

Nebivolol (Nebilet) for chronic heart failure

(ne-BIV-o-lol)

Summary

- Nebivolol is a new selective beta₁-receptor antagonist for treating chronic heart failure.
- Nebivolol is an alternative to bisoprolol, carvedilol, and controlled-release metoprolol but has less robust evidence of survival benefit.
- Although the major trial with nebivolol was conducted in older people (≥ 70 years), there is no evidence that nebivolol is more effective in any age group than other beta blockers used in heart failure.
- Nebivolol is contraindicated in people with hepatic impairment and should be avoided in severe renal impairment.
- Start nebivolol at a low dose (1.25 mg once daily) and slowly titrate to the maximum tolerated dose (up to 10 mg once daily).
- As for other beta blockers, worsening heart failure, bradycardia and dizziness are common during dose titration.
- Avoid stopping nebivolol abruptly, as this can worsen heart failure, or precipitate angina, myocardial infarction or ventricular arrhythmia in people with ischaemic heart disease.

PBS listing

Authority required (streamlined)

For people with moderate to severe heart failure who are stable on standard therapy, which must include an ACE inhibitor or an angiotensin II-receptor antagonist, if tolerated.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of nebivolol on a cost minimisation basis — that is, similar efficacy and cost — compared with bisoprolol, carvedilol and metoprolol.¹

The decision was based on 3 head-to-head trials with carvedilol that compared effects on surrogate measures of heart failure. The PBAC accepted that nebivolol caused similar improvements in surrogate measures (change in left ventricular ejection fraction [LVEF], change in 6-minute walk test and New York Heart Association [NYHA] class improvement) to those of carvedilol, and had a comparable safety profile. The PBAC also considered an indirect comparison with other beta blockers (bisoprolol, carvedilol and metoprolol) versus placebo for evidence of patient-relevant outcomes in heart failure.

Place in therapy

Nebivolol is a selective beta₁-receptor antagonist. It is effective in chronic heart failure when used as an adjunct to ACE inhibitors (or angiotensin II-receptor antagonists) and/or diuretics.^{2–6} Nebivolol is also approved for hypertension but is not PBS listed for this indication.

Nebivolol has been available in Europe for treating hypertension for more than 10 years, and for heart failure for about 2 years. It has been available in the US for hypertension for 2 years. The US Food and Drug Administration's advisory panel recently voted against approval to register nebivolol for heart failure in the US based on insufficient evidence of effectiveness.^{7,8}

Evidence for functional improvement in heart failure is comparable to that of other beta blockers, but nebivolol has less robust evidence of survival benefit. Although the trial investigating patient-relevant outcomes with nebivolol was conducted in an older population than other beta-blocker trials, there is no evidence that nebivolol is more effective in any age group than other beta blockers used in heart failure.

Nebivolol is an alternative to other beta blockers used in heart failure but has less robust evidence of survival benefit

Clinical trials suggest that nebivolol has a similar effect on surrogate outcomes in heart failure to that of bisoprolol, carvedilol, or metoprolol. Nebivolol provides improvements in functional capacity (LVEF % improvement and distance walked over 6 minutes) and symptom severity (improvement in New York Heart Association class [www](#)) comparable to those of carvedilol, with no major differences in the adverse-effect profiles of the two drugs.²⁻⁴

However, evidence for the effect of nebivolol on rate of hospitalisation or death in people with heart failure is less robust than that for other beta blockers. In the only trial to investigate its effects on morbidity and survival (SENIORS), nebivolol marginally reduced the risk of a composite outcome of death or cardiovascular hospitalisation, compared with placebo. But, unlike similar trials with other beta blockers, nebivolol had no effect on death rate alone or on the rate of cardiovascular hospitalisation alone.⁵ No trials have directly compared morbidity and mortality outcomes in heart failure between nebivolol and other beta blockers.

Weighing up the benefits of nebivolol against those of other beta blockers is hampered by differences in study populations

The population studied in the major trial for nebivolol was intended to represent older people with heart failure in the community, a group not well studied in other beta-blocker trials.⁹ People in the SENIORS trial were, on average, older and more were women than in other beta-blocker trials. Unlike people in other major beta-blocker trials¹⁰⁻¹², a proportion had preserved systolic ventricular function (see Table 1).

