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Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	20-838/N022, 024, 025
Drug Name:	Candesartan Cilexetil (ATACAND) Tablets
Indication(s):	Treatment of Heart Failure
Applicant:	Astra Zeneca
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Keywords: Log rank test, Cox regression, subgroup analysis, survival analysis.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Candesartan cilexetil (Candesartan) significantly reduced cardiovascular (CV) death or Chronic Heart Failure (CHF) hospitalization in patients with depressed left ventricular (LV) systolic function and ejection fraction (EF) <= 40% treated with or without an angiotensin converting enzyme (ACE) inhibitor. In the confirmatory analysis, Candesartan also significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI.

In patients with preserved LV systolic function and EF > 40%, Candesartan failed to show that it significantly reduce the risk of CV death or CHF hospitalization. It did not show that Candesartan significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI.

It was not clear whether Candesartan reduced the risk of CV death or CHF hospitalization in patients with depressed or preserved LV systolic function in the oriental subgroup.

Candesartan probably significantly reduced the risk of CV death in patients with depressed LV systolic function and EF <= 40% treated with or without an ACE inhibitor. It failed to show that it significantly reduced the risk of CV death in patients with preserved LV systolic function and EF > 40%.

1.2 Brief Overview of Clinical Studies

The CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and mobility) program consists of 3 pivotal studies (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) with the same primary endpoint and different patient populations. The common primary endpoint was time to the first CV death or CHF hospitalization. Study SH-AHS-0003 treated patients with heart failure who were ACE inhibitor intolerant and had depressed LV function and EF <= 40%, Study SH-AHS-0006 studied patients with heart failure who were treated with ACE inhibitors and had depressed LV systolic function and EF <= 40%, and Study SH-AHS-0007 had patients with heart failure and preserved LV systolic function and EF > 40%. The Sponsor is seeking indication that Candesartan reduces the risk of CV death or CHF hospitalization in the three patient populations based on each of the three studies. The Sponsor is also seeking the indication that Candesartan reduces the risk of all-cause mortality based on the data combining all three studies and the data combining the two studies (SH-AHS-0003 and SH-AHS-0006).

The indication for the patients treated with an ACE inhibitor (SH-AHS-0006) was granted with priority review status and the review was completed in another review. This review considers all the other indications.

Study SH-AHS-0003 (Alternative) was a randomized, double-blind, placebo controlled, parallel group, multicenter study to evaluate the influence of Candesartan cilexetil with a target dose of

32 mg once daily on mortality and morbidity in patients with depressed LV systolic function and EF <= 40% and an intolerance to ACE inhibitors. Male or female patients, over or equal to 18 years old, with symptomatic CHF corresponding to NYHA class II-IV were enrolled in the study. A total of 2028 patients were randomized in a 1:1 ratio into Candesartan group (n = 1013) and placebo group (n = 1015). The median follow-up time was 34 months, and individual follow-up time could last from 25 to 48 months. The design for Studies SH-AHS-0006 (Added) and SH-AHS-0007 (Preserved) was similar to Study SH-AHS-0003 except the patient population. Study SH-AHS-0006 enrolled patients with EF <= 40% and treated with an ACE inhibitor. In this study, a total of 2548 patients were randomized in a 1:1 ratio into Candesartan group (n = 1276) and placebo group (n = 1272). Patient follow-up time ranged from 41 to 48 months, with the median follow-up time of 41 months. Study SH-AHS-0007 had patients with EF > 40% treated with or without ACE inhibitors. The number of randomized patients was 3023, with 1514 patients in the Candesartan group and 1509 patients in the placebo group. The patients were followed from 32 to 48 months, with a median follow-up time of 37 months. All patients remained in the study until the last randomized patient had been in the CHARM program for two years.

1.3 Statistical Issues and Findings

In Study SH-AHS-0003 (Alternative), the primary endpoint, time to the first CV death or CHF hospitalization, achieved statistical significance (P < 0.001) with a relative risk reduction of 23% over placebo. The two secondary endpoints, time to the all-cause mortality or CHF hospitalization and time to CV death or CHF hospitalization or non-fatal MI, also achieved statistical significance with 20% (P = 0.001) and 22% (P < 0.001) relative risk reductions, respectively.

In Study SH-AHS-0006 (Added), the primary endpoint achieved statistical significance with a relative risk reduction of 15% (P = 0.011). The two secondary endpoints also achieved statistical significance. A separate review was completed earlier for Study SH-AHS-0006 since it was granted with priority review status.

In Study SH-AHS-0007 (Preserved), the primary endpoint did not achieve statistical significance, with a p-value = 0.12 and a relative risk reduction of 11%. The two secondary endpoints did not achieve statistical significance either, with both p-values larger than 0.12.

For the combined studies, the primary endpoint was the time to all-cause mortality for the three studies combined, and the secondary endpoint was time to all-cause mortality for the two studies combined (SH-AHS-0003 and SH-AHS-0006). The primary endpoint did not, but was close to, achieve statistical significance with a p-value = 0.055 and a 9% relative risk reduction. This p-value should be compared with 0.049 to account for the alpha adjustment due to the six interim analyses. The secondary endpoint had a 12% relative risk reduction with a nominal p-value = 0.018. The results for the primary and secondary endpoint were primarily driven by the CV

deaths in Studies SH-AHS-0003 and SH-AHS-0006. Strictly speaking, it can't be declared that the secondary endpoint achieved statistical significance based on the pre-specified hierarchical test sequence. However, Candesartan probably significantly reduced the risk of CV mortality in the patient populations in Studies SH-AHS-0003 and SH-AHS-0006 based on the following reasons. Candesartan had no effect in the risk reduction of CV deaths or non-CV deaths in the patient population of Study SH-AHS-0007, but it had relative risk reductions of 15% (P = 0.072) and 16% (P = 0.029) in CV deaths in Studies SH-AHS-0003 and SH-AHS-0006, respectively, and no effect on non-CV deaths in either studies. For CV mortality, the relative risk reductions were quite consistent in the two studies, and the nominal p-value was less than 0.05 in Study SH-AHS-0006. The nominal p-value was bigger than 0.05 in Study SH-AHS-003 for CV deaths, the reason might be that the number of events was much smaller in this study. When the two studies were combined, the relative risk reduction in CV mortality was 16% with a nominal p-value = 0.005.

Six interim analyses were conducted on all-cause mortality and it is not clear how these analyses would affect the Type I error rate for the primary endpoint of each individual study (time to CV death or CHF hospitalization). However, since the allocated Type I error rates were very small for the interim analyses, the effect should be small if any.

In the subgroup analysis of time to CV death or CHF hospitalization, the hazard ratio was 3.73 with a nominal p-value = 0.026 in the oriental subgroup of Study SH-AHS-0007, and the hazard ratios were bigger than 1 in the other two studies in the oriental subgroup. The hazard ratio was 2.14 with a nominal p-value = 0.012 in the oriental subgroup when the three studies were combined (Table 17). Since the sample size was small (n = 133 for three studies combined), further study would be needed for efficacy in this subgroup.

2 INTRODUCTION

2.1 Overview

Candesartan is indicated for the treatment of hypertension and it is available for oral use as tablets containing either 4 mg, 8 mg, 16 mg, or 32 mg of Candesartan cilexetil. In this efficacy supplement application, the Sponsor is seeking indications that Candesartan reduces the combined endpoint of CV mortality or hospitalization for the management of chronic heart failure. Results from the CHARM program are submitted in this application. CHARM was an international (26 countries including the US) program comprised of 3 independent concurrent double-blind, placebo-controlled trials (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) in which a total of 7601 patients (7599 with data) with NYHA class II-IV heart failure. The patients in Study SH-AHS-0003 (CHARM-Alternative) were ACE inhibitor intolerant with depressed LV systolic function and EF <= 40%. Study SH-AHS-0006 (CHARM-Added) studied the patients with depressed LV systolic function and EF <= 40% treated with an ACE inhibitor.

Study SH-AHS-0007 (CHARM-Preserved) enrolled patients with heart failure and preserved LV systolic function and EF > 40%.

2.1.1 HISTORY OF DRUG DEVELOPMENT

The Sponsor was seeking priority review for all 3 pivotal studies. After negotiation with the Sponsor, the Division granted the priority review status for the review of Study SH-AHS-0006. The other two studies are under standard review. The priority review is completed.

2.1.2 SPECIFIC STUDIES REVIEWED

Studies SH-AHS-0003 and SH-AHS-0007 were fully reviewed. Study SH-AHS-0003 enrolled patients with depressed LV systolic function (EF <= 40%) and intolerance to ACE inhibitors. It is also called CHARM-alternative trial. Study SH-AHS-0007 enrolled patients with preserved LV systolic function (EF > 40%) treated or not treated with an ACE inhibitor. It is called CHARM-preserved trial.

2.1.3 MAJOR STATISTICAL ISSUES

The primary endpoint for each of the three studies is the composite of CV mortality and CV hospitalization for the management of CHF, and each study is intended for the indication that Candesartan reduces the risk of the composite endpoint when compared with placebo for its patient population. The data from the two studies, together with Study SH-AHS-0006 in the CHARM program, are also used for the indication that Candesartan reduces the risk of all-cause mortality for the pooled patient population. Six interim analyses were conducted on all-cause mortality at intervals of approximately 6 months over a total of recruitment and follow-up period of around 48 months. In order to stop for efficacy, one required a p-value < 0.0001 for any interim analysis within 18 months, or a p-value < 0.001 for any subsequent interim analysis.

The hypothesis for the primary endpoint is tested at alpha = 0.05 in each study, and the analysis for all-cause mortality is also performed at alpha = 0.05 level based on the pooled data. This is a typical situation for a clinical program consisting of several independent studies, each study has a primary endpoint for an indication and the primary endpoint is tested at alpha = 0.05. There is another primary endpoint for the data combining all the studies, and this primary endpoint is different from the primary endpoint in each study, and it is tested at alpha = 0.05 as well. Strictly speaking, the total alpha is not controlled for the whole program. The data from each study are used twice for the primary analysis, once for the analysis of the primary endpoint in each individual study and once for the analysis of the primary endpoint of the studies combined. It is a complicated issue how to control the total alpha for the whole program.

Since six interim analyses were conducted, some adjustment of the p-value should be made for the all-cause mortality for the pooled data of the 3 studies. After adjusting for the interim analyses, the Type I error rate for the final analysis of all-cause mortality is 0.0492. It is not clear how the interim analyses would affect the alpha level for the analysis of the primary endpoint for each individual study, since the interim analyses were conducted on all-cause mortality which was not the primary endpoint for each individual study. However, the effect should be small since the alpha error rates allocated for the interim analyses were very small.

2.2 Data Sources

This application was submitted electronically. All the materials are located at \\Cdsesub1\n20838\S_022\2004-06-30. The final reports for the three studies and the summary of clinical efficacy for all the 3 studies were fully reviewed. They are located at \\Cdsesub1\n20838\S_022\2004-06-30\clinstat\indication\controlled. The main analyses were independently performed by this reviewer. SAS data sets are located at \\Cdsesub1\n20838\S_022\2004-06-30\crt\datasets .

