Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial

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Summary

Background Angiotensin II type 1 receptor blockers have favourable effects on haemodynamic measurements, neurohumoral activity, and left-ventricular remodelling when added to angiotensin-converting-enzyme (ACE) inhibitors in patients with chronic heart failure (CHF). We aimed to find out whether these drugs improve clinical outcome.

Methods Between March, 1999, and November, 1999, we enrolled 2548 patients with New York Heart Association functional class II–IV CHF and left-ventricular ejection fraction 40% or lower, and who were being treated with ACE inhibitors. We randomly assigned patients candesartan (n=1276, target dose 32 mg once daily) or placebo (n=1272). At baseline, 55% of patients were also treated with β blockers and 17% with spironolactone. The primary outcome of the study was the composite of cardiovascular death or hospital admission for CHF. Analysis was done by intention to treat.

Findings The median follow-up was 41 months. 483 (38%) patients in the candesartan group and 538 (42%) in the placebo group experienced the primary outcome (unadjusted hazard ratio 0·85 [95% CI 0·75–0·96], p=0·011; covariate adjusted p=0·010). Candesartan reduced each of the components of the primary outcome significantly, as well as the total number of hospital admissions for CHF. The benefits of candesartan were similar in all predefined subgroups, including patients receiving baseline β blocker treatment.

Interpretation The addition of candesartan to ACE inhibitor and other treatment leads to a further clinically important reduction in relevant cardiovascular events in patients with CHF and reduced left-ventricular ejection fraction.

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Introduction

Mortality and morbidity among patients with chronic heart failure (CHF) and reduced left-ventricular ejection fraction remain high, despite the use of full conventional treatment, including angiotensin-converting-enzyme (ACE) inhibitors, β blockers, and spironolactone. The addition of an angiotensin II type 1 receptor blocker to an ACE inhibitor is a theoretically attractive treatment strategy in CHF. Angiotensin II can be produced by non-ACE enzymatic pathways in human cardiac tissue and blood vessels, and its generation seems to continue even during chronic, high-dose, ACE-inhibitor treatment in CHF.[1–5] Angiotensin-receptor blockers should, therefore, provide more complete inhibition of the actions of angiotensin II. Conversely, ACE inhibitors also block the breakdown of bradykinin, mediated by kininase II, which is identical to ACE. Bradykinin has direct and indirect vasodilator, antimitotic, and antithrombotic actions that could be of benefit in CHF.[6,7] Consequently, treatment with combined ACE inhibitors and angiotensin-receptor blockers might have advantages over ACE-inhibitor monotherapy.

In several studies, including the Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study,[8] favourable effects on haemodynamic indices, left-ventricular remodelling, and neurohumoral activity in CHF have been reported with combined ACE inhibitors and angiotensin-receptor blockers.[8,9] This combination of treatment also increases exercise capacity and improves New York Heart Association functional class.[10]

In the prospective Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial, part of the CHARM programme,[11–13] we investigated whether combining an angiotensin-receptor blocker, candesartan, with ACE inhibitors also improves clinical outcome. We compared the effect of candesartan with that of placebo among patients with CHF and reduced left-ventricular ejection fraction.

Methods

The design of the CHARM programme has been described in detail elsewhere, including randomisation, monitoring, and follow-up.[11–13]

Patients

Eligible patients were aged 18 years or older, had left-ventricular ejection fraction 40% or lower measured within the past 6 months, New York Heart Association functional class II–IV (if class II, patients had to have admission to hospital for a cardiac reason in the previous 6 months), and treatment with an ACE inhibitor at a constant dose for 30 days or longer. We enrolled patients between March, 1999, and November, 1999 in 618 centres in 26 countries. Investigators were advised of the doses of ACE inhibitors known to reduce morbidity and

mortality in CHF and also asked to state whether each patient was, in their opinion, on an optimum dose of ACE inhibitor, judged individually. The study was approved by ethics committees or institutional review boards in all participating centres and all patients gave written, informed consent.

Methods

We randomly assigned patients, in a double-blind way, candesartan or matching placebo, which could be started at 4 or 8 mg once daily (figure 1), the assignment code being held at an independent centre and by the data safety monitoring board. The treatment dose was doubled every 2 weeks, as tolerated, according to a forced titration protocol, with recommended monitoring of blood pressure, serum creatinine, and potassium. The target dose was 32 mg once daily from 6 weeks onwards. After randomisation, patients were seen at 2, 4, and 6 weeks, at 6 months and, thereafter, at every 4 months until the end of the trial. In a subset of patients enrolled in North America, routine laboratory assessments were done at baseline, 6 weeks, and yearly thereafter for safety reasons.

