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

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Summary

Background Angiotensin-converting-enzyme (ACE) inhibitors improve outcome of patients with chronic heart failure (CHF). A substantial proportion of patients, however, experience no benefit from ACE inhibitors because of previous intolerance. We aimed to find out whether candesartan, an angiotensin-receptor blocker, could improve outcome in such patients not taking an ACE inhibitor.

Methods Between March, 1999, and March, 2001, we enrolled 2028 patients with symptomatic heart failure and left-ventricular ejection fraction 40% or less who were not receiving ACE inhibitors because of previous intolerance. Patients were randomly assigned candesartan (target dose 32 mg once daily) or matching placebo. The primary outcome of the study was the composite of cardiovascular death or hospital admission for CHF. Analysis was by intention to treat.

Findings The most common manifestation of ACE-inhibitor intolerance was cough (72%), followed by symptomatic hypotension (13%) and renal dysfunction (12%). During a median follow-up of 33·7 months, 334 (33%) of 1013 patients in the candesartan group and 406 (40%) of 1015 in the placebo group had cardiovascular death or hospital admission for CHF (unadjusted hazard ratio 0·77 [95% CI 0·67–0·89], p=0·0004; covariate adjusted 0·70 [0·60–0·81], p<0·0001). Each component of the primary outcome was reduced, as was the total number of hospital admissions for CHF. Study-drug discontinuation rates were similar in the candesartan (30%) and placebo (29%) groups.

Interpretation Candesartan was generally well tolerated and reduced cardiovascular mortality and morbidity in patients with symptomatic chronic heart failure and intolerance to ACE inhibitors.

Lancet 2003; **362:** 772–776. Published online Sept 1, 2003
http://image.thelancet.com/extras/03art7418web.pdf
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Introduction

Angiotensin-converting-enzyme (ACE) inhibitors reduce mortality and morbidity among patients with chronic heart failure (CHF) and left-ventricular systolic dysfunction.[1] However, more than one in five patients with left-ventricular systolic dysfunction are not receiving ACE inhibitors. In a registry in Europe and North America, 20% of patients with reduced left-ventricular ejection fraction were not receiving ACE inhibitors, and 9% had a history of ACE-inhibitor intolerance.[2] In European registries, among patients with left-ventricular systolic dysfunction and heart failure, 20% at the time of hospital discharge[3] and 29% in primary care[4] were not receiving ACE inhibitors. Although the use of ACE inhibitors has been steadily and appropriately increasing, intolerance to these drugs frequently prevents their use. The most common manifestation of ACE-inhibitor intolerance leading to discontinuation is cough, representing around 30% to 65% of those people stopping.[2,5,6] The most consistent predictors in patients of non-use of ACE inhibitors are older age and female sex.[2–4]

The use of angiotensin-receptor blockers for patients intolerant to ACE inhibitors is an alternative approach to inhibiting the renin-angiotensin-aldosterone system in CHF. Although short-term treatment with angiotensin-receptor blockers seems to be well tolerated in CHF patients intolerant to ACE inhibitors[6] and may improve symptoms and exercise tolerance in patients not taking ACE inhibitors,[7] their long-term clinical effectiveness on cardiovascular outcomes is not well established.

In the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Alternative study, part of an overall CHARM programme,[8,9] we investigated whether an angiotensin-receptor blocker, candesartan, improves clinical outcome in a population of patients intolerant to ACE inhibitors. The primary objective was to assess the effects of candesartan on the risk of cardiovascular death or hospital admission for heart failure in patients with reduced left-ventricular ejection fraction and symptomatic heart failure not currently treated with an ACE inhibitor because of previous intolerance.

Patients and methods

The design of the CHARM programme has been described in detail elsewhere, including randomisation, monitoring, and follow-up.[8,10]

Patients

Patients aged 18 years and older who had symptomatic heart failure (New York Heart Association Class II–IV) of at least 4 weeks' duration, left-ventricular ejection fraction 40% or less, and intolerance to ACE inhibitors were eligible. We enrolled patients between March, 1999, and March 2001 in 618 centres in 26 countries. ACE-inhibitor intolerance was defined as a having had an ACE

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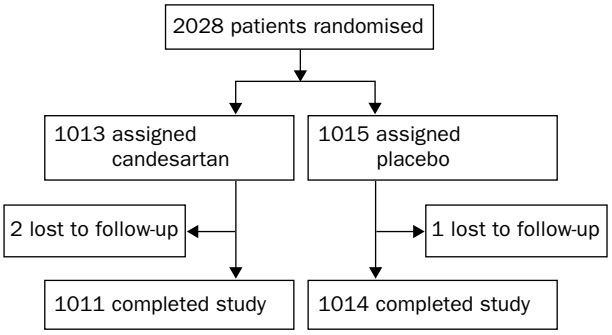

Figure 1: **Trial profile**

inhibitor previously discontinued by a physician because of intolerance, with the specific cause classified. The study was approved by national and local ethics committees in all participating centres, and all patients provided informed consent before randomisation.

