**Aims** Large randomized trials have shown that beta-blockers reduce mortality and hospital admissions in patients with heart failure. The effects of beta-blockers in elderly patients with a broad range of left ventricular ejection fraction are uncertain. The SENIORS study was performed to assess effects of the beta-blocker, nebivolol, in patients ≥70 years, regardless of ejection fraction.
Methods and results We randomly assigned 2128 patients aged ≥ 70 years with a history of heart failure (hospital admission for heart failure within the previous year or known ejection fraction ≤ 35%), 1067 to nebivolol (titrated from 1.25 mg once daily to 10 mg once daily), and 1061 to placebo. The primary outcome was a composite of all cause mortality or cardiovascular hospital admission (time to first event). Analysis was by intention to treat. Mean duration of follow-up was 21 months. Mean age was 76 years (SD 4.7), 37% were female, mean ejection fraction was 36% (with 35% having ejection fraction ≥ 35%), and 68% had a prior history of coronary heart disease. The mean maintenance dose of nebivolol was 7.7 mg and of placebo 8.5 mg. The primary outcome occurred in 332 patients (31.1%) on nebivolol compared with 375 (35.3%) on placebo [hazard ratio (HR) 0.86, 95% CI 0.74–0.99; P = 0.039]. There was no significant influence of age, gender, or ejection fraction on the effect of nebivolol on the primary outcome. Death (all causes) occurred in 169 (15.8%) on nebivolol and 192 (18.1%) on placebo (HR 0.88, 95% CI 0.71–1.08; P = 0.21).

Conclusion Nebivolol, a beta-blocker with vasodilating properties, is an effective and well-tolerated treatment for heart failure in the elderly.

Methods

Study design

The protocol for SENIORS has been published elsewhere.

SENIORS is a parallel group, randomized, double-blind, multicentre, international trial comparing nebivolol with placebo in elderly patients with heart failure on optimal standard therapy. The study was performed in compliance with good clinical practice and followed the recommendations of the Declaration of Helsinki. The relevant national and local ethics review boards and regulatory authorities approved the protocol. Written informed consent was obtained from all patients before enrolment.

Patients

To be eligible, patients had to be aged ≥ 70 years, provide written informed consent, have a clinical history of chronic heart failure with at least one of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure or documented left ventricular ejection fraction ≤ 35% within the previous 6 months. The main exclusion criteria were new drug therapy for heart failure in the 6 weeks prior to randomization, heart failure due primarily to uncorrected valvular heart disease, contraindication or previous intolerance to beta-blockers (e.g. heart rate < 60 beats/min or systolic blood pressure < 90 mmHg), current use of beta-blockers, significant hepatic or renal dysfunction, cerebrovascular accidents within the previous 3 months, and being on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study.
Screening and randomization

Patients were screened for eligibility at participating centres by checking hospital outpatient lists and admissions for heart failure within the previous year. Patients underwent echocardiography after entry into the study but prior to administration of the study drug. A master randomization list stratified by centre was prepared and held securely. Randomization to nebivolol or placebo on a 1:1 basis was carried out by telephone call to a central office (Clinical Data Care, Lund, Sweden). Patients were allocated a treatment number which corresponded to the appropriate study treatment packs.

Study medication

Nebivolol or placebo tablets were provided in identical packaging and tablet appearance. The initial dose was 1.25 mg once daily, and, if tolerated, this was increased to 2.5 and 5 mg, respectively, every 1–2 weeks, reaching a target of 10 mg once daily over a maximum of 16 weeks. Dose titration was performed during a visit to the hospital or clinic, and patients were observed for up to 2 h after taking the new dose to assess tolerability. Up-titration could be stopped or delayed depending on symptoms, possible side-effects, or at the judgement of the local investigator.

Patient follow-up

Following the titration phase, the next two visits were scheduled at 4 and 6 months after randomization, and further visits at 3-monthly intervals until the end of the study. A 30-day safety follow-up visit was planned for all patients after the last study drug administration to document any post-treatment adverse effects. The initial protocol specified a minimum observation period of 6 months for all patients, but this was amended to a minimum of 12 months by the Steering Committee in March 2003 when it was observed in blinded analysis that the composite primary event rate was below the expected rate. The end of the observation period for all patients was set at 15 November 2003. In those patients who did not attend their end of observation follow-up visit, vital status was determined by direct enquiry, national registers of death, and review of practice records.

