**Michael Sampson**

**Antiarrhythmic drugs. Part 3: rate control drugs**

**British Journal of Cardiac Nursing [2019] 14(11)1–11.** [**https://doi.org/10.12968/bjca.2019.0079**](https://doi.org/10.12968/bjca.2019.0079)

|  |
| --- |
| *This is the accepted manuscript version of a published work that appeared in final form in the British Journal of Cardiac Nursing, copyright (c) MA Healthcare, after technical editing by the publisher. To access the final edited and published work see* <https://www.magonlinelibrary.com/doi/abs/10.12968/bjca.2019.0079>. *Originally published November 2019.*  |

**Abstract**

Rate control drugs are used to reduce the ventricular rate during atrial arrhythmias and are widely used in both primary and secondary care. In this final instalment of a three-part series, we evaluate three commonly used rate control agents; bisoprolol, diltiazem, and digoxin. Of these, bisoprolol has the widest range of indications as it is also used in the prevention of ventricular arrhythmias. It has the best safety profile of the three drugs due to its combined renal and hepatic excretion. Diltiazem and digoxin have a narrower range of use, and carry a greater risk of toxicity due to a reliance on either hepatic or renal elimination. These issues are explored alongside consideration of evidence base for use, dosing, and interactions. The focus is on information that supports safe prescribing and administration.

**Key words**

Rate control; beta-blockers; bisoprolol; digoxin; diltiazem; verapamil

**Introduction**

In the first two articles of this three-part series, we examined the principles of antiarrhythmic drug therapy and took a detailed look at three of the most commonly used rhythm control drugs. In this final instalment, we turn our attention to the rate control drugs.

Rate control agents include beta-blockers, the non-dihydropyridine calcium channel blockers, and digoxin. Their principal use in arrhythmia management is to slow the ventricular response during atrial arrhythmias, although some rate control drugs also have rhythm control properties (Bennett, 2013). Like the rhythm control drugs, they are a heterogeneous group with a variety of mechanisms of action, pharmacological features and safety issues. A sound knowledge of their unique features is therefore essential to safe practice.

In this article we examine three of the most commonly used rate control drugs in more detail; bisoprolol, diltiazem and digoxin. As with previous articles in the series, the focus will be on establishing the rationale for drug use, and outlining the information that supports safe prescribing and administration.

**Bisopolol**

**Overview and indications**

Bisoprolol is a beta-adrenergic receptor blocker, more commonly referred to as a beta-blocker (Joint Formulary Committee, 2019). Beta blockers exert their effects by occupying beta-adrenergic receptors on the cell membrane (Fogoros and Mandola, 2018). This prevents adrenaline and noradrenaline from binding to the cell, reducing the effects of the sympathetic nervous system and the “fight or flight” response (Klabunde, 2012). There are two main subtypes of beta-adrenergic receptor; beta 1 receptors and beta 2 receptors. Although many organs contain both subtypes, beta 1 receptors are more common in the heart, GI tract, kidney, brain, and fat cells. Beta 2 receptors predominate in the bronchi, peripheral vasculature, pancreas, uterus and thyroid (Borchard 1998).  Beta-blockers bind to both receptor types.

In the heart, blockade of beta 1 receptors reduces automaticity, electrical conduction speed and contractility (Fogoros and Mandrola, 2018). Beta blockers therefore slow the heart rate, reduce conduction speed through the AV node, and lower cardiac output. Their effect on beta 1 receptors in the kidneys reduces renin production, targeting the start of the renin-angiotensin-aldosterone cascade; this reduces vasoconstriction and fluid retention, lowering the blood pressure (Klabunde, 2012). These effects make beta-blockers useful agents in the management of angina, heart failure, hypertension and arrhythmias (Joint Formulary Committee, 2019).

The effect of beta-blockers on beta 2 receptors is responsible for a range of extra-cardiac effects that may be undesirable, for example bronchospasm (Bain, 2005). Unlike first generation beta-blockers such as propranolol, bisoprolol is cardioselective, meaning that it has a higher affinity for beta 1 receptors than beta 2 receptors (Baker, 2005). This reduces the risk of extra-cardiac side effects but does not eliminate it entirely (Joint Formulary Committee, 2019). It is also dose dependent, with cardioselectivity declining as the dose increases. Unlike some second-generation beta blockers, bisoprolol has no additional vasodilatory properties (Mansour and Kaul, 2009).

