

# **EMPHASIS-HF: The effect of eplerenone versus placebo on cardiovascular mortality or heart failure hospitalization in subjects with NYHA class II chronic systolic heart failure: An analysis of the ‘high-risk groups’**

**Bertram Pitt, M.D., John J.V. McMurray, M.D., Henry Krum, M.B., PhD.,  
Dirk J. van Veldhuisen, M.D.,Ph.D., Karl Swedberg, M.D., Ph.D, Harry Shi, M.S.,  
John Vincent, M.B., PhD., Stuart J Pocock, Ph.D. and Faiez Zannad, M.D., Ph.D.  
for the EMPHASIS-HF Committees and Investigators**

**ClinicalTrials.gov, NCT00232180**

\* 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)

EMPHASIS-HF was funded by Pfizer. Inc. 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.

# EMPHASIS-HF Committees

- **Executive Steering Committee**

- Faiez Zannad (Nancy) (co-chairman)
- Bertram Pitt (Ann Arbor) (co-chairman)
- Helmut Drexler (Hannover) (deceased)
- Dirk J. van Veldhuisen (Groningen)
- Henry Krum (Melbourne)
- John McMurray (Glasgow/Boston)
- Karl Swedberg (Göteborg)

- **Independent Data Safety Monitoring Board**

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- Luigi Tavazzi (Cotignola)
- Stuart Pocock (London)
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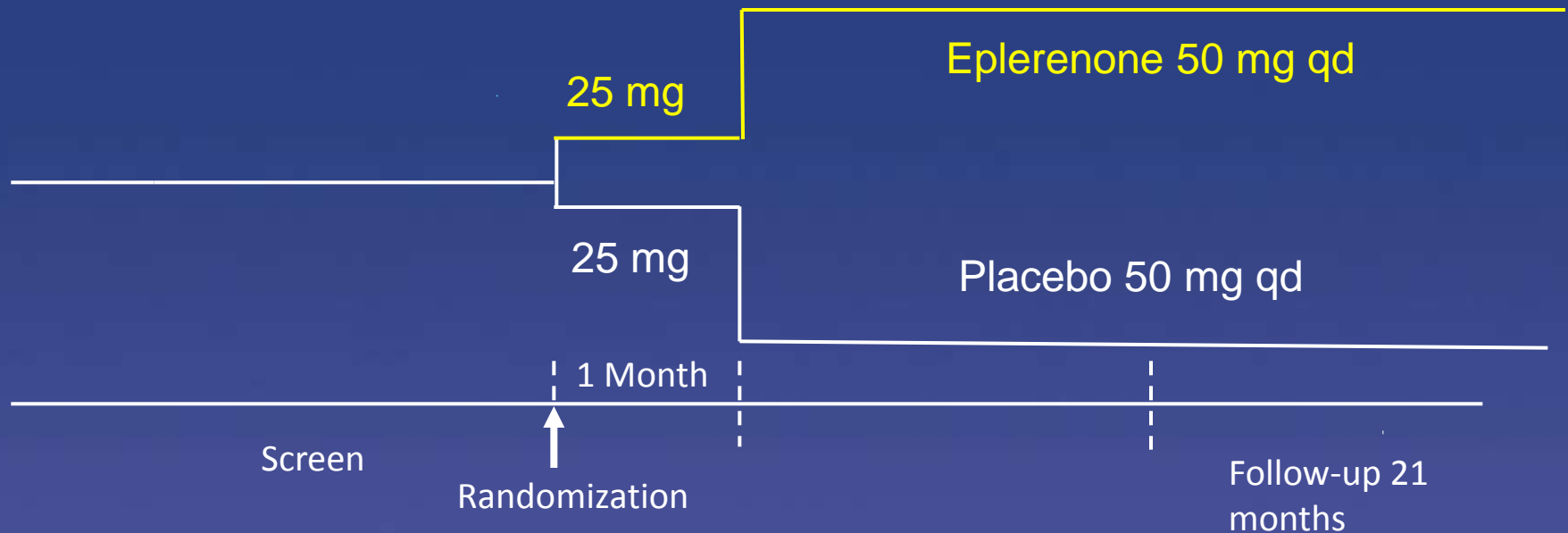
- **Endpoint Adjudication Committee**

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- Andrew Tonkin (Melbourne)
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# Inclusion Criteria

- Inclusion
  - > 55 years of age
  - NYHA functional class II
  - Ejection fraction  $\leq 30\%$  (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  $\geq 250$  pg/ml or NT-pro-BNP  $\geq 500$  pg/ml (males) or 750 pg/ml (females) ]
- Exclusion
  - Serum potassium  $> 5.0$  mmol/L
  - eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>
  - Need for a potassium-sparing diuretic
  - Any other significant comorbid condition

# Study Design



- Primary endpoint: CV death or hospitalization for HF

# Baseline Therapy

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

# Results on Key Clinical Endpoints

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Hazard Ratio (95% CI)	P Value
CV death or HF hospitalization* (Primary Endpoint) (%)	249 (18.3)	356 (25.9)	0.63 (0.54-0.74)	<0.0001
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
Cardiovascular death* (%)	147 (10.8)	185 (13.5)	0.76 (0.61, 0.94)	0.01
Hospitalization for HF* (%)	164 (12.0)	253 (18.4)	0.58 (0.47, 0.70)	<0.0001