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY DESIGN AND ENDPOINT

The three studies (SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007) were randomized, double-blind, placebo controlled, parallel group, multicenter studies to evaluate the influence of Candesartan with a target dose of 32 mg once daily on mortality and morbidity in patients with symptomatic CHF corresponding to NYHA class II-IV. The patient population was male and female patients, over or equal to 18 years of age. Study SH-AHS-0003 enrolled patients with depressed LV systolic function and EF <= 40% and an intolerance to ACE inhibitors, Study SH-AHS-0006 enrolled patients with depressed LV systolic function and EF <= 40% and treated with ACE inhibitors, and Study SH-AHS-007 had patients with preserved LV systolic function and EF > 40%. The patients were randomized in a 1-1 ratio into one of the two treatment groups in each study. In Study SH-AHS-0003, a total of 2028 patients were randomized with n = 1013 in the Candesartan group and n = 1015 in the placebo group. Study SH-AHS-006 randomized 2548 patients with n = 1276 in the Candesartan group and n = 1272 in the placebo group. Study SH-AHS-0007 had 3023 patients with n = 1514 in the Candesartan group and n = 1509 in the placebo group. All patients remained in the study until the last randomized patient had been in the CHARM program for two years. For Study SH-AHS-0003, the patients were followed from 25 to 48 months, with a median follow-up time of 34 months. The study was conducted in 25

countries at a total of 484 sites, including 131 sites in the United States. For Study SH-AHS-0006, the patients were followed from 41 to 48 months, with a median follow-up time of 41 months. The study was conducted in 25 countries at a total of 473 sites, including 123 sites in the United States. In Study SH-AHS-0007, the patients were followed from 32 to 48 months, with a median follow-up time of 37 months. The study was conducted in 26 countries at a total of 514 sites, including 143 sites in the United States. The first patient was randomized on March 22, 1999 and the last patient was completed on March 31, 2003 for each of the three studies.

For each study, the primary endpoint was time to the first CV death or hospitalization due to symptomatic chronic heart failure. Secondary endpoints were time to the first all-cause mortality or hospitalization due to chronic heart failure, time to the first CV death or hospitalization due to chronic heart failure or nonfatal MI.

For the combined studies, the primary endpoint was time to all-cause mortality for the three studies combined. The secondary endpoint was the time to all-cause mortality for the combined studies of SH-AHS-0003 and SH-AHS-0006.

3.1.2 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Tables 1, 2, 3 and 4 are the summaries of the patient participation, demographic and baseline characteristics for Studies of SH-AHS-0003, SH-AHS-0006, SH-AHS-0007 and three studies combined, respectively. Almost everybody completed the study in each group of the studies. The demographic and baseline characteristics seem to be comparable between the two treatment groups for the variables listed in the tables in each of the three studies.

Table 1. Patient Participation, Demographic and Baseline Characteristics (SH-AHS-0003)

	Placebo N = 1015	**Cand. Cil. N = 1013**	**Total N = 2028**
Disposition N (%)			
Completed	1014 (99.9)	1011 (99.8)	2025 (99.9)
Lost to Follow-up	1 (0.1)	2 (0.2)	3 (0.1)
Demographic Characteristics			
Sex N (%)			
Male	691 (68.1)	691 (68.2)	1382 (68.1)
Female	324 (31.9)	322 (31.8)	646 (31.9)
Age Mean (SD) Years	66.8 (10.5)	66.3 (11.0)	66.6 (10.7)
Ethnicity N (%)			
European Origin	901 (88.8)	895 (88.4)	1796 (88.6)
Black	45 (4.4)	28 (2.8)	73 (3.6)
South Asia	15 (1.5)	22 (2.2)	37 (1.8)
Arab/Middle East	6 (0.6)	9 (0.9)	15 (0.7)
Oriental	27 (2.7)	29 (2.9)	56 (2.8)
Malay	10 (1.0)	14 (1.4)	24 (1.2)
Other	11 (1.1)	16 (1.6)	27 (1.3)
Baseline Characteristics			

	Placebo N = 1015	**Cand. Cil. N = 1013**	**Total N = 2028**
Ejection Fraction, Mean (SD)	0.30 (0.07)	0.30 (0.08)	0.30 (0.07)
Diabetes Mellitus, N (%)	270 (26.6)	278 (27.4)	548 (27.0)
Hypertension, N (%)	515 (50.7)	500 (49.4)	1015 (50.0)
Atrial Fibrillation, N (%)	261 (25.7)	254 (25.1)	515 (25.4)
Previous MI, N (%)	618 (60.9)	629 (62.1)	1247 (61.5)
Angina Pectoris, N (%)	592 (58.3)	593 (58.5)	1185 (58.4)
Stroke, N (%)	90 (8.9)	85 (8.4)	175 (8.6)
NYHA II, N (%)	479 (47.2)	487 (48.1)	966 (47.6)
NYHA III, N (%)	499 (49.2)	490 (48.4)	989 (48.8)
NYHA IV, N (%)	37 (3.6)	36 (3.6)	73 (3.6)
Current Smoker, N (%)	127 (12.5)	149 (14.7)	276 (13.8)

Source: Table S1 of the clinical study report of Study SH-AHS-0003 by AstraZeneca.

Table 2. Patient Participation, Demographic and Baseline Characteristics (SH-AHS-0006)

	Placebo N = 1272	**Cand. Cil. N = 1276**	**Total N = 2548**
Disposition N (%)			
Completed	1271 (99.9)	1273 (99.8)	2544 (99.8)
Lost to Follow-up	1 (0.1)	3 (0.2)	4 (0.2)
Demographic Characteristics			
Sex N (%)			
Male	1000 (78.6)	1006 (78.8)	2006 (78.7)
Female	272 (21.4)	270 (21.2)	542 (21.3)
Age Mean (SD) Years	64.1 (11.3)	64.0 (10.7)	64.1 (11.0)
Ethnicity N (%)			
European Origin	1164 (91.5)	1143 (89.6)	2307 (90.5)
Black	62 (4.9)	65 (5.1)	127 (5.0)
South Asia	8 (0.6)	19 (1.5)	27 (1.1)
Arab/Middle East	4 (0.3)	8 (0.6)	12 (0.5)
Oriental	13 (1.0)	22 (1.7)	35 (1.4)
Malay	7 (0.6)	11 (0.9)	18 (0.7)
Other	14 (1.1)	8 (0.6)	22 (0.9)
Baseline Characteristics			
Ejection Fraction, Mean (SD)	0.28 (0.07)	0.28 (0.08)	0.28 (0.07)
Diabetes Mellitus, N (%)	382 (30.0)	376 (29.5)	758 (29.7)
Hypertension, N (%)	619 (48.7)	609 (47.7)	1228 (48.2)
Atrial Fibrillation, N (%)	341 (26.8)	346 (27.1)	687 (27.0)
Previous MI, N (%)	703 (55.3)	714 (56.0)	1417 (55.6)
Angina Pectoris, N (%)	684 (53.8)	666 (52.2)	1350 (53.0)
Stroke, N (%)	112 (8.8)	108 (8.5)	220 (8.6)
NYHA II, N (%)	302 (23.7)	312 (24.5)	614 (24.1)
NYHA III, N (%)	925 (72.7)	931 (73.0)	1856 (72.8)
NYHA IV, N (%)	45 (3.5)	33 (2.6)	78 (3.1)
Current Smoker, N (%)	235 (18.5)	194 (15.2)	429 (16.8)

Source: Table S1 of the clinical study report of Study SH-AHS-0006 by AstraZeneca.

Table 3. Patient Participation, Demographic and Baseline Characteristics (SH-AHS-0007)

	Placebo N = 1509	**Cand. Cil. N = 1514**	**Total N = 3023**
Disposition N (%)			
Completed	1508 (99.9)	1512 (99.9)	3020 (99.9)
Lost to Follow-up	1 (0.01)	2 (0.01)	3 (0.01)
Demographic Characteristics			
Sex N (%)			
Male	891 (59.0)	920 (60.8)	1811 (59.9)
Female	618 (41.0)	594 (39.2)	1212 (40.1)
Age Mean (SD) Years	67.1 (11.1)	67.2 (11.1)	67.2 (11.1)
Ethnicity N (%)			
European Origin	1393 (92.3)	1374 (90.8)	2767 (91.5)
Black	57 (3.8)	69 (4.7)	126 (4.2)
South Asia	11 (0.7)	18 (1.2)	29 (1.0)
Arab/Middle East	5 (0.3)	5 (0.3)	10 (0.3)
Oriental	22 (1.5)	20 (1.3)	42 (1.4)
Malay	8 (0.5)	14 (0.9)	22 (0.7)
Other	13 (0.9)	14 (0.9)	27 (0.9)
Baseline Characteristics			
Ejection Fraction, Mean (SD)	0.54 (0.09)	0.54 (0.09)	0.54 (0.09)
Diabetes Mellitus, N (%)	423 (28.0)	434 (28.7)	857 (28.4)
Hypertension, N (%)	959 (63.6)	984 (65.0)	1943 (64.3)
Atrial Fibrillation, N (%)	442 (29.3)	439 (29.0)	881 (29.1)
Previous MI, N (%)	659 (43.7)	681 (45.0)	1340 (44.3)
Angina Pectoris, N (%)	902 (59.8)	915 (60.4)	1817 (60.1)
Stroke, N (%)	128 (8.5)	140 (9.2)	268 (8.9)
NYHA II, N (%)	905 (60.0)	931 (61.5)	1836 (60.7)
NYHA III, N (%)	584 (38.7)	556 (36.7)	1140 (37.7)
NYHA IV, N (%)	20 (1.3)	27 (1.8)	47 (1.6)
Current Smoker, N (%)	187 (12.4)	222 (14.7)	409 (13.5)

Source: Table S1 of the clinical study report of Study SH-AHS-0007 by AstraZeneca.

Table 4. Patient Participation, Demographic and Baseline Characteristics (Pooled)

	Placebo N = 3796	**Cand. Cil. N = 3803**	**Total N = 7599**
Disposition N (%)			
Completed	3793 (99.9)	3796 (99.8)	7589 (99.8)
Lost to Follow-up	3 (0.01)	7 (0.02)	10 (0.02)
Demographic Characteristics			
Sex N (%)			
Male	2582 (68.0)	2617 (68.8)	5199 (68.4)
Female	1214 (32.0)	1186 (31.2)	2400 (31.6)
Age Mean (SD) Years	66.0 (11.1)	65.9 (11.0)	66.0 (11.0)
Ethnicity N (%)			
European Origin	3458 (91.1)	3412 (89.7)	6870 (90.4)
Black	164 (4.3)	162 (4.3)	326 (4.3)
South Asia	34 (0.9)	59 (1.6)	93 (1.2)

	Placebo N = 3796	**Cand. Cil. N = 3803**	**Total N = 7599**
Arab/Middle East	15 (0.4)	22 (0.6)	37 (0.5)
Oriental	62 (1.6)	71 (1.9)	133 (1.8)
Malay	25 (0.7)	39 (1.0)	64 (0.8)
Other	38 (1.0)	38 (1.0)	76 (1.0)
Baseline Characteristics			
Ejection Fraction, Mean (SD)	0.39 (0.15)	0.39 (0.15)	0.39 (0.15)
Diabetes Mellitus, N (%)	1075 (28.3)	1088 (28.6)	2163 (28.5)
Hypertension, N (%)	2093 (55.1)	2093 (55.0)	4186 (55.1)
Atrial Fibrillation, N (%)	1044 (27.5)	1039 (27.3)	2083 (27.4)
Previous MI, N (%)	1980 (52.2)	2024 (53.2)	4004 (52.7)
Angina Pectoris, N (%)	2178 (57.4)	2174 (57.2)	4352 (57.3)
Stroke, N (%)	330 (8.7)	333 (8.8)	663 (8.7)
NYHA II, N (%)	1686 (44.4)	1730 (45.5)	3416 (45.0)
NYHA III, N (%)	2008 (52.9)	1977 (52.0)	3985 (52.4)
NYHA IV, N (%)	102 (2.7)	96 (2.5)	198 (2.6)
Current Smoker, N (%)	549 (14.5)	565 (14.9)	1114 (14.7)

Source: Table S1 of the clinical study report of pooled clinical study report by AstraZeneca.

