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# Safety and efficacy of valsartan versus enalapril in heart failure patients

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**Abstract**

Although a cornerstone in the treatment of heart failure, angiotensin-converting enzyme inhibitors are under-used, partly due to side effects. If proven at least similarly efficacious to angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers may replace them due to their superior tolerability. We aimed to compare the efficacy and safety of valsartan and enalapril in heart failure patients stabilised on an angiotensin-converting enzyme inhibitor. We randomised 141 patients (mean 68 years, 74% males) with stable mild/moderate heart failure and left ventricular ejection fraction 0.45 or less, to valsartan 160 mg q.d. ($n=70$) or enalapril 10 mg b.i.d. ($n=71$) for 12 weeks. Changes in 6-min-walk test (primary efficacy variable), patients' wellbeing and left ventricular size and function did not differ significantly between the treatment groups. Valsartan was significantly non-inferior to enalapril in walk test distance change: least-square means treatment difference +1.12 m (95% confidence interval −21.9 to 24.1), non-inferiority $P<0.001$. Left ventricular size ($P<0.001$) and function ($P=0.048$) improved significantly only in the valsartan group. Fewer patients experienced adverse events in the valsartan group (50%) than in the enalapril group (63%), although statistically non-significant. Valsartan is similarly efficacious and safe to enalapril in patients with stable, mild/moderate heart failure, previously stabilised on an angiotensin-converting enzyme inhibitor and directly switched to study medication.


*Keywords:* Angiotensin-converting enzyme inhibitor; Angiotensin-receptor blocker; Chronic heart failure; Exercise capacity; Efficacy; Tolerability

## 1. Introduction

In chronic congestive heart failure, inhibition of the renin–angiotensin–aldosterone system by angiotensin-converting enzyme inhibitors improves survival and decreases morbidity [1], and improves exercise capacity [2], quality of life [3], and left ventricular function and size [4,5].

Considerable escape of angiotensin II from angiotensin-converting enzyme inhibition occurs after some time despite effective inhibition of circulating angiotensin-converting enzyme, and appears to be related to the progress and prognosis of heart failure [7,8]. The escape may be due to the actions of non-angiotensin-converting enzyme convertases and/or to ineffective inhibition of myocardial angiotensin-

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converting enzyme [9], and may limit the efficacy of angiotensin-converting enzyme inhibitors. Therefore, specific blockers of the angiotensin type 1-receptor, angiotensin-receptor blockers, may be superior to or add to the effect of angiotensin-converting enzyme inhibitors, by blocking the renin–angiotensin–aldosterone system more effectively [10].

Angiotensin-converting enzyme inhibitors are under-used in clinical practice [11], possibly due to a fear among physicians of side effects [12]. The unspecific action of angiotensin-converting enzyme inhibitors, causing accumulation of bradykinin and substance P, may be at least partly responsible for these side effects [13]. Angiotensin-receptor blockers have a more specific action and side effects on the placebo level [14], and are usually tolerated even by patients who cannot tolerate an angiotensin-converting enzyme inhibitor [15]. Consequently, if angiotensin-receptor blockers could be shown to be similarly efficacious to angiotensin-converting enzyme inhibitors they would probably be used more widely than angiotensin-converting enzyme inhibitors are today.

Studies in heart failure patients indicate that angiotensin-receptor blockers are at least comparable to angiotensin-converting enzyme inhibitors with regard to hemodynamics, neurohormones, exercise capacity and symptoms of heart failure, whereas their side-effect profile is more favourable [14,16–19]. A dose-dependent increase in exercise capacity in response to angiotensin-receptor blocker treatment has been demonstrated [20]. In terms of mortality and morbidity, so far no difference has been shown between angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors [18,21,22].

Valsartan is an orally active, potent and specific competitive angiotensin-receptor blocker. In essential hypertension, valsartan has an anti-hypertensive effect comparable to that of angiotensin-converting enzyme inhibitors and other anti-hypertensive agents, with a more favourable tolerability profile for valsartan [23]. In heart failure patients, valsartan had effects on cardiac hemodynamics similar to lisinopril and was well tolerated in doses ranging from 40 to 160 mg b.i.d. [17].

