Analyses of subgroups:

The treatment effects observed in subgroups in this study generally parallel the findings in the overall population of study SH-AHS-0006 and paralleled the subgroup analysis in the pooled analysis of the three component studies in the CHARM program (SH-AHS-pooled). The beneficial effects of candesartan in reducing CV death and hospitalization due to heart failure was generally consistent across important patient subgroups including sex, race, region, CHF etiology, baseline NYHA class, baseline LVEF and concomitant medications. While there was a statistically significant interaction for age, the direction of the effect was in favor of candesartan across the age groups.

Reviewer's comment: The United States was the country contributing the largest number of patients to the CHARM-Programme studies. In the CHARM-Alternative (SH-AHS-0003) the treatment effect was in the direction favoring candesartan (HR 0.811, 95% CI 0.605 -1.087, P= 0.162). In the CHARM-Added (SH-AHS-0006) study, the HR for the primary efficacy variable was 1.019 (95% CI 0.798-1.303, P=0.877), which is not consistent with the findings of the CHARM-Alternative study. Taken together, studies SH-AHS-0003 and SH-AHS-0006 (pooled analysis) demonstrated a treatment effect in the direction favoring candesartan for the US patients (HR 0.928, 95% CI 0.769 -1.119, P= 0.433).

Resource utilization data for patients hospitalized with a CV diagnosis: number of hospitalizations, length of stay, level of hospital care and any major CV procedures performed

Table 156 summarizes the number of hospitalizations and overall length of stay for hospitalized patients where the primary reason for the hospitalization was stated by the investigator as cardiovascular.

Table 156 Total number and total duration (days) of hospitalizations and percentage of time on each unit of care subdivided with respect to treatment and primary reason for hospitalization. ITT/Safety population (SH-AHS-0003)

		Hospitalisations		Intensive care		Intermediate care		General care		All	
Primary reason[a]	Treatment	N	%	Days	%	Days	%	Days	%	Days	%
Worsening CHF	Placebo	523	27.8	572	11.7	1267	26.0	3041	62.3	4880	100
	Cand.cil.	392	20.8	773	21.3	981	27.0	1873	51.6	3627	100
Myocardial infarction	Placebo	48	2.6	176	38.2	151	32.8	134	29.1	461	100
	Cand.cil.	49	2.6	257	51.8	98	19.8	141	28.4	496	100
Unstable angina	Placebo	93	4.9	122	11.8	571	55.2	341	33.0	1034	100
	Cand.cil.	120	6.4	217	29.8	205	28.1	307	42.1	729	100
Stroke	Placebo	17	0.9	44	33.3	22	16.7	66	50.0	132	100
	Cand.cil.	18	1.0	8	3.7	32	14.7	177	81.6	217	100
TIA	Placebo	13	0.7	9	8.3	26	23.9	74	67.9	109	100
	Cand.cil.	9	0.5	0	0.0	5	7.8	59	92.2	64	100
Hypotension	Placebo	8	0.4	9	11.8	5	6.6	62	81.6	76	100
	Cand.cil.	20	1.1	19	12.0	65	41.1	74	46.8	158	100
Atrial tachyarrhythmia	Placebo	37	2.0	38	6.8	62	11.2	456	82.0	556	100
	Cand.cil.	42	2.2	50	25.3	41	20.7	107	54.0	198	100
Ventricular arrhythmia	Placebo	48	2.6	152	36.5	135	32.4	130	31.2	417	100
	Cand.cil.	41	2.2	138	37.3	116	31.4	116	31.4	370	100
Pulmonary embolism	Placebo	6	0.3	0	0.0	15	22.7	51	77.3	66	100
	Cand.cil.	5	0.3	10	22.7	22	50.0	12	27.3	44	100
Other CV event	Placebo	210	11.2	322	21.7	398	26.8	765	51.5	1485	100
	Cand.cil.	183	9.7	269	25.1	235	22.0	566	52.9	1070	100
All CV events	Placebo	1003	53.3	1444	15.7	2652	28.8	5120	55.6	9216	100
	Cand.cil.	879	46.7	1741	25.0	1800	25.8	3432	49.2	6973	100

[a] As stated by investigator

Information on length of stay by type of ward was recorded for 1,882 hospitalizations (879 in the

candesartan group, 1,003 in the placebo group) where the primary reason for hospitalization was reported as cardiovascular. Patients in the candesartan group spent fewer days in hospital (6,973 days) than patients in the placebo group (9,216 days) (Table 156).

When hospitalized, the candesartan patients spent proportionally more days in more resource intensive care than the placebo patients (intensive care 25.0 vs. 15.7% of days, intermediate care 25.8 vs. 28.8% of days and general care 49.2 vs. 55.6% of days). (Table 156)

Reviewer's comment: This is different than the finding in my review of the CHARM-Added (SH-AHA-0006) study (item 6.1.4.3, page 68) which showed that patients in the candesartan group stayed fewer days (a total of 10,061 days) in hospital compared to patients in the placebo group (a total of 12,073 days), with the candesartan-treated group spending fewer days than the placebo-treated group in higher levels of medical care (intensive care 18.8 vs. 19.4% of days, intermediate care 25.9 vs. 26.2% of days) but not general care (55.3 vs. 54.4% of days).

Drug-drug and drug-disease interactions:

The subgroup analyses showed that the positive effects of candesartan were similar in different age groups, in males and females, diabetics and non-diabetics, and in patients with or without a diagnosis of hypertension.

Candesartan reduced the risk of cardiovascular death or CHF hospitalization in all predefined subgroups and there was no evidence of heterogeneity of treatment effect (Pooled CHARM program report).

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 157 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 ***non-use*** of β-blockers at baseline (RRR =34.3%, P<0.001), during the study (RRR =39.0%, P<0.001) and at the visit preceding the event (RRR=35.1%, P<0.001).

Table 157 CV death or hospitalization due to CHF (confirmed adjudicated) by use of β-blockers in study SH-AHS-0003. 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	
Beta-blocker	No	922	172	232	0.657	0.539	0.800	<0.001
	Yes	1106	162	174	0.904	0.730	1.119	0.354
Beta-blocker during study	No	606	120	165	0.610	0.482	0.772	<0.001
	Yes	1422	214	241	0.861	0.716	1.035	0.111
Beta-blocker at the visit preceding the event	No	1647	147	212	0.649	0.526	0.801	<0.001
	Yes	380	187	193	0.958	0.783	1.172	0.678

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

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving or not receiving β-blockers at baseline. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, I used the definition for high candesartan dose 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): 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 158. It appears that there is a dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving β-blockers and those not receiving β-blockers.

The event rates in patients receiving β-blockers are generally **lower** than in those not receiving β-blockers for the sub-populations of patients receiving “high dose” candesartan, “low dose” candesartan or no candesartan at the visit prior to the event.

Table 158 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-Alternative (SH-AHS-0003) Study

	Beta-blocker at baseline		
Candesartan		**N = 553** **Events = 162 (29.3%)**	
			A
	CC_{HD} n = 343 events = 87 (25.4%) **A1**	CC_{LD} n = 106 events = 51 (48.1%) **A2**	CC_{00} n = 104 events = 24 (23.1%) **A3**
Placebo		**N = 553** **Events = 174 (31.5%)**	
			B
	P_{HD} n = 408 events = 120 (29.4%) **B1**	P_{LD} n = 63 events = 35 (55.6%) **B2**	P_{00} n = 82 events = 19 (23.2%) **B3**
	No beta-blocker at baseline		
Candesartan		**N = 460** **Events = 172 (37.4%)**	
			A
	CC_{HD} n = 252 events = 74 (29.4%) **A1**	CC_{LD} n = 107 events = 67 (62.6%) **A2**	CC_{00} n = 101 events = 31 (30.7%) **A3**
Placebo		**N = 462** **Events = 232 (50.2%)**	
			B
	P_{HD} n = 312 events = 150 (48.1%) **B1**	P_{LD} n = 67 events = 51 (76.1%) **B2**	P_{00} n = 83 events = 31 (37.4%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 159), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 160) also show similar findings.

The above findings suggest that (i) in the absence of candesartan (cells A3), CHF patients treated with β-blockers at baseline have lower event rates than those not treated with β-blockers, and (ii) that when these CHF patients are receiving candesartan at low or high doses, too, those treated with β-blockers at baseline have lower event rates than those not treated with β-blockers.

This finding is also similar to that in my review of the CHARM-Added (SH-AHS-0006) study.

Table 159 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-Alternative (SH-AHS-0003) Study

	Beta-blocker at baseline		
Candesartan		**N = 553** **Events = 176 (31.8%)**	
			A
	CC_{HD} n = 343 events = 96 (28.0%)	CC_{LD} n = 106 events = 55 (51.9%)	CC_{00} n = 104 events = 25 (24.0%)
	A1	**A2**	**A3**
Placebo		**N = 553** **Events = 188 (34.0%)**	
			B
	P_{HD} n = 408 events = 126 (30.9%)	P_{LD} n = 63 events = 40 (63.5%)	P_{00} n = 82 events = 22 (26.8%)
	B1	**B2**	**B3**
	No beta-blocker at baseline		
Candesartan		**N = 460** **Events = 195 (42.4%)**	
			A
	CC_{HD} n = 254 events = 84 (33.1%)	CC_{LD} n = 107 events = 69 (64.5%)	CC_{00} n = 99 events = 42 (42.4%)
	A1	**A2**	**A3**
Placebo		**N = 462** **Events = 245 (53.0%)**	
			B
	P_{HD} n = 313 events = 156 (49.8%)	P_{LD} n = 68 events = 54 (79.4%)	P_{00} n = 81 events = 35 (43.2%)
	B1	**B2**	**B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 160 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-Alternative (SH-AHS-0003) Study

	Beta-blocker at baseline		
Candesartan		**N = 553** **Events = 171 (30.9%)**	
			A
	CC_{HD} n = 345 events = 94 (27.3%)	CC_{LD} n = 106 events = 52 (49.1%)	CC_{00} n = 102 events = 25 (24.5%)
	A1	**A2**	**A3**
Placebo		**N = 553** **Events = 180 (32.6%)**	
			B
	P_{HD} n = 407 events = 124 (30.5%)	P_{LD} n = 64 events = 36 (56.3%)	P_{00} n = 82 events = 20 (24.4%)
	B1	**B2**	**B3**
	No beta-blocker at baseline		
Candesartan		**N = 460** **Events = 182 (39.6%)**	
			A
	CC_{HD} n = 254 events = 82 (32.3%)	CC_{LD} n = 109 events = 69 (63.3%)	CC_{00} n = 97 events = 31 (32.0%)
	A1	**A2**	**A3**
Placebo		**N = 462** **Events = 240 (52.0%)**	
			B
	P_{HD} n = 313 events = 155 (49.5%)	P_{LD} n = 70 events = 55 (78.6%)	P_{00} n = 79 events = 30 (38.0%)
	B1	**B2**	**B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

However, there are many caveats to these findings:

(i) Such "within treatment group" analyses are subject to confounding, which limits the ability to interpret findings.

(ii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

(iii) 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.

(iv) With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β-blockers (Yes/No) or spironolactone (Yes/No).

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

Table 161 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 ***non-use*** of spironolactone at baseline, during the study or at the visit preceding the event.

Table 161 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	1545	224	289	0.742	0.623	0.883	<0.001
	Yes	483	110	117	0.797	0.614	1.034	0.088
Spironolactone during study	No	1193	169	188	0.772	0.627	0.950	0.014
	Yes	835	165	218	0.807	0.659	0.988	0.038
Spironolactone at the visit preceding the event	No	1736	197	251	0.724	0.601	0.873	<0.001
	Yes	291	137	154	0.978	0.776	1.233	0.853

On November 24 2004, the sponsor submitted a response to my request for data related to the primary and principal secondary efficacy endpoints according to dose level of candesartan in relation to patients receiving and not receiving 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 162. It appears that there is a

dose-related response, the event rates being lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups for both patients receiving spironolactone and those not receiving spironolactone.

