7th Advances in Heart Failure

10 e 11 de Outubro

O ADVENTO DO FIM DA FRAÇÃO DE EJEÇÃO?

TERAPÊUTICAS INDEPENDENTES DA FRAÇÃO DE EJEÇÃO

ANTAGONISTAS DOS RECETORES DOS MINERALOCORTICÓIDES NÃO ESTEROIDES?

DISCLOSURES

Consultancy fees, grants and speaker's honoraria from
Astra Zeneca, Bayer, Bial, Boehringer Ingelheim, Novartis, Novo Nordisk
Roche, Sanofi, Servier, CSLVifor.

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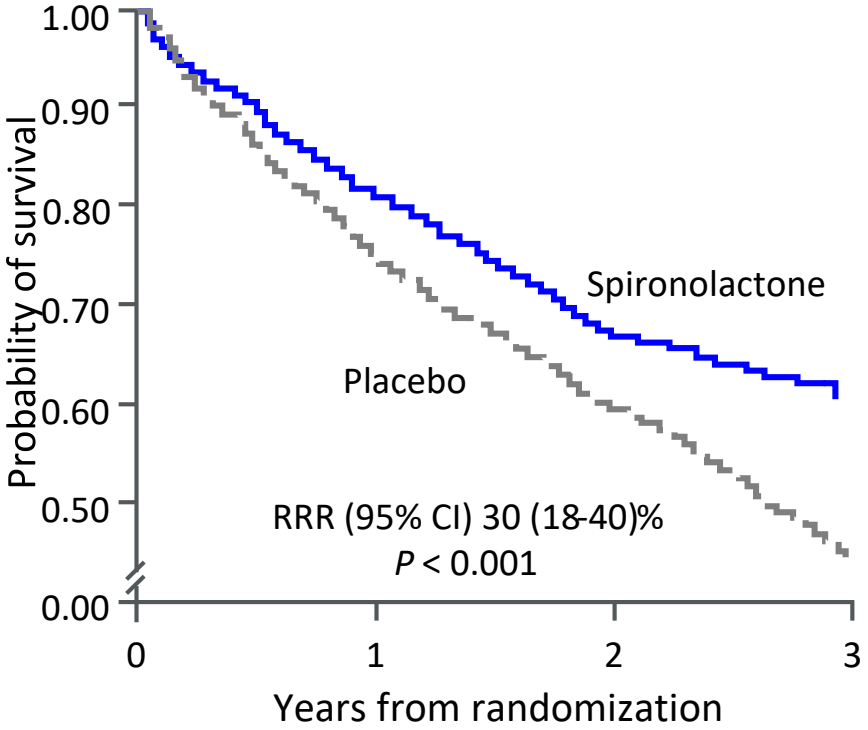
Steroidal MRAs: a pillar of guidelinedirected medical therapy for patients with **HF with reduced ejection fraction**

Class I A

MRA

RALES (1999)

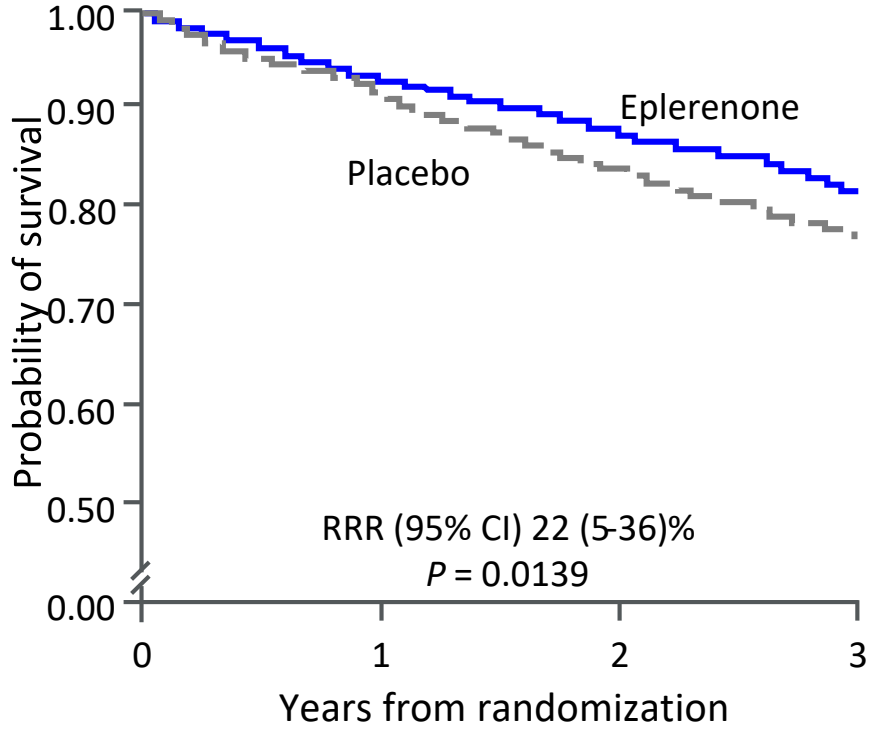
1663 NYHA class III/IV patients
95% ACE-I/10% β-blocker



Pitt B, et al. *N Engl J Med.* 1999;341:709-717.