The aim of the present study was to assess the safety and efficacy—with regard to exercise capacity, quality of life, symptoms of heart failure, and left ventricular size and function—of a direct shift to the angiotensin-receptor blocker valsartan compared to continuing angiotensin-converting enzyme inhibition, in heart failure patients stabilised on an angiotensin-converting enzyme inhibitor.

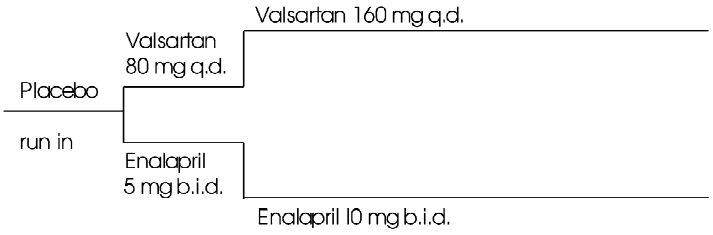
## 2. Materials and methods

### *2.1. Objectives*

The primary objective was to test the hypothesis that valsartan in comparison with enalapril, is at least as effective on exercise capacity, measured as distance walked during a 6-min-walk test, in heart failure patients stabilised on an angiotensin-converting enzyme inhibitor. If non-inferiority was demonstrated, superiority was to be tested. Secondary objectives were to compare the effects of valsartan and enalapril with regard to safety, the dyspnea–fatigue index, quality of life, and left ventricular function and size.

### *2.2. Study design*

This was a multi-centre, double-blind, double-dummy, randomised, parallel-group, enalapril-controlled study in patients with chronic symptomatic heart failure. Fig. 1 shows the study flow schedule. Patients had to be stable during at least 2 weeks prior to inclusion and during a 2-week run-in period. Patients were randomised to valsartan or enalapril for 12 weeks. The last dose of the open angiotensin-converting enzyme inhibitor treatment was taken in the morning of the randomisation day. The first dose of the active study medication was taken in the evening of the randomisation day for patients randomised to enalapril (enalapril 5 mg) and in the morning the day after for patients randomised to valsartan (valsartan 80 mg). After 1 week valsartan was titrated from the starting dose 80 to 160 mg q.d. and enalapril from the starting dose 5 to 10 mg b.i.d.. Titration was forced if standing systolic blood pressure was $>$90 mmHg, there were no symptoms of hypotension, and if serum-creatinine had not increased by $>$50% compared with baseline. All other medication was kept as stable as possible during the entire study.




| VISIT | Week -2 | Week 0 | Week 1 | Week 2 | Week 3 | Week 6 | Week 12 |
|---|---|---|---|---|---|---|---|
| WALK TEST | X | X | | | | X | X |
| MLWHFQ | | X | | | | | X |
| DFI | | X | | | | | X |
| ECHO | X | X | | | | | X |

Fig. 1. Schematic illustration of the study design. Walk test, 6-min-walk test; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; DFI, dyspnea–fatigue index; Echo, echocardiography examination.

The first dose of study medication was always taken in the morning of the study visit day. At all visits the 6-min-walk test was performed 2–4 h after study drug administration, and all tests were always carried out at a similar time of day. Consequently, the efficacy of the interventional drugs was assessed at peak rather than trough.

### 2.3. Patients

Males and females, ≥18 years of age, with stable heart failure, New York Heart Association class II-III, left ventricular ejection fraction ≤0.45, on an angiotensin-converting enzyme inhibitor for heart failure since at least 3 months and able to perform a 6-min-walk test, were eligible. All patients gave written informed consent before inclusion. The study was approved by the respective local ethics committees. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Patients were excluded due to hemodynamically significant primary valvular disease, heart failure due to pulmonary disease, infective cardiomyopathy, recent (within 3 months) myocardial infarction or coronary intervention, unstable coronary disease, severe arrhythmia, recent stroke, serum-creatinine >200 μmol/l or other significant laboratory abnormalities, exercise limiting reason other than heart failure, angiotensin-receptor blocker treatment within 3 months prior to inclusion, persistent standing systolic blood pressure <90 mmHg, and at the investigators discretion.

