GP use of beta blockers in heart failure

General practitioner Mike Mead gives a step-by-step guide on how to treat heart failure in primary care, including how to start patients on beta blockers.

Abstract

This article explains how general practitioners can diagnose and treat heart failure in primary care. Diagnosis is difficult and four diagnostic tests – the electrocardiogram, chest x-ray, blood test for natriuretic peptides and echocardiography – are recommended as being of particular value in confirming the diagnosis in primary care.

A six-step treatment strategy is then given advising i) confirming the diagnosis, ii) excluding other treatable causes of heart failure, iii) giving general advice to the patient, iv) starting treatment with a diuretic, v) then adding an angiotensin-converting enzyme inhibitor, and, vi) finally adding a beta blocker. A 10-point plan explaining in detail how to start beta blockers in primary care concludes the article.

Key words: heart failure, primary care, diuretics, angiotensin-converting enzyme inhibitors, beta blockers.

Introduction

Heart failure affects about 1% of the population and has an appalling prognosis, with half of patients dying within four years of diagnosis. In patients with severe heart failure more than 50% will die within a year.[1]

Heart failure is associated with considerable morbidity in terms of hospitalisation, need for investigation/treatment and effect on the patient's daily life. Even in 1990/91 the cost of heart failure to the NHS was £360 million;[2] hospitalisation accounted for 59.5% of this total. Hospital discharge rates for heart failure now equal or exceed those for myocardial infarction.[2] Patients with heart failure make at least four visits to their general practitioner (GP) each year.[2]

'In primary care the change has been from 'dig and diuretics' to DAB – diuretics, ACE inhibitors and beta blockers'

Mike Mead

Diagnosis

The diagnosis of heart failure is notoriously difficult clinically. Individual symptoms/signs, particularly ankle swelling, can be unreliable with a poor predictive value. The GP will rely on a collection of symptoms and signs to suggest the diagnosis – fatigue, breathlessness, pitting ankle oedema, elevated jugular venous pressure and possibly lung crepitations. Patients with severe heart failure usually have a third heart sound but this is academic to the GP as a diagnostic tool. There are four investigations of particular value in confirming a diagnosis of heart failure:

1. The ECG. A normal electrocardiogram (ECG) is very unusual in patients with heart failure and suggests another diagnosis. Abnormalities commonly found on the ECG include anterior Q waves, left bundle branch block, ischaemic changes, changes suggesting left ventricular hypertrophy, and atrial fibrillation.

2. The chest x-ray. This may show an enlarged heart and pulmonary venous congestion (although it may be normal in patients with heart failure).

3. A blood test for brain natriuretic peptides. This is a very useful blood test since if blood B-natriuretic peptides (BNP's) are normal, it is very unlikely the patient will have heart failure. This test has yet to be widely adopted, but will be, and is a priority for Primary Care Organisation (PCO) support. The BNP test may also save the need for echocardiography, e.g. if BNP is normal and the ECG is normal, it is unlikely the patient has heart failure and an echocardiogram may be less useful.

4. Echocardiography. Echocardiography is, of course, the gold standard in diagnosis and may also detect valvular problems needing surgical intervention. PCOs should have the provision of open-access echocardiography as one of their top cardiovascular priorities for their constituent GPs.

Treatment

A decade ago, the treatment of heart failure was 'dig (digoxin) and diuretics'. Neither of these drugs alter the long-term prognosis, although they may improve symptoms. As research has

Table 1. DAB for heart failure

- **D**. Start with a diuretic
- **A**. Add an ACE inhibitor
- **B**. Add a beta blocker – bisoprolol or carvedilol

progressed, we now have three agents that can actually improve prognosis – angiotensin-converting enzyme (ACE) inhibitors, beta blockers and spironolactone.

In terms of primary care, the change has been from 'dig and diuretics' to DAB (table 1) – diuretics, then add an ACE inhibitor, then add a beta blocker.

The six steps of treatment of a patient with heart failure are:

Step 1. Make sure you are confident of the diagnosis

Consider if you have the right collection of symptoms and signs supported by the investigations at your disposal. In primary care diagnoses are, of course, often multiple with the patient having breathlessness due to chronic obstructive pulmonary disease (COPD), mild anaemia, obesity and heart failure! How much heart failure contributes to the overall clinical symptoms may only be found after a trial of diuretic therapy.

Step 2. Make sure you have excluded other treatable causes of heart failure or exacerbating factors

In most younger patients, heart failure results from myocardial dysfunction secondary to coronary artery disease or myocardial infarction. Systolic hypertension is an important causative factor with age as the heart hypertrophies. Three common factors to exclude are:

- anaemia
- thyroid dysfunction
- valvular abnormalities – a cause of heart failure that should not be missed.

