

## Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme

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### Summary

**Background** Patients with chronic heart failure (CHF) are at high risk of cardiovascular death and recurrent hospital admissions. We aimed to find out whether the use of an angiotensin-receptor blocker could reduce mortality and morbidity.

**Methods** In parallel, randomised, double-blind, controlled, clinical trials we compared candesartan with placebo in three distinct populations. We studied patients with left-ventricular ejection fraction (LVEF) 40% or less who were not receiving angiotensin-converting-enzyme inhibitors because of previous intolerance or who were currently receiving angiotensin-converting-enzyme inhibitors, and patients with LVEF higher than 40%. Overall, 7601 patients (7599 with data) were randomly assigned candesartan (n=3803, titrated to 32 mg once daily) or matching placebo (n=3796), and followed up for at least 2 years. The primary outcome of the overall programme was all-cause mortality, and for all the component trials was cardiovascular death or hospital admission for CHF. Analysis was by intention to treat.

**Findings** Median follow-up was 37.7 months. 886 (23%) patients in the candesartan and 945 (25%) in the placebo group died (unadjusted hazard ratio 0.91 [95% CI 0.83–1.00],  $p=0.055$ ; covariate adjusted 0.90 [0.82–0.99],  $p=0.032$ ), with fewer cardiovascular deaths (691 [18%] vs 769 [20%], unadjusted 0.88 [0.79–0.97],  $p=0.012$ ; covariate adjusted 0.87 [0.78–0.96],  $p=0.006$ ) and hospital admissions for CHF (757 [20%] vs 918 [24%],  $p<0.0001$ ) in the candesartan group. There was no significant heterogeneity for candesartan results across the component trials. More patients discontinued candesartan than placebo because of concerns about renal function, hypotension, and hyperkalaemia.

**Interpretation** Candesartan was generally well tolerated and significantly reduced cardiovascular deaths and hospital admissions for heart failure. Ejection fraction or treatment at baseline did not alter these effects.

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### Introduction

In patients with chronic heart failure (CHF) and reduced left-ventricular ejection fraction (LVEF), results of clinical randomised trials have shown the life-saving and symptomatic benefits of angiotensin-converting-enzyme inhibitors,<sup>1–3</sup>  $\beta$  blockers,<sup>4–7</sup> and, in more selected patients, spironolactone.<sup>8</sup> These findings have led to widespread use of these treatments in appropriate populations.<sup>9</sup> The results have been translated into benefits in clinical practice, since in epidemiological studies and large registries substantial temporally related reductions have been seen in the age-adjusted mortality of patients with heart failure.<sup>10–12</sup> Despite these major successes, the prevalence of heart failure continues to increase, mainly as a consequence of ageing populations, many patients having hypertension, ischaemic heart disease, or both, the two main predisposing disorders for heart failure.<sup>13–15</sup> Indeed, heart failure is the most common reason for hospital admission in patients older than 65 years.<sup>16,17</sup> About 35–50% of patients with signs and symptoms attributed to heart failure do not have substantially reduced LVEF.<sup>17</sup> Irrespective of the cause or presence of left-ventricular dysfunction, once clinically recognised, patients with heart failure are at heightened risk for subsequent hospital admissions and death from cardiovascular causes.

The development of angiotensin II type 1 receptor blockers provides a pharmacologically distinct mechanism of inhibiting the renin-angiotensin-aldosterone system. Angiotensin-receptor blockers offer the potential to improve clinical outcomes for patients with heart failure beyond those seen with angiotensin-converting-enzyme inhibitors, as well as providing an alternative for patients with previous intolerance of angiotensin-converting-enzyme inhibitors.<sup>18</sup> The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme was specifically designed as three parallel, independent, integrated, randomised, double-blind, placebo-controlled, clinical trials comparing candesartan with placebo in three distinct but complementary populations of patients with symptomatic heart failure.<sup>19</sup> Dependent on background use of angiotensin-converting-enzyme inhibitors or LVEF, patients were eligible for one of the three component trials. We designed each trial to find out whether the use of candesartan would reduce the risk of cardiovascular death or hospital admission for CHF management in the specific population. The overarching hypothesis of the CHARM programme prespecified that use of candesartan would reduce the risk of death from any cause in the broad spectrum of patients with heart failure. The population was appropriate to test for consistency of benefits in subgroups and potential safety issues.

### Patients and methods

#### Patients

Eligible patients were women and men aged 18 years or older who had symptomatic heart failure (New York

Heart Association class II–IV) for at least 4 weeks' duration. Major exclusion criteria included serum creatinine  $\geq 265 \mu\text{mol/L}$  or more, serum potassium  $\geq 5.5 \text{ mmol/L}$  or more, known bilateral renal artery stenosis, symptomatic hypotension, women of childbearing potential not using adequate contraception, critical aortic or mitral stenosis, myocardial infarction, stroke, or open-heart surgery in the previous 4 weeks, use of an angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2-year survival, and unwillingness to consent. Other exclusion criteria have been previously described.<sup>19</sup>

Eligible patients were enrolled into one of three trials, done concurrently, according to LVEF higher than 40% (CHARM-Preserved), 40% or lower and being treated with an angiotensin-converting-enzyme inhibitor (CHARM-Added), or 40% or lower and not being treated with an angiotensin-converting-enzyme inhibitor because of previous intolerance (CHARM-Alternative). All patients gave written informed consent before being enrolled. All sites received approval from local ethics committees for the conduct of each of the three component trials.

