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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate, and cost-effective to the NHS.

Guidance for the diagnosis and early management of Acute Coronary Syndromes: unstable angina and non-ST-segment elevation myocardial infarction

This guideline sets out the pharmacological treatment for early management of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) from diagnosis to discharge.

Patients presenting with ST-segment elevation myocardial infarction (STEMI) require immediate reperfusion and are not covered by this guideline. These patients are treated within the Oxford Heart Centre according to local protocol.

Diagnosis [1,2]

The diagnosis should be based on a combination of clinical history, symptoms, vital signs, results from resting 12-lead ECG and cardiac troponin.

Anginal pain in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) can present as:

- Prolonged chest discomfort (more than 20mins) at rest
- New onset angina
- Crescendo angina
- Post-MI angina

Patients who present to A&E with chest pain and suspected acute coronary syndrome (ACS) should have a review of their pre-hospital (if available) and departmental ECG by senior staff within 10 minutes: ST depression, transient ST elevation and T-wave changes are indicative signs of myocardial ischaemia, however the ECG may be normal.

Immediate bloods should be taken, and high-sensitivity cardiac troponin (hs-cTnI) measured.

Classification of diagnosis

NSTEMI: cardiac chest pain with ECG changes (ST or T wave changes) and/or a rise in hs-cTnI.

UA: recent onset and/or crescendo angina with normal or non-diagnostic ECG and a normal hs-cTnl (absence of acute cardiomyocyte injury/necrosis).

All patients with a suspected diagnosis of NSTEMI or UA should be referred to cardiology for review, using the contact numbers below:

Cardiology ANP (JR): bleep 1485
(Mon-Fri 08:00-20:00, Sat-Sun 08:00- 16:00)

Cardiology ANP (Horton): bleep 9608
(Mon-Fri 08:00-16:00)

Or outside of these hours:
Cardiology SpR bleep 4205.

Pharmacological Management

Initial supportive treatment

Oxygen

Administer oxygen if the patient's blood oxygen saturation is below 90% or if the patient is in respiratory distress.[2]

Pain Management

Nitrates

Give sublingual glyceryl trinitrate (GTN) to relieve cardiac chest pain due to myocardial ischaemia. If the pain continues, consider intravenous GTN following advice from cardiology (refer to NHS Injectable Medicines guide for further information). Intravenous GTN requires careful blood pressure monitoring and should only be given when the systolic blood pressure exceeds 90mmHg. Using an infusion solution concentration of 50mg in 50mL, start with an initial dose of 10micrograms/min and titrate upwards in 10microgram/min increments approximately every 30 minutes until symptoms are relieved, unless side effects such as headache or hypotension occur. The usual dose range is 10-200micrograms/min (0.6mL-12mL/hour using a 1mg/mL GTN infusion).[1,2,3]

Nitrates should be avoided in patients who have recently taken a phosphodiesterase type 5 inhibitor (i.e., avoid for 24 hours after taking sildenafil and for 48 hours after taking tadalafil) due to the risk of severe hypotension.[2]

Morphine

Consider intravenous morphine in patients whose ischaemic symptoms are not relieved by nitrates. The usual dose is 5 to 10 mg (reduce dose by half in elderly and frail patients) and patients should have respiratory monitoring (refer to OUH morphine injectable monograph for further information).[2]

Anti-emetic

Give an anti-emetic, such as metoclopramide to patients who have symptoms of nausea and vomiting.

Initial antiplatelet treatment

Aspirin

Aspirin is recommended in all patients presenting with ACS, unless contra-indicated. Prescribe an initial oral loading dose of 300mg followed by a maintenance dose of 75 mg daily.[1,4]

For patients who have a true aspirin allergy (hypersensitivity) consider monotherapy with clopidogrel[4] or ticagrelor as advised by cardiology.

Dual antiplatelet therapy

Following cardiology review and **confirmed diagnosis** of UA or NSTEMI, dual antiplatelet therapy (DAPT) i.e., aspirin plus a $P2Y_{12}$ inhibitor should be prescribed as below.

