South Tees Hospitals NHS
NHS Foundation Trust

Cardiology drug prescribing guidelines & formulary

A guide to common problems

June 2019

Contents

General Information

The following information is written to help guide prescribing by the non-specialist working within and outside the cardiology area. Primary care colleagues may also find it of some help. We intend this to be a user friendly guideline for common and important areas in clinical Cardiology practice.

If, having consulted these guidelines, you still require advice regarding a particular patient, please contact the specialist team (e.g. interventional cardiology, heart failure, cardiac rhythm management), the consultant in charge of the patient, or through the advice and guidance service.

Discharge medication

When writing a discharge prescription, please ensure that the patient has at least 14 days' supply of each medication (please check what supplies are at home). Exceptions to this include courses of antibiotics and steroids, or other courses of drugs. If unsure of what to supply, ask your ward pharmacist.

Out-patient prescribing

When initiating treatment for out-patients please use the approved treatment recommendation form for all green medication. The exceptions are red and amber drugs and any treatment that needs to be started without delay. These should be prescribed from the clinic using the hospital out-patient prescriptions.

Shared care medicines

Medicines are classified by a "traffic light" system as follows:

Green medicines can be freely prescribed by all prescribers within local and national recommendations. Hospital initiated green medicines can be recommended by a specialist for primary care prescribers to prescribe.

Amber medicines should be initiated and stabilised by a specialist but which may then be passed to primary care prescribers for prescribing. Additional information or a shared care agreement may be required to support prescribers.

Red medicine should only be used within secondary care. Primary care prescribers should not be asked to prescribe.

Any medicines classified as red or amber will be highlighted throughout this formulary.

Angina

Treatment of chronic stable angina

See also NICE clinical guideline 126

https://www.nice.org.uk/guidance/cg126

Antiplatelet therapy

All patients with suspected or proven coronary artery disease should receive aspirin 75mg daily unless there is a definite contraindication.

If a patient is allergic to aspirin, clopidogrel 75mg daily is a suitable alternative.

Gastrointestinal (GI) intolerance or bleeding is not the same as an allergy and should not routinely lead to the prescription of clopidogrel (which causes dyspepsia in a similar proportion of patients to aspirin). Consider adding a proton pump inhibitor to aspirin instead.

Practice point 1 - Dyspepsia when taking aspirin:

- Review and modify other contributory factors and medication which might be causing dyspeptic symptoms e.g. excess alcohol, other NSAIDs
- Consider if further investigation is required (refer to other guidelines for dyspepsia)
- Ensure aspirin is taken with food
- Use aspirin 75 mg dispersible once daily
- Combine aspirin with a PPI e.g. lansoprazole 15-30 mg once daily (preferred if treated with clopidogrel) or omeprazole 20 mg once daily
- Enteric coated aspirin is not recommended

History of GI bleeding with aspirin or NSAIDs

Combine the antiplatelet agent with a PPI e.g. lansoprazole 15-30 mg once daily (preferred if treated with clopidogrel) or omeprazole 20 mg once daily.

Clopidogrel (75mg once daily) in combination with aspirin (75mg once daily) is preferred following elective percutaneous coronary intervention (PCI). Duration will be advised at time of discharge and premature cessation should be avoided.

Practice point 2 - Clopidogrel and Proton Pump Inhibitors:

Clopidogrel is a pro-drug which is activated by CYP 450 liver enzymes. PPIs are thought to inhibit these enzymes thus hindering clopidogrel activation. This is a **theoretical** interaction. COGENT, TRITON-TIMI 38 and PLATO trials did not show any increased risk of major adverse cardiovascular events in patients taking PPIs and clopidogrel together. The FDA, MHRA and EMA discourage use of omeprazole and esomeprazole in patients taking clopidogrel.

At James Cook University Hospital, we do not discourage the use of PPIs with clopidogrel and cardiovascular risks should be weighed against the potential gastrointestinal risks. If initiating treatment, lansoprazole is preferred (15 to 30mg once daily). If patients are already taking omeprazole, this treatment can be continued.

Glyceryl TriNitrate (GTN) spray

Prescribe one to two puffs of GTN spray, as required. Advise patients that they should use it prophylactically before activity. A patient information card should routinely be supplied with the first prescription.

Practice point 3 - PDE 5 inhibitors and nitrates:

- When PDE 5 inhibitors, including sildenafil, tadalafil, avanafil and vardenafil, are used in combination with nitrate containing medications it can cause **significant hypotension**.
- Patients initiated on a GTN spray should be counselled on safe concurrent use (as per PIL linked below)
- Patients initiated on long acting nitrate tablets should be sign posted to their GP for alternative erectile dysfunction treatment, or an alternative antianginal agent selected.

MICB5622 - GTN PDE5 Intercation.pdf

Beta-blockers

Beta-blockers are a first-line treatment unless contraindicated because of asthma or high grade AV block.

Use bisoprolol 2.5mg to 10mg daily
or
metoprolol 50mg – 100mg twice to three times daily.

Calcium channel blockers

A rate-limiting calcium channel blocker can be used as an alternative to beta-blockers as a first line.

Use diltiazem (such as Adizem XL) 180mg to 300mg once daily
or
verapamil SR 240mg daily to 240mg twice daily (if preserved left ventricular systolic function).

Continued angina

If symptoms persist despite the above treatment, consider combining a beta-blocker with a dihydropyridine calcium channel blocker.

Practice point 4 - Beta-blocker tolerability and co prescription with calcium antagonists:

Metoprolol is shorter acting so can be used to trial a patient's tolerability to beta blockers. If they are successful in taking metoprolol, treatment can often be switched to bisoprolol.

When combining a calcium channel blocker with a beta blocker, use a dihydropyridine calcium channel blocker, for example, amlodipine, felodipine or slow release nifedipine. An advantage in using beta-blockers as the first line, is that these non-rate limiting calcium antagonists can be safely added. Beta blockers should not be co-prescribed with verapamil.

