PERIOPERATIVE MANAGEMENT OF CARDIOVASCULAR DRUGS

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It is estimated that by 2010 cardiovascular disease will be the leading cause of death worldwide. In some countries more than 1 in 4 people suffer from some form of cardiovascular disease. Many surgical patients take cardiovascular medications and the perioperative management of these medications poses particular challenges for the anaesthetist. Decisions must be made based on a careful risk-benefit analysis for each patient. The risk of stopping some drugs is often greater than the risk of continuing them during surgery, but surgery itself may alter the need for continued therapy for certain conditions. This article offers a guide to the medications you may encounter and provides advice on how they may be used in the perioperative period.

The most commonly prescribed cardiovascular drugs or drug categories are:

- Adrenoceptor antagonists
- Nitrates
- ACE inhibitors
- Anti-arrhythmics
- Angiotensin II receptor antagonists
- Antiplatelet drugs
- Calcium channel blockers
- Anticoagulants
- Diuretics
- Lipid-lowering drugs

Adrenoceptor antagonists
These agents work by blocking the action of catecholamines at \( \alpha \), or \( \beta \), adrenergic receptors, or both.

<table>
<thead>
<tr>
<th>( \beta_1 )-adrenoceptor antagonists (Betablockers)</th>
<th>e.g. the ‘-olols’</th>
</tr>
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<tbody>
<tr>
<td><strong>Classification</strong></td>
<td></td>
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<tr>
<td>- Cardioselective - block ( \beta_1 ) receptors preferentially (eg. atenolol, metoprolol, esmolol, nebivolol)</td>
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<tr>
<td>- Non-cardioselective - block ( \beta_1 ) and ( \beta_2 ) receptors (eg. propanolol, sotalol)</td>
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<tr>
<td>- Dual action at ( \alpha ) and ( \beta_1 ) receptors (labetolol, carvedilol)</td>
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<tr>
<td><strong>Indications</strong></td>
<td></td>
</tr>
<tr>
<td>Angina, post-myocardial infarction (MI), hypertension, supraventricular arrhythmias (especially those associated with increased catecholamine levels)</td>
<td></td>
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<tr>
<td><strong>Mode of action</strong></td>
<td></td>
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<tr>
<td>- Antagonist at ( \beta_1 ) receptors causing reduction in heart rate and force of myocardial contraction, thereby decreasing workload and increasing coronary perfusion time. Improve ischaemia by restoring the myocyte’s oxygen supply demand balance</td>
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<tr>
<td>- Action on ( \beta_1 ) receptors in renal juxtaglomerular cells leads to decreased circulating levels of renin and angiotensin II, resulting in lowering of blood pressure</td>
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<tr>
<td>- As class II antiarrhythmics reduce sinoatrial node automaticity, prolong ventricular conduction and extend the refractory period at the atrioventricular node</td>
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<tr>
<td><strong>Side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Bradycardia, cold peripheries, CNS effects if lipid soluble drug (metoprolol, propanolol), depression, lethargy, bronchospasm</td>
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</table>

**Perioperative management**
- Most centres advocate continuing \( \beta \)-blockers throughout the perioperative period, especially in those at high risk of ischaemic events. Studies have found that \( \beta_1 \) blockers reduce perioperative ischaemia in patients with underlying cardiovascular disease. There is some evidence that \( \beta \)-blockers reduce the risk of perioperative myocardial infarction and death.
<table>
<thead>
<tr>
<th><strong>$\alpha_1$-adrenoceptor antagonists</strong></th>
<th>eg. indoramin and the ‘-azosins’ – doxazosin, prazosin, terazosin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Hypertension, congestive heart failure, Raynaud’s syndrome, benign prostatic hypertrophy</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Prevents $\alpha_1$-mediated vaso-constriction, reduces systemic vascular resistance and blood pressure</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Nausea, postural hypotension, dizziness, headache</td>
</tr>
</tbody>
</table>

**Perioperative management**
- Continue throughout perioperative period
- No intravenous formulations exist, so recommence once oral intake re-established

<table>
<thead>
<tr>
<th><strong>Angiotensin Converting Enzyme Inhibitors (ACEi)</strong></th>
<th>eg. the ‘-prils’ – captopril, lisinopril, enalapril, perindopril, ramipril, cilazapril, fosinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Hypertension, left ventricular dysfunction, post-MI, delaying progression of proteinuria and renal impairment in diabetes</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Angiotensin converting enzyme (ACE) inhibition leads to decreased synthesis of angiotensin II. Angiotensin II normally causes peripheral vasoconstriction and stimulates aldosterone release, resulting in retention of $\text{Na}^+$ and water, and excretion of $\text{K}^+$. Lowering angiotensin II levels results in reduced vascular resistance and reduced fluid retention. Ventricular ejection and cardiac function are therefore improved. Remodelling of the ventricular muscle is also facilitated</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Postural hypotension, dry cough (bradykinin is usually broken down by ACE and so levels rise), rash, angioedema (causing swollen tongue)</td>
</tr>
</tbody>
</table>

