Antiplatelet and antithrombotic therapy in Acute Coronary Syndromes

**ST-Elevation MI**
- PRIMARY PCI
  - Aspirin
  - Clopidogrel
  - +/- GpIIb/IIIa
  - UFH if PCI

**Non-ST-Elevation MI/ACS Late presenting STEMI**
- EARLY ANGIOGRAPHY within 2 hours
  - Aspirin
  - Clopidogrel
  - +/- GpIIb/IIIa
  - UFH if PCI

**CONSERVATIVE STRATEGY**
- DEFERRED ANGIOGRAPHY > 2 hours
  - Aspirin
  - Clopidogrel
  - FONDAPARINUX 2.5mg sc OD for up to 8 days
  - +/- GpIIb/IIIa

**INVASIVE STRATEGY**
- CONSIDER:
  - Aspirin
  - Clopidogrel
  - FONDAPARINUX 2.5mg sc OD for up to 8 days if troponin +ve

**CATH LAB**
- UFH if PCI

**NOTES:**
1. This is not a protocol. Clinical judgement should be applied to weigh individual benefit vs risk of bleeding.
2. For renal impairment with eGFR < 20 ml/min OR Creatinine > 265 µmol/litre give enoxaparin 1mg/Kg sc ONCE daily and NOT fondaparinux.
3. Fondaparinux does not need to be stopped prior to angiography but may be withheld at operator’s discretion.
4. Unfractionated heparin (UFH) should be given at the time of PCI. A dose of 50-100U/kg is recommended depending on concomitant use of a glycoprotein IIb/IIIa inhibitor (GpIIb/IIIa).
5. Closure devices (Angioseal or Terumo bands) allow immediate sheath withdrawal; alternatively sheath removal needs to be delayed until 6 hours after the last dose of fondaparinux (and ACT < 150s if UFH given).
6. Enoxaparin remains the drug of choice for medical and surgical thromboprophylaxis, treatment of DVT/PE and thromboprophylaxis in patients with AF.
Fondaparinux in Acute Coronary Syndromes

Use of antithrombotic heparins has been commonplace in ACS. Unfractionated heparins (UFH) were used initially. Limitations include poor bioavailability at low doses and short half-lives requiring intravenous infusions for prolonged use, with monitoring of therapeutic effect.

Low molecular weight heparins (LMWH), including enoxaparin, have a more predictable dose-effect relationship and can be administered subcutaneously without need for monitoring of coagulation. Maximum plasma levels are achieved 3 to 5 hours after administration subcutaneously. Use of LMWH has been shown to have a lower risk of inducing thrombocytopenia than UFH\(^1\). In ACS, LMWH have been shown superior to UFH\(^2,3\), though the SYNERGY study suggested increased bleeding with crossover from enoxaparin to receiving additional UFH\(^4\).

Bleeding complications remain an important issue in patients presenting with ACS. Patient-related risk factors include increasing age, female sex, a history of bleeding and chronic renal impairment\(^5\). Procedural factors include choice of arterial access for invasive management, and use of antiplatelet and antithrombotic therapy. Major bleeding after both conservative and invasive treatment of ACS is associated with worse outcomes over the short and medium term\(^6\).

The indirect Factor Xa inhibitor fondaparinux has been trialled extensively in ACS. It binds selectively to antithrombin and neutralises Factor Xa at the convergence of the intrinsic and extrinsic coagulation cascade. Generation of thrombin is attenuated, with reduced thrombus formation. Dose-effect relationship is predictable, with a peak plasma concentration less than 2 hours after sc administration, and a plasma half-life of 15 to 17 hours\(^7\). No monitoring of effect is required. A once-daily dose of 2.5mg s.c. is effective for all patients\(^8\). It is excreted unchanged via the kidneys and is contraindicated in those with a CrCl <30ml/min. It does not appear to cross-react with sera from patients with heparin-induced thrombocytopenia, and this complication is thought very unlikely. Protamine does not reverse its effect, though the use of recombinant Factor VIIa may do so\(^9\).

