Effect of Candesartan on Cause-Specific Mortality in Heart Failure Patients

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Program

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Background—Patients with heart failure are at increased risk of sudden death and death attributed to progressive pump failure. We assessed the effect of candesartan on cause-specific mortality in patients enrolled in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program.

Methods and Results—The CHARM program consisted of 3 component trials that enrolled patients with symptomatic heart failure: CHARM-Alternative (n=2028; LVEF≤40% and ACE intolerant), CHARM-Added (n=2548; LVEF≤40%, already on ACE inhibitors), and CHARM-Preserved (n=3023; LVEF >40%). Patients were randomized to candesartan, titrated to 32 mg QD, or placebo and were followed up for a median of 37.7 months. All deaths were reviewed by a blinded adjudication committee and categorized according to prespecified definitions on the basis of a narrative and source documentation. The number and rate of deaths by cause were calculated for each of the component trials and the overall program. Of all the patients, 8.5% died suddenly, and 6.2% died of progressive heart failure. Candesartan reduced both sudden death (HR 0.85 [0.73 to 0.99], $P=0.036$) and death from worsening heart failure (HR 0.78 [0.65 to 0.94], $P=0.008$). These reductions were most apparent in the patients with LVEF≤40%.

Conclusions—Candesartan reduced sudden death and death from worsening heart failure in patients with symptomatic heart failure, although this reduction was most apparent in patients with systolic dysfunction. **(*Circulation*. 2004;110: 2180-2183.)**

Key Words: heart failure ■ candesartan ■ receptor, angiotensin ■ death, sudden

In clinical trials of chronic heart failure (CHF), the majority of patients who die do so suddenly or from progressive pump failure.[1] In heart failure patients, angiotensin-converting enzyme (ACE) inhibitors and β-blockers reduce overall mortality by reducing cardiovascular death, and specifically by reducing sudden death and death attributed to progressive heart failure. In the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program, treatment with an angiotensin receptor blocker (ARB) led to a 12% risk reduction in cardiovascular death and a 9% borderline significant risk reduction in total mortality. We now describe the effect of candesartan on cause-specific mortality in CHARM.

Methods

CHARM consisted of 3 component trials in patients with CHF: CHARM-Alternative (n=2028; LVEF≤40% and ACE intolerant), CHARM-Added (n=2548; LVEF≤40%, already on ACE inhibitors), and CHARM-Preserved (n=3023; LVEF >40%).[2–4] Patients were randomized to candesartan, 4 or 8 mg titrated to 32 mg once daily, or matching placebo and were followed up for a median of 37.7 months. All 3 trials were pooled to provide adequate statistical power to evaluate cause-specific mortality.[5] Only the overall study—not the component trials—was powered to address the effect of candesartan on total mortality.

Deaths were reviewed by a blinded adjudication committee and categorized according to prespecified definitions on the basis of a narrative and source documentation. Deaths were considered cardiovascular unless a specific noncardiovascular cause was identified and were further categorized as sudden or as attributed to myocardial infarction (MI), heart failure, stroke, complications of a procedure, or another cardiovascular cause. Sudden death was defined as the unexpected death of a stable patient. Heart failure death was defined as death in the setting of clinical progressive heart failure with no other apparent cause. MI death required autopsy, cardiac marker, or ECG evidence of infarction. Noncardiovascular deaths were subcategorized as cancer or other cause.

Received May 5, 2004; revision received August 10, 2004; accepted August 18, 2004.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000144474.65922.AA**

Number, Proportion, and Annualized Incidence of Deaths Attributed to Different Causes in the 3 CHARM Trials and the Overall CHARM Program