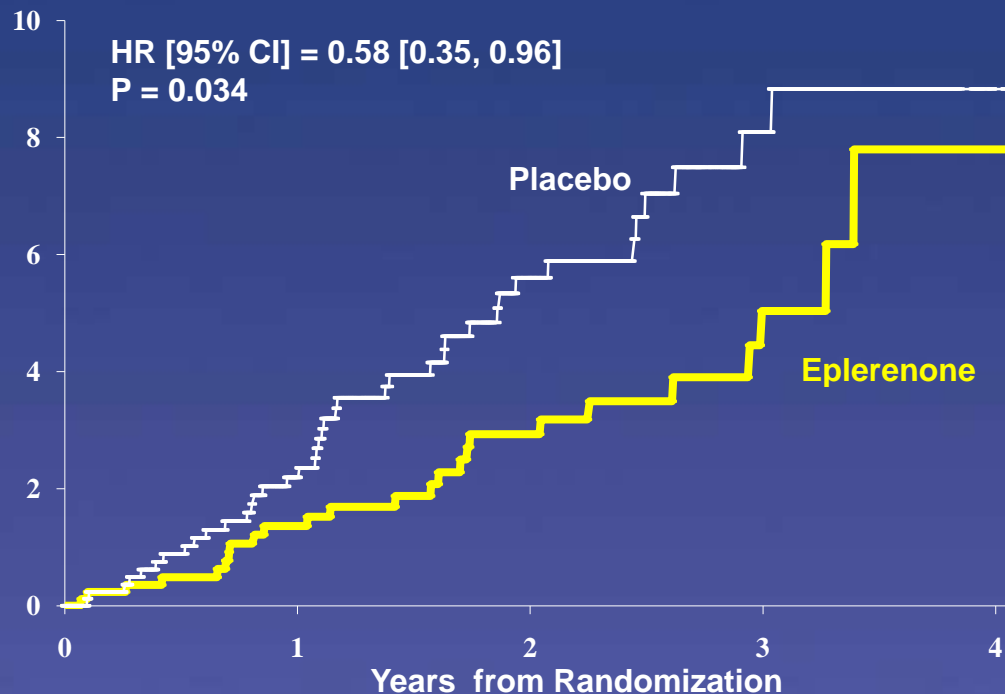
\* NEJM and AHA 2010

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



# New Onset Atrial Fibrillation/Flutter (AFF)

New Onset AFF  
Cumulative Rate (%)



No. at Risk

Placebo	883	611	345	133	1
Eplerenone	911	627	397	162	2



# Safety Results: Serum Potassium and Renal Function

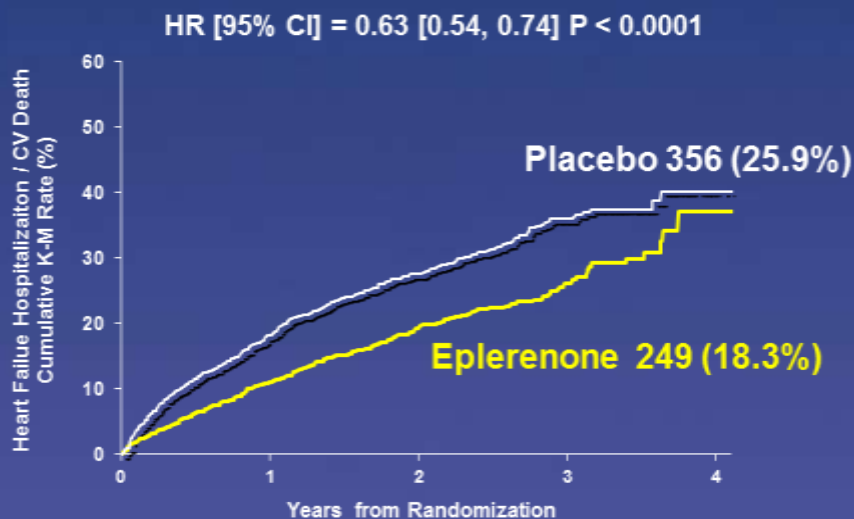
Outcome	Eplerenone	Placebo	p-value
Serum K+>5.5 mmol/l	158/1336 (11.8)	96/1340 (7.2)	<0.001
Serum K+>6.0 mmol/l	33/1336 (2.5)	25/1340 (1.9)	0.29
Hyperkalemia leading to treatment discontinuation	15/1360 (1.1)	12/1373 (0.9)	0.57
Hospitalization for hyperkalemia	4/1360 (0.3)	3/1373 (0.2)	0.85
Serum K+<3.5 mmol/l	100/1336 (7.5)	148/1340 (11.0)	0.002
Hospitalization for worsening renal failure	9/1360 (0.7)	8/1373 (0.6)	0.95

# New Analyses of EMPHASIS-HF

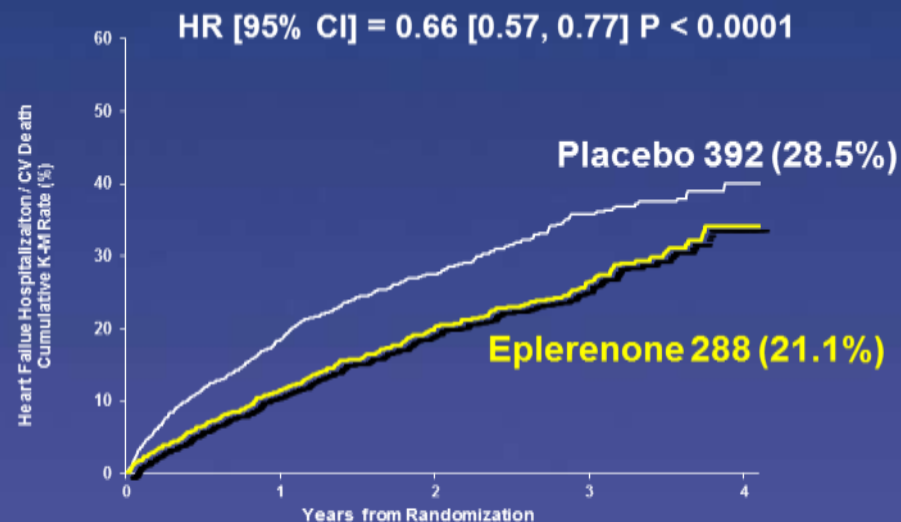
1. Extension of double blind treatment from May 25 to March 18, 2011
2. Recurrent hospitalizations for heart failure (as opposed to time for first hospitalization)
3. Efficacy and safety of eplerenone in high-risk patients

