Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms

EMPHASIS-HF*

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ClinicalTrials.gov, NCT00232180

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* Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure

Disclosure Information

• Faiez Zannad	Grants/contracts, consultant (moderate)
• John JV McMurray	Grants/contracts, consultant (moderate)
• Henry Krum	Grants/Contracts, consultant (moderate)
• Dirk J Van Veldhuisen	Grants/Contracts, consultant (moderate)
• Karl Swedberg	Grants/Contracts, consultant (moderate)
• Harry Shi	Pfizer employee
• John Vincent	Pfizer employee
• Stuart J Pocock	Grants/Contracts, consultant, (moderate)
• Bertram Pitt	Grants/Contracts, consultant, (moderate)

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All analyses were performed or replicated independently at the London School of Hygiene and Tropical Medicine (Tim Collier) .

Eplerenone is approved for treating heart failure after myocardial infarction in 72 countries.

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Angiotensin-converting enzyme inhibitor and spironolactone combination therapy. New objectives in congestive heart failure treatment.

- ACE inhibitors block the RAAS, including aldosterone production.
- Aldosterone antagonists act on the kidney with potassium-sparing diuretic effects
- Combining an aldosterone blocker to an ACE inhibitor is unsafe and can produce hyperkalemia and worsening renal function

ACE inhibitors block the RAAS, including aldosterone production.
Aldosterone antagonists act on the kidney with potassium-sparing diuretic effects

- Aldosterone and ACE inhibitors, independent and distinct effects on ACE inhibitors.
- Aldosterone antagonists exert direct cardiac and vascular effects ….
- Combining an ACE inhibitor and spironolactone may achieve a more complete inhibition of the whole RAAS and may produce further clinical benefits ».

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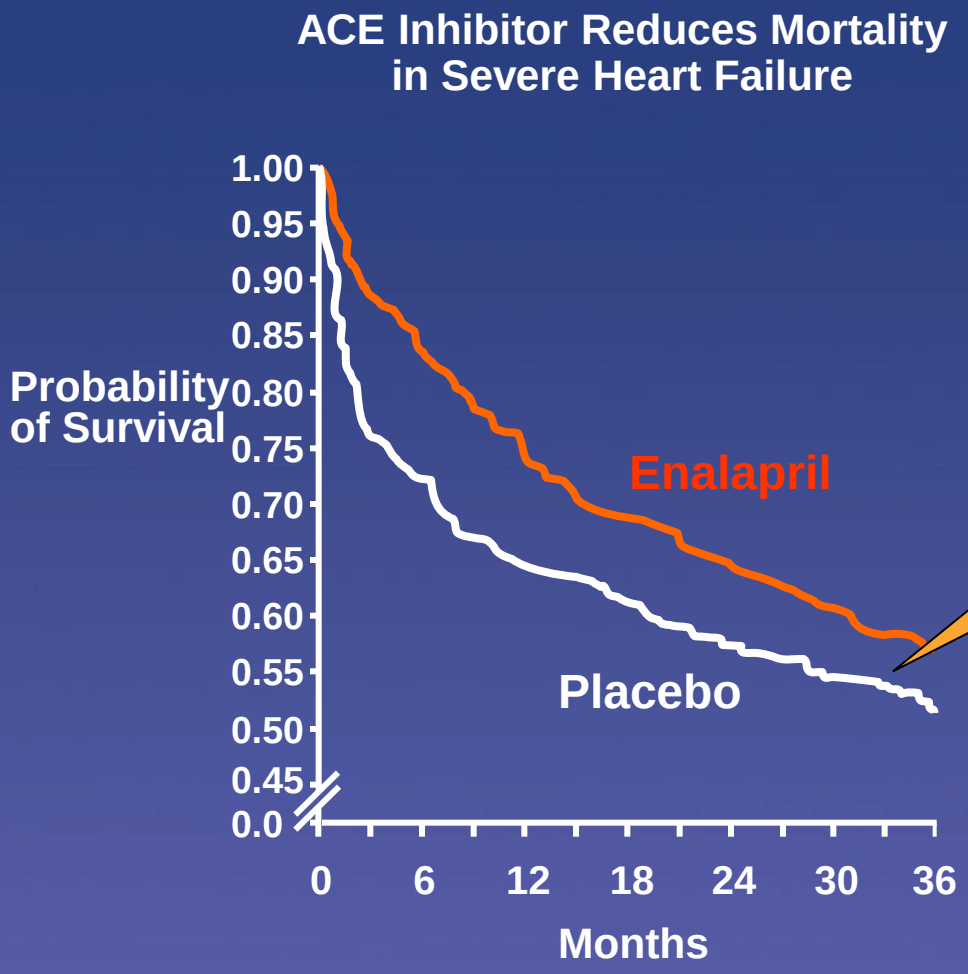
Zannad F, Am J Cardiol. 1993;71:34A-39A.