### 2.4. Primary efficacy variable

#### 2.4.1. 6-min-walk test

The primary efficacy variable was exercise capacity measured as the distance walked during a 6-min-walk test. The patients were instructed to walk as long a distance as possible during 6 min on a premarked walkway. Stops and rests were allowed, if needed, and encouragement was avoided. The first walk test was performed at the start of the run-in period to customise the patients with the procedure. Additional walk tests were performed at randomisation, after 6 weeks of randomised therapy, and at study end. The walk test at the randomisation visit constituted the baseline 6-min-walk test.

### 2.5. Secondary efficacy variables

Quality of life was assessed at the randomisation visit and at study end using the Minnesota Living with Heart Failure Questionnaire [24], applying 20 of 21 questions. The maximum (worst) score was 100. The dyspnea–fatigue index describes the severity of symptoms [25], and was assessed at the randomisation visit and at study end. The score ranges from 0 (worst symptoms) to 12 (no symptoms).

Left ventricular ejection fraction was determined at

the inclusion visit, using the echocardiographic method routinely used at each centre, to secure that the left ventricular ejection fraction was ≤0.45. A standardised echocardiographic examination was performed at randomisation and study end. The examinations were recorded on videotapes and blindly evaluated at a core centre. Left ventricular end-diastolic diameter was measured in two-dimensional mode and left ventricular function was evaluated by determination of the left atrioventricular plane displacement, as described previously [26].

### 2.6. Clinical assessment

At all visits blood pressure, heart rate, body weight, adverse events and medication were recorded. Signs/symptoms of heart failure and New York Heart Association class were assessed at inclusion, at randomisation, after 6 weeks of randomised therapy, and at study end. Medical history was recorded at inclusion. A thorough physical examination was performed at inclusion, at randomisation, and at study end. Blood samples were regularly analysed.

### 2.7. Sample size calculation

A minimum of 65 evaluable patients in each treatment arm were required to test the hypothesis adequately, based on the non-inferiority (equivalence) test, with 80% power for a one-sided test at the 2.5% significance level. Non-inferiority (equivalence) was defined as a treatment effect of valsartan, with respect to mean change from baseline in the distance walked during the 6-min-walk test, better than 45 m less than that of enalapril. This criterion for between-treatment comparability required the entire 95% CI to be above −45 m compared to enalapril. A distance of 45 m was chosen based on an expected average baseline 6-min-walk test distance of 450 m. A difference of 10% in this distance is not considered clinically relevant.

### 2.8. Statistics

Primary efficacy data were analysed by analysis of co-variance using SAS® 6.12 Proc GLM, with centre and treatment as factors and baseline walking distance as covariate. Treatment-by-baseline walking distance interaction was also included in the model. A test for non-inferiority using a one-sided test at the 2.5% significance level was initially performed. The null hypothesis was rejected if the lower limit of the two-sided 95% CI for the adjusted between-treatment difference (based on the least square means and expressed as valsartan minus enalapril) was greater than −45 m. If the test of non-inferiority resulted in rejection of the null hypothesis, a test of superiority of valsartan was performed, using a one-sided test with a significance level of 2.5%. For each of the secondary variables, the change from baseline to endpoint was analysed using analysis of co-variance with centre and treatment as factors and baseline measurement as covariate. Two-sided 95% CIs were calculated for the between-treatment difference in the change from baseline. Descriptive statistics were presented for other secondary efficacy and safety data. Patients who were unable to perform the 6-min-walk test during follow-up due to heart failure or death were assigned a walk distance of 0 m. Data are expressed as mean (S.D.), unless otherwise stated. A two-sided $P$ value $<0.05$ was considered statistically significant.

### 2.9. Patient populations

#### 2.9.1. Intention to treat (full analysis) population

All randomised patients who satisfied the major entry criteria, who received at least one dose of trial medication and from whom at least one measurement after baseline was obtained. This was the primary efficacy population.

#### 2.9.2. Per protocol population

All patients who completed the study without any major deviations from the protocol procedures.

## 3. Results

Of the 146 patients enrolled, 141 were randomised, 70 to valsartan and 71 to enalapril. The intention-to-treat population consisted of 134 patients, 67 in each treatment arm. There were 118 patients in the per protocol population, 61 on valsartan and 57 on enalapril.