However, the event rates in patients receiving spironolactone are generally **higher** than in those not receiving spironolactone for the sub-populations of patients receiving "high dose" candesartan, "low dose" candesartan or no candesartan at the visit prior to the event.

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 163), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 164) also show similar findings.

The above findings suggest that (i) in the absence of candesartan (cells A3), CHF patients treated with spironolactone at baseline had **higher** event rates than those not treated with spironolactone, and (ii) that when these CHF patients are receiving candesartan at low or high doses, too, those treated with spironolactone at baseline have **higher** event rates than those not treated with spironolactone.

This finding is similar to that in my review of the CHARM-Added (SH-AHS-0006) study.

Table 162 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-Alternative (SH-AHS-0003) Study

	Spironolactone at baseline		
Candesartan	**N = 250** **Events = 110 (44.0%)**		
			A
	CC_{HD} n = 107 events = 36 (33.6%)	CC_{LD} n = 79 events = 53 (67.1%)	CC_{00} n = 64 events = 21 (32.8%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 117 (50.2%)**		
			B
	P_{HD} n = 156 events = 74 (47.4%)	P_{LD} n = 39 events = 30 (76.9%)	P_{00} n = 38 events = 13 (34.2%)
	B1	**B2**	**B3**
	No spironolactone at baseline		
Candesartan	**N = 763** **Events = 224 (29.4%)**		
			A
	CC_{HD} n = 488 events = 125 (25.6%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 141 events = 34 (24.1%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 289 (37.0%)**		
			B
	P_{HD} n = 564 events = 196 (34.8%)	P_{LD} n = 91 events = 56 (61.5%)	P_{00} n = 127 events = 37 (29.1%)
	B1	**B2**	**B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 163 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan	**N = 250** **Events = 118 (47.2%)** **A**		
	CC_{HD} n = 107 events = 38 (35.5%) **A1**	CC_{LD} n = 79 events = 56 (70.9%) **A2**	CC_{00} n = 64 events = 24 (37.5%) **A3**
Placebo	**N = 233** **Events = 124 (53.2%)** **B**		
	P_{HD} n = 156 events = 77 (49.4%) **B1**	P_{LD} n = 39 events = 31 (79.5%) **B2**	P_{00} n = 38 events = 16 (42.1%) **B3**
No spironolactone at baseline			
Candesartan	**N = 763** **Events = 253 (33.2%)** **A**		
	CC_{HD} n = 490 events = 142 (29.0%) **A1**	CC_{LD} n = 134 events = 68 (50.8%) **A2**	CC_{00} n = 139 events = 43 (30.9%) **A3**
Placebo	**N = 782** **Events = 309 (39.5%)** **B**		
	P_{HD} n = 565 events = 205 (36.3%) **B1**	P_{LD} n = 92 events = 63 (68.5%) **B2**	P_{00} n = 125 events = 41 (32.8%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 164 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-Alternative (SH-AHS-0003) Study

Spironolactone at baseline			
Candesartan	**N = 250** **Events = 117 (46.8%)** **A**		
	CC_{HD} n = 107 events = 38 (35.5%) **A1**	CC_{LD} n = 81 events = 56 (69.1%) **A2**	CC_{00} n = 62 events = 23 (37.1%) **A3**
Placebo	**N = 233** **Events = 119 (51.1%)** **B**		
	P_{HD} n = 156 events = 76 (48.7%) **B1**	P_{LD} n = 39 events = 30 (76.9%) **B2**	P_{00} n = 38 events = 13 (34.2%) **B3**
No spironolactone at baseline			
Candesartan	**N = 763** **Events = 236 (30.9%)** **A**		
	CC_{HD} n = 492 events = 138 (28.1%) **A1**	CC_{LD} n = 134 events = 65 (48.5%) **A2**	CC_{00} n = 137 events = 33 (24.1%) **A3**
Placebo	**N = 782** **Events = 301 (38.5%)** **B**		
	P_{HD} n = 564 events = 203 (36.0%) **B1**	P_{LD} n = 95 events = 61 (64.2%) **B2**	P_{00} n = 123 events = 37 (30.1%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

However, the same caveats (as that for the dose-response relationship of candesartan to the primary and secondary efficacy endpoints) apply to these findings:

(i) Such "within treatment group" analyses are subject to confounding, which limits the ability to interpret findings.

(ii) Dose level comparisons may not be valid because in the CHARM studies, patients were not randomized to dose level.

(iii) 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.

With regard to other heart failure treatments at baseline, there was no randomization to any treatment including β-blockers (Yes/No) or spironolactone (Yes/No).

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

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 165 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 = 24.1%, P=0.006), during the study (RRR = 26.2%, P<0.001) and at the visit preceding the event (RRR = 19.5%, P=0.025).

Table 165 CV death or hospitalization due to CHF (confirmed adjudicated) by use of digitalis glycoside in study SH-AHS-0003. Comparison of candesartan vs. placebo with Cox regression. ITT/Safety population.

Variable	Group	N	Events cand. cil.	Events plac-ebo	Hazard Ratio	95% CI Lower	95% CI Upper	p-value
Digitalis glycoside	No	1104	149	183	0.769	0.619	0.954	0.017
	Yes	924	185	223	0.759	0.624	0.922	0.006
Digitalis glycoside during study	No	930	116	119	0.865	0.670	1.117	0.266
	Yes	1098	218	287	0.738	0.619	0.880	<0.001
Digitalis glycoside at the visit preceding the event	No	1585	137	160	0.783	0.623	0.983	0.035
	Yes	442	197	245	0.805	0.666	0.973	0.025

Conclusions:

Candesartan significantly reduced CV death or the first occurrence of a CHF hospitalization (P<0.001).

Candesartan significantly reduced all-cause death or the first occurrence of a CHF hospitalization (P= 0.001).

Candesartan significantly reduced all-cause death or the first occurrence of a CHF hospitalization or non-fatal myocardial infarction (P<0.001).

Candesartan significantly reduced cardiovascular death or the first occurrence of a CHF hospitalization or a non-fatal myocardial infarction or a coronary revascularization procedure (P< 0.001).

Candesartan did not reduce all-cause death or the first occurrence of all-cause hospitalization (P= 0.114).

Candesartan did not reduce all-cause death (P= 0.105).

Candesartan did not reduce the first occurrence of hospitalization (P= 0.107).

Candesartan did not reduce the number of fatal and non-fatal MIs (P= 0.199).

Candesartan significantly improved NYHA classification from randomization to the LVCF (P= 0.008).

Summary of Efficacy Results:

Candesartan treatment significantly reduced cardiovascular death or hospitalization due to CHF (HR 0.77, 95% CI 0.67 to 0.89, P< 0.001). This corresponds to a relative risk reduction of 23.2%. The effect appeared early and was sustained throughout the study period. The two secondary outcomes included in the confirmatory analysis were also significantly reduced by treatment with candesartan. The relative risk reduction for all-cause death or hospitalization due to CHF was 20.2% (HR 0.80, 95% CI 0.70 to 0.92, P= 0.001),and for CV death or hospitalization due to CHF or non-fatal MI the relative risk reduction was 21.8% (HR 0.78, 95% CI 0.68 to 0.90, P< 0.001).

The individual components CV death (relative risk reduction 15%, P= 0.072), hospitalization due to CHF (relative risk reduction 32%, P< 0.001) and all-cause death (relative risk reduction 13%, P= 0.105) all contributed to the benefit of candesartan as described by the respective composite endpoints. However, there was no reduction in non-fatal MI.

Symptoms of heart failure according to NYHA classification improved significantly during candesartan treatment compared to placebo (P= 0.008). The incidence of diagnosed onset of diabetes mellitus during the follow-up period was numerically reduced by candesartan (HR 0.79, 95% CI 0.53 to1.18, P= 0.254). Fewer patients in the candesartan group (49, 4.8%) than in the placebo group (70, 6.9%) developed atrial fibrillation (95% CI – 4.1 to 0.0, P= 0.048).

SAFETY RESULTS

Extent of exposure

A total of 2,028 patients (646 females and 1,382 males) were randomized into the study; all were included in the ITT/safety population. Patients who received incorrect investigational product during any part of the study (7 patients) were 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. Duration of treatment was defined as the time from the first day of treatment to the last day of treatment, regardless of temporary discontinuations of the investigational product. The last day of treatment was either the day the patient completed or withdrew from the study or died, or, if the investigational product was discontinued prematurely, the date of the permanent discontinuation. An overview of exposure is presented in Table 166, including data on the number of patients who completed or discontinued the study.

Table 166 Overview of exposure. ITT/Safety population (SH-AHS-0003)

		Placebo (N=1015)		Cand. cil. (N=1013)	
No. (%) of patients evaluable for safety	Male	691	(68.1)	691	(68.2)
	Female	324	(31.9)	322	(31.8)
Age	<65	392	(38.6)	412	(40.7)
	≥65	623	(61.4)	601	(59.3)
	<75	776	(76.5)	780	(77.0)
	≥75	239	(23.5)	233	(23.0)
Race[a]	Caucasian	922	(90.8)	926	(91.4)
	Black	45	(4.4)	28	(2.8)
	Oriental	37	(3.6)	43	(4.2)
	Other	11	(1.1)	16	(1.6)
Exposure by discontinuation due to AE of investigational product and/or study (N and %)	Discontinued investigational product due to AEs	197	(19.4)	220	(21.7)
	Patients who withdrew consent	16	(1.6)	18	(1.8)

[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.

The median duration of patient follow-up in the study was 33.8 months for patients randomized to candesartan and 33.6 months for patients randomized to placebo. The median duration of exposure of the investigational product was 29.5 months in the placebo group and 29.4 months in the candesartan group.

A total of 824 (81.3%) patients in the candesartan group started treatment on 4 mg once daily and 189 (18.7%) patients started on 8 mg once daily at randomization (baseline). A total of 1,313 (64.7%) patients (candesartan 666, 65.8%; placebo 647, 63.7%) received the investigational product for 24 months or more. 52.2% of the candesartan patients (58.9% 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 23.2 mg at 6 months. At the end of treatment (LVCF) 44.1% (60.3% of those still treated with candesartan) received 32 mg candesartan once daily. The mean candesartan LVCF dose was 23.1 mg.

Adverse events

Permanent discontinuations are defined as patients who discontinued treatment with the

investigational product permanently, were alive > 5 days after treatment discontinuation and were not on the investigational product at the closing visit. However, if the investigational product was permanently discontinued, the patient still remained in the study and SAEs were reported during the whole study period.

In the descriptive analyses, patients who had a reduction of the dose of the investigational product and later permanently discontinued the investigational product for the same reason were counted only in the category of discontinuation; whereas, for the exploratory analyze, these patients were counted as having a reduction of the dose of the investigational product as well as having discontinued treatment with the investigational product. As a result of this difference, the rates of dose reductions were higher in the exploratory safety analyses.

Categories of adverse events

AEs were reported by 73.6% (747) of the patients randomized to placebo, and by 73.1% (741) of the patients randomized to candesartan during study. In the placebo group 29.2% (296) of the patients had fatal SAEs and 64.4% (654) of the patients experienced non-fatal SAEs, compared with the candesartan group where 26.3% (266) of the patients had fatal SAEs and 61.1% (619) of the patients had non-fatal SAEs. The investigational product was prematurely discontinued due to AEs for 19.4% (197) of the patients in the placebo group and for 21.7% (220) of the patients in the candesartan group. The investigational product was reduced in dose due to AEs for 76 (7.5%) patients in the placebo group and for 157 (15.5%) patients in the candesartan group. A summary of adverse events by category is presented in Table 167.