Practice point 5 - Choice of antianginal:

There is no evidence that using three or four antianginal drugs achieves greater efficacy than a combination of two drugs at appropriate doses. If significant symptoms persist on two drugs, refer to cardiology for consideration of revascularisation.

Refractory angina

If angina continues despite two drugs and there is no revascularisation option, consider a combination

of beta-blocker and/or calcium channel blocker (see practice point 4)
and isosorbide mononitrate 10 to 20mg twice daily (8am and 2pm)

and/or *ivabradine 5mg to 7.5mg twice daily (2.5mg in elderly)*

and/or *nicorandil 10mg to 30mg twice daily*

and/or *ranolazine MR 375mg to 750mg twice daily*

Practice point 6 - Agents for refractory angina:

If heart rate remains over 70 at rest despite optimal dose of beta-blocker and/or calcium channel blocker, consider the addition of ivabradine 5mg to 7.5mg twice daily (2.5mg in elderly). This can be initiated by a specialist in an out-patient setting. Warn the patient that there can be visual disturbances (e.g. phosphenes – rings or bright lights) which usually recede with continued treatment.

Nicorandil can cause oral, gastrointestinal and anal ulceration. Ensure patients are warned of this potential side effect. Where GI ulceration occurs, an alternative antianginal should be prescribed.

For continuing symptoms, ranolazine MR 375mg to 750mg twice daily can be added. Use with caution if weight < 60kg, in the elderly and in renal impairment (avoid if eGFR <30ml/min). Ranolazine can be initiated by a specialist in an out-patient setting if considered appropriate.

Angina Summary

See also the Rapid Access Chest Pain Clinic guidelines


RACPC referral guidelines.pdf


RACPC referral form.pdf

- ✓ Aspirin – if suspected or proven CAD
- ✓ GTN spray – symptom control
- ✓ Treat hyperlipidaemia – see page 26Initiate or modify antianginal therapy
- ✓ Refer to Rapid Access Chest Pain clinic or Cardiology out patients

Beta blockers or/and calcium channel blockers (see practice point 4)

↓

Beta blockers + calcium channel blockers + isosorbide mononitrate

↓

Beta blockers + calcium channel blockers + isosorbide mononitrate

Plus one of the following:

Ivabradine

Nicorandil

Ranolazine

FURTHER READING

NICE guideline CG 126. Stable angina: Management https://www.nice.org.uk/guidance/cg126/chapter/1-Guidance#anti-anginal-drug-treatment

ESC guidelines on the management of stable coronary artery disease—addenda https://www.escardio.org/static_file/Escardio/Guidelines/publications/ANGINA2013_Stable_Coronary_Artery_Disease_web_addenda.pdf

Specialist Pharmacy Service: Do proton pump inhibitors reduce the clinical efficacy of clopidogrel? https://www.sps.nhs.uk/articles/do-proton-pump-inhibitors-reduce-the-clinical-efficacy-of-clopidogrel-2/

Acute Coronary Syndrome

See also CCU guidelines
http://cardiodocs/guidelines/data/69_04_12_2017_10_26_59_CCUguidelinesDec17.pdf

Antiplatelet therapy

Practice point 7 - Choice of potent antiplatelet:

Ticagrelor	First line for Acute Coronary Syndromes (ACS)
Clopidogrel	First line for elective PCI
	Use if intolerant to ticagrelor in ACS
	Use in triple therapy regimens
	Use in aspirin allergic patients
Prasugrel	Only to be initiated on specialist advice (see below for further details)

Dual Antiplatelet Therapy (DAPT) is the mainstay of ACS management and is usually recommended for 12 months duration. However, both the ACC/AHA (2016) and ESC guidelines (2017) indicate that for patients with a higher risk of bleeding, shorter DAPT duration is reasonable in selected patients. Where PCI has been performed, there is an increasing evidence base for the safety of shorter duration DAPT (e.g. 3-6 months) with contemporary drug-eluting stents. Importantly, the guidelines highlight that decisions about duration of DAPT are best made on an individual basis and should integrate clinical judgment, assessment of the benefit/risk ratio, and patient preference.

Offer PPI cover with lansoprazole 15-30mg once daily in those patients on DAPT when:

- Over 75 years
- On concomitant anticoagulation (warfarin or DOAC)
- Have previous GI bleeding problems
- Have an eGFR < 30ml/min

Ticagrelor

Ticagrelor (90mg twice daily) in combination with low-dose aspirin (75mg once daily) should be given to patients after an index presentation of acute coronary syndrome (ACS) whether treated medically, with percutaneous intervention or following surgical revascularisation. It may also be given if the patient is allergic to clopidogrel, or stent thrombosis has occurred during clopidogrel treatment. Ticagrelor should be initiated by specialist only.

Ticagrelor should be initiated with a loading dose of 180mg followed by 90mg twice daily. **It is contraindicated in patients with a history of intracranial haemorrhage. Ticagrelor is LESS effective when combined with an aspirin dose ≥ 150mg.**

The duration of therapy is variable and will be advised at time of discharge. **Treatment must NOT be stopped prematurely without discussion with the cardiology team.**

Potential adverse effects on ticagrelor initiation			
Adverse effects	**Monitoring**	**Further information**	**Action**
Rise in creatinine	Check at 1 month, then as clinically indicated.	Rise in creatinine is not normally associated with deteriorating renal function – but focus on patients > 75 years, those with moderate/severe renal impairment and those receiving concomitant nephrotoxic drugs.	**> 20%** increase in serum creatinine (or **15%** decline in eGFR) over the pre-procedural baseline – seek advice from the initiating team.
Dyspnoea	None	Dyspnoea is known to occur in up to 20% of patients but tends to be self-limiting.	Discontinuation occurs in approximately **5%** of patients. In these patients, switch to clopidogrel 75mg once daily starting with a loading dose of 300mg or 600mg (depending on patient bleed risk and previous treatment).
Bradycardia	General inpatient observations.	Mainly asymptomatic ventricular pauses noted in early clinical trials. Caution use in patients at high risk of bradycardia e.g. 2nd or 3rd degree AV block.	If significant bradycardia occurs, switch to clopidogrel 75mg once daily starting with a loading dose of 300mg or 600mg (depending on patient bleed risk and previous treatment).