The primary outcome was cardiovascular death or unplanned admission to hospital for the management of worsening CHF. Prespecified secondary outcomes were: cardiovascular death, admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularisation; death (any cause) or admission to hospital for CHF; and development of new diabetes.

We classified all deaths as cardiovascular unless an unequivocal non-cardiovascular cause was established. A CHF hospital admission was defined as admission to hospital necessitated by heart failure and primarily for its treatment. A patient admitted for this reason had to show signs and symptoms of worsening heart failure and require treatment with intravenous diuretics. Evidence of worsening heart failure had to include at least one of the following items: increasing dyspnoea on exertion, orthopnoea, nocturnal dyspnoea, pulmonary oedema, increasing peripheral oedema, increasing fatigue or decreasing exercise tolerance, renal hypoperfusion (ie, worsening renal function), raised jugular venous pressure, and radiological signs of CHF.

A diagnosis of myocardial infarction was made if the following conditions were met: creatine kinase or creatine kinase-MB more than twice the upper limit of normal, or troponin I or T more than twice the upper limit of normal if neither creatine kinase or creatine kinase-MB were available; or three times the upper limit of normal for the same markers within 24 h of percutaneous transluminal coronary angioplasty; or five times the upper limit of normal for the same markers within 24 h of coronary artery bypass grafting surgery. In addition to these marker criteria, a patient had to have experienced electrocardiographic changes in two or more contiguous leads showing new Q waves (or R waves in V1 or V2), left-bundle-branch block, or ischaemic ST-T wave changes, or typical clinical presentation consistent with myocardial infarction defined as one of the following: cardiac ischaemic type pain lasting more than 20 min, pulmonary oedema, or cardiogenic shock not otherwise explained.

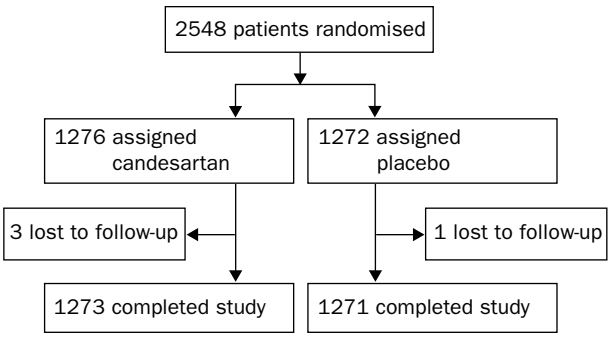


Figure 1: **Trial profile**

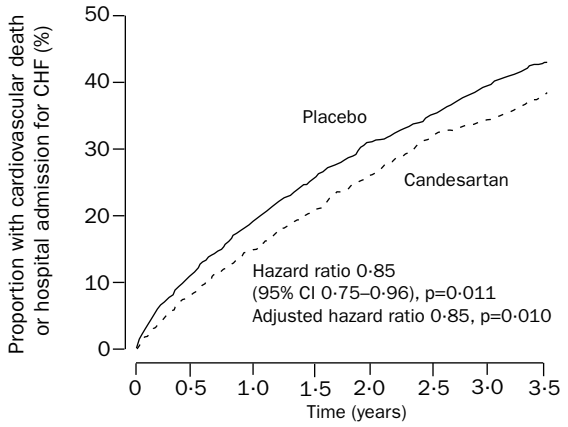
Statistical methods

The planned sample size of 2300 patients was designed to provide around 80% power to detect a 16% relative