Table 167 Number (%) of patients who had at least one adverse event in any category, and total numbers of adverse events. ITT/Safety population (SH-AHS-0003)

Category of adverse events	N (%) of patients who had an adverse event in each category[a]							
	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study[b] (N=1015)		Cand. cil. during study[b] (N=1013)	
Any AEs	724	(71.3)	725	(71.6)	747	(73.6)	741	(73.1)
Serious AEs	675	(66.5)	623	(61.5)	722	(71.1)	682	(67.3)
Serious AEs leading to death	187	(18.4)	165	(16.3)	296	(29.2)	266	(26.3)
Serious AEs not leading to death	611	(60.2)	571	(56.4)	654	(64.4)	619	(61.1)
Discontinuations of investigational product due to AEs	197	(19.4)	220	(21.7)	-	-	-	-
Dose reductions of investigational product due to AEs	76	(7.5)	157	(15.5)	-	-	-	-
	Total number of adverse events							
Any AEs[c]	2302		2402		2780		2894	
Serious AEs[c]	2069		1956		2546		2453	

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.

Most common adverse events**:**

The most commonly reported AEs (Table 168) in the placebo group during study were cardiac failure/cardiac failure aggravated (359, 35.4%), angina pectoris/ angina pectoris aggravated (120,

11.8%), sudden death (106, 10.4%) and renal function abnormal/ renal dysfunction aggravated (50, 4.9%). The most commonly reported AEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (280, 27.6%), hypotension (193, 19.1%) and renal function abnormal/ renal dysfunction aggravated (141, 13.9%).

Table 168 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-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	317	(31.2)	234	(23.1)	359	(35.4)	280	(27.6)
Hypotension	76	(7.5)	190	(18.8)	90	(8.9)	193	(19.1)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	105	(10.4)	120	(11.8)	127	(12.5)
Renal function abnormal/renal dysfunction aggravated[b]	49	(4.8)	136	(13.4)	50	(4.9)	141	(13.9)
Sudden death	85	(8.4)	65	(6.4)	106	(10.4)	80	(7.9)
Pneumonia	64	(6.3)	65	(6.4)	75	(7.4)	83	(8.2)
Myocardial infarction	58	(5.7)	71	(7.0)	68	(6.7)	85	(8.4)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Cerebrovascular disorder	55	(5.4)	41	(4.0)	61	(6.0)	52	(5.1)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	34	(3.4)	57	(5.6)	43	(4.2)
Chest pain	42	(4.1)	37	(3.7)	50	(4.9)	47	(4.6)
Coronary artery disorder	39	(3.8)	38	(3.8)	48	(4.7)	49	(4.8)
Tachycardia ventricular/arrhythmia[b]	31	(3.1)	28	(2.8)	44	(4.3)	39	(3.8)
Cardiomyopathy	29	(2.9)	25	(2.5)	40	(3.9)	37	(3.7)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Hyperkalaemia	16	(1.6)	54	(5.3)	18	(1.8)	54	(5.3)
Dizziness/vertigo[b]	21	(2.1)	43	(4.2)	23	(2.3)	45	(4.4)
Dyspnoea/dyspnoea (aggravated)[b]	39	(3.8)	17	(1.7)	43	(4.2)	22	(2.2)
Syncope	28	(2.8)	26	(2.6)	35	(3.4)	30	(3.0)

a This table uses a cut-off ≥3.0% in total population during study (N=2028).

b Patients having both AEs are counted once only.

Deaths:

562 patients died during the study, of whom 296 (29.2%) were randomized to placebo and 266 (26.3%) randomized to candesartan. For 5 of the patients who died (Site-Patient number: 201-13446, 653-12566, 1006-10801, 1406-22827, 1531-20373), the death was incompletely documented (vital status only without specified cause of death). However, all deaths are included in the analysis. One of the patients in the candesartan group had an SAE with fatal outcome with date of death after the patient's closing visit. Thus, the death of this patient is included in the descriptive safety results, but not in the exploratory results.

The most common fatal SAEs are presented in Table 169. The most commonly reported fatal AE in both treatment groups during study was sudden death, reported for 10.4% (106) of the patients in the placebo group and for 7.9% (80) in the candesartan group. Cardiac failure/ cardiac failure aggravated was the second most common fatal AE, reported for 9.0% (91) of the patients in the placebo group and for 7.6% (77) in the candesartan group, respectively.

Table 169 Number (%) of patients with the most commonly reported[a] AEs leading to death, sorted by descending frequency in the total population during study. ITT/ Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Sudden death	81	(8.0)	64	(6.3)	106	(10.4)	80	(7.9)
Cardiac failure/cardiac failure aggravated[b]	52	(5.1)	37	(3.7)	91	(9.0)	77	(7.6)
Myocardial infarction	10	(1.0)	29	(2.9)	17	(1.7)	38	(3.8)
Cerebrovascular disorder	9	(0.9)	7	(0.7)	14	(1.4)	13	(1.3)
Cardiac arrest	6	(0.6)	7	(0.7)	9	(0.9)	9	(0.9)
Death	3	(0.3)	2	(0.2)	7	(0.7)	9	(0.9)
Pneumonia	3	(0.3)	2	(0.2)	9	(0.9)	6	(0.6)
Fibrillation ventricular	5	(0.5)	4	(0.4)	7	(0.7)	6	(0.6)
Cardiomyopathy	2	(0.2)	1	(0.1)	6	(0.6)	5	(0.5)
Coronary artery disorder	1	(0.1)	3	(0.3)	4	(0.4)	7	(0.7)
Respiratory insufficiency	2	(0.2)	3	(0.3)	5	(0.5)	6	(0.6)
Sepsis	3	(0.3)	2	(0.2)	7	(0.7)	2	(0.2)
Pulmonary carcinoma	2	(0.2)	5	(0.5)	2	(0.2)	6	(0.6)
Tachycardia ventricular/arrhythmia[b]	1	(0.1)	3	(0.3)	3	(0.3)	4	(0.4)
Accident and/or injury	1	(0.1)	2	(0.2)	4	(0.4)	2	(0.2)
Pulmonary oedema	2	(0.2)	2	(0.2)	3	(0.3)	3	(0.3)

a This table uses a cut-off of ≥0.3% in total population during study (N=2028).

b Patients having both AEs are counted once only.

Serious adverse events other than deaths:

Non-fatal SAEs were reported in 64.4% (654) of the patients in the placebo group during study and in 61.1% (619) of the patients in the candesartan group during study. The most common non-fatal SAEs are presented in Table 170.

Table 170 Number (%) of patients with the most commonly reported[a] SAEs other than death, sorted by descending frequency in the total population during study. ITT/Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)		Placebo during study (N=1015)		Cand. cil. during study (N=1013)	
	N	(%)	N	(%)	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	297	(29.3)	209	(20.6)	334	(32.9)	251	(24.8)
Angina pectoris/angina pectoris aggravated[b]	110	(10.8)	100	(9.9)	120	(11.8)	122	(12.0)
Arrhythmia ventricular	64	(6.3)	58	(5.7)	79	(7.8)	73	(7.2)
Pneumonia	62	(6.1)	64	(6.3)	71	(7.0)	81	(8.0)
Hypotension	39	(3.8)	84	(8.3)	51	(5.0)	88	(8.7)
Myocardial infarction	50	(4.9)	46	(4.5)	57	(5.6)	56	(5.5)
Cerebrovascular disorder	50	(4.9)	38	(3.8)	56	(5.5)	46	(4.5)
Arrhythmia atrial	41	(4.0)	44	(4.3)	44	(4.3)	56	(5.5)
Fibrillation atrial	46	(4.5)	32	(3.2)	57	(5.6)	41	(4.0)
Chest pain	41	(4.0)	36	(3.6)	49	(4.8)	45	(4.4)
Coronary artery disorder	39	(3.8)	34	(3.4)	46	(4.5)	42	(4.1)
Tachycardia ventricular/arrhythmia[b]	30	(3.0)	24	(2.4)	42	(4.1)	35	(3.5)
Tachycardia supraventricular	30	(3.0)	27	(2.7)	39	(3.8)	34	(3.4)
Cardiomyopathy	27	(2.7)	24	(2.4)	35	(3.4)	33	(3.3)
Syncope	27	(2.7)	25	(2.5)	34	(3.3)	29	(2.9)

a This table uses a cut-off of ≥3.0% in total population during study (N=2028).

b Patients having both AEs are counted once only.

The most commonly reported non-fatal SAEs in the placebo group during study were cardiac failure/cardiac failure aggravated (334, 33.0%), angina pectoris/angina pectoris aggravated (120, 12.0%) and arrhythmia ventricular (79, 7.8%). The most commonly reported non-fatal SAEs in the candesartan group during study were cardiac failure/cardiac failure aggravated (251, 25.0%), angina pectoris/angina pectoris aggravated (122, 12.0%) and hypotension (88, 8.7%).

Discontinuations due to adverse events:

The investigational product was permanently discontinued due to AEs in 19.4% (197) of the patients in the placebo group and in 21.7% (220) of the patients in the candesartan group. The most common AEs leading to discontinuation of investigational product are presented in Table 171. A patient could have more than one AE, leading to permanent discontinuation of the investigational product, occurring at the same time.

The most commonly reported AEs leading to discontinuation were (a) in the placebo group: cardiac failure/cardiac failure aggravated (72, 7.1%), renal function abnormal/renal dysfunction aggravated (25, 2.5%) and hypotension (14, 1.4%), and (b) in the candesartan group: renal function abnormal/renal dysfunction aggravated (65, 6.4%), cardiac failure/cardiac failure aggravated (53, 5.2%) and hypotension (46, 4.5%).

The preferred term 'renal function abnormal' used in this descriptive safety analysis corresponds to the term increased creatinine used in the exploratory safety analyses. Both terms refer to 'Abnormal renal function, e.g. creatinine increased' pre-specified in the study data collection instrument (CRF).

Table 171 Number (%) of patients with the most commonly reported[a] AEs leading to discontinuation of investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0003)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Cardiac failure/cardiac failure aggravated[b]	72	(7.1)	53	(5.2)
Renal function abnormal/renal dysfunction aggravated[b]	25	(2.5)	65	(6.4)
Hypotension	14	(1.4)	46	(4.5)
Hyperkalaemia	3	(0.3)	21	(2.1)
Myocardial infarction	10	(1.0)	12	(1.2)
Angina pectoris/angina pectoris aggravated[b]	6	(0.6)	10	(1.0)
Pneumonia	9	(0.9)	7	(0.7)
Cerebrovascular disorder	10	(1.0)	4	(0.4)
Dizziness/vertigo[b]	3	(0.3)	11	(1.1)
Coronary artery disorder	7	(0.7)	5	(0.5)
Cardiomyopathy	6	(0.6)	5	(0.5)
Dyspnoea/dyspnoea (aggravated)[b]	8	(0.8)	3	(0.3)
Renal failure acute	3	(0.3)	8	(0.8)
Tachycardia ventricular	7	(0.7)	4	(0.4)
Headache	4	(0.4)	6	(0.6)

a This table uses a cut-off of ≥0.5% in total population on treatment (N=2028).

b Patients having both AEs are counted once only.

Dose reduction due to adverse events:

The investigational product was reduced in dose due to AEs in 7.5% (76) of the patients in the placebo group and in 15.5% (157) of the patients in the candesartan group. The most common AEs leading to dose reduction of the investigational product are presented in Table 172.

The most commonly reported AEs leading to dose reduction in the placebo group were hypotension (27, 2.7%), renal function abnormal (10, 1.0%) and cardiac failure aggravated and dyspnea (7, 0.7%). The most commonly reported AEs leading to dose reduction in the candesartan group were hypotension (85, 8.4%), renal function abnormal (32, 3.2%) and dizziness/vertigo (23, 2.3%).