Methods

We randomly assigned patients candesartan or matching placebo in a double-blind way (figure 1), the assignment code being held by an independent centre and the data safety monitoring board. Starting dose was 4 mg or 8 mg once daily, and the dose was doubled, as tolerated, at a minimum of every 2 weeks, to a target dose of 32 mg once daily. 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. Monitoring of serum potassium and creatinine was recommended during up-titration. In a subset of patients enrolled in North America, routine laboratory assessments to monitor patients' safety were done at baseline, 6 weeks, and 14, 26, and 38 months.

The primary outcome was cardiovascular death or unplanned admission to hospital for the management of worsening CHF. Prespecified secondary outcomes included: 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.

	Candesartan (n=1013)	Placebo (n=1015)
Patients' characteristics		
Mean (SD) age (years)	66·3 (11·0)	66·8 (10·5)
⩾75 years	233 (23·0%)	239 (23·5%)
Men/women	691 (68·2%)/ 322 (31·8%)	691 (68·1%)/ 324 (31·9%)
Ethnic origin		
European	895 (88·4%)	901 (88·8%)
Black	28 (2·8%)	45 (4·4%)
Other	90 (8·8%)	69 (6·8%)
Heart-disease risk factors		
NYHA class		
II	487 (48·1%)	479 (47·2%)
III	490 (48·4%)	499 (49·2%)
IV	36 (3·6%)	37 (3·6%)
Mean (SD) LVEF (%)	29·8 (7·6)	30·0 (7·2)
Mean (SD) heart rate (beats/min)	75·1 (14·2)	73·7 (13·1)
Mean (SD) blood pressure (mm Hg)		
Systolic	129·9 (19·0)	130·3 (18·5)
Diastolic	76·6 (10·9)	76·9 (10·5)
Mean (SD) body-mass index (kg/m^2)	27·4 (4·9)	27·5 (4·8)
Heart-failure cause*		
Ischaemic	706 (69·7%)	679 (66·9%)
Idiopathic	190 (18·8%)	206 (20·3%)
Hypertensive	58 (5·7%)	73 (7·2%)
Medical history		
Hospital admission for CHF	712 (70·3%)	673 (66·3%)
Myocardial infarction	629 (62·1%)	618 (60·9%)
Current angina pectoris	232 (22·9%)	228 (22·5%)
Stroke	85 (8·4%)	90 (8·9%)
Diabetes mellitus	278 (27·4%)	270 (26·6%)
Hypertension	500 (49·4%)	515 (50·7%)
Atrial fibrillation	254 (25·1%)	261 (25·7%)
Pacemaker	97 (9·6%)	88 (8·7%)
Current smoker	149 (14·7%)	127 (12·5%)
PCI	156 (15·4%)	170 (16·7%)
CABG	269 (26·6%)	244 (24·0%)
Implantable cardioverter defibrillator	40 (3·9%)	28 (2·8%)
Cancer	62 (6·1%)	72 (7·1%)
Medical treatment		
Diuretic	864 (85·3%)	869 (85·6%)
β blocker	553 (54·6%)	553 (54·5%)
Spironolactone	250 (24·7%)	233 (23·0%)
Digoxin/digitalis glycoside	455 (44·9%)	469 (46·2%)
Calcium antagonist	178 (17·6%)	153 (15·1%)
Other vasodilators	427 (42·2%)	441 (43·4%)
Oral anticoagulant	320 (31·6%)	299 (29·5%)
Antiarrhythmic agent	124 (12·2%)	149 (14·7%)
Aspirin	578 (57·1%)	595 (58·6%)
Other antiplatelet agent	60 (5·9%)	56 (5·5%)
Lipid-lowering drug	433 (42·7%)	409 (40·3%)
Reason for intolerance		
Cough	704 (69·5%)	751 (74·0%)
Hypotension	143 (14·1%)	119 (11·7%)
Renal dysfunction	134 (13·2%)	100 (9·9%)
Angioedema/anaphylaxis	39 (3·8%)	44 (4·3%)
Other	101 (10·0%)	109 (10·7%)

NYHA=New York Heart Association. LVEF=left-ventricular ejection fraction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. All baseline variables listed, except ethnic origin, heart-failure cause, baseline spironolactone treatment, and reason for intolerance, 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**

