Role of Steroidal and Non-Steroidal MRA in Cardiorenal Diseases

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Disclosures

- Consultant: Amgen, Akebia, AstraZeneca, Novo Nordisk, Medscape, Otsuka, Reata, Vifor
- Advisor: Bayer, Boehringer-Ingelheim, Chinook
- Data Monitoring Committees: Akebia, Otsuka

Role of Steroidal and Non-steroidal MRAs in Cardiorenal Diseases in Diabetes

- Present:
  - Steroidals improve survival in HFrEF
    - Spironolactone and Eplerenone (evidence-based guidelines)
  - Non-Steroidals improve kidney outcomes and reduce hospitalization for HF
    - Finerenone (evidence based-guidelines)

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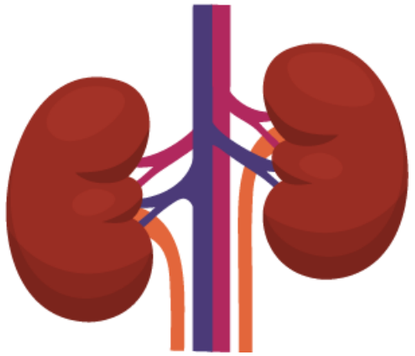
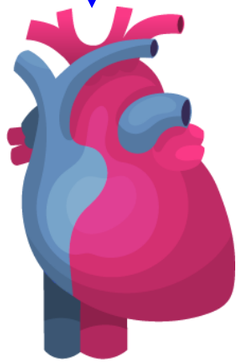
  - Steroidals improve survival in HFrEF
    - Spironolactone and Eplerenone (evidence-based guidelines)
  - Non-Steroidals improve kidney outcomes and reduce hospitalization for HF
    - Finerenone (evidence based-guidelines)
- Future:
  - Ongoing trials in HF and CKD
    - Finerenone and other novel non-steroidals, Spironolactone
    - More studies in cardiorenal space
    - Widespread use

