

Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial

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Summary

Background Half of patients with chronic heart failure (CHF) have preserved left-ventricular ejection fraction (LVEF), but few treatments have specifically been assessed in such patients. In previous studies of patients with CHF and low LVEF or vascular disease and preserved LVEF, inhibition of the renin-angiotensin system is beneficial. We investigated the effect of addition of an angiotensin-receptor blocker to current treatments.

Methods Between March, 1999, and July, 2000, we randomly assigned 3023 patients candesartan (n=1514, target dose 32 mg once daily) or matching placebo (n=1509). Patients had New York Heart Association functional class II–IV CHF and LVEF higher than 40%. The primary outcome was cardiovascular death or admission to hospital for CHF. Analysis was done by intention to treat.

Findings Median follow-up was 36.6 months. 333 (22%) patients in the candesartan and 366 (24%) in the placebo group experienced the primary outcome (unadjusted hazard ratio 0.89 [95% CI 0.77–1.03], $p=0.118$; covariate adjusted 0.86 [0.74–1.0], $p=0.051$). Cardiovascular death did not differ between groups (170 vs 170), but fewer patients in the candesartan group than in the placebo group were admitted to hospital for CHF once (230 vs 279, $p=0.017$) or multiple times. Composite outcomes that included non-fatal myocardial infarction and non-fatal stroke showed similar results to the primary composite (388 vs 429; unadjusted 0.88 [0.77–1.01], $p=0.078$; covariate adjusted 0.86 [0.75–0.99], $p=0.037$).

Interpretation Candesartan has a moderate impact in preventing admissions for CHF among patients who have heart failure and LVEF higher than 40%.

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Introduction

Around 50% of patients with chronic heart failure (CHF) do not have low left-ventricular ejection fraction (LVEF).¹ Although patients with LVEF of 40% or less have poorer outcomes than do patients with higher values, even those with heart failure and LVEF higher than 40% (preserved LVEF) have high rates of mortality and admission to hospital for CHF.¹ In many studies researchers have assessed the effects of angiotensin-converting-enzyme inhibitors,² β blockers,^{3,4} and angiotensin-receptor blockers⁵ in patients with low LVEF but, other than digoxin in one trial,⁶ few treatments have been specifically assessed in CHF patients with LVEF higher than 40%. Consequently, many of the guidelines for the treatment of heart failure do not address this group of patients or simply extrapolate the findings from trials in individuals with low LVEF and heart failure. Whether such extrapolations are justified is unknown.

Inhibitors of angiotensin-converting enzyme reduce mortality and morbidity in patients at high risk of cardiovascular events with preserved LVEF and no CHF.⁷ Therefore, in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved study, part of the CHARM programme,⁸ we tested the hypothesis that another inhibitor of the renin-angiotensin system, an angiotensin-receptor blocker, candesartan, would be of benefit in patients with CHF and preserved LVEF. The primary goal was to assess the effects of candesartan on the composite outcome of cardiovascular mortality or admission to hospital for worsening CHF.

Patients and methods

The design of the CHARM programme has been described in detail elsewhere, including randomisation, monitoring, and follow-up.^{8–10}

Patients

Eligible patients were aged 18 years or older, had New York Heart Association functional class II–IV of at least 4 weeks' duration, had a history of hospital admission for a cardiac reason, and had LVEF higher than 40%. Physicians were free to prescribe all treatments other than angiotensin-receptor blockers. Initially, angiotensin-converting-enzyme inhibitors were not allowed as concomitant treatment, but after publication of the Heart Outcomes Prevention Evaluation trial results,⁷ their use was optional in appropriate patients. The study was approved by the ethics committee or institutional review boards in all participating centres and all patients gave written informed consent.

Methods

We enrolled patients between March, 1999, and July, 2000, in 618 centres in 26 countries. We randomly assigned patients, in a double-blind way, candesartan or

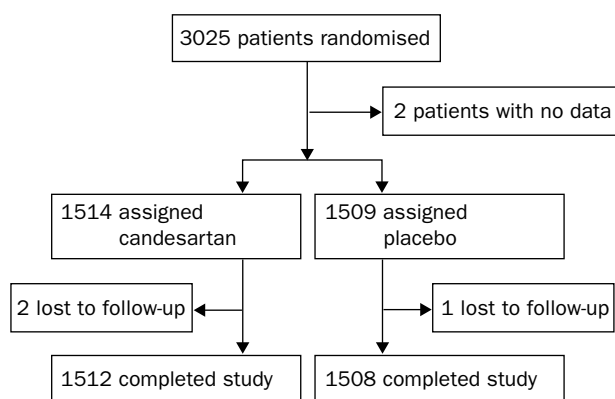


Figure 1: Trial profile

matching placebo (figure 1), which could be started at 4 or 8 mg once daily, the assignment code being held by an independent centre and 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 made at baseline, 6 weeks, and yearly thereafter for safety reasons.

