Failure of an ACE inhibitor to improve exercise tolerance

A randomized study of trandolapril

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Background There has been conflicting evidence of the effect of angiotensin-converting enzyme (ACE) inhibitors on exercise tolerance. Meta-analysis of published results has suggested that a beneficial effect of ACE inhibitors is demonstrated if a trial design is adequate.

Setting Multicentre International Trial.

Methods In a double-blind, randomized, multicentre trial, 292 patients with moderate (New York Heart Association Grades II and III) heart failure were treated with trandolapril or placebo in addition to diuretics, and followed for 16 weeks. Exercise tolerance on a treadmill was assessed at baseline and after 4, 8, 12 and 16 weeks of treatment. Both a modified Bruce and a modified Naughton protocol were used.

Results Exercise tolerance improved in both treatment groups, with no significant benefit from trandolapril treatment.

Conclusion Trandolapril does not improve exercise tolerance as measured by treadmill testing.

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Key Words: ACE inhibitors, exercise duration, heart failure, trandolapril.

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Introduction

Angiotensin converting enzyme (ACE) inhibitors improve mortality and morbidity in patients with heart failure of all degrees of severity, and it seems likely that this is common to all drugs of this class[1–6]. It has, however, been difficult to establish whether ACE inhibitors improve symptoms and exercise capacity: in a review of 35 published double-blind randomized, placebo-controlled trials involving 3411 patients, it was found[7] that active treatment led to an improvement in exercise duration in 23 studies, and that symptoms were improved in 25 of the 33 studies in which symptoms were assessed. The authors of this review concluded that a failure to demonstrate an improvement in exercise capacity with ACE inhibitor treatment was either a chance result in a small trial (a Type 2 error), or was the result of an inappropriate trial design, or the use of a suboptimal method of assessing exercise capacity; all published trials that included more than 50 patients, in which follow-up was more than 3 months, and in which treadmill rather than bicycle testing was used, showed that ACE inhibitor therapy improved both exercise duration and symptoms. This meta-analysis prompts us to describe the results for a previously unpublished trial of trandolapril, for it suggested that we should have found that trandolapril increased exercise duration: in fact it did not.

When our study began in 1991 the effect of ACE inhibitors on the survival of patients with mild to moderate heart failure had not been established with certainty, but since then several trials have been published and trandolapril has been shown in the TRACE Study[6] to improve the survival of patients with impaired left ventricular function following myocardial infarction. There is no reason to suppose that the effects.
of trandolapril on symptoms or exercise tolerance should be different from those of any other ACE inhibitor.

Methods

Study objectives and design

The primary objective of the study was to compare the effects of placebo and trandolapril on exercise tolerance as assessed by the Bruce treadmill protocol after 16 weeks of treatment. Secondary objectives were to compare the effects of placebo and trandolapril with respect to the modified Naughton exercise protocol, and to changes in New York Heart Association (NYHA) functional class. The study was randomized, double-blind, and placebo controlled. It was conducted in eight centres in the United Kingdom and 12 centres in Poland.

Patients

The trial studied patients who complained of breathlessness with heart failure of NYHA Classes II or III. The patients could be male or female and of any age over 18 years. Inclusion criteria were: stable symptoms with no change in diuretic or digoxin dose for at least 2 weeks; a minimum diuretic dose of frusemide 40 mg daily or equivalent; a sitting systolic blood pressure of >90 mmHg and diastolic pressure >50 mmHg; no significant renal disease; evidence of cardiac disease as shown by an enlarged heart on chest X-ray (cardiothoracic ratio >0.5) and/or an end-diastolic left ventricular diameter of >6 ms on echocardiography. Included patients were required to have a maximum exercise tolerance of between 3 and 15 min on the modified Bruce protocol, with a reproducible exercise time (±5%, or ±30 s, whichever was greater) on two consecutive exercise tests (with a minimum of three tests, and a maximum of six).

Exclusion criteria included: heart failure due to obstructive valve disease; a myocardial infarction within the preceding 3 months; a cerebrovascular accident within the preceding 6 months; sustained or symptomatic ventricular tachycardia; uncontrolled atrial fibrillation or other arrhythmias contributing to heart failure; significant chronic lung disease or other significant neurological or musculoskeletal diseases. Treatment with vasodilating drugs other than ACE inhibitors was prohibited.

