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Beta-Blockade With Nebivolol in Elderly Heart Failure Patients With Impaired and Preserved Left Ventricular Ejection Fraction

Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)

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Objectives In this pre-specified subanalysis of the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, which examined the effects of nebivolol in elderly heart failure (HF) patients, we explored the effects of left ventricular ejection fraction (EF) on outcomes, including the subgroups impaired EF (≤35%) and preserved EF (>35%).

Background Beta-blockers are established drugs in patients with HF and impaired EF, but their value in preserved EF is unclear.

Methods We studied 2,111 patients; 1,359 (64%) had impaired (≤35%) EF (mean 28.7%) and 752 (36%) had preserved (>35%) EF (mean 49.2%). The effect of nebivolol was investigated in these 2 groups, and it was compared to explore the interaction of EF with outcome. Follow-up was 21 months; the primary end point was all-cause mortality or cardiovascular hospitalizations.

Results Patients with preserved EF were more often women (49.9% vs. 29.8%) and had less advanced HF, more hypertension, and fewer prior myocardial infarctions (all $p < 0.001$). During follow-up, the primary end point occurred in 465 patients (34.2%) with impaired EF and in 235 patients (31.2%) with preserved EF. The effect of nebivolol on the primary end point (hazard ratio [HR] of nebivolol vs. placebo) was 0.86 (95% confidence interval: 0.72 to 1.04) in patients with impaired EF and 0.81 (95% confidence interval: 0.63 to 1.04) in preserved EF ($p = 0.720$ for subgroup interaction). Effects on all secondary end points were similar between groups (HR for all-cause mortality 0.84 and 0.91, respectively), and no p value for interaction was <0.48.

Conclusions The effect of beta-blockade with nebivolol in elderly patients with HF in this study was similar in those with preserved and impaired EF. (J Am Coll Cardiol 2009;53:2150–8) © 2009 by the American College of Cardiology Foundation

Despite many advances in its management, current large-scale studies of patients with chronic heart failure (HF) indicate that this syndrome still carries a high morbidity and mortality (1,2). Although most large HF studies in the past were conducted in patients with an impaired systolic function and low left ventricular ejection fraction (LVEF), there has been an increased awareness in recent years that many

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patients with symptomatic HF have a (relatively) normal or preserved ejection fraction (EF) (3). Indeed, the prevalence of HF patients with a preserved EF seems to have increased in the last 15 years (4), which is in part related to the aging of the population in the Western world. In terms of survival, patients with HF and preserved EF were previously assumed to have a better outcome, but recent data indicate that survival may be as poor as in patients with a low EF (5).

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For these reasons, HF with preserved EF has received increasing attention in the last 5 to 10 years (6), and several clinical trials have recently reported their results (7–9). Findings from these studies show that neither the angiotensin-converting enzyme (ACE) inhibitor perindopril (8) nor the angiotensin receptor blocker (ARB) candesartan (7,9) caused a statistically significant reduction in their primary end point, that is, a composite of morbidity and mortality. The use of digoxin is also not associated with a beneficial effect in this population (10). In the recent HF Guidelines of the European Society of Cardiology, the high prevalence (>50%) and increasing importance of HF with preserved EF are clearly recognized (11), but it is also acknowledged that no treatment for this patient category has yet been shown convincingly to reduce morbidity and mortality. Although some, albeit not conclusive, data are therefore available for ACE inhibitors and ARBs, no data of similar size regarding the value of beta-blockers in patients with HF and preserved EF are available (6).

The SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial (12) investigated the role of the vasodilating beta-1 receptor antagonist nebivolol in elderly (age ≥70 years) patients with HF and showed evidence of benefit on the composite outcome of death or cardiovascular (CV) hospitalization (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.74 to 0.99 for the comparison of nebivolol with placebo, p = 0.04). Approximately one-third of the patients in the SENIORS trial had an EF >35%. Given that there is very little randomized information about the effects of any beta-blocker in (elderly) patients with HF and in those with preserved systolic function, we undertook further pre-specified analyses of the SENIORS trial data to compare patients with decreased EF (≤35%) with those with (relatively) preserved EF (>35%), that is, to examine the effect of beta-blockade with nebivolol in these 2 groups and also to compare the effect by exploring the interaction of EF with outcome.