In the multi-centre OASIS-5 study\(^10\), over 20,000 patients presenting with NSTEACS were randomised to receive upstream either enoxaparin (1mg/Kg) bd or fondaparinux 2.5mg sc od, in addition to standard antiplatelet therapy. Exclusion criteria were serum creatinine >265µmol/litre, recent haemorrhagic stroke, contraindications to LWMH and indications for anticoagulation other than ACS. Over 12,000 patients went on to have angiography within the study drug period. The study drug was given for up to 8 days, to the point of discharge, or until PCI was performed. It could be restarted after intervention at the discretion of the operator. Consistent with European data, about half of these patients underwent PCI, and represented an intermediate-to-high risk group. Overall, at 9 days, fondaparinux was non-inferior to enoxaparin on the primary efficacy outcome measure of Death/MI/Refractory Ischaemia (5.8% vs 5.7%; HR 1.01, 95% CI 0.90-1.13). The rates of the main secondary outcome of Death or MI at 9 days were similar. (4.1% vs 4.1%) Major bleeding at 9 days, defined by Thrombolysis In Myocardial Infarction criteria, was reduced significantly. (2.2% vs 4.1%; HR 0.52, p<0.001) Largely driven by this reduction in bleeding, there were significant differences noted at 30 days in rates of Death (2.9% vs 3.5%; HR 0.83, p 0.02) and composite Death/MI/Refractory Ischaemia/Major Bleeding (10.2% vs 12.4%; HR 0.82, P=0.001) that persisted out to 180 days. A reduction in bleeding was seen regardless of age, sex, use of additional UFH, the presence of cath lab facilities on-site, or time to revascularisation.
In patients undergoing PCI\textsuperscript{12}, use of fondaparinux was associated at Day 9 with a similar reduction in major bleeding (2.4% vs 5.1%; HR 0.46, \(p=0.001\)) and the composite endpoint of Death/MI/Stroke/Major Bleeding (8.2% vs 10.4%; HR 0.78, \(p=0.004\)). This effect again persisted to 30 and 180 days, as for the study population as a whole. Vascular access site complications including pseudoaneurysm and large haematoma were reduced (3.3% vs 8.1%, \(p<0.001\)).

Subgroup analysis demonstrated reductions in bleeding in all subgroups including those with transradial access, chronic renal impairment, patients undergoing PCI within 24 hours, and the use of clopidogrel and/or glycoprotein inhibitors\textsuperscript{12}.

Patients presenting with ST-elevation MI were studied in the OASIS-6 trial. Relevant to local practice with Primary PCI, no benefit in terms of a reduction in bleeding or the composite endpoint of Death/Re-infarction with the use of fondaparinux over UFH\textsuperscript{13}.

The OASIS-8/FUTURA study\textsuperscript{14} looked specifically at dosing of UFH at the time of PCI in fondaparinux-treated patients who had presented with unstable angina or NSTEMI, with a focus on bleeding complications. 2026 patients were randomised to receive either an “adjunctive standard” dose of 85U/Kg of UFH (60U/Kg if on glycoprotein inhibitors) with further boluses to achieve a target ACT or a low-dose regimen of 50U/Kg irrespective of glycoprotein inhibitor use. Three quarters of patients had presented with NSTEMI. Glycoprotein inhibitors were used in just one quarter of patients, predominantly upfront rather than for bail-out indications. The primary outcome measure was a composite of peri-PCI (within 48 hours) major bleeding, minor bleeding and major access site complications. The main secondary outcome measure was a composite of major bleeding peri-PCI, death, myocardial infarction and target vessel revascularization (TVR). The trial was underpowered for analysis of ischaemic outcomes alone. The incidence of bleeding complications was consistent with those seen in OASIS-5. No differences were noted between the two groups with regard to the primary outcome measure. A benefit in favour of the standard UFH regime just reached a level of significance for the main secondary endpoint (3.9% vs 5.8%, \(p=0.05\)), though pre-specified analysis of the components of this showed no significant differences between the two arms. A reduction in minor bleeding was noted in the low-dose UFH group.

