Table 84 Permanent discontinuation due to pooled adverse events related to abnormal renal function[a] or hypotensive events[b] or hyperkalemia[c] on treatment with candesartan cilexetil or placebo. Specified concomitant medication at the start of the event. ITT/safety population (SH-AHS-0003, -0006, -0007)[d]

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

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

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

As shown in the exploratory analysis, patients discontinued study treatment because of 'increased creatinine' over the entire study period, and the rate was greater for candesartan-treated patients (Figure 24).

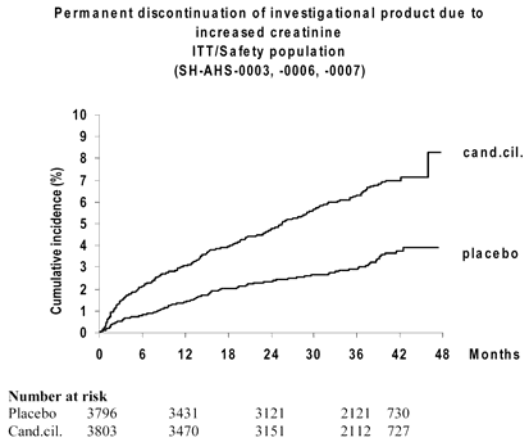


Figure 24 Cumulative incidence (%) of permanent discontinuation of the investigational product due to increased creatinine. ITT/Safety population

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program study with a history of diabetes, investigational product discontinuation for increased creatinine was noted for 57 (5.3%) placebo and 99 (9.1%) candesartan patients (Table 52 and Table 53). Compared to the total population (placebo 3.0%, candesartan 6.2%) (Table 48), diabetic patients were slightly more likely to discontinue the investigational product for increased creatinine levels.

Reviewer's comments with data from the literature: The deterioration in renal function tests is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have low glomerular filtration rates, hypotension and concomitant treatment with ACE-inhibitors and diuretics, all of which may increase the BUN or serum creatinine. The mean serum creatinine concentration in major clinical trials involving patients with congestive heart failure ranges from 1.2 to 1.4 mg/dL (106 to 124 μmol/L), and one third to one half of patients with congestive heart failure have renal insufficiency[20]. Chronic kidney disease is among the strongest predictors of death in patients with congestive heart failure. It may also predispose these patients to hyperkalemia.

It appears that use of ACE inhibitors and/or ARBs may be associated with higher levels of serum creatinine. In stage II of the RESOLVD trial[11] where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of plasma creatinine concentrations ≥ 50% of baseline and above 106μmol/L was found in 4.8% of patients receiving candesartan or enalapril alone, and 2.4% of patients receiving candesartan plus metoprolol or enalapril plus metoprolol; however, this doubled to 9.3% in patients receiving candesartan *plus* enalapril, and 9.0% in patients receiving candesartan *plus* enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.34), it is interesting to note that larger proportions of patients who received *both* candesartan *and* enalapril (with or without metoprolol) had elevated plasma creatinine concentrations. In the Val-HeFT trial[18] where valsartan was compared to placebo with all patients receiving standard therapy for heart failure, significantly (P < 0.001) larger increases were found in the valsartan treated group compared to placebo in BUN (5.9 mg/dl in valsartan group vs. 3.3 mg/dl in placebo group) and serum creatinine (15.9μmol/L in valsartan group and 8.8μmol/L with placebo).

7.3.3 Hyperkalemia

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

Hyperkalemia in CHARM-Alternative (SH-AHS-0003) Study:

At baseline, a slightly higher proportion of patients in the candesartan treatment group had serum potassium levels ≥ 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 61).

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

In Table 39, 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 44). 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 25).

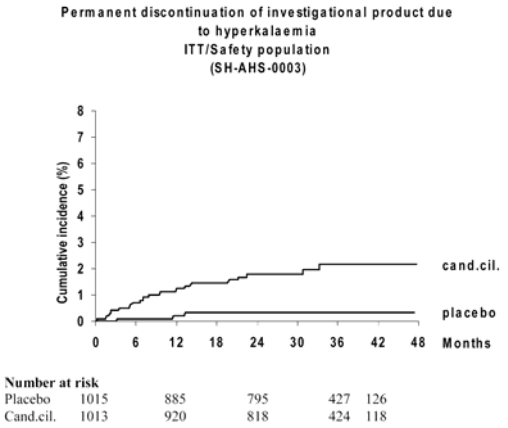


Figure 25 Cumulative incidence (%) of permanent discontinuation of investigational product due to hyperkalemia. ITT/Safety population (Ref. - Table 42).

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.

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

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

Hyperkalemia was reported for 78 patients (2.1%) in the placebo group and 238 patients (6.3%) in the candesartan group on treatment with the investigational product (Table 62).

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

In Table 40, discontinuation of the investigational product because of hyperkalemia occurred more frequently in patients treated with candesartan (placebo 22, 0.6%; candesartan 93, 2.4%). In the exploratory analysis the corresponding numbers were 21 (0.6%) for placebo patients and 85 (2.2%) for candesartan patients (Table 48). The higher rate for hyperkalemia causing discontinuation in the candesartan group could not be explained by between treatment differences in concomitant medications at the start of the event, including potassium – sparing diuretics or baseline serum potassium levels (North American study population) (Table 84).

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

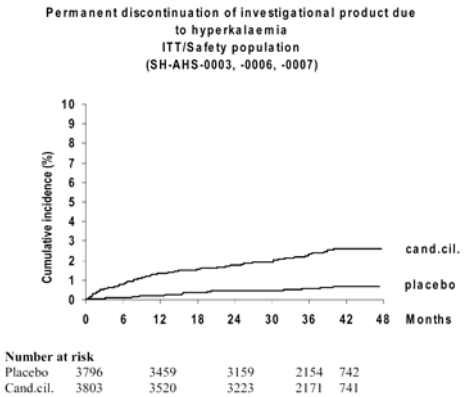


Figure 26 Cumulative incidence (%) of permanent discontinuation of the investigational product due to hyperkalemia. ITT/ Safety population

The discontinuation rate for candesartan-treated patients because of hyperkalemia (Figure 26), presented from exploratory analysis, was somewhat greater during the first 6 to 12 months of treatment, but discontinuations still occurred over the entire study period.

Among the 1,075 (28.3%) placebo patients and 1,088 (28.6%) candesartan patients entering the CHARM Program with a history of diabetes, investigational product discontinuation for the specific preferred term hyperkalemia was noted for 13 (1.2%) placebo and 31 (2.8%) candesartan patients (Table 52 and Table 53).

Reviewer's comments with data from the medical literature: Hyperkalemia is an expected clinical event in patients treated with candesartan, particularly so since these patients with CHF have hypotension (with poor tissue perfusion and metabolic acidosis) and concomitant treatment with ACE-inhibitors, β-blockers and potassium-sparing diuretics (spironolactone) all of which may increase the serum potassium. Also, one third to one half of patients with congestive heart failure have some degree of renal insufficiency[20] in whom a defect in the renal excretion of potassium further increases the risk of hyperkalemia.

Despite this finding that co-morbid renal insufficiency may cause hyperkalemia, physicians do have to use ACE-inhibitors, ARBs and aldosterone-receptor blockers in the treatment of patients with CHF. This is because chronic kidney disease is among the strongest predictors of death in patients with CHF, and these patients (with CHF and chronic renal failure) happen to be the ones who derive the greatest cardiovascular survival and benefits from these drugs. In the situation where CHF and co-morbid chronic renal failure are present, ACE inhibitors and/or ARBs not only treat the heart failure and reduce the risk of a future cardiovascular event and reduce the risk of death, but they also slow the progression of renal disease[21,41,42]. Withholding these drugs on the basis of the level of renal function or fear of causing hyperkalemia will unnecessarily deprive these patients of the cardiovascular benefit and survival benefit that they may obtain from judicious and cautious use of ACE inhibitors and ARBs.

In the OPTIMAAL trial[38], a significant (P=0.01) between-group difference was detected for and serum potassium (increased by 0.19 mmol/l in losartan group vs. 0.22 mmol/L in captopril group), being less with the ARB than with the ACE inhibitor. In the Val-HeFT trial[18] where valsartan was compared to placebo with standard therapy for heart failure, a significantly ($P < 0.001$) larger increase in potassium was found in the valsartan treated group (increase by 0.12 mmol/L) compared to placebo (decrease by 0.07 mmol/L).

In stage II of the RESOLVD trial[11] where patients with NYHA class II-IV and LVEF <0.40 were treated with candesartan alone, enalapril alone, candesartan plus enalapril, candesartan plus metoprolol, enalapril plus metoprolol, or candesartan plus enalapril plus metoprolol, the cumulative incidence of hyperkalemia defined as any observed plasma potassium concentration > 5.5 mmol/L was observed in 4.0% in patients receiving candesartan or enalapril alone, 2.4% in patients receiving candesartan plus metoprolol or enalapril plus metoprolol, 8.1% for patients receiving candesartan plus enalapril, and 7.9% for patients receiving candesartan plus enalapril plus metoprolol. Although the differences between treatment groups were not significantly different (P=0.3), it is interesting to note that larger proportions of patients who received both candesartan and enalapril (with or without metoprolol) had hyperkalemia.

7.3.4 Myocardial ischemia

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

Myocardial ischemia in CHARM-Alternative (SH-AHS-0003) Study:

At baseline, prior to randomization into the 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 between the placebo treatment group (16.4%) and the candesartan group (18.0%) (Table 87).

Table 85 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 86).

Table 86 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). For patients treated with candesartan in CHARM-Alternative study, the hazard ratio for fatal MI was 1.942 (P=0.025).

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

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

The proportions of patients with 'myocardial ischemia' 'on treatment' were approximately equal in the two treatment groups (18.1%, placebo group vs. 16.7% candesartan group) (Table 87).

Table 87 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

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

'Myocardial ischemic' events that were fatal were reported for 70 (1.8%) patients in the placebo group and 97 (2.6%) patients in the candesartan group during study (Table 88).

Table 88 Number (%) of patients with any of the preferred terms angina pectoris/angina pectoris aggravated, myocardial infarction or coronary artery disorder leading to death. ITT/Safety population (SH-AHS-0003, -0006, -0007)

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

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

7.3.5 Angioedema

Angioedema in CHARM-Alternative (SH-AHS-0003) Study

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.

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

During the study 5 cases of angioedema were reported for patients in the candesartan group compared with 3 cases in the placebo treatment group. All patients in the candesartan treatment group were Caucasian. Three of these patients in the candesartan group had a history of previous angioedema reactions while taking ACE-inhibitors. The remaining two patients in the candesartan group had concomitant medication with an ACE-inhibitor at the start of the event.

None of the events was considered life threatening or led to hospitalization. Two patients who developed angioedema required discontinuation of candesartan treatment. For the remaining 3 patients with angioedema, candesartan treatment continued without recurrence of angioedema, and for 1 of these the dose was reduced.

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

The frequency of angioedema as an AE appears to be similar between ARB and ACE-inhibitors. In the VALIANT trial[39] comparing valsartan, valsartan-plus-captopril and captopril, the proportion of patients with angioedema resulting in discontinuation of the study drug are similar; however, more patients in who received captopril or valsartan-plus-captopril reported angioedema resulting in dose reduction (Table 54).

Also, in the OPTIMAAL study[38] comparing losartan vs. captopril in patients with acute MI and evidence of heart failure or LV dysfunction, angioedema was reported significantly (P=0.034) more frequently (Table 55) in the captopril group (22 patients, 0.8%) compared to the losartan group (10 patients, 0.4%); angioedema was also associated with a significantly higher proportion of discontinuation (Table 55) from study drug treatment (14 patients (0.5%) in captopril group versus 4 patients (0.1%) in losartan group, P=0.019). Thus, it appears that angioedema is generally reported more frequently in patients receiving ACE inhibitors than in those receiving ARBs.

7.3.6 Abnormal hepatic function

Abnormal hepatic function in CHARM-Alternative (SH-AHS-0003) Study:

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).

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

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

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

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

7.3.7 Neoplasms

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

Neoplasms in CHARM-Alternative (SH-AHS-0003) Study

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).

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

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

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

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

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 89 and Table 90).

Table 89 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 90 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.

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

Rare adverse events reported include:

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

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

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

Following a Telecon 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.

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

In Table 91, 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 91 The numbers and frequencies of permanent study drug discontinuation due to <u>an adverse event or an abnormal laboratory value</u>[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)

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

In Table 92, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hypotension.

Table 92 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)

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

In Table 93, no relationship is apparent between the dose of candesartan and the numbers and frequencies of permanent study drug discontinuation due to hyperkalemia.

Table 93 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)

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

In Table 94, 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 94 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)

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

In Table 95, 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 95 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)

7.5 Summary of Safety

7.5.1 Summary of safety for CHARM-Alternative (SH-AHS-0003) Study:

Adverse events (AEs) were reported for approximately equal proportions of patients in the two treatment groups, both as analyzed during treatment with the investigational product (placebo 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%) 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.

The following findings are noted between the two treatment groups:

- Candesartan did not influence *time* to permanent discontinuation of the investigational product due to any cause (P =0.735).
- Candesartan did not increase the *number* of permanent discontinuations of the investigational product due to any cause (P =0.509).
- Candesartan did not influence *time* to permanent discontinuation of the investigational product due to an AE or an abnormal laboratory value (P =0.332).
- Candesartan did not increase the *number* of permanent discontinuations of the investigational product 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).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discontinuations and dose reductions attributed to decline in renal function, hypotension and hyperkalemia were more frequent in the candesartan group. Abnormal renal function (placebo, 3.4%; candesartan, 7.4%), hypotension (placebo, 2.5%; candesartan, 5.0%) and hyperkalemia (placebo, 0.6%; candesartan, 3.1%) were the most commonly reported AEs associated with discontinuation of the investigational product. In the candesartan group the frequency of discontinuation for hyperkalemia relative to placebo was greater in the oldest age groups.

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

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

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

Overall conclusions

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

7.5.3 Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor submitted pooled safety data from all CHARM Program studies (SH-AHS-0003, -0006 and -0007). I have presented and discussed the pivotal CHARM-Alternative (SH-AHS-000) study data and the overall CHARM-Pooled data in my safety review above. Safety data from the clinical pharmacology studies and from the non-CHARM studies are generally consistent with data from the CHARM-Pooled studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Rationale, Dosing Regimen and Administration

8.1.1 Prevalence of intolerance to ACE-inhibitors and candidates for treatment with ARBs

Estimates of the incidence of intolerance of ACE inhibitors among patients with heart failure range from 5% to 10%[5,6,7]. A registry of almost 10,000 patients with depressed LV systolic function also showed that 10% of these patients had a history of intolerance to ACE inhibitors[8].

A nationwide survey of patterns of use of ACE inhibitors in patients ≥65 years old who had survived hospitalization for heart failure with left ventricular systolic dysfunction revealed that ACE inhibitors were prescribed to only 68% of this cohort[3]. At least 20% of patients with heart failure do not take ACE inhibitors[4], in part because of intolerance. Similarly, of the 10% of the 10,000 patients with depressed LV systolic function who had a history of intolerance to ACE inhibitors, 6% were found to be both intolerant to ACE inhibitors and candidates for angiotensin II AT_1-receptor blockers (ARBs)[8]. While this is a small percentage, in the United States alone there are an estimated 2 million persons with heart failure[9]; this translates into 120,000 such CHF patients with depressed LV systolic function and intolerance to ACE inhibitors becoming candidates for treatment with ARBs.

8.1.2 Other situations where patients with CHF may be candidates for treatment with ARBs

Patients on ACE-inhibitors may undergo "ACE-escape," in which a gradual elevation of serum angiotensin II and aldosterone levels occurs despite ongoing RAAS inhibition with ACE-inhibitors[22,23]. "ACE-escape" is considered to portend a worse prognosis from CHF[24]. These patients may be candidates to be treated with ARBs which may prevent "ACE-escape"[25,26] because ARBs produce specific angiotensin II blockade via AT_1 receptors and preserve (theoretical) benefits derived from unopposed AT_2 receptor agonism (which is believed to counter the AT_1 response and lead to anti-proliferative, anti-growth and vasodilatory effects[27,28]).

The genetic heterogeneity of the ACE gene may influence the effectiveness of ACE inhibitors. A polymorphism in intron 16 of the ACE gene may cause two alleles (I= insertion; D= deletion) to differ on the presence or absence of a 287 pair-based insertion[29]. The ACE DD genotype, which forms about one-third of the general population, is associated with higher ACE activity[30], and with poor survival for patients with congestive heart failure[31]. In a study of 479 patients with systolic dysfunction (LVEF 0.25±0.08) who were genotyped for the ACE D/I polymorphism[32] and followed to the endpoint of death or cardiac transplantation, 227 patients received ACE inhibitor at "low doses" (≤50% of target dose), 201 patients received "high (standard) dose," and 51 patients received ARBs. The ACE-D allele was associated with an increased risk of events (P=0.026), particularly in the low-dose group (2-year event-free survival percentage: II/ID/DD = 79/66/59, P = 0.032). In the high dose group, this impact was not found (2-year event-free survival percentage: II/ID/DD = 77/70/71, P=0.64). These CHF patients who are not able to tolerate standard doses of ACE inhibitors and are at increased risk of mortality from HF, particularly those with the DD genotype, are potential candidates for ARB treatment.

8.1.3 Can ARBs be tolerated by patients with CHF who are intolerant to ACE inhibitors?

The Study of Patients Intolerant to Converting Enzyme Inhibitors (SPICE)[10] showed that patients with CHF and LVEF <35% who are intolerant to ACE inhibitors were able to tolerate candesartan (4 mg once/day, titrated to 16 mg once/day) similar to those who tolerated placebo (84% vs. 87%); however, the mortality and all-cause hospitalization were not significantly different between the candesartan and placebo groups in this relatively small pilot study of 270 patients. This finding that direct inhibition of the effect of angiotensin is tolerated by patients with a history of intolerance to ACE inhibitors suggests that intolerance to ACE inhibitors is primarily mediated through effects other than those of angiotensin.

ARBs differ from ACE-inhibitors in that they block the effect of angiotensin II at the AT_1 receptor, thus blocking the effects of angiotensin II produced through both ACE-dependent and ACE-independent pathways. Therefore, ARBs may exert a more complete inhibition of the local effects of angiotensin II. Also, blocking AT_1-receptors causes unopposed stimulation of AT_2-receptors which may produce an additional beneficial effect on cardiac remodeling[11] and vascular epithelial changes. Thus, ARBs may be useful in the treatment of CHF with left ventricular dysfunction in patients who are intolerant to ACE inhibitors.

8.1.4 Are all ARBs equal in their clinical effects?

The PK and PD characteristics of ARBs approved in the United States[33] are shown in Table 96.

Table 96 Pharmacokinetic and Pharmacodynamic properties of AT_1 receptor antagonists[33]. (Based on data from Lancet 2000; 355:637-45.)

Drug	In-vitro AT_1-receptor affinity*	Bioavailability (%)	Food effect	Active metabolite	Half-life (h)	Protein binding (%)	Daily dosage (mg)
Losartan (EXP 3174)	IC_{50}:20 nmol/L	33	No	Yes	2 (6–9)	98·7 (99·8)	50–100
Valsartan	IC_{50}:2·7 nmol/L	25	Yes (−40%)	No	9	95	80–320
Irbesartan	IC_{50}:1·3 nmol/L	70	No	No	11–15	90†	150–300
Candesartan cilexetil							
TCV 116		—	No	Yes	3·5–4	—	4–16 (32)
CV11974	K_i:0·6 nmol/L	42			3–11	99·5	
Telmisartan	K_i:3·7 nmol/L	43	No	No	24	>99	40–80
Eprosartan	IC_{50}:1·4–3·9 nmol/L	15	No	No	5–7	98	400–800

*IC_{50}=concentration displacing specifically 50% of the binding of angiotensin II; K_i=inhibition constant.
†Some studies suggest that irbesartan has a greater protein binding (>95%).

The pharmacokinetic and pharmacodynamic differences among ARBs may be clinically relevant. For example, candesartan and valsartan are dose-dependent inhibitors of the AT_1 receptor, with respective receptor affinities approximately 80 and 100 times that of losartan[33]. Valsartan's bioavailability drops if it is taken with food. Losartan is a relatively weaker AT_1 receptor blocker than either valsartan or candesartan, but its active metabolite (EXP3174) is 10-20 times more potent than losartan and is capable of an insurmountable receptor blockade. All six drugs lower BP more effectively than placebo without affecting heart rate, and do so regardless of sex, age or race. However, in a meta-analysis of 43 ranxomised placebo-controlled trials of ARBs in blood pressure studies[34], valsartan 160 mg is superior to losartan 100 mg daily, candesartan at doses of 8 mg and 16 mg daily is superior to losartan at 50 mg and 100 mg daily, and telmisartan 40 mg and 80 mg for 6 weeks reduced 24 hour ambulatory BP significantly more

than losartan 50 mg. While these results suggest differences in efficacy related to control of blood pressure, whether these differences are clinically relevant in terms of morbidity and mortality in patients with CHF remains to be seen.

8.1.5 Do ARBs need to be used at high doses for the treatment of heart failure with depressed LV systolic function?

An insufficient dose of ARBs used in previous clinical trials may have contributed to the observed lack of beneficial effect of ARBs on mortality. In the ELITE[35] and ELITE II[36] studies, the dose of losartan (50 mg q.d.) was chosen based on the effects of losartan in hypertensive patients, where the antihypertensive dose-response curve to losartan peaks at about 50 mg/day and plateaus at higher doses. This dose may not fully block AT_1 receptors throughout the 24-hour dosing interval.

In a study of human volunteers[37] who were given oral doses of placebo, losartan 50 mg or losartan 150 mg, and were subsequently challenged with a pre-determined blood pressure elevating-dose of angiotensin II (to raise radial artery systolic pressure by 20 mmHg), only the higher dose of 150 mg losartan was found adequate to produce a maximum inhibition of the pressor response to angiotensin II (Figure 27). Thus, the dose of 50 mg once/day of losartan used in ELITE[35] and ELITE II[36] may have been insufficient to substantially block the AT_1 receptor. ELITE II showed no survival advantage of losartan over captopril; the insufficient dose of losartan used may, in part, be the reason for this lack of effect.

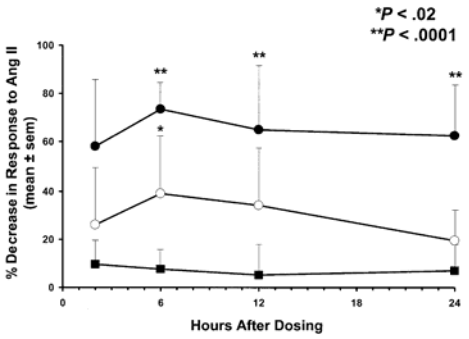


Figure 27 Blockade of the pressor response to intravenous infusions of angiotensin II (Ang II) in normal volunteers after oral administration of placebo (■), losartan 50 mg (○), or losartan 150 mg (●). * P < 0.02, ** P < 0.0001 compared with placebo. (Based on data from J Cardiovasc Pharmacol 2001; 37: 692-6)[37].

In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial[38], losartan (50 mg q.d.) was compared to captopril (150 mg/day) in high-risk patients with acute myocardial infarction (Figure 28). The results were in favor of captopril both for all cause mortality (not significant, P = 0.069) and for cardiovascular mortality (P=0.032). In this case, too, an insufficient dose may, in part, be a reason for the lack of effect of losartan.

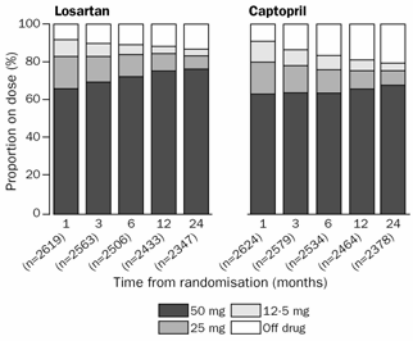


Figure 28 Dose of study drug Losartan was administered once daily and captopril three times daily. (OPTIMAAL Study)[38] (Based on data from Lancet 2002; 360: 752-60.)