3.1.3 STATISTICAL METHODOLOGIES

For each individual study, the primary endpoint, time to the first CV death or hospitalization due to symptomatic chronic heart failure, was compared between the two treatment groups using the log-rank test. The hazard ratio and its 95% CI were obtained by a Cox proportional hazards model. The survival distribution by treatment group was plotted using the Kaplan-Meier product limit estimator. The analyses were conducted on the ITT population, which included all the randomized patients. The two secondary endpoints were analyzed similarly as the primary endpoint. The primary and two secondary endpoints were analyzed based on the principle of closed tests. The analyses were conducted in a hierarchical sequence. The primary endpoint was tested first and the two secondary endpoints were tested sequentially, conditional on a significant result of the preceding test. Changes in the NYHA classification were tested using a Wilcoxon rank-sum test. For continuous variables, the mean change from baseline to last observed value was tested in an ANCOVA model.

The analysis of the combined studies is similar to the analysis of each of the three studies. The primary endpoint was tested first and the secondary endpoint was tested conditional on the significant result of the primary test for the combined studies.

Six interim analyses were conducted on all-cause mortality at intervals of approximately 6 months over a total of recruitment and follow-up period of around 48 months for each individual study and the combined data of the three studies. In order to stop for efficacy, one required a p-value < 0.0001 for any interim analysis within 18 months, or a p-value < 0.001 for any subsequent interim analysis. The hypothesis for the test of the primary endpoint is tested at alpha = 0.05 in each study, and the analysis for all-cause mortality is also performed at alpha =

0.05 level based on the pooled data of the three studies. After adjusting for the interim analyses, the Type I error rate for the final analysis of all-cause mortality is 0.0492. No adjustment was made for the final analysis of the primary endpoint in each individual study.

3.1.4 RESULTS AND CONCLUSION

Tables 5, 6 and 7 present the results for the analysis of the primary endpoint and two secondary endpoints in each individual study, including the analysis of the components of the composite endpoints. The primary endpoint and two secondary endpoints achieved statistical significance in Studies SH-AHS-0003 and SH-AHS-0006 based on the pre-specified hierarchical test sequence. For the primary endpoint, time to the first CV death or CHF hospitalization, Candesartan had relative risk reductions of 23% and 15% over placebo, with p-values < 0.001 and 0.011 for Studies SH-AHS-0003 and SH-AHS-0006, respectively. In these two studies, Candesartan also significantly reduced the risk of the two secondary endpoints. In Study SH-AHS-0003, the relative risk reduction was 20% (P = 0.001) for all-cause death or CHF hospitalization and 22% (P < 0.001) for CV death or CHF hospitalization or nonfatal MI. In Study SH-AHS-0006, the relative risk reduction was 13% (P = 0.021) for all-cause death or CHF hospitalization and 15% (P = 0.010) for CV death or CHF hospitalization or nonfatal MI. The primary endpoint and the two secondary endpoints did not achieve statistical significance in Study SH-AHS-0007. In this study, the relative risk reduction was 11% for the time to the first CV death or CHF hospitalization, with a p-value = 0.12. The nominal p-values were more than 0.12 for both secondary endpoints as well.

Table 8 presents the results for the analysis of the primary endpoint and secondary endpoint of the combined studies. The primary endpoint for the combined studies, the time to all-cause mortality combining the data from the three studies, did not achieve statistical significance with a p-value = 0.055 and 9% relative risk reduction. This p-value should be compared with 0.0492 after adjusting for the interim analyses. The secondary endpoint, the time to all-cause mortality combining the data from Studies SH-AHS-0003 and SH-AHS-0006, had a relative risk reduction of 12% with a nominal p-value = 0.018. Based on the pre-specified hierarchical test sequence, statistical significance can not be declared for the secondary endpoint since the primary endpoint did not achieve statistical significance. However, it can still be argued that Candesartan significantly reduced the risk of CV mortality in Studies SH-AHS-0003 and SH-AHS-0006. In each of the two studies (SH-AHS-0003 and SH-AHS-0006), it had a clear trend in favor of Candesartan with relative risk reductions of 15% (P = 0.072) and 16% (P = 0.029) in CV mortality, respectively. The relative risk reductions were very consistent in the two studies, and the nominal p-value was 0.029 in Study SH-AHS-006. The nominal p-value was bigger than 0.05 in Study SH-AHS-003, the reason might be that there was not enough power to detect the difference since there was smaller number of events in that study. No effects were observed for non-CV deaths in the two studies, with relative risks of 1.01 (P = 0.95) and 1.11 (P = 0.53) for Studies SH-AHS-0003 and SH-AHS-0006, respectively. When the two studies (Study SH-AHS-0003 and Study SH-AHS-0006) were combined, the relative risk reduction for CV mortality was

16% with a nominal p-value = 0.005. In Study SH-AHS-0007, it seemed that the drug had no effect on either CV deaths or non-CV deaths, with relative risks of 0.99 (P = 0.92) and 1.10 (P = 0.59) for CV deaths and non-CV deaths, respectively. Therefore, in my view, Candesartan may have a benefit of reducing the risk of CV mortality in the patient populations of Studies SH-AHS-0003 and SH-AHS-0006, but not in the patient population of Study SH-AHS-0007.

Table 5. Analysis of the Primary and Secondary Endpoints (SH-AHS-0003)

Endpoint	Patients with event		Hazard Ratio (95%CI)	P-value
	Candesartan N = 1013	Placebo N = 1015		
Primary				
CV death or CHF hospitalization	334	406	0.77 (0.67–0.89)	<0.001
Secondary				
All-cause death or CHF hospitalization	371	433	0.80 (0.70-0.92)	0.001
CV death or CHF hospitalization or non-fatal MI	353	420	0.78 (0.68-0.90)	<0.001
Components of the composite endpoints				
CV death	219	252	0.85 (0.71-1.02)	0.072
CHF hospitalization	207	286	0.68 (0.57-0.81)	<0.001
All-cause mortality	265	296	0.87 (0.74-1.03)	0.104
Nonfatal MI	41	36	1.11 (0.71-1.73)	0.66

Source: Table 8 of the Sponsor's summary of clinical efficacy. The results were confirmed independently by this reviewer, with minor difference for nonfatal MI. Nominal P-values were from log-rank test and hazard ratios were from Cox regression model with treatment as the only independent variable.

Table 6. Analysis of the Primary and Secondary Endpoints (SH-AHS-0006)

Endpoint	Patients with event		Hazard Ratio (95%CI)	P-value
	Candesartan N = 1276	Placebo N = 1272		
Primary				
CV death or CHF hospitalization	483	538	0.85 (0.75–0.96)	0.011
Secondary				
All-cause death or CHF hospitalization	539	587	0.87 (0.78-0.98)	0.021
CV death or CHF hospitalization or non-fatal MI	495	550	0.85 (0.76-0.96)	0.010
Components of the composite endpoints				
CV death	302	347	0.84 (0.72-0.98)	0.029
CHF hospitalization	309	356	0.83 (0.71-0.96)	0.013
All-cause mortality	377	412	0.89 (0.77-1.02)	0.086
Nonfatal MI	26	49	0.51 (0.32-0.82)	0.005

Source: Table 8 of the Sponsor's summary of clinical efficacy. The results were confirmed independently by this reviewer, with minor difference for nonfatal MI. Nominal P-values were from log-rank test and hazard ratios were from Cox regression model with treatment as the only independent variable.

Table 7. Analysis of the Primary and Secondary Endpoints (SH-AHS-0007)

Endpoint	Patients with event		Hazard Ratio (95%CI)	P-value
	Candesartan N = 1514	Placebo N = 1509		
Primary				
CV death or CHF hospitalization	333	366	0.89 (0.77–1.03)	0.12
Secondary				
All-cause death or CHF hospitalization	386	411	0.92 (0.80-1.05)	0.22
CV death or CHF hospitalization or non-fatal MI	365	399	0.90 (0.78-1.03)	0.13
Components of the composite endpoints				
CV death	170	170	0.99 (0.80-1.22)	0.92
CHF hospitalization	241	276	0.85 (0.72-1.01)	0.07
All-cause mortality	244	237	1.02 (0.85-1.22)	0.84
Nonfatal MI	49	63	0.77 (0.53-1.12)	0.17

Source: Table 8 of the Sponsor's summary of clinical efficacy. The results were confirmed independently by this reviewer, with minor difference for nonfatal MI. Nominal P-values were from log-rank test and hazard ratios were from Cox regression model with treatment as the only independent variable.

Table 8. Analysis of the Primary and Secondary Endpoints (Pooled)

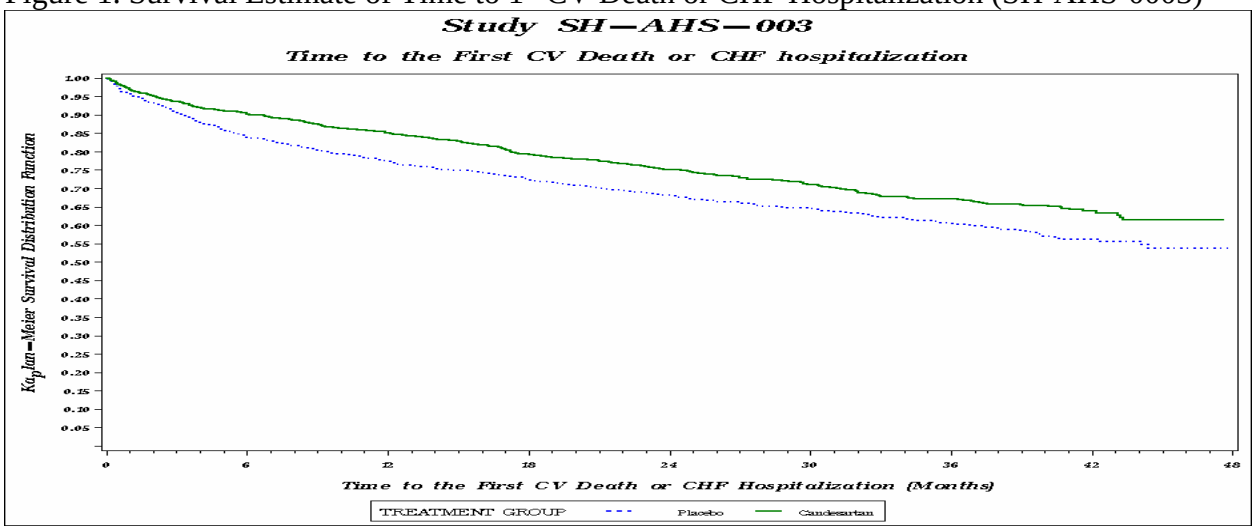
Endpoint	Number of Patients		Hazard Ratio (95%CI)	P-value
	Candesartan n (N)	Placebo n (N)		
Primary				
All-cause death (SH-AHS-0003, -0006, -0007)	886 (3803)	945 (3796)	0.91 (0.83-1.00)	0.055
Secondary				
All-cause death (SH-AHS-0003, -0006)	642 (2289)	708 (2287)	0.88 (0.79-0.98)	0.018
Components				
CV death (SH-AHS-0003, -0006, -0007)	691 (3803)	769 (3796)	0.88 (0.79-0.97)	0.012*
Non-CV death (SH-AHS-0003, -0006, -0007)	195 (3803)	176 (3796)	1.08 (0.88-1.33)	0.452*
CV death (SH-AHS-0003, -0006)	521 (2289)	599 (2287)	0.84 (0.75-0.95)	0.005*
Non-CV death (SH-AHS-0003, -0006)	121 (2289)	109 (2287)	1.07 (0.83-1.39)	0.595*
CV death (SH-AHS-0003)	219 (1013)	252 (1015)	0.85 (0.71-1.02)	0.072*
Non-CV death (SH-AHS-0003)	46 (1013)	44 (1015)	1.01 (0.67-1.53)	0.948*
CV death (SH-AHS-0006)	302 (1276)	347 (1272)	0.84 (0.72-0.98)	0.029*
Non-CV death (SH-AHS-0006)	75 (1276)	65 (1272)	1.11 (0.80-1.55)	0.529*
CV death (SH-AHS-0007)	170 (1514)	170 (1509)	0.99 (0.80-1.22)	0.918*
Non-CV death (SH-AHS-0007)	74 (1514)	67 (1509)	1.10 (0.79-1.52)	0.589

Source: Tables S2, 28, 30 of the Sponsor's pooled clinical study report, Table 55 of the Sponsor's clinical study report of SH-AHS-0003, Table 54 of the Sponsor's clinical study report of SH-AHS-0006, and Table 88 of the Sponsor's clinical study report of SH-AHS-0007. The results were confirmed independently by this reviewer. Nominal P-values were from log-rank test and hazard ratios were from Cox regression model with treatment as the only independent variable. * Nominal P-values were from Cox regression model with treatment as the only independent variable.

