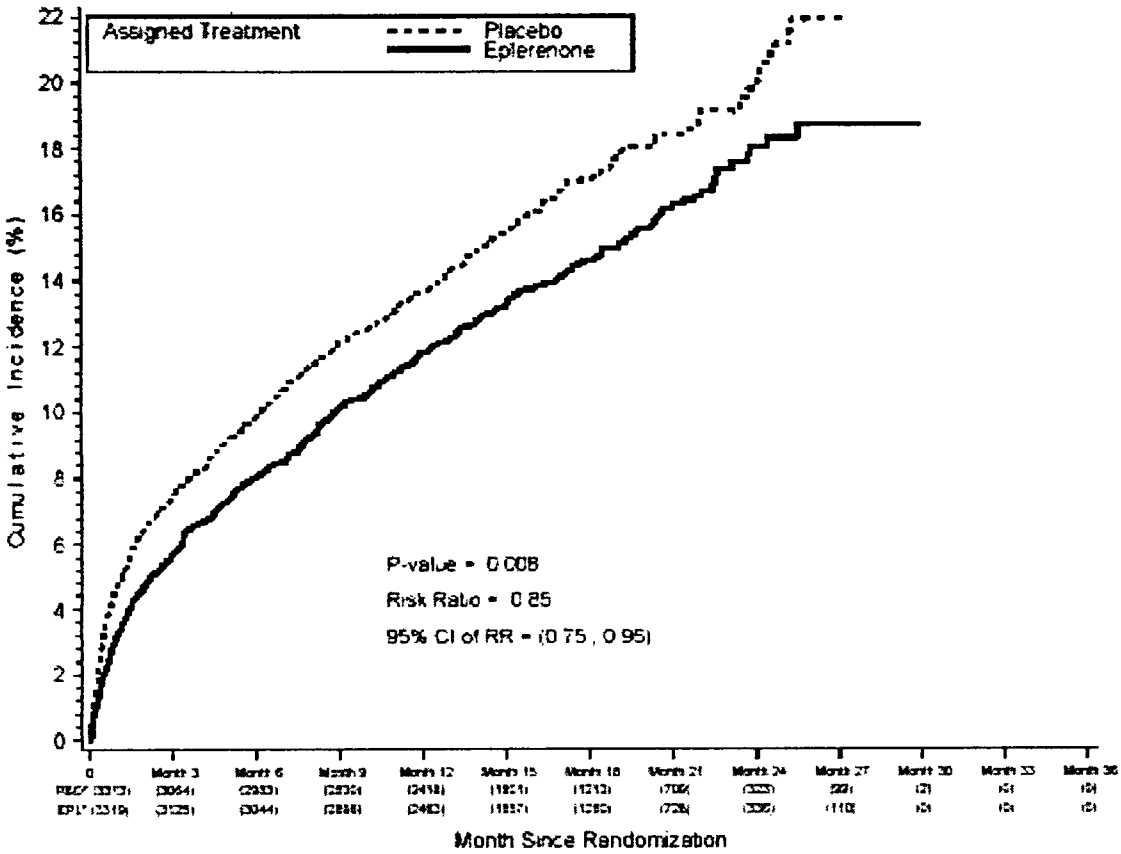

*: Number of Patients at risk

Figure 8: Sponsor's Cumulative Mortality in EPHESUS

The sponsor's analyses use stratification by region. Without this stratification the p-value for the reduction in all-cause mortality is 0.007 and the risk ratio and its confidence intervals remain the same.

The mortality differential is particularly impressive in the first 30 days as shown in the following table.

Table 24: Reviewer's Deaths Within and After 30 Days in EPHESUS

Days	Placebo		Eplerenone		Diff	RR
≤30	158	4.8%	107	3.2%	51	0.68
>30	396	12.6%	371	11.6%	25	0.92

Diff = difference in numbers of deaths; RR = relative risk of death

Two-thirds of the difference in deaths occurred within the first 30 days. There was still a mortality benefit of eplerenone beyond 30 days.

The sponsor's definition of CV hospitalization (progression of HF, MI, stroke, or ventricular arrhythmias) is peculiar and was established very late, shortly before trial completion. If one includes all CV hospitalizations coded by the sponsor (see COMMENT below regarding sponsor's "non-events" that include other CV hospitalizations), then eplerenone remains favorable regarding the combined endpoint of CV mortality and CV hospitalizations (logrank p = 0.028) but the p value exceeds the sponsor's allocated α of 0.01. Furthermore, this combined endpoint is difficult to interpret because eplerenone reduces all cause mortality and CV mortality. While about 83% of the first events for this endpoint are CV hospitalizations, CV deaths constitute about 76% of the difference in numbers of events. The median time to event for CV hospitalizations is shorter for eplerenone (61 days) than for placebo (70 days).

The more meaningful endpoint is all cause hospitalization. The original protocol defined a secondary objective of combined all cause mortality and all cause hospitalizations. For this endpoint, the difference in times to endpoint between eplerenone and placebo is not statistically significant (logrank p = 0.0511). This combined endpoint is also largely determined by the differences in mortality rates between the two groups—there is only a small difference in the rates of any hospitalization (46% of placebo patients and 45% of eplerenone patients.) The rates of patients dying or hospitalized in EPHESUS are summarized in the table below.

Table 25: Reviewer's Rates of Patients Dying or Hospitalized in EPHESUS

Event	Eplerenone n (%)	Placebo n (%)
CV death or CV hospitalization*	1516 (45.7)	1610 (48.6)
CV death†	407 (12.3)	483 (14.6)
CV hospitalization†	1281 (38.6)	1307 (39.5)
All cause death or hospitalization*	1734 (52.2)	1833 (55.3)
Death†	478 (14.4)	554 (16.7)
Hospitalization†	1497 (45.1)	1530 (46.2)

*First event; †Any event

COMMENT: The effect of eplerenone on survival in HF post-MI appears to be both early and sustained. The early benefit is hard to attribute to an improvement in pumping efficiency—One wonders whether it is related to reduced arrhythmia deaths or sudden deaths related to eplerenone's effect upon potassium levels. Note the tabulations of causes of CV death in the next section.

Whether there is a benefit of eplerenone on reducing hospitalizations is less clear. While there is improvement in the combined endpoint of CV mortality and CV hospitalizations with eplerenone, the difference is not statistically significant by the sponsor's allocation of α nor statistically extreme, the difference in the combined endpoint of all cause mortality and all cause hospitalizations is not significant, and mortality difference is the major contributor to these combined endpoints. See also the variations in hospitalization rates by region and gender in Section 3.4.2.3.1.2 below.

My analysis of all hospitalizations includes CV procedures within 14 days of the index MI and those reported by the investigators but adjudicated by the CEC as "non-events". The original CEC charter did not define non-events, but the CEC minutes from August 25, 2000, state the following:

"A MI occurring within 28 days of a previous MI is NOT a new event.

"Coronary Angiography will be categorized as 'Other Cardiovascular, Other, specify' – Angiography.

A 'Non Event' is described as a hospitalization for 'social reasons', 'check-ups', 'physiological testing', 'respite care', etc."

The CEC adjudicated 237, or 3.6% of reported hospitalizations as non-events, with slightly more—17—in the eplerenone group. I checked the coding of a small sample of "non-events". Most were hospitalizations for coronary angiography or other CV catheterizations. Some were one-day hospitalizations. I do not see justification for excluding these events from the category of all hospitalizations. If "non-events" are excluded, the p value for time to first event for all cause mortality and hospitalizations improves to 0.0228.

3.4.2.2. Secondary Endpoints

3.4.2.2.1. CV Mortality and Mortality Causes

A summary of the causes of death, including CV and non-CV deaths, is shown in the following table.

Table 26: Sponsor's Summary of Events Contributing to Mortality in EPHESUS

	Placebo N=3313		Eplerenone 25-50 mg QD N=3319		p-value†	Risk Ratio‡	95% CI for Risk Ratio‡
Deaths - all causes	554	(16.7%)	478	(14.4%)	0.008	0.85	(0.75, 0.96)
CV death	483	(14.6%)	407	(12.3%)	0.005	0.83	(0.72, 0.94)
Sudden cardiac death	201	(6.1%)	162	(4.9%)	0.025	0.79	(0.64, 0.97)
Recurrent AMI	94	(2.8%)	78	(2.4%)	0.187	0.82	(0.61, 1.10)
HF	127	(3.8%)	104	(3.1%)	0.096	0.80	(0.62, 1.04)
Stroke	28	(0.8%)	26	(0.8%)	0.734	0.91	(0.53, 1.55)
Aneurysm	1	(0.0%)	1	(0.0%)	0.988	0.98	(0.06, 15.64)
Pulmonary embolism	4	(0.1%)	4	(0.1%)	0.977	0.98	(0.25, 3.92)
Other CV death	28	(0.8%)	32	(1.0%)	0.672	1.12	(0.67, 1.85)
Non-CV death	54	(1.6%)	60	(1.8%)	0.644	1.09	(0.75, 1.58)
Sepsis	7	(0.2%)	9	(0.3%)	0.657	1.25	(0.47, 3.36)
Pneumonia	8	(0.2%)	10	(0.3%)	0.675	1.22	(0.48, 3.09)
Cancer	19	(0.6%)	20	(0.6%)	0.918	1.03	(0.55, 1.94)
Other non-CV death	20	(0.6%)	21	(0.6%)	0.909	1.04	(0.56, 1.91)
Unwitnessed death#	1	(0.0%)	0				
Unknown cause of death	16	(0.5%)	11	(0.3%)	0.314	0.68	(0.31, 1.46)

Source: Tables T7.1, T8.1, and T8.5

† From a log-rank test for equality of time-to-event distribution stratified by region

‡ Based on a proportional hazards model including treatment as the only factor stratified by region. 95% confidence interval is based on the Wald test.

If patient was not seen for more than 72 hours by anyone. Too few events for calculating risk ratio, p-value, and 95% confidence interval

COMMENT: Note that CV deaths were significantly lower in the eplerenone group. Sudden cardiac deaths, the largest category of CV deaths, were significantly reduced. Deaths due to HF and recurrent MI were also reduced and the risk ratios for sudden death, HF death, and recurrent MI are similar.