ACE Inhibitor Plus Aldosterone Blockade: CONSENSUS 1



48% of pts were taking spironolactone Doses > 75 mg/d

Data derived from the CONSENSUS Trial Study Group. *N Engl J Med.* 1987;316:1429.

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Mineralocorticoid Receptor Antagonists (MRAs) in Heart Failure

Survival
30% RR , P < 0.001

Total Mortality
15% RR, *P*=0.008

HYPOTHESIS:

Eplerenone, added to evidence-based therapy, is associated with improved clinical outcomes in patients with systolic heart failure and mild symptoms

RALES (LVSD, CHF severe symptoms)
Pitt B, Zannad F, Remme WJ, et al. *N Engl J Med.* 1999

EPHESUS (LVSD + HF after MI)
Pitt B, Remme W, Zannad F, et al. *N Engl J Med.* 2003

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Inclusion Criteria

- Inclusion
  - > 55 years of age
  - NYHA functional class II
  - Ejection fraction ≤ 30% (or, if between 31% and 35%, QRS >130 msec)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated).
  - Within 6 months of hospitalization for a cardiovascular reason [or, if no such hospitalization, BNP ≥ 250 pg/ml or NT-pro-BNP ≥500 pg/ml (males) or 750 pg/ml (females)]
- Exclusion
  - Serum potassium > 5.0 mmol/L
  - eGFR < 30 ml/min/1.73 m^2
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition

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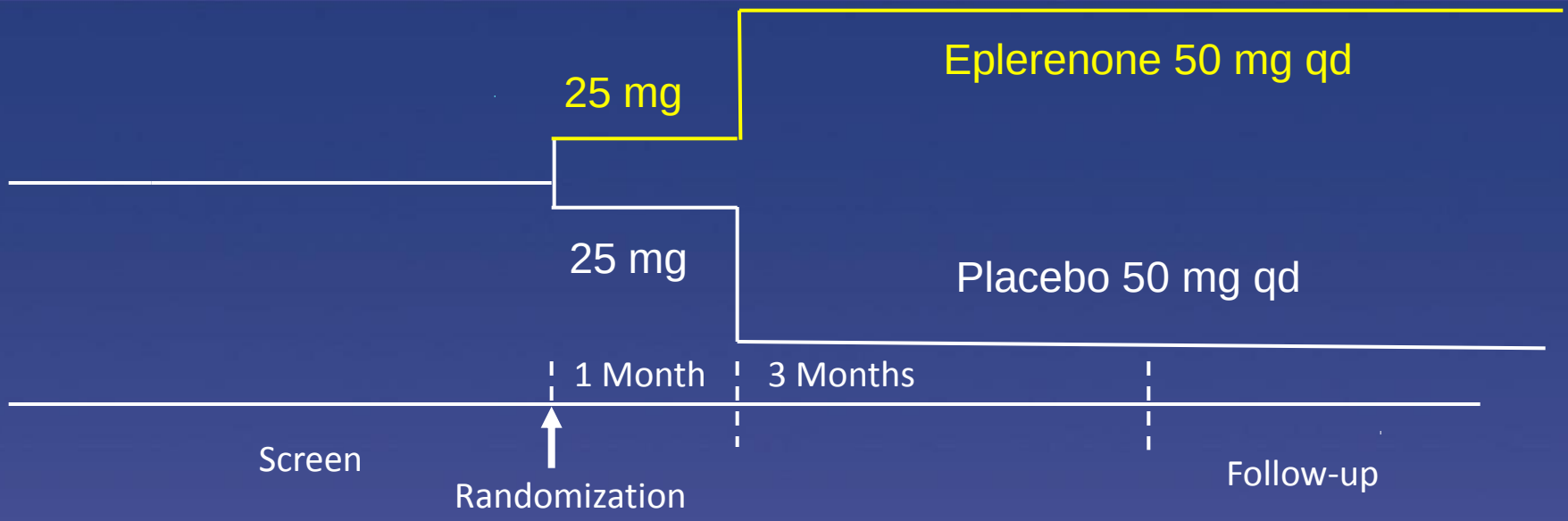
Study Design and Sample Size



- Primary endpoint: CV death or hospitalization for HF
- The initial assumptions :
  - 2584 patients,
  - annual event rate 18% in the placebo group,
  - 813 primary events in 48 months,
  - 80% power to detect an 18% risk reduction (alpha=0.05).
- In June 2009 the overall blinded event rate was lower than expected and the sample size was increased to 3100 patients

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Early Stopping

- May 6th, 2010:
  - DSMC's second planned interim analyses showed overwhelming benefit (two-sided P-value = 0.000001 in favor of eplerenone) beyond the prespecified stopping-boundary for benefit.
- May 9th, 2010 :
  - The Executive Committee agreed to stop patient enrollment.
- May 25th , 2010:
  - Was chosen as the trial cut-off date for the analyses and reporting.