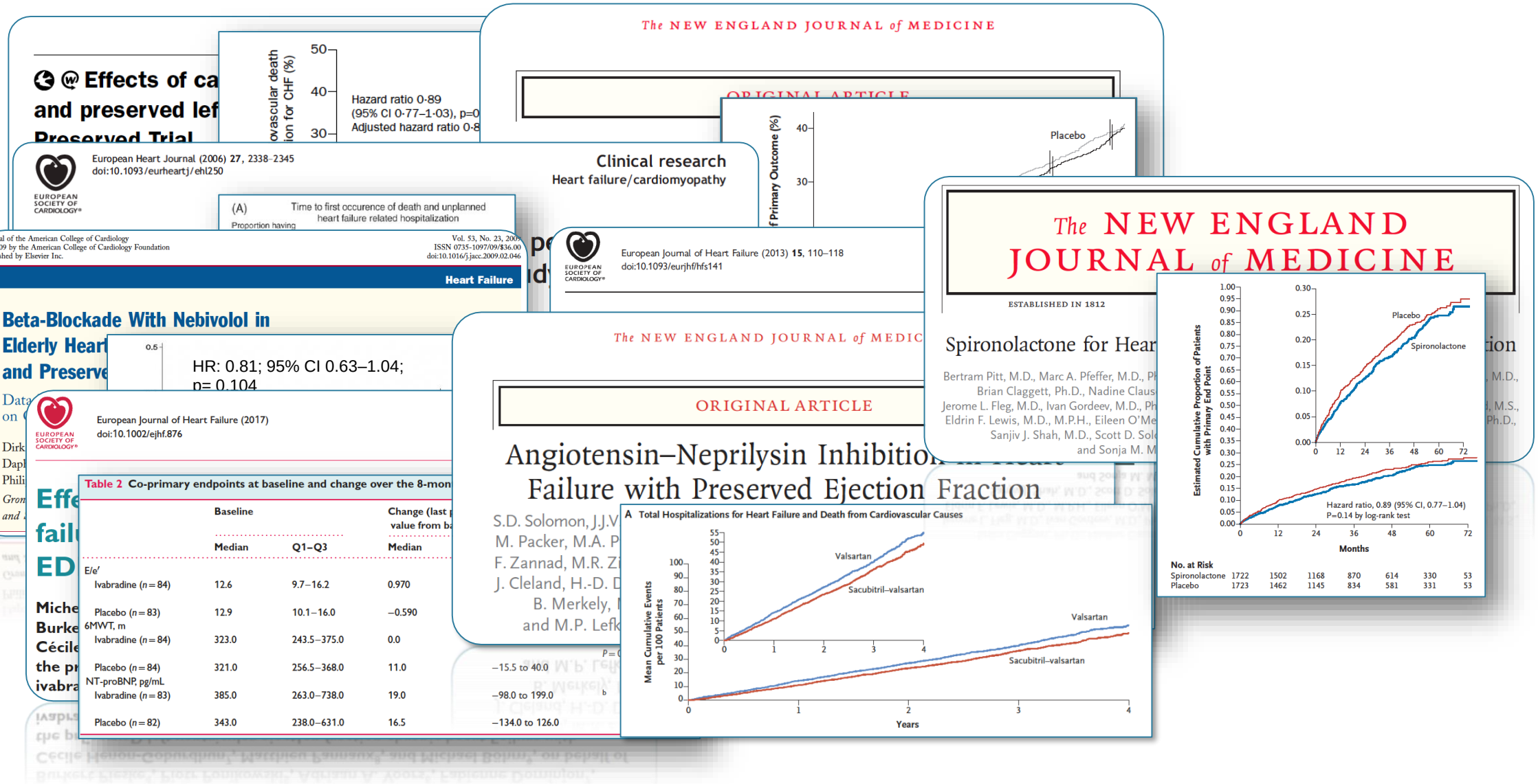
EMPHASIS-HF (2011)

2737 NYHA class II patients
93% ACE-I or ARB/87% β-blocker



Zannad F, et al. *N Engl J Med*. 2011;364:11-21.

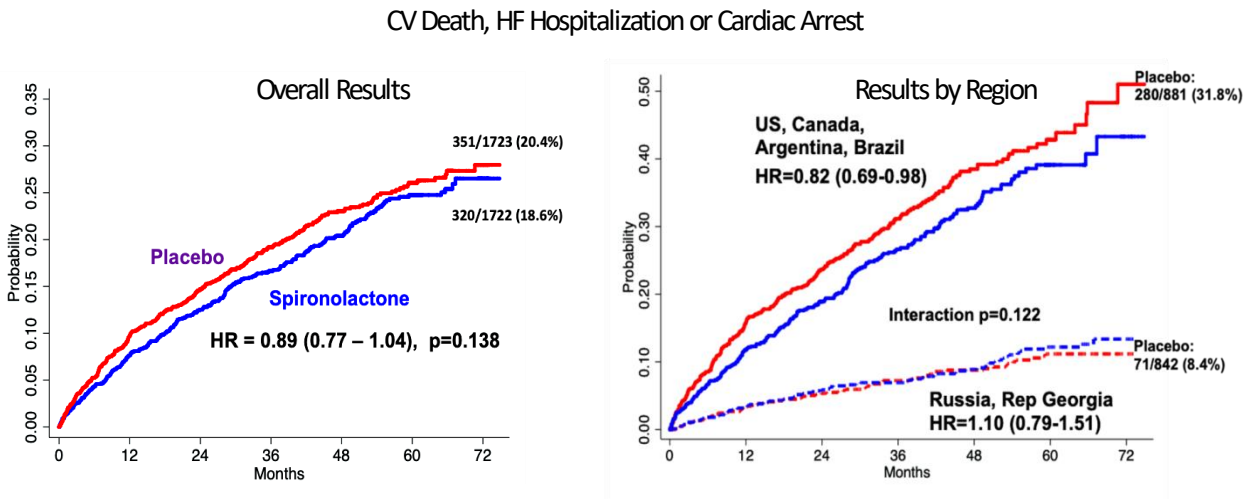
Early RCTs in patients with HFpEF provided minimal support for use of various agents



TOPCAT: A tale of two populations

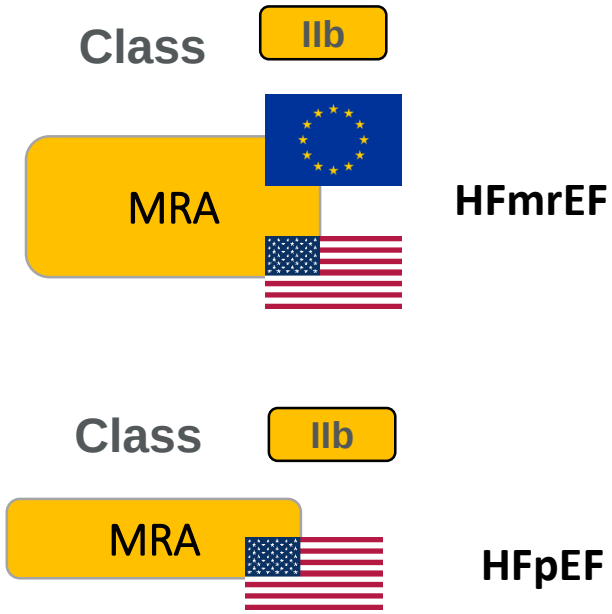
Missed Primary Endpoint in HFpEF but **Suggestive of Benefit in Some Patients**