Table 1
Baseline demographics, clinical findings and medication

| | Valsartan ($n$=70) | Enalapril ($n$=71) |
|---|---|---|
| Males, % ($n$) | 70 (49) | 79 (56) |
| Age (years), mean (range) | 68 (51–90) | 67 (46–89) |
| Weight (kg), mean (range) | 83 (44–130) | 81 (48–118) |
| CHF duration (years), mean (range) | 3.3 (0.3–14.0) | 4.6 (0.3–16.0) |
| Ischemic etiology, % ($n$) | 67 (47) | 55 (39) |
| NYHA class II/III, % | 71/29 | 70/30 |
| Systolic BP (mmHg), mean (S.D.) | 129 (21) | 125 (17) |
| Diastolic BP (mmHg), mean (S.D.) | 75 (10) | 76 (10) |
| Heart rate (beats/min), mean (S.D.) | 70 (10) | 71 (9) |
| ACE inhibitors, % ($n$) | 99 (69)* | 100 (71) |
| Digoxin, % ($n$) | 37 (26) | 45 (32) |
| Diuretics, % ($n$) | 89 (62) | 79 (56) |
| Beta-blockers, % ($n$) | 74 (52) | 79 (56) |

ACE, angiotensin-converting enzyme; BP, blood pressure; CHF, chronic heart failure; NYHA, New York Heart Association.
* All patients in the intention-to-treat population were on an angiotensin-converting enzyme inhibitor at baseline.

### 3.1. Baseline results

Baseline demographics and medication were similar in the two treatment groups (Table 1). At baseline the numbers of patients receiving each of the most frequently used angiotensin-converting enzyme inhibitors were similar in the two treatment groups. Thus, 52 patients received ramipril (median dose 10 mg in both groups), 46 received enalapril (median dose 20 mg in both groups) and 30 patients received captopril (median dose 100 mg in both groups). The efficacy variables measured at baseline were similar in the two treatment groups (Table 2).

Table 2
Baseline efficacy variables

| | Mean (S.D.) | |
|---|---|---|
| | Valsartan ($n$=70) | Enalapril ($n$=71) |
| 6-min-walk test (m) | 418.2 (112.9) | 424.1 (115.1) |
| MLWHFQ (points) | 21.8 (16.4) | 19.2 (13.4) |
| DFI (points) | 6.8 (1.6) | 6.6 (1.6) |
| AVPD (mm) | 8.7 (2.3) | 8.7 (2.2) |
| LVEDD ($mm/m^2$) | 35.7 (11) | 36.8 (11.2) |

AVPD, atrio-ventricular plane displacement; DFI, dyspnea–fatigue index score; LVEDD, left ventricular end diastolic diameter adjusted for body surface; MLWHFQ, Minnesota Living With Heart Failure Questionnaire score.

### 3.2. Efficacy

The two treatment groups were similar with regard to the primary efficacy variable, change in 6-min-walk test distance (Table 3, Fig. 2). In the intention to treat population, valsartan was significantly non-inferior to enalapril: least-square means treatment difference +1.12 m; 95% CI −21.89 to 24.12; non-inferiority $P<0.001$; superiority $P=0.462$. Results of the per protocol analyses were similar. Age (<65 versus ≥65 years), gender, pre-randomisation beta-

Table 3
Results of the 6-min-walk test (m) in different populations at various time-points

| Population, time | Valsartan, mean (S.D.) | | Enalapril, mean (S.D.) | |
|---|---|---|---|---|
| | Post | Change | Post | Change |
| ITT, at endpoint* | 421.1 (119.4) ($n$=67) | 0.6 (47.7) | 426.0 (141.6) ($n$=67) | 0 (79.9) |
| PP, at 6 weeks | 419.3 (115.9) ($n$=61) | −1.1 (39.3) | 437.6 (106.2) ($n$=57) | 3.7 (36.9) |
| PP, at 12 weeks* | 423.7 (118.7) ($n$=61) | 3.3 (45.6) | 447.9 (113.7) ($n$=57) | 14.0 (43.1) |

Endpoint, last available result; ITT, intention to treat; PP, per protocol. In the ITT population, 0 was assigned to patients unable to walk due to heart failure or death.
* $P<0.0001$ for non-inferiority for valsartan versus enalapril.