Ticagrelor **60mg** twice daily can be used in combination with aspirin 75mg once daily when an extended period of DAPT is required. This can be considered for patients following an MI with high risk of another event (see Practice Point 8 below). This recommendation would usually be made by a cardiologist, but would be implemented in primary care. It is not intended for lifelong treatment.

Practice point 8 - Pegasus TIMI 54 trial:

Classed patients at high risk (and therefore potential candidates for extended DAPT) if they had one or more of the following after an ACS.

- Age ≥65 years
- Diabetes requiring medication
- Second prior MI (>1 year ago)
- Multi-vessel CAD
- CrCl <60 mL/min

Main Finding:

Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke but did increase bleeding risk compared to aspirin alone.

Clopidogrel

Clopidogrel (75mg once daily) in combination with aspirin (75mg once daily) is preferred following elective percutaneous coronary intervention (PCI). Duration will be advised at time of discharge and premature cessation should be avoided.

For non-elective PCI, clopidogrel is now reserved for those unable to tolerate ticagrelor or where a combination with an anticoagulant is required.

If a patient is admitted on clopidogrel, review the indication. Routinely, DAPT with ticagrelor will be initiated following ACS. When the DAPT course is completed, clopidogrel may need to be re-instated, for example, if the original indication was a TIA.

Prasugrel

It should be initiated by specialist only and is normally considered when:

- immediate PCI is necessary
- stent thrombosis has occurred during clopidogrel or ticagrelor treatment
- the patient has diabetes **and** is considered high risk
- if use of ticagrelor or clopidogrel is inappropriate and patient is considered high risk
- as an alternative treatment in ST elevation MI.

Prasugrel is contraindicated in patients with a history of stroke or TIA. Use prasugrel initially 60mg as a single dose then 10mg daily (5mg daily if >75 years or body weight <60kg).

Combination anticoagulant and antiplatelet treatment.

Approximately 6–8% of patients undergoing PCI have an indication for long-term oral anticoagulants (OACs) due to various conditions such AF, mechanical heart valves or venous thromboembolism. There are limited data on the combination of an anticoagulant with either dual or single antiplatelet agents.

So called "triple antithrombotic therapy" – DAPT and an oral anticoagulant - is associated with several times higher bleeding risk compared to aspirin alone or DAPT. Because of this, all patients should be prescribed a PPI (Lansoprazole 15 - 30mg once daily, or Ranitidine 300mg twice daily – see practice point 2).

Through estimating the individual risk/benefit ratio, the antithrombotic regimen will be individualised for each patient by the specialist. This will follow these key principles:

- Ensuring that the duration of each agent is clearly stated. Durations of treatment will vary dependent on complexity of coronary artery disease, coronary intervention performed (including stent type), indications for anticoagulation and bleeding risk.
- Avoiding ticagrelor or prasugrel in combination with an anticoagulant. Clopidogrel should be used as it is the most widely studied.
- Warfarin, rivoraxaban, dabigatran and apixaban have published trial data in combination with potent antiplatelets.
- There is increasing evidence that aspirin course can safely be curtailed where an anticoagulant is co-prescribed with clopidogrel. The AUGUSTUS trial demonstrated aspirin increased bleeding without reducing ischaemic events when combined with either warfarin or apixaban. Apixaban was also associated with lower bleeding compared to warfarin.
- In the PIONEER AF trial, a reduced dose of rivaroxaban (15mg once daily) was used in combination with clopidogrel. When clopidogrel has been stopped, the rivaroxaban dose should be reviewed and increased to 20mg once daily if appropriate
- Specialists may use full dose DOAC from initiation depending on patient co-morbidities and indication for anticoagulation.
- Where a patient has a mechanical prosthetic heart valve warfarin will remain the anticoagulant of choice (see practice point 9).

The initiating team will provide clear information regarding durations of treatment at discharge. If unsure or unclear – confirm the plan with the specialist via the Interventional Cardiology Specialist Nurse team.

Secondary Prevention

ACE inhibitors/ARBs, beta-blockers, eplerenone and statin therapy are the mainstay of post MI secondary prevention. Prescribing of these agents is discussed separately.

ACE inhibitors, ARBs and MRAs – See Heart Failure p21
Beta-blockers – See Heart failure p22
Statin therapy – See Hyperlipiaemia p25

FURTHER READING

ESC focussed update on dual antiplatelet therapy (2017). *European Heart Journal, Volume 39, Issue 3, 14 January 2018: 213–260*

CURE study. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST elevation. *N Eng J Med 2001; 345: 494-502*

PLATO study. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Eng J Med 2009; 361: 1045-57*

TRITON TIMI ACS study. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Eng J Med 2007; 357: 2001-15*

WOEST study. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *The Lancet 2013; 381 (9872): 1107-15*

ROCKET AF study. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med 2011; 365:883-891*

PIONEER AF study. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med 2016; 375:2423-2434*

PEGASUS TIMI 54 study. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Eng J Med 2015; 372: 1791-1800*

AUGUSTUS study. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Eng J Med 2019 https://www.nejm.org/doi/full/10.1056/NEJMoa1817083

https://www.nice.org.uk/guidance/conditions-and-diseases/cardiovascular-conditions/acute-coronary-syndromes#panel-pathways

Arrhythmias

Diagnosis of arrhythmias

Appropriate drug treatment of arrhythmias depends on precise diagnosis. A 12-lead ECG recording during an arrhythmia is crucial, and waiting to obtain this is appropriate in all circumstances other than full cardiopulmonary arrest. Any arrhythmia can be associated with haemodynamic collapse, acute heart failure or significantly reduced tissue perfusion e.g. reduced urine output. Emergency DC cardioversion is appropriate when tachyarrhythmia is the cause, regardless of the precise diagnosis.

The CCU guideline contains an approach alongside prescribing information for acute arrhythmia (including post MI arrhythmia, supraventricular tachycardia, and ventricular tachycardia). http://cardiodocs/guidelines/data/69_04_12_2017_10_26_59_CCUguidelinesDec17.pdf

Some arrhythmias, commonly seen outside the acute setting and are discussed below.

