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Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: Data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial

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Background   The SENIORS trial showed that nebivolol reduced the risk of death or cardiovascular (CV) hospitalization in elderly patients with heart failure (HF). We aimed to assess tolerability and dose-related effects of the β-blocker nebivolol in elderly patients from the SENIORS trial.

Methods   Patients assigned to nebivolol (n = 1031) were classified into 4 groups, according to the dose achieved at the end of titration phase (maintenance dose): 0 mg (n = 74), low dose (1.25 or 2.5 mg, n = 142), medium dose (5 mg, n = 127), and target dose (10 mg, n = 688) and compared with those allocated to placebo (n = 1030). Age, sex and ejection fraction were similar between the groups, but prior myocardial infarction, coronary revascularization, and serum creatinine levels were lower in patients who achieved higher maintenance doses of nebivolol.

Results   After adjustment, all-cause mortality or CV hospitalization was significantly reduced in the 10 mg dose group compared with placebo (hazard ratio [HR] 0.75, 95% CI 0.63-0.90) which was similar to the medium dose group (HR 0.73, 95% CI 0.52-1.02). The low dose group had an apparently lower benefit (HR 0.88, 95% CI 0.64-1.20), whereas patients unable to tolerate any dose of nebivolol had an increased risk of death or CV hospitalization (HR 1.95, 95% CI 1.38-2.75).

Conclusions   The benefits of nebivolol in elderly patients with HF appear to be related to the maintenance dose achieved. Patients unable to tolerate any dose have the worst prognosis. (Am Heart J 2007;154:109-15.)

Heart failure (HF) is a major public health problem among the elderly. In Europe, 6% to 10% of people >65 years of age have HF, and the average age of the patient in the community is 76 years.[1-3] The syndrome of HF may arise in presence of either a depressed or apparently normal left ventricular ejection fraction (LVEF).[4] In older patients, HF with preserved LVEF is more common than in younger patients.[5,6]

In elderly patients with HF, the prescription of a β-blocker raises concerns about tolerability and efficacy. Recent data suggest that β-blockers are well tolerated in the elderly,[7] yet target doses may be difficult to achieve in certain subgroups, such as patients with low blood pressure (BP) and those with advanced disease.[8-10] In turn, prescription of low doses may raise concerns over efficacy because older patients may respond differently to medication.[11]

In patients with HF, one randomized trial has shown that β-blockade produces a dose-dependent improvement in

Table I. Baseline characteristics in relation to dose of study medication achieved at the end of titration phase

Baseline characteristics	Placebo (n = 1030)	Nebivolol				P*
		Intolerant to any dose (n = 74)	Low dose (1.25 + 2.5 mg) (n = 142)	Medium dose (5 mg) (n = 127)	High dose (10 mg) (n = 688)	
Demographics and major baseline characteristics						
Age (y)	76 ± 4.5	76.7 ± 5.1	76.6 ± 4.9	76.9 ± 4.9	75.7 ± 4.5	.002
Sex (women) (%)	35.6	40.5	35.2	29.1	40.7	.09
NYHA (III + IV) (%)	41.1	45.9	40.1	40.9	39.7	.47
LVEF (%)	36.2 ± 12.1	34.9 ± 14.5	35.7 ± 13.0	37.4 ± 12.8	35.9 ± 12.1	.98
LVEF ≤35% (%)	64.6	67.6	65.2	63.5	64.1	.68
Heart rate (beat/min)	78.8 ± 13.6	76.7 ± 12.4	72.8 ± 10.1	76.7 ± 13.2	81.0 ± 13.9	<.001
SBP (mm Hg)	139.8 ± 21.1	137.4 ± 23.1	134.2 ± 20.6	135.3 ± 18.6	140.7 ± 19.5	<.001
DBP (mm Hg)	80.8 ± 11.3	77.7 ± 11.2	78.4 ± 10.6	78.7 ± 11.4	81.8 ± 10.5	<.001
Creatinine (μmol/L)	102.7 ± 34.2	110.3 ± 40.5	107.0 ± 39.1	105.3 ± 33.6	98.7 ± 33.3	<.001
Medical history (%)						
Atrial Fibrillation	35.6	29.7	33.8	32.3	33.7	.63
Diabetes	25.0	35.1	31.7	22.8	25.9	.12
Hypertension	62.3	52.7	55.6	57.5	64.7	.004
Myocardial infarct	43.6	56.8	55.6	46.5	40.0	<.001
Prior CABG	8.8	21.6	12.0	10.2	7.8	<.001
Prior PTCA	3.3	9.5	6.3	6.3	2.9	.002
Smoking	5.3	6.8	4.2	6.3	4.5	.49
Medications (%)						
ACE Inhibitors	83.3	78.4	85.2	81.9	82.8	.83
Aldosterone Antagonists	26.0	29.7	35.2	46.5	23.5	<.001
Angiotensin II Antagonists	8.4	10.8	9.9	7.1	7.6	.29
Antiarrhythmics	18.4	29.7	26.8	17.3	10.9	<.001
Aspirin	51.1	56.8	50.7	54.3	53.5	.99
Ca antagonists	14.5	21.6	12.7	11.0	11.0	.07
Cardiac glycoside	43.0	31.1	38.7	42.5	41.3	.25
Diuretics	85.5	89.2	89.4	88.2	85.3	.11
Lipid-lowering drugs	22.3	29.7	22.5	20.5	20.5	.18
Vitamin K antagonists	24.3	20.3	26.1	16.5	21.7	.93