# Primary Endpoints: CV death or HF hospitalization

Primary endpoint until May 25<sup>th</sup> 2010



Primary endpoint until March 18<sup>th</sup>, 2011



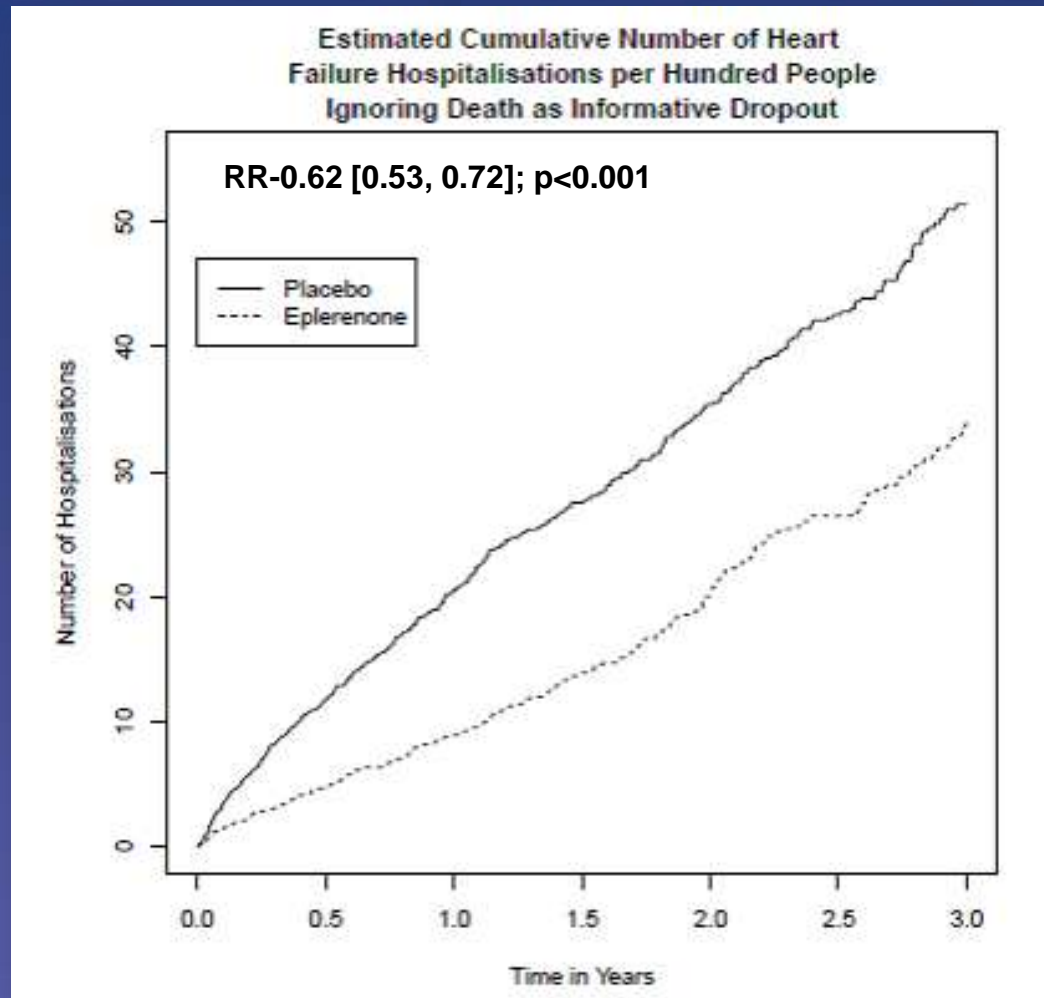
No. at Risk					
Placebo	1373	848	512	199	3
Eplerenone	1364	925	562	232	3

No. at Risk					
Placebo	1376	928	589	307	40
Eplerenone	1367	990	645	338	41

Since the premature stopping of the trial due to efficacy on May 25<sup>th</sup> 2010 (mean follow-up of 21 months), 71 additional primary endpoints were observed while patients (N=1597) remained on double-blind therapy up to March 18<sup>th</sup>, 2011 (mean follow-up of 25 months)



# Repeat hospitalization for Heart Failure



Rate Ratio (RR) = Ratio of hospitalization rates for heart failure

# High Risk Sub Groups

- Age >75 years
- Diabetes Mellitus
- eGFR < 60 ml/min/1.73 m<sup>2</sup>
- LVEF <30%
- Systolic blood pressure <123 mmHg