Concern in patients with worse renal function



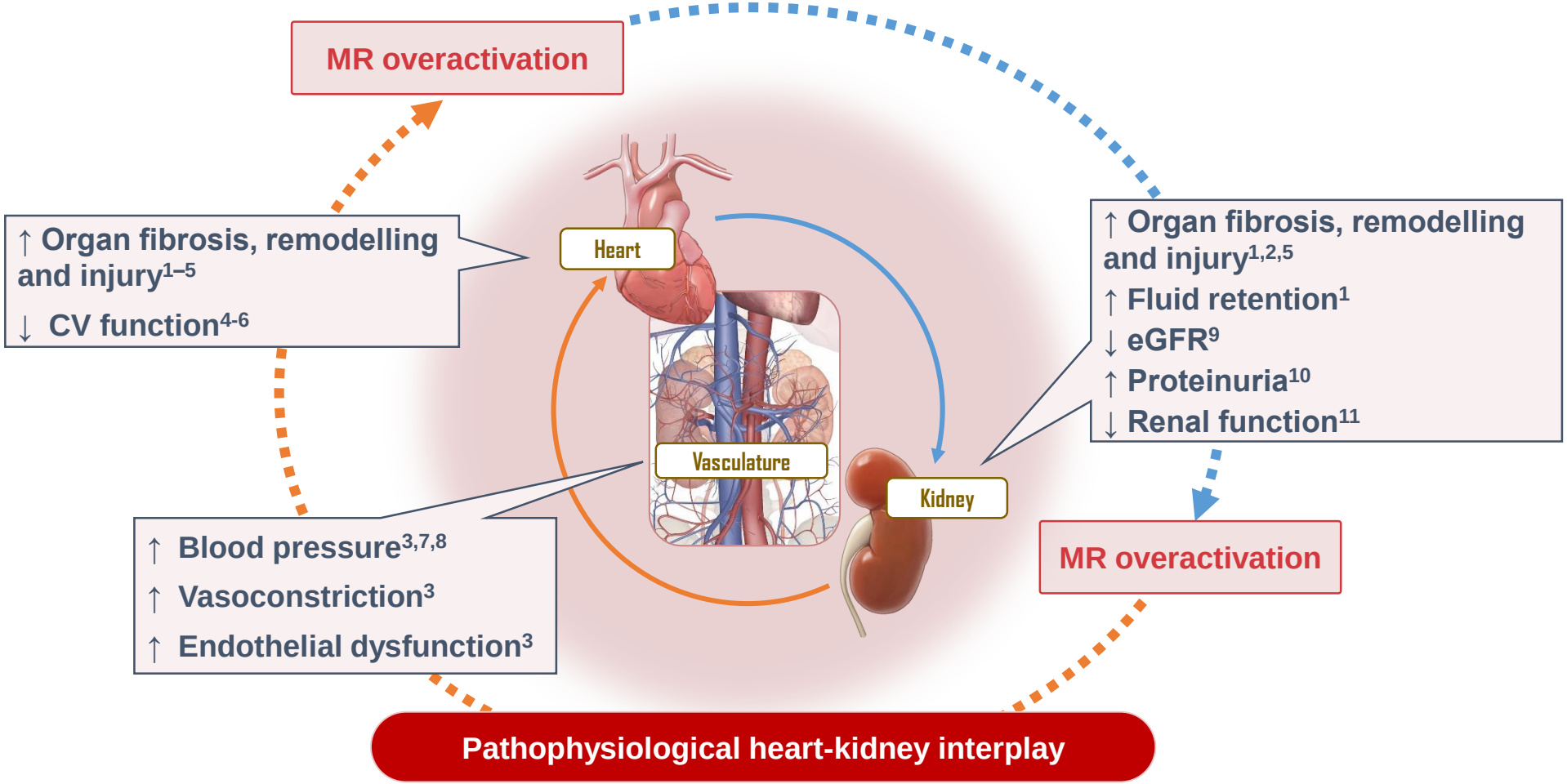
Pitt et al. NEJM 2014;370(15):1383-92

Pfeffer MA et al. Circulation. 2015 Jan 6;131(1):34-42



Beldhuis I et al. JACC 2019

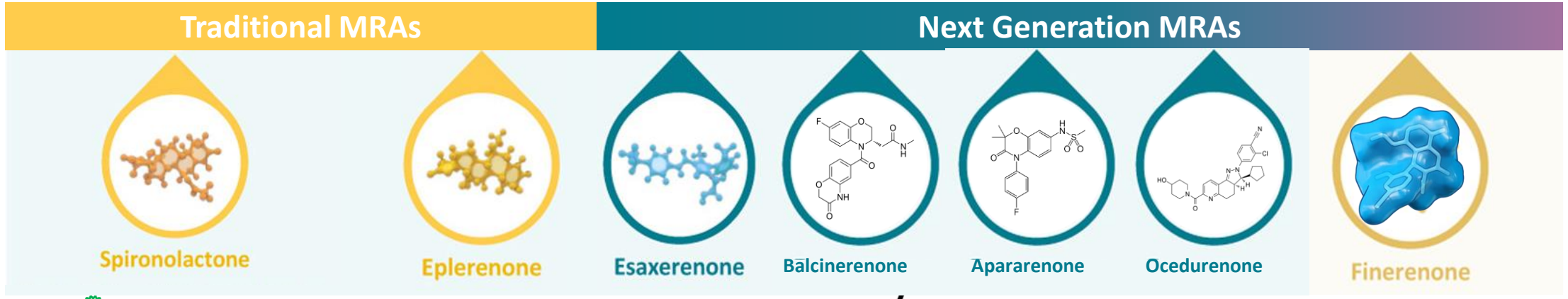
MR overactivation is a key driver of the vicious cycle of heart and kidney diseases, including CKD and HF



CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MR, mineralocorticoid receptor.

1. Savarese G et al. *Diabetologia* 2024;67:246–262; 2. Epstein M, et al. *Am J Kidney Dis* 2022;80:658-666; 3. Gorini S, et al. *Front Endocrinol (Lausanne)* 2019;10:584; 4. Jia G, et al. *Hypertension* 2018;72;537–548; 5. Gomez-Sanchez E & Gomez-Sanchez CE. *Compr Physiol* 2014;4:965–994; 6. van de Heijden CDCC, et al. *Cardiovasc Res* 2018;114:944–953; 7. Buonafine M, et al. *Am J Hypertens* 2018;31:1165–1174; 8. Barrera-Chimal J, et al. *Kidney Int* 2019;96:302–319; Chilton RJ & Silva-Cardoso J. *Cardivasc Endocrinol Metab* 2023;12(3):e0289; 10. Abassi Z, et al. *Front Cardiovasc Med* 2022;9:933215.

