European Journal of Heart Failure (2009) **11**, 872–880
doi:10.1093/eurjhf/hfp104

Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial

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Received 24 June 2009; Revised and accepted 3 July 2009; online publish-ahead-of-print 1 August 2009

Aim To determine the safety and efficacy of nebivolol in elderly heart failure (HF) patients with renal dysfunction.

Methods and results SENIORS recruited patients aged 70 years or older with symptomatic HF, irrespective of ejection fraction, and randomized them to nebivolol or placebo. Patients ($n = 2112$) were divided by tertile of estimated glomerular filtration rate (eGFR). Mean age of patients was 76.1 years, 35% of patients had an ejection fraction of >35%, and 37% were women resulting in a unique cohort, far more representative of clinical practice than previous trials. eGFR was strongly associated with outcomes and nebivolol was similarly efficacious across eGFR tertiles. The primary outcome rate (all-cause mortality or cardiovascular hospital admission) and adjusted hazard ratio for nebivolol use in those with low eGFR was 40% and 0.84 (95% CI 0.67–1.07), 31% and 0.79 (0.60–1.04) in the middle tertile, and 29% and 0.86 (0.65–1.14) in the highest eGFR tertile. There was no interaction noted between renal function and the treatment effect ($P = 0.442$). Nebivolol use in patients with moderate renal impairment (eGFR <60) was not associated with major safety concerns, apart from higher rates of drug-discontinuation due to bradycardia.

Conclusion Nebivolol is safe and has a similar effect in elderly HF patients with mild or moderate renal impairment.

Keywords Heart failure • Renal impairment • Beta-blocker • Nebivolol

Introduction

Decreased renal function has consistently been found to be an independent risk factor for cardiovascular (CV) disease outcomes and all-cause mortality in a large spectrum of patients including those with left ventricular systolic dysfunction and heart failure (HF).[1–3] However, most studies in HF have been conducted in patients with a mean age of 60–65 years and markedly reduced left-ventricular ejection fraction (LVEF), a pattern very dissimilar to the 'average' patient with HF.[4] Data in patients aged more than 70 years or with preserved systolic function are scarce. Altered renal function is also a restriction to the initiation and titration of HF therapy[5] that may limit treatment effectiveness especially in the elderly. Beta-blockers are now considered a routine treatment in patients with symptomatic HF and have been shown to improve ventricular function and reduce morbidity

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† In memoriam

and mortality.[6,7] However, no study has previously assessed the interaction between beta-blocker response and renal function in elderly HF patients.

SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) was undertaken to determine the effect of nebivolol on mortality and morbidity in elderly patients with HF, regardless of ejection fraction, when compared with placebo. The primary outcome (composite of all cause mortality or CV hospital admission) was significantly reduced in those taking nebivolol [31.1% compared with 35.3% on placebo; hazard ratio (HR) 0.86, 95% CI 0.74–0.99; $P = 0.039$].[8] In addition, no significant influence of age or gender was observed and we have recently demonstrated that the efficacy of nebivolol was not dependent on baseline LVEF.[9] The aim of this analysis was to confirm whether nebivolol was effective in participants of SENIORS with mild or moderate renal impairment and determine whether the safety profile was different in these patients.

Methods

The rationale and details of SENIORS have been described previously.[8] Eligible patients were women and men aged 70 years or older who had symptomatic HF (New York Heart Association class II–IV) of at least 4 weeks duration. LVEF was recorded in all participants but was not a specific entry criterion. To ensure that HF patients were recruited, inclusion criteria specified an LVEF of $<35\%$ within 6 months or prior hospitalization for decompensated HF in the previous year whatever the level of LVEF. Participants were randomized on a 1:1 basis to an up-titrating dose (target 10 mg) of nebivolol or placebo. Exclusion criteria included serum creatinine ≥ 250 μmol/L as well as recent change in drug therapy and contraindication/intolerance to beta-blockers.

The primary outcome was the composite of all-cause mortality or CV hospital admission (time to first event) and secondary outcomes included all-cause mortality, all-cause hospital admissions, CV hospital admissions, and CV mortality. For the 2112 participants in this analysis, the mean follow-up period was 20.89 months with a standard deviation (SD) of 9.2 months.

