Historic Evolution of Mineralocorticoid Receptor Antagonism: CV and Renal Protection

Muthiah Vaduganathan, MD MPH

Brigham and Women's Hospital

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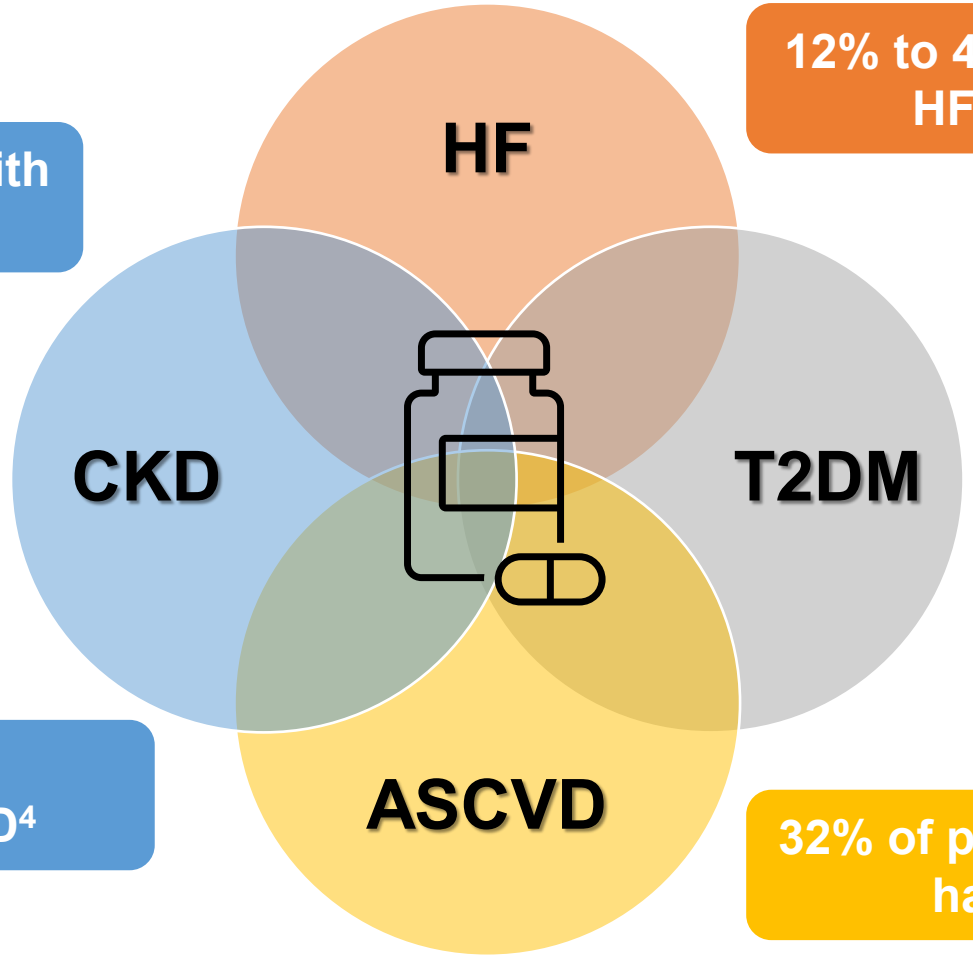
@mvaduganathan

Disclosures: Amgen, American Regent AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Relypsa, and Roche Diagnostics

Substantial Overlap in Cardio-Renal-Metabolic Conditions



12% to 45% of patients with HF have T2DM[1,2]

35% to 45% of patients with HF have CKD[1]

20% to 44% of patients with T2DM have CKD[2,3]

14% of the US population has diabetes[3]

76% of patients with CVD and T2DM have CKD[4]

32% of patients with CAD have T2DM[2]

1. Packer M. *Diabetes Care*. 2018;41:11-13.
2. Wanner C. *Am J Cardiol*. 2017;120:S59-S67.
3. https://www.cdc.gov/nchs/data/databriefs/db319.pdf. Accessed November 7, 2019.
4. Wang T et al. *Diabetes Metab Syndr*. 2019;13:612-615.

Combination Medical Therapy: A New Standard of Cardio-Renal-Metabolic Care

HFrEF

"Quadruple Therapy"

- β-blocker
- ACEi/ARB/ARNI
- *Steroidal* MRA
- SGLT-2 Inhibitor

CKD

"Triple Therapy"

- ACEi/ARB
- *Non-Steroidal* MRA
- SGLT-2 Inhibitor
- Endothelin receptor antagonist
- GLP-1RA

Under-Recognized Prevalence of Hyperaldosteronism

Cross-Sectional Study

4 US Medical Centers

n = 1,015

Oral sodium suppression test

	Normotensive n = 289	Stage 1 HTN n = 115	Stage 2 HTN n = 203	Resistant HTN n = 408
Urine Aldosterone (μg/24h)	6.5 (5.2 – 7.7)	7.3 (5.6 – 8.9)	9.5 (8.2 – 10.8)	14.6 (12.9 – 16.2)
Biochemically Overt Aldosteronism (%)	11.3 (5.9– 16.8)	15.7 (8.6 – 22.9)	21.6 (16.1– 27)	22 (17.2 – 26.8)

CONCLUSION: The prevalence of primary aldosteronism is high and there is a prevalent continuum of renin-independent aldosterone production that parallels the severity of hypertension. These findings redefine the primary aldosteronism syndrome and implicate it in the pathogenesis of "essential" Hypertension (HTN).

Brown JM, Siddiqui M, Calhoun D et al. ***The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study.*** DOI: 10.7326/M20-0065

@ssfarouk

Under-Recognized Prevalence of Hyperaldosteronism

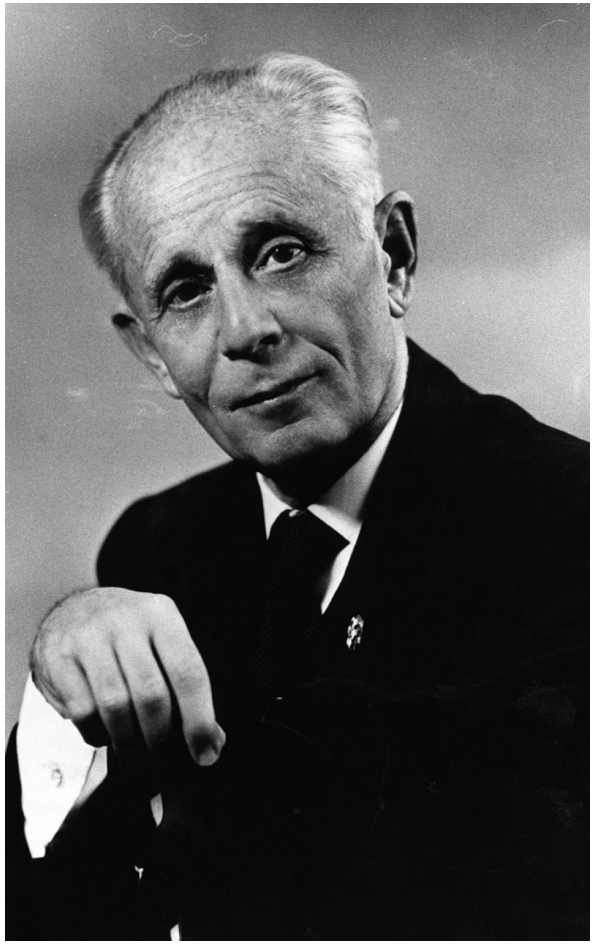
"The prevalence of primary aldosteronism is high and largely unrecognized.

…there is a prevalent continuum of renin-independent aldosterone production that parallels the severity of hypertension.

These findings redefine the primary aldosteronism syndrome and implicate it in the pathogenesis of "essential" hypertension."

--Brown J et al. Ann Intern Med 2020

MR Overactivation as a Central Driver of Inflammation and Fibrosis in the Heart and Kidneys



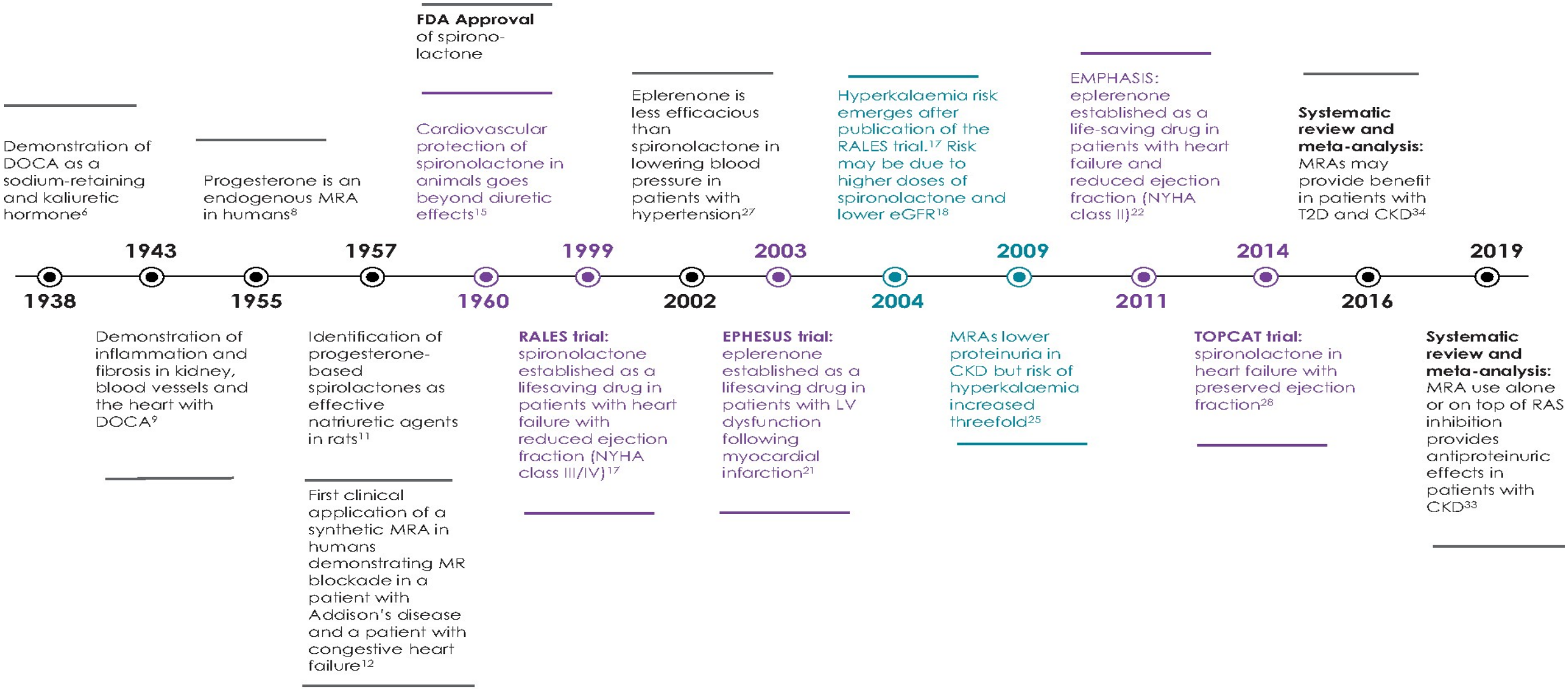
Hans Selye, 1907-1982,
Born Vienna, Austria-Hungary
Source: Wikipedia

MALIGNANT HYPERTENSION
PRODUCED BY TREATMENT WITH
DESOXYCORTICOSTERONE ACETATE
AND SODIUM CHLORIDE*

By Hans Selye, M.D., Ph.D., D.Sc., F.R.S.C.,
C. E. Hall,† M.Sc. and E. M. Rowley, B.Sc.