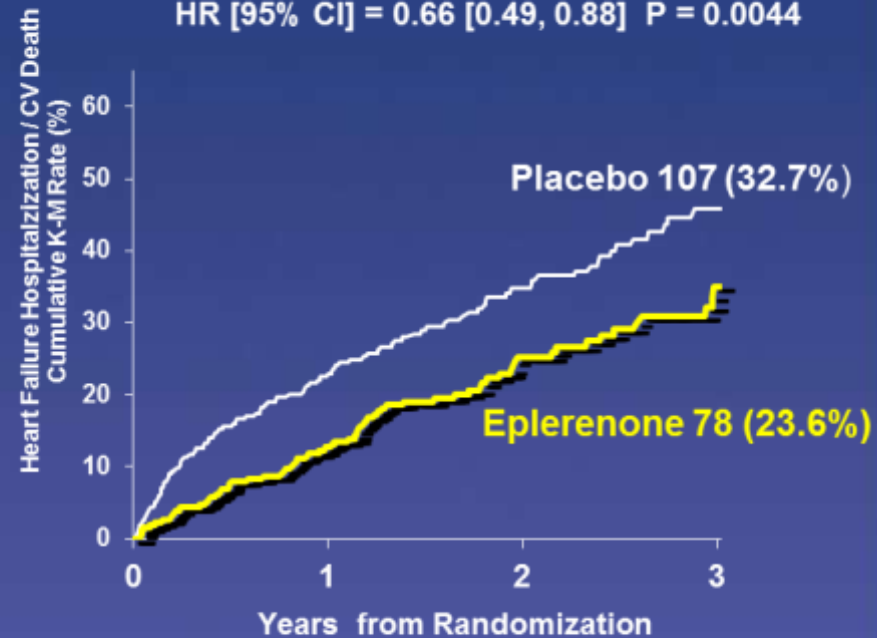
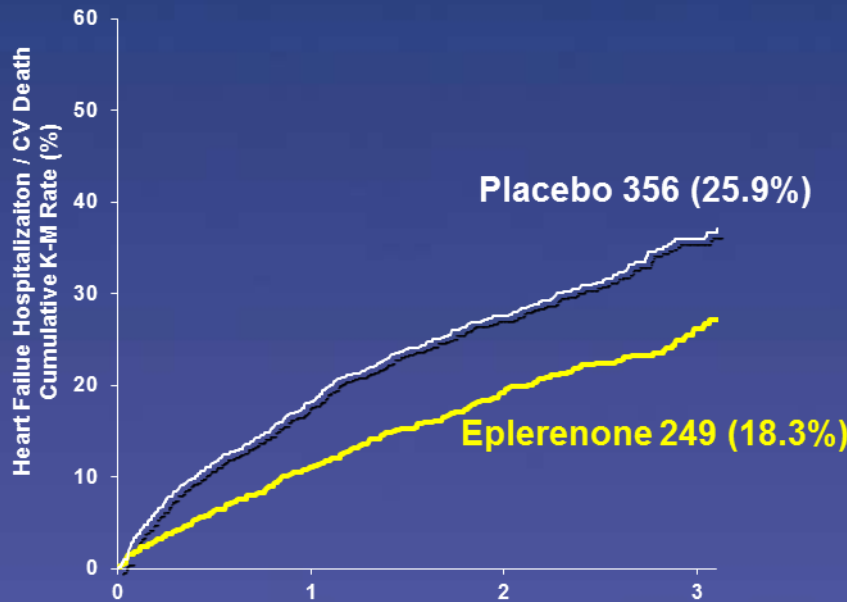
# CV Death or HF Hospitalization

Overall

$\geq 75$  years

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001

HR [95% CI] = 0.66 [0.49, 0.88] P = 0.0044



No. at Risk	Years from Randomization			
	0	1	2	3
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

No. at Risk	Years from Randomization			
	0	1	2	3
Placebo	327	188	112	39
Eplerenone	330	226	122	44

\*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001



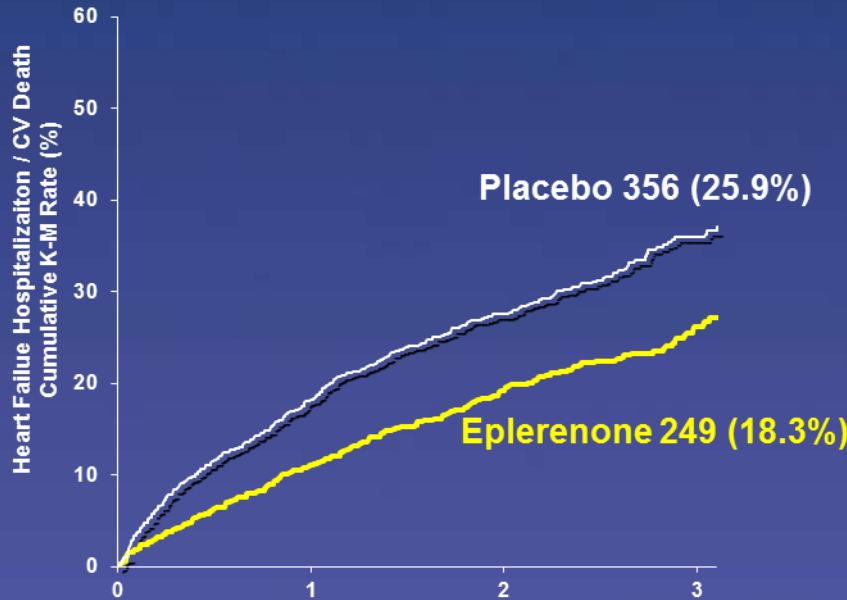
# Safety Results: Serum Potassium and Renal Function in Patients >75 years

Outcome	Eplerenone	Placebo	p-value
Serum K <sup>+</sup> >5.5 mmol/l	40/322 (12.4)	21/318 (6.6)	0.02
Serum K <sup>+</sup> >6.0 mmol/l	7/322 (2.2)	4/318 (1.3)	0.55
Hyperkalemia leading to treatment discontinuation	3/330 (0.9)	3/327 (0.9)	1.00
Hospitalization for hyperkalemia	1/330 (0.3)	1/327 (0.3)	0.98
Serum K <sup>+</sup> <3.5 mmol/l	22/322 (6.8)	34/318 (10.7)	0.09
Hospitalization for worsening renal function	5/330 (1.5)	3/327 (0.9)	0.52

