Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Fondaparinux

Proprietary Product Name: Arixtra

Sponsor: Aspen Pharmacare Australia Pty Ltd

May 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ACT	Activated clotting time
AE	Adverse-event
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ASA	Australian Specific Annex
ATIII	Anti-thrombin III
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration-time curve extrapolated to infinity
AV	Arterio-venous
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCR	Creatinine clearance
CI	Confidence interval
CK-MB	Creatine phosphokinase MB iso-enzyme
CL	Clearance
CL_{ren}	Renal clearance
C_{max}	Peak plasma concentration
CSR	Clinical study report
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ESC	European Society of Cardiology

Abbreviation	Meaning
Fondaparinux	Fondaparinux sodium/Org31540/SR90107A
FUTURA	Fondaparinux trial with UFH during revascularization in acute coronary syndromes
GCP	Good Clinical Practice
GIK	Glucose-insulin-potassium
GPIIb/IIIa	Glycoprotein IIb/IIIb
HIT	Heparin induced thrombocytopaenia
hr	Hour
HR	Hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IIV	Inter-individual variability
INR	International Normalized Ratio
IU	International units
IV	Intravenous
IVRS	Interactive Voice Response System
kg	Kilogram
LMWH	Low molecular weight heparin
MACE	Major Adverse Cardiovascular Events
max	Maximum
mg	Milligram
MI	Myocardial infarction
mL	Millilitre
NS	Not statistically significant
NSAID	Non-steroidal anti-inflammatory drug
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome

Abbreviation	Meaning
NSTEMI	Non-ST segment elevation myocardial infarction
OASIS	Organisation to assess strategies in acute ischemic syndromes
OR	Odds Ratio
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PE	Pulmonary embolism
PF4	Platelet factor 4
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PT	Prothrombin time
QD	Once-daily
RR	Risk Ratio
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
STEMI	ST segment elevation myocardial infarction
$t_{1/2}$	Half-life
TIA	Transient ischaemic attack
T_{max}	Time to reach C_{max}
UA	Unstable angina
UFH	Unfractionated heparin
V1	Volume of central compartment
V2	Volume of peripheral compartment
Vd	Volume of distribution
VTE	Venous thromboembolic event

Abbreviation	Meaning
Vz	Volume of distribution associated with the terminal phase
WGT	Body-weight

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	21 March 2019
Date of entry onto ARTG:	12 April 2019
ARTG numbers:	97800, 97799, 97798, 80279
, *Black Triangle Scheme*	No
Active ingredient:	Fondaparinux
Product name:	Arixtra
Sponsor's name and address:	Aspen Pharmacare Australia Pty Ltd 34-36 Chandos Street St Leonards NSW 2065
Dose form:	Solution for Injection
Strengths:	2.5 mg in 0.5 mL pre-filled syringe 5.0 mg in 0.4 mL pre-filled syringe 7.5 mg in 0.6 mL pre-filled syringe 10.0 mg in 0.8 mL pre-filled syringe
Container:	Pre-filled syringe
Pack sizes:	7, 10, 15 pre-filled syringes
Approved therapeutic use:	*Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.* *Arixtra is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed without any form of initial reperfusion therapy.*
Route of administration:	Subcutaneous (SC) injection
Dosage:	2.5 mg administered once daily for a maximum of 8 days or until hospital discharge (whichever occurs first). For further details, please refer to the Product Information (PI).

Product background

This AusPAR describes the application by Aspen Pharmacare Australia Pty Ltd (the sponsor) to extend the indications for Arixtra solution for injection pre-filled syringe containing fondaparinux to include the following:

- *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 min) invasive management (PCI) is not indicated.*
- *Arixtra is indicated for the 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.*

The current approved indications for Arixtra are:

- *Arixtra is indicated for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery.*
- *Arixtra is indicated for the prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.*
- *Arixtra is indicated for the treatment of acute deep venous thrombosis (DVT) and acute pulmonary embolism (PE).*

Cardiovascular disease is a leading cause of morbidity and mortality in Australia. In 2015, approximately 1 in 3 deaths were due to cardiovascular disease. Based on hospitalisations and mortality data in 2013, 65,300 Australian adults aged ≥ 25 years had a myocardial infarction or unstable angina (about 180 events per day). There was a 29% decline in events between 2007 and 2013, from 534 to 379 events per 100,000 population.[1] In a recent Australian publication that included patients with ST-segment elevation myocardial infarction (STEMI) presenting to regional and urban/city settings between 2009 and 2016, approximately 75% patients underwent a percutaneous coronary intervention (PCI) (about 50% primary PCI), and approximately 32% were thrombolysed.[2]

The available thrombolytics are alteplase, tenecteplase and reteplase. Streptokinase has not been registered in Australia since 2014. Urokinase has not been registered in Australia since 2000. Bivalirudin, enoxaparin and unfractionated heparin (UFH) are antithrombotic agents registered in Australia for use in unstable angina (UA)/ non-ST segment elevation myocardial infarction (NSTEMI) and in STEMI.

The National Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ) guidelines for Acute Coronary Syndrome (2016);[3] recommend either enoxaparin or UFH is recommended in all patients with acute coronary syndrome (ACS) and intermediate to high risk of ischaemic events. Enoxaparin is preferred over UFH because of the need for activated partial thromboplastin time (aPTT) monitoring of UFH. The standard dosing of enoxaparin is 1 mg/kg subcutaneously (SC) twice daily (BD). For UFH a bolus of

[1] Australian Institute of Health and Welfare: Cardiovascular disease snapshot, 24 July 2018 update https://www.aihw.gov.au/reports/heart-stroke-vascular-disease/cardiovascular-health-compendium/contents/how-many-australians-have-cardiovascular-disease last accessed 31 August 2018
[2] Khan E, Brieger D, Amerena J et al *Differences in management and outcomes for men and women with ST-elevation myocardial infarction* Med J Aust 2018; 209 (3): 118-123.
[3] Chew DP, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016. Heart Lung Circ 2016; 25: 895–951.
https://www.heartfoundation.org.au/getmedia/2d0ac5ab-1fc8-436e-9d74-9aa978d02082/acs-guidelines-short-presentation_2016v2.pdf

60 to 70 international units (IU)/kg intravenous (IV) (max 4000 IU) is followed by an infusion with a commencement rate of 12 to 15 IU/kg/hr and a target aPTT 1.5 to 2.5 x control.

Enoxaparin is recommended over UFH as adjunctive pharmacotherapy to thrombolytics. For patients receiving fibrinolysis for STEMI the recommendation is enoxaparin 30 mg IV bolus (if < 75 years of age) then 1 mg SC BD. For patients ≥ 75 years of age a dose of 0.75 mg/kg SC BD with no IV bolus is recommended.

Guidance is provided for patients undergoing PCI after commencing the recommended antithrombin therapy: for those receiving UFH, an IV bolus, dose adjusted for concomitant glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors and for enoxaparin and additional IV bolus only if the PCI occurs ≥ 8 hr after the last enoxaparin dose.

For primary PCI, UFH or enoxaparin are indicated as antithrombin therapy. The guidelines note the use of GPIIb/IIIa inhibitors or alternatively, bivalirudin in this setting.

Fondaparinux is a parenteral, synthetic, pentasaccharide selective antithrombin-dependent inhibitor of Factor Xa (indirect inhibition). It disrupts the coagulation cascade by selectively binding to antithrombin III (ATIII), potentiating the neutralisation of Factor Xa by ATIII. It has no Factor IIa activity. It is not known to interact with platelet factor 4 (PF4), important in the development of heparin induced thrombocytopaenia.

Regulatory status

Fondaparinux was first registered in Australia in 2002. The currently approved indications are described above.

Fondaparinux was first registered in the European Union (EU) in 2002. The indications were extended to include use in UA/NSTEMI and STEMI in 2007. The EU indications for the 2.5 mg dose are at present:

> *Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.*
> *Prevention of Venous Thromboembolic Events (VTE) in adults 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 adult 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 or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (<120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).*
> *Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.*
> *Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see sections 4.2 and 5.1).*

In Canada, extensions of indications similar to those proposed for Australia were approved in 2007. Fondaparinux is registered for the following indications in Canada at present:

Arixtra (fondaparinux sodium) is indicated for:

- *Prophylaxis of venous thromboembolic events (VTE) for up to one-month post-surgery in patients undergoing orthopaedic surgeries of the lower limbs such as hip fracture, knee surgery or hip replacement surgery.*
- *Prophylaxis of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.*
- *Treatment of Acute Deep Vein Thrombosis (DVT) and treatment of Acute Pulmonary Embolism (PE).*
- *Management of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) for the prevention of death and subsequent myocardial infarction.*
- *Management of ST segment elevation myocardial infarction (STEMI) for the prevention of death and myocardial re-infarction in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy*

Fondaparinux was first registered in in the United States of America (USA) in 2001. The US indications are at present:

Arixtra is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- *in patients undergoing hip fracture surgery, including extended prophylaxis:*
- *in patient undergoing hip replacement surgery;*
- *in patients undergoing knee replacement surgery;*
- *in patients undergoing abdominal surgery who are at risk for thromboembolic complications.*

Arixtra is indicated for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium.

Arixtra is indicated for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

Product Information

The Product Information (PI) approved with the submission, which is described in this AusPAR, can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application that are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2017-03032-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2017
First round evaluation completed	2 May 2018

Description	Date
Sponsor provides responses on questions raised in first round evaluation	2 July 2018
Second round evaluation completed	2 August 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	5 September 2018
Sponsor's pre-Advisory Committee response	20 September 2018
Advisory Committee meetings*	4 and 5 October 2018 7 February 2019
Registration decision (Outcome)	21 March 2019
Completion of administrative activities and registration on the ARTG	12 April 2019
Number of working days from submission dossier acceptance to registration decision*	237

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Background

The dossier for the current submission included quality and clinical data, and a risk management plan (RMP).

The EU guidelines of relevance to this submission are:

- CPMP/EWP/570/98 Points to Consider on the Clinical Investigation of New Medicinal Products in the Treatment of Acute Coronary Syndrome (ACS) Without Persistent ST-Segment Elevation Effective: 19 April 2001
- EMEA/CHMP/EWP/311890/2007Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention Effective: 29 June 2009
- CHMP/EWP/185990 Guideline on Reporting the results of Population Pharmacokinetic Analysis Effective: 27 January 2009
- EMA/83874/2014 Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function: Effective: 10 November 2016
- CPMP/ICH/379/95 ICH Topic E 7Note for Guidance on Studies in Support of Special Populations: Geriatrics Effective: 1 January 1995
- EMA/CHMP/ICH/604661/2009 ICH topic E7: Studies in Support of Special Populations: Geriatrics - Questions and Answers For information: 1 June 2014

Quality

The proposed IV injection is a new route of administration of the already registered chemical entity fondaparinux.

The drug substance has not been changed and is the same as that previously approved.

The quality evaluator has recommended approval of the 2.5 mg/0.5 mL strength of fondaparinux solution for injection for IV dosing from a pharmaceutical chemistry perspective.

Nonclinical

No new nonclinical data were provided with this submission. However, the sponsor provided updated statements for the Use in pregnancy; Use in lactation; Carcinogenicity; and Genotoxicity in the PI that were reviewed and considered acceptable by the nonclinical evaluator.

Clinical

The sponsor provided clinical studies to support the proposed indications.

- One new clinical pharmacology study (Study 63107)
- A population pharmacokinetic study (Study CM2006/00139/00)
- Four Phase II studies (the PENTUA, ASPIRE, PENTALYSE trials, and Study ACT2445);
  - The PENTALYSE trial and Study ACT2445 were included for reference but had been evaluated by the TGA previously.
- Two Phase III studies (Oasis 5 and 6 trials) and one Phase III/IV Oasis 8 trial).

Pharmacokinetics

The pharmacokinetics (PK) of fondaparinux in SC dosing has been previously described. The new information about the pharmacokinetics of fondaparinux has been summarised as follows:

- The mean volume of distribution associated with the terminal phase (Vz) in a single 4 mg IV dose in healthy subjects was 8.8 L.
- Peak plasma concentration (C_{max}) and volume of distribution (Vd) were similar in patients with varying renal function given a single IV dose of fondaparinux. There was a linear relationship between fondaparinux clearance and creatinine clearance. Half-life increased 1.4, 2.2 fold (to 29 hr), 5.5 fold (to 72 hr) for creatinine clearance > 60 to 90 mL/min, > 30 to 60 mL/min, and 10 to 30 mL/min compared to creatinine clearance > 90 to 140 mL/min. No PK data were presented for multiple dosing and no data were presented for SC administration in patients with creatinine clearance 20 to 30 mL/min.

Population PK data (popPK)

A two compartmental model with first order elimination from the central compartment best described the PK of fondaparinux. The distributions of the PK parameters and the residual variability were assumed to be lognormal. Age and gender were not identified as significant covariates for fondaparinux PK, weight was identified as a significant covariate for the central and peripheral compartment volumes and were included in the model. Model simulations predicted C_{max} was similar for IV bolus or IV infusion of 2.5 mg of

fondaparinux over 1, 2, 5, and 15 minutes. Time to reach peak plasma concentration (T_{max}) was sufficiently similar for the bolus, 1 and 2 minute infusions to support dosing instructions for a 1 to 2 minute rapid infusion of fondaparinux in 25 to 50 mL of 0.9% sodium chloride as an alternative to IV bolus dosing.

Estimated inter-individual variability for fondaparinux clearance, volume of the central compartment, and volume of the peripheral compartment was 26.1%, 17.4% and 16.9%, respectively.

Pharmacodynamics

The new pharmacodynamics (PD) information from the study of patients indicated there was a 1.07 and 1.5 fold increase in aPTT and bleeding times, respectively, for patients with creatinine clearance 10 to 30 mL/min compared with > 90 to 140 mL/min.

Efficacy

OASIS 5 trial (Study AR1103420)

OASIS 5 (AR1103420) was a randomised, double-blind, double-dummy, parallel-group, active control, event-driven, Phase III non-inferiority study to compare the safety and efficacy of fondaparinux and enoxaparin in 20,078 patients with UA/NSTEMI on background aspirin conducted between April 2003 and December 2005. Patients were eligible if they could be randomised within 24 hr of symptoms consistent with UA/NSTEMI, and at least two of the following: age ≥ 69 years, cardiac troponin T/I or creatine phosphokinase MB iso-enzyme (CK-MB) above upper limit of normal (ULN), or electrocardiogram (ECG) changes consistent with ischaemia. During the study, the inclusion criteria were expanded to included patients aged < 60 years with ECG changes and elevated cardiac enzymes. The key exclusion criteria were age ≤ 21 years, a contraindication to low molecular weight heparin (LMWH), haemorrhagic stroke < 12 months previously, revascularisation already performed for the qualifying event and severe renal insufficiency defined as a serum creatinine of ≥ 265 µmol/L. Patients could undergo any planned PCI or coronary artery bypass graft (CABG).

Patients were mostly European (80.5%), male (62%) with a mean age of 67.1 years (about 25% ≥ aged 75 years). Cardiovascular risk factors included hypertension (67%), diabetes (25%), smoking (54%, current or former), and about 10% had previous PCI or CABG. The mean systolic blood pressure (BP) was 137 mmHg and about 20% had moderate to severe renal impairment. The qualifying events were UA (about 45%) and NSTEMI (about 55%). Most (about 86%) had no clinical evidence of heart failure.

Study treatments were fondaparinux 2.5 mg SC once daily (QD) for 8 days or until discharge and placebo enoxaparin or enoxaparin 1 mg/kg SC BD for 2 to 8 days or until clinically stable and placebo fondaparinux for 8 days or until discharge. Patients undergoing PCI received clopidogrel and aspirin and at least one minute prior to the insertion of the guiding catheter an IV bolus of either fondaparinux or UFH (enoxaparin arm). All patients were followed for a minimum of 90 days and up to maximum of 180 days (95% were followed for more than 90 days). Heparin flushes of the PCI catheter or other vascular access lines were permitted up to 200 IU/day. If undergoing CABG, patients had treatment interruption 24 hr before and for 48 hr after surgery.

Early discontinuations were in 9.8% and 11.6% for the fondaparinux and enoxaparin groups, respectively, most commonly for bleeding events (fondaparinux 1.6%, enoxaparin 4.7%). Major protocol violations resulting in the exclusion from the per-protocol analysis occurred in 2% and 1.9% of the fondaparinux and enoxaparin, groups respectively; over half were patients that did not meet all the inclusion or exclusion criteria.

The non-inferiority margin was 1.185 for the hazard ratio (HR) and the study had about 85% power to detect a 6 to 10% difference for a 6.2% event rate. No adjustments were made for multiple comparisons. Analyses occurred after 1414 events primary efficacy endpoint events accrued.

The primary efficacy endpoint was the first occurrence of adjudicated death, myocardial infarction (MI) or refractory ischaemia (RI) up to and including Day 9:

> Fondaparinux 5.8%, enoxaparin 5.7%; HR fondaparinux versus enoxaparin 1.01 (95% confidence interval (CI) 0.90, 1.13), p = 0.923. No single component of the composite endpoint was the driver of the outcome for either treatment group.
>
> In patients undergoing PCI, events occurred in 8.6% of fondaparinux and 8.4% of enoxaparin patients. In those not undergoing PCI, events occurred in 4.2% fondaparinux and 4.4% of enoxaparin patients.

The key secondary efficacy endpoints were:

- First occurrence of adjudicated death, MI or RI up to and including Days 14, 30, 90 and 180 (see also Figure 1).
- First occurrence of adjudicated death or MI up to and including Days 9, 14, 30, 90 and 180 (see also Figure Figure 2:2).
- Adjudicated death, MI, or RI assessed separately up to and including Days 9, 14, 30, 90 and 180.

Figure 1: OASIS-5 trial; Kaplan-Meier plot, time to first occurrence of death/myocardial infarction/recurrent ischaemia

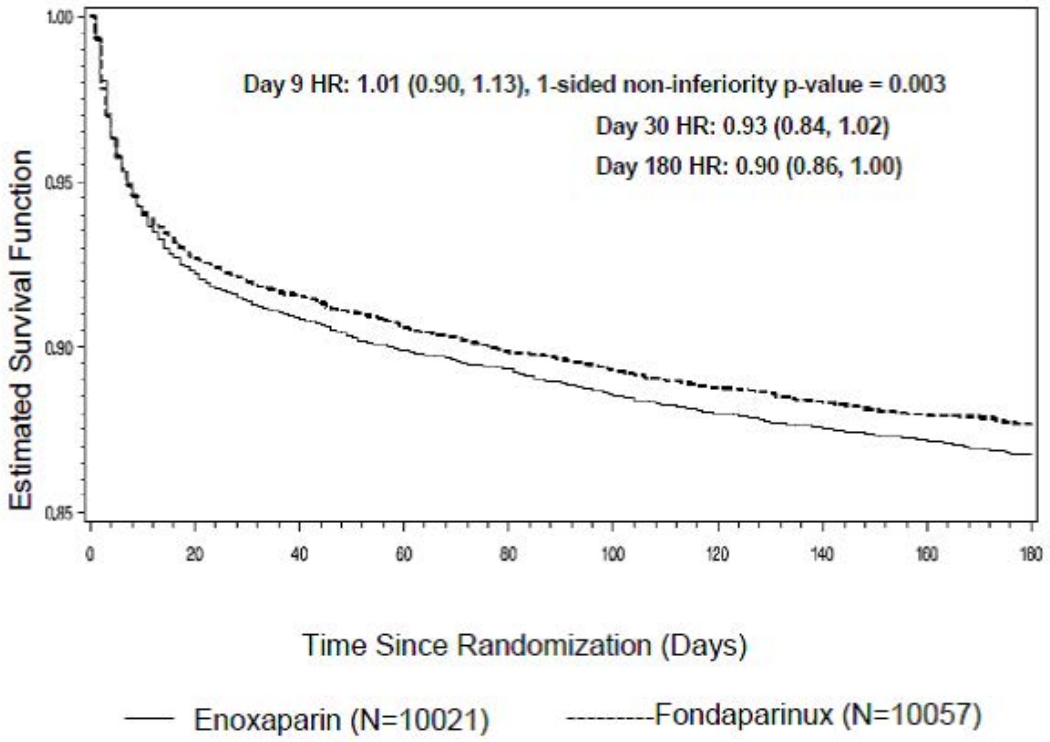
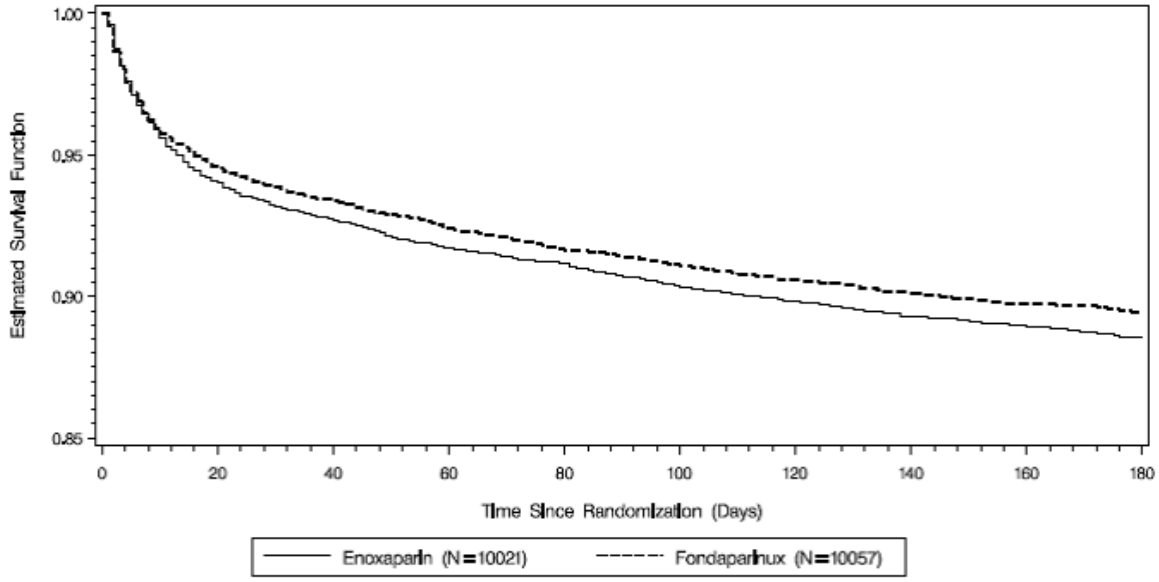


Figure 2: OASIS-5 trial; Kaplan-Meier plot, time to first occurrence of death / myocardial infarction



All key secondary endpoints were overall consistent with the results of the primary endpoint.

