2. Cardiovascular System

2.1 - Positive inotropic drugs

2.1.1 Cardiac glycosides

**Digoxin**

| H - Digoxin specific antibody (Digifab®) |

**Prescribing Points**

- Digoxin is indicated for rate control in atrial fibrillation and as add-on therapy for symptomatic relief of heart failure in sinus rhythm.
- Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea).
- Use with caution in the elderly and in renal impairment due to the higher risk of digoxin toxicity. A lower maintenance dose of digoxin may be required in these patients. Hypokalaemia can also predispose to digoxin toxicity.
- Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems e.g. toxicity, lack of compliance are suspected. For plasma concentration monitoring, blood should ideally be taken at least 6 hours after a dose.
- Toxicity can often be managed by discontinuing digoxin and correcting any electrolyte abnormalities.
- Digifab® is available for reversal of life-threatening overdosage.

2.2 - Diuretics

*Also see Appendix 2A Management of hypertension*


*Also see Appendix 2C Stroke management*

www.fifeadtc.scot.nhs.uk/formulary/sections/FF%20appendix%202C.pdf

2.2.1 Thiazides and related diuretics

<table>
<thead>
<tr>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indapamide 2.5mg</td>
<td>Bendroflumethiazide</td>
</tr>
</tbody>
</table>

**Prescribing Points**

- In the management of hypertension, thiazide diuretics are recommended as 3rd line choices in patients after renin-angiotensin system agents and calcium channel blockers.
- Optimum antihypertensive effect is expected within 4 weeks of starting the diuretic.
- Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus. Indapamide can be used in stroke patients in combination with perindopril.
- Bendroflumethiazide 5mg is not recommended for the treatment of hypertension. Its use should be restricted to the treatment of oedema due to chronic heart failure.
- For all diuretics, monitoring of U&Es is recommended at baseline, 2 weeks after initiation/each dose titration and then annually.

**KEY:-**

| H – Hospital Use Only |
| S – Specialist Initiation or Recommendation |
| R – Restricted Use Only |

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August 2010  
Last amended August 15
2.2.2  

**Loop diuretics**

<table>
<thead>
<tr>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Furosemide</strong></td>
<td><strong>Bumetanide</strong></td>
</tr>
</tbody>
</table>

**Prescribing Points**

- Loop diuretics are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure. If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension (see Appendix 2A), or in patients with impaired renal function or heart failure.
- Loop diuretics are powerful diuretics. Hypokalaemia may develop, and care is needed to avoid hypotension.
- Furosemide and bumetanide both act within 1 hour of oral administration and diuresis is complete within 6 hours. The diuresis associated with these drugs is dose related.
- Furosemide and bumetanide are equally efficacious (furosemide 40mg = bumetanide 1mg). Bumetanide should be restricted to 2nd line use in patients intolerant of furosemide.
- In patients with impaired renal function very large doses may occasionally be needed (Specialist supervision required).
- The lowest dose of diuretic to control symptoms should be used.
- Monitoring of U&Es is recommended at baseline, 2 weeks after initiation/each dose titration and then annually.

2.2.3  

**Potassium-sparing diuretics and aldosterone antagonists**

<table>
<thead>
<tr>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spironolactone</strong></td>
<td><strong>Eplerenone (Inspra®)</strong></td>
</tr>
</tbody>
</table>

**Prescribing Points**

- Hypokalaemia may occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.
- Potassium supplements or potassium-sparing diuretics are seldom necessary when thiazides are used in the routine treatment of hypertension.
- Amiloride is a weak diuretic and not recommended for use.
- Spironolactone is used for oedema in hepatic cirrhosis and heart failure, for resistant hypertension and in Conn’s syndrome. It has been show to reduce mortality in patients with heart failure (NYHA Stage III, Stage IV) who are already prescribed an ACE inhibitor and a diuretic, normally at a dose of 50mg daily.
- Eplerenone is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction. Treatment should be started within 3 – 14 days of an event occurring. It can also be used in patients intolerant of spironolactone or those who develop gynaecomastia.
- Eplerenone is also approved for use in patients who are intolerant of spironolactone, in addition to standard optimal therapy to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%).
- Monitoring of U&Es is recommended at baseline, 2 weeks after initiation/each dose titration and then annually.
Patients with intercurrent fluid losing illness should discontinue these drugs until they have recovered.