Renal function

Plasma creatinine was measured in SENIORS participants at baseline and at the final follow-up visit. Sixteen participants with missing baseline values were not included in this analysis. Renal function was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula. The MDRD four-component equation incorporates age, race, gender, and serum creatinine level and describes estimated glomerular filtration rate (eGFR) in millilitres per minute standardized to a body surface area of 1.73 m^2:

$$\text{eGFR} = 32\,788 \times [\text{creatinine } \mu\text{mol/L}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if Afro-Caribbean}]$$

Estimated GFR was divided into tertiles to maximize the power of the statistical analysis. Ranges for the low, middle, and high eGFR tertiles are <55.5, 55.5–72.8, and >72.8 mL/min respectively. Thus, the low eGFR tertile broadly corresponds to Stage 3 kidney disease (moderately reduced renal function), as categorized by the National Kidney Foundation.[10]

Statistics

Values are reported as mean with SD or numbers (percentage) as appropriate. When assessing the difference between treatment and placebo, continuous variables were compared using two-tailed *t*-tests and categorical variables were assessed using a χ^2 test. For comparisons across tertiles of eGFR, continuous variables were analysed using one-way ANOVA and categorical variables using a χ^2 test. Multivariate analysis was performed using Cox regression methods. Variables for the adjusted multivariate analysis were pre-specified: smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, New York Heart Association (NYHA) class, medical history (diabetes, prior angina, prior stroke, or prior myocardial infarction), and LVEF. To examine extra covariates felt to confound or effect-modify the association of beta-blocker treatment and HF outcomes, we carried out additional *post hoc* adjustments for medication usage, nebivolol dose, and haemoglobin. A *P*-value of <0.05 was considered statistically significant. Analyses were performed on Stata (version 10.1, StataCorp LP).

Results

Baseline characteristics according to renal function

Baseline data for the SENIORS cohort have previously been reported.[8] In brief, SENIORS participants were much older than other beta-blocker trials (mean age 76.1, SD 4.6) with a range of LVEF (mean 36.0%, SD 12.3%) that better represents the clinical population of HF patients. Mean eGFR for the entire cohort was 65.0 (SD 20.4) mL/min. Only 9.9% of patients had normal renal function as defined by eGFR ≥ 90 mL/min. A total of 48.1% of patients had mild renal impairment (eGFR 60–89) and 38.9% moderate impairment (eGFR 30–59). Despite exclusion based on creatinine level, 3.1% of patients had severely reduced kidney function (eGFR <30). *Figure 1* shows the distribution of eGFR according to age and LVEF.

Table 1 presents demographic characteristics by tertile of eGFR. Participants with impaired renal function were more likely to be older, female, with lower LVEF and lower blood pressure (BP). Rates of prior myocardial infarction, coronary revascularization, and diabetes were also higher in those with reduced eGFR. Medication usage (data not shown) was also significantly different according to eGFR tertile; participants with poorer renal function were prescribed more diuretics and angiotensin receptor blockers but less angiotensin converting enzyme inhibitors. The use of aldosterone antagonists, anti-arrhythmics, and lipid-lowering agents was also more common in those with impaired kidney function.

Within-group characteristics were similar between patients allocated to nebivolol or placebo (*Table 1*) despite randomization not stratifying by renal function. The middle eGFR tertile included non-significantly more women allocated to nebivolol, with a small but significantly lower systolic BP (139.0 vs. 142.1 mmHg in the placebo arm; $P = 0.049$). However, all other variables were comparable between treatment groups.