Monitoring, data management, and reporting of adverse events

Study monitoring and data management were performed by the contract research organization Parexel GmbH (Berlin, Germany) under the supervision of the Sponsor. Patient data were recorded on paper case report forms. At regular intervals validation of data was undertaken and all resulting queries were resolved with investigators. Serious adverse events, other than those defined as clinical outcome events, were reported by investigators in an expedited manner and reviewed centrally. An independent and experienced Data and Safety Monitoring Committee regularly examined unblinded data prepared by an independent statistician. In all four interim unblinded analyses, no reason was found for safety concerns.

Independent supervision of the study

The protocol was developed by an independent Steering Committee in collaboration with the Sponsor. The Steering Committee comprised cardiologists from hospitals and academic centres in the participating countries. The responsibilities of the Steering Committee included overseeing the scientific conduct of the study, independent statistical analysis, presentation of the results at scientific meetings, and preparation of manuscripts for publication. The independent Data and Safety Monitoring Committee was responsible for reviewing unblinded study data at regular intervals and ensuring that the Steering Committee was informed of any safety concerns or efficacy issues during the course of the study. All reported deaths and hospital admissions were referred to the independent Clinical Events Review Committee, blinded to treatment, for review of medical records and any other documentation and for final classification of events.

Study outcomes and definitions

The primary outcome was the composite of all cause mortality or cardiovascular hospital admission (time to first event). This outcome was chosen to reflect the potential effect of nebivolol on quality of life in elderly patients in addition to an effect on the risk of death. Secondary outcomes included all cause mortality, the composite of all cause mortality or all cause hospital admissions, all cause hospital admissions, cardiovascular hospital admissions, cardiovascular mortality, the composite of cardiovascular mortality or cardiovascular hospital admissions (time to first event for all of them), functional capacity by New York Heart Association (NYHA) class assessment, and 6-min walk test at 6 months. Deaths were sub-classified by the Clinical Event Review Committee into cardiovascular deaths, non-cardiovascular deaths, or deaths of unknown cause. Hospital admissions were defined as admissions to hospital involving a stay of at least 24 h (excluding hospital admissions planned before randomization and planned admissions for study-related procedures). Cardiovascular admissions included those for cardiac causes (e.g. worsening heart failure, acute coronary syndromes), cerebrovascular causes, or other cardiovascular causes. All other causes of hospital admission were classified as non-cardiovascular or unknown, if relevant information was missing.

Statistical methods

On the basis of previous studies, it was estimated that a sample size of 1700 patients observed for an average 1.5 years (2 years for recruitment and a minimum follow-up of 0.5 years) would provide 90% power to detect a proportional difference of 25% between nebivolol and placebo with a two-sided significance level of 0.05. This assumed a mean annual rate for the primary outcome of 25% in the placebo group and an overall non-compliance rate of 20% in the nebivolol group. To allow for the possibility of lower than expected event rates and higher levels of non-compliance, and losses to follow-up, a total sample of 2000 patients was specified. The sample size was estimated using a time-driven rather than an event-driven approach. The statistical analysis was carried out using the intention to treat according to a plan drawn up before the outcome data were available. The pre-specified primary outcome was analysed using a Cox proportional hazards model with randomized treatment as the major covariate adjusted for baseline age, gender, and ejection fraction. A further analysis was performed with treatment as the sole covariate. Similar analyses were carried out for secondary outcomes unadjusted for multiple comparisons. Whether the effect of nebivolol varied according to five pre-specified risk factors of major interest (Figure 4) was assessed by tests of interaction in Cox-proportional hazard regression analyses adjusted for age, gender, and ejection fraction. A two-sided significance level of
Results

Enrolment and baseline characteristics

The first patient was enrolled in September 2000, the last patient in December 2002. The date of study end was specified as 15 November 2003 for all patients. A total of 2135 patients were enrolled from 11 countries: Czech Republic (312 patients), France (62), Germany (56), Italy (54), Hungary (175), The Netherlands (341), Romania (370), Spain (137), Switzerland (18), Ukraine (457), and the United Kingdom (153). Seven patients were excluded from the final analysis (all six patients recruited at one centre after an audit showed significant deviations from the protocol and poor data quality, and one patient who never took study medication after randomization). A total of 2128 patients (1067 in the nebivolol group and 1061 in the placebo group) were available for analysis (Figure 1).