The evolution of our understanding of the role of the MR has led to the clinical investigation of MRAs for over 60 years



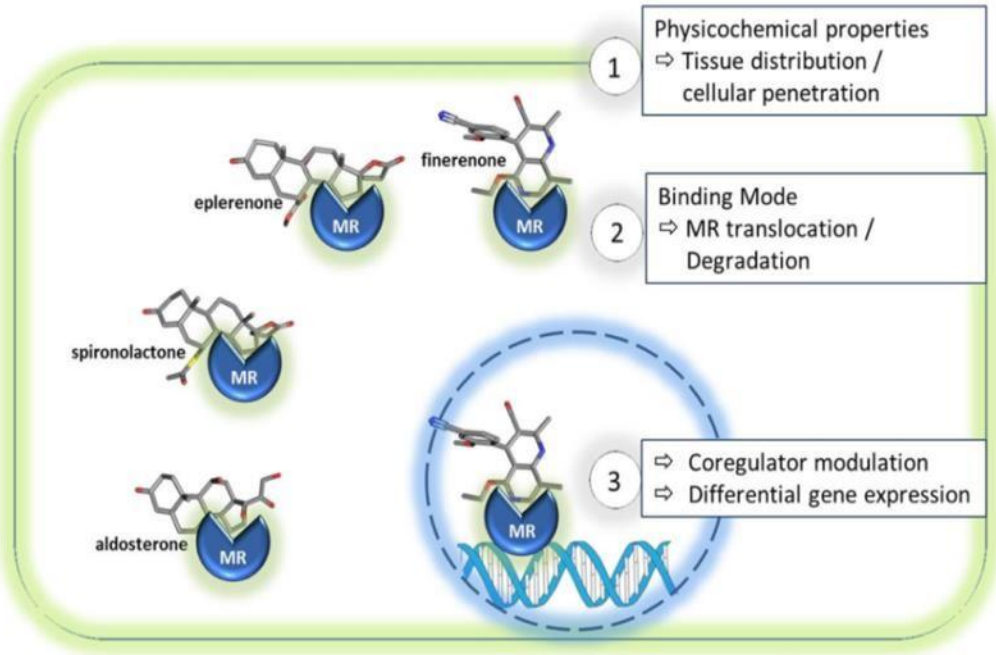
	Spironolactone	Eplerenone	Esaxerenone	Bālcinerenone	Apararenone	Ocedurenone	Finerenone
Indication and key studies	HFrEF Class 1 recommendation[1-3] HFpEF study failed[4]	HFrEF Class 1 recommendation[1-3]	Launched in Japan only in hypertension patients[7]	Failed to reach primary endpoint in patients with HF and CKD[9]	Development discontinued in 2021[10]	Failed in uncontrolled hypertension in CKD[11]	Globally indicated in T2D CKD[2,12] Investigated in HF LVEF ≥40 and patients with CKM[13,14]
Patients investigated in Ph II/III			<2000[8]	<1000[9]			>20,000[15,16]
First launch	1960[5]	2002[6]	2019[7]				2021[16]

CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes.

1. Heidenreich PA, et al. J Am Coll Cardiol 2022;79:e263–e421; 2. McDonagh TA, et al. Eur Heart J 2023;44:3627–3639; 3. McDonagh TA et al. Eur Heart J 2021;42:3599–3726; 4. Pitt B, et al. N Engl J Med 2014;370:1383–1392; 5. NIH. PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Spironolactone (Accessed Aug 2024); 6. NIH. https://drugs.ncats.io/substance/6995V82D0B (Accessed Aug 2024); 7. Daiichi Sankyo Launches "MINNEBRO® Tablets" in Japan. Press Release 2019; 8. Ito S, et al. Hypertension 2020;75:51–58; 9. Lam C, et al. Eur J Heart Fail 2024;doi:10.1002/ejhf.3294; 10. Kolkhof P, et al. Pharmacol Res 2021:172:105859; 11. Novo Nordisk Press Release. https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=168529 (Accessed Aug 2024); 12. Marx N, et al. Eur Heart J 2023;00:1–98; 13. Solomon S, et al. NEJM 2024 [in press]; 14. Vaduganathan M, et al. Nat Med 2024 [in press]; 15. Georgianos PI, et al. Am J Hypertens 2023;36:135–143; 16. Kerendia. PI.

Finerenone is a potent, highly selective **non-steroidal MRA** with Equivalent Heart: Kidney Tissue Distribution and **Potential Safety Advantages over steroidal MRAs**

	Spironolactone	Eplerenone	Finerenone
MRA Class	Steroidal	Steroidal	Non-steroidal
Potency	High	Low	High
Selectivity	Low	Medium	High
Metabolites	Multiple, active	No active	No active
Tissue distribution	Kidney>>heart (>6-fold)	Kidney>heart (~3-fold)	Equivalent (1:1)

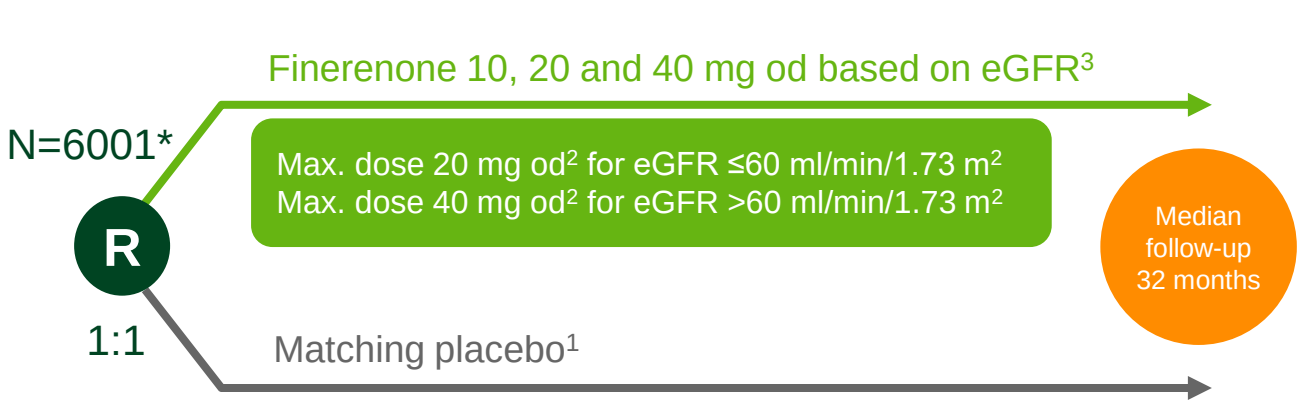


Kolkhof P, NowackC, EitnerF.*Curr OpinNephrolHypertens.*2015;24:417-424

- More selective for MR receptor than spironolactone or eplerenone
- Highly potente
- More balanced Heart/Kidney Distribution than steroidal MRAs

Kolkhof P et al. *Handb Exp Pharmacol.* 2017;243:271-305

FINEARTS-HF evaluated the efficacy and safety of finerenone in patients with HF LVEF ≥40%[1]



Primary endpoint[1]

Number of **CV deaths** and **total HF events†** (first and recurrent)

Secondary endpoints[1]

- **Total HF events†** (first and recurrent)
- Change from baseline to months 6, 9 and12 in **KCCQ-TSS**
- Improvement in **NYHA class** from baseline to Month 12
- **Composite renal endpoint** (sustained decrease in eGFR ≥50%; sustained eGFR decline <15 ml/min/1.73 m²; initiation of dialysis or kidney transplantation)
- **All-cause mortality**