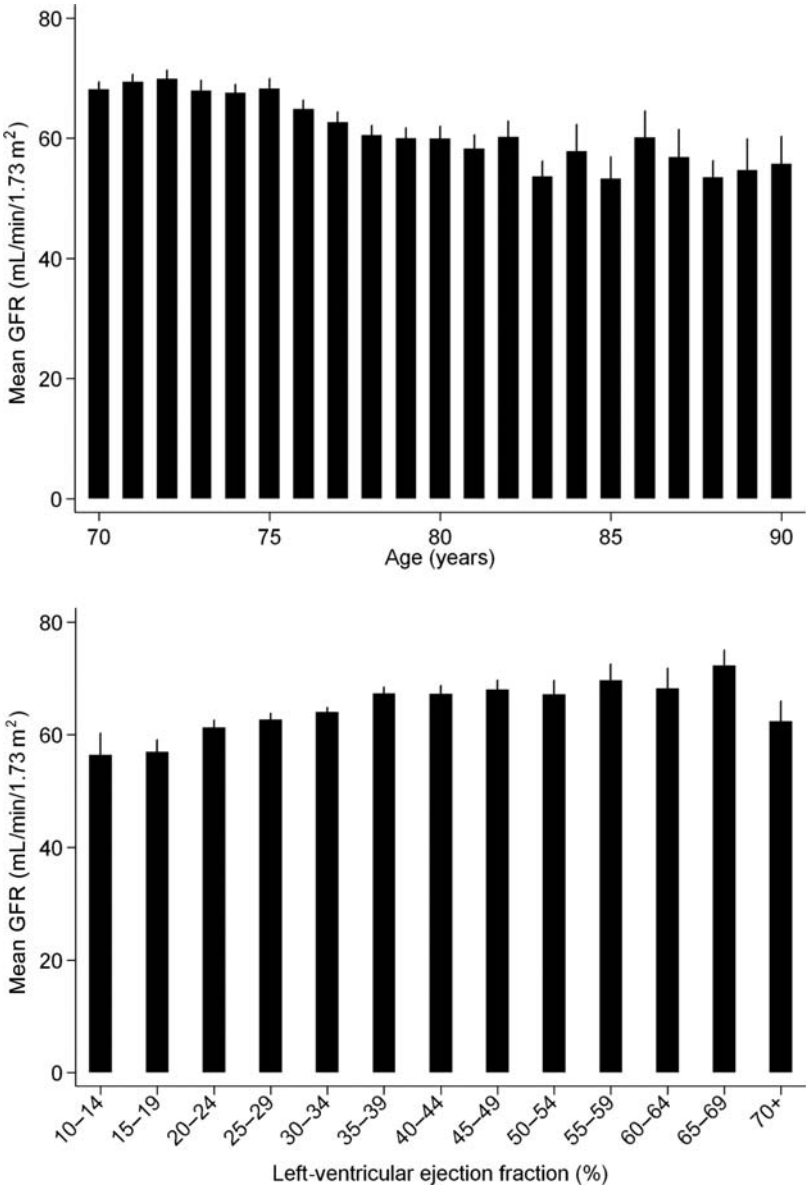

Figure 1 Estimated glomerular filtration rate by age and ventricular function. Renal function divided by age (top, 1-year intervals) and left-ventricular ejection fraction (bottom, 5% intervals), with error bar indicating upper 95% confidence interval.

Renal function and outcomes

Adverse outcomes were significantly more common in SENIORS participants with reduced renal function, confirming higher rates of mortality and HF morbidity in patients with moderate or severe renal impairment (*Figure 2*). The primary outcome (composite of all-cause mortality or CV hospital admission) occurred in 28.7, 31.0, and 40.1% of those in the high, middle, and low eGFR tertiles, respectively (*P*-value for trend <0.001). For all-cause mortality, the rates were 11.9, 15.6, and 23.2% ($P < 0.001$). The risk of death for patients in the lowest eGFR tertile was over twice that seen for patients in the highest eGFR tertile (HR 2.09, 95% CI 1.61–2.72; $P < 0.001$).

Efficacy of nebivolol in patients with impaired renal function

Table 2 presents the primary and main secondary outcomes by tertiles of eGFR. There was no interaction between renal function and the effect of nebivolol on outcome ($P = 0.442$). Similarly for the secondary outcomes, including CV hospitalization and mortality, renal impairment had no effect on the efficacy of nebivolol treatment. *Table 3* describes crude hazard ratios for the primary outcome by eGFR tertile and those adjusted for smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, NYHA class, medical history, and LVEF. *Figure 3* depicts forest plots for these analyses. The degree of renal

Table 1 Demographic characteristics by estimated glomerular filtration rate tertile