	CHARM-Alternative		CHARM-Added		CHARM-Preserved		CHARM-Overall		
Cause of Death	Candesartan (n=1013)	Placebo (n=1015)	Candesartan (n=1276)	Placebo (n=1272)	Candesartan (n=1514)	Placebo (n=1508)	Candesartan (n=3803)	Placebo (n=3796)	Hazard Ratio and 95% CI
Sudden death	80 (7.9)	111 (10.9)	150 (11.8)	168 (13.2)	69 (4.6)	65 (4.3)	299 (7.9)	344 (9.1)	0.85 (0.73–0.99)
Incidence rate*	3.0	4.3	3.9	4.5	1.6	1.5	2.7	3.2	*P*=0.036
Progressive HF	70 (6.9)	89 (8.8)	91 (7.1)	117 (9.2)	48 (3.2)	54 (3.6)	209 (5.5)	260 (6.8)	0.78 (0.65–0.94)
Incidence rate*	2.6	3.5	2.4	3.1	1.1	1.2	1.9	2.4	*P*=0.008
MI	34 (3.4)	17 (1.7)	18 (1.4)	21 (1.6)	9 (0.6)	12 (0.8)	61 (1.6)	50 (1.3)	1.19 (0.82–1.73)
Incidence rate*	1.3	0.66	0.47	0.56	0.20	0.27	0.56	0.47	*P*=0.37
Stroke	13 (1.3)	15 (1.5)	15 (1.2)	13 (1.0)	17 (1.1)	16 (1.1)	45 (1.2)	44 (1.2)	1.00 (0.66–1.52)
Incidence rate*	0.49	0.58	0.39	0.35	0.38	0.36	0.41	0.41	*P*=0.99
Procedure related	6 (0.6)	4 (0.4)	10 (0.8)	2 (0.2)	7 (0.5)	6 (0.4)	23 (0.6)	12 (0.3)	1.87 (0.93–3.77)
Incidence rate*	0.23	0.15	0.26	0.05	0.16	0.14	0.21	0.11	*P*=0.073
Other CV	16 (1.6)	16 (1.6)	17 (1.3)	26 (2.0)	18 (1.2)	17 (1.1)	51 (1.3)	59 (1.6)	0.84 (0.58–1.23)
Incidence rate*	0.60	0.62	0.44	0.70	0.41	0.39	0.47	0.55	*P*=0.37
All CV death	219 (21.6)	252 (24.8)	302 (23.7)	347 (27.3)	170 (11.2)	170 (11.3)	691 (18.2)	769 (20.3)	0.88 (0.79–0.97)
Incidence rate*	8.2	9.8	7.9	9.3	3.8	3.9	6.3	7.2	*P*=0.012
Cancer death	25 (2.5)	18 (1.8)	35 (2.7)	19 (1.5) †	26 (1.7)	22 (1.5)	86 (2.3)	59 (1.5)	1.42 (1.02–1.98)
Incidence rate*	0.94	0.70	0.91	0.51	0.59	0.50	0.79	0.55	*P*=0.037
Other non-CV death	21 (2.1)	26 (2.6)	40 (3.1)	46 (3.6)	48 (3.2)	45 (3.0)	109 (2.9)	117 (3.1)	0.91 (0.70–1.18)
Incidence rate*	0.79	1.01	1.04	1.24	1.08	1.03	1.00	1.09	*P*=0.81
All non-CV death	46 (4.5)	44 (4.3)	75 (5.9)	65 (5.1)	74 (4.9)	67 (4.4)	195 (5.1)	176 (4.6)	1.08 (0.88–1.33)
Incidence rate*	1.7	1.7	2.0	1.8	1.7	1.5	1.8	1.7	*P*=0.45
All deaths	265 (26.2)	296 (29.2)	377 (29.6)	412 (32.4)	244 (16.1)	237 (15.7)	886 (23.3)	945 (24.9)	0.91 (0.83–1.00)
Incidence rate*	10.0	11.5	9.8	11.1	5.5	5.4	8.1	8.8	*P*=0.055

*Per 100 person-years.

The number and rate of deaths by cause were calculated for each of the component trials and the overall program. Hazard ratios were calculated for the treatment differences in the overall program utilizing a Cox proportional hazards model,[6] and the analysis was stratified by individual trial. A formal test for heterogeneity was performed to determine whether the effect of candesartan on individual cause of death was heterogenous among the 3 trials. We used SAS version 8.2 (SAS Institute, Cary, NC) for all statistical analyses.

Results

The demographic details of the CHARM population have been previously reported.[2] Briefly, the mean age was 66 years, 68.4% of patients were male, and 43% had ejection fraction >40%. All-cause and cause-specific mortality results are shown in the Table. Of 1831 deaths, 1460 were cardiovascular. Of all the patients, 8.5% had sudden death (35% of all deaths), and 6.2% died of progressive heart failure (26% of all deaths). Death attributed to MI (1.5% of patients, 6.1% of deaths), stroke (1.2% of patients, 4.9% of deaths), procedures (0.5% of patients, 1.9% of deaths), and other cardiovascular causes (1.4% of patients, 6.0% of deaths) were less common. Of the 371 noncardiovascular deaths (4.9% of patients and 20.3% of deaths), 145 were cancer related (1.9% of patients), and 226 (3.0% of patients) were attributed to other noncardiovascular causes.

The reduction in cardiovascular death with candesartan[2] (HR 0.88 [0.79 to 0.97], $P=0.012$) was largely attributed to a reduction in both sudden death (HR 0.85 [0.73 to 0.99], $P=0.036$) and heart failure death (HR 0.78 [0.65 to 0.94], $P=0.008$). These reductions occurred only in the 2 low-LVEF trials. Noncardiovascular death was not affected by treatment. As previously reported, death attributed to cancer was more frequent in the candesartan group (HR 1.42 [1.02 to 1.98], $P=0.037$). The incidence rates of death and cardiovascular death were considerably lower in the Preserved trial than in the low-LVEF trials. The rates of noncardiovascular death were similar across trials but accounted for a lower proportion of deaths in the patients with LVEF ≤40% (17%) compared with patients in the Preserved trial (29%).

