

7 **Beta-blockers in heart failure**



What will I learn?

In this section you will learn:

- Why beta-blockers should be used in heart failure
- How they improve symptoms and outcomes
- How to start and titrate the dose
- What the possible side effects are and what to do about them

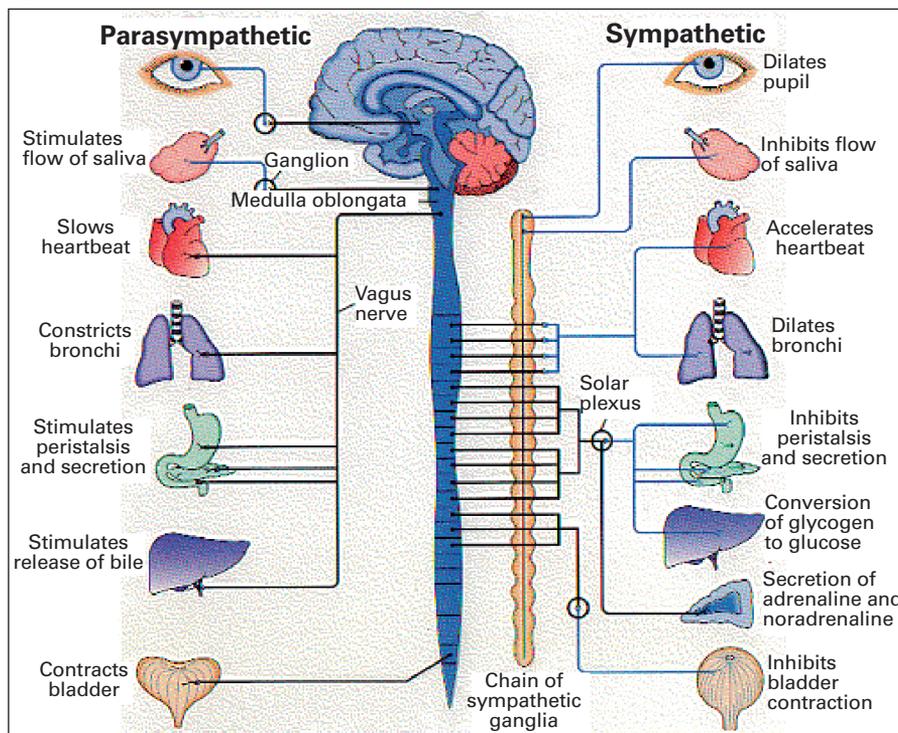
Less than 30 years ago we were taught that beta-blockers were actually contraindicated in heart failure. However, the evidence has been mounting and trials such as CIBIS,¹ MERIT-HF² and SENIORS³ have shown that beta-blockers, when used alongside ACE inhibitors, reduce mortality by up to a third. This is an astonishing figure and yet many people with heart failure are still not treated with beta-blockers.

The successful use of beta-blockers in large, randomised, controlled trials has led the ESC to recommend their use in all suitable patients following ACE inhibition even if they are asymptomatic, unless there is a contraindication to their use. The CIBIS III trial⁴ suggests that beta-blockers may be initiated before ACE inhibition.

How do they improve symptoms and outcomes?

The simple answer to this is that we are not entirely sure! Beta-blockers reduce the effects of the sympathetic nervous system's 'fight or flight' response, which in heart failure has been set off in response to an increase in RAAS activity (Fig. 1). They block stimulation of the beta-receptors in the heart and have a negative inotropic action, which lessens cardiac workload, as the force and rate of the heartbeat is reduced and undesirable remodelling of the heart is minimised.

Figure 1. Effects of the parasympathetic and sympathetic nervous systems.



How should the drugs be started and titrated?

The ESC guidelines suggest the following approach:

As a beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, beta-blockers should be initiated under careful control. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual responses. It is evident therefore that even a low dose of a beta-blocker is superior to a treatment without beta-blocker administration. The introduction of beta-blockers should, therefore, always be attempted even if the titration period has to be prolonged.

Beta-blockers may, however, induce myocardial depression and precipitate heart failure. In addition, beta-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction. Table 1 gives the recommended procedure for the use of beta-blockers in clinical practice and their contraindications. Table 2 shows the titration scheme of the drugs used in most relevant studies.

Table 1. The ESC recommended procedure for starting a beta-blocker.