3.4.2.2.2. Myocardial Infarction

Recurrent MI (fatal or non-fatal) was slightly but not significantly lower in the eplerenone group (8.8%) compared to the placebo group (9.4%). The composite endpoint of CV mortality and nonfatal MI was significantly lower in the eplerenone group (p = 0.009, risk ratio 0.86).

3.4.2.2.3. New Diagnosis of Atrial Fibrillation/Flutter

New diagnosis of atrial fibrillation/flutter was slightly but not significantly lower in the eplerenone group (2.6%) compared to the placebo group (3.0%).

3.4.2.2.4. NYHA Class

By the sponsor's analyses changes in NYHA class were better in the eplerenone group than in the placebo group. The sponsor's analyses of changes in NYHA class are show in the table below.

Table 27: Sponsor's Changes in NYHA Class in EPHESUS

	Placebo N=3313	Eplerenone 25-50 mg QD N=3319	p-value†
Missing‡	169	168	
Baseline NYHA Class#			
I	940 (29.9%)	924 (29.3%)	
II	1629 (51.8%)	1650 (52.4%)	
III	529 (16.8%)	520 (16.5%)	
IV	46 (1.5%)	57 (1.8%)	
Change from baseline			<0.001
Worsened	902 (28.7%)	779 (24.7%)	
No change	1527 (48.6%)	1582 (50.2%)	
Improved	715 (22.7%)	790 (25.1%)	

Source. Table T13

Note. Improvement is defined as a decrease of at least 1 NYHA classification unit and worsening is defined as an increase of at least 1 NYHA classification unit or death. Patients whose baseline NYHA assessment score was missing are excluded from this analysis. Patients who were alive at end of follow-up but did not provide assessments after baseline are also excluded.

† Based on a CMH row-mean score test, stratified by region.

‡ Either baseline assessment missing, postbaseline assessment missing, or patient died within 10 days of randomization without providing baseline assessment.

Baseline NYHA observation was the Week 1 assessment.

COMMENT: Note that more than half (62%) of the difference in the worsened category is accounted for by more deaths with placebo.

3.4.2.2.5. Quality of Life

The following is extracted from the sponsor's summary of a quality of life (QoL) substudy: QoL assessments were conducted in selected countries (Argentina, Belgium, Brazil, Canada, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States) at screening, week 4, months 3, 6, 12, 18, and 24, transition and study termination. Statistically significant within treatment group improvements in Kansas City Cardiomyopathy Questionnaire overall summary scores were observed over the first year of follow-up 14.4 ± 25 for placebo and 15.2 ± 23 for the eplerenone group ($p<0.001$ for both). The primary analysis was a repeated measures analysis of variance with fixed effects for time, region by time and treatment by time with the latter term representing the omnibus hypothesis of treatment effect. This analysis revealed no significant difference in improvement in QoL between patients randomized to placebo or eplerenone ($p = 0.43$).

3.4.2.2.6. Heart Failure and Other CV Markers

The sponsor included in EPHESUS substudies of various HF and other CV markers. I did not examine the raw data from most of these substudies (exceptions are presented in the Safety section below) because the sponsor's analyses did not suggest significant effects of eplerenone on any of them. The sponsor's summary remarks regarding them are included below.

- "For the primary endpoints (N-BNP, CRP, PIIINP, and endothelin), no treatment differences between placebo and eplerenone were observed in patients with a diagnosis of acute AMI with HF and LV dysfunction who were receiving standard therapy. However, both placebo and eplerenone 25-50 mg QD statistically significantly reduced CRP and PIIINP and increased endothelin from baseline. Eplerenone and placebo generally had similar effects on other endothelial markers, cytokines, and collagen markers. As expected, eplerenone significantly increased serum aldosterone levels, while placebo had no effect. Both treatments significantly decreased the levels of PIP and ICTP, TNF-a, IL-6, osteopontin, cortisol and N-ANP. Both treatments significantly increased the levels of soluble e-selectins and TIMP. Vasopressin levels were significantly reduced from baseline in the placebo treatment group. The reductions from baseline in IL-6, PIP, and ICTP were statistically significantly greater in eplerenone patients compared to placebo patients. Similar results were observed in the nondiabetic and diabetic subsets of patients.

- Eplerenone 25-50 mg QD and placebo each had no effect on carotid/femoral PWV or carotid/radial PWV.

- Results of this substudy showed no effect of eplerenone 25-50 mg QD or placebo on PAI-1. Similar reductions from baseline in t-PA were observed in both treatment groups.

- Eplerenone 25-50 mg QD and placebo were equally effective in reducing LVM. No significant changes from baseline within or between treatment groups were observed for ejection fraction, systolic LV volume, diastolic LV volume, or systolic compliance index.

- The effects of placebo and eplerenone 25-50 mg QD on indices of HRV were similar. Improvements in HRV indices were observed in both treatment groups."

The sponsor concluded in the Clinical Overview: "The available EPHESUS substudy results did not confirm a mechanism by which aldosterone blockade reduces all cause mortality and CV mortality/hospitalization."

COMMENT: Eplerenone appears to have a substantial effect upon reducing sudden cardiac death. This effect could be mediated through its effects upon potassium levels.

Whether eplerenone has an effect upon pump failure is not clear. The HF death reductions could also be related to reduced arrhythmia deaths. The negative results on HF markers do not support a substantial effect upon pump failure. The improvements in NYHA class were small.

3.4.2.3. Subgroup Analyses

3.4.2.3.1. Region and Country

3.4.2.3.1.1. Mortality by Region and Country

Mortality rates varied by region, with Latin America having the highest mortality rates as shown in the table below.

Table 28: Reviewer's Mortality Rates by Region in EPHESUS

	Placebo	Eplerenone
Eastern Europe	15.2%	14.1%
Latin America	26.1%	18.8%
Rest of world	14.0%	13.3%
US/Canada	16.2%	16.5%
US	17.3%	15.6%
Canada	13.3%	18.5%
Western Europe	17.4%	12.8%

Note that the differences in the mortality rates are greatest in Latin America and Western Europe. While the combined US/Canada region shows no difference in the mortality rates, the combined neutral rate is actually a combination of a slight benefit of eplerenone in the US with a detriment in Canada.

In a Cox regression including factors for region and region/treatment interactions, the times to death from any cause are significantly different in Latin America ($p = 0.001$). The region/treatment interaction factors are not statistically significant (e.g., $p = 0.075$ for the US-Canada/treatment interaction.)

COMMENT: While the benefit of eplerenone was greatest in two regions, all regions except the US/Canada showed some overall benefit. In Canada 244 patients were enrolled, so the divergent results may be due to chance variation. The US patients did show some benefit. The results appear consistent enough that there is no strong argument for rejecting the overall result.

3.4.2.3.1.2. Hospitalizations by Region and Country

Hospitalization rates varied by region as shown in the following table.

Table 29: Reviewer's Percentages of Patients Hospitalized at Least Once During Follow-up by Region in EPHESUS

	Placebo	Eplerenone
Eastern Europe	38%	36%
Latin America	42%	44%
Rest of world	52%	55%
US/Canada	59%	55%
US	59%	58%
Canada	59%	49%
Western Europe	53%	52%

Note that hospitalization rates by region are discordant with the mortality rates. The Canadian patients show the greatest benefit of eplerenone on hospitalization rates while they showed the greatest detriment on mortality rates. Latin America, also showing a good mortality benefit, shows a hospitalization rate detriment. For US patients the hospitalization rates are similar for the placebo and eplerenone groups. For CV hospitalizations (except elective procedures) the rates are slightly lower for the eplerenone group (43%) than for the placebo group (45%).

In a Cox regression including factors for region and region/treatment interactions, the times to hospitalization are significantly different in Eastern Europe ($p = 0.009$). The region/treatment interaction factors are not statistically significant .

COMMENT: The small differences in hospitalization rates and the discordant results by region compared to mortality rates make it unclear whether eplerenone has a beneficial impact upon hospitalization rates.

3.4.2.3.2. Race

Because the vast majority of patients were white (90%), the numbers of nonwhites are too small to rule out any variations in efficacy by race. However, all racial subgroups identified showed a beneficial impact of eplerenone upon mortality as shown in the following table.

Table 30: Reviewer's Mortality Rates by Race in EPHESUS

	Placebo	Eplerenone
Asian	16%	14%
Black	23%	13%
White	16%	14%
Hispanic	24%	16%
Other	18%	16%

COMMENT: Note the dramatic differences in mortality rates in blacks and Hispanics. The numbers of patients for these racial subgroups are small (74 blacks, 385 Hispanics total).

3.4.2.3.3. Age and Gender

Age group representation in EPHESUS was fairly wide. Eplerenone seems to show reduced efficacy in the elderly as shown in the following table.

Table 31: Reviewer's Mortality Rates by Age Category in EPHESUS

	Placebo	Eplerenone
<50	9%	6%
50-64	12%	9%
65-74	19%	16%
≥75	26%	27%

Average ages were slightly higher in the placebo group. In a Cox regression of survival age is a highly significant covariate. If age is incorporated as a covariate as a continuous variable, then the significance of the treatment is reduced ($p = 0.02$). If age is incorporated as binary factor ≥ 75 or < 75, then the significance of the treatment factor is reduced further ($p = 0.025$).

The effects in the elderly may be more complex than the above table indicates. Mortality through 28 days was lower with eplerenone for the elderly ≥75 (6% vs. 7%). Mortality was higher with eplerenone for the rest of the study in survivors to 28 days (22% vs. 21%).

Causes of death varied by age as shown in the following table.

