

Figure 25 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Exploratory-Analysis: Dose reduction of the investigational product in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

A higher frequency of dose reduction is presented in the exploratory safety analysis which is due to the fact that patients experiencing both dose reduction and later permanent discontinuation for the same reason are counted once in each category in the exploratory analysis. In the descriptive safety analysis above these patients are only included in the discontinuation category.

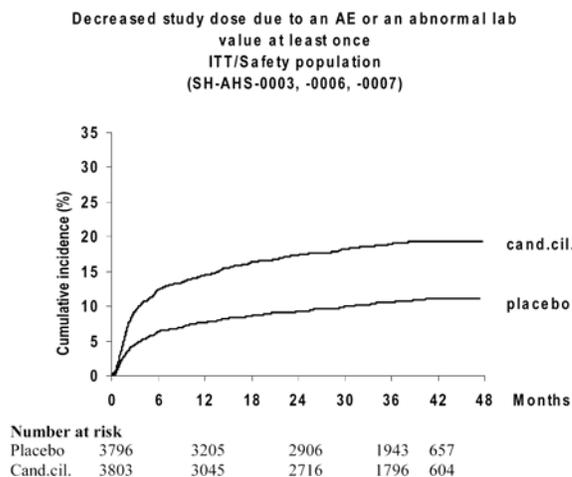


Figure 26 Cumulative incidence (%) of dose reduction of the investigational product due to an AE or an abnormal laboratory value. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 385 (10.1%) patients in the placebo group and 693 (18.2%) patients in the candesartan group (Table 61). This between-treatment difference in dose reductions for an AE of 8.1% was statistically significant ($P < 0.001$), (Table 62). As shown in Figure 26, the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

7.1.4 Common Adverse Events

Adverse events (AEs) collected during the component studies in the total population (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) are described depending on whether they were reported during treatment with the investigational product (referred to as “on treatment” in tables) or reported over the entire study period (referred to as “during study”). AEs during study include all AEs reported for each patient, i.e., those reported on treatment as well as any new-onset AEs during the period following discontinuation of the study drug and new-onset SAEs after the patient completed or withdrew from a component study. AEs are organized according to the AED preferred term level, i.e., AEs of a similar kind share the same preferred term.

7.1.4.1 Appropriateness of adverse event categorization and preferred terms

Categories of adverse events in CHARM-Added (SH-AHS-0006) Study:

AEs were reported by 992 (78.0%) patients randomized to placebo, and by 1,026 (80.4%) patients randomized to candesartan during study. In the placebo group 413 (32.5%) patients had fatal SAEs and 870 (68.4%) patients experienced non-fatal SAEs, compared with the candesartan group where 377 (29.5%) patients had fatal SAEs and 874 (68.5%) patients had non-fatal SAEs. As mentioned in section 7.1.3.2, the investigational product was prematurely discontinued due to AEs for 224 (17.6%) patients in the placebo group and for 310 (24.3%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 123 (9.7%) patients in the placebo group and for 220 (17.2%) patients in the candesartan group. A summary of adverse events by category is presented in Table 71.

Table 71 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0006)

Category of adverse event	N (%) of patients who had an adverse event in each category ^a							
	Placebo on treatment (N=1272)		Cand. cil. on treatment (N=1276)		Placebo during study ^b (N=1272)		Cand. cil. during study ^b (N=1276)	
Any AE	979	(77.0)	1007	(78.9)	992	(78.0)	1026	(80.4)
Serious AEs	930	(73.1)	883	(69.2)	966	(75.9)	969	(75.9)
Serious AEs leading to death	276	(21.7)	210	(16.5)	413	(32.5)	377	(29.5)
Serious AEs not leading to death	842	(66.2)	802	(62.9)	870	(68.4)	874	(68.5)
Discontinuations of investigational product due to AEs	224	(17.6)	310	(24.3)	-	-	-	-
Dose reductions of investigational product due to AEs	123	(9.7)	220	(17.2)	-	-	-	-
	Total number of adverse events							
All AEs ^c	3573		3526		4105		4229	
Serious AEs ^c	3207		2929		3745		3639	

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

^b Only one occurrence of an event during the study period is counted.

^c Events are counted by preferred term, i.e. for patients with multiple events falling under the same preferred term; only one occurrence of the event is counted.

Categories of adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

During study, in the total population AEs were reported by 2,799 (73.7%) patients randomized to placebo, and by 2,841 (74.7%) patients randomized to candesartan. In the placebo group 947 (24.9%) patients had fatal SAEs and 2,487 (65.5%) patients experienced non-fatal SAEs,

compared with the candesartan group where 887 (23.3%) patients had fatal SAEs and 2,432 (63.9%) patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 613 (16.1%) patients in the placebo group and for 799 (21.0%) patients in the candesartan group. The investigational product was reduced in dose due to AEs for 324 (8.5%) patients in the placebo group and for 569 (15.0%) patients in the candesartan group. A summary of AEs by category in the total population is presented in Table 72, and for CHF patients with depressed LV function is given in Table 73.

Table 72 Number (%) of patients with symptomatic CHF with at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Category of adverse event	N (%) of patients who had an adverse event in each category ^a							
	Placebo on treatment		Cand. cil. on treatment		Placebo during study ^b		Cand. cil. during study ^b	
	(N=3796)		(N=3803)		(N=3796)		(N=3803)	
Any AE	2732	(72.0)	2788	(73.3)	2799	(73.7)	2841	(74.7)
Serious AEs	2562	(67.5)	2410	(63.4)	2698	(71.1)	2624	(69.0)
Serious AEs leading to death	616	(16.2)	504	(13.3)	947	(24.9)	887	(23.3)
Serious AEs not leading to death	2369	(62.4)	2246	(59.1)	2487	(65.5)	2432	(63.9)
Discontinuations of the investigational product due to AEs	613	(16.1)	799	(21.0)	-	-	-	-
Dose reductions of the investigational product due to AEs	324	(8.5)	569	(15.0)	-	-	-	-
	Total number of adverse events							
All AEs ^c	9317		9378		10814		11261	
Serious AEs ^c	8390		7730		9895		9634	

- ^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
- ^b Only one occurrence of an event during the study period is counted
- ^c Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

Table 73 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events for the subpopulation ITT/Safety population (SH-AHS-0003, -0006)

Category of adverse event	N (%) of patients who had an adverse event in each category ^a							
	Placebo on treatment		Cand.cil. on treatment		Placebo during study ^b		Cand.cil. during study ^b	
	(N=2287)		(N=2289)		(N=2287)		(N=2289)	
Any AE	1703	(74.5)	1732	(75.7)	1739	(76.0)	1767	(77.2)
Serious AEs	1605	(70.2)	1506	(65.8)	1688	(73.8)	1651	(72.1)
Serious AEs leading to death	463	(20.2)	375	(16.4)	709	(31.0)	643	(28.1)
Serious AEs not leading to death	1453	(63.5)	1373	(60.0)	1524	(66.6)	1493	(65.2)
Discontinuations of investigational product due to AEs	421	(18.4)	530	(23.2)	-	-	-	-
Dose reductions of investigational product due to AEs	199	(8.7)	377	(16.5)	-	-	-	-
	Total number of adverse events							
All AEs ^c	5875		5928		6885		7123	
Serious AEs ^c	5276		4885		6291		6092	

- ^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
- ^b Only one occurrence of an event during the study period is counted.
- ^c Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only one occurrence of the event is counted.

7.1.4.2 Incidence of common adverse events and common adverse event tables

Most common adverse events in CHARM-Added (SH-AHS-0006) Study:

The most commonly reported AEs (Table 74) in the placebo group during study were cardiac failure/cardiac failure aggravated (472, 37.1%), hypotension (184, 14.5%), and sudden death (174, 13.7%). The most commonly reported AEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (421, 33.0%), hypotension (296, 23.2%), and renal function abnormal/renal dysfunction aggravated (196, 15.4%).

Table 74 Number (%) of patients with the most commonly reported^a AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1272)		Cand. cil. on treatment (N=1276)		Placebo during study (N=1272)		Cand. cil. during study (N=1276)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated ^b	435	(34.2)	350	(27.4)	472	(37.1)	421	(33.0)
Hypotension	176	(13.8)	288	(22.6)	184	(14.5)	296	(23.2)
Angina pectoris/angina pectoris aggravated ^b	153	(12.0)	127	(10.0)	169	(13.3)	150	(11.8)
Sudden death	140	(11.0)	114	(8.9)	174	(13.7)	143	(11.2)
Renal function abnormal/renal dysfunction aggravated ^b	115	(9.0)	192	(15.0)	119	(9.4)	196	(15.4)
Arrhythmia ventricular	107	(8.4)	78	(6.1)	121	(9.5)	88	(6.9)
Pneumonia	88	(6.9)	57	(4.5)	108	(8.5)	76	(6.0)
Hyperkalaemia	44	(3.5)	121	(9.5)	46	(3.6)	123	(9.6)
Myocardial infarction	73	(5.7)	60	(4.7)	88	(6.9)	70	(5.5)
Fibrillation atrial	69	(5.4)	52	(4.1)	73	(5.7)	66	(5.2)
Arrhythmia atrial	61	(4.8)	59	(4.6)	71	(5.6)	67	(5.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated ^b	63	(5.0)	52	(4.1)	68	(5.3)	65	(5.1)
Cerebrovascular disorder	48	(3.8)	55	(4.3)	58	(4.6)	69	(5.4)
Chest pain	64	(5.0)	45	(3.5)	71	(5.6)	54	(4.2)
Coronary artery disorder	42	(3.3)	58	(4.5)	50	(3.9)	73	(5.7)
Syncope	45	(3.5)	49	(3.8)	49	(3.9)	59	(4.6)
Tachycardia supraventricular	46	(3.6)	47	(3.7)	50	(3.9)	54	(4.2)
Cardiomyopathy	38	(3.0)	33	(2.6)	48	(3.8)	51	(4.0)
Dizziness/vertigo ^b	35	(2.8)	49	(3.8)	40	(3.1)	57	(4.5)
Pulmonary oedema	41	(3.2)	39	(3.1)	47	(3.7)	48	(3.8)
Renal failure acute	29	(2.3)	45	(3.5)	38	(3.0)	54	(4.2)
Anaemia	36	(2.8)	35	(2.7)	43	(3.4)	46	(3.6)
Accident and/or injury	32	(2.5)	34	(2.7)	43	(3.4)	44	(3.4)
Diabetes mellitus/diabetes mellitus aggravated ^b	41	(3.2)	30	(2.4)	42	(3.3)	37	(2.9)
Dehydration	18	(1.4)	40	(3.1)	22	(1.7)	55	(4.3)

^a This table uses a cut-off of $\geq 3.0\%$ in the total population during study (N=2548).

^b Patients having both AEs are counted once only.

Most common adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The most common AEs (Table 75) in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated (1,187, 31.3% and 1001, 26.3% respectively), angina pectoris/angina pectoris aggravated (506, 13.3% and 490, 12.9%, respectively), hypotension (399, 10.5% and 736, 19.4% respectively) and renal function abnormal/renal dysfunction aggravated (248, 6.5% and 487, 12.8% respectively).

A similar pattern was seen in the subpopulation of patients with depressed LV systolic function.

Table 75 Number (%) of patients with symptomatic CHF with the most commonly reported^a AEs, sorted by descending frequency in the total population during study. ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated ^b	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated ^b	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated ^b	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo ^b	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated ^b	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

^a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).

^b Patients having both or all events are counted once only.

Reviewer's comments: For both the CHARM-Added and CHARM-Pooled study populations, the three most frequent AEs in the placebo and candesartan groups during study were cardiac failure/cardiac failure aggravated, angina pectoris/angina pectoris aggravated and hypotension. For both study populations, too, cardiac failure/cardiac failure aggravated and angina pectoris/angina pectoris aggravated were more frequent in the placebo group than in the candesartan group, whereas hypotension was more frequently reported in the candesartan group than in the placebo group.

7.1.5 Laboratory Findings

Clinical laboratory results in CHARM-Added (SH-AHS-0006) Study:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 477 patients, candesartan 477 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the renin-angiotensin-aldosterone system (RAAS), such as creatinine and potassium.

The mean value for creatinine in the placebo group increased 13.64 µmol/L from the baseline value to the “last value carried forward (LVCF)”. In the candesartan group, the LVCF increased

19.63 $\mu\text{mol/L}$. At baseline, 86 (18.5%) of placebo patients had values above the reference range compared with 83 (17.8%) patients in the candesartan group. For the LCVF that were above the upper level of normal, frequency increased in both treatment groups (placebo 140, 30.4%; candesartan 145, 32.4%). For patients who had serial measurements (placebo 447 patients, candesartan 436 patients) baseline serum creatinine was at least doubled in 27 (6.0%) patients in the placebo group, compared with 32 (7.3%) patients in the candesartan group.

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/L from the baseline value to the LVCF compared with 0.12 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range increased in the placebo group (14, 3.0% at baseline, 20, 4.4% LVCF) and increased from 21 (4.5%) to 31 (6.9%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/L at any time after randomization in 1.1% (5) of 459 patients valid for evaluation in the placebo group and 2.7% (12) of 447 patients in the candesartan group.

Mean sodium measurements increased 0.10 mmol/L for patients treated with placebo and decreased 0.28 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for 5 patients treated with placebo compared with 6 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.30 mmol/L) and candesartan (0.35 mmol/L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was similar for placebo-treated patients (36, 2.8%) compared with candesartan-treated patients (35, 2.7%). One patient (0.2%) in each treatment group had a hemoglobin value below the defined level of abnormality (male ≤ 80 g/L (4.96 mmol/L), female ≤ 70 g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.36%) and candesartan groups (-0.38%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of outliers are in keeping with the expected findings for treatment with inhibitors of the RAAS.

Clinical laboratory results in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

For the total population, serial laboratory data were collected from patients participating at investigational sites in North America (placebo 1,376 patients, candesartan 1,367 patients).

Changes in mean laboratory values were generally small, of minor clinical significance, and occurred primarily in parameters that previously showed changes in studies with inhibitors of the RAAS, such as creatinine and potassium. As a consequence of the large number of observations, some laboratory variables showed statistically significant between treatment differences, even though the absolute differences were small and may not be clinically significant.

From the results for all clinical laboratory tests in the total population, only clinical important abnormalities in the laboratory tests are presented below.

The number of patients with increase in serum creatinine ≥ 2 times from baseline, and of patients with serum potassium ≥ 6 mmol/l after randomization are shown in Table 76 and Table 77 for the total CHARM-Pooled population, and in Table 78 and Table 79 for the subpopulation of CHF patients with LV dysfunction.

Table 76 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1279)		Cand.cil. (N=1263)	
	N	%	N	%
Creatinine	47	3.7	82	6.5

Table 77 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006,-0007)

Abnormal Laboratory variable	Placebo (N=1310)		Cand.cil. (N=1294)	
	N	%	N	%
Potassium	15	1.1	31	2.4

Table 78 Number (%) of patients with increase in serum creatinine ≥ 2 x from baseline value. ITT/Safety population (North America) (SH- AHS- 0003, -0006)

Abnormal Laboratory variable	Placebo (N=754)		Cand.cil. (N=747)	
	N	%	N	%
Creatinine	32	4.2	49	6.6

Table 79 Number (%) of patients with serum potassium to ≥ 6 mmol/L at any time after randomization. ITT/Safety population (North America) (SH-AHS-0003, -0006)

Abnormal Laboratory variable	Placebo (N=774)		Cand.cil. (N=768)	
	N	%	N	%
Potassium	9	1.2	21	2.7

The mean value for creatinine in the placebo group increased 7.7 μ mol/L from the baseline value to the LVCF. In the candesartan group, the mean value increased 17.0 μ mol/L. At baseline, 252 (18.8%) of placebo patients had values above the reference range compared with 251 (18.8%) of patients in the candesartan group. For the last values carried forward that were above the upper level of normal, frequency increased in both treatment groups (placebo 358, 27.3%; candesartan 399, 30.8%). For patients who had baseline value and at least one measurement after randomization (placebo 1279 patients, candesartan 1263 patients) baseline serum creatinine was

at least doubled in 47 (3.7%) patients in the placebo group, compared with 82 (6.5%) patients in the candesartan group (Table 76).

For potassium, the mean value for patients treated with placebo increased 0.02 mmol/L from the baseline value to the LVCF compared with 0.24 mmol/L for patients treated with candesartan. The proportions of patients with values above the reference range increased from 32 (2.4%) to 44 (3.4%) in the placebo group and increased from 38 (2.8%) to 83 (6.4%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/L at any time after randomization in 15 (1.1%) of 1,310 patients valid for evaluation in the placebo group and 31 (2.4%) of 1,294 patients in the candesartan group (Table 77).

AE reports of hypokalemia were rare and occurred more often in the placebo group (placebo 36, 0.9%; candesartan 16, 0.4%).

Mean sodium measurements decreased 0.07 mmol/L for patients treated with placebo and decreased 0.12 mmol/L for patients in the candesartan. The AE term hyponatremia was reported for 13 patients treated with placebo compared with 9 patients treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.18 mmol/L) and candesartan (0.31 mmol/L). The proportion of patients with anemia reported as an AE on treatment with the investigational product was slightly lower for placebo-treated patients (87, 2.3%) compared with candesartan-treated patients (110, 2.9%). One patient in the placebo treatment group and 4 (0.3%) of 1,290 patients in the candesartan group had a hemoglobin value below the defined level of abnormality (male= 80g/L (4.96 mmol/L), female= 70g/L (4.34 mmol/L)).

Glycohemoglobin A_{1c} levels decreased slightly and no major difference was seen between the placebo (-0.31%) and candesartan groups (-0.32%).

In summary, it appears that the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of critical abnormal values was in keeping with the expected findings for treatment with inhibitors of the RAAS.

Reviewer's comments with data from the medical literature: Clinical trials of ARBs in patients with CHF in the medical literature in general also reported small differences in the mean laboratory values between ARBs and the control drug. In the Losartan Intervention For Endpoint reduction (LIFE) trial²³, no significant differences are found in biochemical variables at the end of the study between losartan and atenolol treatment groups. In OPTIMAAL trial²², too, the majority of laboratory tests showed minimal differences between losartan and captopril group except for significant (P=0.01) between-group differences detected for serum uric acid (increased by 46.6 μ mol/L in losartan group vs. 60.8 μ mol/L in captopril group) and serum potassium (increased by 0.19 mmol/L in losartan group vs. 0.22 mmol/L in captopril group).

7.1.6 Vital Signs

For the CHARM Program studies' safety report, vital signs consist of diastolic blood pressure

(DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, only the data for body weight are presented.

Vital signs in CHARM-Added (SH-AHS-0006) Study:

Blood pressure declined in both treatment groups. Mean DBP decreased 2.6 mmHg from the baseline value to the LVCF in the placebo group and 3.5 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 2.5 mmHg for patients treated with placebo and 5.0 mmHg for patients treated with candesartan. The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period.

A DBP < 40 mmHg at any time during the study was reported for 32 (2.5%) patient in the placebo group and 42 (3.3%) patients in the candesartan group. 67 (5.3%) patients treated with placebo and 104 (8.2%) patients treated with candesartan had a recorded SBP < 80 mmHg at any time after randomization.

At LVCF mean heart rate was unchanged in patients in the placebo group and 0.3 bpm lower in patients in the candesartan group compared to baseline

In the placebo group, mean body weight decreased by 0.2 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

Vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Changes in vital signs over time in the total population are shown in Figure 27, Figure 28, Figure 29, and Figure 30.

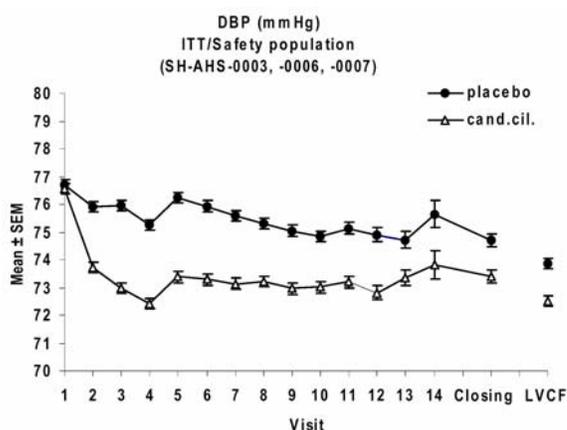


Figure 27 Mean DBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

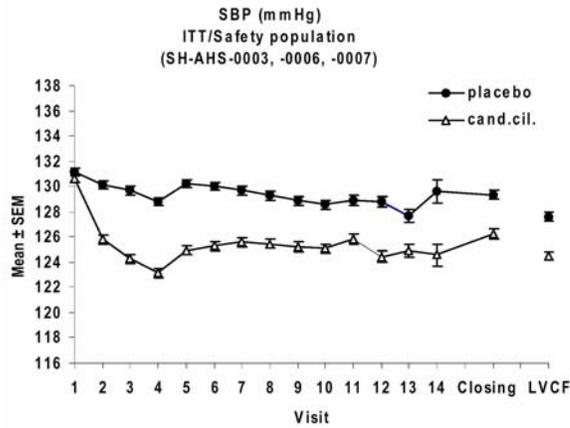


Figure 28 Mean SBP ± SEM (mmHg) by visit for the total population. ITT/Safety population

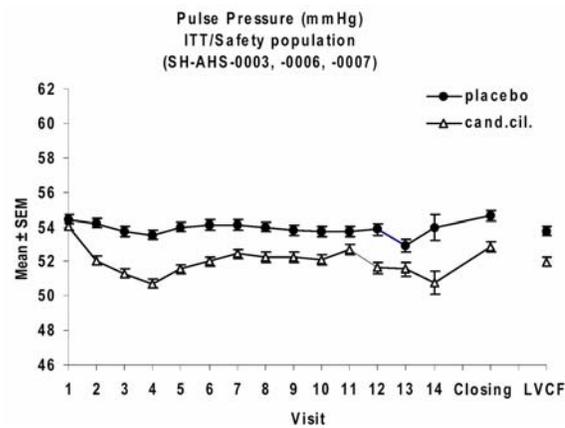


Figure 29 Mean Pulse Pressure ± SEM (mmHg) by visit for the total population. ITT/Safety population

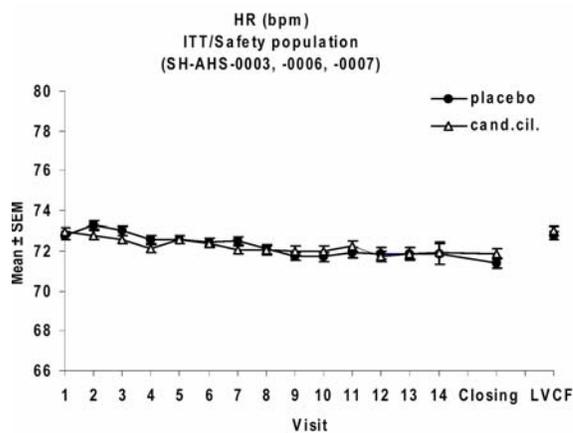


Figure 30 Mean heart rate ± SEM (bpm) by visit for the total population. ITT/Safety population

Changes in vital signs over time in the subpopulation of patients with depressed LV systolic function are shown in Figure 31, Figure 32, Figure 33 and Figure 34.

The number of patients with clinically important changes in vital signs in the total population are shown in (Table 80, Table 81 and Table 82) and the number of patients with clinically important changes in vital signs in the subpopulation of patients with depressed LV systolic function are shown in (Table 83 and Table 84).

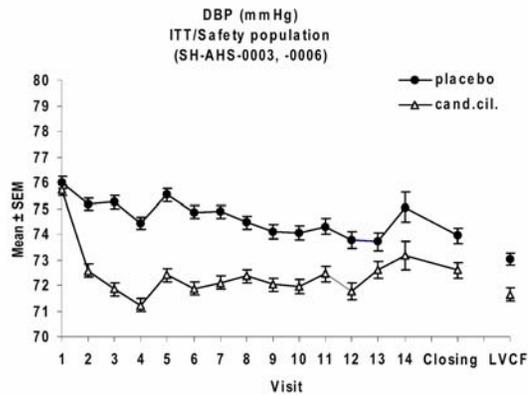


Figure 31 Mean DBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

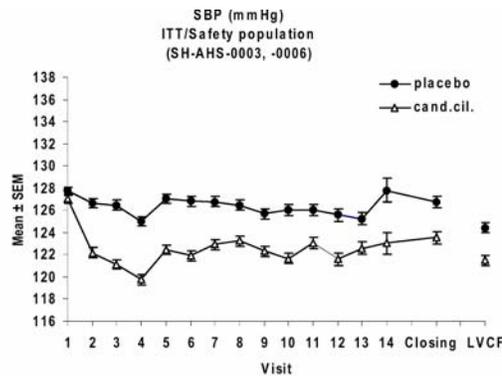


Figure 32 Mean SBP ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

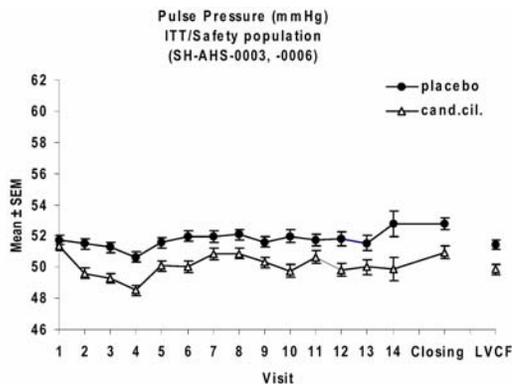


Figure 33 Mean Pulse Pressure ± SEM (mmHg) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

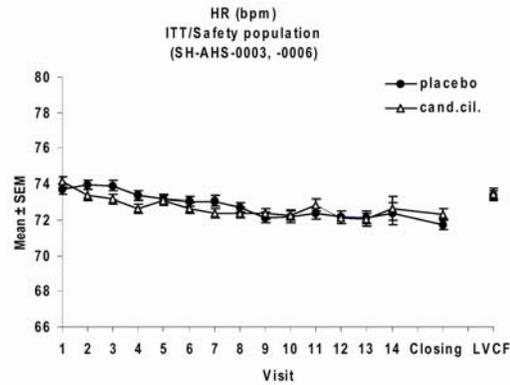


Figure 34 Mean heart rate ± SEM (bpm) by visit for the depressed LV systolic function subpopulation. ITT/Safety population

Table 80 Estimated Means and 95% CI for the change from baseline to LVCF for BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Treat-ment	N	Estimated Mean	95% CI	
				Lower	Upper
DBP (mmHg)	placebo	3755	-2.21	-2.66	-1.75
	cand.cil.	3774	-3.66	-4.10	-3.23
SBP (mmHg)	placebo	3756	-2.69	-3.48	-1.89
	cand.cil.	3774	-5.95	-6.70	-5.19
Pulse Pressure (mmHg)	placebo	3755	-0.42	-1.05	0.21
	cand.cil.	3774	-2.22	-2.83	-1.62
Heart rate (bpm)	placebo	3756	0.22	-0.30	0.73
	cand.cil.	3773	0.37	-0.12	0.86

Table 81 Comparison for Change in BP variables with Region as an ANOVA factor for the total population. ITT/Safety Population. (SH-AHS-0003, -0006, -0007)

Variable	Comparison	Estimated Mean	95% CI		p-value
			Lower	Upper	
DBP (mmHg)	cand.cil. - placebo	-1.45	-2.08	-0.82	<0.001
SBP (mmHg)	cand.cil. - placebo	-3.26	-4.35	-2.16	<0.001
Pulse Pressure (mmHg)	cand.cil. - placebo	-1.81	-2.68	-0.93	<0.001
Heart rate (bpm)	cand.cil. - placebo	0.15	-0.56	0.86	0.680

Table 82 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg or DBP to ≤ 40 mm Hg at any time after randomization for the total population. ITT/safety population. (SH-AHS-0003,-0006, -0007)

Abnormal Vital Sign variable	Placebo (n=3757)		Cand.cil. (n=3774)	
	N	%	N	%
DBP	50	1.3	77	2.0
SBP	109	2.9	201	5.3

Table 83 Number (%) of patients with decrease in SBP to ≤ 80 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2260)		Cand.cil. (n=2271)	
	N	%	N	%
SBP	87	3.8	158	7.0

Table 84 Number (%) of patients with decrease in DBP to \leq 40 mm Hg at any time after randomization for the subpopulation. ITT/safety population. (SH-AHS-0003, -0006)

Abnormal Vital Sign variable	Placebo (n=2259)		Cand.cil. (n=2271)	
	N	%	N	%
DBP	37	1.6	58	2.6

Discussion of vital signs, physical findings and other observations related to safety in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

In the total population, blood pressure declined in both treatment groups. Mean DBP decreased 2.9 mmHg from the baseline value to the LVCF in the placebo group and 4.0 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 3.6 mmHg for patients treated with placebo and 6.1 mmHg for patients treated with candesartan.

The effect on blood pressure in the candesartan group was established during the first 6 months while in the placebo group a trend towards lowering could be seen for a longer time period. Mean heart rate was unchanged during study in both treatment groups. A DBP value less than 40 mmHg at any time during study was reported for 50 (1.4%) patient in the placebo group and 77 (2.0%) patients in the candesartan group. 109 (2.9%) patients treated with placebo and 201 (5.3%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization (Table 82).

In the placebo group, mean body weight decreased by 0.4 kg from baseline to LVCF. In the candesartan population an increase of 0.3 kg was seen.

7.1.7 Overdose Experience

In case reports of overdose (up to 672 mg of candesartan), patient recovery was uneventful. The main manifestation of overdose is symptomatic hypotension and dizziness, which may require placing the patient supine, elevation of legs and, if required, infusion of isotonic saline solution and, sympathomimetic drugs. Candesartan is not removed by hemodialysis.

7.1.8 Postmarketing Experience

The sponsor submits that candesartan has been available in worldwide markets for the treatment of hypertension since 1997. The majority of patients have been treated with 8 to 16 mg dose of candesartan. Since its first approval for treatment of hypertension in 1997, the approved once/day doses of 2 to 32 mg candesartan are available in 84 countries including the United States. In Canada, a 32-mg dose in hypertension was approved in 2002. In 1998, the fixed-dose tablets of candesartan and hydrochlorothiazide was first approved; this formulation is now approved in 56 countries.

During the post marketing period, no unexpected organ-specific toxicity has been reported. Rarely reported reactions include leucopenia, neutropenia, agranulocytosis, hyperkalemia, hyponatremia, increased liver enzymes, abnormal liver function or hepatitis, angioedema, rash, urticaria, pruritus, and renal impairment including renal failure.

7.2 Adequacy of Patient Exposure and Safety Assessments

Please also see section 5.3.1 of the review (Total exposure of candesartan). The sponsor submits that the cumulative exposure to candesartan as of October 2003 exceeds 14 million patient-years.

For this NDA submission, the three pivotal (CHARM Program) efficacy trials comprise 7,601 patients (7,599 patients with data) with NYHA Class II – IV heart failure of at least 4 weeks duration who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The sponsor estimated that the exposure to the investigational product totaled 18,593 patient-years, and exposure to candesartan 9,222 patient-years.