Variable	Low eGFR tertile (<55.5 mL/min/1.73 m^2)			Middle eGFR tertile (55.5–72.8 mL/min/1.73 m^2)			High eGFR tertile (>72.8 mL/min/1.73 m^2)			*P*-value across tertiles
	NEB	PLC	*P*-value	NEB	PLC	*P*-value	NEB	PLC	*P*-value	
n	348	356		346	358		366	338		
eGFR, mL/min (SD)	43.4 (9.1)	43.5 (8.8)	0.899	64.2 (5.1)	64.3 (5.1)	0.779	87.1 (13.3)	87.3 (13.8)	0.791	<0.001
Creatinine, μmol/L (SD)	137.8 (37.0)	137.8 (36.1)	0.995	94.6 (13.2)	96.2 (13.0)	0.109	75.1 (11.8)	75.3 (12.3)	0.853	<0.001
Age, years (SD)	77.3 (5.0)	77.4 (5.1)	0.983	76.1 (4.7)	75.8 (4.3)	0.501	75.0 (4.2)	75.1 (3.8)	0.739	<0.001
Female, %	41.7	39.9	0.631	41.0	34.1	0.056	32.8	31.7	0.749	0.004
Previous MI, %	44.3	48.6	0.248	48.3	46.7	0.667	39.1	35.5	0.328	<0.001
Diabetes, %	29.9	28.7	0.719	25.7	24.9	0.792	24.9	22.2	0.404	0.045
Current smoker, %	4.9	5.9	0.552	3.8	4.8	0.515	6.0	5.3	0.688	0.438
Hyperlipidaemia[a], %	44.8	48.9	0.282	47.1	49.4	0.536	45.9	38.8	0.055	0.073
LVEF, mean % (SD)	34.0 (12.0)	34.4 (12.2)	0.678	35.7 (12.1)	36.2 (11.9)	0.645	38.1 (12.9)	37.4 (11.9)	0.448	<0.001
NYHA class I/II, %	55.5	53.7	0.630	61.0	60.3	0.860	61.8	62.4	0.853	0.009
NYHA class III/IV, %	44.5	46.3	0.630	39.0	39.7	0.860	38.2	37.6	0.853	0.009
Systolic BP, mmHg (SD)	134.3 (20.5)	133.6 (20.2)	0.636	139.0 (19.1)	142.1 (21.8)	0.049	142 (19.9)	143.2 (19.8)	0.485	<0.001
Diastolic BP, mmHg (SD)	78.1 (11.1)	78.0 (10.9)	0.896	81.3 (10.7)	81.3 (11.5)	0.972	82.1 (10.1)	82.7 (10.9)	0.445	<0.001
Body mass index, kg/m^2 (SD)	26.6 (4.6)	26.6 (4.2)	0.777	27.0 (3.9)	26.9 (3.9)	0.808	26.8 (4.0)	26.6 (3.7)	0.544	0.241

NEB, nebivolol; PLC, placebo; MI, myocardial infarction; BP, blood pressure.
[a]Defined as known history of hyperlipidaemia or treatment.