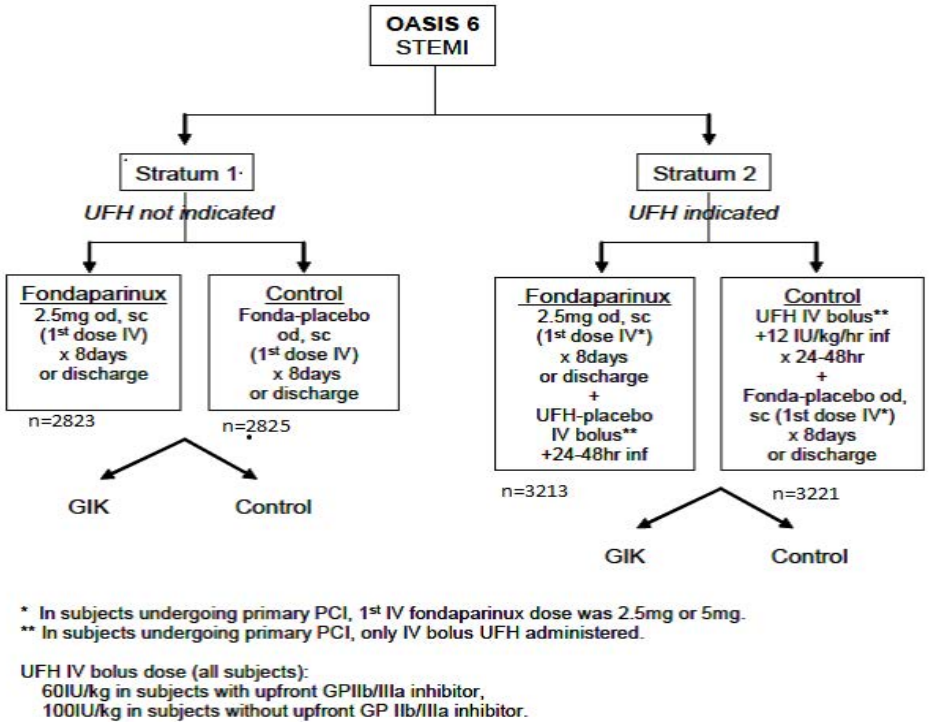
Other efficacy variables included severe ischaemia, stroke, non-fatal cardiac arrest, heart failure and composite death, MI or stroke. A 22% reduction in the overall risk of stroke was reported comparing fondaparinux and enoxaparin but the event numbers were low (1.3% in the fondaparinux group and 1.6% in the enoxaparin group), 0.4% of each treatment group reported stroke at Day 9, and the study was not powered for this comparison.

During their hospital stay, 63% underwent coronary angiography, 34% underwent PCI, and 9% underwent CABG surgery.

OASIS 6 trial (Study AR2103413)

The OASIS 6 trial (Study AR2103413) was a multicentre, multinational, double blind, randomised, controlled, superiority study comparing fondaparinux (n = 6,036) to control therapy (n = 6,056) conducted between August 2003 and January 2006. The following figure describes the study (Figure 3).

Figure 3: OASIS-6 trial; Study schematic



* In subjects undergoing primary PCI, 1st IV fondaparinux dose was 2.5mg or 5mg.
** In subjects undergoing primary PCI, only IV bolus UFH administered.

UFH IV bolus dose (all subjects):
60IU/kg in subjects with upfront GPIIb/IIIa inhibitor,
100IU/kg in subjects without upfront GP IIb/IIIa inhibitor.

There were two strata of initial therapy based on the reperfusion strategy selected by the investigator and the associated need for UFH: Stratum 1: streptokinase or urokinase or placebo, and Stratum 2: thrombolytics (alteplase, reteplase and tenecteplase) requiring UFH to follow the thrombolytic dosage regimen. Once stratified patients could undergo primary PCI, the thrombolytic of investigator choice or could undergo no reperfusion.

Patients were included if they had signs or symptoms of acute myocardial infarction (AMI), ECG changes indicative of a STEMI, and could be randomised within 12 hr of symptom onset. Key exclusion criteria were; age < 21 years, international normalised ratio (INR) > 1.8 on oral anticoagulant, bleeding risk-related contraindication to anticoagulation including haemorrhagic stroke within 12 months, another indication for anticoagulation (not ACS), severe renal insufficiency (serum creatinine ≥ 265 µmol/L), > 5000 IU UFH or LMWH given prior to randomisation, pre-randomisation PCI for the index event as revascularisation or rescue, insulin dependent diabetes (based on insulin requirement and age of onset < 30 years) and serum potassium (K^+) > 5.5 mmol/L. Patients were followed for a minimum of 90 days and a maximum of 180 days. Patients who received thrombolysis and/or UFH therapy prior to randomisation were eligible for the study provided a dose of UFH > 5000 IU had not been received prior to randomisation. Patients were permitted nitrates, angiotensin-converting-enzyme inhibitors (ACEI), beta blockers and antiplatelet agents.

The Stratum 1 study treatments were fondaparinux 2.5 mg QD SC (first dose given IV) or control (placebo given in the same regimen) for up to 8 days or until discharge from the hospital. The Stratum 2 study treatments were fondaparinux 2.5 mg QD SC (first dose given IV) or UFH IV bolus then 12 IU/kg/hr by infusion for 24 to 48 hr titrated to an aPTT of 1.5 to 2 x control and SC placebo for up to 8 days or until discharge. Patients in Stratum 2 undergoing primary PCI received their assigned treatment IV least 1 minute before the insertion of the guiding catheter: either 2.5 mg or 5 mg IV fondaparinux or IV heparin that was dose-adjusted for the use of a GPIIb/IIIa inhibitor.

Most patients were male (72%), of European descent (63%) with a mean age of 61.5 years, and mean weight of 71.5 kg. Most (97%) had ST segment elevation at Baseline, 14% had

heart failure (8.2% more in Stratum 2 than Stratum 1). About 18% had diabetes, 54% had hypertension, 40% were current smokers, and 18% had never smoked. Around 12% had a previous MI, around 3% had previous PCI and 1.2% had previous CABG. The qualifying event occurred 2 to 12 hr prior to randomisation for about 80%. PCI was performed in 31%, 45% received thrombolysis, and 245 did not undergo initial reperfusion.

There were five protocol amendments during the study. Amendment 5 dated March 2005 changed the primary efficacy endpoint assessment from Day 9 to Day 30 and increased the sample size from 10,000 to 12,000 patients to compensate for the endpoint change. A study of 6000 patients in each treatment arm had 84% power to detect a 15% relative HR reduction given a control event rate of 12% and a 5% two-sided α-level. No adjustments were made for multiple comparisons.

Major protocol deviations occurred in 2.2% of the fondaparinux groups and 2.6% of the control groups. Discontinuations occurred in 6.7% of Stratum 1and 9.8% of Stratum 2. The most common single reason was a bleeding event (0.9% for Stratum 1 and 0.4% for Stratum 2).

The primary endpoint was the composite of the time to the first occurrence of death or recurrent MI to Day 30: fondaparinux 9.7%, control 11.1% HR 0.86 (95% CI 0.77, 0.96), p = 0.008.

By strata:

- Stratum 1- fondaparinux versus placebo HR 0.80; 95% CI: 0.69, 0.93; p = 0.003.
- Stratum 2 - fondaparinux versus UFH HR 0.94; 95% CI: 0.79, 1.11; p = 0.460

The Kaplan-Meier (KM) curves for the primary endpoints show divergence early overall and especially for Stratum 1. For Stratum 2 the curves are overlapping to Day 30.

The secondary endpoint of time to death or recurrent MI at each time point measured, that is Day 9, 14, 90 and 180 was favourable for fondaparinux overall but decreased slightly over time (18% risk reduction at Day 9, 12 % risk reduction at Day 180). For Stratum 1 the outcomes were favourable for fondaparinux over placebo, although the upper bound of the HR 95% CI at Day 180 was 1.00. The Stratum 2 the results, while favouring fondaparinux in the proportions of patients with events at each time point, the results were less compelling especially at Day 9 (HR 0.91, 95% CI 0.75, 1.10) and Day 30 (HR 0.94, 95% CI and the point estimates of the HR favoured fondaparinux but the 95% CI all crossed unity.

The secondary endpoint of time to death, recurrent MI or refractory ischaemia at each time point appeared favourable for fondaparinux. Day 9, 14, 90 and 180 was favourable for fondaparinux overall but decreased slightly over time (17% risk reduction at Day 9, 12 % risk reduction at Day 180). The HR for Stratum 2 show the same patterns and very similar results to the secondary endpoint of time to death or recurrent MI and the 95% CI all crossed unity, with very similar results between the two treatment arms to Day 30 and a trend towards fondaparinux at Day 90 and 180. A similar pattern was seen for deaths. The KM curves for fondaparinux and control in Stratum 2 overlap for the first 30 days post intervention for the primary and secondary outcomes.

A *post-hoc* analysis of the results showed benefit of fondaparinux over control for patients not managed with primary PCI. In the same table compared to control the HR for fondaparinux was 0.98 (95% CI 0.67, 1.44) in the subgroup of patients receiving a fibrin specific agent as reperfusion therapy.

OASIS 8 trial (Study AR1108888)

The OASIS 8 trial (Study AR1108888) was a multi-centre, multinational, primary safety study to evaluate the safety of low or standard dose adjunctive IV UFH during PCI in high

risk patients with UA/STEMI after initial treatment with fondaparinux SC and subsequent referral for early coronary angiography conducted between May 2010 and January 2011.

Patients undergoing only coronary angiography were treated with fondaparinux 2.5 mg SC QD and were not randomised. Patients undergoing PCI in addition to coronary angiography were randomised to additional standard dose UFH (85U/kg or 60 U/kg if planned concomitant use of GP IIb/IIIa inhibitor, ACT adjusted) or low dose UFH (50 U/kg with or without GP IIb/IIIa inhibitor, not ACT adjusted) IV bolus. PCI patients also received fondaparinux 2.5 mg SC QD.

Net clinical benefit, relative efficacy of the two dosage regimens during PCI and a comparison of the bleeding and PCI-related complications were the key secondary objectives. Of the 3235 enrolled patients, 2026 patients were randomised and 2017 had index PCI. Including the enrolled patients, the median age was 65.5 years, most were male (64.9%) most were of European descent (72.6%) with a median body mass index (BMI) of 27 kg/m^2 and a median creatinine clearance of 75.72 mL/min. Comparing the randomised and the non-randomised groups there were slightly more males randomised (67.9% versus 49.8% enrolled and there were slightly more subjects of European descent (74.9% versus 68.7% enrolled). Other baseline characteristics were similar. Around a third of patients in each UFH treatment arm discontinued early; the majority due to investigator decision.

The primary endpoint of the composite of peri-PCI major bleeding, minor bleeding, and major vascular access site complications was reported in 4.7% of the low dose UFH group, compared with 5.8% of the standard dose UFH group. The odds ratio was 0.80 (95% CI: 0.54, 1.19; p = 0.267). Comparable event rates occurred in both UFH arms for the individual components of the endpoint. The composite of peri-PCI major bleeding or target vessel revascularisation (TVR) occurred in 5.8% of the low dose UFH group and 3.9% of the standard dose UFH (odds ratio (OR) 1.51 (95% CI: 1.00, 2.28)). The composite of death, MI or TVR to Day 30 occurred in 4.5% of the low dose UFH group and 2.9% of the standard UFH group (OR 1.58 (95% CI: 0.98, 2.53)). Major bleeding and death at Day 30, MI at Day 30 or TVR at Day 30 were similar between the two groups. Catheter thrombosis is discussed in the Safety section, below.

ASPIRE trial (Study AR1104574)

The ASPIRE trial (Study AR1104574) was a Phase IIb pilot study comparing fondaparinux 2.5 mg, fondaparinux 5 mg and UFH, with or without planned IV GPIIb/IIIa inhibition as a primary anticoagulant strategy in 350 patients undergoing PCI either for ACS or as an elective procedure, conducted between June 2003 and January 2004. The dose of UFH was adjusted for the use of GPIIb/IIIa inhibition. The trend for a lower event rate in the 2.5 mg fondaparinux dosage group for the primary outcome of re-infarction, urgent revascularisation, death, or the need for bailout GPIIb/IIIa inhibitor was supportive for the use of this dose in the Phase III studies.

PENTUA trial (Study 63119)

The PENTUA trial (Study 63119) was a multicentre, double-blind, double-dummy, randomised, active-control, dose-ranging study conducted between July 1999 and July 2001 that compared 4 doses of fondaparinux (2.5 mg, 4 mg, 8 mg and 12 mg) and enoxaparin (1 mg/kg BD), in addition to aspirin, in 1147 patients with unstable angina or non-Q wave MI without persistent ST elevation.[4] Patients with a STEMI and those scheduled for PCI within 24 hr of CABG within 48 hr were excluded. Fondaparinux dosing was adjusted for body weight. Patients in the fondaparinux arms received an initial IV

[4] Angina at rest or minimal exertion < 24 hours before screening ECG with either dynamic ST changes or clear ST depression of > = 1 mm +/- serum cardiac troponin (T or I) > 0.1 ng/mL.

bolus of assigned dose on Day 1 with 3 to 7 days of SC dosing. Enoxaparin patients received placebo IV and 3 to 7 days of SC BD dosing thereafter. Patients not on ongoing aspirin were given a 200 to 500 mg oral or IV loading dose as soon as possible after admission, maintenance was oral or IV aspirin 75 to 100 mg in the morning for at least 30 days. The primary endpoint was a composite of all-cause mortality (excluding bleeding), AMI and recurrent symptomatic ischaemia at Day 9. Doses higher than 2.5 mg did not offer a benefit for the primary endpoint at Day 9 or Day 30, and supported the use of a 2.5 mg dose in the subsequent trials.

PENTALYSE trial

The PENTALYSE trial was a multicentre, open-label, randomised, active-control, parallel group, dose-ranging study to assess the safety and tolerability 3 doses of fondaparinux (4 mg, 8 mg and 12 mg) and UFH as adjunctive therapy to recombinant tissue plasminogen activator (rtPA) and aspirin in AMI. This study had been previously evaluated by the TGA and was not re-evaluated.

Safety

An integrated safety summary was not provided. Of the total 29,849 patients in the OASIS 5 and 6 trials, 15,913 were exposed to at least one dose of fondaparinux 2.5 mg. An additional 364 patients were exposed to the 2.5 mg fondaparinux dose in the Phase II studies and 2026 in the OASIS 8 trial. All exposures were of relatively short duration with a median of 6-8 days in the Phase III studies, a median of 3 days in the OASIS 8 trial, and 4 to 5 days in the Phase II studies.

In the OASIS 5 trial, treatment emergent adverse events (TEAEs) were reported for 24% of fondaparinux patients and 28% of enoxaparin patients. The most common events (fondaparinux versus enoxaparin) were headache (2% versus 2%), chest pain (1% versus 1%) and atrial fibrillation (1% versus 1%). In the OASIS 6 trial, overall TEAEs were reported for 32% and 33% of the controls. The most common events were pyrexia (3% versus 3%), atrial fibrillation (3% versus 2%), chest pain (2% versus 1%) and headache (2% versus 2%). In the OASIS 8 trial, in the nonrandomised group, 20.6% reported at least 1 adverse event (AE) but no single events occurred in more than 1.5% of patients. In this group, the most common events were headache (1.5%), gastritis (1.2%) urinary tract infection (1.2%), asthenia (1.1%) and pyrexia (1.1%). In the all randomised group, TEAEs were reported in 21% of patients with no meaningful differences between the low and standard UFH groups. Headache (2.6%), pyrexia (1.3%) and sheath site ooze (1.2%) were the common events. In the ASPIRE trial, the AE profiles were similar across the fondaparinux groups. Compared to UFH events were puncture site haemorrhage (5% versus 7%), angina (4% versus 8%), chest pain (3% versus 3%), headache (3%, versus 6%), coronary artery embolism (3% versus 0%), and syncope vasovagal (3% versus 4%). In the PENTUA trial, AEs occurred in similar proportions in the groups. Common events were headache, constipation, phlebitis, hypercholesterolaemia and back pain.

Deaths were included as part of the efficacy endpoint and were reported as additional efficacy endpoints in the pivotal studies. In the OASIS 5 trial, deaths in the fondaparinux/enoxaparin groups occurred in 1.8%/1.9%, 2.1%/2.4%, 2.9%/3.5%, 4.6%/5.1%, 5.7%/6.4% at Days 9, 14, 30 90 and 180, respectively. In the OASIS 6 trial, overall deaths occurred in 7.8% and 9% of the fondaparinux and control groups: In Stratum 1 9.1% versus 11.3% and in Stratum 2, 6.7% versus 6.7%. In the OASIS 8 trial, deaths at Day 30 occurred in 0.8% of the low dose and 0.6% of the standard dose UFH groups in the randomised population and in the non-randomised population in 2.2% (1.8% cardiovascular, 1.5% re-infarction). In the ASPIRE trial, 2 deaths occurred (one haemorrhagic after an internal iliac artery dissection and one coronary thrombosis; both

after PCI). In the PENTUA trial, there were 12 deaths up to Day 9 of these 10 were cardiac and two were of cause unknown. There was no clear relationship to dose.

In the OASIS 5/OASIS 6 trials, serious adverse events (SAEs) were reported in 4%/3% of the fondaparinux groups and 5%/4% of the control groups. Haemorrhage and procedure complications were the most common. In the OASIS 8 trial, 4% of the non-randomised and 2.4% of the all-randomised had at least one SAE. The most commonly reported across the study were pneumonia, toxic nephropathy (8 in randomised and 2 in non-randomised groups) and acute renal failure (3 each in the randomised and non-randomised groups). In the ASPIRE trial, SAEs were reported for 8%, 13%, and 7% of the fondaparinux 2.5 mg, fondaparinux 5.0 mg and UFH groups, respectively The most commonly reported SAEs by System Organ Class (SOC) were in Cardiac disorders (combined fondaparinux 3%; UFH 3%) and Vascular disorders (1% versus 2%).

Discontinuations due to AEs occurred in 1% of the fondaparinux groups and 2% of the control groups in the OASIS 5 and OASIS 6 trials. The numbers of individual events were small and the types of AEs were similar between the groups; most commonly across both studies were haemorrhagic events, acute renal failure, and pulmonary embolism. In OASIS 8 trials, 0.6% of the 1209 non-randomised patients had SAEs resulting in discontinuation. No two patients reported the same event. Of the 2026 randomised patients, 0.4% had SAEs leading to discontinuation. Renal failure was the only event that occurred in more than one patient (2 patients in the standard UFH group). No discontinuations due to AEs were reported in the ASPIRE trial, and discontinuations due to AEs in the PENTUA trial ranged from 0 in the 2.5 mg group and 1.7% in the 12 mg group and 0.9% in the enoxaparin group. Bleeding occurred in more than on patient in the enoxaparin and fondaparinux groups (1 patient in the 4 mg group, 3 in the 12 mg group and 2 in the enoxaparin group).