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Statistical Analyses

- Efficacy analyses were performed on all randomized patients and according to the intention-to-treat principle.
- Adjusted for the following prespecified baseline prognostic factors
  - Age, eGFR, ejection fraction, body mass index, hemoglobin, heart rate, systolic blood pressure, diabetes mellitus, history of hypertension, prior myocardial infarction, atrial fibrillation, and left bundle branch block or QRS duration >130 milliseconds.
- Unadjusted sensitivity analyses were also performed.

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Results

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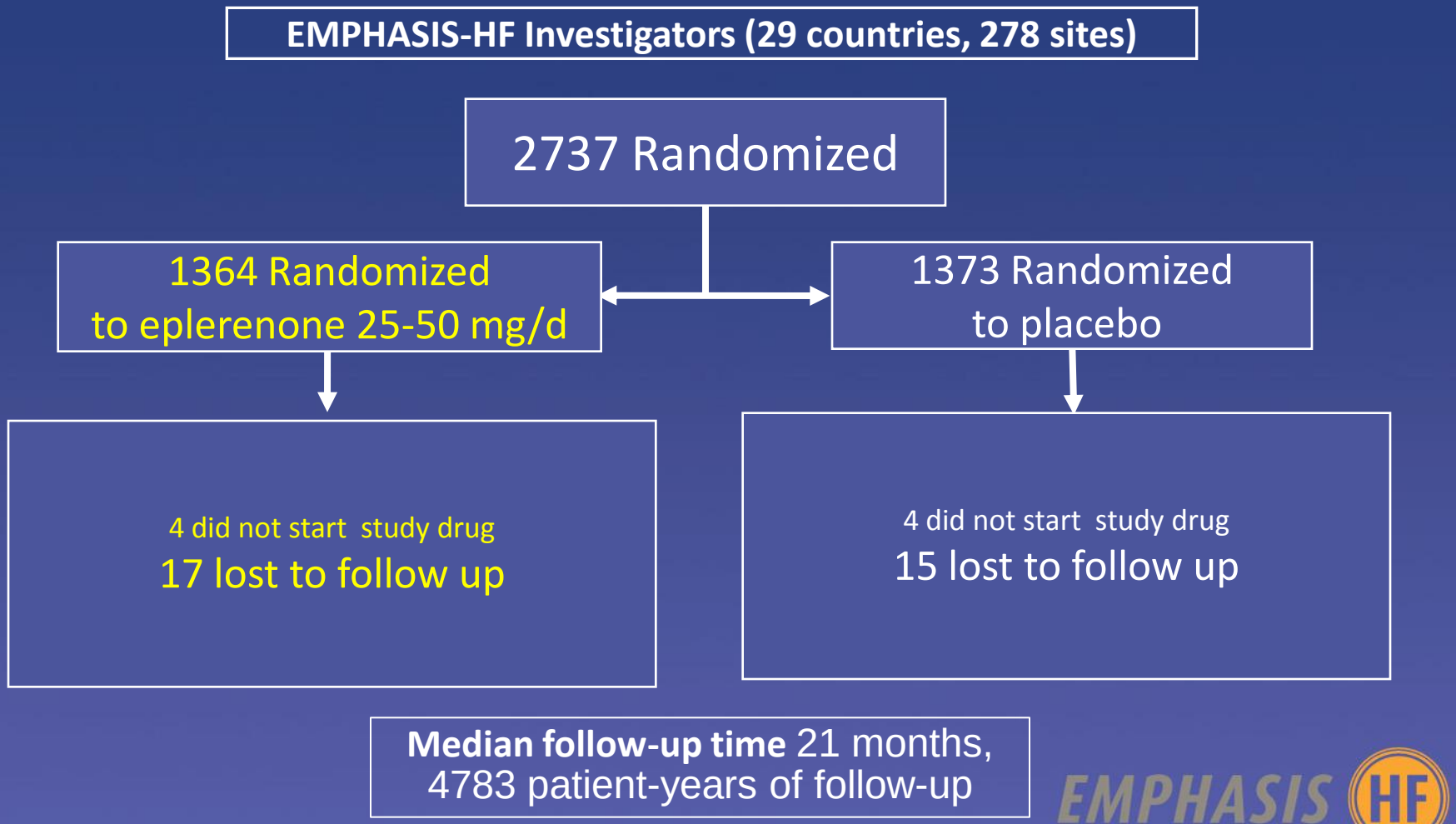
Disposition of Patients