**Perioperative management**
- Often contributes to exaggerated of hypotension on induction and during maintenance of anaesthesia, particularly in presence of hypovolaemia
- Many anaesthetists omit on the morning of surgery particularly if performing neuroaxial blockade (epidural or spinal)
- Some centres recommend stopping ACEi on morning of surgery if part of therapy for LV dysfunction, but continue it if the indication is hypertension

<table>
<thead>
<tr>
<th><strong>Angiotensin II receptor antagonists (ARA’s)</strong></th>
<th>eg. the ‘-sartans’ - losartan, candesartan, irbesartan, valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
| **Mode of action**                            | • Specific angiotensin II type-1 receptor (AT-1) blocker
• Similar cardiovascular actions to ACE inhibitors
• Bradykinin-mediated side effects (eg. dry cough) are avoided since ACE is still active |
| **Side effects**                              | Postural hypotension |

**Perioperative management**
- As for ACEi
### Calcium channel blockers

| Classification | I Phenylacylamines (eg. verapamil)  
|               | II Dihydropyridines (eg. the ‘-dipines’ - nifedipine, amlodipine)  
|               | III Benzothiazepines (eg. diltiazem)  
| Indications   | Hypertension, angina, dysrhythmias  
| Mode of action| • All act on L-type calcium channels present throughout the cardiovascular system  
|               | • Different classes act on the myocardium, cardiac conduction systems and vascular smooth muscle to varying degrees:  
|               |   • Dihydropyridines mainly cause peripheral vasodilation  
|               |   • Verapamil and diltiazem cause some degree of vasodilation, but have far greater cardiac effects, causing decreased myocardial contractility, slowed conduction through AV node and prolonged refractory period. They therefore have class IV antiarrhythmic properties and cause bradycardia  
| Side effects  | Ankle swelling, constipation, headache, flushing, hypotension, dizziness  

**Perioperative management**  
- Continue throughout the preoperative period  
- Available IV if unable to take orally

### Diuretics

| Classification | Thiazides eg. bendroflumethazide, chlorthalidone, metolazone  
|               | Loop diuretics eg. frusemide (furosemide), bumetanide  
|               | Potassium-sparing eg. amiloride, spironolactone  
| Indications   | Hypertension, heart failure, oedema  
| Mode of action| • Thiazides inhibit Na\(^{+}\) and K\(^{+}\) reabsorption in the early portion of the distal convoluted tubule  
|               | • Loop diuretics inhibit the co-transporter (of Na\(^{+}\), K\(^{+}\) and Cl\(^{-}\)) in the thick ascending limb of the loop of Henle  
|               | • Potassium-sparing inhibit Na\(^{+}\) reabsorption in the collecting duct (amiloride) or antagonise the action of aldosterone in the collecting duct (spironolactone)  
| Side effects  | Dehydration, hypokalaemia, postural hypotension, hyponatraemia, hyperuricaemia, gout  
|               | Loop diuretics may also cause deafness if given rapidly intravenously, especially if given with aminoglycoside antibiotics

**Perioperative management**  
- Omit dose on morning of surgery - minimises hypovolaemia, hypokalaemia and other electrolyte disturbances  
- Reintroduce postoperatively when blood pressure, hydration and urine output are adequate

### Nitrates

| eg. glyceryl trinitrate (GTN), isosorbide dinitrate (ISDN)  
| Indications | Angina, heart failure  
| Mode of action | Metabolized to nitric oxide within vascular smooth muscle cells. Nitric oxide acts via guanylate cyclase to cause vascular smooth muscle relaxation in coronary vessels and systemic veins  
| Side effects | Headache, flushing, postural hypotension, dizziness, tachycardia

**Perioperative management**  
- Continue throughout surgery  
- Consider IV or trans-dermal preparations if patient remains nil by mouth
### Anti-arrhythmics

The pharmacology of these agents is described in *(Update 11, Cardiovascular pharmacology)*.