Adverse events of regulatory interest

Bleeding events

In the pivotal studies, bleeding events were the primary safety endpoint. In the OASIS 5 trial;[5] 1.8% versus 3.4% of the fondaparinux and enoxaparin groups had major bleeding on therapy (within 2 days of last dose), and 2.1% versus 4.1% at Day 9. Throughout the study, lower numbers of cumulative major bleeding events occurred in the fondaparinux groups compared to the enoxaparin group (4.1% versus 5.6% at Day 180). In patients undergoing PCI while on the study drug, major bleeding to Day 9 occurred in 1.9% versus 4.3% of fondaparinux versus enoxaparin patients. Fatal haemorrhage occurred in 2.9% versus 3.5%. Similar results were obtained using modified thrombolysis in myocardial infarction (TIMI) criteria for bleeding. [6]

In the OASIS 6 trial, severe bleeding was classified according to the modified TIMI criteria.[6] Across the study, 1.1% versus 1.4% of the fondaparinux and control groups had events. Bleeding events by Strata occurred in 1.0% versus 1.6% (Stratum 1) and 1.3% versus 1.2% (Stratum 2) in the fondaparinux versus control groups. In the 'on-therapy' analysis, events occurred in 1.0% versus 1.3% the fondaparinux group versus control group. There were trends in favour of the placebo group in Stratum 1 but no difference between groups in Stratum 2. ICH occurred in 0.2% of all groups.

[5] In OASIS 5 major bleeding was defined as fatal, symptomatic intracranial haemorrhage (ICH), retroperitoneal haemorrhage, intraocular haemorrhage leading to significant visual loss, or a decrease in haemoglobin (Hb) of > = 3 g/dL or requiring transfusion of > = 2 units of blood. This was revised to include bleeding requiring surgical intervention (removed from minor bleeding criteria). Minor bleeding did not meet the definition of major bleeding but required interruption for > = 24 hours, surgical intervention of 1-unit blood transfusion.
[6] Modified TIMI criteria: fatal haemorrhage, intracranial haemorrhage, cardiac tamponade, or clinically significant bleeding with a decrease in Hb of > 5 g/dL (each transfused unit counting as 1 unit).

In the OASIS 8 trial in the randomised groups, the composite of major bleeding, minor bleeding and major vascular complications occurred in 4.7% and 5.8% with low and standard UFH regimens, respectively. In the ASPIRE trial, 6.4% of the overall fondaparinux and 7.8% UFH groups, and 3.3% of the 2.5 mg and 9.6% of the 5 mg fondaparinux groups. In the PENTUA trial, any bleeding event was reported for 3.9% to 4.5% in the fondaparinux groups and 4.8% in the enoxaparin groups. In the PK study (Study 63119), there was no linear dose response relationship between fondaparinux dose and any bleeding event.

Thrombocytopaenia

Thirty patients in the fondaparinux treatment arms of the OASIS 5 and 6 trials, 20 patients on enoxaparin (OASIS 5 trial) and 6 patients in the OASIS 6 trial control arms developed a thrombocytopaenia AE up to Day 30. Eight patients in the fondaparinux treatment arms of the OASIS 5 and 6 trials, 9 patients on enoxaparin (OASIS 5 trial) and 2 patients in the OASIS 6 trial control arms developed a thrombocytopaenia SAE up to Day 30.

Heparin induced thrombocytopaenia (HIT) was reported for 4 fondaparinux patients and 0 enoxaparin patients in the OASIS 5 trial. In the OASIS 6 trial, 1 case occurred in the UFH arm. All 3 HIT SAEs occurred in the fondaparinux arm of the OASIS 5 trial. In an analysis of events, the sponsor found recent exposure to a heparinoid product as the explanation for HIT seen in a fondaparinux treatment arm.

PCI associated safety

In the OASIS 5 trial, 2854 patients in the fondaparinux group and 2741 in the enoxaparin group had 2888 and 2781 procedures, respectively, during their initial hospitalisation while taking study therapy. Vascular site complications occurred in 3.2% of fondaparinux and 7.2% of enoxaparin patients. Other coronary complications occurred in 12.7% and 10.0% of fondaparinux and enoxaparin patients, including abrupt closure of the coronary artery (1.7% versus 1.3%), new angiographic thrombus (3.2% versus 1.8%), investigator reported catheter thrombus (1.3% versus 0.4%) and catheter thrombus confirmed by adjudication (1.0% versus 0.3%). Death occurred in 0.3% and 0.4% of the respective groups, and stroke occurred in two (< 0.1%) patients in each group.

In the OASIS 6 trial, after at least one dose of study medication, 1862 fondaparinux and 1853 control patients underwent primary PCI and 229 and 215 fondaparinux and control patients, respectively, underwent non-primary PCI. In the OASIS 6 trial, in patients undergoing PCI after at least one dose of fondaparinux adjudicated catheter thrombosis more frequent in the fondaparinux group (22 patients, 1.2%) compared with the UFH group (0%). In the OASIS 6 trial, vascular site complications occurred in 1.7% and 1.9% of the fondaparinux and control groups, respectively. Other coronary complications occurred in 11.2% of the fondaparinux group and 8.6% of the control group.

In the OASIS 8 trial, guiding catheter thrombosis was a prospectively sought outcome; reported for 5 patients (0.5%) in the low dose UFH dose group and one (0.1%) in the standard UFH dose group, and sheath thrombosis occurred in 0.3% and 0.2% of the low UFH and standard UFH dose groups.

Hypersensitivity

Hypersensitivity reactions were uncommon and reported in <1% of patients, however anaphylactic shock was reported for one patient each in the fondaparinux and enoxaparin groups in OASIS 5, and 1 patient in the fondaparinux arm in the OASIS 6 trial. One patient in a control arm of OASIS 6 had an anaphylactoid reaction.

Special populations

The evaluator noted a trend to greater numbers of AEs in the elderly and with creatinine clearance < 20 mL/min, but overall by subgroup in the two pivotal studies event rates were similar across the treatment arms.

Creatinine clearance 20 to 30 mL/min

In the OASIS 5 trial, 241 and 242 patients in the fondaparinux and enoxaparin groups had a creatinine clearance of ≥ 20 to ≤ 30 mL/min. In OASIS 6, 109 fondaparinux patients (54 in Stratum 1 and 55 in Stratum 2) and 105 control patients (54 in Stratum 1 and 51 in Stratum 2) had a creatinine clearance of ≥ 20 to ≤ 30 mL/min. In patients with creatinine clearances, the efficacy outcomes, while numerically in favour of fondaparinux had overlapping confidence intervals, however for major bleeding events a clinically meaningful difference in favour of fondaparinux was seen. In OASIS 6, the sponsor presented an analysis for the whole study cohort by renal function. While little difference was seen for efficacy, a reduction in bleeding events was seen, although there is some overlap of the confidence intervals with the control event result. In a regression analysis there was an interaction between treatment and renal function (p = 0.017), attributed to the greater treatment effect in normal renal function patients for the whole study (HR = 0.77, 95% CI; 0.61, 0.96) compared to patients with moderate renal impairment (HR = 0.90, 95% CI 0.73, 1.12).

Post market

No new safety signals emerged from the Periodic Safety Update Report (PSUR) data presented in this submission.

Risk management plan

The RMP evaluator has reviewed European Union-Risk management plan (EU-RMP) version 2.0 (dated 31 August 2015; data lock point (DLP) 6 December 2013) and Australian specific Annex (ASA) (version 2.0 dated June 2018).

The Summary of safety concerns from the RMP are outlined in Table 2.

Table 2: Summary of safety concerns[7]

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	Bleeding events	ü	–	ü	–
	Off label use (VTE treatment and prevention)	ü	–	ü	–
	Catheter thrombosis during PCI when fondaparinux is used as sole anti-coagulant adjunct to PCI (for the treatment of ACS)	ü	–	ü	–
Important potential risks	Heparin induced thrombocytopenia	ü	–	ü	–
	Use of higher VTE treatment doses (5mg, 7.5mg, 10mg) for treatment of superficial-vein thrombosis	ü	–	ü	–
	Use of fondaparinux 2.5mg in superficial-vein thrombosis patients with concomitant DVT	ü	–	ü	–
Missing information	Use in paediatric patients	ü	ü*	ü	–

*VTE treatment study in paediatric patients (planned - commitment to the US Food and Drug Administration)

The pharmacovigilance and risk minimisation plans listed in the table were considered acceptable. This product is not proposed for the Black Triangle Scheme.

Recommended condition of registration

The RMP evaluator has recommended the following condition of registration.

[7] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;

Meeting other local regulatory agency requirements.

The Arixtra EU-Risk Management Plan (RMP) (version 2.0 (date 31 August 2015; DLP 6 December 2013), with Australian Specific Annex (version 2.0, dated June 2018), included with submission PM, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports should at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

It is recommended that the Consumer Medicine Information (CMI) be updated to include the instructions for use, and the CMI be provided in the box to ensure information on use is readily available to consumers.

Risk-benefit analysis

Delegate's considerations

Efficacy

The sponsor has proposed two separate indications for fondaparinux. These are described below.

Unstable angina and NSTEMI

The efficacy for this extension of indications is primarily supported by evidence from the OASIS 5 trial, a non-inferiority study that compared fondaparinux to enoxaparin, treating patients for the duration of their in-patient stay. The choice of comparator was generalisable to the Australian context.

In this study of approximately 20,000 patients, fondaparinux was non-inferior to enoxaparin for the primary efficacy endpoint of adjudicated death, MI or refractory ischaemia to Day 9 after up to 8 days of treatment (HR 1.01, 95% CI 0.90, 1.13, p = 0.923). Revascularisation with PCI was not a major influence on the efficacy of fondaparinux. The outcomes were generally consistent for the components of the composite endpoint and were not driven by any single component. The secondary efficacy outcomes were consistent. The initial effect was sustained over the 180 days of the study and there was no apparent rebound phenomenon for cardiovascular events after the discontinuation of fondaparinux. Revascularisation with PCI at some time after randomisation was not a major influence on the efficacy of fondaparinux.

The use of an antithrombotic agent is expected to carry a risk of bleeding events. Major bleeding events occurred in 1.8% of the fondaparinux and 3.4% of the enoxaparin patients. In patients undergoing PCI vascular access, site complications were less frequent with fondaparinux while other catheter complications such as catheter thrombosis were more frequent in this group. The other adverse effects showed a safety profile consistent with that previously seen for fondaparinux. Although occasions of HIT, mostly after the treatment period were reported in the fondaparinux group, other explanations were

provided for these cases. Anaphylaxis has been noted as a rare event in post-market reporting, and consistent with these findings, rare events of anaphylaxis were reported in the clinical trial program for the cardiac indications. Some support is provided from the OASIS 8 trial. In particular, it demonstrated how IV UFH could be used in the context of PCI in patients with these diagnoses on fondaparinux. It did not provide a direct comparison of UFH and no UFH in PCI with background fondaparinux. Considering this, the sponsor's proposed dosing instruction to use IV UFH with PCI seems reasonable. Data from the PENTUA trial support fondaparinux 2.5 mg in patients not undergoing PCI.

It is noted that this indication was approved in Canada and the EU in 2007 so there is more than 10 years of international experience with its use in this indication that provides some support. It is also noted that the European Society of Cardiology (ESC) guidelines make specific reference to fondaparinux for this indication.

Overall, fondaparinux was non-inferior to enoxaparin, and when used in accordance with the proposed indication the benefits and risks appear acceptable for the proposed use. The sponsor proposes that it should not be used as the sole antithrombotic agent in PCI, reducing the risk of PCI thrombotic complications.

STEMI

The efficacy for this extension of indications is primarily supported by evidence from a subset of patients in the OASIS 6 trial. This study allowed intervention for index STEMI event based on investigator preference, and patients could be enrolled after an initial intervention of thrombolysis had occurred provided all other inclusion criteria were met. How these patients were included in the analysis is somewhat unclear and clarification is sought from the sponsor.

The study was stratified according to which group of thrombolytics would have been offered if a thrombolytic were the chosen treatment: streptokinase or urokinase (Stratum 1) or fibrinolytic therapy (alteplase, reteplase, tenecteplase; Stratum 2). The strata differed in the anticipated need for UFH following reperfusion therapy, and therefore whether the control group was IV UFH or placebo.

In each group, not all patients underwent the available thrombolysis. About 24 % in each group had no urgent revascularisation and about 31% had a primary PCI. Regardless, the patients in control group of Stratum 1 received placebo and the patients in the control group of Stratum 2 received UFH. The treatments in the control groups between the strata were not equal but they were grouped for the overall comparison of fondaparinux. Because streptokinase and urokinase are no longer available in Australia the generalisability of the study as a whole to the Australian context is uncertain. This raises an issue of generalisability just under half of Stratum 1 received a treatment no longer registered in Australia.

This was a superiority study. While compared to the grouped controls combined, the combined fondaparinux groups were superior to controls for the primary efficacy endpoint, driven by the outcomes from Stratum 1. Across Stratum 2 fondaparinux was not superior to control, but the outcomes were similar and generally numerically in favour of fondaparinux. The efficacy of UFH would be expected to differ from placebo *a priori* and this may have contributed to the different outcomes from the two Strata. The choice of inactive comparator in one Stratum limits the generalisability to current Australian practice.

Bleeding events were similar for fondaparinux and either control treatment. The major difference in safety was in the PCI population where no UFH was given. Catheter thrombosis occurred in 10 fondaparinux patients, 8 of whom were in Stratum 1, and no patients in the control groups. The sponsor does not propose STEMI patients undergoing

primary PCI should be part of the indicated population and this would seem reasonable given the findings.

In the post hoc analysis of the remainder of the study (in which the primary PCI patients were excluded), combined fondaparinux groups had a favourable outcome over the combined controls, although again this was driven by Stratum 1 and results were similar for the two groups for Stratum 2.

There are a number of issues with this study and which weaken the evidence to support the proposed indications. The stratification into thrombolysis group and therefore this activity of the control treatment potentially introduces bias. There was an active control in addition to background therapy in only one Stratum but pooling of active and inactive controls for the overall study. While across the study, superiority of fondaparinux was demonstrated, against active control it was not. Stratum 2 is most generalisable to the Australian context. The use of UFH is mentioned as a treatment option in the Australian guidelines for the management of STEMI, and the thrombolytics that could have been used for patients in Stratum 2 are currently available in Australia and are recommended treatment options in the Australian guidelines. It is reasonable to exclude patients with primary PCI from the indication for safety reasons and the *post-hoc* analysis of the study removing these patients demonstrates similar results to the primary analysis. While the numbers of events are favourable for fondaparinux in Stratum 2, fondaparinux was not superior and the HR 95% CI cross unity. It is recognised that the study was designed to be considered as a whole and interpreted in that manner. However, this exploration of the study design and the issues that this raises reduces confidence in the strength of the evidence that is provided to support the STEMI indication in Australia in 2018. The indication has been approved in the EU and Canada in 2007 so there may be post market experience with its use in this setting. It is noted that in the current ESC guidelines fondaparinux after thrombolytics is not listed as recommended treatment and it is specifically not recommended in the context of primary PCI in STEMI, although it is recommended for non re-perfused patients until coronary revascularisation or hospital discharge. The extent of use for this indication is unknown. As there is no confirmatory Phase III or IV data and the PENTALYSE trial uses different fondaparinux doses and so is of limited support, it is considered that the evidence is not strong to support the proposed indication.

Use in chronic kidney disease

Patients with chronic kidney disease and creatinine clearance 20 to 30 mL/min were eligible for inclusion in the pivotal studies. In these studies, the SC dose was 2.5 mg without dose adjustment. An analysis of this population was limited as are the patient numbers, but there was limited evidence to support the use of fondaparinux for UA/NSTEMI. This is a patient group at increased risk of cardiovascular disease and increased risk of bleeding events. It is expected that any decision to use fondaparinux in this setting would be based on a consideration of the benefits and risks for the individual patient. A precautionary statement to this effect and that the evidence to support this use of fondaparinux in the setting of the proposed indications is limited is proposed for inclusion in the PI.

Adjustment for multiple comparisons

No adjustments for multiple comparisons were made. The sponsor has conducted statistical tests for the primary and secondary endpoints and subcomponents in both the OASIS 5 and 6 trials without adjustment for the overall α-level. This is considered a deficiency in the statistical analysis plan. The claims of statistical significance for the secondary endpoints are viewed with caution and such claims and the p-values should therefore be removed from any description of the clinical trials in the PI.

Dose

The proposed 2.5 mg SC dose is consistent with the dosing in the pivotal studies and is supported. The PK of a single bolus or short infusion supports the proposed IV bolus dose and dilution instructions.

The data from the OASIS 5 and 6 trials support use in patients with creatinine clearance ≥ 30 mL/min without dose adjustment.

Data deficiencies

There are no data regarding drug interactions that may result in the reduced renal clearance of fondaparinux.

There are no data comparing fondaparinux and enoxaparin in patients with STEMI.

Special populations

There is a planned VTE treatment study in paediatric patients noted in the RMP for VTE treatment. There are no planned studies in paediatric patients for the requested indications. This is considered acceptable.

Commentary on the use of fondaparinux in patients with chronic kidney disease is included in the discussion above. The sponsor has proposed that fondaparinux should not be used in patients with a creatinine clearance of < 30 mL/min, consistent with the current recommendations for the approved indications.

Conclusion

Based on the evidence provided and pending any comments from the Advisory Committee on Medicines (ACM) the indication for UA/NSTEMI is proposed for approval.

The evidence is less robust for the proposed indication in STEMI. At this time there is uncertainty regarding the efficacy evidence provided to support this indication; given that the indicated population is derived from a subset of the population studied, and the lack of generalisability of the thrombolytics of Stratum I to the Australian context, the lack of superiority of fondaparinux over IV UFH, and the lack of generalisability of that control treatment to the current Australian context in the Stratum II. The risk of catheter thrombosis in primary PCI is also of concern, although a statement identifying this concern is proposed for the PI. This is countered by over a decade of approval in the EU and Canada. Overall, pending the advice of the ACM, efficacy is uncertain for fondaparinux for this indication. Based on this uncertainty, it is not currently proposed for approval.

Proposed action

The Delegate has no reason to say, at this time, that the application for fondaparinux (Arixtra) should not be approved for the UA/NSTEMI indication

> *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) for whom urgent (< 120 min) invasive management (PCI) is not indicated.*
>
> *Arixtra is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.*

Proposed conditions of registration

The following is the proposed condition of registration for fondaparinux:

> The Arixtra EU-Risk Management Plan (RMP) (version 2.0 date 31 August 2015; DLP 6 December 2013), with Australian Specific Annex (version 2.0, dated June 2018), included with submission PM, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
>
> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports should at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Request for ACM advice (October 2018 meeting)

1. Has sufficient evidence been provided to support the safety and efficacy of fondaparinux for the UA/NSTEMI indication?
2. Has sufficient evidence been provided to support the safety and efficacy of fondaparinux for the proposed STEMI indication? In particular, please comment on:
    a. The reperfusion strategies used in the pivotal studies and the choice of agents in the comparator arms.
    b. A *post-hoc* analysis has identified subgroups with favourable outcome from this study that form the basis of the proposed indication. If PCI patients are excluded from the OASIS 6 trial data set, is the evidence sufficiently robust to support the proposed indication?
    c. The dosing instructions only mention UFH for the STEMI indication, reflecting the clinical trials. Please comment on this approach given other medicines are also approved for this use.
3. Does the committee have any concerns regarding the use of fondaparinux in the peri-PCI period when used in accordance with the proposed dosing instructions? Is the warning about catheter sheath thrombosis sufficient?

Questions for sponsor

1. Regarding the OASIS 6 trial:
    a. Were patients given thrombolytics prior to randomisation considered to have been 'thrombolysed' even though this occurred prior to randomisation or were they considered 'not re-vascularised' because the thrombolysis occurred prior to randomisation? What was the distribution of pre-thrombolysed patients across the four treatment groups?
    b. Please provide a comparison of fondaparinux and control for the overall study and for each of the Strata separately for the patients who were not re-vascularised.

c. Please provide a justification for grouping placebo from Stratum 1 and UFH from Stratum 2 into a single control group given the difference in expected efficacy and safety profile of placebo and heparin.

2. Please explain why there was no adjustment for multiple comparisons (reduction of type I error rate) in the OASIS 5 and 6 trials given that the same data were included in the statistical testing of several endpoints in the studies. In what order did the statistical testing of the subgroups for the primary endpoint and the key secondary endpoints occur?