Figures 1, 2 and 3 are the Kaplan-Meier estimates for time to the first CV death or CHF hospitalization for Studies SH-AHS-0003, SH-AHS-0006 and SH-AHS-0007, respectively. Figures 4 and 5 are the Kaplan-Meier estimates for time to all-cause mortality for three studies combined and two studies combined (SH-AHS-0003 and SH-AHS-0006), respectively. Figures

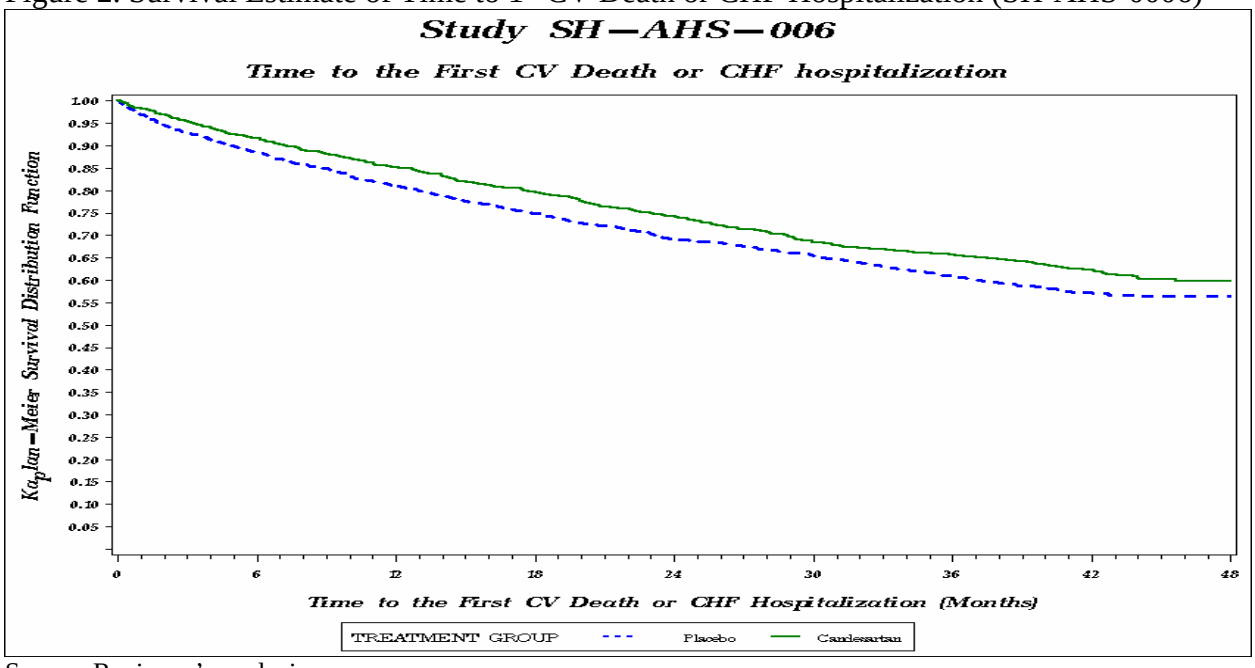
6 and 7 are the Kaplan-Meier estimates for CV and non-CV mortality when the two studies are combined (SH-AHS-0003 and SH-AHS-0006), respectively.

Figure 1. Survival Estimate of Time to 1st CV Death or CHF Hospitalization (SH-AHS-0003)



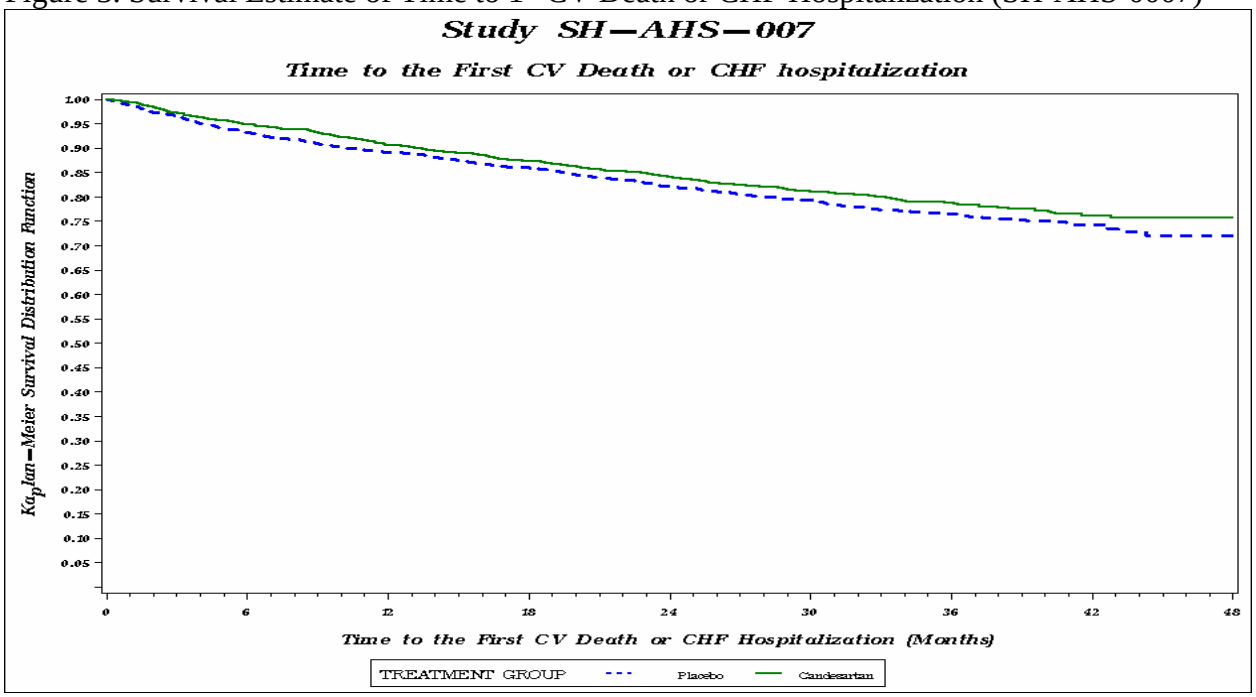
Source: Reviewer's analysis.

Figure 2. Survival Estimate of Time to 1st CV Death or CHF Hospitalization (SH-AHS-0006)



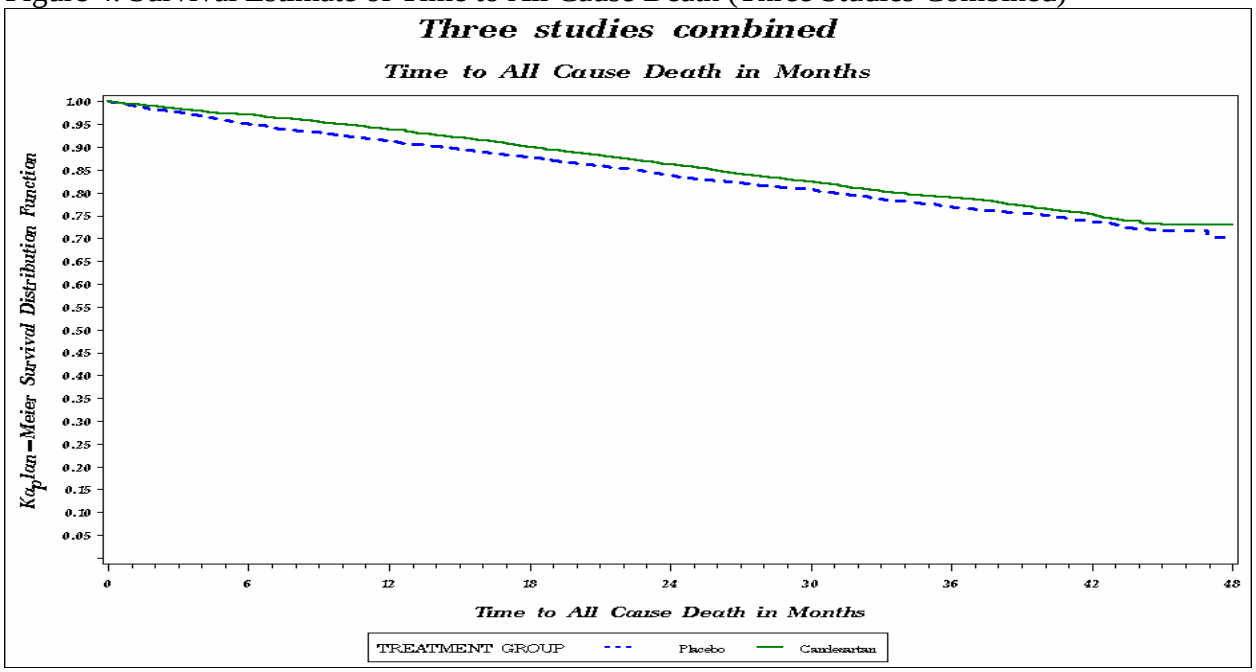
Source: Reviewer's analysis.

