

# PHARMACOTHERAPY IN HEART FAILURE

## BETA-BLOCKADE: FOR WHOM, WHEN AND HOW?

Dr Ken McDonald  
Dr Mark Ledwidge

### Background

This article will continue the theme started in the summer 2003 issue of *HeartWise* on practical issues related to pharmacotherapy in heart failure. Drug therapy in this syndrome is becoming increasingly more complex and it is imperative that proven agents are applied in the correct circumstances to maximise benefit and avoid complications. To underline this point, a recent study of causes of hospitalisation in patients with heart failure found medication-related issues to be the primary precipitant in approximately 20% of cases.

In the last issue, the use of diuretics was explored. The following is a review of the emerging use of beta-blockade in this syndrome. This therapy represents one of the most dramatic reversals of thinking in this syndrome over the last two decades. For many years, the general teaching was that these agents should be avoided in the management of heart failure with reduced systolic function. However, the increasing realisation that heightened activity of sympathetic nervous system is detrimental to outlook has led to a reversal of this teaching with the subsequent demonstration of remarkable prognostic benefit of beta-blockade. This observation has now placed this therapy in the frontline of pharmacological management of heart failure but has also raised practical issues with regard to its application.

### Who to treat?

The first question that needs to be answered when considering beta-blockade is which patient is suitable. The following checklist should be addressed while making this decision.

#### Reduced ejection fraction

The benefit of beta-blockade in heart failure has only been demonstrated in patients with reduced left ventricular systolic dysfunction (defined as a left ventricular ejection fraction <45%). Therefore, it is important to have an estimate of ejection fraction before deciding whether a patient is suitable. Left ventricular systolic function can improve spontaneously (recovery from myocarditis) and also as a result of various interventions in heart failure. For example, revascularisation can result in an increase in ejection fraction. Therefore, it is important to have a recent estimate of LVEF (within four to six weeks of considering beta-blockade) to ensure that systolic

function remains within the range that will derive benefit from beta-blockade.

#### Clinically stable

Beta-blocker therapy should only be prescribed to those with stable heart failure. During periods of clinical instability, the sympathetic nervous system takes on an important temporary stabilising role. To block its effect in such circumstances can lead to further clinical deterioration. Therefore, beta-blocker therapy should be withheld if patients are complaining of progressive symptoms or are demonstrating weight gain even in the absence of symptomatic deterioration. Such circumstances should be dealt with before considering beta-blockers.

If clinical deterioration should occur while on beta-blockers, the dose of beta-blocker should be maintained and other means employed to deal with the clinical problem. The only circumstance where the dose of the beta-blocker should be altered is when there has been a recent increase in dose within days of development of the clinical instability, where reverting to the previous dose can be considered

#### Contraindications to beta-blockade

The major issue in this regard is whether the patient has reversible airways disease. A history of chronic obstructive pulmonary disease (COPD) and/or asthma should be challenged to ensure that the patient does indeed have a contraindication to beta-blockade. In our experience, we have often found that such a diagnosis has been incorrect and, if accepted at face value, would have led to the omission of an important therapy for management of heart failure. Therefore careful review of the evidence supporting the diagnosis of COPD or asthma is recommended and it may be necessary to order a set of pulmonary function tests to clarify whether there is a reversible component to airways disease that may be present.

Other major contraindications to beta-blockade in heart failure are bradycardia or defined conduction disease. However, these are often issues that can be dealt with to allow for the subsequent initiation of beta-blockade. For example, bradycardia may be due to concomitant use of digoxin or calcium channel blockers. Discontinuing these agents can allow heart rate to rise to a level where beta-blockade can be comfortably started. Otherwise, a back-up pacemaker could

be considered, as it could for evidence of significant conduction disease. Peripheral vascular disease is rarely an absolute contraindication to beta-blockade.

## When to treat

### Concomitant therapy for heart failure

Present guidelines suggest that patients with heart failure and left ventricular systolic dysfunction should be first placed on an angiotensin-converting enzyme (ACE) inhibitor before considering beta-blockade. The reason behind this recommendation is simply that all trials with beta-blockade to date, with one exception, have assessed the add-on benefit of beta-blockade to ACEI therapy rather than head-to-head comparison. Indeed it may be that beta-blockade may be as effective as or even more effective than ACEI therapy as monotherapy. However, in practice, this guideline does not prevent most patients receiving both therapies. Recent audit of our experience demonstrates that in excess of 75% of patients with reduced ejection fraction tolerate a combination of both ACEI and beta-blockers in good doses.

When patients are intolerant of ACEI therapy it may be reasonable to first try a beta-blocker rather than an angiotensin receptor blocker, as there are far more data defining the benefit of beta-blockade.