	Candesartan (n=1276)	Placebo (n=1272)
Patients' characteristics		
Mean (SD) age (years)	64·0 (10·7)	64·1 (11·3)
⩾75 years (%)	212 (16·6%)	245 (19·3%)
Men/women	1006 (78·8%)/ 270 (21·2%)	1000 (78·6%)/ 272 (21·4%)
Ethnic origin		
European	1143 (89·6%)	1164 (91·5%)
Black	65 (5·1%)	62 (4·9%)
Other	68 (5·3%)	46 (3·6%)
Heart-disease risk factors		
NYHA class (%)		
II	312 (24·5%)	302 (23·7%)
III	931 (73·0%)	925 (72·7%)
IV	33 (2·6%)	45 (3·5%)
Mean (SD) LVEF (%)	28·0 (7·5)	28·0 (7·5)
Mean (SD) heart rate (beats/min)	73·4 (13·3)	73·7 (12·9)
Mean (SD) blood pressure (mm Hg)		
Systolic	124·7 (18·6)	125·6 (18·6)
Diastolic	75·0 (10·8)	75·2 (10·7)
Mean (SD) body-mass index (kg/m^2)	27·9 (5·5)	27·8 (5·1)
Heart-failure cause*		
Ischaemic	794 (62·2%)	796 (62·6%)
Idiopathic	340 (26·6%)	328 (25·8%)
Hypertensive	87 (6·8%)	79 (6·2%)
Medical history		
Hospital admission for CHF	975 (76·4%)	990 (77·8%)
Myocardial infarction	714 (56·0%)	703 (55·3%)
Current angina pectoris	244 (19·1%)	272 (21·4%)
Stroke	108 (8·5%)	112 (8·8%)
Diabetes mellitus	376 (29·5%)	382 (30·0%)
Hypertension	609 (47·7%)	619 (48·7%)
Atrial fibrillation	346 (27·1%)	341 (26·8%)
Pacemaker	112 (8·8%)	119 (9·4%)
Current smoker	194 (15·2%)	235 (18·5%)
PCI	184 (14·4%)	192 (15·1%)
CABG	326 (25·5%)	298 (23·4%)
Implantable cardioverter-defibrillator	47 (3·7%)	53 (4·2%)
Cancer	78 (6·1%)	75 (5·9%)
Medical treatment		
ACE inhibitor	1276 (100·0%)	1270 (99·8%)
Diuretic	1148 (90·0%)	1146 (90·1%)
β blocker	702 (55·0%)	711 (55·9%)
Spironolactone	222 (17·4%)	215 (16·9%)
Digoxin/digitalis glycoside	735 (57·6%)	753 (59·2%)
Calcium antagonist	123 (9·6%)	144 (11·3%)
Other vasodilators	444 (34·8%)	492 (38·7%)
Oral anticoagulant	484 (37·9%)	487 (38·3%)
Antiarrhythmic agent	166 (13·0%)	154 (12·1%)
Aspirin	652 (51·1%)	659 (51·8%)
Other antiplatelet agent	40 (3·1%)	45 (3·5%)
Lipid-lowering drug	528 (41·4%)	521 (41·0%)

NYHA=New York Heart Association. LVEF=left-ventricular ejection fraction. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. All baseline variables listed, except ethnic origin, heart-failure cause, and baseline spironolactone treatment, used as covariates. *Primary cause assigned by investigator and do not add up to 100% because some causes not listed.

Table 1: **Baseline characteristics of patients**



Number at risk

Candesartan	1276	1176	1063	948	457
Placebo	1272	1136	1013	906	422

Figure 2: **Kaplan-Meier cumulative event curves for primary outcome**

reduction in the primary outcome, assuming an annual placebo event rate of 18%. The analysis was done on an intention-to-treat basis and included all randomised patients. We analysed all major outcomes by time to first event. For the primary analysis we used the logrank test to compare the time-to-event distributions. The hazard ratios were estimated together with 95% CI. In addition, we used a Cox's regression model with treatment and other prospectively defined covariates (table 1) to adjust the hazard ratio for these prespecified baseline factors, which might alter the event rates. We used two-sided p values and took $p<0·05$ to be significant.

Role of the funding source

The sponsor of the study managed the data, and its representatives were involved in the data analysis and data interpretation. All final data analyses were done by the sponsor and verified independently by the statistical centre at the London School of Hygiene and Tropical Medicine, London, UK.

Results

Of 2548 patients enrolled, 1276 were assigned candesartan and 1272 placebo (figure 1). Follow-up was concluded on March 31, 2003. The median duration of follow up was 41 months.

The baseline characteristics, including details of background medical treatment, are given in table 1. Enalapril, lisinopril, captopril, and ramipril were the most commonly used ACE inhibitors, together accounting for 74% of all ACE inhibitors used. The mean daily doses of these drugs in the candesartan group were 16·8, 17·7, 82·2, and 6·8 mg, respectively, and in the placebo group were 17·2, 17·7, 82·7, and 7·3 mg, respectively. Investigators stated that they thought 96% of patients in each group were receiving optimum doses of ACE inhibitor at randomisation. 55% of patients were treated with β blockers at baseline and 17% with spironolactone.[12] By the end of the study, 64% of patients in the candesartan group and 68% in the placebo group were taking β blockers. The proportion of patients taking spironolactone had risen to 20% in the candesartan group and to 25% in the placebo group. Open-label angiotensin-receptor-blocker treatment was being used in 2·3% of the candesartan group and 5·0% of the placebo group by the end of the trial.