In atrial arrhythmias, bisoprolol is used to slow AV node conduction and therefore ventricular rate (Bennett, 2013). This can relieve symptoms such as palpitations, breathlessness and fatigue, and reduces the risk of tachycardia-induced cardiomyopathy (Van Gelder et al, 2016). The aim is to control symptoms, enable exercise, and preserve left ventricular (LV) function, without inducing bradycardia. Guidelines suggest a target heart rate of less than 110 beats per minute at rest for most individuals; a lower heart rate may be needed if symptoms persist, LV function declines, or biventricular pacing is used (Kirchof et al, 2016). Ambulatory monitoring is usually required to assess the response to treatment (Bennett, 2013).

Rate control with beta-blockers may be a standalone treatment, or may complement attempts to control the rhythm using drugs, DC cardioversion or catheter ablation (National Institute for Health and Care Excellence [NICE], 2014). Beta blockers have a limited effect in preventing atrial arrhythmias on their own, although they are more effective when episodes have clear adrenergic triggers such as pain, anxiety or exercise (Grandi and Ripplinger, 2019). They have proven efficacy in reducing atrial fibrillation (AF) following cardiac surgery, and can be used to terminate re-entrant supraventricular tachycardia (SVT) (Frendl et al, 2014; Page et al, 2015).

In the management of ventricular arrhythmia, beta blockers are considered the cornerstone of drug therapy (Priori et al, 2015). They exert a greater rhythm control effect in the abnormal myocardium due to factors including reduced myocardial work and ischaemia, blockade of elevated sympathetic activity, and prevention of adverse ventricular remodelling (Grandi and Ripplinger, 2019). They also have specific antiarrhythmic effects including suppression of abnormal automaticity, and prolongation of the ventricular effective refractory period. Beta blockers reduce sudden arrhythmic death in chronic heart failure (CHF) and following myocardial infarction (MI), and are first line therapies in these conditions (Priori et al, 2015). They also reduce ventricular arrhythmia in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia; the non-selective beta blockers nadolol and propranolol are preferred for this indication because of greater efficacy (Ackerman et al, 2017).

**Dosing and administration**

Bisoprolol has a plasma elimination half-life of 10-12 hours, allowing once daily dosing (Accord Healthcare Ltd, 2019). The drug is well absorbed from the gut with or without food, and undergoes very little first pass metabolism, resulting in a bioavailability of 90%. The usual starting dose is 1.25mg with weekly up titration as required (Joint Formulary Committee, 2019).

In atrial arrhythmias, the dose should be increased until adequate control of the heart rate is achieved, assuming that intolerance or complications do not occur. In the prevention of ventricular arrhythmia in CHF or following MI, the dose of bisoprolol should be increased incrementally, aiming for as near to the maximum dose as the patient can tolerate (NICE 2018; NICE 2013). Careful assessment is required during dose titration as side effects, bradycardia, hypotension or AV block may prevent higher doses from being reached.

The maximum licensed dose of bisoprolol is 10mg daily in CHF, although up to 20mg can be given for other indications (Joint Formulary Committee, 2019).

**Safety**

Because of its negative inotropic effects, bisoprolol is contraindicated in unstable heart failure, cardiogenic shock and symptomatic hypotension (Accord Healthcare Ltd, 2019). Following MI or in newly diagnosed CHF, the drug should only be started once haemodynamic stability has been achieved. In common with other antiarrhythmic drugs, bisoprolol must not be used if there is significant conduction system disease unless a pacemaker is present. It is also contraindicated in untreated pheochromocytoma and metabolic acidosis (Joint Formulary Committee, 2019).

Bisoprolol is usually well tolerated in people with chronic obstructive pulmonary disease, however caution is advised in asthma because of the potential for bronchospasm (Joint Formulary Committee, 2019). Caution is also advised in individuals with peripheral vascular disease as it may decrease peripheral blood flow; it is contraindicated if there is severe occlusive arterial disease or Raynaud’s syndrome. Beta blockers can affect glycaemic control and mask the signs of hypoglycaemia; care is therefore required in diabetes (Accord Healthcare Ltd, 2019).