In a recent trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[39], 14,808 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) plus captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. This study was designed to assess non-inferiority of valsartan relative to captopril. All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan-and-captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Table 97).

Table 97 Cardiovascular mortality and morbidity in VALIANT trial[39] (Based on data from N Engl J Med 2003; 349: 1893-1906.)

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

The VALIANT study[39] showed that valsartan and captopril were equivalent in terms of overall mortality and in terms of the composite endpoint of fatal and nonfatal cardiovascular events, whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival.

The lack of beneficial effect of losartan (ELITE[35], ELITE II[36] and OPTIMAAL[38] trials) and valsartan (VALIANT[39] trial) over ACE inhibitors may be due to the fact that a correct (or high enough) dose of the ARB was not used[40].

In contrast, in two recent clinical trials[41,42] in which the dose of losartan was increased gradually to 100 mg per day in asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy, a significant survival benefit among high-risk patients was observed.

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, 9,193 participants 55-80 years old with essential hypertension and left ventricular hypertrophy ascertained by ECG, were randomly assigned to receive losartan (titrated to 100 mg) or atenolol (titrated to 100 mg) once daily[41]. A significant reduction in relative risk (by 15%, P = 0.009) of the primary composite endpoint of cardiovascular mortality, stroke and MI was found in the subjects treated with losartan (Figure 29).

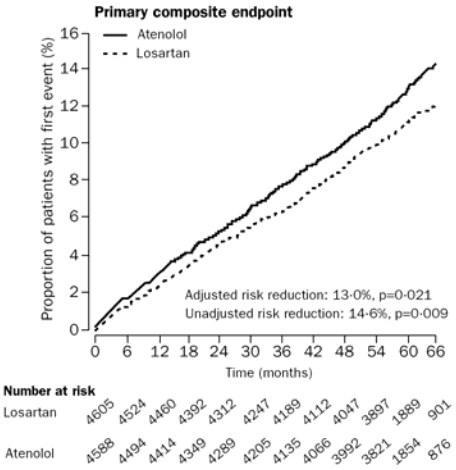


Figure 29 Kaplan Meier curves for primary composite endpoint (LIFE study)[41] (Based on data from Lancet 2002; 359: 995-1003.)

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years[42]. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death. Losartan reduced the primary endpoint significantly (relative risk reduction = 16%, P=0.02), and also reduced the incidence of doubling of serum creatinine concentration (relative risk reduction= 25%, P=0.006) and end-stage renal failure (relative risk reduction= 28%; P=0.002), and <u>also reduced the rate of first hospitalization for heart failure (relative risk reduction= 32%, P=0.005)</u> but had no effect on the rate of death (Table 98).

Table 98 Incidence of the primary composite endpoint and its components in RENAAL study[42] (Based on data from N Engl J Med 2001; 345: 861-9.)

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

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

The above findings suggest that for ARBs to demonstrate a beneficial survival effect in the treatment of patients with heart failure, ARBs must be used at high enough doses that will fully block AT_1 receptors throughout the dosing interval.

8.1.6 Selection of dose of candesartan for the CHARM Program studies

The approved doses of candesartan for treatment of hypertension range from 2 mg to 32 mg once daily. For organ-protective effect (e.g., cardio-protection from remodeling), a higher degree of AT_1-receptor blockade than that required for an anti-hypertensive effect is expected. Thus, higher doses than those optimal for hypertension treatment were thought to be required. The selection of dose of candesartan for treatment of CHF was based on the following studies:

(1) SH-AHS-0001 (RESOLVD) study: In this pilot study of 768 patients with CHF, candesartan 4 mg to 16 mg was found as effective as enalapril 10 mg bid on improving left ventricular function (with or without addition of metoprolol). This study was terminated early because of increased clinical events (deaths) in the treatment groups receiving candesartan and candesartan plus enalapril.

(2) SH-AHS-0002 (SPICE) study: This pilot study of 270 patients with CHF showed that patients intolerant to ACE-inhibitors could be treated for 12 weeks with candesartan 4 mg to 16 mg, with a tolerability similar to placebo.

(3) EC604 study: In this relatively large study of 844 patients with CHF, 4 mg, 8 mg and 16 mg doses of candesartan were given over 12 weeks and, the 16 mg dose was found to improve exercise tolerance (bicycle ergometry only).

(4) SH-AHS-0008 study: In this 8-week study of 98 patients with CHF, candesartan was added to conventional heart failure treatment regimen, starting at 8 mg once daily, titrated at 2-week intervals to doses of 16 mg once daily and to a maximum dose of 32 mg once daily (the highest dose for candesartan in the treatment of essential hypertension approved in the United States). This study showed that the 32 mg dose was generally safe and well-tolerated by these patients with CHF.

In studies conducted prior to the CHARM Program, doses of up to 16 mg once daily were used for treatment of CHF, except in SH-AHS-0008 study which evaluated a target dose of 32 mg once daily. The sponsor's view of the results of these studies was that improvement in the variables tested (left ventricular hemodynamics, neurohormonal changes, exercise tolerance, symptom improvement, etc.) was dose dependent, and maximal at 16 mg dose, that patients with CHF tolerated the 16 mg dose of candesartan well, and that in the tolerability study (SH-AHS-0008), these CHF patients tolerated the 32 mg dose of candesartan as well. Based on this finding, the sponsor decided the target dose of candesartan for the CHARM Program clinical trials as 32 mg once daily.

Also, experience with ACE inhibitors in treatment of heart failure suggests that starting with a low dose is appropriate, and that the dose should then be up-titrated to the target dose.

For this pivotal study SH-AHS-0003 (CHARM-Alternative trial), a starting dose of 4 or 8 mg candesartan was chosen (at the discretion of the clinical investigator), and this was up-titrated by doubling the dose at intervals of 2 weeks up to a maximum dose of 32 mg once daily or the highest tolerated dose to ensure as complete blockade as possible of AT_1-receptors. The protocol specified monitoring serum potassium and creatinine levels at each dose escalation.

The protocol recommended a starting dose of 4 mg once daily for patients:

- with hypovolemia,
- treated with furosemide >40 mg daily or equivalent,
- with NYHA functional class III-IV,
- with systolic BP ≤110 mmHg,
- with serum creatinine >150μmol/L (1.7 mg/dl),
- who were frail, or
- at the investigator's discretion.

The submission (CHARM-Alternative, SH-AHS-0003, study) shows that 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). 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.

8.1.7 Inference on the finding of a relationship between the dose of candesartan and the primary and secondary efficacy outcomes in CHARM-Alternative (SH-AHS-0003) study

Please refer to section 6.1.5 (Is there a relationship between the dose of candesartan and the primary and secondary efficacy outcomes: Pages 49 – 52) of this review for the tables of data submitted by the sponsor on November 24, 2004 in response to my request 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 primary and secondary efficacy endpoints.

For the composite primary efficacy endpoint of CV death or CHF hospitalization, a dose related response was observed with the event rates being significantly (P<0.001) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups (cells A1 vs. A2 in Table 27 and Table 28); however, patients receiving placebo also exhibited the same dose response! (cells B1 vs. B2 in Table 27 and Table 28).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 29 and Table 30), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 31 and Table 32) also show similar findings.

As discussed earlier, 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).

My interpretation of the data provided by the sponsor in Table 27 through Table 32 (in section 6.1.5) is as follows.

(i) <u>Patient sub-populations by severity of CHF (presumed)</u>: Patients in cells A3 (not receiving candesartan prior to event) and B3 (not receiving "double-blind" placebo (perceived by the clinical investigator and the patient as candesartan) prior to event) were, I think, "the most sick" patients who, for some reason (hypotension, hyperkalemia, deterioration in renal function) could not tolerate candesartan for an unknown period of time prior to the primary or secondary efficacy event. Patients in cells A2 (receiving 4 mg or 8 mg candesartan prior to event) and B2 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 4 mg or 8 mg candesartan) prior to event) were "moderately sick" patients who could not tolerate the higher doses of candesartan. Patients in cells A1 (receiving 16 mg or 32 mg candesartan prior to event) and B1 (receiving "double-blind" placebo (perceived by the clinical investigator and the

patient as 16 mg or 32 mg candesartan) prior to event) were "the least sick" patients who tolerated the higher doses of candesartan.

(ii) Effect of no drug – internal consistency: Patients in both treatment groups A3 and B3 were not receiving any investigational drug (candesartan or placebo) and had the same (albeit presumed) severity of CHF. Thus, the events rates in treatment groups A3 and B3 are expected to be similar. The event rates in treatment groups A3 and B3 for the primary and secondary efficacy endpoints are, indeed, similar (Table 27 through Table 32), suggesting internal consistency, and providing some confidence to the logic and integrity of the data.

(iii) Effect of candesartan (1): Comparing the event rates in A2 to B2 allowed the comparison of events in the same population of patients with similar severity of CHF ("moderately sick" patients). A statistically significant reduction in the event rates between A2 vs. B2 for the primary and secondary efficacy endpoints suggests a true difference in this sub-population of moderately sick patients with CHF.

(iv) Effect of candesartan (2): Comparing the event rates in A1 to B1 allow the comparison of event rates in same population of patients with similar degree of CHF ("the least sick" group of patients). A statistically significant reduction in the event rates between A1 vs. B1 for the primary and secondary efficacy endpoints suggests a true difference among patients with the same severity of CHF.

(v) Effect of candesartan (3): The effect of candesartan in the "least sick" and "moderately sick" sub-populations of patients appears to be about the same (for the primary endpoint, a reduction in the relative risk by 34.5% (A1 vs. B1) or 37.6% (A2 vs. B2). This suggests a consistent effect of candesartan for the primary (and also for the secondary) efficacy endpoints.

(vi) Effect of disease: Comparison of the event rates in cells B1 vs. B2 (patients receiving placebo) also shows that the event rates are significantly ($P<0.001$) lower in the "high dose" group compared to the "low dose" group (Table 27 through Table 32). Since neither group (B1 or B2) was receiving candesartan, this finding is clearly due to the severity of CHF.

(vii) Effect of disease severity (or) effect of dose of candesartan? Comparison of cells A1 vs. A2 shows that the event rates are significantly ($P<0.001$) lower in the high dose (16 and 32 mg, A1) candesartan groups compared to the low dose (4 and 8 mg, A2) candesartan groups (Table 27 through Table 32), giving the appearance of a dose-related response. I think that the lower event rate in the "high dose" candesartan group is mainly due to the fact that subjects in cell A1 are "the least sick" of the study population; conversely, the higher event rate in the "low dose" candesartan group is due to the fact that subjects in cell A2 are relatively less sick patients. Thus, rather than a "dose-related" response for candesartan regarding the primary and secondary efficacy endpoints as the data in Table 27 through Table 32 appear to suggest, I think the differences observed between the "high dose" and "low dose" candesartan groups are attributable to the severity of CHF.

8.2 Drug-Drug Interactions

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

CHARM-Alternative (SH-AHS-0003) Study

At the time of randomization, 1,106 (55%) patients were on treatment with a β-blocker, 1,733 (86%) patients were treated with diuretics, 924 (46%) patients with digitalis and 483 (24%) patients were treated with spironolactone, without major differences between treatment groups. Metoprolol and carvedilol were the two most commonly used β-blockers. Four patients were using ACE-inhibitors at randomization.

After randomization, the use of some concomitant medications were more common in the placebo group than in the candesartan group at the closing visit [β-blockers in 480 patients (67%) vs. 476 patients (64%), respectively, spironolactone in 209 patients (29%) vs. 183 patients (25%) respectively, and any diuretics 572 patients (79%) vs. 566 patients (76%), respectively].

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

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

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

The efficacy results of the CHARM-Program studies show that the beneficial effect of candesartan in the CHARM Program was observed in CHF patients with symptomatic CHF (pooled studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) who were receiving ACE-inhibitors, β-blockers or digoxin as part of the conventional treatment for CHF. The beneficial effect of candesartan was observed both for the primary efficacy endpoint of all-cause mortality (Figure 30) and for the composite endpoint of CV death or CHF hospitalization (Figure 31).

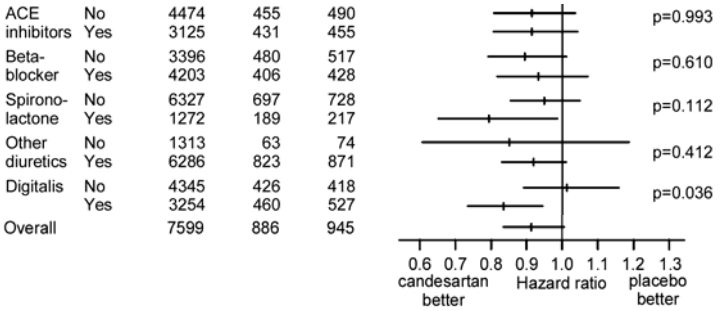


Figure 30 Overall effect of candesartan on all-cause death in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007)

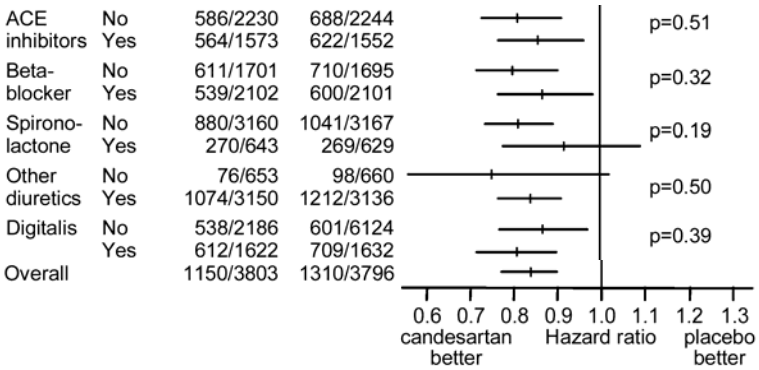


Figure 31 Overall effect of candesartan on CV death or hospitalization in subgroups of conventional CHF treatment. Point estimates of hazard ratios given with 95% confidence interval, and P values. ITT/Safety population (SH-AHS-0003, SH-AHS-0006, SH-AHS-0007).

The beneficial effect of candesartan observed in the CHARM-Program appears to be complementary to the effects of these drugs used in the conventional treatment of CHF.

Within the context of my review of this NDA 20-838 Efficacy Supplement #024, I will present and discuss, in the following sections, the findings reported in clinical trials in the medical literature in comparison with the results from the CHARM-Alternative (SH-AHS-0003) trial.

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

β-blockers have been proven to be effective in reducing mortality from heart failure[43,44,45]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[43] in Europe enrolled 2,647 symptomatic patients in New York Heart Association class III or IV, with LVEF ≤ 35%, receiving standard therapy with diuretics and ACE-inhibitors. Patients were assigned bisoprolol 1·25 mg (n= 1,327) or placebo (n= 1,320) daily, the drug being progressively increased to a maximum of 10 mg per day. Patients were followed up for a mean of 1·3 years. Analysis was by intention to treat.

Table 99 Primary and secondary endpoints and exploratory analyses in CIBIS-II study[43] (Based on data from Lancet 1999; 353: 9-13.)

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0·66 (0·54–0·81)	<0·0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0·80 (0·71–0·91)	0·0006
All cardiovascular deaths	161 (12%)	119 (9%)	0·71 (0·56–0·90)	0·0049
Combined endpoint	463 (35)	388 (29%)	0·79 (0·69–0·90)	0·0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1·00 (0·82–1·22)	0·98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0·56 (0·39–0·80)	0·0011
Pump failure	47 (4%)	36 (3%)	0·74 (0·48–1·14)	0·17
Myocardial infarction	8 (1%)	7 (1%)	0·85 (0·31–2·34)	0·75
Other cardiovascular	23 (2%)	28 (2%)	1·17 (0·67–2·03)	0·58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0·75 (0·37–1·50)	0·41
Unknown cause of death	49 (4%)	23 (2%)	0·45 (0·27–0·74)	0·0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0·64 (0·53–0·79)	0·0001

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

The CIBIS-II study was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit (Table 99). All-cause mortality was significantly lower with bisoprolol than placebo (156 [11·8%] vs. 228 [17·3%] deaths, respectively, with a hazard ratio of 0·66 (95% CI 0·54 – 0·81, P < 0·0001)). There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3·6%] vs. 83 [6·3%] deaths, respectively, with a hazard ratio of 0·56 (95% CI 0·39 – 0·80, P= 0·0011)). Treatment effects were independent of the severity or cause of heart failure.

The relatively large Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[44] enrolled 3,991 patients with CHF in NYHA class II-IV with EF ≤0.40%, stabilized with optimum standard therapy, in a double-blind randomized controlled study. 1,990 patients were randomly assigned metoprolol CR/XL 12·5 mg (NYHA III–IV) or 25·0 mg once daily (NYHA II), and 2,001 patients were assigned placebo. The target dose was 200 mg once daily and doses were up-titrated over 8 weeks. The primary endpoint was all-cause mortality, analyzed by intention to treat. The MERIT-HF study, too, was stopped by the independent safety committee because all-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7·2%, per patient-year of follow-up]) vs. 217 deaths [11·0 %], relative risk 0·66 [95% CI 0·53 – 0·81]; P = 0·00009 or adjusted for interim analyses P = 0·0062). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs. 132, 0·59 [0·45 – 0·78]; P = 0·0002) and fewer deaths from worsening heart failure (30 vs. 58, 0·51 [0·33 – 0·79]; p= 0·0023) (Figure 32).

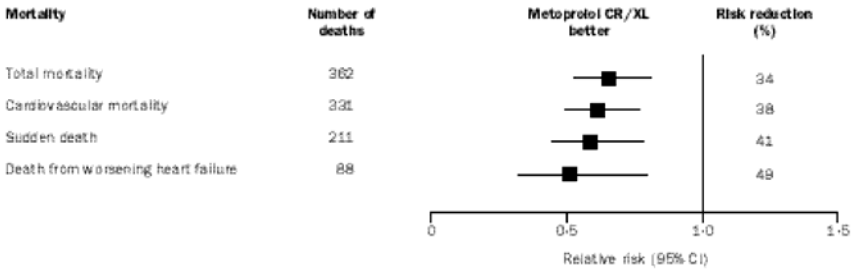


Figure 32 Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure (MERIT-HF study)[44] (Based on data from Lancet 1999; 353: 2001-7.)

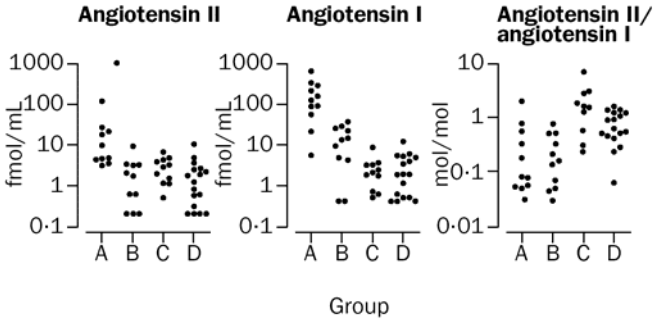


Figure 33 Blood concentrations of angiotensin II and angiotensin I, and angiotensin II/ angiotensin I ratio[48] (Based on data from Lancet 2001; 358: 1609-10.)
Group A= patients with heart failure, receiving ACE inhibitors; Group B= patients with heart failure, receiving ACE inhibitors and β-blockers; Group C= controls; Group D= controls, receiving β-blockers.

β-blockers have been shown to inhibit the activation of the sympathetic nervous system during heart failure and also to reduce renin secretion[46], either of which could result in improved clinical outcome[47]. In a study of two matched groups of patients with NYHA class II-III heart failure receiving maximum tolerated doses of ACE inhibitors, half (11 patients) were randomized to receive β-blockers and the other half (11 patients) did not receive β-blockers[48]. Concentrations of angiotensin II and angiotensin I (Figure 33) were significantly (P<0.01) higher in the group (Group A) that did not receive β-blockers, whereas patients who received β-blockers (Groups B and D) had low levels of angiotensin II (geometric mean 1·1 [95% CI 0·4 - 2·7] vs. 15·5 [4·6 - 52·6] fmol/mL, 95% CI for difference 3 - 59). Thus, reduction of angiotensin II concentrations by β-blockade might contribute to the therapeutic effects of β-blockade in these CHF patients receiving ACE inhibitors.

In stage II of the RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot Study, metoprolol CR was added to the treatment of 426 patients with CHF and dilated cardiomyopathy receiving enalapril alone, candesartan alone or both[11,49]. The proportion of patients receiving target doses of ACE inhibitors, candesartan or both was 95% for the group on enalapril alone, 91 % for the group treated with candesartan and 85% for the group treated with enalapril and candesartan. Metoprolol CR did not affect 6-minute walk distance, NYHA functional class or quality of life in any group. However, Figure 34 shows that improvements were seen in LV ejection fraction (increased by 2.4% in the metoprolol CR-treated group, P=0.001), attenuation in the increase in LVEDV (by 6±61 ml, versus 23±65 ml for

placebo group, P=0.01) and LVESV (reduced by 2±51ml vs. 19±55 ml for placebo group, P<0.001). There were significantly decreased angiotensin II level (P=0.036) and plasma renin activity (P=0.032), and significantly increased N-terminal atrial natriuretic peptide (ANP) level (P=0.001) and brain natriuretic peptide (BNP) level (P=0.002). There were also fewer deaths in the group receiving metoprolol (3.4%, vs. 8.1 % in the placebo group), but the study was not powered to detect differences in clinical endpoints such as death. This study demonstrated that treatment with candesartan, enalapril *and metoprolol* has a more beneficial effect on cardiac volumes and LVEF than treatment with either enalapril alone, candesartan alone or enalapril and candesartan together without a β-blocker.

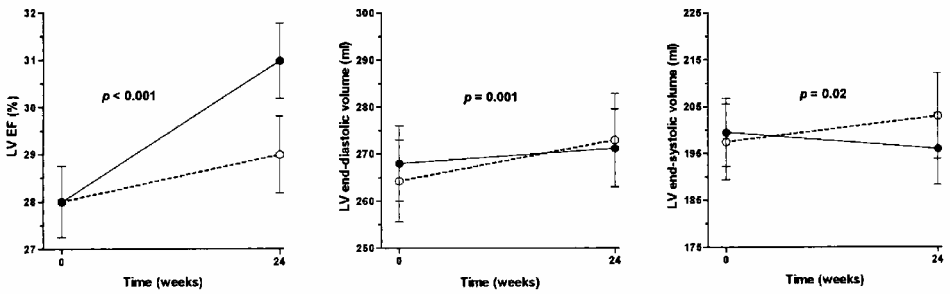


Figure 34 Changes in LVEF and LV volumes in response to metoprolol (●) versus placebo (○) in stage II of the RESOLVD study[49]. Data are mean±SEM. (Based on data from Circulation 2000; 101: 378-84.)

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

In the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) Study[45], a total of 2,289 patients with symptomatic heart failure at rest or minimal exertion and with LVEF <25% were randomized to receive carvedilol or placebo for a mean period of 10.4 months. They also received conventional heart failure therapy including diuretics, ACE inhibitors or ARBs. There were 190 deaths in the placebo group and 130 deaths in the carvedilol group, reflecting a 35% decrease in the relative risk of death with carvedilol (95% CI 0.19 to 0.48, P = 0.0014, Figure 35). There was also a reduction in the relative risk for the combined endpoint of death or hospitalization by 24% (95% CI 0.13 to 0.33, P<0.001, Figure 36). Thus, addition of carvedilol to conventional therapy for heart failure was beneficial in this group of patients with severe heart failure.