Adverse Renal and CV Effects of Aldosterone

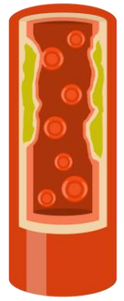
Aldosterone



Glomerulosclerosis
Interstitial fibrosis
Proteinuria
Renal failure



Ventricular hypertrophy
Cardiac fibrosis
Contractile dysfunction
Heart failure

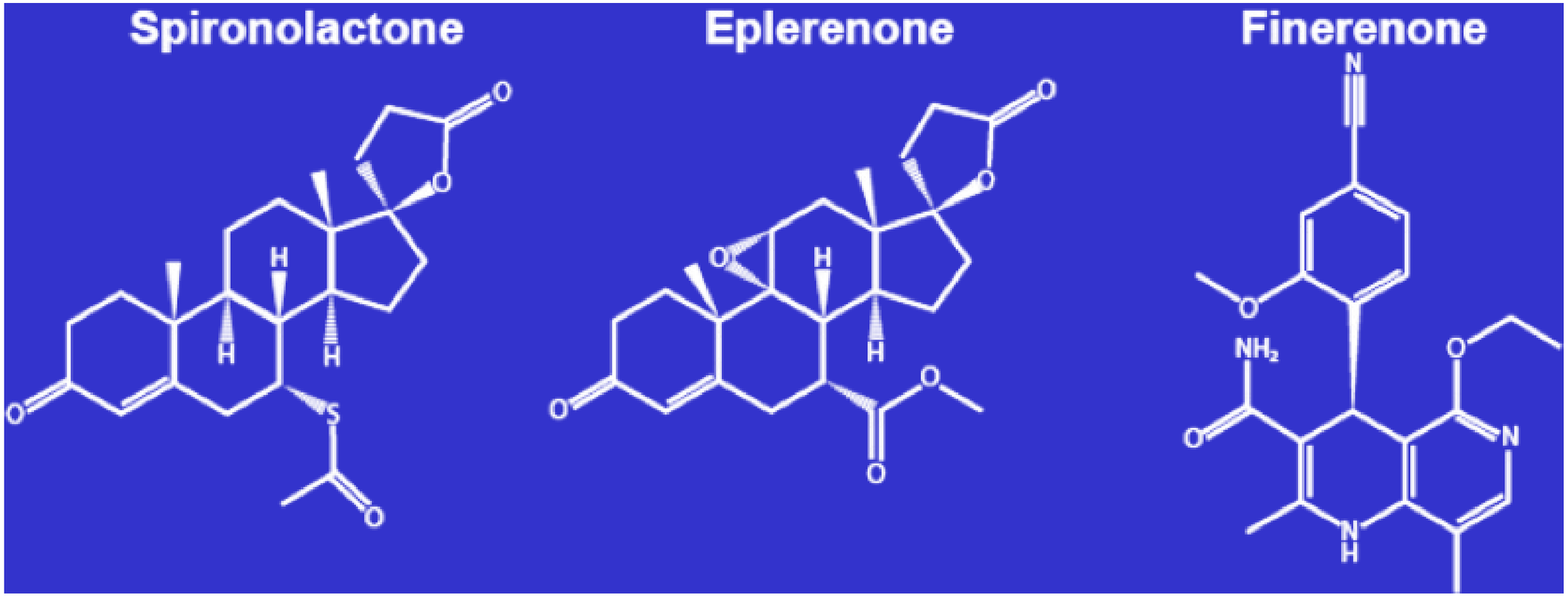


Endothelial dysfunction
Inflammation
Oxidative stress

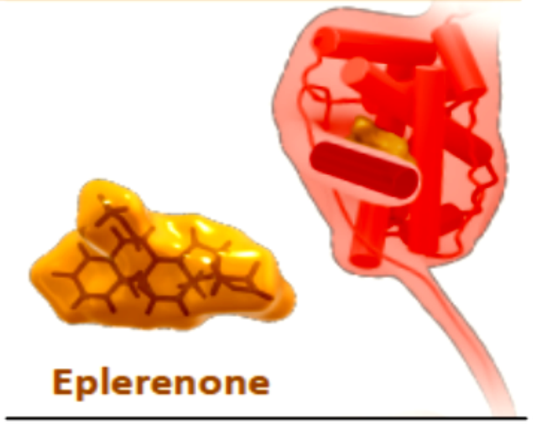
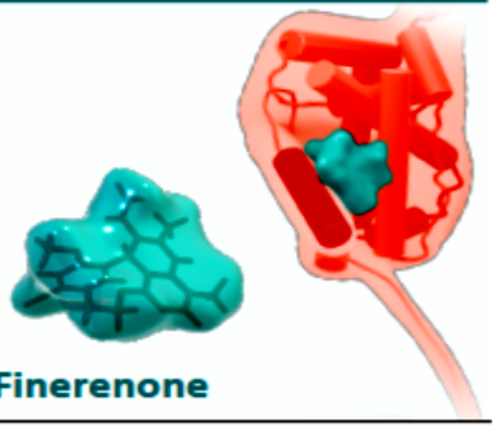
Steroidal vs Non-steroidal MRA

Steroidal MRAs

Non-steroidal MRA



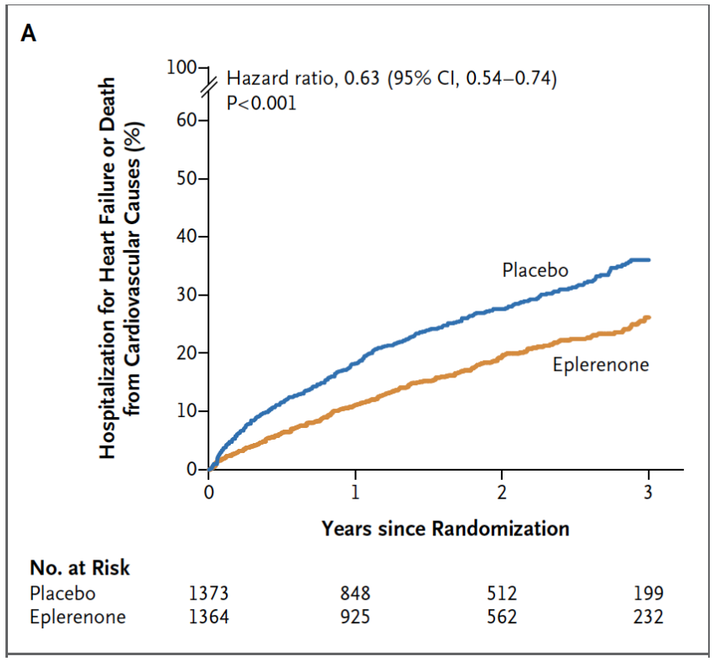
Comparison of MRA Inhibitors: Steroidal and Non-steroidal

	Steroidal MRAs		Finerenone
	 Spironolactone	 Eplerenone	 Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	(+)	-
Half-life	> 20 hours	4-6 hours	2-3 hours
Active metabolites	++	-	-
Effect on BP	+++	++	+

Kintscher U, Bakris GL, and Kolkhof P. *Br J Pharmacol 2021;* DOI: 10.1111/bph.15747.

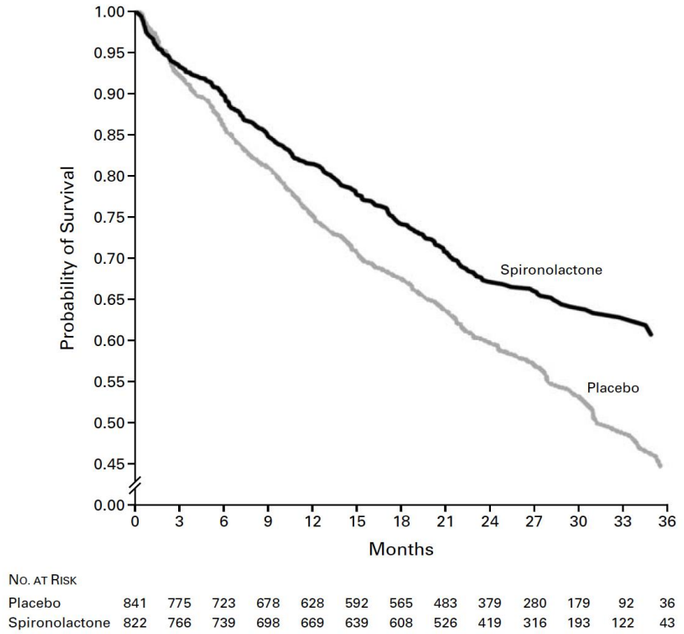
Steroidal MRAs and Systolic Heart Failure