- Potassium supplements must not be given with potassium-sparing diuretics or aldosterone antagonists.
- Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can cause severe hyperkalaemia.

### 2.2.5 Osmotic diuretics

**H** - Mannitol

### 2.3 - Anti-arrhythmic drugs

#### 2.3.2 Drugs for arrhythmias

<table>
<thead>
<tr>
<th>Class I anti-arrhythmics (membrane stabilising drugs)</th>
<th>H - Lignocaine (lidocaine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disopyramide</td>
</tr>
<tr>
<td></td>
<td>Flecainide</td>
</tr>
<tr>
<td></td>
<td>S – Propafenone</td>
</tr>
<tr>
<td>Class II anti-arrhythmics (beta-blockers)</td>
<td>S – Sotalol</td>
</tr>
<tr>
<td>Class III anti-arrhythmics</td>
<td>S – Amiodarone</td>
</tr>
<tr>
<td></td>
<td>R- Dronedarone (Multaq®)</td>
</tr>
<tr>
<td>Class IV anti-arrhythmics (calcium channel blockers)</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Other anti-arrhythmics</td>
<td>H - Adenosine</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

**Prescribing Points**

- All anti-arrhythmic drugs have the potential to cause arrhythmias. These effects are more likely if the patient has hypokalaemia. These drugs, in general, should be only initiated under specialist supervision.
- The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Special care is required if two or more drugs are used.
- Flecainide M/R capsules can be used by patients who are controlled with the immediate release formulation of flecainide. The M/R version allows once daily dosing and is cheaper than using the standard tablets at an equivalent dose.
- Due to the potential of serious side-effects, amiodarone should be reserved for the treatment of life-threatening arrhythmias or when other drugs are contra-indicated or ineffective. Thyroid and liver function should be checked before treatment and then every 6 months during treatment. Patients should be advised to avoid direct sunlight to prevent phototoxic reactions and monitored for signs of shortness of breath (pulmonary fibrosis) and for signs of visual disturbance.
- The normal maintenance dose for amiodarone is 200mg daily.
- Amiodarone may interact with warfarin leading to increased plasma levels of warfarin. This interaction may take several weeks to manifest itself. INR levels should be monitored on a regular basis.
- If a patient develops persistent AF post operatively then amiodarone will be started in hospital. If the AF persists prior to discharge the patient will be continued on amiodarone for 6 weeks. The patient should then be reviewed by a specialist.
- **R** - Dronedarone is approved for restricted use for maintenance of sinus rhythm after successful cardioversion in patients with paroxysmal or persistent AF. Due to safety concerns dronedarone should...
only be prescribed after alternative treatment options have been ineffective, not tolerated or are contraindicated. Dronedarone should not be given to patients with current or previous episodes of heart failure or left ventricular systolic dysfunction. Specialist initiation only.

- Verapamil can have potentially serious interactions if co-administered with IV beta-blockers and digoxin.

2.4 - Beta-adrenoceptor blocking drugs

Also see Appendix 2A Management of hypertension

Also see Appendix 2E Management of Stable angina
www.fifeadtc.scot.nhs.uk/formulary/sections/FF%20appendix%202E.pdf

Also see Appendix 2G Post MI Guidance
www.fifeadtc.scot.nhs.uk/formulary/sections/FF%20appendix%202G.pdf

<table>
<thead>
<tr>
<th>1st Choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol - hypertension, angina, post-MI, heart failure (Class I - III)</td>
<td>Atenolol - hypertension, angina, post-MI</td>
</tr>
<tr>
<td>Carvedilol - heart failure (Class I - IV), oesophageal varices</td>
<td>Nebivolol - systolic hypertension in the elderly, stable heart failure in patients over 70 years</td>
</tr>
<tr>
<td>Propranolol - anxiety, migraine prophylaxis, thyrotoxicosis, tremor, oesophageal varices</td>
<td>S - Labetolol - Pregnancy</td>
</tr>
<tr>
<td>S - Metoprolol - renal impairment, initiation of beta-blockade in coronary care</td>
<td>S - Sotalol (see also section 2.3.2) – arrhythmias</td>
</tr>
<tr>
<td>H - Esmolol - critical care, anaesthesia</td>
<td></td>
</tr>
</tbody>
</table>