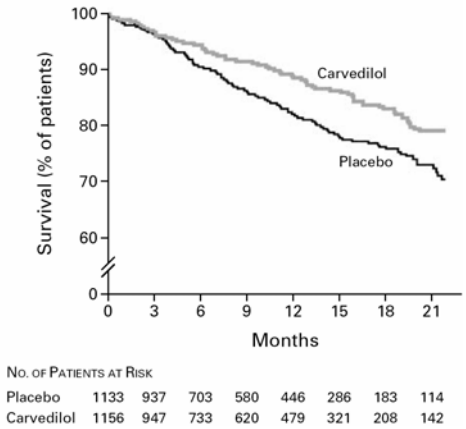


Figure 35 Kaplan-Meier Analysis of Time to Death in Placebo and Carvedilol Groups[45] (Based on data from N Engl J Med 2001; 344: 1651-8.) The 35% lower risk in the carvedilol group was significant: P=0.00013 (unadjusted) and P=0.0014 (adjusted).

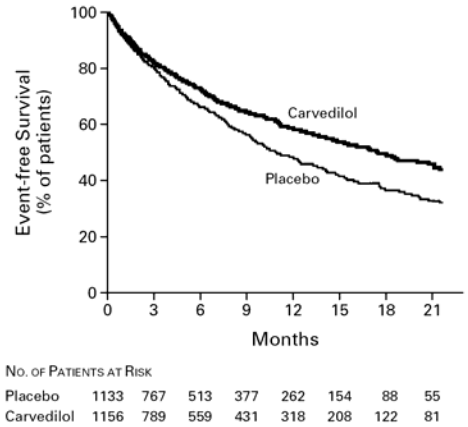


Figure 36 Kaplan-Meier Analysis of Time to Death or First Hospitalization for Any Reason in Placebo and Carvedilol Groups[45]. (Based on data from N Engl J Med 2001; 344: 1651-8.)
The 24 percent lower risk in the carvedilol group was significant (P<0.001).

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

In ELITE II study[36], 3,152 patients with NYHA Class II-IV heart failure and LVEF ≤ 40% were assigned to receive either losartan (50 mg q.d.) or captopril 50 mg t.i.d., and followed up for a median of 1.5 years. Patients were stratified for β-blocker use. The primary and secondary endpoints were all-cause mortality, and sudden death or resuscitated arrest. Median follow-up was 555 days. There were no significant differences in all-cause mortality (11·7 vs. 10·4% average annual mortality rate) or sudden death or resuscitated arrests (9·0 vs. 7·3%) between the losartan and captopril treatment groups (hazard ratios 1·13 [95·7% CI 0·95 – 1·35], p= 0·16 and 1·25 [95% CI 0·98 – 1·60], p= 0·08). No significant interaction was found for concomitant β-blocker use during the study (Figure 37).

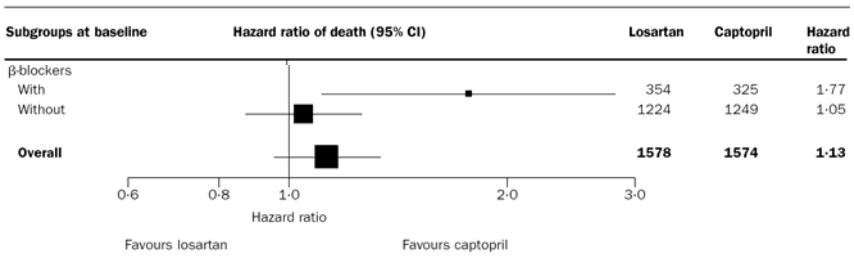


Figure 37 Mortality by subgroup (ELITE II[36]) (Based on data from Lancet 2000; 355: 1582-7.)

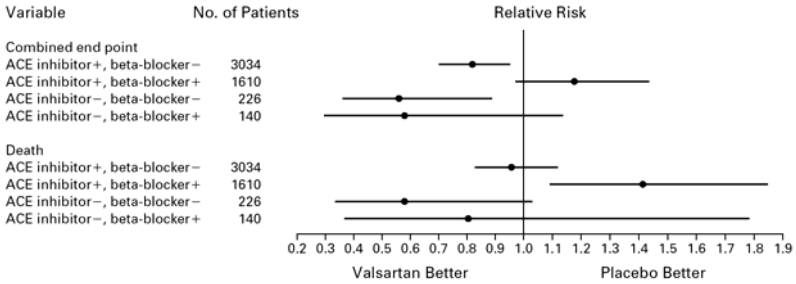


Figure 38 Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, in Val-HeFT study[18]. (Based on data from N Engl J Med 2001; 345: 1667-75.)
ACE denotes angiotensin- converting enzyme, + the use of the drug, and – nonuse.

In the Val-HeFT[18,50] study, 5,010 patients with symptomatic CHF (93% already treated with ACE inhibitors) were randomized to receive valsartan (starting dose 40 mg b.i.d., titrated to a target dose of 160 mg b.i.d.) or placebo, and followed for 1.9 years. The study found that patients taking β-blockers at baseline who were randomized to valsartan (36% of all enrolled) did worse than those randomized to placebo; i.e. the former had a 15% ***increased*** risk or morbidity and mortality (P<0.05). The effect of β-blockers are also derived from two sub-groups (Figure 38): (i) in 1,610 patients given triple therapy with ACE inhibitors, β-blockers and valsartan, there was a significant ***increase*** in mortality (129 vs. 97 deaths, hazard ratio 1.42, 95% CI 1.09-1.85, P = 0.009) compared with 806 patients treated with ACE inhibitors, β-blockers and placebo; and (ii) in 226 patients **not** given ACE inhibitors or β-blockers, there was a 33% reduction in mortality (P=0.012).

These findings in the Val-HeFT[18,50] study could have resulted from the combined treatment of valsartan, an ACE-inhibitor, and a β-blocker causing a reduction in blood pressure of 6 to 7 mmHg in the valsartan group; this drop in BP could have been excessive in patients in whom both the RAS and the β-adrenergic receptors were blocked, leading to ischemic events or worsening of heart failure. This interaction was observed only for the baseline therapy with β-blockers, and did not reflect β-blocker use during the study. The Val-HeFT investigators postulated that extensive blockade of multiple neurohormonal systems in patients with heart failure might be deleterious[51].

There are a number of caveats to the use of β-blockers in heart failure.

One caveat that is unique to the use of β-blockers in heart failure is that they may cause initial worsening before improvement occurs[52]; i.e., initially, β-blockers may worsen symptoms of heart failure, but improvement is seen after long-term therapy. Thus, to avoid deterioration, heart failure patients must first be stabilized on a regimen of digoxin, diuretics and ACE inhibitors and/or ARBs, and β-blockers must be started at low doses and the doses gradually increased over a period of several weeks. Also, data from the ATLAS trial[17], MERIT-HF trial[44] and other β-blocker clinical trials have been computed to show (Table 100) that in patients receiving a low or intermediate dose of an ACE-inhibitor, adding a β-blocker may improve symptoms and reduce the risk of death and hospitalization to a greater magnitude than increasing the dose of the ACE-inhibitor to a maximally tolerated dose[53,54].

Table 100 Comparative Effects of Two Different Treatment Strategies in Patients Receiving Low Doses of Angiotensin-Converting Enzyme (ACE) Inhibitors (Based on data from Am J Med 2001; 110: 81S-94S)[54]

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

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

Secondly, as opposed to the conventional sequence of drug use in the treatment of heart failure (as described above), a small open-label study conducted in Johannesburg, South Africa, showed that initiation of treatment with carvedilol *before* an ACE inhibitor resulted in higher tolerable doses of carvedilol and better improvements in NYHA functional class and LV function. This was a single-center, prospective, randomized trial of initiation of treatment with carvedilol either before (n=39) or after (n=40) perindopril therapy in newly diagnosed patients in NYHA Class II to III heart failure with idiopathic dilated cardiomyopathy, with the addition of the alternative agent after six months[55]. After 12 months, 11 patients died (6 in the group where perindopril was initiated). At 12 months, the group receiving carvedilol as initial therapy achieved a higher tolerable dose of carvedilol (43±17 mg vs. 33±18 mg, P = 0.03), a lower dose of furosemide (P<0.05), and better improvement in symptoms (NYHA functional class, P<0.002), LV ejection fraction (radionuclide: 15±16% vs. 6±13%, P<0.05; echocardiographic, P<0.05), and plasma N-terminal pro-brain natriuretic peptide concentrations (P<0.02) (Table 101).

Table 101 Clinical Parameters and LV Function at 0, 6, and 12 Months of Therapy in Patients With Heart Failure Receiving Either Perindopril (ACEI-First) or Carvedilol (BB-First Group) as Initial Therapy[55] (Based on data from J Am Coll Cardiol 2004; 44: 1825-30.)

Initial Therapy	ACEI-First	BB-First	ACEI-First	BB-First	ACEI-First	BB-First
Months of Treatment	0	0	6	6	12	12
Sample Number	30	27	30	27	30	27
BP (mm Hg)	115 ± 14/76 ± 11	113 ± 15/74 ± 12	121 ± 22/74 ± 16	124 ± 20*/79 ± 15	119 ± 17/73 ± 12	122 ± 19*/75 ± 14
Heart rate (beats/min^{-1})	87 ± 15	88 ± 17	85 ± 16	76 ± 18*‡	76 ± 17*	73 ± 15†
NYHA FC (I/II/II/IV)	4/12/11/1	3/9/12/3	11/11/7/1	13/7/7/0	11/10/9/0	22/3/2/0
LVEDD (mm)	65.5 ± 7.9	65.3 ± 6.8	62.4 ± 7.1	62.0 ± 8.0	62.6 ± 7.9	60.0 ± 11.6†
LVESD (mm)	56.6 ± 7.8	57.6 ± 7.8	53.2 ± 8.2	51.6 ± 10.4†	53.0 ± 8.9	48.5 ± 12.4†
Deceleration time (ms)	154 ± 93	133 ± 45	155 ± 58	207 ± 73†	167 ± 60	204 ± 55†§
E/A	1.46 ± 0.87	1.86 ± 1.25	1.34 ± 0.60	1.27 ± 0.73	1.56 ± 0.79	1.17 ± 0.63*‡

* $p < 0.05$, † $p < 0.005$ versus baseline data; ‡ $p < 0.05$, § $p < 0.01$ versus change from baseline in the ACEI- first group (analysis of covariance). ACEI= angiotensin-converting enzyme inhibitor; BB= beta-blocker; BP= blood pressure; E/A= ratio of E wave to A wave velocity; LVEDD= left ventricular end-diastolic diameter; LVESD= left ventricular end-systolic diameter; NYHA FC= New York Heart Association functional class.

A third caveat is the effect of the ACE D/I polymorphism on heart failure survival. In a study of 479 patients with systolic dysfunction (LVEF 0.25±0.08) who were genotyped for the ACE D/I polymorphism[32] and followed to the endpoint of death or cardiac transplantation, 227 patients received an ACE inhibitor at "low doses" (≤50% of target dose), 201 patients received "high (standard) dose," and 51 patients received ARBs. The ACE-D allele was associated with an increased risk of events and poorer transplant-free survival (1-year percent transplant-free by genotype II/ID/DD = 89/80/74; 2-year = 77/69/62, P=0.026). β-blockers diminished the impact of the ACE-D allele on heart failure survival (reduction in event rate by 29%, P = 0.03), particularly for the DD subjects (relative risk reduction = 53%, P = 0.004) but not for subjects who were ID (RRR = 15%, P=0.46) or II (RRR = 3%, P = 0.94) (Table 102).

Table 102 Relative risk of events by treatment for heart failure in different ACE-genotypes[32] (Based on data from J Am Coll Cardiol 2004; 44: 2019-26.)

	Odds Ratio	95% Confidence Interval	p Value
Beta-blockers			
Overall	0.71	(0.53, 0.96)	0.027
ACE genotype			
II	0.97	(0.47, 2.03)	0.94
ID	0.85	(0.55, 1.31)	0.46
DD	0.47	(0.28, 0.79)	0.004
High-dose ACE inhibitors			
Overall	0.86	(0.64, 1.16)	0.33
ACE genotype			
II	1.35	(0.63, 2.85)	0.44
ID	0.88	(0.57, 1.35)	0.55
DD	0.75	(0.44, 1.27)	0.29
High-dose ACE inhibitors (subject not on beta-blockers)			
Overall	0.88	(0.56, 1.15)	0.24
ACE genotype			
II	1.31	(0.54, 3.22)	0.55
ID	0.86	(0.51, 1.47)	0.59
DD	0.62	(0.33, 1.17)	0.10

ACE = angiotensin-converting enzyme.

CHARM-Alternative (SH-AHS-0003) study

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

Table 103 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

Table 103 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).

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 104. 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.

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 105), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 106) also show similar findings.

Table 104 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%)	CC_{LD} n = 106 events = 51 (48.1%)	CC_{00} n = 104 events = 24 (23.1%)
	A1	**A2**	**A3**
Placebo	**N = 553** **Events = 174 (31.5%)**		
			B
	P_{HD} n = 408 events = 120 (29.4%)	P_{LD} n = 63 events = 35 (55.6%)	P_{00} n = 82 events = 19 (23.2%)
	B1	**B2**	**B3**
	No beta-blocker at baseline		
Candesartan	**N = 460** **Events = 172 (37.4%)**		
			A
	CC_{HD} n = 252 events = 74 (29.4%)	CC_{LD} n = 107 events = 67 (62.6%)	CC_{00} n = 101 events = 31 (30.7%)
	A1	**A2**	**A3**
Placebo	**N = 462** **Events = 232 (50.2%)**		
			B
	P_{HD} n = 312 events = 150 (48.1%)	P_{LD} n = 67 events = 51 (76.1%)	P_{00} n = 83 events = 31 (37.4%)
	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 105 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 106 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%) **A1**	CC_{LD} n = 106 events = 52 (49.1%) **A2**	CC_{00} n = 102 events = 25 (24.5%) **A3**
Placebo	**N = 553** **Events = 180 (32.6%)** **B**		
	P_{HD} n = 407 events = 124 (30.5%) **B1**	P_{LD} n = 64 events = 36 (56.3%) **B2**	P_{00} n = 82 events = 20 (24.4%) **B3**
	No beta-blocker at baseline		
Candesartan	**N = 460** **Events = 182 (39.6%)** **A**		
	CC_{HD} n = 254 events = 82 (32.3%) **A1**	CC_{LD} n = 109 events = 69 (63.3%) **A2**	CC_{00} n = 97 events = 31 (32.0%) **A3**
Placebo	**N = 462** **Events = 240 (52.0%)** **B**		
	P_{HD} n = 313 events = 155 (49.5%) **B1**	P_{LD} n = 70 events = 55 (78.6%) **B2**	P_{00} n = 79 events = 30 (38.0%) **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; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

The above findings suggest that (i) in the absence of candesartan (comparing cells A3 with and without β-blockers), 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 receiving β-blockers at baseline have lower event rates than those not receiving β-blockers.

This finding is also similar to the effect of β-blockers observed in CHF patients treated with ACE inhibitors *plus* candesartan or placebo in the CHARM-Added (SH-AHS-0006) study.

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.

(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).

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

Findings from Clinical Trials in the Medical Literature

Spironolactone has been shown to decrease mortality in NYHA class IV patients with systolic left ventricular dysfunction who were being treated with an ACE inhibitor[56]; this decreased mortality was attributed to a reduction in the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes.

A recent multicenter, randomized, double-blind, placebo-controlled clinical trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) Study) of eplerenone[57] – an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone or androgen receptors – involving 6,632 patients with acute myocardial infarction and left ventricular dysfunction (EF≤40%) and heart failure also supports the above. The EPHESUS study found that eplerenone treatment was associated with reductions in relative risk of all-cause mortality (hazard ratio 0.85, 95% CI 0.75 to 0.96, relative risk reduction 15%, P = 0.008), and cardiovascular death or hospitalization for cardiovascular events (hazard ratio 0.87, 95% CI 0.79 to 0.95, relative risk reduction 13%, P = 0.002). The reduction in cardiovascular mortality (hazard ratio 0.83, 95% CI 0.72 to 0.94, relative risk reduction 15%, P = 0.005), was attributable to a 21% reduction in the rate of sudden death from cardiac causes (hazard ratio 0.79, 95% CI 0.64 to 0.97, relative risk reduction 21%, P = 0.03).

The EPHESUS study also shows that the relative risk for all-cause mortality was significantly (P=0.04) reduced when eplerenone was used together with ACE inhibitors (or ARBs) **and** β-blockers (Figure 39).

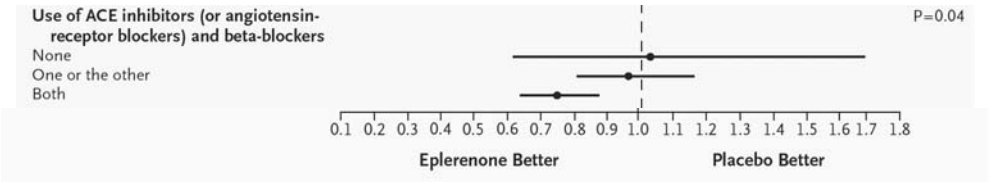


Figure 39 Relative risk of all-cause mortality according to use of and ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[57] (Based on data from N Engl J Med 2003; 348: 1309-21.)

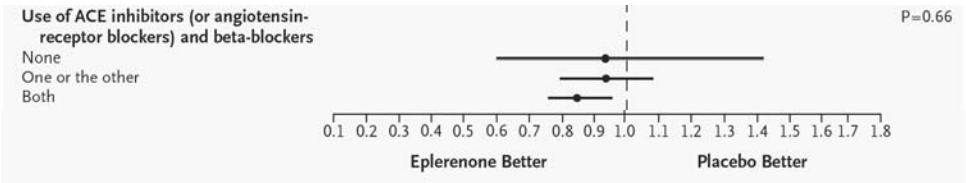


Figure 40 Relative risk of CV death or hospitalization for CV events according to use of an ACE inhibitor (or ARB), a β-blocker or both in EPHESUS study[57] (Based on data from N Engl J Med 2003; 348: 1309-21.)

However, for CV death or hospitalization for CV events, there was no statistically significant reduction in relative risk when eplerenone was used together with an ACE inhibitor or angiotensin receptor blocker (ARB) **and** β-blockers (Figure 40).

In addition, eplerenone produces a number of pharmacodynamic effects that may contribute to myocardial protection in patients with acute MI complicated by left ventricular dysfunction, such as preventing ventricular remodeling and collagen formation[58], reducing coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis[59], reducing oxidative stress and improving endothelial dysfunction[60], etc.

CHARM-Alternative (SH-AHS-0003) Study

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

Table 107 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

Table 107 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.

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

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 108. 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.

Table 108 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 109 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%)	CC_{LD} n = 79 events = 56 (70.9%)	CC_{00} n = 64 events = 24 (37.5%)
	A1	**A2**	**A3**
Placebo	**N = 233** **Events = 124 (53.2%)**		
			B
	P_{HD} n = 156 events = 77 (49.4%)	P_{LD} n = 39 events = 31 (79.5%)	P_{00} n = 38 events = 16 (42.1%)
	B1	**B2**	**B3**
	No spironolactone at baseline		
Candesartan	**N = 763** **Events = 253 (33.2%)**		
			A
	CC_{HD} n = 490 events = 142 (29.0%)	CC_{LD} n = 134 events = 68 (50.8%)	CC_{00} n = 139 events = 43 (30.9%)
	A1	**A2**	**A3**
Placebo	**N = 782** **Events = 309 (39.5%)**		
			B
	P_{HD} n = 565 events = 205 (36.3%)	P_{LD} n = 92 events = 63 (68.5%)	P_{00} n = 125 events = 41 (32.8%)
	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 110 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%)	CC_{LD} n = 81 events = 56 (69.1%)	CC_{00} n = 62 events = 23 (37.1%)
	A1	**A2**	**A3**
Placebo		**N = 233** **Events = 119 (51.1%)**	
			B
	P_{HD} n = 156 events = 76 (48.7%)	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 = 236 (30.9%)**	
			A
	CC_{HD} n = 492 events = 138 (28.1%)	CC_{LD} n = 134 events = 65 (48.5%)	CC_{00} n = 137 events = 33 (24.1%)
	A1	**A2**	**A3**
Placebo		**N = 782** **Events = 301 (38.5%)**	
			B
	P_{HD} n = 564 events = 203 (36.0%)	P_{LD} n = 95 events = 61 (64.2%)	P_{00} n = 123 events = 37 (30.1%)
	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)

However, the event rates are generally **higher** in patients receiving spironolactone 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 109), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 110) also show similar findings.

The above findings suggest that (i) in the absence of candesartan, CHF patients treated with spironolactone at baseline had **higher** event rates than those not treated with spironolactone, and (ii) that for both low and high doses of candesartan, CHF patients treated with spironolactone at baseline have **higher** event rates than those not treated with spironolactone. This finding is similar to the effect of spironolactone observed in CHF patients treated with ACE inhibitors *plus* candesartan or placebo in the CHARM-Added (SH-AHS-0006) study.

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.

(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).

8.2.3 Is there an interaction of candesartan with digoxin?

Findings from Clinical Trials in the Medical Literature

The Digitalis Investigation Group (DIG) Study[61] showed that combination therapy (of digoxin, diuretic and ACE inhibitor) was better than ACE inhibitor alone (Table 111).

In the main trial, patients with LVEF ≤ 0.45 were randomly assigned to digoxin (3,397 patients) or placebo (3,403 patients) in addition to diuretics and ACE-inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months). In an ancillary trial of patients with LVEF > 0.45, 492 patients were randomly assigned to digoxin and 496 to placebo. In the main trial, mortality was unaffected. There were 1,181 deaths (34.8%) with digoxin and 1,194 deaths (35.1%) with placebo (hazard ratio = 0.99; 95% CI, 0.91 to 1.07; P =0.80) (Table 111).

Table 111 Deaths due to study group and cause in the DIG Study[61] (Based on data from N Engl J Med 1997; 336: 525-33.)

Cause of Death	Digoxin (N=3397)	Placebo (N=3403)	Absolute Difference*	Risk Ratio (95% CI)†	P Value
	no. of patients (%)		%		
All	1181 (34.8)	1194 (35.1)	−0.4	0.99 (0.91–1.07)	0.80
Cardiovascular	1016 (29.9)	1004 (29.5)	0.4	1.01 (0.93–1.10)	0.78
Worsening heart failure‡	394 (11.6)	449 (13.2)	−1.6	0.88 (0.77–1.01)	0.06
Other cardiac§	508 (15.0)	444 (13.0)	1.9	1.14 (1.01–1.30)	
Other vascular¶	50 (1.5)	45 (1.3)	0.1	1.11 (0.74–1.66)	
Unknown	64 (1.9)	66 (1.9)	−0.1	0.97 (0.69–1.37)	
Noncardiac and nonvascular	165 (4.9)	190 (5.6)	−0.7	0.87 (0.71–1.07)	

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

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

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

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

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

In the digoxin group, there was a trend (not statistically significant) toward a decrease in the risk of death attributed to worsening heart failure (hazard ratio 0.88; 95% CI, 0.77 to 1.01; P = 0.06)

(Figure 41). However, overall mortality was not reduced because an excess of sudden death and ischemic events were observed in patients randomized to digoxin.

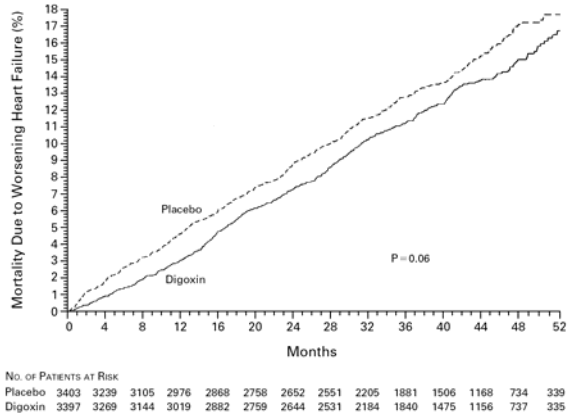


Figure 41 Mortality Due to Worsening Heart Failure in the Digoxin and Placebo Groups[61]. (Based on data from N Engl J Med 1997; 336: 525-33.) The number of patients at risk at each four-month interval is shown below the figure.