Thus, before starting treatment for heart failure, take a full blood count, thyroid function tests and renal function tests (needed for ACE inhibitor monitoring), and listen carefully to the heart (if no echocardiogram is available).

Step 3. Give general advice and stop any drugs that might be contributing to the symptoms

The advice that a GP should give the patient is:

- Reduce salt in the diet if possible (but avoid salt substitutes as these may be high in potassium).
- Reduce weight if obese/overweight.
- Stop smoking.
- Exercise. In patients with chronic stable heart failure, exercise should be encouraged providing it doesn't produce significant symptoms. Strenuous exercise, however, should be avoided.
- Ensure the patient is up to date with influenza and pneumococcal vaccinations.

The drugs to be used with caution or avoided in heart failure include non-steroidal anti-inflammatory drugs (NSAIDs), verapamil, diltiazem, tricyclic antidepressants, steroids and lithium.

Step 4. Start a diuretic

Although a few patients with mild heart failure may respond to bendrofluazide, most will need a loop diuretic like frusemide (but anticipating ACE inhibitor use, co-amilofruse should not be used).

Step 5. Add an ACE inhibitor

ACE inhibitors now have a considerable evidence base behind them, following trials such as CONSENSUS,[3] SOLVD[4] and ATLAS.[5] After excluding contraindications (remember, if a patient has peripheral vascular disease that he or she has a much greater chance of having renal artery stenosis), start an ACE inhibitor with a low dose at night, reducing or withholding diuretics for 24 hours before use depending on need. Make sure the patient is not on an NSAID or a potassium-sparing diuretic and check renal function before starting the ACE inhibitor. The following groups should be referred to a cardiologist to initiate ACE inhibitor therapy (from reference 1):

Table 2. Target levels for ACE inhibitor use in heart failure (from ref 1)

Enalapril 10 mg b.d.
Lisinopril 5–20 mg daily
Perindopril 4 mg daily
Ramipril 2.5–5 mg b.d.
Fosinopril 20 mg daily
Trandolapril 4 mg daily

Adapted from *Eur Heart J* 2001;**22**:1527-60.

- Patients in whom serum creatinine is > 150 µmol/L.
- Patients in whom serum sodium is < 135 mmol/L.
- Patients with severe heart failure.
- Patients with a valvular cause for their heart failure.
- Patients in whom systolic blood pressure (BP) is < 100 mmHg.

A serum potassium > 5.5 mmol/L is a contraindication to ACE inhibitor use. Renal function should be measured after one to two weeks and then one to two weeks after each dose increase, then at three months, and then at six monthly intervals thereafter.[1] A 10–15% rise in serum creatinine may be seen with the use of an ACE inhibitor but these levels may stabilise or fall during treatment. Greater rises than this should prompt a referral. Increase the dose of ACE inhibitors slowly towards target levels which have given the considerable benefit seen in clinical trials (table 2).

Angiotensin II receptor antagonists (AIIRAs) can be considered for those intolerant of ACE inhibitors. While side effects are less with AIIRAs, they have not yet been shown to be superior to ACE inhibitors for this indication.[1] There is also a possible negative interaction with beta blockers.[1] We await with interest the results of studies such as the CHARM-add on study, using an ACE inhibitor and an AIIRA to treat patients with heart failure.

Step 6. Start a beta blocker

The use of beta blockers in patients with heart failure has an even more

impressive evidence base than that for ACE inhibitors. Beta blockers have even greater benefits than afforded by ACE inhibitors.[6] In the CIBIS II trial,[7] for example, over 2,000 patients with symptomatic heart failure on diuretics and ACE inhibitors were randomised to bisoprolol or placebo. The trial was stopped early because mortality was significantly less in the bisoprolol group than in the placebo group. As well as a 34% reduction of all-cause mortality, there was a 44% reduction in sudden death in the bisoprolol group. Fewer patients were hospitalised in the bisoprolol group, there were fewer admissions per patient hospitalised, fewer hospital admissions overall, fewer days spent in hospital and fewer days spent in the most expensive type of ward.[8] Even taking into account drug costs and extra visits for up-titration of the bisoprolol, the costs incurred by the placebo group were greater than the bisoprolol group. The cost-effective use of beta blocker therapy for heart failure in preventing hospital admission again emphasises that this is an agenda which should be supported by a PCO.

There are three beta blockers with an evidence base for use in patients with heart failure – bisoprolol, carvedilol and metoprolol. Only bisoprolol and carvedilol are licensed for heart failure treatment in the UK, and carvedilol is only licensed for initiation in hospital. Hence, bisoprolol will be used when starting a beta blocker in primary care for a patient with heart failure.