Ticagrelor is recommended as part of DAPT for initial management if there are no contra-indications. It is indicated for patients who are being medically managed (no coronary revascularisation) or undergoing coronary angiography with follow-on percutaneous coronary intervention (PCI) as appropriate unless the patient has a high bleeding risk. Prescribe a loading dose of 180mg followed by a maintenance dose of 90mg twice a day in combination with aspirin.[1,4]

Prasugrel may be considered as an alternative to ticagrelor in patients undergoing PCI if ticagrelor is not tolerated or contra-indicated e.g., hypersensitivity, side effects or drug interactions. Prescribe a loading dose of 60mg followed by a maintenance dose of 10 mg daily in combination with aspirin. Prasugrel is not recommended for patients aged 75 years or over due to the increased risk of bleeding. If, after careful consideration a decision is made to use prasugrel the maintenance dose should be reduced to 5mg daily. The maintenance dose should also be reduced for patients who weigh less than 60kg. Prasugrel should not be used in patients with a history of stroke or TIA. [1,4,5]

Prasugrel is not licensed for use in patients who are being medically managed and should only be used in this situation following advice from cardiology. The unlicensed medicine policy should be followed in this instance.

Clopidogrel may be considered as part of DAPT (instead of ticagrelor) for patients who are being medically managed if they have a high bleeding risk. Prescribe a loading dose of 300mg followed by 75mg daily in combination with aspirin. In some patients aspirin alone may also be considered in this situation.[1,4] It is good practice to document the bleeding risks and rationale for choice of DAPT or single antiplatelet therapy (SAPT) in the patient's notes.

For further advice on choice of antiplatelets, especially in patients with intolerances or contraindications, contact the cardiology SpR on bleep 4205.

Duration of antiplatelet therapy

DAPT is continued for up to 12 months in the following groups of patients:

- Patients with a confirmed diagnosis of NSTEMI (medical or PCI management)
- ACS patients managed with PCI.

After 12 months stop the $P2Y_{12}$ inhibitor and continue aspirin indefinitely. For patients with aspirin hypersensitivity or intolerance continue monotherapy with ticagrelor or clopidogrel indefinitely.

For ACS patients who have not undergone a PCI and/or do not have a confirmed diagnosis of NSTEMI continuation of DAPT should be discussed and agreed with cardiology e.g., high-risk UA patients or those being considered for further investigations where diagnosis is uncertain (duration of DAPT will be reviewed at cardiology follow-up).

Antiplatelets and oral anticoagulants

Some patients who require antiplatelets will also have a separate indication for anticoagulation e.g., atrial fibrillation, DVT/PE. In these patients the choice and duration of antiplatelet agent(s) will depend on the NSTEMI/UA management strategy (medical or PCI) together with the patient's bleeding risks and should be discussed with a Cardiologist.

For patients undergoing PCI, DAPT consisting of aspirin and clopidogrel is preferred in combination with an anticoagulant. This is often referred to as 'triple therapy' (DAPT plus anticoagulation). The duration of DAPT should be clearly documented in the patient's notes. Aspirin should be stopped as advised by a Cardiologist at some point after the PCI (usually after 1 month) and clopidogrel continued with the anticoagulant for up to 12 months.[4]

For patients who are being medically managed consider SAPT, usually clopidogrel for up to 12 months in combination with an anticoagulant.[1]

Ticagrelor and Prasugrel should be avoided in combination with anticoagulants, unless specifically advised by a Cardiologist.[1,4]

The recommended plan for antiplatelets and anticoagulants including duration must be clearly documented on the discharge letter to ensure continuity of therapy in primary care.

Extended ticagrelor therapy post MI[6,7]

Following completion of the initial year of DAPT with aspirin and ticagrelor (or other $P2Y_{12}$ inhibitor) extended ticagrelor therapy is indicated in patients who have had a previous MI and are at high risk of further atherothrombotic events (see table below for high-risk criteria). Ticagrelor, at a lower dose of 60 mg twice daily is recommended for up to a maximum of 3 years. Extended treatment is generally initiated by the patient's GP following advice from cardiology (see also Oxfordshire primary care guidance here)

High risk criteria: 1 or more of the following:
Aged 65 years or older
Multi-vessel coronary artery disease
More than one previous MI
Diabetes requiring medication
Chronic non-end stage kidney disease (Creatinine clearance less than 60ml/min)

Antiplatelets and gastroprotection

A proton pump inhibitor (PPI) should be considered for all patients on single or dual antiplatelet therapy, especially those at a high risk of gastrointestinal (GI) bleeds; these include: [1, 8]

- History of gastrointestinal ulcer or haemorrhage
- Dyspepsia / gastro-oesophageal reflux disease
- Helicobacter pylori infection
- Aged 65 years or over
- Chronic alcohol use
- Concomitant use of medicines known to increase risk of GI bleeding, including but not exclusive to:
    - Anticoagulants
    - NSAIDs
    - Corticosteroids
    - Nicorandil
    - Antidepressants (SSRIs)

Lansoprazole and omeprazole are available on the OUH formulary. Prescribe lansoprazole 15mg to 30mg daily or omeprazole 20mg daily (licensed doses indicated for prophylaxis of NSAID associated peptic ulcer disease). For patients taking clopidogrel, consider prescribing lansoprazole due to the potential interaction with omeprazole and clopidogrel.