Prescribing Points

- Bisoprolol is preferred to atenolol as it is less likely to cause side-effects.
- There are differences between beta-blockers e.g. side-effect profiles, licensed indications which may affect choice in an individual patient. Water soluble agents e.g. atenolol, sotalol may be less likely to cause sleep disturbances and nightmares.
- Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.
- Beta-blockers are contra-indicated in patients with second or third-degree heart block. Beta-blockers should also be avoided in patients with worsening, unstable heart failure.
- Beta-blockers should be avoided in patients with a history of asthma or bronchospasm; if there is no alternative, a highly cardioselective beta-blocker e.g. nebivolol, can be used with extreme caution under specialist supervision. Patients with well-controlled chronic obstructive pulmonary disease can be treated with a cardioselective beta-blocker which should be initiated at a low dose by a specialist; the patient should be closely monitored for adverse effects.
- Beta-blockers, especially when combined with a thiazide diuretic, should be avoided in the treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.
- Combination products containing a beta-blocker and a diuretic are not recommended e.g. co-tenidone,
unless compliance is a problem.

- Beta-blockers in combination with diltiazem or verapamil may produce excessive bradycardia. Verapamil should not be given with a beta-blocker.
- In patients with angina or a previous myocardial infarction, a sudden withdrawal of a beta-blocker may cause an exacerbation of symptoms and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped.

Heart failure

- In patients with heart failure, beta-blocker treatment should be started under specialist supervision at a low starting dose and titrated very slowly. Heart failure symptoms may deteriorate initially (first 2-3 days). Patients should be monitored for heart rate, oedema, breathlessness and blood pressure after each dose increase.
- The dose of beta-blocker in patients with heart failure or post-MI should be increased to the target dose (see BNF) or the maximum tolerated dose.
- Bisoprolol only needs to be given once daily whereas carvedilol is given twice daily. Generic bisoprolol is more cost-effective than prescribing carvedilol.

2.5 Hypertension and heart failure

Also see Appendix 2A Management of hypertension

2.5.1 Vasodilator antihypertensive drugs

| Hydralazine |

Prescribing Points

- Hydralazine usually in combination with a nitrate may be used in patients with heart failure who are intolerant of ACE-inhibitors and angiotensin-II receptor antagonists.

2.5.2 Centrally-acting antihypertensive drugs

| Moxonidine |

Prescribing Points

- Moxonidine may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

2.5.4 Alpha-adrenoceptor blocking drugs

| Doxazosin (standard tablets) |

Prescribing Points

- Doxazosin can be used as a fourth-line agent for resistant hypertension.
- Doxazosin can cause first dose hypotension so should be introduced at a low dose and titrated upwards.
- The standard doxazosin tablet offers 24 hour BP control and is considerably cheaper than doxazosin M/R tablets.

2.5.5 Drugs affecting the renin-angiotensin system

Also see Appendix 2A Management of hypertension

**KEY:**

- H — Hospital Use Only
- S — Specialist Initiation or Recommendation
- R — Restricted Use Only

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Also see Appendix 2G Post MI Guidance
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2.5.5.1 Angiotensin-converting enzyme inhibitors

