Finerenone

Rieti 17 giugno 2023

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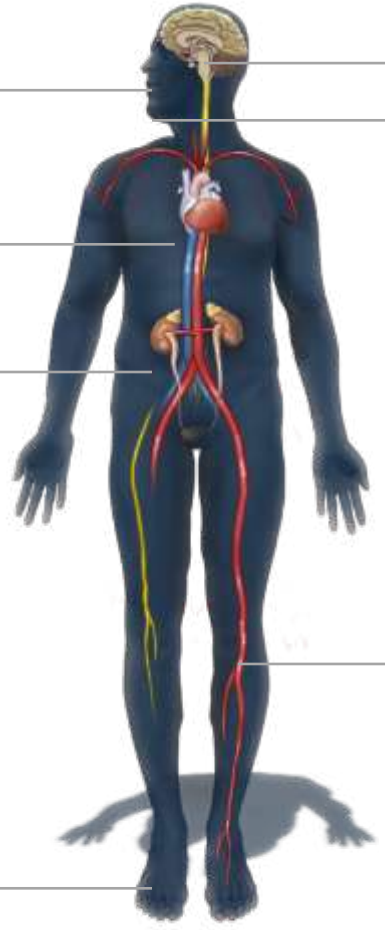
T2D can cause damage to various organs and lead to disease complications, including CKD



Diabetic retinopathy[1,2]
Affects one in three patients with diabetes

Cardiovascular disease[1,2]
Two- to threefold increase in patients with diabetes

CKD in T2D[1]
Diabetes is the leading cause of kidney failure in developed countries[3–5]

10 times higher prevalence of kidney failure in patients with diabetes compared with people without diabetes[1]

Diabetic foot[1,2]
May lead to lower limb amputation

Stroke[1]
56% increased risk of haemorrhagic stroke in patients with diabetes

Oral health issues[1]
Higher risk of periodontal disease

Diabetic neuropathy[1,2]
Nerve damage ranging from numbness in the legs and feet to problems with the digestive system, urinary tract, blood vessels and heart

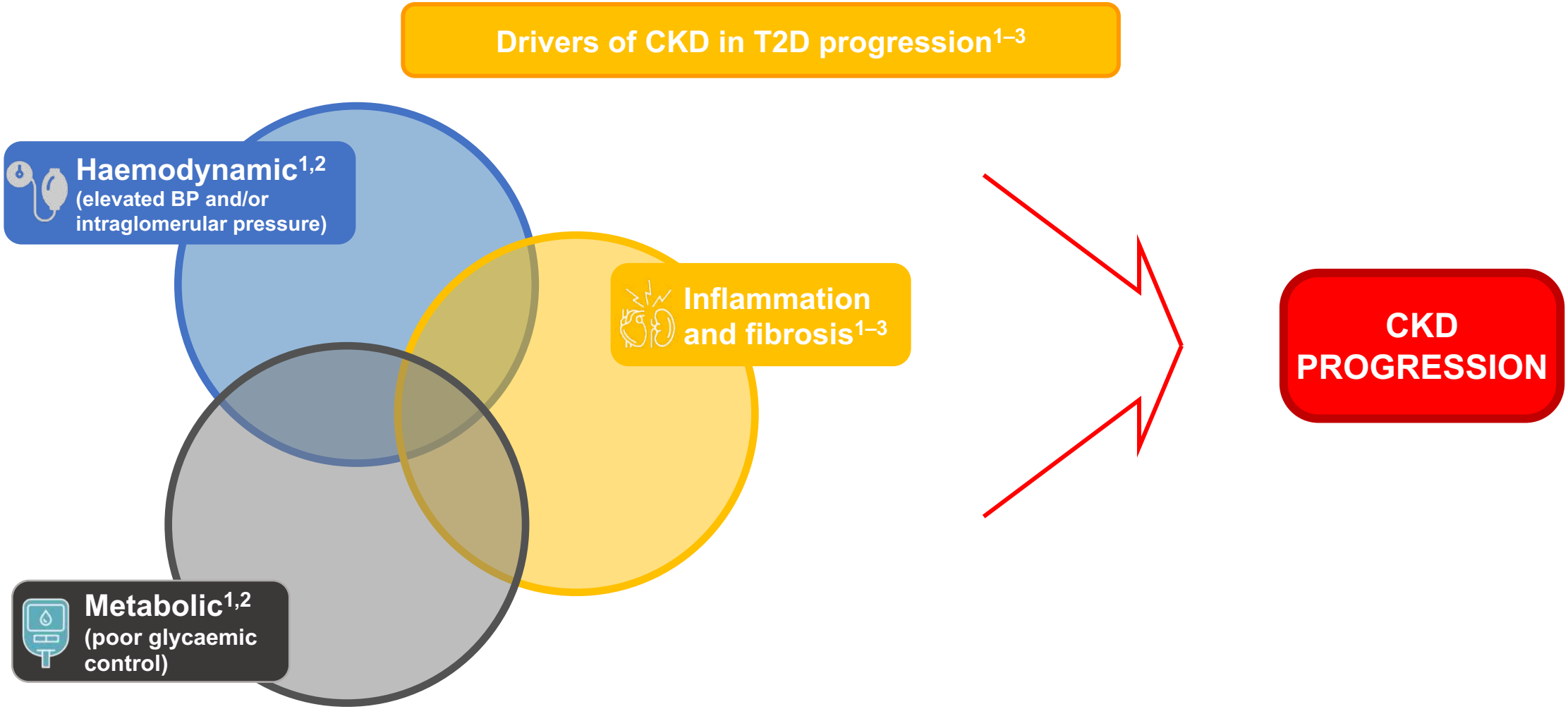
Microvascular complication

Macrovascular complication

T2D, type 2 diabetes; CKD, chronic kidney disease

1. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium; 2019; 2. National Kidney Foundation. National Kidney Foundation. *Am J Kidney Dis* 2007;49(suppl 2):S1–S180; 3. United States Renal Data System. 2018 Annual Data Report. Volume 2, ESKD: Chapter 1; 4. United States Renal Data System. 2018 Annual Data Report. Volume 2, ESKD: Chapter 11; 5. United States Renal Data System. 2019 Annual Data Report. Executive summary