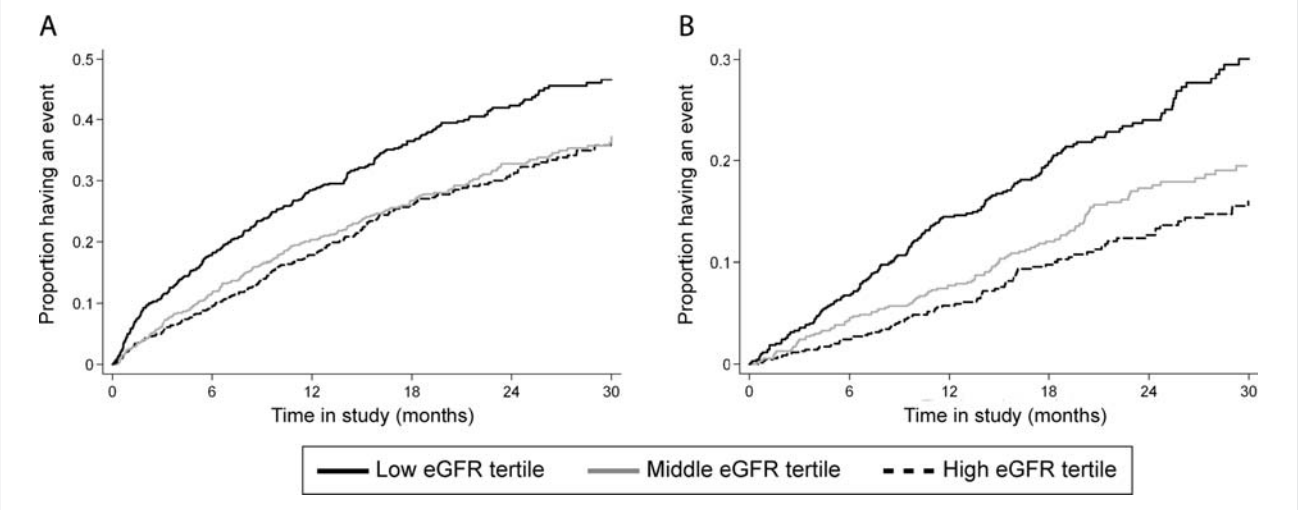

Figure 2 Survival curves for all participants by estimated glomerular filtration rate tertile according to primary outcome (*A*) and all-cause mortality (*B*). Black, solid: low estimated glomerular filtration rate tertile (<55.5 mL/min); Grey, solid: middle estimated glomerular filtration rate tertile (55.5–72.8 mL/min); Black, dashed: high estimated glomerular filtration rate tertile (>72.8 mL/min). Primary outcome was all-cause mortality or cardiovascular hospitalization. Using the high glomerular filtration rate tertile as the reference group, there was no significant difference noted for the middle tertile ($P = 0.486$) but a highly significant increase in the primary outcome for those in the low estimated glomerular filtration rate tertile ($P < 0.001$). Similarly for all-cause mortality, the respective *P*-values are 0.06 and <0.001.

impairment, as divided by eGFR tertiles, did not influence the effect of nebivolol on outcomes. Further adjustment for medication usage had no impact on hazard ratios (data not shown).

Safety of nebivolol in patients with impaired renal function

Nebivolol was very well tolerated in the SENIORS cohort with hypotension being the only significant adverse outcome causing excess drug discontinuation when compared with placebo (4 vs. 0 patients). As the total number of adverse events was very small, *Table 4* lists adverse events and achieved dosage according to an eGFR cut-off of 60 mL/min rather than tertiles of eGFR. In participants randomized to nebivolol, those with moderate renal impairment or worse had a comparable safety profile to participants with normal or mild renal impairment, apart from a marginally significant increase in bradycardia [10 out of 440 patients (2.3%) vs. 5 out of 620 patients (0.8%); $P = 0.046$]. The achieved dose of nebivolol was lower in participants with reduced eGFR but these patients still achieved a clinically appropriate dose of 7.3 (SD 3.7) vs. 8.0 (SD 3.3) mg in those with eGFR > 60 ($P = 0.004$).

Patients in both the treatment and placebo arms experienced a decline in renal function over the course of the 2 year follow-up period. The mean reduction in eGFR was 9.1 (SD 15.4) mL/min in the nebivolol group and 8.7 (SD 14.7) mL/min in the placebo arm (within-group *P*-value for both, <0.001). However, this reduction was not statistically different between the treatment groups ($P = 0.549$).

Discussion

In this paper, *post hoc* analysis of the SENIORS data is presented with respect to baseline renal function. SENIORS was not powered to detect reductions in the primary outcome for the renal sub-groups and hence none of the eGFR tertiles reach statistical significance. However, the interaction analysis between renal function and the effect of nebivolol was not significant, which strongly suggests that the efficacy of nebivolol is not reduced in elderly HF patients with mild or moderate renal impairment. In addition, nebivolol was safe for use in those with renal dysfunction, albeit with a marginal increase in bradycardia-related treatment discontinuation.