<table>
<thead>
<tr>
<th>Prescribing Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Choice</td>
</tr>
<tr>
<td>2nd Choice</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ACE inhibitors are first line agents for hypertension in patients under 55 years (non-black patients) and in patients with type 1 or type 2 diabetes with nephropathy.</td>
</tr>
<tr>
<td>Patients who develop a persistent dry cough on ACE-inhibitors should be switched to an angiotensin II receptor antagonist.</td>
</tr>
<tr>
<td>Renal function and electrolytes should be monitored regularly – at baseline, 2 weeks after initiation / each dose titration and then annually. Hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced.</td>
</tr>
<tr>
<td>Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia.</td>
</tr>
<tr>
<td>Careful monitoring of serum potassium is advised where patients are receiving both an ACE inhibitor and an aldosterone antagonist e.g. spironolactone.</td>
</tr>
<tr>
<td>If serum Creatinine rises by &gt;20% then the ACE inhibitor should be discontinued or if after a dose increase the dose should be reduced to previously tolerated dose. Further investigation could be considered.</td>
</tr>
<tr>
<td>For heart failure, the dose of ACE inhibitor should be titrated to the ‘target’ dose (see BNF) or maximal tolerated dose. The maximum dose of ACE inhibitor provides maximum benefit.</td>
</tr>
<tr>
<td>Patients with nausea and vomiting should be advised to stop their ACE inhibitors for 2-3 days if dehydration is a risk.</td>
</tr>
<tr>
<td>ACE inhibitors are best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly. They should also be used with particular caution in patients with peripheral vascular disease or those with severe generalised atherosclerosis.</td>
</tr>
<tr>
<td>Products containing a combination of an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are not recommended.</td>
</tr>
<tr>
<td>R-Trandolapril is approved for restricted use for prophylaxis after a recent MI in patients with left ventricular dysfunction</td>
</tr>
</tbody>
</table>

2.5.5.2 Angiotensin-II receptor antagonists

Also see Appendix 2A Management of hypertension

Also see Appendix 2G Post MI Guidance
www.fifeadtc.scot.nhs.uk/formulary/sections/FF%20appendix%202G.pdf

<table>
<thead>
<tr>
<th>Prescribing Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Choice</td>
</tr>
<tr>
<td>2nd Choice</td>
</tr>
<tr>
<td>ACE inhibitors are best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly. They should also be used with particular caution in patients with peripheral vascular disease or those with severe generalised atherosclerosis.</td>
</tr>
</tbody>
</table>

KEY:-

H – Hospital Use Only
S – Specialist Initiation or Recommendation
R – Restricted Use Only

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Prescribing Points

- These products should be restricted for use as second line agents, in patients unable to tolerate an ACE inhibitor.
- To achieve a maximal antihypertensive effect the dose of losartan should be titrated to 100mg daily.
- In heart failure, candesartan can be used as an alternative to ACE inhibitors when ACE inhibitors are not tolerated or as an add-on therapy to ACE inhibitors (specialist initiation only).
- Renal function and electrolytes should be monitored regularly - at baseline, 2 weeks after initiation/each dose titration and then annually.
- If serum Creatinine rises by >20% then the AIIRA should be discontinued or if after a dose increase the dose should be reduced to previously tolerated dose. Further investigation could be considered.
- Products containing a combination of an AIIRA with a thiazide diuretic or a calcium-channel blocker are not recommended.
- **R-** Telmisartan is approved for restricted use in patients intolerant of ACE inhibitors, for the prevention of cardiovascular events in patients with established cardiovascular disease.

2.6 - Nitrates, calcium-channel blockers, and other antianginal drugs

Also see Appendix 2E Management of Stable angina

### 2.6.1 Nitrates

<table>
<thead>
<tr>
<th>Glyceryl trinitrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide mononitrate (modified release)</td>
</tr>
<tr>
<td>H - Glyceryl trinitrate IV</td>
</tr>
<tr>
<td>H - Isosorbide dinitrate IV</td>
</tr>
</tbody>
</table>

Prescribing Points

- Modified release versions of isosorbide mononitrate should be prescribed for once daily use. The preferred optimum dose is 60mg daily.
- Glyceryl trinitrate patches are not recommended due to lack of a nitrate free period and due to their cost. They may be useful in patients experiencing dysphagia.