## Where to treat

Beta-blocker titration in patients with documented heart failure has evolved as a somewhat complex process, and is more ideally suited to a specialist unit rather than a GP's

surgery. There are many reasons for this as outlined below. Our routine is to initially confirm suitability for beta-blockade and address the issues outlined above. Beta-blockade is initiated once the systolic blood pressure is greater than 90mmHg and heart rate greater than 60/min. Following the initial dose, patients are observed for at least two hours in the heart failure unit to assess symptomatic and haemodynamic response. If stable, patients are then discharged and asked to return for further titration two weeks later where the above process is repeated. The titration process, in our experience, lasts about 60 days to the achievement of maximally tolerated dose.

During titration, it is important to stress to patients that symptomatic benefit may not occur immediately and indeed there may be some clinical deterioration in the initial weeks. It is therefore important to instruct patients to report changing symptoms and unexplained weight gain. The most commonly observed problems relate to worsening congestion or symptoms related to hypotension. Should these occur, it is equally important not to label the patient intolerant of beta-blockade as temporary adjustment of other therapy may be all that is required.

During beta-blocker titration, adjustment of concomitant medications may be necessary in as many as 30% of patients. The most common change is in diuretic dose to combat congestion. Reduction in the dose of ACE inhibitor or angiotensin receptor blocker dose can be employed to combat hypotension and allow for further titration of beta-blocker. Digoxin therapy is often stopped during titration to minimise

# MERCK

CARDICOR 1.25MG FILM-COATED TABLETS  
CARDICOR 2.5MG FILM-COATED TABLETS CARDICOR  
3.75MG FILM-COATED TABLETS CARDICOR 5MG  
FILM-COATED TABLETS CARDICOR 7.5MG FILM-COATED  
TABLETS CARDICOR 10MG FILM-COATED TABLETS  
bisoprolol

**PRESCRIBING INFORMATION ROI. Indications:** Treatment of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction  $\leq$  35%, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides. **Dosage:** The patients should have stable chronic heart failure without acute failure during the past six weeks and a mainly unchanged basic therapy during the past two weeks. It is recommended that the treating physician should be experienced in the management of chronic heart failure. **Warning:** The treatment of stable chronic heart failure with bisoprolol has to be initiated with a titration phase. **Adults:** Starting dose of 1.25mg a day for one week, then gradual up-titration, if well-tolerated, in defined steps, to a maximum dose of 10mg once daily. **Elderly:** No dosage adjustment required. **Children:** Not recommended. After initiation of treatment with 1.25 mg, the patients should be observed over a period of approximately 4 hours (especially as regards blood pressure, heart rate, conduction disturbances, signs of worsening of heart failure). During the titration phase, in case of worsening of the heart failure or intolerance, it is recommended first to reduce the dose of bisoprolol, or to stop immediately if necessary (in case of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block). Treatment with bisoprolol is not recommended to be stopped abruptly since this might lead to a transitory worsening of heart failure. If discontinuation is necessary, the dose should gradually be decreased. There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired liver or renal function. Up-titration of the dose in these populations should therefore be made with additional caution. **Contra-indications:** Acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy, cardiogenic shock, second or third degree AV block, sick sinus syndrome, sinoatrial block, bradycardia with  $<$  60 beats/min before the start of therapy, hypotension, severe bronchial asthma or severe chronic obstructive pulmonary disease, late stages of peripheral arterial occlusive disease and Raynaud's syndrome, untreated pheochromocytoma, metabolic acidosis, hypersensitivity to bisoprolol or to any of the excipients. **Precautions:** Bronchospasm, bronchial asthma, obstructive airways disease, concomitant treatment with inhalation