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	Candesartan (n=1013)	Placebo (n=1015)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	334 (33·0%)	406 (40·0%)	0·77 (0·67–0·89)	0·0004	0·70 (0·60-0·81)	<0·0001
Cardiovascular death	219 (21·6%)	252 (24·8%)	0·85 (0·71–1·02)	0·072	0·80 (0·66–0·96)	0·02
Hospital admission for CHF	207 (20·4%)	286 (28·2%)	0·68 (0·57–0·81)	<0·0001	0·61 (0·51–0·73)	<0·0001
Cardiovascular death, hospital admission for CHF, MI	353 (34·8%)	420 (41·4%)	0·78 (0·68–0·90)	0·0007	0·72 (0·62–0·83)	<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke	369 (36·4%)	432 (42·6%)	0·80 (0·69–0·91)	0·001	0·74 (0·64–0·85)	<0·0001
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	396 (39·1%)	456 (44·9%)	0·81 (0·71–0·92)	0·002	0·76 (0·66–0·87)	<0·0001

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

Table 2: **Primary and secondary outcomes**

Statistical analysis

The planned sample size of 2000 patients was designed to provide around 80% power to detect an 18% relative reduction in the primary outcome, assuming an annual placebo event rate of 15%. The analysis was based on intention to treat and included all randomised patients. All major outcomes were analysed by time to first event. For the primary analysis we used the logrank test to compare the time-to-event distributions. We estimated the hazard ratios with 95% CI. In addition, a Cox's regression model with treatment and other prospectively defined covariates (table 1) was done to adjust the hazard ratio for prespecified baseline factors that might alter the event rates. We used two-sided p values, and took p<0·05 to be significant.

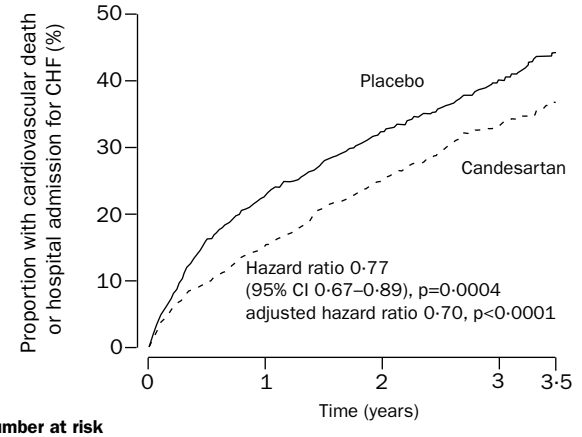
Role of the funding source

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

2028 patients were randomised. Follow-up was concluded on March 31, 2003. The median duration of follow-up was 33·7 months and the vital status at study closure was ascertained in all but three patients (two candesartan and one placebo, figure 1).

The baseline characteristics, including details of background medical treatment, have been previously published[10] and were generally balanced between the treatment groups (table 1). The most common manifestation of ACE-inhibitor intolerance before trial entry was cough (72%), followed by symptomatic hypotension (13%) and renal dysfunction (12%).



Number at risk

Candesartan	1013	929	831	434	122
Placebo	1015	887	798	427	126

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

At baseline, 55% of patients were taking β blockers and 24% spironolactone. At the final visit, 64% in the candesartan group and 67% in the placebo group were taking β blockers, and 25% and 29% spironolactone, respectively. In addition, at the final visit 6% of the candesartan and placebo patients were taking ACE inhibitors, and 9% in each group were taking an open-label angiotensin-receptor blocker.

740 patients experienced the primary outcome of cardiovascular death or hospital admission for CHF: 334 (33%) in the candesartan group and 406 (40%) in the placebo group (table 2). The unadjusted hazard ratio was 0·77 (95% CI 0·67–0·89, p=0·0004), and after covariate adjustment was 0·70 (95% CI 0·60–0·81, p<0·0001; figure 2). The average annual event rates were 13·8% in the candesartan group and 18·2% in the placebo group.

There were consistent reductions in the individual components of the primary outcome of cardiovascular death and of hospital admission for CHF. The unadjusted hazard ratio for cardiovascular death was 0·85 (0·71–1·02, p=0·072), and after covariate adjustment was 0·80 (0·66–0·97, p=0·02). The risk reduction in cardiovascular death and non-fatal cardiovascular outcomes for candesartan was maintained as the composite outcome of cardiovascular death or hospital admission for CHF was expanded in a stepwise way to include non-fatal myocardial infarction, non-fatal stroke, and coronary revascularisation (table 2). The total number of patients who had myocardial infarction was: candesartan 75, placebo 48 (1·52 [1·06–2·18] p=0·025); stroke: candesartan 36, placebo 42 (p=0·42); and coronary revascularisation procedures: candesartan 49, placebo 50 (p=0·79).