Baseline Characteristics

Characteristic	Eplerenone (N=1364)	Placebo (N=1373)
Mean age — yr	68.7 (7.7)	68.6 (7.6)
Female sex — no. (%)	309 (22.7%)	301 (21.9%)
Hx Hypertension — no. (%)	910 (66.7)	909 (66.2)
Blood pressure – mm Hg	124 ±17/75 ± 10	124±17/75±10
Diabetes mellitus— no. (%)	459 (33.7)	400 (29.1)
Serum Creatinine – mg/dl	1.14 (0.30)	1.16 (0.31)
Estimated GFR ml/min/1.73 m^2	71.2 (21.9)	70.4 (21.7)
< 60 ml/min/1.73 m^2 – no. (%)	439 (32.2)	473 (34.5)
Serum Potassium – mmol/liter	4.3 (0.4)	4.3 (0.4)

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Baseline Characteristics

Characteristic	Eplerenone (N=1364)	Placebo (N=1373)
Ischemic heart disease – n (%)	951 (69.7)	935 (68.1)
Hx Myocardial infarction – n (%)	686 (50.3)	695 (50.6)
Hx Hospitalization for HF – n (%)	714(52.3)	726(52.9)
LVEF - %	26.2±4.6	26.1±4.7
Atrial fibrillation or flutter – n (%)	409 (30.0)	435 (31.7)
QRS duration >130 msec in nonpaced baseline ECG – n (%)	298/1167 (25.5)	305/1158 (26.3)
LBB block – n (%)	339 (24.9)	349 (25.4)

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Baseline Therapy

Characteristic – n (%)	Eplerenone (N=1364)	Placebo (N=1373)
ICD	178 (13.0)	184 (13.4)
CRT-P	38 (2.8)	22 (1.6)
CRT-D	74 (5.4)	99 (7.2)
Diuretic	1150 (84.3)	1176 (85.7)
ACEi or ARB or both	1282 (94.0)	1275 (92.9)
Beta-blocker	1181 (86.6)	1193 (86.9)
Digitalis glycosides	363 (26.6)	377 (27.5)
Antiarrhythmic drug	196 (14.4)	192 (14.0)
Antithrombotic drug	1205 (88.3)	1214 (88.4)

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Patient Follow-up and Dosing

	Eplerenone	Placebo
Discontinuations in surviving patients (%)	16.3%	16.6%
Discontinuations for AE – n (%)	188 (13.8%)	222 (16.2%)*
Mean dose at month 5 (mg/day)	39.1 ±13.8	40.8 ±12.9

* p = 0.09

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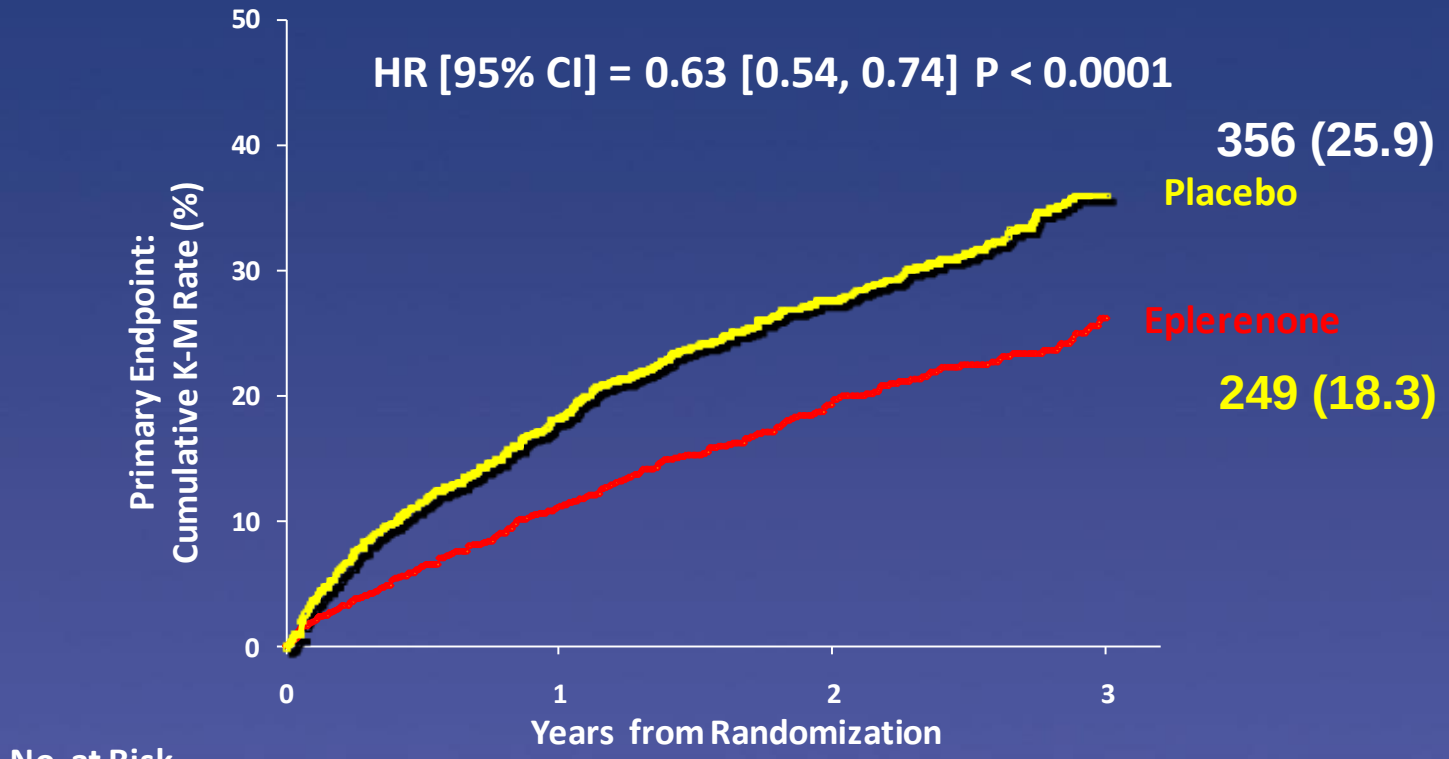
Primary Endpoint Cardiovascular Death or Hospitalization for HF