Methods

The methods and main results of the SENIORS trial have been published previously (12). SENIORS was a parallel-group, randomized, double-blind, multicenter, international trial comparing nebivolol with placebo in elderly patients with HF on optimal standard therapy. To be eligible, patients had to be age ≥70 years, provide written informed consent, and have a clinical history of chronic HF with at least 1 of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive HF or documented LVEF ≤35% within the previous 6 months. The main exclusion criteria were any recent change in CV drug therapy, contraindications to beta-blockers, and significant hepatic or renal dysfunction. Study medication was titrated over a 16-week period from a starting dose of 1.25 mg daily to a target of 10 mg daily. The primary outcome was the composite of all-cause mortality or hospital admissions for a CV cause, and the main secondary outcome was all-cause mortality. Baseline EF was measured by echocardiography in 94%, nuclear imaging in 4%, and magnetic resonance imaging in 2% of patients.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
CI = confidence interval
CV = cardiovascular
EF = ejection fraction
HF = heart failure
HR = hazard ratio
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction

In a subset of patients, echocardiographic measurements were not only taken at baseline, but also after 12 months. These measurements included: EF, left ventricular (LV) end-systolic and -diastolic dimensions, and fractional shortening.

Statistical methods. The influence of EF on the effects of nebivolol in the SENIORS trial population was measured as a dependent variable. Continuous variables were compared between groups using a *t* test or analysis of variance as appropriate. Categorical variables were compared using a chi-square test. The categories were pre-specified as less than or equal to or greater than the median of 35% for EF. In an additional analysis, we also studied 4 groups of EF, investigating patients with EF ≤30%, 31% to 35%, 36% to 46%, and >46% (30% was the median for the impaired EF group, and 46% was the median for the preserved EF group). A Cox proportional hazards model was used to assess the influence of EF with other baseline characteristics (prior myocardial infarction, history of coronary artery disease, age, male sex, diabetes, atrial fibrillation, New York Heart Association functional class, hypertension, systolic blood pressure, and heart rate) to explore any interaction of these variables on outcomes using the original randomized assignment of nebivolol versus placebo. The primary outcome of interest was the composite of all-cause mortality or CV hospital admission (time to first event), and the secondary outcome was all-cause mortality. Other exploratory outcomes, including CV hospitalization as the other component of the primary outcome, are also presented where considered appropriate. We used an intention-to-treat analysis throughout.

Ethics of protocol. The authors confirm that this study complies with the Declaration of Helsinki, the locally ap-