Anticoagulation treatment for ACS

Fondaparinux

All patients with a confirmed diagnosis of ACS should be prescribed fondaparinux,[1,4] unless they have a high bleeding risk or are being considered for immediate angiography. Factors associated with a high bleeding risk include:

- advancing age
- known bleeding complications
- renal or hepatic impairment (see below)
- low body weight (less than 50 kg)

Use of fondaparinux in these patients should be carefully considered. Contact the cardiology SpR on call for further advice if necessary. Patients prescribed fondaparinux for ACS do not need any additional anticoagulant agent for VTE prophylaxis e.g., dalteparin (a VTE risk assessment still needs to be carried out).

The dose of fondaparinux for the treatment of UA/NSTEMI is 2.5 mg once daily administered by subcutaneous injection.[9] For practical purposes a stat dose of fondaparinux may be prescribed on the first day of treatment and thereafter prescribed at 6pm to avoid any complications with surgery or planned/ emergency angiograms (see below). Treatment should be initiated as soon as possible after diagnosis and continued for a maximum of 8 days or until hospital discharge if that occurs sooner. Refer to NHS Injectable Medicines guide for further information.

PCI and surgery: Do not give fondaparinux if the patient is due to undergo a planned PCI on the same day. Unfractionated heparin, as a bolus injection (as per local cardiac catheter lab protocol) should be administered at the time of PCI in patients pre-treated with fondaparinux. If the patient is to undergo coronary bypass graft surgery fondaparinux should be stopped, where possible, 24 hours before surgery.

Fondaparinux and anticoagulation tests: At a dose of 2.5 mg daily, the anticoagulant effects of fondaparinux, cannot be detected by routine anticoagulation tests such as prothrombin time (PT), APPT, activated clotting time (ACT) or international normalised ratio (INR).

Renal Impairment: Fondaparinux is contra-indicated in patients with a creatinine clearance of less than 20 ml/min.[9] Calculate the patient's creatinine clearance using the Cockcroft-Gault equation (here). In these patients consider prescribing dalteparin 80 units/kg twice daily rounded to the nearest 500 units with a maximum dose of 6500 units twice daily. This is two thirds of the normal ACS dosing.[10] This should be administered using dalteparin 10,000 units/1ml graduated syringes to allow for dose manipulation.

Dalteparin should be prescribed for up to eight days or until discharge, whichever is sooner.[10] If the patient is still in hospital after eight days and is awaiting PCI, contact the cardiology SpR for advice regarding ongoing treatment. Dalteparin is renally cleared so care is required when administering to patients with severe renal impairment. Plasma anti-Xa concentration can be used to monitor the anticoagulant effect of dalteparin in these patients to ensure appropriate dosing. For further advice contact Haematology SpR on bleep 5529.

Hepatic Impairment: No dose adjustment of fondaparinux is necessary in patients with hepatic failure. However, use with caution in patients with severe hepatic impairment. This is because there is an increased risk of bleeding due to a deficiency of coagulation factors in these patients.[9]

Secondary Prevention

Secondary prevention medications help reduce the risk of further MI and other manifestations of vascular disease and should be started in all patients with a diagnosis of NSTEMI.[4] Statin therapy is recommended for all patients with cardiovascular disease.[4] Patients should be counselled on the importance of compliance for preventing future cardiovascular events, especially antiplatelets in those who have had PCI. The discharge letter should document a clear management plan including details and timings of any further dose titrations, monitoring of blood pressure and renal function post discharge.

Angiotensin Converting Enzyme Inhibitor [1,4]

Start an Angiotensin Converting Enzyme (ACE) inhibitor as soon as possible when the patient is haemodynamically stable and continue indefinitely.

Ramipril is first line for patients within the OUH Trust. The usual starting dose is 2.5mg daily and should be up titrated depending on blood pressure at short intervals for example every 12 to 24 hours before discharge until maximum tolerated or target dose is reached (see below). Patients with low blood pressure or high risk of side effects may be started on a lower dose of 1.25mg daily. Ramipril can be prescribed in the evening/at night in patients with low blood pressure.