There were 6% fewer hospitalizations overall in the digoxin group than in the placebo group, and fewer patients were hospitalized for worsening heart failure (26.8% vs. 34.7% ; hazard ratio, 0.72; 95% CI, 0.66 to 0.79; P < 0.001) (Table 112). In the ancillary trial, the findings regarding the primary combined outcome of death or hospitalization due to worsening heart failure were consistent with the results of the main trial. Thus, the current concept is that digoxin decreases the need for hospitalization but has not been shown to affect mortality in CHF[61].

Table 112 Patients hospitalized during the DIG study[61], according to study group and reason for hospitalization. (Based on data from N Engl J Med 1997; 336: 525-33.)

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

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

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

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

§This category includes atrioventricular block and bradyarrhythmia.

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

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

CHARM-Alternative (SH-AHS-0003) Study

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

Table 113 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

Table 113 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).

8.3 Special Populations

8.3.1 CHF patients with symptomatic hypotension

Patients with heart failure and symptomatic hypotension may require a reduction in the dose of candesartan. In the CHAR-Alternative (SH-AHS-0003) study, hypotension was one of the most frequently reported adverse event constituting 23% of patients on candesartan versus 13.5% of patients on placebo during the study; the incidence of hypotension leading to drug discontinuation in candesartan-treated patients was 4.5% compared with 1.4% in placebo-treated patients.

8.3.2 CHF patients with impaired renal function (creatinine increase)

In heart failure patients with impaired renal function treated with candesartan, increases in serum creatinine may require dose reduction and/or discontinuation of candesartan. In the CHARM-Alternative (SH-AHS-0003) study, the incidence of "creatinine increase" was 16.1% in patients treated with candesartan versus 8.1% inpatients treated with placebo; the incidence of "creatinine increase" leading to drug discontinuation in candesartan-treated patients was 6.4% compared with 2.5% in placebo-treated patients.

8.3.3 CHF patients with hyperkalemia

In heart failure patients treated with candesartan, hyperkalemia may occur, especially when taken

concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone. In the CHARM-Alternative (SH-AHS-0003) study, the incidence of hyperkalemia was 5.3% in patients treated with candesartan versus 1.6% in patients treated with placebo; the incidence of hyperkalemia leading to drug discontinuation in candesartan-treated patients was 2.1% compared with 0.3% in placebo-treated patients.

8.3.4 Geriatric patients with CHF

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

8.4 Pediatrics

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

8.5 Literature Review

In the sections presented and discussed above, relevant medical literature is referenced throughout the review so that a broad perspective of the scientific background and current thinking related to clinical issues in the treatment of CHF is brought into consideration, and objective conclusions of the efficacy and safety findings can be made. In this literature review section, I will present recent advances in the treatment of CHF following the ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined four stages of heart failure[62].

Instead of the traditional NYHA classification which describes functional limitations the new staging for heart failure is based on its evolution and progression. The stages of heart failure and treatment options for systolic heart failure are shown in Figure 42.

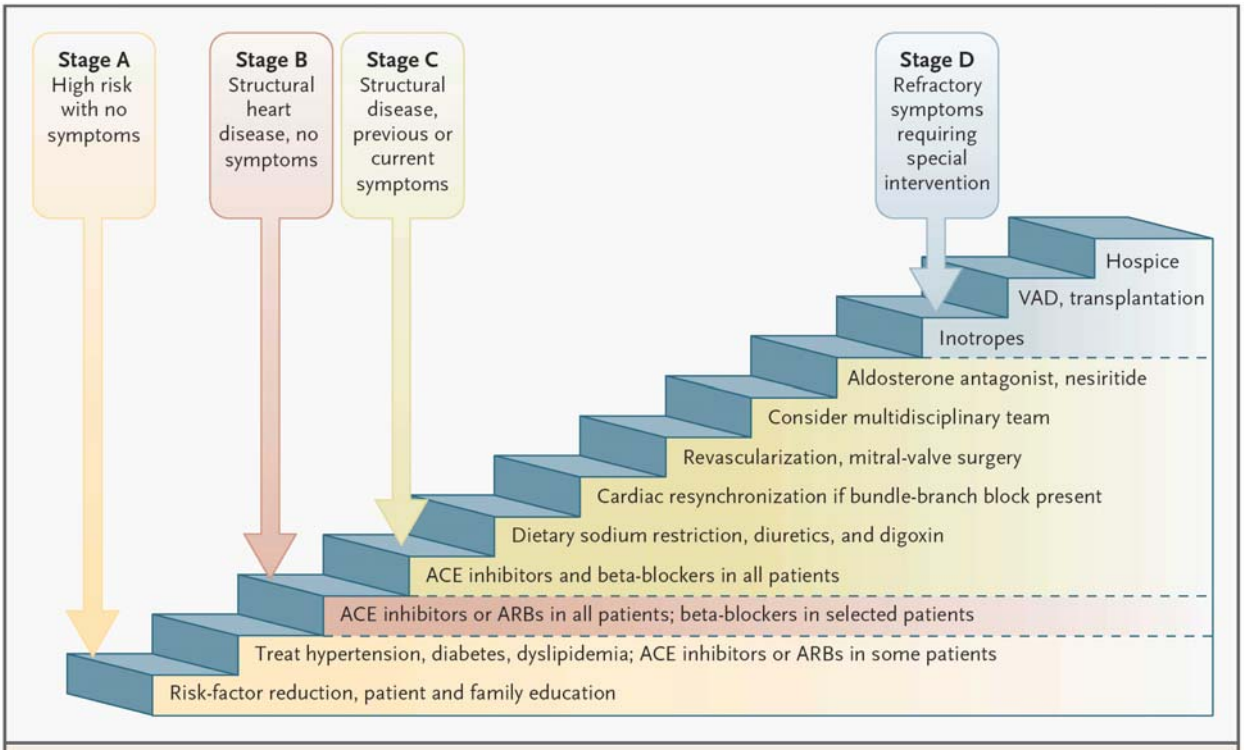


Figure 42 Stages of heart failure and treatment options for systolic heart failure (Based on data from Circulation 2001; 104: 2996-3007)[62].

The states of heart failure may be described as follows:

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

hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction or valvular heart disease, all of whom would be considered to have NYHA class I symptoms.

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

In the context of this NDA review and the new staging of heart failure, I will present for consideration in this section of the review the following issues relevant to the role of ARBs in the treatment of patients with heart failure who are intolerant to ACE inhibitors.

8.5.1 Are angiotensin II-AT_1-receptor blockers (ARBs) comparable to ACE-inhibitors or superior to ACE inhibitors?

This is the primary issue for the CHARM-Alternative (SH-AHS-0003) study. The following information in the medical literature is presented to provide a background for the review of this current NDA supplement (CHARM-Added SH-AHS-0006 study).

8.5.1.1 Effect of Angiotensin (AT_1) receptor blockers (ARBs) on improving survival in patients with heart failure:

The ACC/AHA (American College of Cardiology/American Heart Association) Guidelines for the evaluation and management of CHF which defined the four stages of heart failure[62] did not recommend ARBs as first-line therapy for heart failure of any stage, but that they should be used only in patients who cannot tolerate ACE inhibitors because of severe cough or angioedema.

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

For stage A heart failure: In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, 1,513 patients with type II diabetes and nephropathy were randomized to receive losartan (50-100 mg once daily) or placebo, in addition to conventional antihypertensive treatment, for a mean of 3.4 years[42]. Losartan was found to delay the first hospitalization for heart failure in patients with diabetes mellitus with nephropathy and heart failure (89 (11.9%) patients in the losartan group vs. 127 (16.7%) in the placebo group), for which the relative risk reduction was 32% (P=0.005, Figure 43).

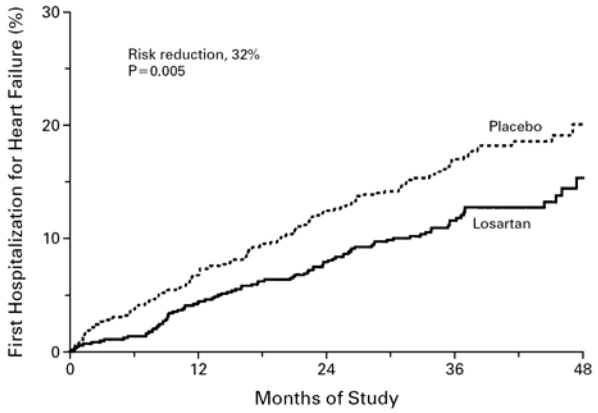


Figure 43 Kaplan-Meier Curves of the Percentage of Patients with a First Hospitalization for Heart Failure in the Losartan and Placebo Groups (RENAAL Study)[42] (Based on data from N Engl J Med 2001;345: 861-9).

For stage B, C or D heart failure: The CHARM-Alternative (SH-AHS-0003) study[63] showed that survival benefits in patients with CHF produced by candesartan (compared to placebo) are in about the same magnitude as that produced by ACE inhibitors described above. In the CHARM-Alternative (SH-AHS-0003) study, 2,028 patients with symptomatic heart failure and LVEF ≤ 40% who were not receiving ACE inhibitors because of previous intolerance were enrolled. Patients were randomly assigned candesartan (target dose 32 mg once daily) or placebo. The sponsor reported a statistically significant 23.2% reduction (hazard ratio= 0.7687; 95% CI 0.67 - 0.89, P = 0.0004) in the relative risk of the composite primary endpoint of cardiovascular death or hospital admission for CHF[63] (Figure 44 and Table 114).

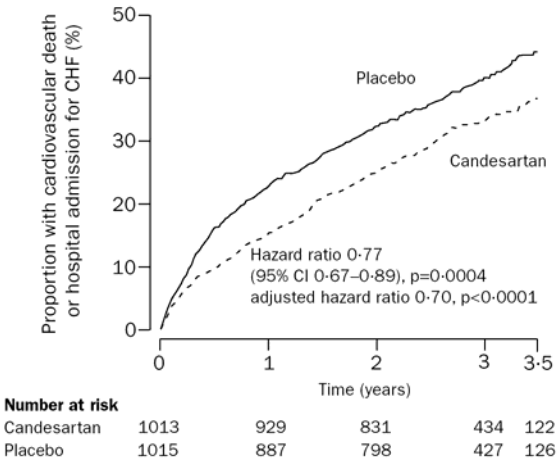


Figure 44 Kaplan-Meier cumulative event curves for primary endpoint (CHARM-Alternative Study)[63] (Based on data from Lancet 2003; 362: 772-6).

Table 114 Primary and secondary endpoints (CHARM-Alternative Study)[63] (Based on data from Lancet 2003; 362: 772-6).

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

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

Table 115 shows the endpoints of the Losartan Intervention for Endpoint reduction (LIFE)[41] study in which 9,193 asymptomatic patients with hypertension and ECG evidence of left ventricular hypertrophy (i.e., stage B heart failure) were randomized to receive losartan or atenolol, and were followed for at least 4 years. Losartan titrated gradually to a dose of 100 mg/day produced a significant reduction (by 13%, P=0.021) in relative risk in the primary composite point of cardiovascular mortality, stroke and MI as well as a decrease (by 25%, P=0.001) in strokes and the incidence of new-onset diabetes (Table 115).

Table 115 Endpoints of LIFE[41] study (Based on data from Lancet 2002; 359: 995-1003).

Endpoint	Losartan (n=4605)		Atenolol (n=4588)		Adjusted hazard ratio (95% CI)†	p	Unadjusted hazard ratio (95% CI)	p
	n	Rate*	n	Rate				
Primary composite endpoint‡	508 (11%)	23·8	588 (13%)	27·9	0·87 (0·77–0·98)	0·021	0·85 (0·76–0·96)	0·009
Cardiovascular mortality	204 (4%)	9·2	234 (5%)	10·6	0·89 (0·73–1·07)	0·206	0·87 (0·72–1·05)	0·136
Stroke	232 (5%)	10·8	309 (7%)	14·5	0·75 (0·63–0·89)	0·001	0·74 (0·63–0·88)	0·0006
Myocardial infarction	198 (4%)	9·2	188 (4%)	8·7	1·07 (0·88–1·31)	0·491	1·05 (0·86–1·28)	0·628
Other prespecified endpoints								
Total mortality	383 (8%)	17·3	431 (9%)	19·6	0·90 (0·78–1·03)	0·128	0·88 (0·77–1·01)	0·077
Admitted to hospital for:								
Angina pectoris	160 (3%)	7·4	141 (3%)	6·6	1·16 (0·92–1·45)	0·212	1·13 (0·90–1·42)	0·284
Heart failure	153 (3%)	7·1	161 (4%)	7·5	0·97 (0·78–1·21)	0·765	0·95 (0·76–1·18)	0·622
Revascularisation	261 (6%)	12·2	284 (6%)	13·3	0·94 (0·79–1·11)	0·441	0·91 (0·77–1·08)	0·292
Resuscitated cardiac arrest	9 (0·2%)	0·4	5 (0·1%)	0·2	1·91 (0·64–5·72)	0·250	1·80 (0·60–5·36)	0·294
New-onset diabetes§	241 (6%)	13·0	319 (8%)	17·4	0·75 (0·63–0·88)	0·001	0·75 (0·63–0·88)	0·001

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

Apart from the CHARM-Alternative study[63] and the LIFE study[41] reviewed above where ARBs are compared to placebo (CHARM-Alternative)[63] or a β-blocker (LIFE)[41], in the medical literature, clinical trials comparing ARBs to ACE inhibitors head-to-head have not shown the superiority in beneficial effects of ARBs over ACE inhibitors.

In 1997, the Evaluation of Losartan in the Elderly (ELITE)[35] trial demonstrated an unexpected survival benefit of losartan (50mg.day) compared to captopril (150 mg/day) in 722 elderly patients with CHF (Figure 45). However, mortality was neither a pre-specified primary nor a pre-specified secondary endpoint of ELITE[35].

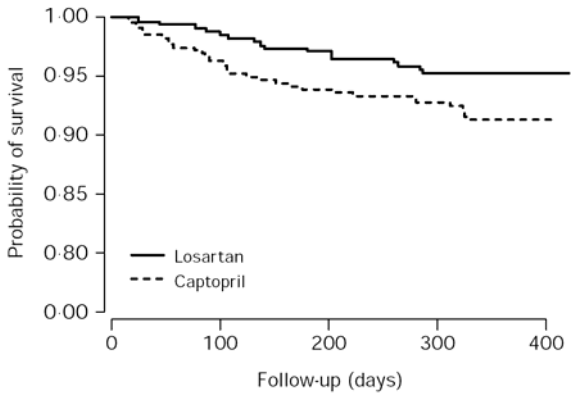


Figure 45 Kaplan-Meier survival curves among patients with CHF in losartan and captopril groups. Patients in losartan group had a 46% lower risk of death than patients in captopril group (p= 0·035). Patients were followed up for 48 weeks (ELITE trial)[35] (Based on data from Lancet 1997; 349: 747-52).

ELITE II[36] was conducted in 3,152 elderly CHF patients with mortality as the primary endpoint. After a mean follow-up of over 500 days, mortality in the captopril group was 15.9%, compared to 17.7% in the losartan group (hazard ratio with captopril 1.13, P = 0.16, Table 116). Thus, ELITE II did not show that losartan was superior to captopril.

Table 116 Endpoint results in ELITE II trial[36] (Based on data from Lancet 2000; 355: 1582-7).

Endpoint	Losartan (n=1578)	Captopril (n=1574)	Hazards ratio (CI)*	p
All-cause mortality (primary endpoint)				
Total mortality	280 (17·7%)	250 (15·9%)	1·13 (0·95–1·35)	0·16
Sudden death	130 (8·2%)	101 (6·4%)	1·30 (1·00–1·69)	
Progressive heart failure	46 (2·9%)	53 (3·4%)	0·88 (0·59–1·30)	
Myocardial infarction	31 (2·0%)	28 (1·8%)	1·11 (0·66–1·85)	
Stroke	18 (1·1%)	11 (0·7%)	1·65 (0·78–3·49)	
Other cardiovascular	5 (0·3%)	6 (0·4%)	0·84 (0·26–2·76)	
Non-cardiovascular	50 (3·2%)	51 (3·2%)	0·99 (0·67–1·47)	
Sudden death or resuscitated cardiac arrest	142 (9·0%)	115 (7·3%)	1·25 (0·98–1·60)	0·08
Combined total mortality or hospital admission for any reason	752 (47·7%)	707 (44·9%)	1·07 (0·97–1·19)	0·18
Hospital admissions				
Any reason	659 (41·8%)	638 (40·5%)	1·04 (0·94–1·16)	0·45
Heart failure	270 (17·1%)	293 (18·6%)	0·92 (0·78–1·08)	0·32

*95·7% CI for total mortality, 95% CI for other endpoints, including components.

In the OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial, losartan (at a dose of 50 mg q.d.) was compared to the ACE inhibitor captopril (at a dose of 150 mg/day) in 5,477 high-risk patients with confirmed acute myocardial infarction and evidence of heart failure or left ventricular dysfunction[38]. The results were in favor of captopril both for all-cause mortality (not significant, P=0.069) and for cardiovascular mortality (P=0.032) (Table 117 and Figure 46).

Table 117 Crude rates and relative risks for pre-specified endpoints in OPTIMAAL Study[38] (Based on data from Lancet 2002; 360: 752-60).

	Losartan (n=2744)	Captopril (n=2733)	Relative risk (95% CI)	p
All-cause mortality	499 (18·2%)	447 (16·4%)	1·13 (0·99–1·28)	0·069
SCD/RCA	239 (8·7%)	203 (7·4%)	1·19 (0·99–1·43)	0·072
Myocardial reinfarction (fatal/non-fatal)*	384 (14·0%)	379 (13·9%)	1·03 (0·89–1·18)	0·722
Other prespecified endpoints				
MI/total mortality	746 (27·2%)	689 (25·2%)	1·10 (0·99–1·22)	0·085
Cardiovascular death	420 (15·3%)	363 (13·3%)	1·17 (1·01–1·34)	0·032
Stroke (fatal/non-fatal)	140 (5·1%)	132 (4·8%)	1·07 (0·84–1·36)	0·587
CABG	404 (14·7%)	375 (13·7%)	1·09 (0·95–1·26)	0·228
PTCA	466 (17·0%)	492 (18·0%)	0·94 (0·83–1·07)	0·358
Revascularisation	845 (30·8%)	827 (30·3%)	1·03 (0·93–1·13)	0·620
First all-cause admission	1806 (65·8%)	1774 (64·9%)	1·03 (0·97–1·10)	0·362
First admission for heart failure	306 (11·2%)	265 (9·7%)	1·16 (0·98–1·37)	0·072
Cardiovascular admission	1480 (53·9%)	1421 (52·0%)	1·06 (0·99–1·14)	0·108
Non-cardiovascular admission	885 (32·3%)	905 (33·1%)	0·98 (0·90–1·08)	0·719

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

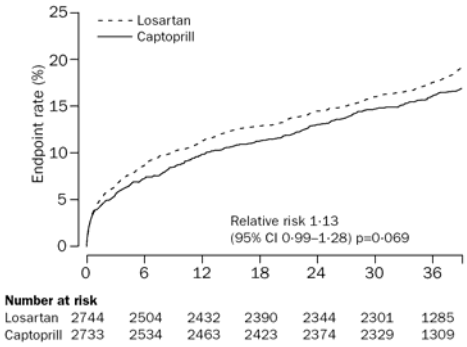


Figure 46 Kaplan- Meier curve for primary endpoint of all-cause mortality. (OPTIMAAL Study)[38] (Based on data from Lancet 2002; 360: 752-60).

The clinical trial of valsartan and captopril in myocardial infarction complicated by heart failure and/or left ventricular dysfunction (VALIANT)[39] was also designed to demonstrate superiority or non-inferiority of valsartan compared to captopril in patients after an acute MI complicated by left ventricular dysfunction and/or heart failure. 14,703 patients were randomized (1:1:1 ratio) to receive either valsartan (titrated to 160 mg b.i.d.), captopril (titrated to 50 mg t.i.d.) or the combination of valsartan (titrated to 80 mg b.i.d.) and captopril (titrated to 50 mg t.i.d.), beginning 12 hours to 10 days after a myocardial infarction, and followed up to a median of 24.7 months. <u>This study was designed to assess non-inferiority of valsartan relative to captopril</u>.

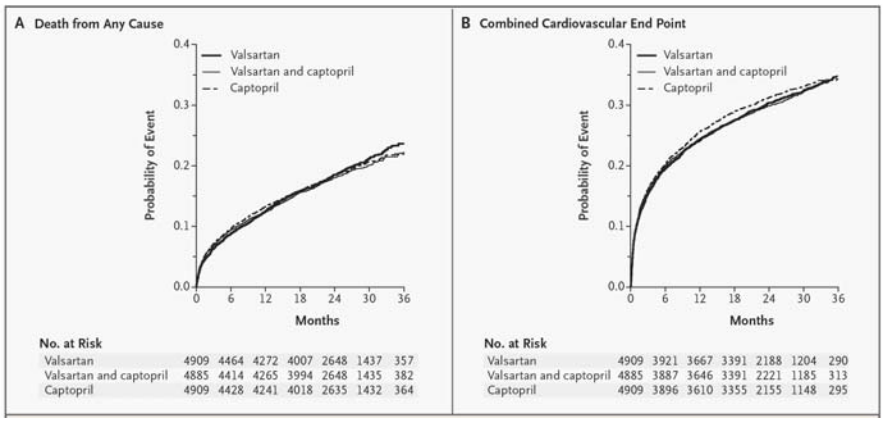


Figure 47 Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group (VALIANT Study)[39] (Based on data from N Engl J Med 2003; 349; 1893-1906).
For the rate of death from any cause, P= 0.98 for the comparison between the valsartan group and the captopril group and P= 0.73 for the comparison between the valsartan-plus-captopril group and the captopril group; for the rate of death from cardiovascular causes, reinfarction or hospitalization for heart failure, P=0.20 for the comparison between the valsartan group and the captopril group and P= 0.37 for the comparison between the valsartan-plus-captopril group and the captopril group.

All-cause mortality was 19.9% in the valsartan group, 19.5% in the captopril group and 19.3% in the combination (valsartan plus captopril) group. The hazard ratio for death in the valsartan group vs. captopril group was 1.00 (97.5% CI: 0.90 to 1.11, P=0.98), and the hazard ratio for death in the valsartan plus captopril group vs. captopril group was 0.98 (97.5% CI: 0.89 to 1.09, P=0.73) (Figure 47 and Table 118). Valsartan and captopril were equivalent in terms of overall mortality and the composite endpoint of fatal and nonfatal cardiovascular events whereas the combination (valsartan plus captopril) therapy resulted in an increase in adverse events without improving overall survival[39] (Table 118).

Table 118 Cardiovascular Mortality and Morbidity* in VALIANT Study[39] (Based on data from N Engl J Med 2003; 349; 1893-1906).

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

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

The lack of superiority in beneficial effect of ARBs (losartan and valsartan, above) over ACE inhibitors has been attributed to not using a high enough dose of the ARB[40]. ACE inhibitors

such as enalapril (at 20 mg/day) also enhanced the pulmonary diffusion capacity of oxygen after 14 days of treatment[64], whereas losartan 50mg/day was without such effect (Figure 48); this improvement in oxygen diffusion capacity across the alveolar surface may have provided benefit to heart failure patients treated with ACE inhibitors, which was not shared by ARBs.

