Cardiovascular therapeutics

Introduction

Cardiology is an expanding area, with a strong evidence base for many of the interventions used. When prescribing for a patient with cardiovascular disease, it is essential to check the diagnosis (several drugs can be used for multiple indications but will be dosed differently) and to check the patient's drug history. When doing this, do not rely upon a previous discharge letter alone nor on a GP letter alone; always use the documents available but also ask the patient what he/she is actually taking. The patient may have varied the dosage, with or without medical advice, and it is crucial to know this to make appropriate adjustments.

This article cannot cover the detailed pathology or management of all cardiac diseases but will highlight some of the recent trends in management and give details of some of the more problematic drugs. Other drugs (diuretics, pain relief and anticoagulants) are the subject of separate articles. Thrombolytic agents and drugs used in emergency management of arrhythmias are covered by hospital protocols and advanced cardiac life support training (www.acls.net) respectively.

There are many detailed guidelines published for individual disorders (*Figure 1*).

Conditions in cardiology

Heart failure

Heart failure treatment has seen several revolutions in the last two decades. The number of patients surviving with heart failure has increased significantly, partly as a result of better treatment and partly because patients are surviving infarctions but with impaired cardiac function.

Old treatments have faded away (digoxin is now restricted in use) and previously contraindicated drugs (e.g. beta blockers) are now encouraged. It was the failure of certain drug trials with cardiac stimulants that caused a complete re-think about the processes involved in heart failure which is now seen as a syndrome that involves the over-activity of stimulatory neurohormonal systems such as the sympathetic nervous system and the renin–angiotensin system. Accordingly, the long-term management of heart failure involves damping down those systems with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers as well as relieving congestive symptoms with diuretics.

Unfortunately, when a patient is acutely unwell it may be inappropriate to introduce new or increased blockade, hence the need to be sure of the drug history. An early senior review is often required.

Ischaemic heart disease

Ischaemic heart disease, presenting as stable angina or an acute coronary syndrome including myocardial infarction, has been subject to much research and there are many trials to guide management. There are good guidelines from National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Network (SIGN), and American learned societies. Each hospital should have local protocols for the management of these conditions.

Hypertension

Hypertension is now primarily an outpatient disorder, although many inpatients will have a background of hypertension. NICE have produced guidelines for general management. One recent change is the move away from beta-blockers as first-line treatment for patients without another indication for their use, such as ischaemic heart disease, because recent data analyses suggest that they may be less effective than other options. Emphasis is now placed on an assessment of the likely role of the renin system in the aetiology of a patient's hypertension. High-renin states (for which ACE inhibitors would be a good first choice) exist more often in the young (<60 years) and in Caucasians. The elderly and black patients respond less well to ACE inhibitors and beta blockers.

Low-dose diuretics, such as bendroflumethiazide 2.5 mg daily, reduce blood pressure well in many patients without the adverse effects on serum electrolytes that higher doses have. They are also beneficial in combination with other drugs although combination with beta-blockers may worsen glycaemic control. Although it is good practice to start treatment with a single agent, most patients will require combination therapy.

Hypertensive emergencies require senior management. There is a need to balance the dangers of acute hypertension with those of lowering pressures rapidly in patients who have adjusted to higher pressures; rapid changes may induce cerebral hypoperfusion or stroke.

Patients who present with a stroke and have raised blood pressure should have their previous medication continued but new medication should not be started until the acute phase (7–10 days) is over unless a senior review indicates that there is immediate danger from the raised blood pressure. Blood pressure is often volatile in acute stroke patients and hypoperfusion may be induced by over-zealous treatment.

Arrhythmias

Arrhythmias are commonly present in sick or elderly patients, mostly as atrial fibrillation, but the management of many arrhythmias is much less dependent on

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Figure 1. Sources of guidelines for individual cardiovascular disorders.

National Institute for Health and Clinical Excellence (NICE www.nice.org.uk) – recent guidelines include interventions in Acute Coronary Syndromes, atrial fibrillation, hypertension and chronic heart failure

Scottish Intercollegiate Guideline Network (SIGN www.sign.ac.uk) – recent guidelines include aspects of coronary heart disease, chronic heart failure and risk estimation and prevention in cardiovascular disease

European Society of Cardiology (ESC www.escardio.org/knowledge/guidelines/)

drugs and is more dependent on electrical intervention (pacing, cardioversion, ablation) in specialist units. There is no good drug treatment for chronic bradyarrhythmias and pacing will be required.

Electrolyte disturbances, especially hypokalaemia, predispose to arrhythmias, and checking and correcting levels is one of the most important roles of a junior doctor.