Patient characteristics at baseline are provided in Table 1. There were no differences among the randomized groups in any of the important baseline characteristics. Mean duration of patient follow-up was 21 months (SD 9; inter-quartile range 14–29 months) with 1863 patient-years of follow-up in the nebivolol group and 1839 in placebo (Table 2). The distribution of patients by age and ejection fraction are shown in Figure 2A and B, respectively.

Compliance to treatment

The mean maintenance dose in the nebivolol group was 7.7 mg (SD 3.6) and 8.5 mg (SD 3.1) in the placebo group. The proportion of patients reaching a dose of ≥5 mg at the end of the titration phase was 80% in the nebivolol group compared with 87% in placebo, and the proportions reaching 10 mg were 68 and 80%, respectively. Premature discontinuation for any reason other than death occurred in 27 and 25%, respectively (Table 2). Discontinuation of treatment occurred mostly at the patients’ request or for other non-clinical reasons, with little difference between the two groups (Table 2).

Haemodynamics

Mean (SD) systolic blood pressure, diastolic blood pressure, and heart rate at the first maintenance visit (~4 months), taking the last observation available for patients with missing data, were 132.3 (19.9) and 135.2 (20.3) mmHg, 76.3 (10.4) and 78.1 (10.2) mmHg, and 68.8 (12.5) and 77.4 (13.6) beats/min in the nebivolol and placebo groups, respectively. Changes from baseline [mean (SD)] in the nebivolol and placebo groups, respectively, for systolic blood pressure were −6.3 (18.2) and −4.3 (17.9) mmHg, for diastolic blood pressure −4.2 (10.6) and −2.4 (10.0) mmHg, and for heart rate −10.3 (14.3) and −1.5 (14.0) beats/min.

Primary outcome

The proportion of patients who suffered death or cardiovascular hospital admission in the nebivolol group was
31.1% compared with 35.3% in the placebo group [hazard ratio (HR) 0.86, 95% CI 0.74–0.99; \( P = 0.039 \); Table 3]. The unadjusted analysis showed an HR of 0.85 with the same CI \( (P = 0.034; \text{Table 3}) \). The absolute risk reduction is 4.2%, suggesting that 24 patients would need to be treated for 21 months to avoid one event. The Kaplan–Meier plot (time to event) suggests that the curves for nebivolol-treated patients compared with placebo for the primary outcome separate after about 6 months and continue to diverge for the duration of follow-up (Figure 3A).

### Primary outcome in subgroups

Results for the primary outcome stratified by major clinical subgroups including gender, ejection fraction, age, diabetes, and prior myocardial infarction are shown in Figure 4. There was no statistically convincing evidence that any of these factors modified the effect of nebivolol. The HR for patients aged less than the median of 75.2 years was 0.79 (95% CI 0.63–0.98) and 0.92 (95% CI 0.75–1.12) in those aged >75.2 years (for interaction test \( P = 0.51; \text{Figure 4} \)). For men, the HR was 0.93 (95% CI 0.78–1.11) and for women, 0.72 (95% CI 0.55–0.93) (for interaction test \( P = 0.11; \text{Figure 4} \)).

### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Nebivolol (n = 1067)</th>
<th>Placebo (n = 1061)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.1 (4.8)</td>
<td>76.1 (4.6)</td>
</tr>
<tr>
<td>Median</td>
<td>75.2</td>
<td>75.3</td>
</tr>
<tr>
<td>Women</td>
<td>410 (38.4%)</td>
<td>375 (35.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Nebivolol (n = 1067)</th>
<th>Placebo (n = 1061)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class I</td>
<td>32 (3.0%)</td>
<td>29 (2.7%)</td>
</tr>
<tr>
<td>II</td>
<td>603 (56.5%)</td>
<td>597 (56.3%)</td>
</tr>
<tr>
<td>III</td>
<td>413 (38.7%)</td>
<td>411 (38.7%)</td>
</tr>
<tr>
<td>IV</td>
<td>19 (1.8%)</td>
<td>24 (2.3%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>683 (64.3%)</td>
<td>686 (64.8%)</td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>&lt;35%</td>
<td>380 (35.7%)</td>
<td>372 (35.2%)</td>
</tr>
<tr>
<td>≥35%</td>
<td>380 (35.7%)</td>
<td>372 (35.2%)</td>
</tr>
</tbody>
</table>