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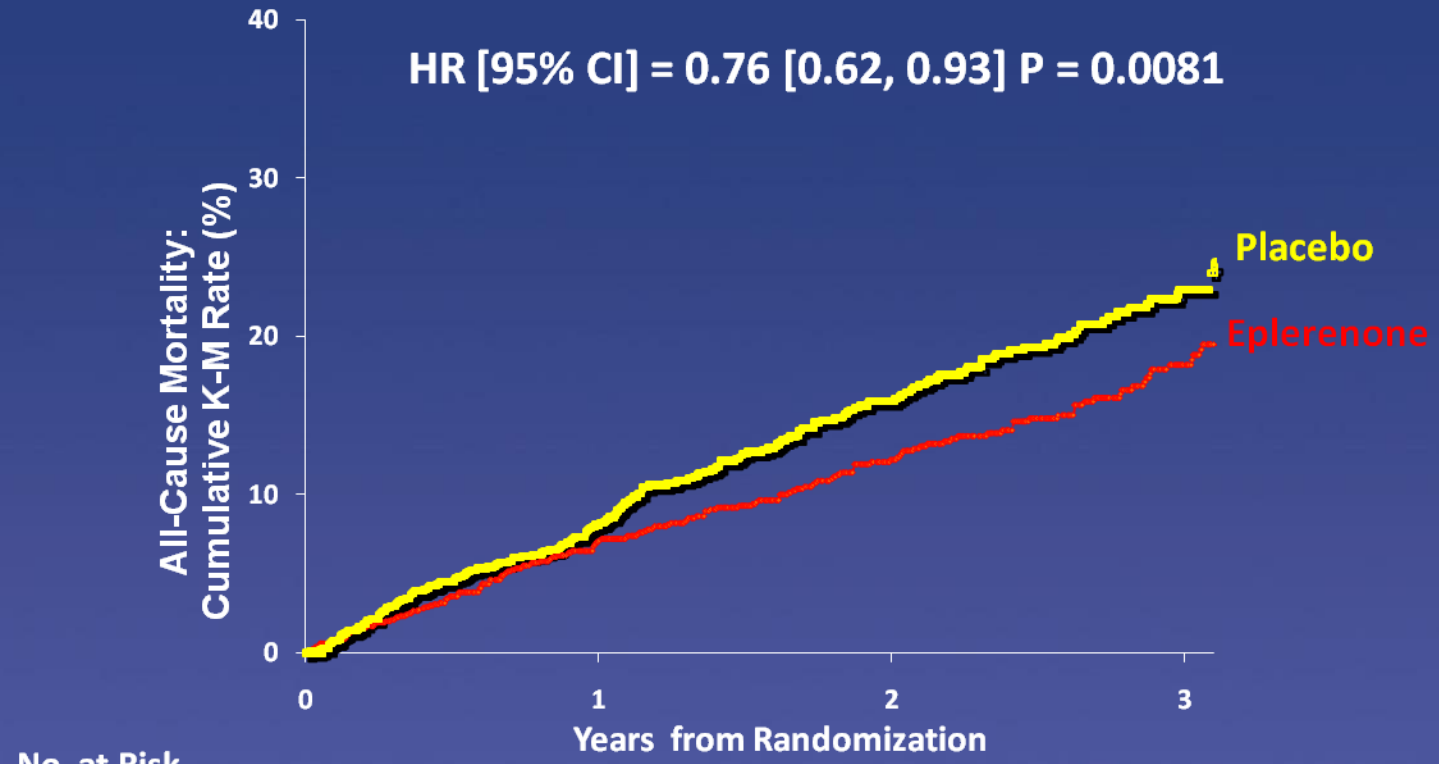
*Unadjusted HR 0.66; 0.56, 0.78; p<0.0001

