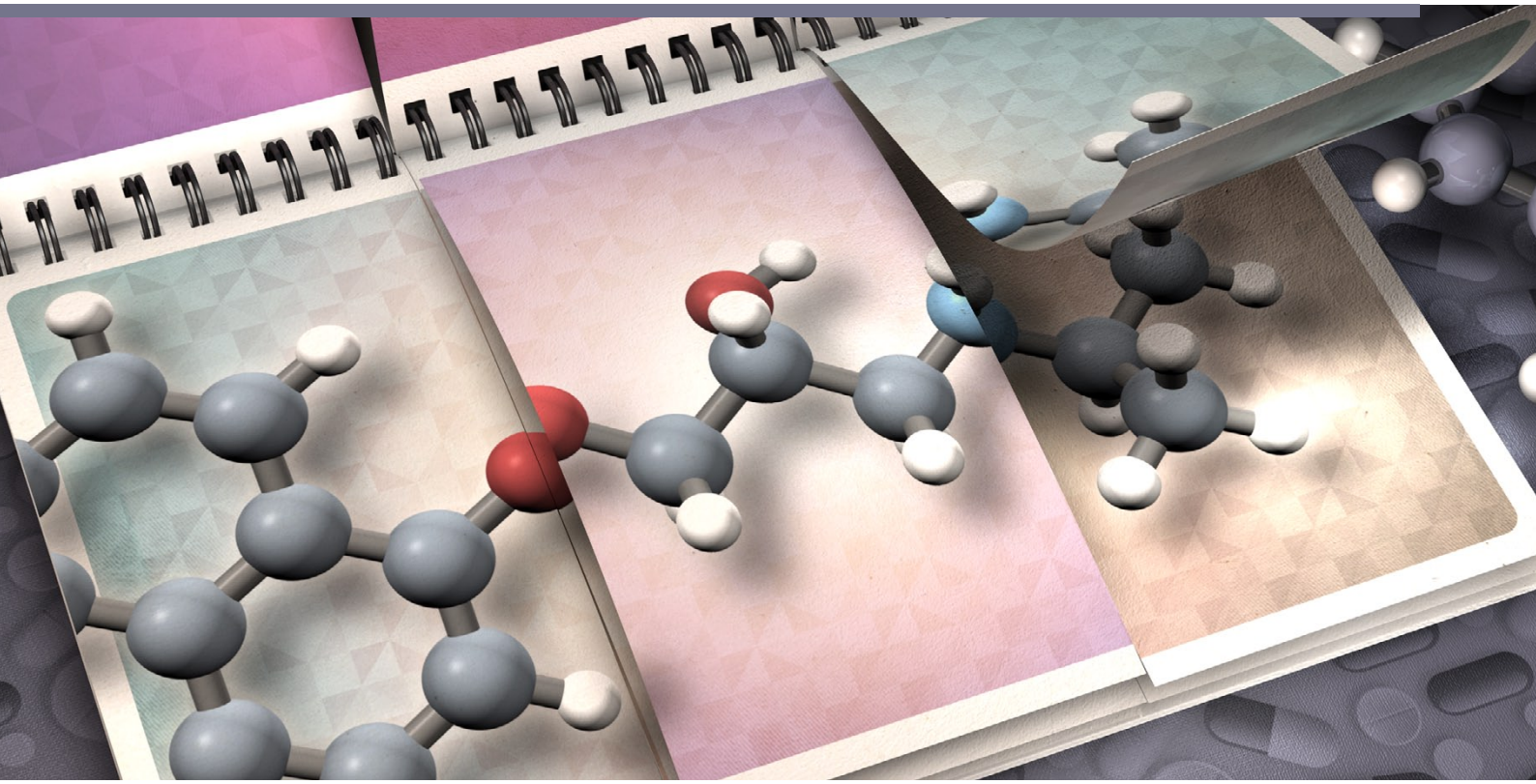

Beta-blockers for cardiovascular conditions: one size does not fit all patients

Metoprolol succinate accounts for almost three-quarters of the beta-blockers dispensed in New Zealand. There is, however, little evidence to support the systematic use of metoprolol succinate over other medicines in this class. Prescribers are encouraged to use the pharmacological diversity of beta-blockers and the clinical characteristics of patients to individualise treatment and optimise care.

