Editorial Comment

# Clinical Use of Nebivolol in the Treatment of Chronic Heart Failure

Evagelos N. Liberopoulos, Moses S. Elisaf

*Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*

Key words:
**Nebivolol, heart failure, beta-blockers, dilated cardiomyopathy, treatment.**

*Address:*
Moses S. Elisaf

*Department of Internal Medicine*
*School of Medicine*
*University of Ioannina*
*45110 Ioannina,*
*Greece*
*e-mail:*
*egepi@cc.uoi.gr*

Chronic heart failure (CHF) is a common cause of morbidity and mortality in the developed world.[1] The goals of CHF treatment are to improve symptoms, prevent hospitalisation and disease deterioration, as well as to prolong survival.[2] CHF is characterised by activation of the sympathetic and the renin-angiotensin-aldosterone systems. Therefore, inhibition of these two systems is the mainstay of current treatment guidelines.[3,4] Substantial data from numerous clinical trials support the use of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, aldosterone blockers and beta-blockers.[2]

Not many years ago beta-blockers were absolutely contraindicated in patients with CHF, because of their negative inotropic effects. However, several randomised, placebo-controlled clinical trials[5-8] have shown unequivocally that treatment with certain beta-blockers results in a significant reduction of the risk of death in patients with CHF and a reduced left ventricular ejection fraction (LVEF). The beta-blockers used in those trials were bisoprolol,[5] carvedilol,[6,7] and metoprolol controlled release/extended release (CR/XL).[8] The decrease in mortality (approximately by 33% compared with placebo) in these trials was accompanied by similarly large and statistically significant reductions in hospital admissions due to CHF worsening. The beneficial effects of beta-blockade in CHF are mainly attributed to the reversal of the beta-adrenergic signal transduction abnormalities as well as to the retardation of the remodelling process.[9] Furthermore, beta-blockers exhibit antiarrhythmic effects, decrease heart rate, blood pressure and myocardial oxygen demand, and increase LVEF.[9] The benefits of beta-blockers in CHF do not seem to represent a class effect. Specifically, therapy with bucindolol demonstrated no benefit,[10] while carvedilol was superior to short-acting metoprolol tartrate in reducing the mortality rate in another trial.[11] Therefore, a particular beta-blocker has to prove its efficacy in large, randomised mortality trials before it can be recommended for the treatment of CHF.

Nebivolol is a third-generation, highly selective beta-1-blocker with vasodilating properties mediated by the endothelial release of nitric oxide (NO).[12] Nebivolol administration decreases peripheral resistance, improves endothelial function, decreases arterial stiffness, reduces preload and afterload due to systemic vasodilation, and increases stroke volume, resulting in the preservation of cardiac output despite reduced heart rate.[13] In addition, nebivolol exhibits anti-proliferative and antioxidant properties.[14] Moreover, we have shown that nebivolol use is associated with a more beneficial metabolic profile compared with atenolol in hypertensive patients with dyslipidaemia.[15]

Nebivolol use is a well-established option in the pharmacotherapy of hyperten-

sion.[12] However, is there clinical evidence to support its use in the treatment of CHF? In a primary study,[16] 22 patients with idiopathic dilated cardiomyopathy (LVEF: 0.15-0.40) were randomly assigned to receive placebo or nebivolol (1-5 mg/day) for 3 months. Nebivolol significantly improved stroke volume, LVEF and left ventricular end-diastolic pressure compared with placebo, by improving systolic contractile performance.[16] In another trial,[17] nebivolol administration (2.5 or 5 mg/day) was accompanied by a trend towards clinical and functional improvement compared with placebo in CHF patients. In a pilot study[18] involving 12 CHF patients (LVEF: 0.13-0.39) nebivolol (2.5 and 5 mg/day) resulted in increased LVEF after 12 weeks, compared with placebo. New York Heart Association (NYHA) class improved in 4 of the 6 patients in the nebivolol group.[18] Furthermore, nebivolol administration for 6 months was associated with a greater haemodynamic improvement compared with atenolol in 26 patients with diastolic CHF and hypertension.[19]