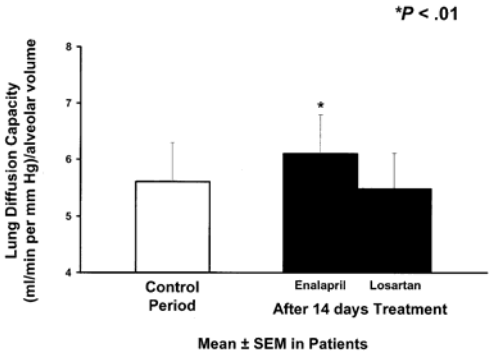


Figure 48 Effect of enalapril or losartan on pulmonary diffusion capacity in heart failure patients[64] (Based on data from J Am Coll Cardiol 2001; 37: 398-406). The bars represent mean±SEM in patients during the control period, after 14 days treatment with enalapril or losartan. * P < 0.01 compared with control period.

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

Recently, two multicenter studies have been initiated in 40 countries to study the effects of ARBs ***and/or*** ACE inhibitors in patients with stage A through D heart failure[65]:

(i) The **T**elmisartan **R**andomized **A**ssessme**N**t **S**tudy in a**CE** i**N**tolerant subjects with cardiovascular **D**isease (TRANSCEND). The TRANSCEND study will enroll 6,000 patients (3,000 patients each to be randomized to telmisartan or placebo) with known intolerance to ACE inhibitors, and with previous vascular event or diabetes mellitus with target organ damage, but controlled blood pressure and without heart failure.

(ii) The **On**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET). The ONTARGET trial plans to enroll 23,400 patients with the same characteristics as TRANSCEND but not ACE intolerant; 7,800 patients each will be randomized to telmisartan or ramipril or telmisartan *plus* ramipril. Seven sub-studies embedded in the main trials are designed to provide insights to the mechanisms of effects of the drugs, and to explore the impact of telmisartan on diabetes mellitus, atrial fibrillation, cognitive decline, erectile dysfunction, etc.

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

I have summarized the issues related to use of ARBs (and other treatments) in heart failure relevant to the review of this NDA supplement in Table 119.

Table 119 Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction

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

8.7 Advisory Committee Meeting

I suggest that the issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction presented in Table 119 be discussed at the Cardio-Renal Drug Advisory Committee Meeting to be scheduled in February, 2005.

8.8 Postmarketing Risk Management Plan

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

8.9 Other Relevant Materials

In the treatment of heart failure, ACE inhibitors, ARBs, β-blockers and spironolactone have contributed to reducing mortality, reducing hospitalizations, and improving functional status. However, large epidemiologic surveys (e.g., Framingham Study still ongoing) have not documented any meaningful change in overall death rates[66]. The reason why the newer and successful therapies failed to result in a meaningful reduction in mortality due to heart failure in the general population may be partly because of structural defects in the heart such as uncorrected valvular disease (aortic stenosis, mitral regurgitation), and partly because many patients have co-morbid diseases such as hypertension, diabetes mellitus, hyperlipidemia, etc.

A nationwide survey of patients ≥65 years who had survived hospitalization for heart failure with LV systolic dysfunction revealed that ACE inhibitors were widely under prescribed despite evidence of their beneficial effect on survival in patients with heart failure[3]. ACE inhibitors were prescribed to only 68% of this cohort, and 76% received either an ACE inhibitor or an ARB. The underutilization of ACE inhibitors is not completely explained by substitution with ARBs. This finding underscores the importance of measures required to translate clinical trial results into actual clinical practice.

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

For ACE inhibitors, randomized trials have shown that there is no difference in mortality between patients receiving high-doses and those receiving low-doses of ACE inhibitors[17,67,68,69]. My review of the CHARM-Added (SH-AHS-0006) study (NDA 20-838 Efficacy Supplement SE1 #022) also finds the same rate of clinical primary efficacy events (CV death or CHF hospitalization) in patients on placebo who received ACE inhibitors at heart failure dose (event rate = 42.4%) or low dose (event rate = 42.1%); similarly for patients on candesartan, the rate of clinical primary efficacy events (CV death or CHF hospitalization) among patients who received ACE inhibitors at heart failure dose (event rate = 36.1%) is about the same as those who received ACE inhibitors at low dose (event rate = 39.7%).

Unlike ACE inhibitors, it appears that a survival benefit is found only when ARBs are used at higher doses than those for the treatment of hypertension. Insufficient dose of ARBs may have contributed to the observed lack of beneficial effect of ARBs on mortality in ELITE II[36], OPTIMAAL[38], Val-Heft[18] and VALIANT[39] trials. (Please also see section 8.1.1 of this review.) A significant survival benefit in high risk patients was observed when relatively larger doses of ARBs were used in LIFE[41] and RENAAL[42] trials.

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

9 OVERALL ASSESSMENT

9.1 Conclusions

CHARM-Alternative (SH-AHS-0003) Study

In patients with CHF, with depressed LV systolic function (LV EF≤40%) and intolerance to ACE-inhibitors, the addition of candesartan significantly (P<0.001) reduced the relative risk of the composite primary efficacy outcome of time to CV death or CHF hospitalization by 23.2%. The effect appeared early and was sustained throughout the duration of the study.

Candesartan treatment also significantly reduced the secondary efficacy outcomes of the relative risks of (i) a composite of time to all-cause mortality or CHF hospitalization (by 20.2%, P=0.001), and (ii) a composite of time to CV death or CHF hospitalization or non-fatal myocardial infarction (MI) (by 21.8%; P<0.001). The reduction in CV death and CHF hospitalization observed with candesartan treatment was also evident in those patients being treated with β-blockers (55% of patients at baseline) and digoxin (46% at baseline).

The symptoms of heart failure as evaluated by the NYHA-classification were reduced by candesartan as compared to placebo.

The magnitude of the benefit (reduction in CV death or CHF hospitalization) translates into a reduction of 7 events per 100 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function treated with candesartan for two years; that is, treating 14 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function for two years with candesartan will prevent one patient from suffering this outcome of CV death or CHF hospitalization.

The reduction in CV death was attributed primarily to a reduction in sudden deaths, which was the most common fatal adverse event in the CHARM-Alternative study. The study was not powered to assess the effect on all-cause mortality.

Dose reduction and discontinuation of the investigational product attributed to aggravated heart failure, decline in renal function, hypotension and hyperkalemia were more common with candesartan than placebo.

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

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

In patients with symptomatic CHF (the total CHARM population) treated with candesartan, an 8.6% reduction in the relative risk of all-cause mortality (P= 0.055) was found. This was attributed to a 12.4% reduction in the relative risk of CV deaths (P= 0.011).

In the two studies in patients with depressed LV systolic function (LVEF ≤40% in SH-AHS-0003 and SH-AHS-0006), those treated with candesartan had an 11.4% reduction in the relative risk of all-cause mortality (P=0.018), resulting from a 15.6% reduction in the relative risk of CV deaths (P= 0.005).

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

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

The beneficial effects of candesartan in the CHARM program were not influenced by treatment with ACE-inhibitors, β-blockers or digoxin. This finding, unlike that observed in the Val-HeFT study[18], suggests benefit of use of an AT_1-receptor blocker in patients already receiving β-blockers and ACE-inhibitors.

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

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

The incidence of new onset diabetes was lower in the candesartan group, an effect observed in other large populations treated with either an ACE inhibitor[70,71] or AT_1-receptor blockers[41].

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

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

9.2 Recommendation on Regulatory Action

Candesartan cilexetil is an angiotensin II type 1 (AT_1)-receptor blocker currently approved in the United States for the treatment of hypertension with an oral starting dose of 16 mg titratable up to 32 mg daily. The CHARM (**C**andesartan cilexetil (candesartan) in **H**eart Failure **A**ssessment of **R**eduction in **M**ortality and Morbidity) Program consists of three pivotal efficacy trials

comprising 7,601 patients with NYHA Class II – IV chronic heart failure (CHF) who were randomized to candesartan (titrated from 4 mg or 8 mg once daily to a target dose of 32 mg once daily as tolerated) or matching placebo, and followed for at least 2 (up to 4) years. The analysis of the CHARM Program was divided into (i) patients with depressed left ventricular (LV) systolic function (ejection fraction (EF) ≤40%) who were intolerant to angiotensin converting enzyme (ACE) inhibitors (CHARM-Alternative), (ii) patients with depressed LV systolic function (EF ≤40%) receiving an ACE inhibitor (CHARM-Added), and (iii) patients with preserved LV systolic function (EF >40%) (CHARM-Preserved). This review pertains to the efficacy supplement #024 (CHARM-Alternative trial).

In CHARM-Alternative (SH-AHS-0003) Study of 2,028 patients with CHF and depressed LV systolic function who were intolerant to ACE inhibitors, candesartan significantly (P<0.001) reduced the relative risk of time to CV death or CHF hospitalization by 23.2% (primary efficacy endpoint). This benefit translates into a reduction of 7 major events per 100 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function treated with candesartan for two years; i.e., treating 14 ACE-inhibitor intolerant patients with CHF and depressed LV systolic function with candesartan for two years will prevent one patient from suffering the outcome of CV death or CHF hospitalization. This beneficial effect was attributed to a reduction in sudden death, which was the most commonly reported fatal AE in both treatment groups, and CHF hospitalization. The study was not powered to assess the effect on all-cause mortality.

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

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

Based on my review limited to NDA 20-838 Efficacy Supplement # 024 with data on the CHARM-Alternative (SH-AHS-0003) study and the overall CHARM Program (SH-AHS-0003, -0006, -0007) studies, I recommend this application as for the indication of treatment of heart failure (NYHA class II-IV) with left ventricular systolic dysfunction (ejection fraction ≤40%) in patients who are intolerant to ACE-inhibitors and receiving other heart failure treatments including β-blockers and digoxin, where candesartan has been shown to reduce the relative risk of time to cardiovascular death or the first occurrence of a hospitalization for heart

failure. I suggest that the issues related to the role and dose of AT_1 receptor blockers in the treatment of patients with heart failure {presented in section 8.6 (Table 119 Issues related to the role of angiotensin receptor blockers in the treatment of patients with heart failure and left ventricular dysfunction)} be discussed at a Cardio-Renal Drug Advisory Committee Meeting.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

I suggest the sponsor institute the following risk management activities:

(i) Analyze data from the CHARM-Program studies to determine dose of candesartan and/or ACE-inhibitor and/or β-blockers and/or spironolactone in relation to AEs (hypotension, hyperkalemia, deterioration of renal function) and study drug discontinuation and/or dose reduction. This information should be provided in the labeling as well as communicated to practicing physicians through educational measures.

(ii) Ensure educational activities regarding the importance of starting with the lowest initial dose of candesartan and of increasing the dose gradually while monitoring the heart rate and blood pressure, serum creatinine, and serum potassium.

9.3.2 Phase 4 Requests

(i) Plan/perform a prospective clinical trial of candesartan in treatment of patients (tolerant and intolerant to ACE inhibitors) with high risk of heart failure without structural heart disease or symptoms (i.e. Stage A heart failure) to determine if candesartan will prevent or delay development of structural heart disease (Stage B), symptomatic heart failure (Stage C) or refractory symptoms of heart failure (Stage D).

(ii) Plan/perform a prospective clinical trial with multiple arms (e.g., for high dose and low dose candesartan, and placebo) to determine the effect of candesartan (high or low dose) in the treatment of CHF in patients who are intolerant to ACE-inhibitors in order to provide the most benefit [survival benefit (all-cause death, CV death, sudden death and CHF death) and clinical benefit (reduced hospitalization, improved symptoms, hemodynamics and exercise tolerance)] with the least risk [of AEs such as aggravated heart failure, hypotension, hyperkalemia, and deterioration of renal function].

9.4 Labeling Review

Please refer to Chapter 9, Item 9.4 (Pages 200-202) 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 labeling review.

9.5 Comments to Applicant

Please also see section 8.6 (Issues related to the role of angiotensin receptor blockers in patients with heart failure and left ventricular dysfunction), section 9.3 (Recommendations on Postmarketing activities) and section 9.3.1 (Risk Management Activity) above. In addition, the following information has been communicated to the sponsor:

(1) Since 44.1% of the CHF patients in the CHARM-Alternative study received the 32 mg/day dose of candesartan, on November 18, 2004, I requested the sponsor to provide information on the CHARM-Alternative (SH-AHS-0003) Study regarding (a) 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 primary and secondary efficacy endpoints, and (b) in the sub-populations of patients receiving or not receiving β-blockers at baseline, (c) in the sub-populations of patients receiving or not receiving spironolactone at baseline, and (d) at which doses of candesartan the adverse events of aggravated heart failure, hypotension, hyperkalemia, deterioration of renal function, study drug discontinuation, and reduction in dose of study drug, were most frequently observed.

On November 24 2004, I received the sponsor's response containing the information requested with preliminary analyses. 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 dose candesartan 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.

My analysis and interpretation of this additional information is presented in this review.

(2) Use the above information to plan a prospective clinical trial to determine the optimal dose of candesartan in CHF patients with depressed LV systolic function who are intolerant to ACE inhibitors, in order to obtain data which will assist in the selection of the dose of candesartan in the treatment of CHF to provide the most benefit (clinical improvement, decrease hospitalization and increased survival) with the least risk (of hypotension, hyperkalemia, deterioration of renal function).

(3) The above comments are made in the context of a concept (not yet proven) that using lower doses of a combination of a β-blocker and an angiotensin AT_1-receptor blocker may improve symptoms and survival and reduce hospitalizations and adverse events to a greater extent than using high doses of one drug such as an angiotensin AT_1-receptor blocker only. This concept is based on the finding that in patients receiving a low or intermediate dose of an ACE inhibitor, adding a β-blocker may improve symptoms and reduce the risk of death and hospitalizations to a greater extent than increasing the dose of the ACE-inhibitor to a maximally tolerated dose[54] (please see Table 100).

10 APPENDICES

10.1 Review of Individual Study Reports

Please refer to Chapter 10 Appendices section (Pages 204-244) of my clinical review for 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 Appendices 10.1.1 through 10.1.18.

The following is a listing of the studies I have reviewed:

10.1.1 Appendix PK1 (Study EC602) *Study of the acute hemodynamic effects of 4mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart Failure – NYHA Class II/III)*

10.1.2 Appendix PK2 (Study EC605-A (PK component)) *Study of the 3- month hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). PK Analysis.*

10.1.3 Appendix PK3 (Study EC608) *A double-blind, multiple-dose, randomized study to evaluate the interaction of 8 mg candesartan cilexetil and 10 mg enalapril after single dosing and as a 3-way crossover at steady state plasma concentration in patient with mild to moderate congestive heart failure (NYHA Class II/III)*

10.1.4 Appendix PK4 (CPH 102) *Pharmacokinetic Evaluation of Candesartan Cilexetil (TCV-116) in Patients with Chronic Congestive Heart Failure*

10.1.5 Appendix PD1 (Study EC602) *Study of the acute hemodynamic effects of 4mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart Failure – NYHA Class II/III)*

10.1.6 Appendix PD2 (Study EC605-A (PD component)) *Study of the 3- month hemodynamic effects of 2 mg, 4 mg, 8 mg and 16 mg candesartan cilexetil in patients with impaired left ventricular function (Heart failure – NYHA class II/ III). PD Data Analysis.*

10.1.7 Appendix PD3 (Study EC604 (STRETCH Study)) *Efficacy and Safety of 4 mg, 8 mg & 16 mg Candesartan Cilexetil (TCV–116) in Patients with Impaired Left Ventricular Function (Mild to Moderate Heart Failure – NYHA Class II/ III)*

10.1.8 Appendix PD4 (Study EC610) *Long Term Safety and Efficacy of 8 mg and 16 mg Candesartan Cilexetil (TCV–116) in Patients with Impaired Left Ventricular Function (Mild to Moderate Heart Failure – NYHA Class II/ III). An open, uncontrolled, multicenter follow-up of study EC604*

10.1.9 Appendix PD5 (Study EC614) *A Six Month Exercise Tolerance Study of Candesartan Cilexetil with a Further Six Month Follow-Up in Patients with Symptomatic Heart Failure (NYHA Class II/III) Intolerant to Angiotensin Converting Enzyme Inhibitors and not Treated with Angiotensin Converting Enzyme Inhibitors.*

10.1.10 Appendix PD6 (SH-AHS-0001) *The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) Pilot study.*

10.1.11 Appendix PD7 (Study OCT105) *Evaluation of the influence of TCV-116 on exercise tolerability and cardiohemodynamics in patients with chronic heart failure (CHF)*

10.1.12 Appendix PD8 (Study OCT106) *Evaluation of the influence of TCV-116 on exercise tolerability and left ventricular function in patients with chronic heart failure*

10.1.13 Appendix PD9 (Study CPH101) *Evaluation of the acute effects of TCV-116 on cardiohemodynamics in patients with chronic heart failure*

10.1.14 Appendix PD10 (Study CPH103) *Evaluation of the Influence of TCV-116 on Exercise Tolerability in Patients with Chronic Heart Failure*

10.1.15 Appendix PD11 (Study CPH104) *Evaluation of the influence of TCV-116 on hormones in patients with chronic heart failure*

10.1.16 Appendix PD12 (Study SH-AHS-0004 (Ellis Study)) *Addition of candesartan to angiotensin converting enzyme inhibitor therapy in patients with chronic heart failure does not reduce levels of oxidative stress*

10.1.17 Appendix PD13 (Study SH-AHS-0005 (Vaile study)) *Effects of angiotensin II (AT1) receptor blockade on cardiac vagal control in heart failure*

10.1.18 Appendix PD14 (Study Hikosaka (Publication)) *Candesartan and Arterial Baroreflex Sensitivity and Sympathetic Nerve Activity in Patients with Mild Heart Failure*

10.1.19 Appendix 1 CHARM-Alternative (SH-AHS-0003) Trial

Clinical Study of candesartan in patients with heart failure who are ACE inhibitor intolerant and have depressed left ventricular systolic function

Study dates
Table 120 shows the chronology of the clinical trials conducted under the CHARM Program.

Table 120 Chronology of the CHARM Program highlights

Original Protocol	November 13, 1998
Amendment #1	December 10, 1998
First Patient randomized	March 22, 1999
Amendment #2	March 31, 1999
Amendment #3	December 21, 1999
Amendment #4	March 7, 2000
Last Patient completed	March 31, 2003
Study Closure	March 31, 2003
Statistical Analysis Plan finalized	April 15, 2003
Database Lock	June 12, 2003
Database Re-Locked	July 4, 2003

Overall Program Title:
"Candesartan Cilexetil (Candesartan) In Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)"

Individual Study Title:

"Clinical Study (SH-AHS-0003) of Candesartan in Patients with Heart Failure Who Are ACE Inhibitor Intolerant and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0006) of Candesartan in Patients with Heart Failure Who Are Treated With ACE Inhibitors and Have Depressed Left Ventricular Systolic Function"

"Clinical Study (SH-AHS-0007) of Candesartan in Patients with Heart Failure and Preserved Left Ventricular Systolic Function"

Objectives of Overall Program (Pooled Analyses):

Primary: To determine whether candesartan, compared to placebo, reduces all cause mortality in the pooled population of patients with symptomatic chronic heart failure (studies SH-AHS-0003, SH-AHS-0006, and SH-AHS-0007).

Secondary: To determine whether candesartan, compared to placebo, reduces all-cause mortality in the pooled population of patients with depressed LV systolic function (studies SH-AHS-0003, SH-AHS-0006).

Objectives Specific to Study SH-AHS-0003 (CHARM Alternative study)

Primary: To determine whether candesartan, compared to placebo, reduces the combined endpoint of cardiovascular (CV) mortality or hospitalization for the management of CHF.

Secondary: To determine whether candesartan, compared to placebo,
- Reduces the combined endpoint of all-cause mortality or hospitalization for the management of CHF
- Reduces the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF or non-fatal myocardial infarction (MI).

Other objectives: To determine whether candesartan, compared to placebo:
- reduced the combined endpoint of cardiovascular mortality, or hospitalization for the management of CHF or non-fatal MI, or coronary revascularization procedures.
- reduced the combined endpoint of all-cause mortality and all-cause hospitalization.
- reduced all-cause mortality.
- reduced all-cause hospitalization.
- reduced the number of fatal and non-fatal MIs.
- affected functional state and symptoms according to NYHA classification.
- was well tolerated and safe by evaluation of drug discontinuation, dose reduction and non-cardiovascular (CV) death and hospitalization.
- influenced the cost of health care.

Study design:

This was a randomized, double- blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan (4 mg titrated to target dose of 32 mg once daily) on mortality and morbidity in patients with depressed LV systolic function and ejection fraction (EF≤ 40%) intolerant to ACE inhibitor. The primary variable for this evaluation was time from randomization to CV mortality or the first occurrence of a hospitalization for CHF. A total of 2028 patients were randomized at 484 sites in 25 countries.

Figure 49 (below) shows the design of the study and the sequence of treatment periods. Randomization was carried out at visit 1. The patients were randomized to candesartan or placebo, and titrated up to 32 mg once daily or to the highest tolerated dose during a 6- week period. Thereafter the patients were scheduled to a visit every 4th month. The information in the CRF for visits 2 to 14 was similar. The recruitment period was 23 months. All patients remained in the study until the last randomized patient had been in the study for at least 2 years. Thus, individual time in the study for surviving patients not lost to follow-up may be 25 to 48 months.

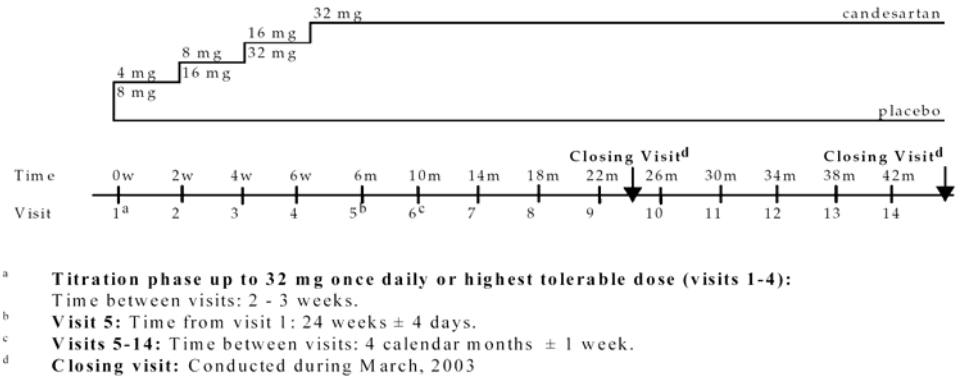


Figure 49 Study design

Therapy with β-blockers or spironolactone:

Patients receive all other treatments for heart failure including β-blockers or spironolactone except other AT1 receptor blockers and, because of intolerance, ACE-inhibitors. The drugs used for these patients' treatment of CHF were initiated and the dose levels stabilized before patients were randomized into the clinical trial.

Inclusion Criteria (Common to all 3 studies in the CHARM Program)

- Male or female, ≥ 18 years old.
- Symptomatic CHF corresponding to NYHA class II-IV for ≥ 4 weeks before randomization.
- Informed consent. (Obtained before any study specific procedures were carried out).

Criteria specific to CHARM Alternative (SH-AHS-0003)

- Documentation of left ventricular ejection fraction (LVEF) ≤ 40% by contrast ventriculography, radionuclide ventriculography or quantitative echocardiography within the previous 6 months. The most recent measurement was used.
- Patients with NYHA Class II must have been of hospitalized for a cardiac reason in the past 6 months.
- No current treatment with an ACE inhibitor because of a history of intolerance (defined as a decision of the attending investigator to discontinue therapy with the ACE inhibitor for what he/she felt was an ACE inhibitor-related AE, including angioedema, anaphylaxis and/or cough and/or symptomatic hypotension and/or renal dysfunction and/or other AEs such as taste disturbance, rash, neutropenia and gastrointestinal upset.