In addition to the 7,601 CHF patients in the CHARM Program clinical trials, the sponsor submitted 24 clinical studies (comprising 4,062 patients with CHF) including:

- (i) 5 randomized, double-blind, placebo-controlled clinical trials with duration of 2 to 12 months, comprising a total of 1,893 patients,
- (ii) one randomized, double-blind, active-treatment (enalapril)-controlled study (RESOLVD) comprising 768 patients, and
- (iii) one open, uncontrolled, long-term (6 month) study comprising 355 patients,
- (iv) 3 clinical pharmacology studies comprising 262 patients,
- (v) 11 clinical studies comprising a total of 677 patients under the Japanese study program (for which FDA granted the sponsor a waiver from providing case report tabulations and case report forms, and 10 studies were pertinent to efficacy), and
- (vi) 4 investigator-initiated clinical studies comprising 107 patients.

Thus, a total of 11,661 patients with CHF have been exposed to candesartan in the treatment of CHF in various clinical trials. About one third of these patients were women, and about 15% (1,736) were 75 years or older. About 90% of the population was Caucasian (white) and 326 patients (2.8%) were black. It appears that a representative population of patients with symptomatic CHF has been exposed to candesartan.

7.2.1 Extent of exposure (dose/duration)

The median time of follow up for the total population of the CHARM-Program studies was 37.7 months, and the longest follow-up time was 47.6 months. The median exposure to double-blind treatment was 34.8 months. A total of 5,360 patients (2,659 patients were in the candesartan group) received study medication for ≥ 24 months. Also, the sponsor stated that from the 6-month visit onwards, $>50\%$ of patients still receiving candesartan were on a dose of 32 mg/day.

Extent of exposure in CHARM-Added (SH-AHS-0006) Study

A total of 2,548 patients (542 females and 2,006 males) were randomized into the study, all of who were included in the ITT/Safety population. Patients who received incorrect investigational

product during any part of the study (6 patients) are included in the analyses according to the group to which they were randomized. An overview of exposure is presented in Table 85, including data on the number of patients who completed or discontinued the study.

The median duration of patient follow-up in the study was 41.1 months for patients randomized to candesartan and 40.9 months for patients randomized to placebo. The median duration of exposure of the investigational product was 40.4 months in the placebo group and 40.3 months in the candesartan group.

Table 85 Overview of exposure. ITT/Safety population (SH-AHS-0006)

		Placebo (N=1272)		Cand. cil. (N=1276)	
No. (%) of patients evaluable for safety	Male	1000	(78.6)	1006	(78.8)
	Female	272	(21.4)	270	(21.2)
Age	<65	636	(50.0)	632	(49.5)
	≥65	636	(50.0)	644	(50.5)
	<75	1027	(80.7)	1064	(83.4)
	≥75	245	(19.3)	212	(16.6)
Race ^a	Caucasian	1176	(92.5)	1170	(91.7)
	Black	62	(4.9)	65	(5.1)
	Oriental	20	(1.6)	33	(2.6)
	Other	14	(1.1)	8	(0.6)
Exposure by discontinuation of investigational product due to AE and/or discontinuation of study (N and %)	Discontinued investigational product due to AEs	224	(17.6)	310	(24.3)
	Patients who withdrew consent	15	(1.2)	25	(2.0)

^aRace is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/ Middle East), Black, Oriental (including Oriental and Malay) and Other.

A total of 1,096 (85.9%) patients in the candesartan group started treatment on 4 mg once daily and 180 (14.1%) patients started on 8 mg once daily at randomization (baseline). A total of 1,756 (68.9%) patients (candesartan 857, 67.2%; placebo 899, 70.7%) received the investigational product for 24 months or more. 53.6% of the candesartan patients (60.5% of those still receiving the investigational product) were treated with the target dose 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan group was 23.5 mg at 6 months. At the end of treatment (LVCF) 41.2% (8.4% of those still treated with candesartan) received 32 mg candesartan once daily. The mean candesartan LVCF dose was 23.1 mg.

Extent of exposure in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

A total of 2,028 patients were randomized into SH-AHS-0003, 2,548 patients to SH-AHS-0006 and 3,025 patients to SH-AHS 0007. The total ITT/safety population for patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006 and SH- AHS-0007) comprised 7,599 patients (2,400 females and 5,199 males) and the corresponding figures for SH-AHS-0003 and SH-AHS-0006 are 4,576 (1,188 females and 3,388 males). Two patients were randomized in error and were therefore excluded from the ITT/safety population in SH-AHS-0007 (because no investigational product was dispensed and no data were collected). Patients who received incorrect investigational product during any part of the studies (22 patients in SH-AHS-0007) are

included in the analyses according to the group to which they were randomized. The incorrect investigational product administration lasted for a maximum of 21 days.

An overview of exposure in the total ITT/safety population including the numbers of patients who completed or discontinued the CHARM Program is presented in Table 86. Table 87 presents the exposure and number of patients by time in the component studies.

A total of 5,360 (70.5%) received the investigational product for 24 months or longer, among which 2,659 (69.9%) on candesartan treatment received the investigational product for 24 months or longer.

Table 86 Overview of exposure in patients with symptomatic CHF. ITT/Safety population (SH-AHS-0003, -0006, -0007)

		Placebo (N=3796)		Cand.cil. (N=3803)	
No. (%) of patients evaluable for safety	Male	2582	(68.0)	2617	(68.8)
	Female	1214	(32.0)	1186	(31.2)
Age (years)	<65	1642	(43.3)	1614	(42.4)
	≥65	2154	(56.7)	2189	(57.6)
	<75	2912	(76.7)	2951	(77.6)
	≥75	884	(23.3)	852	(22.4)
Race ^a	Caucasian	3507	(92.4)	3493	(91.8)
	Black	164	(4.3)	162	(4.3)
	Oriental	87	(2.3)	110	(2.9)
	Other	38	(1.0)	38	(1.0)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	613	(16.1)	799	(21.0)
	Patients who withdrew consent	51	(1.3)	66	(1.7)

^a Race is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/Middle East), Black, Oriental (including Oriental and Malay) and Other. See Section 8.3.

Table 87 Exposure and number of patients with symptomatic CHF by time in the component studies. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Period	Time	Placebo	Cand. cil.	Total	
From baseline to last visit	≥ 0 days	3796	3803	7599	
	≥ 1 months	3765	3779	7544	
	≥ 3 months	3707	3738	7445	
	≥ 6 months	3673	3721	7394	
	≥ 12 months	3464	3563	7027	
	≥ 24 months	3170	3271	6441	
	≥ 36 months	2157	2215	4372	
	≥ 48 months	0	0	0	
	Patient years	10690.3	10938.2	21628.5	
	Mean (months)	33.8	34.5	34.2	
	Median (months)	37.6	37.9	37.7	
	Min/max (months)	0.1/47.4	0.1/47.6	0.1/47.6	
	From baseline to last day on double-blind investigational product	≥ 0 days	3796	3803	7599
		≥ 1 months	3653	3660	7313
≥ 3 months		3501	3475	6976	
≥ 6 months		3451	3419	6870	
≥ 12 months		3105	3071	6176	
≥ 24 months		2701	2659	5360	
≥ 36 months		1766	1715	3481	
≥ 48 months		0	0	0	
Patient years		9371.2	9221.9	18593.1	
Mean (months)		29.6	29.1	29.4	
Median (months)		35.0	34.5	34.8	
Min/max (months)		0.0/47.2	0.0/47.4	0.0/47.4	

The median duration of patient follow-up for the total population in the CHARM Program was 37.9 months for patients randomized to candesartan and 37.6 months for patients randomized to placebo (Table 87). The longest follow-up time was 47.6 months.

Corresponding data for the subpopulation of patients with depressed LV systolic function is shown in Table 88 and Table 89.

The median duration of patient follow-up for the two treatment groups in the subpopulation of patients with depressed LV systolic function were 40.2 and 39.9 months respectively (Table 89).

Table 88 Overview of exposure in the ITT/Safety population for the subpopulation. (SH-AHS-0003, -0006)

		Placebo (N=2287)		Cand.cil. (N=2289)	
No. (%) of patients evaluable for	Male	1691	(73.9)	1697	(74.1)
	Female	596	(26.1)	592	(25.9)
Age	<65	1028	(44.9)	1044	(45.6)
	≥65	1259	(55.1)	1245	(54.4)
	<75	1803	(78.8)	1844	(80.6)
	≥75	484	(21.2)	445	(19.4)
Race ^a	Caucasian	2098	(91.7)	2096	(91.6)
	Black	107	(4.7)	93	(4.1)
	Oriental	57	(2.5)	76	(3.3)
	Other	25	(1.1)	24	(1.0)
Exposure by study completion or	Discontinued investigational	421	(18.4)	530	(23.2)
	Discontinued the study ^b	31	(1.4)	43	(1.9)
	Completed the study	2256	(98.6)	2246	(98.1)

a Race is presented according to the four race groups Caucasian (including European origin, South Asian and Arab/ Middle East), Black, Oriental (including Oriental and Malay) and Other.

b Patients who withdrew consent.

Table 89 Exposure and number of patients for the subpopulation by time in the study. ITT/Safety population. (SH-AHS-0003, -0006)

Period	Time	Placebo	Cand.cil	Total
From Baseline to Last visit	≥ 0 days	2287	2289	4576
	≥ 1 months	2259	2269	4528
	≥ 3 months	2210	2235	4445
	≥ 6 months	2185	2223	4408
	≥ 12 months	2023	2105	4128
	≥ 24 months	1811	1894	3705
	≥ 36 months	1333	1382	2715
	≥ 48 months	0	0	0
	Patient years	6303.2	6503.9	12807.1
	Mean (months)	33.1	34.1	
	Median (months)	39.9	40.1	
	Min/max (months)	0.1/47.4	0.1/47.6	
From Baseline to last day on double-blind study medication	≥ 0 days	2287	2289	4576
	≥ 1 months	2181	2191	4372
	≥ 3 months	2077	2066	4143
	≥ 6 months	2048	2031	4079
	≥ 12 months	1813	1798	3611
	≥ 24 months	1546	1523	3069
	≥ 36 months	1083	1050	2133
	≥ 48 months	0	0	0
	Patient years	5513.3	5420.1	10933.4

The median exposure to the investigational product in the total population was 35.0 months in the placebo group and 34.5 months in the candesartan group.

In the total CHARM-Program population, 3,052 (80.3%) patients in the candesartan group started treatment on 4 mg once daily and 751 (19.7%) patients started on 8 mg once daily at randomization (baseline). Among patients still on the investigational product at 6 months (visit 5), (3,233 patients or 88.9% in the candesartan group and 3,301 patients 92.6% in the placebo group), 62.6% of the candesartan patients were treated with the target dose 32 mg once daily. The mean dose in the candesartan group was 24.0 mg at 6 months. At the end of treatment (LVCF) 62.3% of those still treated with candesartan (2,769, 73.1%) received 32 mg of candesartan once daily. The mean candesartan LVCF dose was 23.9 mg.

7.2.2 Literature

The medical literature reviewed (References, section 10) did not reveal reports of unexpected organ-specific toxicity. In this review, I have presented, with tables and figures where necessary, and discussed the information from the medical literature in the context of the data from the CHARM-Added and CHARM-Pooled Studies under each heading in the safety review template.

7.2.3 Additional submissions, including safety update

The sponsor submitted that there are no on-going clinical studies currently conducted under US IND 50,115, with the exception of an investigator-initiated study (BLO K016) in Germany with a planned recruitment of only 40 patients with CHF. Therefore, the sponsor does not plan to prepare/submit a 4-month safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This section summarizes AEs of special interest relevant to blockade of RAAS in the treatment of CHF by using AT₁-receptor blockers (ARBs) and ACE inhibitors. These AEs of special interest include hypotension, abnormal renal function or worsening of renal function, hyperkalemia, angioedema and myocardial ischemia. In addition, brief descriptions of abnormal hepatic function and neoplasms reported in the safety report are presented.

7.3.1 Hypotensive events

‘Hypotension’ as an adverse clinical event include a composite of the following AAED preferred terms: hypotension; hypotension, postural; dizziness/vertigo; syncope; circulatory failure; and collapse, not otherwise specified (NOS). For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

Hypotensive events in CHARM-Added (SH-AHS-0006) Study:

At baseline, there were a slightly higher proportion of patients in the candesartan group with SBP < 100 mmHg (placebo 54, 4.2%; candesartan 77, 6.0%). AEs suggesting a hypotensive event were reported more frequently for patients in the candesartan group (26.8%) than the placebo group (17.5%) during treatment with the investigational product (Table 90).

Table 90 Number (%) of patients with any of the preferred terms hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/Safety population (SH-AHS-0006)

Placebo on treatment N=1272	Cand. cil. on treatment N=1276	Placebo during study N=1272	Cand. cil. during study N=1276
223 (17.5)	342 (26.8)	236 (18.6)	358 (28.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 176 (13.8%) of patients given placebo and 288 (22.6%) of patients given candesartan (Table 74).

In the candesartan group during treatment, ‘hypotension’ and ‘syncope’ were each reported as an AE that led to death in 1 patient. These hypotensive events that led to death were reported in association with other concomitant events such as myocardial infarction and gastroenterocolitis so that the AE is considered unlikely to be related to candesartan.

The investigational product was discontinued for the specific AE term hypotension in 44 (3.5%) placebo patients and 69 (5.4%) candesartan patients (Table 53). Corresponding figures for the exploratory analysis were 40 (3.1%) placebo patients and 58 (4.5%) candesartan patients (Table 58). The higher proportion of hypotensive events leading to discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started, including diuretics and β-blockers.

Among the patients that discontinued the investigational products due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo 3, 7.5%, candesartan 11, 24.1%).

In patients aged younger than 75 years, discontinuation because of hypotension was reported in 30 (2.9%) of patients in the placebo group and 53 (5.0%) of patients on candesartan.

For patients aged 75 years or older the discontinuation rates were 14 (5.7%) in the placebo group and 16 (7.5%) in the candesartan group.

In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 34 (3.4%) males and 10 (3.7%) females. In the candesartan treatment group there were 59 (5.9%) males and 10 (3.7%) females who were permanently discontinued due to hypotension.

In both treatment groups patients discontinued taking the investigational product because of hypotension over the entire study period; however, the candesartan discontinuation rate, shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 35).

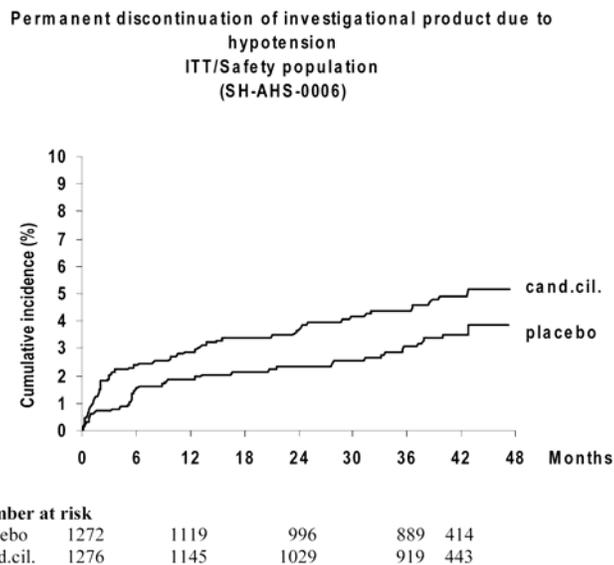


Figure 35 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 56). ITT/Safety population

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 15 (3.9%) placebo patient and 17 (4.5%) candesartan patients.

Hypotensive events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were slightly more patients in the candesartan treatment group with SBP < 100 mmHg (placebo 92, 2.4%; candesartan 126, 3.3%) (North American study population).

AEs suggesting a ‘hypotensive’ event were reported more frequently in the candesartan group (875, 23.0%) than in the placebo group (519, 13.7%) for patients than on treatment with the investigational product (Table 91).

Table 91 Number (%) of patients with any of the preferred terms hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
519 (13.7)	875 (23.0)	560 (14.8)	914 (24.1)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 372 (9.8%) patients given placebo and 714 (18.8%) patients given candesartan (Table 92).

Table 92 Number (%) of patients with symptomatic CHF with the most commonly reported^a AEs, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Preferred term	Placebo on treatment (N=3796)		Cand. cil. on treatment (N=3803)		Placebo during study (N=3796)		Cand. cil. during study (N=3803)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated ^b	1073	(28.3)	831	(21.9)	1187	(31.3)	1001	(26.3)
Hypotension	372	(9.8)	714	(18.8)	399	(10.5)	736	(19.4)
Angina pectoris/angina pectoris aggravated ^b	461	(12.1)	414	(10.9)	506	(13.3)	490	(12.9)
Renal function abnormal/renal dysfunction aggravated ^b	238	(6.3)	474	(12.5)	248	(6.5)	487	(12.8)
Sudden death	282	(7.4)	234	(6.2)	348	(9.2)	291	(7.7)
Pneumonia	243	(6.4)	200	(5.3)	299	(7.9)	261	(6.9)
Myocardial infarction	216	(5.7)	205	(5.4)	257	(6.8)	242	(6.4)
Fibrillation atrial	218	(5.7)	165	(4.3)	249	(6.6)	202	(5.3)
Arrhythmia ventricular	207	(5.5)	159	(4.2)	239	(6.3)	193	(5.1)
Cerebrovascular disorder	189	(5.0)	164	(4.3)	216	(5.7)	203	(5.3)
Coronary artery disorder	170	(4.5)	169	(4.4)	200	(5.3)	205	(5.4)
Chest pain	177	(4.7)	154	(4.0)	202	(5.3)	183	(4.8)
Arrhythmia atrial	175	(4.6)	156	(4.1)	197	(5.2)	187	(4.9)
Hyperkalaemia	78	(2.1)	238	(6.3)	84	(2.2)	242	(6.4)
Tachycardia supraventricular	152	(4.0)	129	(3.4)	177	(4.7)	148	(3.9)
Dizziness/vertigo ^b	107	(2.8)	154	(4.0)	115	(3.0)	168	(4.4)
Accident and/or injury	112	(3.0)	99	(2.6)	143	(3.8)	125	(3.3)
Tachycardia ventricular/arrhythmia/arrhythmia aggravated ^b	110	(2.9)	100	(2.6)	132	(3.5)	128	(3.4)
Syncope	105	(2.8)	121	(3.2)	119	(3.1)	139	(3.7)
Anaemia	87	(2.3)	110	(2.9)	110	(2.9)	145	(3.8)

^a This table uses a cut-off of ≥3.0% in the total population during study (N=7599).

^b Patients having both or all events are counted once only.

A fatal hypotensive event was reported in a comparable proportion of patients in each treatment group (Table 93). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death; notably in the candesartan patients, associated events included electromechanical dissociation, ventricular tachycardia and gastrointestinal bleeding, and were thus assessed by the investigators as unlikely to be related to the investigational product.

Table 93 Number (%) of patients with fatal preferred terms hypotension, hypotension postural, dizziness/ vertigo, syncope, circulatory failure or collapse not otherwise specified (NOS). ITT/ Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N =3803)	Placebo during study (N =3796)	Cand.cil during study (N =3803)
5 (0.1)	6 (0.2)	10 (0.3)	12 (0.3)

As noted in the descriptive analysis for the total population, the investigational product was discontinued for hypotension in 76 (2.0%) placebo patients and 155 (4.1%) candesartan patients (Table 54). Corresponding figures for the exploratory analysis were 66 (1.7%) placebo patients and 132 (3.5%) candesartan patients (Table 61). The higher proportion of permanent discontinuation of the investigational product due to hypotensive events in the candesartan group

could not be explained by higher use of concomitant medication when the event started, including diuretics, β -blockers and ACE-inhibitors. Among the patients that discontinued the investigational product due to hypotensive events, a greater proportion had SBP < 100 mmHg at baseline in the candesartan group (placebo, 7.5%; candesartan, 13.6%).

In patients aged < 75 years, discontinuation because of hypotension was reported in 48 (1.6%) patients in the placebo group and 111 (3.8%) patients on candesartan. For patients aged \geq 75 years the discontinuation rates were 28 (3.2%) patients in the placebo group and 44 (5.2%) patients in the candesartan group. Permanent discontinuation of the investigational product due to hypotension was reported in 56 (2.2%) males and 20 (1.6%) females in the placebo group, and 107 (4.1%) males and 48 (4.0%) females in the candesartan treatment group.

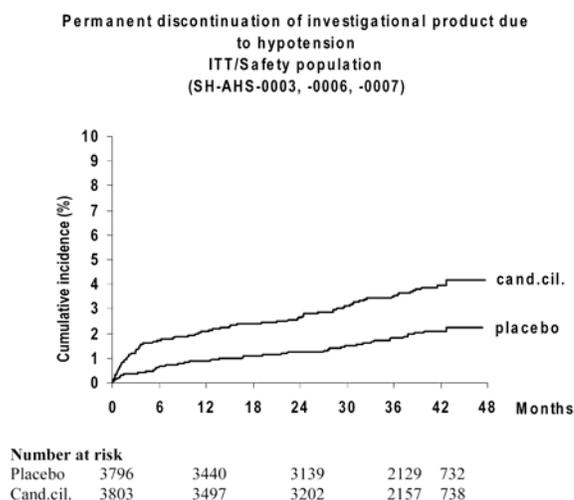


Figure 36 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hypotension. ITT/Safety population

Although patients in both treatment groups discontinued taking the investigational product because of hypotension over the entire study period, the candesartan discontinuation rate shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 36).

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for hypotension was noted for 22 (2.0%) placebo patients and 34 (3.1%) candesartan patients.

Reviewer’s comments with data from the literature: Hypotension is an expected clinical event in this population of patients with chronic heart failure, particularly since they are being treated also with ACE inhibitors, β -blockers, and diuretics all of which may lower the blood pressure. In the VALIANT trial²⁵, where valsartan with or without captopril were given to high risk patients with radiologic evidence of heart failure, left ventricular systolic dysfunction or both, there was a higher incidence of drug-related adverse events (hypotension and renal dysfunction) in the valsartan-plus-captopril group as well as in the valsartan group.

7.3.2 Abnormal renal function

To summarize abnormal renal function, the following AAED preferred terms were selected and analyzed as a single composite event: renal function, abnormal/renal dysfunction, aggravated; renal failure acute; renal failure, NOS; uremia; non-protein nitrogen, increased; renal failure, aggravated; blood urea nitrogen, increased; increased creatinine, acute pre-renal failure and anuria. For this composite AE, patients with multiple events of any of the selected AE terms were counted only once.

Abnormal renal function in CHARM-Added (SH-AHS-0006) Study:

At baseline, prior to study entry, there were a slightly higher proportion of patients in the candesartan group with serum creatinine ≥ 2.0 mg/ dl at baseline (placebo 20, 4.3%; candesartan 26, 5.6%) (North American study population).

AEs suggesting ‘abnormal renal function’ occurred in 151 (11.9%) patients in the placebo group and 231 (18.3 %) patients in the candesartan group during study (Table 94).

Table 94 Number (%) of patients with any of the preferred terms renal function abnormal/ renal dysfunction aggravated, renal failure acute, renal failure not otherwise specified (NOS), uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0006)

Placebo on treatment N=1272	Cand. cil. on treatment N=1276	Placebo during study N=1272	Cand. cil. during study N=1276
139 (10.9)	220 (17.3)	151 (11.9)	231 (18.3)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 118 (9.3%) of patients given placebo and 195 (15.3%) given candesartan during study. Renal failure, acute (placebo, 38 patients, 3.0%; candesartan, 54 patients, 4.2%) and uremia (placebo, 10 patients, 0.8%; candesartan, 18 patients, 1.4%) were also numerically more frequent in patients given active treatment.

A fatal renal function event was reported for a higher proportion of patients in the placebo group, both ‘on treatment’ (placebo, 8 patients; candesartan, 2 patients) and ‘during study’ (placebo, 20 patients; candesartan 15 patients). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis (Table 53), on investigational product discontinuation in the overall study population, “renal function abnormal” was the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 53, 4.2%; candesartan 105, 8.2%).

In the exploratory analysis, increased creatinine was reported for 52 (4.1%) placebo patients and 100 (7.8%) candesartan patients (Table 58). The higher rate for discontinuation of the investigational product due to ‘abnormal renal function’ in the candesartan group could not be

explained by higher use of concomitant medication when the event started. Among the patients who discontinued the investigational product due to ‘abnormal renal function events’, a higher proportion of patients in the placebo group had a serum creatinine level ≥ 2 mg/dL at baseline (placebo 8 (15.4%); candesartan 9 (9.0%)) (North American study population).

In patients aged younger than 75 years, discontinuation because of abnormal renal function was reported in 40 (3.9%) of patients in the placebo group and 82 (7.7%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 13 (5.3%) in the placebo group and 23 (10.8%) in the candesartan group.

In the placebo treatment group 43 (4.3%) males and 10 (3.7%) females discontinued due to renal function abnormal. In the candesartan treatment group 82 (8.2%) males and 23 (8.5%) females discontinued due to abnormal renal function.

In the exploratory analysis, patients discontinued study treatment because of ‘increased creatinine’ over the entire study period, and the rate was greater for candesartan-treated patients (Figure 37).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation because of increased creatinine was noted for 25 (6.5%) placebo and 42 (11.2%) candesartan patients. Compared to the overall population (placebo 4.1%, candesartan 7.8%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 58).

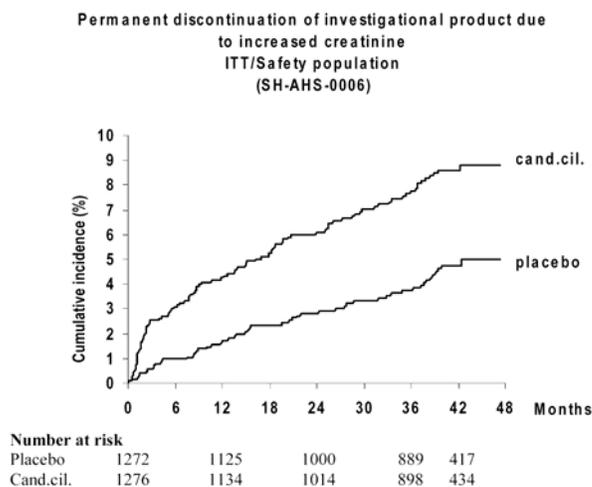


Figure 37 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 56). ITT/Safety population

Abnormal renal function in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were more patients in the candesartan group with serum creatinine > 2.0 mg/ dl (placebo 70, 5.2%; candesartan 84, 6.3%) (North American study population).

AEs suggesting ‘abnormal renal function’ occurred in 349 (9.2%) in the placebo group and 576 (15.1%) patients in the candesartan group during study (Table 95).

Table 95 Number (%) of patients with any of the preferred terms renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006 and -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
316 (8.3)	546 (14.4)	349 (9.2)	576 (15.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 247 (6.5%) of patients given placebo and 485 (12.8%) given candesartan during study. Renal failure, acute (placebo, 91 patients, 2.4%; candesartan, 121 patients, 3.2%) and uremia (placebo, 28 patients, 0.7%; candesartan, 43 patients, 1.1%) were also numerically more frequently in patients given active treatment.

Table 96 Number (%) of patients with fatal renal function, abnormal/renal dysfunction, aggravated, renal failure acute, renal failure, NOS, uremia, non-protein nitrogen increased, renal failure aggravated, blood urea nitrogen increased, acute pre-renal failure or anuria. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand.cil on treatment (N=3803)	Placebo during study (N=3796)	Cand.cil during study (N=3803)
18 (0.5)	7 (0.2)	41 (1.1)	36 (0.9)

Fatal renal function events ‘during study’ and ‘on treatment’ were reported for a higher proportion of patients in the placebo group (Table 96). In both treatment groups, the majority of renal events that led to death were reported in association with other causes of death such as worsening heart failure.

In the descriptive safety analysis, renal function abnormal/renal dysfunction aggravated was the second most common reason for permanent discontinuation of the investigational product (second only to cardiac failure aggravated,) in both treatment groups (placebo 110, 2.9%; candesartan 238, 6.3%) (Table 54). In the exploratory analysis the term increased creatinine was reported for 115 (3.0%) placebo patients and 234 (6.2%) candesartan patients (Table 61). The higher discontinuation rate for ‘abnormal renal function’ in the candesartan group could not be explained by between-treatment differences in concomitant medications when the event started or baseline serum creatinine levels (North American study population) (Table 97).

Table 97 Permanent discontinuation due to pooled adverse events related to abnormal renal function^a or hypotensive events^b or hyperkalemia^c on treatment with candesartan cilexetil or placebo. Specified concomitant medication at the start of the event. ITT/safety population (SH-AHS-0003, -0006, -0007)^d

	Placebo Abn renal N=126		Cand cil Abn renal N=266		Placebo Hypotensive N=93		Cand cil Hypotensive N=188		Placebo Hyperkalae N=22		Cand cil Hyperkalae N=93	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Loop diuretics	117	(92.9)	258	(97.0)	83	(89.2)	169	(89.9)	20	(90.9)	84	(90.3)
Potassium - sparing diuretics	59	(46.8)	105	(39.5)	29	(31.2)	80	(42.6)	10	(45.5)	34	(36.6)
Thiazide diuretics	22	(17.5)	52	(19.5)	22	(23.7)	35	(18.6)	3	(13.6)	11	(11.8)
Any β-blocker	72	(57.1)	146	(54.9)	54	(58.1)	93	(49.5)	13	(59.1)	54	(58.1)
Calcium channel blocker	36	(28.6)	67	(25.2)	11	(11.8)	29	(15.4)	1	(4.5)	23	(24.7)
Any ACE- inhibitor	79	(62.7)	141	(53.0)	63	(67.7)	88	(46.8)	18	(81.8)	59	(63.4)

- a Preferred terms included in abnormal renal function: Renal function abnormal/renal dysfunction aggravated, renal failure acute, renal failure nos, uraemia, non-protein nitrogen increased, renal failure aggravated, acute pre-renal failure or anuria.
 b Preferred terms included in hypotensive events: Hypotension, hypotension postural, dizziness/vertigo, syncope, circulatory failure or collapse not otherwise specified (nos).
 c Hyperkalaemia is a single Preferred term.
 d Exploratory safety analysis

In patients aged younger than 75 years, discontinuation because renal function abnormal/renal dysfunction aggravated was reported in 75 (2.6%) patients in the placebo group and 171 (5.8%) patients in the candesartan group on treatment with the investigational product. For patients aged 75 years or older the discontinuation rates were 35 (4.0%) patients in the placebo group and 67 (7.9%) patients in the candesartan group. In the placebo group the majority of events were seen in male patients (81, 3.1%) compared to 29 (2.4%) female patients. Corresponding values for the candesartan treatment group were 169 (6.5%) males and 69 (5.8%) females. The majority of patients in both treatment groups were Caucasians.

As shown in the exploratory analysis, patients discontinued study treatment because of ‘increased creatinine’ over the entire study period, and the rate was greater for candesartan-treated patients (Figure 38).

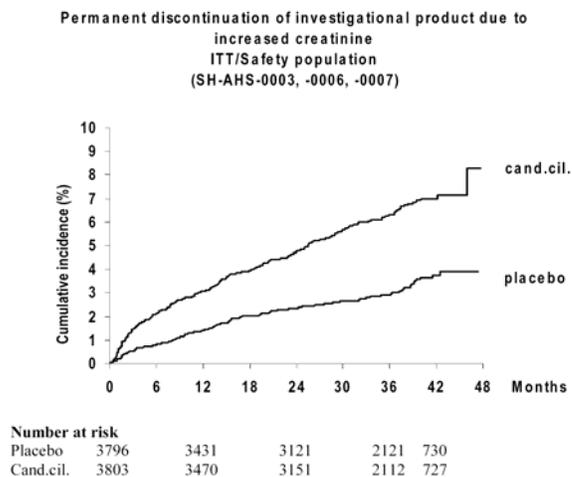


Figure 38 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program study with a history of diabetes, investigational product discontinuation for increased creatinine was noted for 57 (5.3%) placebo and 99 (9.1%) candesartan patients (Table 65 and Table 66). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 61), diabetic patients were slightly more likely to discontinue the investigational product for increased creatinine levels.