3. The RMP evaluator recommended the instructions for use should be included in the CMI and that it should be included in the carton. Please indicate how the sponsor proposes to address this request.

Advisory committee considerations (October 2018 meeting)[8]

The ACM, taking into account the submitted evidence of efficacy and safety, agreed that Arixtra solution for injection in pre-filled syringe containing: 2.5 mg in 0.5 mL; 5.0 mg in 0.4 mL; 7.5 mg in 0.6 mL; 10.0 mg in 0.8 mL of fondaparinux has an overall negative benefit-risk profile for the proposed indications:

> *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.*
>
> *Arixtra is indicated for the 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.*

The ACM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Arixtra in the proposed extended indications.

In providing this advice, the ACM noted the following:

- The clinical evidence to support registration of both proposed indications was from clinical trial data from over ten years ago. The applicability of these trials results were therefore of uncertain clinical relevance given the differences to contemporary standard of care.
- In the OASIS-5 trial, the Phase III study to compare the safety and efficacy of fondaparinux and enoxaparin in patients with UA/NSTEMI, non-inferiority in the primary efficacy endpoint of first occurrence of adjudicated death, MI or refractory ischaemia up to and including Day 9 was demonstrated. Although a lower proportion of patients in the fondaparinux group experienced major bleeding events compared to the enoxaparin group, the ACM considered that these bleeding events appeared to be a likely consequence of femoral artery access (utilised in 88% of patients who

[8] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM), which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

underwent PCI in the OASIS-5 trial). Bleeding complications occur far less commonly in current practice, with the increasing preference for use of radial access.

- Data from the Victorian Cardiac Outcomes Registry Annual Public Report (2017);[9] confirms the increased use of the radial artery for arterial access, and shows that the rate of radial access for acute STEMI was 66% in 2017. The report also describes that in patients undergoing PCI for STEMI, primary PCI (within 12 hours, without preceding thrombolytic) was used in 87.2% of cases. In-hospital major bleeding rates for STEMI was 1.7% and for non-ST elevation -ACS 0.6%.
- The STEMI indication is primarily supported by evidence from a subset of patients in the OASIS-6 trial, which was designed as a superiority study. The treatment pathway described in the OASIS-6 trial does not resemble current practice, that is, only around 31% of STEMI patients had a primary PCI (though this was not defined in the paper, and may or may not be consistent with the time frame defined in current use of the term), while in current practice the vast majority of patients would have primary PCI. Patients in Stratum 1 received thrombolytic treatment that is no longer administered or available in the Australian setting (streptokinase or urokinase). In the subgroup in whom the thrombolytic agent resembles current (though limited) practice (Stratum 2, received alteplase, reteplase and tenecteplase) fondaparinux was not found to be superior to control.
- Fondaparinux has a once daily dosage regimen compared to enoxaparin, which is administered twice daily. In theory, the ACM considered that with its shorter half-life, enoxaparin may afford a benefit with regard to safety in the context of multiple antiplatelet and/or anticoagulant therapies in this population.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. Has sufficient evidence been provided to support the safety and efficacy of fondaparinux for the UA/NSTEMI indication?

The ACM noted that the OASIS-5 trial demonstrated non-inferiority of fondaparinux compared with enoxaparin for the UA/NSTEMI indication, however considered that due to changes in clinical practice since the time the trial was undertaken, particularly with the adoption of radial access as an alternative to femoral access, access-site bleeding has reduced and current enoxaparin use is associated with significantly less bleeding than described in the trial data provided (5.1% reported in enoxaparin arm for major bleeding; Victorian registry data from 2017 reports 0.6% in-hospital major bleeding rate for non-ST elevation ACS).[9] The trial data provided is therefore uninformative with respect to the comparative risk of bleeding between fondaparinux and enoxaparin in the contemporary clinical setting.

2. Has sufficient evidence been provided to support the safety and efficacy of fondaparinux for the proposed STEMI indication? In particular please comment on:

a. The reperfusion strategies used in the pivotal studies and the choice of agents in the comparator arms.

[9] A/Prof Jeffrey Lefkovits, Ms Angela Brennan, Dr Diem Dinh, Prof Andrea Driscoll, Dr Dion Stub, Ms Harriet Carruthers, Mrs Janine Doyle, Dr Kristen Tytler and Prof Chris Reid on behalf of the VCOR. The Victorian Cardiac Outcomes Registry Annual Report 2017. Monash University, SPHPM August 2018, Report No 5, pages 79.

The reperfusion strategies described in the OASIS-6 trial are significantly different to current practice. In particular, it was noted that a relatively low proportion of patients received primary PCI in the trial, and thrombolytic agents were used that are no longer available in the Australian context (streptokinase, urokinase).

b. A *post hoc* analysis has identified subgroups with favourable outcome from this study that form the basis of the proposed indication. If PCI patients are excluded for the OASIS 6 trial data set is the evidence sufficiently robust to support the proposed indication?

The ACM noted that in Stratum 2 of the OASIS-6 trial data set, there was little apparent benefit of fondaparinux in those undergoing primary PCI (which would be the majority of patients in current practice). However, even when excluding these patients from the dataset, the ACM could not identify any subgroup where use of fondaparinux was strongly supported by the data, noting that OASIS-6 trial was designed as a superiority study, and superiority was not demonstrated in the clinically more relevant Stratum 2 subpopulation.

c. The dosing instructions only mention UFH for the STEMI indication, reflecting the clinical trials. Please comment on this approach given other medicines are also approved for this use.

The ACM noted that the National Heart Foundation/Cardiac Society of Australia and New Zealand Guidelines recommend UFH or enoxaparin administration during PCI. The ACM was of the view that the dosing instructions should be consistent with recommended practice.

Overall, the ACM was of the view that sufficient data had not been provided to support efficacy of fondaparinux in the proposed STEMI indication, as the clinical trial followed a treatment algorithm that is significantly different from current practice. Further, the data attributed to the subgroup of the trial that slightly more resembled current treatment (Stratum 2), did not provide robust support of efficacy of fondaparinux in this indication.

3. Does the committee have any concerns regarding the use of fondaparinux in the peri-PCI period when used in accordance with the proposed dosing instructions? Is the warning about catheter sheath thrombosis sufficient?

The ACM noted that use of fondaparinux without other antithrombotic has been associated with guiding catheter thrombosis at higher rates than comparators in PCI. The ACM agreed that if approved for registration, the warning regarding catheter sheath thrombosis in the 'Precautions' section was sufficient.

Delegate's post-ACM considerations

Background

The Delegate sought advice from the ACM in the October 2018 meeting (see ACM Resolution in the section above) regarding the evidence presented to support the registration of fondaparinux for the extension of indications, proposed in submission PM-2017-03032-1-3..

The ACM found the evidence was insufficient to support the registration for each of the proposed indications for reasons of the age of the supportive data presented and generalisability of the data to the Australian context. The ACM noted in its reasoning recent Australian data from the Victorian Cardiac Outcomes Registry (VCOR) (2017) that had been published in August 2018.[9] This information was unavailable to the sponsor at the time of lodging the submission and the sponsor would not have been able to include data from the VCOR in its submission because of the date of publication.

The sponsor was provided the opportunity to review the VCOR publication and provide a response to the ACM advice.

Evaluation of sponsor's response

In this section, comments from the ACM minutes resolution are repeated in italic font, followed by a summary of the sponsor's response to the statement. The Delegate's comments about the response follow.

The clinical evidence to support registration of both proposed indications was from clinical trial data from over ten years ago. The applicability of these trials results were therefore of uncertain clinical relevance given the differences to contemporary standard of care.

Sponsor's response

The sponsor agreed that the trial data were about a decade old. It noted that the ESC and the American College of Cardiology (ACC) guidelines both provide a Class IB recommendation for fondaparinux in non-ST elevation ACS. The sponsor noted the outcomes of the Szummer et al., analysis of Swedish registry data published in 2015 that demonstrated reduced in-hospital severe bleeding;[10] and death;[11] with fondaparinux compared to LMWH. The difference between the fondaparinux and LMWH groups was sustained through 30 and 180 days, even though the anticoagulation was only given during the in-patient stay.

The sponsor noted there are recommendations for therapy in NSTEMI and STEMI in European, American and Australian guidelines based on data that are all now of a similar vintage.

In the OASIS-5 trial, the Phase III study to compare the safety and efficacy of fondaparinux and enoxaparin in patients with UA/NSTEMI, non-inferiority in the primary efficacy endpoint of first occurrence of adjudicated death, MI or refractory ischaemia up to and including Day 9 was demonstrated. Although a lower proportion of patients in the fondaparinux group experienced major bleeding events compared to the enoxaparin group, the ACM considered that these bleeding events appeared to be a likely consequence of femoral artery access (utilised in 88% of patients who underwent PCI in the OASIS-5 trial). Bleeding complications occur far less commonly in current practice, with the increasing preference for use of radial access.

The sponsor presented a post-hoc analysis of bleeding events in OASIS-5 in patients who underwent PCI with radial access. In this patient group major bleeding at 30 days was 1.1% for fondaparinux versus 3.1% for enoxaparin (HR 0.35, 95% CI 0.12, 0.98), and major bleeding at 180 days was 3.9% for enoxaparin and 1.5% for fondaparinux (OR 0.39, 95% CI 0.16, 0.96).

The sponsor noted 69% of patients in the OASIS-5 study did not undergo PCI. The VCOR does not report the number of patients with NSTEMI not undergoing PCI. In the Queensland registry 2016 publication, 57.6% did not undergo PCI. The sponsor concluded that based on the information from the current Australian registries fondaparinux would benefit these patients.

Delegate's comment

Some 2854 fondaparinux patients and 2741 enoxaparin patients underwent 2888 and 2781 PCIs respectively in the OASIS-5 trial while on study drug.

[10] Unadjusted bleeding fondaparinux versus LMWH: OR 0.62, 95%CI 0.52, 0.74
[11] Unadjusted mortality fondaparinux versus LMWH: OR 0.66, 95%CI 0.59, 0.75

A total of 4370 fondaparinux patients and 4294 enoxaparin patients received either PCI or CABG in the whole OASIS-5 trial. The major bleeding rates were 3.0% for fondaparinux and 5.5% for enoxaparin for these patients.

For patients receiving neither PCI nor CABG during the study (5681 in the fondaparinux group and 5726 in the enoxaparin group) major bleeding rates for fondaparinux and enoxaparin were 0.9% and 2.6% respectively.

Between Days 1 to 9, PCI related bleeding occurred in 1.8% of enoxaparin patients and 0.8% of fondaparinux patients. For the same periods, 4.4% of fondaparinux and 9.8% of enoxaparin patients reported any bleeding event with major bleeding in 2.1% of the fondaparinux and 4.1% of the enoxaparin patients.

Regarding efficacy in the same time period death, MI or recurrent ischaemia occurred in 8.7% and 8.1% of the fondaparinux and enoxaparin groups, respectively in patients receiving PCI, and 4.2% and 4.4% in patients not receiving PCI during the study. The non-inferiority study design should be noted when interpreting these results. It is also likely that very high risk patients underwent PCI in this study, which may have contributed to the higher event rates in both groups compared with those not undergoing the intervention.

Data from the Victorian Cardiac Outcomes Registry Annual Public Report 2017 confirms the increased use of the radial artery for arterial access, and shows that the rate of radial access for acute STEMI was 66% in 2017. The report also describes that in patients undergoing PCI for STEMI, primary PCI (within 12 hr, without preceding thrombolytic) was used in 87.2% of cases. In-hospital major bleeding rates for STEMI was 1.7% and for non-ST elevation ACS, 0.6%.

Sponsor's response

The sponsor agreed that the use of radial access is more frequent than reported in the OASIS-5 trial. The sponsor noted 40% of patients in the VCOR registry had PCI using femoral access.

In the Queensland Cardiac Outcomes Registry Annual Public Report 2016, 53% of PCIs were via the radial approach, 44% were the femoral approach and 3% used both. There was heterogeneity across Queensland (20% to 76%) and Victorian hospitals (< 30% to > 90%) for this approach.

The sponsor considers that despite the higher rates of radial access for patients in Australia the results of OASIS-5 trial are still relevant to current practice.

Delegate's comment

The variability in approach is noted. In the Swedish registry, radial access was used in 46.3% of fondaparinux and 36.2% of the LMWH patients. The unadjusted in hospital bleeding rates were 1.1% and 1.8% for fondaparinux and LMWH, respectively.

The STEMI indication is primarily supported by evidence from a subset of patients in the OASIS- 6 trial, which was designed as a superiority study. The treatment pathway described in OASIS-6 does not resemble current practice, that is, only around 31% of STEMI patients had a primary PCI (though this was not defined in the paper, and may or may not be consistent with the time frame defined in current use of the term), while in current practice the vast majority of patients would have primary PCI. Patients in Stratum 1 received thrombolytic treatment that is no longer administered or available in the Australian setting (streptokinase or urokinase). In the subgroup in whom the thrombolytic agent resembles current (though limited) practice (Stratum 2, received alteplase, reteplase and tenecteplase) fondaparinux was not found to be superior to control.

Sponsor's response

The sponsor noted that a substantial number of patients are not eligible for initial reperfusion or are treated with fibrin specific thrombolytics. The sponsor provided a 2013 publication suggesting 38.7% of STEMI patients received primary PCI, 25.2% received thrombolytics and 36.1% received no reperfusion. The sponsor also cited the findings from the 2010 Australian Acute Coronary Syndrome Prospective Audit including normal electrocardiogram on presentation (OR 0.42, P = 0.01), left bundle branch block (OR 0.18, P = 0.001), acute pulmonary oedema (OR 0.34, P < 0.01), history of diabetes (OR 0.54, P < 0.01), and previous lesion on angiogram of > 50% (OR 0.51, P < 0.01). It noted that based on a pre-specified subgroup analysis of STEMI patients in the OASIS-6 trial not receiving initial reperfusion treatment, the proportion of patients with death or re-infarction was 12.2% versus 15.1% for fondaparinux versus control (HR 0.8, 95% CI 0.65, 0.98) without an increase in bleeding or stroke.

While conceding that non-fibrin specific thrombolytics are no longer available in sponsor considers the findings from a pre-specified subgroup analysis from the OASIS 6 trial of patients who received fibrinolytics demonstrate a trend towards lower rates of severe haemorrhage at Day 30 (HR 0.67, 95% CI 0.26, 1.73), but disagrees that fondaparinux was not superior to control. The sponsor notes that statistical significance was not reached for this outcome due to the small sample size, but states that fondaparinux has a unique safety profile, with no increase in severe haemorrhage, irrespective of thrombolytic type compared to heparin and placebo.

Delegate's comment

The primary endpoint was efficacy for the OASIS-6 trial, and the study was conducted in a superiority paradigm, as compared to the OASIS-5 trial, which had a non-inferiority design. In a comparison of the primary efficacy outcome for patients in the fibrinolytic therapy arm (Stratum 2) for reperfusion for fondaparinux versus UFH was HR 0.94; 95% CI: 0.79, 1.11; p = 0.460.

Fondaparinux has a once daily dosage regimen compared to enoxaparin which is administered twice daily. In theory, the ACM considered that with its shorter half-life, enoxaparin may afford a benefit with regard to safety in the context of multiple antiplatelet and/or anticoagulant therapies in this population.

Sponsor's response

The sponsor stated it was unable to locate publications that showed a better safety profile for enoxaparin over fondaparinux related to its shorter half-life. The sponsor reported subgroup analyses for major bleeding at 30 days for use of glycoprotein IIb/IIIa inhibitors (5.2% fondaparinux versus 8.3% enoxaparin, HR 0.6 95% CI 0.46-0.78) and for thienopyridines (3.4% fondaparinux versus 5.4% enoxaparin, HR 0.62, 95% CI 0.52-0.73). The sponsor has calculated a net clinical benefit for each of the groups (glycoprotein IIb/IIIa subgroup 14.8% versus 18.9%, HR 0.77, and thienopyridine subgroup 11.0% versus 13.2%, HR 0.82). No confidence intervals for the comparisons were presented.

Delegate's comment

The Day 30 death, MI or RI for fondaparinux versus enoxaparin in the GP IIb/IIIa group was 11.8% versus 13.2%, and for the same endpoint in the thienopyridine group 8.6% versus 9.2%, and for thienopyridine and aspirin 8.6% versus 9.2%.

The sponsor has also provided comments on the ACM advice to the Delegate on specific issues. The sponsor disagreed that the subgroup analyses that excluded patients who underwent primary PCI from the OASIS-6 data did not show superiority of fondaparinux, stating that its position is that superiority was demonstrated for patients receiving no reperfusion and those receiving thrombolytics. The sponsor noted there was a trend

towards lower rates of the primary safety outcome (severe haemorrhage) (HR 0.67, 95%CI 0.26-1.73) in the 875 patients in the OASIS-6 population who received fibrin specific thrombolytics.

The sponsor agreed with the ACM's comments about the inclusion of dosing instructions for UFH in PCI, and with the ACM's position on the precautionary statement about catheter thrombus.

Evaluation of papers provided with the sponsor's response

It should be noted that these papers were provided as references for statements made in the sponsor's response, rather than as a literature based supplement to its initial submission documents.

Szummer et al., (2015)

Publication

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

Objectives

The aim of the study was to assess the rate of ischaemic and bleeding events in NSTEMI patients given fondaparinux or LMWH during their in-hospital stay, with a specific aim of assessment of the association between fondaparinux and LMWH, and outcome in patients with reduced renal function and in patients undergoing PCI.

Methodology

This was a prospective multicentre cohort study using data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.

The study was conducted between 1 September 2006 and 31 June 2010, with the last follow-up 31 December 2010.

Baseline characteristic data were enhanced from the National Patient registry. Overall, 100 variables including baseline characteristics, medication on admission, in-hospital therapies, complications and discharge medications were collected. In the registry, an annual comparison of the registry data with the medical records showed around 96% agreement.

Entry criteria: All consecutive adult patients with a NSTEMI admitted to a coronary care unit from all 72 hospitals in Sweden that at the time provided care for acute cardiac diseases.

Outcomes**:** The outcomes measured in the study were in-hospital severe bleeding events and death, and 30- and 180-day major bleeding, death, stroke and recurrent myocardial infarction (MI). An in-hospital bleeding event was defined as fatal, cerebral, or bleeding requiring transfusion or surgery. The 30- and 180-day outcomes included readmission due to MI, stroke, or major bleeding events. Death dates were obtained from the Swedish population registry.

Estimated glomerular filtration rate (eGFR) was estimated from serum creatinine admission measurements and included sex and age using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula.

Study participants

Enrolled: 40,616 adult patients with NSTEMI of whom 14,791 (36.4%) received fondaparinux and 25,825 (36.4%) received LMWH (with sex, mean/range age, mean/range of other baseline characteristics if relevant).

Patients treated with fondaparinux were a mean 2 years younger than those treated with LMWH (72 years' versus 74 years), had fewer previous MIs (28.2% versus 32.2%) and previous diagnosis of heart failure (14.5% versus 18.7%). Prior bleeding events and previous haemorrhagic stroke were noted for similar proportions of each group.

Treatments

The exact dosage regimens used were not reported in this paper. PCI adjunctive therapy and was included in the tabulated characteristics.

PCI was available at the hospital for 64.3% of the fondaparinux patients and 58.7% of the LMWH patients. More fondaparinux patients (46.4% versus 38.9%) underwent PCI during the study period. Of the PCI patients given fondaparinux versus those given LMWH, 14.4% versus 17.4% had the PCI on Day 0, 30.2% versus 27.4% on Day 1, and 20.8% versus 18.6% on Day 2. The remainder of PCIs occurred at Day 3 or later. A radial approach was used for 46.3% of the fondaparinux patients versus 36.2% of the LMWH patients.

PCI adjuvant therapy for fondaparinux versus LMWH was given to 77.6% versus 62.7%, LMWH at PCI to 2.6% versus 7.2%, bivalirudin to 22.2% versus 15.3%, and glycoprotein IIb/IIIa blocker to 12.1% versus 23.5%.

At discharge from hospital, dual antiplatelet therapy (DAPT) was prescribed for 78.0% of the fondaparinux and 68.3% of the LMWH patients.

Analysis

The relationship between treatment, confounders and outcome was represented in an acyclic graph. The introduction of fondaparinux at various times in different hospitals was accounted for using calendar time (4-knot-cubic spline) and hospital site (initial model). Adjustment for covariates was performed in a step-wise manner. The second model included the initial model plus age (3-knot-cubic spline), sex, current smoking status, diagnosis of diabetes, hypertension, previous MI, congestive heart failure, peripheral vascular disease, ischaemic stroke, bleeding, chronic obstructive pulmonary disease or cancer, Kilip score > 1, and eGFR. The third model included the second model plus in-hospital PCI or CABG.