Table 172 Number (%) of patients with the most commonly reported[a] AEs leading to dose reduction of investigational product, sorted by descending frequency in the total population on treatment. ITT/Safety population (SH-AHS-0006)

Preferred term	Placebo on treatment (N=1015)		Cand. cil. on treatment (N=1013)	
	N	(%)	N	(%)
Hypotension	27	(2.7)	85	(8.4)
Renal function abnormal	10	(1.0)	32	(3.2)
Dizziness/vertigo[b]	6	(0.6)	23	(2.3)
Cardiac failure aggravated	7	(0.7)	13	(1.3)
Hyperkalaemia	6	(0.6)	12	(1.2)
Dyspnoea	7	(0.7)	1	(0.1)
Abdominal pain	3	(0.3)	4	(0.4)
Fatigue	2	(0.2)	5	(0.5)
Nausea	3	(0.3)	4	(0.4)
Angina pectoris/angina pectoris aggravated[b]	2	(0.2)	4	(0.4)
Diarrhoea	3	(0.3)	3	(0.3)

a The table uses a cut-off of ≥0.3% in total population on treatment (N=2028).

b Patients having both AEs are counted once only.

Exploratory safety variables

Discontinuation of investigational product:

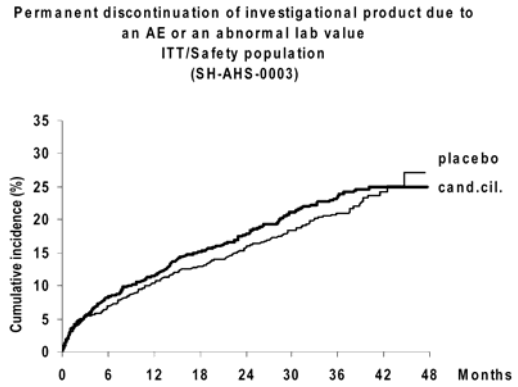
In this exploratory presentation of data the permanent discontinuation of the investigational product due to an AE or abnormal lab value occurred in 196 (19.3%) patients in the placebo group and 218 (21.5%) patients in the candesartan group. Neither the difference in time to event (P= 0.332), (Table 173, Table 174 and (Figure 55) nor the difference in proportions between treatments of 2.2% (P= 0.217) (Table 175 and Table 176) was statistically significant.

Table 173 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. Number of patients with at least one event by treatment group and events per 1000 years of follow-up. Follow-up time is calculated to first event. ITT/Safety population (SH-AHS-0003)

Variable	Treatment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
Permanent investigational product discontinuation due to any cause	Placebo	1013	295	2176.1	135.6	2.1
	Cand. cil.	1011	308	2212.9	139.2	2.2
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	196	2350.3	83.4	2.3
	Cand. cil.	1013	218	2379.8	91.6	2.3
At least one investigational product discontinuation due to any cause	Placebo	1013	456	1973.3	231.1	1.9
	Cand. cil.	1011	489	1933.0	253.0	1.9
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	355	2177.6	163.0	2.1
	Cand. cil.	1013	399	2115.1	188.6	2.1

Table 174 Permanent discontinuation and at least one discontinuation of investigational product due to any cause, an AE or an abnormal laboratory value. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0003)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
Permanent investigational product discontinuation due to any cause	2028	308	295	1.028	0.876	1.207	0.735
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2028	218	196	1.100	0.907	1.334	0.332
At least one investigational product discontinuation due to any cause	2028	489	456	1.090	0.959	1.239	0.187
At least one investigational product discontinuation due to an AE or an abnormal lab value	2028	399	355	1.151	0.997	1.328	0.054



Number at risk					
Placebo	1015	819	712	366	106
Cand.cil.	1013	844	728	366	104

Figure 55 Cumulative incidence (%) of permanent discontinuation of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Specific causes of investigational product discontinuation are noted in Table 175 and Table 176. Hypotension, hyperkalemia and increased creatinine as causes for investigational product discontinuation were statistically significantly more frequent for candesartan; absolute differences in these cause-specific discontinuations relative to placebo were 2.8%, 1.6% and 3.5%, respectively.

The approximate 1.1 fold excess risk for candesartan discontinuation relative to placebo for the entire study population was characteristic of the relative discontinuation rates across most subgroups. The approximate 1.5 fold higher risk of candesartan than placebo discontinuation among patients receiving spironolactone at baseline (placebo 47 patients, candesartan 75 patients) was statistically significant (P= 0.022). Also, the approximate 1.3 fold higher risk for candesartan discontinuation among patients receiving spironolactone at the visit prior to investigational product discontinuation (placebo 74 patients, candesartan 90 patients) was

statistically significant (P= 0.003). However, the 1.1 fold excess risk for candesartan discontinuation for patients having spironolactone recorded as a concomitant medication 'during study' was not significant (P= 0.422).

Dose reduction of the investigational product:

Dose reduction of the investigational product due to an AE or abnormal lab value occurred in 89 (8.8%) patients in the placebo group and 182 (18.0%) patients in the candesartan group (Table 175). This between-treatment difference in dose reductions for an AE of 9.2% was statistically significant (P< 0.001) (Table 176). As shown in Figure 56 the majority of events occurred during the first 6 to 12 months of treatment with the investigational product.

Table 175 Permanent discontinuation, at least one discontinuation and decreased dose of investigational product due to any cause, an AE, an abnormal laboratory value, hypotension, hyperkalemia or increased creatinine. The proportions of patients (%) with an event. ITT/Safety population (SH-AHS-0003)

Variable	Treatment	N	Number of patients with events	Proportion of patients with event	95% CI	
					Lower	Upper
Permanent investigational product discontinuation due to any cause	Placebo	1015	295	29.1	26.3	32.0
	Cand. cil.	1013	308	30.4	27.6	33.3
Permanent investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	196	19.3	16.9	21.9
	Cand. cil.	1013	218	21.5	19.0	24.2
Permanent investigational product discontinuation due to hypotension	Placebo	1015	9	0.9	0.4	1.7
	Cand. cil.	1013	37	3.7	2.6	5.0
Permanent investigational product discontinuation due to hyperkalaemia	Placebo	1015	3	0.3	0.1	0.9
	Cand. cil.	1013	19	1.9	1.1	2.9
Permanent investigational product discontinuation due to increased creatinine	Placebo	1015	27	2.7	1.8	3.8
	Cand. cil.	1013	62	6.1	4.7	7.8
At least one investigational product discontinuation due to any cause	Placebo	1015	456	44.9	41.8	48.0
	Cand. cil.	1013	489	48.3	45.2	51.4
At least one investigational product discontinuation due to an AE or an abnormal lab value	Placebo	1015	355	35.0	32.0	38.0
	Cand. cil.	1013	399	39.4	36.4	42.5
At least one investigational product discontinuation due to hypotension	Placebo	1015	23	2.3	1.4	3.4
	Cand. cil.	1013	72	7.1	5.6	8.9
At least one investigational product discontinuation due to hyperkalaemia	Placebo	1015	9	0.9	0.4	1.7
	Cand. cil.	1013	37	3.7	2.6	5.0
At least one investigational product discontinuation due to increased creatinine	Placebo	1015	37	3.6	2.6	5.0
	Cand. cil.	1013	102	10.1	8.3	12.1
Decreased investigational product dose due to any cause at least once	Placebo	1015	106	10.4	8.6	12.5
	Cand. cil.	1013	201	19.8	17.4	22.4
Decreased investigational product dose due to an AE or an abnormal lab value at least once	Placebo	1015	89	8.8	7.1	10.7
	Cand. cil.	1013	182	18.0	15.6	20.5

Table 176 Permanent discontinuation, at least one discontinuation and decreased dose of investigational product due to any cause, an AE, an abnormal laboratory value, hypotension, hyperkalemia or increased creatinine. The difference in proportion (%) between treatments. Chi-square test. ITT/Safety population (SH-AHS-0003)

Variable	Difference in proportion between treatments	95% CI		p-value
	Cand.cil. - placebo	Lower	Upper	
Permanent investigational product discontinuation due to any cause	1.3	-2.6	5.3	0.509
Permanent investigational product discontinuation due to an AE or an abnormal lab value	2.2	-1.3	5.7	0.217
Permanent investigational product discontinuation due to hypotension	2.8	1.5	4.1	<0.001
Permanent investigational product discontinuation due to hyperkalaemia	1.6	0.7	2.5	<0.001
Permanent investigational product discontinuation due to increased creatinine	3.5	1.7	5.2	<0.001
At least one investigational product discontinuation due to any cause	3.3	-1.0	7.7	0.131
At least one investigational product discontinuation due to an AE or an abnormal lab value	4.4	0.2	8.6	0.040
At least one investigational product discontinuation due to hypotension	4.8	3.0	6.7	<0.001
At least one investigational product discontinuation due to hyperkalaemia	2.8	1.5	4.1	<0.001
At least one investigational product discontinuation due to increased creatinine	6.4	4.2	8.6	<0.001
Decreased investigational product dose due to any cause at least once	9.4	6.3	12.5	<0.001
Decreased investigational product dose due to an AE or an abnormal lab value at least once	9.2	6.3	12.1	<0.001

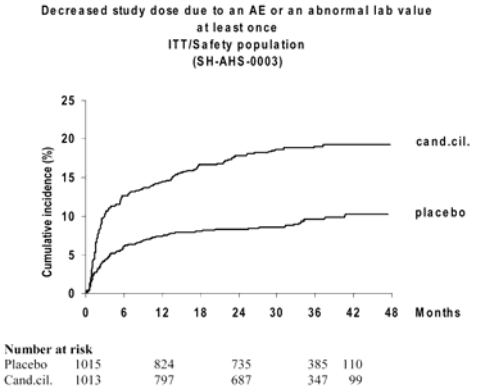


Figure 56 Cumulative incidence (%) of first occurrence of dose decrease of investigational product due to an AE or an abnormal laboratory value. ITT/Safety population

Non-CV death and non-CV hospitalization:

There were no significant differences between the candesartan group and the placebo group in the proportion of patients with non-CV mortality rates (placebo 44, 4.3%; candesartan 46, 4.5%) or non- CV hospitalization rates (placebo 353, 34.8%; candesartan 362, 35.7%).

Adverse events of special interest: This section summarizes AEs relevant to treatment of CHF, AT_1-receptor blockers (ARBs).

Hypotensive events:

To more completely evaluate 'hypotension' as an adverse CE, the following AE terms (AAED preferred terms) were selected and analyzed as a composite AE: 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.

At baseline, slightly more of the study patients randomized to candesartan cited hypotension as their reason for ACE inhibitor intolerance (placebo 119, 11.7%; candesartan 143, 14.1%). Also, there was a slightly higher proportion of patients in the candesartan group with SBP < 100 mmHg (placebo 22, 2.2%; candesartan 31, 3.1%) (North American study population)
AEs suggesting a ‘ hypotensive’ event were reported less frequently for patients in the placebo group (116, 11.4%) than the candesartan group (228, 22.5%) on treatment with the investigational product (Table 177).

Table 177 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
116 (11.4)	228 (22.5)	137 (13.5)	233 (23.0)

The individual AE term contributing the largest numbers to this composite AE was hypotension, which was reported for 76 (7.5%) of patients given placebo and 190 (18.8%) of patients given candesartan (Table 168).

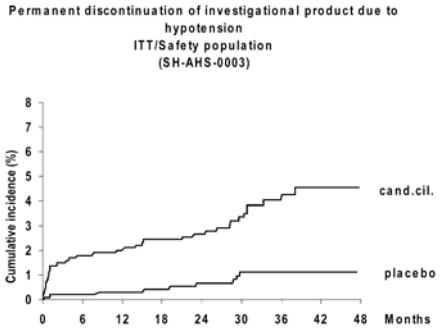
Of the patients in the composite ‘hypotensive’ group, fatal events were reported in the same number of patients in each treatment group (3 in the candesartan group, 3 in the placebo group). In both treatment groups, hypotensive events that led to death were reported in association with other causes of death such as cardiac arrest or failure, ventricular tachycardia and respiratory failure. In the candesartan treated patients, the fatal events occurred well after the titration phase and were assessed by the investigators as related to the investigational product.