Reviewer's comments with data from the literature: The deterioration in renal function tests is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have low glomerular filtration rates, hypotension and concomitant treatment with ACE-inhibitors and diuretics, all of which may increase the BUN or serum creatinine. The mean serum creatinine concentration in major clinical trials involving patients with congestive heart failure ranges from 1.2 to 1.4 mg/dL (106 to 124 $\mu\text{mol/L}$), and one third to one half of patients with congestive heart failure have renal insufficiency¹⁷. Chronic kidney disease is among the strongest predictors of death in patients with congestive heart failure. It may also predispose these patients to hyperkalemia.

It appears that use of ACE inhibitor and ARBs may be associated with higher levels of serum creatinine. In stage II of the RESOLVD trial⁵ where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of plasma creatinine concentrations $\geq 50\%$ of baseline and above 106 $\mu\text{mol/L}$ was found in 4.8% of patients receiving candesartan or enalapril alone, and 2.4% of patients receiving candesartan plus metoprolol or enalapril plus metoprolol; however, this doubled to 9.3% in patients receiving candesartan *plus* enalapril, and 9.0% in patients receiving candesartan *plus* enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.34), it is interesting to note that larger proportions of patients who received *both* candesartan *and* enalapril (with or without metoprolol) had elevated plasma creatinine concentrations. In the Val-HeFT trial¹⁶ where valsartan was compared to placebo with all patients receiving standard therapy for heart failure, significantly (P < 0.001) larger increases were found in the valsartan treated group compared to placebo in BUN (5.9 mg/dl in valsartan group vs. 3.3 mg/dl in placebo group) and serum creatinine (15.9 $\mu\text{mol/L}$ in valsartan group and 8.8 $\mu\text{mol/L}$ with placebo).

7.3.3 Hyperkalemia

Hyperkalemia is reported as observed 'on treatment' rather than 'during study' to present a more clinically meaningful measure of possible relationship to the investigational product.

Hyperkalemia in CHARM-Added (SH-AHS-0006) Study:

At baseline, a slightly higher proportion of patients in the candesartan treatment group had a serum potassium ≥ 5 mmol/L (North American study population).

Hyperkalemia was reported for 44 patients (3.5%) in the placebo group and 121 patients (9.5%) in the candesartan group on treatment with the investigational product Table 74).

Fatal hyperkalemia was reported during the study for 2 patients in the candesartan group and no patient in the placebo group. Patient 155-10493 died of sudden death and hyperkalemia (potassium concentration, 6.2 mmol/ L) after approximately two years of candesartan treatment. Patient 201-12699 had abnormal renal function 20 days after starting treatment with candesartan, and died of sudden death and hyperkalemia (potassium concentration, 6.1 mmol/ L) after 52 days of treatment. Both patients had a concomitant unspecified increase in serum creatinine. These AEs are assessed, respectively, as probably and possibly related to the investigational product.

In Table 53, discontinuation of the investigational product because of hyperkalemia was more frequent with candesartan (placebo 11, 0.9%; candesartan 49, 3.8%). In the exploratory analysis the corresponding numbers were 9 (0.7%) for placebo patients and 44 (3.4%) for candesartan patients (Table 58). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by higher use of concomitant medication when the event started, including potassium-sparing diuretics. There was no between treatment difference regarding baseline serum potassium levels in patients who discontinued investigational product due to hyperkalemia (North American study population).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 8 (0.8%) patients in the placebo group and 31 (2.9%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.2%) in the placebo group and 18 (8.5%) in the candesartan group.

In the placebo group the majority of events were seen in male patients, in the candesartan group the events were equally distributed between.

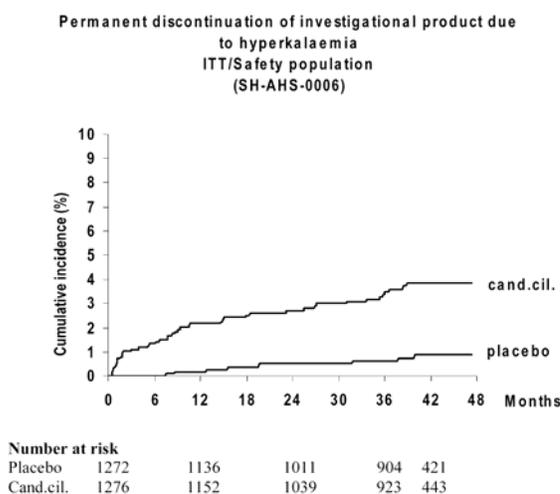


Figure 39 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 56).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, was greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period (Figure 39).

Among the 382 (30.0%) placebo patients and 376 (29.5 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 10 (2.6%) placebo and 31 (8.2%) candesartan patients.

Hyperkalemia in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

At baseline, there were more patients in the candesartan treatment group with serum potassium = 5 mmol/L (placebo 125, 9.3%; candesartan 135, 10.1%) (North American study population).

Hyperkalemia was reported for 78 patients (2.1%) in the placebo group and 238 patients (6.3%) in the candesartan group on treatment with the investigational product (Table 75).

Fatal hyperkalemia ‘during study’ was reported for 2 patients in the candesartan group, and in 1 patient in the placebo group. Both candesartan treated patients were on active treatment in SH-AHS-0006 as described above. The one patient in the placebo group in SH-AHS-0003 was not on treatment with the investigational product and had concomitant renal failure (with an increase in serum creatinine) which could have contributed to the hyperkalemia.

In Table 54, discontinuation of the investigational product because of hyperkalemia occurred more frequently in patients treated with candesartan (placebo 22, 0.6%; candesartan 93, 2.4%). In the exploratory analysis the corresponding numbers were 21 (0.6%) for placebo patients and 85 (2.2%) for candesartan patients (Table 61). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by between treatment differences in concomitant medications at the start of the event, including potassium – sparing diuretics or baseline serum potassium levels (North American study population) (Table 97).

In patients aged younger than 75 years, discontinuation because of the AE term hyperkalemia was reported in 14 (0.5%) patients in the placebo group and 57 (1.9%) patients on candesartan. For patients aged 75 years or older the discontinuation rates were 8 (0.9%) patients in the placebo group and 36 (4.2%) patients in the candesartan group. In the placebo treatment group 16 (0.6%) males and 6 (0.5%) females discontinued due to hyperkalemia. In the candesartan group the majority of events were seen in male patients (72, 2.8%) compared to female patients (21, 1.8%).

The discontinuation rate for candesartan-treated patients because of hyperkalemia, presented from exploratory analysis, (Figure 40), was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.

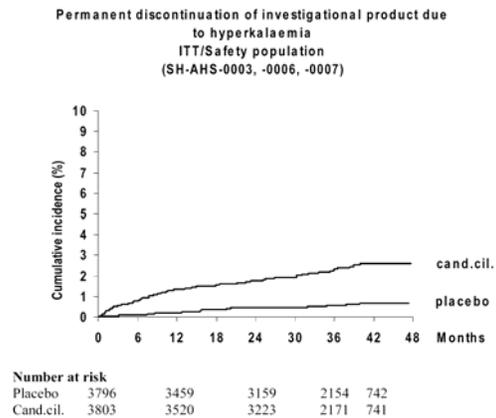


Figure 40 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 13 (1.2%) placebo and 31 (2.8%) candesartan patients (Table 65 and Table 66).

Reviewer’s comments with data from the medical literature: Hyperkalemia is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have hypotension (with poor tissue perfusion and metabolic acidosis) and concomitant treatment with ACE-inhibitors, β -blockers and potassium-sparing diuretics (spironolactone) all of which may increase the serum potassium. Also, one third to one half of patients with congestive heart failure have some degree of renal insufficiency¹⁷ in whom a defect in the renal excretion of potassium further increases the risk of hyperkalemia.

Despite this finding that co-morbid renal insufficiency may cause hyperkalemia, physicians do have to use ACE-inhibitors, ARBs and aldosterone-receptor blockers in the treatment of patients with CHF. This is because chronic kidney disease is among the strongest predictors of death in patients with CHF, and these patients (with CHF and chronic renal failure) happen to be the ones who derive the greatest cardiovascular survival and benefits from these drugs. In the situation where CHF and co-morbid chronic renal failure are present, ACE inhibitors and/or ARBs not only treat the heart failure and reduce the risk of a future cardiovascular event and reduce the risk of death, but they also slow the progression of renal disease^{18,23,24,51,52}. Withholding these drugs on the basis of the level of renal function or fear of causing hyperkalemia will unnecessarily deprive these patients of the cardiovascular benefit and survival benefit that they may obtain from judicious and cautious use of ACE inhibitors and ARBs.

In the OPTIMAAL trial²², a significant (P=0.01) between-group difference was detected for and serum potassium (increased by 0.19 mmol/l in losartan group vs. 0.22 mmol/L in captopril group), being less with the ARB than with the ACE inhibitor. In the Val-HeFT trial¹⁶ where valsartan was compared to placebo with standard therapy for heart failure, a significantly (P <

0.001) larger increase in potassium was found in the valsartan treated group (increase by 0.12 mmol/L) compared to placebo (decrease by 0.07 mmol/L).

In stage II of the RESOLVD trial⁵ where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of hyperkalemia defined as any observed plasma potassium concentration > 5.5 mmol/L was observed in 4.0% in patients receiving candesartan or enalapril alone, 2.4% in patients receiving candesartan plus metoprolol or enalapril plus metoprolol, 8.1% for patients receiving candesartan plus enalapril, and 7.9% for patients receiving candesartan plus enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.3), it is interesting to note that larger proportions of patients who received both candesartan and enalapril (with or without metoprolol) had hyperkalemia.

7.3.4 Angioedema

Angioedema in CHARM-Added (SH-AHS-0006) Study

During the study, two cases of angioedema were reported for patients in the candesartan group. Both patients were Caucasian with concomitant medication with an ACE-inhibitor at the start of the event. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the other patient ACE inhibitor medication was stopped but treatment with candesartan continued.

In the placebo group three patients reported angioedema, in one case leading to discontinuation of the investigational product.

Angioedema in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

During the study 5 cases of angioedema were reported for patients in the candesartan group compared with 3 cases in the placebo treatment group.

All patients in the candesartan treatment group were Caucasian. Three of these patients in the candesartan group had a history of previous angioedema reactions while taking ACE-inhibitors. The remaining two patients in the candesartan group had concomitant medication with an ACE-inhibitor at the start of the event. None of the events was considered life threatening or led to hospitalization. Two patients who developed angioedema required discontinuation of candesartan treatment. For the remaining 3 patients with angioedema, candesartan treatment continued without recurrence of angioedema, and for 1 of these the dose was reduced.

Reviewer's comments with data from the medical literature: Angioedema is an expected clinical event in patients treated with candesartan, particular so since these patients with CHF are receiving concomitant treatment with ACE-inhibitors, and some also had a history of previous angioedema while taking ACE-inhibitors.

The frequency of angioedema as an AE appears to be similar between ARB and ACE-inhibitors.

In the VALIANT trial²⁵ comparing valsartan, valsartan-plus-captopril and captopril, the proportion of patients with angioedema resulting in discontinuation of the study drug are similar; however, more patients in who received captopril or valsartan-plus-captopril reported angioedema resulting in dose reduction (Table 67).

Also, in the OPTIMAAL study²² comparing losartan vs. captopril in patients with acute MI and evidence of heart failure or LV dysfunction, angioedema was reported significantly (P=0.034) more frequently (Table 68) in the captopril group (22 patients, 0.8%) compared to the losartan group (10 patients, 0.4%); angioedema was also associated with a significantly higher proportion of discontinuation (Table 68) from study drug treatment (14 patients (0.5%) in captopril group versus 4 patients (0.1%) in losartan group, P=0.019). Thus, it appears that angioedema is generally reported more frequently in patients receiving ACE inhibitors than in those receiving ARBs.

7.3.5 Myocardial ischemia

Myocardial ischemia in CHARM-Pooled (SH-AHS-0003, -0006,-0007) Studies:

‘Myocardial ischemia’ was evaluated as a composite of the AAED preferred terms: angina pectoris/angina pectoris aggravated, MI and coronary artery disorder. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline prior to enrollment, there were no differences between the treatment groups in the frequencies of patients with previous MI and angina pectoris. Slightly more patients in the candesartan treatment group reported a history of coronary artery bypass grafting (placebo 870, 22.9%; candesartan 921, 24.2%).

The proportions of patients with ‘myocardial ischemia’ ‘on treatment’ were approximately equal in the two treatment groups (18.1% in the placebo group and 16.7% in the candesartan group) (Table 98).

Table 98 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
688 (18.1)	637 (16.7)	774 (20.4)	755 (19.9)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was more frequently reported in the placebo treatment group (placebo 460, 12.1%; candesartan 405, 10.6%). The AE term MI occurred in 216 (5.7%) patients in the placebo group and in 205 (5.4%) in the candesartan group ‘on treatment.’

‘Myocardial ischemic’ events that were fatal were reported for 70 (1.8%) patients in the placebo group and 97 (2.6%) patients in the candesartan group during study (Table 99).

Table 99 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder leading to death. ITT/Safety population (SH-AHS-0003, -0006, -0007)

Placebo on treatment (N=3796)	Cand. cil. on treatment (N=3803)	Placebo during study (N=3796)	Cand. cil. during study (N=3803)
44 (1.2)	66 (1.7)	70 (1.8)	97 (2.6)

Most of the fatal ‘myocardial ischemic’ events ‘during study’ were attributed to fatal MI (57 patients in the placebo group and 77 in the candesartan group).

7.3.6 Abnormal hepatic function

Abnormal hepatic function in CHARM-Added (SH-AHS-0006) Study:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 1 patient; candesartan 6 patients) and hepatic function abnormal (placebo 1 patient; candesartan 4 patients). The AE term hepatic failure was reported for 4 patients in the placebo group and 2 patients in the candesartan group.

Abnormal hepatic function in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

The most common AE terms suggesting liver dysfunction were hepatic enzymes, increased NOS and hepatic function, abnormal; which were reported for 7 and 4 patients, respectively, given placebo treatment and 12 and 10 patients, respectively, given candesartan. The AE term hepatic failure was reported for 5 patients in the placebo group and 6 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis which the investigator and the sponsor considered related to amiodarone (SH-AHS-0003-373-15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (SH-AHS-0003-1476-21109).

Reviewer’s comments: There is no signal that candesartan is associated with increased risk of abnormal liver function tests or hepatic failure.

7.3.7 Neoplasms

AEs indicative of neoplasms, whether benign or malignant, were pooled from the SOC (system organ class) ‘Neoplasms’, plus 3 neoplastic AE terms from other SOCs (Melanoma malignant, Myelomatosis multiple and Pleural mesothelioma).

Neoplasms in CHARM-Added (SH-AHS-0006) Study

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 94.1%; candesartan 93.9%).

Neoplasms were reported for 68 patients (5.3%) in the placebo treatment group compared with 90 (7.1%) in the candesartan group. One patient in the placebo group (Site 1532, Patient number 21520) had both Myeloid dysplasia (included in the SOC Neoplasms) and Myelomatosis

multiple. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 20 patients (1.6%) in the placebo group and 39 patients (3.0%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 7 patients; candesartan, 12 patients), prostatic cancer (placebo, 9 patients; candesartan, 7 patients) and colon cancer (placebo 5 patients; candesartan 8 patients), which are quite typical for patients in this age group.

Neoplasms in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

In the total population slightly more patients in the candesartan treatment group had a history of cancer at baseline (placebo 243, 6.4%, candesartan 270, 7.1%).

Neoplasms were reported for 230 (6.0%) in the placebo group and 244 (6.4%) in the candesartan group. One patient in the placebo group in the component study SH-AHS-0003 (Site 558, Patient number 13436) had Breast neoplasm malignant female and Carcinomatosis (included in the SOC Neoplasms) together with Pleural mesothelioma. One patient in the candesartan group in the component study SH-AHS-0006 (Site 1532, Patient number 21520) had both Myeloid metaplasia (included in the SOC Neoplasms) and Myelomatosis multiple. In the total numbers presented above these patients are counted only once. Neoplasms proved fatal for 59 patients (1.8%) in the placebo group and 84 patients (2.2%) in the candesartan group.

The majority of reported neoplasms were malignant. The most common neoplasm's were prostatic carcinoma (placebo, 27 patients; candesartan, 32 patients), pulmonary carcinoma (placebo, 25 patients; candesartan, 31 patients), colon carcinoma (placebo, 24 patients; candesartan, 26 patients) and breast neoplasm malignant (17 patients in each group). The AE term 'gastrointestinal neoplasm benign' had a higher event rate in the candesartan group during study (placebo, 5; candesartan, 19) whereas 'renal carcinoma' was more frequent in the control group (placebo, 11; candesartan, 5).

7.3.8 Rare Adverse events in CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

Rare adverse events reported include:

- pancytopenia (placebo 1 patient; candesartan 3 patients),
- aplastic anemia (candesartan 1 patient),
- anaphylactic shock and anaphylactoid reaction (placebo 1 patient; candesartan 2 patients),
- Stevens- Johnson syndrome (placebo 2 patients),
- rhabdomyolysis (placebo 2 patients; candesartan 3 patients),
- sarcoidosis (candesartan 2 patients), and
- scleroderma (candesartan 1 patient).

In most cases an alternative cause was identified. There was no sufficient evidence to support a causal relationship to the investigational product.

7.4 Is there is relationship between the dose of candesartan and the important adverse events?

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event or at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving high dose ACE inhibitors and those receiving low dose ACE inhibitors in relation to the adverse events of: (a) aggravated heart failure, (b) hypotension, (c) hyperkalemia, (d) deterioration of renal function, (e) study drug discontinuation, and (f) reduction in dose of study drug

On Nov 12, 2004, I received the sponsor’s response containing the information related to the adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category “no-study drug” was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

7.4.1 Relationship of dose of candesartan to permanent study drug discontinuation due to an adverse event or an abnormal laboratory value

In Table 100, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value.

Table 100 The numbers and frequencies of permanent study drug discontinuation due to an adverse event or an abnormal laboratory value^a in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD} (N=643)			ACEi _{LD} (N=633)		
Candesartan cilexetil^b	CC _{HD} + ACEi _{HFD} N = 426 n = 86 (20.2%)	CC _{LD} + ACEi _{HFD} N = 138 n = 58 (42.0%)	CC ₀₀ + ACEi _{HFD} N = 79 n = 7 (8.9%)	CC _{HD} + ACEi _{LD} N = 393 n = 75 (19.1%)	CC _{LD} + ACEi _{LD} N = 162 n = 64 (39.5%)	CC ₀₀ + ACEi _{LD} N = 78 n = 20 (25.6%)

ACE_{HFD} = ACE inhibitor at heart failure dose; ACE_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Definition used in exploratory safety analyses; ^b Dose of candesartan preceding the event (or at last visit if no event occurred)
 n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.2 Relationship of dose of candesartan to permanent study drug discontinuation due hypotension

In Table 101, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 101 The numbers and frequencies of permanent study drug discontinuation due to hypotension in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose–CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD} (N=643)			ACEi _{LD} (N=633)		
Candesartan cilexetil^b	CC _{HD} + ACEi _{HFD} N = 364 n = 8 (2.2%)	CC _{LD} + ACEi _{HFD} N = 98 n = 13 (13.3%)	CC ₀₀ + ACEi _{HFD} N = 181 n = 1 (0.6%)	CC _{HD} + ACEi _{LD} N = 342 n = 12 (3.5%)	CC _{LD} + ACEi _{LD} N = 131 n = 22 (16.8%)	CC ₀₀ + ACEi _{LD} N = 160 n = 2 (1.3%)

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Definition used in exploratory safety analyses; ^b Dose of candesartan preceding the event (or at last visit if no event occurred)
 n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.3 Relationship of dose of candesartan to permanent study drug discontinuation due to hyperkalemia

In Table 102, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 102 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose–CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD} (N=643)			ACEi _{LD} (N=633)		
Candesartan cilexetil^b	CC _{HD} + ACEi _{HFD} N = 372 n = 16 (4.3%)	CC _{LD} + ACEi _{HFD} N = 94 n = 7 (7.5%)	CC ₀₀ + ACEi _{HFD} N = 177 n = 1 (0.6%)	CC _{HD} + ACEi _{LD} N = 342 n = 12 (3.5%)	CC _{LD} + ACEi _{LD} N = 117 n = 8 (6.8%)	CC ₀₀ + ACEi _{LD} N = 174 n = 0 (0.0%)

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Definition used in exploratory safety analyses; ^b Dose of candesartan preceding the event (or at last visit if no event occurred)
 n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.4 Relationship of dose of candesartan to permanent study drug discontinuation due to increased serum creatinine

In Table 103, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to increased serum creatinine.

Table 103 The numbers and frequencies of permanent study drug discontinuation due to increased creatinine in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose–CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD} (N=643)			ACEi _{LD} (N=633)		
Candesartan cilexetil^b	CC _{HD} + ACEi _{HFD} N = 385 n = 32 (8.3%)	CC _{LD} + ACEi _{HFD} N = 105 n = 20 (19.1%)	CC ₀₀ + ACEi _{HFD} N = 153 n = 2 (1.3%)	CC _{HD} + ACEi _{LD} N = 351 n = 25 (7.1%)	CC _{LD} + ACEi _{LD} N = 127 n = 20 (15.8%)	CC ₀₀ + ACEi _{LD} N = 155 n = 1 (0.7%)

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^a Definition used in exploratory safety analyses; ^b Dose of candesartan preceding the event (or at last visit if no event occurred)
 n = number of patients with one or more events (proportion (%) of patients at the dose)

7.4.5 Relationship of dose of candesartan to dose reductions of study drug due to an adverse event or an abnormal laboratory value

In Table 104, no relationship is apparent between the dose of candesartan and the numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value.

Table 104 The numbers and frequencies of dose reductions of study drug due to an adverse event or an abnormal laboratory value^a in patients who received high or low dose candesartan plus ACE inhibitors at heart failure dose or low dose– CHARM-Added (SH-AHS-0006) Study

	ACEi _{HFD} (N=643)			ACEi _{LD} (N=633)		
Candesartan cilexetil^b	CC_{HD} + ACEi_{HFD} N = 403 n = 88 (21.8%)	CC_{LD} + ACEi_{HFD} N = 83 n = 35 (42.2%)	CC₀₀ + ACEi_{HFD} N = 157 n = 1 (0.6%)	CC_{HD} + ACEi_{LD} N = 380 n = 95 (25.0%)	CC_{LD} + ACEi_{LD} N = 101 n = 43 (42.6%)	CC₀₀ + ACEi_{LD} N = 152 n = 3 (2.0%)

ACEi_{HFD} = ACE inhibitor at heart failure dose; ACEi_{LD} = ACE inhibitor at lower than heart failure dose;
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^aDefinition used in exploratory safety analyses; ^bDose of candesartan preceding the event (or at last visit if no event occurred)
 n = number of patients with one or more events (proportion (%) of patients at the dose)

7.5 Summary of Safety

7.5.1 Summary of safety for CHARM-Added (SH-AHS-0006) Study:

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analyzed during treatment with the investigational product (placebo 979, 77.0%; candesartan 1007, 78.9%) and over the entire study period (placebo 992, 78.0%; candesartan 1026, 80.4%).

Serious adverse events (SAEs) occurred in equal frequency in both treatment groups during study (placebo 75.9%, candesartan 75.9%). Fatal SAEs were less common with candesartan, on treatment with the investigational product (placebo 21.7%; candesartan 16.5%) as well as during the study (placebo 32.5%; candesartan 29.5%). The most common fatal SAEs were CV events and these occurred less frequently in the candesartan treatment group during study (placebo 27.3%; candesartan 23.7%).

24.3% of patients in the candesartan group and 17.6% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding. 17.2% of the patients receiving candesartan and 9.7% receiving placebo required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function (placebo 4.2%; candesartan 8.2%), hypotension (placebo 3.5%; candesartan 5.4%) and hyperkalemia (placebo 0.9%; candesartan 3.8%) were more frequent in the candesartan group.

Differences in mean laboratory values (candesartan compared with placebo) were small and in

keeping with expected values for treatment with inhibitors of the renin-angiotensin-aldosterone system, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups. Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of the investigational product due to any cause ($P < 0.001$).
- Candesartan increased the *number* of permanent discontinuations of the investigational product due to any cause ($P < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value ($P < 0.001$).
- Candesartan increased the *number* of permanent discontinuations of the investigational product due to an AE or an abnormal laboratory value ($P < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value at least once ($P < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

7.5.2 Summary of safety for CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies:

7.5.2.1 Summary of safety in the total population of patients with symptomatic CHF (SH-AHS-0003, 0006, 0007)

In the total population of patients with symptomatic CHF (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) AEs were reported for almost equal proportions of patients in the two treatment groups, both during treatment with the investigational drug (placebo 2732, 72.0%; candesartan 2788, 73.3%) and over the entire study period (placebo 2799, 73.7%; candesartan 2841, 74.7%).

SAEs, fatal and non-fatal, occurred less frequently with candesartan than with placebo on treatment (placebo 67.5%; candesartan 63.4%) as well as during the study, whether on or off treatment (placebo 71.1%; candesartan 69.0%). Fatal SAEs were also less common with candesartan (placebo 16.2%; candesartan 13.3%) on treatment as well as during the study (placebo 24.9%; candesartan 23.3%). The most common fatal SAEs were CV events which occurred less frequently in the candesartan treatment group during study (placebo 20.3%; candesartan 18.2%)

16.1% of patients in placebo group and 21.0% in candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

8.5% of the patients receiving placebo and 15.0% of the patients receiving candesartan required a reduction in the investigational product dose.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Cardiac failure aggravated (placebo 4.9%; candesartan 4.3%), abnormal renal function (placebo 2.9%; candesartan 6.3%), hypotension (placebo 2.0%; candesartan 4.1%) and hyperkalemia (placebo 0.6%; candesartan 2.4%) were the most commonly reported AEs associated with discontinuation of the investigational product.

The differences in mean laboratory values (candesartan compared with placebo), and the frequency of abnormal values were within expected findings for treatment with inhibitors of the RAAS, i.e., slightly higher serum potassium and creatinine levels.

Mean blood pressure from baseline to LVCF (SBP and DBP) was lowered in both treatment groups.

Mean body weight was slightly decreased in the placebo group and increased in the candesartan group.

7.5.2.2 Summary of safety in the population of patients with depressed LV systolic function (SH-AHS 0003, 0006)

The safety findings in the subpopulation of patients with depressed LV systolic function (SHAHS-0003, SH-AHS-0006) were similar to those in the total population, although the absolute AE rate in the patients with depressed LV systolic function were higher than in the total population. Between-treatment differences (candesartan versus placebo) were very similar to those noted for the total population.

AEs were reported for approximately equal numbers of patients in the two treatment groups (placebo 76.0%; candesartan 77.2%), over the entire study period.

SAEs, fatal and non-fatal, occurred less frequently with candesartan treatment (placebo 70.2%; candesartan 65.8%). Fatal SAEs were also less common with candesartan treatment (placebo 20.2%; candesartan 16.4%). The most common fatal SAEs were CV events.

18.4% in the placebo group and 23.2% of the patients in the candesartan group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Abnormal renal function (placebo, 3.4%; candesartan, 7.4%), hypotension (placebo, 2.5%; candesartan, 5.0%) and hyperkalemia (placebo, 0.6%; candesartan, 3.1%) were the most commonly reported AEs associated with

discontinuation of the investigational product. In the candesartan group the frequency of discontinuation for hyperkalemia relative to placebo was greater in the oldest age groups.

The following findings are significantly different between the two treatment groups:

- Candesartan reduced *time* to permanent discontinuation of investigational product due to any cause ($p < 0.001$).
- Candesartan increased the *number* of investigational product discontinuations due to any cause ($p < 0.001$).
- Candesartan reduced *time* to permanent discontinuation of investigational product due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of permanent investigational product discontinuations due to an AE or an abnormal laboratory value ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to any cause ($p < 0.001$).
- Candesartan increased the *number* of dose reductions due to an AE or an abnormal laboratory value ($p < 0.001$).

Thus, candesartan appears to be safe and well tolerated. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

Overall conclusions

Candesartan appears to be safe and well tolerated in this population of patients with chronic heart failure. Discontinuations and dose reductions attributed to a decline in renal function, hypotension and hyperkalemia occur more frequently with candesartan than placebo. The AE profile of candesartan in heart failure patients is consistent with the pharmacology of the drug and the health status of the patients.

7.5.3 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor submitted pooled safety data from all of the CHARM Program studies (SH-AHS-0003, -0006 and -0007). I have presented and discussed the data from this pivotal study (SH-AHS-0006) and the overall CHARM-Pooled data in my safety review above. Safety data from the clinical pharmacology studies and from the non-CHARM studies are generally consistent with data from the CHARM-Pooled studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

8.1.1 Dose of Candesartan (or ARB)

An insufficient dose of ARBs used in previous clinical trials may have contributed to the observed lack of beneficial effect of ARBs on mortality. In the ELITE¹⁹ and ELITE II²⁰ studies, the dose of losartan (50 mg q.d.) was chosen based on the effects of losartan in hypertensive patients, where the antihypertensive dose-response curve to losartan peaks at about 50 mg/day and plateaus at higher doses. This dose may not fully block AT₁ receptors throughout the 24-hour dosing interval.

In a study on human volunteers²¹ where each subject was challenged with a pre-determined blood pressure elevating-dose of angiotensin II (to raise radial artery systolic pressure by 20 mmHg) after oral dosing with placebo, losartan 50 mg or losartan 150 mg, only the higher dose of 150 mg losartan was found adequate to produce a maximum inhibition of the pressor response to angiotensin II (Figure 41). Thus, the dose used in ELITE¹⁹ and ELITE II²⁰ may have been insufficient to substantially block the AT₁ receptor. ELITE II showed no survival advantage of losartan over captopril; the insufficient dose of losartan used may, at least in part, be the reason for this lack of effect.

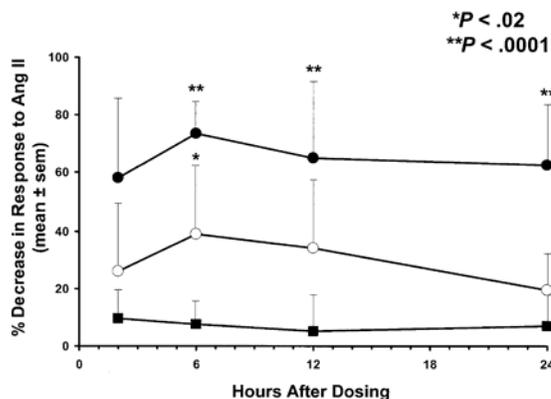


Figure 41 Blockade of the pressor response to intravenous infusions of angiotensin II (Ang II) in normal volunteers after oral administration of placebo (■), losartan 50 mg (○), or losartan 150 mg (●). * P < 0.02, ** P < 0.0001 compared with placebo. (Based on data from J Cardiovasc Pharmacol 2001; 37: 692-6)²¹.