Guidelines for the treatment of HF now include beta-blocker therapy for all symptomatic patients.[6,7] However, uptake of beta-blockers in the clinical setting remains sub-optimal and may reflect a reluctance to prescribe these and other evidence-based medications to a patient group with high levels of co-morbid conditions and advanced age.[11] Furthermore, there is a general concern that the participants of existing randomized controlled trials do not reflect the actual population of HF patients. In particular, trials have often excluded HF patients with preserved systolic function and renal insufficiency.[12] The SENIORS trial enrolled patients with a wide range of LVEF (one-third with ejection fraction >35%) and 50% were aged ≥75 years. Even in this cohort, nebivolol significantly reduced the primary composite outcome of all-cause mortality or CV hospital admission. As demonstrated by the Hypertension in the Very Elderly Trial (HYVET), adequate treatment even in patients of advanced age can result in clinically significant improvements in CV outcomes.[13]

Table 2 Primary and main secondary outcomes by tertile of estimated glomerular filtration rate

Outcome	Low eGFR tertile (<55.5 mL/min/1.73 m^2)			Middle eGFR tertile (55.5–72.8 mL/min/1.73 m^2)			High eGFR tertile (>72.8 mL/min/1.73 m^2)			Interaction *P*-value[a]
	NEB, *n* (%)	PLC, *n* (%)	HR (95% CI)	NEB, *n* (%)	PLC, *n* (%)	HR (95% CI)	NEB, *n* (%)	PLC, *n* (%)	HR (95% CI)	
Primary outcome (all- cause mortality or CV hospitalization)	129 (37.1)	153 (43.0)	0.81 (0.64, 1.03)	98 (28.3)	120 (33.5)	0.83 (0.63, 1.08)	103 (28.1)	99 (29.3)	0.93 (0.70, 1.22)	0.442
All-cause mortality	71 (20.4)	92 (25.8)	0.76 (0.56, 1.03)	57 (16.5)	53 (14.8)	1.14 (0.78, 1.66)	40 (10.9)	44 (13.0)	0.82 (0.53, 1.25)	0.521
CV hospitalization	100 (28.7)	104 (29.2)	0.93 (0.70, 1.22)	72 (20.8)	97 (27.1)	0.74 (0.55, 1.00)	82 (22.4)	73 (21.6)	1.04 (0.76, 1.42)	0.637
CV mortality	49 (14.1)	67 (18.8)	0.72 (0.50, 1.04)	46 (13.3)	43 (12.0)	1.11 (0.74, 1.69)	28 (7.7)	32 (9.5)	0.81 (0.49, 1.35)	0.494

Hazard ratios (HR) represent the effect of nebivolol (NEB) when compared with placebo (PLC). CV, cardiovascular.
[a]Interaction for renal function and effects of nebivolol.

Table 3 Crude and adjusted analysis for the primary outcome according to estimated glomerular filtration rate tertile

Estimated glomerular filtration rate	Number of patients	Primary outcome		Crude			Adjusted		
		Events	Percentage	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Low eGFR tertile	704	282	40	0.81	(0.64, 1.03)	0.087	0.84	(0.67, 1.07)	0.158
Middle eGFR tertile	704	218	31	0.83	(0.63, 1.08)	0.164	0.79	(0.60, 1.04)	0.092
High eGFR tertile	704	202	29	0.93	(0.70, 1.22)	0.597	0.86	(0.65, 1.14)	0.303
Continuous	2112	702	33	0.85	(0.73, 0.99)	0.032	0.85	(0.73, 0.98)	0.030

Hazard ratios (HR) represent the effect of nebivolol when compared with placebo. The adjusted analysis includes smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, NYHA class, medical history (diabetes, prior angina, prior stroke, or prior myocardial infarction) and left-ventricular ejection fraction.

Renal impairment is a common finding in patients with HF and is independently associated with an increased risk of death.[14,15] Our data support this finding in an elderly HF cohort. The link between HF and kidney disease has received considerable attention and likely reflects a number of superimposed factors.[5] For example, renal impairment may indicate a worsened state of HF or paradoxically cause progression of ventricular dysfunction.[16] HF patients with renal impairment are also less likely to be prescribed effective treatment.[17]