Montreal

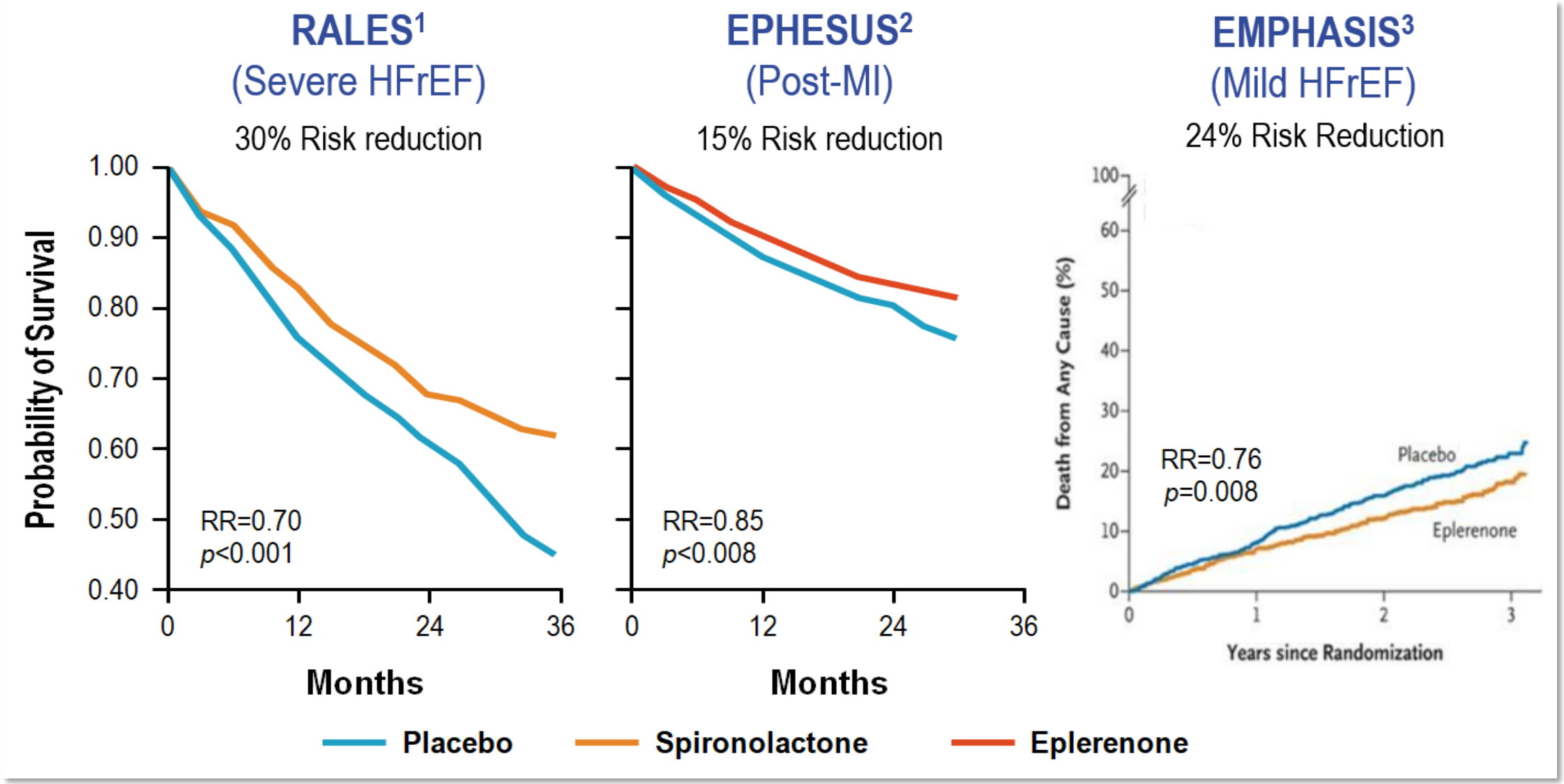
- Selye H, et al. *Can Med Assoc J*. 1943;49:88-92.



Eur Heart J, Volume 42, Issue 2, 7 January 2021, Pages 152–161, https://doi.org/10.1093/eurheartj/ehaa736

OXFORD UNIVERSITY PRESS

Seminal Trials Demonstrating Life-Saving Benefits of MRA in HF with Reduced EF

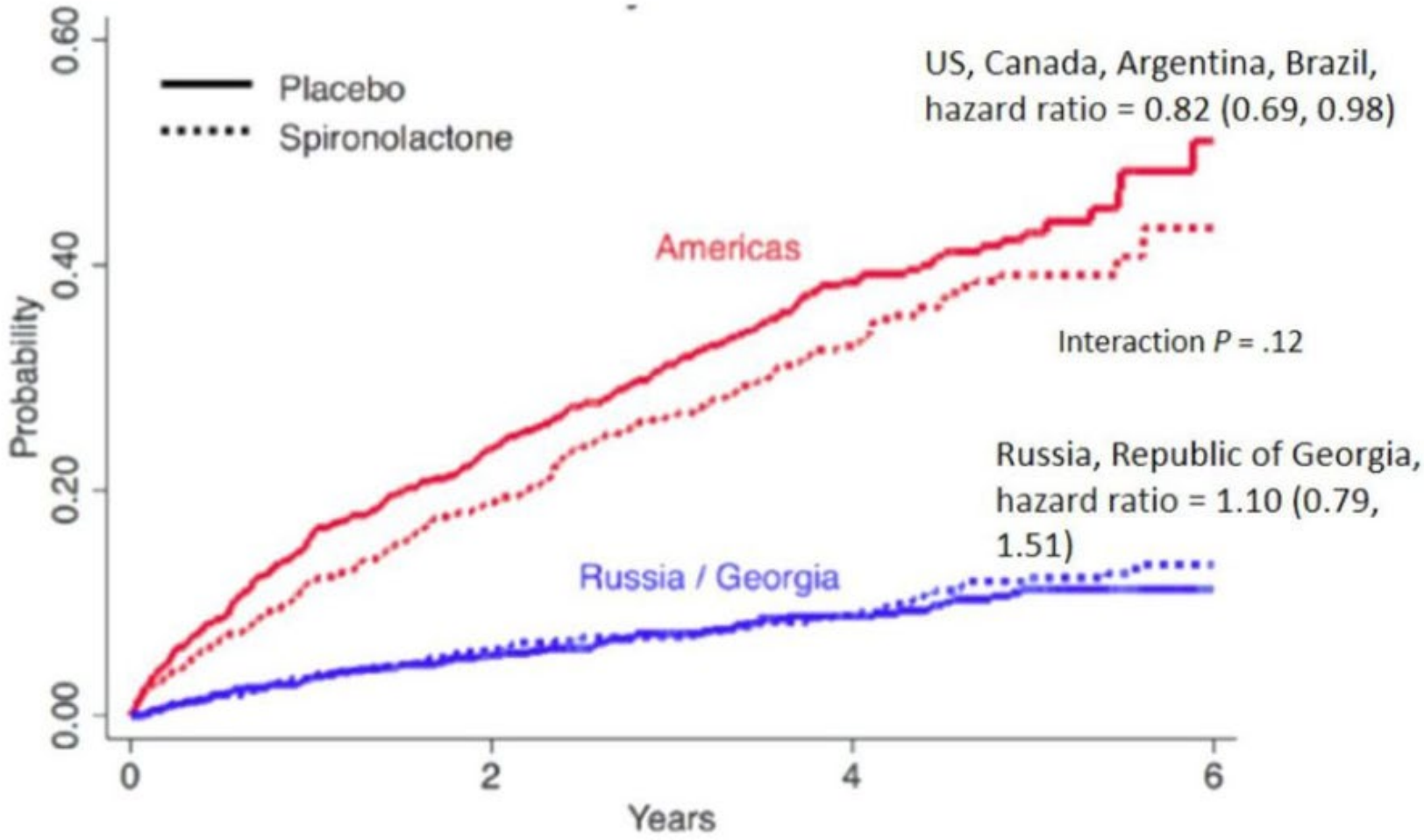


1. Pitt B et al. *N Engl J Med*. 1999:341:709-717.

2. Pitt B et al. *N Engl J Med*. 2003;348:1309-1321.

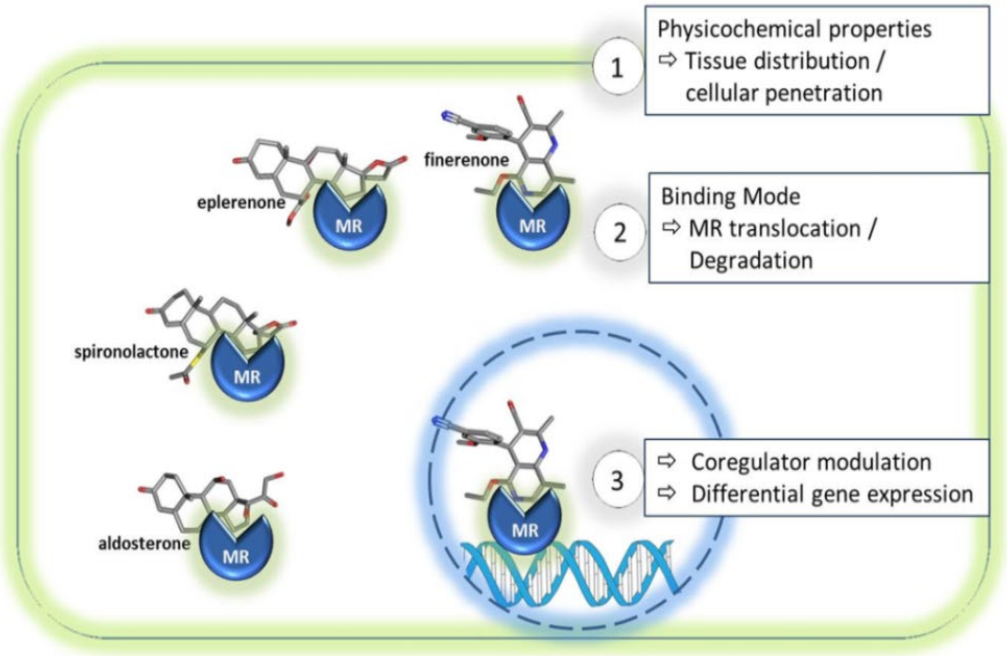
3. Zannad F et al. *N Engl J Med*. 2011;364:11-21.

TOPCAT Trial: Suggestion of Benefit of Spironolactone in HF with Preserved EF



Pfeffer MA, et al. *Circulation*. 2015;131:34-42.

Comparison of Steroidal vs Non-Steroidal MRAs



Kolkhof P, Nowack C, Eitner F. *Curr Opin Nephrol Hypertens.* 2015;24:417-424.