The use of fondaparinux has been reviewed and incorporated into the most recent guidelines regarding NSTEACS. The 2007 ESC guidelines\textsuperscript{15} have given it a Class 1 Recommendation (Level of Evidence A) for anticoagulation in a non-urgent setting, though suggested UFH, bivalirudin or enoxaparin as antithrombotics when emergent invasive treatment is required on presentation. NICE Clinical Guideline 94\textsuperscript{16} recommended its use for cases where angiography was planned to take place more than 24 hours after admission, with UFH as an alternative for more emergent cases. Fondaparinux was thought cost-effective as compared to UFH, easier to administer and superior in clinical outcomes to enoxaparin.
Specific issues

Chronic renal impairment

Patients with renal dysfunction pose a particular problem, with higher risks associated with presentations with ACS and also an increased bleeding risk with current therapy. A subsequent analysis of OASIS-5 indicated that the benefit in reducing bleeding risk of fondaparinux over enoxaparin was actually greatest in those with the most renal impairment (GFR<58ml/min/1.73m^2).\(^\text{15}\)

The definition of renal impairment precluding use of fondaparinux has varied between trials. In OASIS-5 and OASIS-6, fondaparinux was not given to patients with a serum creatinine of >265µmol/litre. The manufacturer’s website reports that it is contraindicated in those with a creatinine clearance less than 30ml/minute, while a creatinine clearance of less than 20ml/min was the cut-off used in OASIS-8. It should be remembered that creatinine clearance will overestimate GFR in severe renal impairment because of tubular secretion and that this measure is not used routinely in clinical practice. Using a more practical measure, the British National Formulary\(^\text{18}\) states that fondaparinux should not be given for treatment of acute coronary syndromes when the estimated GFR is less than 20ml/min/1.73m^2.

Based on the above analysis, NICE guidance recommend unfractionated heparin as an alternative for those with renal dysfunction outside either of these parameters, rather than once-daily enoxaparin (1mg/Kg) given currently. Whilst apparently logical, real-world experience of monitoring of intravenous heparin infusions is now minimal and evidence suggests that supratherapeutic dosing is frequent and commonplace.\(^\text{19}\) It is probable, though not evidence-based, that continuing to use once-daily enoxaparin will remain the most practical antithrombotic to use in patients with a serum creatinine >265µmol/litre or GFR<20ml/min/1.73m^2.

Low Body Weight

Fondaparinux should be used with caution in patients with a body weight < 50kg as elimination is reduced.

Conservatively managed patients

Such patients are currently treated as inpatients for 5 days. OASIS-5 allowed for treatment with fondaparinux for up to 8 days, though the mean duration of therapy was 5.4 days. Current European guidelines suggest continuing therapy until discharge, for a maximum of 8 days.

Late presentation/non-reperfused ST-elevation MI

Around a quarter of patients will present either late or with other reasons precluding reperfusion for STEMI. Equivalent efficacy in terms of Death and Re-infarction has previously been shown for LMWH
as compared to UFH\textsuperscript{20}. Analysis of the OASIS-6 study population presenting with STEMI but not reperfused demonstrated a modest reduction in a composite of Death/Re-infarction at 30 days with fondaparinux over placebo or UFH infusion (12.2\% vs 15.1\%; HR 0.80; 95\% CI 0.65–0.98). There was no difference in severe bleeding between the groups\textsuperscript{21}. This subgroup were older than the OASIS-6 population as a whole, and presented later. Use of dual anti-platelet therapy and statins was limited. Its value in terms of local practice is likely limited, but use of fondaparinux as for NSTEACS appears safe.

**Fondaparinux Dosing prior to Angiography**

Fondaparinux does not need to be stopped prior to angiography. This is supported by the OASIS-8 protocol which aimed for angiography to be undertaken within 18 hours of the previous fondaparinux dose. In the published results, the median time from last dose of fondaparinux to index PCI was 4 hours.

