Pillar approach for the treatment of CKD in T2D: Treat early to help prevent further CV and renal damage

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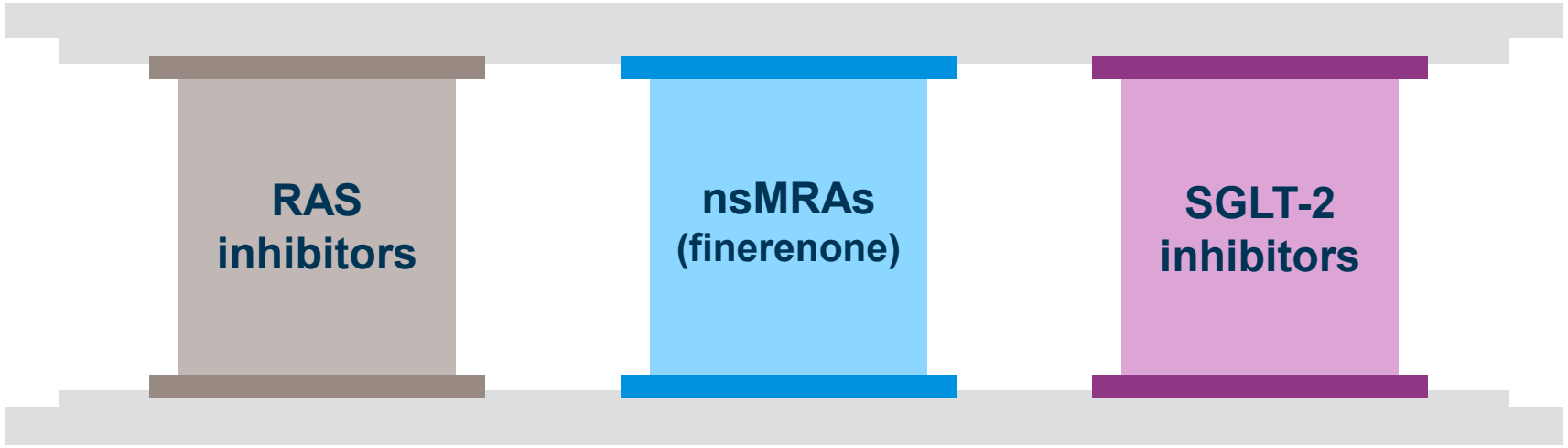
Overview of guideline-recommended treatment options to slow CKD progression and reduce CV events in patients with T2D[1,2]

There are now three distinctly different classes of drugs with a strong evidence base and level A guideline recommendations*:



These drug classes add to the benefits provided by glucose and blood pressure control by slowing CKD progression and significantly reducing CV outcomes

*In addition to glucose and blood pressure control
nsMRA, nonsteroidal mineralocorticoid receptor antagonist

1. Blazek O & Bakris GL. *Am Heart J Plus* 2022;19:100187; 2. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202

Finerenone is the first non-steroidal MRA indicated to reduce risks in patients with CKD associated with T2D

	FIDELIO-DKD[1,2]	FIGARO-DKD[3]
Primary endpoint	**Composite kidney endpoint** Time to kidney failure, sustained ≥40% eGFR decline, or kidney-related death **18% RRR** NNT=29 HR=0.82; *p*=0.001	**Composite CV endpoint** Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF **13% RRR** ARR=2.1% HR=0.87; *p*=0.03
Key secondary endpoint	Same as primary endpoint in **FIGARO-DKD** **14% RRR** NNT=42 HR=0.86; *p*=0.03	Same as primary endpoint in **FIDELIO-DKD** **13% RRR** NNT=47 HR=0.87; *p*=NS
	N=5674 Median follow up **2.6 years**	**N=7352** Median follow up **3.4 years**

ARR, absolute risk reduction; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction; NS, non-significant

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 3. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

FIDELIO-DKD FIGARO-DKD

FIDELITY: Pooled analysis of FIDELIO-DKD and FIGARO-DKD trials

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CV endpoints

Composite CV endpoint
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

14% RRR
NNT=46
HR=0.86; *p*=0.0018

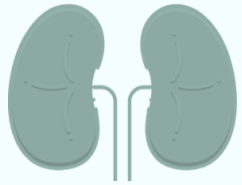
Hospitalisation for heart failure

22% RRR
HR=0.78; *p*=0.003

Kidney endpoints

Composite Kidney endpoint
Time to kidney failure, sustained ≥57% eGFR decline, or kidney-related death