Treatment of arrhythmias

Ectopic beats - ventricular or atrial

Treatment of ventricular or atrial ectopic beats is rarely required but beta-blockers may be considered if a patient is very symptomatic.

e.g. bisoprolol 2.5mg to 10mg daily.

or

verapamil SR 240mg daily to 240mg twice daily

Non-valvular Atrial Fibrillation (NVAF) or flutter

If atrial fibrillation or flutter is acute, exclude any underlying cause (e.g. congestive cardiac failure, electrolyte imbalance, ischaemia or thyrotoxicosis) and treat, if appropriate.

Pharmacological cardioversion should be considered if presentation is within 24 hours of onset. This should take place after specialist advice with appropriate monitoring - refer to CCU guidelines (see above).

Long-term management includes anticoagulation and rate control.

Anticoagulation

All patients with atrial fibrillation or flutter should be considered for early treatment with anticoagulation, using the *CHA_2DS_2-VASC* tool. The utility of bleeding scores are discussed below. DOACs have emerged as the preferred choice in patients commenced on anticoagulation for NVAF, although warfarin can still be used. It is ultimately the patients' choice as to which agent is chosen. Ensure they are fully informed of the risks and benefits before choosing between warfarin or a DOAC..

Anticoagulation is recommended for those with permanent or paroxysmal atrial fibrillation/flutter with a *CHA_2DS_2-VASC* score of 1 or more in men, and 2 or more in women. Other considerations in the decision for anticoagulation include:

- the presence of valvular or other structural heart disease
- thyrotoxicosis
- whether DC cardioversion or ablation is being considered

Practice point 9 - Valvular atrial fibrillation:

DOACs should not be used for mechanical prosthetic heart valves (in any position), bio-prosthetic mitral valve or mitral stenosis. So called "valvular AF" should be treated with warfarin to a target INR range.

Atrial fibrillation following mitral valve repair is more controversial, but our recommendation is that if DOAC is used, treat with apixaban or edoxaban as such patients were included in the pivotal trials for these agents.

Bio-prosthetic valves in the aortic position can be treated with a DOAC.

CHA_2DS_2-VASc and HASBLED Risk Calculators

(adapted from ESC guideline; European Heart Journal (2016) 37, 2893–2962)

CHA_2DS_2-VASC risk calculator	
Risk factor	*Score*
Congestive Heart Failure	**1**
Hypertension	**1**
Age > 75	**2**
Diabetes	**1**
Stroke or TIA	**2**
Vascular disease (e.g. IHD, PVD)	**1**
Age 65-74	**1**
Female **S**ex	**1**

CHA_2DS_2-VASC risk factors - a score of "0" is considered low stroke risk (not no stroke risk) and anticoagulation may not be required. A score greater than 1 in men, and 2 in women suggests moderate-high risk and anticoagulation should be initiated unless contraindicated.

HASBLED risk calculator	
Risk factor	*Score*
Hypertension (uncontrolled – systolic >160 mmHg)	1
Renal disease Dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L	1
Liver disease Cirrhosis or bilirubin >2x normal with AST/ALT/AP >3x normal	1
Prior major bleeding or predisposition to bleeding	1
Stroke or TIA	1
Labile INR Unstable/high INRs, time in therapeutic range <60%	1
Age >65	1
Medication usage predisposing to bleeding Aspirin, clopidogrel, NSAIDs	1
Alcohol use ≥8 drinks/week	1

The HASBLED score includes some of the same factors as CHA_2DS_2-VASC such as age, hypertension and previous stroke. Such a patient would have an *annual* TIA/stroke and systemic embolism risk of between and 6.7-13% dependent on age and gender. Thus, a high HASBLED score should **never** (in isolation) be used to withhold anticoagulation, but instead should lead to the clinician identifying and acting to correct bleeding risk; for example, controlling BP, co-prescription of PPI, a recommendation to reduce alcohol, consideration to stopping NSAIDS and/or antiplatelet therapy, and choosing a DOAC at appropriate dose.

DOAC Dosing Guidance for Non-Valvular AF

Apixaban		
Recommended dose 5mg: twice daily		
Dose recommendation for patients with **two or more** of the following clinical factors:		
Renal Impairment	serum creatinine ≥ 133mmol/L (1.5 mg/dL) and/or creatinine clearance 15-29 mL/min	2.5mg twice daily
Low Body Weight	*≤ 60 kg*	
Age	*>80 years old*	

Edoxaban		
Recommended dose: 60mg once daily		
Dose recommendation for patients with **one or more** of the following clinical factors:		
Renal Impairment	*Moderate or severe (CrCL 15 – 50 mL/min)*	30 mg once daily
Low Body Weight	*≤ 60 kg*	
P-gp Inhibitors	*Ciclosporin, dronedarone, erythromycin, ketoconazole*	

Rivaroxaban		
Recommended dose: 20mg once daily		
Dose recommendation for patients with the following clinical factors:		
Renal Impairment	*Moderate or severe (CrCL 15 – 50 mL/min)*	15mg once daily

Dabigatran		
Recommended dose: 150mg twice daily		
Dose recommendation for patients with **one or more** of the following clinical factors:		
Age	*>80 years old*	110mg twice daily
Patients receiving concomitant verapamil		
Dose *considerations* for patients with **one or more** of the following clinical factors:		
Renal Impairment	moderate renal impairment (CrCL 30-50 mL/min)	110mg twice daily
Age	*75 - 80 years old*	
Patients with gastritis, esophagitis or gastroesophageal reflux		

Practice point 10 - Creatinine clearance (CrCl) vs eGFR:

Studies have demonstrated that use of the Cockcroft-Gault equation allows appropriate dosing of DOACs and minimises the risk of over anticoagulation. Estimated glomerular filtration rate (eGFR) should not be used, as data suggests this can lead to inappropriate dosing in up to 50% of patients. However, the Cockcroft-Gault equation can become inaccurate in extremes of bodyweight, especially the obese. We recommend the use of the MD+CALC Cockcroft-Gault equation, which adjusts for bodyweight in obese patients.

https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation

DOACs have the advantage of a predictable response and fewer monitoring requirements. At this stage, an antidote for dabigatran is available and one for rivaroxaban reversal is awaiting EU approval. Indirect reversal agents (e.g. FFP, beriplex) can be administered for the management of patients with major bleeding (see specialist advice).