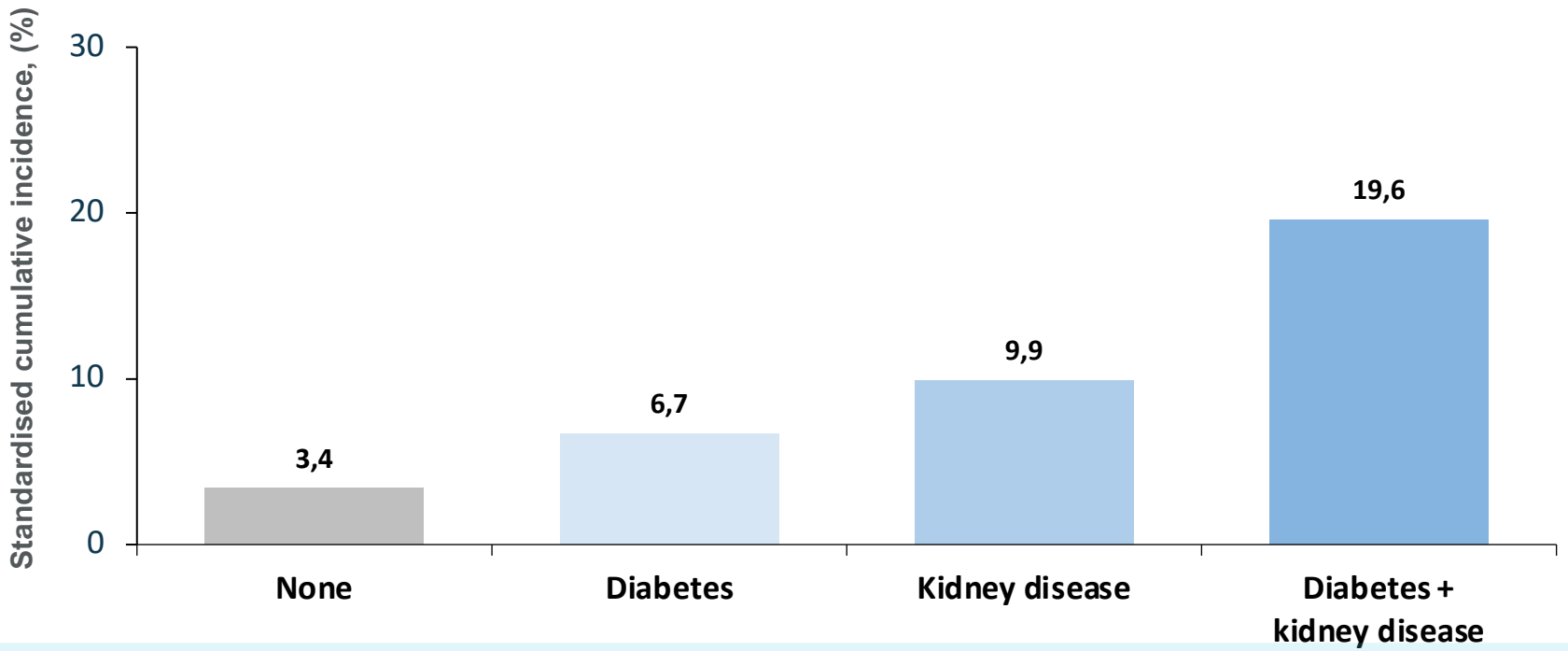
CKD progression in T2D is driven by the combined effects of metabolic, haemodynamic, and inflammatory and fibrotic factors



1. Alicic RZ, et al. *Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, et al. *J Physiol* 2014;18:3997; 3. Bauersachs J, et al. *Hypertension* 2015;65:257–263

Kidney disease approximately triples the risk of CV mortality in patients with CKD and T2D compared to patients with CKD alone[1]

10-year standardised CV mortality (%)

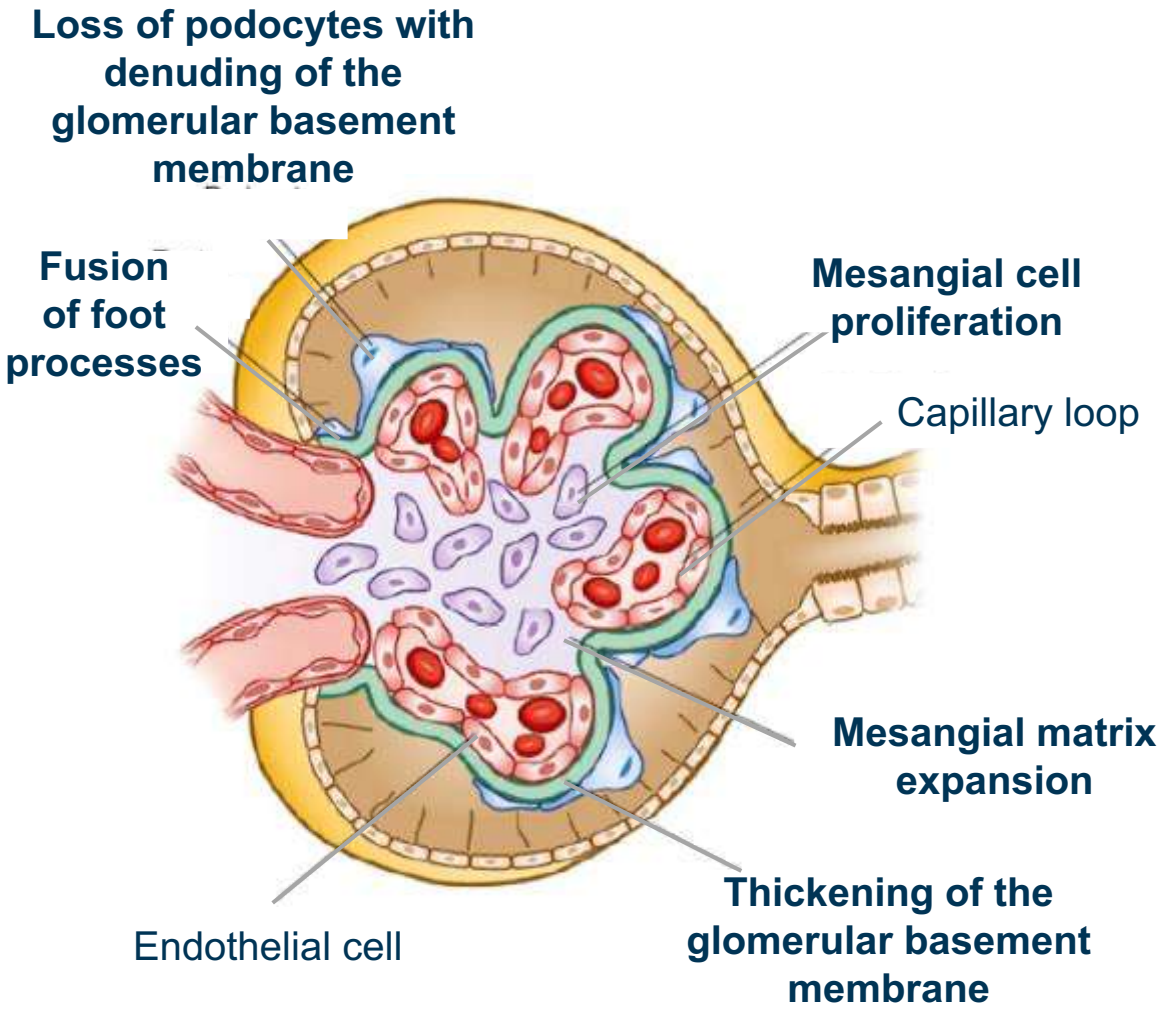


Data from the NHANES III study suggested that excess risk for CVD among patients with diabetes was concentrated among patients with kidney disease (defined as albuminuria, impaired eGFR, or both).[1]