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>Intra-op</th>
<th>Post-op</th>
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</thead>
<tbody>
<tr>
<td>Procainamide</td>
<td>Give the night before surgery</td>
<td>Use IV procainamide or lidocaine (for VT/VF prophylaxis)</td>
<td>Continue IV until able to take oral sips</td>
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<tr>
<td>Disopyramide</td>
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<td>Quinidine</td>
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<tr>
<td>Flecainide</td>
<td>Give on morning of surgery</td>
<td>Give IV if needed</td>
<td>Reinstall once stable (may need levels)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Give on morning of surgery</td>
<td>Continue IV if high risk</td>
<td>Reinstall once stable</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Give the night before surgery</td>
<td>Give IV if needed</td>
<td>Reinstall once stable</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Give on morning of surgery</td>
<td>IV verapamil can be used if needed</td>
<td>Reinstall once stable</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Give normal dose</td>
<td>Give IV if high risk</td>
<td>Reinstall once stable (may need levels)</td>
</tr>
</tbody>
</table>

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## Drugs affecting haemostasis

The decision to continue or stop these drugs is particularly difficult because there are potentially devastating effects from both continuing (increased bleeding) and stopping the drug (cardiovascular events). The balance of risks versus the benefits guides management.

## Antiplatelet drugs

| Classification | Cyclo-oxygenase inhibitors eg. aspirin  
|                | Phosphodiesterase inhibitor eg. dipyridamole  
|                | ADP binding inhibitors eg. clopidogrel, ticlodipine  
|                | Glycoprotein IIb/IIIa receptor antagonists eg. abciximab, eptifibatide, tirofiban |

| Indications | • Act to reduce primary haemostasis by decreasing platelet aggregation and inhibiting thrombus formation. Widely used in primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease. They are effective in the arterial circulation, where anticoagulants have little effect.  
|            | • Aspirin is used in the prophylaxis of MI, ischaemic stroke, transient ischaemic attacks, intermittent ischaemic claudication. Clopidogrel is an alternative  
|            | • Dipyridamole is given to some patients with prosthetic heart valves, in addition to anticoagulants. Also given with low-dose aspirin to reduce risk of recurrent stroke  
|            | • Clopidogrel often given as secondary prevention after an acute ischaemic event  
|            | • Abciximab is given as a bridging medical therapy to angioplasty or coronary artery bypass grafting, when patient has unstable angina or NSTEMI (non ST elevation MI) and is at high risk of further events |

| Mode of action | • Aspirin irreversibly antagonises cyclo-oxygenase reducing thromboxane-mediated platelet aggregation  
|               | • Dipyridamole decreases platelet adenosine uptake, thereby inhibiting adhesion to damaged vessel walls  
|               | • Clopidogrel irreversibly prevents ADP from binding to its receptor on the platelet surface thereby stopping the glycoprotein IIb/IIIa receptor converting into its active form  
|               | • Abciximab (a monoclonal antibody) binds the glycoprotein IIb/IIIa receptor, impeding platelet aggregation |

| Side effects | All can cause GI bleeding (particularly aspirin), hot flushes, tachycardia, headaches (dipyridamole), rarely neutropaenia, thrombocytopaenia (clopidogrel and glycoprotein IIb/IIIa blockers) |

## Perioperative management

Aspirin - stop for at least 7 days prior to surgery where the risks of perioperative bleeding are high (major surgery) or where the risks of even minor bleeding are significant (retinal or intracranial surgery). The risks of bleeding must be balanced against the risks of thromboembolic events, particularly in patients with unstable angina.

- It is safe to perform a subarachnoid block or insert an epidural catheter in the presence of aspirin  
- Most recommend stopping other antiplatelet drugs 7-10 days preoperatively before major surgery or regional anaesthesia. If the risks of coronary thrombosis are high this must be balanced against the benefits of performing a regional block  
- Dipyridamole should be stopped 7-10 days before surgery  
- Abciximab is generally used as a rescue medical therapy before a more permanent re-vascularisation procedure may be performed and it is usually changed to clopidogrel postoperatively
**Anticoagulants**

- eg. warfarin, heparin, and the low molecular weight heparins – tinzaparin, enoxaparin, dalteparin
- Act to inhibit secondary haemostasis and formation of the fibrin clot by interfering directly with the blood coagulation cascade

**Warfarin**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Thrombo-embolism prophylaxis – usually for atrial fibrillation, prosthetic heart valves, thrombophilia, previous thrombembolic disease</th>
</tr>
</thead>
</table>
| Mode of action | • Vitamin K antagonist. Vitamin K is an essential co-factor for the synthesis of clotting factors II, VII, IX and X and also for proteins C and S  
• Takes at least 48-72 hours to achieve its full anticoagulant effect (reflecting the half life of the clotting factors) |
| Side effects | Haemorrhage. Metabolism of warfarin is affected by systemic illness or drug interactions |