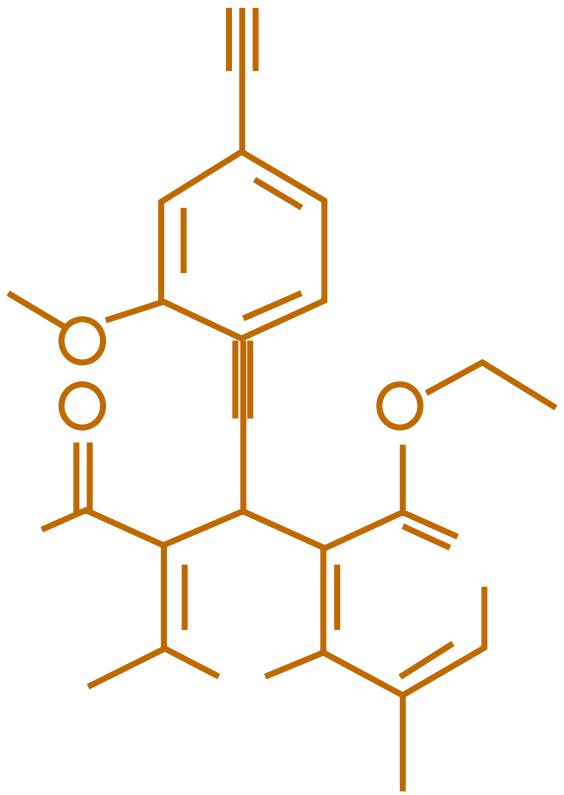
	Spironolactone	Eplerenone	Finerenone
MRA Class	Steroidal	Steroidal	Non-steroidal
Potency	High	Low	High
Selectivity	Low	Medium	High
Metabolites	Multiple, active	No active	No active
Tissue distribution	Kidney>>heart (>6-fold)	Kidney>heart (~3-fold)	Equivalent (1:1)

[a]Half-life of active compound/metabolites; [b]HV = healthy volunteers; [c]In rodents.
Modified from: Kolkhof B, Borden SA. *Mol Cell Endocrinol.* 2012;350:310-317.

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

Can we block the mineralocorticoid receptor but not cause hyperkalemia?

Finerenone is a Non-steroidal Mineralocorticoid Receptor (MR) Antagonist



Bulky, nonsteroidal molecule

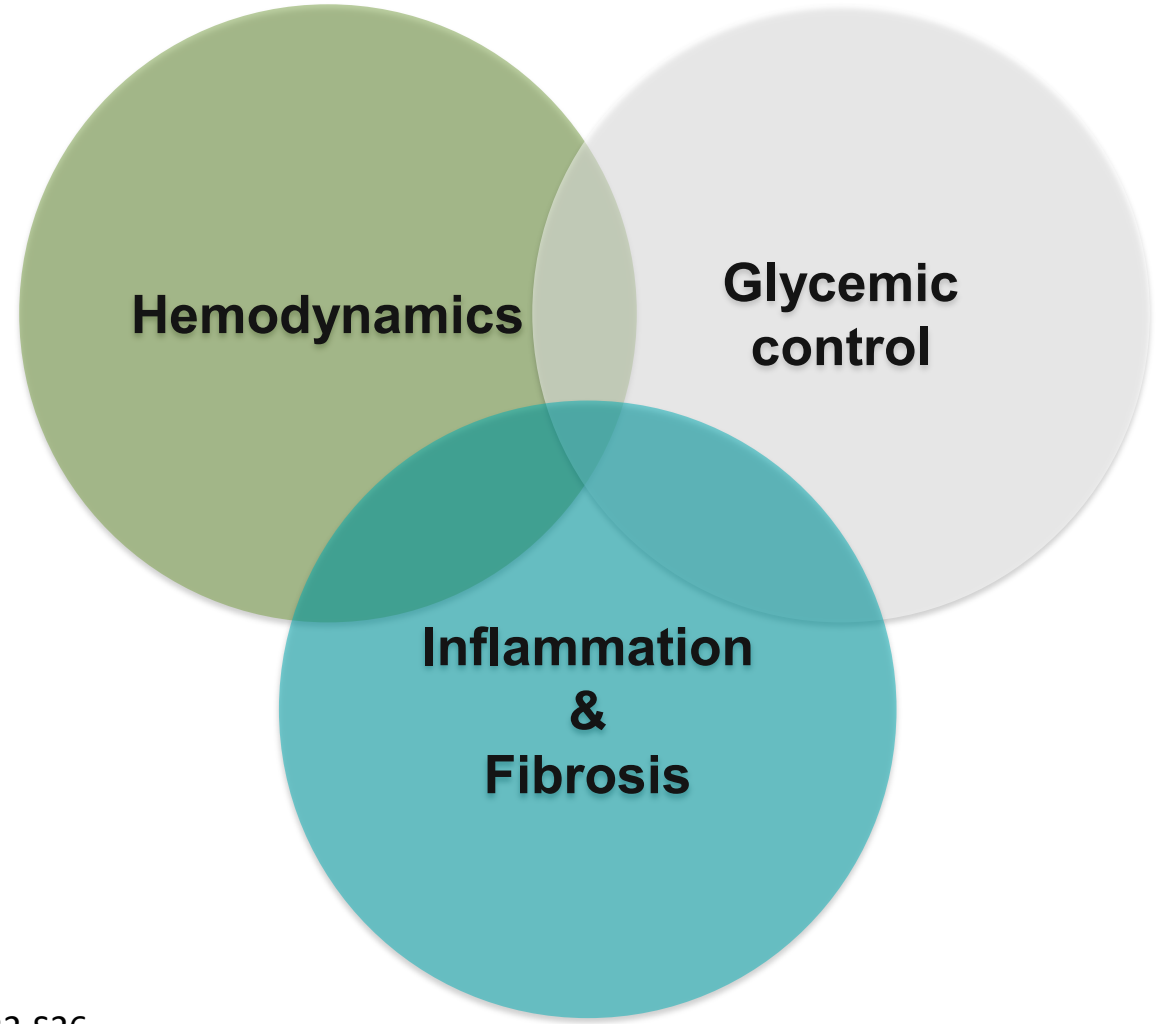
MR antagonist with high selectivity and potency for MR

Distinct structure results in selective and potent interaction with the MR and regulation of gene expression

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

Strategies to Slow Progression of CKD

ACE inhibitors
ARBs

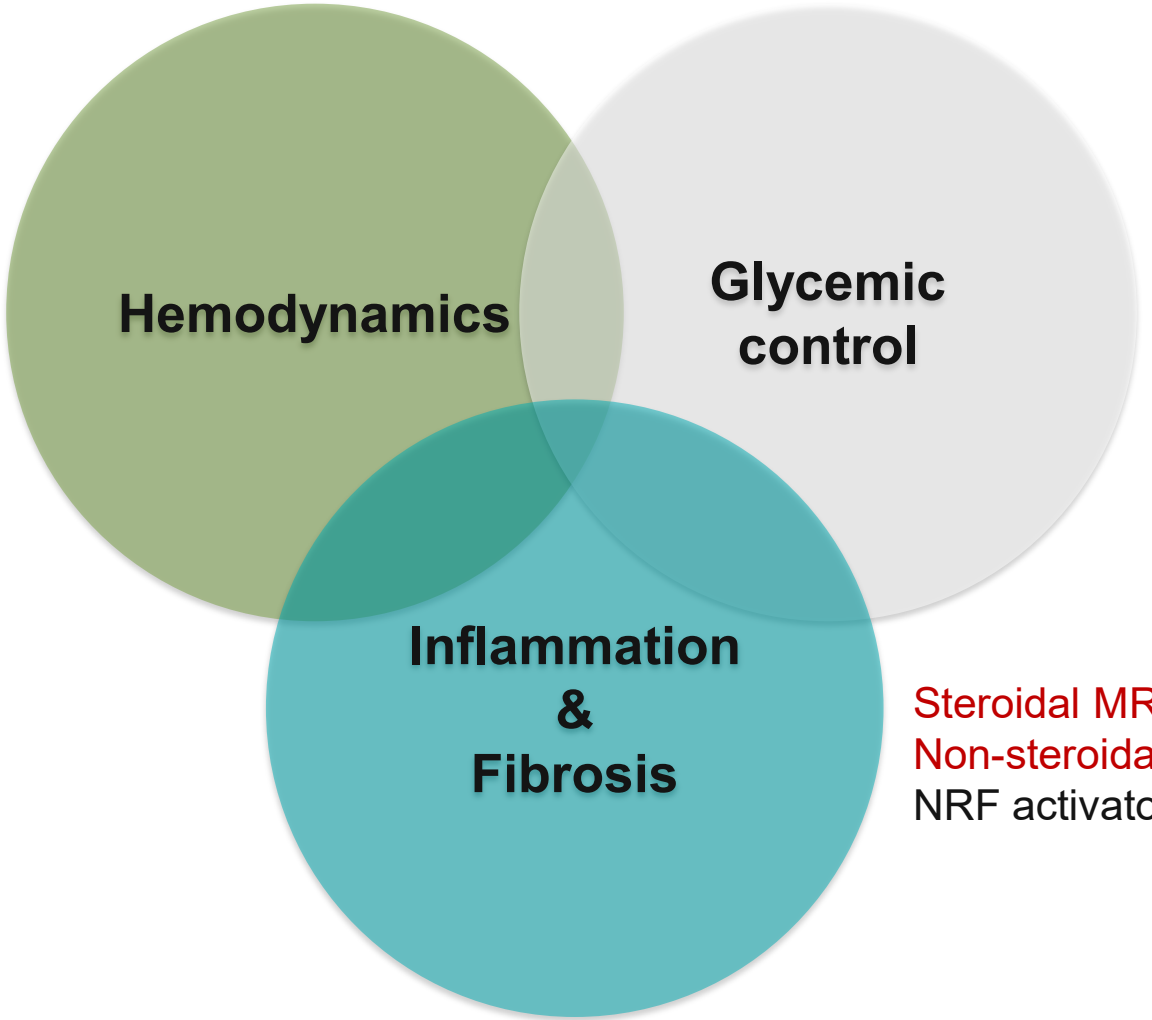


Lowering HbA_{1c}
SGLT2 inhibitors
(several mechanisms may be independent of glucose–lowering)

- Lee SB, et al. *Kidney Int Suppl*. 2010;S22-S26.

Strategies to Slow Progression of CKD

ACE inhibitors
ARBs

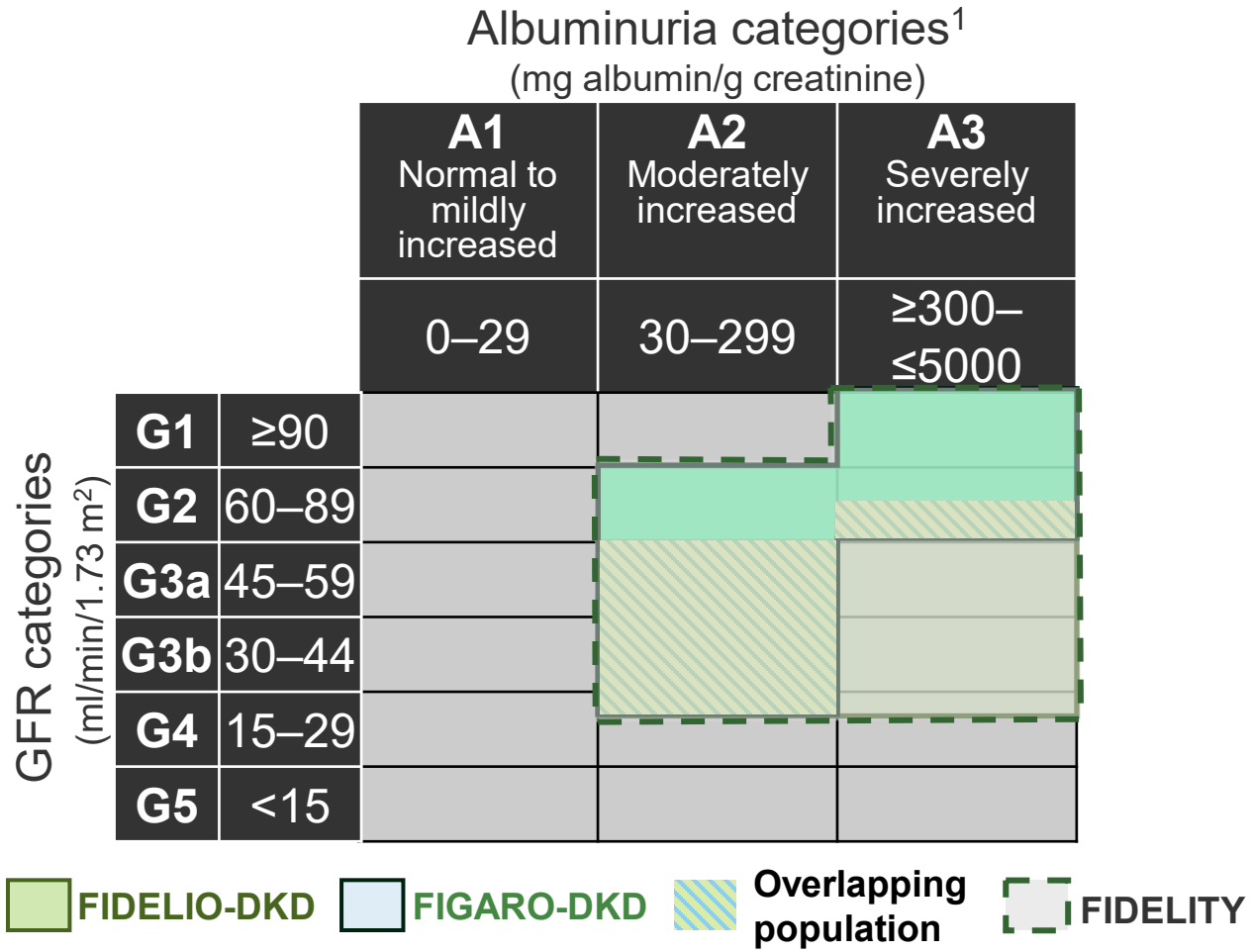


Lowering HbA_{1c}
SGLT2 inhibitors
(several mechanisms may be independent of glucose–lowering)