> ***'The use of beta blockers has an even more impressive evidence base than that for ACE inhibitors'***

In primary care, follow a 10-point plan to using beta blockers in heart failure (figure 1). The plan can be remembered by the mnemonic 'CHECK – COUNSEL – STAPLE'.

Figure 1. Ten-point plan for using beta blockers in heart failure in primary care

'CHECK – COUNSEL – STAPLE'

1. **CHECK** patient is already on a diuretic, ACE inhibitor and possibly digoxin (if appropriate)
2. **CHECK** for contraindications to beta blocker use in heart failure
3. **CHECK** for drug interactions
4. **COUNSEL** the patient
5. **S**tart with bisoprolol 1.25 mg, following manufacturer's recommendations
6. **T**itrate slowly upwards – 'start low and go slow'
7. **A**im to reach a target dose of 10 mg bisoprolol daily
8. **P**ersevere – try to reach target, e.g. by adjusting other drugs and slowing titration
9. **L**eave off bisoprolol slowly if you have to discontinue
10. **E**nsure regular review once stable on bisoprolol

1. Check the patient is already on a diuretic, ACE inhibitor and possibly digoxin (if appropriate)

Diuretics and ACE inhibitors are mandatory but digoxin is now of less relevance. Long-term digoxin therapy, unlike ACE inhibitor and beta blocker therapy, does not improve long-term survival. The main role for digoxin that GPs are likely to see is that it can slow the ventricular rate in atrial fibrillation.[1] It may be used in certain situations when the patient is in sinus rhythm with uncontrolled symptoms and poor ventricular function, but these will tend to be specialist indications.

If digoxin is being used with a beta blocker, the GP must clearly be more aware of the possibility of bradycardia. The important message is that the two – digoxin and a beta blocker – can be used together in heart failure patients (this combination was used in about half the patients in the CIBIS II trial).

For GPs, the priority will be a diuretic plus an ACE inhibitor.

2. Check there are no contraindications to beta blocker use in heart failure

Beta blockers are only indicated for patients with chronic stable heart failure – they should NOT be used in patients with acute heart failure or where there has been any episode of acute heart failure within the past six weeks (including the need for intravenous diuretics). The patient should have been stable on their current therapy for at least two weeks – the safest strategy is to stabilise the patient on an ACE inhibitor and diuretic for at least 6–8 weeks before introducing a beta blocker. GPs may feel happier referring patients with severe heart failure for specialist initiation of beta blocker therapy.

The other major contraindications for using a beta blocker in heart failure in primary care will be:

- Heart block (including 2nd degree heart block).
- Sick sinus syndrome.

- Bradycardia (pulse < 60 per minute before starting the beta blocker).
- Hypotension (systolic BP < 100 mmHg).
- The usual contraindications to beta blocker use – asthma/severe COPD, significant peripheral artery occlusive disease, Raynaud's syndrome.
- Pregnancy or lactation.

Remember, beta blocker use may mask the symptoms of hypoglycaemia in a diabetic patient.

There are a few very rare contraindications, like untreated phaechromocytoma and metabolic acidosis, but it is unlikely GPs will be treating these patients.

3. Check for any possible drug interactions

The main drugs to consider when prescribing beta blockers are:

- Do not use with monoamine oxidase inhibitors, clonidine or calcium antagonists. In particular, remember not to use if the patient is on diltiazem, verapamil or nifedipine.

Take special consideration with other drugs, such as:

- Use of beta blocker eye drops (take into account possibility of additive effects).
- Use of anti-arrhythmic drugs, e.g. amiodarone.
- Use of oral antidiabetic agents or insulin – due to the masking effect of hypoglycaemia.
- Use of tricyclic antidepressants, barbiturates and phenothiazines (beware an increased BP-lowering effect).
- Use of rifampicin: this accelerates the metabolism of bisoprolol.

These precautions are, of course, in addition to the drugs you will be trying to avoid in heart failure anyway – see step 3. Many older patients take quinine for night cramps – quinine can increase digoxin concentration (and hence potentiate bradycardia even further) and itself has numerous cardiovascular side effects (it is best to avoid quinine if a patient is in atrial fibrillation for example).

Before starting a beta blocker, think about the patient's existing therapy and, if there is any uncertainty about any drug interactions or possible additive or detrimental effects, check in the British National Formulary before instituting beta blocker therapy.