Table 1 Baseline Characteristics

Characteristic	LVEF ≤35%				LVEF >35%					
	Nebivolol (n = 678)	Placebo (n = 681)	p Value	Whole Group (n = 1,359)	Nebivolol (n = 380)	Placebo (n = 372)	p Value	Whole Group (n = 752)	All Patients (n = 2,111)	p Value*
Demographics										
Age (yrs)										
Mean	76.1 (4.8)	76.0 (4.5)	0.866	76.1 (4.6)	76.0 (4.8)	76.2 (4.7)	0.826	76.1 (4.7)	76.1 (4.7)	0.837
Median	75.2 (72.1–79.0)	75.3 (72.3–78.9)		75.2 (72.2–78.9)	75.0 (72.2–78.5)	75.3 (72.5–78.6)		75.1 (72.4–78.5)	75.2 (72.3–78.8)	
Women	214 (31.6)	191 (28.1)	0.156	405 (29.8)	193 (50.8)	182 (48.9)	0.147	375 (49.9)	780 (37.0)	<0.001
Clinical										
NYHA functional class										
I	17 (2.5)	18 (2.6)	0.95	35 (2.6)	15 (4.0)	11 (3.0)	0.863	26 (3.5)	61 (2.9)	<0.001
II	360 (53.1)	357 (52.4)		717 (52.8)	236 (62.1)	234 (62.9)		470 (62.5)	1,187 (56.2)	
III	288 (42.5)	290 (42.6)		578 (42.5)	123 (32.4)	119 (32.0)		242 (32.2)	850 (38.8)	
IV	13 (1.9)	16 (2.4)		29 (2.1)	6 (1.6)	8 (2.2)		14 (1.9)	43 (2.0)	
EF (%)										
Mean	28.6 (5.4)	28.8 (5.5)	0.412	28.7 (5.5)	49.3 (10.4)	49.1 (9.7)	0.989	49.2 (10.0)	36.0 (12.3)	<0.001
Median	30 (25–33)	30 (25–33)		30 (25–33)	46 (40.5–55)	47 (41–56)		46 (41–55.5)	33 (28–42)	
Hemodynamics										
Heart rate (beats/min)	79.7 (13.9)	79.1 (14.2)	0.411	79.4 (14.1)	78.1 (13.0)	78.4 (12.7)	0.609	78.3 (12.9)	79.0 (13.7)	0.059
Sitting systolic blood pressure (mm Hg)	135.2 (19.6)	135.9 (20.9)	0.533	135.5 (20.3)	144.6 (19.5)	146.1 (19.9)	0.299	145.4 (19.7)	139.0 (20.6)	<0.001
Sitting diastolic blood pressure (mm Hg)	79.1 (10.7)	79.4 (11.0)	0.615	79.2 (10.9)	83.0 (10.5)	82.9 (11.4)	0.755	82.9 (11.0)	80.5 (11.1)	<0.001
Medical history										
Smoker	43 (6.4)	40 (5.9)	0.713	83 (6.1)	9 (2.4)	14 (3.8)	0.826	23 (3.1)	106 (5.0)	0.002
Prior history of coronary artery disease	439 (64.8)	430 (63.1)	0.537	869 (63.9)	293 (77.1)	285 (76.6)	0.525	578 (76.9)	1,447 (68.6)	<0.001
Prior myocardial infarction	339 (50.0)	323 (47.4)	0.343	662 (48.7)	123 (32.4)	136 (36.6)	0.971	259 (34.4)	921 (43.6)	<0.001
Prior percutaneous coronary intervention	40 (5.9)	23 (3.4)	0.027	63 (4.6)	7 (1.8)	11 (3.0)	0.147	18 (2.4)	81 (3.8)	0.011
Prior coronary artery bypass surgery	86 (12.7)	79 (11.6)	0.541	165 (12.1)	14 (3.7)	14 (3.8)	0.193	28 (3.7)	193 (9.1)	<0.001
Cerebrovascular accident in the previous 3 months	1 (0.2)	0 (0)	0.316	1 (0.1)	0 (0)	0 (0)	0.318	0 (0)	1 (0.1)	0.458
Hypertension	357 (52.7)	364 (53.5)	0.811	721 (53.1)	291 (76.6)	293 (78.8)	0.588	584 (77.7)	13.5 (61.8)	<0.001
Hyperlipidemia	300 (44.3)	312 (45.8)	0.678	612 (45.0)	183 (48.2)	170 (45.7)	0.955	353 (46.9)	965 (45.7)	0.399
Atrial fibrillation	227 (33.5)	237 (34.8)	0.608	464 (34.1)	133 (35.0)	138 (37.1)	0.444	271 (36.0)	735 (34.8)	0.382
Diabetes	196 (28.9)	169 (24.8)	0.089	365 (26.9)	87 (22.9)	96 (25.8)	0.407	183 (24.3)	548 (26.0)	0.205
Medications										
Diuretic	603 (88.5)	595 (87.4)	0.525	1,195 (87.9)	318 (83.7)	307 (82.5)	0.461	625 (83.1)	1,820 (86.2)	0.002
Angiotensin-converting enzyme inhibitor	537 (79.2)	557 (81.8)	0.229	1,094 (80.5)	330 (86,8)	316 (85.0)	0.563	646 (85.9)	1,740 (82.3)	0.002
Angiotensin II antagonist	65 (9.6)	69 (10.1)	0.736	134 (9.9)	22 (5.8)	20 (5.4)	0.849	42 (5.6)	176 (8.3)	0.001
Aldosterone antagonist	223 (32.9)	213 (31.3)	0.524	436 (32.1)	77 (20.3)	63 (16.9)	0.269	42 (5.6)	576 (27.3)	0.001
Cardiac glycoside	282 (41.6)	306 (44.9)	0.214	588 (43.3)	153 (40.3)	151 (40.6)	0.288	304 (40.4)	892 (42.3)	0.206
Antiarrhythmic	99 (14.6)	127 (18.7)	0.045	226 (16.6)	66 (17.4)	67 (18.0)	0.084	133 (17.7)	359 (17.0)	0.536
Lipid-lowering drug	167 (24.6)	191 (28.1)	0.153	358 (26.3)	54 (14.2)	46 (12.4)	0.367	100 (13.3)	458 (21.7)	<0.001