EPHESUS-HF



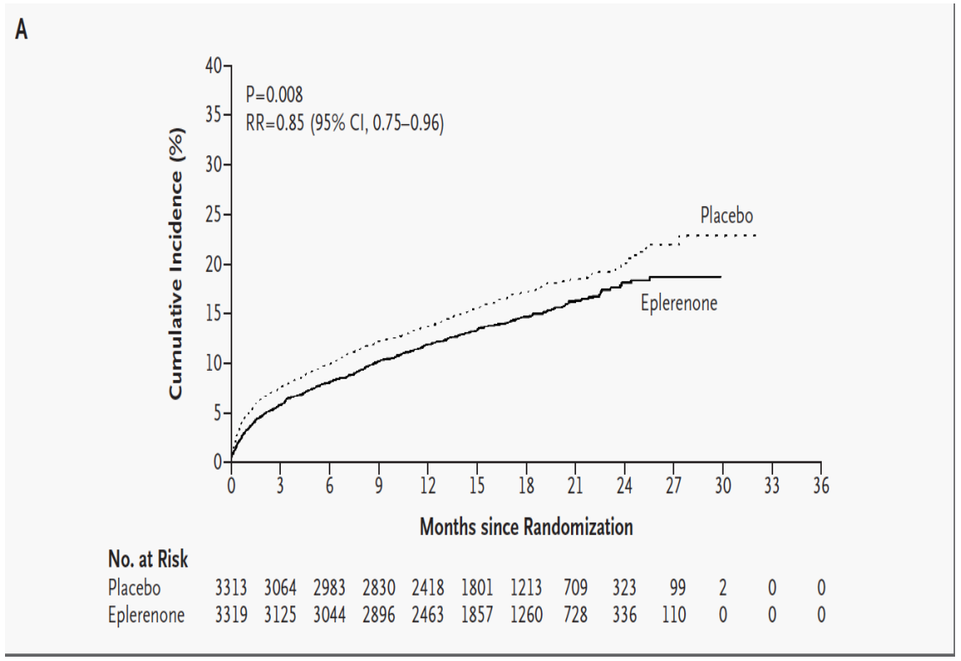
Pitt et al. NEJM 2003

RALES



Pitt et al. NEJM 1999

EPHESUS



Zannad et al. NEJM 2011

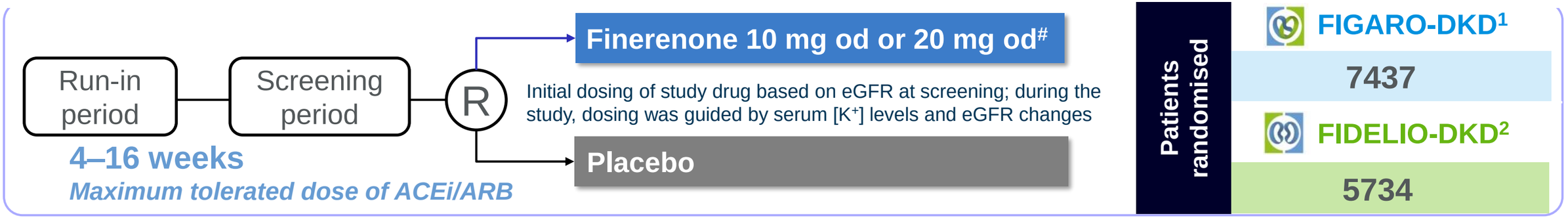
The Finerenone Program

FIDELIO-DKD

FIGARO-DKD

FIDELITY-DKD

FIGARO-DKD and FIDELIO-DKD Investigated the Effects of Finerenone on Kidney and CV Outcomes in Over 13,000 Patients with CKD and T2D[1,2]



	FIGARO-DKD[1]	FIDELIO-DKD[2]
Clinical efficacy primary endpoint	**Composite endpoint:** Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF	**Composite endpoint:** Time to kidney failure,* sustained ≥40% eGFR decline, or renal death
Key secondary endpoint	Same as primary endpoint in **FIDELIO-DKD**	Same as primary endpoint in **FIGARO-DKD**

FIDELITY[3]
Pooled analysis

Key outcomes

CV composite:
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

57% kidney composite:
Time to kidney failure,* sustained ≥57% eGFR decline, or renal death

*Kidney failure defined as initiation of chronic dialysis for ≥90 days or kidney transplantation or sustained eGFR <15 ml/min/1.73 m^2 [2,3]; #patients received an initial dose of finerenone of 10 mg od or 20 od based on an eGFR at the screening visit of 25–<60 or ≥60 ml/min/1.73 m^2, respectively.[1,2] Up-titration to finerenone 20 mg od was permitted at any time after visit 2 (month 1); down-titration to finerenone 10 mg od was permitted at any time after start of treatment. Dose titrations were initiated in response to changes in potassium and eGFR[1,2]

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; od, once daily; T2D, type 2 diabetes

1. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; 2. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 3. Filippatos G. Abstract 7161 presented at the European Society of Cardiology 2021 (ESC 2021)

FIDELITY is a Prespecified Pooled Analysis of Individual Patient Data Set from the FIDELIO-DKD[1] and FIGARO-DKD Trials[2]