The drug list should also be checked for precipitating causes including beta-blockers, diuretics, antidepressants and antihistamines. The latter are among many drugs that can cause a prolongation of the corrected QT interval and render the patient at risk of the dangerous ventricular arrhythmia torsades des pointes. This is most often a problem when antihistamines are combined with an antiarrhythmic such as amiodarone or with a cytochrome enzyme inhibitor such as erythromycin.

It should be remembered that all antiarrhythmic drugs are also proarrhythmic. Beta-blockers are widely used because they reduce the sympathetic drive that underlies many tachyarrhythmias and are well known and relatively safe agents. Amiodarone is also widely used because it is highly effective in many arrhythmias (and has been called cardiological Domestos) but it has many long-term adverse effects (see below). Digoxin is restricted to patients with an element of heart failure and other antiarrhythmics are restricted to specialist prescribers.

Chronic atrial fibrillation may be managed by drugs that return the patient to sinus rhythm (but these are often not successful) or that control ventricular rate. It used to be thought that rate control was inferior to rhythm control but it has now been established that most patients do better on rate control strategies, which are easier to implement and have fewer adverse effects.

Patients who have compromised circulation because of atrial fibrillation or other tachyarrhythmia may need electrical or chemical cardioversion, immediately or in a few weeks. There is a risk of clot formation, and consequent stroke, around cardioversion and local protocols for anticoagulation should be followed.

Detailed advice for some commonly-used and potentially problematic drugs follows.

Drugs in cardiology

Digoxin

Mode of action

Digoxin is a cardiac glycoside with a well-defined role in atrial tachyarrhythmias in the presence of congestive heart failure. It inhibits conduction through the atrioventricular node, thus protecting ventricles from rapid atrial rhythms.

Digoxin has a positive inotropic effect, mainly by inhibiting sodium/potassium triphosphatase (ATPase) which leads to increased intracellular calcium/sodium concentrations, which in turn leads to increased myocardial contractility. This slows sinoatrial node discharge and delays conduction through the atrioventricular node (increasing vagal and diminishing sympathetic drive).

Dosing

Digoxin takes approximately 6 hours to distribute after an oral or intravenous dose and has a half life of 24–36 hours. It can be loaded rapidly (intravenously or orally at 10 mg/kg) or orally over a longer period if there are increased risks of toxicity or reduced urgency.

Digoxin needs careful monitoring with the dose titrated according to therapeutic effect and/or plasma concentrations. Special care must be taken in patients with renal impairment including the elderly who may appear to have normal serum creatinine levels in the presence of reduced renal function. Steady state is reached in about 5 days in the presence of normal renal function.

Pharmaceutical practice points

Digoxin has variable oral absorption and a low therapeutic index. It is available in oral and intravenous dose forms, but they have different bioavailability. If converting oral to intravenous the dose should be reduced by approximately 33%. Drug interactions are relatively common (*Table 1*).

Digoxin is predominantly cleared by the renal system, hence lower maintenance doses will be required in patients with renal impairment and the elderly.

Monitoring

Monitor plasma potassium; aim to keep the level above 4 mmol/litre. Correct baseline potassium levels before starting digoxin. Toxicity may occur when plasma concentrations are within the therapeutic range, especially in the presence of hypokalaemia, hypercalcaemia, hypomagnesaemia, hypothyroidism, hypoxaemia and with acidosis. Blood samples for digoxin concentrations should be taken 6–8 hours after a dose but if this is not possible later samples are better than early ones.

Early signs of toxicity are anorexia, nausea, vomiting, diarrhoea, visual disturbances and CNS disturbances. Arrhythmias and heart block can also develop in acute toxicity.

Amiodarone

Mode of action

Amiodarone is a class 3 antiarrhythmic (prolongs the refractory period of the action potential). It is very effective but is limited by both its short-term and long-term toxicities and its pharmacokinetic profile.

Amiodarone has multiple other actions which contribute to both its antiarrhythmic and proarrhythmic potentials: non-competitive beta-blocking action (weak), some sodium-channel blocking (class 1 action) and some calcium-channel blocking (class 4).

Contraindications

The only absolute contraindication to the administration of amiodarone is allergic reaction (i.e. anaphylaxis).

Amiodarone is relatively contraindicated in pregnancy and individuals with sinus nodal bradycardia, atrioventricular block,

Table 1. Drugs which interact with digoxin

Drug	Effect
Potassium-depleting drugs (e.g. loop or thiazide diuretics)	Increased risk digoxin toxicity
Amiodarone	Increases digoxin concentrations (need to halve digoxin dose if adding amiodarone)
Alternative medicines, e.g. St John's wort (Hypericum)	Can decrease digoxin concentration

and second or third degree heart block who do not have an artificial pacemaker.