Also, in the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial²², losartan (at a dose of 50 mg q.d.) was compared to the ACE inhibitor captopril (at a dose of 150 mg/day) in high-risk patients with acute myocardial infarction (Figure 42). The results were in favor of captopril both for all cause mortality (not significant, P = 0.069) and for cardiovascular mortality (P=0.032). In this case, too, an insufficient dose of losartan can be attributed as a reason for the failure to show superiority of losartan over captopril.

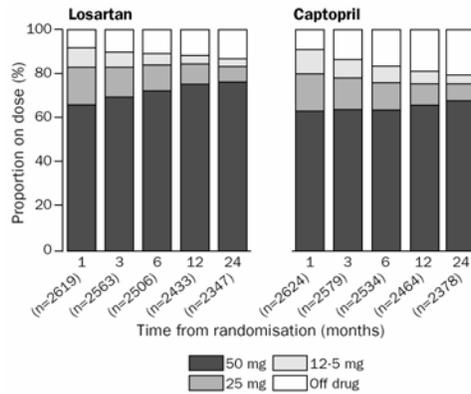


Figure 42 Dose of study drug Losartan was administered once daily and captopril three times daily. (OPTIMAAL Study)²² (Based on data from Lancet 2002; 360: 752-60.)

In contrast, in two recent clinical trials^{23,24} in which the dose of losartan was increased gradually to 100 mg per day in asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy, a significant survival benefit among high-risk patients was observed.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 9,193 participants 55-80 years old with essential hypertension and left ventricular hypertrophy ascertained by ECG, were randomly assigned to receive losartan (titrated to 100 mg) or atenolol (titrated to 100 mg) once daily²³. A significant reduction (by 15%, $P = 0.009$) in the primary composite endpoint of cardiovascular mortality, stroke and MI was found in the subjects treated with losartan (Figure 43).

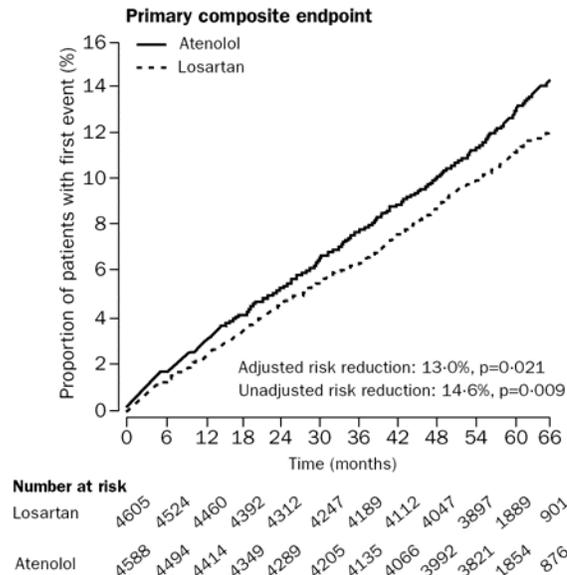


Figure 43 Kaplan Meier curves for primary composite endpoint (LIFE study)²³ (Based on data from Lancet 2002; 359: 995-1003.)

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

(RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years²⁴. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death. Losartan reduced the primary endpoint significantly (relative risk reduction = 16%, P=0.02), and also reduced the incidence of doubling of serum creatinine concentration (relative risk reduction= 25%, P=0.006) and end-stage renal failure (relative risk reduction= 28%; P=0.002), and also reduced the rate of first hospitalization for heart failure (relative risk reduction= 32%, P=0.005) but had no effect on the rate of death (Table 105).

**Table 105 Incidence of the primary composite endpoint and its components in RENAAAL study²⁴
 (Based on data from N Engl J Med 2001; 345: 861-9.)**

END POINT	LOSARTAN GROUP (N=751)		PLACEBO GROUP (N=762)		P VALUE	RISK REDUCTION % (95% CI)
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
Primary composite end point†	327 (43.5)	15.9	359 (47.1)	18.1	0.02	16 (2 to 28)
Doubling of serum creatinine concentration	162 (21.6)	7.9	198 (26.0)	10.0	0.006	25 (8 to 39)
End-stage renal disease	147 (19.6)	6.8	194 (25.5)	9.1	0.002	28 (11 to 42)
Death	158 (21.0)	6.8	155 (20.3)	6.6	0.88	-2 (-27 to 19)
End-stage renal disease or death	255 (34.0)	11.7	300 (39.4)	14.1	0.01	20 (5 to 32)
Doubling of serum creatinine concentration and end-stage renal disease	226 (30.1)	11.0	263 (34.5)	13.2	0.01	21 (5 to 34)

†The primary endpoint was a composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death.

However, when lower doses of ARBs were used, a survival benefit was not found. In a recent trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)²⁵, 14,808 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) plus captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. This study was designed to assess non-inferiority of valsartan relative to captopril. All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan-and-captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Table 106).

Table 106 Cardiovascular mortality and morbidity in VALIANT trial²⁵ (Based on data from N Engl J Med 2003; 349: 1893-1906.)

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value	P Value for Non-inferiority	Hazard Ratio (97.5% CI)	P Value
	<i>number (percent)</i>							
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

The VALIANT study²⁵ showed that valsartan and captopril were equivalent in terms of overall mortality and in terms of the composite endpoint of fatal and nonfatal cardiovascular events, whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival.

It has been suggested that the lack of beneficial effect of losartan (ELITE¹⁹, ELITE II²⁰ and OPTIMAAL²² trials) and valsartan (VALIANT²⁵ trial) over ACE inhibitors may be due to the fact that a correct (or high enough) dose of the ARB was not used²⁶.

CHARM-Added (SH-AHS-0006) Study

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event or at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving high dose ACE inhibitors and those receiving low dose ACE inhibitors in relation to the primary and secondary efficacy endpoints.

On Nov 12, 2004, I received the sponsor’s response containing the information related to the primary and principal secondary efficacy endpoints, and adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category “no-study drug” was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated):

Please refer to section 6.1.5 (pages 72-77) of this review. The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan plus ACE inhibitors at heart failure dose or low are given in Table 41. It appears that there is a relative dose response, the event rates being significantly ($P < 0.001$) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 42).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 43 and Table 44), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 45 and Table 46) also show similar findings.

As discussed earlier, there are many caveats to these findings:

- (i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.
- (ii) Such “within treatment group” analyses are subject to confounding, which limits the ability to interpret findings.
- (iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.
- (iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.
- (v) For the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.
- (vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including ACE inhibitors at recommended dose vs less than heart failure recommended dose.

8.1.2 ACE inhibitor dose

ACC/AHA guidelines recommend ACE inhibitors as the first-line therapy for symptomatic CHF with reduced systolic function and for asymptomatic LV dysfunction²⁷. Treatment with ACE inhibitors has been proven to be effective in reducing mortality in CHF²⁸. However, in a proportion of patients with congestive heart failure, there are increased plasma angiotensin II levels despite ACE inhibitor therapy resulting in death or decompensated heart failure²⁹. While the reasons are not clear, ACE inhibitors block only 13% of the total production of angiotensin II in the human heart due to the existence of ACE-dependent pathways³; thus, it is possible that an effective blockade of the RAAS may require larger than standard doses of ACE inhibitor³⁰. It is generally thought that to achieve a reduction in mortality in CHF patients, ACE inhibitors must

be used at heart failure doses³¹ that have been shown to demonstrate a reduction in mortality and morbidity (Table 107). For the SH-AHS-0006 study, the protocol required that each investigator stated whether the patient was on individualized heart failure dose of ACE inhibitor.

Table 107 Target doses of ACE inhibitors for heart failure used in studies that demonstrate a reduction in mortality and morbidity³¹

ACE inhibitors used in clinical trials in heart failure	Starting dose	Target dose	Clinical Trial	Average dose in study
Captopril	6.25 mg t.i.d.	25 - 50 mg t.i.d.	SAVE	not available
Enalapril	5 mg b.i.d.	10 mg b.i.d.	SOLVD P/T	16-18 mg
Fosinopril	10 mg q.d.	40 mg q.d.	FEST	not available
Lisinopril	2.5 mg q.d.	40 mg q.d.	ATLAS	19 mg
Ramipril	2.5 mg b.i.d.	5 mg b.i.d.	AIRE	not available
Trandalopril	1 mg q.d.	4 mg q.d.	TRACE	not available

The dose of other ACE inhibitors used should be chosen to equate with the above doses.

AIRE = Acute Infarction Ramipril Efficacy; ATLAS = Assessment of Treatment with Lisinopril and Survival; FEST = Fosinopril Efficacy/Safety Trial; SAVE = Survival and Ventricular Enlargement trial; SOLVD P/T = Studies of Left Ventricular Dysfunction (Prevention/Treatment); TRACE = Trandalopril Cardiac Evaluation.

The mean daily dose of enalapril at baseline was 17.0 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)³² and 17.0 mg in Val-HeFT¹⁶. The mean daily dose of lisinopril was 18.0 mg which is also comparable to the 18.0 mg dose in the treatment arm of Val-HeFT¹⁶. However, for those on captopril, the main daily dose in the CHARM-Added study was lower (82 mg/day) compared to the dose used (107 mg/day) VALIANT²⁵ trial. It is possible that in a background of a relatively low dose of an ACE inhibitor (i.e., patients on captopril and patients on low dose ACE inhibitors for reasons of intolerance to higher doses in the CHARM-Added study) there would be more room for improvement with candesartan.

Table 108 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was a statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of ACE inhibitors at baseline (RRR = 14.9%, P=0.010), during the study (RRR = 14.8%, P=0.011), and at the visit preceding the event (RRR = 11.8%, P=0.046). Also, a statistically significant reduction in relative risk the primary endpoint of CV death or hospitalization due to CHF for patients treated with candesartan was associated with use of recommended heart failure dose of ACE inhibitors at baseline (RRR = 20.6%, P=0.010), during the study (RRR = 19.08%, P=0.010), and at the visit preceding the event (RRR = 17.7%, P=0.026).

Table 108 CV death or hospitalization due to CHF (confirmed adjudicated) by use of ACE-inhibitors in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac- ebo	Hazard Ratio	95% CI		p- value
						Lower	Upper	
ACE inhibitors	No	2	0	0				
	Yes	2546	483	538	0.851	0.753	0.963	0.010
ACE inhibitors: Recommended heart failure dose	No	1257	251	263	0.915	0.770	1.088	0.314
	Yes	1291	232	275	0.794	0.666	0.945	0.010
ACE inhibitors during study	No	1	0	0				
	Yes	2547	483	538	0.852	0.753	0.963	0.011
ACE inhibitors during study: Recommended heart failure dose	No	1012	213	208	0.910	0.751	1.101	0.331
	Yes	1535	270	330	0.810	0.689	0.951	0.010
ACE inhibitors at the visit preceding the event	No	1527	0	0				
	Yes	1021	483	538	0.882	0.779	0.998	0.046
ACE inhibitors at the visit preceding the event: Recommended heart failure dose	No	479	233	246	0.947	0.791	1.134	0.556
	Yes	542	250	292	0.823	0.694	0.977	0.026

The reduction in relative risk of cardiovascular death or CHF hospitalization (primary efficacy endpoint) was present in patients taking recommended heart failure dose of ACE inhibitors as shown in Figure 44 below.

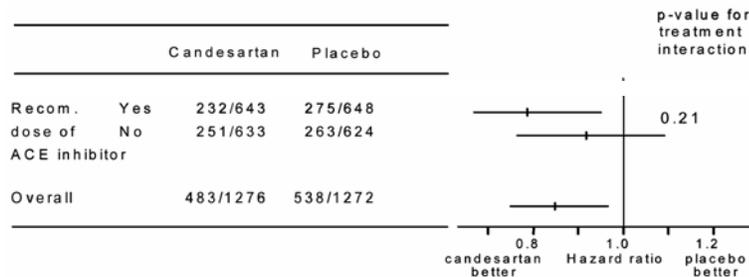


Figure 44 Effect of candesartan compared with placebo on primary outcome in all patients, and patients taking or not taking recommended dose of ACE inhibitors at baseline.

However, I do not think that it is appropriate to just compare the mean daily dose of ACE inhibitors used. As mentioned above, the CHARM-Added (SH-AHS-0006) study consists of CHF patients on “heart-failure doses” of ACE inhibitors and those on “low doses” of ACE inhibitors. One would expect that in a background of a relatively low dose of an ACE-inhibitor, there would be more room for improvement with additional Renin-Angiotensin System (RAS) blockade produced by candesartan. The study’s findings contradict this concept (Table 109, below); i.e., candesartan treatment on top of ACE inhibitor treatment was associated with a significant reduction in CV deaths or CHF hospitalizations in the sub-group of CHF patients

receiving high-dose ACE inhibitors (A vs. C in Table 109), and NOT in those receiving low-dose ACE inhibitors (B vs. D in Table 109).

Table 109 Comparison of the primary efficacy endpoints for patients treated with candesartan versus those treated with candesartan plus an ACE inhibitor

Primary Efficacy Endpoint	Overall Study AHS-0006	Cc on top of ACEi _{HFD}	Cc + ACEi _{LD}	Cc in AHS-0003	ACEi _{HFD} on top of Cc	ACEi _{HFD} vs. ACEi _{LD}	CC + ACEi _{HFD} vs. ACEi _{LD}
	A+B vs. C+D	A vs. C	B vs. D	~B vs. ~D	A vs. B	C vs. D	A vs. D
CV deaths or CHF hospitalizations:							
Hazard Ratio	HR = 0.853;	HR = 0.794	HR = 0.915	HR = 0.768	HR = 0.874	HR = 1.006	HR = 0.799
Relative Risk Reduction	RRR = 14.7%	RRR = 20.6%	RRR = 8.5%	RRR = 23.2%	RRR = 12.6%	RRR = NA	RRR = 20.1%
P	P = 0.011	P = 0.010	P = 0.314	P < 0.001	P = NA	P = NA	P = 0.0127

A, B, C and D = Reference to cells in Table 37.

This finding in the CHARM-Added study is difficult to explain. The ATLAS (Assessment of Treatment with Lisinopril and Survival)¹² study evaluated the effect of high dose lisinopril (32.5 to 35 mg/day, n = 1,568) versus low dose lisinopril (2.5 to 5 mg/day, n = 1,596) in the treatment of 3,164 patients with CHF (NYHA class III and LVEF ≤ 0.30) with a 39 – 58 months follow-up time. This study showed that all-cause mortality was NOT statistically significant between groups, but high dose lisinopril produced a significant 12% reduction (P=0.002) in the relative risk of the composite endpoint of death or hospitalization for any reason, and significantly (P<0.001) reduced the relative risk for the composite endpoint of all-cause deaths or CHF hospitalizations by 15%, compared with the low-dose regimen (Table 110).

Table 110 Effect of high and low dose lisinopril on major clinical events (ATLAS Study)¹² (Based on data from Circulation 1999; 100: 2312-8.)

	Low-Dose	High-Dose	Hazard Ratio	P
All-cause mortality	717 (44.9)	666 (42.5)	0.92 (0.82–1.03)	0.128
Cardiovascular mortality	641 (40.2)	583 (37.2)	0.90 (0.81–1.01)	0.073
All-cause mortality+hospitalization for any reason	1338 (83.8)	1250 (79.7)	0.88 (0.82–0.96)	0.002
All-cause mortality+hospitalization for cardiovascular reason	1182 (74.1)	1115 (71.1)	0.92 (0.84–0.99)	0.036
All-cause mortality+hospitalization for heart failure*	964 (60.4)	864 (55.1)	0.85 (0.78–0.93)	<0.001
Cardiovascular mortality+hospitalization for cardiovascular reason	1161 (72.7)	1088 (69.4)	0.91 (0.84–0.99)	0.027
Fatal and nonfatal myocardial infarction+hospitalization for unstable angina	224 (14.0)	207 (13.2)	0.92 (0.76–1.11)	0.374

Values in parentheses indicate percentage or range. P values determined by log-rank test. Hazard ratios represent 95% CI, except for all-cause mortality, shown as 96.1% CI.

*Analysis not specified in protocol before breaking the blind.

In contrast, the NETWORK (Clinical Outcome with Enalapril in Symptomatic Chronic Heart Failure)³³ trial found no differences between high-dose and low-dose treatment groups for any of the endpoints measured among 1,532 patients with NYHA class II (65% of patients) to class III/IV (35% of patients) heart failure randomized to receive enalapril 2.5 mg b.i.d., 5 mg b.i.d. or 10 mg b.i.d., followed up for 24 weeks. It is possible that even maximally recommended doses of ACE inhibitors do not completely prevent ACE-mediated formation of angiotensin II in CHF³⁴.

In a study of 75 patients with CHF randomized to low- (5 mg daily) and high-dose (40 mg daily) enalapril in a double-blind trial¹³, the cardiac dimensions did not change with either high- or low-dose enalapril with the exception of the thickness of the interventricular septum (Table 111).

Table 111 Echocardiographic Characteristics of the CHF Patients Participating in the Low-Dose (5 mg/ day) Versus High-Dose (40 mg/ day) Enalapril Study¹³

		Baseline Mean	End of Study Mean	Change From Baseline (mean [SD])
LV ED (cm)	Low	7.1	7.3	0.1 (0.6)
	High	7.1	6.9	-0.2 (1.1)
LV ES (cm)	Low	6.1	6.1	-0.0 (0.6)
	High	6.2	5.9	-0.1 (0.8)
IVS (cm)	Low	0.98	0.99	-0.01 (0.23)
	High	1.01	0.91	-0.12 (0.25)*
LVPW (cm)	Low	1.01	1.02	0.02 (0.27)
	High	1.02	0.99	-0.08 (0.20)
LV EF (%)	Low	24.4	27.1	3.6 (8.5)
	High	21.0	26.3	3.6 (12.8)

LV ED and LV ES = left ventricular end diastolic and systolic dimensions, respectively; IVS = interventricular septum thickness; LVPW = left ventricular posterior wall thickness; LV EF = left ventricular ejection fraction.
 *p < 0.05 versus baseline.

The High Enalapril Dose Study Group¹⁴ enrolled 248 patients with advanced CHF who were randomized to receive a maximal tolerated dose of enalapril, up to 20 mg/day in Group 1 (mean dose achieved 17.9 ± 4.3 mg/ day, n=122) and 60 mg/day in Group 2 (mean dose achieved 42 ± 19.3 mg/day, n=126). There were 22 deaths (18.03%) in Group 1, and 23 deaths (18.25%) in Group 2 (hazard ratio = 0.998; confidence interval [CI 0.556 to 1.790, p=0.995) (Figure 45).

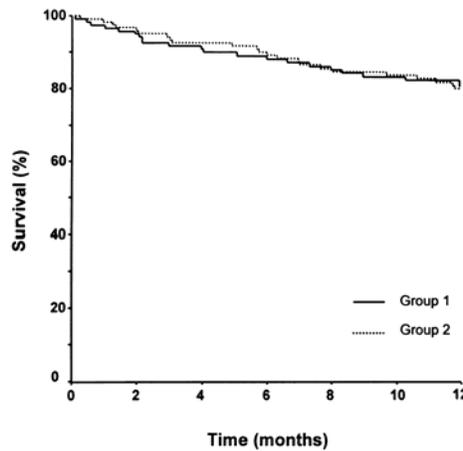


Figure 45 Cumulative mortality in Groups 1 and 2 of High Enalapril Dose Study¹⁴. (Based on data from (J Am Coll Cardiol 2000; 36: 2090-5.)

No statistically significant differences in survival were observed in subgroup analyses in terms of age, etiology of heart failure, SBP, ejection fraction and HR when using high dose enalapril as a covariant for each subgroup. No difference was found when death and hospital admission were used as a composite end point for statistical analysis (p=0.645, log-rank test) (Figure 46).

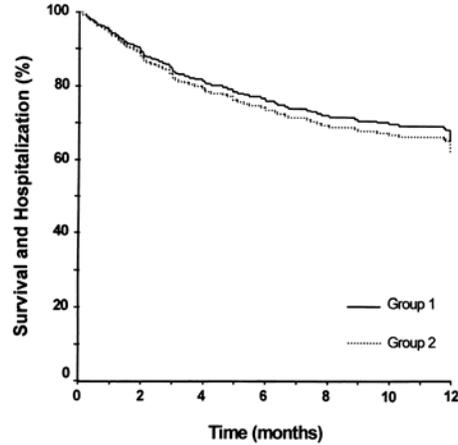


Figure 46 Cumulative incidence of composite end point of mortality and hospital admission in the two treatment groups in High Enalapril Dose Study¹⁴. (Based on data from (J Am Coll Cardiol 2000; 36: 2090-5.)

The above findings need to be considered in the context of actual clinical practice where the doses of ACE inhibitors used are often less than those demonstrated to be of benefit in clinical trials, mostly because of concern for perceived adverse effects at higher doses. Currently, most physicians are of the opinion that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be small. The ACC/AHA recommended that patients with CHF should not generally be maintained on very low doses of an ACE inhibitor unless these are the only doses that can be tolerated²⁷. Thus, the survival benefit of candesartan that is seen in patients receiving full “heart-failure doses” of ACE inhibitors may not be translated into actual clinical practice in the management of chronic heart failure at the primary care level.

The results in the CHARM-Added (SH-AHS-0006) study suggest that the CHF patients in the CHARM studies who were on “low doses” of ACE inhibitors may have been at an optimal dosage that they could just tolerate, and thus were obtaining a balanced mortality/morbidity benefit without accruing any potential adverse effects that could have arisen from the addition of ARBs to ACE inhibitors in their clinically delicate condition. As discussed above, randomized trials of ACE inhibitors have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors^{12,13,14,15}.

8.2 Drug-Drug Interactions

In general, patients in the CHARM Program studies were also receiving aggressive heart failure treatment with combinations of diuretics, β -blockers and digitalis as well as individually optimized doses of ACE inhibitors prior to randomization.

CHARM-Added (SH-AHS-0006) Study

At the time of randomization, 99.9% of the patients were on treatment with ACE-inhibitors (as required by the protocol), 56% were on treatment with a β -blocker, 90% with diuretics, 58% with digitalis and 17% were treated with spironolactone, without major differences between treatment groups.

Enalapril, lisinopril, captopril and ramipril were the most commonly used ACE inhibitors, together accounting for 74% of all ACE inhibitors used. In the candesartan group, the mean daily doses of these ACE inhibitors were 16.8, 17.7, 82.2 and 6.8 mg, respectively, and in the placebo group, 17.2, 17.7, 82.7 and 7.3 mg, respectively. Slightly more than 50% of the patients received the recommended ACE inhibitor dose for treatment of heart failure.

Metoprolol and carvedilol were the two most commonly used β -blockers. The mean daily doses of metoprolol were 88.8 mg in the candesartan group and 84.1 mg in the placebo group, and the mean daily doses of carvedilol were 28.6 in the candesartan group and 27.5 mg in the placebo group.

After randomization, the use of some concomitant medications were more common in the placebo group than in the candesartan group at the closing visit [β -blockers in 586 patients (67.8%) vs. 577 patients (64.3%), spironolactone in 216 patients (25.0%) vs. 182 patients (20.3%) and ACE inhibitors in 727 patients (84.1%) vs. 709 patients (79.0%)]. The proportion of patients using β -blockers and spironolactone increased during the study period while the proportional usage of ACE inhibitors decreased.

CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

At the time of randomization, the CHF patients in the total CHARM-Pooled population were receiving conventional heart failure treatments including diuretics (6,286, 83%), β -blockers (4,203, 55%), digoxin (3,254, 43%), ACE-inhibitors (3,125, 41%) and spironolactone (1,272, 17%). The most frequently used β -blockers were metoprolol and carvedilol that were taken, respectively, by 26% (1,945 patients) and 13% (980 patients) of the patient population. These two β -blockers accounted for about 70% of the β -blocker use within this patient population.

At the closing visit, there were more patients in the placebo group receiving diuretics (2,195, 77% vs. 2,171, 75%), β -blockers (1,812, 64% vs. 1,765, 61%), digoxin (1,018, 36% vs. 978, 34%), ACE-inhibitors (1,110, 39% vs. 1,051, 36%) and spironolactone (625, 22% vs. 501, 17%).

The efficacy results of the CHARM-Program studies show that the effects on the primary efficacy endpoints (reduction in relative risk of CV death or CHF hospitalization for CHARM-

Added (SH-AHS-0006) and reduction in the relative risk of all-cause mortality for CHARM-Pooled (SH-AHS-0003, -0006, -0007) studies) were present also in patients taking β -blockers or digoxin.

Within the context of my review of this NDA 20-838 Efficacy Supplement #022, I will present and discuss the findings reported in clinical trials in the medical literature in comparison with the results from the CHARM-Added (SH-AHS-0006) trial.

8.2.1 Is there an interaction of candesartan with β -blockers?

β -blockers have been proven to be effective in reducing mortality from heart failure^{35,36,37}. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)³⁵ in Europe enrolled 2,647 symptomatic patients in New York Heart Association class III or IV, with LVEF \leq 35%, receiving standard therapy with diuretics and ACE-inhibitors. Patients were assigned bisoprolol 1.25 mg (n= 1,327) or placebo (n= 1,320) daily, the drug being progressively increased to a maximum of 10 mg per day. Patients were followed up for a mean of 1.3 years. Analysis was by intention to treat.

The CIBIS-II study was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit (Table 112). All-cause mortality was significantly lower with bisoprolol than placebo (156 [11.8%] vs. 228 [17.3%] deaths, respectively, with a hazard ratio of 0.66 (95% CI 0.54 – 0.81, P < 0.0001)). There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs. 83 [6.3%] deaths, respectively, with a hazard ratio of 0.56 (95% CI 0.39 – 0.80, P= 0.0011)). Treatment effects were independent of the severity or cause of heart failure.

Table 112 Primary and secondary endpoints and exploratory analyses in CIBIS-II study³⁵ (Based on data from Lancet 1999; 353: 9-13.)

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0.66 (0.54-0.81)	<0.0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0.80 (0.71-0.91)	0.0006
All cardiovascular deaths	161 (12%)	119 (9%)	0.71 (0.56-0.90)	0.0049
Combined endpoint	463 (35)	388 (29%)	0.79 (0.69-0.90)	0.0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1.00 (0.82-1.22)	0.98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0.56 (0.39-0.80)	0.0011
Pump failure	47 (4%)	36 (3%)	0.74 (0.48-1.14)	0.17
Myocardial infarction	8 (1%)	7 (1%)	0.85 (0.31-2.34)	0.75
Other cardiovascular	23 (2%)	28 (2%)	1.17 (0.67-2.03)	0.58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0.75 (0.37-1.50)	0.41
Unknown cause of death	49 (4%)	23 (2%)	0.45 (0.27-0.74)	0.0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0.64 (0.53-0.79)	0.0001

Numbers refer to patients who presented at least once with given event. For hospital admissions, numbers refer to patients admitted at least once with any cause.

The relatively large Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)³⁶ enrolled 3,991 patients with CHF in NYHA class II-IV with EF ≤0.40%, stabilized with optimum standard therapy, in a double-blind randomized controlled study. 1,990 patients were randomly assigned metoprolol CR/XL 12.5 mg (NYHA III-IV) or 25.0 mg once daily (NYHA II), and 2,001 patients were assigned placebo. The target dose was 200 mg once daily and doses were up-titrated over 8 weeks. The primary endpoint was all-cause mortality, analyzed by intention to treat. The MERIT-HF study, too, was stopped by the independent safety committee because all-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%, per patient-year of follow-up]) vs. 217 deaths [11.0%], relative risk 0.66 [95% CI 0.53 – 0.81]; p= 0.00009 or adjusted for interim analyses p= 0.0062). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs. 132, 0.59 [0.45 – 0.78]; p= 0.0002) and fewer deaths from worsening heart failure (30 vs. 58, 0.51 [0.33 – 0.79]; p= 0.0023) (Figure 47).

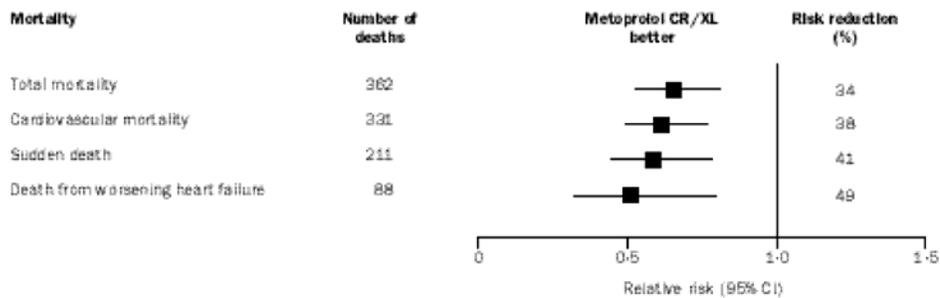


Figure 47 Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure (MERIT-HF study)³⁶ (Based on data from Lancet 1999; 353: 2001-7.)

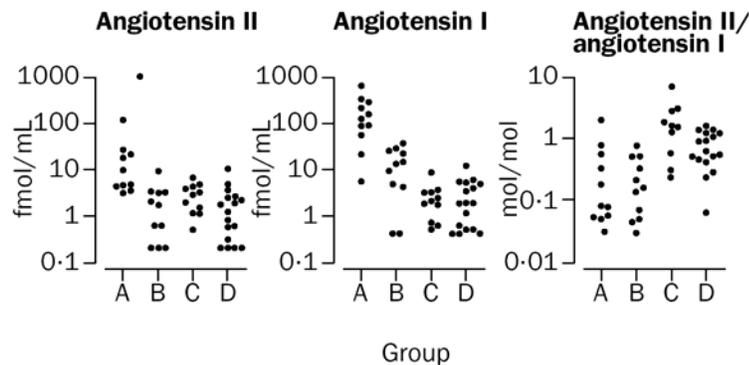


Figure 48 Blood concentrations of angiotensin II and angiotensin I, and angiotensin II/ angiotensin I ratio²⁹ (Based on data from Lancet 2001; 358: 1609-10.)

Group A= patients with heart failure, receiving ACE inhibitors; Group B= patients with heart failure, receiving ACE inhibitors and β -blockers; Group C= controls; Group D= controls, receiving β -blockers.

β -blockers have been shown to inhibit the activation of the sympathetic nervous system during heart failure and also to reduce renin secretion³⁸, either of which could result in improved clinical outcome³⁹. In a study of two matched groups of patients with NYHA class II-III heart failure receiving maximum tolerated doses of ACE inhibitors, half (11 patients) were randomized to receive β -blockers and the other half (11 patients) did not receive β -blockers²⁹. Concentrations

of angiotensin II and angiotensin I (Figure 48) were significantly ($P < 0.01$) higher in the group (Group A) that did not receive β -blockers, whereas patients who received β -blockers (Groups B and D) had low levels of angiotensin II (geometric mean 1.1 [95% CI 0.4 - 2.7] vs. 15.5 [4.6 - 52.6] fmol/mL, 95% CI for difference 3 - 59). Thus, reduction of angiotensin II concentrations by β -blockade might contribute to the therapeutic effects of β -blockade in these CHF patients receiving ACE inhibitors.