Table 32: Reviewer's Causes of Death by Age Category in EPHESUS

	Age <75				Age ≥75			
	Placebo		Eplerenone		Placebo		Eplerenone	
	n	%	n	%	n	%	n	%
sudden	152	5.8%	109	4.0%	49	6.9%	53	8.6%
mi	56	2.2%	44	1.6%	38	5.4%	34	5.5%
hf	70	2.7%	66	2.4%	57	8.0%	38	6.2%
stroke	17	0.7%	18	0.7%	11	1.5%	8	1.3%
aneurysm	1	0.0%	1	0.0%	0	0.0%	0	0.0%
pe	2	0.1%	2	0.1%	2	0.3%	2	0.3%
other cv	22	0.8%	25	0.9%	6	0.8%	7	1.1%
sepsis	5	0.2%	5	0.2%	2	0.3%	4	0.6%
pneumonia	6	0.2%	4	0.1%	2	0.3%	6	1.0%
cancer	12	0.5%	18	0.7%	7	1.0%	2	0.3%

	Age <75				Age ≥75			
	Placebo		Eplerenone		Placebo		Eplerenone	
	n	%	n	%	n	%	n	%
other non-cv	12	0.5%	12	0.4%	8	1.1%	9	1.5%
unwitnessed	1	0.0%	0	0.0%	0	0.0%	0	0.0%
unknown	11	0.4%	9	0.3%	5	0.7%	2	0.3%
alive	2236	85.9%	2390	88.4%	523	73.7%	451	73.2%

pe = pulmonary embolus

Note that sudden death rates were substantially lower in patients < 75 with eplerenone and HF death rates were slightly lower. Sudden death rates were higher in patients ≥ 75 with eplerenone while HF death rates were substantially lower.

Hospitalization rates were also slightly higher in the age ≥ 75 category with eplerenone. While age is a highly significant covariate in a Cox regression of survival, a treatment-age ≥ 75 interaction term is not a significant factor in a Cox regression of survival. It is a significant factor ($p = 0.001$) in a Cox regression of the sponsor's coprimary endpoint, combined CV mortality and CV hospitalization.

Mortality rates were higher in females, likely because the mean age of females (68.5) is substantially higher than of males (62.1). Both genders showed reduced mortality with eplerenone as shown in the following table.

Table 33: Reviewer's Mortality Rates by Gender in EPHESUS

	Placebo	Eplerenone
female	19.8%	16.2%
male	15.4%	13.7%

Causes of death varied by gender as shown in the following table.

Table 34: Reviewer's Causes of Death by Gender in EPHESUS

	Female				Male			
	Placebo		Eplerenone		Placebo		Eplerenone	
	n	%	n	%	n	%	n	%
sudden	60	6.1%	54	5.8%	141	6.0%	108	4.5%
mi	35	3.6%	23	2.4%	59	2.5%	55	2.3%
hf	54	5.5%	35	3.7%	73	3.1%	69	2.9%
stroke	9	0.9%	13	1.4%	19	0.8%	13	0.5%
aneurysm	1	0.1%	0	0.0%	0	0.0%	1	0.0%
pe	2	0.2%	1	0.1%	2	0.1%	3	0.1%
other cv	12	1.2%	12	1.3%	16	0.7%	20	0.8%
sepsis	3	0.3%	3	0.3%	4	0.2%	6	0.3%
pneumonia	1	0.1%	1	0.1%	7	0.3%	9	0.4%
cancer	3	0.3%	4	0.4%	16	0.7%	16	0.7%

	Female				Male			
	Placebo		Eplerenone		Placebo		Eplerenone	
	n	%	n	%	n	%	n	%
other non-cv	6	0.6%	4	0.4%	14	0.6%	17	0.7%
unwitnessed	1	0.1%	0	0.0%	0	0.0%	0	0.0%
unknown	7	0.7%	2	0.2%	9	0.4%	9	0.4%
alive	785	80.2%	787	83.8%	1974	84.6%	2054	86.3%

pe = pulmonary embolus

COMMENT: Note that the beneficial effect of eplerenone on HF and MI deaths was greater in females while the beneficial effect of eplerenone on sudden death rates was greater in males. However, these subset differences may be chance occurrences.

Hospitalization rates were slightly higher in females treated with eplerenone than with placebo as shown in the following table.

Table 35: Reviewer's Hospitalization Rates by Gender in EPHESUS

	Placebo	Eplerenone
female	47%	49%
male	46%	44%

COMMENT: These analyses suggest that there may be reduced efficacy of eplerenone in patients 75 or older. There appears to be reasonable consistency in age differences between the effects on mortality and the effects on hospitalizations. The differences in causes of death and in effects by gender are more difficult to interpret, although the inconsistent hospitalization rates by gender casts doubt on an eplerenone benefit for hospitalization rates.

3.4.2.3.4. Other Subgroups

I examined the following other baseline factors for their relationships to mortality and eplerenone treatment:

- Eplerenone was associated with reduced mortality for all baseline Killip classes except class 1 (eplerenone 11.2% vs placebo 10.5%).

- Eplerenone was associated with reduced mortality for all baseline (week 1) NYHA functional classes, although mortality rates in the 89 class 4 patients were similarly high (eplerenone 49% vs. placebo 52%).

- Eplerenone was not associated with reduced mortality in the patients for which inclusion criterion 3 (clinical evidence of HF) was not documented because of diabetes (eplerenone 16% vs placebo 15%). A history of diabetes was associated with higher mortality rates. Eplerenone mortality rates were lower than placebo rates

both in patients with a history of diabetes and those without, although the benefit was slightly lower in patients with a history of diabetes as shown in the following table.

Table 36: Reviewer's Mortality Rates by History of Diabetes in EPHESUS

Hx of diabetes	Placebo	Eplerenone
No	15%	12%
Yes	21%	19%

The relationship between mortality and diabetics without clinical evidence of HF is complex. While for the entire study diabetics without clinical evidence of HF did not show a mortality benefit with eplerenone, short term they do show a slight benefit (28 day CV mortality 3.6% vs. 2.8%).

- Of the three measures defining clinical evidence of HF (pulmonary congestion by exam, by x-ray, or an S_3) only the S_3 appears to be completely unrelated to mortality. The mortality rates are virtually identical (eplerenone 14.4% and placebo 16.7%) regardless of the presence or absence of an S_3. Mortality rates for patients with pulmonary congestion by either exam or x-ray were higher than for patients without pulmonary congestion. For overall all-cause or CV mortality eplerenone did not show a benefit in patients without pulmonary congestion. However, short term patients without pulmonary congestion show a benefit from eplerenone as shown in the following table.

Table 37: Reviewer's 28-Day CV Mortality by Baseline Pulmonary Congestion in EPHESUS

Pulmonary Congestion*	Placebo	Eplerenone	RR
no	3.1%	2.2%	0.71
yes	4.7%	3.1%	0.66

*by exam or chest x-ray; RR = relative risk

After 28-days the eplerenone mortality benefit was only evident in patients with baseline pulmonary congestion as shown in the following table.

Table 38: Reviewer's Post 28-Day CV Mortality by Baseline Pulmonary Congestion in EPHESUS

Pulmonary Congestion*	Placebo	Eplerenone	RR
no	8.1%	8.2%	1.02
yes	11.5%	10.1%	0.87

*by exam or chest x-ray; RR = relative risk

- Eplerenone was not associated with reduced mortality for patients with a baseline history of renal insufficiency (eplerenone 31% vs. placebo 30%) or for patients with a baseline estimated creatinine clearance ≤30 ml/min (both 42%). Difference in mortality was small for patients with baseline estimated creatinine clearance of 31-50 ml/min (eplerenone 26% vs. placebo 27%).

- Eplerenone was associated with reduced mortality for all patients with baseline SBP >90 mm Hg, while eplerenone mortality was higher than placebo for patients with baseline SBP ≤90 (26% vs. 13%). Above 90 placebo mortality rates did not vary consistently.

- Eplerenone was not associated with reduced mortality for patients without a history of hypertension at baseline. The mortality rates by treatment group and history of hypertension are shown in the following table.

Table 39: Reviewer's Mortality Rates by History of Hypertension in EPHESUS

Hx of hypertension	Placebo	Eplerenone
No	14%	14%
Yes	18%	14%

However, the CV mortality rate was slightly lower in the eplerenone group in patients without a history of hypertension. Mean blood pressures increased from baseline during the study, with the increases slightly greater in the placebo group vs. the eplerenone group. The changes were similar regardless of a history of hypertension at baseline. See the Safety section below for a more detailed discussion of the BP changes during the study. Patients without a history of hypertension did show a short term benefit from eplerenone (28 day CV mortality 4.5% vs. 2.9%).

- Mortality, and in particular CV mortality showed an U-shaped relationship to baseline potassium levels, as shown in the following table.

Table 40: Reviewer's CV Mortality Rates by Baseline Potassium in EPHESUS

Baseline potassium	Placebo	Eplerenone
≤3.3	21%	21%
3.31-3.5	24%	14%
3.51-3.7	16%	14%
3.71-3.9	15%	12%
3.91-4.1	13%	8%
4.11-4.5	14%	13%
4.51-5	14%	12%
>5	16%	20%

CV mortality shows a similar U-shaped relationship to last, minimum, or average potassium levels. For the last, minimum, or average potassium levels, the

distributions of levels for the eplerenone group are shifted to higher values compared to the placebo group. Note that eplerenone shows lower CV mortality rates for all potassium levels except the two extremes, which have few patients.

The relationship of CV mortality within 28 days to baseline potassium levels is more intriguing as shown in the following table.

Table 41: Reviewer's 28-Day CV Mortality Rates by Baseline Potassium in EPHESUS

Baseline potassium	Placebo	Eplerenone
≤3.3	10%	4%
3.31-3.5	8%	3%
3.51-3.7	5%	4%
3.71-3.9	6%	4%
3.91-4.1	4%	3%
4.11-4.5	4%	3%
4.51-5	4%	3%
>5	2%	2%

Mortality increases perhaps slightly with decreasing potassium levels with eplerenone but more dramatically with decreasing potassium levels with placebo.

COMMENT: While these are post hoc subgroup analyses, some of the suggestions are intriguing. There does appear to be a difference between eplerenone effects on short-term, i.e., 28-day, compared to long term mortality. The strongest effect appears to be on short-term mortality and it appears unrelated to HF measures but strongly associated with lower baseline potassium levels. Because the short-term mortality differences are largely due to differences in sudden death and MI, one wonders whether these short-term effects are due to potassium increase with eplerenone mitigating cardiac arrhythmias. The relationship of mortality to potassium levels is explored further in connection with RALES.