✓ Key inclusion criteria:[2]

- Aged ≥40 years
- HF diagnosis; NYHA class II–IV (ambulatory or hospitalised primarily for HF)
- LVEF ≥40% measured within last 12 months
- Structural heart abnormalities within last 12 months
- Diuretics in 30 days prior to randomization
- NT-proBNP ≥300 pg/mL or BNP ≥100 pg/mL (sinus rhythm); NT-proBNP ≥900 pg/mL or BNP ≥300 pg/mL (atrial fibrillation)

✗ Key exclusion criteria:[2]

- eGFR <25 ml/min/1.73 m²
- Serum plasma potassium >5.0 mmol/l
- MI or any event that could have reduced the EF
- Acute inflammatory heart disease, CABG, stroke or TIA within last 90 days or PCI in the last 30 days
- Alternative causes of HF symptoms
- SBP ≥160 mmHg‡

Finerenone is indicated for the treatment of chronic kidney disease (with albuminuria) associated with T2D in adults.[4] For prescribing information please refer to the SmPC of the product applicable in your country. Finerenone is not indicated for the treatment of heart failure. 40 mg od is not a licensed dosage of finerenone.

*6016 randomized, 6001 included in efficacy analysis[1]; †Worsening HF events defined as either an unplanned HHF or an urgent heart failure visit; ‡If not on treatment with ≥3 blood pressure lowering medications or ≥180 mmHg irrespective of treatments.

BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; od, once daily; PCI, percutaneous coronary intervention; R, randomisation; SBP, systolic blood pressure; TIA, transient ischemic attack; T2D, type 2 diabetes.

1. Solomon S, et al. *NEJM* 2024 [in press]; 2. Solomon S, et al. *NEJM* 2024 [in press] (Suppl 1); 3. Bayer AG. https://clinicaltrials.gov/ct2/show/NCT04435626 [accessed August 2024]; 4. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed August 2024].

FINEARTS-HF

7th Advances in Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE 2024

ORIGINAL ARTICLE

Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

FINEARTS-HF

Baseline Characteristics - FINEARTS-HF and other HFpEF trials

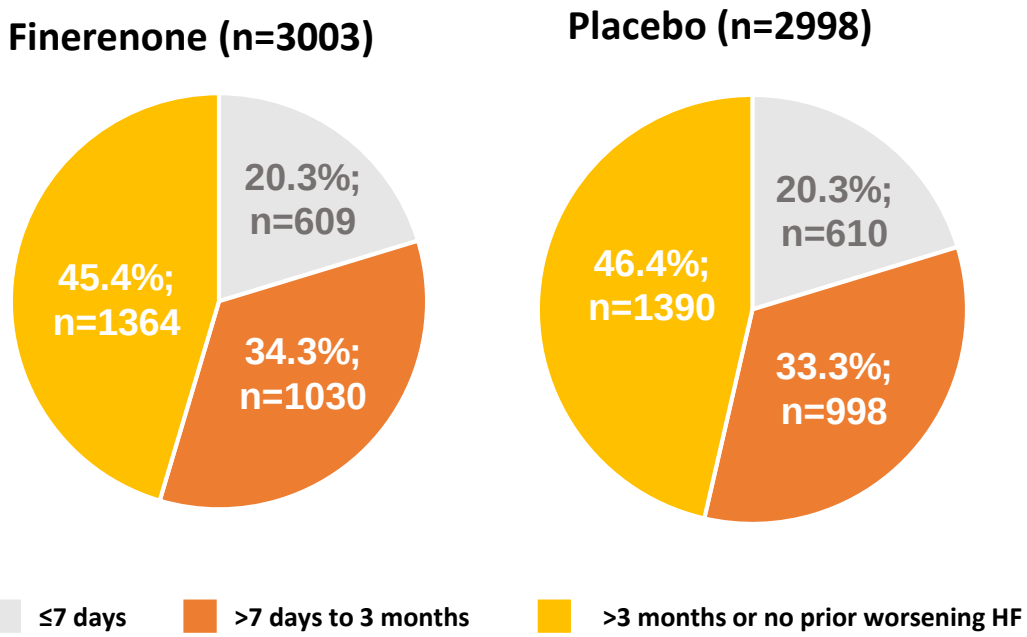
	CHARM Preserved (n=3023)	EMPEROR Preserved (n=5988)	PARAGON-HF (n=4822)	TOPCAT (n=3445)	DELIVER HF (N=6263)	FINEARTS-HF (N=6014)
Age (years)	67±11	72±9	73±8	69±10	72±10	71±12
Women (%)	40	45	52	52	44	45
NYHA II (%)	61	82	72	63	75	69
NYHA III (%)	38	18	27	33	25	30
NYHA IV (%)	2	0.3	0.6	<1	0.3	0.7
LVEF (%)	54±9	54±9	58±8	57±7	54±9	53±8
Hypertension (%)	64	90	96	91	89	89
Diabetes (%)	28	49	43	32	45	41
Hx of MI (%)	44	29	23	26	26	26
Hx of AF (%)	29	52	52	35	56	55
Stroke (%)	9	10	10	8	9	14
Baseline NT-proBNP (pg/mL) – median	NA	971 (499-1740)	885 (863-908)	950 (588-1920)	1011 (623-1751)	1502
eGFR (mL/min)	NA	61±20	63±19	68±20	61±19	62±20