Data are shown as mean ± SD for continuous variables and as percentages for discrete variables. *ACE,* Angiotensin-converting enzymes.
*Resulting from the logistic regression model having nebivolol dose as response and each baseline characteristic as a covariate.

survival.[12] In contrast, subgroup analyses in major β-blocker trials have not shown a clear dose-response effect.[13,14] The average age of the patients in these trials was 63 years, and patients with LVEF >40% were excluded.

The SENIORS trial assessed the effects of the β-blocker nebivolol in elderly patients (age ≥70 years) with HF. About one third of the patients had a preserved LVEF.[15] Nebivolol was initiated with a low dose and, if tolerated, was carefully up-titrated to a target dose of 10 mg daily. Overall, nebivolol reduced the combined end point of death or cardiovascular (CV) admission. This outcome represented an average-dose effect of nebivolol, as the trial was not designed as a dose-response study. As yet, there have been no studies relating dose response to outcome in an elderly population with HF; in this study, we aimed to assess tolerability and dose-related effects of nebivolol in patients from the SENIORS trial.

Methods

Patients

The study design and main findings of SENIORS have been published previously.[15,16] Briefly, 2128 patients ≥70 years of age and with a history of HF were randomly assigned to nebivolol (1067 patients) or placebo (1061 patients). The initial dose of nebivolol was 1.25 mg once daily and, if tolerated, was increased to 2.5 and 5 mg, respectively, every 1 to 2 weeks, aiming to reach a target of 10 mg once daily over a maximum of 16 weeks. Up-titration could be stopped or delayed depending on symptoms, side effects, or the judgment of the local investigator. Overall, nebivolol reduced the combined end point of death or CV admission compared with placebo (hazard ratio [HR] 0.86, 95% CI 0.74-0.99, P = .039).

This study includes all those patients who reached a maintenance dose or who did not tolerate any dose by the end of titration phase. We analyzed the data by classifying the patients assigned to nebivolol into 4 groups, according

Table II. Relative risk of outcome events with nebivolol compared with placebo

| | | Nebivolol | | | | | | | |
| | | Intolerant to any dose (n = 74) | | Low dose (1.25 +2.5 mg) (n = 142) | | Medium dose (5 mg) (n = 127) | | High dose (10 mg) (n = 688) | |
Outcomes	Placebo (n = 1030)	%	HR*	%	HR	%	HR	%	HR
All-cause mortality or CV hospitalization	34.7	52.7	1.95 (1.38-2.75)	31.7	0.88 (0.64-1.20)	29.9	0.73 (0.52-1.02)	27.6	0.75 (0.63-0.90)
All-cause mortality or all-cause hospitalization	41.1	62.2	2.11 (1.54-2.89)	43.0	1.04 (0.79-1.36)	37.8	0.77 (0.57-1.04)	33.9	0.78 (0.66-0.92)
CV mortality or CV hospitalization	32.4	48.6	2.30 (1.61-3.30)	28.9	0.86 (0.62-1.19)	29.1	0.75 (0.53-1.06)	25.1	0.73 (0.60-0.88)

