Editorial

Making sense of SENIORS

John McMurray

Department of Cardiology, Western Infirmary, Glasgow G11 6NT, UK

Online publish-ahead-of-print 11 January 2005

This editorial refers to ‘Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)’ by M.D. Flather et al., on page 215.

Recently, three landmark, prospective, randomized, placebo-controlled trials demonstrated, unequivocally, that a relatively short period of treatment with certain beta-blockers (bisoprolol, target dose 10 mg once daily; carvedilol, target dose 25 mg twice daily; and metoprolol CR/XL, target dose 200 mg once daily) led to a comparable reduction in the risk of death (relative risk reduction ∼33%) in patients with chronic heart failure (CHF) and a reduced left ventricular ejection fraction (LVEF).1–3 The decrease in mortality in these trials due, mainly, to a pronounced reduction in death from cardiovascular causes, was seen irrespective of symptom severity and was accompanied by similarly large and statistically significant reductions in cardiovascular hospital admissions, especially those due to worsening CHF.4–6

How should we interpret the findings of the new and important SENIORS (study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure) study7 in light of these prior trials? Looking at outcomes that can be compared across the trials, it is hard to conclude that, in SENIORS, nebivolol was as effective as bisoprolol, carvedilol, or metoprolol CR/XL, as dosed in CIBIS (cardiac insufficiency bisoprolol study)2, COPERNICUS (carvedilol prospective randomized cumulative survival), or MERIT-HF [metoprolol CR/XL (controlled release) randomized intervention trial in heart failure], respectively (Table 1). While it could be argued that all cause mortality is not the most important endpoint in the very elderly, there also appeared to be less effect on hospital admissions in SENIORS. Why might this be? There are several possibilities. The particular beta-blocker used might be important. By design, SENIORS randomized older patients; this might also be significant. Alternatively, the inclusion of patients with an LVEF > 0.35 could have influenced the response to treatment. For one or more of these reasons, SENIORS may have lacked statistical power to show a difference between placebo and nebivolol. The duration of follow-up was also much longer in SENIORS than in any of the prior trials, which is a good thing, and this too could be important.

Looking at each of these possibilities in turn, the particular molecule, formulation, and dose of a beta-blocker may all be important, as suggested by recent trials.8,9 Consequently, it is quite possible that nebivolol, at the dose used in SENIORS, is inferior to the other proven treatment regimens described earlier. Older patients may respond differently to drugs, including those affecting the sympathetic nervous and renin-angiotensin systems, both in terms of efficacy and tolerability.10 A weakness of the prior beta-blocker (and other) trials, and the strength of SENIORS, was the inclusion of many truly elderly patients.11–13 Could the age difference between these trials explain the apparent differences in outcome? It would seem not, for in retrospective subgroup analyses of CIBIS 2 and MERIT-HF, older patients seemed to derive as much benefit as younger ones.14,15 For example, in MERIT-HF, the relative risk reduction (RRR) in all cause mortality with metoprolol CR/XL was 37% in those aged >65 compared with 30% in those <65 years and 29% in those aged >75 (overall RRR 34%).15 In CIBIS 2, the RRR in mortality in those ≥71 years was 32% compared with 31% in those <71 years (overall RRR 34%).14

Patients with CHF but without a marked reduction in LVEF have a different natural history (and better survival) than those with a low LVEF.16–18 How patients without a marked reduction in LVEF respond to treatments known to be effective in low LVEF CHF is uncertain.19,20 It is quite possible that inclusion of a substantial proportion of patients with LVEF > 0.35 in SENIORS, which was
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of outcomes in CIBIS 2, MERIT-HF, COPERNICUS, and SENIORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean follow-up (years)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>CIBIS 2</td>
<td>1.3</td>
</tr>
<tr>
<td>(1320 placebo, 1327 bisoprolol)</td>
<td></td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>1.0</td>
</tr>
<tr>
<td>(2001 placebo, 1990 metoprolol CR/XL)</td>
<td></td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>0.87</td>
</tr>
<tr>
<td>(1133 placebo, 1156 carvedilol)</td>
<td></td>
</tr>
<tr>
<td>SENIORS</td>
<td>1.75</td>
</tr>
<tr>
<td>(1061 placebo, 1067 nebivolol)</td>
<td></td>
</tr>
<tr>
<td>^Primary end-point in SENIORS.</td>
<td></td>
</tr>
<tr>
<td>P, placebo; BB, beta-blocker; CV, cardiovascular. For events, each cell shows (where published), number of events, odds ratio, hazard ratio, or relative risk (with 95% confidence intervals) and P-value (odds ratios for COPERNICUS calculated from numbers of events).</td>
<td></td>
</tr>
</tbody>
</table>
both a good and brave strategy, could account for the small effect of nebivolol. It would, therefore, be of interest to see an analysis of mortality in SENIORS after exclusion of patients with LVEF \(>0.35\). I calculate the odds ratio for the primary end-point in these patients is 0.83, which is less impressive than in MERIT-HF or COPERNICUS (Table 1).

One way in which inclusion of patients with LVEF \(>0.35\) could have influenced the findings of SENIORS was by reducing statistical power since these patients have fewer cardiovascular events. The event rate in SENIORS was surprisingly low. However, it is mainly the number of events, rather than rate of events, that influences power and, although SENIORS was not an event driven trial, the number of deaths, for example, was not greatly different than in CIBIS 2 or COPERNICUS, yet the effect of treatment clearly was.

Lastly, SENIORS had the longest follow-up of all the large beta-blocker trials described (and twice as long as that of COPERNICUS). All the other trials were also stopped prematurely. Early stopping for benefit and short-term follow-up tends to exaggerate the apparent treatment effect-size and this too may account for some of the apparent difference between SENIORS and the prior studies (though this is not obvious from inspection of the Kaplan–Meier curves in SENIORS).

What are we to conclude from all of this? The authors are to be congratulated on an excellently conceived and conducted study though the interpretation of the results of SENIORS is difficult (and some more important information has yet to be presented, e.g. the effect of treatment on symptoms, functional class, and quality of life). Treatment with a different beta-blocker, inclusion of patients with a different type of heart failure (preserved LVEF), use of a different primary endpoint, and longer duration of follow-up mean that comparing SENIORS with the prior beta-blocker trials in CHF involves a lot more than just comparison of age. For the reasons outlined, it would be wrong to suggest that SENIORS shows that beta-blockers are less effective in the elderly with low LVEF CHF. Indeed, all the evidence from other trials is to the contrary. It might be wise, however, to stick to beta-blockers that we know definitely work in CHF. What is disappointing is to see how infrequently elderly patients are prescribed these effective treatments.

References