### 2.6.2 Calcium channel blockers

Also see Appendix 2A Management of hypertension

Also see Appendix 2E Management of Stable angina

<table>
<thead>
<tr>
<th>Dihydropyridines</th>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amlodipine</td>
<td>Lercanidipine</td>
</tr>
</tbody>
</table>
Rate limiting
1st Choice Verapamil
2nd Choice Diltiazem
H - Nimodipine

Prescribing Points
- Amlodipine is the first choice calcium channel blocker for hypertension.
- Lercanidipine can be used in hypertensive patients who develop ankle oedema with amlodipine.
- For dihydropyridines, side-effects associated with vasodilatation such as flushing and headache and ankle swelling are common.
- Verapamil can be used post-MI or in angina where beta-blockers are not tolerated or are inappropriate. Verapamil should not be co-prescribed with a beta-blocker due to the risk of bradycardia.
- Diltiazem may be used in angina in patients for whom beta-blockers are contra-indicated or ineffective. Due to the risk of bradycardia it should be used with caution in combination with beta-blockers.
- Modified release diltiazem (except the 60mg strength) should be prescribed by brand name due to differences in bioavailability between brands.
- There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of angina.
- Nimodipine is used for prevention of vascular spasm following subarachnoid haemorrhage.

2.6.3 Other antianginal drugs

Also see Appendix 2E Management of Stable angina
www.fifeadtc.scot.nhs.uk/formulary/sections/FF%20appendix%202E.pdf

Ivabradine (Procoralan®)
Nicorandil

Prescribing Points
- Ivabradine is used for rate control when patients have a contra-indication to or are intolerant of beta-blockers and rate limiting calcium channel blockers.
- Ivabradine can be added to beta blockers to control symptoms.
- Ivabradine is also approved for specialist initiation only for the treatment of chronic heart failure (class II – IV) in patients whose heart rate is ≥ 75 beats per minute (bpm), in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.
- Nicorandil can be used in combination with other drugs to control symptoms of angina.
- Unlike the nitrates, patients do not develop tolerance with nicorandil.
- Oral and anal ulceration has been reported with nicorandil requiring withdrawal of treatment.

2.6.4 Peripheral vasodilators and related drugs

Naftidrofuryl oxalate
Nifedipine (standard capsules)
Prescribing Points

- Naftidrofuryl can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl should be assessed for improvement after 3–6 months.
- The SMC has not recommended the use of cilostazol (Pletal®) in NHS Scotland for the treatment of intermittent claudication.
- Management of Raynaud's Syndrome includes avoidance of exposure to cold and stopping smoking. More severe symptoms may require vasodilator treatment with naftidrofuryl or nifedipine.
- Other vasodilators are not recommended for the treatment of intermittent claudication or Raynaud’s syndrome due to lack of efficacy.

2.7 - Sympathomimetics

2.7.1 Inotropic sympathomimetics

- H - Dobutamine
- H - Dopamine
- H - Isoprenaline

2.7.2 Vasoconstrictor sympathomimetics

- H - Ephedrine hydrochloride
- H - Metaraminol
- H - Noradrenaline (Norepinephrine)
- H - Phenylephrine

2.7.3 Cardiopulmonary resuscitation

- Adrenaline (Epinephrine)

Prescribing Points

- Sympathomimetics are used to optimise cardiovascular function in critical care and anaesthesia.

2.8 - Anticoagulants and protamine

2.8.1 Parenteral anticoagulants

- Heparin
  - S - Dalteparin
  - H - Epoprostenol
  - S - Fondaparinux
  - R - Argatroban
  - R - Tinzaparin

Prescribing Points

- LMWH are now 1st choice for thromboprophylaxis and treatment of DVT and PE.
- Unfractionated heparin is used when immediate effect or reversibility is required. Monitoring of APTT is necessary.
- Epoprostenol is used in haemofiltration and heparin allergy.
- Fondaparinux is used first line in acute coronary syndrome patients.
- Dalteparin is approved for extended treatment of symptomatic venous thromboembolism (VTE) and prevention of its recurrence in patients with solid tumours.
- **R** — Argatroban is approved for restricted hospital specialist use only in adult patients with renal impairment who have heparin induced thrombocytopenia.
- **R** — Tinzaparin is approved for restricted hospital use in renal patients only for the prevention of clotting in patients undergoing haemodialysis.