*Hazard ratio (95% CI) adjusted for age, sex, heart rate, SBP, DBP, creatinine, hypertension, myocardial infarction, prior CABG, prior PTCA, aldosterone antagonists, antiarrhythmics and calcium antagonists.

to the dose achieved by the end of titration phase (maintenance dose): 0 mg (patients who could not tolerate any dose), low dose (1.25 or 2.5 mg), medium dose (5 mg), and target dose (10 mg). A total of 67 patients (36 in the nebivolol group and 31 in the placebo group) were excluded from this analysis. These were patients who discontinued the study before the end of titration phase (16 weeks) despite initial tolerance of study drug. In the nebivolol group, discontinuation took place because of the following reasons: patient request (16), death (11), loss to follow-up (4), adverse event (stroke) (1), hospitalization (2), and worsening HF (2). In the placebo group, discontinuation took place as follows: patient request (17), death (9), loss to follow-up (1), adverse event (myocardial infarction) (1), patient not taking medication correctly (2), and mandatory indication for β-blocker (1). Most patients who died during the titration phase achieved only small doses of nebivolol. The population of the present study consisted therefore of 1031 patients in the nebivolol group and 1030 patients in the placebo group.

Clinical outcomes

The primary outcome was the composite of death or CV hospitalization. Secondary outcomes included the composite of all-cause mortality or all-cause hospitalization and the composite of CV mortality or CV hospitalization.

Statistical analysis

Logistic regression analysis was used to assess the relationship between each baseline characteristic and nebivolol dose groups. The association between dose of nebivolol and clinical outcomes was assessed using multivariate Cox proportional hazards models. We controlled for baseline characteristics that had an independent association with the dose achieved up to $P < .10$. Adjustment was performed with the following variables at baseline: age; sex; heart rate; systolic BP (SBP); diastolic BP (DBP); creatinine; history of hypertension; history of myocardial infarction; prior coronary artery bypass grafting (CABG); prior percutaneous coronary intervention (PTCA); and prescription of aldosterone antagonists, antiarrhythmics, and calcium antagonists. In the Cox proportional analysis, we compared each dose group with all

placebo patients that reached a maintenance dose or did not tolerate a maintenance dose (n = 1030). Results are expressed as HRs with 95% CI. Survival curves were estimated by the Kaplan-Meier method. Statistical analysis was performed by using SAS software (version 9.1, SAS Institute, Cary, NC).

Results
Baseline patient characteristics

Patient characteristics at baseline are shown in Table I. In the nebivolol group (n = 1031), a total of 688 (67%) patients reached the target dose, whereas 127 (12%) and 142 (14%) reached medium and low doses, respectively. Thus, about 90% of patients were able to tolerate a dose of nebivolol after the titration with about 80% achieving doses of ≥5 mg. A total of 74 (7%) patients were unable to tolerate a dose of nebivolol by the end of titration phase. Patients who only tolerated lower doses were older, had lower BPs, lower heart rates, and higher creatinine levels. Patients only tolerating low doses of nebivolol were also those who had a higher prevalence of myocardial infarction as the underlying cause of HF, whereas history of hypertension was more frequent among those tolerating target doses. No significant difference was observed across the 4 groups with regard to LVEF and New York Heart Association (NYHA) class, but a higher percentage of patients in NYHA III to IV were unable to tolerate a maintenance dose. In addition, there was no significant difference in associated comorbidities, such as atrial fibrillation or diabetes. The use of antiarrhythmics and calcium antagonists was higher among patients tolerating low doses, whereas a similar proportion received angiotensin-converting enzyme inhibitors or digitalis.

Approximately 70% of the patients remained on the same maintenance dose until the end o the study.