Figure 3. Survival Estimate of Time to 1st CV Death or CHF Hospitalization (SH-AHS-0007)



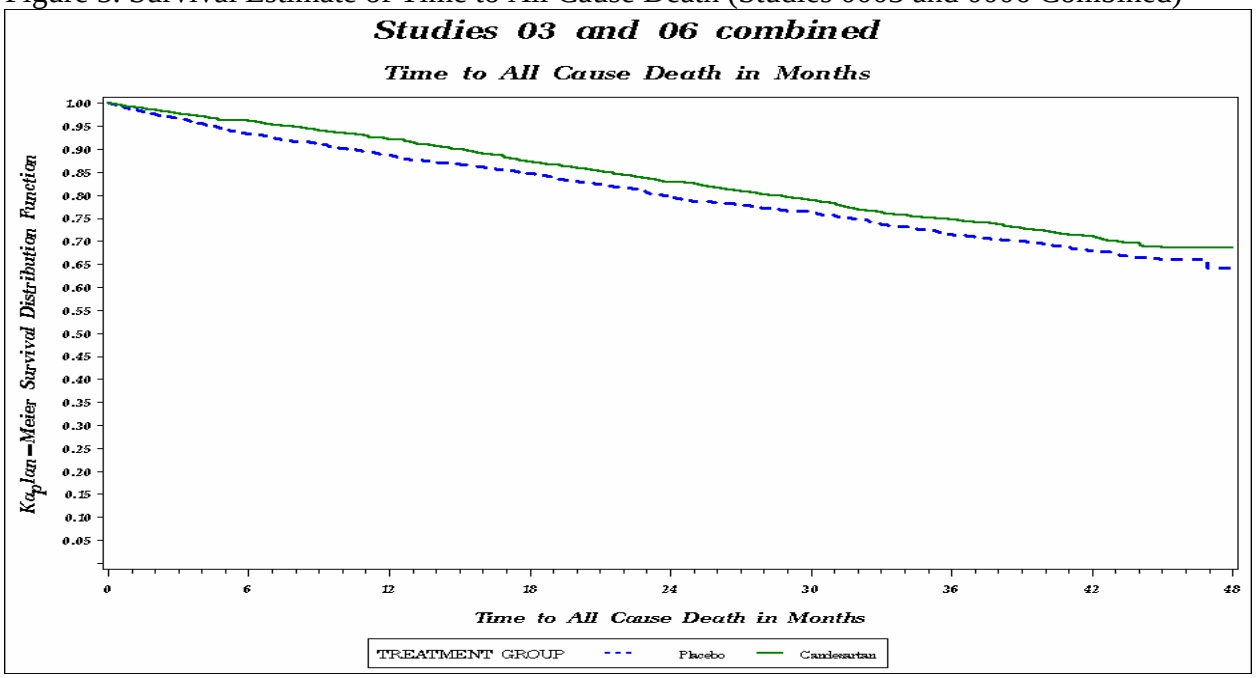
Source: Reviewer's Analysis.

Figure 4. Survival Estimate of Time to All Cause Death (Three Studies Combined)



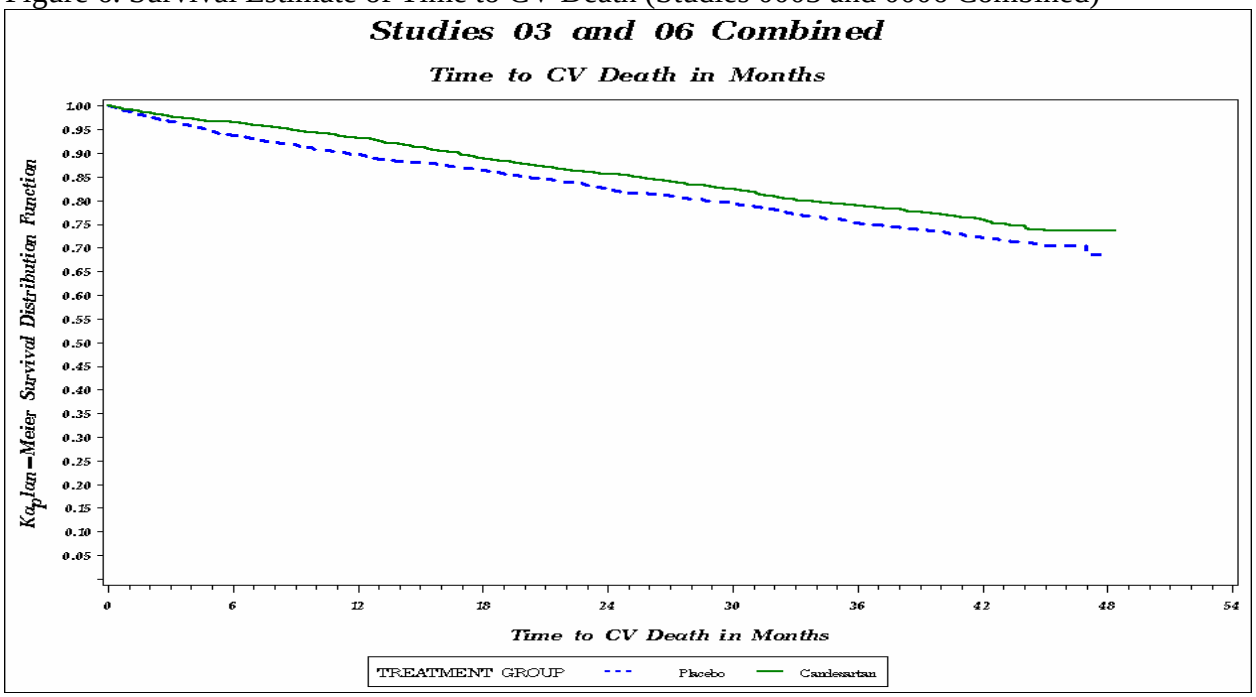
Source: Reviewer's Analysis.

Figure 5. Survival Estimate of Time to All Cause Death (Studies 0003 and 0006 Combined)



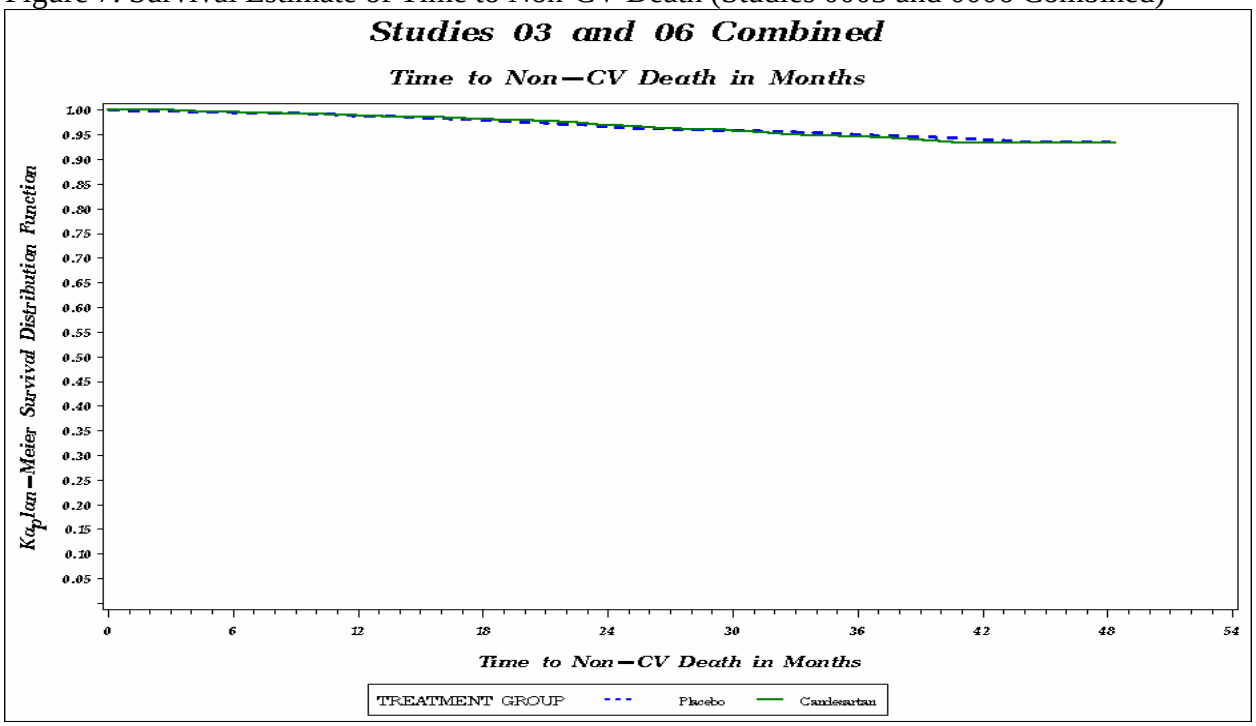
Source: Reviewer's Analysis.

Figure 6. Survival Estimate of Time to CV Death (Studies 0003 and 0006 Combined)



Source: Reviewer's Analysis.

Figure 7. Survival Estimate of Time to Non-CV Death (Studies 0003 and 0006 Combined)



Source: Reviewer's Analysis.

3.2 Evaluation of Safety

The most commonly reported adverse events (AE) are in Tables 9, 10, 11, 12 and 13 for Studies SH-AHS-0003, SH-AHS-0006, SH-AHS-0007, three studies combined and two studies combined (SH-AHS-0003 and SH-AHS-0006), respectively. The tables use a cut-off of 3% AEs in the total population during the study. It seemed that most of reported AEs are comparable among the two treatment groups. Among the AEs that occurred more in the Candesartan group during the study, Hypotension, Renal function abnormal/renal dysfunction aggravated occurred more in Candesartan group than Placebo group in each of the three studies, and Hyperkalaemia occurred more in Candesartan group than Placebo group in Studies SH-AHS-0003 and SH-AHS-0006.

Table 9. Most Commonly Reported AEs (SH-AHS-0003)

Preferred Term	**Placebo** on treatment (N = 1015) n %	**Candesartan** on treatment (N = 1013) n %	**Placebo** during study (N = 1015) n %	**Candesartan** during study (N = 1013) n %
Cardiac failure/cardiac failure aggravated	317 (31.2)	234 (23.1)	359 (35.4)	280 (27.6)
Hypotension	76 (7.5)	190 (18.8)	90 (8.9)	193 (19.1)
Angina pectoris/angina pectoris aggravated	110 (10.8)	105 (10.4)	120 (11.8)	127 (12.5)
Renal function abnormal/renal dysfunction aggravated	49 (4.8)	136 (13.4)	50 (4.9)	141 (13.9)

Preferred Term	**Placebo** on treatment (N = 1015) n %	**Candesartan** on treatment (N = 1013) n %	**Placebo** during study (N = 1015) n %	**Candesartan** during study (N = 1013) n %
Sudden death	85 (8.4)	65 (6.4)	106 (10.4)	80 (7.9)
Pneumonia	64 (6.3)	65 (6.4)	75 (7.4)	83 (8.2)
Myocardial infarction	58 (5.7)	71 (7.0)	68 (6.7)	85 (8.4)
Arrhythmia ventricular	64 (6.3)	58 (5.7)	79 (7.8)	73 (7.2)
Cerebrovascular disorder	55 (5.4)	41 (4.0)	61 (6.0)	52 (5.1)
Arrhythmia atrial	41 (4.0)	44 (4.3)	44 (4.3)	56 (5.5)
Fibrillation atrial	46 (4.5)	34 (3.4)	57 (5.6)	43 (4.2)
Chest pain	42 (4.1)	37 (3.7)	50 (4.9)	47 (4.6)
Coronary artery disorder	39 (3.8)	38 (3.8)	48 (4.7)	49 (4.8)
Tachycardia ventricular/arrhythmia	31 (3.1)	28 (2.8)	44 (4.3)	39 (3.8)
Cardiomyopathy	29 (2.9)	25 (2.5)	40 (3.9)	37 (3.7)
Tachycardia supraventricular	30 (3.0)	27 (2.7)	39 (3.8)	34 (3.4)
Hyperkalaemia	16 (1.6)	54 (5.3)	18 (1.8)	54 (5.3)
Dizziness/vertigo	21 (2.1)	43 (4.2)	23 (2.3)	45 (4.4)
Dyspnoea/dyspnoea (aggravated)	39 (3.8)	17 (1.7)	43 (4.2)	22 (2.2)
Syncope	28 (2.8)	26 (2.6)	35 (3.4)	30 (3.0)

Source: Table S4 of the Sponsor's clinical study report of study SH-AHS-0003.
On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 10. Most Commonly Reported AEs (SH-AHS-0006)