	Candesartan (n=1276)	Placebo (n=1272)
Number of patients (%)*		
None	953 (74·7)	890 (70·0)
1	184 (14·4)	184 (14·5)
2	76 (6·0)	100 (7·9)
⩾3	63 (4·9)	98 (7·7)
Number of patients admitted to hospital (number of admissions)	323 (607)	382 (836)

*Investigator reported, with CHF as primary reason. †p=0·002 test for difference in distribution of CHF hospital admissions.

Table 3: **Number of hospital admissions for worsening heart failure***

483 (38%) patients in the candesartan group and 538 (42%) in the placebo group experienced the primary outcome of cardiovascular death or admission to hospital for CHF (unadjusted hazard ratio 0·85 [95% CI 0·75–0·96], p=0·011; covariate adjusted p=0·010; figure 2). The annual event rates were 14·1% in the candesartan group and 16·6% in the placebo group.

Other outcomes are shown in table 2. Candesartan reduced cardiovascular mortality and the risk of admission to hospital for CHF individually, as well as the risk of each of the secondary composite outcomes. There were 302 (24%) cardiovascular deaths in the candesartan group compared with 347 (27%) in the placebo group (unadjusted 0·84 [0·72–0·98], p=0·029; covariate adjusted p=0·021). Candesartan also reduced the proportion of patients experiencing a first hospital admission for CHF after randomisation, the proportion of patients with multiple admissions for CHF, and the total number of hospital admissions for CHF (table 3). The total number of patients who had myocardial infaraction was candesartan 44, placebo 69 (p=0·012); stroke: candesartan 47, placebo 41 (p=0·62); and coronary revascularisation procedures: candesartan 69, placebo 75 (p=0·46).

The number of deaths from any cause in the candesartan group was 377 (30%) compared with 412 (32%) in the placebo group (unadjusted 0·89 [0·77–1·02], p=0·086; covariate adjusted p=0·105). 539 (42%) patients treated with candesartan and 587 (46%) with placebo died from any cause or were admitted for CHF (unadjusted 0·87 [0·78–0·98], p=0·021). In the candesartan group, 852 patients had 2462 hospital admissions for any reason and 858 placebo patients had 2798 admissions (p=0·7 for patients and p=0·023 for admissions). 72 (6%) patients in the candesartan group

	Candesartan (n=1276)	Placebo (n=1272)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	483 (37·9%)	538 (42·3%)	0·85 (0·75–0·96)	0·011	0·85 (0·75–0·96)	0·010
Cardiovascular death	302 (23·7%)	347 (27·3%)	0·84 (0·72–0·98)	0·029	0·83 (0·71–0·97)	0·021
Hospital admission for CHF	309 (24·2%)	356 (28·0%)	0·83 (0·71–0·96)	0·014	0·83 (0·71–0·97)	0·018
Cardiovascular death, hospital admission for CHF, MI	495 (38·8%)	550 (43·2%)	0·85 (0·76–0·96)	0·010	0·85 (0·75–0·96)	0·007
Cardiovascular death, hospital admission for CHF, MI, stroke	512 (40·1%)	559 (43·9%)	0·87 (0·77–0·98)	0·020	0·86 (0·76–0·97)	0·015
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	548 (42·9%)	596 (46·9%)	0·87 (0·77–0·97)	0·015	0·87 (0·77–0·98)	0·018

MI=myocardial infarction. *Covariate-adjusted model for variables shown in table 1.