23% RRR
NNT=59
HR=0.77; *p*=0.0002



Dialysis

20% RRR
HR=0.80; *p*=0.04

Median follow-up: 3 Years

Baseline characteristics	
Number of patients	13,026
Gender (M/F)	70%/30%
Age	65 years
HBA1c	7.7%
BP	137/76 mmHg
Prior HF	7.7%
RAS inhibitors (ACEi/ARB)	99.8%
Statins	72.2%

Finerenone is indicated for the treatment of CKD (with albuminuria) associated with T2D in adults

Agarwal R, *et al*. *Eur J Heart* 2022;43:474–484

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Julia has T2D and newly diagnosed CKD with persistent albuminuria

Julia*

- 67-year-old female
- T2D for 6 years
- Newly diagnosed CKD

- HbA1c 7.8%
- Blood pressure 137/84 mmHg

- eGFR 54 ml/min/1.73 m^2
- UACR 380 mg/g
- Serum [K^+] 4.3 mmol/l

- Glycaemic control including SGLT-2i
- Anti-hypertensive treatment including maximum tolerated dose of RASi

Albuminuria categories (mg albumin/g creatinine)[1]

GFR categories (ml/min/1.73 m^2)		A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
		<30 mg/g <3 mg/mmol	**30–300 mg/g** (3–30 mg/mmol)	**>300 mg/g** (>30 mg/mmol)
G1	**≥90**			
G2	**60–89**			
G3a	**45–59**			
G3b	**30–44**			
G4	**15–29**			
G5	**<15**			

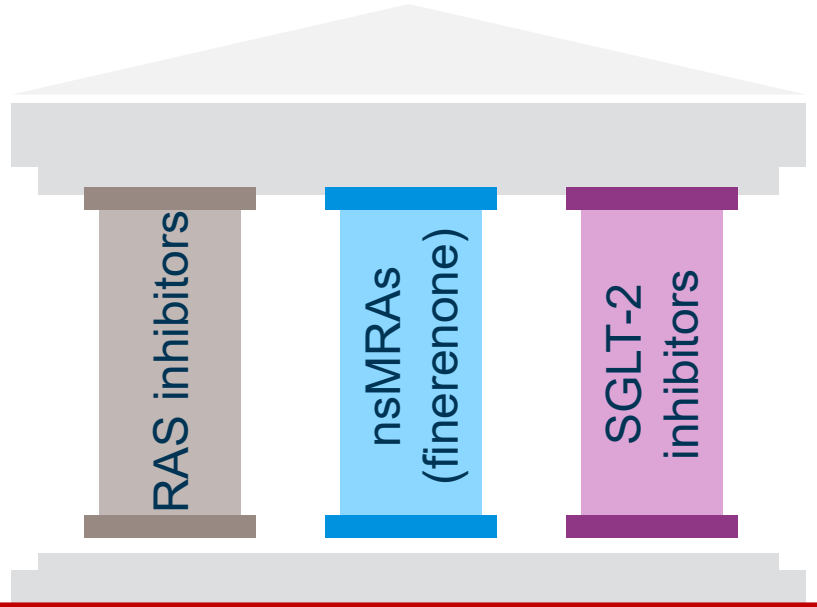
What would be the expected benefits of adding finerenone to Julia's treatment regimen?

*Fictitious patient case
GFR, glomerular filtration rate

1. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2022;102:S1–S128

Based on evidence from recent clinical trials, a ‘pillar approach’ has been proposed for the treatment of patients with CKD and T2D*

Proposed pillar approach[1]



Maximum tolerated doses of RASi with an SGLT-2i and finerenone should provide maximal benefit to slow CKD progression and reduce CV outcomes#