The trial investigated the efficacy and safety of nebivolol compared with placebo in people aged ≥ 70 years with a clinical history of heart failure (discharged from hospital in the previous 12 months with a diagnosis of congestive heart failure or with an LVEF $\leq 35\%$ in the previous 6 months). Nebivolol was started at 1.25 mg daily and titrated as tolerated to a maximum of 10 mg once daily with a mean follow-up of 21 months.

Compared with placebo, nebivolol marginally reduced the proportion of people who experienced the composite endpoint of death or cardiovascular hospital admission (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74 to 0.99). However, there was no difference between nebivolol and placebo on death rate alone.⁵ In contrast, other major trials of beta blockers have consistently found more than a 30% reduction in death rate after 1 year of treatment¹³ (see Table 2).

Differences in patient populations may account for the discrepancy in survival benefit between nebivolol and other beta blockers. A post hoc analysis of a subgroup from SENIORS, which more closely matched other trial populations (< 75.2 years with an ejection fraction $\leq 35\%$, $n = 684$), found a similar mortality benefit with nebivolol to that of other beta blockers (HR 0.62, 95% CI 0.43 to 0.89).⁵ However, the results of this unplanned analysis should be interpreted with caution. Further research is needed to confirm the survival benefit of nebivolol.

Table 1: Patient characteristics in major trials of beta blockers in heart failure^{5,10-12}

Drug and trial	Age mean (years)	Female (%)	LVEF mean (%)
Nebivolol SENIORS $n = 2128$	76	38	36
Carvedilol COPERNICUS $n = 2289$	63	21	20
Bisoprolol CIBIS-II $n = 2647$	61	19	28
Metoprolol-CR MERIT-HF $n = 3991$	64	23	28

Table 2: Effect of beta blockers on all cause mortality in heart failure^{5,10-12}

Trial	Drug	Treatment effect* (95% CI)
SENIORS	Nebivolol	0.88 (0.71 to 1.08) [†]
COPERNICUS	Carvedilol	0.65 (0.52 to 0.81)
CIBIS-II	Bisoprolol	0.66 (0.54 to 0.81)
MERIT-HF	Metoprolol-CR	0.66 (0.53 to 0.81)

* Hazard ratios with 95% confidence intervals, except for MERIT-HF, reported as relative risk
† Not significant

[www](#) Refer to this review at www.npsradar.org.au for more information about New York Heart Association classification of heart failure.

Nebivolol is no more effective than other beta blockers in older people

Despite the SENIORS trial population being markedly older than people in other beta-blocker trials, there is no evidence to suggest that nebivolol is more effective in this age group than other beta blockers. In the SENIORS population, the effect of nebivolol appeared to be independent of age, gender, or LVEF.¹⁴ Nebivolol's vasodilatory properties (thought to be due to nitric oxide modulation) are of unknown clinical relevance.¹⁴

Safety issues

The adverse-effect profile of nebivolol is similar to those of other beta blockers used in heart failure.^{2,3,5,6} The most common adverse effects reported in the SENIORS trial for nebivolol and placebo, respectively, were:¹⁴

- bradycardia (11% versus 2%)
- dizziness (14% versus 13%)
- hypotension (7% versus 7%)
- fatigue (6% versus 5%).

Worsening heart failure was reported in about 20% of patients in each group.¹⁴ Most adverse events with nebivolol were reported during the titration period (see below).¹⁴

Nebivolol is contraindicated in people with hepatic impairment, because of limited experience in this population. Patients with liver enzyme levels ≥ 3 times the upper limit of normal were excluded from the SENIORS trial.⁹ Avoid use in people with severe renal impairment (serum creatinine concentration ≥ 250 micromol/L), as there is no experience in these patients.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Monitor vital signs closely when starting or titrating nebivolol

Do not start nebivolol in people who have had acute heart failure in the past 6 weeks.¹⁴ Assess heart rate, blood pressure and clinical status before starting nebivolol and before increasing the dose. Do not increase the dose unless the patient is stable (see below). Discuss each of the common adverse effects of nebivolol with the patient and what to do if they experience them (see Information for patients).