There were 265 deaths from any cause in the candesartan group, and 296 in the placebo group (unadjusted 0·87 [0·74–1·03], p=0·11; covariate adjusted 0·83 [0·70–0·99], p=0·033). All-cause mortality or hospital admission for CHF occurred in 371 patients in the candesartan group and 433 in the placebo group (0·80

	Candesartan (n=1013)	Placebo (n= 1015)
Number of patients (%)†		
None	801 (79·1)	724 (71·3)
1	110 (10·9)	155 (15·3)
2	49 (4·8)	65 (6·4)
⩾3	53 (5·2)	71 (7·0)
Number of patients admitted to hospital (number of admissions)	212 (445)	291 (608)

*Investigator reported, with heart failure as primary reason. †p=0·0001 test for difference in distribution of hospital admissions for chronic heart failure.

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

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	Candesartan (n=1013)	Placebo (n=1015)	p
Cause of discontinuation*			
Hypotension			
All	37 (3·7%)	9 (0·9%)	<0·0001
Intolerance due to previous hypotension	13/143 (9·1%)	5/119 (4·2%)	
Increase in creatinine			
All	62 (6·1%)	27 (2·7%)	<0·0001
Intolerance due to previous renal dysfunction	31/134 (23·1%)	12/100 (12%)	
Hyperkalaemia			
All	19 (1·9%)	3 (0·3%)	0·0005
Intolerance due to previous renal dysfunction	8/134 (13·6%)	1/100 (1·0%)	
Cough			
All	2 (0·2%)	4 (0·4%)	0·69
Intolerance due to previous cough	2/704 (0·3%)	4/751 (0·5%)	
Angioedema			
All	1 (0·1%)	0	0·50
Intolerance due to angioedema/anaphylaxis	1/39 (2·6%)	0/44	
Any adverse event or laboratory abnormality	218 (21·5%)	196 (19·3%)	0·23

*More than one reason for discontinuation possible.

Table 4: **Permanent study-drug discontinuation for adverse events, by reason for previous ACE-inhibitor intolerance**

[0·70–0·92], p=0·001). The number of patients admitted to hospital for CHF and the total numbers of hospital admissions primarily for CHF were lower in the candesartan group than in the placebo group (table 3). In the candesartan group, 610 patients had 1718 hospital admissions for any reason, and 643 placebo patients had 1835 hospital admissions (p=0·16 for patients and p=0·06 for admissions). Among patients without a prestudy diagnosis of diabetes, 44 in the candesartan group and 53 in the placebo group developed diabetes (0·79 [0·53–1·18], p=0·254).

The effect of candesartan on cardiovascular death or hospital admission for CHF was generally consistent across prespecified subgroups. No major subgroup showed a significant interaction of subgroup and treatment effect.

The initial dose of study drug was 4 mg in 81% and 8 mg in 19% of patients. At 6 months, the mean daily doses for those taking study drugs were 23 mg for candesartan and 27 mg for placebo. Of patients taking study medication at that time, 59% of the candesartan and 73% of the placebo group reached the target dose of 32 mg once daily. 30% of candesartan and 29% of placebo patients permanently discontinued study drug (p=0·53). By the end of the study, 24% of the candesartan survivors and 22% of the placebo survivors were no longer taking study medication (p=0·49). Reasons for permanent discontinuation are shown in table 4. Patients were more likely to stop taking candesartan than placebo for renal dysfunction, hyperkalaemia, and hypotension. Patients in both groups who had previous intolerance because of renal dysfunction were more likely to have study drug discontinued because of increased creatinine.

Angioedema occurred in three candesartan patients and no placebo patient. None of the three cases was deemed life threatening or led to hospital admission, and in two cases candesartan was continued without recurrence. All three cases occurred in the 39 patients in the candesartan group who had history of ACE-inhibitor intolerance because of angioedema or anaphylaxis. Thus, among patients with history of angioedema on an ACE inhibitor, this event recurred leading to candesartan discontinuation in one of 39 patients.

By 6 months, blood pressure was lowered from baseline by 4·4 mm Hg systolic and 3·9 mm Hg diastolic more in the candesartan group than in the placebo group (p<0·0001 for both values). Serum creatinine at least doubled in 5·5% of the 311 patients with serial measures in the candesartan group, compared with 1·6% of the 307 patients in the placebo group (p=0·015). Potassium increased to 6 mmol/L or higher in 3% of the 321 patients in the candesartan group and 1·3% of the 315 patients in the placebo group (p=0·26).