# CV Death or HF Hospitalization

## Overall

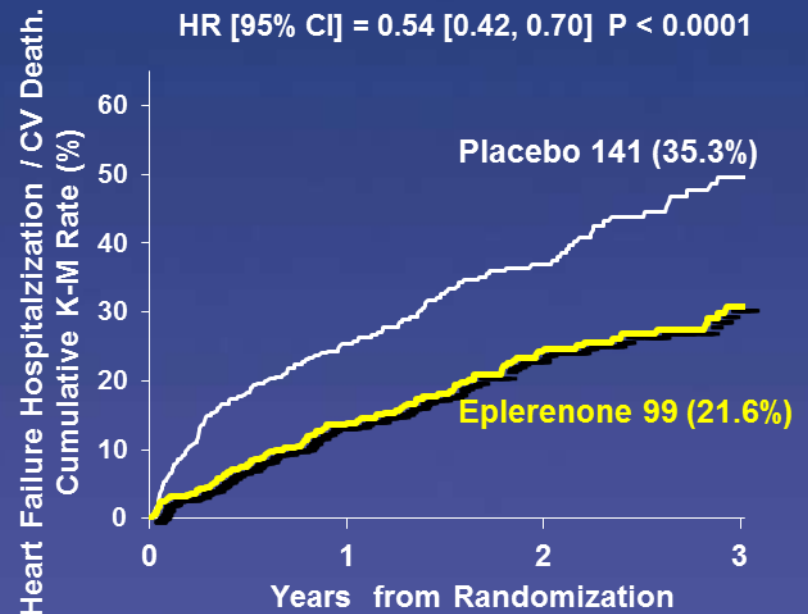
HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



No. at Risk	Years from Randomization			
	0	1	2	3
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

## Diabetes Mellitus

HR [95% CI] = 0.54 [0.42, 0.70] P < 0.0001



No. at Risk	Years from Randomization			
	0	1	2	3
Placebo	400	218	123	42
Eplerenone	459	294	175	74

\*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001

# Safety Results: Serum Potassium and Renal Function in Patients with Diabetes Mellitus

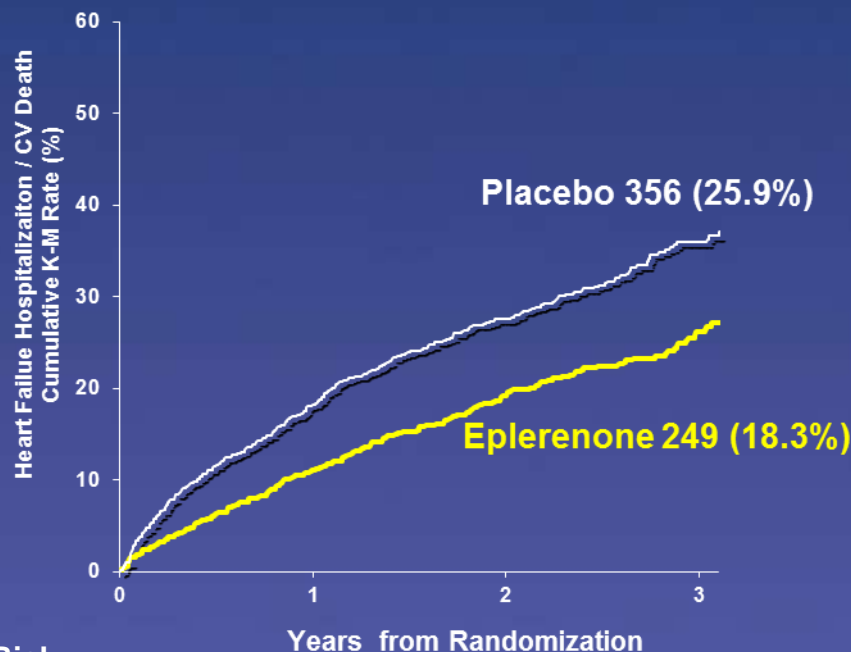
Outcome	Eplerenone	Placebo	p-value
Serum K <sup>+</sup> >5.5 mmol/l	63/447 (14.1)	33/387 (8.5)	0.01
Serum K <sup>+</sup> >6.0 mmol/l	17/447 (3.8)	8/387 (2.1)	0.16
Hyperkalemia leading to treatment discontinuation	9/459 (2.0)	3/400 (0.8)	0.15
Hospitalization for hyperkalemia	4/459 (0.9)	2/400 (0.5)	0.55
Serum K <sup>+</sup> <3.5 mmol/l	31/447 (6.9)	46/387 (11.9)	0.016
Hospitalization for worsening renal function	5/459 (1.1)	7/400 (1.8)	0.39