The component trials were all done at the same 618 sites in 26 countries, with use of uniform procedures, definitions, and forms, and one data coordinating centre, management, and leadership team. An independent data safety monitoring board was established to oversee the safety of patients enrolled in the trial and to monitor trial progress. This board had access to all data through an independent statistical centre. Predefined stopping rules for efficacy or safety concentrated on mortality from the overall trial programme. An independent clinical-event committee adjudicated all study endpoints.

## Methods

Between March, 1999, and March, 2001, patients were randomly assigned, in a double-blind way, candesartan or matching placebo (figure 1) according to computer-generated assignment, stratified by site and component trial, and provided through a coordinating telephone centre. The assignment code was held at an independent centre and by the data safety monitoring board. The initial dose used could be 4 mg or 8 mg candesartan once daily or matching placebo, decided by the study physician.<sup>19</sup> Study-drug dose could be doubled, as tolerated, at a minimum of every 2 weeks, to the target dose of 32 mg once daily, with recommended monitoring of blood pressure and serum potassium and creatinine. Study medication could be increased or decreased in response to the patients' clinical status, and algorithms were provided as guidelines for management of hypotension or renal dysfunction. After the titration phase, visits were scheduled every 4 months, with a minimum planned duration of 2 years. Routine safety laboratory assessments were done in North American patients at baseline, 6 weeks, 14 months, and yearly thereafter. Use of conventional heart-failure treatments, such as  $\beta$  blockers, diuretics, digitalis, spironolactone, and, if appropriate, angiotensin-converting-enzyme inhibitors, were allowed. After the results of the Heart Outcomes Prevention Evaluation trial<sup>20</sup> were available, physicians were permitted to use angiotensin-converting-enzyme inhibitors in CHARM-Preserved patients who had similar demographic features. Patients were free to discontinue their participation in the study at any time. Discontinuations because of patients' preference or physicians' decision were recorded and these patients were followed up for outcomes if possible, according to the intention-to-treat principle.

The primary outcome of the overall programme was all-cause death. The outcomes in the three component trials were: cardiovascular death or unplanned admission to hospital for the management of worsening CHF (primary outcome); 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 or when heart failure became a major component of the patient's hospital admission. 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.

## Statistical methods

Each component trial independently estimated its respective sample size based on the anticipated event rate for the combined outcome of cardiovascular death or admission to hospital for CHF. We designed the overall

