

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Nebivolol

Nebivolol is the newest addition to the range of beta blockers used for heart failure. This selective beta-1 receptor antagonist has been used in many countries for the treatment of hypertension, and more recently for heart failure.

The Australian Therapeutics Goods Administration (TGA) recently approved nebivolol for use in chronic heart failure in addition to other standard therapies. Three studies have directly compared nebivolol with carvedilol, a non-selective beta and alpha-1 blocker. Results demonstrated that the two agents were comparable in efficacy and safety; however, the outcomes tested were based on surrogate endpoints, such as improvements in left ventricular function, a six-minute walk test, and improvements in exercise capacity.

Mortality and rates of hospital admissions were outcomes measured in the SENIORS trial. In comparison to previous beta blocker trials in heart failure patients, this trial was designed to include an older patient population (≥ 70 years old). Subjects were included if they had a diagnosis of heart failure and, either a documented Left Ventricular Ejection Fraction (LVEF) $\leq 35\%$, or a hospital admission for heart failure within the previous year. In this study, 2135 patients were enrolled and randomized to either nebivolol 1.25mg daily or placebo. This dose was titrated over 16 weeks to a maximum of 10mg daily, as tolerated, with the mean maintenance dose of 7.7mg daily.

The combined primary outcome of all cause mortality or hospital admission was significantly reduced in the nebivolol group by 14%; however, the secondary outcome of all cause mortality alone was not significantly reduced. Studies of other beta blockers have shown greater than 30% reductions in mortality in heart failure patients. There have not been any randomised controlled trials comparing mortality outcomes of nebivolol to other beta blockers; however, a post-hoc analysis of the SENIORS trial including only those patients with similar characteristics to previous beta blocker studies (< 75.2 years with an ejection fraction of $\leq 35\%$) found similar mortality benefits. This suggests the lack of mortality benefits in the nebivolol group may be a result of the older population included in the SENIORS trial.

When adjusting for various factors, including ejection fraction, there was no change in the combined primary outcome of the SENIORS trial. This is an important finding, considering there is little data regarding the treatment of heart failure patients with preserved systolic function; however, further research in this area is warranted.

Adverse effects in the SENIORS trial were similar to those seen in other beta blocker trials, with bradycardia, dizziness, hypotension, and fatigue being the most common. Nebivolol is metabolised through Cytochrome P450 2D6; therefore, potential interactions may occur with enzyme inhibitors such as paroxetine and fluoxetine. The use of nebivolol is contraindicated in severe hepatic and renal insufficiency due to limited data in these patients.

In comparison to other beta blockers, nebivolol is unique because it modulates the release of nitric oxide (NO). Lack of nitric oxide bioavailability has been implicated in arterial stiffness. Hence, it has been suggested that nebivolol may have further advantages for treating cardiovascular disease; however, these potential benefits have not been proven.

This E-Bulletin is based on work by Heather Forbes, Utility Pharmacist, RGH

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