Bisoprolol should not be stopped suddenly, especially in coronary heart disease as this can produce rebound ischaemia; gradual dose reduction over a number of days is recommended (Bain, 2018). The drug should be continued during surgery whenever possible. Common side effects include fatigue, dizziness, headache, cold hands and feet and gastrointestinal disturbances (Fogoros and Mandrola, 2018).

Bisoprolol is eliminated by two routes; 50% is converted to inactive metabolites by the liver prior to renal excretion, while the other half is excreted unchanged by the kidneys (Accord Healthcare Ltd, 2019). Because of this dual elimination, dose reduction is not required if there is renal or hepatic impairment, and there are no drugs interactions caused by shared hepatic pathways. Combined with a broad therapeutic index, these features give bisoprolol a good safety profile (Bain, 2018). Important drug interactions do occur because of additive effects, and these must be taken into account - see table 1 for more details.

|  |  |  |
| --- | --- | --- |
| **Drug** | **Effect of co-administration** | **Recommendation** |
| Verapamil (and to a lesser extent diltiazem) | Additive effects on inotropy and AV conduction: increased risk of hypotension, bradycardia, AV block and heart failure. | Concomitant use not recommended |
| Centrally acting antihypertensives, e.g. clonidine, methyldopa, moxonodine, rilmenidine | Additive effect on sympathetic tone: increased risk of bradycardia, hypotension, heart failure. | Concomitant use not recommended |
| Class I antiarrhythmic drugs, e.g. flecainide | Additive effects on inotropy and AV conduction: increased risk of hypotension, bradycardia and AV block. | Concomitant use not recommended in heart failure; use with caution in angina and hypertension |
| Antihypertensives and drugs with blood pressure lowering potential, e.g. tricyclic antidepressants, barbiturates, phenothiazines | Additive effects on blood pressure; increased risk of hypotension | Use with caution |
| Class III antiarrhythmics, e.g. amiodarone | Additive effect on AV conduction: increased risk of bradycardia and AV block. | Use with caution |
| Topical beta blockers e.g. timolol eye drops | Additive effects possible | Use with caution |
| Digoxin, parasympathomimetic drugs | Additive effect on AV conduction: increased risk of bradycardia and AV block. | Use with caution |
| Insulin and hypoglycaemic agents | May increase effects and mask signs of hypoglycaemia | Use with caution |

**Table 1. Drugs with important additive effects to bisoprolol (Accord Healthcare Ltd, 2019)**

**Diltiazem**

**Overview and indications**

Diltiazem is one of a heterogeneous group of drugs described as calcium channel blockers (Joint Formulary Committee, 2019). The group can be subdivided into two main drug types - the dihydropyridine drugs, which include amlodipine, nifedipine and nicardipine; and the non-dihydropyridine drugs, which comprise diltiazem and verapamil. All calcium channel blockers reduce the influx of calcium through voltage-gated L-type calcium channels, which are found in multiple organs including the heart, blood vessels, and gut (Abernethy and Schwartz, 1999).

In the blood vessels, reduced calcium entry causes smooth muscle relaxation and vasodilatation, lowering blood pressure and increasing coronary artery blood flow. This makes calcium channel blockers useful drugs in the management of hypertension and angina (Joint Formulary Committee, 2019).

In the heart, calcium channel blockade reduces contractility and slows the depolarisation of cells within the cardiac conduction system. This reduces the sinus rate and slows conduction through the AV node. The magnitude of these cardiac effects varies between the two groups of calcium channel blockers; the dihydropyridine drugs have little negative inotropic action, and do not affect electrical function *in vivo* (Abernethy and Schwartz, 1999).In contrast, diltiazem and verapamil have a more profound negative inotropic effect and slow depolarisation of the sinus and AV nodes (Padial et al, 2016).

The AV node slowing properties of diltiazem make it a useful drug for the rate control of atrial arrhythmias in people without significant left ventricular dysfunction (Van Gelder et al, 2016). Although the drug is not licensed for this use, it is a first-line agent for rate control in AF guidelines, alongside beta-blockers (Kirchof et al, 2016; NICE, 2014). The evidence base for its use is limited, but in a cross-over study of 60 patients with permanent AF, diltiazem controlled heart rate more effectively, both at rest and during exercise, than verapamil, metoprolol or carvedilol (Ulimoen et al, 2013). The drug was also superior in terms of symptom management. Unlike beta-blockers, diltiazem can be used safely in asthma, and may cause less fatigue (Bennett, 2013).