Continued on next page

Table 1 Continued

Characteristic	LVEF ≤35%				LVEF >35%				All Patients (n = 2,111)	p Value*
	Nebivolol (n = 678)	Placebo (n = 681)	p Value	Whole Group (n = 1,359)	Nebivolol (n = 380)	Placebo (n = 372)	p Value	Whole Group (n = 752)		
Vitamin K antagonist	182 (26.8)	200 (29.4)	0.301	382 (28.1)	51 (13.4)	61 (16.4)	0.134	112 (14.9)	494 (23.4)	<0.001
Aspirin	335 (49.4)	334 (49.1)	0.893	669 (49.2)	223 (58.7)	200 (53.8)	0.351	423 (56.3)	1,092 (51.7)	0.002
Calcium antagonist	57 (8.4)	82 (12.0)	0.027	139 (10.2)	72 (19.0)	70 (18.8)	0.129	142 (18.9)	281 (13.3)	<0.001
Renal function										
Creatinine (μmol/l)	105.8 (34.1)	106.6 (34.4)	0.692	106.2 (34.3)	95.3 (36.1)	98.0 (35.4)	0.322	96.7 (35.8)	102.8 (35.1)	<0.001
GFR by MDRD	63.3 (19.3)	63.6 (19.7)	0.793	63.5 (19.5)	68.7 (21.8)	66.7 (21.4)	0.515	67.7 (21.7)	64.7 (21.7)	<0.001

Data are number of patients and percentage, n (%). *The p value for comparison of whole group ejection fraction (EF) ≤35% and whole group EF >35%.
GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; NYHA = New York Heart Association.

pointed ethics committees have approved the research protocol, and informed consent has been obtained from the participants.

Results

The SENIORS trial enrolled 2,128 patients age ≥70 years with stable HF. The EF measurement at baseline was available in all but 17 patients, and therefore the present study consisted of 2,111 patients. Mean EF in the whole population was 36% (median EF 33%), and about one-third of patients had an EF >35%. Baseline characteristics for patients with an EF ≤35% (mean 28.7%) or >35% (mean 49.2%) are shown in Table 1. As expected, patients with an EF >35% were more often women, had a better functional class according to the New York Heart Association classification, had a higher blood pressure, and had hypertension more often and coronary artery disease less often in their medical history. Use of background medication was also slightly different between the groups. ACE inhibitors were used by >80% of patients in both groups, but ARBs (5.6% vs. 9.9%) and particularly aldosterone antagonists (5.6% vs. 32.1%) were used by fewer patients with relatively preserved EF, as compared with HF patients with impaired EF. There was no significant difference between the nebivolol dose achieved in the high and low EF groups (7.6 ± 3.7 mg vs. 7.4 ± 3.5 mg, respectively, p = 0.398). During the study, drop-in use of beta-blockers was extremely low (<1%); drop-out rates, however, were significant (around 25%, similar in nebivolol and placebo groups), but there were no significant differences between the 2 EF groups.

Influence of EF on outcome. The relationship between EF and the primary end point of all-cause death or CV hospitalization is shown in Figure 1. In HF patients with EF ≤35%, the HR for nebivolol versus placebo was 0.86 (95% CI: 0.72 to 1.04, p = 0.117), and in patients with EF >35% the HR was 0.81 (95% CI: 0.63 to 1.04, p = 0.104); the p value for subgroup interaction was p = 0.720, that is, there was no difference in the effect of nebivolol versus placebo between the 2 EF groups (Table 2). In addition, the p value for interaction between the impaired (EF ≤35%) and preserved (EF >35%) groups were not significant for any of the secondary end points comparing nebivolol versus placebo (all values p > 0.48). Results for the 4 EF groups for the primary and secondary end points showed overall similar results across the 4 subcategories. For the primary end point, the HRs in these 4 EF subgroups were: for patients with EF ≤30%, 0.81 (95% CI: 0.64 to 1.03); for patients with EF 31% to 35%, 0.92 (95% CI: 0.69 to 1.22); for patients with EF 36% to 46%, 0.84 (95% CI: 0.59 to 1.20); and for patients with EF >46%, 0.76 (95% CI: 0.52 to 1.11). There was no significant interaction between treatment effect and EF when the latter was taken as a continuous variable (p = 0.720). For the secondary end points, none of the p values for interaction were statistically significant (Table 2).