Steroidal MRA: spironolactone, epleronone
Non-steroidal MRA: finerenone, esaxerenone
NRF activators: bardoxolone

- Kolkhof P, et al. *Mol Cell Endocrinol*. 2012;350:310–317; Kolkhof P, et al. *J Endocrinol*. 2017;234:T125-T140.

Evaluation of Finerenone Across the Spectrum of Kidney Disease in Type 2 Diabetes



FIDELITY[4]
N=13,171

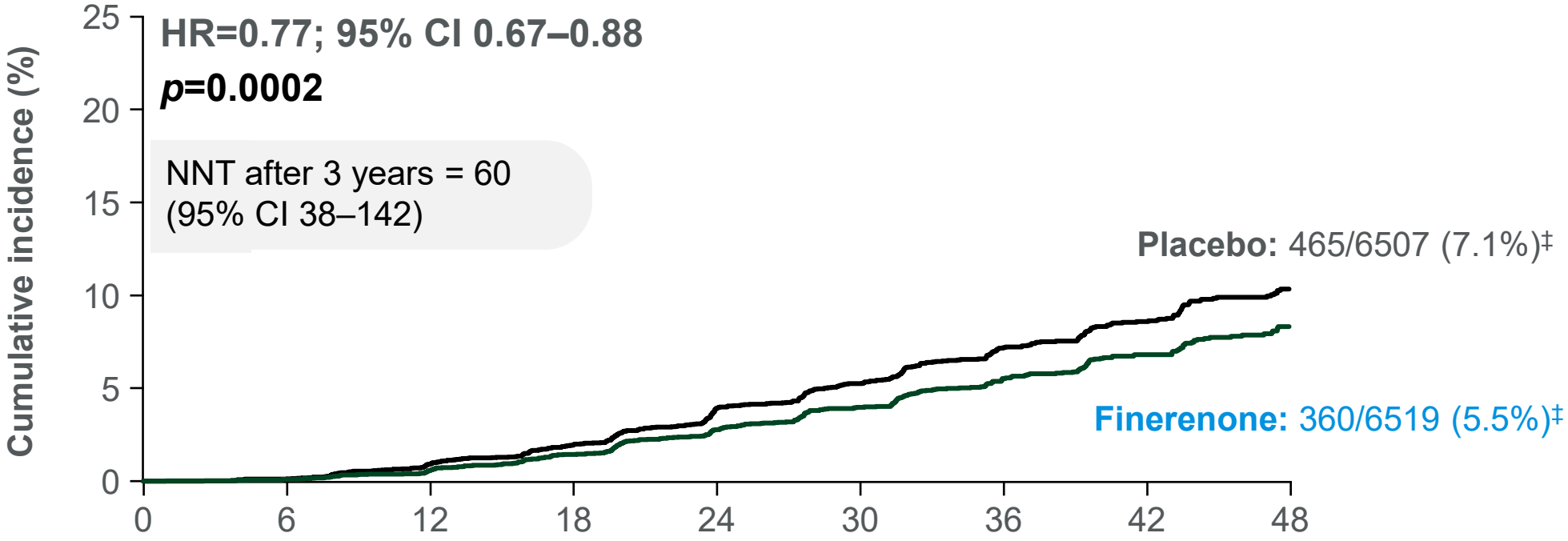
FIDELIO-DKD[2]
N=5734

FIGARO-DKD[3]
N=7437

1. *Kidney Int* 2013;3:1–150; 2. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 3.

Finerenone Delays Progression to End Stage Kidney Disease

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or renal death#



No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

Agarwal R, *et al*. Manuscript in development

FIDELITY pooled analysis: Effects of finerenone on the components of the ≥57% eGFR kidney composite outcome

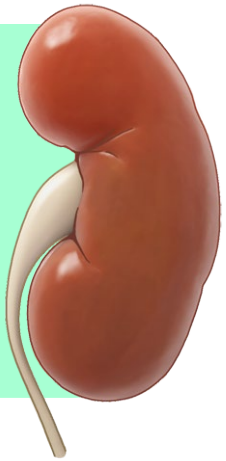
Outcome	Finerenone (n=6519)		Placebo (n=6507)		HR (95% CI)	*p*-value
	n (%)	n per 100 PY	n (%)	n per 100 PY		
≥57% eGFR kidney composite outcome	**360 (5.5)**	**1.96**	**465 (7.1)**	**255**	**0.77 (0.67–0.88)**	**0.0002**
Kidney failure*	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040‡
Sustained# decrease in eGFR to <15 ml/min/1.73 m^2	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026‡
Sustained# ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.459

*Kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 ml/min/1.73 m^2; #confirmed by two eGFR measurements ≥4 weeks apart; ‡analyses for *p*-values not prespecified

FIDELITY pooled analysis: NNT to prevent one kidney outcome event at 3 years

HR (95% CI)	ARR (95% CI) at 36 months	NNT (95% CI) at 36 months
0.77 (0.67–0.88)	–1.7% (–2.6 to –0.7)	60 (38–142)

- **Hazard ratio = 0.77** – equivalent to a **23% relative risk reduction**
- **Absolute risk reduction = 1.7%** at 3 years
- **NNT** to **prevent one kidney outcome event** was **60** at 3 years



Pooled Safety Data from 2 Pivotal RCTs of Finerenone in CKD

Finerenone had a modest effect on blood pressure

Overall difference in mean SBP between groups:

	Month 4	Month 12
FIDELIO-DKD[1]	–3.9 mmHg	–3.0 mmHg
FIGARO-DKD[2]	–3.5 mmHg	–3.0 mmHg
FIDELITY[3]	–3.7 mmHg	–3.0 mmHg

HbA1c levels and body weight were similar in both groups throughout the study

There were no differences in acute kidney injury between groups

Sexual side effects (e.g. gynaecomastia) were rare and balanced between groups

Finerenone Dosing and Monitoring

1 INITIATE

Measure serum potassium

Do not initiate KERENDIA if serum potassium >5.0 mEq/L.

If >4.8 to 5.0 mEq/L, initiation may be considered with additional potassium monitoring within the first 4 weeks based on clinical judgment and serum potassium levels.

Measure eGFR to determine recommended starting dose

10 mg	eGFR ≥25 to <60 mL/min/1.73 m^2
20 mg	eGFR ≥60 mL/min/1.73 m^2
Not recommended	eGFR <25 mL/min/1.73 m^2

2 CHECK LABS

After initiation, restart, or dose adjustment of KERENDIA:

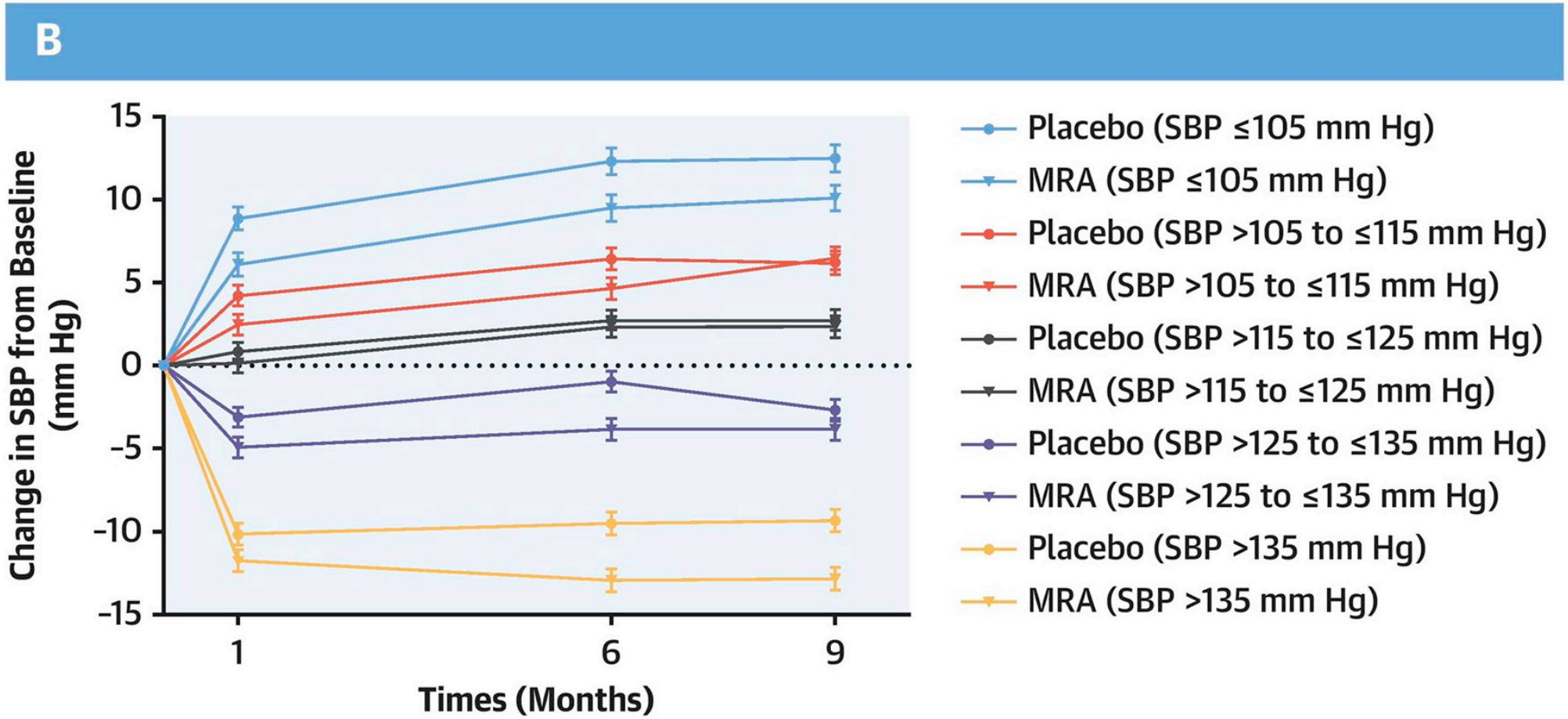
In 4 weeks, check serum potassium

3 ADJUST: Target daily dose of KERENDIA is 20 mg daily

Current serum potassium (mEq/L)	Current dose 10 mg once daily	Current dose 20 mg once daily
≤4.8	Increase the dose to 20 mg once daily*	Maintain 20 mg once daily
>4.8 to 5.5	Maintain 10 mg once daily	Maintain 20 mg once daily
>5.5	Withhold KERENDIA. Consider restarting at 10 mg once daily when serum potassium ≤5.0 mEq/L	Withhold KERENDIA. Restart at 10 mg once daily when serum potassium ≤5.0 mEq/L