Use of beta-blockers in HF patients with kidney disease is known to improve outcomes.[17–19] Mechanistically, this improvement may be linked to reduction in activity of the renin–angiotensin system, improvement in renal blood flow, and improved natriuresis in response to volume loading.[20] However, only a few studies have compared the effects of beta-blockade in HF patients with and without renal dysfunction. The Cooperative Cardiovascular Project was a non-randomized observational study using propensity score matching in patients over 65 years who survived a myocardial infarction. In the 2613 participants on beta-blockers, a greater benefit was noted for patients with serum creatinine levels of 2.0 mg/dL [176.8 μmol/L] or greater ($P = 0.02$).[21] Subgroup analysis of CIBIS (Cardiac Insufficiency Bisoprolol) II, a randomized controlled trial of bisoprolol in symptomatic patients with ejection fraction $\leq$35% and mean age 61 years, showed similar benefit for beta-blocker treatment in those with creatinine clearance <60 and ≥ 60 mL/min.[22] Finally, a sub-analysis of MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure) is considered in which 3991 participants with LVEF $\leq$40% and mean age of 64 were randomized to controlled-release metoprolol or placebo.[23] Renal function, divided into MDRD eGFR groups, was a strong and independent predictor of outcomes. The benefit of beta-blockade was noted in all eGFR groups, with no significant interaction for renal function and total mortality (interaction *P*-value = 0.095). Our analysis confirms the latter two results and for the first time extends these conclusions to an HF population more typical of clinical practice, that is older and with a wide range of LVEF. The number needed to treat (NNT) with nebivolol for the primary outcome in the whole cohort was 24. Patients in the lowest tertile of eGFR had a similar NNT of 17, although we were underpowered to detect differences between the eGFR tertiles. However, as CV outcomes were more common in those with impaired renal function, the absolute clinical benefit may actually be greater in these patients.

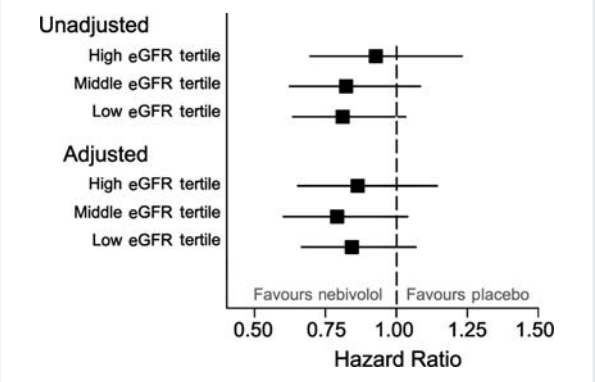

Figure 3 Forest plot for primary outcome by estimated glomerular filtration rate tertile. Adjusted analysis includes smoking, gender, ethnicity, age, heart rate, systolic blood pressure, diastolic blood pressure, NYHA class, medical history (diabetes, prior angina, prior stroke or prior myocardial infarction), and left-ventricular ejection fraction.

The good renal tolerance of nebivolol even in this group of patients may be explained by its unique ability to vasodilate renal arteries via endothelial-dependent nitric oxide,[24] independently of effects on adreno-receptors.[25] Nebivolol has a higher degree of beta-1 selectivity than any other beta-blocker, explaining the minimal effects noted on the airways of asthmatic patients or insulin sensitivity in those with diabetes.[26] Metabolism and elimination of nebivolol is almost entirely through hepatic cytochrome P450 enzymes, although the minimal amount of drug excreted unchanged in the urine can be important in patients with severe renal impairment.[26] This may explain the higher rate of bradycardia seen in those with low eGFR in our study.

The effect of beta-blockers on the natural history of renal function in patients with HF remains largely unknown. Beta-blockade has the potential to improve renal function, presumably by

Table 4 Safety data by estimated glomerular filtration rate and treatment group

Event	Nebivolol			Placebo			Whole group		
	eGFR < 60	eGFR ≥ 60	*P*-value	eGFR < 60	eGFR ≥ 60	*P*-value	Nebivolol	Placebo	*P*-value
Number	440	620		446	606		1060	1052	
Final dose at end of titration	7.3 ± 3.7	8.0 ± 3.3	0.004	8.2 ± 3.3	8.7 ± 2.9	0.003	7.7 ± 3.5	8.5 ± 3.1	<0.001
Hypotension[a]	2 (0.5)	2 (0.3)	0.730	0 (0)	0 (0)	–	4 (0.4)	0 (0)	0.046
Renal failure[a]	0 (0)	1 (0.2)	0.399	0 (0)	1 (0.2)	0.391	1 (0.1)	1 (0.1)	0.996
Bradycardia[a]	10 (2.3)	5 (0.8)	0.046	3 (0.7)	5 (0.8)	0.391	15 (1.4)	8 (0.8)	0.147
HF[a]	12 (2.7)	9 (1.5)	0.142	9 (2.0)	5 (0.8)	0.095	21 (2.0)	14 (1.3)	0.242
Any event[a]	23 (5.2)	15 (2.4)	0.015	11 (2.5)	10 (1.7)	0.350	38 (3.6)	21 (2.0)	0.027