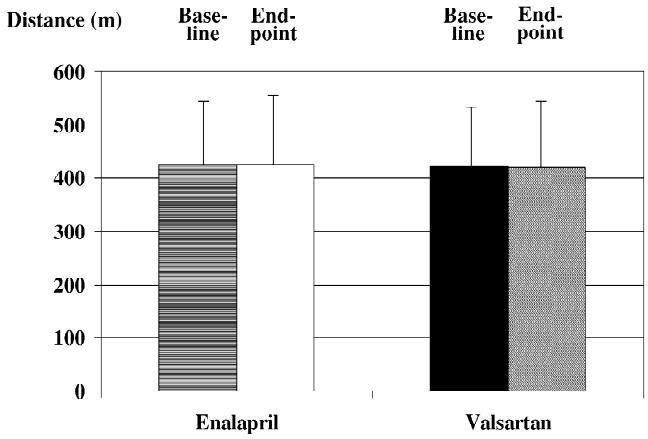



Fig. 2. Results of the 6-min-walk test as analysed in the intention-to-treat population. Standard deviations are indicated. There were no significant within- or between-group changes.

blocker use, New York Heart Association class, and aetiology of heart failure, had no influence on the change in 6-min-walk test distance from baseline to endpoint (last available test) for the intention to treat population.

There were no significant differences between the two groups with regard to change in any of the secondary efficacy variables (Table 4). The Minnesota Living with Heart Failure Questionnaire and the dyspnea–fatigue index showed no significant within-group changes in either group. However, in the valsartan group the left ventricular end diastolic diameter improved significantly: mean change −4.1 (1.0) mm/m$^2$; 95% CI −2.17 to −5.98; $P<0.001$. Also atrioventricular plane displacement improved significantly in the valsartan group: mean change 0.32 (0.16) mm; 95% CI 0.00–0.63, $P=0.048$. In the enalapril group there were no significant within-group changes of these variables.

Table 5
Deaths and adverse events

| | % (*n*) | |
|---|---|---|
| | Valsartan (*n*=70) | Enalapril (*n*=71) |
| Deaths | 1.4 (1) | 7.6 (5) |
| All AEs | 50 (35) | 63 (45) |
| Premature withdrawal* | 7.1 (5) | 12.7 (9) |
| Worsened CHF | 5.7 (4) | 1.4 (1) |
| Headache | 5.7 (4) | 1.4 (1) |
| Diarrhea | 4.3 (3) | 2.8 (2) |
| Dizziness | 4.3 (3) | 8.5 (6) |

AE, adverse event; CHF, chronic heart failure.
* Including death.

### *3.3. Safety*

The total proportion of patients with an adverse event was 50% in the valsartan group and 63% in the enalapril group ($P$=NS) (Table 5). The cause of death was heart failure in the single patient who died in the valsartan group. The deaths in the enalapril group were caused by congestive heart failure ($n=1$), myocardial infarction ($n=1$), sudden death ($n=2$), and pneumonia ($n=1$). In the valsartan group, other

Table 4
Results of the secondary efficacy variables in the intention-to-treat population

| Variable | Treatment group | *n* | Mean baseline value | LSM change (S.E.) | LSM treatment difference (95% CI) |
|---|---|---|---|---|---|
| MLWHFQ (points) | Valsartan | 67 | 21.1 | 0.7 (1.3) | −0.2 (−3.8–3.4) |
| | Enalapril | 64 | 18.2 | 0.9 (1.3) | |
| DFI (points) | Valsartan | 67 | 6.9 | 0.24 (0.16) | −0.02 (−0.45–0.41) |
| | Enalapril | 64 | 6.7 | 0.26 (0.16) | |
| AVPD (mm) | Valsartan | 67 | 8.7 | 0.32 (0.16) | −0.02 (−0.42–0.46) |
| | Enalapril | 64 | 8.8 | 0.30 (0.16) | |
| LVEDD (mm/m$^2$) | Valsartan | 67 | 35.7 | −4.1 (1.0) | −2.24 (−4.9–0.4) |
| | Enalapril | 63 | 37.0 | −1.8 (1.0) | |

AVPD, atrio-ventricular plane displacement; CI, confidence interval; DFI, dyspnea–fatigue index score; LSM, least-square mean; LVEDD, left ventricular end diastolic diameter adjusted for body surface; MLWHFQ, Minnesota Living With Heart Failure Questionnaire score; S.E., standard error. The differences between the two groups were not significant.

reasons for premature withdrawal were adverse events ($n=2$) and withdrawn consent ($n=2$), and in the enalapril group adverse events ($n=3$) and withdrawn consent ($n=1$). A total of six patients (9%) in the valsartan group and 11 (16%) in the enalapril group experienced serious adverse events, including deaths.