### 2.8.2 Oral anticoagulants

*Also see Appendix 2H Guidance on Newer anticoagulants*


<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
</table>

#### Prescribing Points

**Warfarin**

- Oral anticoagulants take at least 48 to 72 hours for the anticoagulant effect to develop fully. If an immediate effect is required, heparin must be given concomitantly.
- Warfarin dose should be adjusted according to target International Normalised Ratio (INR) levels (see BNF). INR levels should be monitored regularly during treatment.
- Patients initiated on warfarin therapy should have a target INR range and treatment duration documented in their Anticoagulant Treatment Booklet. Copies of the booklet can be obtained from Pharmacies and from The Scottish Office Home and Health Department, Room 64, St. Andrew’s House, Edinburgh, EH1 3DH.

#### Management of bleeding and excessive anticoagulation with warfarin

| INR < 6.0 | 1. Reduce or withhold Warfarin  
2. Restart when INR < 5.0 |
|-----------|-----------------|
| INR 6.0- 8.0 (No bleeding or Minor Bleeding) | 1. Withhold Warfarin  
2. Restart when INR < 5.0 |
| INR > 8.0 (No bleeding or Minor Bleeding) | 1. Withhold Warfarin  
2. Restart when INR < 5.0  
3. If other risk factors for bleeding give 0.5 - 2.5mg Vit K IV or orally* |
| **MAJOR BLEEDING** | 1. Stop Warfarin  
2. Give Octaplex 50units/kg up to a maximum dose of 3000units |

* Vitamin K takes 4 - 6 hours to exert an effect, whether by IV or oral administration. If doses less than 10mg are to be administered orally the preferred presentation is Konakion MM Paediatric 2mg / 0.2ml which is not licensed for this indication but is formulated and packaged for oral administration.

**Rivaroxaban**

- Rivaroxaban is approved for the prevention of venous thromboembolism in adults undergoing elective hip replacement or knee replacement surgery.

**KEY:**

- **H** — Hospital Use Only
- **S** — Specialist Initiation or Recommendation
- **R** — Restricted Use Only

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Rivaroxaban is approved as a 2nd line choice for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Restricted to patients in whom there is poor INR control with warfarin unrelated to compliance or in patients who are genuinely intolerant of warfarin/coumarins. (See Appendix 2H for further advice).

Rivaroxaban is approved as a 1st line choice for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. Approved for first presentation of DVT for up to 6 months duration. Specialist initiation only. (See Appendix 2H for further advice).

Rivaroxaban is also approved as the 1st line choice treatment of pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults. Anticipated duration for the majority of patients is 6 months. Treatment for up to 12 months may be appropriate for some patients. Specialist initiation only.

Rivaroxaban is not recommended by the Scottish Medicines Consortium (SMC) for co-administration with aspirin alone or with aspirin plus clopidogrel for the prevention of atherothrombotic events in patients after an acute coronary syndrome. Requires submission and approval of an IPTR before prescribing for this indication.

Patients prescribed rivaroxaban should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

2.8.3 Protamine Sulphate

**H - Protamine**

**Prescribing Points**

- Protamine reverses the effects of unfractionated heparin but only partially reverses those of LMWH.

2.9 - Antiplatelet drugs

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipyridamole (modified release) (Persantin® Retard)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>R</strong>- Prasugrel (Efient®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>R</strong>- Ticagrelor (Brilique®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>H</strong>- Tirofiban</td>
<td></td>
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</tbody>
</table>

**Prescribing Points**

- Aspirin is no longer recommended for the primary prevention of cardiovascular disease or in diabetics without underlying cardiovascular disease.
- The normal dose of aspirin to prevent cardiovascular events is 75mg daily. The dispersible formulation is preferred. Enteric coated (EC) aspirin is more expensive, may have lower bioavailability and does not provide protection against gastric irritation.
- Patients with a history of GI upset or high GI risk should be prescribed aspirin with a prophylactic dose of PPI (omeprazole or lansoprazole). Clopidogrel should only be prescribed if a combination of aspirin + PPI is not tolerated.
- Clopidogrel is licensed for secondary prevention only. It should not be prescribed for primary prevention.
- Patients with hypersensitivity / true intolerance to aspirin should be prescribed clopidogrel instead.
- GI risk with clopidogrel is similar to that with aspirin.
- The co-prescribing of clopidogrel with omeprazole or esomeprazole should be avoided due to the potential

**KEY:-**

- **H** – Hospital Use Only
- **S** – Specialist Initiation or Recommendation
- **R** – Restricted Use Only

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antagonism of the anti-platelet effect.