13,171 patients randomized

3 years' median follow-up

48 countries

Maximal Tolerated Doses of RAS Blockade

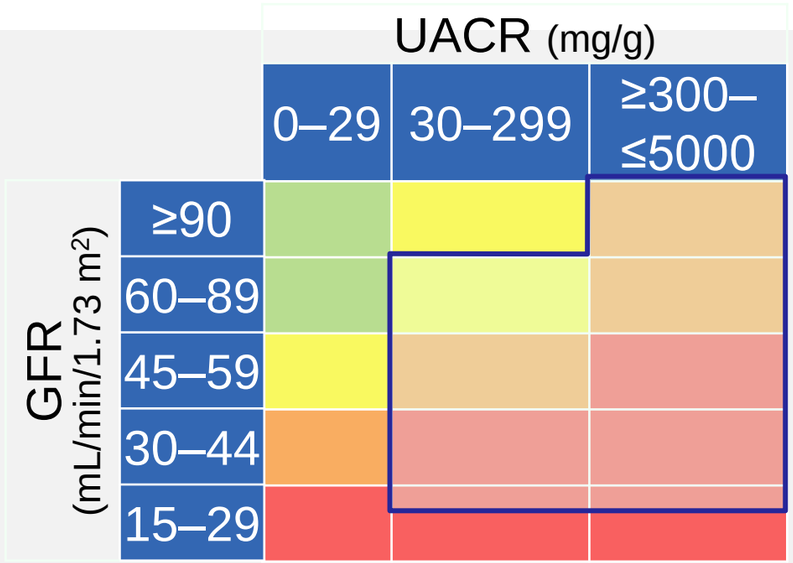
R

Finerenone 10 or 20 mg od*

Placebo

Key eligibility criteria

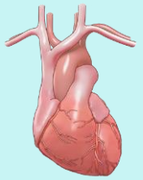
- ✓ **T2D**
- ✓ **CKD**
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol/L
- ✗ Symptomatic HFrEF



Key outcomes

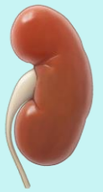
CV composite

Time to CV death, non-fatal MI, non-fatal stroke, or HHF



≥57% eGFR kidney composite

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



Aim of this subgroup analysis: To explore the treatment effect of finerenone in patients with and without concomitant SGLT-2i use at baseline

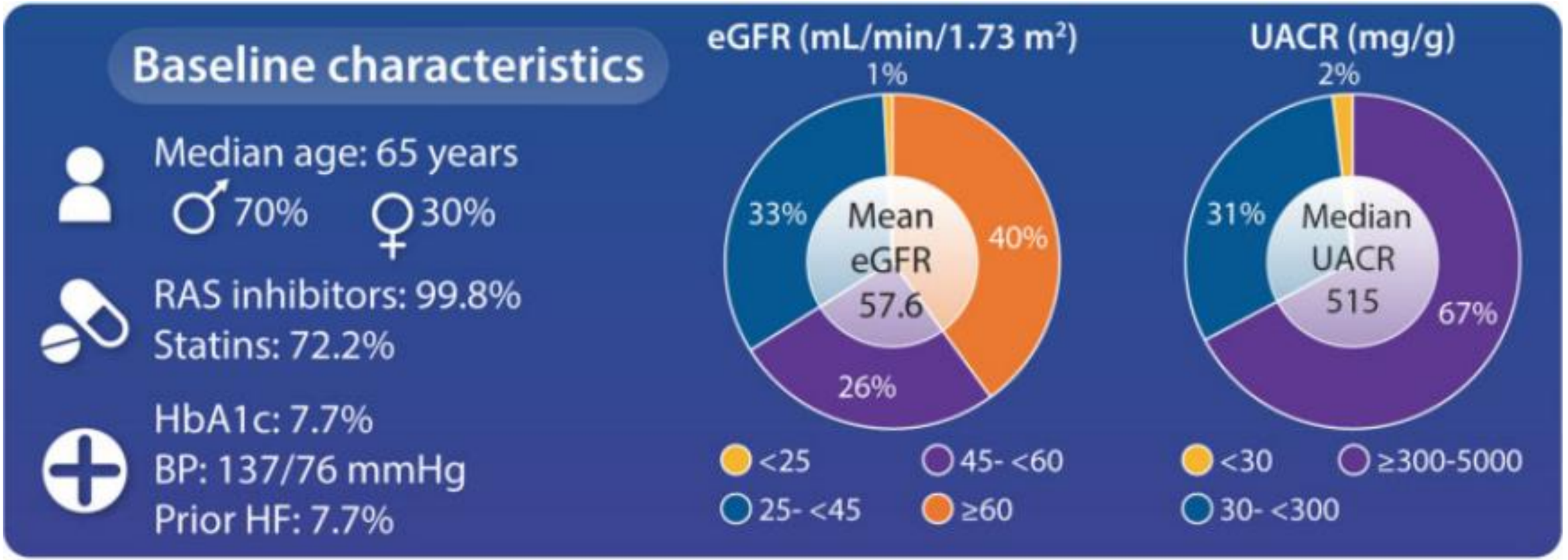
*10 mg if screening eGFR 25–<60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m², up-titration encouraged from month 1 if serum [K^+] ≤4.8 mEq/L and eGFR stable; #kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 mL/min/1.73 m².

CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HHF, hospitalisation for heart failure; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; MI myocardial infarction; od, once daily; RASi, renin–angiotensin system inhibitor; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021;doi:10.1056/NEJMoa2110956.

Agarwal R et al. *Eur Heart J*. 2022;43(6):474-484.

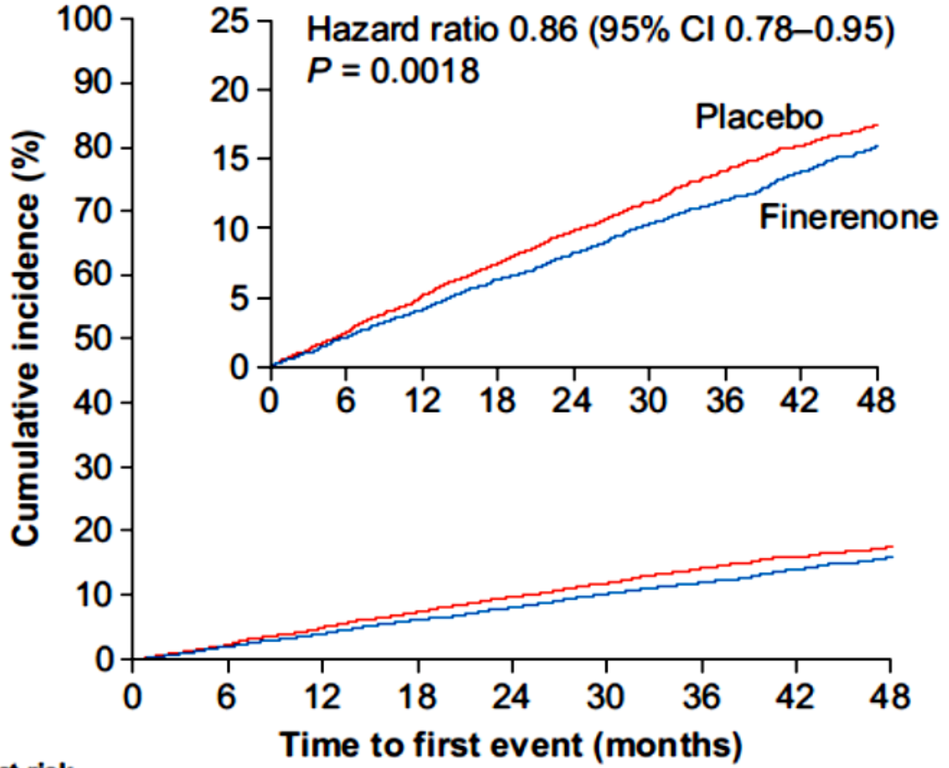
FIDELITY Pooled Analysis: Baseline Characteristics



Agarwal R et al. *Eur Heart J*. 2022;43(6):474-484.

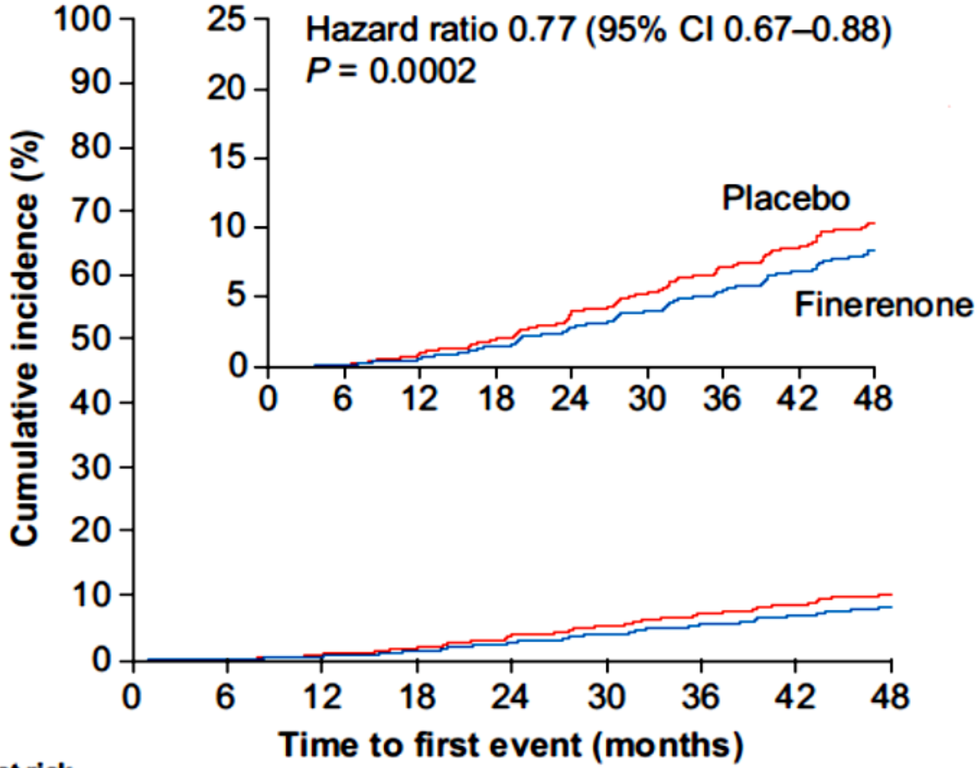
Time to Efficacy Outcomes

(A) The composite CV outcome defined as CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure.