Figure 1
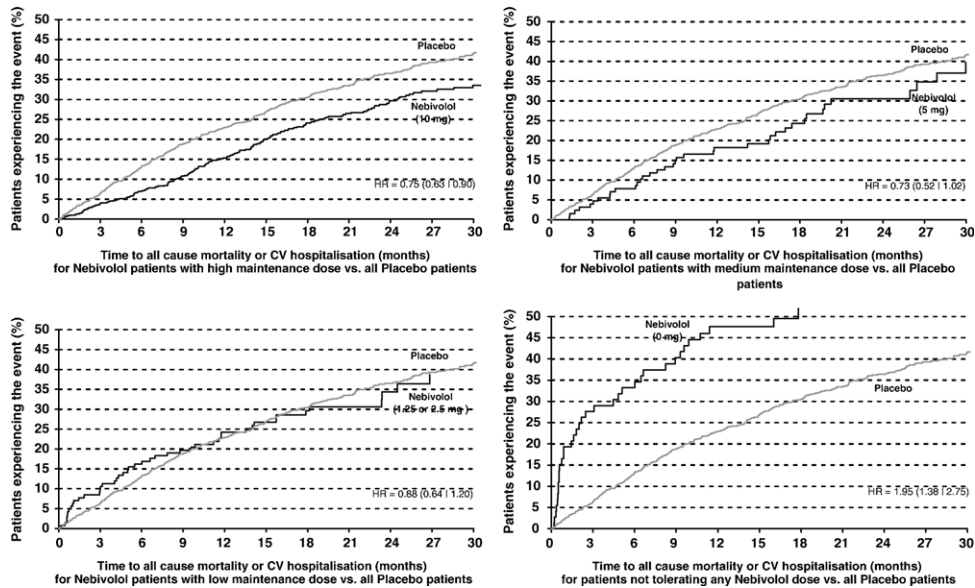
Kaplan-Meier survival curves in patients receiving placebo and nebivolol at different maintenance doses. Hazard ratio is given by the multivariate Cox analysis adjusted for baseline differences.

Clinical outcomes

In a univariate survival analysis, nebivolol at the target dose (10 mg) was associated with a significant reduction of all-cause mortality or CV hospitalization compared with placebo (HR 0.74, 95% CI 0.62-0.88). Nebivolol in medium (5 mg) and low dose (1.25 or 2.5 mg) was associated with a nonsignificant benefit (HR 0.81, 95% CI 0.58-1.13, and HR 0.94, 95% CI 0.69-1.29, respectively). Patients unable to tolerate any dose of nebivolol had a higher risk of death or CV admission (HR 2.15, 95% CI 1.55-3.00) compared the placebo group.
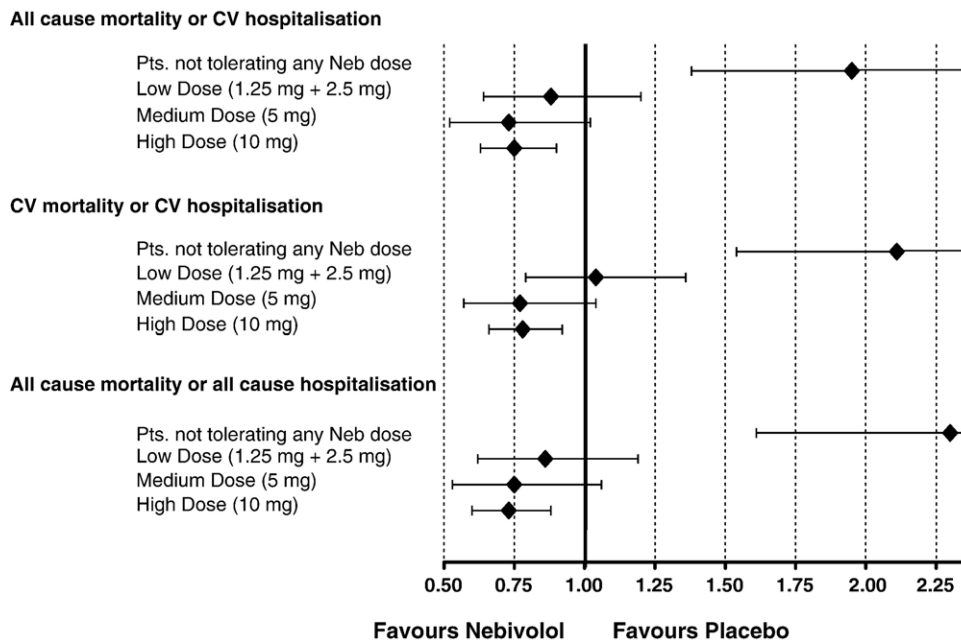
After adjustment, nebivolol in target dose remained associated with a significant reduction of all-cause mortality or CV hospitalization (HR 0.75, 95% CI 0.63-0.90) (Table II). The benefit on this composite measure was due to an improved outcome on both all-cause mortality and CV hospitalization (HR 0.84, 95% CI 0.65-1.08, and HR 0.76, 95% CI 0.62-0.94, respectively). Nebivolol in medium dose had a similar benefit to the target dose on all-cause mortality or CV hospitalization (HR 0.73, 95% CI 0.52-1.02), whereas nebivolol in low dose had an apparently lower benefit (HR 0.88, 95% CI 0.64-1.20). Other adjusted analyses are presented in Table II and are similar to the findings of the unadjusted analyses. The proportion of patients who suffered death or CV admission decreased with an increasing dose of nebivolol. Similarly, a higher proportion of patients on low doses experienced the composite secondary outcomes.