### Table 2 Compliance to treatment and reasons for discontinuation

<table>
<thead>
<tr>
<th>Nebivolol (n = 1067)</th>
<th>Placebo (n = 1061)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-years of follow-up</td>
<td>1863</td>
</tr>
<tr>
<td>Patient-years (%) observed/total*</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

### Table 3 Reasons for drug discontinuation\*

<table>
<thead>
<tr>
<th>Nebivolol (n = 285)</th>
<th>Placebo (n = 261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance dose level achieved</td>
<td>( \geq 5 \text{ mg} )</td>
</tr>
<tr>
<td>Other</td>
<td>( 83 ) (7.8%)</td>
</tr>
</tbody>
</table>

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\* Data are number of patients (%).
\*\* Considering untraced patients as followed until 15 November 2003.
\*\*Median (first quartile–third quartile).
\*\* Up to 4 months after first drug intake.
\*\* At second maintenance visit, \( \sim 6 \) months after first drug intake.
\*\* At fourth maintenance visit, \( \sim 12 \) months after first drug intake.
\*\* Reasons other than death. Percentages of the whole ITT population. Reason not known for four and two patients in nebivolol and placebo group, respectively.

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Data are number of patients (%).
\* Considering untraced patients as followed until 15 November 2003.
\* Median (first quartile–third quartile).
\* Up to 4 months after first drug intake.
\* At second maintenance visit, \( \sim 6 \) months after first drug intake.
\* At fourth maintenance visit, \( \sim 12 \) months after first drug intake.
\* Reasons other than death. Percentages of the whole ITT population. Reason not known for four and two patients in nebivolol and placebo group, respectively.
The HR for patients with left ventricular ejection fraction \( \leq 35 \) and \( >35\% \) were 0.87 (95% CI 0.73–1.05) and 0.82 (95% CI 0.63–1.05), respectively (for interaction test \( P = 0.42; \) Figure 4).

### All cause mortality

The proportion of deaths was 15.8 and 18.1% in the nebivolol and placebo groups, respectively (HR 0.88, 95% CI 0.71–1.08; \( P = 0.21; \) Table 3). Time to all cause death is shown in Figure 3B. The proportion of cardiovascular deaths which might be considered sudden deaths was 36% in the nebivolol group and 48% in the placebo group.

### Other secondary outcomes

The proportions of cardiovascular hospital admissions were 24.0 and 26.0% in the nebivolol and placebo groups, respectively (HR 0.90, 95% CI 0.76–1.06). Other secondary outcomes including total mortality, cardiovascular mortality, or all cause mortality and all cause hospitalization are shown in Table 3.

### Analyses which were not pre-specified

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 ejection

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**Table 3** Primary and main secondary outcomes (time to first event)a

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nebivololb (n = 1067)</th>
<th>Placebo b (n = 1061)</th>
<th>HRa</th>
<th>95% CI</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality or CV hospitalization</td>
<td>332 (31.1%)/20.3</td>
<td>375 (35.3%)/23.9</td>
<td>0.86</td>
<td>0.74–0.99</td>
<td>0.039</td>
</tr>
<tr>
<td>All cause mortality contributing to primary outcomec</td>
<td>76 (7.1%)/4.1</td>
<td>99 (9.3%)/5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV hospitalizations contributing to primary outcomec</td>
<td>256 (24.0%)/16.3</td>
<td>276 (26.0%)/18.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome, unadjusted analysis</td>
<td>332 (31.1%)/20.3</td>
<td>375 (35.3%)/23.9</td>
<td>0.85</td>
<td>0.74–0.99</td>
<td>0.034</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>169 (15.8%)/9.1</td>
<td>192 (18.1%)/10.4</td>
<td>0.88</td>
<td>0.71–1.08</td>
<td>0.21</td>
</tr>
<tr>
<td>CV mortality</td>
<td>123 (11.5%)/6.9</td>
<td>145 (13.7%)/8.2</td>
<td>0.84</td>
<td>0.66–1.07</td>
<td>0.17</td>
</tr>
<tr>
<td>Sudden cardiac deathc,d</td>
<td>44 (4.1%)/2.5</td>
<td>70 (6.6%)/4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CV mortalityc</td>
<td>26 (2.4%)/1.5</td>
<td>20 (1.9%)/1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown/not classifiedc,e</td>
<td>20 (1.9%)/1.1</td>
<td>27 (2.5%)/1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>256 (24.0%)/16.3</td>
<td>276 (26.0%)/18.3</td>
<td>0.90</td>
<td>0.76–1.06</td>
<td>0.20</td>
</tr>
<tr>
<td>CV mortality or CV hospitalization</td>
<td>305 (28.6%)/19.4</td>
<td>350 (33.0%)/23.2</td>
<td>0.84</td>
<td>0.72–0.98</td>
<td>0.027</td>
</tr>
<tr>
<td>All cause hospitalization</td>
<td>359 (33.6%)/24.4</td>
<td>364 (34.3%)/25.7</td>
<td>0.96</td>
<td>0.82–1.10</td>
<td>0.47</td>
</tr>
<tr>
<td>All cause mortality or all cause hospitalization</td>
<td>408 (38.2%)/26.6</td>
<td>443 (41.8%)/30.1</td>
<td>0.90</td>
<td>0.78–1.02</td>
<td>0.082</td>
</tr>
</tbody>
</table>