- eGFR 54 ml/min/1.73 m^2
- UACR 380 mg/g

- RASi
- Finerenone
- SGLT-2i

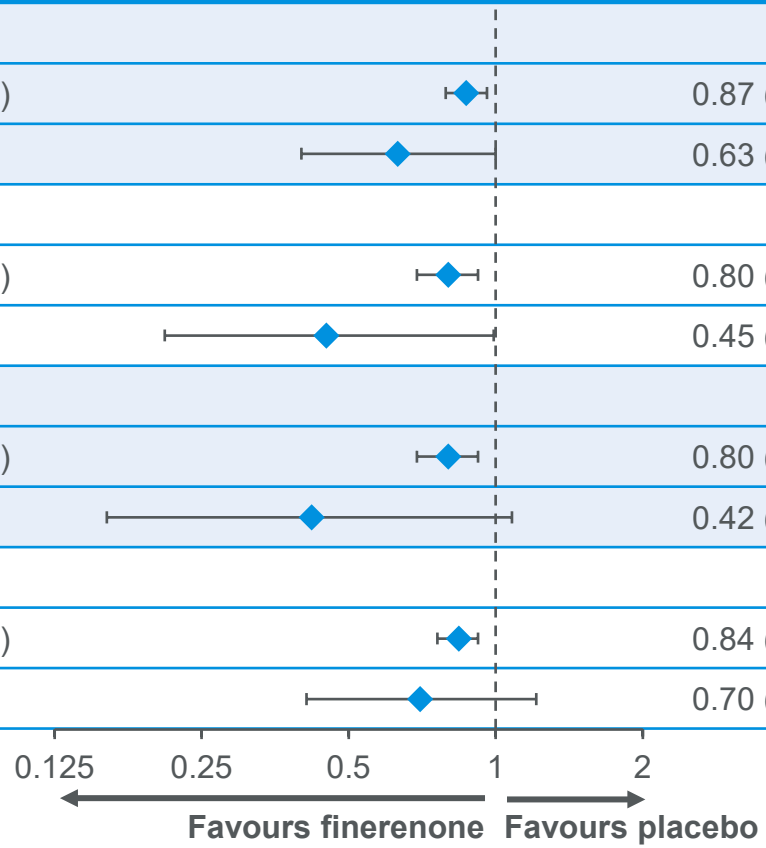
*Patients with diagnosed HFrEF and NYHA II-IV were excluded from the finerenone phase III clinical studies (see section 5.1 of Kerendia (finerenone) SmPC);[2] #the CV outcomes referred to pertain to HHF risk in particular

NYHA, New York Heart Association

1. Blazek O & Bakris GL *Am Heart J Plus* 2022;19:100187; 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 23 March 2023]

In FIDELITY, the CV and kidney benefits of finerenone were consistent irrespective of SGLT-2i use at baseline

Endpoint	Finerenone n/N (n/100 PY)	Placebo n/N (n/100 PY)	Adjusted HR (95% CI)*	p-value for interaction
CV composite#				
No SGLT-2i	786/6081 (4.4)	887/6068 (5.1)	0.87 (0.79–0.96)	0.41
SGLT-2i	39/438 (3.0)	52/439 (4.1)	0.63 (0.40–1.00)	
HHF				
No SGLT-2i	246/6081 (1.4)	303/6068 (1.7)	0.80 (0.68–0.95)	0.16
SGLT-2i	10/438 (0.7)	22/439 (1.7)	0.45 (0.21–0.99)	
eGFR ≥57% kidney composite‡				
No SGLT-2i	351/6081 (2.1)	448/6068 (2.6)	0.80 (0.69–0.92)	0.29
SGLT-2i	9/438 (0.7)	17/439 (1.4)	0.42 (0.16–1.08)	
eGFR ≥40% kidney composite§				
No SGLT-2i	818/6081 (5.0)	961/6068 (5.9)	0.84 (0.76–0.92)	0.59
SGLT-2i	36/438 (2.9)	34/439 (2.8)	0.70 (0.41–1.21)	



*Adjusted HR for HbA1c, SBP, UACR at baseline (log-transformed) and eGFR at baseline; #composite of CV death, non-fatal MI, non-fatal stroke or HHF; ‡eGFR ≥57% kidney composite outcome defined as kidney failure (ESKD or eGFR <15 ml/min/1.73 m^2), a sustained ≥57% decrease in eGFR from baseline (equivalent to a doubling of serum creatinine) for ≥4 weeks, or renal death; §eGFR ≥40% kidney composite outcome defined as kidney failure (ESKD or eGFR <15 ml/min/1.73 m^2), a sustained ≥40% decrease in eGFR from baseline maintained for ≥4 weeks, or renal death
PY, patient-years; SBP, systolic blood pressure
Rossing P, *et al. ASN* 2021; oral presentation.

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How might adopting the pillar approach be beneficial to a patient with CKD and T2D like Julia?