Date snapshot: 08 Mar 2023 Source: J-Review

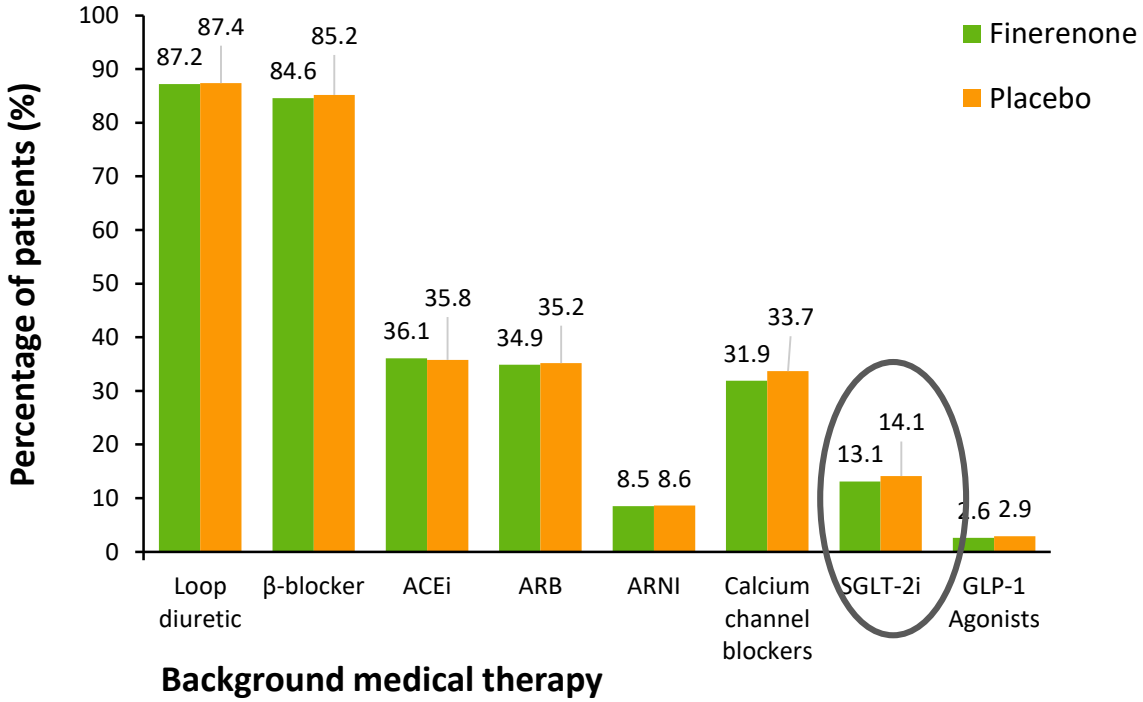
The **FINEARTS-HF** patient population was largely consistent with other contemporary HF trials, but patients had **more acute HF**

In FINEARTS-HF, 20% of participants were randomized during or within 7 days of a worsening HF event

Randomization timing relative to the most recent worsening HF event



Background medication use was robust and consistent between treatment arms



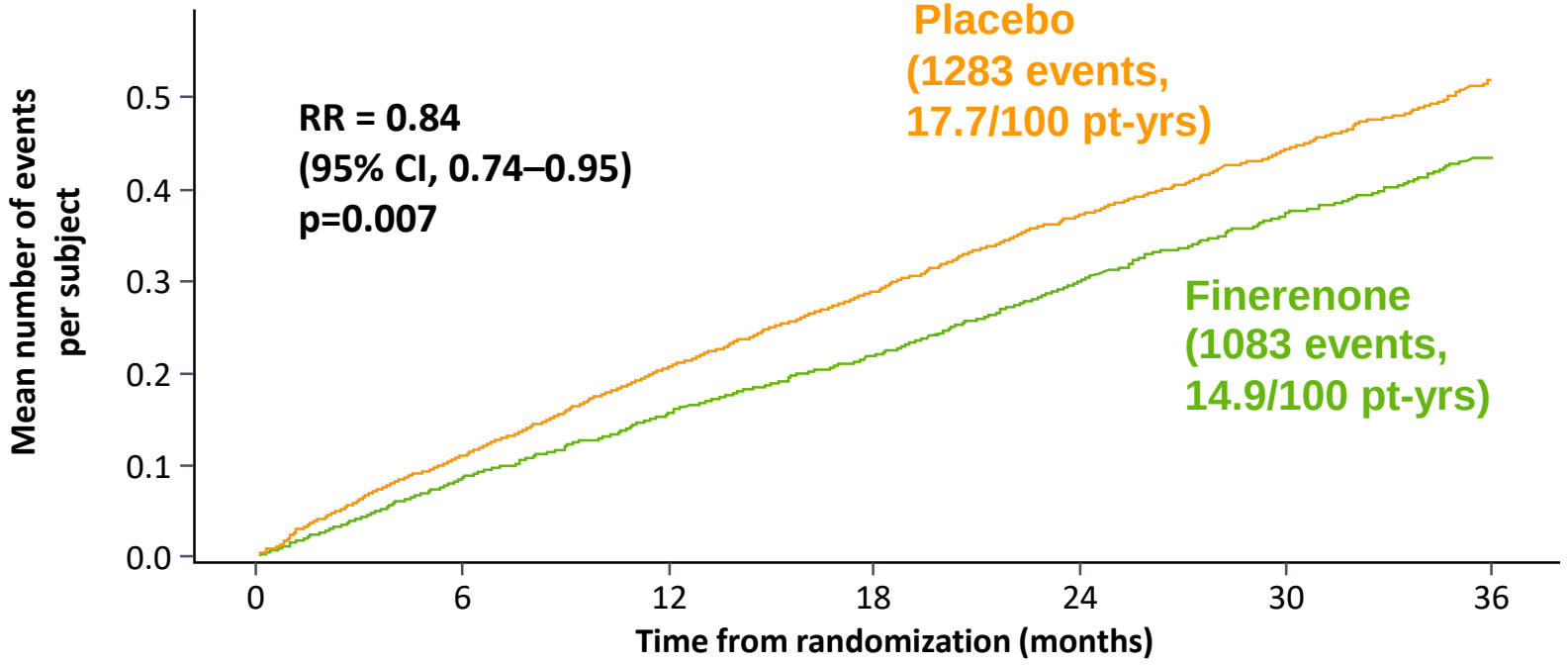
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GLP-1, glucagon-like peptide 1; HF, heart failure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

Solomon S, et al. *NEJM* 2024 [in press].

FINEARTS-HF

Finerenone demonstrated a clinically **meaningful 16% relative risk reduction** in the composite of **CV deaths and total HF events**

Primary endpoint: Number of CV deaths and total HF events[1]



Differences in treatment effect on the composite CV outcome were observed early and remained consistent throughout FINEARTS-HF

CI, confidence interval; CV, cardiovascular; HF, heart failure; PY, patient year; RR, rate ratio.

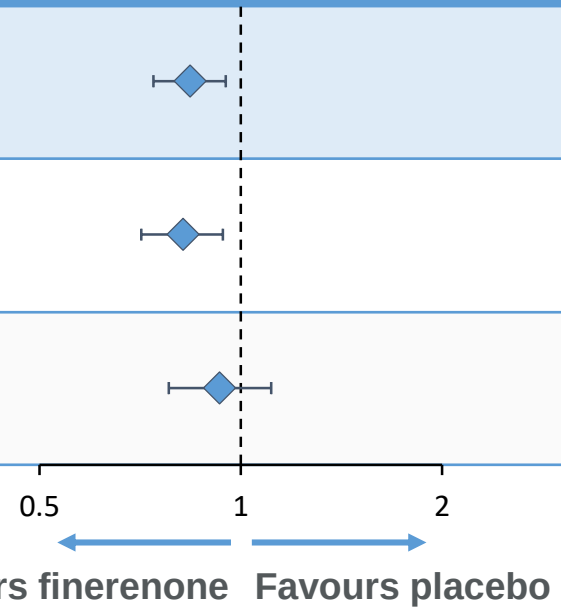
1. Solomon S, et al. *NEJM* 2024 [in press]