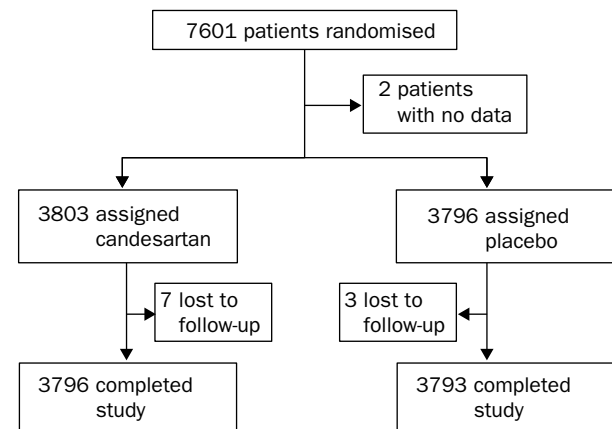


Figure 1: Trial profile

	Candesartan (n=3803)	Placebo (n=3796)
<b>Patients' characteristics</b>		
Mean (SD) age (years)	65.9 (11.0)	66.0 (11.1)
≥75 years	852 (22.4%)	884 (23.3%)
Men/women	2617 (68.8%)/ 1186 (31.2%)	2582 (68.0%)/ 1214 (32.0%)
Ethnic origin		
European	3412 (89.7%)	3458 (91.1%)
Black	162 (4.3%)	164 (4.3%)
Other	229 (6.0%)	174 (4.6%)
<b>Heart-disease risk factors</b>		
NYHA class		
II	1730 (45.5%)	1686 (44.4%)
III	1977 (52.0%)	2008 (52.9%)
IV	96 (2.5%)	102 (2.7%)
Mean (SD) LVEF (%)	38.8 (14.9)	38.8 (14.9)
<30	1073 (28.2%)	1045 (27.5%)
≥30–39	1083 (28.5%)	1123 (29.6%)
≥40–49	667 (17.5%)	655 (17.3%)
≥50	980 (25.8%)	973 (25.6%)
Mean (SD) heart rate (beats/min)	73.0 (13.3)	72.8 (12.8)
Mean (SD) blood pressure (mm Hg)		
Systolic	130.6 (19.3)	131.1 (19.0)
Diastolic	76.6 (10.9)	76.7 (10.6)
Mean (SD) body-mass index (kg/m <sup>2</sup> )	28.3 (5.6)	28.2 (5.3)
<b>Medical history</b>		
Hospital admission for CHF	2725 (71.7%)	2701 (71.2%)
Myocardial infarction	2024 (53.2%)	1980 (52.2%)
Current angina	872 (22.9%)	936 (24.7%)
Stroke	333 (8.8%)	330 (8.7%)
Diabetes mellitus	1085 (28.6%)	1075 (28.3%)
Hypertension	2093 (55.0)	2093 (55.1%)
Atrial fibrillation	1039 (27.3%)	1044 (27.5%)
Pacemaker	313 (8.2%)	324 (8.5%)
Current smoker	565 (14.9%)	549 (14.5%)
PCI	575 (15.1%)	653 (17.2%)
CABG	921 (24.2%)	870 (22.9%)
Implantable cardioverter defibrillator	98 (2.6%)	93 (2.4%)
Previous cancer	270 (7.1%)	243 (6.4%)
<b>Medical treatment</b>		
ACE inhibitor	1573 (41.4%)	1552 (40.9%)
β blocker	2102 (55.3%)	2101 (55.3%)
Diuretic	3150 (82.8%)	3136 (82.6%)
Spirinolactone	643 (16.9%)	629 (16.6%)
Digoxin/digitalis glycoside	1622 (42.7%)	1632 (43.0%)
Calcium antagonist	768 (20.2%)	774 (20.4%)
Other vasodilators	1437 (37.8%)	1527 (40.2%)
Oral anticoagulants	1182 (31.1%)	1156 (30.5%)
Antiarrhythmic agents	443 (11.6%)	450 (11.9%)
Aspirin	2105 (55.4%)	2141 (56.4%)
Other antiplatelet agent	181 (4.8%)	175 (4.6%)
Lipid-lowering drug	1578 (41.5%)	1575 (41.5%)

NYHA=New York Heart Association. ACE=angiotensin-converting enzyme. 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.

Table 1: Baseline characteristics of patients

study to address the question of all-cause mortality in all randomised patients, with its sample size being based on the sum of the three trials. We estimated an annual overall mortality in the placebo group of 8% and, on that basis, the programme of investigation had more than 85% power to detect around a 14% reduction in mortality at a significance level of 0.05, based on the logrank test. All analyses were done by intention to treat, and p values were two-sided. Cardiovascular death, hospital admission for heart failure, or non-fatal myocardial infarction, for the primary and secondary analyses were based on the adjudicated approved events. The hierarchical secondary analyses also included the non-adjudicated outcomes of non-fatal stroke and coronary revascularisation procedures. Investigator-reported outcomes and new onset of diabetes mellitus were prespecified additional outcomes. All time-to-event variables were analysed with

the logrank test and displayed on Kaplan-Meier plots according to treatment. We estimated the hazard ratios and 95% CI comparing treatments, stratified by trial, with a stratified logrank test. In addition, a covariate-adjusted Cox's regression model was fitted with the prespecified baseline covariates shown in table 1 to adjust the hazard ratio for other factors that might affect prognosis. Prespecified subgroup analyses were done, each using a test for heterogeneity to assess for possible interactions between treatment and baseline variables. We combined data from the two studies of patients with LVEF 40% or less because this subgroup was prespecified as clinically important. We grouped major non-cardiovascular events by specific cause and for safety analyses. We compared the rates and proportions of patients who discontinued blinded study medication overall, as well as for specific reasons such as hypotension, increased creatinine, and hyperkalaemia for safety and tolerability assessments.

### 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 London School of Hygiene and Tropical Medicine, London, UK.

### Results

7601 patients were randomised, although no data were available on two patients incorrectly assigned randomisation numbers and, therefore, the results are based on 7599 patients (3803 candesartan, 3796 placebo, figure 1). The programme was completed as planned with follow-up concluding on March 31, 2003, 2 years after the last patient was randomised. The median duration of follow-up was 37.7 months and the vital status of all but ten (0.1%) patients was ascertained at study closure. The baseline characteristics of the placebo and candesartan groups are shown in table 1.<sup>21</sup>

886 (23%) in the candesartan group and 945 (25%) in the placebo group died from any cause (unadjusted hazard ratio 0.91 [95% CI 0.83–1.00], p=0.055; covariate adjusted 0.90 [0.82–0.99], p=0.032, figure 2). Annual mortality rates (events per 100 years of follow-up) were 8.1% and 8.8%, respectively. This lower mortality in the candesartan group was attributable to fewer cardiovascular deaths: 691 (18%) in the candesartan compared with 769 (20%) in the placebo group (unadjusted 0.88 [0.79–0.97], p=0.012; covariate adjusted 0.87 [0.78–0.96], p=0.006, figure 2). This treatment difference in cardiovascular death was most striking in the first year but was maintained without additional divergence in subsequent years.