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

Preferred Term	**Placebo** on treatment (N = 1272) n %	**Candesartan** on treatment (N = 1276) n %	**Placebo** during study (N = 1272) n %	**Candesartan** during study (N = 1276) n %
Accident and/or injury	32 (2.5)	34 (2.7)	43 (3.4)	44 (3.4)
Diabetes mellitus/diabetes mellitus aggravated	41 (3.2)	30 (2.4)	42 (3.3)	37 (2.9)
Dehydration	18 (1.4)	40 (3.1)	22 (1.7)	55 (4.3)

Source: Table S4 of the Sponsor's clinical study report of study SH-AHS-0006.
On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 11. Most Commonly Reported AEs (SH-AHS-0007)

Preferred Term	**Placebo** on treatment (N = 1509) n %	**Candesartan** on treatment (N = 1514) n %	**Placebo** during study (N = 1509) n %	**Candesartan** during study (N = 1514) n %
Cardiac failure/cardiac failure aggravated	321 (21.3)	247 (16.3)	356 (23.6)	300 (19.8)
Angina pectoris/angina pectoris aggravated	198 (13.1)	182 (12.0)	217 (14.4)	213 (14.1)
Hypotension	120 (8.0)	236 (15.6)	125 (8.3)	247 (16.3)
Renal function abnormal/renal dysfunction aggravated	74 (4.9)	146 (9.6)	79 (5.2)	150 (9.9)
Pneumonia	91 (6.0)	78 (5.2)	116 (7.7)	102 (6.7)
Atrial fibrillation	103 (6.8)	79 (5.2)	119 (7.9)	93 (6.1)
Myocardial infarction	85 (5.6)	74 (4.9)	101 (6.7)	87 (5.7)
Coronary artery disorder	89 (5.9)	73 (4.8)	102 (6.8)	83 (5.5)
Cerebrovascular disorder	86 (5.7)	68 (4.5)	97 (6.4)	82 (5.4)
Chest pain	71 (4.7)	72 (4.8)	81 (5.4)	82 (5.4)
Tachycardia supraventricular	76 (5.0)	55 (3.6)	88 (5.8)	60 (4.0)
Arrhythmia atrial	73 (4.8)	53 (3.5)	82 (5.4)	64 (4.2)
Sudden death	57 (3.8)	55 (3.6)	68 (4.5)	68 (4.5)
Accident and/or injury	49 (3.2)	46 (3.0)	63 (4.2)	59 (3.9)
Dizziness/vertigo	51 (3.4)	62 (4.1)	52 (3.4)	66 (4.4)
Anaemia	35 (2.3)	46 (3.0)	47 (3.1)	63 (4.2)
Dyspnoea/dyspnoea (aggravated)	48 (3.2)	39 (2.6)	51 (3.4)	46 (3.0)

Source: Table S4 of the Sponsor's clinical study report of study SH-AHS-0007.
On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 12. Most Commonly Reported AEs (Three Studies Pooled)

Preferred Term	**Placebo** on treatment (N = 3796) n %	**Candesartan** on treatment (N = 3803) n %	**Placebo** during study (N = 3796) n %	**Candesartan** during study (N = 3803) n %
Cardiac failure/cardiac failure aggravated	1073 (28.3)	831 (21.9)	1187 (31.3)	1001 (26.3)
Hypotension	372 (9.8)	714 (18.8)	399 (10.5)	736 (19.4)
Angina pectoris/angina pectoris aggravated	461 (12.1)	414 (10.9)	506 (13.3)	490 (12.9)
Renal function abnormal/renal dysfunction aggravated	238 (6.3)	474 (12.5)	248 (6.5)	487 (12.8)
Sudden death	282 (7.4)	234 (6.2)	348 (9.2)	291 (7.7)
Pneumonia	243 (6.4)	200 (5.3)	299 (7.9)	261 (6.9)
Myocardial infarction	216 (5.7)	205 (5.4)	257 (6.8)	242 (6.4)
Atrial fibrillation	218 (5.7)	165 (4.3)	249 (6.6)	202 (5.3)
Arrhythmia ventricular	207 (5.5)	159 (4.2)	239 (6.3)	193 (5.1)

Preferred Term	**Placebo** on treatment (N = 3796) n %	**Candesartan** on treatment (N = 3803) n %	**Placebo** during study (N = 3796) n %	**Candesartan** during study (N = 3803) n %
Cerebrovascular disorder	189 (5.0)	164 (4.3)	216 (5.7)	203 (5.3)
Coronary artery disorder	170 (4.5)	169 (4.4)	200 (5.3)	205 (5.4)
Chest pain	177 (4.7)	154 (4.0)	202 (5.3)	183 (4.8)
Arrhythmia atrial	175 (4.6)	156 (4.1)	197 (5.2)	187 (4.9)
Hyperkalaemia	78 (2.1)	238 (6.3)	84 (2.2)	242 (6.4)
Tachycardia supraventricular	152 (4.0)	129 (3.4)	177 (4.7)	148 (3.9)
Dizziness/vertigo	107 (2.8)	154 (4.0)	115 (3.0)	168 (4.4)
Accident and/or injury	112 (3.0)	99 (2.6)	143 (3.8)	125 (3.3)
Tachycardia ventricular/arrhythmia/ arrhythmia aggravated	110 (2.9)	100 (2.6)	132 (3.5)	128 (3.4)
Syncope	105 (2.8)	121 (3.2)	119 (3.1)	139 (3.7)
Anaemia	87 (2.3)	110 (2.9)	110 (2.9)	145 (3.8)

Source: Table S4 of the Sponsor's clinical study report of pooled data.
On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

Table 13. Most Commonly Reported AEs (Studies SH-AHS-0003 and SH-AHS-0006 Combined)

Preferred Term	**Placebo** on treatment (N = 2287) n %	**Candesartan** on treatment (N = 2289) n %	**Placebo** during study (N = 2287) n %	**Candesartan** during study (N = 2289) n %
Cardiac failure/cardiac failure aggravated	752 (32.9)	584 (25.5)	831 (36.3)	701 (30.6)
Hypotension	252 (11.0)	478 (20.9)	274 (12.0)	489 (21.4)
Angina pectoris/angina pectoris aggravated	263 (11.5)	232 (10.1)	289 (12.6)	277 (12.1)
Renal function abnormal/renal dysfunction aggravated	164 (7.2)	328 (14.3)	169 (13.7)	143 (11.2)
Sudden death	225 (9.8)	179 (7.8)	280 (12.2)	223 (9.7)
Arrhythmia ventricular	171 (7.5)	136 (5.9)	200 (8.7)	161 (7.0)
Pneumonia	152 (6.6)	122 (5.3)	183 (8.0)	159 (6.9)
Myocardial infarction	131 (5.7)	131 (5.7)	156 (6.8)	155 (6.8)
Hyperkalaemia	60 (2.6)	175 (7.6)	64 (2.8)	177 (7.7)
Cerebrovascular disorder	103 (4.5)	96 (4.2)	119 (5.2)	121 (5.3)
Fibrillation atrial	115 (5.0)	86 (3.8)	130 (5.7)	109 (4.8)
Arrhythmia atrial	102 (4.5)	103 (4.5)	115 (5.0)	123 (5.4)
Chest pain	106 (4.6)	82 (3.6)	121 (5.3)	101 (4.4)
Coronary artery disorder	81 (3.5)	96 (4.2)	98 (4.3)	122 (5.3)
Tachycardia ventricular/arrhythmia/ arrhythmia aggravated	94 (4.1)	80 (3.5)	112 (4.9)	104 (4.5)
Tachycardia supraventricular	76 (3.3)	74 (3.2)	89 (3.9)	88 (3.8)
Cardiomyopathy	67 (2.9)	58 (2.5)	88 (3.8)	88 (3.8)
Syncope	73 (3.2)	75 (3.3)	84 (3.7)	89 (3.9)
Dizziness/vertigo	56 (2.4)	92 (4.0)	63 (2.8)	102 (4.5)
Pulmonary oedema	67 (2.9)	59 (2.6)	77 (3.4)	75 (3.3)
Accident and/or injury	63 (2.8)	53 (2.3)	80 (3.5)	66 (2.9)
Anaemia	52 (2.3)	64 (2.8)	63 (2.8)	82 (3.6)
Renal failure acute	41 (1.8)	69 (3.0)	57 (2.5)	85 (3.7)

Source: Table 146 of the Sponsor's clinical study report of study SH-AHS-pooled.
On treatment = on treatment with investigational product; During study = total study period, irrespective of treatment with investigational product or not.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Subgroup analysis of the primary endpoint was performed by age, gender and ethnic group. For the analysis of time to CV death or CHF hospitalization, the results are presented in Tables 14, 15, 16 and 17 for Studies SH-AHS-0003, SH-AHS-0006, SH-AHS-0007 and three studies combined, respectively. For the analysis of all-cause mortality, the results are in Tables 18 and 19 for three studies combined and two studies (SH-AHS-0003 and SH-AHS-0006) combined, respectively.

For the time to CV death or CHF hospitalization, the hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the oriental, South Asian, Arab/Middle East subgroups in each of the three studies, and for blacks in Study SH-AHS-0007. The sample sizes were small in these subgroups, and the nominal p-values were larger than 0.05 except for the oriental group in Study SH-AHS-0007. The hazard ratio was 3.73 with a nominal p-value = 0.026 in the oriental subgroup of Study SH-AHS-0007 (Table 16 and Figure 8), and the hazard ratios were bigger than 1 in the oriental subgroup in the other two studies with the nominal p-values larger than 0.05. The hazard ratio was 2.14 with a nominal p-value = 0.012 in the oriental subgroup when the three studies were combined (Table 17).

For all-cause mortality, the hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the oriental, Arab/Middle East subgroups in the three studies combined and two studies combined (SH-AHS-0003 and SH-AHS-0006). Again, the sample sizes were small in these subgroups and the nominal p-values were larger than 0.05.