Julia*

- 67-year-old female
- T2D for 6 years
- Newly diagnosed CKD

- eGFR 54 ml/min/1.73 m^2
- UACR 380 mg/g

Prescribed medication

- RASi
- SGLT-2i#
- Finerenone# — Added to treatment regimen

As opposed to a conventional sequencing approach to treatment, the pillar approach suggests initiating treatment with the recommended drug classes as early as safely possible after diagnosis‡,[1,2]

Applying this approach could reduce UACR and consequently reduce persistent risk of CKD progression and CV outcomes in this patient population[1,2]

*Fictitious patient case; #on top of a maximum tolerated dose of RASi; ‡finerenone or SGLT-2i can be initiated as soon as a stable dose of RASi has been achieved; however, the two drug classes cannot be initiated simultaneously (additional details in back-up slide)

1. Blazek O & Bakris GL *Am Heart J Plus* 2022;19:100187; 2. DeFronzo RA, *et al. Diabetes Obes Metab* 2022;24:1197–1205

Prior to initiation of finerenone treatment, serum [K^+] and eGFR must be measured

If serum [K^+] ≤5.0 mmol/l*

Julia's serum [K^+]: 4.3 mmol/l

If eGFR ≥25 ml/min/1.73 m^2

Julia's eGFR: 54 ml/min/1.73 m^2

Julia can initiate treatment with finerenone

Starting dose: **10 mg** od

(if eGFR is <60 ml/min/1.73 m^2)

Target and maximum recommended dose: **20 mg** od

(and starting dose if eGFR ≥60 ml/min/1.73 m^2)

Treatment can be **maintained** in patients with an **eGFR ≥15 ml/min/1.73 $m^{2\#}$**

*If serum [K^+] is >4.8–5.0, initiation of finerenone may be considered with additional serum potassium monitoring within the first 4 weeks based on patient characteristics and serum [K^+]; #if eGFR falls below 15 ml/min/1.73 m^2, treatment should be discontinued

Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 1 Mar 2023]

Animated slide

After treatment initiation, eGFR and serum [K⁺] should be measured periodically and the dose of finerenone should be adjusted accordingly

eGFR after 1 month	Current serum [K⁺] (mmol/l)	Finerenone dose adjustment
eGFR decline <30%	≤4.8	10 → 20 ← 20 Increase to* or maintain **20 mg od**
	>4.8–5.5	**Maintain current dose**
	>5.5	**Withhold treatment** Restart at 10 mg od when serum [K⁺] is ≤5.0 mmol/l

If at 1 month, Julia's serum [K⁺] remains below 4.8 mmol/l and her eGFR has not declined by >30%, her dose of finerenone can be increased to 20 mg od

If Julia's serum [K⁺] increases to 5.0 mmol/l, her dose of finerenone should be maintained at 20 mg od

At follow-up, if Julia's serum [K⁺] has increased to 5.6 mmol/l, treatment with finerenone should be withheld

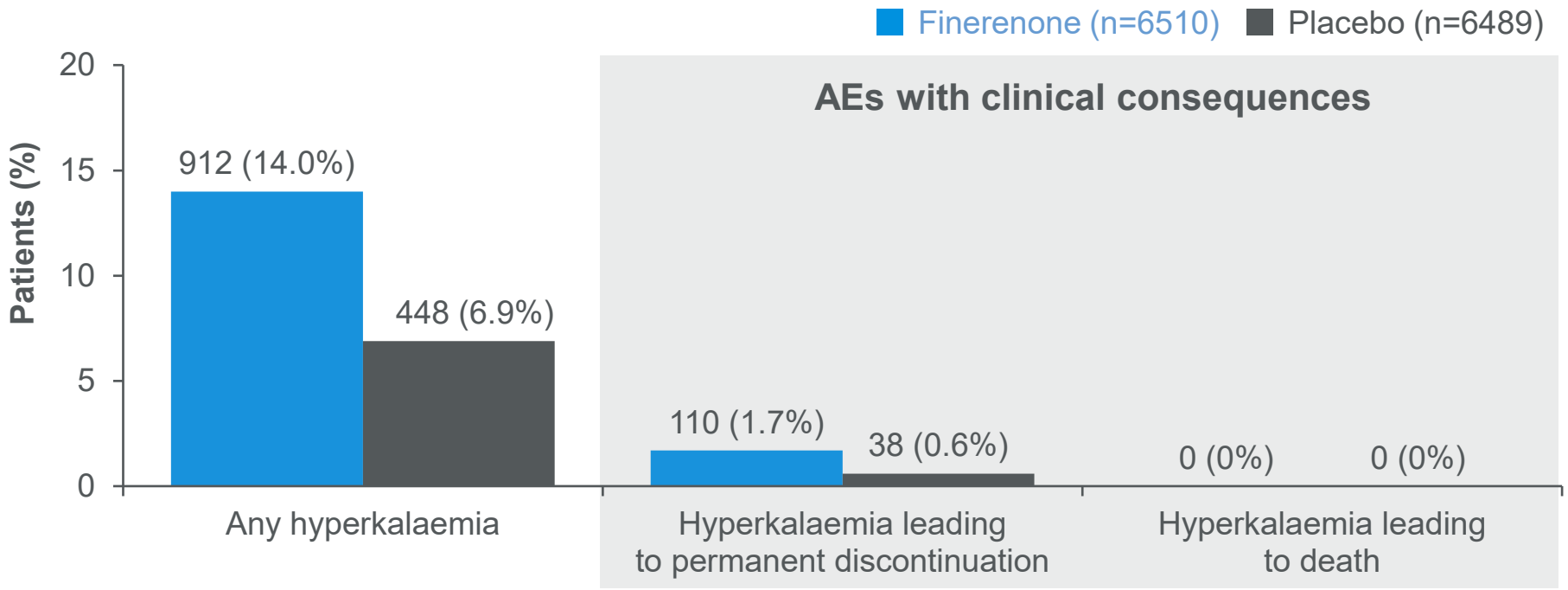
Serum [K⁺] and eGFR should be remeasured 4 weeks after initiation or after restarting finerenone treatment, or after an increase in dose#