No. at risk									
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087

(B) The composite kidney outcome: kidney failure, sustained ≥ 57% decrease in eGFR from baseline over >_4 weeks, or renal death

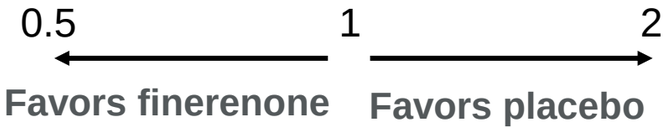


No. at risk									
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959

Agarwal R et al. *Eur Heart J*. 2022;43(6):474-484.

FIGARO-DKD was a Successful HF Prevention Trial 29% ↓ Risks of Hospitalizations for HF

Outcome	Finerenone (n=3686)		Placebo (n=3666)		HR (95% CI)	p-value
	n (%)	n/100 PY	n (%)	n/100 PY		
Primary composite CV outcome*	**458 (12.4)**	**3.87**	**519 (14.2)**	**4.45**	**0.87 (0.76–0.98)**	**0.03**
CV death	194 (5.3)	1.56	214 (5.8)	1.74	0.90 (0.74–1.09)	–
Non-fatal MI	103 (2.8)	0.85	102 (2.8)	0.85	0.99 (0.76–1.31)	–
Non-fatal stroke	108 (2.9)	0.89	111 (3.0)	0.92	0.97 (0.74–1.26)	–
Hospitalisation for HF	117 (3.2)	0.96	163 (4.4)	1.36	0.71 (0.56–0.90)	–



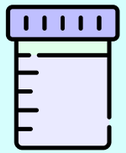
Bakris GL on behalf of FIDELIO-DKD Investigators. *N Engl J Med*. 2020 Dec 3;383(23):2219-2229.

Predictors of Hyperkalemia Derived from Clinical Trials

- eGFR <45 ml/min/1.73 m^2
- Serum potassium of >4.5 mEq/L
- eGFR <45 ml/min/1.73m^2 + serum [K+] >4.5 mEq/L (HIGHEST PREDICTOR)

Lazich I and Bakris G. *Sem Nephrol* 2014;34:333-339; Khosla N et.al. *Am J Nephrol* 2009;30:418-423; Clase, C. M., et al. *Kidney Int 2020;97(1): 42-61*.

Practical Considerations for Finerenone Use



Measure UACR

To identify patients at highest risk of CKD progression and CV events[1] and who stand to benefit from finerenone treatment[2,3]

Measure eGFR[2,3]

Starting dose of finerenone depends on a patient's eGFR*

Measure serum [K+] regularly to minimize risk of hyperkalemia[2–4]

During treatment, the dose of finerenone depends on a patient's serum [K+]#

Temporarily withhold finerenone if serum [K+] >5.5 mmol/l‡

Continue standard of care therapy, including RASi and blood glucose lowering drugs[5]

*10 mg od for patients with an eGFR <60 ml/min/1.73 m^2, 20 mg od for patients with an eGFR ≥ 60 ml/min/1.73 m^2; #serum [K+] ≤4.8 mmol/l, 20 mg od; serum [K+] >4.8–≤5.0 mmol/l, maintain dose (10 mg od or 20 mg od); ‡restart treatment at 10 mg od when serum [K+] <5.0 mmol/l.

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al*. *N Engl J Med* 2021; doi: 10.1056/NEJMoa2110956; 4. Agarwal R. *WCN* 2021; abstract WCN21-0607; 5. American Diabetes Association. *Diabetes Care* 2021;44:S151–S167.

Steroidal and Non-Steroidal Mineralocorticoid Receptor Access in CKD and HFrEF

CKD

"Triple Therapy"

- **ACEi/ARB**
- ***Non-Steroidal* MRA**
- **SGLT-2 Inhibitor**

"Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies."