Study procedures

Exercise testing

A modified Bruce protocol was used as the principle mode of assessment: this involved the standard Bruce protocol plus three 3-min low-level stages (2.7 kph at 0, 1.3 and 2.6). This test was always performed first; after an absolute minimum of 30 min rest (but with a maximum permitted interval of 48 h) a second test using a modified Naughton protocol was used (2 min stages at 1.6 and 2.4 kph, then three 2-min stages at 3.2 kph, then four 2-min stages at 4.8 kph and two 2-min stages at 5.5 kph, with slopes of 0, 0, 2, 4, 6, 4.3, 5.7, 7.5, 8.5, 8 and 9°).

The patients were initially given (single-blind) placebo capsules and attended weekly for exercise testing (Bruce protocol only) until the inclusion criteria were satisfied: the variation in exercise times between two consecutive tests had to be within ±5% or ±30 s, whichever was greater. If this degree of consistency was not achieved within 6 weeks the patient was excluded from the study. Randomization was only performed when consistency of exercise testing had been demonstrated.

Medication

At their first visit patients were given a test dose of trandolapril 0.5 mg (single-blind) 1 h prior to exercise testing. Any patient who developed symptomatic hypotension was considered ineligible to proceed further. During the run-in phase of the study, in which consistency of exercise tolerance was developed, patients were treated with two placebo capsules daily (single-blind).

After randomization patients were given increasing doses of study medication corresponding to trandolapril 1 mg (dose A), 2 mg (dose B), or 4 mg (dose C), or placebo in similarly labelled blister packs. After a week on dose A the patient was seen and clinically assessed, and if there had been no adverse events he or she was given the next blister pack, labelled dose B. After a further 2 weeks and another clinical assessment the patient was advanced to dose C, the maximum for the trial. Patients unable to tolerate an increase of dose were reduced to the previous lower dose, and this was maintained for the rest of the study.

Statistical considerations

Study size

Previous studies had shown that patients with heart failure of the NYHA Classes II–III have a standard deviation of exercise duration on the Bruce protocol of about 200 s. If this were to hold for the patients included in this trial, 210 patients (105 per group) would be sufficient to give 90% power to detect a difference between the treatment groups of 90 s in exercise time at the 5% significance level. To allow for an unpredictable number of withdrawals, and also to permit some confidence in the evaluation of the secondary objectives, it was decided that a total of some 300 patients would be included.

Methods of evaluation

The primary efficacy variable was change in exercise duration from baseline to end-point using the modified...
Bruce treadmill test. The main analysis was based on an intention to treat analysis, including all randomized patients who received at least one dose during the treatment phase, and who were evaluated at least once while on treatment. A per-protocol analysis of the primary efficacy variable was also planned in which patients who were major protocol violators would be excluded. In both analyses, for patients who did not complete the course of treatment the last assessment while on treatment was taken as the study end-point ('carry forward' technique).

Statistical methods
All statistical tests were based on two-sided alternative hypotheses and were performed at the 5% level. Variables in the efficacy assessments were tested for normality by examination of residuals, which comprised inspecting the plots of residuals against normal scores and residuals against predicted values, as well as considering the Kolomogorov D-statistic, stem and leaf and normal probability plots.

Summary statistics for demographic variables were compared to identify any treatment and country imbalances with respect to age, weight, and height using a two-sample t-test and a chi-squared test for sex and race.

For the modified Bruce and Naughton protocols, the treatments were compared for change from baseline at end-point and week 16 using an analysis of covariance with baseline exercise time as a covariate. Other factors included were the use of digoxin, and country of origin of the patient, as well as interactions with treatment. If the interaction terms were not significant they were removed from the model and the analysis repeated. For descriptive purposes, the analyses were repeated at weeks 4, 8 and 12 for patients with observation at the those time points, and again with the last observation carried forward. Within-treatment comparisons for change from baseline at each assessment were made using paired t-tests.

For analysis of NYHA class, changes from baseline to week 16 and to end-point were categorized as ‘no change’, ‘worsening’, or ‘improvement’. Treatment comparisons for these changes were analysed using a Mantel-Haenszel test. Changes in symptoms and signs were analysed by scoring plus-1 for each symptom or sign which improved, 0 for each showing no change, and minus-1 for each which deteriorated. Thus each patient had a total score between minus-5 and plus-5. Treatment comparisons for the composite scores were analysed using a Mantel–Haenszel test.