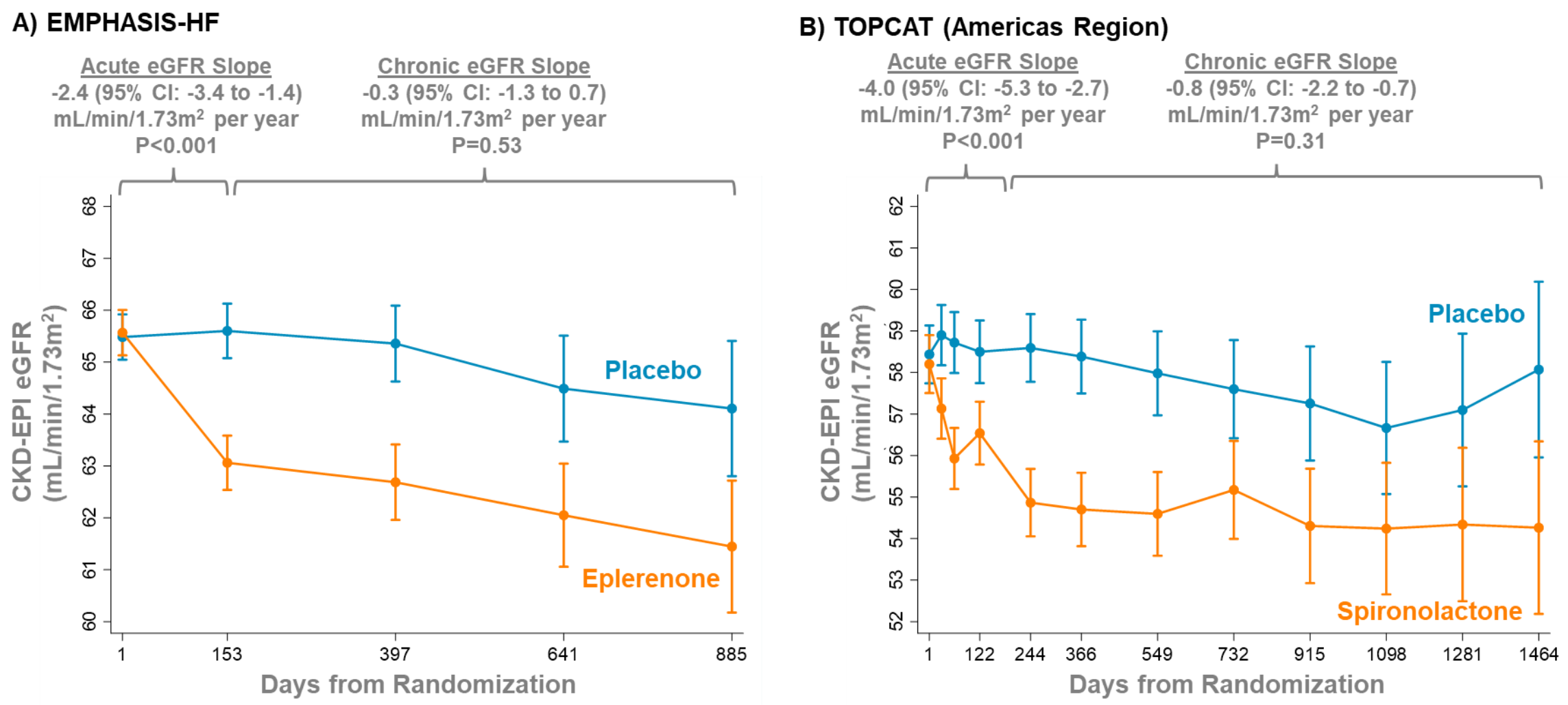
*if eGFR has decreased by more than 30% compared to previous measurement, maintain 10 mg dose.

MRAs "Hemodynamically Neutral" in High-Risk Patients with Low Starting Blood Pressure



Serenelli, M. et al. J Am Coll Cardiol HF. 2020;8(3):188-98.

MRAs Induce an Expected and Reversible 'eGFR Dip" within Days of Initiation (Similar to ACEi/ARB/SGLT2i)

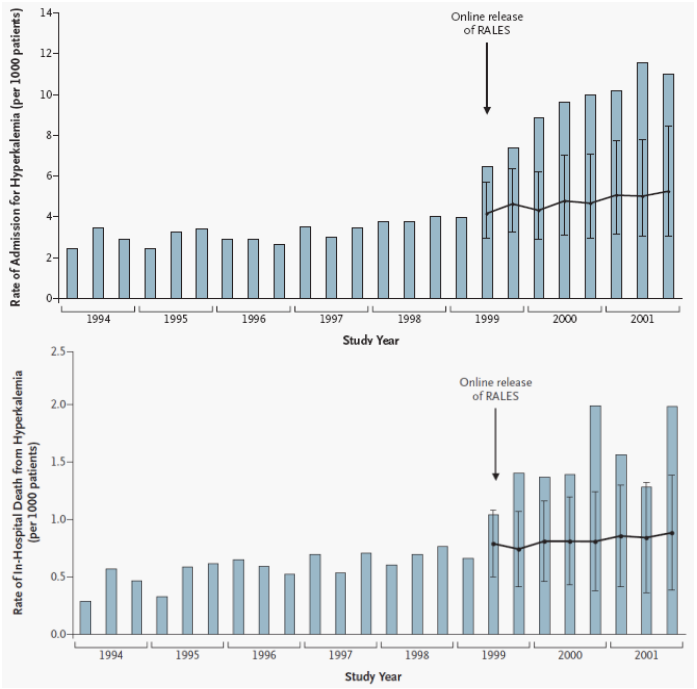


Vaduganathan M, Ferreira JP, et al. In Progress

Hyperkalemia Limits a Broader Use of the Steroidal MRAs: Spironolactone and Eplerenone

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study [a]

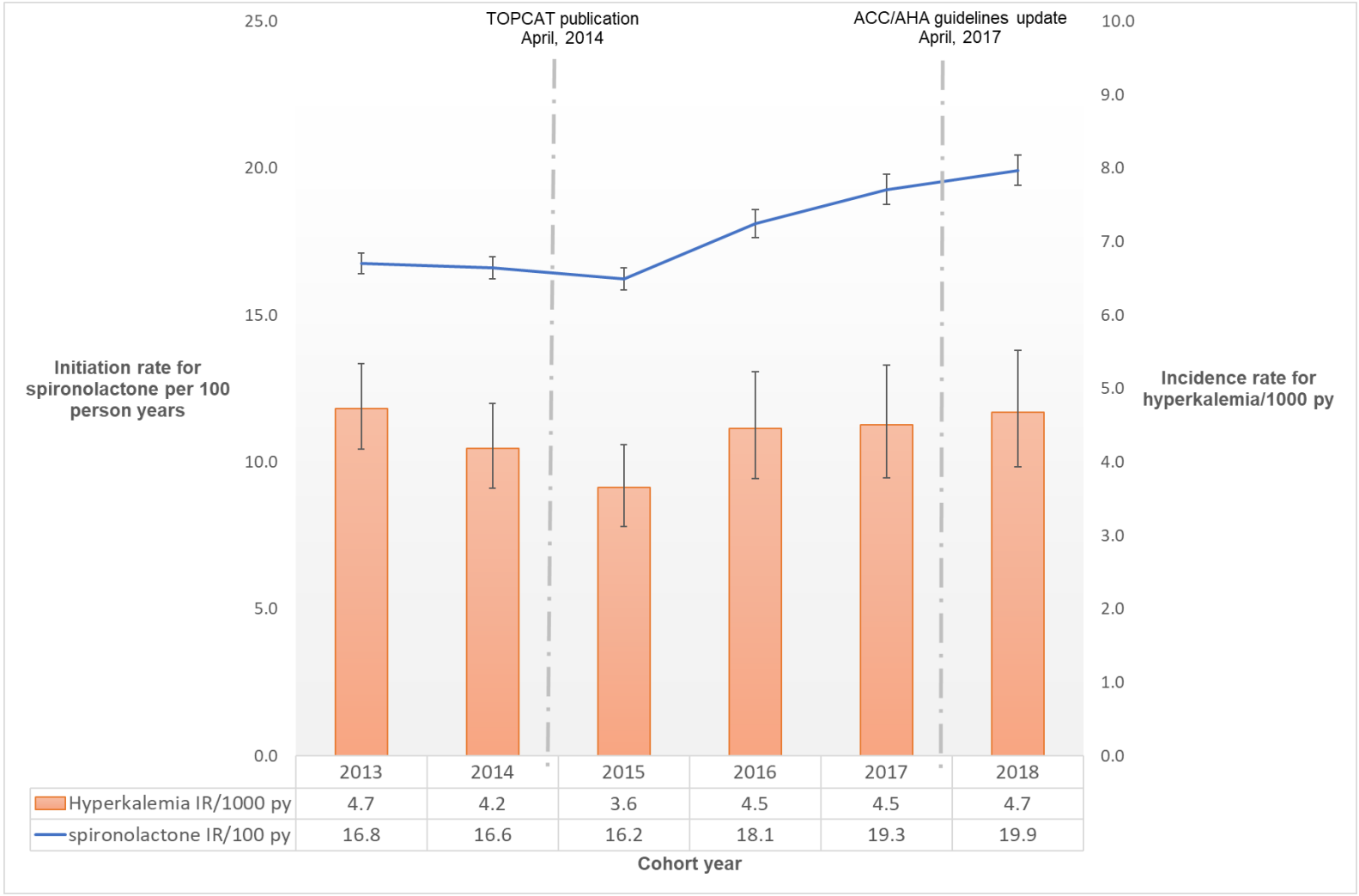
David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.



EPLERENONE[b]
Contraindicated in patients with a serum potassium of >5.5 mEq/L
Contraindicated in patients with type 2 diabetes with microalbuminuria Contraindicated in men with a serum creatinine of >2.0 mg/dL and in women with a serum creatinine of >1.8 mg/dL Contraindicated in patients with a creatinine clearance of <50 mL/min
Contraindicated in patients treated concomitantly with potassium supplements or other potassium-sparing diuretics

- a. Juurlink DN, et al. *N Engl J Med*. 2004;351:543-551; b. Sica DA. *J Clin Hypertens (Greenwich).* 2002;5:441-445.