Discussion

Among patients with CHF and left-ventricular systolic dysfunction clinically judged unable to tolerate an ACE inhibitor, candesartan significantly reduced cardiovascular death and hospital admission for heart failure. The effect appeared early and was sustained throughout the 3 years of the trial. Candesartan was well tolerated, without a significant excess in need for discontinuation compared with placebo, despite this population's history of intolerance to another inhibitor of the renin-angiotensin system.

The 23% relative risk reduction in cardiovascular mortality or hospital admission for heart failure with candesartan is similar to the 26% relative reduction in these outcomes reported for enalapril in the Study of Left Ventricular Dysfunction treatment trial,[11] and in an overview of large trials of ACE inhibitors for patients with left-ventricular systolic dysfunction, with or without heart failure.[12] We have shown prospectively that an angiotensin-receptor blocker has an important benefit as an inhibitor of the renin-angiotensin system, which seems to be similar to the benefit seen with ACE inhibitors.

We studied an angiotensin-receptor blocker compared with placebo among patients with CHF who were receiving no background ACE-inhibitor treatment. In the Valsartan Heart Failure trial,[13] a subset of 366 patients—only 7% of the overall trial population—was not taking background ACE-inhibitor treatment. The large reduction in mortality and morbidity with valsartan in that post-hoc subgroup was promising,[14] but, as has been seen in other subgroup findings,[15–17] could be misleading.

We did not design CHARM-Alternative to detect moderate differences in all-cause mortality. Nevertheless, the reduction in cardiovascular death and hospital admission for CHF was accompanied by lower all-cause mortality than in the placebo group, which in the covariate-adjusted analysis reached significance.

We found candesartan to be well tolerated, nearly as well tolerated as placebo, which was consistent with our pilot experience.[6] Even among patients who had intolerance because of symptoms other than cough, tolerability was good. Because we did not require rechallenge with an ACE inhibitor, some of these patients might have tolerated another exposure to ACE inhibitors. Consistent with the overall programme, discontinuation because of renal insufficiency, hyperkalaemia, or hypotension was more common with candesartan than placebo. Although patients with previous ACE-inhibitor discontinuation because of renal insufficiency and hypotension were more likely to have recurrence while taking candesartan than placebo, most patients with these histories tolerated candesartan. However, because the discontinuation rate was higher because of recurrence, physicians should be particularly careful to monitor patients with a history of renal insufficiency, hyperkalaemia, or hypotension.

Although angioedema has been reported with the use of angiotensin-receptor blockers,[18] the incidence of

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recurrent angioedema among patients who initially had developed angioedema on ACE inhibitors is not well documented.[19] In CHARM-Alternative, the occurrence of angioedema was infrequent, and only one of 39 patients in the candesartan group with a history of angioedema on ACE inhibitors had recurrence leading to permanent drug discontinuation. In this case, the angioedema did not lead to hospital admission and was not life threatening. Thus, history of angioedema or anaphylaxis on an ACE inhibitor should prompt caution but does not seem to be a contraindication to use of an angiotensin-receptor blocker.

Although patients were required to have a documented previous discontinuation of an ACE inhibitor because of intolerance, the definition was practical and was based on the practising physician's judgment. Determination of intolerance is sometimes subjective, and efforts should be made to assure that as many patients as possible are receiving ACE inhibitors since these drugs extend survival. However, for intolerant patients, we show that candesartan can be an alternative treatment.

Over the duration of the trial, 33% of candesartan compared with 40% of placebo patients had cardiovascular death or first admission to hospital for CHF. This absolute reduction of seven major events per 100 patients treated corresponds to the need to treat 14 patients with candesartan to prevent one patient from having cardiovascular death or hospital admission for heart failure. In addition, multiple CHF hospital admissions were reduced. Adequate attempts should be made to place patients with CHF and reduced left-ventricular ejection fraction on ACE inhibitors and β blockers. However, irrespective of the tolerance of an ACE inhibitor, the addition of candesartan improves outcome. In conclusion, candesartan was generally well tolerated and reduced cardiovascular mortality and morbidity in patients with symptomatic CHF who were not receiving ACE inhibitors because of intolerance.

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.

Acknowledgments

This study was supported by AstraZeneca R&D, Mölndal, Sweden. We thank our patients for their participation, Ann-Britt Johansson and Angela Moscaritolo for secretarial assistance, Peter Johansson for statistical help in the analysis, and Gunilla Ohlin for important input during the initiation of CHARM.

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