There also appears to be a longer-term survival benefit from eplerenone. Whether this apparent benefit is real (the small differential in age between the two groups is a contributory factor) and what the mechanism is are difficult to determine from these data. The mortality rates by history of hypertension suggest that one mechanism of action may be blood pressure reduction or better blood pressure control. The blood pressure changes are difficult to interpret because the baseline readings were obtained in the immediate post-MI period and likely don't reflect the patient's usual BP readings. One can also not rule out a potassium-related effect or some other mechanism such as prevention of fibrosis or inhibition of remodeling.

What to recommend regarding patients without pulmonary congestion is problematic. While for overall mortality they do not show a benefit, they do for 28-day mortality. Ideally this issue needs further study.

3.4.2.3.5. Interactions with Other CV Drugs

Other baseline or concurrent CV drug use was usually associated with lower CV mortality in both groups. One notable exception is spironolactone use at any time: It was associated with higher mortality in both groups, slightly lower in the eplerenone group than the placebo group.

For the following analyses any use within 14 days of the index MI was counted as baseline use. Any use on or after day 28 (the day at which eplerenone could be increased to 50 mg daily) was counted as concurrent use. I defined concurrent use as on or after day 28 to avoid counting transient use of medications in the immediate post-infarction period. Deaths and CV deaths within the first 28 days were less frequent in the eplerenone group regardless of the baseline use of CV medications. Because duration of therapy with eplerenone is an important issue, I also examined mortality rates in patients who survived the first 28 days.

The eplerenone group usually showed lower rates than the placebo group regardless of the baseline or concurrent CV drug use. Exceptions to the pattern that the eplerenone group mortality was lower regardless of baseline or concurrent drug use are the following:

- Mortality was slightly higher in the eplerenone group in patients not treated at baseline with beta blockers (24% vs. 23%) and CV mortality was identical (20%). For concurrent beta blocker use as well, the benefit from eplerenone appears to be greater in the patients receiving beta blockers as shown in the following table.

  Table 42: Reviewer's CV Mortality Post 28 Days by Concurrent Beta Blocker Use in EPHESUS

Beta blocker	Placebo	Eplerenone
no	17%	17%
yes	9%	8%

- CV mortality post 28 days was slightly higher in the eplerenone group in patients treated concurrently with ARBs (10% vs. 9%) while total mortality was virtually identical (12%). The numbers of patients treated with ARBs is relatively low (577 total). For ACE inhibitor use or combined ACEI/ARB use, the benefit from eplerenone appears to be greater in the patients receiving ACEI/ARB as shown in the following table, although the number of patients not receiving ACEI/ARB is relatively low (839).

  Table 43: Reviewer's CV Mortality Post 28 Days by Concurrent ACE Inhibitor Use in EPHESUS

ACEI	Placebo	Eplerenone
no	11%	13%
yes	11%	9%

If one crosses ACEI use with beta blocker use, the eplerenone benefit remains in the largest group, that receiving both an ACEI and a beta blocker as shown in the following table.

Table 44: Reviewer's CV Mortality Post 28 Days by Concurrent ACEI/ARB and Beta Blocker Use in EPHESUS

ACEI/BB	Placebo	Eplerenone	N
none	17%	23%	204
BB only	9%	10%	635
ACEI/ARB only	17%	16%	969
both	9%	8%	4573

Note that the numbers of patients are relatively low for those patients receiving neither type of drug or beta blockers alone.

- CV mortality post 28 days was similar in both groups in patients not treated with a diuretic as shown in the following table.

Table 45: Reviewer's CV Mortality Post 28 Days by Concurrent Diuretic Use in EPHESUS

Diuretic	Placebo	Eplerenone
no	5%	5%
yes	13%	12%

- CV mortality post 28 days was similar in both groups in patients not treated with a digitalis preparation as shown in the following table.

Table 46: Reviewer's CV Mortality Post 28 Days by Concurrent Digitalis Use in EPHESUS

Digitalis	Placebo	Eplerenone
no	8%	8%
yes	20%	17%

However, most patients (89%) that received a digitalis preparation also received a diuretic. If one crosses diuretic use with dig use, the following CV mortality rates are observed:

Table 47: Reviewer's CV Mortality Post 28 Days by Concurrent Diuretic and Digitalis Use in EPHESUS

Dig/diuretic	Placebo	Eplerenone	N
none	4%	4%	2045
dig only	16%	10%	160
diuretic only	10%	10%	2942
both	21%	18%	1234

Note that eplerenone benefit appears only to be seen with digitalis use.

Medication use varied by age. The mean ages of patients by baseline medication use are shown in the following table.

Table 48: Reviewer's Mean Ages of Patients by Baseline CV Medication Use in EPHESUS

Baseline Use	No	Yes
Beta blocker	67	63
ACE inhibitor	63	64
ARB	64	67
Aspirin	66	64
Digitalis	63	67
Loop diuretic	61	67
Other diuretic	64	65

COMMENT: Note that beta blocker use declined with increasing age. Some of the apparent lack of efficacy of eplerenone in patients without baseline beta blocker use may be explained by their greater age because eplerenone efficacy appears to be reduced in the very elderly.

While these post-hoc subset analyses are somewhat difficult to interpret, they do seem to suggest that eplerenone reduces CV mortality in patients receiving approved treatments, i.e., an ACE inhibitor and a beta blocker. The interactions with digitalis and diuretics are more difficult to interpret. While they could be chance, one wonders whether eplerenone is reducing arrhythmias associated with diuretic use, digitalis, or the combination.

3.4.3. Safety

3.4.3.1. Exposure

Exposure to study drug is summarized in Section 3.4.1.3.3.1. Overall there were about 3,800 patient-exposure years to eplerenone in EPHESUS. The average exposure time was about 1.2 years. The mean dose was 43.5 mg.

3.4.3.2. Serious Adverse Events

3.4.3.2.1. Deaths

All cause mortality was the first primary endpoint in EPHESUS and CV mortality was part of the sponsor's coprimary endpoint. The mortality results, including mortality causes, are presented in Section 3.4.2 above. Rates of CV death, and sudden cardiac death in particular, were significantly lower in the eplerenone group. Note that there were no causes of death significantly more frequent in the eplerenone group.

3.4.3.2.2. Hospitalizations

Hospitalizations were a secondary endpoint in EPHESUS and CV hospitalizations were incorporated into the sponsor's coprimary endpoint. Hospitalization rates are discussed in Section 3.4.2 above. Overall hospitalizations were slightly lower in the eplerenone group and reasons for hospitalizations were similar between the two groups as shown in the following table.

Table 49: Reviewer's Reasons for Hospitalizations in EPHESUS

	Placebo	Eplerenone
Angina, stable	100	100
Angina, unstable	398	405
Atrial arrhythmias	107	98
Elective CV surgery	353	351
Heart failure	621	478
Hypotension	31	34
MI	269	268
PVD	36	48
Stroke	54	73
Ventricular arrhythmia	63	58
Other CV	447	383
COPD	23	21
Pneumonia	75	39
Other pulmonary	27	30
Diabetes	38	29
Renal dysfunction	18	34
Electrolytes	6	13
Elective non-CV surgery	48	70
Other non-CV	527	504
Total	3241	3044

CV = cardiovascular; MI = myocardial infarction;
PVD = peripheral vascular disease;
COPD = chronic obstructive pulmonary disease

Note that there are some differences in reasons for hospitalizations between the two groups. The eplerenone group had substantially fewer hospitalizations for HF, pneumonia, and diabetes but more hospitalizations for PVD, stroke, renal dysfunction, electrolyte disturbances, and elective non-CV surgery. The table above shows events, i.e., one patient may have more than one hospitalization for the same reason or different reasons. Differences in the numbers of patients with any hospitalization were statistically significant for pneumonia, renal dysfunction, and elective non-CV surgery.

3.4.3.2.3. Other Serious Adverse Events

Serious adverse events (SAEs) were more frequent in the placebo group (51% of patients) than in the eplerenone group (49%). SAEs experienced by one percent or more

of patients in either treatment group or with a statistically significant difference between the two groups are shown in the table below.

Eplerenone shows significantly lower rates of sudden death, HF, dyspnea, pneumonia, hypertension, pericarditis, and accident SAEs. Eplerenone shows significantly greater rates of dehydration, leg arterial thromboses, increased creatinine, and pyelonephritis SAEs.

COMMENT: The lower rate of accident SAEs with eplerenone in this study is presumably a chance variation and illustrates the problem of overinterpreting any of the observed differences. However, the higher rate of leg arterial thromboses is interesting in view of possible effects of eplerenone on the fibrinolytic system.

In addition to the SAEs noted in the above table, there was also a greater but not significantly greater rate of hyperkalemia SAEs in the eplerenone group (19 eplerenone vs. 11 placebo.) See Section 3.4.3.6.1 for a discussion of hyperkalemia

Table 50: Sponsor's Patients with Serious Adverse Events in EPHESUS

Body System Adverse Event	Placebo (N=3301)	Eplerenone 25-50 mg QD (N=3307)	p-value†
Any event	1689 (51.2%)	1604 (48.5%)	0.032
Autonomic Nervous System Disorders			
Hypertension Aggravated	25 (0.8%)	11 (0.3%)	0.020
Hypotension	32 (1.0%)	25 (0.8%)	-
Syncope	37 (1.1%)	46 (1.4%)	-
Body as a Whole - General Disorders			
Chest Pain Non-Cardiac	74 (2.2%)	76 (2.3%)	-
Injury - Accidental	19 (0.6%)	7 (0.2%)	0.019
Sudden Death	184 (5.6%)	123 (3.7%)	<0.001
Cardiovascular Disorders - General			
Cardiac Failure	383 (11.6%)	324 (9.8%)	0.019
Cardiac Failure Left	176 (5.3%)	144 (4.4%)	-
Unstable Angina	283 (8.6%)	279 (8.4%)	-
Heart Rate and Rhythm Disorders			
Cardiac Arrest	46 (1.4%)	38 (1.1%)	-
Fibrillation Atrial	79 (2.4%)	68 (2.1%)	-
Fibrillation Ventricular	34 (1.0%)	35 (1.1%)	-
Tachycardia Ventricular	45 (1.4%)	51 (1.5%)	-
Metabolic and Nutritional Disorders			
Dehydration	5 (0.2%)	15 (0.5%)	0.041
Myo, Endo, Pericardial, and Valve Disorders			
Angina Pectoris	184 (5.6%)	190 (5.7%)	-
Coronary Artery Disorder	80 (2.4%)	89 (2.7%)	-
Myocardial Infarction	276 (8.4%)	271 (8.2%)	-
Pericarditis	24 (0.7%)	6 (0.2%)	<0.001
Platelet, Bleeding and Clotting Disorders			
Thrombosis Arterial Leg	2 (<0.1%)	11 (0.3%)	0.022
Respiratory System Disorders			
Dyspnea	97 (2.9%)	71 (2.1%)	0.042
Pneumonia	82 (2.5%)	49 (1.5%)	0.004
Urinary System Disorders			
Creatinine Increase	1 (<0.1%)	9 (0.3%)	0.021
Pyelonephritis	0 (0.0%)	6 (0.2%)	0.031
Renal Function Abnormal	29 (0.9%)	41 (1.2%)	-
Vascular (Extracardiac) Disorders			
Cerebrovascular Disorder	90 (2.7%)	91 (2.8%)	-

3.4.3.3. Events Leading to Discontinuation

AEs led to withdrawal at similar rates in both treatment groups (eplerenone 4.9%, placebo 4.7%). Those with at least a 0.2% rate in either group are shown in the table below.