CV, cardiovascular; NHANES III, Third National Health and Nutritional Examination Survey; CKD, chronic kidney disease; T2D, type 2 diabetes; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate

1. Afkarian M et al. *J Am Soc Nephrol.* 2013;24:302-308.

T2D causes structural changes in the kidney glomerulus[1]



Other diabetes induced changes

Glomerulosclerosis[1–3]
Thickened glomerular basement membrane and mesangial expansion are accompanied by accumulation of AGEs, leading to glomerulosclerosis[2]

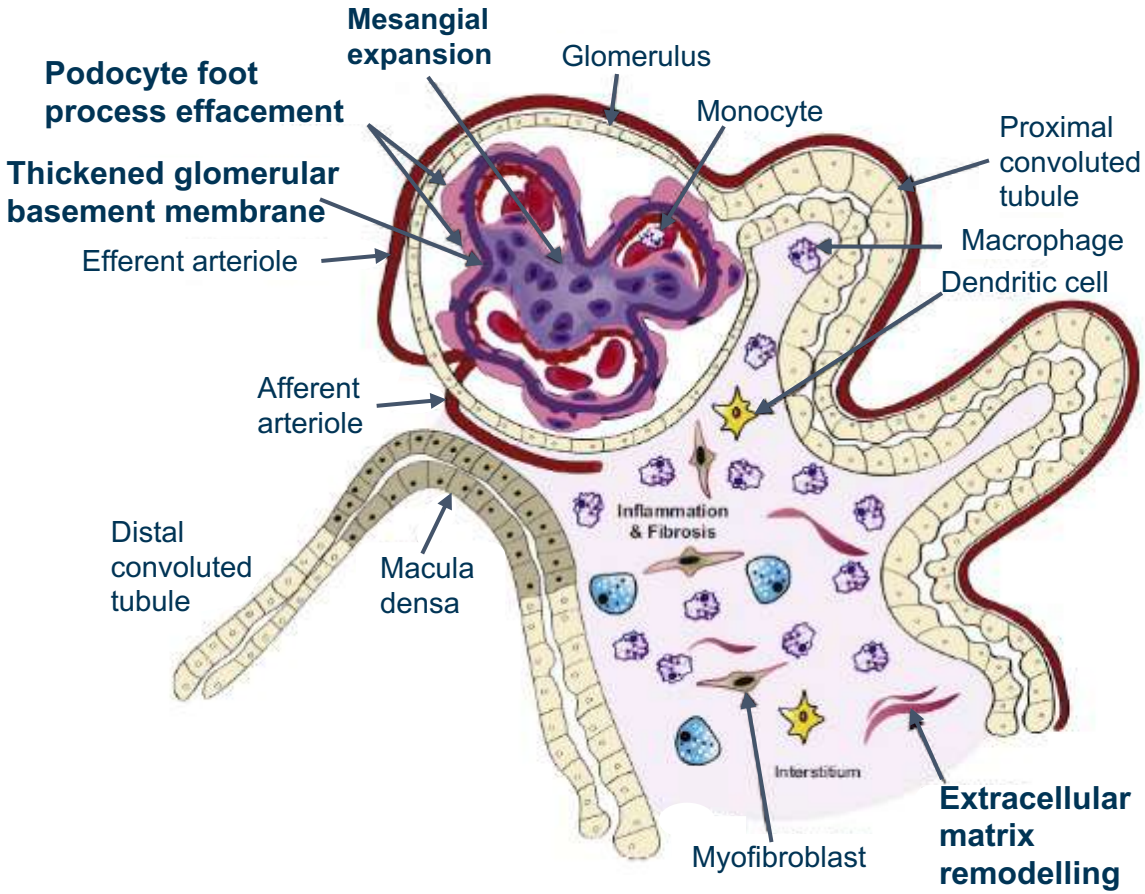
Glomerular hypertrophy[1–4]
Glomerular hypertrophy is associated with an increase in eGFR, mainly caused by increased plasma flow and glomerular capillary hydrostatic pressure

T2D, type 2 diabetes; AGE, advanced glycation end-product; GFR, glomerular filtration rate

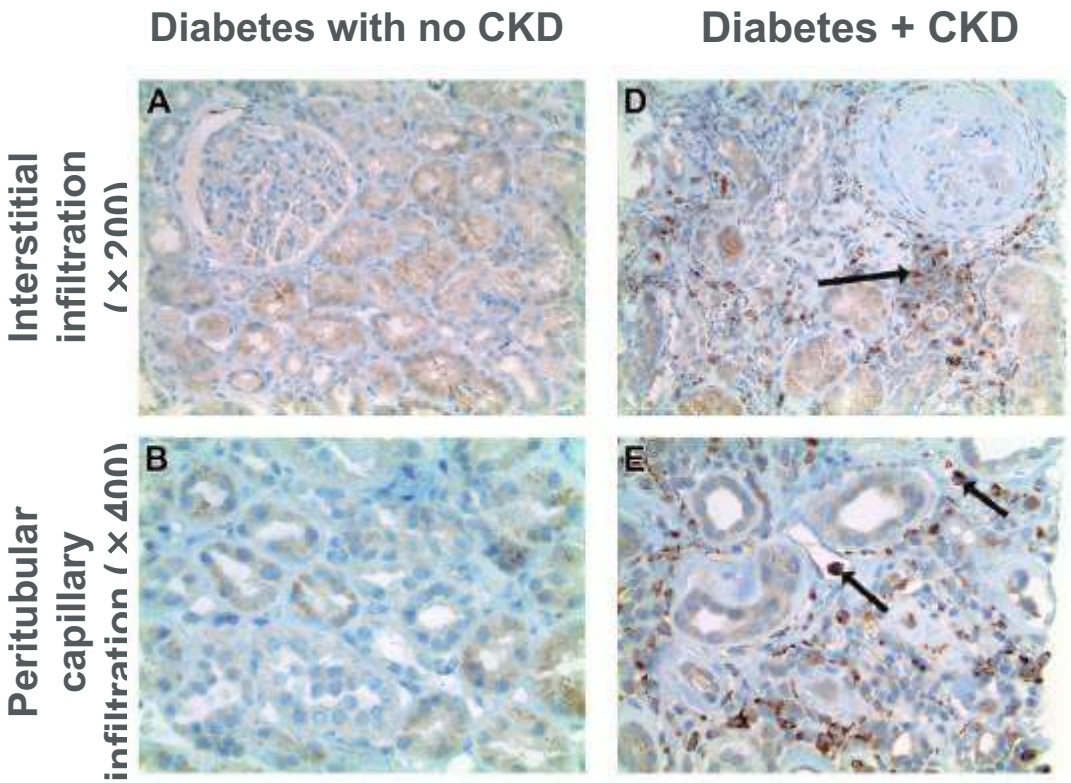
1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263;
4. Wolf G & Ziyadeh FN. *Kidney Int* 1999;56:393-405