Dosing

Amiodarone needs loading over a long period (see British National Formulary for dosing guidelines). In acute tachyarrhythmias intravenous loading and maintenance infusion needs to be followed and overlapped with oral loading as the two forms exert different pharmacodynamic effects. Oral loading (over 2–3 weeks according to local policy) requires divided daily dosing because of gastrointestinal adverse effects, which are more likely in elderly patients.

Amiodarone has variable oral bioavailability (20–80%), and a very long half life (1–3 months). Aim to keep the maintenance dose low to reduce adverse effects.

Adverse effects

Adverse effects appear to be mostly dose related; however, plasma concentration monitoring seems to be of limited benefit (toxicity can occur within the therapeutic range). The extensive half life makes adverse effects slow to resolve when therapy is stopped. The maximal effects of dose changes will take 1–3 months to be seen.

Adverse effects include photosensitivity (this is very common, and patients should be warned about this), hyper-/hypothyroidism, benign corneal microdeposits (may interfere with night driving but otherwise not a problem), skin pigmentation changes, nausea or altered taste (especially at loading doses), peripheral neuropathy and sleep disturbances. Elevation of hepatic transaminases leading to liver failure, and pulmonary fibrosis or alveolitis are uncommon but severe adverse effects that may be fatal.

Monitoring

Monitor hepatic and thyroid function before starting treatment and 6-monthly throughout, and take a baseline chest X-ray.

Interactions

Amiodarone can reduce digoxin clearance (halve digoxin dose on starting amiodarone), and inhibit warfarin and phenytoin metabolism. It can increase the risk of arrhythmia when coadministered with drugs that prolong the QT interval, such as tricyclic antidepressants, some selective serotonin-re-uptake inhibitor antidepressants, clarithromycin, erythromycin, voriconazole and some antipsychotics.

Clinical practice points

Amiodarone given intravenously is incompatible with sodium chloride 0.9%, and must be infused through a large or central vein with glucose 5% via a non-PVC giving set.

ACE inhibitors and angiotensin-receptor blockers

Comparative modes of action

The action of ACE inhibitors on angiotensin-converting enzyme prevents the conversion of angiotensin I to angiotensin II and prevents bradykinin inactivation. The reduction in angiotensin II production in tissues results in relaxation of blood vessels, reduced force of cardiac contraction, reduction of the angiotensin trophic effect on cardiovascular tissues and reduced aldosterone release (subsequent to sodium loss and potassium retention). Angiotensin II may be produced by other routes and so ACE inhibitors do not prevent its action completely.

The increased kinin levels may contribute usefully to vasodilatation but may cause an irritating dry cough that leads some patients to abandon the drug.

Although angiotensin-receptor blockers have similar properties to ACE inhibitors, there are few large or long studies to compare their efficacy. Unlike ACE inhibitors they do not inhibit the breakdown of bradykinin and other kinins, but they do act as a blocker at the final receptor, regardless of the route of angiotensin II production. It is not therefore safe to assume they can be interchanged with ACE inhibitors but it is reasonable to use an angiotensin-receptor blocker when the patient has not tolerated an ACE inhibitor. There is some rationale for combining the treatments in a few patients.

Precautions

Most ACE inhibitors and angiotensin-receptor blockers are renally excreted and doses need to be reduced in renally impaired patients. They can impair renal function in their own right, especially in the presence of renal artery stenosis.

Dosing

ACE inhibitors and angiotensin-receptor blockers are used in lower doses in heart failure than in hypertension, and must be initiated much more cautiously in heart failure.

The most notable side effects are first dose hypotension (especially in elderly patients and heart failure), skin rashes and rarely angioedema (early or delayed onset). Patients should be appropriately counselled regarding hypotensive risks when initiating and increasing dose. It may be appropriate to give initial doses at bedtime if the patient is unlikely to need to get out of bed until normal waking hours. Antihypertensive therapy should revert to morning dosing once treatment is stabilized.

Monitoring

Baseline electrolytes should be checked 1–2 weeks post initiation of therapy and with each dose increment. Check for renal impairment on initiation (patients may have previously unsuspected renal artery stenosis).

Interactions

Both classes are associated with increased plasma potassium levels, so one must beware of accumulation with potassium-sparing diuretics or potassium supplementation.

There is an increased risk of renal failure if used in combination with diuretics and non-steroidal anti-inflammatory drugs.