- **R** - Prasugrel in combination with aspirin is approved for restricted use in patients requiring an emergency stent, in patients who experience an in-stent thrombosis whilst on clopidogrel or have previous clopidogrel intolerance or sensitivity. The combination should be given for 12 months. Specialist initiation only.

- **R** - Ticagrelor in combination with aspirin is approved for restricted use in high risk patients with a non-ST elevated myocardial infarction (NSTEMI) for the prevention of an atherothrombotic event. Specialist initiation only.

**Stroke prevention**

- Clopidogrel should be prescribed for all patients who experience an event (stroke/TIA).

- Patients who cannot tolerate clopidogrel monotherapy should be prescribed aspirin and dipyridamole modified release.

**Use of aspirin & clopidogrel in acute coronary syndrome**

<table>
<thead>
<tr>
<th>ST elevation</th>
<th>Non ST elevation</th>
<th>Stent insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin &amp; clopidogrel for 1 month then continue long-term aspirin.</td>
<td>Aspirin &amp; clopidogrel for at least 3 months then continue long-term aspirin.</td>
<td>Aspirin &amp; clopidogrel for 3 months then continue long-term aspirin.</td>
</tr>
<tr>
<td>Bare metal stent</td>
<td>Drug eluting stent</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment duration with antiplatelet agents should follow advice given by the supervising cardiologist.

- The co-prescribing of clopidogrel with aspirin increases GI risk four-fold.

**2.10 – Stable angina, acute coronary syndromes and fibronolysis**

**2.10.2 Fibrinolytic Drugs**

<table>
<thead>
<tr>
<th></th>
<th><strong>S</strong> - Tenecteplase</th>
<th><strong>H</strong> - Alteplase</th>
<th><strong>H</strong> - Streptokinase</th>
<th><strong>H</strong> - Urokinase</th>
</tr>
</thead>
</table>

**Prescribing Points**

- Alteplase is approved for the fibrinolytic treatment of acute ischaemic stroke. For use within 4.5 hours after onset of the stroke symptoms and after exclusion of intracranial haemorrhage.

- Alteplase 2mg/2ml vial formulation is approved for use in unblocking occluded central venous access devices including those used for haemodialysis. Only to be used when alteplase is the product of choice for this indication.

**2.11 - Antifibrinolytic drugs and haemostatics**

**Tranexamic acid**

**Prescribing Points**

- Tranexamic acid is used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis and in the management of menorrhagia.
Blood products

The following blood products are available through the hospital Blood Bank at Victoria Hospital and Queen Margaret Hospital. GP requests should be directed to Victoria Hospital.

- Red cell concentrate
- Platelets
- Fresh frozen plasma
- Cryoprecipitate
- DEFIX concentrate

Prescribing Points

- The blood banks keep small supplies of recombinant Factor VIII and recombinant Factor IX for emergency treatment of haemophiliacs under guidance of the South East Scotland Haemophilia Centre. Any enquiries regarding supplies of concentrate for home treatment should be directed to the South East Scotland Haemophilia Centre at Edinburgh Royal Infirmary or the East of Scotland Haemophilia Centre at Ninewells for patients attending there from North East Fife.

The blood products listed below are now considered as medicines and are available from the Pharmacy Departments at Victoria and Queen Margaret Hospitals. GP requests should be directed to Victoria Hospital.

Normal Human Immunoglobulin
Albumin solution 4.5%
Albumin solution 20%
Hepatitis B Immunoglobulin
Hyperimmune antivaricella Immunoglobulin
Human tetanus Immunoglobulin
Anti-D Immunoglobulin

- It should be remembered that all blood products present a possible infective risk and doctors should be advised to make judgements on the necessity to use these products in the light of potential risk.
- The use of many blood products is governed by protocols or guidelines but advice may be sought from one of the consultant haematologists.