CKD in T2D is associated with chronic inflammation

Chronic inflammation underlies structural and functional changes in CKD in T2D



Kidney biopsy shows influx of macrophage-lineage cells* in patients with CKD and diabetes



*CD-68 immunohistochemistry
CKD, chronic kidney disease; T2D, type 2 diabetes
Alicic RZ, *et al. Adv Chronic Kidney Dis* 2018;25:181–191

CKD progression in T2D is driven by the combined effects of metabolic, haemodynamic and inflammatory and fibrotic factors

DIABETES

Pathogenic mechanisms for kidney injury[1]

Metabolic factors[1,2]

- Kidney responds to **hyperglycaemia** by prompting diverse intracellular processes, including:
  - Alteration in cellular **energy production (↑NADPH)**
  - Activation of different enzymes (e.g. **PKC**)
  - Enhanced **flux of polyols** and hexosamine
  - Generation of **AGEs and ROS**
  - Activation of **transducer signalling pathways (↑TGF-β)**

Haemodynamic factors[1]

- **Hyperglycaemia** induces activation of local kidney **RAAS**, leading to:
  - **Systemic hypertension**
  - **Intraglomerular hypertension**
  - **Glomerular hyperfiltration**
  - **Impaired kidney vascular regulation**
  - **Altered sodium/fluid balance**

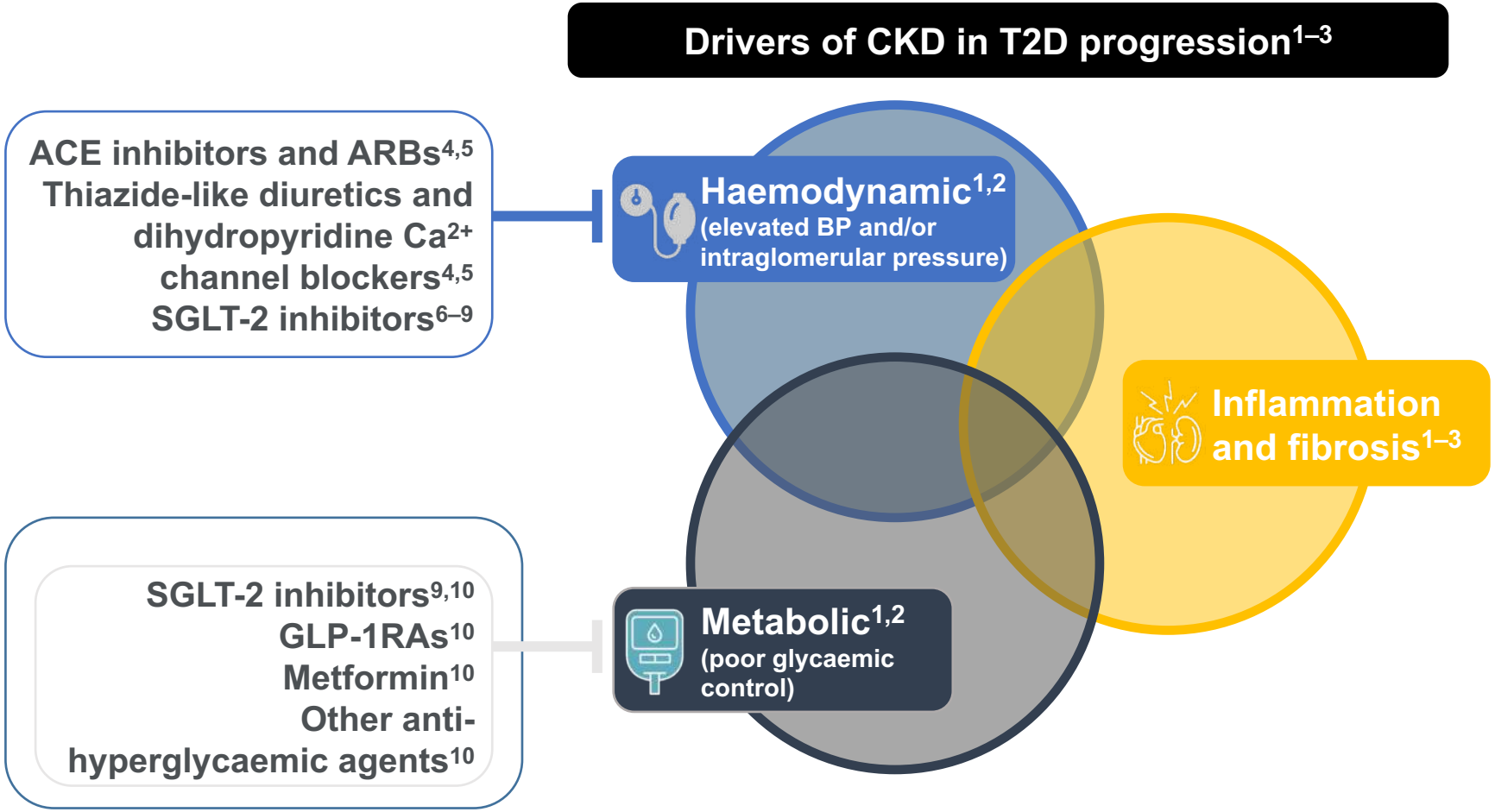
Inflammatory and fibrotic factors[3]

- Metabolic and haemodynamic abnormalities induced by diabetes, including **hyperglycaemia and AGEs**, lead to release of **proinflammatory cytokines (e.g. IL-1 IL-6, TNF-α)**
- Other activated inflammatory molecules and pathways include:
  - Chemokines
  - Innate immune cells
  - Adhesion molecules

AGE, advanced glycation end-product; CKD, chronic kidney disease; IL-1, interleukin-1; IL-6; interleukin-6; NADPH, nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; T2D, type 2 diabetes; TGF-β, transforming growth factor beta; TNF-α, tumour necrosis factor alpha