CV, cardiovascular.

*aHR (and P-value) calculated on time to event. Analyses adjusted by gender, age, and left ventricular ejection fraction, unless otherwise specified.

*bEach cell in these columns contains the number of events, the percentage of events, and the annual rate as number of events per 100 patient-years of follow-up at risk.

*cNot pre-specified analyses.

*dConsidered within CV mortality.

*eUnknown/not classified category includes: not witnessed, not sudden cardiac death, not classified, vital status information from patients who prematurely terminated the study.
fractions, we identified the subgroup of patients most similar to the previous major outcome trials. In this sub-
group, defined as patients of less than median age (75.2 years) with an ejection fraction $\geq 35\%$ ($n = 342$ for nebi-
volol and $n = 342$ for placebo), the HR for the primary
outcome was 0.73 (95% CI 0.56–0.96). For all cause mor-
tality alone, the HR was 0.62 (95% CI 0.43–0.89). This
suggests an efficacy for nebivolol similar to that seen in
similar patient cohorts for metoprolol-controlled
release, bisoprolol, and carvedilol. If an ejection fraction
threshold of 40% rather than 35% was used, there was no
material difference to the results for the subgroup com-
parisons. For the primary endpoint, in the population
with ejection fraction $> 40\%$, HR $= 0.86$ (95% CI
0.73–1.03; $P = 0.095$) for ejection fraction $< 40\%$, HR $= 0.83$ (95% CI 0.62–1.11; $P = 0.203$). As age was a
particular focus of the SENIORS trial, we also analysed
patient cohorts between median age (75.2 years) and
85 years ($n = 459$ for nebivolol and $n = 482$ for placebo)
where the HR for the primary endpoint was 0.91 (95%
CI 0.74–1.13) and for patients $> 85$ years ($n = 69$ for nebi-
volol and $n = 54$ for placebo) where the HR was 1.32 (95%
CI 0.73–2.37). There was no difference between the
groups for hospitalization for heart failure [placebo 144
(13.7%), nebivolol 145 (13.9%), HR = 0.99 (95% CI
0.79–1.25; $P = 0.95$)].

Adverse events

Adverse events are shown in Table 4. There were no
differences other than those expected of a beta-
blocker, namely, an increased incidence of bradycardia
and a decrease of angina pectoris and unstable angina.
Bradycardia was associated with withdrawal from
blinded treatment in 18 and 4 nebivolol and placebo
treated patients, respectively.

Discussion

The SENIORS study shows that treating elderly patients
with heart failure with nebivolol reduces the composite
risk of all cause mortality or cardiovascular hospital
admission compared with placebo. The beneficial
effects appear after 6 months of treatment and the risk
reduction continues to increase with longer treatment.
A broad range of patients on standard currently rec-
ommended treatment were included (one-third with
ejection fraction $> 35\%$, 37% females, and 50% aged
$> 75$ years). Study medication was well tolerated and
the majority of patients were able to reach a mainten-
ance dose of $10\, mg$ once daily after careful titration.
The observed reductions in heart rate and blood pressure
were as anticipated from treatment with a beta-blocker.

