Long-term survival in severe heart failure in patients treated with enalapril

Ten year follow-up of CONSENSUS I

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Background The CONSENSUS trial was the first study to show prognostic improvement by an ACE inhibitor. Patients in NYHA class IV heart failure were treated with enalapril or placebo. After study completion (average 183 days) all patients were offered open-label enalapril therapy. This paper reports on the survival at the 10-year follow up of the patients randomized in the CONSENSUS trial.

Methods All 35 participating centres in CONSENSUS I were asked to complete a questionnaire on the survival status at 1 November 1996 of patients randomized in CONSENSUS.

Results At 10-year follow up, one patient was lost to follow-up. Five patients, all in the enalapril group, were long-term survivors \( (P = 0.004) \). Averaged over the duration of the trial (double-blind plus open-label extension) the risk reduction was 30% \( (P = 0.008) \), with a 95% confidence interval of 11% to 46%. At the end of the double-blind study period, mortality was considerably higher among patients who did not receive open ACE inhibitor therapy compared to those who did.

Conclusion After a treatment period of, on average, 6 months, enalapril was shown to be effective. The effect was sustained for at least 4 years i.e. for another 3.5 years. The present follow-up is the first heart failure trial where the full life-cycle has been followed from randomization. In severe heart failure, mortality is significantly reduced by enalapril. On average, the beneficial effect is maintained for several years and overall survival time is prolonged by 50% (from 521 to 781 days).

Key Words: Congestive heart failure, prognosis, ACE inhibitors.

See page 85 for the Editorial comment on this article

Introduction

The prognosis for survival in heart failure remains serious and modern therapy has had little impact on survival in the community[1]. However, among patients with severe heart failure followed in a tertiary centre and treated with angiotensin converting enzyme (ACE) inhibitors, prognosis may have improved[2]. The effect on long-term prognosis on patients in severe heart failure has been less well defined.

The CONSENSUS trial was the first study, in severe heart failure, to show a prognostic improvement by medical therapy, and by an ACE inhibitor in particular[3]. The reduction in the risk of mortality was 50% over the first 6 months (95% confidence interval 34% to 67%), and 46% over 12 months (95% confidence interval 11% to 63%). After study completion (average 183 days) all patients were offered open-label enalapril therapy. In a 2-year follow-up we found that 83% of the patients had received an ACE inhibitor[4].

This paper reports on survival at the 10-year follow-up of the patients randomized in the CONSENSUS trial.

Methods

All 35 participating centres in CONSENSUS I were asked to complete a questionnaire on the survival status at 1 November 1996 of patients randomized in
Table 1  Follow-up of the patients randomized in CONSENSUS

<table>
<thead>
<tr>
<th>Patients included</th>
<th>Placebo (n=126)</th>
<th>Enalapril (n=127)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients alive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at end of trial</td>
<td>58</td>
<td>77</td>
<td>0.002</td>
</tr>
<tr>
<td>at 2-years</td>
<td>40</td>
<td>61</td>
<td>0.006</td>
</tr>
<tr>
<td>at year 10, 1 December 1996</td>
<td>5</td>
<td>5</td>
<td>0.008</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-values are based on the whole study period.

CONSENSUS. The follow-up information could be retrieved from central statistics, by record confirmation or telephone contact. For all patients who had died, the date of death was recorded.

CONSENSUS was stopped on 14 December 1986 following a recommendation from the Safety Committee that all patients be treated with enalapril due to a highly significant beneficial effect on survival.

Statistical methods

The results of the open-label follow-up period were analysed in two different ways. First, all 253 randomized patients were included in an analysis of the time from randomization to death, with data from the double-blind and open-label periods pooled. Next, the 135 survivors of the double-blind period were included in an analysis of the time from the end of the double-blind period to death. Note that this analysis is potentially biased, since survivors in the enalapril group are not necessarily comparable to survivors in the placebo group. The treatment groups were compared by the logrank test[5].