Table 14. Subgroup Analysis of Time to CV Death or CHF Hospitalization (SH-AHS-0003)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	804	120	116	0.973 (0.754, 1.256)	0.833
	>= 65 -< 75	752	123	165	0.711 (0.563, 0.898)	0.004
	>= 75	472	91	125	0.647 (0.494, 0.848)	0.002
Age (Years)	< 75	1556	243	281	0.818 (0.689, 0.971)	0.022
	>= 75	472	91	125	0.647 (0.494, 0.848)	0.002
Sex	Male	1382	231	285	0.750 (0.630, 0.892)	0.001
	Female	646	103	121	0.813 (0.625, 1.057)	0.122
Ethnic Group	European	1796	286	354	0.750 (0.642, 0.877)	<0.001
	Black	73	6	19	0.450 (0.179, 1.127)	0.088
	South Asian	37	14	9	1.211 (0.523, 2.803)	0.655
	Arab/Middle East	15	3	2	1.142 (0.191, 6.850)	0.884
	Oriental	56	14	9	1.672 (0.721, 3.875)	0.231
	Malay	24	7	6	0.850 (0.285, 2.533)	0.770
	Other	27	4	7	0.277 (0.081, 0.953)	0.042
Region	Western Europe	924	146	173	0.787 (0.632, 0.981)	0.033
	Eastern Europe	198	32	44	0.733 (0.465, 1.157)	0.182

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
	North America (US and Canada)	677	114	141	0.765 (0.598, 0.979)	0.034
	USA	470	82	99	0.811 (0.605, 1.087)	0.162
	Asia	73	24	16	1.168 (0.620, 2.201)	0.631
	Russia	53	5	9	0.552 (0.185, 1.649)	0.287
	Other	103	13	23	0.457 (0.231, 0.902)	0.024
NYHA	II	966	115	147	0.720 (0.564, 0.920)	0.008
	III	989	195	234	0.790 (0.653, 0.955)	0.015
	IV	73	24	25	0.817 (0.465, 1.436)	0.483
LVEF	< 0.25	453	110	118	0.756 (0.583, 0.981)	0.035
	>= 0.25	1574	224	288	0.750 (0.630, 0.894)	0.001

Source: Table 107 of the Sponsor's clinical study report of study SH-AHS-0003, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Table 15. Subgroup Analysis of Time to CV Death or CHF Hospitalization (SH-AHS-0006)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	1268	192	211	0.879 (0.723, 1.069)	0.197
	>= 65 -< 75	823	176	193	0.782 (0.637, 0.959)	0.018
	>= 75	457	115	134	0.945 (0.736, 1.212)	0.654
Age (Years)	< 75	2091	368	404	0.842 (0.732, 0.970)	0.017
	>= 75	457	115	134	0.945 (0.736, 1.212)	0.654
Sex	Male	2006	387	427	0.862 (0.752, 0.990)	0.035
	Female	542	96	111	0.815 (0.620, 1.072)	0.143
Ethnic Group	European	2307	427	490	0.845 (0.742, 0.962)	0.011
	Black	127	24	29	0.655 (0.381, 1.126)	0.126
	South Asian	27	11	4	1.264 (0.400, 3.998)	0.690
	Arab/Middle East	12	3	0		
	Oriental	35	10	4	1.804 (0.564, 5.768)	0.320
	Malay	18	5	3	1.104 (0.263, 4.636)	0.892
	Other	22	3	8	0.573 (0.152, 2.165)	0.412
Region	Western Europe	1193	194	255	0.739 (0.613, 0.891)	0.002
	Eastern Europe	219	41	43	0.825 (0.538, 1.266)	0.378
	North America (US and Canada)	954	205	204	0.984 (0.811, 1.194)	0.870
	USA	597	128	128	1.019 (0.798, 1.303)	0.877
	Asia	59	19	8	1.282 (0.561, 2.930)	0.556
	Russia	15	2	5	0.787 (0.152, 4.073)	0.775
	Other	108	22	23	0.800 (0.446, 1.435)	0.454
ACE at baseline	Recommended Dose	1291	232	275	0.794 (0.666, 0.945)	0.010
	Not Recommended Dose	1257	251	263	0.915 (0.770, 1.088)	0.314
ACE During Study	Recommended Dose	1535	270	330	0.810 (0.689, 0.951)	0.010
	Not Recommended Dose	1012	213	208	0.910 (0.751, 1.101)	0.331
NYHA	II	614	93	104	0.841 (0.636, 1.112)	0.225
	III	1856	367	399	0.868 (0.753, 1.000)	0.051

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
	IV	78	23	35	0.847 (0.500, 1.435)	0.536
LVEF	< 0.25	770	186	203	0.851 (0.698, 1.039)	0.113
	>= 0.25	1778	297	335	0.849 (0.726, 0.993)	0.040

Source: Table 102 of the Sponsor's clinical study report of study SH-AHS-0006, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Table 16. Subgroup Analysis of Time to CV Death or CHF Hospitalization (SH-AHS-0007)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	1184	72	86	0.901 (0.659, 1.232)	0.513
	>= 65 -< 75	1032	117	118	0.901 (0.698, 1.164)	0.424
	>= 75	807	144	162	0.815 (0.651, 1.020)	0.074
Age (Years)	< 75	2216	189	204	0.923 (0.757, 1.125)	0.429
	>= 75	807	144	162	0.815 (0.651, 1.020)	0.074
Sex	Male	1811	195	205	0.909 (0.747, 1.106)	0.341
	Female	1212	138	161	0.867 (0.691, 1.089)	0.220
Ethnic Group	European	2767	289	336	0.845 (0.722, 0.989)	0.036
	Black	126	16	11	1.203 (0.558, 2.592)	0.637
	South Asian	29	6	2	2.263 (0.456, 11.242)	0.318
	Arab/Middle East	10	2	2	1.291 (0.180, 9.240)	0.799
	Oriental	42	10	4	3.730 (1.166, 11.928)	0.026
	Malay	22	5	5	0.508 (0.147, 1.757)	0.285
	Other	27	5	6	0.836 (0.255, 2.744)	0.768
Region	Western Europe	1377	125	143	0.872 (0.686, 1.108)	0.262
	Eastern Europe	196	18	12	1.388 (0.669, 2.882)	0.379
	North America (US and Canada)	1112	142	167	0.827 (0.661, 1.034)	0.096
	USA	734	95	105	0.853 (0.646, 1.126)	0.261
	Asia	70	17	9	1.555 (0.693, 3.494)	0.285
	Russia	132	9	10	0.816 (0.331, 2.008)	0.658
	Other	136	22	25	0.889 (0.501, 1.578)	0.689
ACE at baseline	Recommended Dose	306	43	41	0.855 (0.557, 1.311)	0.473
	Not Recommended Dose	2717	290	325	0.887 (0.757, 1.039)	0.137
ACE During Study	Recommended Dose	519	63	79	0.810 (0.582, 1.129)	0.213
	Not Recommended Dose	496	70	82	0.882 (0.641, 1.214)	0.441
NYHA	II	1836	151	164	0.883 (0.708, 1.101)	0.269
	III	1140	166	195	0.870 (0.707, 1.070)	0.188
	IV	47	16	7	1.602 (0.657, 3.905)	0.300
LVEF	< 0.50	1072	106	131	0.778 (0.602, 1.005)	0.055
	>= 0.50	1951	227	235	0.951 (0.793, 1.142)	0.592

Source: Table 102 of the Sponsor's clinical study report of study SH-AHS-0007, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Table 17. Subgroup Analysis of Time to CV Death or CHF Hospitalization (Pooled)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
All	All	7599	1150	1310	0.836 (0.772, 0.905)	<0.001

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	3256	384	413	0.910 (0.792, 1.046)	0.185
	>= 65 -< 75	2607	416	476	0.787 (0.690, 0.898)	<0.001
	>= 75	1736	350	421	0.802 (0.696, 0.924)	0.002
Age (Years)	< 75	5863	800	889	0.853 (0.775, 0.938)	0.001
	>= 75	1736	350	421	0.802 (0.696, 0.924)	0.002
Sex	Male	5199	813	917	0.837 (0.762, 0.920)	<0.001
	Female	2400	337	393	0.835 (0.722, 0.966)	0.015
Ethnic Group	European	6870	1002	1180	0.816 (0.750, 0.888)	<0.001
	Black	326	46	59	0.714 (0.484, 1.054)	0.090
	South Asian	93	31	15	1.362 (0.731, 2.538)	0.330
	Arab/Middle East	37	8	4	1.724 (0.511, 5.821)	0.380
	Oriental	133	34	17	2.135 (1.185, 3.845)	0.012
	Malay	64	17	14	0.769 (0.378, 1.566)	0.469
	Other	76	12	21	0.504 (0.243, 1.046)	0.066
Region	Western Europe	3494	465	571	0.787 (0.696, 0.889)	<0.001
	Eastern Europe	613	91	99	0.854 (0.643, 1.136)	0.279
	North America (US and Canada)	2743	461	512	0.872 (0.769, 0.989)	0.033
	USA	1801	305	332	0.904 (0.773, 1.056)	0.201
	Asia	202	60	33	1.299 (0.848, 1.991)	0.230
	Russia	200	16	24	0.707 (0.374, 1.340)	0.288
	Other	347	57	71	0.712 (0.502, 1.010)	0.057
NYHA	II	3416	359	415	0.814 (0.707, 0.938)	0.004
	III	3985	728	828	0.846 (0.766, 0.935)	0.001
	IV	198	63	67	0.930 (0.656, 1.317)	0.682
LVEF	< 0.50	5645	923	1075	0.813 (0.744, 0.887)	<0.001
	>= 0.50	1953	227	235	0.951 (0.793, 1.142)	0.592

Source: Table 12.1.9.4.40 of the Sponsor's clinical study report, Appendix 12.1.3, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Table 18. Subgroup Analysis of All-Cause Mortality (Three Studies Pooled)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	3256	233	266	0.858 (0.719, 1.022)	0.087
	>= 65 -< 75	2607	348	330	0.984 (0.847, 1.144)	0.837
	>= 75	1736	305	349	0.887 (0.761, 1.035)	0.127
Age (Years)	< 75	5863	581	596	0.939 (0.838, 1.053)	0.282
	>= 75	1736	305	349	0.887 (0.761, 1.035)	0.127
Sex	Male	5199	638	678	0.911 (0.817, 1.015)	0.090
	Female	2400	248	267	0.924 (0.778, 1.099)	0.373
Ethnic Group	European	6870	790	856	0.914 (0.829, 1.006)	0.067
	Black	326	27	30	0.889 (0.527, 1.499)	0.658
	South Asian	93	18	14	0.659 (0.325, 1.338)	0.249
	Arab/Middle East	37	5	2	1.786 (0.340, 9.369)	0.493
	Oriental	133	24	13	1.619 (0.819, 3.199)	0.166
	Malay	64	16	14	0.729 (0.355, 1.499)	0.390
	Other	76	6	16	0.315 (0.121, 0.820)	0.018

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Region	Western Europe	3494	405	440	0.917 (0.801, 1.049)	0.207
	Eastern Europe	613	70	79	0.847 (0.614, 1.169)	0.313
	North America (US and Canada)	2743	306	330	0.919 (0.786, 1.073)	0.284
	USA	1801	199	215	0.927 (0.764, 1.124)	0.442
	Asia	202	44	31	0.898 (0.566, 1.425)	0.648
	Russia	200	16	13	1.470 (0.700, 3.089)	0.309
	Other	347	45	52	0.760 (0.509, 1.133)	0.178
NYHA	II	3416	281	282	0.961 (0.815, 1.134)	0.637
	III	3985	553	611	0.890 (0.793, 0.999)	0.047
	IV	198	52	52	1.037 (0.703, 1.528)	0.856
LVEF	< 0.25	1223	225	261	0.781 (0.653, 0.934)	0.007
	>= 0.25	6375	660	684	0.956 (0.859, 1.064)	0.410

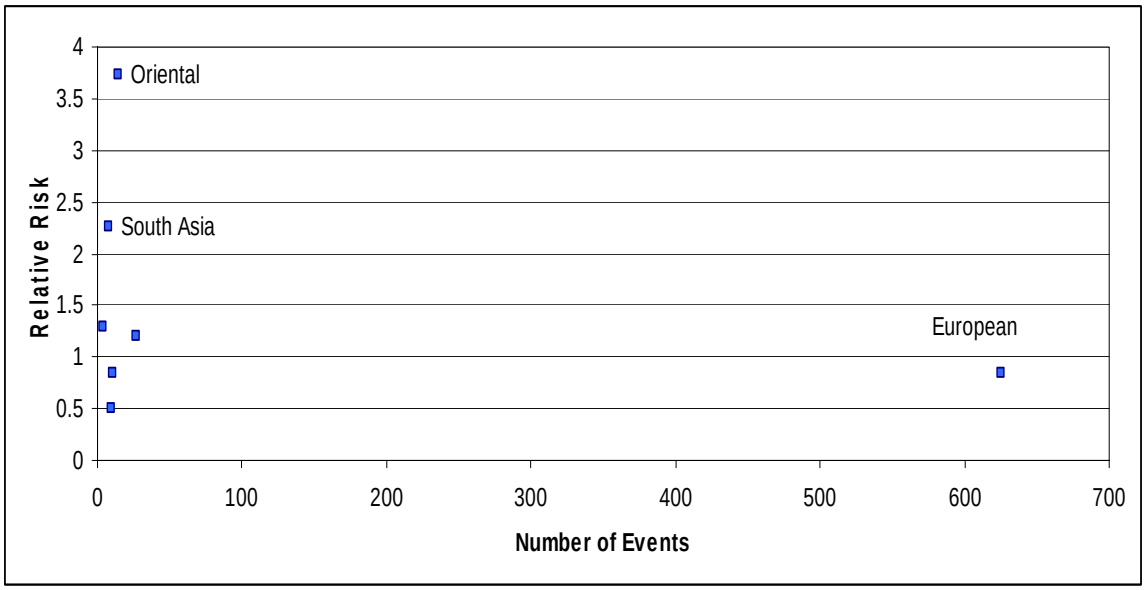
Source: Table 12.1.9.4.49 of the Sponsor's clinical study report, Appendix 12.1.3, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Table 19. Subgroup Analysis of All-Cause Mortality (SH-AHS-0003 and -0006 Pooled)