## 4. Discussion

The present study investigated the effects of a direct shift from angiotensin-converting enzyme inhibitor treatment to randomised treatment with either valsartan or enalapril, in patients with chronic congestive heart failure. During a 12-week intervention, valsartan and enalapril were similarly efficacious in terms of the effect on exercise capacity, symptoms of heart failure, quality of life, and left ventricular function and size.

This is one of few studies comparing the safety and efficacy of an angiotensin-receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure patients stabilised on an angiotensin-converting enzyme inhibitor prior to inclusion [16,19]. It is the first study comparing valsartan and an angiotensin-converting enzyme inhibitor in this context. No prior study comparing an angiotensin-receptor blocker and an angiotensin-converting enzyme inhibitor has included a population of heart failure patients with such an up to date medication as the present study. Besides all patients being on an angiotensin-converting enzyme inhibitor at baseline, more than three of four patients were treated with a beta-blocker. This is especially important since there has been some discussion regarding the safety and efficacy of angiotensin-receptor blockers in heart failure patients on beta-blocker treatment.

Importantly, these patients were all stabilised on and tolerant to an angiotensin-converting enzyme inhibitor. Withdrawal of the angiotensin-converting enzyme inhibitor in such angiotensin-converting enzyme inhibitor responders is liable to cause deterioration, and any agent replacing the angiotensin-converting enzyme inhibitor stands an obvious risk of working less well than the angiotensin-converting enzyme inhibitor, at least in the short term. Furthermore, side effects from the angiotensin-converting enzyme inhibitor are expected to appear less frequently than in an unselected group of heart failure patients. Despite these biases working against valsartan, there were no signs of an inferior efficacy of valsartan compared with enalapril. Also with regard to safety, the study result was reassuring for valsartan. In the valsartan group fewer patients experienced an adverse event, and there were fewer deaths, serious adverse events and patients discontinuing due to adverse events, although these between-group differences were not statistically significant.

The primary endpoint, change in 6-min-walk test distance, did not differ between the two treatment groups as regards the primary efficacy analysis in the intention to treat population. However, patients who could not perform the walk test due to heart failure or death were assigned a walk distance of 0 m at endpoint, and since more patients in the enalapril arm were unable to perform an endpoint walk test due to those reasons, this could potentially have obscured a difference between the two groups. However, since the per protocol analysis showed a similar result this was not the case.

None of the secondary efficacy parameters differed significantly between the two treatment regimens with regard to change from baseline to endpoint. The Minnesota Living with Heart Failure Questionnaire and the dyspnea–fatigue index showed essentially no changes in either group. Although left ventricular size and atrioventricular plane displacement improved significantly only in the valsartan group, the between-group difference was not statistically significant.

Most patients were in New York Heart Association class II, which is a potential limitation to a study designed to detect deterioration. Another potential limitation is that there were two uncontrolled active study groups.

### *4.1. Comparison with prior similar studies*

The results of the present study are in accordance with other similar studies in heart failure patients [14], such as a 16-week study comparing losartan and enalapril [16]. Although not all patients were previously stabilised on an angiotensin-converting enzyme inhibitor and patients were more symptomatic in that study, the effect of the intervention was quite similar

in terms of exercise capacity and symptoms of heart failure. The results of the present study are also in accordance with those of a fairly large study comparing candesartan and enalapril [21].