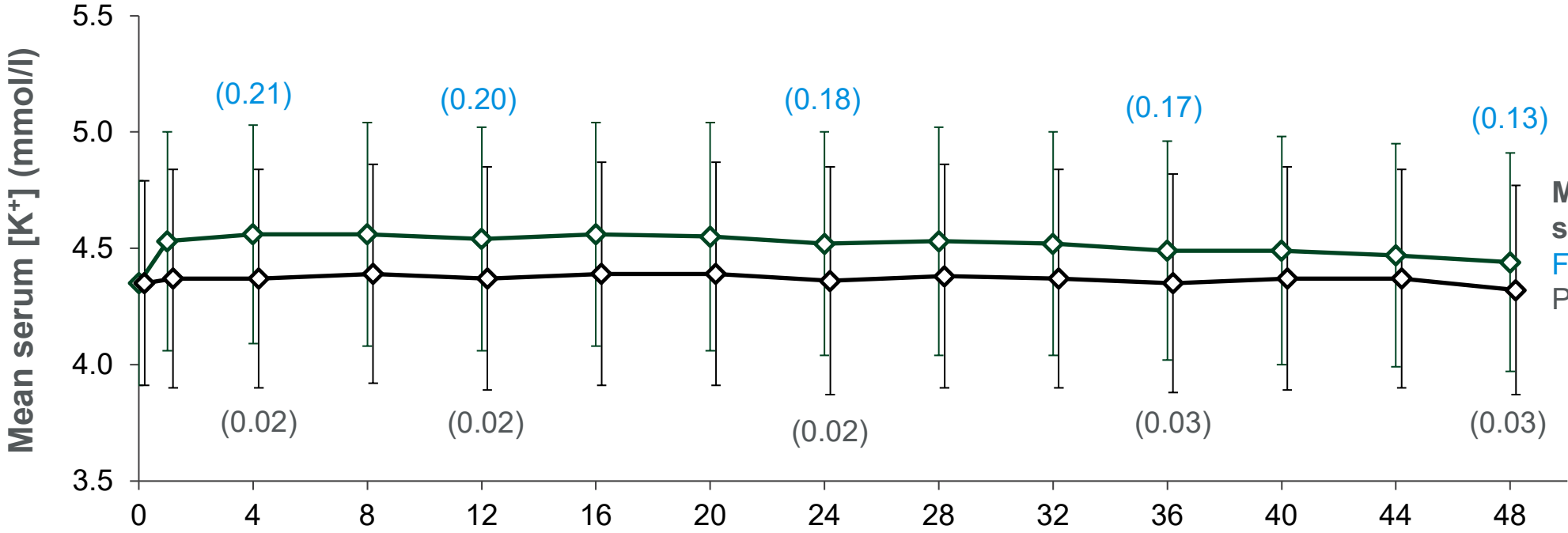
Spironolactone Initiation and Hyperkalemia Incidence in Patients in HFpEF in Medicare from 2013 to 2018



R Desai, M Vaduganathan et al. In Process

Finerenone Impact on Potassium in Pivotal RCTs

The maximum difference in mean serum [K^+] between groups was 0.17 mmol/l at month 16*

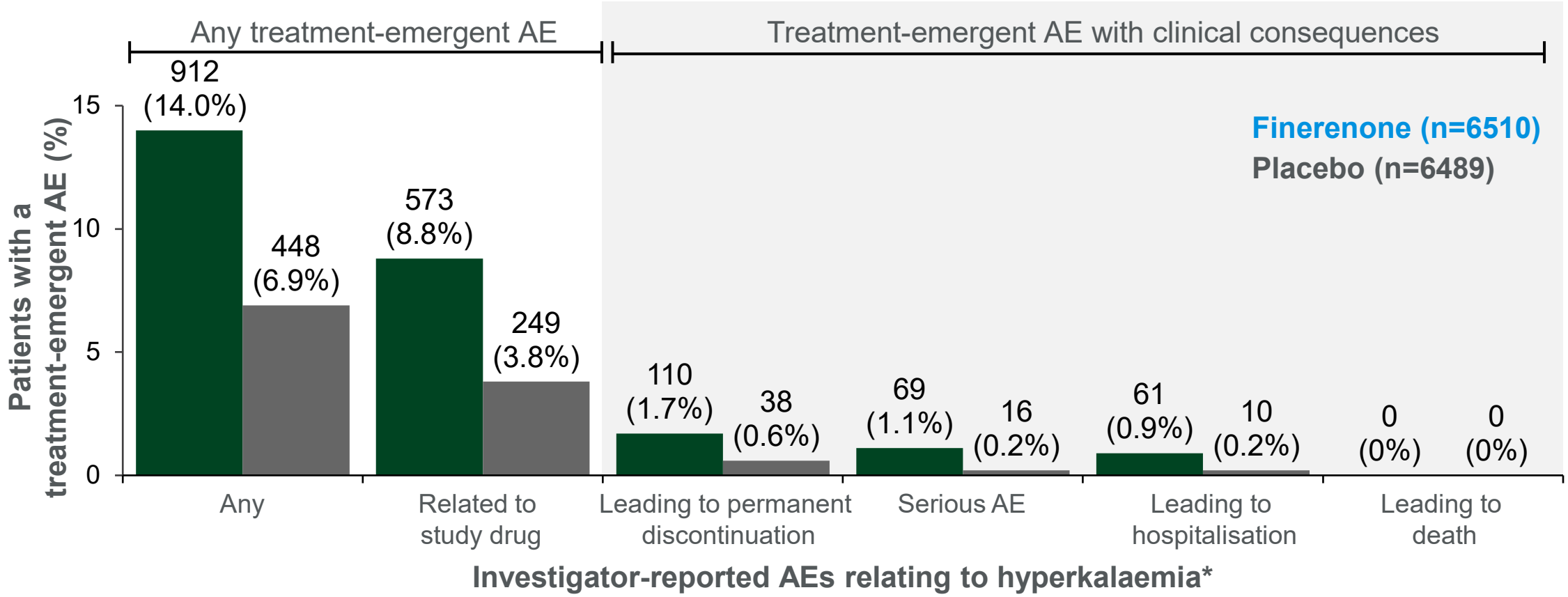


Mean baseline serum [K^+]
Finerenone: 4.35±0.44
Placebo: 4.35±0.44

Patients (n):						
Finerenone	6510	6234	5990	4916	2781	912
Placebo	6487	6229	5965	4878	2759	887

Numbers in parentheses show change from baseline; error bars show standard deviation
*Based on a mean change of 0.21 mmol/l in the finerenone and 0.04 mmol/l in the placebo group
Agarwal R, *et al*. Manuscript in development

Finerenone Impact on Hyperkalemia in Pivotal RCTs



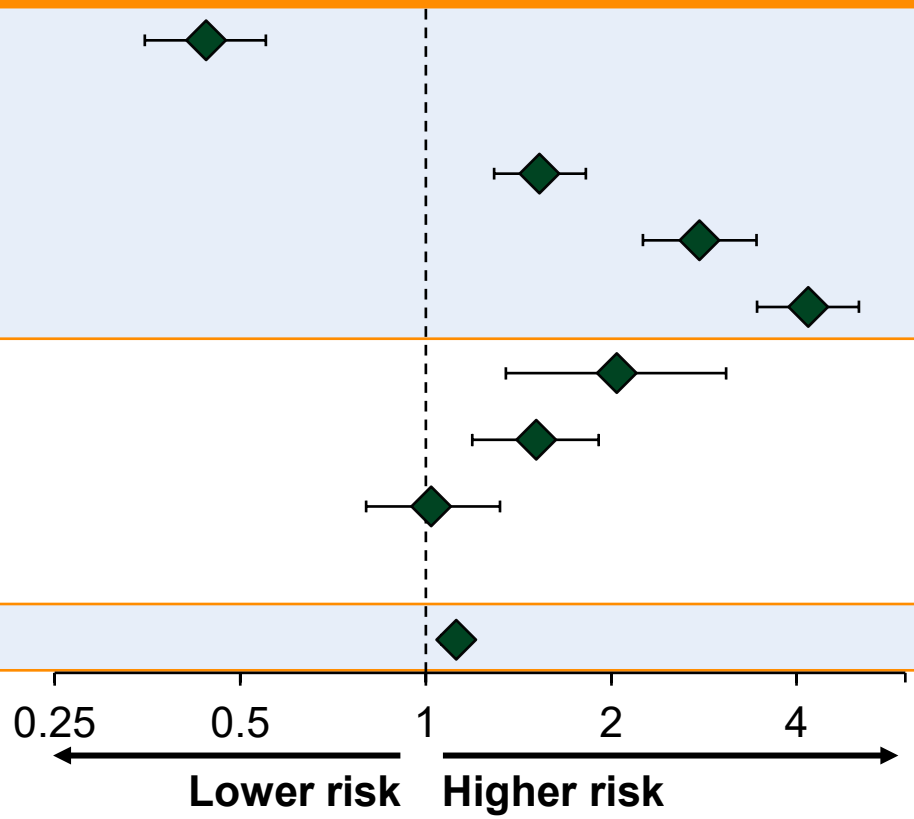
There were no deaths due to hyperkalaemia, and the incidences of treatment discontinuation or hospitalisation due to hyperkalaemia were low

*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'.
MedDRA, Medical Dictionary for Regulatory Activities

Higher baseline [K^+], lower eGFR and higher UACR were associated with higher risk of hyperkalaemia*

FIDELIO-DKD

Variable (%#)		HR (95% CI)	*p*-value
Baseline serum [K^+], mmol/l	≤4.1 (30%)	0.44 (0.35–0.55)	<0.0001
	>4.1–≤4.5 (36%)	Reference	
	>4.5–≤4.8 (20%)	1.53 (1.29–1.82)	
	>4.8–≤5.0 (7%)	2.78 (2.25–3.44)	
	>5.0 (7%)	4.18 (3.45–5.05)	
Baseline eGFR, ml/min/1.73 m^2	<25 (2%)	2.04 (1.35–3.07)	<0.0001
	25–<45 (53%)	1.51 (1.19–1.91)	
	45–<60 (34%)	1.02 (0.80–1.32)	
	≥60 (12%)	Reference	
Log2 of baseline UACR‡		1.12 (1.06–1.17)	<0.0001



After adjustment for age, sex, baseline UACR, baseline eGFR, baseline serum [K^+], baseline medication use (diuretic use, β-blocker use and SGLT-2i use) and treatment assignment (finerenone vs placebo); #

Frequency of potassium monitoring

Finerenone USPI label recommendations regarding potassium measurement[1]

- **Measure serum potassium** and **eGFR** in **all patients before initiation of treatment with finerenone** and **dose accordingly**. **Do not initiate finerenone** if **serum potassium is >5.0 mmol/l**
- **Measure serum potassium periodically** during **treatment with finerenone** and **adjust dose accordingly**
- **More frequent monitoring** may be necessary for patients at **risk for hyperkalaemia**, including those on **concomitant medications** that impair potassium excretion or increase serum potassium

		Current finerenone dose	
		10 mg once daily	20 mg once daily
Current serum potassium (mmol/l)	≤4.8	Increase the dose to 20 mg once daily*	Maintain 20 mg once daily
	>4.8 – 5.5	Maintain 10 mg once daily	Maintain 20 mg once daily
	>5.5	Withhold finerenone. Consider restarting at 10 mg once daily when serum potassium ≤5.0 mmol/l	Withhold finerenone. Restart at 10 mg once daily when serum potassium ≤5.0 mmol/l

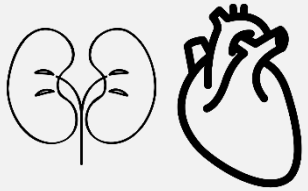
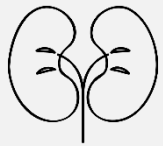
KDIGO practical guidance[2]

- Changes in **BP, serum creatinine, and serum potassium** should be checked **within 2–4 weeks of initiation** or increase in the dose of a RASi, depending on the current eGFR and serum potassium.
- In patients at **risk for hyperkalemia**, measuring **serum potassium before and at 1–2 weeks after initiation of RASi is recommended**

ESC guidance[3,4]

- Check **blood chemistry** at **1 and 4 weeks after starting/up-titrating MRA**
- **Potassium binders may be considered** in patients with **HF with or without CKD** to **manage hyperkalaemia**
- **Potassium binders** may be **considered** in selected **patients with HF with or without CKD** to allow **up-titration of MRAs** while avoiding hyperkalaemia

Finerenone Phase II Program: Less Serum K Change with Finerenone Compared to Spironolactone