# CV Death or HF Hospitalization

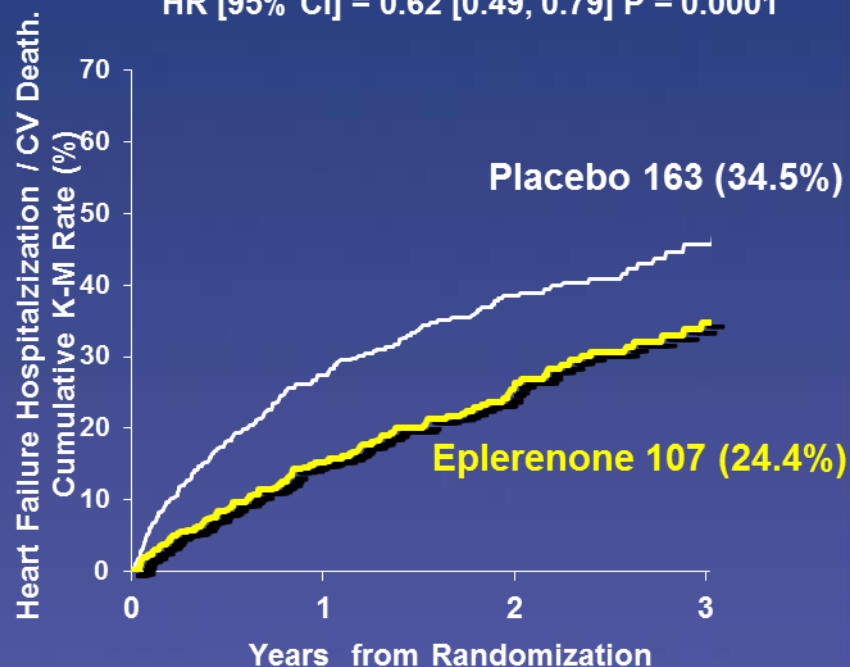
Overall

eGFR < 60 ml/min/1.73m<sup>2</sup>

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



HR [95% CI] = 0.62 [0.49, 0.79] P = 0.0001



\*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001



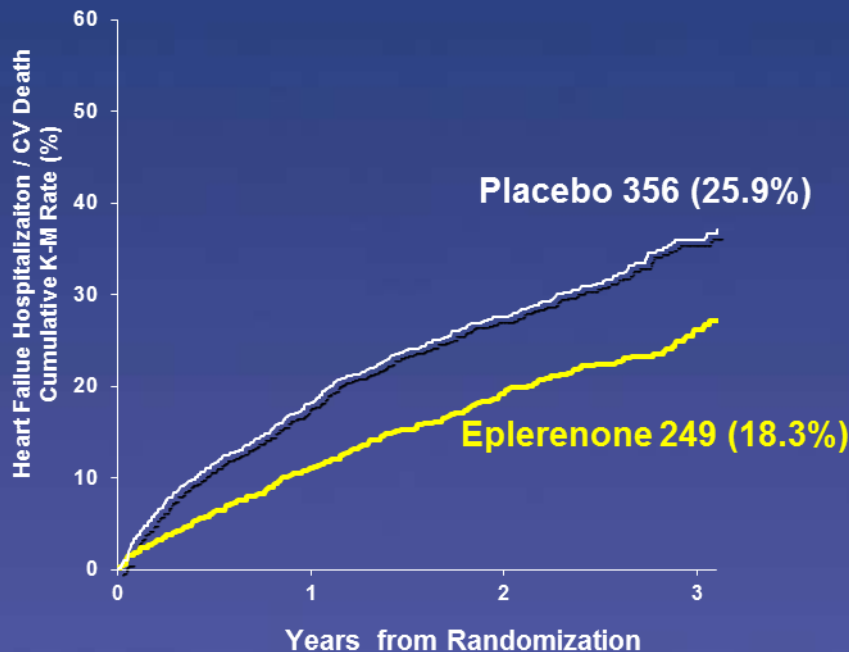
# Safety Results: Serum Potassium and Renal Function - eGFR<60 ml/min/1.73m<sup>2</sup>

Outcome	Eplerenone	Placebo	p-value
Serum K <sup>+</sup> >5.5 mmol/l	70/422 (16.6)	43/461 (9.3)	0.002
Serum K <sup>+</sup> >6.0 mmol/l	8/422 (1.9)	15/461 (3.3)	0.29
Hyperkalemia leading to treatment discontinuation	5/439 (1.1)	10/473 (2.1)	0.30
Hospitalization for hyperkalemia	1/439 (0.2)	2/473 (0.4)	0.57
Serum K <sup>+</sup> <3.5 mmol/l	26/422 (6.2)	46/461 (10.0)	0.048
Hospitalization for worsening renal function	5/439 (1.1)	8/473 (1.7)	0.32

# CV Death or HF Hospitalization

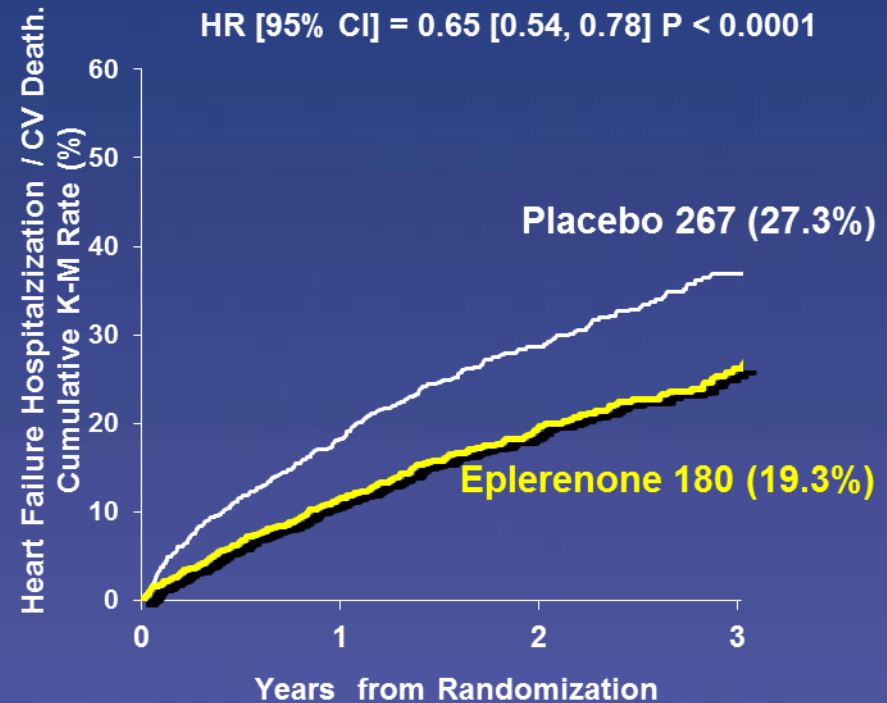
## Overall

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



## LVEF < 30 %

HR [95% CI] = 0.65 [0.54, 0.78] P < 0.0001



### No. at Risk

Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

### No. at Risk

Placebo	978	616	367	146
Eplerenone	934	653	406	179

\*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001



# Safety Results: Serum Potassium and Renal Function in Patients with a LVEF<30%

Outcome	Eplerenone	Placebo	p-value
Serum K+>5.5 mmol/l	106/926 (11.5)	75/961 (7.8)	0.008
Serum K+>6.0 mmol/l	19/926 (2.1)	21/961 (2.2)	0.87
Hyperkalemia leading to treatment discontinuation	7/934 (0.7)	10/978 (1.0)	0.47
Hospitalization for hyperkalemia	2/934 (0.2)	2/978 (0.2)	1.00
Serum K+<3.5 mmol/l	76/926 (8.2)	120/961 (12.5)	0.003
Hospitalization for worsening renal function	4/934 (0.4)	6/978 (0.6)	0.52