Ethics
All patients gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee of each participating centre, and the study was conducted in accordance with the Declaration of Helsinki.

Results
Two hundred and ninety-two patients were randomized into the study, 108 from the U.K. Centres and 184 from the Polish Centres. One hundred and forty-eight patients were randomized to receive placebo and 144 trandolapril.

Baseline characteristics
Table 1 shows the characteristics of patients in the placebo and trandolapril groups at randomization. The average age of those in the placebo group was 57.5 years compared with 59 years in the trandolapril group. There was a predominance of males in the study group as a whole, but the treatment groups were imbalanced in that the placebo group contained 124 (84%) males compared with 98 (68%) in the trandolapril group. Patients in the placebo group were significantly heavier (mean weight 79.2 kg compared with 76.8 kg), than those in the trandolapril group. One hundred and eleven patients (75%) in the placebo group and 114 (79%) in the trandolapril group were in NYHA functional Class II; the remainder were in Class III.

Approximately half the patients had a chest X-ray at the time of randomization and the cardiothoracic ratio was 0.57 and 0.56 in the placebo and trandolapril groups, respectively. Three-quarters of the patients had an echocardiogram, and the mean left ventricular end diastolic diameter was 6.3 cm in the placebo group and 6.5 cm in the trandolapril group.

Protocol violations
Eight patients, all from one centre, had to be excluded from all analyses because during the course of the study the treadmill was incorrectly re-programmed and exercise times on different occasions could not be compared. Fourteen patients were included in the intention to treat analyses, but excluded from the per-protocol analyses because of (consistent) incorrect treadmill programming, limitation of exercise by angina which developed during the study, or poor compliance.

Dose titration
At end-point (the last exercise test taken by the patient) 90% of the placebo and 81% of the trandolapril group were on Dose C (trandolapril 4 mg daily or placebo). Five per cent and 7% were taking Dose B (trandolapril 2 mg daily or placebo) and 5% and 12% were on Dose A (trandolapril 1 mg or placebo). The main reason for Dose C not being achieved was low blood pressure and/or dizziness.

Withdrawals
A total of 38 patients withdrew from the study (17 placebo, 21 trandolapril); 10 of these withdrew during
the titration phase (6 placebo, 4 trandolapril) and 28 during exercise phase (11 placebo, 17 trandolapril). The reasons for withdrawal were diverse, with no particular problems being attributable to either treatment. The total of withdrawals includes 8 deaths (6 placebo, 2 trandolapril).

### Efficacy

Two hundred and eighty four of the 292 randomized patients were included in the intention to treat analysis (148 placebo, 144 trandolapril) and 273 in the per-protocol analyses (139 placebo, 134 trandolapril).

**Exercise assessed by Bruce Treadmill Protocol**

At baseline the two treatment groups (intention to treat) had a similar exercise tolerance on the Bruce protocol (placebo 605 s, trandolapril 591 s). In the placebo group there was a mean improvement in exercise time at the end-point of 139 s, compared with 116 s in the trandolapril group (Fig. 1). This difference between groups was not statistically significant, although the increased exercise time seen in both groups was highly significant ($P=0·001$).

There was no significant difference between the treatment groups in the changes in exercise time from baseline to week 16 (intention to treat analysis), in changes from baseline to end-point (per-protocol analysis) or from baseline to week 16 (per-protocol analysis).

**Exercise assessed by the Naughton Protocol**

The two treatment groups (intention to treat analysis) had similar exercise times at baseline (placebo 576 s, trandolapril 539 s) and the increase in exercise time at end-point was similar (mean improvement of 87 s in the placebo and 80 s in the trandolapril group, Fig. 2). The difference from baseline in both treatment groups was highly significant ($P=0·0001$) but there was no significant difference between the treatment groups. Essential identical results were obtained in the per-protocol analysis.