Table 51: Sponsor's AEs Causing Permanent Discontinuation in EPHESUS

Body System Adverse Event	Placebo (N=3301)	Eplerenone 25-50 mg QD (N=3307)
Any event	155 (4.7%)	163 (4.9%)
Autonomic Nervous System Disorders		
Hypotension	2 (<0.1%)	7 (0.2%)
Cardiovascular Disorders - General		
Cardiac Failure*	27 (0.8%)	12 (0.4%)
Cardiac Failure Left	6 (0.2%)	7 (0.2%)
Central and Peripheral Nervous System Disorders		
Dizziness	2 (<0.1%)	6 (0.2%)
Gastrointestinal System Disorders		
Diarrhea	5 (0.2%)	8 (0.2%)
Dyspepsia*	6 (0.2%)	0 (0.0%)
Nausea	3 (<0.1%)	7 (0.2%)
Metabolic and Nutritional Disorders		
Hyperkalemia*	10 (0.3%)	22 (0.7%)
Myo Endo Pericardial and Valve Disorders		
Myocardial Infarction	7 (0.2%)	13 (0.4%)
Respiratory System Disorders		
Dyspnea	4 (0.1%)	5 (0.2%)
Urinary System Disorders		
Renal Function Abnormal	13 (0.4%)	13 (0.4%)
Vascular (Extracardiac) Disorders		
Cerebrovascular Disorder	8 (0.2%)	12 (0.4%)

3.4.3.4. Laboratory Test Value Changes

Small but statistically significant differences in changes from baseline for several lab test values for the eplerenone group compared to the placebo group were observed. Lab tests with significantly different changes included hematocrit, red blood cell count (RBC), potassium, total protein, albumin, alkaline phosphatase, LDH, sodium, inorganic phosphorous, total bilirubin, creatinine, and BUN. The majority of the mean changes were very small and likely not clinically significant, e.g., mean RBCs were 4.36 (x 10^{12}/L) in the placebo group and 4.34 in the eplerenone group at baseline and increased 0.2 in the placebo group and 0.15 in the eplerenone group by the last visit ($p < 0.001$).

One difference that may have some clinical relevance is the difference in potassium values. The mean serum potassium level at baseline was 4.26 mmol/L in the placebo group and 4.27 mmol/L in the eplerenone group. Mean potassium increased by 0.17 in the placebo group and 0.26 in the eplerenone group by the last visit ($p < 0.001$). A significantly greater percentage of eplerenone-treated patients had extreme potassium values (defined as potassium >5.5 mmol/L) compared to placebo-treated patients for the final visit (2.8% vs 2.0%, $p = 0.044$) and maximum value (15.7% vs 11.3%, $p<0.001$).

The other lab test change difference worth noting is the difference in renal function tests. Serum creatinine is the best measure of renal function available on study patients, but EPHESUS was an international study with creatinine measured in different labs with different units. The sponsor compensated for the different units by converting all lab values to SI units in the data sets provided in the NDA. However, there appear to be minor residual problems with unit conversions for creatinine, e.g., values consistently about 0.02 mg/dL (when expressed in typical US units) for one site. I corrected obvious errors in unit conversions. Some value peculiarities remain, e.g., random values of <0.4 at foreign sites with all other values for the patients in the more typical range of >0.7. The values given below reflect the corrected values.

The mean creatinine level at baseline was 1.13 mg/dL in the placebo group and 1.13 mg/dL in the eplerenone group. Mean creatinine increased by 0.04 in the placebo group and 0.08 in the eplerenone group by the last visit ($p < 0.001$). Creatinine changes varied by gender as shown in the following table.

Table 52: Reviewer's Creatinine Changes by Gender in EPHESUS

	Placebo	Eplerenone
female	0.04	0.11
male	0.04	0.06

(creatinine mg/dL)

While females appear to show a greater change in renal function as estimated by creatinine, the differences are less prominent when changes are viewed as creatinine clearance estimated by the Cockcroft-Gault equation as shown in the following table.

Table 53: Reviewer's Creatinine Clearance Changes by Gender in EPHESUS

	Placebo	Eplerenone
female	-1.9	-5.1
male	-1.3	-2.7

(creatinine clearance ml/min)

Creatinine clearance shows better fit than creatinine in linear regression analyses of change in creatinine or creatinine clearance by baseline value, treatment, and gender. Gender is a highly significant baseline covariate in such analyses but an interaction term

for treatment and gender is insignificant. Renal function changes varied inconsistently by age without any obvious interaction between treatment and age. Increase in creatinine increased by age while decreases in creatinine clearance varied inconsistently by age.

3.4.3.5. Vital Sign Changes

Because the baseline measurements in EPHESUS were in the immediate post-MI period usually in hospital, the baseline measurements may not reflect the patients' usual basal state. I believe that this limitation is particularly important for vital signs. In EPHESUS mean blood pressures increased from the baseline to the last visit. The increases were significantly lower for eplerenone than for placebo as shown in the following table.

Table 54: Sponsor's Vital Sign Changes in EPHESUS

	Placebo		Eplerenone 25-50 mg QD		p-value†
	Baseline	(Mean change)	Baseline	(Mean change)	
Sitting SBP (mmHg)	120.6	(6.2)	120.8	(3.2)	<0.001
Sitting DBP (mmHg)	72.5	(3.5)	73.2	(2.0)	<0.001
Sitting Pulse (bpm)	76.3	(-5.5)	76.6	(-6.4)	0.021

A significantly greater percentage of eplerenone-treated patients experienced a low extreme sitting systolic BP value (defined as a =15% decrease from baseline) compared to placebo-treated patients (10.0% vs 8.1%) at the final visit. Significantly greater percentages of placebo-treated patients experienced high extreme sitting SBP (31.2% vs 26.0%) or DBP (27.9% vs 25.4%) values (defined as a =15% increase from baseline) compared to eplerenone-treated patients at the final visit.

3.4.3.6. Events of Special Interest

3.4.3.6.1. Hyperkalemia and Hypokalemia

Hyperkalemia was more frequent with eplerenone treatment. The sponsor's summary of elevated potassium levels by treatment is shown in the following table.

Table 55: Sponsor's Summary of Elevated Potassium Levels in EPHESUS

Potassium Criteria	Placebo N=3237	Eplerenone 25-50 mg QD N=3251	p-value†
>5.5 mmol/L	363 (11.2%)	508 (15.6%)	<0.001
≥6.0 mmol/L	126 (3.9%)	180 (5.5%)	0.002
>5.5 mmol/L at least 2 consecutive occasions	55 (1.7%)	99 (3.0%)	<0.001

Elevated potassium levels were more frequent with reduced baseline renal function as shown in the following table.

Table 56: Reviewer's Mean Changes in Potassium Levels by Baseline Creatinine Clearance in EPHESUS

CrCl	Placebo	Eplerenone
≤30	0.22	0.36
31-50	0.19	0.34
51-70	0.16	0.29
71-100	0.16	0.23
>100	0.14	0.22

CrCl = baseline creatinine clearance, ml/min
(potassium changes mmol/L)

Hyperkalemia SAEs were also more frequent with reduced baseline renal function as shown in the following table.

Table 57: Reviewer's Patients with Hyperkalemia SAEs by Baseline Creatinine Clearance in EPHESUS

CrCl	Placebo	Eplerenone
≤30	2.1%	1.2%
31-50	0.3%	1.0%
51-70	0.3%	0.9%
71-100	0.3%	0.4%
>100	0.2%	0.0%

CrCl = baseline creatinine clearance, ml/min

In one hypertension study patients with diabetes and microalbuminuria appeared to have a greatly increased risk of hyperkalemia with eplerenone treatment. While the precise definition of diabetes and microalbuminuria from the hypertension study is not duplicated in EPHESUS, a history of diabetes and urine protein on the baseline urinalysis do appear to be risk factors for increase potassium as shown in the following table.

Table 58: Reviewer's Mean Changes in Potassium Levels by History of Diabetes and Baseline Urine Protein in EPHESUS

	Placebo	Eplerenone
neither	0.13	0.19
urine protein	0.22	0.36
history of diabetes	0.18	0.31
both	0.25	0.40

(potassium changes mmol/L)

The mean changes in potassium levels are similar with proteinuria and diabetes even for patients with relatively normal renal function, e.g., baseline creatinine clearances >70 or

>100. Hyperkalemia SAEs were more frequent particularly with the combination of diabetes and baseline proteinuria as shown in the following table.

Table 59: Reviewer's Patients with Hyperkalemia SAEs by History of Diabetes and Baseline Urine Protein in EPHESUS

	Placebo	Eplerenone
neither	0.3%	0.4%
urine protein	0.2%	0.2%
history of diabetes	0.2%	0.5%
both	1.0%	2.5%

However, there is a mortality differential favoring eplerenone regardless of the categories of urine protein and history of diabetes in the above table.

Potassium increases were also greater with ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) use as shown in the following table.