The models stratified for renal function stage were adjusted in the main analysis, and the association between treatment and outcome by renal function was tested for linear trend. The association between treatment and outcome was assessed in PCI patients. PCI adjusted data were adjusted in accordance with the initial and second models and then for the variables of use of UFH, LMWH, bivalirudin GP IIb/IIIa blockers use of closure device and time from arrival to CCU to PCI in categories of 0,1, 2, and ≥ 3 days.

Missing data were imputed using multiple imputations with the method of chained equation. Current smoking status had missing data in 8.8%. All applicable covariates and outcome variables were used to predict the value for the missing covariate.

Three sensitivity analyses were conducted:

- Only patients with a complete data set
- Propensity score matched analysis with exact matching on calendar time and in-hospital PCI (described in detail in the paper)
- Only first MI included (patients with previous MI excluded)

Results

The use of fondaparinux increased from 0.7% in the first calendar year to 84.7% in the last calendar year (Table 3). Fondaparinux for the NSTEMI indication was approved in the EU on 29 August 2007.

Table 3: Distribution of fondaparinux and enoxaparin treated patients in the matching strata: calendar-time (quarters) and PCI

		No PCI		PCI	
		LMWH	Fondaparinux	LMWH	Fondaparinux
2006	First quarter	1423	1	837	0
	Second quarter	1488	1	908	0
	Third quarter	1293	11	779	5
	Fourth quarter	1426	21	882	27
2007	First quarter	1480	48	930	35
	Second quarter	1463	56	920	42
	Third quarter	1287	53	808	60
	Fourth quarter	1318	130	895	102
2008	First quarter	1093	266	768	256
	Second quarter	807	530	525	379
	Third quarter	560	707	402	523
	Fourth quarter	469	774	321	665
2009	First quarter	391	885	240	745
	Second quarter	323	886	215	734
	Third quarter	297	837	214	727

		No PCI		PCI	
		LMWH	Fondaparinux	LMWH	Fondaparinux
	Fourth quarter	239	820	167	793
2010	First quarter	203	954	168	886
	Second quarter	167	903	119	92

Table 4: The association of fondaparinux and LMWH with various outcomes

	No. Events/No. All (%)		OR (95% CI)			
				Adjusted		
Events	Fondaparinux	Low-Molecular-Weight Heparin	Unadjusted	Model 1: Hospital and Calendar Time	Model 2: Hospital, Calendar Time, Baseline Characteristics[a]	Model 3: Model 2+PCI or CABG
In-Hospital						
Bleeding	165/14 791 (1.1)	461/25 825 (1.8)	0.62 (0.52-0.74)	0.47 (0.36-0.60)	0.54 (0.42-0.70)	0.54 (0.42-0.70)
Death	394/14 791 (2.7)	1022/25 825 (4.0)	0.66 (0.59-0.75)	0.59 (0.49-0.70)	0.75 (0.63-0.89)	0.76 (0.63-0.89)
Bleeding or death	549/14 791 (3.7)	1429/25 825 (5.5)	0.65 (0.58-0.72)	0.54 (0.47-0.63)	0.67 (0.58-0.78)	0.68 (0.58-0.79)
30 Days						
MI	1326/14 791 (9.0)	2463/25 825 (9.5)	0.93 (0.87-1.00)	0.93 (0.83-1.04)	0.94 (0.84-1.06)	0.95 (0.85-1.06)
Stroke	75/14 791 (0.5)	153/25 825 (0.6)	0.86 (0.65-1.13)	1.02 (0.68-1.13)	1.11 (0.74-1.65)	1.12 (0.75-1.68)
Death	628/14 791 (4.2)	1508/25 825 (5.8)	0.72 (0.65-0.79)	0.65 (0.57-0.75)	0.82 (0.71-0.95)	0.83 (0.72-0.96)
MI, stroke, or death	1921/14 791 (13.0)	3932/25 825 (15.2)	0.83 (0.78-0.88)	0.79 (0.72-0.86)	0.87 (0.79-0.95)	0.88 (0.80-0.96)
Bleeding	204/14 791 (1.4)	547/25 825 (2.1)	0.65 (0.55-0.76)	0.49 (0.39-0.62)	0.56 (0.44-0.70)	0.56 (0.44-0.70)
Bleeding or death	807/14 791 (5.5)	1987/25 825 (7.7)	0.69 (0.64-0.75)	0.60 (0.53-0.68)	0.74 (0.65-0.84)	0.74 (0.65-0.84)
MI, stroke, death, or bleeding	2077/14 791 (14.0)	4331/25 825 (16.85)	0.81 (0.77-0.86)	0.75 (0.68-0.82)	0.83 (0.75-0.90)	0.83 (0.76-0.91)
180 Days						
MI	2100/14 791 (14.2)	4077/25 825 (15.8)	0.88 (0.83-0.93)	0.92 (0.84-1.01)	0.97 (0.89-1.06)	0.98 (0.89-1.07)
Stroke	258/14 791 (1.7)	511/25 825 (2.0)	0.88 (0.76-1.02)	0.90 (0.72-1.12)	0.98 (0.79-1.22)	0.99 (0.80-1.23)
Death	1234/14 791 (8.3)	3041/25 825 (11.8)	0.68 (0.64-0.73)	0.63 (0.56-0.70)	0.76 (0.68-0.85)	0.77 (0.69-0.86)
MI, stroke, or death	3188/14 791 (21.6)	6704/25 825 (26.0)	0.78 (0.75-0.82)	0.76 (0.70-0.82)	0.85 (0.79-0.92)	0.86 (0.79-0.93)
Bleeding	285/14 791 (1.9)	712/25 825 (2.8)	0.69 (0.60-0.80)	0.54 (0.44-0.66)	0.60 (0.50-0.74)	0.60 (0.50-0.74)
Bleeding or death	1458/14 791 (9.9)	3598/25 825 (13.9)	0.68 (0.63-0.72)	0.60 (0.54-0.72)	0.71 (0.65-0.72)	0.72 (0.65-0.80)
MI, stroke, death, or bleeding	3352/14 791 (22.7)	7103/25 825 (27.5)	0.77 (0.74-0.81)	0.73 (0.67-0.78)	0.81 (0.75-0.88)	0.82 (0.76-0.89)

Abbreviation: MI, myocardial infarction.

[a] Baseline characteristics: age; sex; diabetes; hypertension; current smoking status; previous myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, bleeding, chronic obstructive pulmonary disease, or cancer; Killip classification greater than 1; and estimated glomerular filtration rate. Model 2 is the main model presented in the Results section.

The ORs of in-hospital bleeding and 30-day bleeding events by eGFR were similar for fondaparinux and enoxaparin for patients with an eGFR ≥ 30 mL/min/1.73 m^2, and favoured fondaparinux in the ≥60 – 90 group in-hospital and both ≥ 60 to 90 mL/min/1.73 m^2 and > 90 mL/min/1.73 m^2 at 30 days. There was no clear difference between fondaparinux and enoxaparin in the analysis of 30-day mortality, although this favoured fondaparinux in hospital in the ≥30 to 60 mL/min/1.73 m^2 group. For the combination of MI, stroke or death there was no difference for the individual eGFR groups although overall was favourable for fondaparinux, and was favourable overall and for the > 90

mL/min/1.73 m^2 group in an analysis of MI, stroke, bleeding or death by treatment groups and renal function.

Evaluator's comments

The authors note two subgroups of patients that received special attention in the post hoc analyses of the OASIS-5 trial. The reduction in events was largest in patients with moderately reduced renal function treated with fondaparinux compared with LMWH.

The commencement of the study pre-dates the approval of fondaparinux by the EMA on 29 August 2007, so the use of fondaparinux is clustered in 2008 to 2010. Although catheter thrombosis with fondaparinux was recognised in publications in 2007, a mechanism was identified in 2011, and a review article was published in 2010. The interpretation of the results of this study therefore should be interpreted in this context.

Hammon et al 2011

Publication

Hamon M, Mehta S, Steg PG, Faxon D, Kerkar P, Rupprecht HJ, et al. Impact of transradial and transfemoral coronary interventions on bleeding and net adverse clinical events in acute coronary syndromes. EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2011; 7(1):91-7.

Objectives

To compare the impact of transradial and transfemoral PCI approaches on PCI-related bleeding and patient outcomes in patients with ACS in the OASIS-5 trial.

Methodology

Design: This was a *post-hoc* analysis of patients enrolled in the OASIS-5 trial who underwent an early PCI.

Entry criteria: OASIS-5 was a non-inferiority study comparing enoxaparin or fondaparinux in 20,078 patients with ACS but not STEMI.

Treatments: Angiography could be performed at the investigator's discretion and there could be triage to PCI, CABG or medical treatment. PCI patients received clopidogrel or aspirin at least six hr before the procedure.

Outcomes: Composite ischaemia (death from any cause, MI or refractory ischaemia) and major bleeding;[12] at 9 days, 30 days and 6 months were the endpoints for this analysis. Stroke was compared in the two groups and a net clinical benefit calculation of the composite ischaemia and major bleeding endpoints was calculated.

Analysis: Descriptive statistics, Chi-square test for categorical variables, Wilcoxon rank sum test for continuous variables, a Cox proportional hazards model adjusted with a propensity score for the radial approach to PCI (based on age, sex, diabetes, ST segment changes, prior MI, glycoprotein inhibitor use, elevated cardiac enzymes and baseline variables), and a time to event display using Kaplan-Meier methodology were all used for the analyses. This was not an intention to treat analysis: if one access method failed and the patient crossed to a second (for example, failed radial access) the result was analysed according to the site used.

[12] Major bleeding defined as intracranial, retroperitoneal, intraocular, a decrease in haemoglobin of at least 3 g/dL (each transfused unit counted as 1 g/dL of haemoglobin) or requiring transfusion of ≥ 2 U of red blood cells

Study participants

Enrolled: 14,159 patients were catheterised, and the 7,885 who underwent PCI by radial or femoral access at the time of initial catheterisation were included in this analysis. Overall the femoral approach was more common (90%, 12,761 patients) than the radial approach (10%, 1,398).

There were significant differences between the radial and femoral populations at Baseline (Table 5).

Table 5: Baseline characteristics of patients according to radial or femoral access

Radial Femoral *p* value (N=1,398) (N=12,761)			
Age (years)	64.4±11.3	65.3±10.6	NS
Male (%)	70.9	65.3	<0.001
Medical history			
Diabetes (%)	21.5	25.4	<0.001
Myocardial infarction (%)	21.0	23.9	0.016
PCI (%)	13.3	13.4	0.908
CABG (%)	4.1	9.0	<0.001
Heart failure (%)	7.4	9.4	0.079
High-risk features			
ST-segment depression ≥1mm (%)	42.4	44.8	0.083
CKMB-Trop. elevated (%)	78.7	74.1	<0.001
In-hospital medications			
Aspirin (%)	97.8	97.9	0.682
Clopidogrel (%)	79.5	72.4	<0.001
GPIIb/IIIa inhibitor (%)	33.1	23.6	<0.001
Beta-blocker (%)	88.2	89.0	0.346

Radial	Femoral	*p* value	(N=1,398) (N=12,761)
ACE inhibitor (%)	60.0	69.2	<0.001
Statin (%)	85.3	82.3	0.005
CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; Trop.: troponin; ACE: angiotensin converting enzyme			

Results

The radial approach was safer than the femoral approach overall. There were fewer net clinical adverse events with the radial approach (adjusted OR = 0.83 (95% CI: 0.62, 0.99), p = 0.03), driven by a reduction in major bleeding at day 9 (adjusted OR = 0.45 (95% CI: 0.26, 0.77), p=0.003). Favourable results were sustained over the 6 month period.

Evaluator's comments

The significant differences in baseline characteristics were not unexpected given this was a post hoc analysis and because of the large difference between the number of patients in each treatment group. Significantly, more patients in the radial group were taking clopidogrel, a GPIIb/IIIa inhibitor or statin but fewer were taking an ACEI. More patients in the radial group had an elevated CKMB or troponin.

There was no randomisation specifically for this study. Allocation of access site was based on the investigator preference. This may have introduced bias. The authors have attempted to address this using a propensity score adjustment for common factors that may influence choice of access site.

The safety results were favourable for radial access over femoral access, and overall efficacy was similar. This was the objective of the study. Some results were presented for major bleeding events related to fondaparinux and enoxaparin; however, no absolute numbers of patients were presented. From the OASIS 5 study, result 275 enoxaparin patients and 319 fondaparinux patients had PCI by the radial route. It is unclear whether all of these patients were included in the study. This limits the conclusions that can be drawn, but is overall supportive of the safety of the radial approach with fondaparinux in the NSTEMI population.

Garrahy et al 2016

Publication

Garrahy P. Queensland Cardiac Outcomes Registry 2016 Annual Report – State wide cardiac clinical network. 2016.

Objectives

This was the 2016 annual report from the Queensland Cardiac Outcomes Registry. It reported outcomes for cardiac surgery, heart failure support services and interventional cardiology. Data were from patients treated in seven of the eight Queensland public hospitals with a cardiac catheter laboratory. Only the interventional cardiology outcomes of direct relevance to the management of STEMI and NSTEMI in this context of this submission are mentioned in this document.

Methodology

This is the 2016 audit of data collected in the QCOR. It collected diagnostic and interventional cardiology from 7 sites, cardiac surgery from 3 sites, heart failure from 24 sites, thoracic surgery from 4 sites, echocardiography form 3 sites, electrophysiology, ICDs and ablations from 8 sites and cardiac rehabilitation information from 52 sites.

Two of the seven sites in the interventional cardiology audit were tertiary metropolitan centres, with the remainder large regional centres.

Entry criteria: Not clear from the report.

Study participants

Enrolled: Of the total 11,334 cases contributing to the 2016 report, 3,563 were PCI cases (31%). The median age of PCI patients was 64 years (median age range 61-67 years depending on the centre). The median age of NSTEMI cases for women was 67 years compared to 64 years for men (overall median 65 years). The median age of STEMI patients was 61 years: the range of medians across the participating hospitals was 58 to 64 years. The median age for women, 65 years, was higher than for men, 60 years.

Analysis: No detailed account of the methods of analysis was presented in the report. The majority of the statistics are descriptive.

Results

Of the total 2,165 patients with NSTEMI, 45% received a PCI. However, NSTEMI PCI represented 28% of the PCI caseload. Inter-hospital transfer for the intervention occurred in 57%. Among NSTEMI patients, 54% of those transferred from another hospital met the 72 hr target to angiography, compared with 77% who were admitted directly to the facility.

There were 1,253 documented STEMI, 56% presented as primary PCI cases, and 27% received thrombolysis. Overall 81.7% underwent a PCI. A radial approach was used in 53% of cases but that varied between 20 – 70% depending on the institution. Only 3% of patients required a dual approach.

Of the total cases, 23% of the PCI was elective, 52% was urgent (typically for NSTEMI) and 24% was emergent (typically for STEMI). The final category was salvage (3%): a treatment of last resort such as patient in cardiogenic shock at the start of the procedure, or within the previous 10 minutes had received chest compressions or unanticipated extracorporeal support.

Drug eluting stents were the most commonly used stent group (78%), followed by bare metal stent (22%) and bioresorbable vascular scaffolds (<1%, reported as 0% in the total but 1 – 2% at some centres). The mean number of stents per case was 1.5.

Adverse events were analysed as a composite endpoint and as individual event. Only major adverse cardiovascular events (MACE) events and radiation safety were presented. Overall 99.8% of diagnostic procedures and 97.7% of PCI procedures observed a safe radiation dose of ≤ 5 Gy. There were 20 cases with MACE events (0.56%), of which coronary artery perforation occurred in 0.34%, in-laboratory death in 0.14%, cerebrovascular event in 0.06% and emergency CABG in 0.03%.

Evaluator's comments

This report only includes outcomes from public hospitals. As noted from the Victorian registry data (see below) the likelihood of intervention and the access approach differed between the two settings. This limitation was noted by the authors, who also noted that the seven participating sites represents 50% of all of the cardiac catheter laboratories in Queensland.

The authors also, very reasonably, caution against extrapolation of the safety findings to non-participating sites.

This study provides an overview of the types of procedures undertaken in the public hospital system in Queensland and their timing, and adds to the overall context in which injectable anticoagulants are used in ACS, but does not directly inform the use of fondaparinux which is not registered for this use in Australia currently.

Chew et al., (2013)

Publication

Chew DP, French J, Briffa TG, Hammett CJ, Ellis CJ, Ranasinghe I, et al. Acute coronary syndrome care across Australia and New Zealand: the SNAPSHOT ACS study. The Medical journal of Australia. 2013; 199(3):185-91.

Objectives

This was a prospective audit of all patients hospitalised with suspected or confirmed ACS between 14 and 27 May 2012.

Methodology

Design: This was an observational study.

Entry criteria: Patients with suspected or confirmed ACS between 14 and 27 May 2012 inclusive from 286 sites representing all Australian states and territories and New Zealand were tracked for the duration of their acute care for that episode, including tracking of transfers between hospitals.

Treatments: There were no specific allocated treatments.

Outcomes: The outcomes were the rates of guideline-recommended investigations and therapies, and in-hospital clinical events (death, new or recurrent myocardial infarction, stroke, cardiac arrest and worsening congestive cardiac failure).

Study participants

Enrolled: 4398 patients in Australia and New Zealand. Of those 65.7% presented to a principal referral hospital or a hospital in a major city. The median Global Registry of Acute Coronary Events (GRACE) risk score was 119 (IQR 96-114) across the population and 138 (IQR 114-161) in patients with a diagnosis of MI.

Analysis: To increase the sample size for some comparisons data from the smaller states and territories groups were combined. Descriptive statistics were used for the variables. Propensity score-adjusted estimates taking into account the influence of hospital classification and health jurisdiction on angiography provision, compliance with guideline medication on discharge, referral to cardiac rehabilitation and MACE events were obtained using logistic regression. Propensity scores used age, sex, GRACE score, diagnostic group, heart failure at presentation, renal impairment, diabetes, hypertension, nursing home residence, dementia or cognitive impairment, private insurance, and primary language other than English were constructed for the likelihood of living in each jurisdiction and presenting to a hospital of each classification.

Results

Of the 421 patients with STEMI/ left bundle branch block (LBBB) 25.2% were thrombolysed, 38.7% received primary PCI and 36.1% received no reperfusion therapy. Non-principal referral hospitals less frequently provided the guideline-recommended investigations and therapies. There were differences in the median (IQR) time to angiography across jurisdictions [overall for Australia and New Zealand 40 hr (17,73) ranging from median of 26 hr in South Australia, 29 hr in Victoria and Western Australia,

to 37 in the Northern Territory/Tasmania and 47 in Queensland]. Reduced provision of invasive management with increasing risk, as estimated by the GRACE score was evident (GRACE score <100, 90.1% versus 101-150, 81.3% versus 151-200, 49.4% versus > 200 36.1%, p<0.001).

Inpatient recurrent MI occurred in 5.1% and the in hospital mortality rate was 4.5%.

Interaction terms used for each jurisdiction and hospital classification were not found to be significant.

Evaluator's comments

This study provides a snapshot of ACS care in 2012. It provides evidence of the variability of care depending on type of hospital (private versus public), location of the hospital (principal referral versus others) and regional differences in care. It also provided evidence of differences in approach to invasive care based on risk (GRACE score). It is uncertain the impact of this study on the delivery of care in subsequent years.

There is no comparison of pharmacotherapies. This study does not directly inform the use of fondaparinux or of other parenteral anticoagulants in this setting.

Huynh et al., (2010)

Publication

Huynh LT, Rankin JM, Tideman P, Brieger DB, Erickson M, Markwick AJ, et al. Reperfusion therapy in the acute management of ST-segment-elevation myocardial infarction in Australia: findings from the ACACIA registry. Medical Journal of Australia. 2010; 193(9):496-501.

Objectives

To describe the management and outcomes of patients presenting with STEMI in Australia from a prospective audit of ACS conducted in 39 remote, rural and metropolitan hospitals across Australia between 1 November 2005 and 31 July 2007.

Methodology

Design: This was an observational study, which analysed data from the Australian Acute Coronary Syndrome Prospective Audit from 1 November 2005 to 31 July 2007.

Entry criteria: Patients were included as STEMI if they presented with angina or angina-equivalent and persistent > 1mm ST elevation in two contiguous leads, or new or presumed new LBBB.

Outcomes: The analysis considered factors associated with the use of reperfusion therapy, the timely use of reperfusion and the mortality outcomes with reperfusion in a 12 month follow-up period.