In this issue of the *Hellenic Journal of Cardiology*, Patrianakos et al[20] report the effect of nebivolol on cardiac performance and exercise capacity in patients with non-ischaemic dilated cardiomyopathy (LVEF<0.45, NYHA class II-III). In this well-organised study, patients (n=60, age 55.0 ± 9.5 years) were randomised to receive placebo or nebivolol (1.25 to 5 mg/day) and were followed for 3 months. Nebivolol administration resulted in a significant improvement in NYHA class (p=0.001), LVEF (p=0.01), left ventricular end-systolic volume (p=0.046), resting heart rate (p=0.03), as well as in systolic and diastolic blood pressure (p<0.001), compared with placebo. In addition, nebivolol improved markers of diastolic cardiac function. Drug withdrawal rates were not different between the two groups (13.3% on nebivolol vs. 16.6% on placebo) and nebivolol was well-tolerated. The target dose of 5 mg nebivolol/day was achieved in 68% of patients. On the other hand, maximum exercise duration significantly (p=0.01) decreased in the nebivolol group compared with placebo, possibly due to a decrease (p<0.001) in maximum heart rate during exercise. This may offset the favourable haemodynamic effects achieved by improved contractility.[9] In contrast, nebivolol did not reduce the exercise capacity of CHF patients in other studies.[17,18] Moreover, metoprolol increased the exercise time non-significantly (p=0.08) in patients with CHF due to ischaemic or idiopathic dilated cardiomyopathy compared with placebo.[21] Differences in study participant characteristics, initial LVEF, therapy duration, aetiology of CHF and dose of beta-blocker used may account for the effects observed.

Nebivolol may also exert some pleiotropic effects in CHF by increasing endothelial NO release. Indeed, CHF is associated with endothelial dysfunction by different mechanisms, such as reduced synthesis and release of NO and increased NO degradation.[22] Notably, this endothelial dysfunction is associated with an increased mortality risk in subjects with both ischaemic and non-ischaemic CHF.[23]

Although the above studies provided evidence that nebivolol improves cardiac performance in patients with CHF, data regarding the effect of this drug on mortality and hospital admissions were lacking. The recent Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS)[24] was undertaken to address those issues. SENIORS differed from other studies with beta-blockers[5-8,10,11] in that it included older patients (≥70 years) regardless of their LVEF. Patients with a history of CHF (n=2128, 68.2% of whom had a history of coronary artery disease) were randomly assigned to receive nebivolol (titrated from 1.25 to 10 mg/day) or placebo and were followed up for 21 months. The primary outcome was a composite of all cause mortality or cardiovascular hospital admission (time to first event). The primary outcome occurred in 332 patients (31.1%) on nebivolol compared with 375 patients (35.3%) on placebo (relative risk reduction: 14%, hazard ratio [HR]: 0.86, 95% confidence interval [CI]: 0.74-0.99, p=0.039). The beneficial effects appeared after 6 months of treatment and the risk reduction continued to increase with longer treatment. There was no significant influence of age, gender, prior myocardial infarction or LVEF on the effect of nebivolol on the primary outcome. All-cause death occurred in 169 patients (15.8%) on nebivolol and 192 patients (18.1%) on placebo (HR: 0.88, 95% CI: 0.71-1.08, p=0.21).[24] Cardiovascular hospital admissions were 24% and 26% in the nebivolol and placebo groups, respectively (HR: 0.90, 95% CI: 0.76-1.06, p=0.20). In SENIORS, the magnitude of the beneficial effects of nebivolol appears to be less than that observed in other similar trials (15% vs. 33% relative risk reduction, respectively).[25] Differences in the age of patients recruited, LVEF at study outset, duration of follow-up, as well as in the particular beta-blocker used may be possible explanations. In order to put the results of SENIORS in the context of previous beta-blocker trials, which recruited younger patients and excluded patients with higher LVEF, the investigators identified the subgroup of pa-

tients most similar to the previous major outcome trials. In a post-hoc analysis, the HR for the primary outcome was 0.73 (95% CI: 0.56-0.96) in this subgroup (n=684). For all cause mortality alone, the HR was 0.62 (95% CI: 0.43-0.89). This suggests an efficacy for nebivolol equal to that seen in similar patient cohorts for metoprolol CR/XL, bisoprolol and carvedilol. Furthermore, study medication in SENIORS was well tolerated and many patients (68%) were able to reach a maintenance dose of 10 mg once daily after careful titration.