Mortality From Any Cause



No. at Risk				
Placebo	1373	947	587	242
Eplerenone	1364	972	625	269

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*Unadjusted HR, 0.78; 0.64, 0.95; p=0.01

Hospitalization From Any Cause

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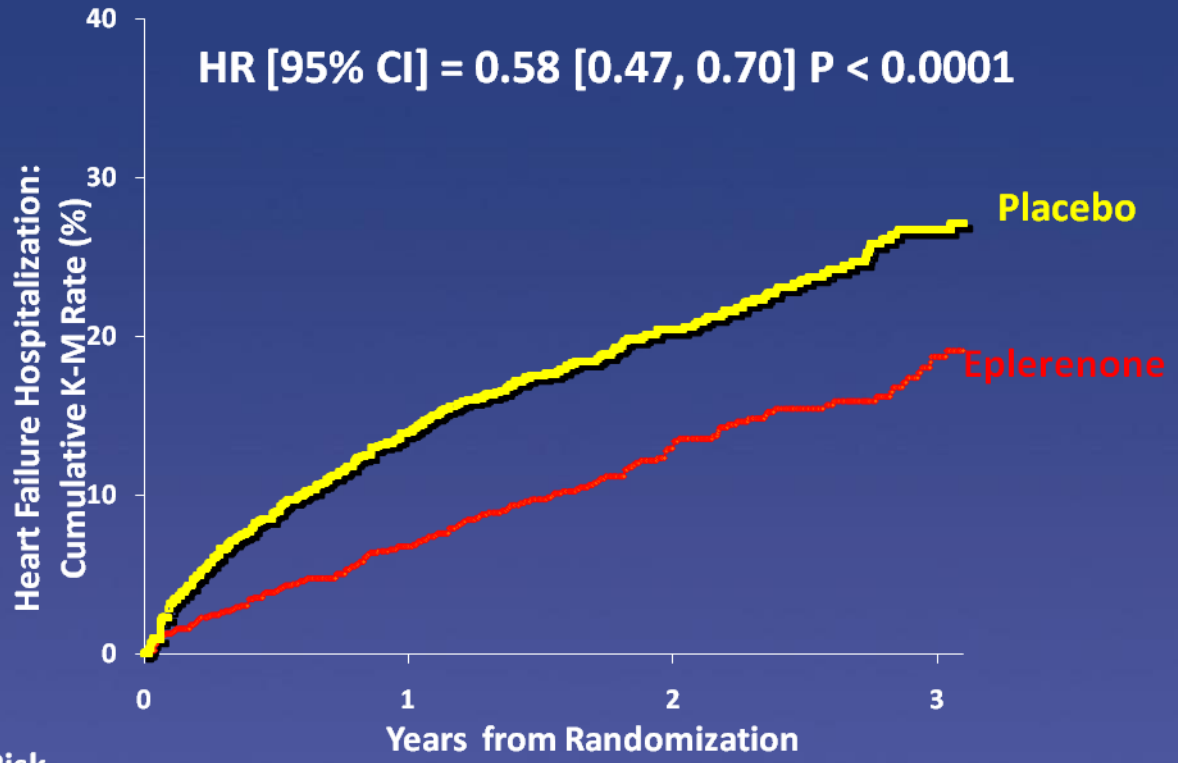
*Unadjusted HR, 0.78; 0.69, 0.89; p <0.0001

Heart Failure Hospitalization



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

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*Unadjusted HR, 0.61; 0.50, 0.75; p <0.0001

Other Adjudicated Secondary Outcomes

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Hazard Ratio (95% CI)	P Value
Secondary outcomes				
Death from any cause	171 (12.5)	213 (15.5)	0.76 (0.62, 0.93)	0.008
Hospitalization from any cause	408 (29.9)	491(35.8)	0.77 (0.67, 0.88)	<0.0001
Hospitalization for heart failure	164 (12.0)	253 (18.4)	0.58 (0.47, 0.70)	<0.0001
Death from any cause or hospitalization for heart failure	270 (19.8)	376 (27.4)	0.65 (0.55, 0.76)	<0.0001
Death from heart failure or hospitalization for heart failure	170 (12.5)	262 (19.1)	0.58 (0.48, 0.70)	<0.0001
Cardiovascular death	147 (10.8)	185 (13.5)	0.76 (0.61, 0.94)	0.01