Study participants

755 patients with STEMI enrolled in the registry, 131 from remote (n= 17) and rural (n=114) hospitals (for the analysis considered 'rural') and the remainder from metropolitan hospitals.

Results

Most (505/755, 66.9%) received some form of reperfusion therapy: 198 (39.2%) with thrombolysis, and 307 (60.8%) with primary PCI (one patient received both). Of the 85 rural patients re-perfused, 63/85 (74.1%) received thrombolysis, compared with 135/419 patients (32.2%) in metropolitan hospitals. The remaining 284 re-perfused metropolitan patients received PCI.

Angiography was performed for 575/624 metropolitan patients and 96/131 rural patients during the initial admission (although there was a significant difference between rural and metropolitan patients, overall 89% received angiography).

For the whole cohort, 4% died during the index admission, 4.8% at 30 days and 7.8% at 12 months (this is presumed to be cumulative although not explicitly stated). Compared with no reperfusion, reperfusion of any kind was associated with a reduction in mortality during the year of follow-up (HR death 0.44 (95% CI 0.25, 0.78). Compared with no reperfusion, PCI had a benefit (HR death 0.33, 95% CI 0.18, 0.61) but not compared with thrombolysis (HR 0.66 95% CI 0.26 – 1.68).

Of the 199 patients that received thrombolysis the door to needle time was ≤ 30 minutes for 34.7% (69), and for patients with PCI the door to balloon time was ≤ 90 minutes for 36.5%.

Timely reperfusion compared with late or no reperfusion, after adjustment by baseline GRACE score for the 12-month follow-up period decreased the odds of death (HR 0.22, 95% CI 0.05-0.95, p=0.04).

Evaluator's comments

The paper presents data from an audit that is now 11- 13 years old and cannot be considered representative of contemporary practice in Australia.

Rural patients were less likely than the metropolitan patients to receive any reperfusion therapy. In their discussion, the authors note that more patient complexity was associated with less reperfusion. The authors also noted that 70% of patients presenting with LBBB and typical chest pain were not re-perfused despite guideline recommendations to the contrary.

In the discussion, the authors note the type of treating unit appeared to influence on the use of reperfusion therapy, and the authors noted this had implications for rural regions where specialist cardiology services are limited.

This was an overview of the reperfusion strategies for patients from a selection of hospitals in Queensland. It highlights that in 2005 to 2007, there were differences in strategy between metropolitan, rural, and remote centres, and that reperfusion and angiography was offered to fewer patients in rural communities. As the VCOR 2017 report indicates, there have been changes over time with PCI approach, and an increasing proportion of patients with a door to balloon time meeting the guideline recommendations over a three-year period. The proportion of patients not receiving reperfusion therapy in Queensland in 2018 is difficult to estimate from the QCOR paper.

Olgren et al., (2009)

Publication

Olgren J, Wallentin L, Afzal R, Bassand J-P et al Effects of fondaparinux in patients with ST-segment elevation acute myocardial infarction not receiving perfusion treatment. European Heart Journal. 2008. 29:315-323

Objectives

This was an analysis of patients with STEMI who did not receive reperfusion therapy in the OASIS-6 study.

Methodology

Design: This was a stratified, double blind, and randomised controlled trial. Patients were stratified based on investigator preference for type of thrombolytic (non-fibrin specific or fibrin specific) they would use if thrombolytics were to be given. Patients were then randomised to receive fondaparinux or placebo in Stratum 1 or fondaparinux or

unfractionated heparin (UFH) in Stratum 2. Results for the combined fondaparinux group and the combined control groups were analysed together.

Entry criteria: The initial protocol allowed for entry into the study up to 24 hr after a STEMI; however after about 4300 patients were enrolled the window after infarction was decreased to < 12 hr. Patients were contraindicated if they had a contraindication to anticoagulation, such as a high risk of bleeding, were receiving oral anticoagulants or had a creatinine of ≥ 3.0 mmol/L.

Treatments: This paper is an analysis of the 2867patients who did not receive any reperfusion treatment; in Stratum 1 received fondaparinux or placebo and in Stratum 2 received fondaparinux or UFH.

Outcomes: The primary composite outcome from the OASIS 6 study was death or myocardial re-infarction at 30 days, although analyses were also performed at day 9, and a minimum of 90 and a maximum of 180 days. As of 21 March 2005, the follow up was only for 90 days. The definition of the bleeding events was the same as the Peters paper.

Study participants

These were patients from the OASIS 6 study, described previously. A comparison of the patients not re-perfused with patients in the study who received reperfusion is presented below (Table 6). It is noted that the patients were older and with a longer mean time from onset of symptoms to randomisation. The non-reperfusion groups had a greater proportion of patients with previous stoke, previous myocardial infarction and heart failure than the group who were re-perfused.

Table 6: Baseline characteristics and medications from patients not receiving reperfusion in the OASIS 6 study

Table 1 Baseline characteristics and medications within 7 days prior to randomization

	Control (n = 1409)		Fondaparinux (n = 1458)		OASIS-6 receiving reperfusion treatment (n = 9225)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	65.0	12.7	64.6	12.4	60.5	12.0
Body mass index (kg/m^2)	26.5	4.5	26.7	4.5	26.5	4.3
Onset to randomization (h)	10.7	6.5	10.7	6.4	5.3	4.2
Heart rate (beats/min)	77.6	14.1	77.4	14.2	75.8	14.5
Diastolic blood pressure (mm Hg)	80.9	14.0	81.5	13.9	81.4	14.5
Systolic blood pressure (mm Hg)	134.1	23.6	135.3	23.3	133.9	23.3
	n	%	n	%		
Men	903	64.1	955	65.5	6888	74.7
Previous myocardial infarction	231	16.4	240	16.5	1047	11.3
Previous stroke	146	10.4	147	10.1	508	5.5
Hypertension	899	63.8	969	66.5	4713	51.1
Heart failure	387	27.5	376	25.8	921	10.0
Diabetes	250	17.7	253	17.4	1649	17.9
Anterior myocardial infarction	730	51.8	711	48.8	4162	45.1
New left bundle branch block	37	2.6	31	2.1	50	0.5
Aspirin	815	57.8	851	58.4	5803	62.9
Clopidogrel	123	8.7	112	7.7	1566	17.0
UH heparin	150	10.6	179	12.3	1458	15.8
LMW heparin	44	3.1	46	3.2	131	1.4
Oral anticoagulants	2	0.1	4	0.3	23	0.2

Table 7: Medications from randomisation to discharge OASIS 6 trial patients not undergoing reperfusion

Table 2 Medications from randomization to discharge

	Control		Fondaparinux		OASIS-6 receiving reperfusion treatment	
	n = 1409	%	*n* = 1458	%	*n* = 9225	%
Aspirin	1334	94.7	1390	95.4	8956	97.1
Non-study UF heparin	119	8.4	103	7.1	1110	12.0
LMW heparin	86	6.1	79	5.4	541	5.9
GP IIb/IIIa	57	4.0	62	4.3	1773	19.2
Clopidogrel	360	25.6	375	25.7	5765	62.5
Ticlopidine	63	4.5	60	4.1	914	9.9
Oral anticoagulants	37	2.6	35	2.4	216	2.3
Beta blockers	1136	80.6	1190	81.7	7840	85.0
Calcium channel blockers	203	14.4	211	14.5	849	9.2
ACE inhibitors	1075	76.3	1149	78.9	7201	78.1
ARB agents	55	3.9	55	3.8	292	3.2
Spironolactone/eplerenone	181	12.8	153	10.5	873	9.5
Loop diuretics	554	39.3	555	38.1	2547	27.6
Statins	805	57.1	830	57.0	7291	79.0

UF, unfractionated; LMW, low molecular weight; GP, glycoprotein; ACE, angiotensin converting enzyme.
ARB, angiotensin II receptor blocker.

Results

In this analysis, 1226 patients were from Stratum I with a placebo control whereas 1641 patients were from Stratum II with a UFH control. Patients in either Stratum received fondaparinux for 8 days. The primary composite endpoint was death or myocardial re-infarction at Day 30. In Stratum I the HR for this endpoint was 0.88 (95% CI 0.65-1.19) and for Stratum II was 0.74 (95% CI 0.57 – 0.97).

Table 8: Outcomes for combined Stratum I and Stratum II with combined control groups, OASIS 6 study, patients not undergoing reperfusion

Table 3 Outcomes at 30 days

	Control (*n* = 1409)		Fondaparinux (*n* = 1409)		HR	95% CI
	n	%	*n*	%		
Death	176	12.5	153	10.5	0.83	0.67–1.04
Myocardial re-infarction (MI)	49	3.7	34	2.5	0.66	0.43–1.02
Stroke	17	1.3	11	0.8	0.62	0.29–1.33
Severe haemorrhage	21	1.5	18	1.3	0.82	0.44–1.55
Death/MI	212	15.1	178	12.2	0.80	0.65–0.98
Death, MI, stroke	225	16.0	185	12.7	0.78	0.64–0.95
Death/MI/severe haemorrhage	215	15.3	183	12.6	0.81	0.67–0.99

At Day 3 the composite endpoint of death or myocardial re-infarction in Stratum I was fondaparinux versus placebo HR 0.76; 95% CI 0.48-1.20 and in Stratum II fondaparinux versus UFH HR 0.79, 95% CI 0.53-1.16 (p=0.91 for heterogeneity).

There was a trend for reduced in severe bleeding events between fondaparinux or either of the controls at Day 3 or Day 30, although confidence intervals for the estimates are wide and all include unity (Table 9).

Table 9: Severe bleeding events fondaparinux / controls at Day 3 or Day 30

Day	Stratum I HR (95% CI)	Stratum II HR (95% CI)
3	0.39 (0.08 – 2.00)	0.72 (0.30 – 1.71)
30	0.78 (0.21 – 2.89)	0.84 (0.41 - 1.72)

Evaluator's comments

This was a post-hoc analysis of a subset of the population studied from the OASIS 6 study. There was no difference between fondaparinux and placebo for the primary outcome at Day 3, whereas there appeared to be a benefit when comparing fondaparinux and UFH at Day 30. The comparisons of fondaparinux over control for death, MI stroke and death, MI and severe haemorrhage all suggest a benefit of fondaparinux over control. This is difficult to interpret in that the control groups are a combination of active and inactive control. A more meaningful comparison would be for these endpoints against placebo and UFH, separately. There was no difference in severe bleeding events between the two groups, although there was a favourable trend for fondaparinux. Again, this comparison is difficult to interpret given active and inactive comparators are combined, and the rates of haemorrhage may differ between the two.

Peters et al., (2007)

Publication

Peters RJ, Joyner C, Bassand JP, Afzal R, Chrolavicius S, Mehta SR, et al. The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. European heart journal. 2008; 29(3):324-31.

Objectives

This is a post-hoc subgroup analysis of patients confined to the patients who received thrombolytics in the OASIS 6 trial.

Methodology

Design: This was a stratified, double blind, and randomised controlled trial. Patients were stratified based on investigator preference for type of thrombolytic (non-fibrin specific or fibrin specific) they would use if thrombolytics were to be given. Patients were then randomised to receive fondaparinux or placebo in Stratum 1 or fondaparinux or unfractionated heparin (UFH) in Stratum 2. Results for the combined fondaparinux group and the combined control groups were analysed together. Not all patients in each Stratum were thrombolysed.

Entry criteria: The initial protocol allowed for entry into the study up to 24 hr after a STEMI; however after about 4300 patients were enrolled the window after infarction was decreased to < 12 hr. Patients were contraindicated if they had a contraindication to anticoagulation such as a high risk of bleeding, were receiving oral anticoagulants or had a creatinine of ≥ 3.0 mmol/L.

Treatments: Patients in Stratum 1 received fondaparinux or matching placebo as a 2.5 mg IV initial dose then 2.5 mg SC daily for up to 8 days or until discharge. The patients received 5 mg IV if undergoing PCI without GP IIb/IIIa inhibitor use.

Patients in Stratum 2 received fondaparinux or placebo, as above but the placebo group received an IV dose of 60 IU/kg followed by an infusion of 12 IU/kg for 24 – 48 hr, adjusted to an APTT 1.5 to 2.0 times the control. Higher doses could be used during PCI.

Outcomes: The primary outcome was death or MI at 30 days. Patients were followed for 3 (minimum) to 6 (maximum) months. Bleeding was the safety outcome and in study

analysis was classified severe (fatal, ICH, cardiac tamponade or clinically significant haemorrhage with a decrease in Hb of ≥ 5 g/dL) or minor (overt haemorrhage with a decrease in Hb of 3.0 – 5.0 g/dL that did not meet other criteria for 'severe'.) Each transfused unit of blood was counted as 1g of Hb.

The author state 'the primary outcomes of the main trial were used in this study (that is, rate of death or MI and severe bleeding at 30 days').

Study participants

Enrolled: Of the total of 12,092 patients, 5658 were in Stratum 1 and 6434 were in Stratum II. Of 5436 who received thrombolytic therapy, 4415 were in Stratum 1 and 1021 in Stratum II. Twenty patients in Stratum I received fibrin specific thrombolytics and 166 patients in Stratum II received non-fibrin specific thrombolytics (Table 10).

Table 10: Thrombolytic therapy administered in OASIS-6

Table 1 Numbers of patients who received thrombolytic therapy

OASIS-6	Stratum I		Stratum II		Total
	Placebo 2835	Fonda 2823	UFH 3221	Fonda 3213	12 092
Non-fibrin specific thrombolytics	2216	2179	83	83	4561
Fibrin specific thrombolytics	9	11	436	419	875
Any thrombolytic	2225	2190	519	502	5436

UFH, unfractionated heparin.

Around 16% of Stratum II received a non-fibrin specific thrombolytic, so a total of 875 patients received fibrin specific thrombolytics. The most commonly used thrombolytic was streptokinase (3829 patients, 73%).

Baseline characteristics for the whole cohort of thrombolysed patients (regardless of Stratum) showed they were slightly younger (mean age 60.1 years versus 61.5 years for the whole cohort), less likely to have been taking background aspirin (53.2% versus 61.8%), less likely to be taking clopidogrel (8.4% versus 46.5%), less likely to have non-study UFH (6.8% versus 14.8%), or GPIIb/IIIa inhibitors (0.3% versus 1.9%) but with similar (1.6% versus 1.8%) use of LMWH and oral anticoagulants (0.2% each). They were randomised slightly earlier: mean 5.7 hr versus 6.6 hr.

Results

The results are presented in the text and tables. There is some confusion in the cross referencing of the tables in the text. The study results appear to be presented three times with differing results. In the text, Table 2 (reproduced below as Table 11) is mentioned in context of the 1021 patients in Stratum II. Table 4 (reproduced below as Table Table 112) is mentioned in the context of baseline characteristics of all patients and those treated with thrombolytics (these characteristics are included in Table 3 of the paper), and Table 6 (represented below as Table 13) is mentioned as a presentation of antithrombotic therapies started after randomisation.

Table 11: Study endpoints at 30 days in OASIS-6 by thrombolytic agent

Table 2 Study endpoints at 30 days by type of thrombolytic agent

Death/MI	*n*	Control, *n* (%)	Fondaparinux, *n* (%)	HR	95% CI	*P*-value for interaction
Death/MI						
NFS lytics	4561	318 (13.8)	241 (10.7)	0.76	0.64 0.90	0.175
FS lytics	875	54 (12.1)	52 (12.1)	1.01	0.69–1.48	
Severe haemorrhage						
NFS lytics	4561	45 (2.0)	27 (1.2)	0.60	0.37–0.97	0.846
FS lytics	875	11 (2.5)	7 (1.7)	0.67	0.26–1.73	

FS, fibrin specific thrombolytic agents; NFS, non-fibrin specific thrombolytic agents; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 12: Incidence of death and MI at 30 days in OASIS-6 by type of thrombolytic agent

Table 4 Incidence of death and MI at 30 days by type of thrombolytic agent

Death/MI	*n*	Control, *n* (%)	Fondaparinux, *n* (%)	HR	95% CI	*P*-value for interaction
Death/MI						
NFS lytics	4561	260 (11.3)	194 (8.6)	0.75	0.62–0.90	0.046
FS lytics	875	33 (7.4)	39 (9.1)	1.24	0.78–1.97	
MI						
NFS lytics	4561	71 (3.3)	57 (2.6)	0.80	0.56–1.13	0.359
FS lytics	875	26 (6.1)	14 (3.5)	0.57	0.30–1.08	

FS: fibrin specific thrombolytic agents, NFS: non-fibrin specific thrombolytic agents, HR: hazard ratio, 95% CI: 95% confidence interval.

The endpoints for this paper and the primary OASIS-6 study show a favourable outcome for fondaparinux if both thrombolytic strata are grouped and placebo and UFH are considered a single comparator group [death/MI fondaparinux 10.9% versus control 13.6% HR 0.79 (0.68, 0.92)].

The results for the primary endpoint are presented by Stratum below.

Table 13: Primary endpoints at 30 days for thrombolysed patients in OASIS – 6 by Stratum

Table 6 Primary endpoints at 30 days by stratum

	n	Control, *n* (%)	Fondaparinux, *n* (%)	HR	95% CI	*P*-value for interaction
Death/MI						
Stratum 1	4415	308 (13.8)	237 (10.8)	0.77	0.65–0.91	0.414
Stratum 2	1021	64 (12.3)	56 (11.2)	0.91	0.63–1.30	
Severe haemorrhage						
Stratum 1	4415	42 (2.0)	27 (1.3)	0.65	0.40–1.05	0.680
Stratum 2	1021	14 (2.7)	7 (1.4)	0.52	0.21–1.29	

FS: fibrin specific thrombolytic agents, NFS: non-fibrin specific thrombolytic agents, HR: hazard ratio, 95% CI: 95% confidence interval.

Table 11 is only noted in reference to the patient numbers in each Stratum, and Table 12 is mentioned in the context of baseline characteristics of all patients and those treated with thrombolytics. Both appear to be presenting the same outcome and for the same analysis but have different results. The reasons for the difference between the outcomes for death/MI are not explained in the paper. A Forest plot of the outcomes of the OASIS study is included using results by Stratum rather than by type of thrombolytic received and another presenting the results seen in Table 2 of the study (.Table 11 in this document).

Evaluator's comments

There are different results presented for the primary endpoint of this study using apparently the same data set without explanation of the reasons for the difference.

It can be seen that the death/MI endpoint has a point estimate HR of 1.24 for the composite of death/MI (95% CI 0.78-1.97). Although acknowledged that this is a post-hoc analysis of the study and that it was not specifically powered for the endpoint, the HR for the composite endpoint of death/MI was 1.24, with the upper bound of the 95% CI of 1.97 and this is of concern. This finding is not discussed in the text of the study and as noted previously there are issues with the cross-referencing of the tables in the study. The same study endpoint for fibrin specific thrombolytics in the preceding table has a point estimate of 1.01 (95% CI 0.69-1.48), suggesting equivalence to rather than superiority over UFH in this comparison.

Because not all thrombolysed patients in Stratum 1 had NFS thrombolytics and not all patients in Stratum 2 had FS, the difference in the findings are of interest. Although the numbers are smaller there is no apparent benefit of fondaparinux over control, and there a possible influence of including results from patients who received non-fibrin thrombolytics into this group.

The authors claim the study suggests fondaparinux is superior to placebo or control based on the point estimates, noting the wide confidence intervals, but note that 'a large trial would be required; evaluating fondaparinux and UFH in patients treated with FS agents'.

Overall, this study raises uncertainty about using fondaparinux with fibrin specific thrombolytics, rather than providing reassurance. This analysis is not considered sufficiently robust to support the use of fondaparinux for STEMI in the Australian setting.

Jolly et al., (2009)

Objectives

This study was an analysis of the OASIS-5 study to evaluate the relative efficacy and safety in patients also receiving glycoprotein (GP) IIb/IIIa inhibitors or thienopyridines.

Methodology

Design: This analysis is set in the OASIS-5 study. A non-inferiority study comparing fondaparinux and enoxaparin in 20,078 patients with unstable angina or NSTEMI. The overall study design has been described elsewhere in the Request for ACM's advice and the second round clinical evaluation report for submission PM-2017-03032-1-3.

Entry criteria: Patients met the entry criteria for OASIS-5.

Treatments: Use of GPIIb/IIa inhibitors or thienopyridines was discretionary for the treating physician.

Outcomes: Major bleeding was the main safety outcome. Time to ischaemic events (death, MI and refractory ischaemia) was the primary outcome, and was the primary outcome for the main study. A net clinical outcome calculation of a combination of the main safety and efficacy outcomes was also presented. The definitions of the events were the same as those used in the main study.