### *4.2. Angiotensin type-1 receptor blockade versus angiotensin-converting enzyme inhibition*

Despite effective inhibition of circulating angiotensin-converting enzyme, plasma levels of angiotensin II after some time return to abnormally high levels in many patients during chronic angiotensin-converting enzyme inhibition [6–8]. Experimentally myocardial angiotensin II formation was almost completely maintained despite effective suppression of circulating angiotensin II [27]. This angiotensin-converting enzyme inhibitor escape appears to be related to progress of the cardiovascular disease [6], and confers a substantially worse prognosis [8]. The escape may be due to the actions of alternative enzymes catalysing the conversion of angiotensin I to angiotensin II, such as human heart chymase, CAGE, cathepsin G, and trypsin [9], and/or incomplete blockade of tissue-bound angiotensin-converting enzyme, e.g. in the myocardium. Since angiotensin-converting enzyme inhibitors do not completely inhibit the harmful effects of angiotensin II, angiotensin-receptor blockers may have an advantage by effectively blocking the angiotensin type-1 receptor.

In contrast to angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers do not inhibit the breakdown of bradykinin. This may be advantageous since bradykinin might cause harm and side effects [28–30], but it may also be a disadvantage since bradykinin has potentially beneficial effects [31,32].

Experimental studies indicate that angiotensin II may exert beneficial effects via the angiotensin type-2 receptor [33–35], which is up-regulated under certain pathological conditions with tissue damage [32,36]. During treatment with angiotensin-receptor blockers the type-2 receptor is open to stimulation by angiotensin II, which could be yet another advantage for angiotensin-receptor blockers over angiotensin-converting enzyme inhibitors. Angiotensin II levels are high because angiotensin-converting enzyme is not inhibited, especially since there is no negative feedback on the formation of renin, which is normally seen due to stimulation of the angiotensin type-1 receptor by angiotensin II.

Angiotensin-converting enzyme inhibitors increase nitric oxide levels via bradykinin. Experimental studies indicate that nitric oxide production may be increased also during treatment with angiotensin-receptor blockers [37–42], without increased bradykinin levels. Furthermore, through the type-1 receptor angiotensin II causes formation of free oxygen radicals that can degrade nitric oxide [43]. Consequently, angiotensin-receptor blockers may increase nitric oxide levels by decreasing free oxygen radical formation. Thus, the increased availability of nitric oxide seen with angiotensin-converting enzyme inhibitor treatment may also be present during treatment with angiotensin-receptor blockers.

As indicated above, angiotensin-receptor blockers have a potential to inhibit deleterious effects of the renin–angiotensin–aldosterone system activation seen in heart failure patients, more effectively than angiotensin-converting enzyme inhibitors. At present, little is known about whether this is true also in humans. In the present study it is unlikely that any major angiotensin-converting enzyme inhibitor escape was present, since patients were stable and mostly had mild symptoms of heart failure. However, it is not possible to conclude if the study result was due to any differences or similarities between the two treatment regimens with regard to effects on the different angiotensin receptors, bradykinin, or nitric oxide.

The present study gives no information about a possible difference between angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors with regard to long-term morbidity and mortality. The only mortality trial performed up to now directly comparing an angiotensin-receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure patients, the ELITE II trial [22], showed no significant difference between losartan and captopril in terms of mortality or morbidity. The recently reported Valsartan in Heart Failure Trial [44], showed that there was an additional morbidity benefit of further blockade of the renin–angiotensin–aldosterone system by valsartan, in patients receiving standard heart failure therapy including angiotensin-

converting enzyme inhibitors. No conclusions, however, can be drawn from that trial regarding the relative efficacy of angiotensin-receptor blockers versus angiotensin-converting enzyme inhibitors.

## 5. Conclusion

During a 12-week intervention period, valsartan 160 mg q.d. was as effective in terms of exercise capacity as enalapril 10 mg b.i.d. in patients with stable, mild to moderate heart failure, previously stabilised on an angiotensin-converting enzyme inhibitor and directly switched to study medication. Symptoms of heart failure, quality of life, left ventricular function and left ventricular size changed slightly and similarly in both treatment groups. Valsartan tended to be better tolerated than enalapril, although the difference was not statistically significant. Thus, if there is any reason to stop angiotensin-converting enzyme inhibitor treatment in patients like those in the present study, a shift can be safely made from the angiotensin-converting enzyme inhibitor to valsartan without causing any clinical problems during at least 3 months. The long-term impact on morbidity and mortality should be examined in future studies.

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