Diltiazem does not reduce sympathetic activity or slow conduction within the myocardium, and therefore has no intrinsic antiarrhythmic properties. It is not used in heart failure because of its negative inotropic effects (Padial et al, 2016). Although diltiazem and verapamil may supress idiopathic ventricular tachycardia, they have no role in the management of ventricular arrhythmia secondary to structural heart disease, and are not used in the prevention of sudden cardiac death (Brugada and Diez, 2010). Diltiazem and verapamil are effective alternatives to adenosine in the acute termination of re-entrant SVT; verapamil is used in this context because diltiazem is not available in intravenous form in the UK (Joint Formulary Committee, 2019).

**Dosing and administration**

Diltiazem is well-absorbed orally, however a large first-pass effect reduces bioavailability to around 40% (Accord-UK Ltd, 2018). With standard preparations, plasma half-life is only 4-8 hours, meaning that three times daily administration is required (Joint Formulary Committee, 2019). To improve adherence, modified or sustained release preparations are typically used, allowing once or twice daily dosing. In AF, twice daily dosing is commonly employed, using a sustained-release preparation such as Tildiem Retard, which has an elimination half-life of 7-8 hours (Sanofi, 2019). Preparations from different manufacturers have different pharmacokinetic profiles and are therefore not interchangeable.

Because diltiazem is not licensed for AF, manufacturers recommendations on dosing are not available (Accord-UK Ltd, 2018; Sanofi, 2019). A typical starting dose is 90mg twice daily using a sustained release preparation; this should be reduced to 60mg in the elderly, or if there is renal or hepatic impairment (Sanofi, 2019). Dosing should be guided by clinical response; as with beta-blockers, the aim is to control symptoms and enable the patient to exercise, without producing bradycardia, hypotension or intolerable side effects (Van Gelder et al, 2016).

In hypertension and angina, the maximum licensed doses of diltiazem for are 360mg and 480mg respectively (Accord-UK Ltd, 2018). Up to 360mg daily has been used in clinical studies of AF rate control, although unwanted effects were more likely at this dose (Padial et al, 2016).

**Safety**

Diltiazem should not be given if there is significant conduction system disease unless a pacemaker is present (Joint Formulary Committee, 2019). The drug is contraindicated in pregnancy and breastfeeding; congestive heart failure; severe aortic stenosis; cardiogenic shock; and severe hypotension (Sanofi, 2019). Common side effects include headache, dizziness, flushing, constipation and ankle oedema (Accord-UK Ltd, 2018).

Diltiazem is deactivated in the liver, with only 5% excreted unchanged in the urine (Abernethy and Schwartz, 1999). Despite this small renal involvement, plasma levels increase during both hepatic and renal impairment, requiring dose reduction (Sanofi, 2019). Diltiazem is primarily metabolised by CYP3A4, and also inhibits this enzyme (Accord-UK Ltd, 2018). Interactions occur when diltiazem is coadministration with drugs metabolised by, or affecting, CYP3A4. Additive effects occur with drugs that decrease blood pressure or cardiac conduction. Important interactions are outlined in table 2.

|  |  |  |
| --- | --- | --- |
| **Drug** | **Effect of co-administration** | **Recommendation** |
| Alpha antagonists, nitrates | Additive hypotensive effect | Use with caution, monitor blood pressure. |
| Amiodarone | Additive effect on AV conduction: increased risk of bradycardia, AV block. | Use with caution – close supervision and ECG monitoring |
| Anti-H2 agents (cimetidine, ranitidine) | Increase in diltiazem plasma levels | Careful monitoring and dose reduction if necessary |
| Atorvastatin, simvastatin | Increased statin plasma levels; muscle toxicity possible | Change to a statin not metabolised by CYP3A4, e.g. pravastatin, rosuvastatin |
| Beta blockers | Additive effects on cardiac conduction and inotropy – increased risk of bradycardia, AV block, heart failure | Use with caution – close supervision and ECG monitoring  |
| Carbamazepine | Increased plasma levels of carbamazepine | Check plasma levels and adjust dose if necessary |
| Ciclosporin | Increase in ciclosporin plasma levels | Use reduced dose of ciclosporin and monitor plasma levels and renal function. |
| Dantrolene | Ventricular fibrillation when dantrolene coadministered with verapamil. | Concomitant use contraindicated |
| Digoxin | Additive effect on AV conduction: increased risk of bradycardia and AV block. Increased digoxin plasma level. | Use with caution – close supervision and ECG monitoring  |
| Ivabradine | Additive effect on sinus rate – risk of significant bradycardia | Concomitant use contraindicated |
| Lithium | Increased risk of lithium-induced neurotoxicity | Use with caution |
| Rifampicin | May decrease plasma levels of diltiazem | Monitor rate control |
| Theophylline | Increase in circulating theophylline levels | Use with caution |