Results of the multivariate analysis showed that the effect of nebivolol was not significantly affected regarding the

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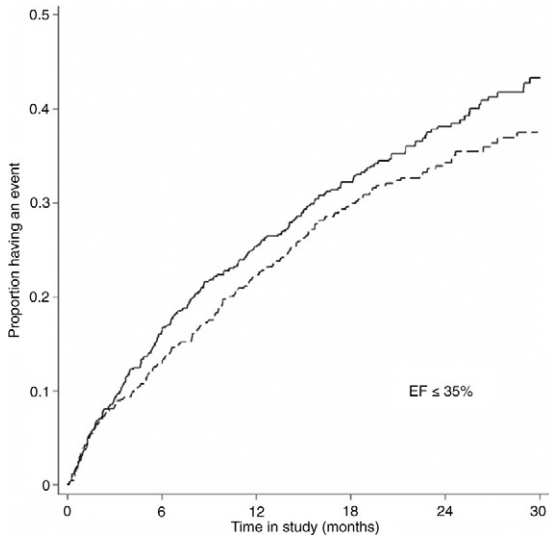

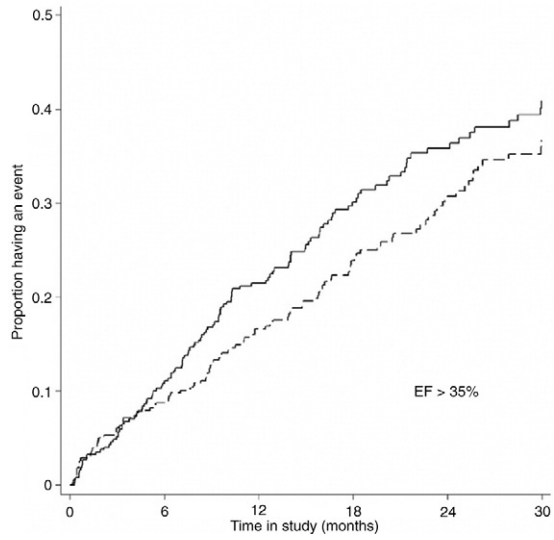

Figure 1 **Kaplan-Meier Curve of Primary Outcome**

Kaplan-Meier curve of primary outcome (all-cause mortality or cardiovascular hospitalization) for impaired (≤35%) and preserved (>35%) ejection fraction (EF) group for nebivolol **(dotted line)** versus placebo **(solid line)**.

primary outcome. This was the case when EF was entered as a continuous variable, and also when using the 35% cutoff. No secondary outcomes showed nebivolol to have a statistically significant effect ($p > 0.400$ in all cases).

Additional post-hoc analyses. Additional exploratory post-hoc analyses were conducted to investigate specific questions. Although we used 35% as a cutoff for preserved versus impaired EF (based on main study) (11), an EF of 40% is also often used. We thus investigated the effect of nebivolol versus placebo in 643 patients with LVEF ≥40% (Table 3). Results for both the primary outcome (HR: 0.82) as well as the secondary end points (only main secondary outcomes shown) were similar to those with EF ≥35%.

We also explored the influence of baseline heart rate on the subsequent effect of the beta-blocker (Table 4). The net reduction in heart rate by nebivolol (vs. placebo) in the whole population was 8.8 beats/min. This reduction was observed both in patients with impaired EF (net effect vs. placebo −9.7 beats/min) and in patients with preserved EF (net effect vs. placebo −6.9 beats/min) (both $p < 0.001$). For the whole population, there was no apparent influence of baseline heart rate (HRs for heart rate ≤80 and >80 beats/min: 0.85 and 0.83, respectively). In patients with EF ≤35%, the effect of nebivolol was larger in patients with higher than in those with lower heart rates (HR: 0.77 vs. 0.93), but in patients with an EF >35%, the reverse was observed (HR: 0.98 vs. 0.71). None of these interactions were statistically significant (Table 4). We also explored a possible association between the effect of nebivolol on blood pressure and outcome parameters in the 2 groups, but we could not find such an association.