Several large randomized trials and meta-analyses of
previous trials have shown that beta-blockers reduce
the risk of death or hospitalization in patients with
heart failure.$^{10–14}$ In those studies the mean age was 63
years and the estimated mean ejection fraction was
25% (most studies had an upper limit for ejection fraction
of 35 or 40%). Subgroup analyses of some of the large
studies indicated this benefit was present in
patients $> 65$ years,$^{13,20,21}$ but there was little infor-
mation in those $> 70$ years and those patients with ejec-
tion fraction $> 35\%$. The need for additional data has
been emphasized.$^{8,11,22,23}$ SENIORS extends the evidence
of benefit of beta-blockade to a broad range of elderly
patients with heart failure including those with mild
left ventricular dysfunction or preserved ventricular
function. The patients in the SENIORS study more
closely resemble the general population of patients
with heart failure, where the mean age is 76 years.$^{2,3}$

Other observational studies have assessed the effects
of beta-blockers in elderly patients$^{24,25}$ but no previous ran-
donized controlled trial has had the power to demon-
strate efficacy in elderly heart failure patients
specifically.

The estimated HR for the primary outcome in SENIORS
was 0.85, suggesting a lesser degree of risk reduction
compared with previous large trials. Nevertheless, both
components of the primary outcome (all cause mortality
and cardiovascular hospital admission) show a similar and
consistent effect indicating that the results are robust
with a 15% proportional and 4% absolute reduction in
risk. We undertook a subanalysis which was not pre-
specified (age less than median and ejection fraction ≤35%) in order to determine the result for patients most similar to those recruited in previous trials. The findings were similar to the results from previous trials, with significant 27 and 38% reductions in the primary composite endpoint and all-cause mortality, respectively, indicating that nebivolol has beneficial effects of a magnitude similar to those of other beta-blockers proved to have major outcome benefits in heart failure.

SENIORS explored the effects of nebivolol in several clinically important subgroups of patients. Given the overall P-value for the primary endpoint of 0.039 there was, of course, limited power to detect potential interactions. Despite advanced age being an inclusion criterion one important potential interaction was still that of age itself. The increased risk of dying from a natural cause in the elderly may compete with the potential benefits of a treatment. Thus, it is plausible that there is a threshold of biological age, rather than chronological age, beyond which the benefit of treatment is difficult to show. Although the benefits of nebivolol appeared to be less in patients ≥75 years, age as a continuous variable did not significantly affect the treatment effect. It is possible that beta-blockers, or indeed any treatments, are in reality less effective in the very elderly.
Heart failure with preserved systolic function is common in population samples of heart failure patients, especially in the older age groups.26 Previous mortality and morbidity studies both for ACE inhibitors and for beta-blockers have typically excluded such patients. One trial within the CHARM programme27 investigating the effects of candesartan did not show a significant effect on its primary endpoint. SENIORS showed both a significant overall treatment effect and a virtually identical point estimate of risk reduction for patients with low and preserved ejection fraction. This is the best evidence to date of a treatment likely to be effective in the substantial proportion of the elderly population with heart failure who have a broad range of ventricular dysfunction, and suggests the beta-blocker nebivolol can be recommended for heart failure, irrespective of ejection fraction.

Nebivolol is a beta-1-selective blocker with vasodilator properties which appear to be due to modulation of nitric oxide release that reduces peripheral vascular resistance.15–17 Nebivolol has been extensively investigated in hypertension and has received approval in many jurisdictions for this indication. The exact mechanisms of benefit in heart failure are not known, but may include reduction in ventricular wall stress,28 reduction in adverse neurohormonal stimulation, and reduction in incidence of acute coronary events, especially as half of the patients had a prior myocardial infarction. In SENIORS, patients were started on a dose of 1.25 mg once daily and titrated to a target dose of 10 mg over a mean of 7 weeks. Elderly patients are at higher risk of hypotension, bradycardia, and other side-effects of beta-blockers when compared with younger patients. Nevertheless, 68% of patients in the nebivolol group reached the maximum dose, with only 6% not tolerating any dose. This good tolerability may, in part, be related to the vasodilating properties of nebivolol so that results may not be generalizable to other beta-blockers when used in elderly heart failure patients. Previous studies have raised the possibility that beta-blockers in heart failure need to be evaluated separately and the effects of one cannot be extrapolated to another.29,30 It has been estimated that the probability of receiving beta-blocker therapy is substantially lower in the elderly31,32 and the most quoted reasons for this are concerns that physicians are less convinced by the body of evidence in this age group.33,34 The SENIORS study should allay this concern.

The SENIORS trial shows that the beta-1-selective vasodilating beta-blocker nebivolol is well tolerated and effective in reducing mortality and morbidity in patients of age >70 years with heart failure, regardless of the initial ejection fraction. Nebivolol can be used in this common group of patients for the treatment of heart failure.

Acknowledgements

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Appendix

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