Table 60: Reviewer's Mean Change in Potassium By ACEI/ARB Use at Any Time after 27 Days in EPHESUS

ACEI/ARB	Placebo	Eplerenone
None	0.05	0.20
Any	0.17	0.27

(potassium changes mg/dL)

The 24 hyperkalemia SAEs after 27 days were reported only in patients who at some time had received an ACE inhibitor or an ARB as shown in the following table.

Table 61: Reviewer's Patients with Hyperkalemia SAEs By ACEI/ARB Use at Any Time after 27 Days in EPHESUS

ACEI/ARB	Placebo	Eplerenone
None	0.0%	0.0%
Any	0.2%	0.6%

All 30 hyperkalemia SAEs occurred in patients who at some time were given an ACEI or ARB regardless of the duration of treatment in EPHESUS.

Hypokalemia AEs were reported in 21 (0.6%) eplerenone patients and in 53 (1.6%) placebo patients ($p < 0.001$). Hypokalemia AEs were slightly more frequent with reduced baseline renal function and less frequent with eplerenone treatment regardless of the baseline renal function. The association of hypokalemia AEs with reduced renal function is likely related to the increased used of diuretics with reduced renal function. Hypokalemia AEs were strongly associated with diuretic use in the absence of eplerenone treatment as shown in the following table.

Table 62: Reviewer's Patients with Hypokalemia AEs By Diuretic Use at Any Time after 27 Days in EPHESUS

Diuretic	Placebo	Eplerenone
None	0.5%	0.4%
Any	2.2%	0.7%

COMMENT: The hyperkalemia risk factors appear to be consistent with those identified in the hypertension studies. Eplerenone appears to reduce the frequency of hypokalemia AEs.

3.4.3.6.2. Sex Hormone-Related Adverse Events

Sex hormone-related adverse events were uncommon and occurred at similar rates in the two treatment groups as shown in the following table. The median time to development of gynecomastia in the eplerenone group was 491 days, with an interquartile range of 372 to 674 days. One hint that eplerenone may cause clinically significant sex hormone related AEs is that five of the eplerenone gynecomastia events were considered serious while only one of the placebo gynecomastia events was considered serious.

Table 63: Sponsor's Other Events of Special Interest in EPHESUS

Body System Adverse Event	Placebo N=3301	Eplerenone 25-50 mg QD N=3307
Disorders, Female	(N=975)	(N=937)
Breast pain female	3 (0.3%)	1 (0.1%)
Menstrual disorder	4 (0.4%)	4 (0.4%)
Disorders, Male	(N=2326)	(N=2370)
Gynecomastia	14 (0.6%)	12 (0.5%)
Male breast pain	3 (0.1%)	3 (0.1%)
Excluding male breast pain	11 (0.5%)	9 (0.4%)
Libido decreased	1 (<0.1%)	0 (0.0%)
Impotence	20 (0.9%)	21 (0.9%)

The other differences in AEs that could be related to sex-hormone effects are differences in cancers, discussed in the next section.

3.4.3.6.3. Neoplasms

While the absolute numbers of cancers was low and the total numbers of patients with cancer were similar between the two treatment groups, there are some interesting

differences regarding specific cancer types between the two groups as shown in the following table.

Table 64: Reviewer's Patients with Cancers or Neoplasms in EPHESUS

	Placebo		Eplerenone	
	N	%	N	%
Treated patients	3301		3307	
All cancers*	59	1.8%	62	1.9%
Neoplasms#	11	0.3%	10	0.3%
Lung cancer	12	0.4%	15	0.5%
Gastrointestinal cancer	8	0.2%	17	0.5%
Esophageal cancer	0	0.0%	4	0.1%
Bladder cancer	5	0.15%	5	0.15%
Renal cancer	0	0.00%	1	0.03%
Renal mass	3	0.1%	0	0.00%
Adrenal adenoma	0	0.00%	2	0.06%
Thyroid cancer	0	0.0%	1	0.03%
Females	975		937	
Breast cancer	0	0.0%	3	0.3%
Breast neoplasm	1	0.1%	1	0.1%
Cervical cancer	0	0.0%	1	0.1%
Ovarian cancer	0	0.0%	1	0.1%
Vulvar/vaginal cancer	3	0.3%	0	0.0%
Males	2326		2370	
Prostate cancer	9	0.4%	1	0.04%
Benign prostatic hypertrophy	24	1.0%	24	1.0%

* Excluding non-melanoma skin cancer
# Neoplasms = tumors not identified clearly as benign or malignant or site

The differences that are statistically significant are the differences in prostate cancer rates ($p = 0.037$ by Fisher's exact test for prostate cancer sponsor coding and $p = 0.011$ for the prostate cancer expanded coding.) The placebo prostate cancer patients include three patients with the AE noted at 6, 7, and 14 days. The only prostate cancer death was in an eplerenone patient who had a history of prostate cancer at baseline (not included in the above table.)

COMMENT:

- Note that prostate cancers are less frequent and breast cancers more frequent with eplerenone, suggesting an estrogen-like effect.

- Note that two adrenal adenomas or nodular hypertrophy were reported in eplerenone patients. One was an "incidentaloma" found on CT scan of the thorax. The other was found after a brief episode of lumbar pain and was eventually excised. A third eplerenone patient who died after one day of therapy had an adrenal adenoma noted at

autopsy, an occurrence which highlights the problem of dealing with incidentalomas. Note also the three renal masses in placebo patients. While listed as renal masses, it is possible that one or more of these could have been adrenal masses.

- Note the one thyroid cancer in an eplerenone patient and see the next section.

3.4.3.6.4. Thyroid Disorders

Both hyperthyroidism and hypothyroidism AEs were slightly more frequent with eplerenone treatment than with placebo as shown in the following table.

Table 65: Reviewer's Patients with Thyroid Adverse Events in EPHESUS

	Placebo		Eplerenone	
	N	%	N	%
Treated patients	3301		3307	
Hyperthyroidism	9	0.3%	15	0.4%
Hypothyroidism	8	0.2%	15	0.5%
Goiter	7	0.2%	6	0.2%
Thyroid cancer	0	0%	1	0.03%

COMMENT: These event rates are suggestive that eplerenone has an effect upon thyroid function. However, the event rates are low and the effect not proven such that no additional studies or lab monitoring seem needed.

3.4.3.6.5. Thrombotic Events

Arterial thromboses were uncommon but significantly more frequent with eplerenone therapy, and thrombophlebitis was slightly more frequent with eplerenone, as shown in the following table.

Table 66: Reviewer's Patients with Thrombotic Adverse Events in EPHESUS

	Placebo		Eplerenone	
	N	%	N	%
Treated Patients	3301		3307	
Myocardial infarction	270	8.2%	267	8.1%
Stroke/TIA	110	3.3%	113	3.4%
Arterial thromboses	5	0.2%	15	0.5%
Thrombophlebitis	12	0.4%	16	0.5%
Pulmonary embolism	14	0.4%	9	0.3%

Other major thrombotic events, e.g., myocardial infarction and stroke, occurred with similar frequencies in the two treatment groups.

COMMENT: These rates are suggestive that eplerenone has an effect upon peripheral arterial thromboses. However, the event rates are low and the effect not proven such that no additional studies or patient monitoring seem needed.

3.4.3.7. Overall Adverse Events

Treatment-emergent adverse events were experienced by 80% of patients in the placebo group and 79% of patients in the eplerenone group. All significant differences in AE rates between eplerenone and placebo have been commented upon in the previous sections.

3.4.3.8. Overdose

Overdose with eplerenone was not reported in EPHESUS.

3.5. Summary

3.5.1. Efficacy Summary

Eplerenone appears to show solid efficacy in improving survival in HF patients post-MI. In EPHESUS the mortality risk reduction was about 15% with a p value of 0.008. The survival curves separate early and the separation is maintained throughout the duration of the study. The follow-up rate for vital status was excellent (99.7%), baseline risk factors were well-balanced, and other aspects of the trial design and conduct appear good.

Two-thirds of the difference in deaths occurred within the first 30 days. There was still a mortality benefit of eplerenone beyond 30 days (relative risk 0.92). The major contributor to the difference in deaths was sudden death, although there were also similar relative risk reductions in recurrent MI and HF deaths.

There are no subgroup variations that suggest major issues with validity of the survival benefit. The variations in mortality rates by region and country, while not the ideal ones because the US shows less benefit than other countries, are within chance variation. The vast majority of patients were white, so variations in efficacy by race are impossible to estimate. Both genders showed a survival benefit with eplerenone, while the variations by age do not suggest validity issues but may represent a noteworthy subgroup variation as discussed next.

The following subgroup differences are of clinical interest:

- Efficacy appears to be lacking in patients aged 75 and over (eplerenone 27% vs. placebo 26%). That this is a real effect is suggested by the continuous reduction in benefit from younger to older ages and the significance of age as a covariate in Cox regressions.

- Eplerenone was not associated with reduced mortality in diabetics without clinical evidence of HF (eplerenone 16% vs placebo 15%). (Diabetics were the one subgroup that could be eligible without clinical evidence of HF.)

- Eplerenone was not associated with reduced mortality for patients with a baseline history of renal insufficiency (eplerenone 31% vs. placebo 30%) or for patients with a baseline estimated creatinine clearance ≤ 30 ml/min (both 42%). Difference in mortality was small for patients with baseline estimated creatinine clearance of 31-50 ml/min (eplerenone 26% vs. placebo 27%).

- Eplerenone was not associated with reduced mortality for patients without a history of hypertension at baseline (both 14%). Eplerenone was also not associated with reduced mortality for patients with baseline SBP <100.

The eplerenone group usually showed lower mortality rates than the placebo group regardless of baseline or concurrent CV drug use. Mortality was slightly higher in the eplerenone group in patients not treated at baseline with beta blockers (24% vs. 23%) and CV mortality was identical (20%). This difference is likely related to the fact that the average age of patients not taking beta blockers was higher than those taking them (67 vs. 63). There is an intriguing relationship that eplerenone benefit after 28 days was only seen in patients receiving a digitalis preparation.

The evidence is not convincing for the following reasons:

- The sponsor's definition of the CV hospitalization component (progression of HF, MI, stroke, or ventricular arrhythmias) is not clinically relevant because many CV causes, such as atrial arrhythmias and angina, are excluded.