Beta blockers

Mode of action

This class has a wide range of actions and indications, including hypertension, angina, heart failure and arrhythmias.

These drugs competitively block beta receptors in the heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain and liver. Beta-1 receptors are relatively cardio-selective but although some drugs are described as selective for these receptors, no drug is entirely specific.

Contraindications

Reversible airways disease (e.g. asthma – in particular brittle asthma) is usually a contraindication. Chronic obstructive pulmonary disease may not be a contraindication but does require caution in case a significant component is reversible.

Peripheral vascular disease requires caution (although a trial of a beta-1 selective agent may prove less problematic).

Interactions
Avoid combination with verapamil because of the risk of severe bradycardia and heart block.

Clinical practice points
Beta-blockers may mask signs of acute hypoglycaemia (e.g. tachycardia and tremor) and delay recovery. They can alter lipid and glucose metabolism (again beta-1 selective agents are preferred).

Abrupt withdrawal of beta-blocker treatment can cause a rebound phenomenon which can precipitate rebound hypertension, myocardial infarction, ventricular arrhythmia or angina. The dose should be reduced gradually over 8–14 days.

Nitrates

Mode of action
These are used in stable and unstable angina and heart failure, exerting a nitric oxide-mediated vasodilatory effect (predominantly venodilatory), reducing venous return and preload to the heart and reducing myocardial oxygen requirement. Nitrates can be used for acute management or maintenance and also prophylactically for activities likely to precipitate anginal episodes.

Products
There are a number of different nitrate formulations. They can be sublingual, most commonly as glyceryl trinitrate spray, and intravenous for acute use. Immediate release or sustained release oral tablets (usually isosorbide mononitrate) and sustained release transdermal patches (glyceryl trinitrate) are used in maintenance therapy.

Adverse effects
A throbbing headache and postural hypotension (as a result of vasodilation) are the most commonly reported adverse effects. It is important to counsel patients about sitting down before using sublingual glyceryl trinitrate for acute treatment. Paracetamol may be used to relieve headache.

Interactions
Avoid sildenafil (Viagra) and similar agents in patients taking nitrates because of the risk of severe hypotension.

Clinical practice points
A common issue across all nitrate treatments is the necessity for asymmetric dosing to prevent the development of tolerance. A 'nitrate-free' period each day (at least 14 hours between doses of isosorbide mononitrate tablets) should be arranged by, for example, dosing at 8am and 2pm. Tolerance can develop quickly and lead not only to withdrawal or rebound symptoms in the absence of the drug, but to a loss of beneficial response. Patches are usually applied at breakfast and removed at bedtime (unless the patient usually experiences symptoms more frequently overnight). Patients with allergies to adhesives may be unable to use these preparations.

Antiplatelet agents

Aspirin and clopidogrel are widely used for inpatients and outpatients, and injectable agents are used in acute coronary syndromes and cardiac surgery.

Mode of action
Each one works at one of several points in the chain of events that activates platelets and causes them to aggregate in response to tissue injury. Because they work at different points they may be used separately or in combination. Antiplatelet agents are used particularly in arterial disease, where anticoagulants are less effective.

Products
Aspirin is available in 300 mg and 75 mg (incorrectly called 'junior', 'baby' or 'paediatric') tablets. Aspirin is contraindicated in children up to 16 years because of the risk of precipitating Reye's syndrome.

Clopidogrel is available in 75 mg tablets. Dipyridamole is available as 25 mg and 100 mg tablets, 200 mg modified release tablets and as a combination product with aspirin. It is indicated for secondary prevention of ischaemic events in combination with aspirin.

Abciximab, eptifibatide and tirofiban are injectable glycoprotein IIb/IIIa antagonists.

Adverse effects
Haemorrhage is the main risk for all these agents. All are contraindicated in patients with recent severe haemorrhage or who are at risk of such.

Aspirin and clopidogrel increase the risk of gastrointestinal bleeding, dyspepsia and abdominal pain, especially in the elderly, and there is debate about the relative risk. While clopidogrel is considered to be slightly safer, the difference is small and in vulnerable patients a proton pump inhibitor may be used to prevent damage.

Interactions
Most of the clinically important interactions involve products which promote bleeding or gastrointestinal damage.

Adenosine (for management or diagnosis of arrhythmias) should not be given to patients taking dipyridamole because of increased vasodilatation.

Monitoring
Baseline clotting tests and platelet counts should be performed and repeated once therapy has started. Abciximab requires particular attention because of the frequency of immune-mediated adverse effects. (See local protocol for all aspects of dosing and monitoring.)