**Symptoms and signs**

After 16 weeks treatment, 27 of 132 (20%) of patients in the placebo group, and 28 of 124 (22%) in the trandolapril group had improved one NYHA Class. This difference was not statistically significant. On the basis of the composite score of five symptoms and signs, 16% of patients in the placebo group compared with 23% of patients in the trandolapril group had shown at least a mild improvement at week 16; corresponding end-point figures were 15% and 23% for placebo and trandolapril respectively.

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<tr>
<th>Table 1 Characteristics at baseline of patients randomized to placebo or trandolapril treatment</th>
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<td>Placebo (n=148)</td>
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<td><strong>Age (mean)</strong></td>
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<td><strong>Sex (male)</strong></td>
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<td><strong>Weight (mean (kg))</strong></td>
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<tr>
<td><strong>Aetiology</strong></td>
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<td>Hypertension</td>
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<td>Valvular disease</td>
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<td><strong>Duration of heart failure</strong></td>
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<td>3 months–1 year</td>
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<td><strong>NYHA functional class</strong></td>
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<td>III</td>
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<td><strong>Signs</strong></td>
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<td>Mean cardiothoracic ratio</td>
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<td>Echocardiogram performed</td>
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<td>Mean LV end-diastolic diameter (cm)</td>
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Analysis of covariance
None of the covariates defined in the protocol (baseline exercise time, use of digoxin, country of origin of the patient) affected the results.

Exploratory analysis
In view of the lack of effect of trandolapril on exercise duration, a single subgroup analysis was performed which was not pre-defined in the protocol. The treatment groups were compared in the 65 patients (35 placebo, 30 trandolapril) who had symptoms of NYHA Class III at baseline. As with the total study group, exercise time increased with both the Bruce and Naughton protocols but there was no significant difference between the patients treated with placebo or trandolapril.

Discussion
In this study trandolapril did not increase exercise time as measured on a treadmill, nor did it lead to an improvement in NYHA Class. However, trandolapril treatment probably improved other symptoms and signs of heart failure in our patients. This failure to improve exercise capacity was unexpected, particularly as the design of our study fulfilled all the criteria necessary for a benefit from ACE inhibitor therapy[7].

It seems unlikely that our study failed to demonstrate a difference between active and placebo treatment that actually existed: with nearly 300 patients this was one of the three or four largest exercise studies in heart failure, and there was not even a non-significant trend in favour of active treatment. The results were similar among the patients included in the U.K. and Poland. It seems most unlikely that a larger study would have led to a different result. Despite considerable efforts to achieve a stable baseline of exercise tolerance, the increase in exercise time seen with placebo treatment during the course of the study was quite marked and this could have made it more difficult to demonstrate an improvement with trandolapril; however, the improvement seen with placebo treatment is well within the range of other published studies. The overview of Narang et al[7] suggested that an increase in exercise time can only be demonstrated in the more severely affected patients (NYHA Grade III) but the analysis of our patients with heart failure of this degree of severity suggests that this is not the case.

There is no reason to suppose that trandolapril is any less effective than other ACE inhibitors. It improves survival after myocardial infarction in patients with impaired left ventricular function (TRACE)[6] and it is an effective anti-hypertensive. The dose of trandolapril used in our study was comparable to that used in TRACE and the fact that 19% of our patients were unable to tolerate the highest dose suggests we could not have increased it.

We used two different treadmill protocols, one with a slow and one with a relatively fast build-up of workload, and the results were identical. The type of exercise test therefore cannot be critical. We have to conclude that treadmill testing is not a particularly useful way of studying the effect of ACE inhibitors in heart failure.

We have to ask whether any form of exercise testing is a useful surrogate for an improvement in symptoms or survival. Although others have found a reasonable correlation between symptoms and exercise testing, this was not the case in our study. The VHeFT-II Study showed that the combination of hydralazine and a nitrate led to a greater improvement
in exercise testing than did enalapril, whereas the ACE inhibitor led to a greater reduction in fatality\[8\]. Drugs such as milrinone, enoximone, flosequinan, and ibopamine have all been shown to improve symptoms and treadmill exercise times yet have been found to cause an increase rather than a decrease in fatality in heart failure patients\[9–13\]. Digoxin improved symptoms but has a neutral effect on fatality\[14\]. We now have an example of a drug that improves survival in heart failure yet does not improve exercise tolerance. Trials must be specifically designed to study the effect of drugs on symptoms, exercise duration, or survival.

References


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