KDIGO 2022 Guideline for Diabetes in CKD

HFrEF & HFmrEF

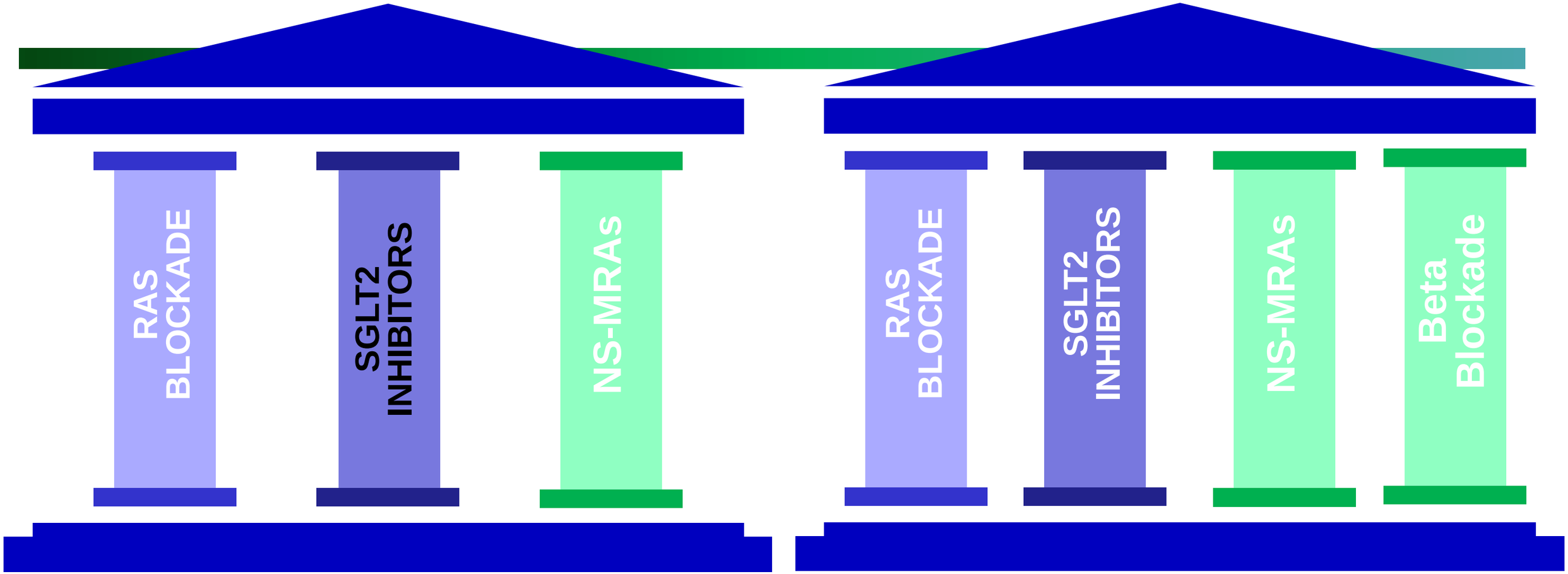
"Quadruple Therapy"

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

"In patients with HFrEF and NYHA class II to IV symptoms MRA (spironolactone or eplerenone)… to reduce morbidity and mortality if eGFR is >30 mL/min/1.73 m^2 and serum K is <5.0 mEq/L."

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure
Circ 145;18. e895 2022

Pillars of Therapy to Reduce Cardiorenal Risk



Slowing DKD progression and reducing CV risk

RAS = renin-angiotensin system; SGLT = sodium-glucose cotransporter; MRA = magnetic resonance angiogram; NS = non-steroidal.

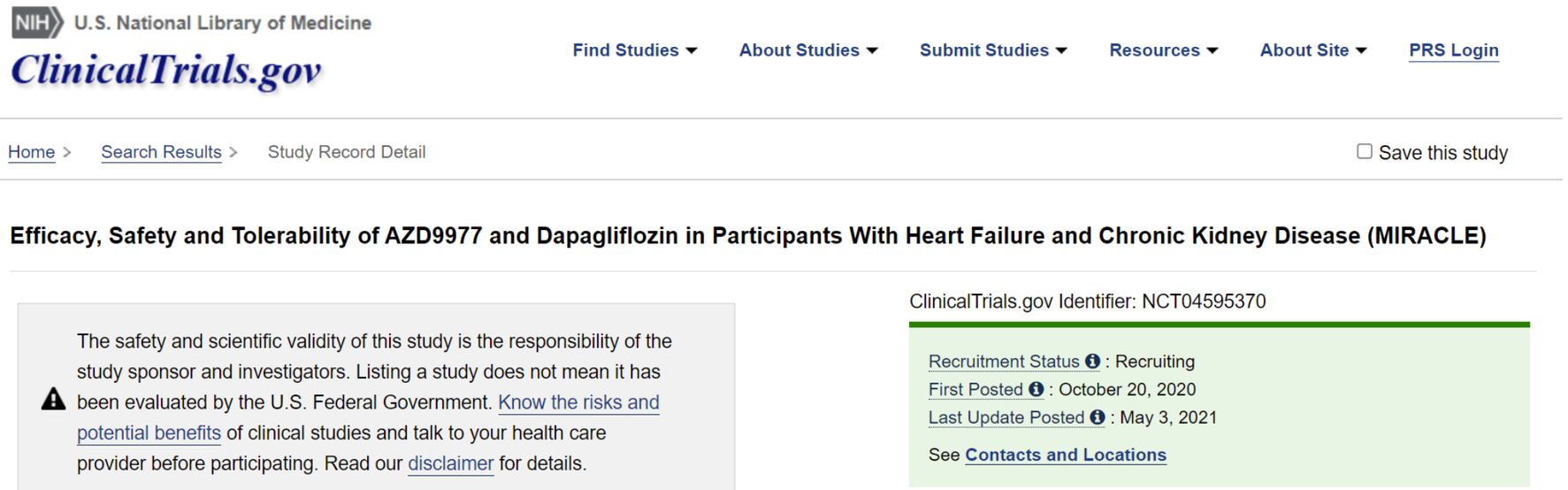
Courtesy of George L Bakris, MD.

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

FIND-CKD = Finerenone In Non-Diabetic Chronic Kidney Disease; FINEARTS-HF = FINerenone trial to investigate Efficacy and sAfetysuperioR to placebo in paTientS with Heart Failure; SPIRIT-HF = Spironolactone In The Treatment of Heart Failure; SPIRRIT = Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction.

Combination SGLT2i + MRA Being Formally Tested in HF + CKD: MIRACLE



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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.