Exclusion Criteria (Common to all 3 studies in the CHARM Program)

Any of the following was regarded as a criterion for exclusion:

1. Treatment with an angiotensin II type 1 (AT_1) receptor blocker within 2 weeks before randomization.
2. Known hypersensitivity to AT_1-receptor blocker.
3. Current serum-creatinine ≥ 265 μmol/L (≥ 3 mg/dL). If the patient was in a stable condition the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.

4. Current serum-potassium ≥ 5.5 mmol/L (≥ 5.5 mEq/L) or a history of marked ACE inhibitor induced hyperkalemia resulting in either a serum-potassium ≥ 6.0 mmol/L (≥ 6.0 mEq/L) or a life-threatening adverse event. If the patient was in a stable condition, the sample could be taken within one month before randomization. For unstable patients a new sample was recommended.
5. Known bilateral renal artery stenosis.
6. Current symptomatic hypotension.
7. Persistent systolic or diastolic hypertension (systolic >170 mmHg; diastolic >100 mmHg) despite use of antihypertensive therapy.
8. CHF secondary to any of the following conditions: a) Critical aortic or mitral stenosis b) Non-cardiac disease (e.g., uncorrected thyroid disease) c) Pericardial disease.
9. Stroke, acute myocardial infarction or open-heart surgery within the last 4 weeks before randomization.
10. History of severe obstructive, restrictive or other chronic pulmonary disease.
11. Significant liver disease.
12. The following procedures: a) Planned cardiac surgery expected to be performed within 4 weeks after randomization. b) Previous heart transplants; or heart transplants expected to be performed within the next 6 months
13. Presence of any non-cardiac disease (e.g., cancer) that was likely to significantly shorten life expectancy to <2 years.
14. Pregnant or lactating women or women of childbearing potential who were not protected from pregnancy by an accepted method of contraception, such as the oral contraceptive pill, an intrauterine device or surgical sterilization (all women of childbearing potential must have a negative pregnancy test before randomization).
15. Any condition that in the opinion of the investigator would jeopardize the evaluation of efficacy or safety or be associated with poor adherence to the protocol.
16. Treatment with any investigational agents within 4 weeks before randomization.

Protocol Amendments:

The protocol amendments to the CHARM program are summarized in Table 121 below. The table below includes the specific date of implementation of each amendment and its relationship to patient recruitment. Particular attention to be paid to Amendment 4 that is highlighted in the table below. The change involved increasing the sample size in the overall CHARM program by 950 patients (15% increase). The increase in sample size affected each component of CHARM differentially. This change occurred more than 15 months after the original protocol was first approved and approximately 12 months after the first patient was randomized.

Table 121 Summary of Protocol Amendments in the CHARM program

Number (date of internal approval)	Key details of amendment (Section of this report affected)	Reason for amendment	Persons who initiated Amendment
Amendment made before the start of patient recruitment			
1 (10 December 1998)	Another secondary objective was added: To determine whether candesartan, compared to placebo, reduced the combined endpoint of all-cause death and hospitalization for the management of CHF. Changes in the primary analysis were made to reflect changes in the secondary endpoint described above.	To meet planned changes in European guidelines for heart failure studies, recommending that "all-cause death" is part of any combined Endpoints.	AstraZeneca Clinical Study Team
Amendments made after the start of patient recruitment			
2 (31 March 1999)	No substantive changes made via this amendment. There were no changes to the primary/secondary endpoints, analysis, inclusion/exclusion criteria that were made	Editorial/Clarification changes	Executive Committee AstraZeneca Clinical Study Team
3 (21 December 1999)	A reference was made to the Clinical Endpoint Committee Manual of Operations (adjudication plan). Inclusion criteria (Section 5.3.1) ACE inhibitors were allowed as concomitant treatment for patients fulfilling the HOPE-study inclusion criteria.	The detailed adjudication plan had not been developed at the time of the original protocol. Publication of the HOPE-study results	Executive Committee
4 (7 March 2000)	The number of randomized patients in the overall CHARM program was <u>increased by 950 patients</u> (6500 to 7450). For CHARM Alternative this increase was 300 patients. For CHARM Added (0006) this was 250 patients. For CHARM Preserved this was 400 patients.	To safeguard statistical power due to lower than expected event rates in blinded data.	Executive Committee

Note: Data in this table adapted from Table 12 of SH-AHS-0007 study report

Statistical Considerations

Please refer to the Statistical Review by Dr. Charles Le for a more detailed discussion.

Primary Analyses (of each component study of CHARM):

The primary variable (time from randomization to a CV event or the first occurrence of a CHF hospitalization) was to be analyzed by a two-sided log rank test. For patients with multiple occurrences of events, the time to first occurrence was to be used. A P-value below 0.05 was to be considered statistically significant.

To meet the secondary objectives in each study a log rank test was to be performed to first compare the incidence curves for the combined endpoint of all cause mortality or CHF hospitalization and then for the combined endpoint of CV mortality, CHF hospitalization or non-fatal MI. A statistically significant difference was to be declared if the P-value was below 0.05.

The primary and secondary endpoints were to be analyzed using a step down procedure in which if and only if the previous analysis was significant at a P value below 0.05, were subsequent analyses of the secondary endpoints were to occur.

Primary Pooled Analyses (CHARM studies pooled):

Data on all cause mortality was to be pooled from all three component studies of the CHARM Program (SH-AHS-0003, SH-AHS-0006, and SH-AHS-0007). The primary endpoint of the pooled analysis was to determine if candesartan, compared to placebo, reduces all cause mortality in this patient population. A p-value less than 0.05 for the two-sided log-rank test was to be considered as a confirmation of different incidence curves for the pooled population.

It was estimated that the annual event rate in the overall CHARM program would be approximately 11%. It was anticipated that the event rates in the patient population with a depressed ejection fraction would be higher: 14% and 11.6% for studies SH-AHS-0003 and SH-AHS-0006 respectively. It was anticipated that the annual event rate in the patients with preserved ejection fraction would be 8.3%. It was also anticipated that candesartan arm would reduce the incidence of all cause mortality relative to the placebo by a minimum of 16%. Under these assumptions the power of the study was greater than 90% (even if one were to assume an even smaller overall event rate of 9%). It was originally expected that 6,500 patients would be required to achieve the endpoint. However, as discussed above in the protocol amendments section, the sample size was increased approximately 1 year after the initiation of the overall CHARM program.

CHARM-Alternative (SH-AHS-0003) Study Review

The current study is one of three component studies in the CHARM program (SH-AHS-0003, SH-AHS-0006, and SH-AHS-0007). This program was designed to investigate the effects of candesartan on mortality and morbidity in patients with CHF.

STUDY OBJECTIVES

Primary objective:

To determine whether candesartan, compared to placebo, reduces the combined endpoint of

cardiovascular mortality or hospitalization for the management of CHF.

Secondary objectives:

To determine whether candesartan, compared to placebo:
- reduced the combined endpoint of all-cause mortality or hospitalization for the management of CHF.
- reduced the combined endpoint of cardiovascular mortality or hospitalization for the management of CHF or non-fatal myocardial infarction (MI).

Other objectives:

To determine whether candesartan, compared to placebo:
- reduced the combined endpoint of cardiovascular mortality, or hospitalization for the management of CHF or non-fatal MI, or coronary revascularization procedures.
- reduced the combined endpoint of all-cause mortality and all-cause hospitalization.
- reduced all-cause mortality.
- reduced all-cause hospitalization.
- reduced the number of fatal and non-fatal MIs.
- affected functional state and symptoms according to NYHA classification.
- was well tolerated and safe by evaluation of drug discontinuation, dose reduction and non-cardiovascular (CV) death and hospitalization.
- influenced the cost of health care.

STUDY PLAN AND PROCEDURES

This was a randomized, double-blind placebo controlled parallel group multicenter study to evaluate the influence of candesartan (4 mg titrated to target dose of 32 mg once daily) on mortality and morbidity in patients with depressed LV systolic function and ejection fraction (EF) ≤ 40% intolerant to ACE inhibitors. The primary variable for this evaluation was time from randomization to CV mortality or the first occurrence of a hospitalization for CHF. A total of 2028 patients were randomized at 484 sites in 25 countries.

The patient recruitment period was 23 months. All patients were to remain in the study until the last randomized patient had been in the study for at least two years. Individual time in the study for surviving patients not lost to follow-up could last from 25 to 48 months depending on when a patient was randomized. The closing visits were conducted during March 2003.

The Steering and Executive Committees supervised the progress of the study. The LSHTM group conducted the interim analyses and the SC evaluated the data. A Clinical Endpoint Committee (CEC) classified clinical events (CEs).

AstraZeneca, Sweden, manufactured all investigational products, i.e., candesartan 4 and 16 mg tablets and matching placebo.

The investigational products were packed by Quintiles Ltd. in Edinburgh, Scotland and

distributed to the investigational sites by Quintiles or its depots around the world.

The QTONE ™ system, an Interactive Voice Response System (IVRS), was used to manage the central randomization, supply and re-supply of investigational product.

There was a shortage of medication during Spring 2002, as expiring stock (1 September and 1 October 2002) was inadvertently marked as available in IVRS. **As a consequence 8 patients took expired drug (**Table 122**)**. However, additional stability testing suggested that the drug was still within specifications

Table 122 Patients on expired drug

Country	Site	Pat no	Bottle no	Expiry date	Days on expired drug
France	506	13567	792324	2002-10-01	47
Germany	1076	11354	770754	2002-10-01	5
	1092	12153	614623	2000-11-01	19
Poland	607	12641	602451	2000-11-01	76
	610	12716	621388	2000-11-01	76
	611	12636	659926	2000-11-01	8
South Africa	1855	15239	743817	2002-09-01	3
Sweden	113	11075	680524	2002-09-01	1

Assigning patients to treatment groups: Investigational Products, AstraZeneca R& D Mölndal, Sweden provided a computer generated randomization list (block size = 2) of identifiers to Quintiles. Using this list Quintiles via the QTONE ™ system assigned each patient a patient number and the patient was randomized to treatment with candesartan or placebo at 1: 1 ratio.

Methods for breaking the blind:

During the study individual treatment codes were available to the investigators or pharmacists at the study site through a 24-hour telephone service by QTONE™ .

The treatment code was only to be broken when the appropriate management of the patient necessitated knowledge of the treatment randomization. Quintiles reported to AstraZeneca any breaking of the treatment code. AstraZeneca retained the right to break the code for serious adverse events that were causally related to treatment and potentially required expedited reporting to regulatory authorities.

Pre-study, concomitant and post-study treatment:

Candesartan was added to optimum conventional CHF treatment, with the exception of ACE inhibitors to which patients were intolerant. Before randomization the investigator was asked to optimize therapy for each patient. Therapy with a β-blocker or spironolactone, if required, was initiated and dose levels stabilized before randomization.

Treatment with non-study AT_1-receptor blockers (ARBs) was avoided. All other medication considered necessary for the patient's safety and well-being could be given at the discretion of the investigator and recorded in the case report forms (CRFs).

Upon completion of the study patients were switched to a low dose of an ARB, beginning the

day after the last dose of the CHARM investigational product; this treatment was continued for 2 weeks, after which the decision to up-titrate or to discontinue the ARB.

Primary efficacy variable: The primary efficacy variable was the time from randomization to mortality or the first occurrence of a CHF hospitalization, whichever occurred first.

The secondary efficacy variable: The secondary efficacy variable was all-cause death or hospitalization due to CHF whichever occurred first. The other secondary outcome variable was cardiovascular death or hospitalization due to CHF or non-fatal MI, whichever occurred first.

Clinical endpoints identified by the investigator as possible primary or secondary endpoints required a central adjudication. The process was blinded regarding any information relating to randomization group. All adjudicated endpoints were classified according to pre-specified definitions by the CEC (Clinical Endpoint Committee). Events matching the criteria were classified as 'confirmed adjudicated'.

Definitions:

Cardiovascular death: All deaths were considered CV unless an unequivocal non-CV cause was established. CV deaths include sudden deaths, death due to MI, death due to heart failure, death due to stroke, death due to CV investigation/procedure/operation (procedure-related death), death due to other CV causes (specified), presumed CV deaths and deaths from unknown causes.

First occurrence of CHF hospitalization: A hospitalization was defined as any overnight stay in a hospital (different dates for admission and discharge). A CHF hospitalization was defined as admission to hospital necessitated by heart failure and primarily for the treatment of heart failure. In other words, a patient admitted for this reason demonstrated signs and symptoms of worsening heart failure (see below) and required treatment with intravenous diuretics. Evidence of worsening heart failure had to include at least one of the following items:

- Increasing dyspnea on exertion.
- Orthopnea.
- Nocturnal dyspnea.
- Increasing peripheral edema.
- Increasing fatigue/decreasing exercise tolerance.
- Renal hypoperfusion (i.e. worsening renal function).
- Elevated jugular venous pressure (JVP).
- Radiological signs of CHF.

All-cause death: Death from any cause was considered to be a secondary endpoint. For patients who were lost to follow- up, i.e., without any follow-up data on vital status at the end of the study, the last date known to be alive was used in the analysis.

Myocardial infarction: A diagnosis of MI required at least one of the following conditions:

- Creatine kinase (CK) or creatine kinase muscle-brain (CK-MB) > twice the upper limit of normal.

- CK > 3 times the upper limit of normal immediately following a percutaneous transluminal coronary angioplasty.
- A troponin I or troponin T > 2 times the upper limit of normal in hospitals where CK measurement is not available and ECG demonstrated development of pathological Q-waves and/ or the development or disappearance of localized ST-elevations combined with the development of T-inversion in at least two of the routine standard leads and/ or clinical history consistent with MI.

NYHA Classification of Heart Failure: NYHA classification at each scheduled visit Functional class and symptomatic status were evaluated at each scheduled visit according to the NYHA classification, as follows:

NYHA Class I	No limitation: Ordinary physical exercise does not cause undue fatigue, dyspnea or palpitations.
NYHA Class II	Slight limitation of physical activity: Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnea.
NYHA Class III	Marked limitation of physical activity: Comfortable at rest but less than ordinary activity results in symptoms.
NYHA Class IV	Unable to carry out any physical activity without discomfort: Symptoms of CHF are present even at rest with increased discomfort with any physical activity.

Coronary revascularization procedures: Coronary revascularization procedures included coronary artery bypass grafting and percutaneous transluminal coronary interventions with or without stents.

Patient-Reported Outcomes measurements and variables: Data on patient-reported outcomes measurements and variables were collected in each study in the CHARM program. The results are presented in the pooled report of the study program.

Health Economics measurements and variables. For assessment of economic impact of candesartan in treatment of heart failure the study included variables to capture resource utilization. Since cost and cost-effectiveness analyses are based partly on the resource utilization and partly on data (primarily unit cost) from other sources such analyses are extrapolations from the findings of this study.

Number of hospitalizations: A hospitalization was defined as any overnight stay in a hospital (different dates for admission and discharge). For each hospitalization the investigator indicated the primary reason for hospitalization. For hospitalizations where the primary reason was not a CV-related one, only the fact that a hospitalization occurred is used as a marker of resource utilization.

Resource utilization data for patients hospitalized with a cardiovascular diagnosis: For hospitalizations where the primary reason was CV-related, further data was collected on length of stay by type of ward. Three categories of ward were used, general, intermediate and intensive.

The following definitions were used to guide the categorization of each level of care.

- Intensive care: Highest level of observation and intervention available (e.g., Intensive Care Unit, Coronary-Care Unit).
- Intermediate care: Level of intervention less than in Intensive Care but more than general nursing. Includes cardiac monitoring (e.g., Step Down Care, Telemetry, Coronary Step Down Care).
- General care: Care consists of general nursing observation. No cardiac monitoring.

The reporting of CV procedures included coronary artery bypass grafting, percutaneous transluminal coronary intervention without stent, percutaneous transluminal coronary intervention with stent, implantation of cardioverter defibrillator, implantation of pacemaker, ventricular assist device, heart transplantation, cardiac catheterization including angiography, other cardiac surgery for heart failure, and other CV procedure/ operation.

Adverse events

(a) Definitions

An adverse event (AE) was any unintended and unfavorable sign (e.g., an abnormal laboratory finding), symptom or disease temporally associated with the use of a pharmaceutical product, whether or not considered causally related to the product. A serious adverse event (SAE) was an AE that at any dose:

- resulted in death
- was life-threatening ("Life-threatening" meant that the patient was at immediate risk of death from the AE as it occurred. "Life-threatening" did not mean that had an AE occurred in a more severe form, it might have caused death)
- required in-patient hospitalization or prolongation of existing hospitalization (Outpatient treatment in an emergency room was not in itself a SAE, although the reasons for it might have been (e.g., bronchospasm, laryngeal edema). Hospital admissions and/ or surgical operations planned before or during a study were not considered adverse events if the illness or disease existed before the patient was randomized in the study, provided that it did not deteriorate in an unexpected way during the study)
- resulted in persistent or significant disability/ incapacity, or
- was a congenital anomaly/birth defect

A permanent discontinuation was defined as patients who discontinued treatment with the investigational product permanently, were alive > 5 days after treatment with the investigational product and were not on the investigational product at the closing visit.

AEs considered as 'Other major events during hospitalization' were also collected in the CRF. In the safety analysis these AEs are treated as serious AEs although information on seriousness was not collected.

Pregnancy in itself was not regarded as an AE unless there was a suspicion that the

investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) was to be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities, birth defects and spontaneous miscarriages were to be recorded as SAEs. Elective abortions without complications were not to be considered as AEs.

Serious adverse events reporting:

The investigator had to inform the CoC within one working day from the time- point when the investigator received information of any SAE/clinical event (CE) that occurred in the course of the study. The CoC was to also receive a completed SAE Form/CE form within 14 calendar days. All SAEs/CEs had to be reported to the CoC, whether or not considered causally related to the investigational product.

The investigator was required to assess the causal relationship to the investigational products for each SAE as "probable", "possible", or "unlikely".

SAEs/CEs were classified as reported by the investigator, independent of the adjudication of clinical endpoints by the CEC, and were not harmonized with endpoints with regards to classification. All SAE reports were reviewed by the SC who was responsible for monitoring safety in the study and for reporting to AstraZeneca if any events raised safety concerns.

Laboratory safety measurements and variables: Laboratory assessments were made at sites in Canada and USA. The measurements were done at visit 1, 4, 7, 10, 13 and/ or at closing visit, depending on how many visits the patient had. Laboratory assessment made at an extra visit was only included in the analysis if it was a last value carried forward (LVCF).

During evaluation of data, levels for clinically important abnormalities in hematology (hemoglobin) and clinical chemistry (creatinine and potassium) were defined as: Hemoglobin ≤ 80 g/ L (4.96 mmol/ L) for males, ≤ 70 g/ L (4.34 mmol/ L)] for females; creatinine ≥ 2 x baseline value; and potassium ≥ 6 mmol/ L.

Quest Diagnostics was to call the investigator if values reached a predefined limit for the following measurements: creatinine, ASAT, ALAT, alkaline phosphates, hematocrit and hemoglobin.

Laboratory tests were done at local hospital laboratories at the discretion of the investigators when deemed necessary. The investigator was to check creatinine and potassium approximately 2 weeks after each increase in dose.

Urine collected in North America and a subset of European countries was also analyzed for microalbuminuria at a central laboratory.

Other safety measurements and variables: Body weight, heart rate and blood pressure were

measured during the study. Changes in heart rate and blood pressure recorded during the course of the study, which caused investigational product discontinuation or dose reduction were considered as AEs.

Clinically important abnormalities in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as: SBP ≤ 80 mmHg and DBP ≤ 40 mmHg.

Quality Assurance:

The sponsor undertook a GCP audit program to ensure compliance with its procedures and to assess the adequacy or its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, were directed towards all aspects of the clinical study process and its associated documentation.

Monitoring:

The sponsor's monitors regularly visited with the investigational sites to confirm that the facilities remained acceptable, that the investigational teams were adhering to the protocol, that data were being accurately recorded in the CRF and faxed to the CoC, and to provide information and support to the investigator. Source data verification (SDV) was also done. The monitors ensured that drug accountability was carried out. The monitors also assisted the CoC in study issues by checking that relevant photocopies of medical records/ hospital notes were sent to the CEC and the Co-coordinating site as soon as additional information had been requested.

Data management:

The data were entered into an electronic database using DataFax, a direct fax- to- computer data capture system, which was used for data transmission, data entry validation and query handling. Complete CRFs and SAE reports were sent by fax from the investigational sites directly to a computer at the CoC at AstraZeneca R& D Mölndal, Sweden. Handwritten data were manually entered and other information from the CRFs was checked against the fax pages at the CoC. Data were then transferred from DataFax to a Statistical Analysis System (SAS) study database. The sponsor's single patient output listing application (SPOLA) system was used regularly to run quality checks on the study database. Data Clarification Forms (DCFs) were generated and referred to the investigator for clarification. Answered DCFs or corrected CRF pages were faxed to DataFax and the database was updated with the correct validated data. The study database was used for data listings and status reports throughout the study.

The endpoint adjudication process done by the CEC, was handled electronically through the Clinical Endpoint Management System (CEMS). There were predefined CRF pages required for adjudication of each event type. Validated CRF pages for endpoint candidates were collected within the system and sent electronically to the CEC via CEMS. The CEC reviewers adjudicated the endpoints through forms available electronically in CEMS. The adjudication forms were dependent on event type. A QC of the CECs adjudication was carried out to ensure that the reviews were consistent between reviewers and for the same reviewer.

The sponsor submitted that all data editing, data coding and data validation, including logical checks between records in the database were done on blinded data. Before database lock was declared, QC checks on the data were completed and error rates reported, and all decisions on the ability to evaluate of the data from each individual patient were made and documented.

The randomization code was broken after declaration of database lock.

Statistical evaluation:

The statistical analyses were made by the Bio statistics group at AstraZeneca R& D Mölndal, Sweden. The software used was SAS ® Version 8.2.

The analyses included the following SAS ® procedures: LIFETEST (method = KM) for the Log rank test; PROC PHREG with the Wald statistic for estimates and confidence intervals (CIs) for hazard ratios (HR); PROC FREQ (chi sq binomial risk diff) in the analyses of proportions; PROC NPAR1WAY (Wilcoxon) for the analyses of frequency of events and the change in NYHA classes; and PROC MIXED for change from baseline variables. In the analyses of prognostic and other explanatory factors, PROC PHREG (selection = stepwise) was used for time to event variables, PROC LOGISTIC (selection = stepwise) for dichotomous outcome variables, and PROC REG (selection = stepwise, slstay = 0.05) for multivariate regression analyses.

- All tests were two-sided and statistical significance was concluded if the p-value was below 0.05, unless otherwise specified.
- All CIs had a confidence level of 95%.
- All p-values and confidence levels were presented as nominal without any adjustment for multiple comparisons.
- All analyses for the primary and secondary objectives were based on the confirmed adjudicated events.
- If an event could be concluded to have occurred in a specific time interval but no date was recorded, the midpoint of the interval was used as the date of occurrence.
- The LVCF principle was used when data was missing after some visit, e.g., for DBP, SBP, HR and NYHA class.
- For composite endpoints, time to event was defined as the time to the first occurrence of any of the components.
- The following definitions apply throughout this report:
    - Relative risk reduction: (1- hazard ratio) x 100%
    - Cumulative incidence function: (1-Kaplan-Meier survival estimates at time ‘t’) x 100% (Note, these figures are generally referred to as Kaplan-Meier curves in the text in this report.)
    - Estimated hazard rate: Total number of events/1000 patient years.
    - Annualized incidence rates: Total number of events/100 patient years.

- Follow- up time: The time a patient is at risk for an event, i.e., the time until death, the event, or last known to be alive.

Censoring of observations and imputation of dates for deaths:

Data collection from patients in the study was finished during the planned common closing visit period, 3 March to 31 March 2003.

SAEs and Endpoints were reported up to each patient's individual closing visit date. However, a few patients came to the visit prior to or after the closing visit period.

Three patients were lost to follow up at the closing visit for various reasons.