KEY PRACTICE POINTS:

- Beta-blockers are a diverse group of medicines and prescribers should consider their different properties, along with the presence of co-morbidities, to individualise care for patients with cardiovascular conditions
- When a beta-blocker is initiated, a slow upwards titration of dose is recommended to minimise adverse effects. Beta-blockers should also be withdrawn slowly, ideally over several months, to prevent rebound symptoms such as resting tachycardia.
- From 6-12 months onwards post-myocardial infarction, consider withdrawing beta-blockers for patients without heart failure or arrhythmias, if re-vascularisation has occurred
- Bisoprolol is an alternative to metoprolol succinate in many cases; both are once-daily cardioselective beta-blockers that are less likely to cause fatigue and cold extremities than non-specific beta-blockers and are often preferred for patients with co-existing chronic obstructive pulmonary disorder (COPD) because they cause less bronchoconstriction

Metoprolol succinate is the most frequently prescribed beta-blocker in New Zealand

In 2016, 325 000 people received a beta-blocker from a community pharmacy in New Zealand:[1]

- 72% were prescribed metoprolol succinate; the seventh most prescribed medicine in New Zealand
- 7% were prescribed bisoprolol
- 5% were prescribed atenolol
- 4% were prescribed carvedilol or propanolol

This pattern of prescribing is different to other countries, such as Australia where less than 5% of patients are prescribed metoprolol succinate.[2]

Why is metoprolol succinate prescribed so widely?

It is likely that metoprolol succinate is the beta-blocker of choice among New Zealand prescribers because it has a wide range of indications, i.e. angina, arrhythmia, heart failure, hypertension and post-myocardial infarction, it is dosed once-daily and it is cardioselective (see below). The innovator brand (Betaloc)

was also heavily marketed in New Zealand before alternative options, e.g. bisoprolol, were subsidised.

Reliance on one medicine may cause problems

The recent disruption of the supply of metoprolol succinate where dispensing was limited to fortnightly or monthly amounts highlights the risk of depending on one beta-blocker. A review of the different properties of beta-blockers, their role in different cardiovascular conditions and co-morbidities is therefore timely.

The pharmacology of beta-blockers

All beta-blockers produce competitive antagonism of beta-adrenoceptors in the autonomic nervous system.[3] This prevents the "flight or fight" response induced by adrenaline and noradrenaline.[3] It is the pharmacological differences, such as beta-adrenergic selectivity, lipid solubility and dual receptor activity, which make each beta-blocker unique. Research is ongoing into the complex ways in which these properties translate into treatment effects for patients.

Non-selective, cardioselective and vasodilating beta-blockers

Beta-blockers are classified according to their adrenoceptor binding affinities (Table 1), the degree of which varies within each class.

There are three main sub-types of beta-adrenoceptors:[3]

- Beta$_1$-adrenoceptors (75%) are located in the heart
- Beta$_2$-adrenoceptors are located in vascular and bronchial smooth muscle
- Beta$_3$-adrenoceptors are located on adipocytes and are thought to be involved with fatty acid metabolism

Some beta-blockers, e.g. carvedilol, also bind to alpha-adrenoceptors and prevent contraction of vascular smooth muscle.

Non-selective beta-blockers, e.g. propanolol, block beta$_1$ and beta$_2$-adrenoceptors equally.

Cardioselective beta-blockers, e.g. atenolol, bisoprolol and metoprolol, have a greater affinity for beta$_1$-adrenoceptors and are less likely to cause constriction of airways or peripheral vasculature and are preferred in patients with respiratory disease. Bisoprolol is reported to be more cardioselective than metoprolol and atenolol.[4]

Vasodilating beta-blockers, e.g. carvedilol, reduce peripheral resistance by binding to alpha-adrenoceptors, causing vasodilation without affecting cardiac output.[3] It has been suggested that this may be preferable in patients with insulin resistance, although strong evidence of a benefit is lacking.[3] In addition to alpha$_1$-blockade, carvedilol binds non-selectively to beta$_1$ and beta$_2$-adrenoceptors.[3]

Celiprolol and pindolol have intrinsic sympathomimetic activity (ISA) and therefore simultaneously block and stimulate beta-adrenoceptors causing less bradycardia and peripheral vasoconstriction.[5] This may be desirable in patients with peripheral artery disease but less beneficial in patients with heart failure or angina.