A committee unaware of treatment assignment and which component of the CHARM programme was being undertaken adjudicated the cause of death, first myocardial infarctions, and first hospital admissions for heart failure. The adjudicated outcomes were the basis of the formal analyses, but we had specified that investigator-reported events would also be analysed. 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

	Candesartan (n=1514)	Placebo (n=1509)
Patients' characteristics		
Mean (SD) age (years)	67.2 (11.1)	67.1 (11.1)
≥75 years	407 (26.9%)	400 (26.5%)
Men/women	920 (60.8%)/ 594 (39.2%)	891 (59.0%)/ 618 (41.0%)
Ethnic origin		
European	1374 (90.8%)	1393 (92.3%)
Black	69 (4.6%)	57 (3.8%)
Other	71 (4.6%)	59 (3.9%)
Heart-disease risk factors		
NYHA class		
II	931 (61.5%)	905 (60.0%)
III	556 (36.7%)	584 (38.7%)
IV	27 (1.8%)	20 (1.3%)
Mean (SD) LVEF mean (%)	54.0 (9.4)	54.1 (9.4)
41–49%	536 (35.4%)	536 (35.5%)
50–59%	545 (36.0%)	511 (33.9%)
≥60%	433 (28.6%)	462 (30.6%)
Heart rate (beats/min)	71.2 (12.4)	71.4 (12.5)
Mean (SD) blood pressure (mm Hg)		
Systolic	136.0 (18.6)	136.3 (18.3)
Diastolic	77.8 (10.9)	77.8 (10.5)
Mean (SD) body-mass index (kg/m ²)	29.3 (5.9)	29.0 (5.6)
Heart-failure cause*		
Ischaemic	854 (56.4%)	852 (56.5%)
Idiopathic	131 (8.7%)	132 (8.7%)
Hypertensive	337 (22.3%)	347 (23.0%)
Medical history		
Hospital admission for CHF	1038 (68.6%)	1038 (68.8%)
Myocardial infarction	681 (45.0%)	659 (43.7%)
Current angina pectoris	396 (26.2%)	436 (28.9%)
Stroke	140 (9.2%)	128 (8.5%)
Diabetes mellitus	434 (28.7%)	423 (28.0%)
Hypertension	984 (65.0%)	959 (63.6%)
Atrial fibrillation	439 (29.0%)	442 (29.3%)
Pacemaker	104 (6.9%)	117 (7.8%)
Current smoker	222 (14.7%)	187 (12.4%)
PCI	235 (15.5%)	291 (19.3%)
CABG	326 (21.5%)	328 (21.7%)
Implantable cardioverter defibrillator	11 (0.7%)	12 (0.8%)
Cancer	130 (8.6%)	96 (6.4%)
Signs and symptoms of CHF		
Oedema	459 (30.3%)	442 (29.3%)
Orthopnoea	286 (18.9%)	303 (20.1%)
Paroxysmal nocturnal dyspnoea	184 (12.2%)	181 (12.0%)
Rest dyspnoea	144 (9.5%)	152 (10.1%)
Third heart sound	81 (5.4%)	81 (5.4%)
Basal crackles	232 (15.3%)	227 (15.0%)
Jugular venous pressure >6 cm	100 (6.6%)	122 (8.1%)
Cardiomegaly	238 (15.7%)	256 (17.0%)
Upper-zone redistribution	31 (2.0%)	54 (3.6%)
Medical treatment		
ACE inhibitor	296 (19.6%)	280 (18.6%)
β blocker	847 (55.9%)	837 (55.5%)
Diuretic	1138 (75.2%)	1121 (74.3%)
Spironolactone	171 (11.3%)	181 (12.0%)
Digoxin/digitalis glycoside	432 (28.5%)	410 (27.2%)
Calcium antagonist	467 (30.8%)	477 (31.6%)
Other vasodilators	566 (37.4%)	594 (39.4%)
Oral anticoagulants	378 (25.0%)	370 (24.5%)
Antiarrhythmic agent	153 (10.1%)	147 (9.7%)
Aspirin	875 (57.8%)	887 (58.8%)
Other antiplatelet agent	81 (5.4%)	75 (5.0%)
Lipid-lowering drug	617 (40.8%)	645 (42.7%)