Clinical practice points
Aspirin and clopidogrel are dosed at 75 mg per day but a loading dose of 300 mg is given in acute coronary syndromes (including myocardial infarction) unless the patient is over 75 years (where caution is needed because of gastrointestinal effects).

Clopidogrel should be substituted for aspirin only if the patient is proven to be intolerant of low-dose aspirin.

Clopidogrel is given with aspirin for a fixed period after acute coronary syndrome, myocardial infarction or stenting procedures. Dipyridamole is also given for 2 years after the last event. Check the local policy for both drugs and, on discharge, ensure the GP is informed of the length of treatment. Aspirin will be continued for life. Gastric discomfort from aspirin should be managed with antacid treatment rather than by changing to clopidogrel.

Abciximab should only be given once to any patient, to reduce the risk of thrombocytopenia.

Statins

Mode of action
Statins are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (HMG-CoA reductase). This is a rate-limiting enzyme in the hepatic production of cholesterol and isoprenoids.

Statins reduce levels of total cholesterol and most sub-types but increase levels of high-density lipoprotein cholesterol. They are the most effective lipid-lowering agents available and are beneficial for primary and secondary prevention of coronary artery disease.

In addition to lipid lowering, statins are known to stabilize plaques, inhibit thrombus formation and reduce plasma viscosity as well as having further pleiotropic effects such as antioxidant, immunomodulatory and anti-inflammatory activity. These pleiotropic properties may well be very important in the drugs' clinical effect but they are less well characterized than the lipid-lowering properties. It is possible that the drugs may be differentiated by these effects but at present the statins are assumed to have a class effect and therefore the choice of drug depends on cost and convenience.

Dosing

Early work encouraged the use of low starting doses and upward titration but more recent studies have confirmed the safety of starting at higher doses (e.g. simvastatin 40 mg daily) unless there are drug interactions (see below). In secondary prevention of coronary artery disease the drugs are used without regard to the patient's serum cholesterol level; the assumption is that a reduction will be good, whatever the starting value. The same is not necessarily true in primary prevention where the risk–benefit ratio is different.

Doses are normally given at night to match the diurnal rhythm of cholesterol synthesis but atorvastatin can be given equally effectively in the morning.

Adverse reactions and drug interactions

Statins lead to muscle aches and abnormal liver function tests, especially elevations of serum transaminases. In a few patients the liver disturbances are clinically important (transaminase levels more than three times the upper limit of normal with or without clinical signs) and in rare cases the myopathy may develop into rhabdomyolysis. This risk is greater in the elderly, those with renal impairment or untreated hypothyroidism, and those who abuse alcohol.

The risk is also increased if another lipid-lowering agent is co-prescribed (such cases should be referred to specialist clinics) or if there are interactions affecting the metabolism of the statin.

Atorvastatin and simvastatin are metabolized by cytochrome P4503A4 and there are many drugs which inhibit this enzyme and increase the risk of statin toxicity (*Table 2*). Simvastatin is most affected but atorvastatin should be used with caution where simvastatin is restricted or contraindicated. Grapefruit juice is also contraindicated with simvastatin.

Fluvastatin (one of the older statins) is metabolized by a different cytochrome (CYP2C9) and may be affected by ketoconazole or fluconazole.

Important clinical point

Low-dose simvastatin is now available for sale in UK pharmacies. Check for this when taking medication histories. Also enquire about the patient's compliance with statins and any general symptoms of myalgia which are early symptoms of rhabdomyolysis. **BJHM**

Conflict of interest: Dr Shakur is a council member for the Royal Society of Medicine's Research and Pharmaceutical section.

Table 2. Interactions and dose reductions with simvastatin

Drugs	Prescribing actions
HIV protease inhibitors, azole antifungals, erythromycin, clarithromycin, other potent CYP3A4 inhibitors, grapefruit juice	Avoid simvastatin
Ciclosporin, gemfibrozil, niacin	Limit simvastatin to 10 mg/day
Verapamil, amiodarone	Limit simvastatin to 20 mg/day
Diltiazem	Limit simvastatin to 40 mg/day

Atorvastatin should be used very cautiously wherever simvastatin is restricted. Pravastatin is generally safe but levels are known to rise with some of these interacting drugs so caution should be exercised. Monitor serum transaminase and creatine kinase levels.

KEY POINTS

- Guidelines abound for cardiology and are updated frequently. Check the websites listed.
- Polytherapy is almost universal. Make sure patients know what they are to take and why they are to take it. Make treatments as simple as possible.
- Check with the patient what dose of medication he/she is actually taking – it may well differ from what is on the label or the last hospital prescription.