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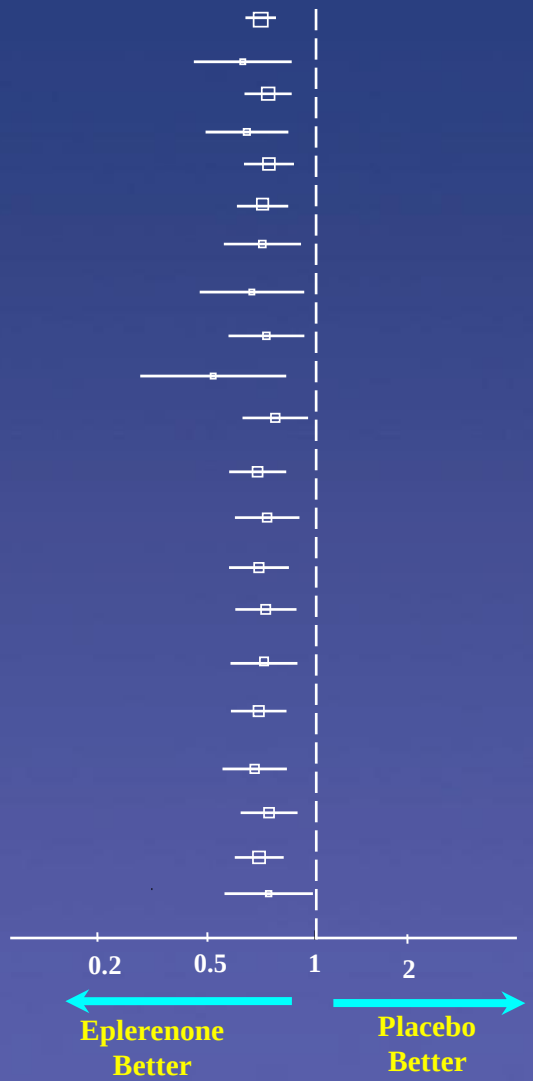
All results are adjusted for prespecified baseline characteristics. Unadjusted analyses revealed similar results

Subgroup Analysis – Primary endpoint

Baseline Variable	Subgroup	No. of Patients	P-value for Interaction
Overall		2,737	
Gender	Female	610	0.36
	Male	2,127	
Age	< 65 yr	883	0.37
	>= 65 yr	1,854	
Age	< 75 yr	2,080	1.00
	>= 75 yr	657	
Region	Asia/Middle East/ Africa	380	0.46
	East Europe	911	
	South/North America	346	
	West Europe / Australia	1,100	
Systolic BP	< Median	1,352	0.65
	>= Median	1,384	
Pulse Pressure	< Median	1,272	0.75
	>= Median	1,464	
Heart Rate	< Median	1,340	0.79
	>= Median	1,383	
eGFR	< 60 ml/min/1.73m2	912	0.50
	>= 60 ml/min/1.73m2	1,821	
Primary Diagnosis	Ischaemic Heart Failure	1,886	0.73
	Non-Ischaemic Heart Failure	846	



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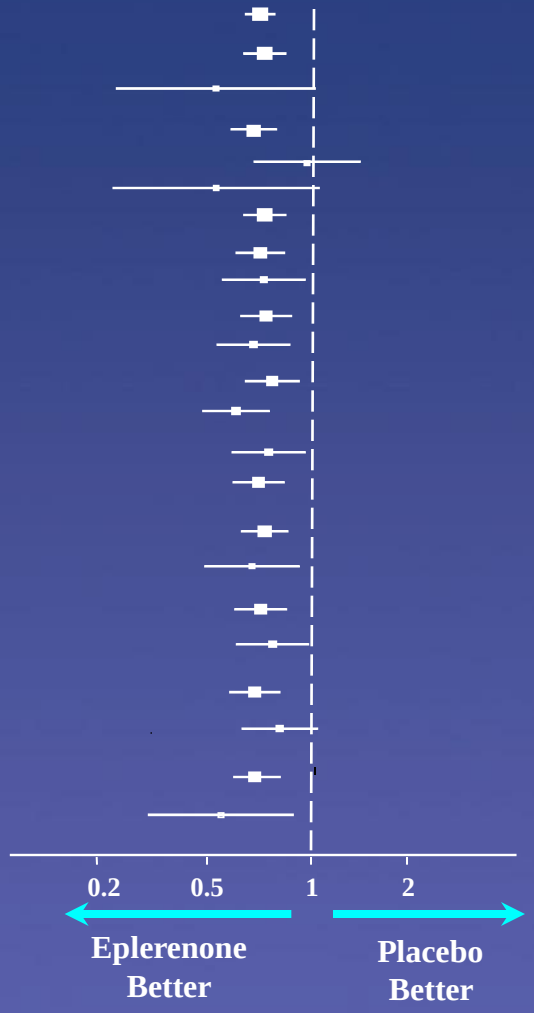
Subgroup Analysis – Primary endpoint (cont'd)