In stage II of the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study, metoprolol CR was added to the treatment of 426 patients with CHF and dilated cardiomyopathy receiving enalapril alone, candesartan alone or both^{5,40}. The proportion of patients receiving target doses of ACE inhibitors, candesartan or both was 95% for the group on enalapril alone, 91% for the group treated with candesartan and 85% for the group treated with enalapril and candesartan. Metoprolol CR did not affect 6-minute walk distance, NYHA functional class or quality of life in any group. However, Figure 49 shows that improvements were seen in LV ejection fraction (increased by 2.4% in the metoprolol CR-treated group, $P = 0.001$), attenuation in the increase in LVEDV (by 6 ± 61 mL, versus 23 ± 65 mL for placebo group, $P = 0.01$) and LVESV (reduced by 2 ± 51 mL vs. 19 ± 55 mL for placebo group, $P < 0.001$). There were significantly decreased angiotensin II level ($P = 0.036$) and plasma renin activity ($P = 0.032$), and significantly increased N-terminal atrial natriuretic peptide (ANP) level ($P = 0.001$) and brain natriuretic peptide (BNP) level ($P = 0.002$). There were also fewer deaths in the group receiving metoprolol (3.4%, vs. 8.1% in the placebo group), but the study was not powered to detect differences in clinical endpoints such as death. This study demonstrated that treatment with candesartan, enalapril *and metoprolol* has a more beneficial effect on cardiac volumes and LVEF than treatment with either enalapril alone, candesartan alone or enalapril and candesartan together without a β -blocker.

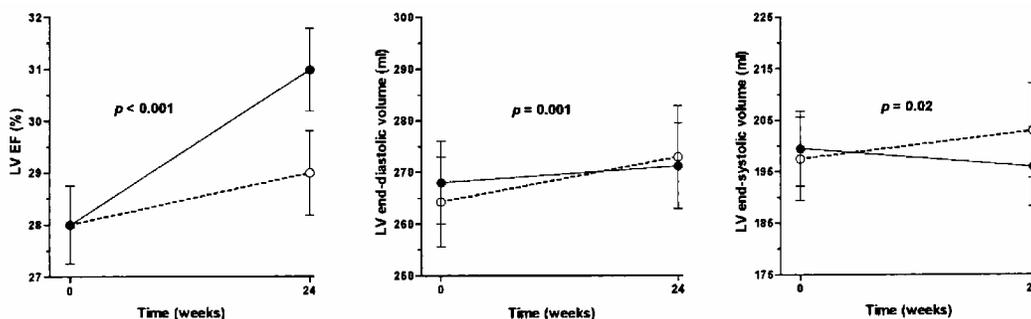


Figure 49 Changes in LVEF and LV volumes in response to metoprolol (●) versus placebo (○) in stage II of the RESOLVD study⁴⁰. Data are mean ± SEM. (Based on data from *Circulation* 2000; 101: 378-84.)

In a later communication dated 16-Sep-2004, the sponsor submitted that there are no other studies on the hemodynamic effects of candesartan in combination with an ACE inhibitor and a β -blocker in patients with heart failure. Also, there are no other reported studies in the medical literature of the hemodynamic effect of this combination treatment in patients with heart failure.

In the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) Study³⁷, a total of 2,289 patients with symptomatic heart failure at rest or minimal exertion and with LVEF

<25% were randomized to receive carvedilol or placebo for a mean period of 10.4 months. They also received conventional heart failure therapy including diuretics, ACE inhibitors or ARBs. There were 190 deaths in the placebo group and 130 deaths in the carvedilol group, reflecting a 35% decrease in the relative risk of death with carvedilol (95% CI 0.19 to 0.48, P = 0.0014, Figure 50). There was also a reduction in the relative risk for the combined endpoint of death or hospitalization by 24% (95% CI 0.13 to 0.33, P<0.001, Figure 51). Thus, addition of carvedilol to conventional therapy for heart failure was beneficial in this group of patients with severe heart failure.

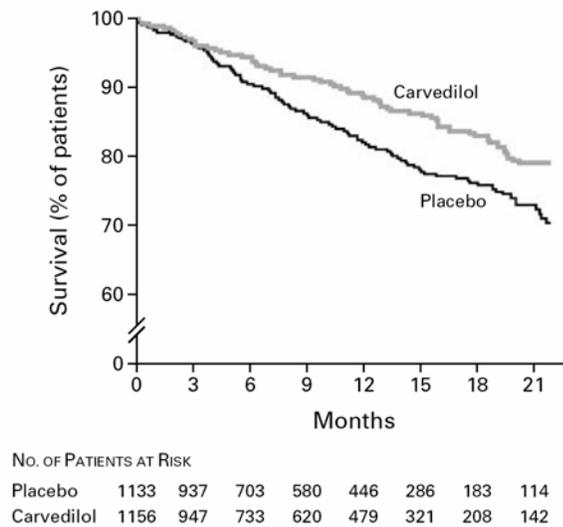


Figure 50 Kaplan-Meier Analysis of Time to Death in Placebo and Carvedilol Groups³⁷ (Based on data from N Engl J Med 2001; 344: 1651-8.) The 35% lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).

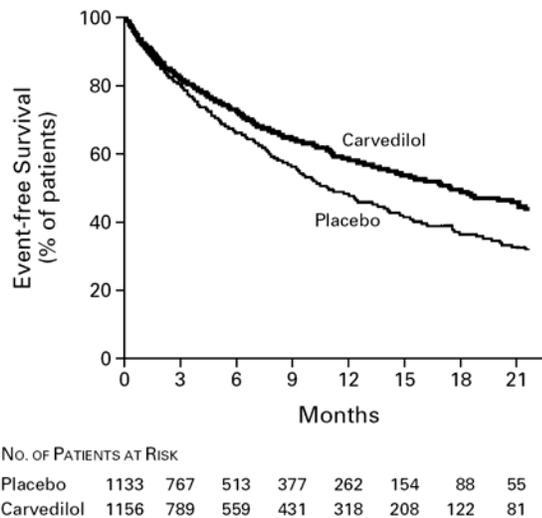


Figure 51 Kaplan-Meier Analysis of Time to Death or First Hospitalization for Any Reason in Placebo and Carvedilol Groups³⁷. (Based on data from N Engl J Med 2001; 344: 1651-8.) The 24 percent lower risk in the carvedilol group was significant (P<0.001).

On the other hand, other studies in the medical literature show contradictory findings.

In ELITE II study²⁰, 3,152 patients with NYHA Class II-IV heart failure and LVEF ≤ 40% were assigned to receive either losartan (50 mg q.d.) or captopril 50 mg t.i.d., and followed up for a median of 1.5 years. Patients were stratified for β-blocker use. The primary and secondary endpoints were all-cause mortality, and sudden death or resuscitated arrest. Median follow-up was 555 days. There were no significant differences in all-cause mortality (11.7 vs. 10.4% average annual mortality rate) or sudden death or resuscitated arrests (9.0 vs. 7.3%) between the losartan and captopril treatment groups (hazard ratios 1.13 [95.7% CI 0.95 – 1.35], p= 0.16 and 1.25 [95% CI 0.98 – 1.60], p= 0.08). No significant interaction was found for concomitant β-blocker use during the study (Figure 52).

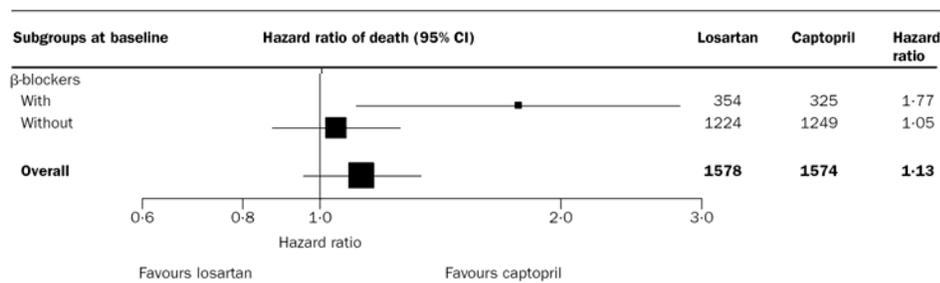


Figure 52 Mortality by subgroup (ELITE II²⁰) (Based on data from Lancet 2000; 355: 1582-7.)

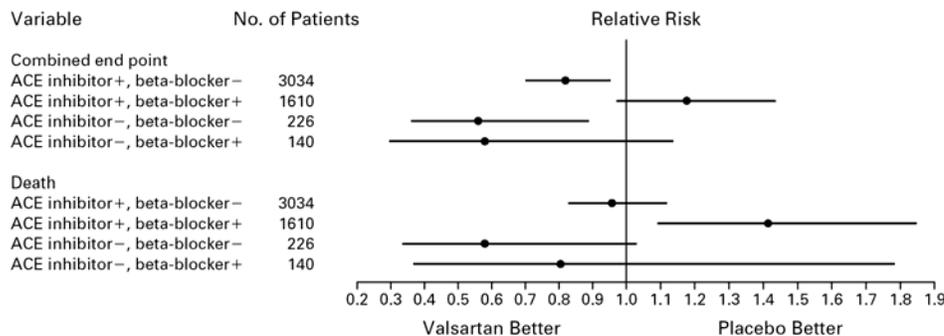


Figure 53 Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, in Val-HeFT study¹⁶. (Based on data from N Engl J Med 2001; 345: 1667-75.)
 ACE denotes angiotensin- converting enzyme, + the use of the drug, and – nonuse.

In the Val-HeFT^{16,41} study, 5,010 patients with symptomatic CHF (93% already treated with ACE inhibitors) were randomized to receive valsartan (starting dose 40 mg b.i.d., titrated to a target dose of 160 mg b.i.d.) or placebo, and followed for 1.9 years. The study found that patients taking β-blockers at baseline who were randomized to valsartan (36% of all enrolled) did worse than those randomized to placebo; i.e. the former had a 15% **increased** risk or morbidity and mortality (P<0.05). The effect of β-blockers are also derived from two sub-groups (Figure 53): (i) in 1,610 patients given triple therapy with ACE inhibitors, β-blockers and

valsartan, there was a significant **increase** in mortality (129 vs. 97 deaths, hazard ratio 1.42, 95% CI 1.09-1.85, p = 0.009) compared with 806 patients treated with ACE inhibitors, β -blockers and placebo; and (ii) in 226 patients **not** given ACE inhibitors or β -blockers, there was a 33% reduction in mortality (P=0.012).

These findings in the Val-HeFT^{16,41} study could have resulted from the combined treatment of valsartan, an ACE-inhibitor, and a β -blocker causing a reduction in blood pressure of 6 to 7 mmHg in the valsartan group; this drop in BP could have been excessive in patients in whom both the RAS and the β -adrenergic receptors were blocked, leading to ischemic events or worsening of heart failure. This interaction was observed only for the baseline therapy with β -blockers, and did not reflect β -blocker use during the study. The Val-HeFT investigators postulated that extensive blockade of multiple neurohormonal systems in patients with heart failure might be deleterious⁴².

One caveat that is unique to the use of β -blockers in heart failure is that they may cause initial worsening before improvement occurs⁴³; i.e., initially, β -blockers may worsen symptoms of heart failure, but improvement is seen after long-term therapy. Thus, to avoid deterioration, heart failure patients must first be stabilized on a regimen of digoxin, diuretics and ACE inhibitors and/or ARBs, and β -blockers must be started at low doses and the doses gradually increased over a period of several weeks. Also, data from the ATLAS trial¹², MERIT-HF trial³⁶ and other β -blocker clinical trials have been computed to show (Table 113) that in patients receiving a low or intermediate dose of an ACE-inhibitor, adding a β -blocker may improve symptoms and reduce the risk of death and hospitalization to a greater magnitude than increasing the dose of the ACE-inhibitor to a maximally tolerated dose^{31,44}.

Table 113 Comparative Effects of Two Different Treatment Strategies in Patients Receiving Low Doses of Angiotensin-Converting Enzyme (ACE) Inhibitors (Based on data from Am J Med 2001; 110: 81S-94S)⁴⁴

	Increasing ACE Inhibitor to Maximal Doses	Adding a β Blocker to the ACE Inhibitor
Effect on symptoms	No change	Improved
Effect on risk of death	8% reduction	30%–40% reduction
Effect on risk of death and hospitalization	12% reduction	20%–40% reduction

Data from the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial were used to predict the effect of increasing the dose of the ACE inhibitor from low dose to maximal doses. Data from the MERIT-HF (Metoprolol Controlled Release Randomized Intervention Trial in Heart Failure), PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise), and MOCHA (Multicenter Oral Carvedilol in Heart Failure Assessment) trials were used to predict effect of adding a β -blocker to the regimen of patients already taking low to intermediate doses of an ACE inhibitor.

CHARM-Added (SH-AHS-0006) study

The protocol specified that for patients for whom therapy with a β -blocker or spironolactone was considered, these treatments were initiated and the dose levels stabilized before patients were randomized into the clinical trial to receive candesartan or placebo.

Table 114 CV death or hospitalization due to CHF (confirmed adjudicated) by use of β -blockers in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
						Lower	Upper	
Beta-blocker	No	1135	260	264	0.933	0.786	1.107	0.427
	Yes	1413	223	274	0.774	0.649	0.924	0.005
Beta-blocker during study	No	723	186	175	0.948	0.771	1.165	0.609
	Yes	1825	297	363	0.793	0.680	0.924	0.003
Beta-blocker at the visit preceding the event	No	1966	222	217	0.946	0.785	1.141	0.561
	Yes	582	261	321	0.860	0.730	1.014	0.072

Table 114 shows that for the primary endpoint of CV death or CHF hospitalization, there was a statistically significant reduction in relative risk (RRR) for patients treated with candesartan which was associated with use of β -blockers at baseline (RRR =22.6%, P=0.005) or during the study (RRR =20.7%, P=0.003), but not at the visit preceding the event (RRR=14.0%, P=0.072).

The reduction in relative risk of CV death or CHF hospitalization (primary efficacy endpoint) was present in patients taking β -blockers as shown in Figure 54 below.

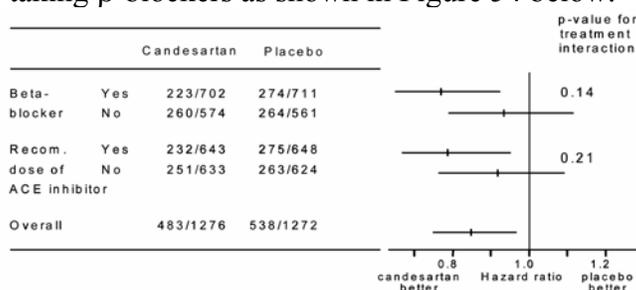


Figure 54 Effect of candesartan compared with placebo on primary outcome in all patients, and patients taking or not taking β -blockers, and/or recommended dose of ACE inhibitors at baseline.

For the component of death in the composite endpoints, there were 175/702 (24.9%) deaths in the candesartan group and 195/711 (27.4%) deaths in the placebo group, with a hazard ratio of 0.88 (95% CI 0.72 to 1.08) in patients treated with a β -blocker at baseline. In patients not treated with a β -blocker at baseline there were 202/574 (35.2%) deaths in the candesartan group and 217/561 (38.7%) deaths in the placebo group, with a hazard ratio of 0.88 (95% CI 0.73 to 1.07). Thus, it appears that candesartan reduced the relative risk of CV death or CHF hospitalization in patients treated with β -blocker in addition to an ACE inhibitor (recommended dose or low dose) at baseline.

Relationship of dose of candesartan to use or non-use of β -blockers in the treatment of CHF

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients

receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event or at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving or not receiving β -blockers at baseline.

On Nov 12, 2004, I received the sponsor’s response containing the information related to the primary and principal secondary efficacy endpoints. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category “no-study drug” was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

Table 115 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive β -blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β -blocker at baseline			Not on β -blocker at baseline		
Candesartan cilexetil^b	CC_{HD} + BB N = 445 n = 146 (32.8%) I ₁	CC_{LD} + BB N = 104 n = 41 (39.4%) I ₂	CC₀₀ + BB N = 153 n = 36 (23.5%) I ₃	CC_{HD} + NB N = 328 n = 138 (42.1%) J ₁	CC_{LD} + NB N = 122 n = 74 (60.7%) J ₂	CC₀₀ + NB N = 124 n = 48 (38.7%) J ₃

BB = receiving β -blocker at baseline; NB = not receiving β -blocker at baseline
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 116 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive β -blockers at baseline on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(I ₁ + J ₁) vs (I ₂ + J ₂)	36.9	0.631	(0.508, 0.784)	< 0.001
I ₁ vs J ₁	--	0.723	(0.573, 0.912)	0.006
I ₁ vs I ₂	19.0	0.810	(0.573, 1.145)	0.233
I ₁ vs J ₂	59.8	0.402	(0.303, 0.531)	<0.001
J ₁ vs I ₂	--	1.122	(0.791, 1.590)	0.519
J ₁ vs J ₂	44.2	0.558	(0.421, 0.741)	< 0.001
I ₂ vs J ₂	--	0.500	(0.341, 0.732)	< 0.001

^a Note: P=0.092 for test for interaction between high/low dose candesartan and baseline covariate (cells I₁, J₁, I₂ and J₂ only)
 Cells I₁, J₁, I₂ and J₂ = Reference to cells in Table 115.

Table 117 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive β -blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β -blocker at baseline			Not on β -blocker at baseline		
Candesartan cilexetil^b	CC_{HD} + BB N = 447 n = 164 (36.7%) K ₁	CC_{LD} + BB N = 105 n = 44 (41.9%) K ₂	CC₀₀ + BB N = 150 n = 44 (29.3%) K ₃	CC_{HD} + NB N = 375 n = 155 (45.3%) L ₁	CC_{LD} + NB N = 122 n = 77 (63.1%) L ₂	CC₀₀ + NB N = 123 n = 61 (49.6%) L ₃

BB = receiving β -blocker at baseline; NB = not receiving β -blocker at baseline
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 118 Comparison of the effect of high or low dose candesartan plus on CHF patients who did or did not receive β -blockers at baseline on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(K ₁ + L ₁) vs (K ₂ + L ₂)	34.0	0.660	(0.535, 0.810)	< 0.001
K ₁ vs L ₁	--	0.749	(0.600, 0.936)	0.011
K ₁ vs K ₂	15.0	0.850	(0.610, 1.186)	0.340
K ₁ vs L ₂	57.0	0.430	(0.328, 0.564)	<0.001
L ₁ vs K ₂	--	1.133	(0.810, 1.587)	0.465
L ₁ vs L ₂	42.4	0.576	(0.437, 0.759)	<0.001
K ₂ vs L ₂	--	0.512	(0.353, 0.743)	<0.001

^a Note: P=0.070 for test for interaction between high/low dose candesartan and baseline covariate (cells K₁, L₁, K₂ and L₂ only)
 Cells K₁, L₁, K₂ and L₂ = Reference to cells in Table 117.

Table 119 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who did or did not receive β -blockers at baseline – CHARM-Added (SH-AHS-0006) Study

	Receiving β -blocker at baseline			Not on β -blocker at baseline		
Candesartan cilexetil^b	CC_{HD} + BB N = 445 n = 149 (33.5%) M ₁	CC_{LD} + BB N = 107 n = 45 (42.1%) M ₂	CC₀₀ + BB N = 150 n = 34 (22.7%) M ₃	CC_{HD} + NB N = 330 n = 144 (43.6%) N ₁	CC_{LD} + NB N = 122 n = 76 (62.3%) N ₂	CC₀₀ + NB N = 122 n = 47 (38.5%) N ₃

BB = receiving β -blocker at baseline; NB = not receiving β -blocker at baseline
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 120 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive β -blockers at baseline on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(M ₁ + N ₁) vs (M ₂ + N ₂)	37.7	0.632	(0.504, 0.770)	< 0.001
M ₁ vs N ₁	--	0.707	(0.562, 0.889)	0.003
M ₁ vs M ₂	23.4	0.766	(0.549, 1.070)	0.118
M ₁ vs N ₂	60.3	0.397	(0.301, 0.523)	<0.001
N ₁ vs M ₂	--	1.085	(0.777, 1.517)	0.631
N ₁ vs N ₂	43.8	0.562	(0.426, 0.743)	< 0.001
M ₂ vs N ₂	--	0.520	(0.359, 0.752)	<0.001

^a Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells M₁, N₁, M₂ and N₂ only)
 Cells M₁, N₁, M₂ and N₂ = Reference to cells in Table 119.

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan with or without concomitant β -blockers at baseline are given in Table 115. It appears that there is a relative dose response, the event rates being significantly ($P < 0.001$) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both groups of patients receiving heart failure doses and low doses of ACE inhibitors (Table 116).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 117 and Table 118), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 118 and Table 120) also show similar findings.

However, there are many caveats to these findings:

- (i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.
- (ii) Such “within treatment group” analyses are subject to confounding, which limits the ability to interpret findings.
- (iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.
- (iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.
- (v) For the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.
- (vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β -blockers (Yes/ No).

8.2.2 Is there an interaction of candesartan with spironolactone or aldosterone blockers?

Findings from Clinical Trials in the Medical Literature

Spironolactone has been shown to decrease mortality in NYHA class IV patients with systolic left ventricular dysfunction who were being treated with an ACE inhibitor⁴⁵; this decreased mortality was attributed to a reduction in the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes.

A recent multicenter, randomized, double-blind, placebo-controlled clinical trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) Study) of eplerenone⁴⁶ – an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone or androgen receptors – involving 6,632 patients with acute

myocardial infarction and left ventricular dysfunction (EF≤40%) and heart failure also supports the above. The EPHEBUS study found that eplerenone treatment was associated with reductions in relative risk of all-cause mortality (hazard ratio 0.85, 95% CI 0.75 to 0.96, relative risk reduction 15%, P = 0.008), and cardiovascular death or hospitalization for cardiovascular events (hazard ratio 0.87, 95% CI 0.79 to 0.95, relative risk reduction 13%, P = 0.002). The reduction in cardiovascular mortality (hazard ratio 0.83, 95% CI 0.72 to 0.94, relative risk reduction 15%, P = 0.005), was attributable to a 21% reduction in the rate of sudden death from cardiac causes (hazard ratio 0.79, 95% CI 0.64 to 0.97, relative risk reduction 21%, P = 0.03).

The EPHEBUS study also shows that the relative risk for all-cause mortality was significantly (P=0.04) reduced when eplerenone was used together with ACE inhibitors (or ARBs) **and** β-blockers (Figure 55).

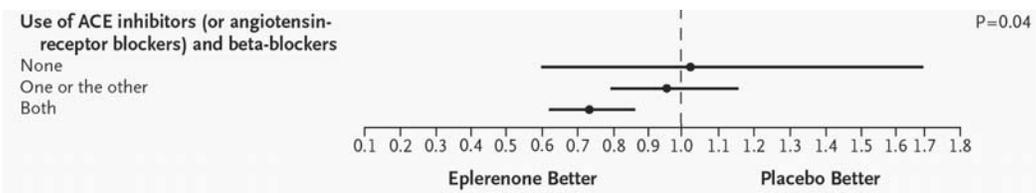


Figure 55 Relative risk of all-cause mortality according to use of and ACE inhibitor (or ARB), a β-blocker or both in EPHEBUS study⁴⁶ (Based on data from N Engl J Med 2003; 348: 1309-21.)

However, for CV death or hospitalization for CV events, there was no statistically significant reduction in relative risk when eplerenone was used together with an ACE inhibitor or angiotensin receptor blocker (ARB) **and** β-blockers (Figure 56).

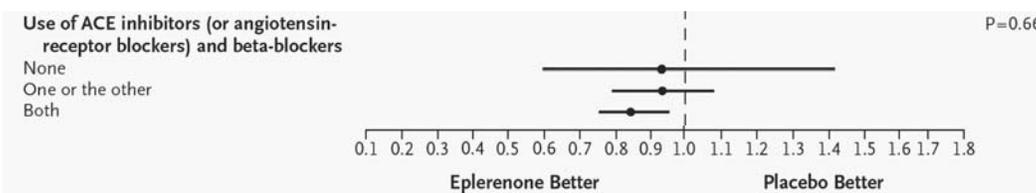


Figure 56 Relative risk of CV death or hospitalization for CV events according to use of an ACE inhibitor (or ARB), a β-blocker or both in EPHEBUS study⁴⁶ (Based on data from N Engl J Med 2003; 348: 1309-21.)

In addition, eplerenone produces a number of pharmacodynamic effects that may contribute to myocardial protection in patients with acute MI complicated by left ventricular dysfunction, such as preventing ventricular remodeling and collagen formation⁴⁷, reducing coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis⁴⁸, reducing oxidative stress and improving endothelial dysfunction⁴⁹, etc.

CHARM-Added (SH-AHS-0006) Study

The sponsor submitted that for patients for whom therapy with a β-blocker or spironolactone was considered, these treatments were initiated and the dose levels stabilized before patients were randomized into the clinical trial to receive candesartan or placebo.

Table 121 CV death or hospitalization due to CHF (confirmed adjudicated) by use of spironolactone in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac- ebo	Hazard Ratio	95% CI		p- value
						Lower	Upper	
Spironolactone	No	2111	378	441	0.819	0.714	0.940	0.004
	Yes	437	105	97	1.005	0.763	1.325	0.971
Spironolactone during study	No	1572	258	285	0.833	0.704	0.986	0.034
	Yes	976	225	253	0.896	0.749	1.073	0.233
Spironolactone at the visit preceding the event	No	2246	330	389	0.812	0.701	0.940	0.005
	Yes	302	153	149	0.834	0.664	1.048	0.119
ACE inhibitors or beta-blocker or Spironolactone	Yes	2548	483	538	0.853	0.754	0.964	0.011
ACE inhibitors or beta-blocker or Spironolactone during study	Yes	2548	483	538	0.853	0.754	0.964	0.011

Table 121 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was no statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of spironolactone at baseline, during the study or at the visit preceding the event. However, when candesartan use was analyzed in conjunction with use of an ACE inhibitor or β -blockers or spironolactone at baseline or during the study, there was a statistically significant ($P=0.011$) reduction (by 14.7%) in relative risk of CV death or hospitalization due to CHF.

Relationship of dose of candesartan to the primary and secondary efficacy endpoints in patients receiving or not receiving spironolactone

Following a Telecon with the sponsor on Nov 2, 2004, I requested the sponsor to provide information on the CHARM-Added (SH-AHS-0006) Study regarding the proportion of patients receiving low dose (4 or 8 mg) or high dose (16 or 32 mg) candesartan *at the time of the event or at the last visit (if no event occurred)* in the each of the sub-populations of patients receiving or not receiving aldosterone antagonists at baseline.

On Nov 12, 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, high candesartan dose is defined as 16 mg or 32 mg and low dose candesartan as 4 mg or 8 mg. Dose level was determined as described in the submission as a patient's last dose (if the patient had no event), or, if the patient had an event, as the last dose prior to the event. The category "no-study drug" was used to classify patients who were not on study drug at the visit prior to the event or not on study drug at the last visit if they had no event.

Table 122 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

Candesartan cilexetil ^b	Receiving spironolactone at baseline			Not on spironolactone at baseline		
	CC _{HD} + SS N = 111 n = 49 (44.1%) O ₁	CC _{LD} + SS N = 57 n = 35 (61.4%) O ₂	CC ₀₀ + SS N = 54 n = 21 (38.9%) O ₃	CC _{HD} + NS N = 662 n = 235 (35.5%) P ₁	CC _{LD} + NS N = 169 n = 80 (47.3%) P ₂	CC ₀₀ + NS N = 223 n = 63 (28.3%) P ₃

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 123 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive spironolactone at baseline on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(O ₁ + P ₁) vs (O ₂ + P ₂)	36.9	0.631	(0.508, 0.784)	< 0.001
O ₁ vs P ₁	--	1.321	(0.971, 1.798)	0.076
O ₁ vs O ₂	38.1	0.619	(0.401, 0.955)	0.030
O ₁ vs P ₂	11.4	0.886	(0.620, 1.264)	0.504
P ₁ vs O ₂	54.2	0.458	(0.321, 1.653)	< 0.001
P ₁ vs P ₂	33.1	0.669	(0.519, 0.862)	0.002
O ₂ vs P ₂	--	1.442	(0.969, 2.146)	0.071

^a Note: P=0.708 for test for interaction between high/low dose candesartan and baseline covariate (cells O₁, P₁, O₂ and P₂ only)
 Cells O₁, P₁, O₂ and P₂ = Reference to cells in Table 122.

Table 124 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

Candesartan cilexetil ^b	Receiving spironolactone at baseline			Not on spironolactone at baseline		
	CC _{HD} + SS N = 111 n = 52 (46.9%) Q ₁	CC _{LD} + SS N = 58 n = 37 (63.8%) Q ₂	CC ₀₀ + SS N = 53 n = 22 (41.5%) Q ₃	CC _{HD} + NS N = 665 n = 261 (39.3%) R ₁	CC _{LD} + NS N = 169 n = 84 (49.7%) R ₂	CC ₀₀ + NS N = 220 n = 83 (37.7%) R ₃

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline
 CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit
^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 125 Comparison of the effect of high or low dose candesartan plus on CHF patients who did or did not receive spironolactone at baseline on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(Q ₁ + R ₁) vs (Q ₂ + R ₂)	34.0	0.660	(0.535, 0.810)	< 0.001
Q ₁ vs R ₁	--	1.268	(0.942, 1.708)	0.118
Q ₁ vs Q ₂	37.3	0.627	(0.411, 0.956)	0.030
Q ₁ vs R ₂	10.4	0.896	(0.634, 1.267)	0.535
R ₁ vs Q ₂	51.6	0.484	(0.343, 0.683)	<0.001
R ₁ vs R ₂	29.5	0.705	(0.551, 0.901)	0.005
Q ₂ vs R ₂	--	1.435	(0.975, 2.114)	0.067

^a Note: P=0.586 for test for interaction between high/low dose candesartan and baseline covariate (cells Q₁, R₁, Q₂ and R₂ only)
 Cells Q₁, R₁, Q₂ and R₂ = Reference to cells in Table 124.

Table 126 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who did or did not receive spironolactone at baseline – CHARM-Added (SH-AHS-0006) Study

Candesartan cilexetil ^b	Receiving spironolactone at baseline			Not on spironolactone at baseline		
	CC _{HD} + SS N = 112 n = 50 (44.6%) S ₁	CC _{LD} + SS N = 57 n = 36 (63.2%) S ₂	CC ₀₀ + SS N = 53 n = 20 (37.7%) S ₃	CC _{HD} + NS N = 663 n = 243 (36.7%) T ₁	CC _{LD} + NS N = 172 n = 85 (49.4%) T ₂	CC ₀₀ + NS N = 219 n = 61 (27.9%) T ₃

SS = receiving spironolactone at baseline; NS = not receiving spironolactone at baseline

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC₀₀ =Not on candesartan at event or last visit

^b Dose of study drug preceding the event (or at last visit if no event occurred)

Table 127 Comparison of the effect of high or low dose candesartan on CHF patients who did or did not receive spironolactone at baseline on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression^a – CHARM-Added (SH-AHS-0006) Study

Comparison	Relative risk reduction	Hazard ratio	95% confidence interval	P-value (Wald)
(S ₁ + T ₁) vs (S ₂ + T ₂)	37.7	0.632	(0.504, 0.770)	< 0.001
S ₁ vs T ₁	--	1.293	(0.954, 1.753)	0.098
S ₁ vs S ₂	39.0	0.610	(0.397, 0.937)	0.024
S ₁ vs T ₂	15.0	0.850	(0.600, 1.206)	0.364
T ₁ vs S ₂	53.9	1.461	(0.325, 0.655)	<0.001
T ₁ vs T ₂	34.4	0.656	(0.513, 0.840)	< 0.001
S ₂ vs T ₂	--	1.409	(0.954, 2.082)	0.085

^a Note: P=0.719 for test for interaction between high/low dose candesartan and baseline covariate (cells M₁, N₁, M₂ and N₂ only)

Cells M₁, N₁, M₂ and N₂ = Reference to cells in Table 126.