The manufacturer recommends that people starting nebivolol or receiving a dose increase are observed under the supervision of an experienced doctor for at least 2 hours to ensure that they remain clinically stable¹⁴, which is consistent with the SENIORS protocol. A similar recommendation was included in the product information for other beta blockers when first approved for heart failure, but has since been removed.¹⁵ There appears to be no pharmacological reason why monitoring during the dose titration of nebivolol should be different from that of other beta blockers used in heart failure.

Worsening heart failure, bradycardia and dizziness can sometimes be managed without stopping nebivolol

If worsening heart failure or intolerance (e.g. low heart rate, hypotension, dizziness) is experienced during dose titration, consider reducing the dose stepwise and extending the dose titration interval (see Dosing issues).¹⁴ Adjusting the dose of concomitant diuretic or ACE inhibitor first may be more appropriate for some symptoms (e.g. pulmonary oedema).^{16,17} Try not to stop nebivolol abruptly, because this can worsen heart failure, or precipitate angina, myocardial infarction or ventricular arrhythmia in people with ischaemic heart disease.¹⁴ To stop nebivolol, gradually reduce the dose by halving it each week.¹⁴

However, if symptoms are severe (e.g. severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic bradycardia or AV block), consider stopping nebivolol and closely monitor the patient. Hospital admission is probably indicated in such cases.

Limited experience in severe heart failure

Most patients treated with nebivolol in the SENIORS trial were NYHA grade II or III (94%), and only about 2% had severe heart failure (NYHA grade IV). Another placebo-controlled study with nebivolol had a similar proportion of people with NYHA grade IV heart failure.⁶ Head-to-head trials with nebivolol have excluded people with severe heart failure.²⁻⁴

Some SSRIs may increase the risk of adverse effects with nebivolol

Cytochrome P450 2D6 inhibitors such as paroxetine and fluoxetine may increase plasma concentrations of nebivolol. This could increase the risk of bradycardia and other adverse effects¹⁴, particularly if cytochrome P450 2D6 inhibitors are started after titrating the nebivolol dose.

Dosing Issues

Start with 1.25 mg once daily for 1–2 weeks. Titrate up in a stepwise manner to the maximum tolerated dose (up to 10 mg daily).¹⁴ Nebivolol can be taken with or without food.¹⁴

Titrate slowly according to patient tolerance

If the starting dose is tolerated and the patient is stabilised, increase the dose to 2.5 mg once daily for 1–2 weeks*, then, as tolerated, to 5 mg once daily for 1–2 weeks, then, as tolerated, to the maximum of 10 mg once daily.

Note that nebivolol is also indicated for hypertension, but has a different dosing regimen for this indication.

Individual tolerance may vary

In the SENIORS trial, 68% of patients treated with nebivolol reached a dose of 10 mg daily and a further 12% reached 5 mg daily.⁵ No special dosage adjustment is required in older people, in people with mild to moderate renal impairment, or in poor metabolisers of nebivolol.[†] The dose of nebivolol should always be titrated to the maximum tolerated dose (no more than 10 mg once daily) for the individual. Poor metabolisers, who have about 1.4 times the plasma concentration of nebivolol and active metabolites as extensive metabolisers, may not tolerate nebivolol as well and may require a lower ultimate dose.

* NICE guideline on heart failure suggests doubling the dose of beta blockers at not less than 2-weekly intervals.¹⁷

† Metabolism of nebivolol depends on cytochrome P450 2D6, which is subject to genetic polymorphism

Information for patients

Advise patients¹⁸:

- that nebivolol improves symptoms of heart failure and reduces the risk of dying or being admitted to hospital with heart problems
- that initial worsening of some symptoms of heart failure is common. Patients should promptly see their doctor if they experience breathlessness, tiredness, or increased swelling in their legs or stomach
- to go immediately to the Emergency department at their local hospital if they experience severe lightheadedness, dizziness or fainting
- that they will start on a low dose that is then gradually increased over a number of weeks to the dose best for them
- to stand up slowly when getting out of bed or up from a chair, to lessen dizziness or lightheadedness
- that they must drink enough water when exercising and in hot weather, to avoid sudden drops in blood pressure (lightheadedness)
- that they must not stop taking nebivolol without speaking to their doctor, because abruptly stopping could make their condition worse.

Discuss the Nebilet consumer medicine information (CMI) leaflet with the patient.

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Date published: March 2010

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