Variable	Group	Total N	Candesartan # of events	Placebo # of Events	Hazard Ratio (95% CI)	P-value
Age(Years)	< 65	2072	198	223	0.853 (0.705, 1.033)	0.105
	>= 65 -< 75	1575	253	259	0.916 (0.770, 1.089)	0.320
	>= 75	929	191	226	0.894 (0.737, 1.084)	0.255
Age (Years)	< 75	3647	451	482	0.892 (0.784, 1.014)	0.080
	>= 75	929	191	226	0.894 (0.737, 1.084)	0.255
Sex	Male	3388	494	541	0.884 (0.783, 0.999)	0.048
	Female	1188	148	167	0.864 (0.692, 1.078)	0.195
Ethnic Group	European	4103	575	637	0.890 (0.795, 0.996)	0.042
	Black	200	18	27	0.683 (0.375, 1.244)	0.213
	South Asian	64	14	12	0.578 (0.265, 1.264)	0.170
	Arab/Middle East	27	4	1	2.330 (0.260, 20.886)	0.450
	Oriental	91	17	10	1.298 (0.592, 2.848)	0.515
	Malay	42	11	9	0.866 (0.358, 2.095)	0.750
	Other	49	3	12	0.193 (0.053, 0.704)	0.013
Region	Western Europe	2117	299	330	0.900 (0.769, 1.052)	0.186
	Eastern Europe	417	56	72	0.747 (0.527, 1.060)	0.103
	North America (US and Canada)	1631	221	238	0.916 (0.763, 1.100)	0.348
	USA	1067	147	153	0.979 (0.780, 1.227)	0.852
	Asia	132	30	22	0.796 (0.458, 1.382)	0.418
	Russia	68	7	8	1.319 (0.472, 3.685)	0.597
	Other	211	29	38	0.621 (0.383, 1.008)	0.054
NYHA	II	1580	158	171	0.888 (0.715, 1.103)	0.283
	III	2845	442	490	0.874 (0.769, 0.994)	0.041
	IV	151	42	47	0.989 (0.650, 1.503)	0.957
LVEF	< 0.25	1223	225	261	0.781 (0.653, 0.934)	0.007
	>= 0.25	3352	416	447	0.923 (0.807, 1.054)	0.237

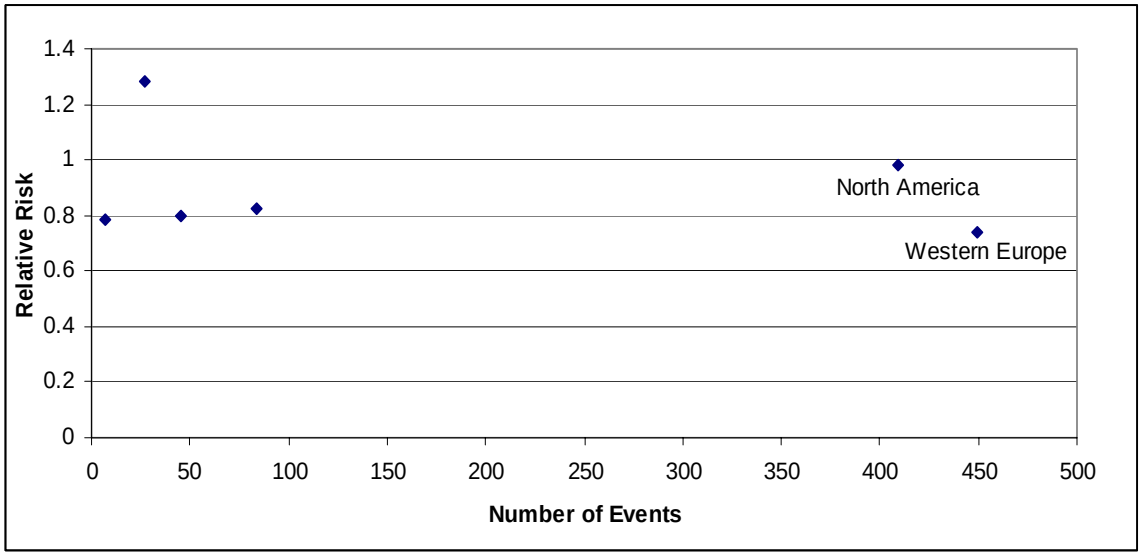
Source: Table 12.1.9.4.135 of the Sponsor's clinical study report, Appendix 12.1.3, independently confirmed by this reviewer. The nominal P-value, hazard ratio and CI were from Cox regression model.

Figure 8. Time to CV Death or CHF Hospitalization by Ethnicity (Study SH-AHS-0007)



Source: Reviewer's analysis.

Figure 9. Time to CV Death or CHF Hospitalization by Region (Study SH-AHS-0006)



Source: Reviewer's analysis.

4.2 Other Subgroup Populations

The results of subgroup analysis of the primary endpoint by region, classification of NYHA and LVEF are presented in Tables 14 - 19. For time to CV death or CHF hospitalization, the hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the Asia subgroup in each of the three studies, the USA subgroup in Study SH-AHS-0006 and Eastern Europe in Study SH-AHS-0007. The sample sizes were small in Asia and Eastern Europe. The estimate of the hazard ratio was 1.02 in the USA subgroup (0.98 in North America) in Study SH-AHS-0006 (Table 15), which seemed not to be consistent with the overall results. However, as Figure 9 indicates, North America does not deviate from other regions dramatically in Study SH-AHS-0006. In the other two studies, the results in the USA were quite consistent with the overall results. When the three studies were combined, the hazard ratio in the USA group was consistent with the overall results (Table 17).

For all-cause mortality, the hazard ratios were less than 1 (in favor of Candesartan) in all the subgroups except for the Russia subgroup in the three studies combined and two studies combined (SH-AHS-0003 and SH-AHS-0006). Again, the sample sizes were small in the subgroups and the nominal p-values were larger than 0.05.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In Study SH-AHS-0003 (Alternative), the primary endpoint, time to the first CV death or CHF hospitalization, achieved statistical significance ($P < 0.001$) with a relative risk reduction of 23% over placebo. It seemed that both CV death and CHF hospitalization contributed the benefits. The two secondary endpoints, time to the all-cause mortality or CHF hospitalization and time to CV death or CHF hospitalization or non-fatal MI, also achieved statistical significance with 20% ($P = 0.001$) and 22% ($P < 0.001$) relative risk reductions, respectively.

Studies SH-AHS-0006 (Added) and SH-AHS-0007 (Preserved) have the same primary and secondary endpoints as Study SH-AHS-0003. In Study SH-AHS-0006, the primary endpoint achieved statistical significance with a relative risk reduction of 15% ($P = 0.011$). The two secondary endpoints also achieved statistical significance. A separate review was completed earlier for Study SH-AHS-0006 since it was granted with priority review status.

In Study SH-AHS-0007, the primary endpoint did not achieve statistical significance, with a p-value = 0.12 and a relative risk reduction of 11%. The two secondary endpoints did not achieve statistical significance either, with both p-values larger than 0.12.

For the combined studies, the primary endpoint was the time to all-cause mortality for the three studies combined, and the secondary endpoint was time to all-cause mortality for the two studies combined (SH-AHS-0003 and SH-AHS-0006). The primary endpoint did not, but was close to, achieve statistical significance with a p-value = 0.055 and a 9% relative risk reduction. This p-value should be compared with 0.049 to account for the alpha adjustment due to the six interim analyses of the all-cause mortality. The secondary endpoint had a 12% relative risk reduction with a nominal p-value = 0.018. The results of the primary and secondary endpoints were primarily driven by the CV deaths in Studies SH-AHS-0003 and SH-AHS-0006. Strictly speaking, it can't be declared that the secondary endpoint achieved statistical significance based on the pre-specified hierarchical test sequence. However, Candesartan probably significantly reduced the risk of CV mortality in the patient populations in Studies SH-AHS-0003 and SH-AHS-0006 based on the following reasons. Candesartan had no effect in CV death or non-CV death in Study SH-AHS-0007 (the relative risks were 0.99 (P = 0.92) and 1.10 (P = 0.59) for CV deaths and non-CV deaths, respectively), but it had relative risk reductions of 15% (P = 0.072) and 16% (P = 0.029) in CV death in Studies SH-AHS-0003 and SH-AHS-0006, respectively. The relative risk reductions were very consistent in the two studies, and the nominal p-value was less than 0.05 in Study SH-AHS-006. The nominal p-value was bigger than 0.05 in Study SH-AHS-003, the reason might be that the number of events was much smaller in this study. When the two studies were combined, the relative risk reduction was 16% in CV mortality with a nominal p-value = 0.005. No effects were observed for non-CV deaths in the two studies (the relative risks were 1.01 (P = 0.95) and 1.11 (P = 0.53) in Studies SH-AHS-0003 and SH-AHS-0006, respectively).

Six interim analyses were conducted on all-cause mortality and it is not clear how these analyses would affect the Type I error rate for the primary endpoint of each individual study (time to CV death or CHF hospitalization). However, since the allocated Type I error rates were very small for the interim analyses, the effect should be small.

In the subgroup analysis of time to CV death or CHF hospitalization, the hazard ratio was 3.73 with a nominal p-value = 0.026 in the oriental subgroup of Study SH-AHS-0007, and the hazard ratios were bigger than 1 in the oriental subgroup in the other two studies. The hazard ratio was 2.14 with a nominal p-value = 0.012 in the oriental subgroup when the three studies were combined (Table 17).

5.2 Conclusions and Recommendations

Candesartan significantly reduced the risk of CV death or CHF hospitalization in patients with depressed LV systolic function and EF < 40% treated with or without an ACE inhibitor. Candesartan also significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI in the same patient population. In patients with preserved LV systolic function and EF > 40%, Candesartan failed to show that it significantly reduced the risk of CV death or CHF hospitalization. It did not show that

Candesartan significantly reduced the risk of all-cause death or CHF hospitalization, and the risk of CV death or CHF hospitalization or non-fatal MI.

In the oriental subgroup, it was not clear that Candesartan reduced the risk of CV death or CHF hospitalization in patients with depressed or preserved LV systolic function.

Candesartan probably significantly reduced the risk of CV mortality in patients with depressed LV systolic function and EF <= 40% treated with or without an ACE inhibitor. It failed to show that it significantly reduced the risk of all-cause or CV mortality in patients with preserved LV systolic function and EF > 40%.