**Table 2. Important drug interactions with diltiazem (Accord-UK Ltd, 2018)**

**Digoxin**

**Overview and indications**

Digoxin is one of the oldest cardiovascular medicines. The drug is extracted from the Foxglove plant *digitalis lanata,* which has been used for centuries in traditional remedies for “dropsy”, an archaic term for oedema (Stucky and Goldberger, 2015). In the 18th century, William Withering investigated the properties of digitalis, publishing a paper on its clinical use in 1785. From then until the mid-twentieth century, digitalis preparations were the only effective drug therapy for heart failure and AF; digoxin, the pharmaceutical compound prepared from the digitalis plant, continues to be used in these two conditions, although its use has declined in recent years (Wyse, 2014).

Digoxin binds to the sodium-potassium pump in the cell membrane, occupying the receptor site for potassium (Stucky and Goldberger, 2015). Inhibition of the pump causes an increase in intracellular sodium; this affects the sodium-calcium exchange mechanism, resulting in increased levels of intracellular calcium. In the cardiac myocyte, increased calcium levels produce a positive inotropic effect. The same mechanism in nerve cells increases parasympathetic tone, slowing sinus node activity and conduction through the AV node (Accord-UK Ltd, 2019). This reduces the heart rate during sinus rhythm and slows the ventricular response to atrial tachyarrhythmias.

The positive inotropic effects of digoxin can be useful in chronic heart failure, although its use is no longer recommended until first- and second-line therapies have been optimised (Ponikowski et al, 2016). In the DIG study, a large randomised controlled trial of heart failure patients, digoxin had a neutral effect on mortality when compared to placebo, but reduced hospitalisation for heart failure by 28% (Digitalis Investigation Group, 1997).

The effect of digoxin on AV node conduction is widely exploited in the rate control of atrial arrhythmias, in particular AF (Kirchof et al, 2016). As with heart failure, other drugs are considered first-line (beta blockers and non-dihydropyridine calcium channel blockers) however digoxin can be a useful adjunct to these agents. The use of digoxin as monotherapy is not recommended unless the patient is sedentary, as it does not control the heart rate during exercise (Van Gelder et al, 2016). Digoxin has no intrinsic antiarrhythmic activity, and has no additional indications in arrhythmia management.

**Dosing and administration**

Although digoxin can be given intravenously, its predominant use is in long term oral therapy. Typical doses are 125 – 250micrograms once daily, although smaller doses may be required in elderly patients and in heart failure; 62.5 microgram tablets are available (Joint Formulary Committee, 2019).

Peak plasma levels are reached 2-6 hours after oral administration; however, the drug has a large volume of distribution so it takes some days to achieve steady state plasma levels (Accord-UK Ltd, 2019). A more rapid clinical response can be achieved by oral loading, for example 0.75 to 1.5mg over 24 hours in divided doses (Joint Formulary Committee, 2019). Absorption is slowed when digoxin is taken with food, but bioavailability is unaffected at around 63% (Accord-UK Ltd, 2019).

Although a small fraction of digoxin is metabolised in the liver, the majority is excreted unchanged by the kidneys; the dose should therefore be reduced when renal function is impaired. Elimination half-life in people with normal renal function is 30-40 hours (Accord-UK Ltd, 2019).

**Safety**

Although digoxin is a useful rate control agent, a number of safety issues affect its use. These include a risk of drug toxicity, concerns about increased mortality, and multiple interactions.

Digoxin has a narrow therapeutic index, meaning that toxic effects can develop rapidly if over-dosing or drug accumulation occurs (Bennett, 2013). Risk factors for toxicity include renal impairment and the coadministration of drugs that reduce digoxin clearance, for example amiodarone or verapamil (Accord-UK Ltd, 2019). Toxicity is also more likely when there is hypokalaemia because the drug competes with potassium for binding sites on the sodium-potassium pump (Klabunde, 2012). People with heart failure are a high-risk group for digoxin toxicity because they often have impaired renal function, and are frequently treated with diuretics, which can cause hypokalaemia (Wang et al, 2010).