Figure 1 shows the Kaplan-Meier survival curves in patients receiving nebivolol at different doses or placebo. The beneficial effects of target and medium doses of nebivolol on primary outcome appeared early after the end of titration phase and were constant during follow-up. Patients intolerant to any dose of nebivolol had a markedly higher risk of death or CV hospitalization compared with placebo. Similar results were obtained on secondary outcomes (Table II and Figure 2).

Discussion

The present study shows that nebivolol is well tolerated in elderly patients with HF, with about 80% of patients reaching a maintenance dose of ≥5 mg. Only 7% of patients were unable to tolerate any maintenance dose of nebivolol. The data show a significant reduction in the risk of all-cause mortality and CV hospitalization when the target dose of nebivolol was compared with placebo. The beneficial effects appeared early after the beginning of treatment and were constant during follow-up. The 5 mg dose appeared to have a similar benefit as the 10 mg dose, whereas low doses achieved no benefit. However, the numbers of patients in these groups were too small to allow firm conclusions. An important novel finding of the present study is that patients unable to tolerate a maintenance dose of nebivolol had the worst outcome, with 2 times higher risk of death or CV hospitalization. Similar results were obtained on secondary outcomes.

Figure 2

All cause mortality or CV hospitalisation

Pts. not tolerating any Neb dose
Low Dose (1.25 mg + 2.5 mg)
Medium Dose (5 mg)
High Dose (10 mg)

CV mortality or CV hospitalisation

Pts. not tolerating any Neb dose
Low Dose (1.25 mg + 2.5 mg)
Medium Dose (5 mg)
High Dose (10 mg)

All cause mortality or all cause hospitalisation

Pts. not tolerating any Neb dose
Low Dose (1.25 mg + 2.5 mg)
Medium Dose (5 mg)
High Dose (10 mg)

0.50   0.75   1.00   1.25   1.50   1.75   2.00   2.25

Favours Nebivolol   Favours Placebo

Primary and secondary outcomes (HR with 95% CI) in patients receiving placebo versus nebivolol at different maintenance doses.

The tolerability of nebivolol is likely to have been influenced by clinical factors because patients unable to tolerate high doses had lower SBP and DBPs and lower heart rates. Further, they were slightly older and had a higher prevalence of renal dysfunction and diabetes. It is of note that patients unable to tolerate any dose did not differ significantly in mean LVEF and NYHA class, although a higher proportion of NYHA III to IV patients were included in this group. This finding agrees with previous data which showed that severity of HF per se did not predict successful β-blocker titration in patients with idiopathic dilated cardiomyopathy. Instead, that study showed that only low BP predicted which patients will develop problems during titration.[17] Other studies have also reported pretreatment BP as a predictor of β-blocker tolerability in patients with HF.[7,18-20] Although the tolerability of nebivolol (as with many drug treatments) may be dependent on a more favorable clinical profile, it is also possible that physicians were more likely to withhold the treatment if side effects occurred in "sicker" patients. Our data show that given the markedly increased risk on all outcomes in these patients, increased efforts should be made to initiate and maintain β-blocker therapy wherever possible in elderly patients with HF.[21]