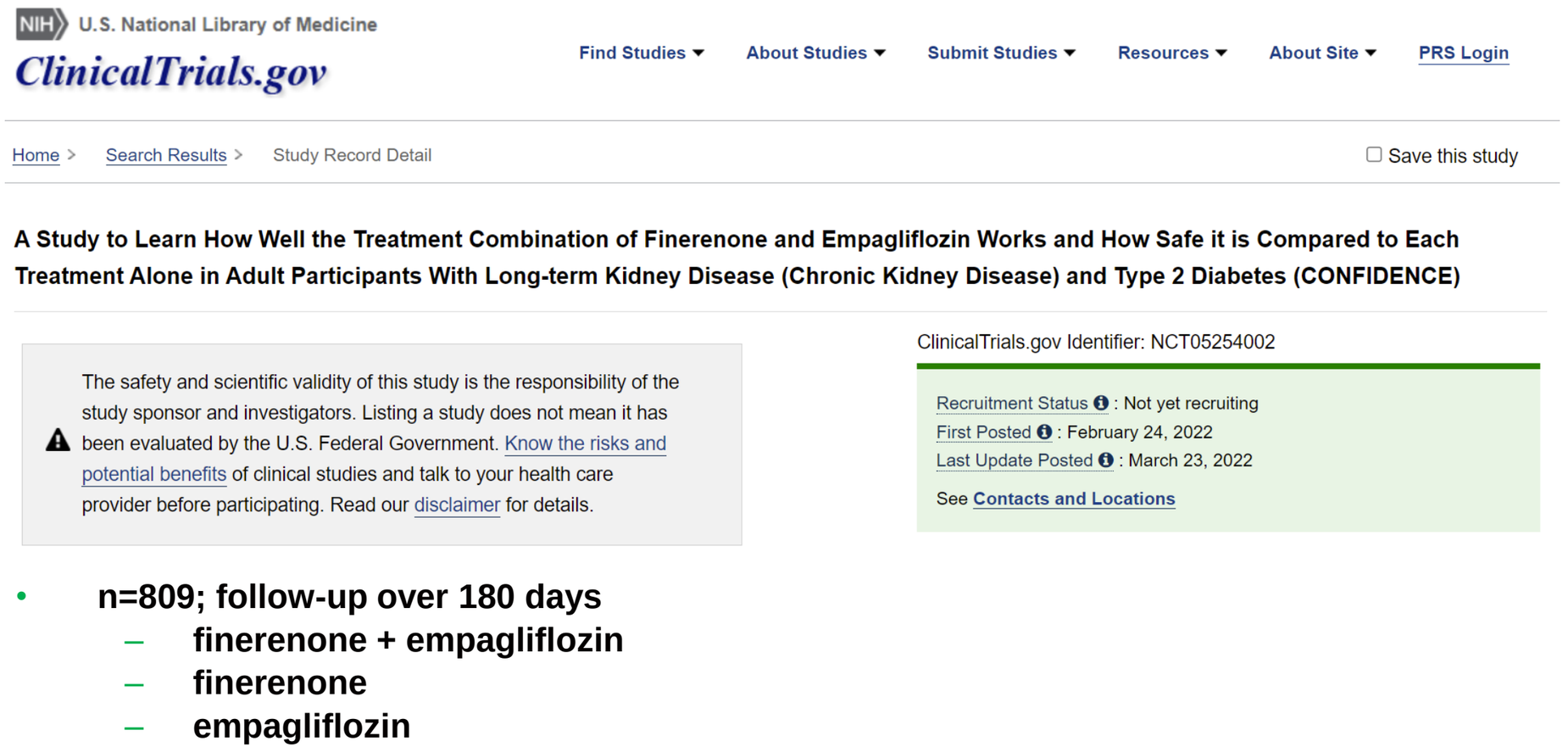
ClinicalTrials.gov Identifier: NCT04595370

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

See Contacts and Locations

- **n=500; follow-up over 12 weeks**
  - **AZD9977 Dose A + dapagliflozin 10 mg**
  - **AZD9977 Dose B + dapagliflozin 10 mg**
  - **AZD9977 Dose C + dapagliflozin 10 mg**
  - **Dapagliflozin 10 mg**

Combination SGLT2i + MRA Being Formally Tested in CKD:CONFIDENCE



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Save this study

A Study to Learn How Well the Treatment Combination of Finerenone and Empagliflozin Works and How Safe it is Compared to Each Treatment Alone in Adult Participants With Long-term Kidney Disease (Chronic Kidney Disease) and Type 2 Diabetes (CONFIDENCE)

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: NCT05254002

Recruitment Status : Not yet recruiting
First Posted : February 24, 2022
Last Update Posted : March 23, 2022

See Contacts and Locations

- **n=809; follow-up over 180 days**
  - **finerenone + empagliflozin**
  - **finerenone**
  - **empagliflozin**

Role of Steroidal and Non-steroidal MRAs in Cardiorenal Diseases in Diabetes

- Present:
  - Steroidals improve survival in HFrEF
    - Spironolactone and Eplerenone (evidence-based guidelines)
  - Non-Steroidals improve kidney outcomes and reduce hospitalization for HF
    - Finerenone (evidence based-guidelines)
- Future:
  - Ongoing trials in HF and CKD
    - Finerenone and other novel non-steroidals, Spironolactone
    - More studies in cardiorenal space
    - Widespread use