NYHA=New York Heart Association. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. All baseline variables listed, except ethnic origin, heart-failure cause, signs and symptoms of CHF, 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

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

	Candesartan (n=1514)	Placebo (n=1509)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	333 (22.0%)	366 (24.3%)	0.89 (0.77–1.03)	0.118	0.86 (0.74–1.00)	0.051
Cardiovascular death	170 (11.2%)	170 (11.3%)	0.99 (0.80–1.22)	0.918	0.95 (0.76–1.18)	0.635
Hospital admission for CHF	241 (15.9%)	276 (18.3%)	0.85 (0.72–1.01)	0.072	0.84 (0.70–1.00)	0.047
Cardiovascular death, hospital admission for CHF, MI	365 (24.1%)	399 (26.4%)	0.90 (0.78–1.03)	0.126	0.87 (0.75–1.00)	0.051
Cardiovascular death, hospital admission for CHF, MI, stroke	388 (25.6%)	429 (28.4%)	0.88 (0.77–1.01)	0.078	0.86 (0.75–0.99)	0.037
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	460 (30.4%)	497 (32.9%)	0.91 (0.80–1.03)	0.123	0.91 (0.80–1.03)	0.130

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

Table 2: **Primary and secondary outcomes**

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

Assuming an annual event rate for the primary outcome of 11%, the planned sample size of 2900 patients would provide a power of 80% to detect a relative risk reduction of 18% at an α level of 0.05. If, however, the relative risk reduction was 16%, the power would decrease to 70%.

We used two-sided p values and took $p < 0.05$ to be significant. A covariate-adjusted model was also fitted with use of prespecified baseline characteristics (table 1) to adjust for imbalances in factors that might affect outcomes. Investigator-reported outcomes were used as a supportive analysis and new onset of diabetes mellitus was a prespecified additional outcome.

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

3025 patients were enrolled, including two patients who mistakenly received randomisation numbers but had no other data recorded and never received study medication. Therefore, 3023 patients were randomised—1514 were assigned candesartan and 1509 placebo. Two candesartan patients and one placebo patient were lost to follow-up (figure 1). Follow-up was concluded on March 31, 2003, with a median duration of 36.6 months. Baseline characteristics are presented in table 1. Several baseline characteristics associated with a poorer prognosis were slightly more common in the candesartan group than in the placebo group: previous myocardial infarction, stroke, current smoking, hypertension, diabetes, cancer, and use

	Candesartan (n=1514)	Placebo (n=1509)
Number of patients (%)		
None	1284 (84.8%)	1230 (81.5%)
1	132 (8.7%)	157 (10.4%)
2	54 (3.6%)	59 (3.9%)
≥3	44 (2.9%)	63 (4.2%)
Number of patients admitted to hospital (number of admissions)	230 (402)	279 (566)

*Investigator reported, with CHF as primary reason ($p=0.014$ for distribution).

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

of digitalis and diuretics. Conversely, various characteristics or treatments associated with lower mortality were slightly less common in the candesartan group than in the placebo group, including previous percutaneous coronary intervention, and use of lipid-lowering drugs, aspirin, and spironolactone (table 1).

At baseline 296 (20%) in the candesartan group and 280 (19%) in the placebo group were taking angiotensin-converting-enzyme inhibitors, and 847 (56%) and 837 (56%) were taking β blockers. The doses (number of patients) of the most commonly used β blockers for candesartan and placebo, respectively, were: metoprolol 87 mg and 94 mg (393 and 379); atenolol 53 mg and 53 mg (189 and 173); carvedilol 31 mg and 34 mg (96 and 109); bisoprolol 6 mg and 6 mg (72 and 65); sotalol 152 mg and 177 mg (36 and 64); various other β blockers (57 and 49). By the end of the study, 298 (20%) in the candesartan and 340 (23%) in the placebo group were receiving angiotensin-converting-enzyme inhibitors, 712 (47%) and 748 (50%) were receiving β blockers, and 136 (9%) and 201 (13%) were receiving spironolactone. Non-study angiotensin-receptor blockers were used in 3% of patients in each of the two groups.