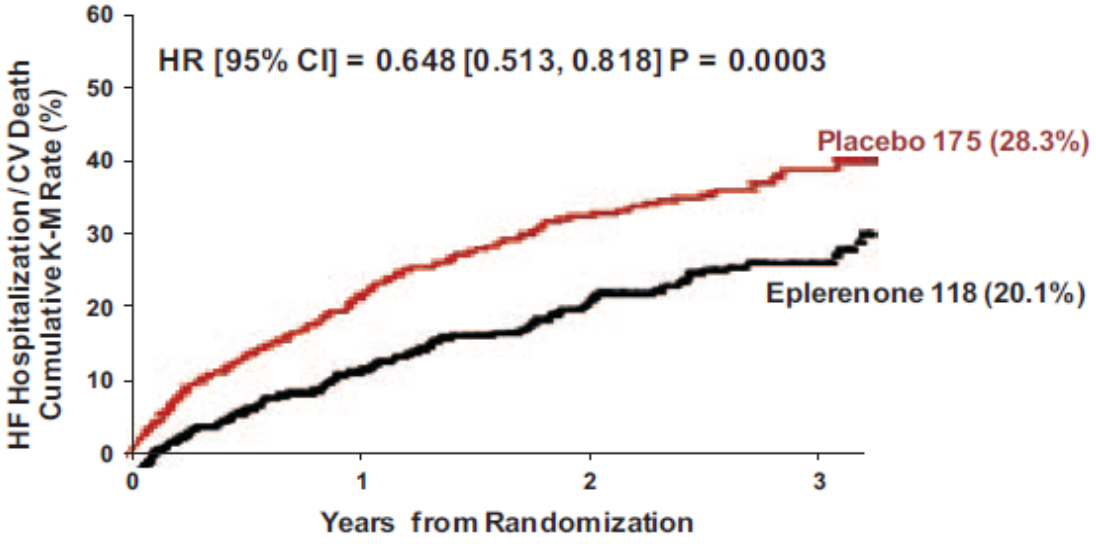
Program	Patients	Comparator	Δ Serum K
ARTS[a] 	CKD and HF	Spironolactone	↓
ARTS-HF[b] 	HFrEF	Eplerenone	↔
ARTS-DN[c] 	CKD + A2/A3	Placebo	↑

- Bakris GL, et al. *JAMA.* 2015;314:884-894; Filippatos G, et al. *Eur Heart J*. 2016;37:2105-2114; Pitt B, et al. *Eur Heart* J. 2013;34:2453-2463.

MRA Clinical Benefits Not Influenced by Background Therapy

EMPHASIS-HF
Benefits of MRA Irrespective of Background ACEi/ARB or BB

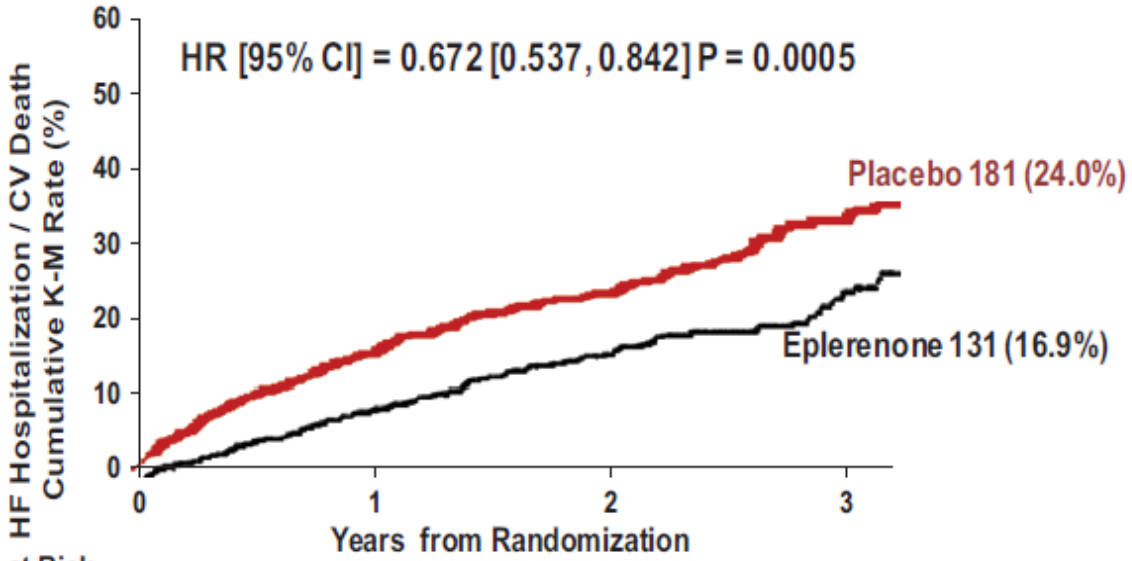
< 50% Target Dose



No. at Risk

Placebo	619	350	194	82
Eplerenone	588	387	219	87

≥ 50% Target Dose



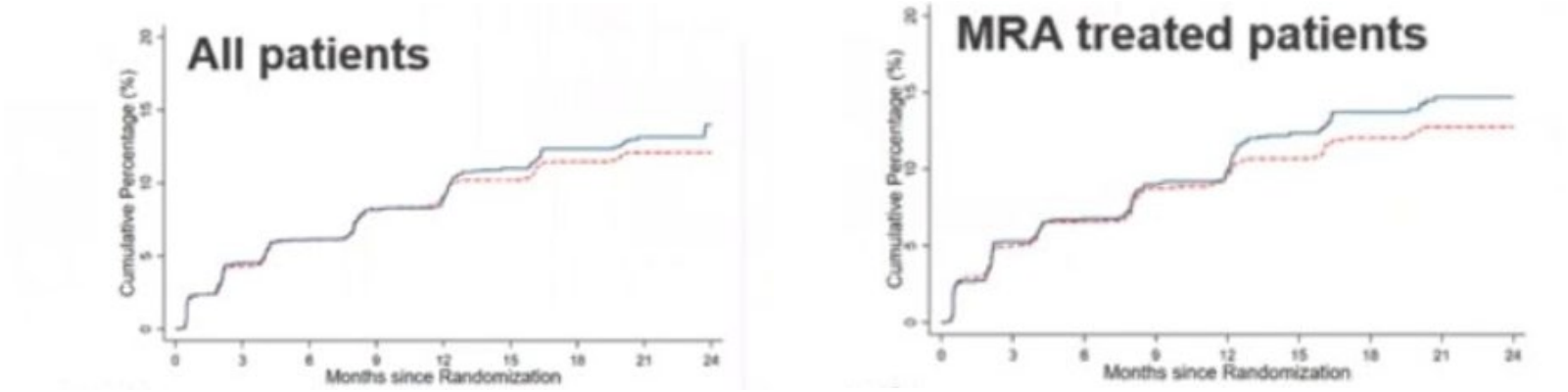
No. at Risk

Placebo	754	498	318	117
Eplerenone	776	538	343	145

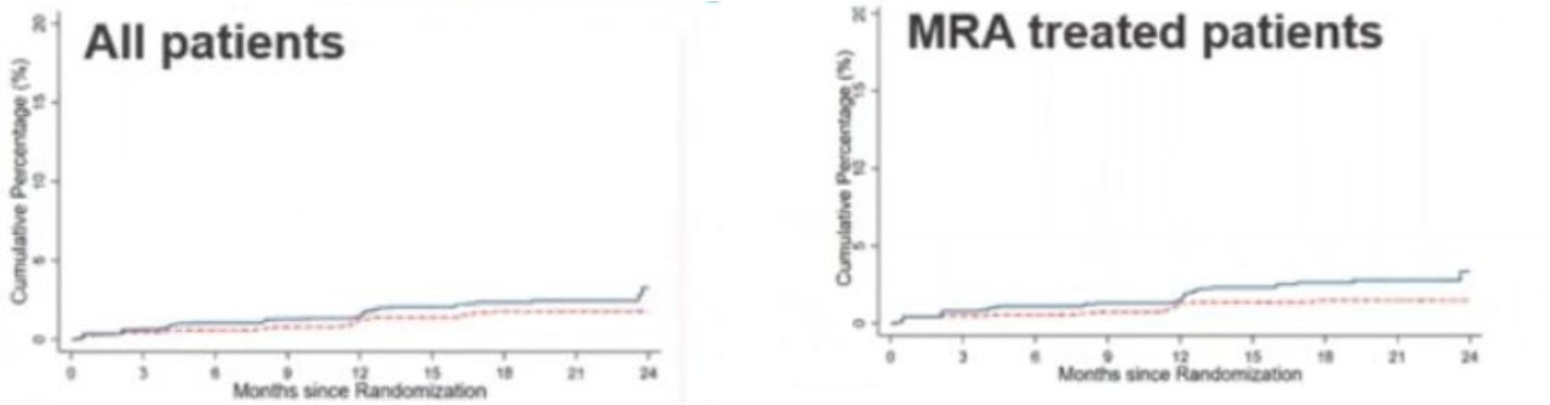
Synergistic Potential: SGLT2i and MRAs
One Drug May Facilitate the Use of Another

In patients taking an MRA at baseline, the incidence of moderate-severe hyperkalemia (potassium > 6.0 mmol/L) was significantly lower in the dapagliflozin group compared with the placebo group (p = 0.010)

Incidence of Hyperkalemia (> 5.5 mmol/L)



Incidence of Hyperkalemia (> 6.0 mmol/L)

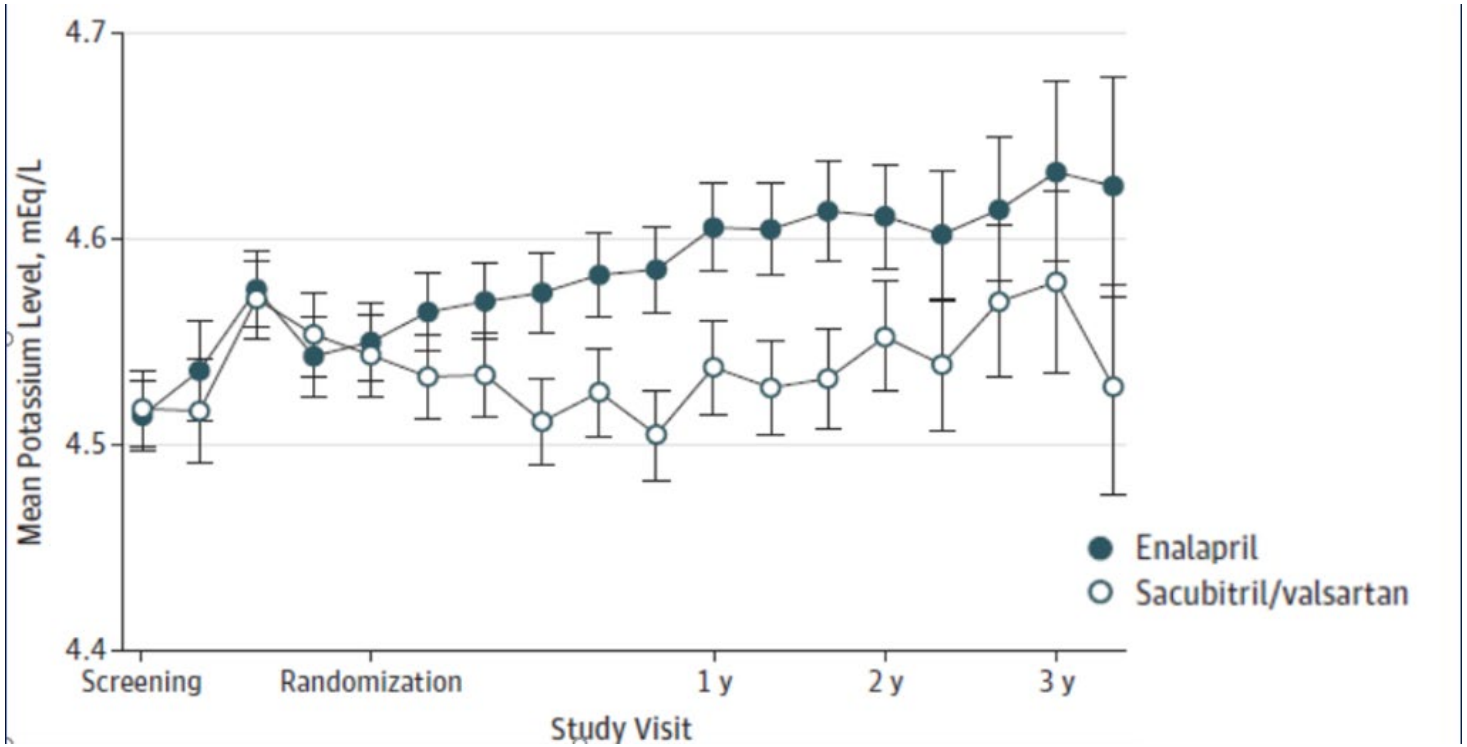


Kristensen SL, et al. ESC Congress 2020.
https://academic.oup.com/euroheartj/article/41/Supplement_2/ehaa946.0939/6003930