What is the difference between metoprolol succinate and metoprolol tartrate?

At a molecular level the succinate and tartrate salts of metoprolol are very similar and the active ingredient of the two formulations is identical. The doses of metoprolol succinate and tartrate are slightly different due to the difference in weight of the two salts, but they are therapeutically equivalent, e.g. metoprolol succinate 23.75 mg is equal to metoprolol tartrate 25 mg. It is important, however, not to confuse the different formulations of metoprolol when they are prescribed. Metoprolol succinate is an oral modified-release formulation taken once daily while most formulations of metoprolol tartrate are immediate-release,* taken twice daily.

* N.B. A 200 mg modified-release form of metoprolol tartrate, taken once daily, is available fully subsidised in New Zealand.

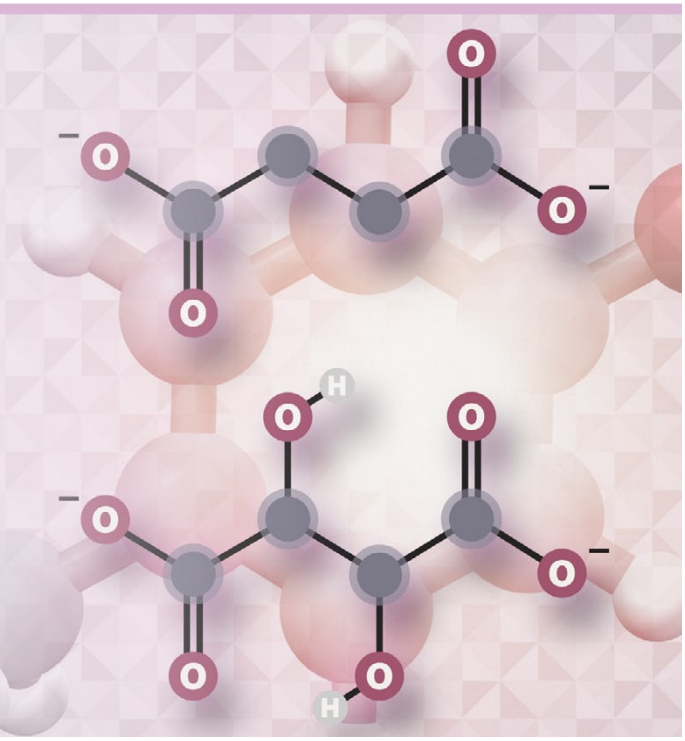

Table 1: Properties of beta-blockers subsidised in New Zealand.

Beta-blocker	Selectivity	Vasodilation	ISA*	Lipid solubility	Excretion
Atenolol	β_1 selective	No	No	Low	Renal
Bisoprolol	β_1 selective++	No	No	Yes	Renal / hepatic
Carvedilol	Non-selective	Yes	No	Yes	Hepatic
Celiprolol	Non-selective	Mild	Yes	Low	Renal
Metoprolol	β_1 selective+	No	No	Yes	Hepatic
Nadolol	Non-selective	No	No	Low	Renal
Pindolol	Non-selective	No	Yes	Yes	Hepatic
Propranolol	Non-selective	No	No	Yes+	Hepatic
Sotalol	Non-selective	No	No	Low	Renal
Timolol	Non-selective	No	No	Yes	Hepatic

* Intrinsic sympathomimetic activity

Beta-blockers can be water or lipid soluble

Water-soluble beta-blockers, e.g. atenolol, are excreted via the kidneys and dose reductions may be necessary in patients with reduced renal function.[3, 5] Lipid-soluble beta blockers, e.g. carvediolol or metoprolol, are metabolised in the liver and may be better tolerated by patients with reduced renal function.[3]

Bisoprolol is processed by both the liver and kidneys therefore does not require dose adjustments for patients with either renal or liver dysfunction,[6] and is also less likely to interact with other medicines.

Beta-blockers may influence other medicines

All beta-blockers can potentiate bradycardia, hypotension and cardiac effects caused by other medicines, e.g. diltiazem. Beta-blockers that are metabolised by hepatic enzymes may also interact with medicines that are metabolised via the same pathway.