Table 2: **Primary and secondary outcomes**

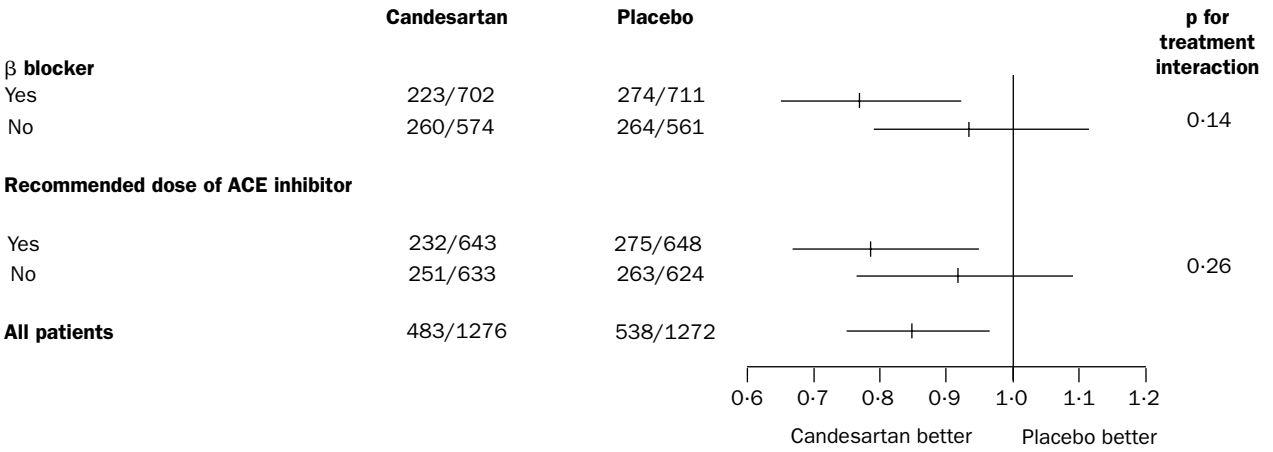


Figure 3: **Effect of candesartan compared with placebo on primary outcome in all patients and patients taking or not taking β blocker and taking or not taking recommended dose of ACE inhibitors at baseline**
Recommended daily doses: benazepril 20 mg, captopril 150 mg, enalapril 20 mg, fosinopril 20 mg, lisinopril 20 mg, perindopril 4 mg, quinapril 20 mg, ramipril 10 mg, and trandolapril 2 mg.

and 72 (6%) in the placebo group developed new diabetes (unadjusted 0·98 [0·70–1·35], p=0·88).

Candesartan reduced the risk of cardiovascular death or admission to hospital for CHF in all predefined subgroups, with no evidence of heterogeneity of treatment effect.[13] In particular, candesartan reduced this risk in patients treated with β blockers in addition to an ACE inhibitor at baseline (figure 3). Among these patients, 175 (25%) of 702 died in the candesartan group and 195 (27%) of 711 died in the placebo group (0·88 [0·72–1·08], p=0·22). The numbers of deaths in patients not taking a β blocker at baseline were 202 (35%) of 574 in the candesartan group and 217 (39%) of 561 in the placebo group (0·88 [0·73–1·07], p=0·20). Candesartan was as effective among patients taking a recommended dose of ACE inhibitor as in those taking lower doses (figure 3).

86% of patients started on 4 mg and 14% on 8 mg of candesartan or placebo daily. The mean daily doses for patients taking study drug at 6 months were 24 mg in the candesartan and 27 mg in the placebo group. 61% of the candesartan and 73% of the placebo group reached the target dose of 32 mg within 6 months of randomisation.

At the final study visit, 220 (25%) survivors in the candesartan group and 155 (18%) in the placebo group were no longer taking study medication for any reason. Overall, 309 (24%) patients in the candesartan group and 233 (18%) patients in the placebo group permanently discontinued study medication because of an adverse event or an abnormal laboratory value (p=0·0003, table 4).

In 32 (7%) of 436 in the candesartan group, creatinine at least doubled from baseline, compared with in 27 (6%) of 447 in the placebo group (p=0·5). Among patients taking spironolactone at baseline, serum creatinine at least doubled from baseline in eight (11%) of 73 patients in the candesartan group and three (4%) of 71 in the placebo group (p=0·21).

	Candesartan (n=1276)	Placebo (n=1272)	p
Cause of discontinuation			
Hypotension	58 (4·5)	40 (3·1)	0·079
Increase in creatinine	100 (7·8)	52 (4·1)	0·0001
Hyperkalaemia	44 (3·4)	9 (0·7)	<0·0001
Any adverse event or laboratory abnormality	309 (24·2)	233 (18·3)	0·0003

Table 4: **Permanent study-drug discontinuation for adverse events**

In the candesartan group, 12 (3%) of 447 patients developed potassium concentrations 6 mmol/L or higher compared with five (1%) of 459 in the placebo group (p=0·089). For patients taking spironolactone at baseline, three (4%) of 74 in the candesartan group developed potassium concentrations of 6 mmol/L or higher compared with one (1%) of 71 in the placebo group.