anaesthetics, diabetes mellitus, strict fasting, ongoing desensitisation therapy, first degree AV block, Prinzmetal's angina, peripheral arterial occlusive disease, psoriasis, thyrotoxicosis. Allergic reactions may be worsened. **Pregnancy and lactation:** Bisoprolol should not be used during pregnancy unless clearly necessary. Use during breastfeeding is not recommended. **Drug interactions:** Calcium antagonists, clonidine, monoamineoxidase-A inhibitors, class-I and class-III antiarrhythmic drugs, parasympathomimetic drugs, other  $\beta$ -blockers, insulin and oral antidiabetic drugs, anaesthetic agents, digitalis glycosides, prostaglandin synthetase inhibiting drugs, ergotamine derivatives, sympathomimetic agents, tricyclic antidepressants, barbiturates, phenothiazines, other antihypertensive agents, rifampicin, mefloquine. **Side effects:** **Common:** Coldness or numbness in the extremities, tiredness, dizziness, headache, GI disturbances. **Uncommon:** Muscular weakness/cramps, bradycardia, AV-stimulus disturbances, worsening of heart failure, orthostatic hypotension, sleep disturbances, depression, bronchospasm. **Rare:** Nightmares, hallucinations, hypersensitivity reactions, increased liver enzymes, hepatitis, increased triglycerides, potency disorders, hearing impairment, allergic rhinitis, dry eyes, psoriasis-like rash, alopecia. **Presentations:** Cardicor film-coated tablets contain either 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg or 10mg bisoprolol fumarate (2:1). Calendar Pack 28 tablets. Price in Republic of Ireland: 1.25mg €8.76; 2.5mg €8.11; 3.75mg €10.01; 5mg €10.51; 7.5mg €12.13; 10mg €13.43. **Product licence no.:** PL 0493/0179-84. **Product authorisation number and holder:** PA 654/7/1-6; Merck Pharmaceuticals, (A Division of Merck Ltd), Harrier House, High Street, West Drayton, Middlesex UB7 7QG, United Kingdom. **Legal category:** POM. **Date of preparation:** January 2003. Full prescribing information available on request from: Merck Pharmaceuticals, (A Division of Merck Ltd), 2004A Orchard Avenue, Citywest Business Campus, Naas Road, Dublin 24. Tel: 01 466 1900. **Reference 1.** CIBIS II, *Lancet* 1999; 353 (9146): 9-13.



problems related to bradycardia.

Despite the above complexities, the time invested in beta-blocker titration is worthwhile given the significant prognostic benefit of this therapy. Patients with heart failure and reduced ejection fraction who are not on beta-blockers should be referred to your local heart failure unit for assessment and titration. If patients have a reduced ejection fraction without ever having features of heart failure, beta-blockers can be prescribed in a manner similar to their use in other cardiovascular conditions and do not need referral.

### Are all beta-blockers the same?

The short answer is 'no', in that the therapy with bucindolol was not effective. However, all other beta-blockers assessed have been found to be effective. The bulk of the data relate to bisoprolol (Cardicor), carvedilol (Eucardic) and Metoprolol XL (not available in Ireland). A recent direct comparison between carvedilol and Metoprolol XL demonstrated superiority for carvedilol but otherwise little comparative data are available. We routinely use both bisoprolol and carvedilol and have found no significant difference. Intolerance to one beta-blocker does not mean intolerance to the class and it is worthwhile challenging patients with an alternative beta-blocker if significant symptoms occurred with the initial agent.

### Discontinuing beta-blockers

In almost all cases, therapy is lifelong. Follow up echocardiography may reveal definitive improvement in

ejection fraction, often to values above 45%, the normal criterion for initiating beta-blocker therapy. Even in these circumstances, one would be reluctant to wean off therapy as the natural history of this group is unclear. In some circumstances, where the presentation is typical of acute myocarditis, subsequent improvement may reflect the natural history of the disease process and discontinuing beta-blocker therapy and ACEI therapy may be possible under specialist review.

Abrupt discontinuation of beta-blockade due to concomitant medical illnesses should be avoided if possible. For example, a respiratory infection with evidence of mild bronchospasm should not precipitate immediate withdrawal of beta-blockade unless the clinical situation deteriorates. The concern with immediate withdrawal is the potential for malignant arrhythmias.







### Summary

Beta-blockade represents a remarkable development in the management of heart failure associated with left ventricular systolic dysfunction. It is now firmly established as a first line therapy and should be considered in all patients with reduced left ventricular ejection fraction. Titration of these agents can be complex and time consuming and is best achieved in the setting of a specialist heart failure unit.

*Dr Ken McDonald and Dr Mark Ledwidge, Heart Failure Unit, St Vincent's University Hospital, Dublin.*

# ADD CARDICOR ADD LIFE

## SETTING STANDARDS IN CHF TREATMENT

-  The first beta<sub>1</sub>-selective, beta-blocker with proven power to prolong life in CHF<sup>1</sup>
-  Significant 32% reduction in all-cause mortality versus placebo ( $p < 0.0001$ ) with Cardicor led to early discontinuation of CIBIS II<sup>1</sup>
-  Significant 42% reduction v. placebo in sudden deaths ( $p = 0.0011$ ) and 26% reduction in cardiovascular deaths ( $p = 0.0049$ )<sup>1</sup>
-  Significant 33% reduction ( $p < 0.0001$ ) v. placebo in hospitalisations for worsening heart failure<sup>1</sup>
-  Significantly fewer admissions for ventricular dysrhythmias ( $p = 0.006$ )<sup>1</sup>
-  Cardicor is a simple 'once daily' dose

Once Daily  
**Cardicor**  
bisoprolol 

Add Cardicor. Add Life.