Synergistic Potential: Sacubitril/Valsartan & MRAs
One Drug May Facilitate the Use of Another

PARADIGM-HF

Serum Potassium Level by Study Visit in Patients Treated with an



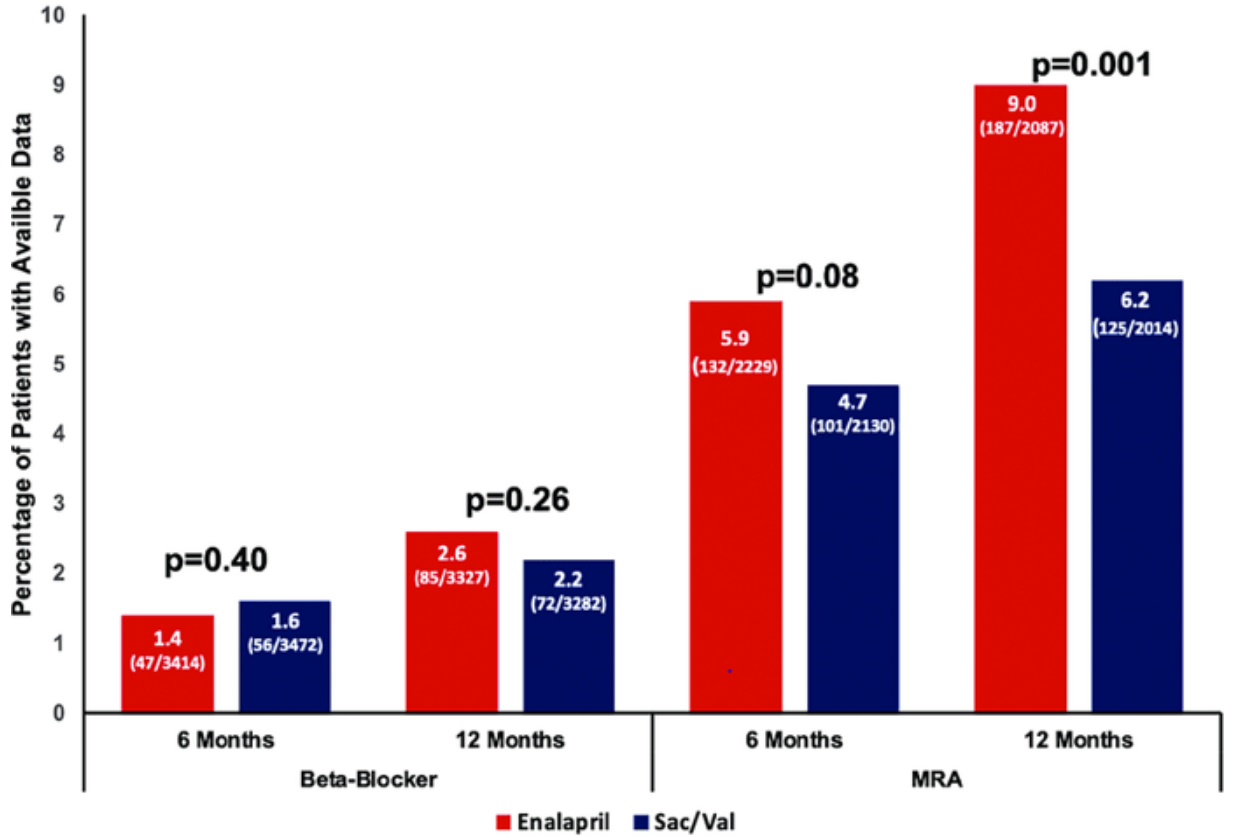
In symptomatic HFrEF treated with an MRA, hyperkalemia was less likely with sacubitril/valsartan than with an ACEI

Desai AS, et al. *JAMA Cardiol*. 2017;2(1):79-85.

Synergistic Potential: Sacubitril/Valsartan Facilitated Sustained MRA Use in HF

- Use of sacubitril/valsartan (when compared with enalapril) may promote sustained MRA use in follow-up.
- Use of sacubitril/valsartan did not lead to greater discontinuation or down-titration of other key guideline-directed medical therapies.

PARADIGM-HF Discontinuations by Treatment Allocation Over Time

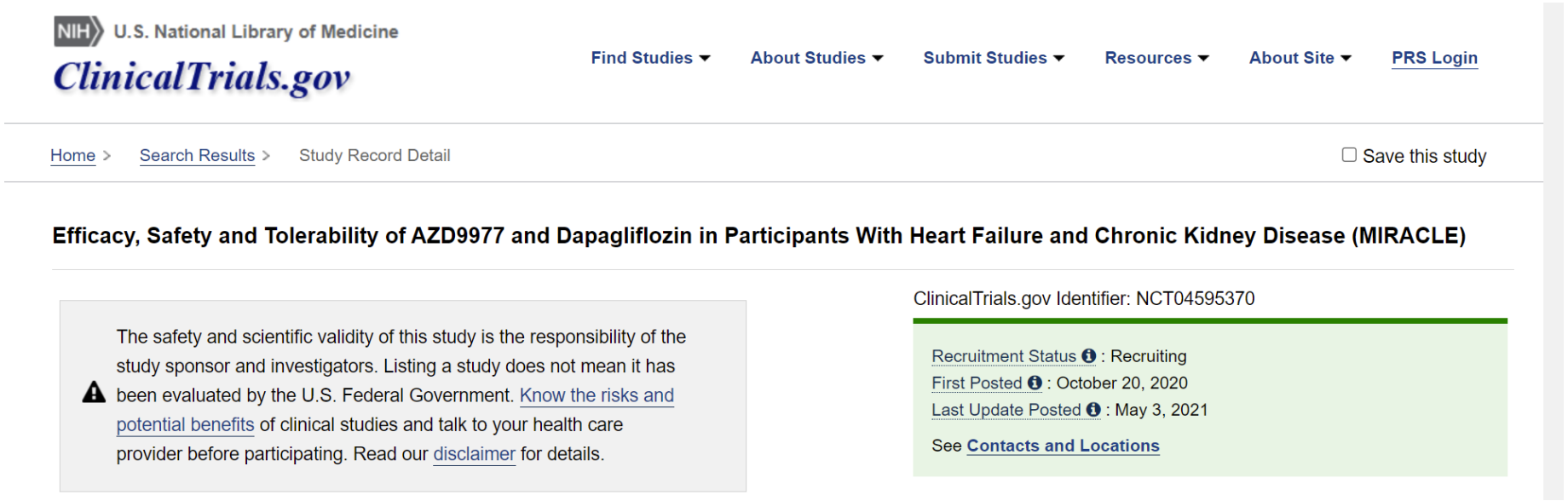


Bhatt AS, et al. *Eur J Heart Fail*. 2021;23:1518-1524.

Ongoing Trials of MR Antagonism in HF and CKD Anticipated to Complete 2022-2024

	SPIRIT-HF	SPIRRIT	FINEARTS-HF	FIND-CKD
Therapy	Spironolactone	Spironolactone	Finerenone	Finerenone
Sample Size	1300	3200	5500	1500
Population	HF and LVEF ≥ 40%	HF and LVEF ≥ 40%	HF and LVEF ≥ 40%	Non-diabetic CKD
Primary Endpoint	CV Death + Total HF Hospitalization	CV Death + Total HF Hospitalizations	CV Death + Total HF Events	Change in eGFR Slope
Estimated Completion Date	2024	2022	2024	TBD

Combination SGLT2i + MRA Being Formally Tested in HF



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Save this study

Efficacy, Safety and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease (MIRACLE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04595370

Recruitment Status : Recruiting
First Posted : October 20, 2020
Last Update Posted : May 3, 2021

See Contacts and Locations

n=540; ~140; ~12 countries; 3–4-week run-in / washout, follow-up over 12 weeks

- **AZD9977 Dose A + dapagliflozin 10 mg**
- **AZD9977 Dose B + dapagliflozin 10 mg**
- **AZD9977 Dose C + dapagliflozin 10 mg**
- **AZD9977 Dose C**
- **Dapagliflozin 10 mg**
- **Placebo**

Combination SGLT2i + MRA Being Formally Tested in CKD

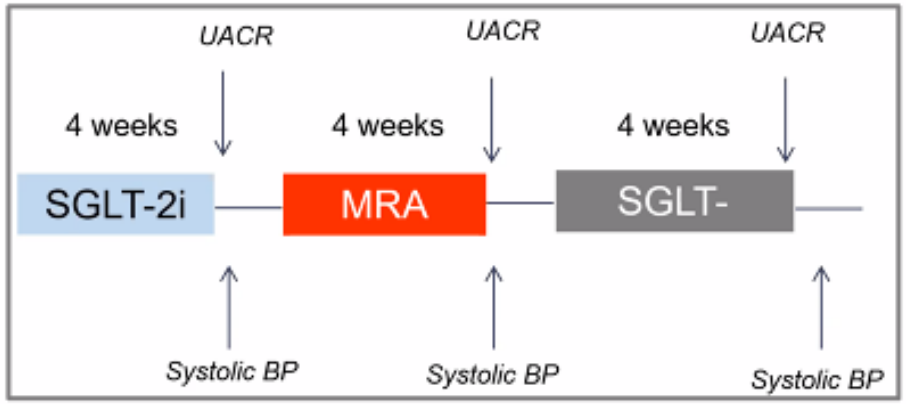
ROTATE-3: Combination of SGLT-2i and MRA

Primary objective:
- Effects on albuminuria

Primary endpoint:
- Change in albuminuria from baseline to end of treatment

Status (Q3/2020):
Included: 44
Total required: 46

DBL: June 2021



Trial design:
Multicenter, open label, randomised, 3-period cross-over study

Population:
- Patients with CKD with and without type 2 diabetes
- UACR >100 mg/g (11.7 mg/mmol)
- eGFR >25 ml/min/1.73m^2

Secondary objectives:
Effects on:
- Blood pressure
- Potassium

Conclusions

- Mineralocorticoid receptor over-activation is a central driver of progression of heart and kidney disease
- Steroidal MRAs (spironolactone and eplerenone) form backbone therapy for patients with HFrEF, but do potentiate hyperkalemia
- Nonsteroidal MRAs (finerenone) slows kidney disease progression in CKD and may have lower risks of hyperkalemia
- MRAs can be easily combined with other effective therapies in HF and CKD
- Ongoing trials are underway evaluating finerenone in HFpEF and non-diabetic CKD