4. Counsel the patient

The success of any therapy depends on counselling the patient. The important issues will be:

- Counsel about the considerable benefit of beta blocker use and that it is worth persevering and trying to manage any side effects, for the long-term gain.
- Counsel concerning the ways patients can help in improving their prognosis (see step 3) and that includes continuing their other prescribed medication (i.e. diuretic, ACE inhibitor and possibly digoxin) as well as the beta blocker.
- Counsel on the need for up-titration and the need to attend the nurse/doctor for regular review.
- Counsel on possible side effects – the more the patient understands their therapy, the more likely is compliance.

5. Start therapy with 1.25 mg bisoprolol

Since the only beta blocker licensed for primary care initiation is bisoprolol, start with 1.25 mg bisoprolol. More precisely, one should start with Cardicor®, since this is the only bisoprolol preparation actually licensed for use in heart failure and it is also the only bisoprolol tablet available as a 1.25 mg strength. By prescribing by brand, this will also ensure the patient gets a whole tablet rather than a prescription being dispensed as generic 5 mg bisoprolol broken up into quarters.

The licence for Cardicor® states that the treating physician (in this case the GP) should be experienced in the management of chronic heart failure. This is now, as this article details, well within the capacity of most GPs, but any GP at all unsure about the basic treatment principles should ask a partner with more experience to initiate treatment.

When starting bisoprolol in the surgery, the licence recommends a four-hour period of observation to monitor pulse, BP and any dizziness, dyspnoea or other signs of cardiac failure. In practice, this is not a difficult problem to overcome if the patient attends for the first appointment in the morning and brings some reading material with them. After giving the 1.25 mg of bisoprolol, the nurse should measure heart rate and BP every hour for the first three hours.

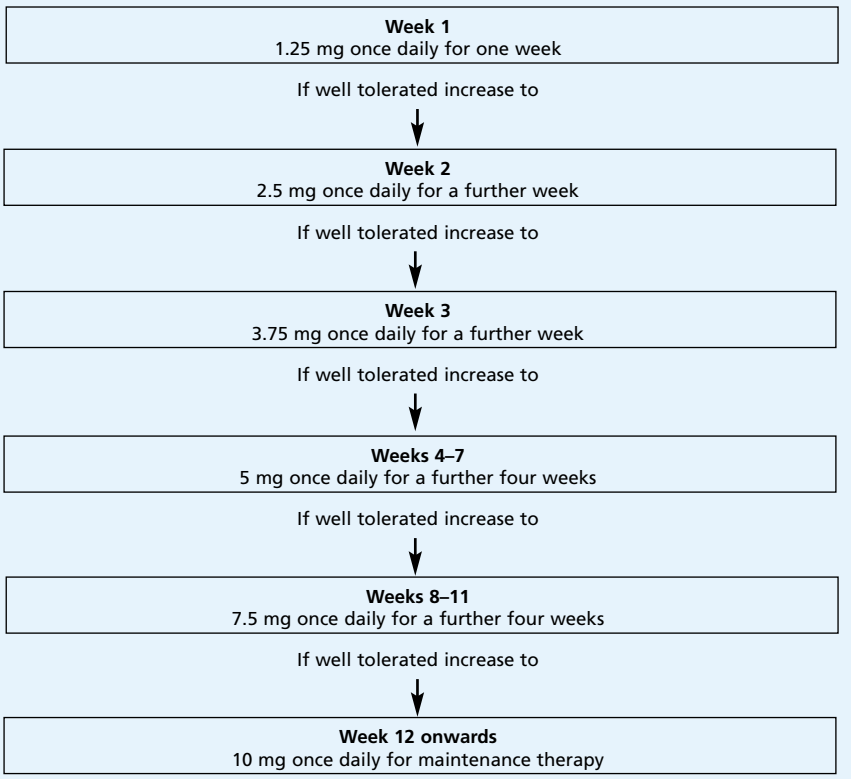
In a study of starting bisoprolol 1.25 mg in 264 patients and monitoring them for the first four hours, there were no serious adverse events, no cases of symptomatic bradycardia or syncope and no patient became more breathless at rest.[9] The average fall in systolic BP in these patients was 8 mmHg. In 14 patients out of the 264, the systolic BP fall was > 20 mmHg but 13 of these experienced no symptoms and only one patient, with severe heart failure, had symptomatic dizziness as a result of the fall in systolic BP. The authors concluded that adverse events in initiating beta blocker therapy are unlikely to occur more frequently than in 1.4% of patients.[9] The authors suggest that for patients with mild to moderate heart failure, it may even be possible to initiate beta blockers at home, with another adult in attendance instructed on how to manage any side effects. Clearly, the four-hour observation period should not be a barrier to starting beta blockers in heart failure, particularly considering the possible benefits.