- If one includes all CV hospitalizations, then the difference in the times to CV death or first CV hospitalization is not significant ($p = 0.028$) compared to the sponsor's allocated α of 0.01. CV deaths constitute about 76% of the difference in numbers of events. The median time to event for CV hospitalizations is shorter for eplerenone (61 days) than for placebo (70 days).

- Times to first hospitalization or death (all causes for both) were not significantly different between the two groups ($p = 0.0511$).

- All hospitalizations were not significantly reduced (46% of placebo patients and 45% of eplerenone patients.)

- Mortality and hospitalization rates were not consistent by subgroups, e.g., region or gender. For regions, mortality benefit was greatest in Latin America while hospitalizations were higher for eplerenone there. For gender, both genders showed mortality benefit with eplerenone but females had higher hospitalization rates with eplerenone.

An EPHESUS quality of life (QoL) substudy using the Kansas City Cardiomyopathy Questionnaire did not show significant differences in improvement in QoL between eplerenone and placebo. Changes in NYHA class were better in the eplerenone group, but differences were small (worsened 25% eplerenone vs 29% placebo) and more than half (62%) of the difference in the worsened category is accounted for by deaths.

EPHESUS substudies examined a wide range of HF biomarkers--N-BNP, CRP, PIIINP, endothelin, PIP, ICTP, TNF-a, IL-6, osteopontin, N-ANP, soluble e-selectins, TIMP, carotid/femoral PWV, carotid/radial PWV, PAI-1, t-PA, LVM, ejection fraction, systolic LV volume, diastolic LV volume, systolic compliance index, and HRV. The sponsor concluded "The available EPHESUS substudy results did not confirm a mechanism by which aldosterone blockade reduces all cause mortality and CV mortality/ hospitalization."

The relationship of baseline potassium levels to 28-day CV mortality, the excess of placebo sudden and MI deaths early, and the lack of relationship to HF measures such as pulmonary congestion suggests that one mechanism of action may be effect of eplerenone on potassium levels reducing arrhythmic deaths. Whether a longer term mechanism related to HF or to BP reduction is operative is less clear.

3.5.2. Safety Summary

EPHESUS represents about 2,880 patient-ears of exposure to eplerenone. The mean dose was 43.5 mg. Overall adverse event rates for eplerenone were similar to placebo (AEs in 79% of eplerenone patients vs. 80% of placebo patients.) Serious AEs were more frequent in the placebo group (51%) than in the eplerenone group (49%), with most of the difference due to a lower rate of HF SAEs in the eplerenone group. The noteworthy AEs related to eplerenone in EPHESUS are the following:

- Hyperkalemia was more frequent with eplerenone. Both lab measures of potassium, e.g., any value >5.5 mmol/L in 16% of eplerenone patients and 11% of placebo patients, and reported AEs, e.g., 3.6% of eplerenone patients and 2.3% of placebo patients, were higher in the eplerenone group. Hyperkalemia was more frequent with reduced renal function, e.g., mean increase in potassium was 0.36 mmol/L in eplerenone patients with baseline creatinine clearance (CrCl) ≤30 ml/min vs. 0.22 in

placebo patients with CrCl ≤30, 0.22 in eplerenone patients with CrCl >100, and 0.14 in placebo patients with CrCl >100. Hyperkalemia was also more frequent in patients with a history of diabetes or proteinuria on the baseline urinalysis and most frequent with both and eplerenone treatment. Hyperkalemia was more frequent with ACE inhibitor or angiotensin II receptor blocker use; hyperkalemia SAEs were reported only in patients who received these drugs.

- Hypokalemia was less frequent with eplerenone. Hypokalemia AEs were reported in 0.6% of eplerenone patients and in 1.6% of placebo patients.

- Sex hormone-related adverse events were uncommon and occurred at similar rates in the two treatment groups, e.g., gynecomastia was reported in 0.5% of eplerenone-treated males and in 0.6% of placebo-treated males. The median time to development of gynecomastia in the eplerenone group was 491 days.

- Both hyperthyroidism (0.4% vs 0.3%) and hypothyroidism (0.5% vs. 0.2% placebo) AEs were slightly more frequent with eplerenone treatment than with placebo. One thyroid cancer was reported in an eplerenone patient.

- Two adrenal adenomas were reported in eplerenone patients and none in placebo patients.

- Prostate cancers were reported significantly less frequently in eplerenone-treated males (0.4%) compared to placebo-treated males (0.04%). Breast cancer was only reported in eplerenone females (0.3%).

3.5.3. Conclusions

Eplerenone appears to be effective in improving survival in patients with HF post-MI, with a relative risk reduction of about 15%. The potential adverse effects, such as hyperkalemia, do not appear to interfere with this survival improvement. Sex-hormone related AEs were not a major problem in EPHESUS. The possibilities of effects on sex-hormone-related neoplasms, adrenal adenomas, or thyroid function are not major issues for this HF post-MI indication; they may be for the hypertension indication.

4. RALES, Study IG5-94-02-004

Study IG5-94-02-004 is entitled "Randomized Aldactone® Evaluation Study (RALES): Comparison of Spironolactone vs. Placebo on Mortality in Patients with Severe Heart Failure." It is referenced in this review as RALES. It was an international, randomized, double-blind, placebo-controlled, parallel-group study of spironolactone in addition to standard treatment in patients with severe heart failure (HF), NYHA class III or IV.

Because spironolactone is another aldosterone receptor antagonist, this study provides additional information on the effects of such drugs in HF.

COMMENT: Note that the patient population for RALES (class III-IV HF) is slightly different than for EPHESUS (LVEF = 40% and diabetic or clinical evidence of HF post MI).

4.1. Sites and Investigators

One hundred ninety-five investigators enrolled 1,663 patients at 195 sites in 15 countries. The number of patients by country and treatment are shown in the following table.

Table 67: Reviewer's Patients by Country in RALES

Country	Placebo	Spironolactone	Total	Percent
Belgium	64	66	130	8%
Brazil	188	184	372	22%
Canada	32	32	64	4%
France	195	187	382	23%
Germany	9	11	20	1%
Japan	8	6	14	1%
Mexico	17	20	37	2%
Netherlands	119	117	236	14%
New Zealand	8	9	17	1%
South Africa	10	9	19	1%
Spain	130	124	254	15%
Switzerland	9	8	17	1%
United Kingdom	14	13	27	2%
United States	26	24	50	3%
Venezuela	12	12	24	1%
Total	841	822	1663	100%

The mean number of patients per site was 8.5 (median 7, range 1 to 64). The five sites contributing the most patients (29 to 64) were all in Western Europe. Overall 64% of the patients were from Western Europe and 26% were from Latin America.

COMMENT: Note that few patients were enrolled in the US.

4.2. Background

4.2.1. Initial Protocol

The earliest protocol provided in the NDA is dated July 10, 1995. It incorporated the first four amendments and three administrative changes. The protocol was amended further

five times and administratively changed two more times prior to completion of the study as described in the next section.

4.2.2. Protocol Amendments

- Amendment 1, dated 20 December 1994, allowed increase of the spironolactone dose to 50 mg QD after the week 8 visit.

- Amendment 2, dated 16 January 1995, clarified inclusion criterion number five regarding the prestudy time limitation for the diagnosis of HF.

- Amendment 3, dated 25 March 1995, specified an interim analysis plan and added CRF 702.

- Amendment 4, dated 10 May 1995, described the difference in packaging of clinical supplies for the Japanese study sites to accommodate Japanese Regulatory Requirements and modified CRFs accordingly.

- Amendment 5, dated 25 October 1995, allowed for six month proANF sample to be collected and revised CRF 800 used by the Primary Endpoint Committee. Other cardiovascular death was changed from "Including renal-artery thrombosis, endocarditis, pulmonary emboli, bronchitis and concomitant heart failure, occlusion of femoral arterial graft, and heart failure associated with melena (gastric ulcer)" to "Including renal-artery thrombosis, endocarditis, pulmonary emboli, and occlusion of femoral arterial graft."

- Amendment 6, dated 2 February 1996, excluded patients taking Ibopamine.

- Amendment 7, dated 22 March 1996, revised the date of study termination to December 1993, deleted the performance of an interim analysis by G.D. Searle and allowed the DSMB to establish rules for interim analyses and early termination, redefined a "completed" patient from one whose is receiving study medication at the time the study is terminated to one whose vital status can be determined at the end of the study, changed the sample size estimates to use SOLVD and CONSENSUS trial results.

- Administrative Change 4, dated 10 April 1996, added Concurrent Medications and Adverse Signs and Symptoms CRFs, Telephone Contact CRFs, CRFS for months 42, 48, and 45, and CRF600 for transitioning from visit to telephone contact, and revised the end of study CRF and the sudden death definition.

- Amendment 8, date 7 October 1996, added a quality of life questionnaire in Brazil, Canada, and France.

- Amendment 9, dated 19 November 1996, revised secondary objectives to include sub-categories for HF aggravation, atrial flutter/fibrillation or supraventricular tachycardia, stable angina, and stroke; dropped HF signs and symptoms from the Signs and Symptoms CRFs; determined "expectedness" for serious adverse events based on spironolactone prescribing information; revised the sudden cardiac death definition to include unwitnessed deaths and shortened the other cardiovascular death definition; revised CRF 801 categorizations and format; included unnumbered Concurrent Medications CRF; and added a sodium retention substudy in Brazil.

- Administrative Change 5, dated 3 February 1998, revised instructions for unused clinical supplies destruction and revised the product package insert for ex-US sites.

4.2.3. Study Dates

The first patient was randomized on March 24, 1995, and the last on December 31, 1996. The study was terminated on August 24, 1998, because of a statistically significant and clinically meaningful reduction in mortality in the spironolactone-treated group compared to the placebo group as determined by the DSMB.

4.3. Study Design

RALES was an international, randomized, double-blind, placebo-controlled, parallel-group study of spironolactone 25 mg once daily vs. placebo in addition to standard treatment (loop diuretic, ACE inhibitor if tolerated) in patients with NYHA class III or IV heart failure. Patients returned for evaluation every four weeks for the first three months, every three months for the remainder of the first year, and every six months thereafter. Patients were followed for deaths and hospitalizations for the duration of the trial.