FINEARTS-HF

The statistically significant reduction in the composite CV outcome was **driven by a reduction in HF events**

Primary endpoint: Components of composite CV outcome

Outcome	Finerenone (N=3003) n	Placebo (N=2998) n	Ratio or difference (95% CI)	p-value
Composite CV outcome	**1083**	**1283**	**RR=0.84 (0.74–0.95)**	**0.007**
Total (first and recurrent) HF events*	842	1024	RR=0.82 (0.71–0.94)	0.006
CV death	242	260	HR=0.93 (0.78–1.11)	NR



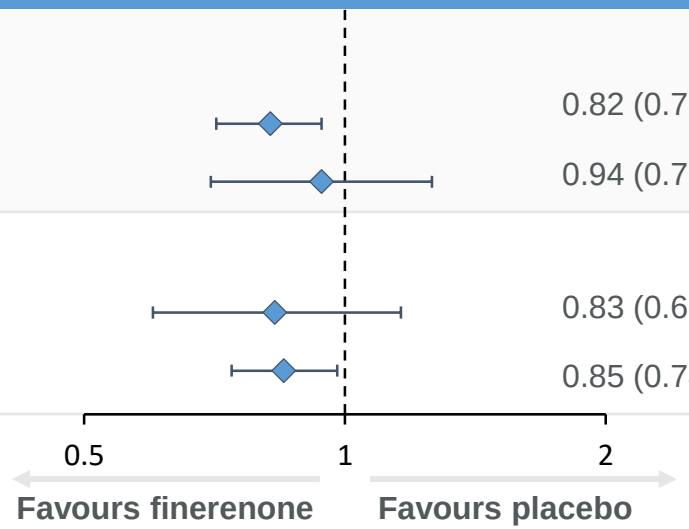
*One patient in each group was reported as having a HF event on the same day as a CV death and was counted as only one composite event in the primary analysis.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NR, not reported; RR, rate ratio.

Solomon S, et al. *NEJM* 2024 [in press].

The effects of **finerenone** on the **primary outcome** were consistent **regardless of LVEF** and background therapy at baseline, including **SGLT-2i** use

Category	Finerenone Events[1]	Placebo Events[1]	RR (95% CI)[1]
LVEF			
<60%	877	1061	0.82 (0.71–0.94)
≥60%	206	222	0.94 (0.70–1.26)
SGLT-2i			
Yes	176	234	0.83 (0.60–1.16)
No	907	1049	0.85 (0.74–0.98)



Rate ratios for the primary endpoint **across all 17 pre-specified subgroups** were in favour of finerenone and there were no significant interaction p-values[1,2]

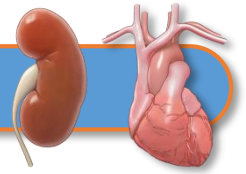
CI, confidence interval; LVEF, left ventricular ejection fraction; RR, rate ratios; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

1. Solomon S, et al. *NEJM* 2024 [in press]; 2. Solomon S, et al. ESC 2024. Hot Line Presentation 7.

FINEARTS-HF

Finerenone demonstrated significant benefits in the **secondary efficacy endpoints** of total HF events and patient-reported health status

Secondary endpoints



Outcome	Finerenone (n=3003) n	Placebo (n=2998) n	Ratio or Difference (95% CI)	p-value
Total (first and recurrent) HF events*	842	1024	RR: 0.82 (0.71–0.94)	0.006 ✓
Change in KCCQ-TSS LS mean (SE)	8.0 (0.32)	6.4 (0.32)	Difference: 1.6 (0.8–2.3)	<0.001 ✓
Improvement in NYHA class from baseline to month 12†	557‡ (18.6%)	553 (18.4%)	OR: 1.01 (0.88–1.15)	*Testing hierarchy stops*
Composite kidney outcome†	75 (2.5%)	55 (1.8%)	HR 1.33 (0.94–1.89)	*Not applicable*
All-cause death†	491 (16.4%)	522 (17.4%)	HR 0.93 (0.83–1.06)	*All-cause death was tested outside hierarchy*

*One patient in each group was reported as having a HF event on the same day as a CV death and was counted as only one composite event in the primary analysis.†The secondary hypotheses were tested hierarchically as follows based on the rejection of the primary null hypothesis: total HF events; KCCQ total symptom score improvement and NYHA class improvement; and the composite kidney endpoint. All-cause death was tested outside this hierarchy, if the primary null hypothesis was rejected, at a nominal two-sided significance level of 5%. ‡Result based on n=3002.

CI, confidence interval; HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LS, least square; NYHA, New York Heart Association; OR, odds ratio; SE, standard error

FINEARTS-HF

The overall incidence of **serious AEs was similar** between the finerenone and placebo groups

	Finerenone (N=2993)	Placebo (N=2993)
Type of treatment-emergent safety outcome	**n (%)**	**n (%)**
Any SAE	1157 (38.7%)	1213 (40.5%)

20.4% and 20.6% of patients receiving finerenone and placebo respectively, discontinued the trial drug for reasons other than death

Treatment emergent defined as all safety outcomes that occurred in patients who received at least one dose of study drug and up until 3 days following permanent discontinuation.
AE, adverse event; SAE, serious adverse event.
Solomon S, et al. *NEJM* 2024 [in press].

Finerenone increased the risk of manageable hyperkalemia and the incidence of hypokalemia was numerically lower compared to placebo

	Finerenone (N=2993)	Placebo (N=2993)
Type of treatment-emergent safety outcome	**n (%)**	**n (%)**
Investigator-reported hyperkalemia	**289 (9.7%)**	**125 (4.2%)**
Leading to hospitalization	16 (0.5%)	6 (0.2%)
Leading to death	0 (0%)	0 (0%)
Serum potassium		
>5.5 mmol/l	413 (14.3%)	199 (6.9 %)
>6.0 mmol/l	86 (3.0%)	41 (1.4%)
<3.5 mmol/l	**127 (4.4%)**	**281 (9.7%)**
Systolic blood pressure <100 mmHg	538 (18.5%)	361 (12.4%)

[K+]

Hypokalemia (serum potassium <3.5 mmol/l) incidence was numerically lower for finerenone compared to placebo

FINEARTS-HF was the first trial to include finerenone 40 mg dosing

40 mg od is not a licensed dosage of finerenone, please consult local prescribing information for more detail. Treatment emergent defined as all safety outcomes that occurred in patients who received at least one dose of study drug and up until 3 days following permanent discontinuation.
eGFR, estimated glomerular filtration rate.
Solomon S, et al. *NEJM* 2024 [in press].