- Patients should be on a background therapy with ACE inhibition, if not contraindicated.
- The patient should be in a relatively stable condition without the need for intravenous inotropic therapy and without signs of marked fluid retention.
- Start with a very low dose (Table 2) and titrate up to maintenance dosages shown to be effective in large trials. The dose may be doubled every one to two weeks if the preceding dose was well tolerated. Most patients can be managed as outpatients.
- Transient worsening failure, hypotension or bradycardia may occur during the titration period or thereafter:
 - monitor the patient for evidence of heart failure symptoms, fluid retention, hypotension and symptomatic bradycardia
 - if worsening of symptoms, first increase the dose of diuretics or ACE inhibitor; temporarily reduce the dose of beta-blockers if necessary
 - if hypotension, first reduce the dose of vasodilators; reduce the dose of beta-blockers if necessary
 - reduce or discontinue drugs that may lower heart rate in the presence of bradycardia; reduce dose of beta-blockers if necessary but discontinue only if clearly necessary
 - always consider the reintroduction and/or uptitration of the beta-blocker when the patient becomes stable.
- If inotropic support is needed to treat a decompensated patient on beta-blockade, phosphodiesterase inhibitors should be preferred because their haemodynamic effects are not antagonised by beta-blocker agents.

The following patients should be referred for specialist care:

- severe heart failure class III–IV
- heart failure of unknown aetiology
- relative contraindications: asymptomatic bradycardia and/or low blood pressure
- intolerance to low doses
- previous use of beta-blocker and discontinuation because of symptoms
- suspicion of bronchial asthma or severe pulmonary disease.

Contraindications to beta-blockers in patients with heart failure

- bronchial asthma
- severe bronchial disease
- symptomatic bradycardia or hypotension.

Table 2. Initiating dose, target dose and titration scheme of beta-blocking agents as used in recent large, controlled trials.

Beta-blocker	First dose (mg)	Increments (mg/day)	Target dose (mg/day)	Titration period
Bisoprolol	1.25	2.5, 3.75, 5, 7.5, 10	10	Weeks–month
Metoprolol succinate CR	12.5/25	25, 50, 100, 200	200	Weeks–month
Carvedilol	3.125	6.25, 12.5, 25, 50	50	Weeks–month
Nebivolol	1.25	2.5, 5, 10	10	Weeks–month

Daily frequency of administration as in the clinical trials



In this case study we met William, who has heart failure. He has been prescribed 12.5 mg carvedilol and 40 mg furosemide daily. He is currently asymptomatic but is complaining of increasing tiredness, which concerns him as he has found a part-time caretaker's job in a small block of flats. Dr Jones is due to see him in the clinic today. How should she manage his medication at his review?

What are the possible side effects?

Beta-blockers can be divided into two classes:

- *non-selective beta-blockers* which block both β_1 and β_2 receptors in the heart, lungs and around the body.
- *cardio-selective beta-blockers* which focus their activity on the heart. The use of these cardio-selective beta-blockers, such as bisoprolol, carvedilol, metoprolol and nebivolol have led to fewer side effects, such as bronchoconstriction, but other side effects, such as depression, erectile dysfunction and cold peripheries may still be experienced.

Overall, most people tolerate them well but all patients being treated for heart failure should be warned about the risk of a temporary exacerbation in symptoms after starting on a beta-blocker.



For more information on how beta-blockers work go to cvpharmacology.com/cardioinhibitory/beta-blockers.htm

For more information on why we use beta-blockers go to www.tcd.ie/tsmj/2003/beta.htm

For general advice on treating heart failure go to www.cks.library.nhs.uk



What you need to know

- Beta-blockers should be used in heart failure because, when used with ACE inhibitors and diuretics, they reduce mortality by a third.
- Beta-blockers improve symptoms and outcomes by impacting on the RAAS and the sympathetic nervous system to reduce cardiac workload and diminish fluid and salt retention.
- Beta-blockers should be initiated on a 'start low, go slow' basis when the patient is stable, in order to reduce the risk of adverse events.
- Possible side effects are reduced by opting for cardio-selective beta-blockers, but include cold extremities, depression and erectile dysfunction. Beta-blockers should never be stopped suddenly, however.



Self-assessment questions

Take a minute to test your knowledge:

1. Describe a possible drug and dose regime for initiating a beta-blocker.
2. What advice should be given to someone starting on a beta-blocker?
3. How would you explain to a patient the purpose of starting treatment with a beta-blocker?

References

1. Le Jemtel TH. Review of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II). *Curr Cardiol Rep* 1999; **1**(1): 29–30.
2. Merit HF investigators. Effect of metoprolol CR/XL in chronic heart failure. *Lancet* 1999; **335**(9169): 2001–2007.
3. Flather MD, et al. Randomised trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**(3): 215–225.
4. Willenheimer R, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomised cardiac Insufficiency Bisoprolol Study (CIBIS) III *Circulation* 2005; **112**(16): 2426–2435.