Discussion

The majority of deaths in CHARM, which included a wide range of patients with CHF, were cardiovascular, and most were sudden or attributed to heart failure. The overall reduction in cardiovascular mortality associated with candesartan[2] was attributed to fewer sudden deaths and heart failure deaths, with no reduction in deaths attributed to MI or stroke, although these were relatively infrequent. The reductions in both sudden and heart failure death attributed to candesartan were predominantly observed in the patients with LVEF ≤40%.

The low rate of death from MI and stroke is consistent with other trials in patients with low-LVEF CHF.[7,8] CHARM also

provides additional information on the causes of death in patients with CHF and preserved LVEF. Overall mortality was lower in these patients compared with patients with reduced LVEF, and the proportion of noncardiovascular deaths was higher. Neither the absolute number nor the proportion of deaths attributed to MI or stroke was higher in the Preserved trial, even though these patients were older and more hypertensive than in the reduced-LVEF trials.[5] The proportion of cardiovascular deaths that were sudden or attributed to heart failure was similar across the 3 trials.

The mechanisms by which an ARB may reduce the likelihood of progressive heart failure leading to death are well established and similar to the mechanisms postulated for the benefit observed with ACE inhibitors. These include a myriad of hemodynamic and neurohormonal actions,[9] reduction in ventricular dilatation and remodeling,[10] and reduction in sympathetic tone.[11] The mechanisms whereby ARBs reduce the incidence of sudden death in patients with CHF remain less clear (as they are also for ACE inhibitors). Overall improvement in hemodynamic status and attenuation of ventricular remodeling may directly and indirectly decrease the propensity to fatal ventricular arrhythmia.[12] ARBs, like ACE inhibitors, are potassium sparing, and relative increases in serum potassium may further reduce the arrhythmia risk. Reductions in the incidence of sudden death have been observed in trials with ACE inhibitors,[13] and in the Randomized ALdactone (spironolactone) Evaluation Study for congestive heart failure (RALES) and Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study (EPHESUS) trials with the aldosterone antagonists.[8,14] That ARBs should display effects with regard to sudden death and death due to progressive heart failure that are similar to the effects of ACE inhibitors is even less surprising in light of recent data from the post-MI VALsartan In Acute myocardial iNfarction Trial (VALIANT) trial in which, in a direct comparison, the ARB valsartan was similar to captopril with regard to all primary end points.[15]

Although the effect of candesartan on sudden death and death due to progressive heart failure appears to be most pronounced in the low-LVEF populations, it is important to note that only the pooled CHARM overall study was designed and adequately powered to address the effect of candesartan on total mortality. The primary end point in the component trials, in contrast, was heart failure hospitalization or cardiovascular death. We have thus reported the hazard ratios and 95% confidence intervals for the individual causes of death only in the overall results. Because of the lack of power in the component trials, we resist drawing conclusions from the numeric differences in causes of death among the various component trials. Indeed, a formal statistical test of heterogeneity did not reveal any heterogeneity in any of the individual cause-of-death end points between trials, although we cannot exclude the possibility that with larger sample sizes we may have seen differences in the effect of candesartan in the different populations.

Some limitations of this analysis should be noted. The ability to classify cause of death is always limited by the accuracy and availability of clinical information, standardization of the adjudication process, and consistency across the trial. The central adjudication methodology used in CHARM was designed to ensure consistency. Sudden death in a clinical trial does not imply causality, and there is inherent uncertainty in this classification. Although arrhythmia is presumed in many patients who die suddenly, other causes of sudden death include acute myocardial infarction, pulmonary embolism, aortic dissection, and stroke. In autopsied patients in the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, myocardial infarction was a frequent cause of death in autopsied patients who died suddenly.[16] Autopsy data were available in only a minority of patients in CHARM. It is, however, likely that some of the deaths classified as "sudden death" were fatal infarctions. Finally, although this study was not powered to address differences in the effect of candesartan on total mortality in the component trials, we also lack the statistical power to detect moderate increases or reductions in mortality from events such as MI, stroke, or procedure-related deaths, where the event rate was very low.

In summary, the reduction in cardiovascular deaths produced by candesartan in a broad spectrum of CHF patients can be attributed to both reduced sudden death and death attributed to heart failure, but not death attributed to MI, stroke, procedures, or other cardiovascular causes. This benefit was observed primarily in patients with reduced ejection fraction.

Disclosure

Drs Solomon, Pfeffer, Swedberg, Granger, McMurray, and Yusuf have served as consultants to or received research grants and honoraria from AstraZeneca and other major cardiovascular pharmaceutical companies. Drs Pocock, Wang, Skali, Finn, and Zornoff have received research support form AstraZeneca. Dr Michelson is an employee of AstraZeneca.

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