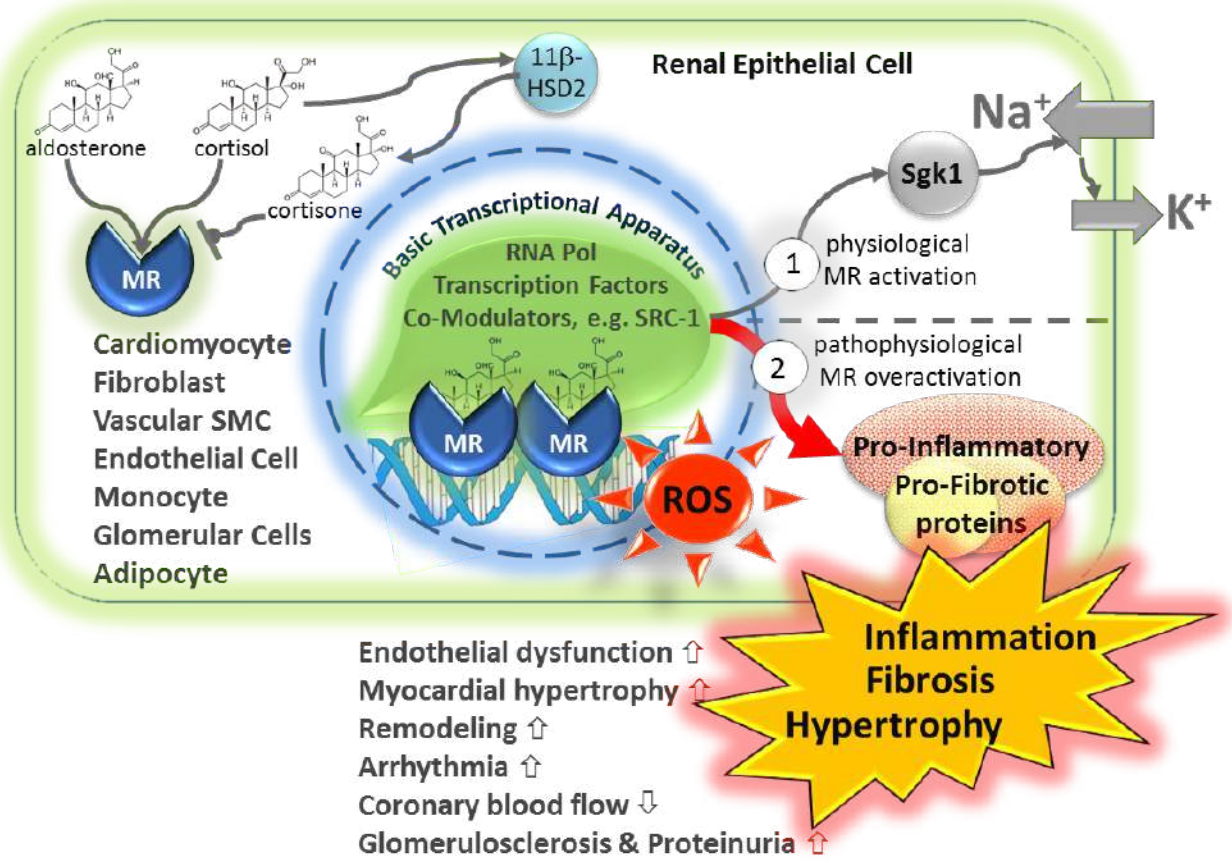
1. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 2. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 3. Alicic RZ, *et al. Adv Chronic Kidney Dis* 2018;25:181–191

Current treatments for patients with CKD and T2D primarily target haemodynamic and metabolic factors



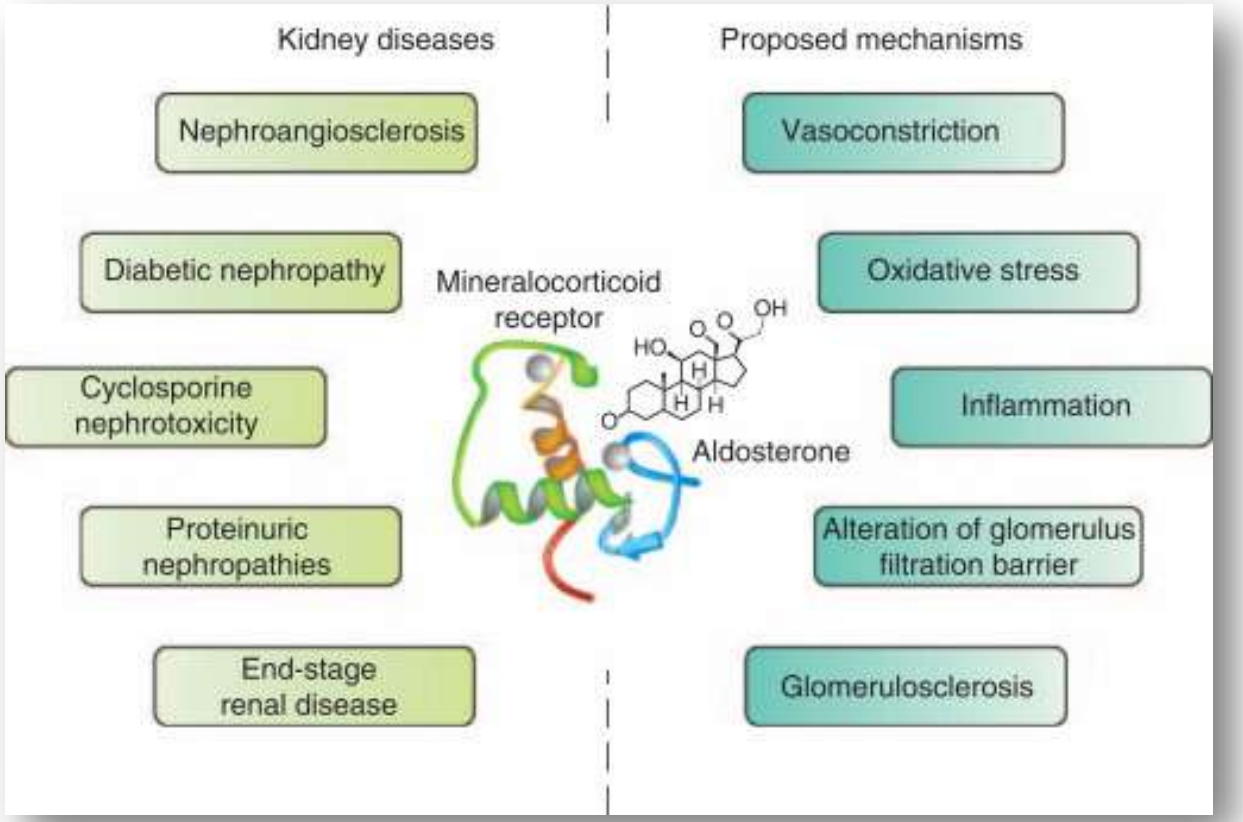
1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263;
4. American Diabetes Association. *Diabetes Care* 2020;43:S135-151; 5. American Diabetes Association. *Diabetes Care* 2020;43:s111–1340; 6. Kidokoro K, *et al. Circulation* 2019:140;303–315; 7. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 9. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434; 10. American Diabetes Association. *Diabetes Care* 2020;43:S98–S110