By 6 months, blood pressure was lowered from baseline by 4·6 mm Hg systolic (p=0·007) and 3·0 mm Hg diastolic (p=0·004) more in the candesartan group than in the placebo group. The reduction in blood pressure with candesartan was not greater among patients treated with β blockers at baseline than among those not treated with β blockers.

There were two cases of angioedema in the candesartan group and three in the placebo group. All affected patients were taking an ACE inhibitor at the time and two required hospital admission (one placebo and one candesartan). One patient taking candesartan had study medication discontinued.

Discussion

Among patients with CHF and a low left-ventricular ejection fraction, the addition of candesartan to an ACE inhibitor decreased the risk of cardiovascular death, and admission to hospital for CHF. This beneficial effect of candesartan was seen in all prespecified subgroups of patients, including those treated with β blockers and other treatments, with no evidence of treatment heterogeneity.

Our findings are consistent with the evidence that angiotensin II continues to be produced despite chronic ACE-inhibitor treatment,[1–5] and mechanistic studies showing favourable neurohumoral, haemodynamic, and left-ventricular remodelling effects from adding an angiotensin-receptor blockers in patients already treated with an ACE inhibitor.[8,9] These potentially beneficial effects are also seen in patients treated with β blockers and ACE inhibitors. For example, in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study,[14] the greatest left-ventricular reverse remodelling was seen with the combination of enalapril, metoprolol, and candesartan. Our results extend those observations to improvements in important clinical outcomes.

Our findings may superficially seem to be in conflict with those of Valsartan Heart Failure Trial (Val-HeFT),[15] although direct comparisons between trials are difficult to

make. In Val-HeFT, the addition of valsartan to conventional treatment, including ACE inhibitors in 93% of patients, β blockers in 35%, and spironolactone in 5%, reduced the risk of the composite co-primary outcome of death or cardiovascular morbidity (admission for CHF, ⩾4 h intravenous treamtent for CHF without admission, or cardiac arrest with resuscitation) by 13·2%. This effect on the composite outcome was principally explained by a 27·5% reduction in CHF hospital admission, since valsartan had no effect on cardiovascular mortality or total mortality. Unexpectedly, in the 1610 (35%) patients treated with both ACE inhibitors and β blockers at baseline, valsartan was associated with a worse outcome. This latter finding has caused concern about excessive neuroendocrine inhibition and led guidelines to discourage triple neurohumoral blockade.[16–19] We believe our results can remove these concerns.

Comparison of the overall Val-HeFT population—nearly all of whom were treated with ACE inhibitors—with our population is most approriate. The findings of the two trials show consistently that adding an angiotensin-receptor blocker to conventional treatment has incremental clinical benefit. The apparent differences between our trial and Val-HeFT might be explained by the particular type or dose of angiotensin-receptor blocker used. Alternatively, underpowered analyses of small subgroups in Val-HeFT might have led to the difference.

The benefits of candesartan were evident in our study among patients treated with recommended doses of ACE inhibitors. For example, the mean daily dose of enalapril taken at baseline was 17·0 mg, which compares favourably with 16·6 mg in those taking the drugs in the treatment group of the Studies Of Left Ventricular Dysfunction[20] and 17·0 mg in Val-HeFT.[15] We also show clearly that this benefit is clinically important. Over the mean 3·0 years duration of the trial, 37·9% of patients in the candesartan group experienced a cardiovascular death or first admission to hospital for CHF compared with 42·3% in the placebo group. This absolute reduction of 4·4 patients with events per 100 patients treated corresponds to a number needed to treat of 23 to prevent one first event of cardiovascular death or CHF admission. It is not only first events that are reduced. Multiple CHF admssions, which are common, distressing, and costly, are also reduced.[21,22] These benefits are obtained at the expense of infrequent adverse effects that are characteristic of drugs inhibiting the renin-angiotensin-aldosterone system. The higher rates of withdrawals for renal dysfunction and hyperkalaemia in the candesartan group indicate the need for careful monitoring of renal function and serum potassium. In conclusion, the addition of candesartan to an ACE inhibitor and other treatments, including a β blocker, is generally well tolerated in patients with CHF and a low left-ventricular ejection fraction and leads to a clinically important reduction in cardiovascular mortality and morbidity.

Conflict of interest statement

M A Pfeffer, K Swedberg, C B Granger, J J V McMurray, and S Yusuf have served as consultants to or received research grants from AstraZeneca and other major cardiovascular pharmaceutical companies. J Östergren has served as a consultant and received research grants from AstraZeneca. P Held, E L Michelson, and B Olofsson are employees of AstraZeneca.

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