The symptoms of digoxin toxicity are non-specific and include fatigue, nausea, weight loss, headache and confusion (Stucky and Goldberger, 2015). As serum levels increase, xanthopsia, a yellowing of the vision, may occur. This is commonly known as the “Van Gogh” effect after the famous painter. Van Gogh was treated with digitalis compounds, and it has been speculated that his “yellow-period” work was influenced by drug toxicity. Digoxin toxicity is associated with arrhythmia development including frequent ectopic beats, atrial tachycardia with 2:1 AV block, and junctional rhythms. Ventricular tachycardia can also occur, which can cause cardiac arrest (Bennett, 2013).

Because of the risk of toxicity and proarrhythmia, regular blood tests for renal function and plasma digoxin levels are recommended in people taking digoxin (Accord-UK Ltd, 2016). Toxicity is more likely at plasma concentrations above 2.0ng/ml, but can occur at lower concentrations (Stucky and Goldberger, 2015). Guidance from the European Society of cardiology recommends a target serum digoxin level of 0.5–0.9 ng/mL (Kirchof et al, 2016). Blood for digoxin levels should be taken at least six hours after the last dose of the drug (Accord-UK Ltd, 2016).

Increased mortality in patients taking digoxin has been debated for many years (Wyse, 2014). Although this was not seen in the DIG trial of heart failure patients, subsequent studies of people with AF have demonstrated a higher death rate in individuals taking digoxin (Wyse, 2014). These trials were mainly retrospective cohort studies, and therefore at risk of bias. Ziff et al (2015) perfomed a meta-analysis of the available data, concluding that there was a neutral effect on mortality in randomised controlled trails, although these were all of patients with heart failure. Considerable prescription bias was found in the retrospective studies of AF patients; individuals taking digoxin were older, sicker and more likely to be taking diuretics and antiarrhythmic drugs. Ziff et al (2015) concluded that the increase in mortality was probably due to confounding, and not the effect of digoxin. Other authors have pointed to data linking increased mortality with higher serum digoxin levels, suggesting that any excess mortality risk might be mitigated by careful dosing and monitoring of drug levels (Lopes et al, 2018; Wyse, 2014).

Digoxin is contraindicated in significant conduction system disease (unless a pacemaker is present), myocarditis, Wolff-Parkinson-White syndrome, and ventricular arrhythmias (Joint Formulary Committee, 2019). The drug has multiple interactions; readers are referred to manufacturer’s guidance (Accord-UK Ltd, 2019). Among those most relevant to cardiac nurses are interactions with other rate control drugs, which result in additive effects on heart rate and AV conduction (Bennett, 2013). ACE inhibitors, amiodarone, angiotensin receptors blockers, atorvastatin and calcium channels blockers may all increase digoxin plasma levels. Diuretics cause electrolyte depletion, increasing the risk of digoxin toxicity (Accord-UK Ltd, 2019).

**Conclusion**

The rate control drugs are a diverse group with various mechanisms of action, pharmacological properties, and safety profiles. Bisoprolol has the widest range of indications, being useful in both atrial and ventricular arrhythmia, and has a good safety profile if additive effects with other cardiovascular drugs are taken into account. Diltiazem has a narrower range of use, but is an effective alternative in the rate control of AF, especially in patients with asthma or intolerance to beta-blockers. Digoxin is largely used as an adjunct as it fails to control heart rate during exercise. The drug suffers from a narrow therapeutic index, multiple interactions, and renal excretion. This results in a risk of toxicity, which can produce life-threatening arrhythmia. Some studies have linked the drug to an increase in mortality, although there is no clear consensus on this issue.

All medicines have the potential for adverse events, especially if they are used without adequate assessment or monitoring of the patient. Antiarrhythmic drugs can produce life threatening complications, so an understanding of their uses, pharmacology, and interactions is especially important. This series has highlighted the key issues in the use of these drugs, and described six commonly used drugs in detail. Although important safety information has been highlighted, clinicians should augment this with their own investigation of product literature, especially when prescribing.