Several review and oversight committees were involved in the conduct of this study. In addition to a Steering Committee, an Executive Committee and a DSMB, a Primary Endpoint Committee classified the cause of death for each patient who died during the trial and a Non-Fatal Hospitalization Endpoint Committee classified the cause of non-fatal hospitalization for each patient who was hospitalized during this trial.

4.3.1. Objectives

The primary objective was to evaluate the safety and efficacy of spironolactone plus standard therapy vs. placebo plus standard therapy on long-term mortality (minimum three year follow-up) in patients with severe HF. The secondary objectives were to compare the efficacy of spironolactone vs. placebo by assessing the following:

1. Cardiac mortality (i.e., sudden cardiac death, myocardial infarction, progressive HF)

2. Incidence of cardiac mortality plus hospitalization for cardiac reasons defined as hospitalization for HF aggravation, atrial flutter/ fibrillation or supraventricular tachycardia, ventricular arrhythmias, angina, myocardial infarction, or stroke, as well as for each category analyzed separately

3. Incidence of hospitalization for cardiac reasons

4. Changes in NYHA functional classification

5. Quality of life

4.3.2. Number of Subjects, Randomization, and Blinding

Randomization used a standard permutated-block randomization scheme with a block size of four. Ultimately 1,663 subjects were randomized, 822 to spironolactone and 841 to placebo.

Study medication was provided by the sponsor through the Searle Pharmacy in U.S., through [redacted], and through [redacted]) in Europe. It was provided as spironolactone 25 mg tablets and matching placebo tablets identical in appearance, color, and taste. Two-part labels were computer-generated for the double-blind treatment. One part of the label, containing study and patient information was attached to the container; the other part was a tear-off portion containing the same information plus a sealed pouch with the identity of the assigned treatment. The randomization code could be broken if an emergency situation arose that in the investigator's opinion required knowledge of the code and the medical monitor could not be reached. The date and reason(s) for breaking the code must have been submitted to the sponsor by the investigator.

4.3.3. Inclusion and Exclusion Criteria

Inclusion criteria were the following:

1. Male or female at least 21 years of age
2. If female of childbearing potential, employing adequate contraceptive measures
3. Not pregnant
4. All of the following evidence of severe HF:

   a. ejection fraction (EF) =35% (based on contrast ventriculography, radionuclide scan, or echocardiography) within the six months prior to the first dose of study medication (with no significant intercurrent event);
   b. a history of NYHA functional classification IV within the six months prior to the first dose of study medication; and
   c. a NYHA functional classification of III or IV at the time of the first dose of study medication;
5. Diagnosed with HF regardless of etiology at least six weeks prior to the first dose of study medication
6. Receiving the following conventional medical therapy at the time of the first dose of study medication:
   a. a loop diuretic; and
   b. for patients not previously found to be intolerant of such therapy, an ACE inhibitor;
7. Willing and capable of complying with the requirements of the protocol
8. Informed consent

Exclusion criteria were the following:

1. Any life-threatening disease, other than HF, (including patients with known, or suspected, myocarditis or with automatic implanted cardioverter/defibrillators) or had primary hepatic failure
2. Active malignancy of any type, or history of malignancy (except basal cell)
3. Heart transplant or likely to have heart transplant surgery
4. Clinically significant, operable valvular disease other than mitral or tricuspid regurgitation
5. Congenital heart disease
6. Unstable angina at the time of the first dose of study medication
7. Intrinsic renal disease at the time of the first dose of study medication (defined as a serum creatinine level >220 mmol/L or >2.5 mg/dL; for patients with a baseline serum creatinine level >160 mmol/L or >1.8 mg/dL, increases within the previous week were not to exceed 25%)
8. Potassium levels above 5.0 mEq/L at the time of the first dose of study medication
9. Other clinically significant abnormalities in biochemistry values at the time of the first dose of study medication that the investigator judged would interfere
10. Potassium-sparing diuretic within the previous two weeks
11. Any investigational medication within 30 days or scheduled to receive an investigational drug other than study medication during the course of the study
12. Known hypersensitivity to spironolactone or related compounds
13. Previously been admitted to this study or to the spirono lactone dose-ranging study
14. Currently on ibopamine

4.3.4. Dosage and Administration

Patients were started on spironolactone 25 mg orally once daily (QD) or matching placebo. Following a one- to four-week stabilization period, patients who were tolerant of the initial dosage regimen continued on the initial dose (one 25 mg tablet of spironolactone or placebo QD). Patients who were intolerant of the initial dosage regimen had their dose decreased to one tablet every other day (QOD; spironolactone 25 mg or placebo). Patients who were tolerant of one tablet QD at week 8 may have had their dose increased to two tablets QD (spironolactone 50 mg or placebo) at the discretion of the investigator.

4.3.5. Safety and Efficacy Endpoints

The primary efficacy endpoint was all cause mortality. Secondary efficacy endpoints included the measures listed under 4.3.1 Objectives above. Safety measures included physical examination, clinical laboratory tests (particularly creatinine, potassium, and sodium), and adverse events.

4.3.6. Statistical Considerations

4.3.6.1. Sample Size Calculations

This study was originally designed as an event-driven trial (540 deaths, estimated enrollment of 1400 patients.) However, it was later changed to a maximum duration trial. The designed duration of this study became 57 months (starting in March 1995 and ending in December 1999). The event rate (deaths) for the placebo group in the RALES study was based on the results of two previous studies, SOLVD and CONSENSUS. Sample size estimates based on the log-rank test with 90% power ranged from 2092 with 20% treatment effect, 25% in NYHA class IV, and 1037 deaths to 652 with 25% treatment effect, 100% in NYHA class IV, and 456 deaths.

The DSMB met regularly to examine efficacy and safety data. It monitored mortality with a stopping rule based on a Lan-DeMets use function and an O'Brien-Fleming boundary with a two-tailed a of 0.05. At each of its meetings, the DSMB calculated the cumulative type I error with respect to efficacy. At the fifth planned interim analysis (with 620 deaths), the observed effect of spironolactone on the risk of death from all causes exceeded the prespecified critical z value. Hence the trial was stopped on August 24, 1998, at the recommendation of the DSMB. Ultimately 1663 patients were randomized and 670 were dead at the end of study.

4.3.6.2. Analysis Cohorts and Missing Data

For deaths and hospitalizations all randomized patients were to be followed for the duration of the trial. For deaths, missing data are handled by censoring with the log-rank test.

4.3.6.3. Pre-specified Analyses

The log-rank test was specified for the analysis of the primary endpoint, mortality.

4.4. Results

4.4.1. Study Implementation

4.4.1.1. Disposition of Subjects

The disposition of subjects is shown in the following table.

Table 68: Sponsor's Disposition of Patients in RALES

	Placebo N=841		Spironolactone N=822		Total N=1663	
Patients with at least one dose	839	(99.8%)	819	(99.6%)	1658	(99.7%)
Alive at end of study	455	(54.1%)	538	(65.5%)	993	(59.7%)
Not on study medication at end of study	100	(11.9%)	114	(13.9%)	214	(12.9%)
Reason for stopping study medication						
Adverse sign or symptom	22	(2.6%)	36	(4.4%)	58	(3.5%)
Noncompliance	52	(6.2%)	48	(5.8%)	100	(6.0%)
Pre-existing violation	3	(0.4%)	3	(0.4%)	6	(0.4%)
Treatment failure	14	(1.7%)	11	(1.3%)	25	(1.5%)
Unknown	9	(1.1%)	16	(1.9%)	25	(1.5%)
On study medication at end of study	337	(40.1%)	411	(50.0%)	748	(45.0%)
Unknown	18	(2.1%)	13	(1.6%)	31	(1.9%)
Dead at end of study	386	(45.9%)	284	(34.5%)	670	(40.3%)
Died while not on study medication	111	(13.2%)	110	(13.4%)	221	(13.3%)
Reason for stopping study medication						
Adverse sign or symptom	20	(2.4%)	27	(3.3%)	47	(2.8%)
Noncompliance	24	(2.9%)	23	(2.8%)	47	(2.8%)
Pre-existing violation	3	(0.4%)	2	(0.2%)	5	(0.3%)
Treatment failure	6	(0.7%)	4	(0.5%)	10	(0.6%)
Unknown	58	(6.9%)	54	(6.6%)	112	(6.7%)
Died while on study medication	275	(32.7%)	172	(20.9%)	447	(26.9%)
Unknown	0	(0.0%)	2	(0.2%)	2	(0.1%)
Heart transplants	11	(1.3%)	8	(1.0%)	19	(1.1%)

Thirty-five (4%) placebo and 37 (4%) spironolactone patients not known to have died have last follow-up dates prior to the study cutoff date of August 24, 1998. The median length of missing follow-up is 365 days (mean 405 days), with an interquartile range of 90 to 646.

COMMENT: The follow-up rate in RALES is only fair.

4.4.1.2. Subject Demographics and Baseline Characteristics

4.4.1.2.1. Overall Baseline Characteristics

Subject demographics were well balanced between the two groups as shown in the following table.

Table 69: Reviewer's Subject Demographics in RALES

	Placebo	Spironolactone
Mean age	65.2	65.3
Median age	67	67
Age range	22-91	21-90
Age < 50, %	10%	11%
Age ≥ 65, %	59%	59%
Age ≥ 75, %	20%	22%
Male, %	73%	73%
White, %	87%	87%
Black	8%	7%

Other baseline characteristics were also well-balanced between the two groups as shown in the following table.

Table 70: Reviewer's Other Baseline Characteristics in RALES

	Placebo	Spironolactone
Mean ejection fraction	0.25	0.26
Mean pulse	81	81
Mean SBP	121.6	122.8
Mean DBP	74.5	74.7
Diabetic, %	23%	21%
Hypertensive, %	24%	23%
History of MI, %	29%	28%
History of stroke, %	6%	4%
History of afib, %	10%	11%
NYHA class II, %	0.4%	0.5%
NYHA class III, %	69%	72%
NYHA class IV, %	31%	27%
Ischemic etiology, %	54%	55%

COMMENT: Note that the typical patient was an older white male. Baseline characteristics appear to have been well-balanced between the two groups, although slightly more placebo patients were NYHA class IV.