# CV Death or Hospitalization

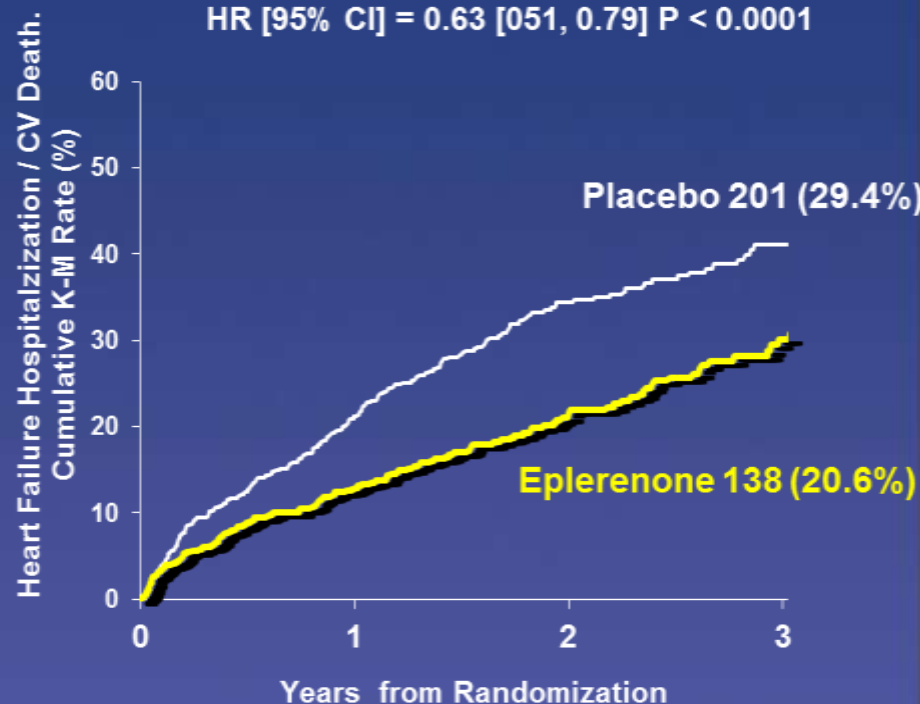
Overall

HR [95% CI] = 0.63 [0.54, 0.74] P < 0.0001



Systolic BP < Median (123 mmHg)

HR [95% CI] = 0.63 [0.51, 0.79] P < 0.0001



No. at Risk

Placebo	1373	848	512	199
Eplerenone	1364	925	562	232

No. at Risk

Placebo	683	392	220	86
Eplerenone	669	449	257	98

\*Un-adjusted HR [95% CI] = 0.66 [0.56, 0.78] P < 0.0001



## Safety Results: Serum Potassium and Renal Function in Patients with a Systolic BP <Median (123 mmHg)

Outcome	Eplerenone	Placebo	p-value
Serum K+>5.5 mmol/l	72/658 (10.9)	48/660 (7.3)	0.02
Serum K+>6.0 mmol/l	14/658 (2.1)	16/660 (2.4)	0.85
Hyperkalemia leading to treatment discontinuation	8/669 (1.2)	5/683 (0.7)	0.42
Hospitalization for hyperkalemia	2/669 (0.3)	2/683 (0.3)	0.99
Serum K+<3.5 mmol/l	51/658 (7.8)	77/660 (11.7)	0.02
Hospitalization for worsening renal function	3/669 (0.4)	5/683 (0.7)	0.44

# Summary/Conclusions

- The efficacy and safety of eplerenone in addition to standard therapy in patients with systolic heart failure and mild symptoms was relatively consistent across a number of pre-specified, high-risk subgroups
- The beneficial effect of eplerenone on the primary endpoint after the premature stopping of enrollment into the trial due to efficacy (mean follow-up 21 months) remained significant over an additional follow-up up-to 10 months (total of mean follow-up 25 months) on double-blind therapy