Aldosterone and Mineralocorticoid Receptor in Physiology and Pathophysiology



Kolkhof, Jaisser, Kim, Filippatos, Nowack & Pitt. Handb Exp Pharmacol. 2016

Mechanisms and contribution of MR in kidney diseases



Bertocchio, Warnock, & Jaisser, Kidney International, 2011, 25

Clin Exp Nephrol (2015) 19:1098–1106
DOI 10.1007/s10157-015-1106-2

ORIGINAL ARTICLE

Anti-albuminuric effects of spironolactone in patients with type 2 diabetic nephropathy: a multicenter, randomized clinical trial

Sawako Kato[1] · Shoichi Maruyama[1] · Hirofumi Makino[2] · Jun Wada[2] · Daisuke Ogawa[2] · Takashi Uzu[3] · Hisazumi Araki[3] · Daisuke Koya[4] · Keizo Kanasaki[4] · Yutaka Oiso[5] · Motomitsu Goto[5] · Akira Nishiyama[6] · Hiroyuki Kobori[6] · Enyu Imai[7] · Masahiko Ando[8] · Seiichi Matsuo[1]

Conclusions Spironolactone reduced albuminuria along with conventional RAS inhibitors in patients with diabetic nephropathy. Our study suggests that spironolactone exerts anti-albuminuric effects independent of systemic hemodynamic alterations.

activity in the kidney. In conclusion, our study suggests that spironolactone could be recommended as a second-line treatment for patients with type 2 diabetes and nephropathy, when the control of blood pressure or albuminuria is insufficient under the RAS blocker-based therapy.

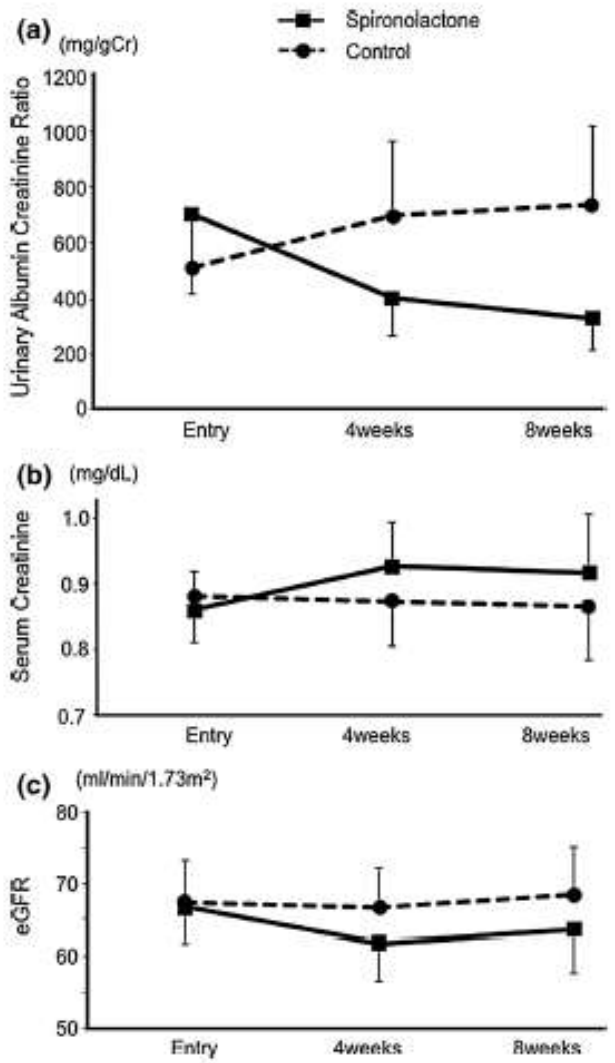
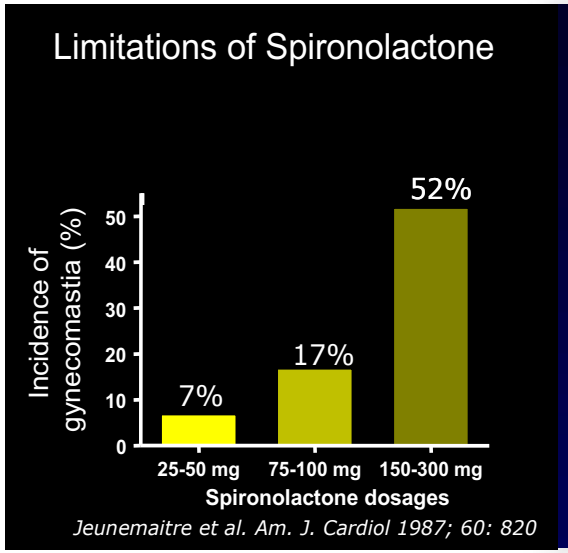
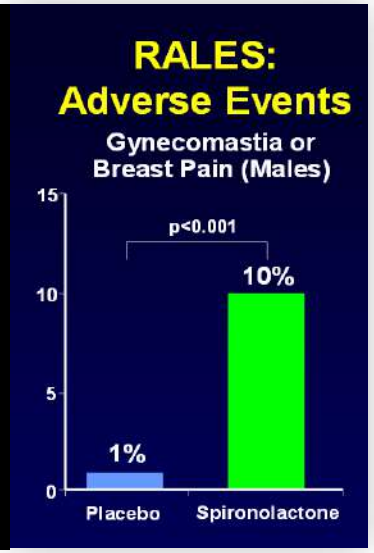
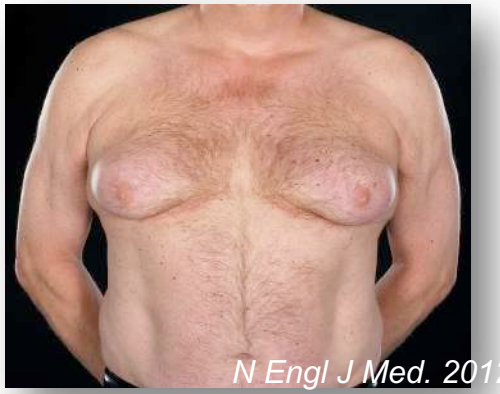


Fig. 1 Line plot showing mean urinary albumin-to-creatinine ratio (**a**), mean serum creatinine (**b**) and mean estimated glomerular filtration rate (**c**). The *squares* represent the control group (Group C) and the *circles* represent the spironolactone group (Group S)