Measure of LV function and changes over time. In approximately 1,500 patients, echocardiographic measurements were performed at baseline and after 12 months. Table 5 shows these measures of LV function for the whole group as well as for patients with EF ≤35% and >35%. Overall, nebivolol had a significant effect on LV end-systolic dimension (mean change −0.18 cm on nebivolol vs. −0.10 cm on placebo, difference $p = 0.013$) and on LVEF (change +4.9% on nebivolol. vs. +3.2% on placebo, $p = 0.002$), whereas no effect was observed for LV end-diastolic dimension and a borderline significant difference for fractional shortening.

When the groups were analyzed according to their baseline EF, changes over time were overall more pronounced in patients with EF ≤35% than in those with EF >35%, but the effect between nebivolol and placebo was in general similar in the 2 groups. In both groups, a significant difference on EF favoring nebivolol was observed ($p = 0.013$ and $p = 0.027$, respectively).

Discussion

The main finding of the present study is that the effect of the beta-blocker nebivolol seemed to be of similar magnitude between HF patients with impaired EF and patients with preserved EF. Although the SENIORS trial was not powered to show a statistically significant effect of nebivolol in the EF subgroups, the HRs are similar with no apparent evidence of interaction in any subgroup analysis, which supports the hypothesis that there is a similar beneficial effect in patients with impaired and preserved EF.

Beta-blockers are standard drugs for patients with HF and decreased EF (11), and together with ACE inhibitors and ARBs, they form the cornerstone of its treatment. Although >10,000 HF patients with EF ≤35% have been studied in large outcome trials, it is surprising that no larger trial has examined the effect of beta-blockade in patients with EF >35%. Given this absence of supportive data,

Table 2 Primary and Main Secondary Outcomes (Time to First Event) for High and Low EF

Outcomes	EF ≤35%				EF >35%				p Value (Subgroup Interaction)
	Nebivolol (n = 678)	Placebo (n = 681)	HR	95% CI	Nebivolol (n = 380)	Placebo (n = 372)	HR	95% CI	
Primary outcome (all-cause mortality or CV hospitalization)	218 (32.2)	247 (36.3)	0.86	0.72–1.04	110 (29.0)	125 (33.6)	0.81	0.63–1.04	0.720
Secondary outcomes									
All-cause mortality	115 (17.0)	135 (19.8)	0.84	0.66–1.08	52 (13.7)	55 (14.8)	0.91	0.62–1.33	0.718
All-cause mortality or HF hospitalization	170 (25.1)	181 (26.6)	0.94	0.76–1.15	81 (21.3)	88 (23.7)	0.87	0.65–1.18	0.734
CV mortality	88 (13.0)	104 (15.3)	0.84	0.63–1.12	33 (8.7)	39 (10.5)	0.82	0.52–1.30	0.932
Sudden cardiac death	34 (5.0)	51 (7.5)	0.66	0.43–1.02	9 (2.4)	18 (4.8)	0.49	0.22–1.08	0.510
Non-CV mortality	14 (2.1)	13 (1.9)	1.07	0.50–2.27	12 (3.2)	7 (1.9)	1.65	0.65–4.19	0.485
Unknown/not classified	13 (1.9)	18 (2.6)	0.70	0.34–1.43	7 (1.8)	9 (2.4)	0.75	0.28–2.02	0.889
CV hospitalization	169 (24.9)	180 (26.4)	0.92	0.75–1.14	85 (22.4)	94 (24.3)	0.83	0.62–1.11	0.593
CV mortality or CV hospitalization	204 (30.1)	234 (34.4)	0.86	0.71–1.03	97 (25.5)	113 (30.4)	0.79	0.59–1.03	0.648
All-cause hospitalization	229 (33.8)	232 (34.1)	0.98	0.82–1.17	127 (33.4)	130 (35.0)	0.89	0.70–1.14	0.586
All-cause mortality or all-cause hospitalization	265 (36.3)	153 (41.1)	0.91	0.77–1.08	138 (36.3)	153 (41.1)	0.83	0.66–1.04	0.553

CI = confidence interval; CV = cardiovascular; EF = ejection fraction; HF = heart failure; HR = hazard ratio.

current HF guidelines do not advocate the use of beta-blockers in these patients, but nevertheless, these drugs are used frequently in this population (13,14). In an Italian Registry study (13), beta-blockers were used more in HF patients with preserved EF than in impaired EF, and a recent study from the U.S. showed that beta-blockers were used in >60% of patients with EF >40% (14).