*Maintain 10 mg od if eGFR has decreased by >30% compared with the previous measurement; #Thereafter, serum [K⁺] should be remeasured periodically and as needed based on patient characteristics and serum [K⁺]

Bayer AG. KERENDIA® (finerenone) Summary of Product Characteristics. 2023. https://www.ema.europa.eu/documents/product-information/kerendia-epar-product-information_en.pdf [accessed 1 Mar 2023]

Finerenone increased hyperkalaemia, but the clinical impact was minimal[1]

Investigator-reported hyperkalaemia adverse events[1]*



Max difference in mean serum [K⁺] between finerenone and placebo[1]

0.19 mmol/l at month 4

Hyperkalaemia risk factors:[2]
High baseline [K⁺], lower eGFR, higher UACR, ß-blocker use

With a robust [K⁺] management strategy guided by regular serum [K⁺] monitoring,[3] there were no hyperkalaemia-related deaths in ~13,000 people over 3 years' median follow-up

*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalaemia' and 'blood potassium increased'
AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 2. Agarwal R, *et al. J Am Soc Nephrol* 2022;33:225–237;
3. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; Supplementary appendix

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Summary

Finerenone slows CKD progression and reduces CV risk in a broad range of patients with **CKD and T2D**[1]

The **pillar approach** to the treatment of patients with CKD and T2D:

- Allows for **early treatment initiation** with RASis, SGLT-2is and finerenone[2,3]
- Is recommended to improve kidney and CV outcomes[2]

Eligibility for finerenone treatment initiation is based on **serum [K^+] and eGFR**

After initiation, serum [K^+] and eGFR must be measured periodically to allow for **finerenone dose adjustments** if needed[4]

*On top of a maximum tolerated dose of RASi

1. Naaman SC & Bakris GL. In: Chronic Kidney Disease and Type 2 Diabetes. Arlington: American Diabetes Association; 2021. p28–32; 2. Blazek O & Bakris GL *Am Heart J Plus* 2022;19:100187; 3. DeFronzo RA, *et al. Diabetes Obes Metab* 2022;24:1197–1205; 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 01 Mar 2023]

CHECK is a multidisciplinary collaboration aiming to raise awareness of kidney health and the need for early UACR testing for people with T2D

CHECK | Collaborate for Healthy Kidneys

Visit www.check-kidneys.com

to access information and resources for **HCPs, health system decision-makers and patients**

Our vision

- For all people with T2D to know the status of their kidneys
- For healthcare professionals to take action with annual UACR testing to safeguard CV and kidney health

Multidisciplinary CHECK group

Lori Berard, Christoph Wanner, Joseph Vassalotti, Alice Cheng, Peter Rossing, Katharina Schütt, Boris Klanger, Yvonne Böhler, Oriol Sola Morales, Olivier Wong, Patient representatives