The NZF interactions checker provides details on medicine interactions, including their clinical significance, available from: **www.nzf.org.nz**

Cardiovascular indications for beta-blockers

The indications for beta-blockers have shifted over the years. Originally widely prescribed for hypertension and contraindicated for the treatment of heart failure, beta-blockers now have a limited role in the treatment of hypertension and are routinely prescribed to patients with heart failure. The benefits of beta-blockers post-myocardial infarction are also no longer as clear as they once were.

Stable angina: preference and co-morbidities determines treatment choice

Beta-blockers or calcium channel blockers are recommended as the first-line anti-anginal medicines.[7] There is no evidence that one beta-blocker is superior to another or that beta-blockers are superior to calcium channel blockers.[8] The choice of beta-blocker is largely determined by the presence of co-morbidities, prescriber experience and the patient's preference for frequency of dosing and their likely adherence to treatment. A cardioselective beta-blocker such as bisoprolol or metoprolol succinate will provide the maximum effect with the minimum amount of adverse effects. Beta-blockers that reduce resting heart rate less than others (due to ISA) tend not to be used for angina, e.g. celiprolol and pindolol.

Information on the management of stable angina is available from: **www.bpac.org.nz/BPJ/2011/october/angina.aspx**

Arrhythmias: bisoprolol and metoprolol succinate are often preferred

Beta-blockers are the first-line treatment for long-term symptomatic rate control in patients with a range of cardiac arrhythmias, including atrial fibrillation and ventricular tachycardia.[9, 10] Bisoprolol* or metoprolol succinate are first-choice beta-blockers for patients with atrial fibrillation as they are prescribed once-daily and do not require dose adjustment in patients with renal impairment. Bisoprolol is preferred as it is more cardioselective than metoprolol and may cause more bradycardia.

Sotalol should not be used for rate control in atrial fibrillation due to its pro-arrhythmic action. Sotalol is used exclusively for rhythm control in patients with supraventricular and ventricular arrhythmias, but use has declined since the SWORD (survival with oral d-sotalol) study in the 1990s was discontinued when it was found that sotalol was associated with a higher rate of sudden death when administered to patients after myocardial infarction.[11] Alternatives for rhythm control include flecainide in younger patients or amiodarone in older patients.

* Unapproved use

Information on the management of atrial fibrillation from bpac^{nz} is due to be updated shortly and will be available from: **www.bpac.org.nz**

Heart failure: evidence for bisoprolol, carvediolol and metoprolol succinate

Beta-blockers are initiated alongside an ACE inhibitor in all patients with heart failure with reduced ejection fraction (HF-REF) after a diuretic has reduced the patient's fluid overload. Bisoprolol, carvedilol or metoprolol succinate are generally prescribed for heart failure in New Zealand; there is no strong evidence of effectiveness for one over another.[12] In practice, carvedilol is usually first-line if heart failure is associated with atrial fibrillation, followed by bisoprolol or metoprolol succinate. Any of these three choices are appropriate if heart failure is associated with ischaemic heart disease, but it is important that the beta-blocker is slowly titrated to maximum tolerated dose (see Page 5).

Patients with heart failure with preserved ejection fraction (HF-PEF) may also be prescribed a beta-blocker if they have other cardiovascular co-morbidities, such as atrial fibrillation or hypertension.[12]

Information on the management of heart failure is available from: **www.bpac.org.nz/BPJ/2013/february/managing-heart-failure.aspx**

Hypertension: beta-blockers are fourth-line

For patients with uncomplicated hypertension beta-blockers are generally a fourth-line option as angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), diuretics or calcium channel blockers are associated with better outcomes.[13] Beta-blockers may be more effective in younger patients with hypertension than older patients and may be used to manage hypertension in females of reproductive age. There is no evidence that one beta-blocker is superior to any other for the management of hypertension.[13] If a beta-blocker is prescribed the choice is based on the presence of co-morbidities, prescriber experience and the patient's preference for frequency of dosing and their likely adherence to treatment.

Information on the management of hypertension is available from: **www.bpac.org.nz/BPJ/2013/August/hypertension.aspx**

Post-myocardial infarction: initiated in secondary care, but when should they be stopped?