Current European guidelines on HF treatment recommend initiation of β-blocker therapy with a small dose, and a gradual increase in dosage until target dose used in large clinical trials is achieved.[22] However, for obvious reasons most randomized controlled trials with β-blockers in HF were not designed as dose-response studies. To date, only the MOCHA trial, a relatively small, 6-month study was designed to evaluate the dose-related effects of carvedilol in patients with mild to moderate HF.[12] The study found a dose-related improvement in mortality and LVEF which broadly supports our findings on dose and clinical outcomes. In contrast to these findings, however, are subgroup analyses from both MERIT-HF and CIBIS II trials, which did not show a dose-response effect of metoprolol and bisoprolol on survival when compared with placebo.[13,14] However, it is difficult to examine from such post hoc analyses a true dose-response effect because sicker patients have higher levels of adrenergic activation,[23] and in such patients, lower β-blocker doses may already be sufficient to achieve a significant benefit. One other study in which the dose-response relation was examined was the COMET trial. This study showed a greater benefit of target versus subtarget doses of β-blockers, but these subtarget doses included patients on both medium and low doses.[24] In most of these trials, the mean age of the patients was much lower than in SENIORS (63 compared with 75 years), and patients with LVEF >40% were excluded.

Data from observational studies, which included patients with a broad range of LVEF, may be even

more difficult to interpret in relation to our findings. Two such studies found a similar benefit on survival with prescription of high- and low-dose β-blocker therapy.[25,26] In contrast, in the EuroHeart Failure Survey patients who were treated with high doses of β-blockers achieved a higher benefit than patients treated with low doses, but the biases in these analyses are likely to be larger than in our analysis.[27] In a cohort of patients with advanced HF and preserved LVEF, a higher benefit of high-dose versus low-dose β-blocker therapy was also observed.[28] However, in observational studies, high dose was defined as ≥50% of target dose achieved in randomized controlled trials, and therefore, no clear distinction between the effect of target-, medium-, and low-dose therapy was made. The results of these studies suggest that patients who achieve at least "medium" doses do better than those on "lower" doses, although there are no widely accepted definitions for these terms. Compared to the randomized trial setting, which use careful up-titration schedules to reach target doses, in clinical practice, a lower percentage of patients may actually receive target doses, and many patients only receive medium or low doses.[28] The important finding of the present study is that medium doses of 5 mg nebivolol may be effective in an elderly HF population.

A high proportion of patients (67%) reached the target dose of nebivolol in the SENIORS trial. Nebivolol is a β1-selective blocker whose mechanism of action combines β-adrenergic blocking activity with vasodilating properties mediated by nitric oxide modulation on endothelial cells.[29,30] This seemingly good tolerability of nebivolol may be related to its vasodilating properties.

Our study has a number of limitations. First, because it is a post hoc analysis, patients were not randomized to receive different doses of nebivolol, and the dose prescribed was influenced by patients' characteristics and physicians' decisions. Thus, the comparison between nebivolol-treated and control patients may have a number of biases. Second, medium- and low-dose groups included a small number of patients, and the analysis may have lacked the power to demonstrate a statistically significant effect. Third, there was some overlap on the maintenance doses of medication during follow-up, as well as a crossover in therapy that might have influenced the results. Finally, we assessed only composite outcomes as primary and secondary end points because the number of events in medium and low-dose nebivolol groups was too small for appropriate analysis of simple outcomes.

In conclusion, our analysis indicates that higher doses of nebivolol (medium to target) appear to give better results than lower doses. Nebivolol is also well tolerated in elderly patients with HF. Future randomized studies prospectively addressing the issue of dose and outcome are needed in a wide range of therapeutic areas.