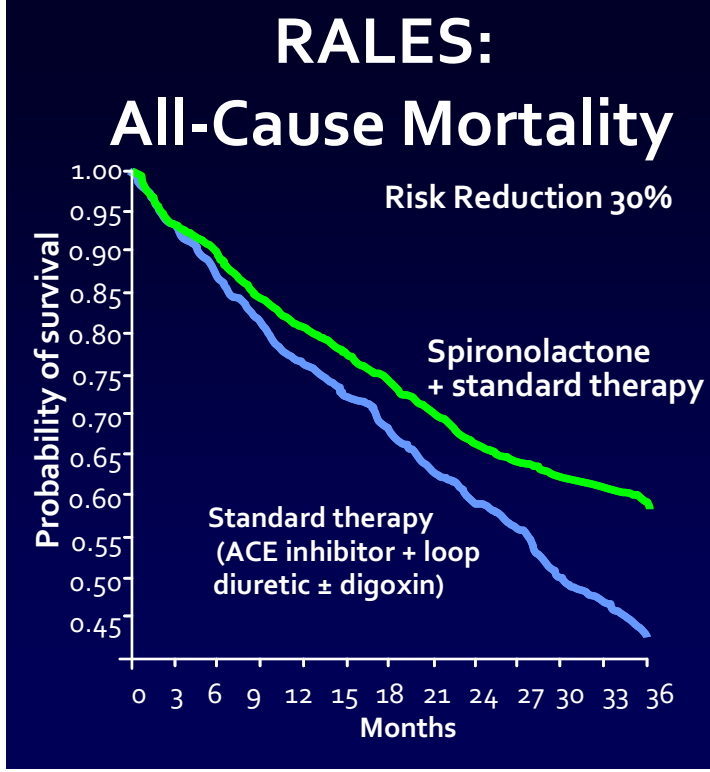
Spironolactone is a non-selective steroidal MRA





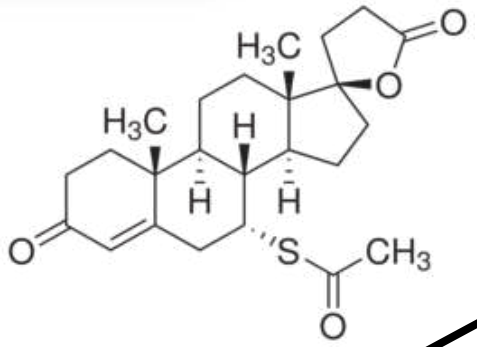


gynecomastia



menstrual irregularities

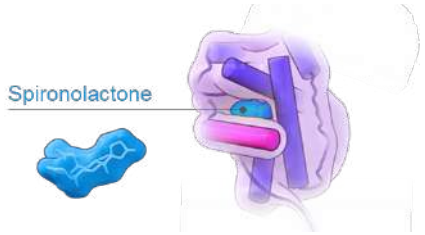
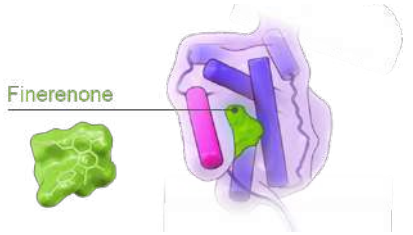
impotence



spironolactone

- **Significant increase in the risk of hyperkalemia with the addition of spironolactone to ACEi and/or ARB (relative risk 3.06, 95% CI 1.26, 7.41).**

Differential MR binding of steroidal MRAs vs finerenone results in distinct effects on gene expression

	Aldosterone antagonists		Finerenone
			
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)[1,5]
Potency to MR	High[4,10]	Moderate[1,4,10]	High[1,2,10]
Selectivity to MR	Low[4,10]	Moderate[4,10]	High[1,2,10]
CNS penetration	Yes	Yes	No based on preclinical data[3]
Gynecomastia	Yes[4]	Less than spironolactone[4]	No signal in phase II studies[7-9]
Hyperkalaemia	Yes[4]	Yes[4]	Moderately increased*[,7-9]
Tissue distribution	Kidney > heart (at least 6-fold)[6,10]	Kidney > heart (~3-fold)[6,10]	Balanced kidney : heart (1:1)[6,10]

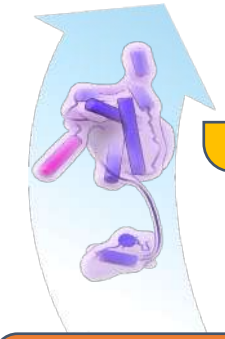
Based on preclinical data and ARTS phase II programme

MR, mineralocorticoid receptor

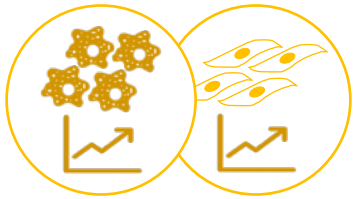
1. Bärfacker L, *et al. ChemMedChem* 2012;7:1385–1403; 2. Pitt B, *et al. Eur J Heart Fail* 2012;14:668–675; 3. Kolkhof P, *et al. J Cardiovasc Pharmacol* 2014;64:69–78; 4. Sica DA. *Heart Fail Rev* 2005;10:23–29; 5. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889; 6. Kolkhof P, *et al. Curr Opin Nephrol Hypertens* 2015;24:417–424; 7. Pitt B, *et al. Eur Heart J* 2013;34:2453–2463; 8. Bakris GL, *et al. JAMA* 2015;314:884–894; 9. Filippatos G, *et al. Eur Heart J* 2016;37:2105–2114; 10. kolkhof P, *et* al. *Handb Exp Pharmacol*. 2017;243:271-305

MR overactivation, which contributes to inflammation and fibrosis, is a potential treatment target to slow CKD progression

Kidney and heart diseases are associated with MR overactivation [4,7,8]