The primary outcome of cardiovascular death or admission to hospital for heart failure occurred in 333 (22%) patients in the candesartan group and 366 (24%) in the placebo group [relative risk reduction 11%, adjusted hazard ratio 0.89 [95% CI 0.77–1.03], $p=0.118$; covariate adjusted 0.86 [0.74–1.00], $p=0.051$; tables 2 and 3 and figure 2). The annual event rates were 8.1% in the candesartan group and 9.1% in the placebo group.

The analyses of various prespecified composites are summarised in table 2 and generally yielded results similar to the effects on the primary outcome. The number of individuals experiencing cardiovascular deaths were

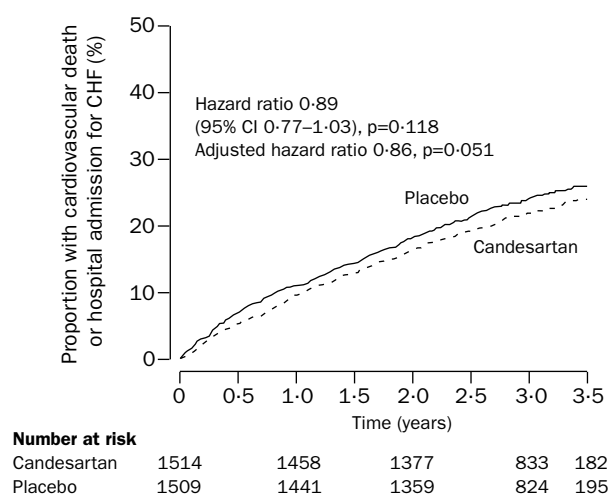


Figure 2: **Time to cardiovascular death or hospital admission for CHF**

	Candesartan (n=1514)	Placebo (n=1509)	p
Cause of discontinuation			
Hypotension	37 (2.4%)	17 (1.1%)	0.009
Increase in creatinine	72 (4.8%)	36 (2.4%)	0.0005
Hyperkalaemia	22 (1.5%)	9 (0.6%)	0.029
Any adverse event or laboratory abnormality	270 (17.8%)	204 (13.5%)	0.001

Table 4: Permanent study-drug discontinuation for adverse events

similar in the two treatment groups (170 *vs* 170, 0.99 [0.80–1.22], $p=0.92$), as were non-cardiovascular deaths (74 *vs* 67, 1.10 [0.79–1.52], $p=0.59$).

The number of individuals who were admitted to hospital for CHF (as a primary cause reported by the investigator) at least once was lower in the candesartan group than in the placebo group (230 *vs* 279; $p=0.017$). In addition, the number of individuals admitted more than once for heart failure was also lower in the candesartan group (98 *vs* 122; $p=0.093$); therefore, the total number of admissions for CHF was 402 in the candesartan group and 566 in the placebo group ($p=0.014$, table 3). The total number of patients with myocardial infarction was: candesartan 57, placebo 73 ($p=0.15$); stroke: candesartan 58, placebo 63 ($p=0.60$); and coronary revascularisation procedures: candesartan 118, placebo 116 ($p=0.96$). In the candesartan group, 912 patients had 2510 admissions for any reason and 922 placebo patients had 2545 admissions ($p=0.63$ for patients and $p=0.79$ for admissions).

Directionally similar results were obtained in the additional prespecified analyses with use of the investigator-reported outcomes. However, the reduction in the composite outcome of cardiovascular death and admission to hospital for heart failure was clearer than in the formal analysis and nominally significant (324 in the candesartan group *vs* 372 in the placebo group, 0.85 [0.73–0.98]; $p=0.028$). 40% fewer individuals were diagnosed as having new diabetes in the candesartan group than in the placebo group (47 *vs* 77, 0.60 [0.41–0.86], $p=0.005$). There was no heterogeneity of treatment effects in the subgroups, which are described in detail in the overall results of the CHARM programme.¹⁰

The initial dose of study medication was 4 mg in 2260 (75%) and 8 mg in 763 (25%) patients. By 6 months, study medication had been discontinued in 157 (11%) candesartan patients and 113 (8%) placebo patients ($p<0.007$). Of those taking study medication at that time, 876 (67%) of candesartan patients were at the target dose of 32 mg once daily and 1061 (79%) of the placebo group were titrated to the same dose. By 6 months, the mean daily doses were 25.0 mg and 27.8 mg, respectively, in the candesartan and placebo groups, and were similar at subsequent visits. By the end of the study, 268 (22%) of the survivors in the candesartan group and 220 (18%) in the placebo group were no longer taking study medication. 270 (18%) patients in the candesartan group and 204 (14%) in the placebo group had permanently discontinued study medications for adverse events or abnormal laboratory values ($p=0.001$, table 4).