A Cox proportional hazards model was used to compare efficacy, safety and net clinical outcome, for patients taking GPIIb/IIIa inhibitors, thienopyridines or both.

The analysis was repeated in the subgroup of patients undergoing PCI in those that received GPIIb/IIIa inhibitors, those that received thienopyridines at least 6 hr before PCI, and both. In the PCI group, outcomes by type of GPIIb/IIIa inhibitor and loading dose of clopidogrel were compared between the fondaparinux and enoxaparin groups. A propensity score was developed for the use of GPIIb/IIIa inhibitors and included variables

such as age, sex, diabetes, ST-segment deviation, elevated cardiac enzymes, and 'other baseline variables'. This was used to adjust the Cox model. A second propensity sore, developed similarly was used for thienopyridines in the Cox model.

Study participants

20,078 patients were in the main study, 3,630 patients received GPIIb/IIIa inhibitors and 13,531 received thienopyridines.

Numerous differences between patients receiving and not receiving GPIIb/IIIa inhibitors are demonstrated below (Table 14).

Table 14: Baseline characteristics for GPIIb/IIIa inhibitors use in the OASIS-5 trial

Table 1 Baseline Characteristics for Patients Treated With and Without GP IIb/IIIa Inhibitors

Characteristic	GP IIb/IIIa Use (n = 3,630)	No GP IIb/IIIa Use (n = 16,448)	p Value
Geographic region			
North America	853 (39)	1,309 (61)	<0.001*
Latin America	189 (10)	1,738 (90)	
Western Europe	2,058 (29)	4,952 (71)	
Eastern Europe	306 (5)	6,477 (95)	
Australia	139 (27)	384 (73)	
South Africa	15 (8)	181 (92)	
Asia	70 (5)	1,407 (95)	
Age (mean)	65	67	<0.001
Age ≥75 yrs	737 (20)	4,297 (26)	<0.001
Male sex	2,591 (71)	9,788 (60)	<0.001
Prior MI	787 (22)	4,377 (27)	<0.001
Diabetic	913 (25)	4,165 (25)	0.83
Prior coronary bypass surgery	376 (10)	1,267 (8)	<0.001
Prior PCI	546 (15)	1,786 (11)	<0.001
Troponin/CK-MB >ULN	3,097 (85)	11,041 (67)	<0.001
ST-segment depression ≥1 mm	1,554 (43)	8,688 (53)	<0.001
Transient ST-segment elevation >2 mm	333 (9)	820 (5)	<0.001
T-wave inversion (≥2 mm)	754 (21)	4,235 (26)	<0.001
Medications after randomization			
Aspirin	3,576 (99)	16,000 (97)	<0.001
Clopidogrel	3,159 (87)	9,351 (57)	<0.001
Beta-blocker	3,210 (88)	14,348 (87)	0.049
ACE inhibitor	2,427 (67)	11,636 (71)	<0.001
Statin	3,121 (86)	12,541 (76)	<0.001
Intravenous heparin	833 (23)	1,988 (12)	<0.001
Revascularization during initial hospitalization			
PCI	2,592 (71)	4,297 (26)	<0.001
Coronary bypass surgery	367 (10)	1,495 (9)	0.06

*Data are presented as n (%). The p value refers to difference in use of GP IIb/IIIa inhibitor between the different geographic regions.
ACE = angiotensin-converting enzyme; CK-MB = creatine kinase myocardial band; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

In addition, in the comparison of baseline characteristics numerous statistically significant differences were found between the patients receiving and not receiving thienopyridines (Table 15).

Table 15: Baseline characteristics for thienopyridine use in the OASIS-5 trial

Table 4 Baseline Characteristics for Patients Treated With and Without Thienopyridines

Characteristic	Thienopyridine Use (n = 13,532)	No Thienopyridine Use (n = 6,545)	p Value
Geographic region			
North America	1,783 (82)	379 (18)	<0.001*
Latin America	1,434 (74)	493 (26)	
Western Europe	5,591 (80)	1,419 (20)	
Eastern Europe	3,058 (45)	3,725 (55)	
Australia	332 (63)	191 (37)	
South Africa	38 (19)	158 (81)	
Asia	1,296 (88)	181 (12)	
Age (mean)	66	68	<0.001
Age ≥75 yrs	3,187 (24)	1,847 (28)	<0.001
Male sex	8,792 (65)	3,587 (55)	<0.001
Prior MI	3,382 (25)	1,782 (27)	<0.001
Diabetic	3,423 (25)	1,655 (25)	0.98
Prior coronary bypass surgery	1,264 (9)	379 (6)	<0.001
Prior PCI	1,910 (14)	422 (6)	<0.001
Troponin/CK-MB >ULN	10,035 (74)	4,103 (63)	<0.001
ST-segment depression ≥1 mm	6,655 (49)	3,587 (55)	<0.001
Transient ST-segment elevation >2 mm	874 (7)	279 (4)	<0.001
T-wave inversion (≥2 mm)	3,283 (24)	1,706 (26)	0.006
Medications after randomization			
Aspirin	13,193 (98)	6,383 (98)	0.95
Beta-blocker	11,960 (88)	5,598 (86)	<0.001
ACE inhibitor	9,311 (69)	4,752 (73)	<0.001
Statin	11,266 (83)	4,396 (67)	<0.001
Intravenous heparin	2,138 (16)	683 (10)	<0.001
GP IIb/IIIa inhibitors	3,246 (24)	384 (6)	<0.001
Revascularization during initial hospitalization			
PCI	6,650 (49)	239 (4)	<0.001
Coronary bypass surgery	1,111 (8)	751 (11)	<0.001

Data are presented as n (%). *The p value refers to difference in use of thienopyridines between the different geographic regions.
Abbreviations as in Table 1.

Results

The use of GP IIb/IIIa inhibitors had little impact on the composite primary endpoint but may have slightly increased the risk of death in the analysis for the overall study population (Table 16.
Table 16:).

Table 16: Efficacy, safety and net clinical outcome for GP IIb/IIIa inhibitor use, OASIS-5 trial

Table 2 Death, MI, Refractory Ischemia, Major Bleeding, and Net Clinical Outcome at 30 Days in Those Treated With a GP IIb/IIIa Inhibitor

Outcome	GP IIb/IIIa Use (n)	Fondaparinux (%)	Enoxaparin (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p Value*
Death, MI, refractory ischemia	Yes (3,630)	220 (11.8)	232 (13.2)	0.89 (0.74 1.07)	0.87 (0.72 1.06)	0.63
	No (16,448)	585 (7.1)	632 (7.7)	0.93 (0.83-1.04)	0.93 (0.82-1.04)	
Death	Yes (3,630)	58 (3.1)	64 (3.6)	0.85 (0.60-1.22)	0.85 (0.59-1.23)	0.89
	No (16,448)	237 (2.9)	288 (3.5)	0.83 (0.70-0.98)	0.79 (0.66-0.95)	
MI	Yes (3,630)	118 (6.4)	129 (7.4)	0.86 (0.67-1.10)	0.83 (0.64-1.07)	0.46
	No (16,448)	269 (3.3)	282 (3.5)	0.96 (0.81-1.14)	0.99 (0.83-1.17)	
Major bleeding	Yes (3,630)	96 (5.2)	146 (8.3)	0.61 (0.47 0.79)	0.60 (0.46 0.78)	0.86
	No (16,448)	218 (2.7)	349 (4.3)	0.62 (0.53-0.74)	0.62 (0.52-0.73)	
Net clinical outcome†	Yes (3,630)	278 (14.9)	333 (18.9)	0.77 (0.66-0.90)	0.76 (0.65-0.90)	0.42
	No (16,448)	748 (9.1)	906 (11.0)	0.83 (0.75-0.91)	0.81 (0.74-0.90)	

*Interaction p value for unadjusted analysis. †Net clinical outcome is defined as composite of death, MI, refractory ischemia, or major bleeding.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

For the PCI subgroup the results were tabulated by agent used (Table 17). The authors note that the use of up-front GP IIb/IIIa inhibitors alone did not reduce the risk of catheter thrombus in the fondaparinux or enoxaparin groups (0.7% [15/2,028] not receiving up-front GP IIb/IIIa versus. 1.3% [14/1,077] receiving up-front GP IIb/IIIa, p = 0.12) and enoxaparin groups (0.3% [5/1,987] not receiving up-front GP IIb/IIIa versus. 0.3% [3/1,085] receiving up-front GP IIb/IIIa,
p=0.9).

Table 17: Efficacy, safety and net clinical outcome by use of clopidogrel loading dose or GP IIb/IIIa inhibitor

Table 3 Death, MI, or Refractory Ischemia or Major Bleeding in Patients Undergoing PCI by Loading Dose of Clopidogrel or Type of GP IIb/IIIa Inhibitor

Outcome	Fondaparinux (%)	Enoxaparin (%)	Unadjusted HR (95% CI)*
Death, MI, or refractory ischemia			
Tirofiban (n = 1,102)	62 (11.2)	70 (12.8)	0.87 (0.62–1.22)
Eptifibatide (n = 773)	35 (9.1)	31 (7.9)	1.15 (0.71–1.87)
Abciximab (n = 686)	60 (16.6)	42 (12.9)	1.32 (0.89–1.96)
Clopidogrel loading dose 300 mg (n = 2,977)	155 (10.4)	143 (9.6)	1.09 (0.87–1.37)
Clopidogrel loading dose 600 mg (n = 145)	6 (8.8)	5 (6.5)	1.40 (0.43–4.58)
Major bleeding			
Tirofiban (n = 1,102)	21 (3.8)	25 (4.6)	0.83 (0.46–1.48)
Eptifibatide (n = 773)	9 (2.4)	28 (7.2)	0.32 (0.15–0.68)
Abciximab (n = 686)	16 (4.5)	23 (7.1)	0.62 (0.33–1.17)
Clopidogrel loading dose 300 mg (n = 2,977)	47 (3.2)	77 (5.2)	0.61 (0.42–0.87)
Clopidogrel loading dose 600 mg (n = 145)	1 (1.5)	2 (2.6)	0.57 (0.05–6.32)

*Interaction p values are nonsignificant for these subgroups (p > 0.05).
Abbreviations as in Table 2.

More patients were treated with thienopyridines than without during their initial hospitalisation. Unlike the GP IIb/IIIa inhibitors, above, outcomes were similar with and without their addition (Table 18).

Table 18: Efficacy, safety and net clinical outcome for thienopyridine use OASIS-5

Table 5 Death, MI, Refractory Ischemia, Major Bleeding, and Net Clinical Outcome at 30 Days in Those Treated With Thienopyridines

Outcome	Thienopyridine Use (n)	Fondaparinux n (%)	Enoxaparin n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Interaction p Value*
Death, MI, or refractory ischemia	Yes (13,532)	596 (8.6)	616 (9.1)	0.94 (0.84–1.05)	0.94 (0.84–1.06)	0.61
	No (6,545)	219 (6.7)	248 (7.5)	0.89 (0.74–1.07)	0.87 (0.72–1.05)	
Death	Yes (13,532)	178 (2.6)	218 (3.2)	0.81 (0.66 0.98)	0.79 (0.61 0.96)	0.59
	No (6,545)	117 (3.6)	134 (4.1)	0.88 (0.69–1.13)	0.84 (0.65–1.10)	
MI	Yes (13,532)	291 (4.3)	305 (4.6)	0.94 (0.80–1.11)	0.95 (0.81–1.12)	0.85
	No (6,545)	96 (3.0)	106 (3.3)	0.91 (0.69–1.20)	0.92 (0.69–1.21)	
Major bleeding	Yes (13,532)	229 (3.4)	360 (5.4)	0.62 (0.53–0.73)	0.62 (0.52–0.73)	0.92
	No (6,545)	85 (2.6)	135 (4.2)	0.63 (0.48–0.83)	0.62 (0.47–0.83)	
Net clinical outcome†	Yes (13,532)	749 (11.0)	892 (13.2)	0.82 (0.75–0.91)	0.82 (0.74–0.90)	0.78
	No (6,545)	277 (8.5)	347 (10.6)	0.80 (0.68–0.93)	0.78 (0.66–0.92)	

*Interaction p value for unadjusted analysis. †Net clinical outcome is defined as composite of death, MI, refractory ischemia, or major bleeding.
Abbreviations as in Table 2.

In PCI patients treated with GP IIb/IIIa inhibitor and pre-treated with a thienopyridine the composite efficacy endpoint was 11.0% versus 12.2% for those treated and 10.3% and 9.3% for those not treated in the fondaparinux and enoxaparin groups, respectively. Major bleeding occurred in 2.9% versus 5.9% for those treated and 2.8% and 5.4% for those not treated in the fondaparinux and enoxaparin groups, respectively. The net clinical outcome occurred in 13.2% versus 16.1% for those treated and 12.3% and 13.6% for those not treated in the fondaparinux and enoxaparin groups, respectively. HRs for these comparisons are not tabulated or presented in the text but are depicted graphically in a Forest plot (Figure 4).

Figure 4: Efficacy, safety and net clinical outcome for patients undergoing PCI treated with GP IIb/IIIa inhibitors or pre-treated with thienopyridines or both, OASIS-5

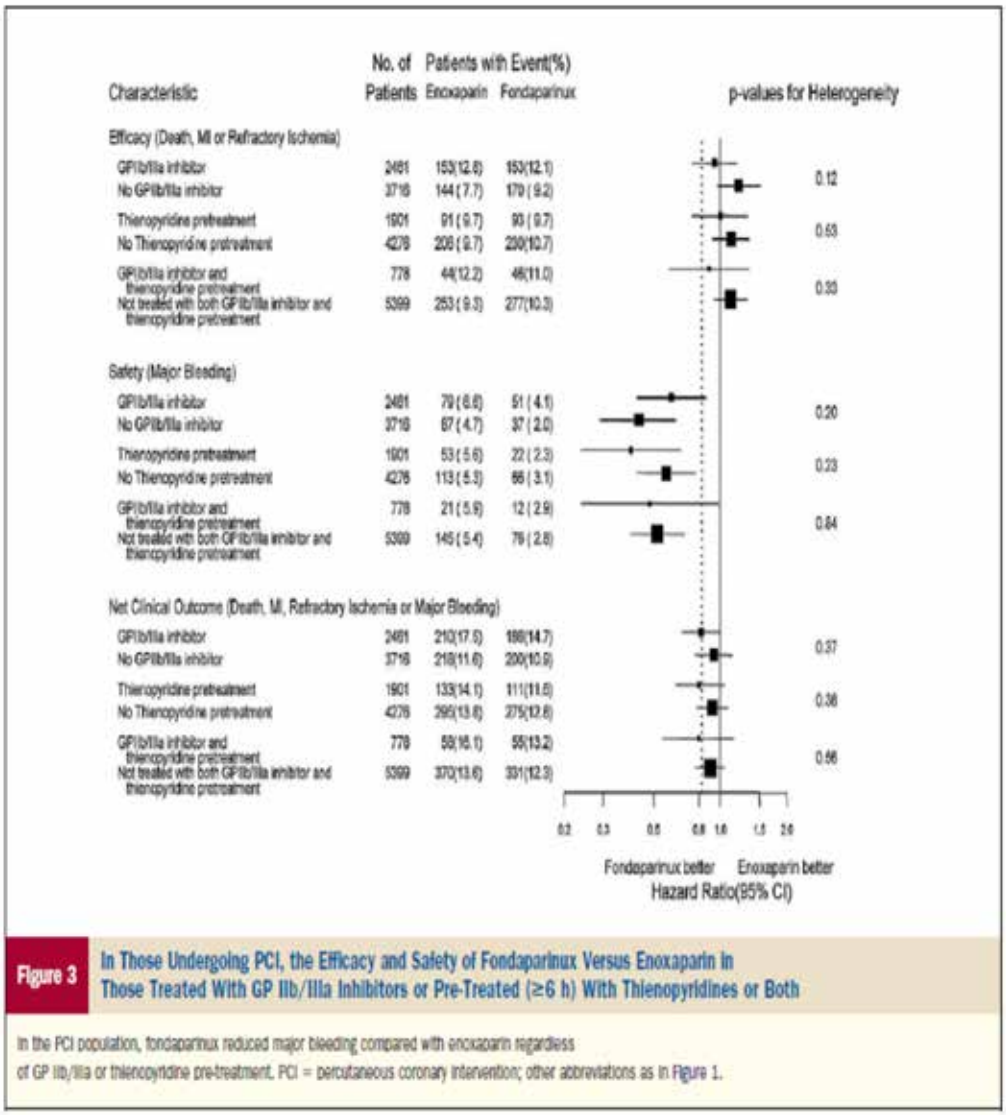


Figure 3 **In Those Undergoing PCI, the Efficacy and Safety of Fondaparinux Versus Enoxaparin in Those Treated With GP IIb/IIIa Inhibitors or Pre-Treated (≥6 h) With Thienopyridines or Both**

In the PCI population, fondaparinux reduced major bleeding compared with enoxaparin regardless of GP IIb/IIIa or thienopyridine pre-treatment. PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

Evaluator's comments

This analysis provides some reassurance that the use of GP IIb/IIIa inhibitors and thienopyridines do not substantially affect the safety of fondaparinux as compared with enoxaparin. Although not specifically powered for the analysis, the outcomes suggest more favourable efficacy outcomes for fondaparinux when these agents are used. Overall, this study does not suggest any compromise of the efficacy or safety of fondaparinux when used in conjunction with these agents.

Discussion

The sponsor was invited to provide commentary on the ACM minutes. The sponsor has responded disagreeing with some of the outcomes and providing its own expert opinion regarding the potential use of fondaparinux in the Australian context. Two expert opinions were provided, both supporting the use of fondaparinux for NSTEMI. Regarding the use in STEMI one expert was more cautious in his support and the other did not offer comment.

The sponsor, as requested, has provided copies of the references cited in the response and these have been summarised in this report.

The sponsor's responses and references can be divided into registry reports from Australia and audits of ACS treatment in Australia, presentation of real-world comparative data comparing fondaparinux with LMWH, and additional analyses from the OASIS-5 and OASIS-6 trials.

The sponsor reviewed the VCOR 2017 data, data from Queensland 2016 and earlier audits of Australian clinical practice in the management of ACS. These were aimed at two issues:

- how widespread the use of the radial approach in PCI was, and therefore how generalisable the OASIS-5 PCI subset data is to the Australian context; and
- to establish whether there is a patient population to which the OASIS-6 study subgroup analyses was generalisable.

Although there was an increasing use over time of the radial approach in Victoria this was not universal and about half of private patients had PCI by a femoral approach. In Queensland, there was considerable heterogeneity within hospitals for the access site of PCI. From the VCOR regional STEMI data a patient group was identified that did not have reperfusion therapy, although more than 80% of patients, regardless of whether or not they were re-perfused, were transferred to a PCI capable centre, suggesting for these patients the intention was for assessment for intervention. Older data identified patient groups that had not been re-perfused, although there were instances where this was inconsistent with the general recommendations at the time. It is unclear whether some of these publications had resulted in amendments to clinical practice and the offer of intervention to more patients. Overall, the sponsor has highlighted that the availability of services and their utilisation may not be uniform across Australia, or even between services in the same state.

Regarding the comment about the age of the data, the sponsor has noted that other aspects of cardiac care are based on data of similar age, and notes ongoing support for the use of fondaparinux in international guidelines.

The additional analyses of the PCI approach from the OASIS-5 trial data consistently demonstrated a difference in safety for both fondaparinux and enoxaparin for the radial approach (0.9% versus 2.4%) compared to the femoral approach (2.3% versus 4.8%). Differences between the major bleeding, overall bleeding, large haematoma, pseudo-aneurysm, and gastrointestinal and other site bleeding were seen between radial and femoral approaches. A second paper based on the OASIS-5 trial considered the impact of GP IIb/IIIa, thienopyridine use, and the impact of both on efficacy and safety. No safety concerns arose from these analyses. There was also no compromise of efficacy, with the point estimate risks of the efficacy more closely approximating unity with enoxaparin with the use of GP IIb/IIIa and/or thienopyridine.

The Swedish registry data provided additional support for the efficacy and safety of fondaparinux compared with enoxaparin. In this study, 46.4% of the fondaparinux and 38.9% of the LMWH patient underwent PCI. Of those, over half received their PCI in the first two days of admission to hospital. For PCI, a radial approach was used for 46.3% and 36.2% of the LMWH patients. Adjuvant PCI therapy was given for over 3 quarters of the fondaparinux patients, although only 2.6% received adjuvant LMWH. In hospital for bleeding, death or a combination of bleeding and death favoured fondaparinux. By 30 and 180 days, the outcomes were similar when adjusted for calendar time, baseline characteristics, PCI or CABG. For patients with kidney dysfunction, identified by brackets of estimated glomerular filtration rate, no concerns were raised for safety or efficacy compared with enoxaparin. A safety signal for catheter thrombosis in patients receiving fondaparinux as their only anticoagulant at the time of PCI was identified. These data are 8 years old but they track both the introduction of fondaparinux as an anticoagulant option in Sweden and also the changing likelihood of receiving PCI during admission, and analyses presented made adjustments for calendar time.