References

1. Cowie MR, Wood DA, Coats AJ, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000;83:505‐10.
2. Kupari M, Lindroos M, Iivanainen AM, et al. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 1997; 241:387‐94.
3. Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; the Rotterdam study. Eur Heart J 1999;20:447‐55.
4. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001;344:17‐22.
5. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol 2003;41:217‐23.
6. Pernenkil R, Vinson JM, Shah AS, et al. Course and prognosis in patients > or =70 years of age with congestive heart failure and normal versus abnormal left ventricular ejection fraction. Am J Cardiol 1997;79:216‐9.
7. Krum H, Hill J, Fruhwald F, et al. Tolerability of beta-blockers in elderly patients with chronic heart failure: the COLA II study. Eur J Heart Fail 2006;8:302‐7.
8. Baxter AJ, Spensley A, Hildreth A, et al. Beta blockers in older persons with heart failure: tolerability and impact on quality of life. Heart 2002;88:611‐4.
9. Tandon P, McAlister FA, Tsuyuki RT, et al. The use of beta-blockers in a tertiary care heart failure clinic: dosing, tolerance, and outcomes. Arch Intern Med 2004;164:769‐74.
10. Macdonald PS, Keogh AM, Aboyoun CL, et al. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. J Am Coll Cardiol 1999;33:924‐31.
11. Lamy PP. Physiological changes due to age. Pharmacodynamic changes of drug action and implications for therapy. Drugs Aging 1991;1:385‐404.
12. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 1996;94:2807‐16.
13. Simon T, Mary-Krause M, Funck-Brentano C, et al. Bisoprolol dose-response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). Eur Heart J 2003;24:552‐9.
14. Wikstrand J, Hjalmarson A, Waagstein F, et al. Dose of Metoprolol CR/XL and clinical outcomes in patients with heart failure—analysis of the experience in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). J Am Coll Cardiol 2002;40:491‐8.
15. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215‐25.
16. Shibata MC, Flather MD, Bohm M, et al. Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS). Rationale and design. Int J Cardiol 2002;86:77‐85.

17. Anthonio RL, Van Veldhuisen DJ, Breekland A. et al. Beta-blocker titration failure is independent of severity of heart failure. Am J Cardiol 2000;85:509-12, A11.

18. Rouleau JL, Roecker EB, Tendera M, et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. J Am Coll Cardiol 2004;43:1423-9.

19. Butler J, Young JB, Abraham WT, et al. Beta-blocker use and outcomes among hospitalized heart failure patients. J Am Coll Cardiol 2006;47:2462-9.

20. Estep JD, Mehta SK, Uddin F, et al. Beta-blocker therapy in patients with heart failure in the urban setting: moving beyond clinical trials. Am Heart J 2004;148:958-63.

21. Waagstein F. Beta-adrenergic blockade in dilated cardiomyopathy, ischemic cardiomyopathy, and other secondary cardiomyopathies. Heart Vessels Suppl 1991;6:18-28.

22. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:1115-40.

23. Clark AL, Cleland JG. The control of adrenergic function in heart failure: therapeutic intervention. Heart Fail Rev 2000;5:101-14.

24. Metra M, Torp-Pedersen C, Swedberg K, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259-68.

25. Sin DD, McAlister FA. The effects of beta-blockers on morbidity and mortality in a population-based cohort of 11,942 elderly patients with heart failure. Am J Med 2002;113:650-6.

26. Dobre D, DeJongste MJL, Lucas C, et al. Effectiveness of beta blocker therapy in daily practice patients with advanced chronic heart failure; is there an effect-modification by age? Br J Clin Pharmacol 2007;63:356-64.

27. Lenzen MJ, Boersma E, Reimer WJ, et al. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials: a report from the Euro Heart Survey on Heart Failure. Eur Heart J 2005;26:2706-13.

28. Dobre D, Van Veldhuisen DJ, Dejongste ML, et al. Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival. Eur J Heart Fail 2007;9:280-6.

29. Ignarro LJ, Byrns RE, Trinh K, et al. Nebivolol: a selective beta(1)-adrenergic receptor antagonist that relaxes vascular smooth muscle by nitric oxide- and cyclic GMP–dependent mechanisms. Nitric Oxide 2002;7:75-82.

30. Ignarro LJ. Experimental evidences of nitric oxide-dependent vaso-dilatory activity of nebivolol, a third-generation beta-blocker. Blood Press Suppl 2004;1:2-16.