After discharge the dose should be further up titrated to ensure the maximum tolerated or target dose (5mg twice daily) is reached within 4-6 weeks of starting.

Consider an Angiotensin Receptor Blocker as an alternative in patients who are intolerant to ACE inhibitors.

Baseline renal function, electrolytes and blood pressure should be taken and re-measured after 1-2 weeks of starting treatment and then as appropriate.

Beta Blocker

Start a beta blocker as soon as possible when the patient is haemodynamically stable. Bisoprolol is first line within the OUH Trust. The usual starting dose is 2.5 mg daily. Patients with low blood pressure or at high risk of side effects may be started on a lower dose of 1.25mg. Gradually up titrate the dose, to achieve a resting heart rate of 60 beats per minute, to the maximum tolerated or target dose of 10 mg daily.[1,4] Cardio-selective beta blockers such as bisoprolol, may be used cautiously under supervision, if no alternative, in patients with a history of asthma or obstructive airways disease.[11]

Beta-blockers should be continued indefinitely in patients with reduced left ventricular ejection fraction (LVEF). There is a lack of evidence for continuing beta-blockers beyond 12 months in patients without reduced LVEF and therapy should be reviewed and potential benefits and risks of stopping or continuing beta-blockers beyond 12 months discussed with patients.[4]

Statins[12,13]

Unless contraindicated, all patients with coronary artery disease should be started on atorvastatin 80 mg daily. Consider a lower dose where there is:

- Potential interactions (e.g., concomitant use of ciclosporin, elbasvir with grazoprevir, amiodarone, see BNF for full details and list of interactions)
- High risk of adverse effects (e.g., chronic kidney disease (CKD)*
- Patient preference
- Previous side effects / intolerances

Baseline measurements of total cholesterol, HDL cholesterol and non-HDL cholesterol should be taken with a target of 40% reduction in non-HDL cholesterol at 3 months (or target of non-HDL cholesterol of less than 2.5mmol/L if baseline measurements not available). Treatment initiation should not be delayed before taking these measurements. Also take baseline Liver Function Tests (LFTs) and continue treatment unless liver transaminases are more than three times the upper limit of normal. Retest LFTs and lipid profiles at 3 and 12 months to monitor ongoing treatment.

*Consider starting patients with CKD on 20 mg daily. The dose can be increased if a greater than 40% reduction is not achieved after 3 months and if eGFR is 30ml/min/1.73m2 or more. Patients with an eGFR of less than 30 ml/min/1.73m2 should have higher doses agreed with renal specialist.

Do not routinely measure creatine kinase in patients taking statins unless they have or have had generalised, unexplained, muscle pain in the past. In patients who are intolerant to statins, aim to treat with the maximum tolerated dose and inform the patient that any statin at any dose will reduce the risk of cardiovascular disease.

In patients who have previous intolerance try stopping therapy and restarting once symptoms resolve (after 4 to 6 weeks) to see if they are related to statin treatment. When restarting use a lower dose and gradually up titrate as tolerated e.g., atorvastatin 10mg to

0mg daily. Patients should be advised to seek medical attention if they develop muscle pain, tenderness, or weakness.

In patients who are intolerant to atorvastatin, consider ezetimibe 10mg daily or alternative statin e.g., rosuvastatin 5mg to 10mg daily (currently non-formulary and approval needed before initiation).

Patients who have a total cholesterol of 7.5 mmol/L or more should be referred to the lipid clinic. Patients who do not reach the target of 40% reduction in non-HDL cholesterol at 3 months or are intolerant to statins should also be referred to the lipid clinic.

Glyceryl Trinitrate

All patients, unless there are contraindications, should have a glyceryl trinitrate (GTN) 400microgram sublingual spray prescribed on discharge and be counselled on how to use it.[4]

Smoking Cessation

Offer patients who smoke advice on how to quit. Information on smoking cessation and prescribing Nicotine Replacement Therapy (NRT) can be found in *MIL vol. 10 no. 9: Nicotine Replacement Therapy (NRT) for Smoking Cessation*. Patients should be supplied with 2 weeks NRT at discharge.

Cardiac Rehabilitation

All patients diagnosed with NSTEMI should be referred to the cardiac rehabilitation team before discharge. To refer please contact the team on Ext. 20251 with enough time prior to discharge to allow the team to see the patient as an in-patient.

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