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

Argentina – D. R. Nul, J.L. Serra, J. M. Thierer (LI); Australia - D.B. Cross, A.P. Sindone (LI), B. B. Singh; Belgium – J.L. Boreux, F. P.P. Charlier, P. Dendale, G. De Keulenaer, B. Marchandise, P. Marechal, F. Marenne, W.V. Mieghem, A. C. Van Dorpe, J. Vanhaecke (LI); Canada – J. M. Arnold, D. Dion, T. Huynh, S. M. Kouz, S. Lepage, R. S. McKelvie, E. O'Meara (LI), G. Proulx, C. Sauve; Czech Republic - M. Aschermann, D. Brecka, J. Filipovsky, L. Groch, O. Jerabek, I. Jokl, H. Linkova, Z. Motovska, J. Munz, M. Penicka, D. Rucka, J. Smid, R. Spacek, J. Spinar (LI), R. Stipal, J. Vojacek; France – P. Attali, A. Bonneau, J.P. Bousser, L. Dutoit, F. Funck, M. P. Galinier, P. Gibelin, B. D. Hautefeuille, L. Hittinger, Y. Jobic, P. Jourdain, M. Komajda (LI), E. Maupas, T. Olive, A. Philiat, G. Roul, F. Rouleau, J.N. Trochu; Germany – M. Boehm, L. Bruch, H. Drexler, H. Engelhardt, S. Erbs, A. Foerster, N. Franz, R. Hambrecht, H. Heuer, U. Krueger, U. Landmesser, R. Leischik, V. Mitrovic, S. Moehlenkamp, J. Monti, J. Mueller-Ehmsen, C. Oezcelik, S. Philipp, B. Pieske, J. U. Roehnisch, H. Schunkert, R. Schwinger, R. Wachter, R. Willenbrock (LI), B. R. Winkelmann, R. Winkler, K. C. Wollert; Greece - S. Adamopoulos, I. Kalikazaros, A. Karavidas, H. Karvounis, D. Kremastinos (LI), A. J. Manolis, I. Nanas, K. Sotirellos, K. Vasiliadis, C. Zabolis; Hong Kong – S. Lee (LI), C. M. Yu; Hungary – C. Czibok, I. Édes (LI), T. Forster, I. Preda, K. Simon, J. Takacs, K. Zámolyi; India - K. S. S. Bhagavatula (LI), K. Chockalingam, N. Desai, S. S. Iyengar, S. M. Jayadev, A. S. Mullasari, S. P. Sathe, N. Sinha, P. S. Vadagenalli, G. S. Wander; Ireland - K. M. McDonald (LI), P. Nash, C. J. Vaughan; Italy - P. Agostoni, G. B. Ambrosio, G. Bittolo Bon, G. Boffa, L. Cacciavillani, A. Capucci, M. Chiariello (LI), V. Cirrincione, G. F. Gensini, F. Masini, M. G. Modena, I. Monte, P. Perrone Filardi, G. M. C. Rosano, M. Senni, G. Sinagra, C. Tamburino, P. Terrosu, G. Q. Villani, M. Volterrani; Korea - S. C. Chae, C. W. Ha, J.W. Ha, J.H. Shin; Mexico – E. Bayram-Llamas, J. C. Calvillo, A. Cruz-Diaz, L. Delgado-Leal, M. M. Estrada-Gomez, D. Kosturakis (LI), F. Petersen-Aranguren R. G. Velasco-Sanchez; Netherlands - M. C.G. Daniëls, A. Dirkali, P. H. J. M. Dunselman (LI), E. P. de Kluiver, J. A. Kragten, D. J.A. Lok, A. H.E.M. Maas, H. R. Michels, D. M. Nicastia, I. Stoel, J. B.R.M. de Swart, H. J.M. Thijssen, L. H.J. Van Kempen, A. A. Voors, F. F. Willems; Poland - M. Dłużniewski (LI), Z. Gaciong, K. Kawecka-Jaszcz, R. Jozwa, J. Korewicki, M. Krzeminska-Pakula, M. Kurowski, M. Ogorek, M. Pempera, A. Rynkiewicz, M. Ujda, M. Wierzchowiecki; Portugal – Á. Abreu, A. Andrade, M. Carrageta, C. Fonseca, F. Franco, V. M. Gil, N. Lousada, C. Mendonca, I. Moreira, F. P. Padua, L. Providência, J. C. Silva Cardoso (LI), M. Tráfulo; Russia - G. P. Aroutyunov (LI), K. Gindin, Y. B. Karpov, V. A. Kostenko, Y. P. Nikitin, G. Igorevna Obraztsova, N. P. Shilkina, E. V. Shlyakhto, A. Skvortsov; Singapore – Z.P. Ding, D. P. S. Yeo; Slovakia – V. Ambrovicova, L. Gaspar, E. Goncalvesova, P. Kycina, J. Litvinova, Z. Mikes, J. Murin (LI), P. Poliacik, R. Uhliar; South Africa – E. A. Lloyd, D. Marx, D. P. Naidoo, H. W. Prozesky, K. Sliwa-Hahnle H. Theron; Spain – M. Anguita, E. De Teresa, E. Galve, J. R. G. Juanatey (LI), P. M. M. Orbe, M. Vida; Sweden - U. Ahremsmark, B. Andersson (LI), U. Axelsson, S. Berglund, K. Boman, U. Dahlstrom, M. Fu, L. Holm Orndahl, A. Johansson, M. Lindgren, C. Nemeček, H. Prantare, V. Roussine, G. Stehn, A. Stenberg, K. Swedberg, P. Vasko; Ukraine - A. Bazylevych, O. I. Dyadyk, G. V. Dzyak, O. M. Girina, G. A. Ignatenko, L. G. Kononenko, V. F. Kubyshev, O. V. Kuryata, A. N. Parkhomenko (LI), M. V. Perepelytsya, T. O. Pertseva, G. S. Popik, M. V. Rishko, I. I. Sakharchuk, V. I. Tseluyko, S. A. Tykhonova, V. Vizir, L. G. Voronkov; United Arab Emirates – N. Al Khaja, W. A. Almahmeed, N. Bazargani; United Kingdom – A. A. J. Adgey, A. Al-Mohammad, P. Banerjee, M. Barlow, A. B. Bridges, N. Brooks, E. C. Connolly, M. A. Denvir, R. M. Egdell (LI), A. Kardos, P. J. Keeling, A. A. Khokhar, J. J. McMurray, R. Senior, S. G. Williams; United States - I. S. Anand, J. L. Anderson, M. R. Berk, B. D. Bertoleto, J. D. Bisognano, R. D. Blonder, C. S. Breburda, D. B. Canaday, R. C. Capodilupo, M. D. Chouinard, W. S. Colucci, R.J. Dahiya, S. H. Dunlap, L. K. Essandoh, A. R. Flores, D. A. Henderson, W. R. Herzog Jr., R. J. Katz, E. J. Kosinski, I. N. Labin, F. L. Lally, J. A. Lash, F. A. McGrew III, S. M. Mohiuddin, D. Moraes, S. C. Murali, M. Nallasivan, E. Philbin, S. Prabhu, D. S. Primack, R. Ramani, D. Rawitscher, R. Sangrigoli, C. M. Schmalzfuss, L. Stoletniy, M. H. Strong, U. Thadani, C. B. Treasure II, R. M. Vicari, C. D. Vogel, M. N. Walsh, D. Wencker, S. A. Wilson, E. Winkel, A. H. Wiseman, L. Y. Zoiopoulos; Venezuela – J.R.G. Mancebo, I. Mendoza, S.T. Waich (LI)