2.12 - Lipid-regulating drugs

Also see Appendix 2F Management of Cholesterol
http://www.fifeadtc.scot.nhs.uk/formulary/support%20info/Management%20of%20Cholesterol.pdf

<table>
<thead>
<tr>
<th>Statins</th>
<th>Simvastatin</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice</td>
<td>Pravastatin (primary prevention only, in patients intolerant of simvastatin)</td>
<td></td>
</tr>
<tr>
<td>3rd Choice</td>
<td>Rosuvastatin (Crestor®) (secondary prevention only, high risk patients)</td>
<td></td>
</tr>
</tbody>
</table>

Prescribing Points

- A statin is the drug of first choice for primary and secondary prevention of cardiovascular disease, treating hypercholesterolaemia and moderate hypertriglyceridaemia.

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Fife Formulary

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Last amended August 15
Simvastatin 40mg is recommended as the 1st choice statin for primary prevention and in secondary prevention for patients with stable cardiovascular disease.

There is a 10 fold difference in benefits in using statins in secondary prevention compared to primary prevention.

In primary prevention there is no need to chase a cholesterol target level.

Pravastatin 40mg (primary prevention) or rosuvastatin (secondary prevention) should be used in patients who are intolerant of simvastatin.

In secondary prevention, atorvastatin 40mg should be used if there is an inadequate response to simvastatin 40mg.

The usual starting dose for rosuvastatin is 10mg but patients of Asian origin and the elderly should start on 5mg. Titration from 20mg to 40mg should only be done under specialist supervision.

Pravastatin and rosuvastatin are not metabolised by the cytochrome P450 system. They can be used as alternatives in patients who require long-term treatment with drugs that may interact with simvastatin and atorvastatin e.g. verapamil, amiodarone.

Simvastatin (all doses) should not be used with the following medications: itraconazole; ketoconazole; clarithromycin; telithromycin and HIV protease inhibitors.

More than 10mg of simvastatin should not be used with gemfibrozil, ciclosporin or danazol.

More than 20mg of simvastatin should not be used with amiodarone, amlodipine, diltiazem or verapamil.

Simvastatin 80mg is associated with increased risk of myopathy/rhabdomyolysis compared to the use of lower doses of simvastatin and possibly other statins.

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness.

Fibrates, bile acid sequestrants, or nicotinic acid should not normally be used in combination with a statin.

**Bile acid sequestrants**

**S - Colestyramine**

**Prescribing Points**

- Used in secondary prevention where patients are intolerant of or have inadequate response to statins.
- Bile acid sequestrants reduce LDL-cholesterol but can aggravate hypertriglyceridaemia.
- Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, and K may be required when treatment is prolonged.
- Other drugs should be taken at least 1 hour before or 4-6 hours after bile acid sequestrants to reduce possible interference with absorption.

**Ezetimibe**

**Ezetimibe (Ezetrol®)**

**Prescribing Points**

- Ezetimibe should be reserved for use in secondary prevention in patients intolerant of statins and/or a fibrate or in combination with a statin in those patients having an inadequate response to maximally tolerated doses of statins. (Check patient concordance with statin).

**Fibrates**
Prescribing Points

- Fibrates are indicated in isolated hypertriglyceridaemia (serum triglyceride level > 10mmol/litre) or in secondary prevention in patients intolerant of statins.
- A fibrate can be added to statin therapy if triglycerides remain high even after the LDL-cholesterol concentration has been reduced adequately.
- Combination of a statin with a fibrate carries an increased risk of side-effects and should be used under specialist supervision.
- In type 2 diabetes a fibrate can be added to a statin for those with a serum-triglyceride concentration exceeding 2.3 mmol/litre, despite 6 months of treatment with a statin and optimal glycaemic control.

Other Agents

- Omega-3 fatty acid compounds may be used to reduce triglycerides, in addition to a statin, in patients with mixed hyperlipidaemia not adequately controlled with a statin alone. There is little clinical trial evidence that the triglyceride lowering effect decreases the risk of cardiovascular disease.
- The SMC has not recommended Omacor® for use within NHS Scotland for the treatment of hypertriglyceridaemia.

2.13 - Local sclerosants

- H - Ethanolamine oleate
- H - Sodium tetradecyl sulfate