**Key points**

* Bisoprolol, diltiazem and digoxin are useful drugs in the management of heart rate during atrial arrhythmia.
* Bisoprolol has additional indications in the management of ventricular arrhythmia, and confers a mortality benefit in chronic heart failure and following myocardial infarction. It has a broad therapeutic index, with few interactions, making it a relatively safe drug providing additive effects are taken into account.
* Diltiazem is a useful alternative in the rate control of atrial arrhythmia, although it has no significant place in the management of ventricular arrhythmia. Unlike bisoprolol, it can be given to patients with asthma, but suffers from more interactions due to its hepatic elimination. Diltiazem is contraindicated in heart failure because of its negative inotropic effects.
* Digoxin is a second line drug in rate control, and can be a useful adjunct in heart failure. It does not control heart rate during exercise, so is generally used in conjunction with a beta blocker or diltiazem. There is a risk of drug toxicity that increases in renal impairment and hypokalaemia - monitoring of renal function and serum digoxin levels are therefore important aspects of safe management.
* Antiarrhythmic drugs have the potential for adverse events, especially if they are used unwisely or without sufficient assessment or follow up. Understanding the key features of each drug, its recommended uses, and the potential for interaction with other medicines are important aspects of ensuring that antiarrhythmic drug therapy is delivered safely.

**CPD questions**

1. Rate control agents often produce side effects such as fatigue and breathlessness (beta blockers) and ankle swelling (diltiazem). How would you identify these as unwanted drug effects, rather than symptoms of the patients underlying heart problem?
2. How would you monitor the effect of rate control agents on heart rate? What range is desirable, and what problems should you be looking out for?
3. Digoxin often produces characteristic ST depression on the 12-lead ECG. Would you recognise these changes? What effect might they have on the diagnosis of acute myocardial ischaemia?

**References**

Abernethy DR, Schwartz JB (1999) Calcium-antagonist drugs, *New England Journal of Medicine*,

341(19), 1447-57.

Accord Healthcare Ltd (2019*) Summary of product characteristics: bisoprolol 2.5mg film-coated*

*tablet*, <https://www.medicines.org.uk/emc/product/6126/smpc> accessed 09/07/2019.

Accord-UK Ltd (2018) *Summary of product characteristics: Diltiazem Hydrochloride Tablets 60mg*

*(pack size 84),* [https://www.medicines.org.uk/emc/product/5774/smpc accessed 16/07/2019](https://www.medicines.org.uk/emc/product/5774/smpc%20accessed%2016/07/2019)

Accord-UK Ltd (2019) *Summary of product characteristics: Digoxin tablet BP 125 micrograms,*

<https://www.medicines.org.uk/emc/product/5772/smpc>accessed 17/07/2019

Ackerman MJ, Priori SG, Dubin AM, Kowey P, Linker NJ, Slotwiner D, Triedman J, Van Hare GF, Gold

MR (2017) Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic

ventricular tachycardia: Are all beta-blockers equivalent? *Heart Rhythm*. 14(1):e41-4.

Antzelevitch C, Burashnikov A. (2011) Overview of basic mechanisms of cardiac arrhythmia. *Cardiac Electrophysiology Clinics*. 3(1):23-45.

Bain A (2018) Beta-blocker use in cardiovascular disease, *British Journal of Cardiac Nursing*, 13(10):491-7.

Baker JG (2005) The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and

beta3 adrenoceptors, *British Journal of Pharmacology*, 144, 317-322.

Bennett DH (2013) *Bennett’s Cardiac Arrhythmias: Practical notes on interpretation and treatment*. 8th ed. London: Hodder Arnold.

Borchard U (1998) Pharmacological properties of beta-adrenoceptor blocking drugs, *Journal of Clinical and Basic Cardiology*, 1, 5-9.

Brugada J, Diez PD (2010) How to recognise and manage idiopathic ventricular tachycardia, *E-journal of the ESC Council of Cardiology Practice*, 8 (26), <https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-8/How-to-recognise-and-manage-idiopathic-ventricular-tachycardia> accessed 16/07/2019.

Dan GA, Martinez-Rubio A, Agewall S, Boriani G, Borggrefe M, Gaita F, van Gelder I, Gorenek B, Kaski JC, Kjeldsen K, Lip GY (2018) Antiarrhythmic drugs–clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace.* Feb 9.

Digitalis Investigation Group (1997) The effect of digoxin on mortality and morbidity in patients with heart failure, *New England Journal of Medicine*, 336:525–533.