Overall, the additional data supported the similarity between fondaparinux and enoxaparin when used in NSTEMI, and were consistent with the overall outcomes of non-inferiority of fondaparinux and enoxaparin in NSTEMI found in the OASIS-5 trial.

The sponsor provided two subgroup analyses from the OASIS-6 trial of patients with STEMI. The Delegate and the ACM had significant concerns about this study. The STEMI patients were initially stratified by the type of thrombolytic agent (non-fibrin specific or fibrin specific preferred by the site investigator) then randomised to either fondaparinux or control. Only the stratum in which fibrin-specific thrombolytics were the agent of choice had an active (UFH) control and in the other stratum, the control group received placebo. The outcomes for all the fondaparinux and all the control groups were combined in the primary efficacy analysis, although *a priori* the outcomes would not be expected to be similar for efficacy or safety between placebo and an active control. There was a concern about a lack of generalisability of the data to the Australian context because non-fibrin specific thrombolytics are no longer registered. In addition, there was a much higher primary PCI rate across the treatment arms in Stratum 2 compared with Stratum 1. It is noted from the OASIS-6 trial clinical study report, that around 64% of Stratum 2 had a PCI prior to discharge, compared to 6.4-6.7% of Stratum 1. In Stratum 2, around 59% had primary PCI, compared to 0.2 to 0.4% of Stratum 1. In-hospital non-protocol UFH was given to 13% of Stratum 2 and 7.3 to 8.2% of Stratum 1. Overall Stratum 2 was more closely aligned with Australian practice.

The sponsor has proposed that patients receiving primary PCI should not be included in the indication, and this is reasonable. Two additional analyses of the remaining two population subsets of the OASIS-6 trial were provided as separate publications: those receiving thrombolytics and those receiving no reperfusion therapy.

In the publication by Peters et al., providing an analysis of the thrombolysed patients from the OASIS-6 trial, 4415 patients in Stratum 1 (non-fibrin specific thrombolytic Stratum) and 1021 patients in Stratum 2 (fibrin-specific thrombolytic Stratum) received thrombolytic as their reperfusion strategy. Of the patients in Stratum 2, 166 patients received non-fibrin thrombolytics, leaving 875 (including 20 patients from Stratum 1) who received fibrin-specific thrombolytics, and therefore generalisable to the Australian context. There may have been editing issues with the paper because the results by fibrinolytic used were reported twice and in one comparison the HR for the primary efficacy outcome (death or MI) was 1.24, for fondaparinux versus UFH with the upper bound of the 95% CI 1.97, although the lower bound was 0.78. The other analysis indicated similar outcomes for fondaparinux and UFH. However, this was a superiority study and although this is a sub-group analysis and the study was not specifically powered for this comparison, the superiority of fondaparinux over UFH for efficacy was not demonstrated. When compared by Stratum, and including patients receiving non fibrin-specific thrombolytics in the Stratum 2 analysis the HR was 0.91 (95% CI 0.63 to 1.30). This does not lead to a conclusion of superiority for fondaparinux. Overall, this study does not provide reassurance about the efficacy of fondaparinux given with fibrin-specific thrombolytics as would be the case in current Australian practice. While not clearly superior to UFH for severe haemorrhage in this analysis, as the sponsor has stated there was a trend in favour of fondaparinux.

In a separate publication (describing the analysis of patients not receiving reperfusion in the OASIS-6 trial at Day 9), similar outcomes between the Strata but was favourable for fondaparinux compared with UFH in the Stratum 2 analysis at 30 days for the primary study outcome. Although the reason it was superior to control in Stratum 2 but not Stratum 1 with an inactive control is unclear. Benefit was seen when both strata were combined for composite endpoints of death and MI, death, MI and stroke, and death MI and severe haemorrhage, not driven by any one of the individual components for which a trend but not clear superiority for fondaparinux was seen. For severe bleeding at Day 3

and Day 30, there is a trend in favour of fondaparinux in both strata, but the confidence intervals are very wide indicating considerable uncertainty in the results and for all comparisons the HRs cross unity.

Conclusion

The sponsor has provided additional data, including a registry based study that demonstrated the introduction of fondaparinux for NSTEMI into another country. These data supplement the OASIS-5 study and provide reassurance of the efficacy and safety when used in the real world, and the additional analysis provides reassurance of the efficacy and safety of fondaparinux in combination with commonly used medications such as thienopyridines and GPIIb/IIIa inhibitors. Consistently severe haemorrhage occurred less frequently with fondaparinux than enoxaparin. Overall, the data are generally supportive of its use for NSTEMI.

The sponsor has provided two additional publications of subgroups analyses from the OASIS-6 trial. The analysis of STEMI patients re-perfused with thrombolytics does not offer compelling evidence to support the efficacy and safety in this indication. While there are trends towards safety, efficacy is less convincing.

Interpretation of the additional analysis of patients undergoing no reperfusion is difficult. While with a single positive finding for efficacy for fondaparinux in Stratum 2, the subgroup analysis was underpowered for the comparisons and the outcomes were inconsistent with the remainder of the study and against an inactive control, but favourable when both strata are combined for analysis for composite endpoints.
The sponsor has proposed that the STEMI indication is limited to patients not undergoing primary PCI, but the analysis of thrombolysed patients and the uncertainty about the non-re-perfused patients does not provide sufficient support for the STEMI indication as proposed.

The question has been raised as to whether fondaparinux has a place in therapy in the non-re-perfused patients for whom a higher risk of bleeding that may occur with UFH or the more commonly used enoxaparin. The evidence to support the efficacy and safety to support this proposal would be based on a subgroup analysis of a single study with issues with generalisability and internal validity. It is therefore not clear whether, despite favourable outcomes for fondaparinux being found, the evidence is sufficiently robust to support an indication. The ACM will be requested to provide its view on this proposal.

Review of relevant findings of the 2017 Annual report of the VCOR (Victorian Cardiac Outcomes Registry)

This paper is the 2017 Annual Report from the VCOR registry (https://vcor.org.au/sites/default/files/VCOR%20Annual%20Report%202017.pdf), cited by the ACM, and from which evidence questioning the relevance of the findings of the submission was partly drawn.

The registry is based in Victoria, supported by the Department of Health and Human Services Victoria, and Monash University. Some contributing staff received salary support by a National Health and Medical Research Council (NHMRC) Fellowship.

In 2017, the registry included data from all 30 public and private hospitals in Victoria.

The report was divided into four main parts: PCI (all 30 hospitals participated); acute STEMI (10 regional hospitals participated); heart failure (presented as a 4-week snapshot of management); and the use, safety and quality of cardiac implanted electronic devices. The PCI and STEMI sections are of the most relevance to the requested indications and are described in this section.

PCI

The PCI data set included collected data from 10,792 procedures performed for 9,552 patients (61.5% in the public system).

In the overall data set, the median age for males was 66 years (interquartile range 57, 74) and for females 71 years (interquartile range 62, 78). The peak frequency of PCI procedures occurred in the seventh decade for males and eighth decade for females.

Most patients undergoing PCI were male (76%), with a mean age of 66 years. Private patients were about 6 years older than the public patients. About 20% were performed after hours.

About half of the PCI cases presented with ACS, (21% with STEMI and 30% with non-ST elevation ACS); 77% to a public hospital. For patients with stable (non-ACS disease), 65% had stable angina, with a PCI indicator of high grade stenosis in 91% and positive functional test in 49% (81% had at least two of these three indicators).

Early revascularisation for non-ST elevation ACS is an Australian guideline recommendation. About 49% had PCI within 24 hr of hospital admission, 22% in 24 to 47 hr, 13% within 48 to 72 hr and 16% more than 72 hr of admission. Most (87.8%) PCI for non-ST elevation ACS cases occurred in normal working hours.

About 90% of stents were drug eluting stents (DES) (88% public, 92% private), with an overall 5% increase from the previous year.

Radial artery access occurred in 61% of cases, and varied between hospitals (68% public, 50% private), with lower rates in females versus males (56% versus 63%) and in the elderly (49% > 80 years versus 62% < 80 years).

Primary PCI for acute STEMI was 13% of the overall PCI, and most were in the public sector (92%), and most used radial access (66%). A door to needle time of < 90 minutes was achieved in 77% and the median door to balloon time was 63 minutes.

The overall risk-adjusted 30 day mortality was 2.9%. The major adverse coronary events (MACE) total mortality was 1.8% in hospital and 2.2% at 30 days (hospital events inclusive).

Major bleeding was defined according to BARC definitions;[13] category 3;[14] and category 5.[15] The median in-hospital major bleeding was 0.7% (0.5% radial access, versus 0.9% femoral access versus 11.8% brachial access). Major bleeding in STEMI occurred in 1.7%, 0.6% in non-ST elevation ACS and 0.3% in non-ACS patients. The median 30 day unplanned re-admission rate was 3.6% (similar in public versus private sectors).

Regional hospital STEMI

The 2017 cohort included 287 patients with suspected STEMI from 10 Victorian regional health services, of whom 88 (31%) were ineligible for thrombolysis, 50.5% received thrombolysis either in hospital or pre-hospital, and a further 16.7% were triaged to primary PCI in a PCI capable hospital. Most (94%) of patients who were thrombolysed were transferred to a PCI-capable hospital within 24 hr (median time from referral for

[13] Bleeding Academic Research Consortium: Standardized Bleeding Definitions for Cardiovascular Clinical Trials; A Consensus Report From the Bleeding Academic Research Consortium. Circulation. 2011;123:2736–2747 https://doi.org/10.1161/CIRCULATIONAHA.110.009449

[14] Category 3 bleeding is divided into three subgroups: a) overt bleeding plus haemoglobin (Hb) drop of 3 to < 5g/dL; transfusion with over bleeding, b) overt bleeding plus haemoglobin drop of ≥ 5 g/dL; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents, c) intracranial haemorrhage (not microbleeds or haemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy, imaging or lumbar puncture; intraocular bleed compromising vision

[15] Category 5 bleeding is divided into two subgroups; a) probable fatal bleeding (no autopsy or imaging confirmation but clinically suspicious), b) definite fatal bleeding (overt or autopsy or imaging confirmation)

transfer to actual transfer was 2.3 hr), and 82% of the whole cohort (regardless of thrombolysis eligibility) were transferred to a PCI-capable hospital. Of those, 57% had a subsequent PCI and 6% underwent CABG.

The mean age in the regional cohort was 67 years (± 15) and most patients were male (64.1%). The median time from pain onset to first ambulance/medical contact was 110 minutes, the median time for ambulance arrival was 16 minutes and the median transport time was 54 minutes. The median door to needle time to thrombolytics was 48 minutes (29% received this in 30 minutes).

Hospital mortality (before transfer) overall in this cohort was 6%. Mortality in patients with cardiogenic shock was 34%.

Major bleeding occurred in 0% patients treated with primary PCI (N = 31), 9.1% with rescue PCI (N = 11), 2.0% with PCI ≤ 24 hr of lysis (N = 50) and 5.3% with PCI > 24 hr of lysis (N = 19). The small case and event numbers are noted.

Delegate's request for ACM's advice (February 2019 meeting)

Issues

- Whether taking into account the evidence provided in the submission and the evidence provided in the response to the ACM resolution, there is sufficient evidence now to support an indication for use in patients with NSTEMI.
- Whether the subgroup analyses of the OASIS-6 trial in patients are sufficient to support the requested STEMI indication.

Revised indications

The sponsor has modified its requested indications:

> *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.*
>
> *Arixtra is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed without primary percutaneous coronary intervention (PCI)*

Summary of issues

This request for advice should be considered an addendum to the previous Request for Advice-(Delegate's overview) for this submission.

The key points are outlined below. Regarding the requested indication for NSTEMI not undergoing urgent PCI (< 120 minutes):

- The OASIS-5 trial was a non-inferiority study comparing fondaparinux and enoxaparin that met is primary endpoint of time to death, MI or recurrent ischaemia. There were no specific safety concerns compared with enoxaparin and overall major bleeding rates were favourable for fondaparinux.
- Concerns were raised about the generalisability of the study because of the high use of the femoral approach and the low use of the radial approach to PCI.
  - Although the radial approach was used in only 10% of patients 14,159 patients who underwent angiography, outcomes were consistently favourable for safety for fondaparinux over enoxaparin.
  - Australian registry data indicate the femoral approach is still used for coronary angiography and PCI, so the safety information would still be applicable in those patients

  - Australian registry data indicate increasing use of a radial approach but this is not universal and varies between states and centres.

- Efficacy and safety of fondaparinux do not appear compromised by the use of GP IIb/IIIa inhibitors and/or thienopyridines.
- Data from the Swedish cardiac registry support the safety and efficacy of fondaparinux as compared to LMWH.
- ESC guidelines provide a Class Ib recommendation for its use in NSTEMI

Regarding the requested indication for STEMI patients not undergoing primary PCI

- The OASIS-6 trial was the single supportive studies and had a number of design issues. This was a superiority study in two non-randomised Strata based on the investigator preference for non-fibrin specific (Stratum 1) or fibrin specific thrombolytics (Stratum 2). Patients in each stratum were randomised to fondaparinux or control (inactive in Stratum 1 and UFH in stratum 2).
- Stratum 2 is more generalisable to the Australian context; fibrinolytic therapy is available and the use of primary or early PCI was substantially higher.
- Stratum 1 is not generalisable to the Australian context; non-fibrin specific thrombolytics are not available and the use of primary of early PCI was very low.
- In Stratum 2 fondaparinux was not superior to control (UFH) for efficacy
- For patients re-perfused with fibrin specific thrombolytics fondaparinux was not superior to control (UFH) for efficacy
- Fondaparinux was favourable for non re-perfused patients in Stratum 2 compared to control (UFH), but although there was a favourable trend it was not superior to placebo in a corresponding analysis of stratum 1, raising questions about the strength of the evidence this provides
- Australian registry data suggest there may be a small proportion of patients that are not re-perfused post STEMI, so there is a question as to whether fondaparinux would be suitable, however the evidence supporting this proposal has a number of limitations
- Consistently lower rates of severe/major bleeding than comparators

Preliminary conclusions

Taking into account the new and previously submitted evidence presented to support the indication:

> *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.*

The preliminary conclusion is that insufficient evidence has been provided to support this indication as written.

The indication includes patients re-perfused with thrombolytics and patients who receive no reperfusion. A single study has been provided to support the indication. The new publications are sub analyses of relevant patient subgroups from the OASIS-6 trial and not new studies. The new analysis of the thrombolysed subgroup of patients is not persuasive of benefit, particularly for efficacy, for the stratum relevant to the Australian context. There is uncertainty about the robustness of the evidence for fondaparinux for the non re-perfused patients; however, the ACM is requested to consider whether the evidence is sufficiently robust.

Request for ACM advice (February 2019 meeting)

The advice of the ACM is sought on the following:

1. Has sufficient support for safety and efficacy of fondaparinux for the proposed indication for use in NSTEMI now been provided?
2. Has sufficient support for safety and efficacy of fondaparinux for the proposed indication for use in STEMI now been provided?

The committee is invited to provide comment on any other matter(s) that arise(s) from the review of this information.

Advisory committee considerations (February 2019 meeting)

The ACM, taking into account the submitted evidence of efficacy, safety and quality, considered Arixtra, pre-filled syringe containing fondaparinux 2.5 mg in 0.5 mL, 5.0 mg in 0.4 mL, 7.5 mg in 0.6 mL or 10.0 mg in 0.8 mL for 2.5 mg daily dosing to have an overall positive benefit-risk profile for the revised indications:

- *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.*
- *Arixtra is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed without primary percutaneous coronary intervention (PCI).*

In providing this advice, the ACM noted that:

- The sponsor has modified the proposed indication for use of Arixtra in STEMI based on comments from the October 2018 ACM meeting, and provided additional evidence in support of their revised indication.
- The initially proposed indication for use in STEMI was:
  - *Arixtra is indicated for the 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*
- The sponsor's proposed indication for NSTEMI has not changed. There is no further concern regarding the NSTEMI indication following review of the additional evidence supplied by the sponsor, as below.
- The sponsor has provided additional data including a registry-based study that demonstrated the introduction of fondaparinux for NSTEMI patients in another country. The data showed that fondaparinux was favourable in relation to decreasing bleeding and showed a favourable trend for efficacy.
- The sponsor also provided data to support the conclusion that the results of the OASIS-5 trial are still relevant to current practice, despite the higher rates of radial access for patients in Australia (based on the VCOR report).
- The use of Arixtra in STEMI is less straightforward.
- A key concern regarding the use of Arixtra in patients undergoing primary PCI is the increased risk of catheter tip thrombosis. The ACM discussed whether this risk should warrant inclusion of a black box warning, but concluded that:
  - appropriately qualified and experienced treating physicians should already be aware of this risk without the need for specific warning; and
  - the revised indication should be sufficient to avoid this circumstance occurring.

- The sponsor has provided analyses, which show that Day 30 outcomes for Arixtra used in STEMI patients with no initial reperfusion are improved compared to other anticoagulants or placebo. While the ACM considers that there are issues with these analyses, overall it was agreed that they do show a favourable trend for safety for Arixtra and some evidence of non-inferiority in terms of efficacy.
- Given this, the ACM agreed with the sponsor that the revised indication for use of Arixtra in STEMI for patients not undergoing primary PCI would provide a potentially beneficial additional treatment option.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- A statement in the Dosage and Administration section of the PI and relevant sections of the CMI to specify that the initial dose of Arixtra must be given intravenously for the STEMI indication, in keeping with practice from the reference studies.
- A statement in the Dosage and Administration, Precautions and Contraindications sections of the PI and relevant sections of the CMI to ensure that precautions and exclusions for the use of Arixtra in patients with renal failure be reviewed in the context of the enrolment criteria in the OASIS-5 and 6 trials.

Specific advice

The Delegate requested advice on specific questions on this submission. The ACM advised the following in response to the Delegate's questions:

1. ***Whether, taking into account the evidence provided in the submission and the evidence provided in the response to the ACM resolution, there is sufficient evidence now to support an indication for use in patients with NSTEMI.***

The ACM agreed that there is now sufficient overall evidence to support an indication for use of Arixtra in patients with NSTEMI. The evidence provided in the submission, coupled with the evidence provided by the sponsor in response to the outcomes of the October 2018 ACM meeting, were considered sufficient to support this indication.

The ACM considered that the new evidence provided by the sponsor, including a registry-based study, supplemented the OASIS-5 trial and provided reassurance of the efficacy and safety when used in real world situations. Furthermore, the additional analysis submitted by the Sponsor provided reassurance of the efficacy and safety of fondaparinux in combination with commonly used medications such as thienopyridines and GPIIb/IIIa inhibitors. The ACM noted that consistently severe haemorrhage occurred less frequently with fondaparinux than enoxaparin.

2. ***Whether the subgroup analyses of the OASIS-6 trial in patients are sufficient to support the requested STEMI indication.***

The ACM considered that the evidence provided in support of the revised STEMI indication remains sub-optimal, in particular with respect to non-reperfused patients.

However, the ACM noted that the sub-group analysis of the 2,867 patients with STEMI who did not receive reperfusion therapy in the OASIS-6 trial, while underpowered, does appear to show benefit for the use of fondaparinux in this setting.

When combined with observational data from overseas jurisdictions (EU and Canada) where Arixtra is approved for use in STEMI in patients who are managed with thrombolytics or who are initially to receive no form of reperfusion therapy, that do not show signals of harm from over 10 years of use in practice, the ACM concluded that there is now sufficient evidence to support the use of Arixtra for the revised STEMI indication as follows:

> *…for patients who are managed without primary percutaneous coronary intervention.*

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Arixtra fondaparinux 2.5 mg in 0.5 mL pre-filled syringe; 5.0 mg in 0.4 mL pre-filled syringe; 7.5 mg in 0.6 mL pre-filled syringe and 10.0 mg in 0.8 mL pre-filled syringe for SC injection, indicated for:

> *Arixtra is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.*
>
> *Arixtra is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed without any form of initial reperfusion therapy*

Specific conditions of registration applying to these goods

- The Arixtra EU-Risk Management Plan (EU-RMP), version 2.0, dated 31 August 2015; DLP 6 December 2013, with Australian Specific Annex (version 2.0, dated June 2018) included with submission PM-2017-03032-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Arixtra approved with the submission, which is described in this AusPAR, is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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