Beta-blockers are given acutely as first-line treatment post-myocardial infarction to decrease infarct size, increase the threshold for ventricular arrhythmias, and in the long-term, to prevent dysfunctional ventricular remodelling and heart failure.[14] Bisoprolol or metoprolol succinate are usually prescribed as they are the most cardioselective beta-blockers, but there is evidence of benefit for a number of other beta-blockers and international guidelines do not specify which beta-blocker to prescribe.[15, 16]

The optimal duration of treatment post-myocardial infarction is uncertain

There are two reasons why the optimal duration of beta-blocker treatment post-myocardial infarction is uncertain:[16]

1. Reperfusion techniques and the routine use of statins and anti-platelet medicines post-myocardial infarction mean that patients now gain less benefit from the use of beta-blockers than they did decades ago
2. There are no recent prospective randomised studies assessing the long-term benefits of beta-blockers in patients with uncomplicated myocardial infarction

A systematic review of sixty trials that divided studies into either the reperfusion era or the pre-reperfusion era, found that beta-blockers reduced mortality in patients post-myocardial infarction in the pre-reperfusion era, but not the reperfusion era.[17] Beta-blockers in the reperfusion era do, however, reduce the risk of subsequent angina (number needed to treat [NNT] 26) and the risk of recurrent myocardial infarction (NNT 209).[17]

Guidelines support the use of a beta-blocker for one to three years post-myocardial infarction,[18, 19] but in practice they are now being stopped earlier in patients who are otherwise well, with no signs of angina or heart failure.

Withdrawal of beta-blockers may be appropriate at 6–12-months post-myocardial infarction if re-vascularisation has occurred

At 6–12-months post-myocardial infarction prescribers are encouraged to consider withdrawing beta-blockers from patients without atrial fibrillation or heart failure, if re-vascularisation occurred while they were being treated for their myocardial infarction. If re-vascularisation did not occur the beta-blocker is likely to be required long term to prevent angina or if there is poor ventricular function. This is an evolving area of research and increasingly the evidence appears to support the withdrawal of beta-blockers from patients without other indications for treatment, e.g. heart failure or arrhythmias (see: "The optimal duration of treatment post-myocardial infarction is uncertain").

Information on the management of acute coronary syndromes is available from: **www.bpac.org.nz/BPJ/2015/April/coronary.aspx**

Minimising the adverse effects of beta-blockers

The adverse effect profile varies between beta-blockers according to their properties (Table 1). Tolerance to treatment may be improved with a slow upward titration of the beta-blocker until the maintenance dose is established. Approximately 3 – 5% of patients can be expected to be intolerant to beta-blocker treatment due to hypotension or bradycardia.[20]

Table 2 summarises recommended choices of beta-blocker, depending on the indication, patient co-morbidities and adverse effects.

Initiating beta-blockers: start low and go slow if treating heart failure

Beta-blockers should be started at a low dose and slowly titrated to maximum tolerated dose when used to treat patients with heart failure. For atrial fibrillation, the starting

Table 2: Summary of indications, recommendations and considerations for the use of beta-blockers for cardiovascular conditions in New Zealand.

Indication	Recommendation	Co-morbidities and considerations
Angina	All beta-blockers are considered to be equally effective although bisprolol or metoprolol may be preferred. Celiprolol and pindolol tend not to be used	Cardioselective beta-blockers, e.g. bisoprolol or metoprolol, are less likely to cause adverse effects, e.g. cold extremities or fatigue Celiprolol and pindolol have ISA which may reduce bradycardia or peripheral vasoconstriction Water soluble beta-blockers, e.g. atenolol, celiprolol or nadolol, are less likely to cause CNS adverse effects, such as sleep disturbances Polypharmacy: bisoprolol is less likely to interact with other medicines Renal dysfunction: consider dose adjustments for water-soluble beta-blockers, e.g. atenolol, celiprolol and nadolol; bisoprolol may be preferred Respiratory disease: cardioselective beta-blockers, e.g. bisoprolol and metoprolol, are preferred
Arrhythmias	Metoprolol or bisoprolol	
Heart failure	Bisoprolol, carvedilol or metoprolol	
Hypertension	All beta-blockers are considered to be equally effective (as fourth-line treatment)	
Post-myocardial infarction	Bisoprolol or metoprolol; consider withdrawal after 6–12 months if re-vascularised and no other indications.	

dose of the beta-blocker depends on the patient's heart rate and co-morbidities, e.g. a starting dose of 23.75 mg metoprolol succinate may be appropriate for a patient with moderately elevated heart rate, but 47.5 mg may be required for a patient with a significantly elevated heart rate. For other conditions, e.g. angina, a beta-blocker can usually be started at a standard dose.