The investigational product was discontinued for the specific AE term hypotension in 14 (1.4%) placebo patients and 46 (4.5%) candesartan patients (Table 169). Corresponding figures for the exploratory analysis were 9 (0.9%) placebo patients and 37 (3.7%) candesartan patients (Table 175). The higher proportion of hypotensive events leading to discontinuation in the candesartan group could not be explained by between treatment differences in baseline blood pressure or concomitant medications when the event started, including diuretics and β-blockers As noted above, more candesartan patients had a history of hypotension on an ACE inhibitor.

In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 30 (2.9%) of patients in the placebo group and 53 (5.0%) of patients on candesartan. In patients aged younger than 75 years, discontinuation because of the preferred term hypotension was reported in 11 (1.4%) of patients in the placebo group and 32 (4.1%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 3 (1.3%) in the placebo group and 14 (6.3%) in the candesartan group. In the placebo group, permanent discontinuation of the investigational product due to hypotension was reported in 11

(1.6%) males and 3 (0.9%) females. In the candesartan treatment group there were 34 (4.9%) males and 12 (3.7%) females who were permanently discontinued due to hypotension). The majority of patients were Caucasians.

Although over the entire study period patients in both treatment groups discontinued taking the investigational product because of hypotension, the candesartan discontinuation rate, shown in the exploratory analysis, was greatest during the first 6 to 12 months of treatment (Figure 57).



Number at risk					
Placebo	1015	885	793	421	125
Cand.cil.	1013	915	817	421	116

Figure 57 Cumulative incidence (%) of permanent discontinuation of investigational product due to hypotension (Ref. - Table 173). ITT/Safety population

Among the 270 (26.6%) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hypotension was noted for 1 (0.4%) placebo patient and 11 (4.0%) candesartan patients.

Abnormal renal function:

To summarize abnormal renal function, the following AE terms (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; acute pre-renal failure and anuria. For this composite AE, patients with multiple events including any of the selected AE terms were counted only once.

At baseline, prior to study entry, more patients randomized to candesartan (placebo 100, 9.8 %; candesartan 134, 12.8 %) cited ‘renal dysfunction’ as the reason for ACE-inhibitor intolerance. Also, there were a slightly higher proportion of patients in the candesartan group with serum creatinine > 2.0 mg/dl at baseline placebo 26, 7.8%; candesartan 30, 9.2%)(North American study population).

AEs suggesting ‘abnormal renal function’ occurred in 82 (8.1%) in the placebo group and 163 (16.1 %) patients in the candesartan group during study (Table 178).

Table 178 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-0003)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
74 (7.3)	157 (15.5)	82 (8.1)	163 (16.1)

The AE terms that predominately contributed to this composite AE term was renal function abnormal which was reported in 50 (4.9%) of patients given placebo and 141 (13.9%) given candesartan during study. Renal failure, acute (placebo, 19 patients, 1.9%; candesartan, 31 patients, 3.1%) and uremia (placebo, 7 patients, 0.7%; candesartan, 14 patients, 1.4%) were also numerically more frequent in patients given active treatment.

Among the patients with 'abnormal renal function', similar numbers in both treatment group had an event, which proved a fatal renal function event 'during study' (8 in the candesartan group, 9 in the placebo group). 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 or respiratory failure.

In the descriptive safety analysis (Table 171), on investigational product discontinuation in the overall study population, the specified AE term renal function abnormal/renal dysfunction aggravated was, second to aggravation of cardiac failure, the most common reason for permanent discontinuation of the investigational product in both treatment groups (placebo 25, 2.5%; candesartan 65, 6.4%). In the exploratory analysis the term increased creatinine was reported for 27 (2.7%) placebo patients and 62 (6.1%) candesartan patients (Table 175). The higher rate for discontinuation of the investigational product due to '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). As noted above, more candesartan than placebo patients gave a history of ACE inhibitor intolerance because of abnormal renal function.

In patients aged younger than 75 years, discontinuation because of the AE term renal function abnormal/renal dysfunction aggravated was reported in 20 (2.6%) of patients in the placebo group and 44 (5.6%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 5 (2.1%) in the placebo group and 21 (9.4%) in the candesartan group. In the placebo group the majority of events were seen in male patients (24, 3.5%) compared to only one female. In the candesartan treatment group 47 (6.8%) males and 18 (5.6%) females reported the renal event. The vast majority of patients in both treatment groups were Caucasians.

In the exploratory analysis, patients discontinued study treatment because of the term 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 58).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the

study with a history of diabetes, investigational product discontinuation for the specific term increased creatinine was noted for 12 (4.4%) placebo and 25 (9.0%) candesartan patients. Compared to the overall population (placebo 2.7%, candesartan 6.1%) diabetics were slightly more likely to discontinue the investigational product for increased creatinine levels (Table 175 and Table 176).

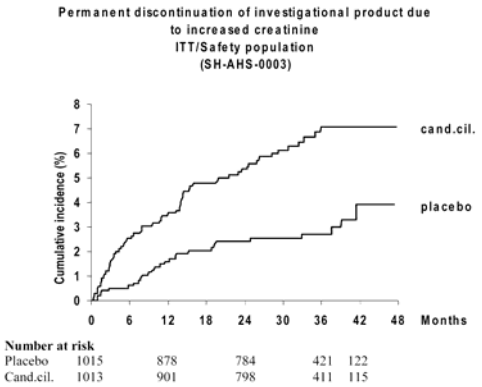


Figure 58 Cumulative incidence (%) of permanent discontinuation of investigational product due to increased creatinine (Ref. - Table 173). ITT/Safety population

Hyperkalemia:

In this section hyperkalemia is discussed 'on treatment' rather than 'during study' as a more clinically meaningful measure of possible relationship to the investigational product.

At baseline, there was no notable difference between the treatment groups in the proportions of patients with serum potassium ≥ 5 mmol/ L (North American study population).

Hyperkalemia was reported for 16 patients (1.6%) in the placebo group and 54 patients (5.3%) in the candesartan group on treatment with the investigational product (Table 168).

Fatal hyperkalemia 'on treatment' was not reported for any patients in the candesartan group or the placebo group.

In Table 171, discontinuation of the investigational product because of hyperkalemia was predominately limited to patients treated with candesartan (placebo 3, 0.3%; candesartan 21, 2.1%). In the exploratory analysis the corresponding numbers were 3 (0.3%) for placebo patients and 19 (1.9%) for candesartan patients (Table 175). 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).

In patients < 75 years old, discontinuation because of the AE term hyperkalemia was reported in 2 (0.3%) patients in the placebo group and 11 (1.4%) of patients on candesartan. For patients aged 75 years or older the discontinuation rates were 1 (0.4%) in the placebo group and 10

(4.5%) in the candesartan group. In the placebo group there was a low frequency of events for both genders, in the candesartan treatment group the majority of events were seen in male patients (17, 2.5%) compared to females (4, 1.2%). The vast majority of patients in both treatment groups were Caucasians.

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 59).

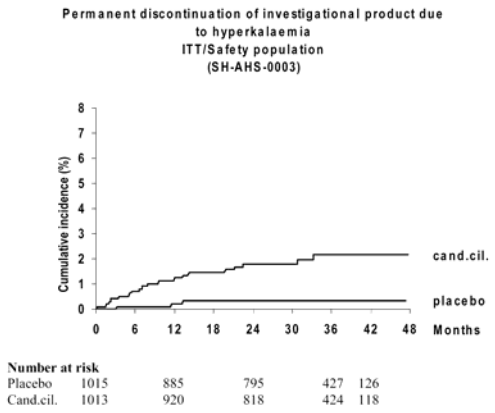


Figure 59 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 173).

Among the 270 (26.6 %) placebo patients and 278 (27.4 %) candesartan patients entering the study with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 3 (1.1%) placebo and 5 (1.8%) candesartan patients.

Myocardial ischemia

'Myocardial ischemia' was evaluated as a composite of the following AE terms (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 only counted once.

At baseline, prior to study there were no major 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 bypass grafting (placebo 244, 24.0 %; candesartan 269, 26.5 %).

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal in the two treatment groups (16.4% in the placebo group and 18.0% in the candesartan group) (Table 179).

Table 179 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
166 (16.4)	182 (18.0)	190 (18.7)	217 (21.4)

The AE term accounting for the greatest number of patients in this composite AE was angina pectoris which was also reported for essentially equal proportions of patients in the two groups (placebo 109, 10.7%; candesartan 105, 10.4%). The AE term MI occurred in 58 (5.7%) patients in the placebo group and in 71 (7.0%) in the candesartan group 'on treatment.'

The risk of 'myocardial ischemic' events during candesartan therapy could not be explained by concomitant medication at the start of the event. AEs related to hypotension, reported at the same time as angina pectoris or MI, were more frequent in the candesartan group (angina pectoris 9 patients, MI 7 patients) than in the placebo group (angina pectoris 2 patients, MI 0 patients). For coronary artery disorder there was no difference.

'Myocardial ischemic' events that were fatal were reported for 21 (2.1%) patients in the placebo group and 48 (4.7%) patients in the candesartan group during study (Table 180).

Table 180 Table 79 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)

Placebo on treatment N=1015	Cand. cil. on treatment N=1013	Placebo during study N=1015	Cand. cil. during study N=1013
11 (1.1)	35 (3.5)	21 (2.1)	48 (4.7)

Most of the fatal 'myocardial ischemic' events 'during study' were attributed to fatal MI (17 patients in the placebo group and 38 in the candesartan group).

Abnormal hepatic function:

The most common AE terms suggesting liver dysfunction during treatment were hepatic enzymes increased (placebo 4 patients; candesartan 2 patients) and hepatic function abnormal (placebo 3 patients; candesartan 3 patients). The AE term hepatic failure was reported for 1 patient in the placebo group and 2 patients in the candesartan group.

In the candesartan group there was one fatal case of hepatic necrosis considered related to amiodarone (Site 373, Patient number 15108), and one fatal case of cholestatic hepatitis considered related to septic cholangitis (Site 1476, Patient number 21109; this patient is not included in the listings of AEs of special interest).

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 were reported for 59 patients (5.8%) in each treatment group. One patient in the placebo group (Site 558, Patient number 13436) had breast neoplasm, malignant, female and carcinomatosis together with pleural mesothelioma. In the total numbers presented above this patient is counted only once. Neoplasms proved fatal for 18 patients (1.8%) in the placebo group and 23 patients (2.3%) in the candesartan group.

In the overall study population, the majority of patients did not have a history of cancer at baseline (placebo 92.9%; candesartan 93.9%).

The majority of reported neoplasms were malignant. The most common neoplasms during study were pulmonary cancer (placebo, 3 patients; candesartan, 10 patients), colon cancer (6 patients in each group), prostatic cancer (placebo, 3 patients; candesartan, 8 patients) and breast neoplasm malignant female (placebo 4 patients; candesartan 5 patients).

Permanent discontinuation and dose reduction of investigational product according to reason for ACE-inhibitor intolerance

Reasons for ACE-inhibitor intolerance, as noted at study entry, were not common reoccurrences as causes for permanent discontinuation or dose reduction of the investigational product (Table 181 and Table 182).

Table 181 Reasons for permanent discontinuation of investigational product compared to reason for ACE inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who permanently discontinued treatment with investigational product
Cough	751	4 (<1.0)	704	2 (<1.0)
Hypotension	119	5 (4.2)	143	13 (9.0)
Renal dysfunction[a]	100	12 (12.0)	134	31 (23.0)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	9 (8.3)	101	8 (7.9)
Any reason	1015	295 (29.1)	1013	308 (30.4)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product included was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Table 182 Reasons for the first dose reduction of investigational product compared to reason for ACE- inhibitor intolerance at baseline. ITT/Safety Population (SH-AHS-0003)

	Treatment			
	Placebo (N=1015)		Cand. cil. (N=1013)	
Reason for ACE inhibitor intolerance at baseline	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product	Number of patients, who were intolerant at baseline	Number of patients (%), who had at least one dose reduction of investigational product
Cough	751	3 (<1.0)	704	4 (<1.0)
Hypotension	119	6 (5.0)	143	25 (17.4)
Renal dysfunction[a]	100	3 (3.0)	134	22 (16.4)
Angioedema	44	0 (0)	39	1 (2.6)
Other[b]	109	1 (<1.0)	101	17 (16.8)
Any reason	1015	106 (10.4)	1013	201 (19.8)

a Reason for ACE-inhibitor intolerance was defined as renal dysfunction. Reason for permanent discontinuation of investigational product was defined as abnormal renal function.
b Includes any adverse event, lab value, or unknown reason.