Safety data in the SENIORS trial according to renal function and treatment arm.
[a]Leading to drug discontinuation. Nebivolol dose described as mean dose (mg) ± SD; other variables are total number (percentage).

improvement in cardiac output and a concomitant increase in renal perfusion,[27] supplementing the direct glomerular effects of beta-1 receptor antagonism. In a small double-blind crossover study, nebivolol preserved renal blood flow when compared with atenolol, the latter causing a significant drop in GFR.[28] In the setting of reduced renal perfusion in HF, venous congestion is also a determinant of GFR[29] and another target for agents that block sympathetic activation. Our data, the first involving an elderly HF cohort, found no improvement over 2 years in renal function, but did confirm that nebivolol was as safe as placebo with regards to longer term kidney function, even in those patients with moderate impairment at baseline. However, these issues can only be fully addressed in a prospective controlled trial or an individual patient meta-analysis of all beta-blocker trials, which is currently being explored.[30]

Analysis of the dose of nebivolol achieved has identified that lower doses may have less impact on outcomes and those intolerant of beta-blockers have a significantly higher risk of death or CV admission when compared with placebo (adjusted hazard ratio 1.95, 95% CI 1.38–2.75).[31] Anaemia is also a powerful independent predictor of HF outcomes[32] and is associated with impaired renal function through inadequate erythropoietin production.[33] Previous studies have not reported the association of baseline haemoglobin with renal function in HF and the subsequent effects on beta-blocker efficacy. To account for these potential modifiers on the effect of nebivolol in participants with reduced eGFR, we further adjusted our multivariate analysis for dose and baseline haemoglobin. In the low eGFR tertile (<55 mL/min), the hazard ratio for the primary outcome was unchanged when compared with the pre-specified analysis (0.87, 95% CI 0.68–1.11; $P = 0.250$).

Limitations of study

This analysis is based on subgroups from the SENIORS cohort and is thus liable to the usual limitations of such methods. In particular, we were statistically underpowered to detect significant improvement in the primary outcome for the eGFR subgroups. Nevertheless, each tertile had a trend towards benefit, and interaction *P*-values were consistently non-significant across the secondary outcomes. Another limitation was the exclusion of patients with a creatinine level of >250 μmol/L. This level was a pre-determined exclusion criterion based on licensing restrictions for nebivolol in some of the countries participating in SENIORS recruitment. As such the conclusions for this analysis cannot be extended to patients with severe renal impairment. We chose to describe renal function in terms of the MDRD formula, which has been validated in HF patients.[34,35] Although eGFR by this technique is higher than with other methods,[36] supplementary analysis of the SENIORS data based on serum creatinine and Cockroft-Gault clearance resulted in identical conclusions.

Conclusions

In elderly HF patients with a wide range of ejection fraction, mild and moderate impairment of renal function did not interact with the effect of nebivolol on clinical outcomes. Furthermore, nebivolol was well tolerated in participants of the SENIORS trial with moderate renal impairment. Thus, mild to moderate renal dysfunction, even in the elderly, should not present a limitation to the use of nebivolol in HF patients.

Funding

The SENIORS study was funded by a grant from Menarini Ricerche SpA. The Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London, received a grant from Menarini Ricerche to support statistical analyses and preparation of secondary manuscripts. Funding to pay the Open Access publication charges for this article was provided by Menarini Farmaceutica Internazionale, Florence.

Conflict of interest: All members of the Steering Committee of SENIORS and authors of this paper (except M.R. and D.B.) have received honoraria for speaking on aspects of heart failure and beta-blockers at meetings funded by companies in the pharmaceutical industry, including Menarini and its subsidiaries. The authors confirm that the study complies with the Declaration of Helsinki (2008), the locally appointed ethics committees have approved the research protocol and that informed consent has been obtained from the participants.

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