Despite this apparent rather widespread use of beta-blockers in HF patients with (relatively) preserved EF, only a few data from smaller studies are available to support this strategy. Aronow et al. (15) examined the effect of propranolol in 158 older patients with HF and LVEF ≥40%, and found a reduction of mortality from 76% to 56%. Bergström et al. (16) investigated 113 patients with HF, an LVEF ≥45%, and echocardiographic evidence of diastolic dysfunction, but observed no effect of carvedilol on clinical end points. In another comparative study in only 26 patients with "diastolic HF" (LVEF >50%) (17), nebivolol was associated with a greater improvement of invasive hemodynamics than atenolol, but the effect on exercise parameters was similar. One larger study is the J-DHF (Japanese Diastolic Heart Failure Study) study, which plans to evaluate the effect of carvedilol in 800 HF patients with preserved EF (18). Apart from these randomized studies, observational data also support the use of beta-blockers in HF patients with a normal EF (19,20).

The present study examined the effect of nebivolol on clinical end points in HF patients with impaired and preserved EF, and provides only limited information on mechanisms. One factor that may be associated with a better outcome in HF is the achieved dose of a beta-blocker, as shown in the SENIORS trial (21). Patients with EF >35% had a higher blood pressure than those with EF ≤35%, and blood pressure is one of the most powerful parameters for predicting tolerability (21,22). In the SENIORS trial, patients with higher EF were not getting higher doses of nebivolol (21), so dose probably did not play a role. It has also been assumed that patients with a higher heart rate at baseline would benefit more from beta-blockade, but 2 recent studies of HF patients with impaired EF did not confirm this (23,24). In HF patients with preserved EF, baseline heart rate may theoretically be more relevant (25), given the effect of slowing heart rate on increased diastolic filling, and one small study with the

Table 3 Primary and Main Secondary Outcomes (Time to First Event) for LVEF ≥40%

Outcome	LVEF ≥40%		
	Nebivolol (n = 320)	Placebo (n = 323)	HR (95% CI)
Primary outcome (all-cause mortality or CV hospitalization)	92 (28.8)	108 (33.4)	0.82 (0.62–1.08)
All-cause mortality	44 (13.8)	48 (14.9)	0.92 (0.61–1.36)
All-cause mortality or HF hospitalization	67 (20.9)	75 (23.2)	0.88 (0.63–1.23)
CV mortality	28 (8.8)	35 (10.8)	0.80 (0.49–1.32)

LVEF = left ventricular ejection fraction; other abbreviations as in Table 2.

Table 4 Effect of Baseline Heart Rate (≤80 or >80 Beats/Min) on the Primary Outcome (All-Cause Mortality or Cardiovascular Hospitalizations)

Primary Outcome	Heart Rate ≤80 Beats/Min	Heart Rate >80 Beats/Min	All Patients
LVEF ≤35%	0.93 (0.73–1.17)	0.77 (0.58–1.02)	0.86 (0.72–1.04)
LVEF >35%	0.71 (0.52–0.99)	0.98 (0.65–1.49)	0.81 (0.63–1.04)
All patients	0.85 (0.70–1.03)	0.83 (0.66–1.06)	0.84 (0.73–0.98)

LVEF = left ventricular ejection fraction.