In 33 (6%) of candesartan patients and 15 (3%) of placebo patients, creatinine at least doubled on surveillance laboratory assessments ($p=0.007$). Potassium concentrations of 6 mmol/L or higher were noted in ten (2%) candesartan and six (1%) placebo patients ($p=0.32$). No other unexpected or clinically important changes in laboratory values were seen. By 6 months, blood pressure was lowered from baseline by 6.9 mm Hg systolic and 2.9 mm Hg diastolic more in the candesartan group than in the placebo group ($p<0.0001$).

Discussion

We show a trend in favour of candesartan towards fewer cardiovascular outcomes among patients with preserved LVEF, although the difference in the composite of cardiovascular mortality or CHF hospital admissions between the candesartan and placebo group is moderate and of borderline significance. The numbers of individuals admitted one or more times for heart failure was reduced, which reinforces the fact that candesartan is of some clinical benefit in this population.

Heart failure at entry to the trial was diagnosed based on the physician's judgment, but we documented various clinical characteristics that are part of the syndrome of heart failure. Compared with patients in the two trials of low LVEF in the CHARM programme,^{11,12} patients with preserved LVEF were older (mean age 67.2 years), a higher proportion were women (40%), were more likely to be in New York Heart Association class II (61%), have a history of hypertension (64%), and less likely to report having a previous myocardial infarction (44%). The proportion of patients who had peripheral oedema was higher (30%), whereas the proportions with a third heart sound (5%), cardiomegaly (16%), and upper-lobe vascular distribution (3%) were lower than among patients in the other two trials. Fewer patients received digoxin (28%), diuretics (75%), spironolactone (12%), or oral anticoagulants (25%). However, two-thirds of the patients had been previously admitted to hospital for heart failure. These characteristics at entry suggest that the patients we studied probably had heart failure.

The unadjusted p value for the comparison of the adjudicated primary outcome was around 0.10, whereas the adjusted p value, using pre-specified variables in a Cox's regression model, was 0.051, with an estimate of the apparent treatment effect increasing from 11% to 14%. This finding is similar to the results based on the events reported by the clinical site investigators (15%) and is closer to the results of the other two CHARM component trials (15% and 23% relative risk reductions in the CHARM-Added and CHARM-Alternative trials, respectively).

Our results should be viewed in the context of the whole CHARM programme, and the effects of candesartan on the primary composite outcome in the component trials were consistent in direction, with no evidence of statistical heterogeneity. Additionally, the clear differences in investigator-reported outcomes provide further direct evidence of the benefit of candesartan among patients with preserved LVEF. Therefore, the borderline statistical difference between candesartan and placebo in this study is supported by additional analyses within the trial and the clear results in the two companion trials.

In contrast to the effects among patients with low LVEF, we noted no apparent impact on cardiovascular death, and the benefit we did see was chiefly in preventing admissions to hospital for CHF. However, the CI for the impact on cardiovascular death are wide, and longer treatment and follow-up might be necessary for the full effects of candesartan to emerge in this population.¹³

We found a significant reduction in the development of new diabetes. Although the effects seem larger in this trial than in the other two CHARM component trials, the differences in effect size could have been exaggerated by chance. The real benefits might be closer to those seen in the overall programme—ie, a risk reduction of 22% rather than the apparent 40% we report. Nevertheless, this impact in preventing diabetes is similar to that seen in the Heart Outcomes Prevention Evaluation trial¹⁴ with

ramipril, and in the Losartan Intervention For Endpoint reduction in hypertension study¹⁵ with losartan. Collectively, the consistent findings from these studies and CHARM suggest that blocking the renin-angiotensin system with inhibitors of angiotensin-converting enzyme or angiotensin-receptor blockers prevents the progression to diabetes. We saw an increase in the proportion of patients who had raised creatinine or hyperkalaemia, reinforcing the need for monitoring.

Current recommendations for the management of patients with preserved LVEF and heart failure are based on sparse data and extrapolations from trials involving patients with related disorders (eg, low LVEF and CHF or preserved LVEF and no CHF). Our trial provides direct information on this large group of patients with heart failure, albeit a moderate benefit, based on statistically borderline results. Among patients with CHF and preserved LVEF who have no contraindications, however, candesartan reduces the number of hospital admissions for CHF.

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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