FINEHEART

FINE-HEART was powered to assess heart and kidney outcomes in patients with a high burden of CKM multimorbidity

Finerenone has been studied in RCTs of patients with T2D and CKD and separately in patients with HF (± T2D, ± kidney disease). Individually**, these trials were not powered to evaluate treatment effects on CV death or efficacy in key subgroups**[1]

FINEARTS-HF

FIDELIO-DKD

FIGARO-DKD

FINEHEART

FINE-HEART was able to more robustly assess the safety profile and efficacy of finerenone on CV death and other heart and kidney outcomes compared to the individual trials alone[1]

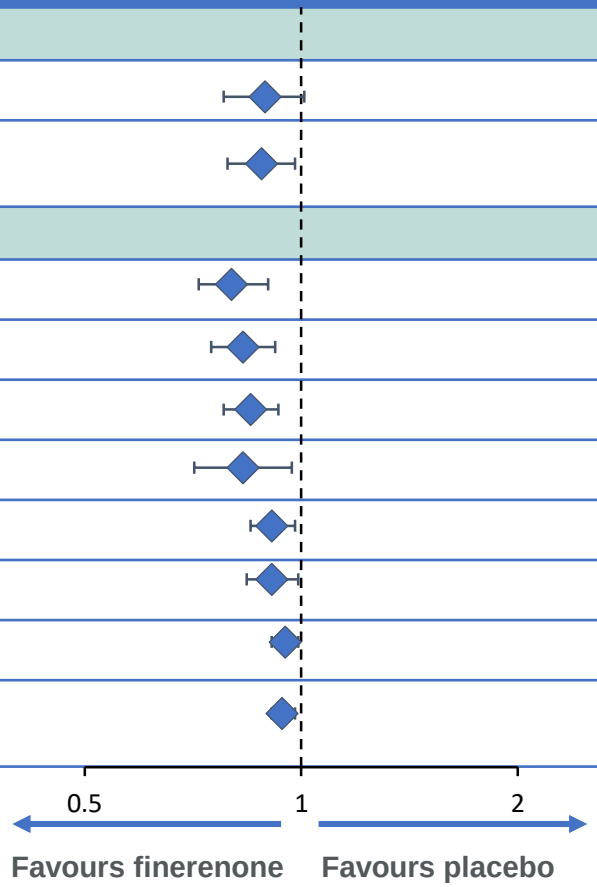
Finerenone is indicated for the treatment of chronic kidney disease (with albuminuria) associated with T2D in adults.2 For prescribing information please refer to the SmPC of the product applicable in your country. Finerenone is not indicated for the treatment of heart failure.

CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; RCT, randomized controlled trial; T2D, type 2 diabetes.

1. Vaduganathan M, et al. *Nat Med* 2024 [in press]; 2. Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed August 2024].

FINE-HEART: Finerenone was associated with significantly improved kidney outcomes compared to placebo

Outcome	Finerenone (n=9,501) n (%)	Placebo (n=9,490) n (%)	HR (95% CI)	p-value
Primary endpoint				
CV death (excluding unknown death)	421 (4.4)	471 (5.0)	0.89 (0.78–1.01)	0.076
Prespecified sensitivity analysis: CV death (including unknown death)	627 (6.6)	703 (7.4)	0.88 (0.79–0.98)	0.025
Secondary endpoints				
Kidney composite endpoint	557 (5.9)	685 (7.2)	0.80 (0.72–0.90)	<0.001
HHF	705 (7.4)	839 (8.8)	0.83 (0.75–0.92)	<0.001
CV death or HHF	1009 (10.6)	1168 (12.3)	0.85 (0.78–0.93)	<0.001
New onset atrial fibrillation	286 (3.0)	345 (3.6)	0.83 (0.71–0.97)	0.018
Major adverse CV events	1428 (15.0)	1554 (16.4)	0.91 (0.85–0.98)	0.010
All-cause death	1042 (11.0)	1136 (12.0)	0.91 (0.84–0.99)	0.027
All-cause hospitalization	4261 (44.8)	4401 (46.4)	0.95 (0.91–0.99)	0.025
All-cause death or all-cause hospitalization	4467 (47.0)	4653 (49.0)	0.94 (0.91–0.98)	0.007



CI, confidence interval; CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio.

Vaduganathan M, et al. *Nat Med* 2024 [in press].

Finerenone is the first and only MRA to demonstrate definitive CV benefits in a broad population of patients with HF and LVEF ≥40%

Finerenone demonstrated a statistically significant **16% relative risk reduction in the composite CV outcome** (number of CV deaths and HF events) in patients with **HF and LVEF ≥40%,** compared to placebo

The effects of finerenone on the CV composite outcome were **consistent across a broad population**, regardless of baseline use of an SGLT-2i or LVEF status

Finerenone demonstrated significant **benefits in the secondary efficacy endpoints of total HF events and patient-reported health status**

Finerenone was well tolerated, **confirming the well-known safety profile**, with a comparable incidence of treatment-emergent SAEs to placebo

CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SAE, serious adverse event; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

Solomon S, et al. *NEJM* 2024 [in press].

FINEHEART

7th Advances in Heart Failure

10 e 11 de Outubro

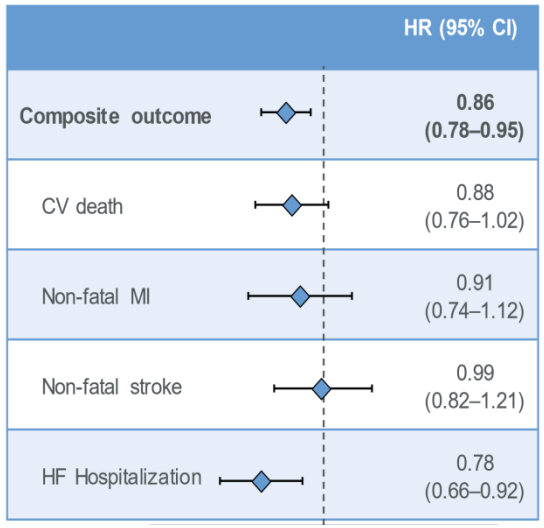
O ADVENTO DO FIM DA FRAÇÃO DE EJEÇÃO?

TERAPÊUTICAS INDEPENDENTES DA FRAÇÃO DE EJEÇÃO

ANTAGONISTAS DOS RECETORES MINERALOCORTICÓIDES NÃO ESTEROIDES?

Benefícios comprovados:

- EFpEF / EFmrEF
- ⬇ eventos CV na DM2 e DRC



FIDELIO DKD and FIGARO DKD pooled analysis. Agarwal R, et al. Eur Heart J 2022

- **Sem evidencia (RCTs) na EFrEF**
- Efeito de classe?
- FIEARTS-HF & Guidelines?