Baseline Variable	Subgroup	No. of Patients	P-value for Interaction
Overall		2,737	
Prior Beta Blocker + ACEI + ARB	No	2,584	0.40
	Yes	153	
Prior Beta Blocker	Yes	2,421	0.06
	No	316	
Prior ACEI or ARB	N o	141	0.34
	Yes	2,596	
LVEF	< 30%	1,912	0.89
	>= 30%	819	
Hx. of Atrial Fibrillation	No	1,891	0.59
	Yes	844	
Hx. of Diabetes	No	1,877	0.10
	Yes	859	
Hx. of Hypertension	No	917	0.69
	Yes	1,819	
Prior CRT or ICD Procedures	No	2,120	0.62
	Yes	615	
QRS	<= 130 msec	1,811	0.61
	> 130 msec	871	
LBB Block Present	No	2,048	0.29
	Yes	688	
Enrolment Criterion	Prior Hosp <180 Days	2,282	0.39
	Met BNP / ProBNP Criterion	385	



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Safety – Relevant adverse events

(Investigator reported events)

	Patients with an adverse event — no. (%)		
Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	979 (72)	1007 (73.6)	0.37
Hyperkalemia – n (%)	109 (8)	50 (3.7)	<0.001
Hypokalemia – n (%)	16 (1.2)	30 (2.2)	0.05
Renal failure – n (%)	39 (2.9)	42 (3.1)	0.82
Hypotension – n (%)	46 (3.4)	37 (2.7)	0.32
Gynecomastia and other breast disorders – n (%)	10 (0.7)	14 (1.0)	0.54

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Safety – drug discontinuation due to AEs

(Investigator reported events)

	Patients with an adverse event leading to drug withdrawal — no. (%)		
Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
All	188 (13.8)	222 (16.2)	0.09
Hyperkalemia – n (%)	15 (1.1)	12 (0.9)	0.57
Hypokalemia – n (%)	0	3 (0.2)	0.25
Renal failure – n (%)	4 (0.3)	6 (0.4)	0.75
Hypotension – n (%)	0	3 (0.2)	0.25
Gynecomastia and other breast disorders – n (%)	2 (0.1)	2 (0.1)	1.00

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Safety – Prespecified Adjudicated events

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Hazard Ratio (95% CI)	P Value
Hospitalization for worsening renal failure	9 (0.7)	8 (0.6)	0.97 (0.37, 2.58)	0.95
Hospitalization for hyperkalemia	4 (0.3)	3 (0.2)	1.15 (0.25, 5.31)	0.85

No death was attributed to these hospitalizations.

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Safety - Potassium related issues

(Investigator reported events)

	Patients with an adverse event leading to drug withdrawal — no. (%)		
Outcome	Eplerenone (N=1360)	Placebo (N=1373)	P Value
Hyperkalemia (investigator reported AE)	109 (8)	50 (3.7)	<0.001
Hyperkalemia leading to drug discontinuation	15 (1.1)	12 (0.9)	0.57
Serum K+ > 5.5 mmol/L	158 (11.8)	96 (7.2)	<0.001
Serum K+ > 6.0 mmol/L	33 (2.5)	25 (1.9)	0.29
Hospitalization for hyperkalemia (adjudicated)	4 (0.3)	3 (0.2)	0.85

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Summary and Conclusions

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Summary

- The addition of eplerenone to recommended treatment resulted in a
  - 37% reduction in the rate of the composite outcome of death from cardiovascular causes or hospitalization for heart failure.
  - 24% reduction in the rate of death from any cause
  - 23% reduction in the rate of hospitalization from any cause
  - 42% reduction in the rate of hospitalization for heart failure
- The effect of eplerenone on the primary outcome was consistent across all prespecified subgroups.
- NNT
  - To prevent one patient experiencing the primary endpoint, per year of follow up, is 19
  - To postpone one death, per year of follow up, is 51

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Conclusions

- In patients with systolic heart failure and mild symptoms, the addition of eplerenone to recommended medical therapy
  - was well tolerated,
  - improved survival,
  - and prevented hospitalization.

- We believe that the robustness of these findings, in conjunction with the consistent results from the earlier RALES and EPHESUS trials, provides compelling evidence to change medical practice.

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Post-MI LVSD	Preserved LVSF	LVSD Mild CHF	LVSD Moderate CHF	LVSD Severe CHF
AIRE/SAVE	PEP-CHF (Perindopril)	SOLVD		CONSENSUS
CAPRICORN	SENIORS	US Carvedilol/ MERIT/CIBIS/SENIORS		COPERNICUS
OPTIMAAL (Losartan) VALIANT (Valsartan)	CHARM I-PRESERVE	ELITE HEAAL (Losartan) VALHeft/CHARM (Valsartan/Candesartan)		-----?------
EPHESUS (eplerenone)	TOPCAT (Spironolactone)	EMPHASISE-HF (Eplerenone)		RALES (spironolactone)

Changing practice: HF + Low EF

ACEi (ARB)

Beta-Blocker

MR Antagonist (eGFR>30 ml/min)

Device (selected pts)

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Article (10.1056/NEJMoa1009492) published on November 14, 2010, at NEJM.org

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ORIGINAL ARTICLE

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EMPHASIS HF

EMPHASIS-HF: 2737 patients in 29 countries, 278 Investigators

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