Effects of 12 Weeks of Ramipril Treatment on the Quality of Life in Patients with Moderate Congestive Heart Failure: Results of a Placebo-Controlled Trial

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Summary. The assessment of quality of life (QoL) has become recognized as an important tool for evaluating heart failure therapy. The angiotensin-converting enzyme inhibitor ramipril (mean dose 8 mg) was evaluated in 223 patients with moderate chronic congestive heart failure at 24 centers in 4 Nordic countries following a randomized, double-blind, placebo-controlled, parallel group design. The follow-up period was 12 weeks. QoL was evaluated using a questionnaire with 47 items, including the disease-specific Severe Heart Failure Questionnaire, the Sleep Dysfunction Scale, and the Psychological General Well-Being Index. In both treatment groups the total score increased from baseline to 12 weeks for both the Severe Heart Failure Questionnaire and for the Psychological Well-Being Index, reflecting relief of symptoms and improved well-being. However, no significant differences between the placebo and ramipril groups could be detected. Only a trend toward improvement in sleep on ramipril compared with placebo therapy was observed. In conclusion, in this placebo-controlled trial no significant effects of 12-week ramipril treatment on QoL could be demonstrated in patients with moderate congestive heart failure.

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Key Words. heart failure, quality of life, ACE inhibitors, questionnaire

The aim of treating patients with chronic congestive heart failure (CHF) is to increase the survival rate and to reduce symptoms, thereby improving well-being and the ability to function in day-to-day activity, that is, to improve quality of life (QoL). Results of several clinical trials indicate that angiotensin-converting enzyme (ACE) inhibitors may be superior to other vasodilators in the treatment of heart failure, and they have been shown to improve prognosis [1-3], in addition to offering exercise-related benefits [4-10].

There is also good evidence of symptomatic improvement with treatment with ACE inhibitors in heart failure, and several studies have demonstrated that the New York Heart Association (NYHA) class improves over time in groups of patients treated with ACE inhibitors compared with others on placebo treatment [4-8]. Attenuated progression of heart failure might be one mechanism for improved symptoms [11]. Beneficial effects on dyspneic symptoms as well as on QoL have been more difficult to demonstrate [12].

In the Ramipril Multicenter Study [13], the primary objective was to evaluate the effect of 12-week ramipril treatment on maximal exercise time in patients with mild or moderately severe chronic CHF. As a secondary objective, the effect of treatment on QoL was evaluated.

Materials and Methods

Study protocol

This was a double-blind, randomized, placebo-controlled, multicenter study of the effects of ramipril in patients with mild or moderate chronic CHF. A parallel-group design was applied, and the study was performed at 24 centers in four Nordic countries: Sweden, Denmark, Finland and Norway. The study started with a single-blind placebo run-in period of

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weeks of treatment using a set of standard question-

Quality of life was assessed at baseline and after 12

weeks before the start of the placebo run-in period

2-6 weeks, when baseline evaluation was carried out.

The follow-up period of blinded therapy was 12 weeks,

and the mean dose of ramipril was 8 mg (1.25–10 mg).

Patients with stable chronic congestive heart fail-

ure in class II or III, according to New York Heart

Association (NYHA) classification [9], for at least 2

months with treatment with diuretics and digitalis or
diuretics alone were included (Table 1). Patients
treated with vasodilators (except long-acting nit-

rates), calcium antagonists, or potassium-sparing di-
uretics that could not safely be withdrawn at least 2
weeks before the start of the placebo run-in period
were excluded from the study [13].

Heart failure was due to ischemic heart disease,
hypertensive heart disease, or dilated cardiomyopa-
thy, with or without secondary mitral insufficiency.
The patients had cardiomegaly on chest radiograph
and/or an ejection fraction <40% estimated by echo-
cardiography. The study groups were comparable at
baseline [13] (Table 1). The study was approved by
the ethics committees at all centers.

### Quality of life

Quality of life was assessed at baseline and after 12
weeks of treatment using a set of standard question-

naires. The questionnaires were all self-administered,
were completed at home 1 or 2 days before the next
visit to the clinic, and the investigator physician or
the study nurse checked that all the questions had
been fully answered. The questionnaires were trans-
lated into the native language of each of the four par-

Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo (n = 108)</th>
<th>Ramipril (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (range)</td>
<td>64.6 (41–79)</td>
<td>64.4 (38–79)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>79.5 (14.9)</td>
<td>75.4 (11.9)*</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>173 (9)</td>
<td>172 (10)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>79 (73)</td>
<td>81 (70)</td>
</tr>
<tr>
<td>Women</td>
<td>29 (27)</td>
<td>34 (30)</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>8 (7)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>IIB</td>
<td>57 (53)</td>
<td>66 (57)</td>
</tr>
<tr>
<td>IIIA</td>
<td>33 (31)</td>
<td>35 (31)</td>
</tr>
<tr>
<td>IIIB</td>
<td>10 (9)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Cause of CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>68 (63)</td>
<td>69 (60)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>21 (19)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>19 (18)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis alone</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diuretics alone</td>
<td>38 (35)</td>
<td>44 (38)</td>
</tr>
<tr>
<td>Digitalis and diuretics</td>
<td>67 (62)</td>
<td>70 (61)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>37 (34)</td>
<td>39 (34)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>28 (26)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Ejection fraction %, mean (SD)</td>
<td>33 (8)</td>
<td>35 (7)</td>
</tr>
</tbody>
</table>

*p = 0.009.
SD = standard deviation; NYHA = New York Heart Association; CHF = congestive heart failure.

The primary objective of the study was to evaluate
the effect of ramipril treatment on maximal exercise
time. In order to detect a difference in maximal exer-
cise time of 60 seconds, with an assumed standard
device sign for this difference of 150 seconds with alpha
= 0.05 and 1 - beta = 0.80, it was necessary for the
total number of patients to be 200. To compensate
for withdrawals, 223 patients were randomized.

Comparisons for continuous variables were per-
formed in an analysis of variance model. The model
included the treatment of factors, center, and their
interaction, and the effects were estimated by least-
square means. The ramipril group was compared with
the placebo group at the end of treatment using analy-

Statistical methods

The disease-specific Severe Heart Failure Question-
naire (QLQ-SHF) included 18 questions with 6
graded response options [14]. The combined questions
gave a mean point score but could also focus upon
subjective cardiovascular symptoms (six items), day-
to-day activity (seven items), and the psychological
impact of the disease (five items). The higher the nu-
meric point score value, the better the patient felt.

Sleep disturbance was evaluated using the Sleep
Dysfunction Scale based upon five 6-graded questions
about sleep disturbance [15]. Higher score values indi-
cated a lack of sleep problems. A control question
(item 25) was included to check if the use of sleeping
medication had changed.

The patients were also asked to give an overall
global evaluation of the effect of therapy in a question
(item 25) taken from Sharpe et al. [16]. Before analy-
thesis the scale was reversed by subtracting the value
from 8, making the score comparable with the other
scales, that is, the higher the value, the better the
patient felt.

Well-being was assessed using the Psychological
General Well-Being (PGWB) index [17], consisting of
22 6-graded questions. Apart from giving a summary
score, six dimensions provided details on anxiety (five
questions), depression (three questions), well-being
(four questions), health (three questions), self-control
(three questions), and vitality (four questions). A score
of 22 indicated the lowest possible well-being, while
132 signified the best possible well-being.

Analysis of variance included assessments at 4 and
8 weeks, but primarily 12 weeks of treatment in rela-
tion to baseline, and the ramipril group was compared
with the placebo group. The correlations of QoL ver-
sus time until end of exercise were calculated at 12
weeks for the two treatment groups.