The reductions in death, particularly cardiovascular death, were seen among patients with LVEF of 40% or less, with significant reductions in all-cause mortality (0.88 [0.79–0.98], p=0.018) and cardiovascular deaths (0.84 [0.75–0.95], p=0.005). There was, however, no significant heterogeneity across the three trials in the impact of candesartan on all-cause mortality (figure 3) or cardiovascular deaths or hospital admission for CHF (interaction test, p=0.37 and p=0.43, respectively).

There were slightly more non-cardiovascular deaths in the candesartan group than in the placebo group (195 [5%] vs 176 [5%]; p=0.45), which was due to a difference in cancer deaths (86 [2.3%] vs 59 [1.6%], p=0.038). The incidence of non-fatal neoplasms detected during the programme was, however, similar in the two treatment groups (185 [5.1%] vs 194 [4.6%], p=0.49).

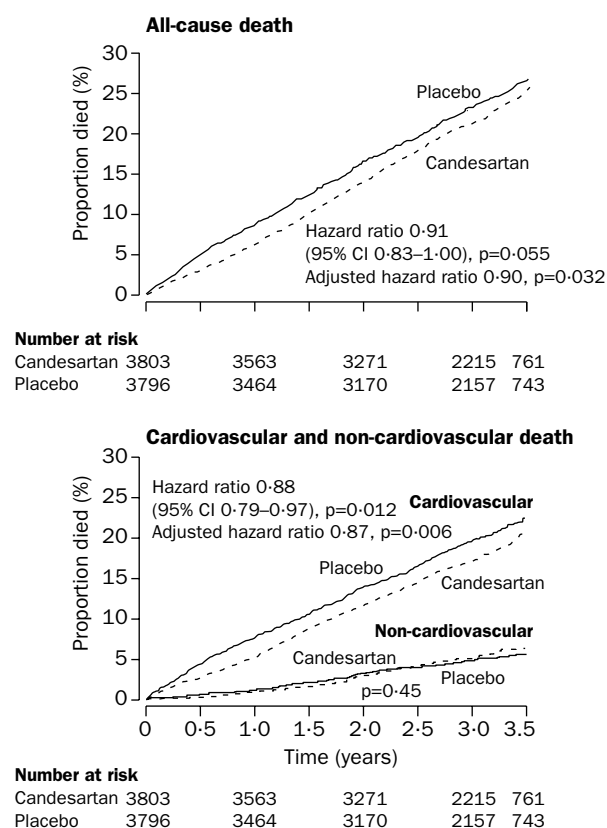


Figure 2: Kaplan-Meier curves of all-cause death and cardiovascular or non-cardiovascular deaths

Overall, time to cardiovascular death or hospital admission for CHF, the primary outcome for each of the three component trials, was reduced by 16% (candesartan 30%, placebo 35%, adjusted 0.84 [0.77–0.91],  $p<0.0001$ ; covariate adjusted 0.82 [0.75–0.88],  $p<0.0001$ , figure 4). This reduction in risk with candesartan was consistent across all trials (heterogeneity  $p=0.33$ , figure 3).<sup>22–24</sup> Risk of cardiovascular death and risk of first hospital admission for CHF were each significantly reduced: 757 (20%) of candesartan patients compared with 918 (24%) placebo patients had at least one adjudicated hospital admission for CHF ( $p<0.0001$ ). Moreover, there were 1454 investigator-reported hospital admissions for CHF as the primary cause in the candesartan patients compared with 2010 in the placebo group ( $p<0.0001$ ). Two or more hospital admissions for heart failure were reported in 339 (9%) candesartan and 456 (12%) placebo patients ( $p<0.0001$ ). This risk reduction in time to cardiovascular death and non-fatal cardiovascular outcomes by

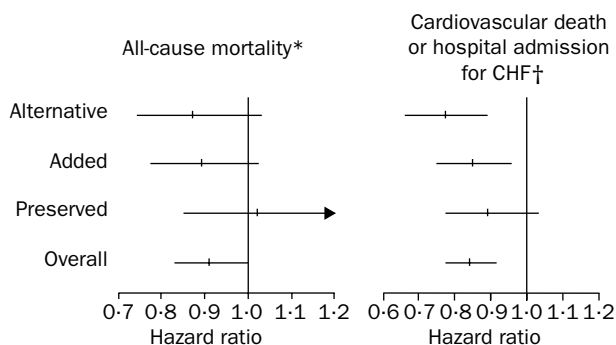


Figure 3: Effects of candesartan on all-cause mortality, cardiovascular death, or hospital admission for CHF

\*p for heterogeneity 0.37. †p for heterogeneity 0.33.