Warfarin can still be used for AF where there is a patient preference. Patients should be "slow loaded" (e.g. 1 or 2mg daily and check the INR on day 7) to avoid the risk of high INRs and increased bleeding. The target INR is 2.5 for atrial fibrillation.

Whichever anticoagulant is used, patients should still be counselled on the importance of adherence to therapy, carrying an anticoagulant alert card, and educated about the signs of bleeding. For inpatients, the pharmacy team should be contacted prior to discharge in order to provide a counselling service.

Rate control

If the ventricular rate at rest is greater than 90bpm and early cardioversion is not an option, the condition should be controlled with an oral beta-blocker

e.g. bisoprolol 2.5mg to10mg daily

or verapamil SR 120 to 240mg daily

plus digoxin, if necessary.

NB. Verapamil increases digoxin levels, so be aware of the potential for toxicity, and consider reducing the digoxin dose.

Practice point 11 – How to start treatment with Digoxin:

Start treatment with digoxin using an oral loading dose of 500 to 1,000micrograms over 24 hours in divided doses, followed by a maintenance dose of 62.5 to 250 microgram daily, depending on the patient's age and renal function. Do not use IV digoxin unless the patient is truly nil by mouth.

If a patient's condition is resistant to the above measures, early specialist cardiac referral is appropriate. If urgent cardioversion is essential, it should be undertaken without delay but specialist opinion may be warranted to advise on long-term therapy.

Paroxysmal atrial fibrillation

If the patient is symptomatic consider a beta-blocker

e.g. bisoprolol 2.5mg to 10mg daily.

If a beta-blocker fails and a rhythm control strategy is being considered, this should be done after specialist advice.

For those with no or minimal structural abnormality of the heart, consider:

flecainide, starting dose 50mg twice daily

Amiodarone may be preferred for patients with impaired left ventricular systolic function (see below for dosing and further guidance).

For very infrequent episodes (e.g. fewer than three episodes per year) patients may prefer a "pill in the pocket" strategy.


Flecainide - Pill in the pocket protocol.pdf

Where patients are symptomatic of PAF, AF ablation can be considered as an option. Specialist cardiac referral is appropriate in this situation to discuss the merits of a procedural approach to this arrhythmia.

Amiodarone

Amiodarone remains a commonly prescribed and potent antiarrhythmic. Patients may be treated with amiodarone as treatment/prophylaxis against ventricular tachycardia and atrial fibrillation. It reduces the incidence of arrhythmias by increasing the duration and refractory period of the cardiac action potential and prolonging the QT interval.

Regular monitoring is essential because it does have potentially serious side effects that can be minimised with appropriate identification and prompt withdrawal. Amiodarone has a very long half-life (an average of 58 days) and so its effects may continue for some time (possibly months) after stopping therapy.

Patients receiving amiodarone should have their liver and thyroid function checked at baseline and then every 6 months (see prescribing guidance below, and BNF, for further information on monitoring).

Amiodarone is metabolised via the CYP3A4 isoenzyme and is a strong P-glycoprotein inhibitor meaning it has numerous drug interactions often requiring dose reductions. Please refer to the amiodarone prescribing guidance (below), the current BNF or SmPC for further information.


prescribing guidance amiodarone cardiolog

It is essential that patients are aware of the possible adverse effects of amiodarone as well as the benefits. Consider giving them the "Information for patients and carers" leaflet.


MICB5351 V2 - Amiodarone.pdf

FURTHER READING

ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal (2016) 37, 2893–2962

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal (2018) 00, 1–64

Heart failure

Treatment of heart failure should be aimed at relieving symptoms, reducing hospitalisation and prolonging life.

An accurate diagnosis is crucial in deciding upon appropriate therapy. B-type natriuretic peptide (BNP) levels may aid diagnosis at the time of first presentation. An ECHO should be performed to confirm left ventricular dysfunction. All recommendations below refer to patients with proven left ventricular systolic dysfunction. Please read in conjunction with the latest South Tees Heart Failure Service Guideline (2018).


SOUTH TEES HF SERVICE final.doc


NICE HF guideline NG106 2018.pdf

Management of heart failure

ACE inhibition

All patients should be considered for Angiotensin Converting Enzyme (ACE) inhibition regardless of symptoms.

For ease of titration the first choice ACE inhibitor in heart failure is:

perindopril - initiate at 2mg once daily and if tolerated titrate to the target dose of 4mg once daily.

A common alternative is:

ramipril - initiate at 2.5mg once daily and titrate to 10mg once daily

Serum urea and electrolytes should be checked before and 48 hours to one week after initiating ACE inhibitor therapy, and one week after any dose increase. The degree of further monitoring depends on the patient's clinical circumstances but should be at least annual.

If creatinine rises by >50% consider discontinuing or reducing to previously tolerated lower dose and seek specialist advice.

Patients intolerant of ACE inhibitors because of side effects, such as intolerable cough, can be treated with the angiotensin II receptor antagonist (ARB or "sartan")

candesartan at a dose of 4 to 32mg daily.

Beta-blockade

Beta-blockade should be considered early in the management of heart failure. It requires specialist assessment and monitoring. Careful dose titration is required.

Bisoprolol is recommended, with a starting dose of 1.25mg daily, titrated at two-weekly intervals to a target of 10mg daily.

If a patient is already taking a beta blocker for a co-morbidity (e.g. atenolol) switch to a beta-blocker licensed for heart failure. For example, if on atenolol 50mg daily switch to bisoprolol 5mg daily and titrate if necessary.

Carvedilol 3.125mg to 25mg twice daily or nebivolol 1.25mg to 10mg once daily are alternatives for more severe disease or if bisoprolol is not tolerated.