Refer to the New Zealand Formulary for individual beta-blocker dosing regimens: **www.nzf.org.nz**

Titrating dose in heart failure

Begin treatment with a beta-blocker at a low dose and gradually increase this to the recommended dose or the maximum tolerated dose. Record the patient's heart rate and blood pressure before treatment is initiated and continue to monitor these as the dose is titrated upwards.[12] Adverse effects will often resolve and patients can be encouraged to persist with treatment as long as their systolic blood pressure does not fall too low, e.g. less than 100 mmHg. If adverse effects do not resolve, drop back to the previous dose and assess symptom control.

Beta-blockers are usually not recommended in patients with asthma

Beta-blockers should generally be avoided in patients with asthma.[21] This is because they may prevent sympathetic stimulation of the pulmonary beta$_2$-adrenoceptors thus causing bronchoconstriction and reducing the effectiveness of bronchodilators.[22]

If a beta-blocker must be used in a patient with asthma, cardioselective beta-blockers, e.g. bisoprolol and metoprolol, are better tolerated than non-selective beta-blockers, although they are still associated with a decrease in lung function and adverse effects.[22]

Cardioselective beta-blockers are generally safe and beneficial in patients with COPD

There is evidence that beta-blockers are under-prescribed to patients with COPD, yet they provide significant benefit to those with co-existing heart failure;[23] cardioselective beta-blockers are preferred. A systematic review which included 15 studies with a follow-up period ranging from one to seven years found that beta-blockers in patients with COPD significantly decreased overall mortality and exacerbation of COPD.[24]

Cardioselective beta-blockers may reduce peripheral vasoconstriction and fatigue

Cardioselective beta-blockers, e.g. bisoprolol and metoprolol succinate, are less likely to cause fatigue and cold extremities than non-selective beta-blockers.[21] However, peripheral vasoconstriction may still occur due to the reduction in cardiac output.[21] If patients report cold extremities when taking a beta-blocker, a dihydropyridine calcium channel blocker can be added to their treatment regimen, e.g. amlodipine. If the patient's blood pressure is "on target", the beta-blocker can be reduced, otherwise it should be left at the same dose.

Water soluble beta-blockers are less likely to cause sleep disturbances

Malaise, vivid dreams, nightmares and in rare cases hallucinations may be caused by lipid-soluble beta-blockers crossing the blood brain barrier.[21] If a patient reports adverse effects related to the central nervous system that cannot be managed with a dose reduction, consideration may be given to switching treatment to a water-soluble beta-blocker, e.g. atenolol, celiprolol or nadolol.

Withdrawal of beta-blockers is sometimes appropriate

Treatment with beta-blockers is generally long-term, but it should not be regarded as indefinite. Occasionally it may be necessary to temporarily withdraw treatment, e.g. if the patient develops lower limb ulcers. In the long-term, the emergence of co-morbidities may make management more complex and it is appropriate to periodically review the benefits and risks of treatment with beta-blockers.

Stopping treatment: go slow to get low

Beta-blockers should be withdrawn slowly to prevent the onset of a withdrawal syndrome which in serious cases may include ischaemic cardiac symptoms, e.g. chest pain, even in those with no history of coronary heart disease. The risk of myocardial infarction is increased for older patients during the first month of withdrawal from cardioselective beta-blockers and this increased risk continues for six months.[25] Heart rate and blood pressure should be monitored as the dose is reduced and the patient's cardiac receptors and sympathetic nerve activity down-regulate.[3, 26]

There are no specific guidelines for withdrawing beta-blockers. A practical approach would be to reduce the patient's dose over several months, e.g. down titrating a twice daily dose to once daily for one month and then further reducing the dose to every second day for another month, before stopping treatment completely at the time when the patient's next prescription would be due. The dose could be halved every week for patients who needed to withdraw from treatment more rapidly.

Further information on beta-blockers is available in the podcast: the "Rational use of beta-blockers" with Dr Linda Bryant: **www.goodfellowunit.org/podcast/rational-use-beta-blockers-linda-bryant**

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