**Dosing of UFH at the time of PCI**

The results of OASIS-8 suggest that there is no evidence to support a routine use of low-dose UFH in all fondaparinux-treated patients. The “adjunctive standard” regime used in the trial protocol mandated an initial bolus of 85U/Kg, with further doses up to a maximum of 10000 Units. Further dosing was guided by measurement of ACT at 5 minutes, aiming for an ACT of 250-300 seconds on a Hemotech device (300 to 350 seconds on a Hemochron).

It is recommended by both the authors of OASIS-5\textsuperscript{11,21} (and NICE) that patients undergoing PCI are given UFH at a dose of 50-100U/Kg as per standard treatment in the cath lab, and not additional intravenous doses of fondaparinux. Current European guidelines follow the OASIS-8 protocol more closely, recommending an initial bolus of 85U/Kg and ACT-guided further doses as described above.

**Glycoprotein IIb/IIIa inhibitors (GpIIb/IIIa)**

In OASIS-5, around 40\% of those undergoing an invasive strategy were on glycoprotein inhibitors. Post-hoc analysis\textsuperscript{12} demonstrated a statistically significant 40\% reduction in Major Bleeding and composite clinical outcomes consistent with the study results as a whole.

As per OASIS-8 and current European guidelines\textsuperscript{15}, an UFH dose of 60U/Kg should be given in those undergoing PCI who are treated with GpIIb/IIIa inhibitors, aiming for a target ACT of 200 seconds.

**Guide catheter thrombosis**

In OASIS-5, this was reported in both study arms, though with an excess in those given fondaparinux (0.3\% vs 1.2\%). This did not appear to impact on the rate of PCI-related coronary complications (8.6 vs. 9.5\%, RR 1.11 95\% CI 0.94–1.29, p=0.21) for enoxaparin vs. fondaparinux. Interventional
operators were reminded that the protocol allowed for the unblinded use of UFH at their discretion. The final 1758 cases were analysed specifically for this. Use of UFH at a mean dose of 47U/Kg appeared to reduce this complication. In those fondaparinux-treated patients documented as having developed catheter thrombosis after the protocol amendment, nine events occurred when no UFH was given prior to PCI and the remaining case occurred in a patient who received a low dose of open-label UFH of 5 U/Kg\textsuperscript{11}.

In support of the use of additional UFH at the time of PCI, patients undergoing non-Primary PCI after STEMI in the OASIS-6 trial\textsuperscript{17} (250 on fondaparinux and 239 controls) were mandated to receive UFH prior to PCI. No catheter thrombosis was noted in either group. In the much larger OASIS-8 population, guide catheter thrombosis was rare in both groups and very rare (0.1%) in the group receiving standard doses of UFH\textsuperscript{14}.

Management of vascular access after angiography/PCI

No change is required in the use of femoral artery closure devices or the removal of radial artery sheaths. If a femoral puncture is not suitable for closure device, or the sheath left in at the discretion of the operator, then the sheath should remain until at least 6 hours\textsuperscript{21} after the last dose of fondaparinux, and manual compression/Femstop applied in the usual way. If felt clinically appropriate, fondaparinux can be continued 2 hrs after sheath removal, providing there has been a delay of at least 18 hours after the last dose\textsuperscript{14}.

Management of bleeding complications whilst on fondaparinux

The effect of fondaparinux is non reversible and unless there is a life threatening bleed or a bleed into a critical site like the CNS management is supportive only. Anti-Xa levels will allow an assessment of the residual activity of Fondaparinux in the patient.

Recombinant Factor VIIa (rVIIa) is a therapeutic option should only be used with extreme caution due to the increased risk of thromboembolic complications and high cost and is only available from blood bank after discussion with the duty Haematologist.

Protamine is not effective in reversal of Fondaparinux.

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References


12. Jolly SS, Faxon DP, Fox KA et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein Ilb/llla inhibitors or thienopyridines:


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