Fogoros RN, Mandrola JM (2018) *Fogoros' electrophysiologic testing*. 6th ed. Oxford: Wiley Blackwell; 2018.

Frendl G, Sodickson AC, Chung MK, Waldo AL, Gersh BJ, Tisdale JE, Calkins H, Aranki S, Kaneko T,

Cassivi S, Smith SC, Darbar D, Wee JO, Waddell TK, Amar D, Adler D (2014) 2014 AATS guidelines for

the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical

procedures, *Journal of Thoracic and Cardiovascular Surgery*, 148:e153-93

Garcia TB (2015) *12-lead ECG: The Art of Interpretation.*  2nd Edition. Burlington, Ma : Jones and Bartlett

Grandi E, Ripplinger CM (2019) Antiarrhythmic mechanisms of beta blocker therapy, *Pharmacological Research, 146,* 104274. doi.org/10.1016/j.phrs.2019.104274

Joint Formulary Committee (2019) *British National Formulary*, 77th edition, London: BMJ Group and Pharmaceutical Press.

Kirchhof P, Benussi S, Kotecha D et al (2016) ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, *European Heart Journal*, 37, 2893–2962.

Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, Ridefelt P, Lawrence JH, De Caterina R, Vinereanu D, Hanna M (2018) Digoxin and mortality in patients with atrial fibrillation. *Journal of the American College of Cardiology*, 71(10):1063-74.

Mansoor AH, Kaul U (2009) Beta-blockers in cardiovascular medicine, *Journal of the Association of Physicians of India*, 57:7-12.

National Institute for Health and Care Excellence (2013) *Myocardial infarction: cardiac*

*rehabilitation and prevention of further cardiovascular disease. NICE clinical guideline CG172.*

Available at <https://www.nice.org.uk/guidance/cg172>

National Institute for Health and Care Excellence (2014) *Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 180.* Available at <https://www.nice.org.uk/guidance/cg180>

National Institute for Health and Care Excellence (2018) *Chronic heart failure in adults: diagnosis and management. NICE guideline NG106*. Available at <https://www.nice.org.uk/guidance/ng106>

Padial LR, Baron-Esquivias G, Madrid AH, Martín DM, Pallares-Carratala V, de la Sierra A (2016) Clinical experience with diltiazem in the treatment of cardiovascular diseases, *Cardiology and Therapy*, 5(1):75-82.

Page RL, Joglar JA, Halperin JL & Levine GN (2015) 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia, *Circulation*, <http://dx.doi.org/10.1016/j.hrthm.2015.09.019>

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González‐Juanatey JR, Harjola VP, Jankowska EA, Jessup M (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, *European Journal of Heart Failure,* 18(8):891-975.

Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, Elliott PM, Fitzsimons

D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N,

Norekva TM, Spaulding C, Van Veldhuisen DJ (2015) 2015 ESC Guidelines for the management of

patients with ventricular Arrhythmias and the prevention of sudden cardiac death: The Task Force

for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac

Death of the European Society of Cardiology (ESC), *European Heart Journal*, 36, 2793–2867.

Prichard BN (1987) Bisoprolol: a new beta-adrenoceptor blocking drug, *European Heart Journal*,

8(suppl\_M):121-9.

Sanofi (2019) *Summary of product characteristics: Tildiem Retard 90mg Prolonged-Release Tablets,* [https://www.medicines.org.uk/emc/product/4970/smpc accessed 16/07/2019](https://www.medicines.org.uk/emc/product/4970/smpc%20accessed%2016/07/2019)

Stucky MA, Goldberger ZD (2015) Digoxin: its role in contemporary medicine, *Postgraduate Medical Journal*, 91(1079):514-8.

Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A (2013) Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation, *American Journal of Cardiology,* 111(2):225-30.

Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B (2016) Rate control in atrial fibrillation*. The Lancet*. 388(10046):818-28.

Wang MT, Su CY, Chan AL, Lian PW, Leu HB, Hsu YJ (2010) Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population‐based study, *British Journal of Clinical Pharmacology*, 70(2):258-67.

Wyse DG (2014) Death and digoxin: stop me if you've heard this one before, *Canadian Journal of*

*Cardiology*, 30(10):1145-7.

Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D (2015)

Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled

trial data, *BMJ,* 351:h4451.