Endpoints occurring after 31 March 2003 but before the closing visit if the visit for some reason took place after March 31 were not included in the statistical analysis.

A few patients came to their last visit during January and February 2003. This visit date concluded the recording of endpoints for these patients. To conclude the study and finish data recording, the date of 31 March 2003 served to censor observations. Censoring of observations and/ or imputation of date was implemented in the following situations.

Patients lost to follow-up/ incomplete patient data:

Patient status	Censoring/ imputation
Date of death unknown	Death date estimated by imputation
Date of death after March 31	Analyzed as being alive 31 March
Patients not reported dead	Last date known to be alive was used in the analyses

Patients who withdrew the consent:

Patient status	Censoring/ imputation
Status alive up to 31 March	Patient analyzed as being alive 31 March
Dead patient	Death date estimated by imputation

When month of death was unknown, if occurring before 31 March, a death date was estimated by imputation using the following rule: The death date was allocated to a date exactly between the date of withdrawal of consent (alternatively last date known to be alive) and 31 March 2003. **In the present study there was only one patient for whom the date of death was unknown i.e., the procedure of imputation was only applied in one case.**

Primary and secondary efficacy endpoints included in the confirmatory analyses were adjudicated and verified by the CEC according their Manual of Operations.

Intention-to-Treat (ITT) Population: All randomized patients.

Safety population: The safety population is identical to the ITT population.

Per Protocol (PP) population: A PP analysis was made for the primary endpoint. The PP population included patients who were on the investigational product at the time of a confirmed adjudicated event or were on the investigational product at the closing visit for patients completing the study without a confirmed, adjudicated event. Patients taking non-study AT1-receptor blocker (ARB) were excluded from the PP analysis.

Protocol deviations were determined prior to unblinding and are listed together with the corresponding patient numbers.

Method of statistical analysis: The primary efficacy endpoint whether candesartan, compared to placebo, reduced the combined endpoint of CV death or hospitalization for the management of CHF, as translated into a hypothesis problem: time from randomization to the combined endpoint CV death or CHF hospitalization, whichever occurs first.

The null hypothesis (H0) was:
H0: The distribution function for the time from randomization to the combined endpoint when treated with candesartan equals the distribution function for the time from randomization to the combined endpoint when treated with placebo.

The alternative hypothesis (H1) was:
H1: The distribution functions differ.

The null hypothesis was tested using the two-sided Log rank test for comparing the time from randomization to event distributions. **A P-value in this test less than 0.05 was considered as a confirmation that there was a true difference between the two distributions.**

In addition, estimates of the treatment hazards were calculated as the number of events per 1000 patient years. The size of treatment effect was estimated by means of a Cox proportional hazards model with treatment as the only factor. The hazard ratio, with a 95% confidence interval based on the Wald estimate of standard error, and corresponding relative risk reduction estimate are reported.

The two secondary efficacy endpoints were translated into null hypotheses:
- Time from randomization to the combined endpoint all-cause death or CHF hospitalization.
- Time from randomization to the combined endpoint CV death or, CHF hospitalization or, non-fatal MI, respectively.

The null hypothesis was equality of the distribution functions for the time from randomization to the combined event for candesartan and placebo versus the alternative hypothesis that they were different.

The null-hypotheses were tested with a Log rank test in the same way as described above for the primary efficacy endpoint, and the treatment hazards were estimated and the hazard ratios were calculated in a Cox regression model.

If the p-value for the first of these tests was less than 0.05 and if the test for the primary variable was significant at the 0.05 level, then this test was also considered as a confirmation of a true treatment effect. Similarly, if this occurred and the second p- value was also less than 0.05, then the second combined event distributions were also concluded to be confirmed to be different. **This follows from the theory of closed test procedures and will guarantee a multiple alpha level of 0.05 (**Bauer, 1991).

The Kaplan-Meier estimated time from randomization to event distribution was plotted for each treatment. This graph was used to interpret the likely differences in the true distributions.

Determination of sample size:

In the original study protocol the sample size was calculated as **1,700** patients based on a two-sided Log rank test for the primary variable time from randomization to CV death or a hospitalization due to CHF, whichever occurred first. **The significance level was set to 0.05.**

The study protocol allowed for the possibility of lower event rates (based on overall event rates in blinded data) than assumed in the initial sample size assumptions and permitted additional patients and/or longer follow- up time if required so as to preserve statistical power. Accordingly, the sample size for the study was adjusted in a protocol amendment (# 4 of 4-March-2000), for a total of **2,000** patients in the study.

Interim analyses:

The protocol specified that the Safety Committee formally compared the treatment groups in the CHARM Program trials with regard to all-cause death. While the total mortality in the three CHARM trials combined was the emphasis, the data from the treatment groups were compared at approximately 6-months intervals with a logrank test, stratified by study.

In order to stop the trials for benefit in the overall population, the stopping rule required $P<0.0001$ for analyses performed within 18 months of the first patient randomized, and $P<0.001$ for all subsequent analyses. If the test for heterogeneity between trials indicated a differential benefit of candesartan across the individual trials, consideration was to be given to continuing randomization or follow- up for those trials in which findings were less pronounced.

In order to stop for safety, should candesartan exhibit greater mortality, the same general principles applied except that the plan required $p< 0.001$ for analyses performed within 18 months of the first patient randomized and $p< 0.01$ for any subsequent analysis.

In addition, the logrank test for a treatment difference in mortality was performed separately for each trial at each interim analysis.

Stopping a single trial for benefit required (1) the same boundary values as for the overall analysis, and (2) statistical evidence of heterogeneity between trials of sufficient strength to justify termination of the trial. The results of 6 interim analyses are summarized in (Table 123).

Table 123 Interim results for CHARM-Pooled

Interim report number	Date of database delivery	Total deaths	Hazard ratio (95% CI)			Nominal p-value	Early stopping criterion
	09 Aug '99	12					
1	27 Mar '00	199	0.63	(0.49,	0.80)[a]	0.00069	0.0001
2	27 Jul '00	331	0.66	(0.53,	0.82)	0.00020	0.0001
3	01 Mar '01	599	0.76	(0.64,	0.89)	0.00064[b]	0.001
4	09 Aug '01	861	0.80	(0.70,	0.91)	0.00103	0.001
5	22 Feb '02	1187	0.86	(0.77,	0.96)	0.00851	0.001
6	01 Aug '02	1438	0.88	(0.79,	0.98)	0.01472	0.001
Final	31 Mar '03	1831	0.91	(0.83,	1.00)	0.055	0.0492

[a]Data taken from source other than CHARM Interim Reports (personal communication).
[b]Boundary crossed for efficacy.
N.B. First patient randomized was 22 March 1999. The initial meeting of the SC was on 22 August 1999 where no formal analyses were performed due to the small number of events observed.

The stopping boundary for efficacy was crossed at the third interim analysis. However, the Committee recommended that the program continue based on the following considerations:-

- The treatment difference in mortality was most marked in one study (66 vs100 deaths [p= 0.006 by logrank test], SH-AHS-0003; CHARM-Alternative Study)) and not statistically significant in the other two (140 vs. 168 deaths [p= 0.070], SH-AHS-0006 (CHARM-Added) study; and, 54 vs. 71 deaths [p= 0.136], SH-AHS-0007 (CHARM-Preserved) Study).
- At that point in time, data on the primary study endpoint, CV death or hospitalization, were incomplete with many such endpoints awaiting adjudication, thus making it difficult to reliably assess the totality of evidence for efficacy.

Data and safety monitoring committees

Safety Committee (SC): The SC functioned independently of all other individuals and bodies associated with the conduct of the CHARM program, including the investigators, the Steering Committee and the program sponsor.

The SC was charged with the following responsibilities:

- To monitor patient safety in the study.
- To monitor efficacy at interim analyses of results.

The SC received safety data on a monthly basis and was responsible for reviewing the safety data continually during the program. A monthly letter was sent from the SC to the CHARM program chairmen and to the sponsor, stating that they had reviewed the data and whether there were any safety concerns or not. Interim efficacy analyses were made every six months. The SC reviewed relevant data and had to make a recommendation to the Steering Committee and the sponsor as to stopping the study for benefit or for harm.

Clinical study protocol amendments and other changes in the conduct of the study:

The original clinical program protocol was dated 13 November 1998.

There were four amendments to the protocol.

The first amendment was made to improve the scientific quality of the study, and came into effect before any patients were recruited. The addition of another secondary objective brought the study into line with forthcoming European guidelines for studies in heart failure as discussed with regulatory agencies. The change made use of endpoints that were collected but had not been combined in the original protocol. Consequently the first amendment did not affect the study procedure as such, only the analysis of the result.

Three further amendments were made after the start of patient recruitment.

The second amendment was made twelve days after the first patient had been included. The changed text reflects that time points for urine sampling were changed and that neutropenia was recognized as an ACE inhibitor-related AE not related to anaphylaxis or angioedema.

The third amendment was made nine months after the first patient was randomized, after the detailed adjudication plan had been developed. The plan describes the procedures for adjudication of clinical endpoints by the Endpoint Committee (CE). These procedures had been followed for all CEs occurring before the plan was final. Thus, the same criteria of evaluation of CEs were applied throughout the study.

The fourth amendment was made one year after the first patient was randomized. The increase in sample size was intended to safeguard the statistical power of the study due to a lower than expected event rate in blinded data.

In addition, there were a total of 21 local amendments (Canada 1, Czech Republic 1, Finland 1, France 6, Germany 1, Ireland 1, the Netherlands 2, Portugal 1, South Africa 1, Spain 3, Sweden 2 and USA 1) to meet planned changes in European guidelines for heart failure studies, recommending that "all-cause death" is part of any combined endpoints. None of these affected the design or analysis of the study. No other changes to the conduct of the study were made.

The amendments were approved by IRBs and Medical Agencies as appropriate, prior to implementation.

Changes to planned analyses:

Prior to unblinding of data:

- In amendment, the closed test procedure was changed due to an addition to the secondary objective. The original closed test procedure was modified to contain three steps with one primary and two secondary variables in a hierarchical order.
- In amendment 4 **a re-calculation of the power was done due to a decision to increase the sample sizes in the two other component studies in the CHARM program (SH-AHS-0003 and SH-AHS-0007).**

- Several efficacy and safety variables were added for analyses to those described in the study protocol, and were finalized before database lock was declared.
- Additional analyses were made for the time to event variables adjusting for 33 pre-specified covariates used in the interim analyses. This was decided before un-blinding the study and is included as a part of the analysis plan for the manuscripts approved by the Executive Committee.
- Analyses in subgroups were made even if the p- value for the interaction treatment by subgroup was greater than 0.1. The interaction p-values were calculated in a regression model for each subgroup separately.
- The non-CV death component, cancer death was included as a separate analysis.
- The planned calculation of medians and percentiles for the cumulative incidence curves were not performed.

After unblinding of data:

- Analyses of CHF as the primary reason for hospitalization were also made.
- An additional analysis for NYHA class was made where class III and IV constituted one class.
- Analyses of hospitalizations due to non-CV cause as a primary reason were added.
- An analysis of time to event variables comparing US versus non- US was performed.

Re-opening of study database:

Shortly before the Clean File meeting and Database Lock on 12 June 2003, death reports and other CRF-pages for patients classified as 'withdrew consent' were removed from the database.

However, based on a recommendation from the Executive Committee the data were re-entered and database was revised to include these data and database lock was declared on July 4, 2003. The cases re-entered into the study database were adjudicated by the endpoint committee as done for all other cases.

In three cases the death reports sent in were crossed out by the investigator with a comment that the information should not be entered into the database. In these cases the information in the reports was not used and it was decided by the Study Team that the date of death was to be estimated by imputation. The number of patients with events added or reclassified in the study database is shown in Table 124.

Table 124 Number of patients with events added (+) or subtracted (-) due to reclassification at the re- opening of the database.

Event	Treatment		Comments
	Placebo	Cand.cil.	
Confirmed, adjudicated CV-deaths	+2	+4	Seven death reports were added. As a result six patients with CV-deaths were re-classified based on this new information.
Non adjudicated deaths	-2	-5	Due to the new death reports the number of non-adjudicated deaths decreased, they were re-adjudication to CV death.
Confirmed, adjudicated non-CV-deaths	0	+1	One of the seven deaths was re-classified as non-CV death.
Confirmed, adjudicated CHF-hospitalisations	0	+1	One CHF hospitalisations was agreed after adjudication.
Non-fatal MI	0	0	No difference.
Other SAE:s	0	+1	Six SAE-reports were added, but only one patient was re-classified as "other SAE".

STUDY PATIENTS

In total 2,028 patients were recruited from 484 sites. The first patient was randomized in the study on 22 March 1999, and the last patient completed the study on 31 March 2003. Of the 2,028 patients recruited, 1,013 were randomized to candesartan and 1,015 to placebo. All 2028 patients were analyzed for safety and efficacy. Overall, the treatment groups were comparable for demographic characteristics and baseline data.

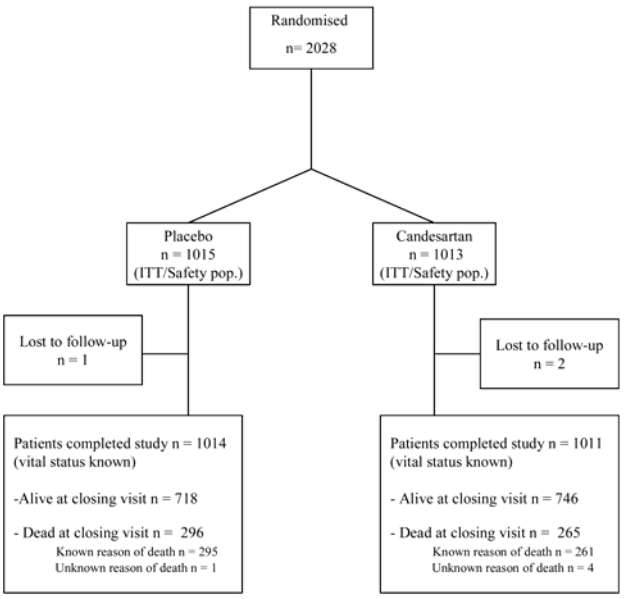


Figure 50 Patient disposition (completion or discontinuation)

Disposition: The disposition of study patients is summarized in Figure 50.

Protocol deviations: The number of patients with protocol deviations in each treatment group are summarized in Table 125. (N.B. One patient could have more than one protocol deviation through out the study.)

Table 125 Number of patients with protocol deviations

	Placebo (N=73)	Cand. cil. (N=63)
Inclusion criteria deviation	6	9
Exclusion criteria deviation	31	28
Patient's consent withdrawn (continued in study or with investigational product)	0	0
Patient pregnant	0	0
Investigational product given without randomisation	0	0
Investigational product never given	0	0
Wrong investigational product given, wrong bottle and wrong investigational product	1	6
Wrong investigational product given, wrong bottle and correct investigational product	12	4
Wrong dose of investigational product given (dose <4 or >32 mg)	0	4
Incorrect dose of investigational product given (dose ≠4, 8, 16, 32 mg)	2	0
Pre-randomisation (randomisation date before visit 1)	16	6
Treatment code prematurely broken	5	4
Less than two years in the study (patients lost to follow up)	0	2

Patient populations analyzed:

All analyses were based on the ITT/Safety population, which was defined before the treatment code was broken. The ITT/Safety population included all randomized patients.

Table 126 Reasons for exclusion from PP population and number of patients excluded

Reason for exclusion[a]	Placebo	Cand. cil.
No investigational product at the confirmed, adjudicated CV death or hospitalisation for the management of CHF, whichever occurred first	66	86
Open label AT_1-receptor blocker taken at any time point before the confirmed, adjudicated CV death or hospitalisation for the management of CHF, whichever occurred first	11	7
ACE inhibitor taken at any time point before the confirmed, adjudicated CV death or hospitalisation for the management of CHF, whichever occurred first	17	7
No investigational product at closing visit – patients without confirmed, adjudicated CV death or hospitalisation for the management of CHF	92	123
Open label AT_1-receptor blocker taken at any time point during the study - patients without confirmed, adjudicated CV death or hospitalisation for the management of CHF	58	66
ACE inhibitor taken at any time point during the study - patients without confirmed, adjudicated CV death or hospitalisation for the management of CHF	48	53

The reasons for exclusion from the PP population are given in Table 126. (One patient could be listed for more than one reason in this table.) PP analyses were performed only for the primary variable. The PP population included patients who were on investigational product at the time of a confirmed adjudicated event or were on the investigational product at the closing visit for patients completing the study without a confirmed, adjudicated event. Patients taking non-study

ARBs were excluded from the PP analyses. All decisions on the inclusion or exclusion of patients from the PP efficacy analysis population were made while the data were still blinded.

The study populations analyzed, and the number of patients in each population, are summarized in Figure 51.

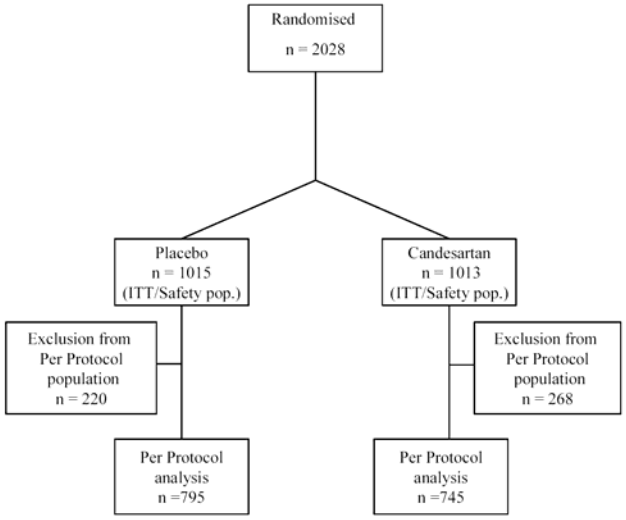


Figure 51 Study populations

Demographic and other patient characteristics:

The treatment groups were generally well balanced with regard to baseline characteristics. However, more patients in the candesartan group had a previous hospitalization for CHF (70.3% vs. 66.3%) and more frequently had a LVEF below 25% (23.6% vs. 21.1%).

Cough was the most common reason for ACE intolerance in both treatment groups. It was more common in the placebo group than in the candesartan group (751, 74.0% vs. 704, 69.5%). ACE intolerance due to hypotension or renal dysfunction was more common in the candesartan group (143, 14.1% vs. 119, 11.7%, and 134, 13.3% vs. 100, 9.9% respectively) (Table 127).

Table 127 Reasons for ACE inhibitor intolerance at randomization. ITT/Safety Population (SH-AHS-0003)

Reason for ACE inhibitor intolerance at randomisation[a]	Treatment	
	Placebo (N=1015)	Cand. cil. (N=1013)
	Number of intolerant patients at randomisation, N (%)	Number of intolerant patients at randomisation, N (%)
Cough	751 (74.0)	704 (69.5)
Hypotension	119 (11.7)	143 (14.1)
Renal dysfunction	100 (9.9)	134 (13.3)
Angioedema	44 (4.3)	39 (3.8)
Other[b]	109 (10.7)	101 (10.0)

[a] A patient may have more than one reason for intolerance
[b] Includes any AE, lab value, or unknown reason.

Treatment compliance:

Compliance was assessed (> 80%, 20- 80% or < 20%) by estimation of returned tablets and after

discussion with the patient. Pill- counts were not done unless required by local regulatory authorities. The majority of patients had a compliance of > 80% at all visits with no apparent difference between treatment groups.

Use of concomitant medication at randomization:

In general, patients were also receiving aggressive heart failure treatment with combinations of diuretics, β-blockers and digitalis.

More than half of patients (1,106, 55%) received β-blockers, 86% (1,733 patients) were treated with diuretics, 46% (924 patients) with digitalis and 24% (483 patients) were treated with spironolactone. Patients were ACE inhibitor intolerant but they were being treated with other therapeutic agents known to provide beneficial effects for the treatment of CHF.

N.B. ACE inhibitors were used by 4 patients at randomization.

Use of concomitant medications after randomization:

The use of some concomitant medications were more common in the placebo group than in the candesartan group at the closing visit [β-blockers in 480 patients (67%) vs. 476 patients (64%), spironolactone in 209 patients (29%) vs. 183 patients (25%) and diuretics in 572 patients (79%) vs. 566 patients (76%)].

EFFICACY RESULTS

Primary efficacy endpoint: Time from randomization to cardiovascular death or hospitalization due to CHF

During the follow-up period, 740 patients experienced the primary outcome of CV death or CHF hospitalization, 334 (33.0%) in the candesartan group and 406 (40.0%) in the placebo group. The average annualized events rates were 13.8% and 18.2% respectively (Table 128).

Table 128 Confirmed adjudicated CV death or hospitalization due to CHF. 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	Treat-ment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
CV death or hospitalisation due to CHF (confirmed adjudicated)	Placebo	1015	406	2229.2	182.1	2.2
	Cand. cil.	1013	334	2418.9	138.1	2.4

The relative risk was significantly (P<0.001) reduced by 23.2% for the primary outcome of CV death or hospitalization due to CHF, whichever came first, by candesartan treatment (Table 129).

Table 129 Confirmed adjudicated CV death or hospitalization due to CHF. 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	
CV death or hospitalisation due to CHF (confirmed adjudicated)	2028	334	406	0.768	0.665	0.888	<0.001

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 52).

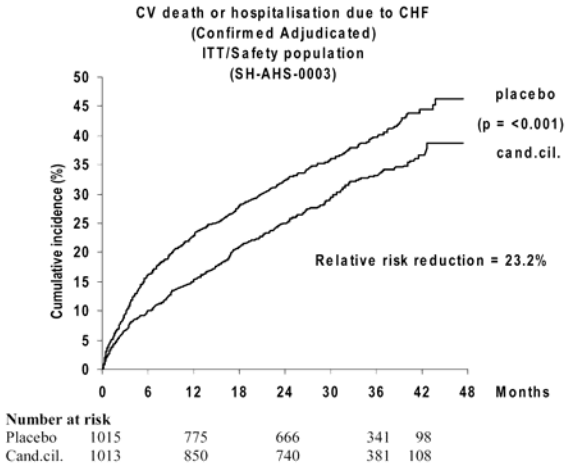


Figure 52 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.972).

Secondary variable: Time from randomization to all-cause death or hospitalization due to CHF

During the follow-up period, 804 patients experienced the secondary outcome of all-cause death or CHF hospitalization, 371 (36.6%) in the candesartan group and 433 (42.7%) in the placebo group. The average annualized events rates were 15.3% and 19.4%, respectively (Table 130).

Table 130 Confirmed adjudicated all-cause death or hospitalization due to CHF. 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)

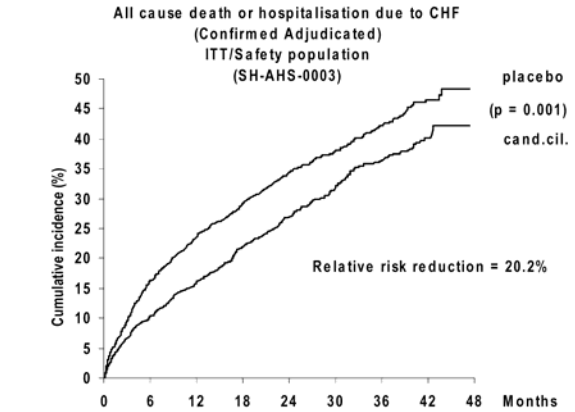
Variable	Treat-ment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	Placebo	1015	433	2229.2	194.2	2.2
	Cand. cil.	1013	371	2418.9	153.4	2.4

The relative risk for the secondary outcome of all cause death or hospitalization due to CHF, whichever came first, was significantly reduced by 20.2% by candesartan treatment (Table 131).

Table 131 Confirmed adjudicated all- cause death or hospitalization due to CHF. 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	
All-cause death or hospitalisation due to CHF (confirmed adjudicated)	2028	371	433	0.798	0.695	0.917	0.001

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 53).