SENIORS extended the evidence of the benefit of beta-blockade to a broad range of elderly patients with CHF, including those with mild left ventricular dysfunction or preserved ventricular function. Based on these results, nebivolol can be recommended for the treatment of CHF irrespective of age and initial LVEF. Nevertheless, patients (especially the elderly) are not frequently prescribed these effective drugs.[26] What may be more important than selecting a certain beta-blocker is to implement trial results in clinical practice. As with statins in patients with acute coronary syndrome,[27] the inpatient initiation of a beta-blocker is beneficial for stable patients who are hospitalised with CHF.[28]

## References


1. Haldeman GA, Croft JB, Giles WH, Rashidee A: Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999; 137: 352-360.
2. Yan AT, Yan RT, Liu PP: Narrative review: Pharmacotherapy of chronic heart failure: Evidence from recent clinical trials. Ann Intern Med 2005; 142: 132-145.
3. Remme WJ, Swedberg K: Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Eur J Heart Fail 2002; 4: 11-22.
4. Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2001. Accessed at www.acc.org/clinical/guidelines/ failure/hf_index.htm.
5. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9-13.
6. Packer M, Bristow MR, Cohn JN, et al: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334: 1349-1355.
7. Packer M, Coats AJ, Fowler MB, et al: Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-1658.
8. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001-2007.
9. Satwani S, Dec GW, Narula J: β-Adrenergic blockers in heart failure: Review of mechanisms of action and clinical outcomes. J Cardiovasc Pharmacol Ther 2004; 9: 243-255.
10. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001; 344: 1659-1667.
11. Poole-Wilson PA, Swedberg K, Cleland JG, et al: Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003; 362: 7-13.
12. Cockcroft J: Nebivolol: A review. Expert Opin Pharmacother 2004; 5: 893-899.
13. Zanchetti A: Clinical pharmacodynamics of nebivolol: New evidence of nitric-oxide mediated vasodilating activity and peculiar haemodynamic properties in hypertensive patients. Blood Press Suppl 2004; 1:17-32.
14. Kuroedov A, Cosentino F, Luscher TF: Pharmacological mechanisms of clinically favorable properties of a selective beta1-adrenoceptor antagonist, nebivolol. Cardiovasc Drug Rev 2004; 22: 155-168.
15. Rizos E, Bairaktari E, Kostoula A, et al: The combination of nebivolol plus pravastatin is associated with a more beneficial metabolic profile compared to that of atenolol plus pravastatin in hypertensive patients with dyslipidaemia: A pilot study. J Cardiovasc Pharmacol Ther 2003; 8: 127-134.
16. Wisenbaugh T, Katz I, Davis J, et al: Long-term (3-month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. J Am Coll Cardiol 1993; 21: 1094-1100.
17. Uhlir O, Dvorak I, Gregor P, et al: Nebivolol in the treatment of cardiac failure: A double-blind controlled clinical trial. J Card Fail 1997; 3: 271-276.
18. Brehm BR, Wolf SC, Gorner S, Buck-Muller N, Risler T: Effect of nebivolol on left ventricular function in patients with chronic heart failure: A pilot study. Eur J Heart Fail 2002; 4: 757-763.
19. Nodari S, Metra M, Dei Cas L: Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized comparison of the long-term effects of atenolol vs. nebivolol. Eur J Heart Fail 2003; 5: 621-627.
20. Patrianakos AP, Parthenakis FI, Mavrakis HE, et al: Effects of nebivolol on left ventricular function and exercise capacity in patients with non-ischemic dilated cardiomyopathy. A randomised placebo-controlled study. Hell J Cardiol 2005; 46: 199-207.
21. Waagstein F, Stromblad O, Andersson B, et al: Increased exercise ejection fraction and reversed remodelling after long-term treatment with metoprolol in congestive heart failure: A randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischemic or idiopathic dilated cardiomyopathy. Eur J Heart Fail 2003; 5: 679-691.
22. Tousoulis D, Charakida M, Stefanadis C: Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure. Int J Cardiol 2005; 100: 347-353.
23. Katz SD, Hryniewicz K, Hriljac I, et al: Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005; 111: 310-314.
24. Flather M, Shibata M, Coats A, et al: Randomized trial to determine the effect of nebivolol on mortality and cardiovascu-

lar hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005; 26: 215-225.
25. McMurray J: Making sense of SENIORS. Eur Heart J 2005; 26: 203-206.
26. Komajda M, Follath F, Swedberg K, et al: Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme-a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003; 24: 464-474.
27. Liberopoulos EN, Daskalopoulou SS, Mikhailidis DP: Early statin therapy in patients with acute coronary syndrome. Hell J Cardiol 2005; 46: 5-8.
28. Ventura HO: Benefits of inpatients initiation of β-blockers. Am Heart J 2004; 148: 944-950.