CHF Patients who received high or low dose candesartan with or without spironolactone at baseline

Primary efficacy endpoint of CV mortality or CHF hospitalization (confirmed, adjudicated): The proportion of patients who reached the primary efficacy endpoint while on high or low dose candesartan with or without spironolactone are shown in Table 122. It appears that there is a relative dose response, the event rates being significantly (P<0.001) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for patients receiving heart failure doses or low doses of ACE inhibitors (Table 123).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 124 and Table 125), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 126 and Table 127) also show similar findings.

However, there are many caveats to these findings:

- (i) The findings are restricted to patients in the candesartan treatment group, i.e., they cannot be analyzed with corresponding placebo groups.
- (ii) Such “within treatment group” analyses are subject to confounding, which limits the ability to interpret findings.
- (iii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

- (iv) The observation time will differ by dose level, particularly because the protocol-specified dose escalation treatment regimen means that after the first dose level, the experience at subsequent dose levels is conditional on the experience at the prior dose levels. For example, a patient hospitalized for CHF in the first 2 weeks would be assigned to the 4 mg dose level and is removed from the risk set. The patient is now no longer at equal risk for hospitalization at any other dose level. Furthermore, this same patient could complete the study at a higher dose and appear in the candesartan high-dose group for the endpoint of discontinuation for an adverse event.
- (v) For the primary and secondary endpoints, the group with the least events is that receiving NO candesartan at the visit preceding the event or at the last visit if no event occurred.
- (vi) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including spironolactone (Yes/No).

8.2.3 Is there an interaction of candesartan with digoxin?

Findings from Clinical Trials in the Medical Literature

The Digitalis Investigation Group (DIG) Study⁵⁰ showed that combination therapy (of digoxin, diuretic and ACE inhibitor) was better than ACE inhibitor alone. In the main trial, patients with LVEF ≤ 0.45 were randomly assigned to digoxin (3,397 patients) or placebo (3,403 patients) in addition to diuretics and ACE-inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with LVEF > 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo. In the main trial, mortality was unaffected. There were 1,181 deaths (34.8%) with digoxin and 1,194 deaths (35.1%) with placebo (hazard ratio = 0.99; 95% CI, 0.91 to 1.07; P = 0.80) (Table 128).

Table 128 Deaths due to study group and cause in the DIG Study⁵⁰ (Based on data from N Engl J Med 1997; 336: 525-33.)

CAUSE OF DEATH	DIGOXIN	PLACEBO	ABSOLUTE DIFFERENCE*	RISK RATIO (95% CI)†	P VALUE
	(N = 3397)	(N = 3403)			
	no. of patients (%)		%		
All	1181 (34.8)	1194 (35.1)	-0.4	0.99 (0.91-1.07)	0.80
Cardiovascular	1016 (29.9)	1004 (29.5)	0.4	1.01 (0.93-1.10)	0.78
Worsening heart failure‡	394 (11.6)	449 (13.2)	-1.6	0.88 (0.77-1.01)	0.06
Other cardiac§	508 (15.0)	444 (13.0)	1.9	1.14 (1.01-1.30)	
Other vascular¶	50 (1.5)	45 (1.3)	0.1	1.11 (0.74-1.66)	
Unknown	64 (1.9)	66 (1.9)	-0.1	0.97 (0.69-1.37)	
Noncardiac and nonvascular	165 (4.9)	190 (5.6)	-0.7	0.87 (0.71-1.07)	

*Absolute differences were calculated by subtracting the percentage of deaths in the placebo group from the percentage of deaths in the digoxin group (before values were rounded).

†Risk ratios and confidence intervals (CI) were estimated from the Cox proportional-hazards model.

‡This category includes patients who died from worsening heart failure, even if the final event was an arrhythmia.

§This category includes deaths presumed to result from arrhythmia without evidence of worsening heart failure and deaths due to atherosclerotic coronary disease, bradyarrhythmias, low-output states, and cardiac surgery. Although this outcome was not prespecified, P = 0.04 for the comparison of study groups with respect to death from other cardiac causes.

¶This category includes deaths due to stroke, embolism, peripheral vascular disease, vascular surgery, and carotid endarterectomy.

In the digoxin group, there was a trend (not statistically significant) toward a decrease in the risk

of death attributed to worsening heart failure (hazard ratio 0.88; 95% CI, 0.77 to 1.01; P = 0.06) (Figure 57). However, overall mortality was not reduced because an excess of sudden death and ischemic events were observed in patients randomized to digoxin.

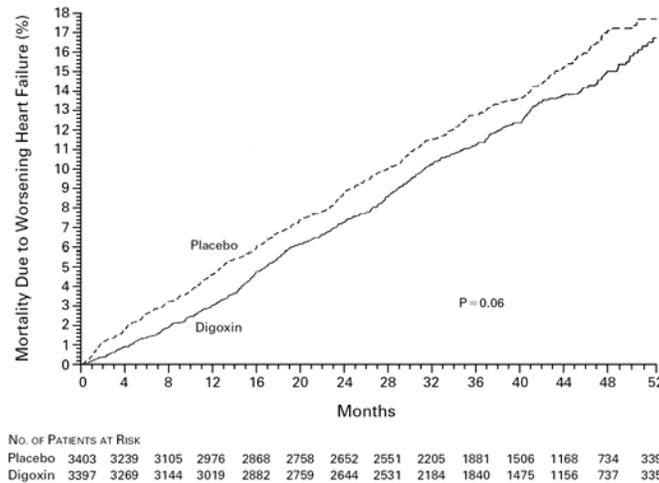


Figure 57 Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups⁵⁰. (Based on data from N Engl J Med 1997; 336: 525-33.) The number of patients at risk at each four-month interval is shown below the figure.

Table 129 Patients hospitalized during the DIG study⁵⁰, according to study group and reason for hospitalization. (Based on data from N Engl J Med 1997; 336: 525-33.)

REASON FOR HOSPITALIZATION*	DIGOXIN (N = 3397)	PLACEBO (N = 3403)	ABSOLUTE DIFFERENCE†	RISK RATIO (95% CI)‡	P VALUE
	no. of patients (%)		%		
Cardiovascular	1694 (49.9)	1850 (54.4)	-4.5	0.87 (0.81-0.93)	<0.001
Worsening heart failure	910 (26.8)	1180 (34.7)	-7.9	0.72 (0.66-0.79)	<0.001
Ventricular arrhythmia, cardiac arrest	142 (4.2)	145 (4.3)	-0.1	0.98 (0.78-1.24)	
Supraventricular arrhythmia§	133 (3.9)	152 (4.5)	-0.6	0.87 (0.69-1.10)	
Atrioventricular block, bradyarrhythmia	14 (0.4)	9 (0.3)	0.1	1.56 (0.68-3.61)	
Suspected digoxin toxicity	67 (2.0)	31 (0.9)	1.1	2.17 (1.42-3.32)	<0.001
Myocardial infarction	195 (5.7)	201 (5.9)	-0.2	0.97 (0.79-1.18)	
Unstable angina	399 (11.7)	398 (11.7)	0.1	1.01 (0.87-1.16)	
Stroke	157 (4.6)	164 (4.8)	-0.2	0.95 (0.77-1.19)	
Coronary revascularization¶	83 (2.4)	71 (2.1)	0.4	1.17 (0.85-1.61)	
Cardiac transplantation	25 (0.7)	16 (0.5)	0.3	1.57 (0.84-2.94)	
Other cardiovascular	452 (13.3)	381 (11.2)	2.1	1.20 (1.05-1.38)	
Respiratory infection	238 (7.0)	252 (7.4)	-0.4	0.94 (0.79-1.12)	
Other noncardiac and nonvascular	1126 (33.1)	1079 (31.7)	1.4	1.06 (0.98-1.15)	
Unspecified	20 (0.6)	18 (0.5)	0.1	1.11 (0.59-2.10)	
No. of patients hospitalized	2184 (64.3)	2282 (67.1)	-2.8	0.92 (0.87-0.98)	0.006
No. of hospitalizations	6356	6777			

*Data shown include the first hospitalization of each patient for each reason.

†Absolute differences were calculated by subtracting the percentage of patients hospitalized in the placebo group from the percentage of patients hospitalized in the digoxin group (before values were rounded).

‡Risk ratios and confidence intervals (CI) were estimated from a Cox proportional-hazards model that used the first hospitalization of each patient for each reason.

§This category includes atrioventricular block and bradyarrhythmia.

¶This category includes coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty.

||This category includes embolism, venous thrombosis, peripheral vascular disease, hypertension, other vascular surgery, cardiac catheterization, other types of catheterization, pacemaker implantation, installation of automatic implantable cardiac defibrillator, electrophysiologic testing, transplant-related evaluation, nonspecific chest pain, atherosclerotic heart disease, hypotension, orthostatic hypotension, and valve operation.

There were 6% fewer hospitalizations overall in the digoxin group than in the placebo group, and

fewer patients were hospitalized for worsening heart failure (26.8% vs. 34.7% ; hazard ratio, 0.72; 95% CI, 0.66 to 0.79; P < 0.001) (Table 129). In the ancillary trial, the findings regarding the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial. Thus, the current concept is that digoxin decreases the need for hospitalization but has not been shown to affect mortality in CHF⁵⁰.

CHARM-Added (SH-AHS-0006) Study

The sponsor submitted that patients who were on digitalis glycosides had their dose levels stabilized before they were randomized into the clinical trial to receive candesartan or placebo.

Table 130 CV death or hospitalization due to CHF (confirmed adjudicated) by use of spironolactone in study SH-AHS-0006. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac- ebo	Hazard Ratio	95% CI		p- value
						Lower	Upper	
Digitalis glycoside	No	1060	172	185	0.873	0.709	1.074	0.200
	Yes	1488	311	353	0.844	0.725	0.983	0.030
Digitalis glycoside during study	No	897	133	134	0.923	0.726	1.173	0.513
	Yes	1651	350	404	0.833	0.722	0.962	0.013
Digitalis glycoside at the visit preceding the event	No	1856	159	170	0.874	0.704	1.085	0.222
	Yes	692	324	368	0.885	0.762	1.029	0.112

Table 130 shows that for the primary endpoint of CV death or hospitalization due to CHF, there was a statistically significant reduction in relative risk for patients treated with candesartan which was associated with use of digitalis glycosides at baseline (RRR = 15.6%, P=0.030) or during the study (RRR = 16.7%, P=0.013), but not at the visit preceding the event (RRR = 11.5%, P=0.112).

8.3 Special Populations

8.3.1 CHF patients with symptomatic hypotension

Patients with heart failure and symptomatic hypotension may require a reduction in the dose of candesartan. In the CHARM program, hypotension was the second most frequently reported adverse event constituting 18.8% of patients on candesartan versus 9.8% of patients on placebo; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.1% compared with 2.0% in placebo-treated patients.

8.3.2 CHF patients with impaired renal function (creatinine increase)

In heart failure patients with impaired renal function treated with candesartan, increases in serum creatinine may require dose reduction and/or discontinuation of candesartan. In the CHARM program, the incidence of “creatinine increase” was 12.5% in patients treated with candesartan versus 6.3% in patients treated with placebo; the incidence of “creatinine increase” leading to drug discontinuation in candesartan-treated patients was 6.3% compared with 2.9% in placebo-treated patients.

8.3.3 CHF patients with hyperkalemia

In heart failure patients treated with candesartan, hyperkalemia may occur, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM program, the incidence of hyperkalemia was 6.3% in patients treated with candesartan versus 2.1% in patients treated with placebo; the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.4% compared with 0.6% in placebo-treated patients.

8.3.4 Geriatric patients with CHF

Of the 7,599 patients with heart failure in the 3 trials of the CHARM program, 4,343 (57 %) were ≥ 65 years old and 1,736 (23 %) were ≥ 75 years old. The pharmacokinetics of candesartan remained linear in patients with CHF; however, the AUC was almost doubled in patients > 65 years old compared to healthy, younger patients. In patients ≥ 75 years of age, the incidence of drug discontinuations due to adverse events was higher for those treated with candesartan or placebo compared with patients < 75 years of age. In these patients, the most common adverse events leading to drug discontinuation at an incidence of at least 3%, and more frequent with candesartan than placebo, were abnormal renal function (7.9% vs. 4.0%), hypotension (5.2% vs. 3.2%) and hyperkalemia (4.2% vs. 0.9%). Thus, greater sensitivity of older individuals with heart failure to candesartan must be considered.

8.4 Pediatrics

The sponsor requested a pediatric waiver from assessing the safety and effectiveness of candesartan for the treatment of heart failure in pediatric patients. By letter dated 26-Aug-2004, the division granted a waiver for the requirement of pediatric studies for all age groups for the applications contained in the CHARM program (S-022, S-024, and S-025).

8.5 Literature Review

In the sections presented and discussed above, relevant medical literature is referenced throughout the review so that a broad perspective of the scientific background and current thinking related to clinical issues in the treatment of CHF is brought into consideration, and objective conclusions of the efficacy and safety findings can be made. In this literature review section, I will present recent advances in the treatment of CHF following the ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined four stages of heart failure²⁷.

Instead of the traditional NYHA classification which describes functional limitations the new staging for heart failure is based on its evolution and progression. The stages of heart failure and treatment options for systolic heart failure are shown in Figure 58.

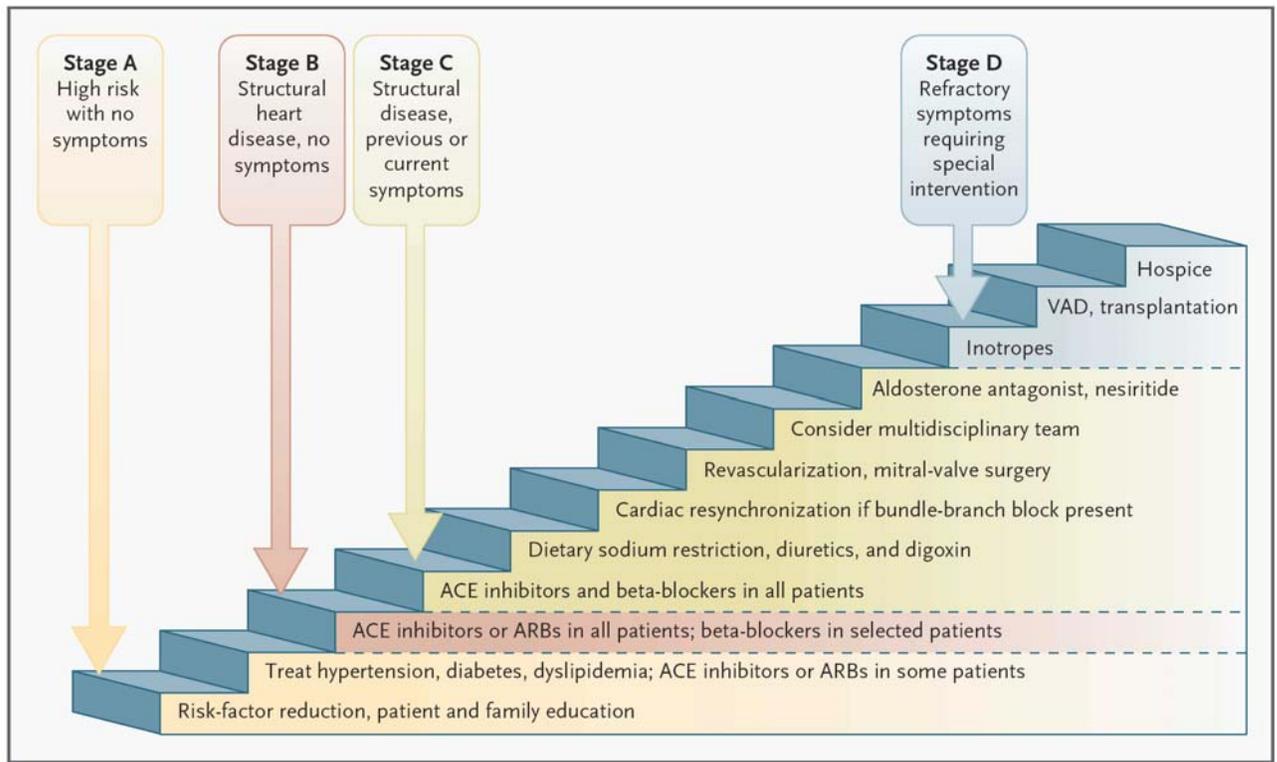


Figure 58 Stages of heart failure and treatment options for systolic heart failure (Based on data from Circulation 2001; 104: 2996-3007)²⁷

The states of heart failure may be described as follows:

- Patients with stage A heart failure are at high risk for the development of heart failure but have no apparent structural abnormality of the heart. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy.
- Patients with stage B heart failure have a structural abnormality of the heart but have never

had symptoms of heart failure. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction or valvular heart disease, all of whom would be considered to have NYHA class I symptoms.

- Patients with stage C heart failure have a structural abnormality of the heart and current or previous symptoms of heart failure. Their symptoms may be classified as NYHA class I, II, III or IV.
- Patients with stage D heart failure have end-stage symptoms of heart failure that are refractory to standard treatment (maximal medical therapy), are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA class IV symptoms.

In the context of this NDA review and the new staging of heart failure, I will present for consideration in this section of the review the following issues relevant to the role of ACE-inhibitors and ARBs in the treatment of heart failure:

8.5.1 Are angiotensin II-AT₁-receptor blockers (ARBs) comparable to ACE-inhibitors or superior to ACE inhibitors?

This is primarily the issue for the CHARM-Alternative (SH-AHS-0003) study, and this will be addressed in detail later in the review for NDA 20-838 Supplement S-024. The following information in the medical literature is presented to provide a background for the review of this current NDA supplement (CHARM-Added SH-AHS-0006 study).

8.5.1.1 Effect of ACE inhibitors on improving survival in patients with heart failure:

For stage A heart failure, the goal of treatment is to prevent remodeling.

In the Heart Outcomes Prevention Evaluation (HOPE) trial, 9,297 asymptomatic high-risk patients (55 years of age or older) with vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomized to receive either ramipril (10 mg once per day orally) or placebo for 5 years^{51,52}. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

A total of 651 patients who were assigned to receive ramipril (14.0%) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8%); thus ramipril reduced the combined rate of CV death, MI and strokes by 22% (relative risk, 0.78; 95% CI, 0.70 to 0.86; P< 0.001). Ramipril also reduced the rates of death from cardiovascular cause, all-cause death, myocardial infarction and stroke (Table 131) in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.

Table 131 Incidence of the primary outcome and deaths from any cause in HOPE study⁵¹ (Based on data from N Engl J Med 2000; 342: 145-53)

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE†
	no. (%)				
Myocardial infarction, stroke, or death from cardiovascular causes‡	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	-4.87	<0.001
Death from cardiovascular causes§	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	-3.78	<0.001
Myocardial infarction§	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	-3.63	<0.001
Stroke§	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	-3.69	<0.001
Death from noncardiovascular causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	-2.79	0.005

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡In the substudy, 34 of 244 patients (13.9 percent) assigned to take a low dose of ramipril (2.5 mg per day) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12.7 percent) and 41 of 244 assigned to placebo (16.8 percent). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95 percent confidence interval, 0.70 to 0.86).

§All patients with this outcome are included.

In the European Trial on the Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA), 12,218 patients were randomized to receive either perindopril (long acting ACE inhibitor with a terminal half-life of 25-30 h) 8 mg once daily (n=6,110) or placebo (n=6,108)⁵³. 65% had previous MI, 50% had coronary artery disease on angiography, and 23% were men with a positive stress test. The mean follow-up was 4.2 years. The primary endpoint was cardiovascular death, myocardial infarction or cardiac arrest. Analysis was by intention to treat. Perindopril reduced the combined frequency of cardiovascular death, MI and cardiac arrest within 4.2 years by 20% (from 603 patients (9.9%) in placebo group to 488 patients (8.0%) in perindopril group (P=0.0003) (Table 132). There was also a non-significant 14% reduction in cardiovascular mortality and a significant 22% reduction in non-fatal MI (P=0.001), and a significant 14% reduction in the composite endpoint of total mortality, non-fatal MI, unstable angina and cardiac arrest (P=0.0009) (Table 132). These benefits were achieved on a background of high usage of aspirin, β-blockers and lipid-lowering agents.

Table 132 Frequency of primary and selected secondary outcomes (EUROPA study)⁵³ (Based on data from Lancet 2003; 362: 782-8)

	Perindopril (n=6110)	Placebo (n=6108)	Relative risk reduction (95% CI)	p
Cardiovascular mortality, MI, or cardiac arrest	488 (8.0%)	603 (9.9%)	20% (9 to 29)	0.0003
Cardiovascular mortality	215 (3.5%)	249 (4.1%)	14% (-3 to 28)	0.107
Non-fatal MI	295 (4.8%)	378 (6.2%)	22% (10 to 33)	0.001
Cardiac arrest	6 (0.1%)	11 (0.2%)	46% (-47 to 80)	0.22
Total mortality, non-fatal MI, unstable angina, cardiac arrest	904 (14.8%)	1043 (17.1%)	14% (6 to 21)	0.0009
Total mortality	375 (6.1%)	420 (6.9%)	11% (-2 to 23)	0.1

The Second Australian National Blood Pressure Lowering Trial (ANBP2)⁵⁴ enrolled 6,083 subjects with hypertension (65 to 84 years of age, receiving health care at 1,594 family practices) in a randomized, open-label study of patients treated with ACE inhibitors vs. those treated with diuretics. Subjects were followed for a median of 4.1 years, and the total numbers of cardiovascular events in the two treatment groups were compared with the use of multivariate proportional-hazards models. There were 695 cardiovascular events or deaths from any cause in the ACE-inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient-years; thus, treatment with an ACE inhibitor was associated with a significant reduction in CV events compared with a diuretic-based regimen for the same reduction in blood pressure (the hazard ratio for a cardiovascular event or death with ACE-inhibitor treatment was 0.89 [95% CI, 0.79 to 1.00]; P= 0.05)) (Table 133).

Table 133 Primary endpoints and cause-specific first events in ANBP2 Study⁵⁴ (Based on data from N Engl J Med 2003; 348: 583-92)

Event	ACE-Inhibitor Group (N=3044)		Diuretic Group (N=3039)		Hazard Ratio (95% CI)	P Value
	No. of Events	Rate per 1000 Patient-yr	No. of Events	Rate per 1000 Patient-yr		
Primary end points						
All cardiovascular events or death from any cause	695	56.1	736	59.8	0.89 (0.79–1.00)	0.05
First cardiovascular event or death from any cause	490	41.9	529	45.7	0.89 (0.79–1.01)	0.06
Death from any cause	195	15.7	210	17.1	0.90 (0.75–1.09)	0.27
Cause-specific first events						
First cardiovascular event†	394	33.7	429	37.1	0.88 (0.77–1.01)	0.07
Coronary event	173	14.3	195	16.2	0.86 (0.70–1.06)	0.16
Myocardial infarction	58	4.7	82	6.7	0.68 (0.47–0.98)	0.04
Other cardiovascular event	134	11.0	144	11.9	0.90 (0.71–1.14)	0.36
Heart failure	69	5.6	78	6.4	0.85 (0.62–1.18)	0.33
Cerebrovascular event	152	12.5	163	13.6	0.90 (0.73–1.12)	0.35
Stroke	112	9.2	107	8.8	1.02 (0.78–1.33)	0.91

* Hazard ratios are for the event in the group assigned to angiotensin-converting-enzyme (ACE) inhibitors as compared with the diuretic group and are adjusted for age and sex. CI denotes confidence interval.

† Myocardial infarction is a subcategory of coronary events; heart failure is a subcategory of other cardiovascular events; and stroke is a subcategory of cerebrovascular events. Patients were counted once for each type of first cardiovascular event they had, but patients who had more than one type of event were counted only once for the overall category of first cardiovascular event.

Among male subjects, the hazard ratio was 0.83 (95% CI, 0.71 to 0.97; P= 0.02); among female subjects, the hazard ratio was 1.00 (95% CI, 0.83 to 1.21; P= 0.98); the P value for the interaction between sex and treatment-group assignment was 0.15 (Figure 59). This led to the recommendation that initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents despite similar reductions of blood pressure.

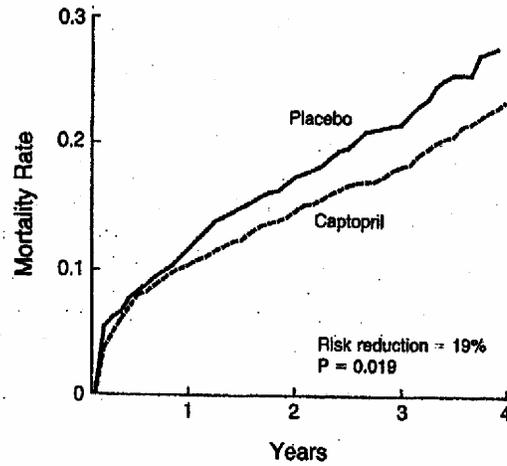


Figure 59 Primary endpoints among all subjects, male subjects and female subjects (ANBP2 Study)⁵⁴ (Based on data from N Engl J Med 2003; 348: 583-92). ACE denotes angiotensin-converting enzyme, and CI confidence interval.

For stage B, C or D heart failure, the goal is to improve survival, slow the progression of disease, alleviate symptoms and minimize risk factors. ACE inhibitors decrease the conversion of angiotensin I to angiotensin II, minimizing the multiple pathophysiological effects of angiotensin II, and decrease the degradation of bradykinin. Bradykinin promotes vasodilatation in the vascular endothelium, and cause natriuresis in the kidney. Thus, ACE inhibitors improve survival, reduce the rate of hospitalization, improve symptoms, cardiac performance, neurohormonal levels and reverse remodeling after MI⁵⁵. Recent studies suggest ACE inhibitors may prevent diabetes mellitus, atrial fibrillation and dementia^{56,57}.

Four major trials provided evidence of the favorable effects of ACE inhibitor treatment after acute myocardial infarction with stage B or stage C heart failure:

- (i) The Survival and Ventricular Enlargement (SAVE)⁵⁸ trial examined the effect of captopril in 2,231 patients within 3 – 16 days after myocardial infarction, with LVEF ≤40% and without overt heart failure or symptoms of myocardial ischemia. Captopril-treated patients (n=1,115) compared to placebo-treated patients (n=1,116) had a 19% (95% CI 3% - 32%, P=0.019) reduction in the relative risk of all-cause mortality (Figure 60), 21% (95% CI 5% - 35%, P=0.014) reduction in the relative risk of CV deaths, 37% (95% CI 20% - 50%, P<0.001) reduction in the relative risk of severe heart failure, 22% (95% CI 4% - 37%, P=0.019) reduction in the relative risk of heart failure requiring hospitalization, and a 25% (95% CI 5% - 40%, P=0.015) reduction in the relative risk of recurrent MI (Figure 61). Thus, in patients with asymptomatic LV dysfunction after MI, long-term treatment with captopril was associated with improved survival and reduced morbidity and mortality due to cardiovascular events, and this benefit was seen in patients who received thrombolytic therapy, aspirin or β-blockers.



Placebo	1116	987	915	809	282
Captopril	1115	1000	938	614	288

Figure 60 Cumulative mortality from all causes in the study groups in SAVE trial⁵⁸ (Based on data from N Engl J Med 1992; 327: 669-77). The number of patients at risk at the beginning of each year is shown at the bottom

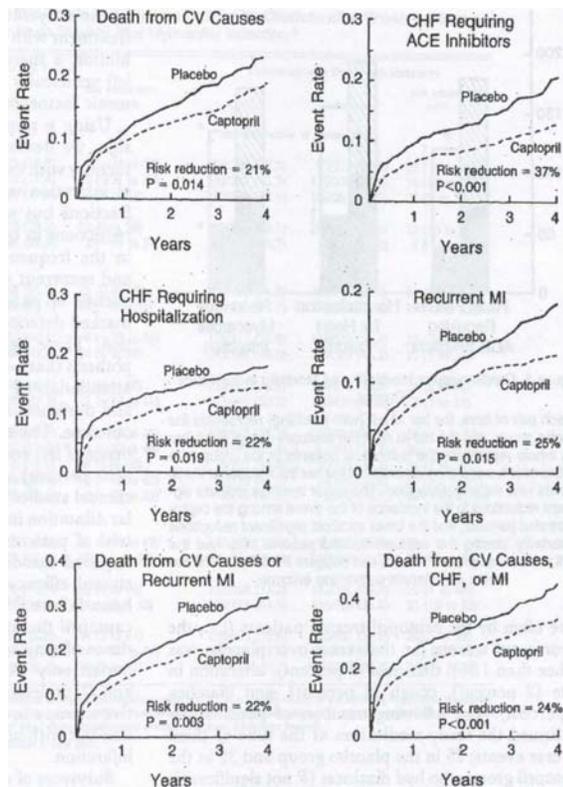


Figure 61 Life tables for cumulative fatal and non-fatal cardiovascular events in SAVE trial⁵⁸ (Based on data from N Engl J Med 1992; 327: 669-77). CV denotes cardiovascular, CHF congestive heart failure, MI myocardial infarction. The bottom right panel shows the following events: death from cardiovascular causes, severe heart failure requiring ACE inhibitors or hospitalization, or recurrent myocardial infarction. For all combined analyses, only the time to the first event was used.

- (ii) The Acute Infarction Ramipril Efficacy (AIRE)⁵⁹ trial enrolled 2,006 patients (in 144 centers in 14 countries) with overt signs of heart failure (except NYHA class IV) after

an acute MI. Patients were randomized to either ramipril (n=1,014) or placebo (n=992) on day 3 to day 10 after AMI, and followed to a minimum of 6 months (average = 15 months). Patients treated with ramipril had a 27% (95%CI 11% - 40%, P=0.02) reduction in the relative risk of all-cause mortality (Figure 62) and a 19% (35% CI 5% - 31%, P=0.008) reduction in the relative risk of progression to the first validated event in a composite outcome of death, severe/resistant heart failure, myocardial infarction or stroke. This study shows that administration of ramipril to patients with clinical evidence of either transient or ongoing heart failure reduced premature death from all causes.

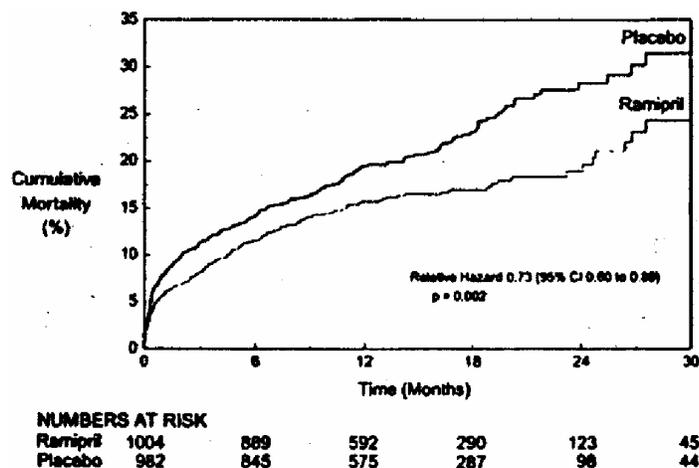


Figure 62 Mortality curves illustrating the primary endpoint of all-cause mortality analyzed by intention-to-treat in AIRE trial⁵⁹ (Based on data from Lancet 1993; 342: 821-8). Most patients were followed for <18 months, and the curves have been terminated at 30 months because of the small numbers of patients with prolonged follow-up.