6. Titrate slowly upwards

Once the patient has been started on bisoprolol, figure 2 shows the schedule for up-titration.

Note Cardicor® is a once-daily tablet, so does not add unduly to the compliance difficulties inherent in patients already on polypharmacy. Cardicor® has a patient information leaflet insert informing the patient of the different available strengths.

Figure 2. Schedule for up-titration of bisoprolol in general practice



7. Aim to reach the 10 mg target dose

As with ACE inhibitor therapy, the aim is to titrate up to the doses used in clinical trials to produce the best protective effect.

In the CIBIS II trial of symptomatic heart failure patients on a diuretic and ACE inhibitor, 564 patients reached the 10 mg dose, 152 reached 7.5 mg and 176 reached 5 mg. Thus, by slowly and methodically up-titrating the dose of bisoprolol, realistically over half of patients can be expected to reach the maximum 10 mg dose.

8. Persevere!

While up-titrating, the patient may experience side effects. The commonest side effects are:

- dizziness
- bradycardia
- hypotension
- fatigue.

There is also the possibility of an initial worsening of heart failure. However, because there is likely to be long-term improvement in symptoms and prognosis with beta blocker use, it is worthwhile persevering to see if maintenance therapy can be achieved with a target, or near as possible target, dose. If worsening heart failure or intolerance due to side effects occurs during the up-titration, any heart failure symptoms should be managed with a diuretic and an ACE inhibitor; the beta blocker dose should be slightly reduced. Once the patient is stable again, consider re-introduction or further up-titration of the beta blocker. Be guided by the clinical situation. Some patients actually report feeling 'better' quite quickly on starting bisoprolol (usually manifested as having 'more energy'), although responses are subjective. Even if patients do not feel substantially better, an improved ejection fraction can be objectively measured. Having warned the patient that they may initially feel marginally worse, it is a positive result if initially they feel the same on the beta blocker.

9. Leaving off the beta blocker

In cases of severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or atrioventricular block, you may have to stop the beta blocker immediately. However, the general rule, if the situation is not an emergency but discontinuation is still considered necessary, is not to stop the beta blocker abruptly as this itself may lead to a transitory worsening of heart failure. Reduce the dose gradually, dividing into halves weekly. If the patient is sufficiently intolerant of a beta blocker to necessitate discontinuation, it is worth referring to a specialist to see if the beta blocker can be re-introduced in a hospital setting. The withdrawal rate in using beta blockers in heart failure is, in fact, quite low, at less than 10%.

10. Ensure regular review of the patient

As with any chronic condition, follow-up of the patient, titrating treatment with symptoms, is part of good clinical practice.

'PCOs may wish to consider a special heart failure team or support a GP with an interest in cardiology to deliver a 'heart failure service' locally'

Spironolactone

The RALES study[10] showed that ACE inhibitor plus loop diuretic plus low-dose spironolactone (12.5–50 mg) can improve survival in patients with advanced heart failure, irrespective of cause. Initiating spironolactone therapy is a specialist decision, but GPs need to be aware of the need for monitoring renal function and potassium if ACE

Key messages

- ECG, chest x-ray, brain natriuretic peptide test and echocardiography are particularly helpful in confirming the diagnosis of heart failure
- Be confident of the diagnosis of heart failure and exclude any other treatable causes or exacerbating factors
- Advise the patient to reduce salt, reduce weight (in the obese/overweight), stop smoking, and to have influenza and pneumococcal vaccinations. Encourage exercise
- Start the patient on a diuretic, then add an ACE inhibitor (or an AIIRA in cases of intolerance)
- Start a beta blocker – (bisoprolol) – following the CHECK-COUNSEL-STAPLE plan

inhibitors and spironolactone are being used together (stop spironolactone if serum potassium is > 5.5 mmol/L). Gynaecomastia develops in about 10% of patients on spironolactone.

Warfarin

Many patients with heart failure will be on warfarin for atrial fibrillation or post-valve replacement.

Conclusion

The treatment of heart failure in primary care is now standardised, with a solid evidence base, but inevitably will involve more input from the doctor and nurse in initiating and monitoring treatment. Although cost-effective, particularly in terms of saving hospital admission, the cost-effectiveness is seen in the hospital side of the budget rather than in primary care workload. With primary and secondary care working together, there will need to be resource allocation to give GPs and nurses the time and support (including access to investigations like echocardiography) to maximise patient care in this important area. PCOs may also wish to consider a special heart failure team or support of a GP with an interest in cardiology to deliver a 'heart failure service' locally to those practices without the time or expertise to deliver the service 'in house'. As with most clinical areas, we need to look at more imaginative ways of delivering care within the community.

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