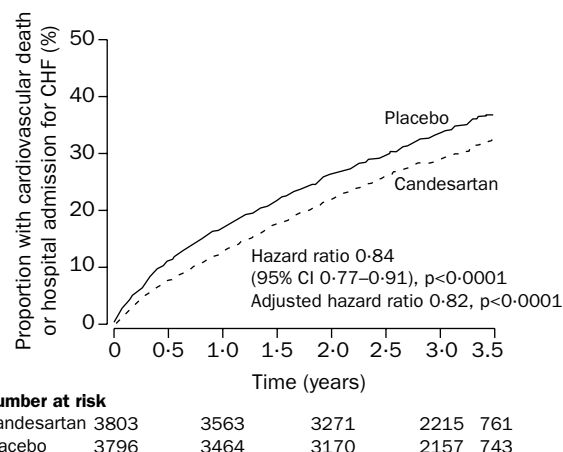


Figure 4: Effect of candesartan on cardiovascular mortality or hospital admission for CHF

candesartan was maintained as the composite outcome of cardiovascular death or hospital admission for CHF was expanded in a prespecified stepwise way to include non-fatal myocardial infarction, non-fatal stroke, and coronary revascularisation procedures (table 2). The total number of patients with myocardial infarction was: candesartan 176, placebo 190 ( $p=0.33$ ); stroke: candesartan 141, placebo 146 ( $p=0.63$ ); and coronary revascularisation procedure: candesartan 236, placebo 241 ( $p=0.62$ ). In the candesartan group, 2374 patients had 6690 hospital admissions for any reason compared with 2423 placebo patients who had 7178 admissions ( $p=0.2$  for patients and  $p=0.015$  for admissions).

Overall, 1398 (37%) candesartan and 1541 (41%) placebo patients died (any cause) or were admitted for CHF (0.86 [0.80–0.93],  $p<0.0001$ ). In patients without a prestudy diagnosis of diabetes, the number of patients in the candesartan group who during the programme were newly diagnosed as having diabetes was significantly lower than that in the placebo group: candesartan 163 (6%) of 2715 and placebo 202 (7%) of 2721 (0.78 [0.64–0.96],  $p=0.020$ ; test for heterogeneity between trials,  $p=0.163$ ).

The reduction in risk of cardiovascular death or hospital admission for heart failure with candesartan was similar in men and women (figure 5). Similarly, the 1736 patients aged 75 years or older showed as great a benefit with candesartan as did younger patients. Particularly noteworthy was the similar effectiveness of candesartan in patients with LVEF higher or lower than 40% (figure 5). The relative reductions in risk were similar across New York Heart Association classes and among patients with or without a history of diabetes at baseline (figure 5). The beneficial effect of candesartan was consistent irrespective of baseline concomitant medications used. Specifically, similar benefits were noted whether or not ACE inhibitors,  $\beta$  blockers, spironolactone, any diuretic, digitalis glycoside, aspirin, or lipid-lowering drugs were used at baseline (figure 5).

The initial dose of study medication was 4 mg in 80% and 8 mg in 20% of patients. At the 6-month visit, study medication had been discontinued in 404 (11%) of the candesartan patients and 265 (7%) of placebo patients ( $p<0.0001$ ). Of those taking study medication at that time, 2025 (63%) of candesartan patients were at the target dose (32 mg once daily) compared with 2489 (75%) of the placebo group. At 6 months, the mean daily doses were 24 mg and 27 mg, respectively, and were similar at subsequent visits. By the end of the studies, 660 (23%) of candesartan survivors and 529 (19%) of placebo

	Candesartan (n=3803)	Placebo (n=3796)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admissions for CHF	1150 (30.2%)	1310 (34.5%)	0.84 (0.77–0.91)	<0.0001	0.82 (0.75–0.88)	<0.0001
Cardiovascular death	691 (18.2%)	769 (20.3%)	0.88 (0.79–0.97)	0.012	0.87 (0.78–0.96)	0.006
Hospital admission for CHF	757 (19.9%)	918 (24.2%)	0.79 (0.72–0.87)	<0.0001	0.77 (0.70–0.84)	<0.0001
Cardiovascular death, hospital admission for CHF, MI	1213 (31.9%)	1369 (36.1%)	0.84 (0.78–0.91)	<0.0001	0.82 (0.76–0.89)	<0.0001
Cardiovascular death, hospital admission for CHF, MI, stroke	1269 (33.4%)	1420 (37.4%)	0.85 (0.79–0.92)	<0.0001	0.83 (0.77–0.90)	<0.0001
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	1404 (36.9%)	1549 (40.8%)	0.86 (0.80–0.93)	<0.0001	0.85 (0.79–0.92)	<0.0001

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

Table 2: Secondary outcomes hierarchically ordered

survivors were no longer taking study medication for any reason ( $p=0.0001$ ). Permanent discontinuations for adverse events or abnormal laboratory values were more frequent with candesartan (table 3). Angioedema was reported in five (0.13%) candesartan-assigned patients and three (0.08%) patients in the placebo group.