Cough was the most frequently cited reason for ACE-inhibitor intolerance at baseline (73.9% of placebo-treated patients; 69.5% of candesartan-treated patients) but was associated with a discontinuation rate < 1% in both groups for a recurring event during study. Of patients with a history of symptomatic hypotension as a reason for ACE-inhibitor intolerance, 4.2% in the placebo group and 9.0% in the candesartan group discontinued because of hypotension. Renal dysfunction as a recurrent event was reported for 12.0% of patients in the placebo group compared with 23.0% in the candesartan group.

Regarding dose reductions, the rate for cough was < 1% in both treatment groups for a recurring event during study. In the candesartan group, compared to discontinuation, it was more common to have a dose reduction for recurring hypotension, while it was more common to permanently discontinue candesartan treatment if abnormal renal function was the recurring event.

Angioedema:

During study, three cases of angioedema were reported for patients in the candesartan group. All 3 patients were Caucasian with a history of previous angioedema reactions while taking ACE-inhibitors. None of the three events was considered life threatening or led to hospitalization.

Thirty-nine patients in the candesartan group had a history of ACE-inhibitor intolerance due to angioedema. One of these patients developed angioedema that required discontinuation of candesartan treatment. For the two remaining patients with angioedema, candesartan treatment continued without recurrence, and for one of these the dose was reduced. For two patients, the reaction occurred one month after randomization, and for the third patient the angioedema occurred more than a year after administration of the first dose of candesartan.

Of 44 patients in the placebo group who had a history of angioedema, none discontinued investigational product because of angioedema.

Discussion of deaths, serious adverse events, discontinuation due to adverse events, and other significant adverse events:

Both CV mortality and overall mortality were lower for patients given candesartan. There were no statistically significant differences between the candesartan group and the placebo group in proportion of patients with non-CV death or non-CV hospitalization.

SAE reports were a common occurrence during the study, an expected finding for a study population with CHF and a long follow-up period. SAEs were reported for more than two thirds of study patients (placebo 71.1%, candesartan 67.3%) and most SAEs were CV disorders, reflecting the underlying conditions and risk factors of the study population.

Greater than one fourth of study patients died during the study (placebo 29.2%; candesartan 26.3%), but overall mortality was lower with candesartan treatment. As expected, most deaths were attributed to CV causes, the most frequent of which were sudden death; cardiac failure/cardiac failure, aggravated; and MI.

Among CV deaths, specific causes such as sudden death and death from heart failure were less common with candesartan treatment. This is an expected finding given that candesartan significantly reduced overall CV death and the most common causes of death in patients with CHF are typically sudden (arrhythmic) death and death from heart failure. Prevention of these causes of CV death is consistent with the survival beneficial effect of candesartan treatment observed in patients with CHF.

Among CV deaths, specific causes such as sudden death and death from heart failure were less common with candesartan treatment. This is an expected finding given that candesartan significantly reduced overall CV death and the most common causes of death in patients with CHF are typically sudden (arrhythmic) death and death from heart failure. Prevention of these causes of CV death is consistent with the beneficial effect of candesartan treatment in patients with CHF. Death from MI, a less common cause of death in this population, appeared to occur more frequently in the candesartan group; however, the incidence of non-fatal MI (placebo 4.9%, candesartan 4.5%) as well as all ischemic events (MI, angina pectoris, angina pectoris aggravated, coronary artery disorder) was approximately the same in the candesartan and placebo groups (18.7% myocardial ischemic events in the placebo group, and 21.4% in the candesartan group). An excess of non-fatal MI events would have been expected if the fatal MI events were due to a general pro-ischemic effect. Furthermore, given the relatively few MI events in the present study, the effect of candesartan on fatal and non-fatal MI may be best estimated by the effects in the overall CHARM programme. In this total population the difference in fatal MI events originated from the study SH-AHS-0003 and the frequency of non-fatal MI events was lower in the candesartan group (placebo 4.9%, candesartan 4.1%).

The mortality findings in the study population were relatively consistent across subgroups on the basis of age, gender and race. As expected, mortality was higher in older patients.

Also, as expected, the most common non-fatal SAEs were CV (cardiac failure/cardiac failure aggravated; angina pectoris and arrhythmia ventricular), and they generally occurred less frequently in patients in the candesartan group. Pneumonia, also an expected finding in an older population with CHF, was frequently cited as an AE with an approximately equal frequency in the 2 treatment groups (placebo 7.4 %; candesartan 8.2 %). ‘Renal failure acute’ as a non-fatal SAE was reported for 18 of placebo-treated patients and for 30 of candesartan-treated patients during study.

There was no difference in frequency between treatment groups for AE terms suggesting liver dysfunction. The two fatal cases (hepatic necrosis, cholestatic hepatitis) in the candesartan group were not considered related to the investigational product. Of 1013 candesartan-treated patients in the study, 23 (2.3%) died of cancer; 18 (1.8%) of 1015 placebo-treated patients also died from malignancy. Equal proportions reported a neoplasm during the study (59 patients, 5.8%). The types of cancer (lung, prostate, breast, colon) were typical for patients in the age group of the study population.

Tolerability of the investigational product in this population with CHF and a history of ACE-

inhibitor intolerance, was not remarkably different between patients treated with candesartan and patients treated with placebo. Overall, 70.2% of patients completed participation in the study without discontinuing treatment (70.9% in the placebo and 69.6% in the candesartan groups). Small differences existed between treatment groups for specific causes of investigational product discontinuation. Discontinuation due to aggravation of cardiac failure was more common in placebo-treated patients (7.1% compared with 5.2% for candesartan). Abnormal renal function, hypotension and hyperkalemia were cited more frequently as reasons for discontinuation with candesartan treatment (6.4% compared with 2.5%; 4.5% compared with 1.4% and 2.1% compared with 0.3%, respectively). Discontinuation of candesartan because of these three reasons was most notable in the first 6 to 12 months of treatment. Hypotension, progressive renal dysfunction and hyperkalemia are well recognized as likely AEs in patients with CHF, particularly when they are treated with inhibitors of the RAAS. It should also be noted that the study data collection instrument (CRF) included hypotension, increased creatinine and hyperkalemia as pre-specified reason for discontinuation. Furthermore, the majority of AEs reported for these events did not lead to discontinuation of the investigational product.

For hypotension, abnormal renal function and hyperkalemia the rates increased with age in the candesartan treatment group but not for patients in the placebo group. In patients aged younger than 75, discontinuation because of abnormal renal function was reported in 47 (6.0%) of patients on candesartan. Higher incidences were seen for patients aged 75 years or older where 24 patients (10.8%) in the candesartan group discontinued. A similar trend was shown for hypotension and hyperkalemia. Generally the frequency of events was higher for males in both treatment groups. However, the relative risk for renal function impairment with candesartan treatment was increased in women. The proportion of Caucasians in the study was dominant (placebo 90.8 %; candesartan 91.4 %). Only 4.4% in the placebo group and 2.8% on candesartan treatment were Blacks and the number of events were correspondingly small. There was a significant increase in discontinuation rates in the candesartan group for patients treated with spironolactone both at baseline and at the visit preceding the event. This could be expected from another inhibitor of the RAAS. However, concomitant medication with β-blockers and/or spironolactone at the time of the event did not seem to essentially affect the outcome regarding the AEs specifically studied.

For patients with a history of diabetes the between-treatment difference in frequency of discontinuations caused by increase in creatinine was slightly higher compared to the total population in the study. This is not an unexpected finding in a subpopulation with possible underlying renal dysfunction and autonomic dysregulation.

Patients with previous ACE-inhibitor discontinuation because of renal dysfunction and hypotension were more likely to have recurrence while taking candesartan than placebo, most patients with these histories tolerated candesartan. Importantly, cough (the most common reason for patients not taking an ACE-inhibitor due to ACE-inhibitor intolerance) led to discontinuation and/or dose reduction in only a few patients in each treatment group.

Angioedema occurred in only three patients, all with previous hypersensitivity to ACE inhibitors.

Study investigators chose to reduce the dose of the investigational product to manage AEs for 15.5% of candesartan-treated patients and 7.5% of placebo-treated patients. In general, AEs cited as prompting investigational product discontinuation were also cited as reasons for dose reductions (hypotension, hyperkalemia and abnormal renal function). However, dose reduction due to aggravated cardiac failure was comparatively rare.

In this study of patients with an established history of ACE-inhibitor intolerance, candesartan was safe, given that it reduced CV-mortality without off-setting non-CV mortality. It was also well tolerated; almost equal proportions of patients in the two treatment groups had AEs leading to permanent discontinuation of the investigational product. As expected for an inhibitor of the RAAS, events relatively specific to candesartan such as hypotensive events, hyperkalemia and increased creatinine occurred. Importantly, for most patients, reactions that prohibited patients from taking ACE inhibitors did not lead to discontinuation of the investigational product.

Clinical laboratory results:

Serial laboratory data were collected from patients participating at investigational sites in North America (placebo 334 patients, candesartan 326 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, such as creatinine and potassium.

The mean value for creatinine in the placebo group decreased 4.73 µmol/L from the baseline value to the LVCF (two extreme values were present at baseline but not at LVCF explaining the decrease). In the candesartan group, the value increased 17.9 µmol/L. At baseline, 75 (22.4%) of placebo patients had values above the reference range compared with 78 (23.9%) 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 94, 29.8%; candesartan 120, 37.3%).m For patients who had serial measurements (placebo 307 patients, candesartan 311 patients) baseline serum creatinine was at least doubled in 5 (1.6%) patients in the placebo group, compared with 17 (5.4%) 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 0.24 mmol/L for patients treated with candesartan. During the study, the proportions of patients with values above the reference range remained approximately the same in the placebo group (6, 1.8% at baseline, 7, 2.2% LVCF) and increased from 7 (2.1%) to 22 (6.8%) in the candesartan group. Potassium levels increased to ≥ 6 mmol/ L at any time after randomization in 1.3% (4) of 315 patients valid for evaluation in the placebo group and 2.8% (9) of 321 patients in the candesartan group.

Mean sodium measurements increased 0.03 mmol/L for patients treated with placebo and decreased 0.39 mmol/L for patients in the candesartan group. The AE term hyponatremia was reported for four patients (Site – Patient number: 358 – 10453, 455 – 16036, 943 – 14360, 1515 – 20840) treated with placebo compared with one patient (Site 1480, Patient number 23729)

treated with candesartan.

Minor decreases were seen for mean hemoglobin values for patients treated with placebo (0.13 mmol/L) and candesartan (0.24 mmol/ L). The proportion of patients with anemia reported as an AE during treatment with the investigational product was slightly lower for placebo-treated patients (16, 1.6%) compared with candesartan-treated patients (29, 2.9%). No patients in the placebo treatment group and 1 (0.3%) of 320 patients valid for evaluation in the candesartan 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 (-0.39%) and candesartan groups (-0.25%).

In summary, both the small differences in mean laboratory values (candesartan compared with placebo) and the frequency of outliers was in keeping with the expected findings for treatment with inhibitors of the renin-angiotensin-aldosterone system, i.e., effects on serum creatinine and potassium levels.

Discussion of vital signs, ECG, physical findings and other observations related to safety:

Vital signs consist of diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure and heart rate. For physical findings, data for body weight are presented.

At LVCF mean heart rate was 0.7 bpm lower in patients in the placebo group and 1.8 bpm lower in patients in the candesartan group compared to baseline.