Diuretics

Diuretics should be used for any patient with symptomatic heart failure (e.g. dyspnoea with effort or peripheral oedema). Loop diuretics are most effective and furosemide 40 to 80mg daily is the drug of choice. Higher doses are rarely necessary unless there is concomitant renal failure, in which case, the patient should be referred. Bumetanide is alternative loop diuretic that may be considered for patients not responding; bumetanide 1mg is approximately equivalent to furosemide 40mg.

Further measures

Mineralocorticoid receptor antagonists (MRA)

In severe LVSD or those with continuing symptoms (NYHA II to IV)

Add a mineralocorticoid receptor antagonist (MRA) eplerenone 25mg once daily (titrated to 50mg once daily after four weeks if tolerated) or spironolactone 25 mg once daily (no further titration).

Careful monitoring of plasma potassium is required when used in conjunction with an ACE inhibitor or ARB.

Practice point 12 – Monitoring of eplerenone or spironolactone:

Check U&Es at week 1 and 4, then four weekly for 3 months, then 3 monthly for one year and 6 monthly thereafter. At discharge, communicate this information to the GP. A plasma potassium of 6mmol/L is acceptable in this situation.

Sacubitril valsartan

Sacubitril valsartan is indicated for the treatment symptomatic heart failure in adult patients with a reduced ejection fraction and already taking a stable dose of ACE inhibitor or ARB. It should be used **instead of** an ACE inhibitor or ARB. It improves mortality and reduces hospital admissions compared to ACE inhibitor.

As recommended by NICE (see NICE guideline above), Sacubitril valsartan should only be initiated by a heart failure specialist.

See prescribing guideline (below) for further details regarding suitable candidates, initiation and monitoring of therapy.

sacubitril valsartan prescribing guidance

Practice point 13 - Sacubitril valsartan and the risk of angioedema or renal impairment:

Sacubitril/valsartan **must not** be co-administered with an ACE inhibitor or Angiotensin Receptor Blocker (ARB) (due to the increased risk of angioedema) or Aliskiren (due to increased risk of renal impairment).

Ensure that you allow a **36 hour washout** of the patient's ACE inhibitor, ARB or Aliskiren.

Sacubitril valsartan should be prescribed using the **generic name** to avoid concomitant prescribing of ACE inhibitor or ARB therapy.

Ivabradine

If resting heart rate remains above 75bpm

Add ivabradine 5mg twice daily

NICE TA267 ivabradine.pdf

Warn the patient that there can be visual disturbances which usually recede with continued treatment.

ACE inhibitor and ARB

It is highly unlikely in current practice for ACE inhibitors to be recommended in combination with an ARB in treatment of heart failure. **Triple therapy (ACE inhibitor + ARB + MRA) is contra-indicated and should not be used due to the increased risk of hyperkalaemia.**

Practice point 14 – Medicines sick day rules:

If a patient is unwell with any of the following: fevers, sweats and shaking, vomiting or diarrhoea (unless only minor) then consider temporarily stopping the medicines listed below.

- ACE inhibitors e.g. perindopril, ramipril, enalapril, lisinopril, captopril
- ARBs e.g. candesartan, losartan, valsartan, irbesartan, olmesartan
- Diuretics e.g. furosemide, bumetanide, bendroflumethiazide
- Sacubitril valsartan (Entresto)
- Eplerenone or spironolactone
- NSAIDs e.g. ibuprofen, naproxen, diclofenac
- Metformin

Restart at their usual dose after 24-48 hours of eating and drinking normally.

FURTHER READING

European Society of Cardiology guideline – heart failure
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure

Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. The Lancet. 2003. 362(9386):772-776.

Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction N Engl J Med 2003; 348:1309-21.

Management of acute heart failure

Refer to JCUH Acute Heart Failure guideline and CCU guidelines.

JCUH Acuteheartfailureman

http://cardiodocs/guidelines/data/69_04_12_2017_10_26_59_CCUguidelinesDec17.pdf

Hyperlipidaemia

Lowering LDL cholesterol and raising HDL cholesterol is effective in the primary and secondary prevention of coronary heart disease. Statins are the drug of choice in all patients. Drug treatment must be combined with appropriate diet, weight loss, smoking cessation, and blood pressure reduction. Details of treatment of obesity are available in the diabetes and endocrinology section of the trust formulary.

See also NICE pathway – lipid modification for preventing cardiovascular disease

NICE lipid modification 2018.pdf

Primary prevention

To achieve cost-effective primary prevention, statin therapy is recommended by NICE for all adults who have a 10% or greater 10 year risk of developing CVD. The level of risk should be estimated using the recommended CVD risk equations (e.g. https://qrisk.org/three/) or by clinical assessment in people for whom these are not available or appropriate (e.g. people aged > 84 years).

Drug treatment should only be considered after hypercholesterolaemia has been confirmed by repeated measurement and assay of the fasting lipid profile (i.e. total cholesterol, HDL cholesterol and triglycerides) to enable accurate risk stratification.

A target for total or LDL cholesterol is not recommended for primary prevention of CVD.

Use atorvastatin 20mg daily.

For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction.

For patients with Type 1 or 2 diabetes, or chronic kidney disease a statin should be offered. Refer to NICE guidance.

A very high cholesterol (>7.5mmol/L) may be indicative of familial hypercholesterolaemia and referral to a lipid specialist should be considered.

Secondary prevention

Treatment with a statin is recommended for all patients with proven vascular disease and for all type II diabetics aged over 40 years.

Use atorvastatin 40-80mg once daily

All patients with acute coronary syndrome should be initiated on a high intensity statin.

Use atorvastatin 80mg daily

Use atorvastatin 40mg if there are potential drug interactions, there is a high risk of adverse effects, or patient preference.

If the 40mg dose proves intolerable, reduce the dose further rather than changing agent. If a patient is truly intolerant of small doses of atorvastatin , then other statins (e.g. rosuvastatin, simvastatin, pravastatin) should be tried. With continued intolerance ezetimibe 10mg daily may be offered.

Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment after 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

- discuss adherence and timing of dose
- optimise adherence to diet and lifestyle measures
- consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

For severe hypercholesterolaemia, ezetimibe 10mg daily can be added to an optimal statin dose. Ezetimibe can also be used in combination with a low dose of statin when side effects produced by high statin doses prevent optimal lipid control.

Try atorvastatin 20mg with ezetimibe 10mg daily initially.

Avoid simvastatin 80mg once daily as this is associated with a higher rate of adverse effects including myopathy, with no extra benefit.

Statin interactions

High dose statins should be avoided in combination with drugs that interact with cytochrome P450 metabolism.
Adapted from https://www.gov.uk/drug-safety-update/statins-interactions-and-updated-advice-for-atorvastatin

Interacting drug	What happens?	Comments/Action
amiodarone	↑ statin levels that may cause increase side effects e.g. muscle ache	Reduce the dose of statin: *simvastatin – maximum 20mg daily* *atorvastatin – maximum 40mg daily*
amlodipine	↑ statin levels with ↑ risk of side-effects	Reduce the dose of statin: *simvastatin – maximum 20mg daily*
potent CYP3A4 inhibitors: including clarithromycin, itraconazole, ketoconazole, erythromycin, telithromycin, and HIV protease inhibitors	Inhibits metabolism leading to ↑ statin levels with ↑ risk of side-effects	Avoid if possible: *simvastatin – omit whilst taking interacting agent* *atorvastatin – maximum 20mg daily whilst taking interacting agent*
ciclosporin	↑ statin levels with ↑ risk of side-effects	Interacts with all statins: *simvastatin – maximum 10mg daily* *atorvastatin – maximum 10mg daily* *Contraindicated with rosuvastatin*
diltiazem	↑ statin levels with ↑ risk of side-effects	*simvastatin – maximum 20mg daily* *atorvastatin – maximum 40mg daily*
grapefruit juice	↑ statin levels with ↑ risk of side-effects	*Limit intake of grapefruit juice to very small quantities (or avoid altogether)*
verapamil	↑ statin levels with ↑ risk of side-effects	*simvastatin – maximum 20mg daily* *atorvastatin – maximum 40mg daily*
warfarin	↑INR	*Variable response of INR between patients. Monitor INR more closely.*

Monitoring

Cholesterol and LFTs (ALT and AST) should be measured before initiation, at 3 months and at 12 months. Do not measure again unless clinically indicated. Stop treatment if serum transaminases rise to and persist at more than three times the upper limit of normal. Routine creatine kinase (CK) monitoring is not required but if myopathy is suspected, CK should be measured. The statin should be stopped if CK levels are more than five times the upper limit of normal. Muscle pain without elevated CK is not a reason to stop the drug, unless severe and disabling.

Hypertriglyceridaemia

A fasting lipid profile must be measured before determining need for treatment of hypertriglyceridaemia. Dietary and other lifestyle modifications are the mainstay of treatment.

In isolated severe hypertriglyceridaemia, a fibrate is usually more appropriate than a statin. However, mixed hyperlipidaemia should be treated with a statin, initially. Combination therapy with a statin and a fibrate should only be considered after specialist assessment.

The recommended fibrate treatment is gemfibrozil 600mg twice daily.

If combination therapy with a statin is being considered, use fenofibrate 200mg daily but be aware that there may be an increased risk of myositis.

Further treatment

For patients with suspected familial hyperlipidaemia, referral to a lipid specialist via the Diabetes Care Centre at JCUH. Consider specialist referral where hyperlipidaemia is not well controlled despite the above measures.

Practice point 15 - PCSK9 inhibitors - Evolocumab and Alirocumab:

These drugs are monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9), which slows the degradation of low density lipoprotein receptors in the liver. This helps to reduce levels of low density lipoprotein (LDL) cholesterol.

NICE have approved their use for treating familial and primary hypercholesterolaemia/mixed dyslipidaemia under certain circumstances. Any patients who are being considered for treatment should be referred to Dr Arutchelvam, Diabetes and Endocrinology Consultant.

FURTHER READING

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
https://www.nice.org.uk/guidance/ta393

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
https://www.nice.org.uk/guidance/ta394

Hypertension

See also NICE clinical guideline CG127 – Hypertension

NICE hypertension CG127.pdf

Lifestyle advice should be offered initially and then periodically to all patients with hypertension. They should:

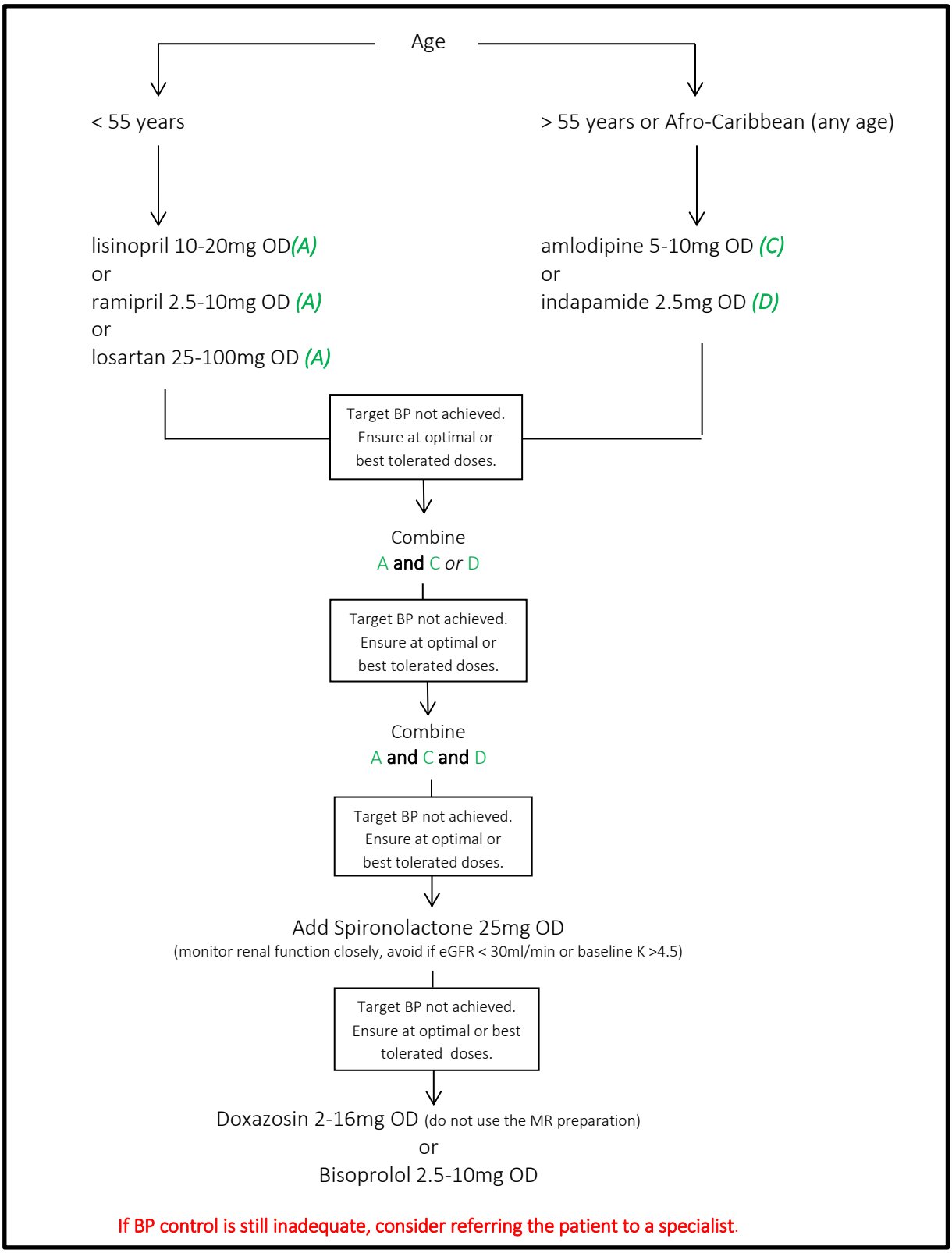
- Stop smoking
- Reduce alcohol intake
- Aim for ideal weight and healthy diet - follow the ”five-a-day” message
- Reduce sodium intake
- Take regular aerobic exercise
- Discourage the excessive intake of coffee or caffeine-rich products

Drug therapy

The choice of antihypertensive used is often dictated by comorbidity such as concomitant renal failure, diabetes, ischaemic heart disease or heart failure. For example, a diuretic and ACE inhibitor may be preferred in heart failure. If there are no other factors to consider, use the flow chart overleaf to guide your choice.

Allow at least four weeks for a full response to take place to each change in therapy.

How to choose an antihypertensive



Practice point 16 – Antihypertensives – considerations:

If a patient experiences cough or multiple side effects induced by an ACE inhibitor, consider using losartan 25-100mg daily instead.

Do not combine an ACE inhibitor with an ARB to treat hypertension.

Thiazides and ACE inhibitors are contraindicated in pregnancy. Use labetolol 200mg twice daily if pregnant. Consider bisoprolol 5mg daily as an alternative first line drug for women of childbearing age.

If a patient has hypokalaemia at baseline or if it is readily induced by therapy with low dose diuretics, refer them promptly for further investigation, as this could be a sign of hyperaldosteronism. If potassium <4.5 and eGFR >60ml/min add spironolactone to their treatment rather than giving a potassium supplement.

If amlodipine causes peripheral oedema in a patient, substitute it with diltiazem (e.g. Adizem XL 180mg daily).

Statins

Add a statin if the patient's cardiovascular disease risk is > 10% over 10 years.

Use atorvastatin 20mg daily.

FURTHER READING

Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014; 100: ii1–ii67.

JBS3-Guidelines-report.pdf

Secondary prevention post-MI

All patients should be considered for long-term secondary prevention therapy after a myocardial infarction. This consists of:

Aspirin - 75mg dispersible tablet one daily with or after food.

If a patient has true aspirin allergy, they can be given clopidogrel 75mg daily instead of aspirin.

Atorvastatin - 80mg daily.

If not tolerated consider a lower dose or simvastatin 40mg daily.

Bisoprolol – (aim for) 10mg daily.

If the patient cannot tolerate this and has preserved left ventricular systolic function, use verapamil SR 120 to 240mg daily, or diltiazem up to 300mg daily.

Ramipril – (aim for) 10mg daily.

Eplerenone - 25 to 50mg daily.

Only use eplerenone if there is clinical heart failure and moderate-to-severe or severe left ventricular systolic dysfunction on echocardiography. However, close monitoring of renal function is required - refer to the heart failure nurse.

Check U&Es at week 1 and 4, then four weekly for 3 months, then 3 monthly for one year and 6 monthly thereafter. At discharge, communicate this information to the GP. A plasma potassium of 6mmol/L is acceptable in this situation.

FURTHER READING

NICE: Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease

https://www.nice.org.uk/guidance/cg172

NICE CG172 - myocardial-infarction-

Further advice

If, having consulted these guidelines, you require advice regarding a particular patient, please contact the consultant or specialist nurse team in charge of the patient or through the advice and guidance service.

Interventional Cardiology Specialist Nurse team:
Tel: 01642 850850 ext 54922

Heart Failure Specialist Nurse team:
Tel: 01642 835865

Cardiac Rhythm Management Specialist Nurse team:
Tel: 01642 282806 (0800hr to 1600hr), 01642 850850 ext 53048 (after 1600hr)

Advice and Guidance service:
This can be accessed via "Choose & Book" under "Advice and Guidance". Your query will be sent via email to the consultant cardiologist in clinic on that or the following day.

Any comments?

If you have comments to make about this formulary, please email them to:

Dr David Austin, Consultant Cardiologist
The James Cook University Hospital
(david.austin@nhs.net)

and to

John Stapleton, Clinical Pharmacist
The James Cook University Hospital
(j.stapleton@nhs.net).