Surveillance blood safety analyses were done in 2743 North American patients. Between baseline and 6 weeks, serum creatinine changed slightly in the two treatment groups (8  $\mu\text{mol/L}$  increase in the candesartan group and 1  $\mu\text{mol/L}$  decrease in the placebo group). Creatinine doubled in 82 (6%) of 1263 candesartan patients and 47 (4%) of 1279 of placebo patients with surveillance laboratory assessments ( $p=0.002$ ). At 6 weeks, there was a 0.14 mmol/L increase in serum potassium ( $p<0.0001$ ) in the candesartan group with no overall change in the placebo group. A potassium concentration of 6.0 mmol/L or higher was seen in 31 (2%) of 1294 candesartan and 15 (1%) of 1310 placebo patients ( $p=0.017$ ). No other unexpected or clinically important changes in laboratory values were noted.

By 6 months, blood pressure was lowered from baseline by 5.2 mm Hg systolic and 3.0 mm Hg diastolic more in the candesartan group than in the placebo ( $p<0.001$  for both), with more lowering of blood pressure in CHARM-Preserved (test for heterogeneity for systolic  $p=0.025$ , for diastolic  $p=0.021$ ).

## Discussion

Our results show that treatment of a broad spectrum of patients with symptomatic heart failure with candesartan resulted in a reduction in deaths, albeit of borderline significance, notably because of a significant 12% reduction in cardiovascular deaths. In the overall CHARM programme, the risk of death and, particularly, death attributed to cardiovascular causes was

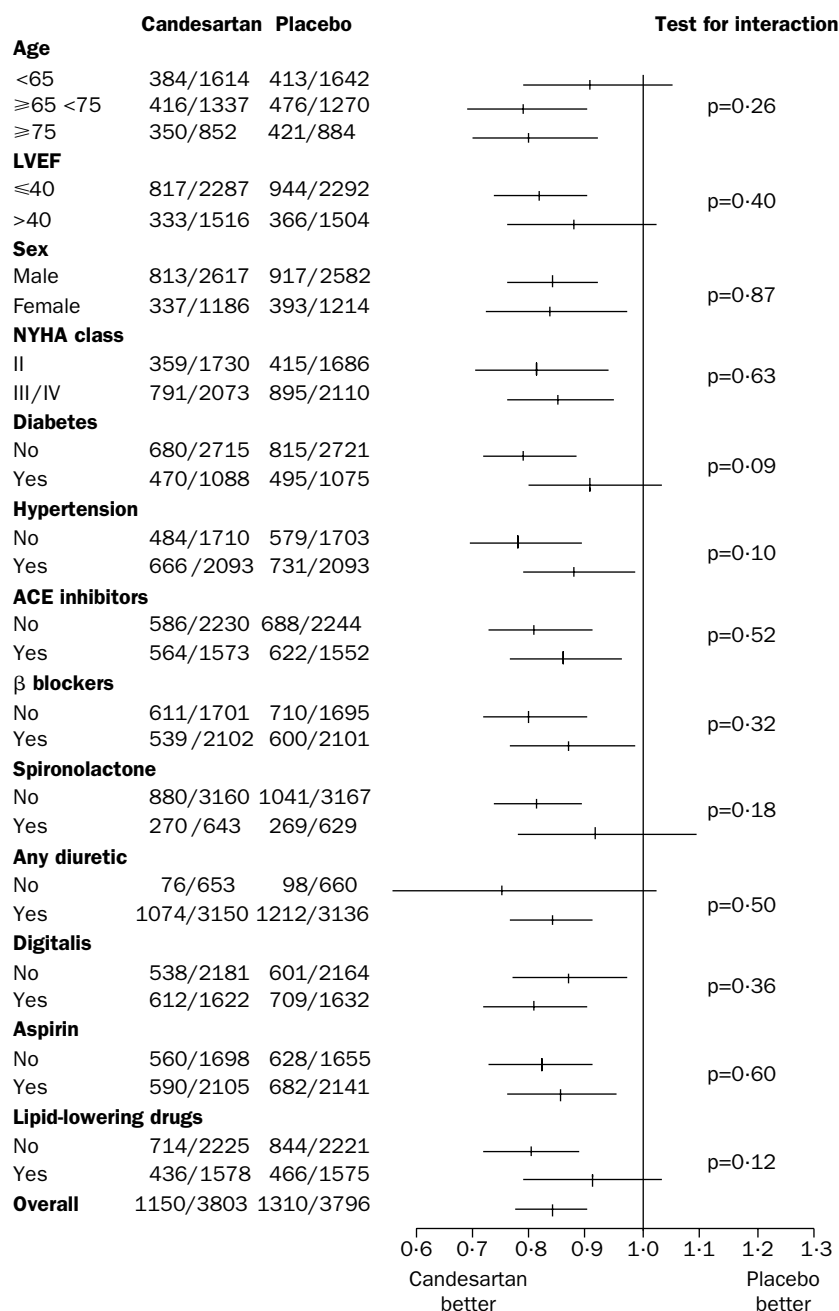


Figure 5: Overall effect of candesartan on cardiovascular death or first admission for CHF in prespecified subgroups

Point estimates of hazard ratios given with 95% CI. p values are for heterogeneity.