Number at risk					
Placebo	1015	775	666	341	98
Cand.cil.	1013	850	740	381	108

Figure 53 Cumulative incidence (%) of confirmed adjudicated all- cause death or hospitalization due to CHF over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.721).

<u>Secondary variable: Time from randomization to cardiovascular death, or hospitalization due to CHF or non-fatal MI</u>

During the follow-up period, 773 patients experienced the secondary outcome of CV death or CHF hospitalization or non-fatal MI, 353 (34.8%) in the candesartan group and 420 (41.4%) in the placebo group. The average annualized events rates were 14.8% and 19.1%, respectively (Table 132).

Table 132 Confirmed adjudicated CV death or hospitalization due to CHF or nonfatal MI. 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)

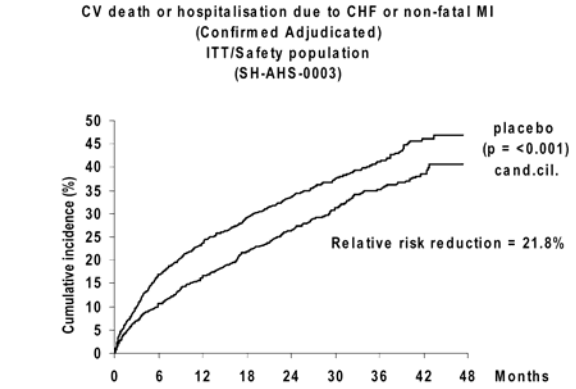
Variable	Treat-ment	N	Events (No of patients)	Total follow-up time (years)	Events / 1000 follow-up years	Mean follow-up time (years)
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	Placebo	1015	420	2196.4	191.2	2.2
	Cand. cil.	1013	353	2389.2	147.8	2.4

The relative risk for the secondary outcome of CV death or CHF hospitalization or non-fatal MI, whichever came first, was significantly reduced by 21.8% by candesartan treatment (Table 133).

Table 133 Confirmed adjudicated CV death or hospitalization due to CHF or non-fatal MI. 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	
CV death or hospitalisation due to CHF or non-fatal MI (confirmed adjudicated)	2028	353	420	0.782	0.679	0.901	<0.001

The Kaplan-Meier plot implies that the benefit of candesartan appeared early and was maintained throughout the study period (Figure 54).



Number at risk					
Placebo	1015	767	654	333	95
Cand.cil.	1013	841	728	371	106

Figure 54 Cumulative incidence (%) of confirmed adjudicated CV death or hospitalization due to CHF or non- fatal MI over time. ITT/Safety population

The treatment effect of candesartan was similar across geographical regions (test for interaction; P= 0.983).

<u>Is there a dose response of the dose of candesartan (plus heart failure dose or low dose of ACE-inhibitors) on the primary and secondary efficacy outcomes?</u>

The submission shows that 1,756 (68.9%) patients (candesartan = 857, 67.2%; placebo = 899, 70.7%) received the investigational product for 24 months or more. A total of 1,096 (85.9%) patients in the candesartan group started treatment on 4 mg once daily, and 180 (14.1%) patients started on 8 mg once daily. 53.6% of patients treated with candesartan were receiving the target dose of 32 mg once daily at 6 months (visit 5). Also, the sponsor stated that from the 6-month visit onwards, >50% of patients still receiving candesartan were on a dose of 32 mg/day. The mean dose in the candesartan treatment group was 23.5 mg at 6 months.

In Table 134 and Table 135, the proportions of patients who developed the primary efficacy endpoint events appear to be less in the candesartan-treated groups than the placebo-treated groups, particularly at the lower doses of 4 mg and 8 mg candesartan where the relative risk reduction with candesartan vs. placebo was significant (Table 135). However, the results in the table do not take into consideration whether patients were receiving heart failure doses or low doses of ACE-inhibitors.

Table 134 CV death or CHF hospitalization by subgroup: dose of study drug, (events per 1000 years of follow-up), Study SH-AHS-0003

Variable	Group	Treatment	N	Events (number of patients)	Total follow-up time (years)	Events/1000 follow-up years	Mean follow-up time (years)
Dose of study drug (at the visit preceding the event) (at last visit if no event)	4 mg	Placebo	78	57	108.0	527.9	1.4
		Candesartan	127	71	285.1	249.0	2.2
	8 mg	Placebo	89	57	158.8	358.9	1.8
		Candesartan	99	44	247.8	177.6	2.5
	16 mg	Placebo	151	69	349.1	197.6	2.3
		Candesartan	185	75	469.8	159.6	2.5
	32 mg	Placebo	776	295	2123.8	138.9	2.7
		Candesartan	588	209	1629.0	128.3	2.8
	No study drug	Placebo	178	60	494.9	121.2	2.8
		Candesartan	277	84	789.9	106.3	2.9

Table 135 CV death or CHF hospitalization by subgroup: dose of study drug (Cox regression), Study SH-AHS-0003

Variable	Group	N	Events candesartan	Events placebo	Hazard ratio	95% CI	p-value
Dose of study drug (at the visit preceding the event) (at last visit if no event)	4 mg	205	71	57	0.534	0.376, 0.758	<0.001
	8 mg	188	44	57	0.533	0.359, 0.791	0.002
	16 mg	336	75	69	0.823	0.593, 1.141	0.243
	32 mg	1364	209	295	0.927	0.776, 1.106	0.399
	No study drug	455	84	60	0.872	0.626, 1.214	0.418

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 primary and secondary efficacy endpoints.

On November 24 2004, I received the sponsor's response containing the information related to the primary and principal secondary efficacy endpoints, and adverse event endpoints according to dose level of candesartan. These analyses consider dose level of candesartan consistent with the sub-group analyses presented in the submission. For the dose analyses, 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 plus ACE inhibitors at heart failure dose or low are given in Table 136. It appears that there is a relative dose response, the event rates being significantly (P<0.001) lower in the high dose (16 and 32 mg) candesartan groups compared to the low dose (4 and 8 mg) candesartan groups; however, patients receiving and placebo also exhibited the same dose response! (Table 137).

The secondary efficacy endpoint of all-cause mortality or CHF hospitalization (Table 138 and Table 139), and for secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (Table 140 and Table 141) also show similar findings.

Table 136 The numbers and event rates (primary efficacy endpoint of CV mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 371 (36.6%)** **A**	
	CC_{HD} n = 597 events = 180 (30.2%) **A1**	CC_{LD} n = 213 events = 124 (58.2%) **A2**	CC_{00} n = 203 events = 67 (33.0%) **A3**
Placebo		**N = 1015** **Events = 433 (42.7%)** **B**	
	P_{HD} n = 721 events = 282 (39.1%) **B1**	P_{LD} n = 131 events = 94 (71.8%) **B2**	P_{00} n = 163 events = 57 (35.0%) **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; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 137 Comparison of the effect of high or low dose candesartan on the primary endpoint of time to CV mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression– CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	23.2	0.768	(0.665, 0.888)	<0.001
A_1 vs B	40.7	0.593	(0.494, 0.712)	<0.001
A_1 vs A_2	64.5	0.355	(0.280, 0.451)	<0.001
A_2 vs B	-	1.652	(1.346, 2.028)	<0.001
A_1 vs B_1	34.5	0.655	(0.539, 0.796)	<0.001
A_2 vs B_2	37.6	0.624	(0.472, 0.825)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 136.

Table 138 The numbers and event rates (secondary efficacy endpoint of all-cause mortality or CHF hospitalization, confirmed, adjudicated) of patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 371 (36.6%)** **A**	
	CC_{HD} n = 597 events = 180 (30.2%) **A1**	CC_{LD} n = 213 events = 124 (58.2%) **A2**	CC_{00} n = 203 events = 67 (33.0%) **A3**
Placebo		**N = 1015** **Events = 433 (42.7%)** **B**	
	P_{HD} n = 721 events = 282 (39.1%) **B1**	P_{LD} n = 131 events = 94 (71.8%) **B2**	P_{00} n = 163 events = 57 (35.0%) **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; [a] Dose of study drug preceding the event (or at last visit if no event occurred)

Table 139 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of all-cause mortality or CHF hospitalization (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	20.2	0.798	(0.695, 0.917)	0.001
A_1 vs B	38.2	0.618	(0.519, 0.735)	<0.001
A_1 vs A_2	62.7	0.373	(0.297, 0.470)	<0.001
A_2 vs B	-	1.631	(1.336, 1.992)	<0.001
A_1 vs B_1	30.2	0.698	(0.579, 0.841)	<0.001
A_2 vs B_2	40.1	0.599	(0.458, 0.784)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 138.

Table 140 The numbers and event rates (secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI, confirmed, adjudicated) of patients who received high or low dose candesartan – CHARM-Alternative (SH-AHS-0003) Study

Candesartan		**N = 1013** **Events = 353 (34.9%)** **A**	
	CC_{HD} n = 599 events = 176 (29.4%) **A1**	CC_{LD} n = 215 events = 121 (56.3%) **A2**	CC_{00} n = 199 events = 56 (28.1%) **A3**
Placebo		**N = 1015** **Events = 420 (41.4%)** **B**	
	P_{HD} n = 720 events = 279 (38.8%) **B1**	P_{LD} n = 134 events = 91 (67.9%) **B2**	P_{00} n = 161 events = 50 (31.1%) **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)

Table 141 Comparison of the effect of high or low dose candesartan on the secondary efficacy endpoint of CV mortality or CHF hospitalization or non-fatal MI (confirmed, adjudicated) using Cox Regression[a] – CHARM-Alternative (SH-AHS-0003) Study

Comparison	Relative risk reduction (%)	Hazard ratio	95% confidence interval	p-value (Wald)
A vs B	21.8	0.782	(0.679, 0.901)	<0.001
A_1 vs B	37.9	0.621	(0.521, 0.741)	<0.001
A_1 vs A_2	62.1	0.379	(0.301, 0.478)	<0.001
A_2 vs B	-	1.620	(1.323, 1.983)	<0.001
A_1 vs B_1	30.9	0.691	(0.572, 0.834)	<0.001
A_2 vs B_2	39.5	0.605	(0.460, 0.795)	<0.001

Cells A, B, A_1, B_1, A_2 and B_2 = Reference to cells in Table 140.

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).

My interpretation of the data provided by the sponsor in Table 136 through Table 141 is as follows.

(i) Patient sub-populations by severity of CHF (presumed): Patients in cells A3 (not receiving candesartan prior to event) and B3 (not receiving "double-blind" placebo (perceived by the clinical investigator and the patient as candesartan) prior to event) were, I think, "the most sick" patients who, for some reason (hypotension, hyperkalemia, deterioration in renal function) could not tolerate candesartan for an unknown period of time prior to the primary or secondary efficacy event. Patients in cells A2 (receiving 4 mg or 8 mg candesartan prior to event) and B2 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 4 mg or 8 mg candesartan) prior to event) were "moderately sick" patients who could not tolerate the higher doses of candesartan. Patients in cells A1 (receiving 16 mg or 32 mg candesartan prior to event) and B1 (receiving "double-blind" placebo (perceived by the clinical investigator and the patient as 16 mg or 32 mg candesartan) prior to event) were "the least sick" patients who tolerated the higher doses of candesartan.

(ii) Effect of no drug – internal consistency: Patients in both treatment groups A3 and B3 were not receiving any investigational drug (candesartan or placebo) and had the same

(albeit presumed) severity of CHF. Thus, the events rates in treatment groups A3 and B3 are expected to be similar. The event rates in treatment groups A3 and B3 for the primary and secondary efficacy endpoints are, indeed, similar (Table 136 through Table 141), suggesting internal consistency, and providing some confidence to the logic and integrity of the data.

(iii) Effect of candesartan (1): Comparing the event rates in A2 to B2 allowed the comparison of events in the same population of patients with similar severity of CHF ("moderately sick" patients). A statistically significant reduction in the event rates between A2 vs. B2 for the primary and secondary efficacy endpoints suggests a true difference in this sub-population of moderately sick patients with CHF.

(iv) Effect of candesartan (2): Comparing the event rates in A1 to B1 allow the comparison of event rates in same population of patients with similar degree of CHF ("the least sick" group of patients). A statistically significant reduction in the event rates between A1 vs. B1 for the primary and secondary efficacy endpoints suggests a true difference among patients with the same severity of CHF.

(v) Effect of candesartan (3): The effect of candesartan in the "least sick" and "moderately sick" sub-populations of patients appears to be about the same (for the primary endpoint, a reduction in the relative risk by 34.5% (A1 vs. B1) or 37.6% (A2 vs. B2). This suggests a consistent effect of candesartan for the primary (and also for the secondary) efficacy endpoints.

(vi) Effect of disease: Comparison of the event rates in cells B1 vs. B2 (patients receiving placebo) also shows that the event rates are significantly (P<0.001) lower in the "high dose" group compared to the "low dose" group (Table 136 through Table 141). Since neither group (B1 or B2) was receiving candesartan, this finding is clearly due to the severity of CHF.

(vii) Effect of disease severity (or) effect of dose of candesartan? Comparison of cells A1 vs. A2 shows that the event rates are significantly (P<0.001) lower in the high dose (16 and 32 mg, A1) candesartan groups compared to the low dose (4 and 8 mg, A2) candesartan groups (Table 136 through Table 141), giving the appearance of a dose-related response. I think that the lower event rate in the "high dose" candesartan group is mainly due to the fact that subjects in cell A1 are "the least sick" of the study population; conversely, the higher event rate in the "low dose" candesartan group is due to the fact that subjects in cell A2 are relatively less sick patients. Thus, rather than a "dose-related" response for candesartan regarding the primary and secondary efficacy endpoints as the data in Table 27 through Table 32 appear to suggest, I think the differences observed between the "high dose" and "low dose" candesartan groups are attributable to the severity of CHF.

Components of primary and secondary variables

The individual components of 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. There was no reduction in non-fatal MI (Table 142 and Table 143).

Table 142 Components of primary and secondary variables. 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 pati-ents)	Total follow-up time (years)	Events/ 1000 follow-up years	Mean follow-up time (years)
CV death (confirmed adjudicated)	Placebo	1015	252	2582.4	97.6	2.5
	Cand. cil.	1013	219	2658.1	82.4	2.6
Hospitalisation due to CHF (confirmed adjudicated)	Placebo	1015	286	2229.2	128.3	2.2
	Cand. cil.	1013	207	2418.9	85.6	2.4
All-cause death (confirmed adjudicated)	Placebo	1015	296	2582.4	114.6	2.5
	Cand. cil.	1013	265	2658.1	99.7	2.6
Non-fatal MI (confirmed adjudicated)	Placebo	1015	36	2534.5	14.2	2.5
	Cand.cil.	1013	41	2619.5	15.7	2.6

Table 143 Components of primary and secondary variables. Comparison of candesartan versus placebo with Cox regression. ITT/Safety population (SH-AHS-0006)

Variable	N	Events cand. cil.	Events placebo	Hazard Ratio	95% CI		p-value
					Lower	Upper	
CV death (confirmed adjudicated)	2028	219	252	0.847	0.707	1.015	0.072
Hospitalisation due to CHF (confirmed adjudicated)	2028	207	286	0.677	0.566	0.810	<0.001
All-cause death (confirmed adjudicated)	2028	265	296	0.872	0.739	1.029	0.105[a]
Non-fatal MI (confirmed adjudicated)	2028	41	36	1.107	0.708	1.733	0.656[b]

[a] Logrank test p=0.104
[b] Logrank test p=0.655

Time from randomization to all-cause death:

Time from randomization to all-cause death is a component of a secondary variable, and is presented in Table 142 and Table 143.

Time from randomization to all-cause hospitalization:

During the follow-up period, 610 (60.2%) patients in the candesartan group and 643 (63.3%) patients in the placebo group were hospitalized due to any cause. The average annualized events rates were 36.3% and 40.0% respectively (Table 144). The relative risk of all-cause hospitalization was non-significantly (P= 0.107) reduced by candesartan treatment (Table 145).

Table 144 Confirmed adjudicated all- cause hospitalization. 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)
All-cause hospitalisation	Placebo	1015	643	1606.2	400.3	1.6
	Cand. cil.	1013	610	1681.6	362.7	1.7

Table 145 Confirmed adjudicated all-cause hospitalization. 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	
All-cause hospitalisation	2028	610	643	0.913	0.817	1.020	0.107

Number of patients with fatal or non-fatal MI:

There were significantly fewer patients with fatal or non-fatal MI in the placebo group (48,4.7%) than in the candesartan group (75, 7.4%) (Table 146 and Table 147).

Table 146 The proportion of patients (%) with confirmed adjudicated fatal or nonfatal MI. ITT/Safety population (SH-AHS-0003)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Fatal or non-fatal MI (confirmed adjudicated)	Placebo	1015	48	4.7	3.5	6.2
	Cand. cil.	1013	75	7.4	5.9	9.2

Table 147 The difference in proportion (%) of patients with confirmed adjudicated fatal or non- fatal MI 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	
Fatal or non-fatal MI (confirmed adjudicated)	2.7	0.6	4.7	0.012

NYHA classification of heart failure:

Improvement in NYHA functional class by 1 or 2 NYHA classes was observed in 359 (35.7%) patients in the candesartan group compared to 298 (29.7%) in the placebo group (P= 0.008, Wilcoxon rank-sum test) (Table 148).

Table 148 Number of patients and change from baseline to LVCF in NYHA class by treatment. ITT/Safety population (SH-AHS-0003)

Visit	NYHA class	Placebo	Cand. cil.	Total
Baseline	NYHA II	479 (47.2%)	487 (48.1%)	966 (47.6%)
	NYHA III	499 (49.2%)	490 (48.4%)	989 (48.8%)
	NYHA IV	37 (3.6%)	36 (3.6%)	73 (3.6%)
	Total	1015	1013	2028
LVCF	NYHA I	95 (9.5%)	144 (14.3%)	239 (11.9%)
	NYHA II	521 (51.9%)	493 (49.0%)	1014 (50.4%)
	NYHA III	337 (33.6%)	332 (33.0%)	669 (33.3%)
	NYHA IV	51 (5.1%)	37 (3.7%)	88 (4.4%)
	Total	1004	1006	2010
Change from baseline to LVCF[a]	NYHA improved by 3 classes	0	2 (0.2%)	2 (0.1%)
	NYHA improved by 2 classes	33 (3.3%)	40 (4.0%)	73 (3.6%)
	NYHA improved by 1 class	265 (26.4%)	319 (31.7%)	584 (29.1%)
	NYHA same as baseline	597 (59.5%)	544 (54.1%)	1141 (56.8%)
	NYHA deteriorated by 1 class	106 (10.6%)	93 (9.2%)	199 (9.9%)
	NYHA deteriorated by 2 classes	3 (0.3%)	8 (0.8%)	11 (0.5%)
	Total	1004	1006	2010

[a] Wilcoxon rank-sum test, p=0.008

The shift in NYHA functional class from baseline to last known class is presented in Table 149.

Table 149 NYHA class shift table by treatment. ITT/Safety Population. (SH-AHS-0003)

Change in NYHA class from baseline to LVCF	Number of patients (%)	
	Placebo (N=1015)	Cand.cil. (N=1013)
from II to Unknown	4 (0.4%)	4 (0.4%)
from II to I	71 (7.0%)	112 (11.1%)
from II to II	328 (32.3%)	294 (29.0%)
from II to III	73 (7.2%)	69 (6.8%)
from II to IV	3 (0.3%)	8 (0.8%)
from III to Unknown	4 (0.4%)	2 (0.2%)
from III to I	24 (2.4%)	30 (3.0%)
from III to II	184 (18.1%)	189 (18.7%)
from III to III	254 (25.0%)	245 (24.2%)
from III to IV	33 (3.3%)	24 (2.4%)
from IV to Unknown	3 (0.3%)	1 (0.1%)
from IV to I	0	2 (0.2%)
from IV to II	9 (0.9%)	10 (1.0%)
from IV to III	10 (1.0%)	18 (1.8%)
from IV to IV	15 (1.5%)	5 (0.5%)

Time from randomization to diagnosed onset of diabetes:

Analyses include only patients without a pre-study diagnosis of diabetes. During the follow-up period 44 (6.0%) patients in the candesartan group and 53 (7.1%) patients in the placebo group had a diagnosed onset of diabetes during the follow-up period. The average annualized events rates were 2.3% and 2.9% respectively (Table 150). There is a nonsignificant (P= 0.254) relative risk reduction of 20.8% for developing diabetes with candesartan treatment (Table 151).

Table 150 Diagnosed onset of diabetes. Number of patients with an 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)
Diagnosed onset of diabetes	Placebo	745	53	1831.6	28.9	2.5
	Cand. cil.	735	44	1921.0	22.9	2.6

Table 151 Diagnosed onset of diabetes. 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	
Diagnosed onset of diabetes	1480	44	53	0.792	0.531	1.182	0.254 [a]

[a] Logrank test p=0.252

Number of patients who developed atrial fibrillation:

Significantly fewer patients in the candesartan group than in the placebo group developed atrial fibrillation (candesartan 49, 4.8%, placebo 70, 6.9%, P= 0.048) during the follow-up period (Table 152 and Table 153).

Table 152 Development of atrial fibrillation. The proportions of patients (%) with an event. ITT/ Safety population (SH-AHS-0003)

Variable	Treatment	N	Number of patients with event	Proportion of patients with event	95% CI	
					Lower	Upper
Development of atrial fibrillation	Placebo	1015	70	6.9	5.4	8.6
	Cand. cil.	1013	49	4.8	3.6	6.3

Table 153 Development of atrial fibrillation. 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	
Development of atrial fibrillation	-2.1	-4.1	0.0	0.048

Frequency of hospitalizations:

The effects on hospitalizations for various reasons are presented in Table 154 and Table 155. The number of patients hospitalized for CHF as well as the total numbers of hospital admissions primarily for CHF were reduced by treatment with candesartan.

Table 154 Total number of clinical events by variable and treatment. ITT/ Safety population (SH-AHS-0003)

Variable	Treatment	N	Number of patients with events	Total number of events	Total number of follow-up years	Mean (number of events / follow-up year) by patients	Events / 1000 follow-up years
Coronary revascularisation procedure	Placebo	1015	50	66	2582.4	0.04	25.6
	Cand. cil.	1013	49	62	2658.1	0.03	23.3
All-cause hospitalisation	Placebo	1015	643	1835	2582.4	1.44	710.6
	Cand. cil.	1013	610	1718	2658.1	1.04	646.3
Non-fatal stroke	Placebo	1015	29	34	2582.4	0.06	13.2
	Cand. cil.	1013	25	28	2658.1	0.01	10.5
Non-fatal MI	Placebo	1015	61	92	2582.4	0.12	35.6
	Cand. cil.	1013	62	110	2658.1	0.11	41.4
Hospitalisation due to CHF	Placebo	1015	329	716	2582.4	0.66	277.3
	Cand. cil.	1013	257	539	2658.1	0.44	202.8
Hospitalisation due to CHF (primary reason only)	Placebo	1015	291	608	2582.4	0.53	235.4
	Cand.cil.	1013	212	445	2658.1	0.38	167.4
Number of days alive in hospital	Placebo	1015	586	16008	2582.4	8.11	6199
	Cand. cil.	1013	559	14687	2658.1	7.27	5525

Table 155 Difference between treatments by variable. Wilcoxon rank-sum test. ITT/Safety population (SH-AHS-0003)

Variable	Mean (number of events / follow-up year) by patients.		p-value
	Placebo	Cand. cil.	
Coronary revascularisation procedure	0.04	0.03	0.930
All-cause hospitalisation	1.44	1.04	0.062
Non-fatal stroke	0.06	0.01	0.594
Non-fatal MI	0.12	0.11	0.842
Hospitalisation due to CHF	0.66	0.44	<0.001
Hospitalisation due to CHF (primary reason only)	0.53	0.38	<0.001
Number of days alive in hospital	8.11	7.27	0.176