**Perioperative management**

- For patients at low risk of thromboembolism (eg. uncomplicated atrial fibrillation without prior history of thromboembolic events), warfarin should be discontinued 4-5 days before surgery. An INR (international normalized ratio) of 1.5 is generally considered safe for surgery  
- Warfarin may be continued perioperatively in certain minor operations (eg. cataract and dental surgery)  
- For other elective surgery weigh the risks and benefits of continuous anticoagulation for each patient. If anticoagulation is deemed necessary, warfarin is replaced intravenous heparin, from the time that the INR falls below the therapeuatic range for the underlying problem.  
- An infusion of heparin is started at 1000units/hour and then adjusted to keep the APTT ratio between 1.5 and 2.5  
- The heparin infusion is stopped 6 hours prior to surgery and restarted 6-12 hours after surgery, if there is no clinical evidence of bleeding. This should be continued until warfarin therapy is restarted and the INR is greater than 2.0  
- For emergency surgery, the effects of warfarin may be reversed by giving fresh frozen plasma (10-15ml/kg), or clotting factors. Intravenous vitamin K (1-2mg up to 10mg) may be used in life threatening haemorrhage, but the effects make re-anticoagulation difficult

**Unfractionated Heparin**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Prophylaxis and treatment of DVT, PE, MI, unstable angina, vaso-occlusive disease</th>
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</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Antithrombin III agonist, which binds to and potentiates antithrombin III action, causing inactivation of thrombin and other clotting factors (especially Xa)</td>
</tr>
<tr>
<td>Side effects</td>
<td>Haemorrhage, heparin-induced thrombocytopaenia (HITS)</td>
</tr>
</tbody>
</table>

**Perioperative management**

- Heparin has a much shorter half-life (1 hour) than warfarin and is often used as a substitute bridging therapy for those patients at high risk of thromboembolism undergoing surgery (see above)  
- If emergency reversal of heparin-induced haemorrhage is needed, protamine is used
Lipid-lowering drugs

**Classification**
- HMGCoA reductase inhibitors eg. the ‘-statins’ - simvastatin, atorvastatin, fluvastatin
- Anion exchange resins eg. cholestyramine
- Fibric acid derivatives eg. the ‘-fibrates’ - clofibrate, bezafibrate, ciprofibrate
- Nicotinic acid derivative eg. acipimox

**Indications**
Hyperlipidaemia, hypercholesterolaemia, patients with cardiac risk factors

**Mode of action**
Statins reversibly inhibit HMGCoA reductase, the rate-limiting enzyme in cholesterol synthesis by the liver. The liver responds by increasing its expression of lower density lipoprotein (LDL) receptors, thereby increasing its uptake of LDLs from the circulation. Also thought to decrease cardiac disease via an unknown mechanism

Cholestyramine acts by sequestering bile acids in the intestine, preventing their reabsorption and enterohepatic circulation

Fibrates stimulate the enzyme lipoprotein lipase, converting triglycerides into fatty acids and glycerol

Acipimox causes a reduction in very low density lipoproteins (VLDL) and thus LDL

**Side effects**
Generally well-tolerated, but reversible myositis, headache and GI disturbance can occur. Rhabdomyolysis is rare

**Perioperative management**
- Most lipid-lowering drugs can be continued throughout the perioperative period.
- Although manufacturers advise stopping ‘statins’ pre-operatively, it is now thought prudent to continue them in the perioperative period. Many myocardial infarcts are caused by coronary plaque rupture, thrombus formation and vessel occlusion. Statins stabilize plaques and therefore may be beneficial in preventing perioperative myocardial infarcts

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Low Molecular Weight Heparins (LMWH)

| **Indications** | As for heparin |
| **Mode of action** | More effective inhibition of factor Xa, but less effective inactivation of thrombin, compared to heparin |
| **Side effects** | Haemorrhage, reduced risk of thrombocytopaenia |

**Perioperative management**
- Used in place of heparin
- No monitoring necessary
- Last dose should be 12 hours before surgery, including those patients undergoing regional blocks (spinal or epidural)
- Protamine may be used to reverse the effects of LMWHs, although this may be less effective

In this review of perioperative prescription of cardiac medications, we have attempted to summarise the available information to provide a reference guide for daily use. The advice is not always clear-cut and the decision for each drug that a patient is taking must be considered carefully, and judged by weighing the relative risks of continuing or stopping the therapy.