	Candesartan (n=3803)	Placebo (n=3796)	p
<b>Cause of discontinuation</b>			
Hypotension	132 (3.5%)	66 (1.7%)	<0.0001
Increase in serum creatinine	234 (6.2%)	115 (3.0)	<0.0001
Hyperkalaemia	85 (2.2%)	21 (0.6%)	<0.0001
Any adverse event or laboratory abnormality	797 (21.0%)	633 (16.7)	<0.0001

Table 3: Permanent study-drug discontinuations for adverse events

strongly affected by left-ventricular systolic function. The annual cardiovascular death rate among the placebo group who had reduced LVEF was around 9%<sup>22,23</sup> and was only 4% in the placebo group of CHARM-Preserved.<sup>24</sup> However, the annual non-cardiovascular death rate of about 2% per year in the placebo group was similar in all component trials. In the patients with LVEF higher than 40%, who had a substantially lower risk of dying of a cardiovascular cause than did patients with lower LVEF, candesartan did not seem to alter survival. However, the absence of heterogeneity in treatment effect across trials and by LVEF, and the reduction in hospital admissions for heart failure in this lower-risk group, does provide an indication that worthwhile clinical benefits were derived from candesartan.

Our prespecified analysis of the mortality results from the two low LVEF trials shows a clear prolongation in survival with candesartan, a significant reduction in all deaths, and a 16% lower rate of cardiovascular death. This reduction in cardiovascular deaths was complemented by significant reductions in hospital admissions for the management of heart failure in all component trials.

The concept that inhibition of the renin-angiotensin system by blockade at the angiotensin II type 1 receptor can result in more complete inhibition of the adverse cardiovascular effects of angiotensin II while leaving unopposed other potentially desirable actions modulated by different angiotensin II receptors has stimulated much interest and clinical investigation. Angiotensin-receptor blockers effectively reduce important non-fatal clinical events in hypertensive patients who have diabetes and nephropathy,<sup>25,26</sup> hypertensive patients with electrocardiographic evidence of left-ventricular hypertrophy,<sup>27</sup> elderly patients with hypertension,<sup>28</sup> and those with symptomatic heart failure and depressed ejection fraction.<sup>29</sup> However, a survival advantage produced by angiotensin-receptor blockers in patients with heart failure and reduced LVEF has not been clearly shown,<sup>29,30</sup> nor in any other high-risk population studied. We show that candesartan offers survival benefits in patients with CHF and reduced LVEF. However, we cannot tell to what extent this improvement in survival was related to the 32 mg daily target dose of candesartan or other potentially distinctive pharmacological properties.<sup>31</sup>

In patients with heart failure and reduced LVEF, it has been suggested that additional survival benefits could not be achieved with angiotensin-receptor blockers among those already taking proven effective treatments, including angiotensin-converting-enzyme inhibitors and  $\beta$  blockers.<sup>32</sup> Our two cohorts of patients with symptomatic heart failure (LVEF  $\leq$ 40%) prespecified by use of angiotensin-converting-enzyme inhibitor and with substantial  $\beta$ -blocker use, is particularly well suited to address this question. The reductions in cardiovascular death with candesartan were similar in patients taking angiotensin-converting-enzyme inhibitors and not taking them because of intolerance. Similarly, the similarity of

clinical-outcome benefits irrespective of  $\beta$  blocker use suggests that candesartan offers additive benefits and complementary mechanisms to these other proven treatments.

The primary outcome of all the component CHARM trials, time to cardiovascular death or adjudicated hospital admission for CHF, was consistently reduced in symptomatic heart-failure patients. This finding, based on more than 20 000 patient-years and more than 2450 events, is robust, and suggests that patients who have symptomatic heart failure will derive important clinical benefits from candesartan. The absence of heterogeneity in results underscores that this benefit was achieved across a broad spectrum of patients. Subgroup analyses must be interpreted cautiously since the most rigorous test of the study hypothesis is derived from the entire population, in which consistency of this benefit was seen. Similar reductions in mortality and morbidity outcomes with the use of candesartan were obtained in women and men, those with and without diabetes, and importantly, across age-groups, a substantial number of patients being older than 75 years. The beneficial effects of candesartan in the CHARM programme were not altered by baseline use of  $\beta$  blockers, spironolactone, digoxin, aspirin, and lipid-lowering treatments. This added efficacy on top of  $\beta$  blockers is particularly noteworthy, since 55% of CHARM patients at baseline were receiving these drugs, and a previous subgroup analysis from the Valsartan Heart Failure Trial<sup>29</sup> suggested less benefit of an angiotensin-receptor blocker in patients already receiving  $\beta$  blockers.