- (iii) The Survival of Myocardial Infarction Long-Term Evaluation (SMILE)⁶⁰ trial randomized 1,556 patients in Italy within 24 hours after an acute anterior MI to receive zofendopril (n=772) or placebo (n=784) for 6 weeks.

Table 134 Incidence of Severe Congestive Heart Failure or Death as the Combined Primary End Point of the SMILE Study⁶⁰ (Based on data from N Engl J Med 1995; 332: 80-5).

EVENT	PLACEBO GROUP	ZOFENOPRIL	REDUCTION IN RISK	
	(N = 784)	GROUP (N = 772)	(95% CI)*	P VALUE
	no. of patients (%)		%	
Severe congestive heart failure†	32 (4.1)	17 (2.2)	46 (11 to 71)	0.018
Death	51 (6.5)	38 (4.9)	25 (-11 to 60)	0.19
Combined end point	83 (10.6)	55 (7.1)	34 (8 to 54)	0.018

*CI denotes confidence interval.

†At least three of the following had to be present: third heart sound, bilateral pulmonary rales, radiologic evidence of pulmonary congestion, or peripheral edema despite the concomitant administration of digoxin, diuretics, and vasodilators other than ACE inhibitors and necessitating open-label treatment with an ACE inhibitor.

Table 134, Figure 63 and Figure 64 shows that in patients treated with zofendopril, a

34% (95% CI, 8 to 54 percent; P=0.018) reduction in the relative risk of death or severe heart failure was observed at 6 weeks, and a 29% (95% CI, 6% to 51%; P=0.011) reduction in the relative risk of mortality was observed after 1 year.

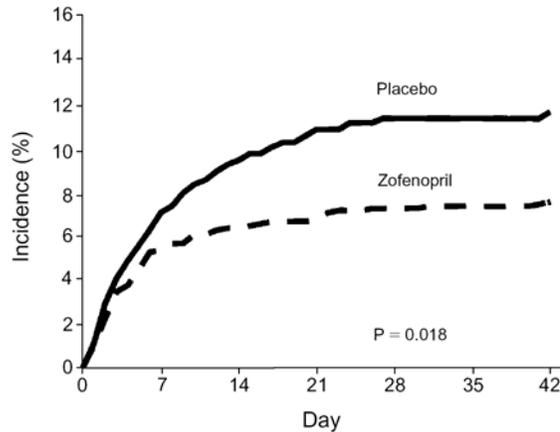


Figure 63 Incidence of Death or Severe Congestive Heart Failure during Six Weeks of Treatment with Zofenopril or Placebo in Patients with Acute Myocardial Infarction (SMILE Study)⁶⁰ (Based on data from N Engl J Med 1995; 332: 80-5).

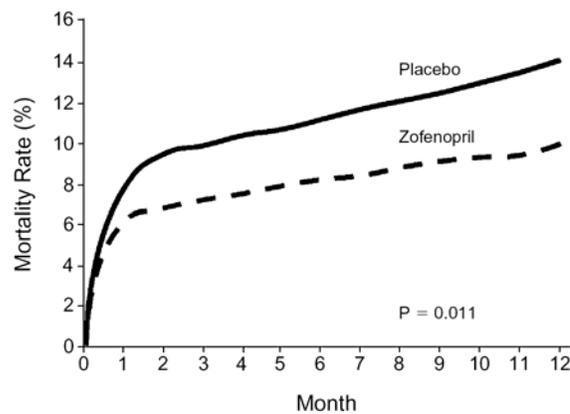
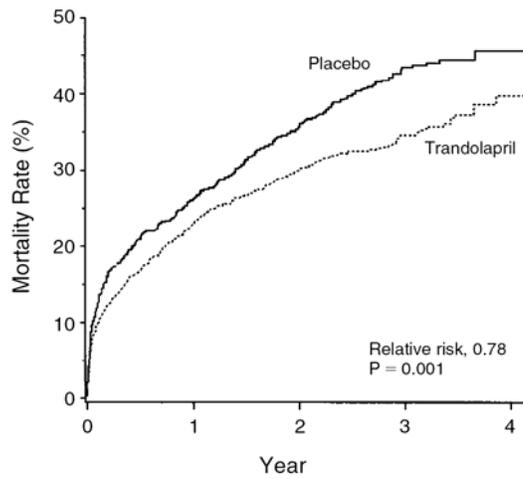


Figure 64 Cumulative Mortality during One Year of Follow-up among Patients with Acute Myocardial Infarction Treated for Six Weeks with Zofenopril or Placebo (SMILE Study)⁶⁰ (Based on data from N Engl J Med 1995; 332: 80-5).

- (iv) The Danish TRAndolapril Cardiac Evaluation (TRACE)⁶¹ study evaluated the effect of trandolapril on patients with an LVEF ≤ 0.35 after MI. 6,676 patients with 7001 myocardial infarctions confirmed by enzyme studies were screened. A total of 2,606 patients had echocardiographic evidence of left ventricular systolic dysfunction (LVEF $\leq 35\%$). On days 3 to 7 after infarction, 1,749 patients were randomly assigned to oral trandolapril (n=876 patients) or placebo (n=873 patients).



NO. AT RISK					
Trandolapril	876	677	613	319	20
Placebo	873	647	562	280	22

Figure 65 Cumulative Mortality from All Causes among Patients Receiving Trandolapril or Placebo (TRACE Study)⁶¹ (Based on data from N Engl J Med 1955; 333: 1670-6).

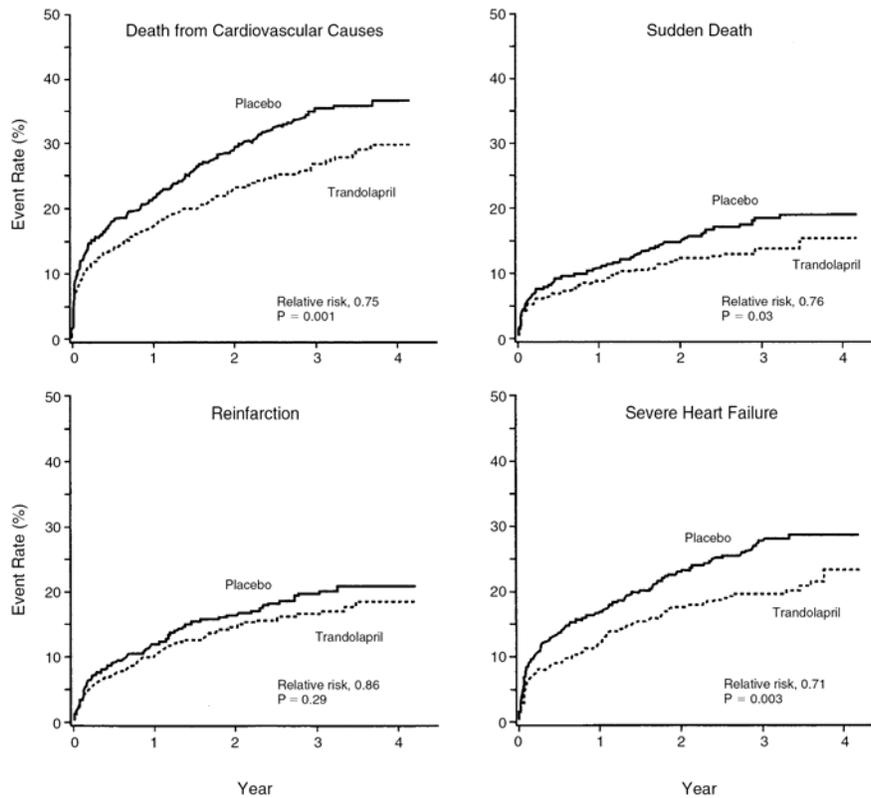


Figure 66 Event Rates for the Secondary End Points of Death from Cardiovascular Causes, Sudden Death, Reinfarction, and Severe or Resistant Heart Failure among Patients Receiving Trandolapril or Placebo (TRACE Study)⁶¹ (Based on data from N Engl J Med 1955; 333: 1670-6).

The duration of follow-up was 24 to 50 months. Patients assigned to treatment with trandolapril had a 22% (hazard ratio 0.78; 95% CI 0.67 to 0.91, P=0.001) reduction in the relative risk of death from all causes (Figure 65), 25% (hazard 0.75; 95% CI 0.63 to 0.89; P=0.001) reduction in the relative risk of death from cardiovascular causes, and 24% (hazard ratio 0.76; 95% CI 0.59 to 0.98; P=0.03) reduction in relative risk of sudden death (Figure 66). The relative risk of progression to advanced heart failure was decreased by 29% (hazard ratio 0.71; 95% CI 0.55 to 0.89; P=0.003) with trandolapril, whereas the drug had no effect on the risk of recurrent MI (Figure 66). The TRACE study shows that long-term treatment with trandolapril in patients with reduced left ventricular function soon after myocardial infarction significantly reduced the relative risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure⁶¹.

The above information needs to be considered from a clinical practice point of view, particularly in primary care settings where primary care physicians (internists, family practitioners, geriatricians) encounter most patients with Stage A through C heart failure. While ACE inhibitors are recommended for many patients with Stage A heart failure, and also for Stage B, Stage C or Stage D heart failure, there is widespread under-use of ACE inhibitors by physicians as reported in a nation-wide survey of patterns of use of ACE inhibitors in patients with heart failure and left ventricular systolic dysfunction⁶².

8.5.1.2 Effect of Angiotensin (AT₁) receptor blockers (ARBs) on improving survival in patients with heart failure:

The ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined the four stages of heart failure²⁷ did not recommend ARBs as first-line therapy for heart failure of any stage, but that they should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.

Information from clinical trials of ARBs suggests that ARBs may be as useful as ACE inhibitors.

For stage A heart failure: In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years²⁴. Losartan was found to delay the first hospitalization for heart failure in patients with diabetes mellitus with nephropathy and heart failure (89 (11.9%) patients in the losartan group vs. 127 (16.7%) in the placebo group), for which the relative risk reduction was 32% (P=0.005, Figure 67).

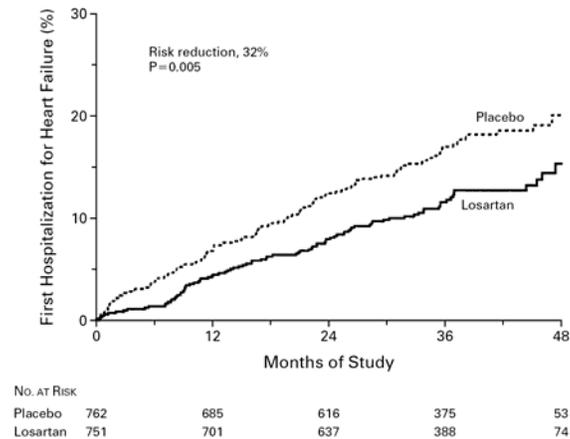


Figure 67 Kaplan-Meier Curves of the Percentage of Patients with a First Hospitalization for Heart Failure in the Losartan and Placebo Groups (RENAAL Study)²⁴ (Based on data from N Engl J Med 2001;345: 861-9).

For stage B, C or D heart failure: The CHARM-Alternative (SH-AHS-0003) study⁶³ showed that survival benefits in patients with CHF produced by candesartan (compared to placebo) are in about the same magnitude as that produced by ACE inhibitors described above. In the CHARM-Alternative (SH-AHS-0003) study, 2,028 patients with symptomatic heart failure and LVEF ≤ 40% who were not receiving ACE inhibitors because of previous intolerance were enrolled. Patients were randomly assigned candesartan (target dose 32 mg once daily) or placebo. The sponsor reported a statistically significant 23% reduction (hazard ratio= 0.77; 95% CI 0.67 - 0.89, P = 0.0004) in the relative risk of the composite primary endpoint of cardiovascular death or hospital admission for CHF⁶³ (Figure 68 and Table 135). This will be reviewed and discussed in detail in my review of the CHARM-Alternative (SH-AHS-0003) study in NDA 20-838 Supplement #024.

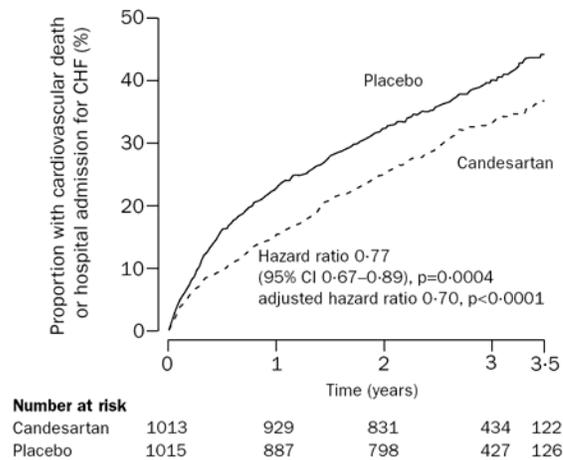


Figure 68 Kaplan-Meier cumulative event curves for primary endpoint (CHARM-Alternative Study)⁶³ (Based on data from Lancet 2003; 362: 772-6).

Table 135 Primary and secondary endpoints (CHARM-Alternative Study)⁶³ (Based on data from Lancet 2003; 362: 772-6).

	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 136 shows the endpoints of the Losartan Intervention for Endpoint reduction (LIFE)²³ study in which 9,193 asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy (i.e., stage B heart failure) were randomized to receive losartan or atenolol, and were followed for at least 4 years. Losartan titrated gradually to a dose of 100 mg/day produced a significant reduction (by 13%, P=0.021) in relative risk in the primary composite point of cardiovascular mortality, stroke and MI as well as a decrease (by 25%, P=0.001) in strokes and the incidence of new-onset diabetes (Table 136).

Table 136 Endpoints of LIFE²³ study (Based on data from Lancet 2002; 359: 995-1003).

Endpoint	Losartan (n=4605)		Atenolol (n=4588)		Adjusted hazard ratio (95% CI)†	p	Unadjusted hazard ratio (95% CI)	p
	n	Rate*	n	Rate				
Primary composite endpoint‡	508 (11%)	23.8	588 (13%)	27.9	0.87 (0.77–0.98)	0.021	0.85 (0.76–0.96)	0.009
Cardiovascular mortality	204 (4%)	9.2	234 (5%)	10.6	0.89 (0.73–1.07)	0.206	0.87 (0.72–1.05)	0.136
Stroke	232 (5%)	10.8	309 (7%)	14.5	0.75 (0.63–0.89)	0.001	0.74 (0.63–0.88)	0.0006
Myocardial infarction	198 (4%)	9.2	188 (4%)	8.7	1.07 (0.88–1.31)	0.491	1.05 (0.86–1.28)	0.628
Other prespecified endpoints								
Total mortality	383 (8%)	17.3	431 (9%)	19.6	0.90 (0.78–1.03)	0.128	0.88 (0.77–1.01)	0.077
Admitted to hospital for:								
Angina pectoris	160 (3%)	7.4	141 (3%)	6.6	1.16 (0.92–1.45)	0.212	1.13 (0.90–1.42)	0.284
Heart failure	153 (3%)	7.1	161 (4%)	7.5	0.97 (0.78–1.21)	0.765	0.95 (0.76–1.18)	0.622
Revascularisation	261 (6%)	12.2	284 (6%)	13.3	0.94 (0.79–1.11)	0.441	0.91 (0.77–1.08)	0.292
Resuscitated cardiac arrest	9 (0.2%)	0.4	5 (0.1%)	0.2	1.91 (0.64–5.72)	0.250	1.80 (0.60–5.36)	0.294
New-onset diabetes§	241 (6%)	13.0	319 (8%)	17.4	0.75 (0.63–0.88)	0.001	0.75 (0.63–0.88)	0.001

*Per 1000 patient-years of follow-up. †For degree of left ventricular hypertrophy and Framingham risk score at randomisation. ‡Cardiovascular mortality, stroke, and myocardial infarction (numbers of patients with a first primary event). §In patients without diabetes at randomisation (losartan, n=4019; atenolol, n=3979).

Apart from the CHARM-Alternative study⁶³ and the LIFE study²³ reviewed above, in the medical literature, most clinical trials comparing ARBs to ACE inhibitors head-to-head have not shown the superiority in beneficial effects of ARBs over ACE inhibitors.

In 1997, the Evaluation of Losartan in the Elderly (ELITE)¹⁹ trial demonstrated an unexpected survival benefit of losartan (50mg.day) compared to captopril (150 mg/day) in 722 elderly patients with CHF (Figure 69). However, mortality was neither a pre-specified primary nor a pre-specified secondary endpoint of ELITE¹⁹.

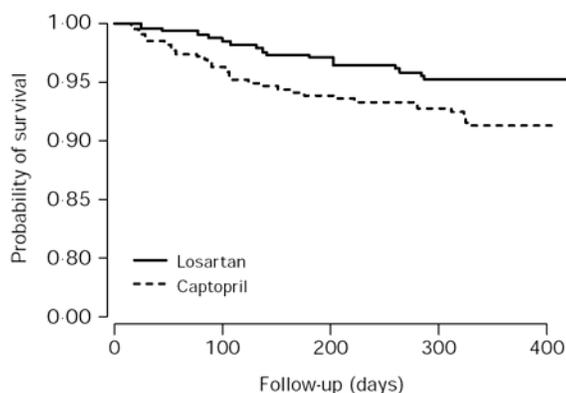


Figure 69 Kaplan-Meier survival curves among patients with CHF in losartan and captopril groups. Patients in losartan group had a 46% lower risk of death than patients in captopril group (p= 0.035). Patients were followed up for 48 weeks (ELITE trial)¹⁹ (Based on data from Lancet 1997; 349: 747-52).

ELITE II²⁰ was conducted in 3,152 elderly CHF patients with mortality as the primary endpoint. After a mean follow-up of over 500 days, mortality in the captopril group was 15.9%, compared to 17.7% in the losartan group (hazard ratio with captopril 1.13, P = 0.16, Table 137). Thus, ELITE II did not show that losartan was superior to captopril.

Table 137 Endpoint results in ELITE II trial²⁰ (Based on data from Lancet 2000; 355: 1582-7).

Endpoint	Losartan (n=1578)	Captopril (n=1574)	Hazards ratio (CI)*	p
All-cause mortality (primary endpoint)				
Total mortality	280 (17.7%)	250 (15.9%)	1.13 (0.95–1.35)	0.16
Sudden death	130 (8.2%)	101 (6.4%)	1.30 (1.00–1.69)	
Progressive heart failure	46 (2.9%)	53 (3.4%)	0.88 (0.59–1.30)	
Myocardial infarction	31 (2.0%)	28 (1.8%)	1.11 (0.66–1.85)	
Stroke	18 (1.1%)	11 (0.7%)	1.65 (0.78–3.49)	
Other cardiovascular	5 (0.3%)	6 (0.4%)	0.84 (0.26–2.76)	
Non-cardiovascular	50 (3.2%)	51 (3.2%)	0.99 (0.67–1.47)	
Sudden death or resuscitated cardiac arrest	142 (9.0%)	115 (7.3%)	1.25 (0.98–1.60)	0.08
Combined total mortality or hospital admission for any reason	752 (47.7%)	707 (44.9%)	1.07 (0.97–1.19)	0.18
Hospital admissions				
Any reason	659 (41.8%)	638 (40.5%)	1.04 (0.94–1.16)	0.45
Heart failure	270 (17.1%)	293 (18.6%)	0.92 (0.78–1.08)	0.32

*95.7% CI for total mortality, 95% CI for other endpoints, including components.

In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial, losartan (at a dose of 50 mg q.d.) was compared to the ACE inhibitor captopril (at a dose of 150 mg/day) in 5,477 high-risk patients with confirmed acute myocardial infarction and evidence of heart failure or left ventricular dysfunction²². The results were in favor of captopril both for all-cause mortality (not significant, P=0.069) and for cardiovascular mortality (P=0.032) (Table 138 and Figure 70).

Table 138 Crude rates and relative risks for pre-specified endpoints in OPTIMAAL Study²² (Based on data from Lancet 2002; 360: 752-60).

	Losartan (n=2744)	Captopril (n=2733)	Relative risk (95% CI)	p
All-cause mortality	499 (18.2%)	447 (16.4%)	1.13 (0.99–1.28)	0.069
SCD/RCA	239 (8.7%)	203 (7.4%)	1.19 (0.99–1.43)	0.072
Myocardial reinfarction (fatal/ non-fatal)*	384 (14.0%)	379 (13.9%)	1.03 (0.89–1.18)	0.722
Other prespecified endpoints				
MI/total mortality	746 (27.2%)	689 (25.2%)	1.10 (0.99–1.22)	0.085
Cardiovascular death	420 (15.3%)	363 (13.3%)	1.17 (1.01–1.34)	0.032
Stroke (fatal/ non-fatal)	140 (5.1%)	132 (4.8%)	1.07 (0.84–1.36)	0.587
CABG	404 (14.7%)	375 (13.7%)	1.09 (0.95–1.26)	0.228
PTCA	466 (17.0%)	492 (18.0%)	0.94 (0.83–1.07)	0.358
Revascularisation	845 (30.8%)	827 (30.3%)	1.03 (0.93–1.13)	0.620
First all-cause admission	1806 (65.8%)	1774 (64.9%)	1.03 (0.97–1.10)	0.362
First admission for heart failure	306 (11.2%)	265 (9.7%)	1.16 (0.98–1.37)	0.072
Cardiovascular admission	1480 (53.9%)	1421 (52.0%)	1.06 (0.99–1.14)	0.108
Non-cardiovascular admission	885 (32.3%)	905 (33.1%)	0.98 (0.90–1.08)	0.719

SCD=sudden cardiac death; RCA=resuscitated cardiac arrest; MI=myocardial infarction; CABG=coronary-artery bypass grafting; PTCA=percutaneous transluminal coronary angioplasty. *Definite or probable as defined by endpoint classification committee.

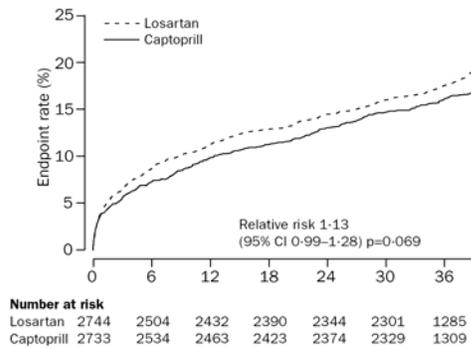


Figure 70 Kaplan- Meier curve for primary endpoint of all-cause mortality. (OPTIMAAL Study)²² (Based on data from Lancet 2002; 360: 752-60).

The clinical trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)²⁵ was also designed to demonstrate superiority or non-inferiority of valsartan compared to captopril in patients after an acute MI complicated by left ventricular dysfunction and/or heart failure. 14,703 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) and captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. This study was designed to assess non-inferiority of valsartan relative to captopril.

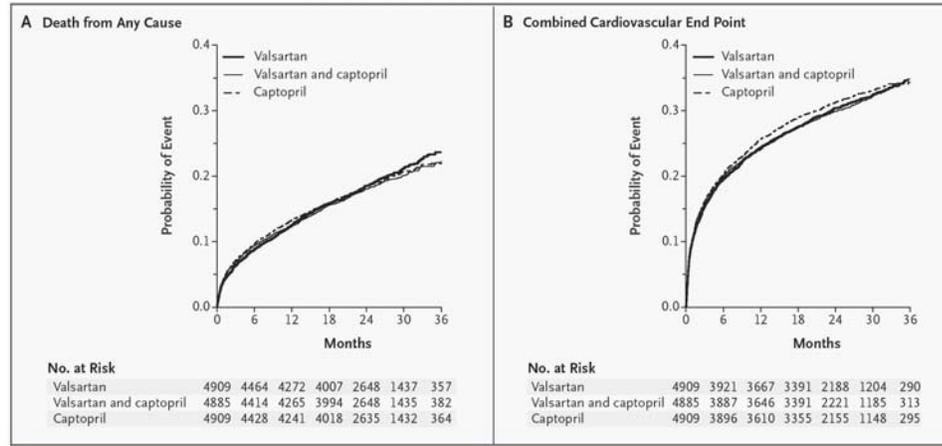


Figure 71 Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group (VALIANT Study)²⁵ (Based on data from N Engl J Med 2003; 349; 1893-1906).

For the rate of death from any cause, P= 0.98 for the comparison between the valsartan group and the captopril group and P= 0.73 for the comparison between the valsartan-plus-captopril group and the captopril group; for the rate of death from cardiovascular causes, reinfarction or hospitalization for heart failure, P=0.20 for the comparison between the valsartan group and the captopril group and P= 0.37 for the comparison between the valsartan-plus-captopril group and the captopril group.

All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan plus captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Figure 71 and Table 139). Valsartan and captopril were equivalent in terms of overall mortality and the composite endpoint of fatal and nonfatal cardiovascular events whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival²⁵ (Table 139).

Table 139 Cardiovascular Mortality and Morbidity* in VALIANT Study²⁵ (Based on data from N Engl J Med 2003; 349; 1893-1906).

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value	P Value for Non-inferiority	Hazard Ratio (97.5% CI)	P Value
	<i>number (percent)</i>							
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

* Heart failure denotes hospitalization for the management of heart failure, and CI confidence interval.

The lack of superiority in beneficial effect of ARBs (losartan and valsartan, above) over ACE inhibitors has been attributed to not using a high enough dose of the ARB²⁶. ACE inhibitors such as enalapril (at 20 mg/day) also enhanced the pulmonary diffusion capacity of oxygen after 14 days of treatment⁶⁴, whereas losartan 50mg/day was without such effect (Figure 72); this improvement in oxygen diffusion capacity across the alveolar surface is likely to have provided benefit to heart failure patients treated with ACE inhibitors, which was not shared by ARBs.

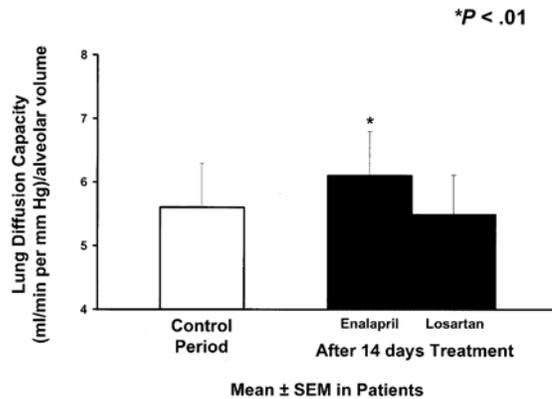


Figure 72 Effect of enalapril or losartan on pulmonary diffusion capacity in heart failure patients⁶⁴ (Based on data from J Am Coll Cardiol 2001; 37: 398-406). The bars represent mean±SEM in patients during the control period, after 14 days treatment with enalapril, and after 14 days treatment with losartan. * P < 0.01 compared with control period.

Thus, the findings from reports of clinical trials in the medical literature and the findings from clinical trials in this NDA may lend support to the use of ARBs as an alternative to ACE inhibitors when patients cannot tolerate ACE inhibitors. But there is no consistent evidence that ARBs are superior to ACE inhibitors.

8.5.2 Are the effects of ARBs additive on top of ACE-inhibitors?

That is, can incremental survival benefits be achieved in heart failure by using two inhibitors (ACE-inhibitors and AT₁-receptor blocking agents) of the renin-angiotensin system?

This question arose because it has been suggested that additional survival benefits could not be achieved with ARBs among those already taking proven effective treatments such as ACE inhibitors and β -blockers⁶⁵.

For Stage A heart failure: I have not yet found in the medical literature any study where an ACE inhibitor and an ARB are used together in patients who are at high risk for the development of heart failure but have no apparent structural abnormality of the heart (i.e., no studies of use of ACE an inhibitor and an ARB together among patients with hypertension and/or diabetes mellitus, and/or dyslipidemia without an apparent structural abnormality of the heart for the prevention of heart failure).

For Stage B, C or D heart failure: As discussed above, in the Valsartan Heart Failure Trial (Val-HeFT)¹⁶ of 5,010 patients, the addition of valsartan to conventional treatment (including ACE inhibitors in 93% of patients, β -blockers in 35% and spironolactone in 5%) reduced the risk of the composite co-primary outcome of death or cardiovascular morbidity (admission for CHF, ≥ 4 hour intravenous treatment for CHF without admission, or cardiac arrest with resuscitation) by 13.2%. This effect on the composite outcome was explained primarily by a 27.5% reduction in CHF hospital admissions, since valsartan showed no effect on cardiovascular mortality or total mortality.

In a subpopulation of 1,610 (35%) patients treated with both ACE inhibitors and β -blockers at baseline, valsartan was associated with a worse outcome. This finding raised concerns about excessive neuroendocrine inhibition^{31,66} and led to guidelines to discourage triple neurohumoral blockade^{67,68}.

In the Valsartan in Acute Myocardial Infarction Trial (VALIANT)²⁵, as discussed above, 14,703 patients with myocardial infarction complicated by heart failure and/or left ventricular dysfunction were randomized to receive either valsartan (titrated to 160 mg b.i.d., 4,909 patients), captopril (titrated to 50 mg t.i.d., 4,909 patients) or the combination of valsartan (titrated to 80 mg b.i.d.) and captopril (titrated to 50 mg t.i.d.) (4,885 patients), beginning 12 hours to 10 days after a myocardial infarction, and followed to a median of 24.7 months. All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan plus captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Figure 71 and Table 139).

In the VALIANT study valsartan and captopril were found to be equivalent in terms of overall mortality and in terms of the composite endpoint of fatal and nonfatal cardiovascular events²⁵. The combination (valsartan plus captopril) did not produce any added survival benefit, but resulted in an increase in the rate of adverse events (hypotension, renal

dysfunction and hyperkalemia). It is possible that in the unstable situation after myocardial infarction, the combination of valsartan plus captopril could have lowered the blood pressure too aggressively. On the other hand, this lack of superiority in beneficial effect of losartan over captopril has been attributed to not using a high enough dose of valsartan²⁶.

In a meta-analysis of 17 randomized, parallel-group, blinded clinical trials of ARBs (five trials had background ACE inhibitor treatment) involving 12,469 patients with NYHA functional class II-IV heart failure, with treatment duration of ≥ 4 weeks, the following all-cause mortality results were reported⁶⁹:

- (i) Between the ARB group (n=7,060) and control group (n=5,409), the pooled mortality rate (hazard ratio=0.96; 95% CI:0.75-1.23) was not statistically different (Figure 73).