Table 5 Echocardiographic Parameters at Baseline and Follow-Up

Baseline to 12 Months	n	Baseline Mean ± SD	Baseline p Value	12 Months Mean ± SD	12 Months p Value	Difference p Value
Echocardiography measurements for all patients						
LVESD						
Nebivolol	760	4.72 ± 1.10	0.912	4.54 ± 1.05	0.141	0.013
Placebo	742	4.72 ± 1.06		4.62 ± 1.06		
LVEDD						
Nebivolol	775	5.89 ± 0.99	0.869	5.84 ± 0.96	0.503	0.449
Placebo	755	5.91 ± 0.94		5.87 ± 0.94		
LVEF						
Nebivolol	784	35.9 ± 11.9	0.887	40.8 ± 12.6	0.023	0.002
Placebo	758	36.1 ± 11.9		39.3 ± 12.4		
FS						
Nebivolol	759	20.5 ± 9.7	0.814	22.7 ± 10.6	0.115	0.050
Placebo	739	20.6 ± 8.9		21.9 ± 9.8		
Echocardiography measurements for LVEF ≤35%						
LVESD						
Nebivolol	480	5.15 ± 0.98	0.344	4.89 ± 0.98	0.312	0.010
Placebo	480	5.09 ± 0.92		4.95 ± 0.98		
LVEDD						
Nebivolol	493	6.18 ± 0.93	0.561	6.08 ± 0.93	0.979	0.414
Placebo	491	6.14 ± 0.89		6.08 ± 0.95		
LVEF						
Nebivolol	504	28.9 ± 5.3	0.588	35.5 ± 9.9	0.037	0.013
Placebo	494	29.1 ± 5.4		34.2 ± 9.3		
FS						
Nebivolol	479	17.1 ± 8.1	0.752	19.8 ± 10.3	0.753	0.050
Placebo	479	17.3 ± 6.9		18.7 ± 8.6		
Echocardiography measurements for LVEF >35%						
LVESD						
Nebivolol	278	3.98 ± 0.88	0.495	3.93 ± 0.86	0.262	0.483
Placebo	260	4.03 ± 0.94		4.01 ± 0.92		
LVEDD						
Nebivolol	280	5.39 ± 0.88	0.357	5.41 ± 0.86	0.260	0.813
Placebo	263	5.46 ± 0.86		5.49 ± 0.79		
LVEF						
Nebivolol	280	48.7 ± 9.9	0.623	50.3 ± 11.3	0.155	0.027
Placebo	264	49.1 ± 9.4		48.4 ± 11.8		
FS						
Nebivolol	278	26.3 ± 9.5	0.626	27.6 ± 9.3	0.891	0.486
Placebo	259	26.7 ± 8.9		27.5 ± 9.1		

FS = fractional shortening; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension.

calcium antagonist verapamil confirmed this (26). The present data from the SENIORS trial do not support this concept, however. Direct improvement of LV function may be a third potential mechanism by which nebivolol might exert a beneficial effect in HF patients. In the present study, EF slightly increased in both groups, but it is unclear whether this effect was associated with the clinical findings. In a previous, more detailed (but smaller) echocardiographic substudy from the SENIORS trial, nebivolol was not found to have a beneficial effect on diastolic function parameters such as E/A ratio and E-wave deceleration time (27). Nevertheless, ischemia (particularly in the subendocardium) probably plays an important role in the pathophysiology of HF (28), which may be even more prominent in patients with preserved EF (with or without LV hypertrophy) (29). Beta-blockade may improve diastolic filling, thereby enhancing perfusion and metabolism (30). The increased nitric oxide release, specifically induced by nebivolol, may cause an additional improvement of early relaxation (31,32). Consequently, a reduction of (subendocardial) ischemia by nebivolol in the present study is a potential mechanism for explaining the clinical effect.

Study limitations. The overall effect size of nebivolol in the SENIORS trial on death/CV hospitalization had a p value of 0.04, thus the power to detect interactions between EF and outcomes are limited and prone to the play of chance. Nevertheless, if this interaction were present, we expect that at least a trend would have been observed, but of course a demonstration of a similar effect in subgroups is not the same as clear results from a properly powered clinical trial. Some patients in the group of assumed HF with preserved EF may not have had HF, and a recent careful analysis of the CHARM-Preserved (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) trial showed that up to one-third of patients may not have had diastolic dysfunction (33). These patients had symptoms suggestive of HF, but that may not have been caused by HF but by other comorbidities, and it has been suggested that treatment should focus on these comorbidities (34). Lastly, current findings with nebivolol should not be extrapolated automatically to other beta-blockers (17,31).

Conclusions

The present analysis suggests that the effect of beta-blockade (with nebivolol) is similar in HF patients with preserved and impaired EF. This finding is particularly important for patients with preserved EF because no (pharmacologic) treatment has yet been shown to improve outcome in this population. Some positive data for the use of ACE inhibitors and ARBs are available in these patients (7,8), but the current study provides the first large-scale data for a potentially beneficial effect of beta-blockade in HF patients with a preserved EF, and is the only one in elderly HF patients. Larger, adequately powered studies with beta-blockers in this population are clearly needed.

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