Blood pressure declined in both treatment groups. Mean DBP decreased 3.5 mmHg from the baseline value to the LVCF in the placebo group and 4.8 mmHg from the baseline value to the LVCF in the candesartan group. Corresponding values for SBP were 4.4 mmHg for patients treated with placebo and 6.5 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 value less than 40 mmHg at any time during the study was reported for 5 (0.5%) patient in the placebo group and 16 (1.6%) patients in the candesartan group. 20 (2.0%) patients treated with placebo and 54 (5.4%) patients treated with candesartan had a recorded SBP value less than 80 mmHg at any time after randomization.

In the placebo group, mean body weight decreased by 0.5 kg from baseline to LVCF. In the candesartan population an increase of 0.7 kg was seen.

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

Following a Telecon on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) 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 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 November 24, 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, I used the definition for high candesartan dose 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.

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

In Table 183, 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 183 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 218 (21.5%)**	
			A
	CC_{HD} n = 626 events = 97 (15.5%)	CC_{LD} n = 260 events = 100 (38.5%)	CC_{00} n = 127 events = 21 (16.5%)
	A1	**A2**	**A3**
Placebo		**N = 1015** **Events = 196 (19.3%)**	
			B
	P_{HD} n = 748 events = 124 (16.6%)	P_{LD} n = 140 events = 60 (42.9%)	P_{00} n = 127 events = 12 (9.5%)
	B1	**B2**	**B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; n = number of patients with one or more events (proportion (%) of patients at the dose)
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)

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

In Table 184, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 184 The numbers and frequencies of permanent study drug discontinuation due to hypotension[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 37 (3.7%)**	**A**
	CC_{HD} n = 556 events = 9 (1.6%) **A1**	CC_{LD} n = 207 events = 24 (11.6%) **A2**	CC_{00} n = 250 events = 4 (1.6%) **A3**
Placebo		**N = 1015** **Events = 9 (0.9%)**	**B**
	P_{HD} n = 666 events = 5 (0.8%) **B1**	P_{LD} n = 102 events = 4 (3.9%) **B2**	P_{00} n = 247 events = 0 (0.0%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; n = number of patients with one or more events (proportion (%) of patients at the dose)
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)

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

In Table 185, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 185 The numbers and frequencies of permanent study drug discontinuation due to hyperkalemia[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 19 (1.9%)**	**A**
	CC_{HD} n = 557 events = 10 (1.8%) **A1**	CC_{LD} n = 192 events = 8 (4.2%) **A2**	CC_{00} n = 264 events = 1 (0.4%) **A3**
Placebo		**N = 1015** **Events = 3 (0.3%)**	**B**
	P_{HD} n = 665 events = 3 (0.5%) **B1**	P_{LD} n = 98 events = 0 (0.0%) **B2**	P_{00} n = 252 events = 0 (0.0%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; n = number of patients with one or more events (proportion (%) of patients at the dose)
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)

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

In Table 186, 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 186 The numbers and frequencies of permanent study drug discontinuation due to increased creatinine[a] in patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 62 (6.1%)**	**A**
	CC_{HD} n = 578 events = 32 (5.5%) **A1**	CC_{LD} n = 209 events = 26 (12.4%) **A2**	CC_{00} n = 226 events = 4 (1.8%) **A3**
Placebo		**N = 1015** **Events = 27 (2.7%)**	**B**
	P_{HD} n = 675 events = 16 (2.4%) **B1**	P_{LD} n = 106 events = 9 (8.5%) **B2**	P_{00} n = 234 events = 2 (0.9%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; n = number of patients with one or more events (proportion (%) of patients at the dose)
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)

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

In Table 187, 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 187 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 – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 182 (18.0%)**	**A**
	CC_{HD} n = 621 events = 120 (19.3%) **A1**	CC_{LD} n = 171 events = 60 (35.1%) **A2**	CC_{00} n = 221 events = 2 (0.9%) **A3**
Placebo		**N = 1015** **Events = 89 (8.8%)**	**B**
	P_{HD} n = 693 events = 64 (9.2%) **B1**	P_{LD} n = 97 events = 25 (25.8%) **B2**	P_{00} n = 225 events = 0 (0.0%) **B3**

CC_{HD} =candesartan high dose (16 mg, 32 mg) CC_{LD} =candesartan low dose (4 mg, 8 mg); CC_{00} =Not on candesartan at event or last visit; n = number of patients with one or more events (proportion (%) of patients at the dose)
[a] Definition used in exploratory safety analyses; [b]Dose of candesartan preceding the event (or at last visit if no event occurred)

Conclusions on safety results:

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.

Standard safety assessments included serious adverse events, serious and non-serious adverse events causing discontinuation of investigational product or dose reduction, clinical laboratory data (North America), vital signs and physical examination. The following were found:

- Serious adverse events occurred in equal frequency in both treatment groups during study (placebo 71.1%, candesartan 67.3%).
- 21.7% of the patients in the candesartan group and 19.4% of the placebo group permanently discontinued treatment with the investigational product due to an AE or an abnormal laboratory finding.
- 15.5% of the patients receiving candesartan and 7.5% receiving placebo 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.
- Differences in mean laboratory values across the treatment groups were small and in keeping with expectations for inhibitors of the renin-angiotensin-aldosterone system, i.e. increase in creatinine and potassium.
- 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.
- Candesartan did not influence time to permanent investigational product discontinuation due to any cause (P=0.735).
- Candesartan did not increase the number of investigational product discontinuations due to any cause (P= 0.509).
- Candesartan did not influence time to permanent investigational product discontinuation due to an AE or an abnormal laboratory value (P= 0.332).
- Candesartan did not increase the number of permanent investigational product discontinuations due to an AE or an abnormal laboratory value (P= 0.217).
- Candesartan increased the number of dose reductions due to an AE or an abnormal laboratory value at least once (P≤ 0.001).
- Candesartan did not influence time to non-CV death (P= 0.948).
- Candesartan did not increase the number of non-CV deaths (P= 0.822).
- Candesartan did not increase the number of non-CV hospitalizations (P= 0.652).

8.1 Summary of safety

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

724, 71.3%; candesartan 725, 71.6%) and over the entire study period (placebo 747, 73.6%; candesartan 741, 73.1%)

Serious adverse events (SAEs), fatal and non-fatal, occurred less frequently on treatment with candesartan (placebo 675, 66.5%; candesartan 623, 61.5%) as well as during the study, whether on or off treatment (placebo 722, 71.1%; candesartan 682, 67.3%). Fatal SAEs were also less common with candesartan, on treatment with the investigational product (placebo 187, 18.4%; candesartan 165, 16.3%) as well as during the study (placebo 296, 29.2%; candesartan 266, 26.3%). The most common fatal SAEs were cardiovascular events and these occurred less frequently in the candesartan treatment group during study (placebo 252, 24.8%; candesartan 219, 21.6%).

A total of 417 (20.6%) of the patients permanently discontinued taking the investigational product because of an AE or abnormal laboratory value (placebo 197, 19.4%; candesartan 220, 21.7%).

Study investigators chose to reduce the investigational product dose because of an AE for 76 (7.5%) of patients taking placebo and 157 (15.5)% taking candesartan.

Apart from cardiac failure aggravated (placebo 72, 7.1%; candesartan 53, 5.2%), abnormal renal function (placebo 25, 2.5%; candesartan 65, 6.4%), hypotension (placebo 14, 1.4%; candesartan 46, 4.5%) and hyperkalemia (placebo 3, 0.3%; candesartan 21, 2.1%) were the most commonly reported AE, given as reasons for discontinuing the investigational product.

Cough (the most common reason for patients not taking an ACE-inhibitor due to drug intolerance) led to discontinuation in only a few patients in each treatment group. Also most patients with ACE-inhibitor intolerance for other reasons at study entry, including hypotension, renal dysfunction and angioedema were able to tolerate candesartan treatment. Angioedema, specifically, occurred in none of the placebo patients and in 3 patients in the candesartan group. One of 39 candesartan patients with a history of angioedema when taking an ACE-inhibitor permanently discontinued candesartan because of angioedema.

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.

DISCUSSION AND OVERALL CONCLUSIONS

Discussion

In patients with CHF and clinically considered intolerant to an ACE inhibitor candesartan significantly reduced CV mortality or hospitalization due to heart failure. The effect appeared early and was sustained throughout the duration of the study. Also the other outcomes included in the confirmatory analysis; all-cause mortality or hospitalization for heart failure as well as CV

mortality or hospitalization due to heart failure or non-fatal MI were significantly reduced. There were substantial reductions in the individual components of the composite outcomes except for non-fatal MI. Moreover, symptoms of heart failure as evaluated by the NYHA-classification and development of atrial fibrillation were reduced.

This study evaluated candesartan in a population unable to receive standard ACE inhibitor therapy due to intolerance to this class of drugs. Importantly, the 23% relative risk reduction in CV mortality and heart failure hospitalization with candesartan parallels closely the reduction in mortality and heart failure hospitalization observed with the ACE inhibitor enalapril in the earlier SOLVD study[72] and in an overview of large studies of ACE inhibitors for patients with depressed LV systolic function with or without heart failure[51]. The magnitude of the benefit seen from treatment with candesartan was achieved despite modern concomitant treatment with other effective heart failure drugs such as β-blockers and spironolactone, agents which were not widely prescribed at the time of the earlier ACE-inhibitor trials. The present study has prospectively shown that candesartan provides an important treatment benefit, which appears to be of similar magnitude as that achieved with ACE inhibitors.

There were consistent and clinically important reductions in CHF hospitalizations with candesartan. In addition to prolongation of time to hospitalization due to heart failure, the number of patients admitted to hospital for CHF and the total numbers of hospital admissions primarily for CHF were lower in the candesartan group than in the placebo group.

Over the duration of the trial, 33% of candesartan patients compared with 40% of placebo patients reached the endpoint of CV mortality or first hospitalization due to heart failure. This absolute reduction of 7 major events per 100 patients treated corresponds to the need to treat 14 patients with candesartan to prevent one patient from suffering this outcome.

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. All fatal CV events except fatal MI were lower after treatment with candesartan. Although death due to MI was infrequent compared to death from heart failure-related causes, fatal MI was significantly more common in the candesartan group. There was, however no between- treatment difference in the incidence of non- fatal MI. Furthermore results from all three component studies included in the CHARM programme did not show differences between the treatment groups regarding fatal or non-fatal MI. Non-CV death was not influenced by candesartan.

Candesartan was well tolerated, without a notably increased need for discontinuation overall compared to placebo, despite these patients having a prior history of intolerance to another inhibitor of the renin- angiotensin-aldosterone system. This is consistent with our pilot experience[10]. As may be expected, discontinuation due to renal function impairment, hyperkalemia, or hypotension was more common with candesartan than placebo. This distribution of events could be expected from the pharmacodynamic profile of candesartan and the underlying conditions in the CHF population. Monitoring patients for these risks, especially those receiving concomitant therapy with diuretics or other inhibitors of the RAAS, is an already well-established practice for care of the CHF patient. While patients with prior ACE-inhibitor

discontinuation due to renal insufficiency and hypotension were more likely to have recurrence during treatment with candesartan compared with placebo, the vast majority of these patients were able to tolerate candesartan.

Importantly, cough (the most common reason for patients not taking an ACE-inhibitor due to ACEI-intolerance) led to discontinuation in only a few patients in each treatment group in the current study. Thus, patients who experienced cough as a reason for discontinuation of ACE inhibitor treatment did not experience recurrence of cough during treatment with candesartan.

Although angioedema has been reported with the use of AT1-receptor blockers[73], the incidence of recurrent angioedema among patients who initially had developed angioedema on ACE inhibitors is not well documented[74]. In the present study, the occurrence of angioedema was infrequent, and only 1 of 39 (2.6%) of the patients with a history of angioedema during treatment with ACE inhibitors had recurrence of angioedema leading to permanent discontinuation of treatment with candesartan, and this patient did not require hospitalization nor was the adverse event life threatening.