The use of candesartan in patients with symptomatic heart failure did not significantly reduce the risk of myocardial infarction, stroke, or use of coronary revascularisation procedures. However, the significant benefits of candesartan treatment were maintained when these non-fatal cardiovascular events were incorporated with admission to hospital for heart failure and cardiovascular death in a prespecified analysis of time to first event. Lowering of blood pressure was more pronounced in CHARM-Preserved than in the other component trials and did not seem to be related to improved clinical outcome. The frequency of new diabetes was lower in the candesartan group than in the placebo group, which is an effect that has been seen in other large populations treated with inhibitors of angiotensin-converting enzyme<sup>33</sup> and angiotensin-receptor blockers.<sup>27,28</sup>

Candesartan was generally well tolerated but was associated with a greater occurrence of discontinuation of study medication than was placebo because of hypotension, hyperkalaemia, and an increase in serum creatinine, underscoring the need to monitor patients. Although more cancer deaths occurred in the candesartan group, we attributed this imbalance to the play of chance, since the investigator-reported rate of non-fatal neoplasms did not differ between treatment groups. Moreover, including CHARM together with the entire previous candesartan placebo-controlled trial experience (AstraZeneca, data on file), there were 523 (144 fatal) investigator-reported neoplasms, including cancers, during 20 692 patient-years of exposure to candesartan compared with 491 (125 fatal) in 20 135 patient-years with placebo ( $p=0.6$  and  $p=0.4$ , respectively). No consistent differences in fatal or non-fatal neoplasms at different sites have been noted between candesartan and placebo.

Our findings show that candesartan, given in titrated doses as tolerated, can prolong survival, particularly in patients with LVEF of 40% or less, and provide

incremental clinical benefits across the broad spectrum of patients with symptomatic heart failure, including reductions in hospital admissions for heart failure and prevention of diabetes. This effect is consistent for the combined cardiovascular mortality and morbidity outcome, irrespective of other effective concomitant treatments, ejection fraction, age, and sex. The clinical effectiveness we report for candesartan in the treatment of chronic heart failure offers the opportunity to further reduce cardiovascular mortality and morbidity in this expanding segment of our ageing population.

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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 served as consultant and received research grants from AstraZeneca. P Held, E L Michelson, and B Olofsson are employees of AstraZeneca.

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#### References

- 1 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**: 1429–35.
- 2 The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; **325**: 293–302.
- 3 Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995; **273**: 1450–56.
- 4 Packer M, Bristow MR, Cohn JN, et al, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996; **334**: 1349–55.
- 5 CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**: 9–13.
- 6 MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353**: 2001–07.
- 7 Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002; **106**: 2194–99.
- 8 Pitt B, Zannad F, Remme WJ, et al, for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**: 709–17.
- 9 Bart BA, Ertl G, Held P, et al. Contemporary management of patients with left ventricular systolic dysfunction: results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) registry. *Eur Heart J* 1999; **20**: 1182–90.
- 10 MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation* 2000; **102**: 1126–31.
- 11 Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**: 1397–402.
- 12 Swedberg K, Köster M, Rosén M, Schaufelberger M, Rosengren A. Decreasing one-year mortality from heart failure in Sweden: data from the Swedish Hospital Discharge Registry—1988 to 2000. *J Am Coll Cardiol* 2003; **41** (suppl A): 190a (abstr).
- 13 Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003; **89**: 49–53.
- 14 Redfield MM. Heart failure: an epidemic of uncertain proportions. *N Engl J Med* 2002; **347**: 1442–44.
- 15 Braunwald E. Shattuck lecture: cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; **337**: 1360–69.
- 16 American Heart Association. Heart disease and stroke statistics: 2003 updates. Dallas, TX: American Heart Association, 2002.
- 17 Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003; **348**: 2007–18.
- 18 Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996; **334**: 1649–54.
- 19 Swedberg K, Pfeffer M, Granger C, et al, for the CHARM-Programme Investigators. Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM)—rationale and design. *J Card Fail* 1999; **5**: 276–82.
- 20 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, for the The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342**: 145–53.
- 21 McMurray J, Östergren J, Pfeffer M, et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail* 2003; **5**: 261–70.
- 22 Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function and intolerant to ACE inhibitors: the CHARM-Alternative Trial. *Lancet* 2003 **362**: 772–76.
- 23 McMurray JJV, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function treated with an ACE inhibitor: the CHARM-Added trial. *Lancet* 2003 **362**: 767–71.
- 24 Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left ventricular systolic function: the CHARM-Preserved Trial. *Lancet* 2003 **362**: 777–81.
- 25 Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851–60.
- 26 Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–69.
- 27 Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
- 28 Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**: 875–86.
- 29 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667–75.
- 30 Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial: the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**: 1582–87.
- 31 Nishikawa K, Naka T, Chatani F, Yoshimura Y. Candesartan cilxetil: a review of its preclinical pharmacology. *J Hum Hypertens* 1997; **11** (suppl 2): S9–17.
- 32 Massie BM. Neurohormonal blockade in chronic heart failure: how much is enough? Can there be too much? *J Am Coll Cardiol* 2002; **39**: 79–82.
- 33 Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. *JAMA* 2001; **286**: 1882–85.