Results

At the end of the trial, of the 253 randomized patients (126 to placebo, 127 to enalapril) there were 58 and 77 survivors in the two treatment groups, respectively (P=0.002) as presented in Table 1. At the 10-year follow-up one patient was lost to follow-up. Five patients, all in the enalapril group, were long-term survivors (P=0.004). The Kaplan–Meier curves are depicted in Fig. 1; averaged over the entire duration of the trial (double-blind plus open-label extension) the risk reduction was 30% (P=0.008), with a 95% confidence interval of 11% to 46%. Figure 1 illustrates that the effect of enalapril during the double-blind portion of the trial persisted for the entire 10-year follow-up period. Figure 2 shows that the enalapril group continued to accrue benefit from their double-blind therapy for approximately 3 additional months after the end of the double-blind period.

Figure 1  Kaplan–Meier survival curves for the two treatment groups in CONSENSUS from randomization to the end of the 10-year follow-up. ——=placebo; – – –=enalapril.

Figure 2  Kaplan–Meier survival curves from end of trial. ——=placebo; – – –=enalapril.

Figure 3  Kaplan–Meier curves from the end of the trial grouped by original allocation group and depending on the open-label use of an ACE inhibitor after the end of the double-blind study period. ——=placebo; – – –=enalapril.

Figure 3 demonstrates the mortality rates in the two treatment groups from the time the double-blind period ended to the end of the 10-year follow-up. However, the curves also illustrate the outcome in
relation to whether a patient received open-label ACE-inhibitor therapy at the conclusion of the double-blind period. Mortality was considerably higher among patients who were not treated compared to those who were treated with an ACE inhibitor. In both groups there is a suggestion of a carry-over effect by enalapril from the double-blind period as it seems to take 6–12 months for the curves to merge among non-users as well as users of ACE inhibitors.

Discussion

This long-term follow-up over a 10-year period, of patients in severe heart failure NYHA class IV, shows that a beneficial treatment effect obtained during a treatment period of, on average, 6 months is sustained for at least 4 years i.e. for another 3–5 years. We have previously reported the significant effect on morbidity as expressed by hospitalizations in CONSENSUS. Morbidity has not been evaluated in our long-term follow-up. As the need for hospitalization for heart failure is closely associated with mortality and prognosis we believe that a sustained survival effect is also associated with an improvement in morbidity.

Furthermore, the present follow-up is the first controlled, prospective heart failure trial where the full life-cycle has been followed from randomization. As all patients in the group initially allocated to placebo died, we have complete information on long-term survival in these patients. At a previous follow-up of the same study patients at 2 years, we showed that both allocation groups had a similar use of ACE inhibitors of around 80%. There is strong support that the beneficial treatment effect by enalapril in severe congestive heart failure observed during the double-blind phase carries over to the follow-up period. In contrast, those who stopped treatment in the enalapril group or did not start treatment with enalapril in the placebo group after the double-blind phase, had a very grim outcome. Figure 3 demonstrates the importance of continued treatment with an ACE inhibitor. Starting treatment with an ACE inhibitor, in patients previously not treated, confers the same mortality as for patients previously taking enalapril. There are several reasons why high-risk patients are not taking ACE inhibitors, terminal illness is one. However, many of the patients in the non-ACE-inhibitor group lived for 2–3 years which makes this unlikely as the sole reason. Coughing may be bothersome, but was rarely a reason for discontinuation in the trial. Doctor compliance and motivation for treatment is an important factor and may explain the lack of treatment in some of the patients. The under-use of ACE inhibitors has been reported in several recent surveys and the present study reflects its serious consequences.

The maintained treatment effect in the CONSENSUS trial suggests that ACE-inhibitor therapy is involved in the important pathophysiological process leading to progression of heart failure. Enalapril has been documented to be favourably associated with neuroendocrine activation, remodelling and manifestations of coronary disease. Our findings suggest that these factors are important and may be modified in severe heart failure, resulting in long-term beneficial effects on mortality and morbidity.

Since there are no survivors in the placebo group it is possible to calculate the average survival in this group, which was 521 days. There are five survivors in the enalapril group. The average survival for the 10 years of follow up was 781 days, representing a more than 50% increase in survival time over the placebo group.

Because of the pronounced treatment effects by enalapril in severe congestive heart failure, only six patients need to be treated for each patient life saved. On average the beneficial effect is maintained for several years and overall survival time is prolonged by 50% by treatment with enalapril. The long-term effect in this follow-up suggests that the already low cost per life saved by the use of enalapril in heart failure is further reduced as the treatment effect is maintained over several years.

We are grateful to all the CONSENSUS investigators for their contribution.

References

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