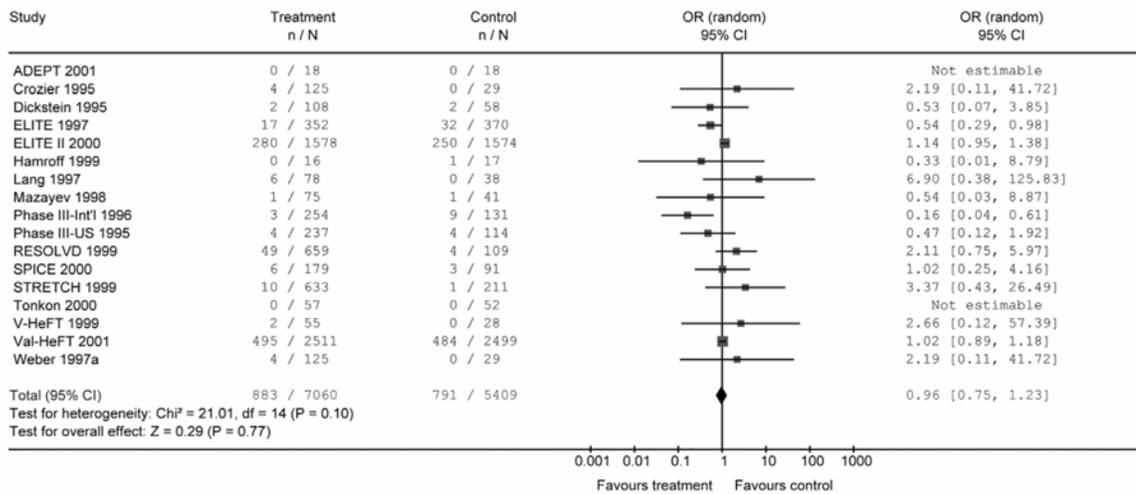


Figure 73 Comparison of angiotensin receptor blockers versus controls on all-cause mortality. (Based on data from J Am Coll Cardiol 2002; 39: 463-70)⁶⁹ Controls were either placebo or angiotensin-converting enzyme inhibitor (ACEI). Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

- (ii) Among trials where background ACE inhibitors were not given, the pooled estimate favored ARBs (n=1,628) over placebo (n=631) in improving survival (hazard ratio: 0.68; 95% CI: 0.38 to 1.22) although the sample size was too small to produce statistical significance (Figure 74). The data from the CHARM-Alternative (SH-AHS-0003) study appears to be in conformity with this finding⁶³.

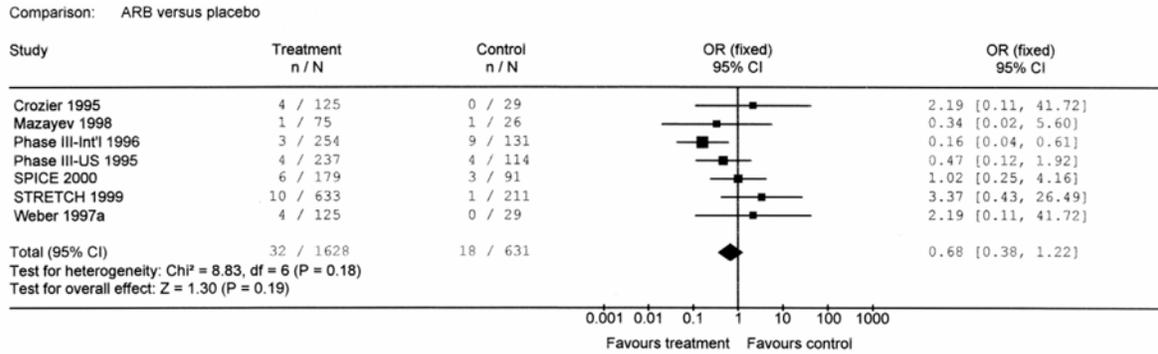


Figure 74 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)⁶⁹. ARB vs. placebo. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

- (iii) Among trials that directly compared ARBs (n=2,518) with ACE inhibitors (n=2,164), head-to-head, ARBs were not superior in improving survival (hazard ratio = 1.09; 95% CI 0.92-1.29) (Figure 75).

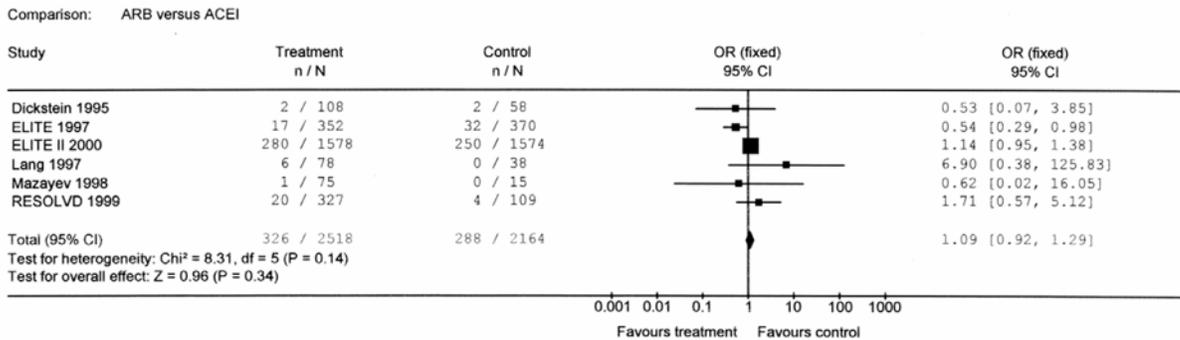


Figure 75 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)⁶⁹. ARB versus angiotensin-converting enzyme inhibitors (ACEI). Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

- (iv) When the combination therapy of ARBs plus ACE inhibitors (n = 2,989) was compared with ACE inhibitors (n = 2,723) alone, the risks of death were virtually identical (hazard ratio = 1.04; 95% CI: 0.91-1.20) (Figure 76). This meta-analysis does not include the data from the CHARM-Added (SH-AHS-0006) study under review, which showed a survival benefit of treatment with candesartan in patients with CHF already taking ACE-inhibitors.

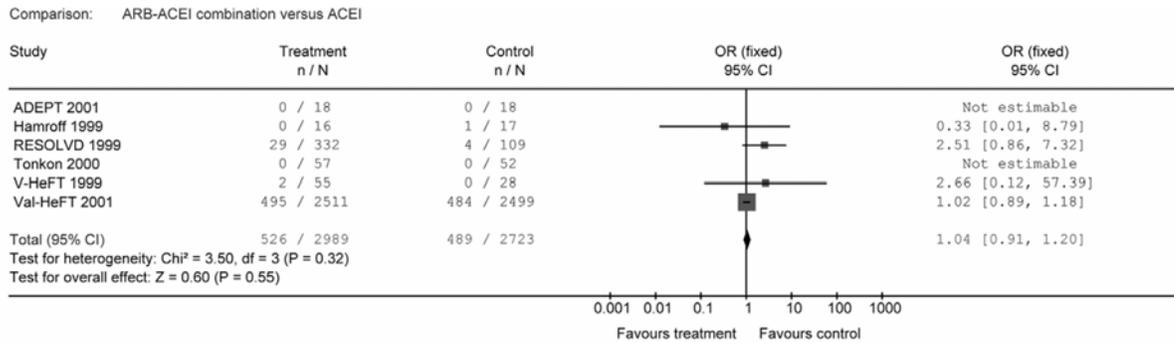


Figure 76 Stratified comparisons of angiotensin receptor blockers (ARB) on all-cause mortality: (Based on data from J Am Coll Cardiol 2002; 39: 463-70)⁶⁹. ARB plus angiotensin-converting enzyme inhibitors (ACEI) combination versus ACEI. Odds ratios (OR) and the 95% confidence intervals (CI) are shown on a logarithmic scale, with box size proportional to the sample size. The diamond represents the pooled effect.

Comparing the survival benefits found in CHARM-Added (SH-AHS-0006) study with other ARB/ACE inhibitor trials in CHF: The CHARM-Added (SH-AHS-0006) study enrolled 2,548 patients with NYHA functional class II-IV CHF and LVEF $\leq 40\%$ and treated with ACE inhibitors. Patients were randomly assigned candesartan (target dose 32 mg once daily) or placebo. The median follow-up was 41 months. The primary efficacy composite outcome of time to CV death or CHF hospitalization, was reduced significantly by candesartan (by 14.7%, $P=0.011$). The secondary efficacy outcomes in this (SH-AHS-0006 (CHARM-Added)) study were also reduced consistently by candesartan: “all-cause death or CHF hospitalization” was reduced by 12.9% ($P=0.021$), and “CV death or CHF hospitalization or non-fatal MI” was reduced by 14.8% ($P=0.008$). The reductions in these composite efficacy endpoints in CHF patients with LV systolic dysfunction may be attributable to reductions in the individual components of CHF hospitalizations (by 17.5%, $P = 0.014$), non-fatal MI (by 48.8%, $P = 0.006$), CV deaths (by 15.8%, $P = 0.029$), and CHF deaths (by 24.8%, $P = 0.041$).

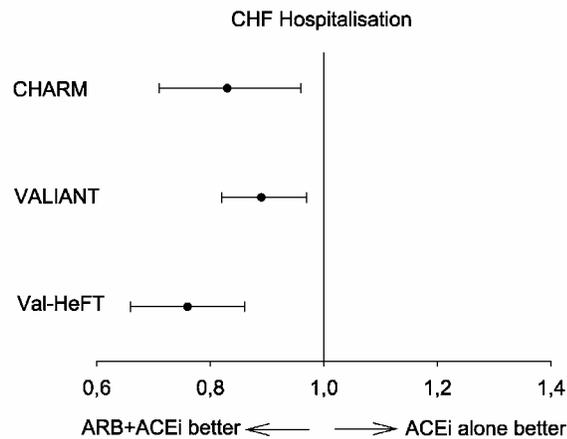


Figure 77 CHF hospitalisation⁷⁰ in CHARM-added, VALIANT (added) and Val-HeFT (Based on data from International Journal of Cardiology 2004 (In press; personal communication with Prof. A. A. Voors).

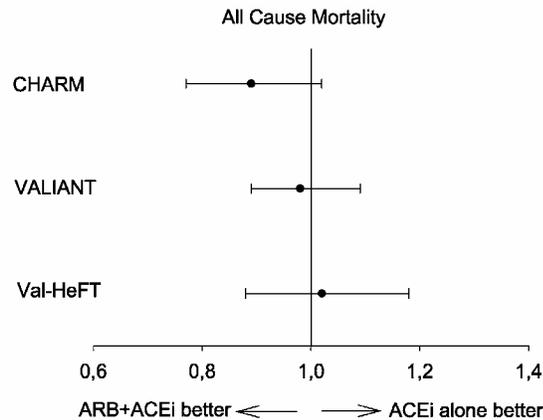


Figure 78 All-cause mortality⁷⁰ in CHARM-added, VALIANT (added) and Val-HeFT (Based on data from International Journal of Cardiology 2004 (In press; personal communication with Prof A. A. Voors).

At this point in time, the CHARM-Added study is the **only** study which shows that incremental survival benefits are achieved with two inhibitors of the renin-angiotensin system (ACE-inhibitors and AT₁-receptor blocking agents) used together (Figure 77 and Figure 78).

The reasons for this disparity of results between the CHARM-Added (SH-AHS-0006) study and the Val-HeFT and VALIANT trials have been postulated as follows⁷⁰:

1. The VALIANT trial studied patients with acute MI complicated by LV dysfunction, which is very different from established CHF studied in patients in the Val-HeFT and CHARM-Added trials. In the early phase after acute MI during which remodeling occurs, ACE inhibitors might adequately suppress angiotensin II levels and therefore effectively reverse remodeling and contribute to a large extent in improving survival. Thus, the add-on effects of valsartan on captopril in the VALIANT trial will be less than that found with candesartan on ACE-inhibitors in CHARM-Added trial that was not designed to enroll patients with heart failure during the early phase of acute MI.
2. The doses of ACE inhibitors used were lower in CHARM (captopril 82 mg, enalapril 17 mg, lisinopril 18 mg) and Val-HeFT (captopril 82 mg, enalapril 17 mg, lisinopril 18 mg) trials compared to VALIANT (captopril 107 mg) trial. In a background of a relative low dose of an ACE inhibitor, there would be more room for improvement with additional renin-angiotensin-system blockade with ARBs.

However, the NETWORK (Clinical Outcome with Enalapril in Symptomatic Chronic Heart Failure)³³ trial found no differences between high-dose and low-dose ACE-inhibitor treatment groups for any of the endpoints measured. Also, most randomized trials of ACE inhibitors have shown no difference in mortality between patients receiving high-dose ACE inhibitors and those receiving low-dose ACE inhibitors^{12,13,14,15}.

3. There could be possible structural differences between losartan, valsartan and candesartan, although there is no large-scale data to support such differences at this time.
4. The proportion of patients in the VALIANT trial that was no longer taking study medication at one year was 16.8% in the captopril group and 19.0% in the combination group. Based on the intent-to-treat analyses, the effects of the combination might be underestimated.

In the CHARM-Added study, 53.6% of patients treated with candesartan were receiving the target dose of 32 mg once daily at 6 months (visit 5). The mean dose in the candesartan treatment group was 23.5 mg at 6 months. 67.2% of patients in the candesartan treatment group and 70.7% of patients in the placebo group received the investigational product for 24 months or more.

5. The effects of the combination of an ARB and an ACE inhibitor might only be expected in the subgroup of patients with increased concentrations of angiotensin II despite treatment with the ACE inhibitor. On the other hand, it has been suggested that even maximally recommended doses of ACE inhibitors do not completely prevent ACE-mediated formation of angiotensin II in CHF^{3,4}.

The above postulations should be viewed in the context of the fact that ACE inhibitors only partially block the production of angiotensin II. One or more ACE-independent pathways^{1,2} for the synthesis of angiotensin II has been demonstrated, including the “chymase pathway” which produces angiotensin II at the tissue level, about 90% of angiotensin produced in the heart being believed to be produced via this pathway^{3,4}. Thus, local production of angiotensin II can occur despite the use of an ACE inhibitor.

AT₁-receptor blockers, by inhibiting angiotensin II at the AT₁-receptor level, may exert a more complete inhibition of the local adverse effects of angiotensin II. Also, blocking AT₁-receptors causes unopposed stimulation of AT₂-receptors which may produce an additional beneficial effect on cardiac remodeling⁵ and vascular epithelial changes.

Thus, hypothetically, ACE inhibitors and AT₁-receptor blockers such as candesartan may exert different effects at the cardiac and vascular levels, which may be complementary in the treatment of CHF⁶. This may explain the incremental clinical benefits observed with two inhibitors of the renin-angiotensin system (ACE-inhibitors and candesartan) in the CHARM-Added (SH-AHS-0006) study.

While a reduction in the relative risk of hospitalization for CHF was found in Val-HeFT and CHARM-Added trials, and a reduction in the relative risk of cardiovascular mortality was demonstrated in CHARM-Added trial, ***no effect on all-cause mortality has been demonstrated*** in any one of these Val-HeFT, VALIANT or CHARM-Added trials (except in the CHARM-Pooled data for CHF patients with depressed left ventricular systolic function, as a secondary efficacy endpoint).

This inconsistency between the results of VALIANT and CHARM/Val-HeFT trials, and the uncertainty concerning the added protective effects of ARBs when used in combination with ACE inhibitors in less high-risk populations with controlled hypertension have led to the development and initiation of two multicenter studies in 40 countries to study the effects of ARBs and ACE when used together in patients with stage A through D heart failure⁷¹:

- (i) The **Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND)**. The TRANSCEND study will enroll 6,000 patients (3,000 patients each to be randomized to telmisartan or placebo) with known intolerance ACE inhibitors, and with previous vascular event or diabetes mellitus with target organ damage, but controlled blood pressure and without heart failure.
- (ii) The **Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)**. The ONTARGET trial plans to enroll 23,400 patients with the same characteristics as TRANSCEND but not ACE intolerant; 7,800 patients each will be randomized to telmisartan or ramipril or telmisartan plus ramipril. Seven sub-studies are embedded in the main trials; they are designed to obtain insights to mechanisms of the effects of the drugs, and to explore the impact of telmisartan on diabetes mellitus, atrial fibrillation, cognitive decline, erectile dysfunction, etc.

8.6 Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction

I have summarized the issues related to use of ARBs (and other treatments) in heart failure relevant to the review of this NDA supplement in Table 140.

Table 140 Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction

Issue	Evidence from Clinical Trials		
	Stage A	Stage B, C, D	
		CHF	Post-MI
Are ARBs useful in the treatment heart failure (better than placebo)? Yes		CHARM	
No		STRETCH, SPICE, Weber	
Are ARBs as useful as ACEi in ACE-intolerant patients with heart failure? Yes		CHARM-0003	
No			
Are ARBs as useful as ACEi in the treatment of heart failure? Yes	LIFE, RENAAL	CHARM-0003, ELITE II, RESOLVD 1999	VALIANT
No			
Are ARBs superior to ACEi in the treatment of heart failure? Yes		ELITE I, CHARM-0003	
No		ELITE II	OPTIMAAL, VALIANT
Are ARBs additive over ACEi for survival in heart failure? Yes	?RENAAL	Val-HeFT, CHARM-0006	Val-HeFT
No			VALIANT
Are ARBs additive when used with ACEi and β-blockers in the treatment of heart failure? Yes		CEBIS-II, MERIT-HF, RESOLVD, CHARM, COPERNICUS,	
No		ELITE II, Val-HeFT	Val-HeFT
Are ARBs additive when used with ACEi and alsoosterone-antagonists in the treatment of heart failure? Yes		EPHESUS	
No		?CHARM	
Are ARBs additive when used with ACEi and digoxin in the treatment of heart failure? Yes		DIG, CHARM	
No			
Are ARBs additive when used with ACEi, β-blockers, spironolactone and digoxin in the treatment of heart failure? Yes		CHARM	
No			
Is dose of ACEi important for the treatment of heart failure? Yes			
No		NETWORK, CHARM	
Dose not addressed		HOPE, EUROPA, ANBP2	SAVE, AIRE, SMILE, TRACE
Is dose of ARB important for the treatment of heart failure? Yes			VALIANT
No		?CHARM	
Future studies of ARBs in CHF: (i)telmisartan in ACE intolerant patients	TRANSCEND	TRANSCEND (Stage B)	
(ii) in ACE tolerant patients (telmisartan or ramipril or telmisartan plus ramipril)	ONTARGET	ONTARGET (Stage B)	

8.7 Advisory Committee Meeting

I suggest that the issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction presented in Table 140 be discussed at the Cardio-Renal Drug Advisory Committee Meeting to be scheduled in February, 2005.

8.8 Postmarketing Risk Management Plan

The sponsor has not submitted a postmarketing risk management plan with the NDA supplement.

8.9 Other Relevant Materials

In the treatment of heart failure, ACE inhibitors, ARBs, β -blockers and spironolactone have contributed to reducing mortality, reducing hospitalizations, and improving functional status. However, large epidemiologic surveys (e.g., Framingham Study still ongoing) have not documented any meaningful change in overall death rates⁷². The reason why the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure in the general population may be partly because of structural defects in the heart such as uncorrected valvular disease (aortic stenosis, mitral regurgitation), and partly because many patients have co-morbid diseases such as hypertension, diabetes mellitus, hyperlipidemia, obesity, etc.

A nationwide survey of patients ≥ 65 years who had survived hospitalization for heart failure with LV systolic dysfunction revealed that ACE inhibitors were widely under prescribed despite evidence of their beneficial effect on survival in patients with heart failure⁶². ACE inhibitors were prescribed to only 68% of this cohort, and 76% received either an ACE inhibitor or an ARB. The underutilization of ACE inhibitors is not completely explained by substitution with ARBs. This finding underscores the importance of measures required to translate clinical trial results into actual clinical practice.

The dose of ACE inhibitors and ARBs for the treatment of heart failure remains to be an issue. Uncertainties regarding use of the optimal dose of ACE inhibitors (as perceived by general practitioners as well as practicing cardiologists) remain an unresolved issue in clinical practice.

For ACE inhibitors, randomized trials have shown that there is no difference in mortality between patients receiving high-doses and those receiving low-doses of ACE inhibitors^{12,13,14,15}. (Please also see the discussion in section 8.1.2 of this review.) The CHARM-Added study also shows the same rate of clinical primary efficacy events (CV death or CHF hospitalization) in patients on placebo who received ACE inhibitors at heart failure dose (event rate = 42.4%) or low dose (event rate = 42.1%); similarly for patients on candesartan, the rate of clinical primary efficacy events (CV death or CHF hospitalization) among patients who received ACE inhibitors at heart failure dose (event rate = 36.1%) is about the same as those who received ACE inhibitors at low dose (event rate = 39.7%).

For ARBs, it appears that a survival benefit is found only when higher doses than that for the treatment of hypertension are used. Insufficient dose of ARBs may have contributed to the

observed lack of beneficial effect of ARBs on mortality in ELITE II²⁰, OPTIMAAL²², Val-Heft¹⁶ and VALIANT²⁵ trials. (Please also see section 8.1.1 of this review.) A significant survival benefit in high risk patients was observed when relatively larger doses of ARBs were used in LIFE²³ and RENAAL²⁴ trials.

I think that only when there is a consensus of opinion about using ACE inhibitors for any type of heart failure regardless of the dose will there be an impetus to facilitate the concept that ACE inhibitors and ARBs are useful and beneficial in the treatment of all stages of heart failure to improve survival and reduce hospitalizations. Further surveys and educational activities in this aspect of heart failure treatment are necessary.

9 OVERALL ASSESSMENT

9.1 Conclusions

CHARM-Added (SH-AHS-0006) Study

In patients with CHF, with 99.9% of them using an ACE-inhibitor, the addition of candesartan significantly ($P=0.011$) reduced the relative risk of the composite primary efficacy outcome of CV death or CHF hospitalization by 14.7%. The effect appeared early and was sustained throughout the duration of the study.

Candesartan treatment also significantly reduced the secondary efficacy outcomes of the relative risks of (i) a composite of all-cause mortality or CHF hospitalization (by 12.9%, $P=0.021$), and (ii) a composite of CV death or CHF hospitalization or non-fatal myocardial infarction (MI) (by 14.8%; $P=0.008$). The symptoms of heart failure as evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

This reduction in CV death and CHF hospitalization observed with candesartan treatment was also evident in those patients being treated with recommended doses of ACE- inhibitors as well as in those treated with β -blockers (56% of patients at baseline), suggesting that there is no negative interaction between the AT_1 -receptor blocker candesartan, ACE-inhibitors and β -blocker therapy as was seen with valsartan in Val-HeFT¹⁶.

The sponsor submits that the benefit of candesartan in this study was evident in the presence of background treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg (in those taking drug) in the treatment arm of the Studies Of Left Ventricular Dysfunction (SOLVD)³² and 17 mg in Val-HeFT¹⁶. The mean daily dose of lisinopril was 18 mg which is also comparable to the 18 mg dose in the treatment arm of Val-HeFT¹⁶. However, for those on captopril, the main daily dose in the CHARM-Added study was lower (82 mg/day) compared to the dose used (107 mg/day) VALIANT²⁵ trial. It is possible that in a background of a relatively low dose of an ACE inhibitor (i.e., patients on captopril and patients on low dose ACE inhibitors for reasons of intolerance to higher doses in the CHARM-Added study) there would be more room for improvement with candesartan.

The findings of the CHARM-Added study may also be clinically important. The magnitude of the benefit in reducing cardiovascular death or CHF hospitalization translates into an absolute reduction of 4.4 events per 100 patients treated over a period of two years, which suggests that treating 23 patients for two years with candesartan will prevent one patient from suffering this outcome (of CV death or CHF hospitalization).

The reduction in CV death was attributed primarily to a reduction in sudden deaths and deaths due to heart failure, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

Dose reduction and discontinuation of investigational product were more common with candesartan than placebo. This was primarily attributable to renal function impairment, hyperkalemia, or hypotension all of which could be expected from inhibitors of the RAAS and the underlying conditions in the CHF population. Monitoring patients for these expected events is therefore necessary in the care of the CHF patient.

More cancer deaths occurred in the candesartan group, but the investigator-reported rate of non-fatal neoplasms was more equal between treatment groups. In the total CHARM population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007) no significant differences in the incidence of neoplasms were identified.

CHARM-Pooled (SH-AHS-0003, -0006, -0007) Studies

In patients with symptomatic heart failure (i.e., the entire CHARM study population) treated with candesartan a statistically borderline 8.6% reduction in the relative risk of all-cause mortality ($P=0.055$) was found. This was attributed to a 12.4% reduction in the relative risk of CV deaths ($P=0.011$).

In the two studies in patients with depressed LV systolic function ($LVEF \leq 40\%$ in SH-AHS-0003 and SH-AHS-0006), those treated with candesartan had an 11.4% reduction in the relative risk of all-cause mortality ($P=0.018$), resulting from a 15.6% reduction in the relative risk of CV deaths ($P=0.005$). The all-cause mortality result in the overall (three) study pooled analysis was influenced by the neutral treatment effect in the population with preserved left ventricular systolic function (Study SH-AHS-0007).

The reduction in the relative risk of CV death was attributed primarily to reductions in the relative risks of sudden deaths (by 19.9%; $P=0.013$) and deaths due to heart failure (by 24.2%; $P=0.008$), which are the most common modes of death in patients with CHF. Candesartan did not affect non-CV deaths.

There was also a reduction in the relative risk of hospitalization due to heart failure found in each of the component studies of the CHARM Program.

The beneficial effects of candesartan in the CHARM program were not influenced by treatment with ACE-inhibitors, β -blockers or digoxin. This finding, unlike that observed in the Val-HeFT study¹⁶, suggests benefit of use of an AT_1 -receptor blocker in patients already receiving β -blockers and ACE-inhibitors.

The most common causes of death for the heart failure patient, sudden death and death due to CHF, were both reduced by candesartan when compared to placebo. The most common cause of non-cardiovascular death was pneumonia in both the candesartan-treated and the placebo-treated groups.

More cancer deaths occurred in the candesartan group but the investigator-reported rate of non-fatal neoplasms was not different between treatment groups.

The incidence of new diabetes was lower in the candesartan group, an effect observed in other large populations treated with either an ACE inhibitor^{51,52} or AT₁-receptor blockers²³.

Symptoms of heart failure, as classified by the NYHA-classification, improved more in patients treated with candesartan than in patients treated with placebo (P= 0.004).

Overall, there was no significant safety issue associated with candesartan treatment of CHF other than the expected adverse event findings typical of the class of drugs and the clinical findings expected for the study populations. Discontinuation due to renal dysfunction, hyperkalemia, or hypotension was more common with candesartan than placebo. This distribution of events could be expected from inhibitors of RAAS and the underlying conditions in the CHF population. Monitoring patients for these risks is, therefore, an important consideration in care of the CHF patient.

9.2 Recommendation on Regulatory Action

Candesartan cilexetil is an angiotensin II type 1 (AT₁)-receptor blocker currently approved in the United States for the treatment of hypertension with an oral starting dose of 16 mg titratable up to 32 mg daily. The CHARM (Candesartan cilexetil (candesartan) in Heart Failure Assessment of Reduction in Mortality and Morbidity) Program consists of three pivotal efficacy trials comprising 7,601 patients with NYHA Class II – IV chronic heart failure (CHF) who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The analysis of the CHARM Program was divided into (i) patients with depressed left ventricular systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed left ventricular systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with Preserved left ventricular systolic function (EF >40%) (CHARM-Preserved). This efficacy supplement #022 pertains to CHARM-Added trial which received priority review.

In CHARM-Added (SH-AHS-0006) Study of 2,548 patients with CHF who were receiving an ACE inhibitor, candesartan significantly (P=0.011) reduced the relative risk of time to CV death or CHF hospitalization by 14.7% (primary efficacy endpoint). This benefit translates into a reduction of 4.4 events per 100 patients treated for two years; i.e., treating 23 patients with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. The reduction in CV death was attributed to a reduction in sudden death and CHF death, which are the most common modes of death in patients with CHF. The study was not powered to assess the effect on all-cause mortality.

The benefit of candesartan was evident in the presence of treatment with ACE inhibitors at recommended doses. The mean daily dose of enalapril at baseline was 17 mg, which compares to 16.6 mg in the treatment arm of the **Studies Of Left Ventricular Dysfunction (SOLVD)**³² and 17 mg in the **Valsartan Heart Failure Trial (Val-HeFT)**¹⁶. This benefit was also evident in patients

treated with β -blockers, suggesting that there is no negative interaction between the AT₁-receptor blocker candesartan, ACE-inhibitors and β -blockers as reported with valsartan in Val-HeFT¹⁶.

The CHARM Program (Combined SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007 Studies) failed to reach statistical significance for the primary efficacy endpoint of time to all-cause mortality (reduction in relative risk = 8.6%; P= 0.055) in patients with symptomatic CHF; a significant (P= 0.018) reduction in time to all-cause mortality by 11.4% was seen in the sub-population of CHF patients with depressed LV systolic function (secondary efficacy endpoint). This was attributed to a 12.4 -15.6% relative risk reduction in CV death (P= 0.011), subsequently attributed to reductions in relative risks of sudden death (by 15.2 - 19.9%; P=0.013) and CHF death (by 21.7 - 24.2%; P=0.008). The beneficial effects of candesartan were also evident in patients treated with ACE inhibitors, β -blockers or digoxin, unlike that reported in Val-HeFT.

There were no significant safety issues associated with candesartan treatment of CHF other than the expected adverse events (AEs) consistent with the pharmacology of the drug and the health status of patients. Discontinuation or dose reduction of study drug attributed to a decline in renal function, hypotension or hyperkalemia occurs more frequently with candesartan than placebo.

Based on my review limited to NDA 20-838 Efficacy Supplement # 022 with data on the CHARM-Added (SH-AHS-0006) study and the overall CHARM Program (SH-AHS-0003, -0006, -0007) studies, I recommend this application as for the indication of treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction \leq 40%) in patients who are receiving other heart failure treatments including ACE-inhibitors or β -blockers, where candesartan has been shown to reduce the relative risk of time to cardiovascular death or the first occurrence of a hospitalization for heart failure. I suggest that the issues related to the role and dose of AT₁ receptor blockers in the treatment of patients with heart failure presented in section 8.6 (Table 140 Issues related to the role of angiotensin receptor blockers in the treatment of patients with heart failure and left ventricular dysfunction) be discussed at a Cardio-Renal Drug Advisory Committee Meeting.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

I suggest the sponsor institute the following risk management activities:

- (i) Analyze data from the CHARM-Program studies to determine dose of candesartan and/or ACE-inhibitor and/or β -blockers and/or spironolactone in relation to AEs (hypotension, hyperkalemia, deterioration of renal function) and study drug discontinuation and/or dose reduction. This information should be provided in the labeling as well as communicated to practicing physicians through educational measures.
- (ii) Ensure educational activities regarding the importance of starting with the lowest initial dose of candesartan and of increasing the dose gradually while monitoring the heart rate and blood pressure, serum creatinine, and serum potassium.

9.3.2 Phase 4 Requests

- (i) Plan/perform a prospective clinical trial of candesartan in treatment of patients (tolerant and intolerant to ACE inhibitors) with high risk of heart failure without structural heart disease or symptoms (i.e. Stage A heart failure) to determine if candesartan will prevent or delay development of structural heart disease (Stage B), symptomatic heart failure (Stage C) or refractory symptoms of heart failure (Stage D).
- (ii) Plan/perform a prospective clinical trial (with multiple arms for multiple (e.g., high vs low) doses of candesartan and multiple (recommended heart failure dose vs low) doses of ACE-inhibitors) to find the optimal dose combination of ACE-inhibitor (high or low dose) and candesartan (high or low dose) in the treatment of CHF which will provide the most benefit [survival benefit (all-cause death, CV death, sudden death and CHF death) and clinical benefit (reduced hospitalization, improved symptoms, hemodynamics and exercise tolerance)] with the least risk [of AEs such as aggravated heart failure, hypotension, hyperkalemia, and deterioration of renal function].