Overall conclusions

Candesartan reduces mortality and hospitalization due to heart failure and improves symptoms in patients with CHF and intolerance to treatment with ACE inhibitors. The reduction in mortality is attributed to the reduction in CV deaths. Candesartan is 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. Most patients with a history of prior ACE inhibitor intolerance are able to tolerate candesartan.

10.1.20 Appendix 2 CHARM-Pooled studies

Please refer to Chapter 10, Item 10.1.20, Appendix 16 (Pages 314-366) of my clinical review of the efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my reviews of the individual clinical studies in the CHARM-Program.

10.2 Line-by-Line Labeling Review

Please refer to Chapter 10, Item 10.2 (Pages 367-394) of my clinical review of the efficacy supplement SE 1 #022 of NDA 20-838 (CHARM-Added (SH-AHS-0006) study) in which I presented my line-by-line labeling review.

11 REFERENCES

[1] Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995; 273 (18): 1450-6.
[2] Honig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation 1997; 95:1115-8.
[3] Masoudi FA, Rathore SS, Wang lY, Havranek EP, Curtis JP, Foody JAM, Krumholz HM. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. Circulation 2004; 110: 724-731.
[4] Bart BA, Ertl G, Held P, Kuch J, Maggioni AP, McMurray J, et al for the SPICE Investigators. Contemporary management of patients with left ventricular systolic dysfunction: results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) registry. Eur Heart J 1999; 20: 1182-90.
[5] Clinical Quality Improvement Network Investigation. Mortality risk and patterns of practice in 4606 acute care patients with congestive heart failure: the relative importance of age, sex and medical therapy. Arch Intern Med 1996; 156: 1669-73.
[6] Bart BA, Gattis WA, Diem SJ, O'Connor CM. Reasons for underuse of angiotensin-converting enzyme inhibitors in patients with heart failure and left ventricular dysfunction. Am J Cardiol 1997; 79: 1118-20.
[7] The Large State Peer Review Organization Consortium Heart failure treatment with angiotensin-converting enzyme inhibitors in hospitalized Medicare patients in 10 large states. Arch Intern Med 1997; 157:1103-8.
[8] Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB Jr., Kohn RM, et al. Adverse effects of enalapril in the studies of left ventricular dysfunction (SOLVD). Am Heart J 1996; 131(2):350-5.
[9] Konstam M, Dracup K, Battarff M, et al. Heart failure evaluation and care of patients with left ventricular systolic dysfunction. Clinical Practice Guideline No 11. HCPRA Publication No. 94-0612, Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services, June 1994.
[10] Granger CB, Ertl G, Kuch J, Maggioni AP, McMurray J, Rouleau J-L, Stevenson LW, Swedberg K, Young J, Yusuf S, Califf RM, Bart BA, Held P, Michelson EL, Sellers MA, Ohlin G, Sparapani R, Pfeffer, MA for the Study of Patients Intolerant to Converting Enzyme Inhibitors (SPICE) Investigators. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. Am Heart J 2000; 139; 609-17.
[11] McKelvie RS, Rouleau J-L, White M, Afzal R, Young JB, Maggioni AP, et al. Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure. Eur Heart J 2003; 24(19): 1727- 1734.
[12] CPMP Committee for proprietary medicinal products (EMEA). Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure. CPMP/EWP, 235/95, Rev 1.
[13] Solomon, SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S, Pfeffer MA. Effect on candesartan on cause-specific mortality in heart failure patients. The Candesartan in Heart failure Assessment and Reduction in Mortality and morbidity (CHARM) Program. Circulation 2004; 110: 2180-3.
[14] Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition o sudden cardiac death in patients following acute myocardial infarction: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1999; 33: 598-604
[15] St John Sutton M, Lee D, Rouleau JL, Goldman S, Plappert T, Braunwald E, Pfeffer MA. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. Circulation 2003; 107: 2577-2582.
[16] Uretsky BF, Thygesen K, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, Poole-Wilson PA, Ryden I. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. Circulation 2000; 102: 611-616.
[17] Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, on behalf of the ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999; 100: 2312-8.

[18] Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; 345: 1667-1675.
[19] Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction: the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med 1995; 332: 80-85.
[20] Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. Ann Intern Med 2003; 138: 917-924.
[21] Palmer, BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004; 351: 585-592.
[22] Struthers AD. Aldosterone escape during ACE inhibitor therapy in chronic heart failure. Eur Heart J 1995; 16 Suppl N:103-6.
[23] MacFadyen RJ, Lee AFC, Morton JJ, Pringle SD, Struthers AD. How often are angiotensin Ii and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? Heart 1999; 82: 57-61.
[24] Roig E, Perez-Villa F, Morales M, et al. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. Eur Heart J 2000; 21: 53-7.
[25] Urata H, Healy B, Stewart RW, Bumpus M, Hussain A. Angiotensin II-forming pathways in normal and failing human hearts. Circ Res 1990; 66: 883-90.
[26] Petrie MC, Padmanabhan N, McDonald JE, Hillier C, Connell JMC, McMurray JJV. Angiotensin converting enzyme (ACE) and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. J Am Coll Cardiol 2001; 37: 1056-61.
[27] Nakajima M, Hutchinson HG, Fujinaga M, et al. The angiotensin II type 2 (AT_2) receptor antagonizes the growth effects of the AT_1 receptor: gain of function study using gene transfer. Proc Natl Acad Sci 1995; 92: 10663-7.
[28] Unger T. The role of the renin-angiotensin system in the development of cardiovascular disease. Am J Cardiol 2002; 89: Suppl:3A-10A.
[29] Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990; 86: 1343-6.
[30] Danser AH, Derkx FH, Hense HW, Jeunemaitre X, Riegger GA, Schunkert H. Angiotensinogen (M235T) and angiotensin-converting enzyme (I/D) polymorphisms in association with plasma renin and prorenin levels. J Hypertens 1998; 16: 1879-83.
[31] Andersson B, Sylven C. The DD genotype of the angiotensin-converting enzyme gene is associated with increased mortality in idiopathic heart failure. J Am Coll Cardiol 1996; 29: 162-7.
[32] McNamara DM, Holubkov R, Postava L, Janosko K, MacGowan GA, Mathier M, Murali S, Feldman AM, London B. Pharmacogenetic insertions between angiotensin-converting enzyme inhibitor therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. J Am Coll Cardiol 2004; 44: 2019-26.
[33] Burnier M, Brunner HR. Angiotensin II receptor antagonists. Lancet 2000; 355: 637-45.
[34] Reeves RA, Lin CS, Kassler-Taub K, Pouleur H. Dose-related efficacy of irbesartan for hypertension: an integrated analysis. Hypertension 1998: 31: 1311-16.
[35] Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI: Randomized trial of losartan vs. captopril in patients over 65 years with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; 349:747-752.
[36] Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial – the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355:1582-1587
[37] Berlowitz MS, Latif F, Hankins SR, Ennezat PV, Moskowitz R, Tandon S, Colombo PC, Le Jemtel TH: Dose-dependent blockade of the angiotensin II type 1 receptor with losartan in normal volunteers. J Cardiovasc Pharmacol 2001; 37:692-696.
[38] Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagoinst Losartan. Lancet 2002; 360: 752-760.

[39] Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau J-L, et al for Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. N Engl J Med 2003; 349: 1893-1906.
[40] Mann DL, Deswal A. Angiotensin-receptor blockade in acute myocardial infarction – a matter of dose. N Engl J Med 2003; 349: 1963-5.
[41] Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995-1003.
[42] Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-869.
[43] CIBIS- II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS- II): a randomized trial. Lancet 1999; 353(9146): 9-13.
[44] MERIT- HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353(9169): 2001-7.
[45] Packer M, Coats AJS, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL: for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-1658
[46] Buhler FR, Laragh JH, Baer L, Vaughan ED, Brunner HR. Propranolol inhibition of renin secretion: a specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. N Engl J Med 1972; 287:1209-1214.
[47] Sharpe N. Benefit of beta-blockers for heart failure: proven in 1999. Lancet 1999; 353: 1988-1989.
[48] Campbell DJ, Aggarwal A, Esler M, Kaye D. β-blockers, angiotensin II and ACE inhibitors in patients with heart failure. Lancet 2001; 358: 1609-10.
[49] The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy – The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study. Circulation 2000; 101:378-384.
[50] Thackray, SDR, Witte KKA, Khand A, Dunn A, Clark AL, Cleland JGF. Clinical trials update: highlights of the scientific sessions of the American Heart Association year 2000: Val HeFT, COPERNICUS, MERIT, CIBIS-II, BEST, AMIOVIRT, V-MAC, BREATHE, HEAT, MIRACL, FLORIDA, VIVA and the first human cardiac skeletal muscle myoblast transfer for heart failure. Eur J Heart Failure 2001;3:117-124.
[51] Flather MD, Yusuf S, Kober L, et al. Long-term ACE inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355: 1575-1581.
[52] Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995; 25: 1154-1161.
[53] Klein L, O'Connor CM, Gattis WA, Zampino M, de Luca L, Vitarelli A, Fedele F, Gheorghiade M. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations. Am J Cardiol 2003; 91 (suppl): 18F-40F.
[54] Packer M. Current role of β-adrenergic blockers in the management of chronic heart failure. Am J Med 2001; 110: 81S-94S.
[55] Sliwa K, Norton GR, Kone N, Candy G, Kachope J, Woodiwiss AJ, Libhaber C, Sareli P, Essop R. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. J Am Coll Cardiol 2004; 44: 1825-30.
[56] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341(10): 709-17.
[57] Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348(14): 1309-1321.

[58] Suzuki G, Morita H, Mishima T, et al. Effects of long-term monotherapy with eplerenone, a novel aldosterone blocker, on progression of left ventricular dysfunction and remodelling in dogs with heart failure. Circulation 2002; 106: 2967-72.
[59] Rocha R, Rudolph AE, Frierdich GE, et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol 2002; 283: H1802-H1810.
[60] Bauersachs J, Heck M, Fraccarollo D, et al. Addition of spironolactone to angiotensin-converting enzyme inhibition in heart failure improves endothelial vasomotor dysfunction: role of vascular superoxide anion formation and endothelial nitric oxide synthase expression. J Am Coll Cardiol 2002; 39: 351-8.
[61] The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336(8): 525-33.
[62] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, et al. CCC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2001. circulation 2001; 104: 2996-3007.
[63] Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, for the CHARM Investigators. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003; 362: 772-776.
[64] Gaizzi M, Agostoni P, Gauzzi MD: Modulation of alveolar-capillary sodium handling as a mechanism of protection of gas transfer by enalapril, and not by losartan, in chronic heart failure. J Am Coll Cardiol 2001; 37: 398-406.
[65] The ONTARGET/TRANSCENT Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/ Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease (ONTARGET/TRANSCEND) trials. Am Heart J 2004; 148: 52-61.
[66] Jessup M, Brozena S. Heart Failure. N Engl J Med 2003; 348:2007-2018.
[67] Gullestad L, Aukrust P, Ureland T, et al. Effect of high- versus low-dose angiotensin converting inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol 1999; 34: 2061-6.
[68] Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. J Am Coll Cardiol 2000; 36: 2090-5.
[69] Tang WH, Vegelos RH, Yee YG, et al. Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. J Am Coll Cardiol 2002; 39: 70-8 [Erratum: J Am Coll Cardiol 2002; 39: 746].
[70] The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-53.
[71] The Heart Outcomes Prevention Evaluation(HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in patients with diabetes mellitus: results of the HOPE study and MICRO-Hope sub-study. Lancet 2000; 355: 253-9. [Erratum, Lancet 2000; 356: 860-1]
[72] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325(5): 293-302.
[73] Warner KK, Viscontin JA, Tschampel MM. Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. Ann Pharmaco 2000; 34(4): 526-8.
[74] Gavras I, Gavras H. Are patients who develop angioedema with ACE inhibition at risk of the same problem with AT1 receptor blockers? Arch Intern Med 2003; 163(2): 240-1.