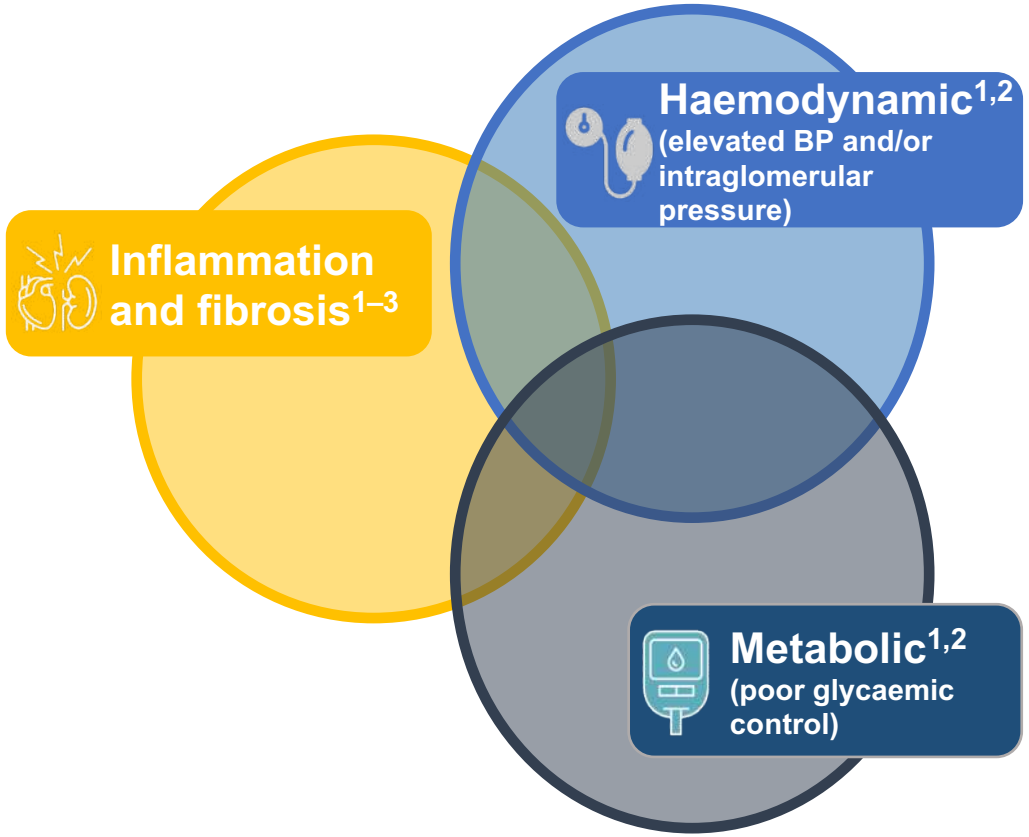
Increased gene expression of pro-inflammatory and pro-fibrotic factors [3–8]



Blocking MR overactivation may slow CKD progression mediated through inflammatory and fibrotic pathways,[3,7] which are largely unaddressed by current therapies[1,9]

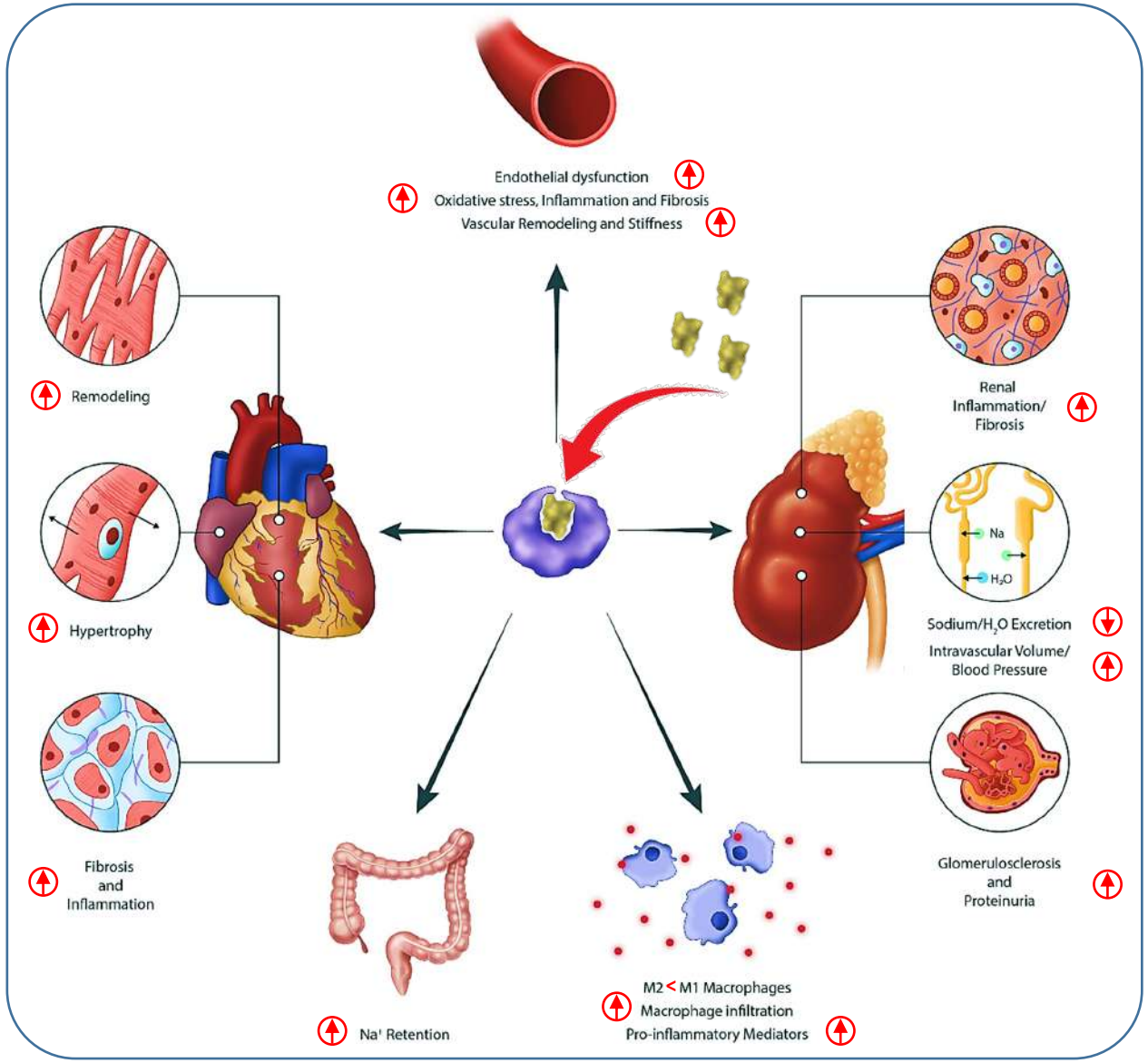
KIDNEY AND HEART PROTECTION

Drivers of CKD in T2D progression[1–3]



1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263;
4. Buonafine M, *et al. Am J Hypertension* 2018;31:1165–1174; 5. Brown NJ. *Nat Rev Nephrol* 2013;9:459–469; 6. Biwer LA, *et al. Am J Hypertension* 2019;32:123–134;
7. Barrera-Chimal J, *et al. Kidney Int* 2019;96:302–319; 8. Kolkhof P, *et al. Handb Exp Pharmacol* 2017;243:271–305; 9. Alicic RZ, *et al. Adv Chronic Kidney Dis* 2018;25:1941–191

MR overactivation causes kidney and cardiovascular damage

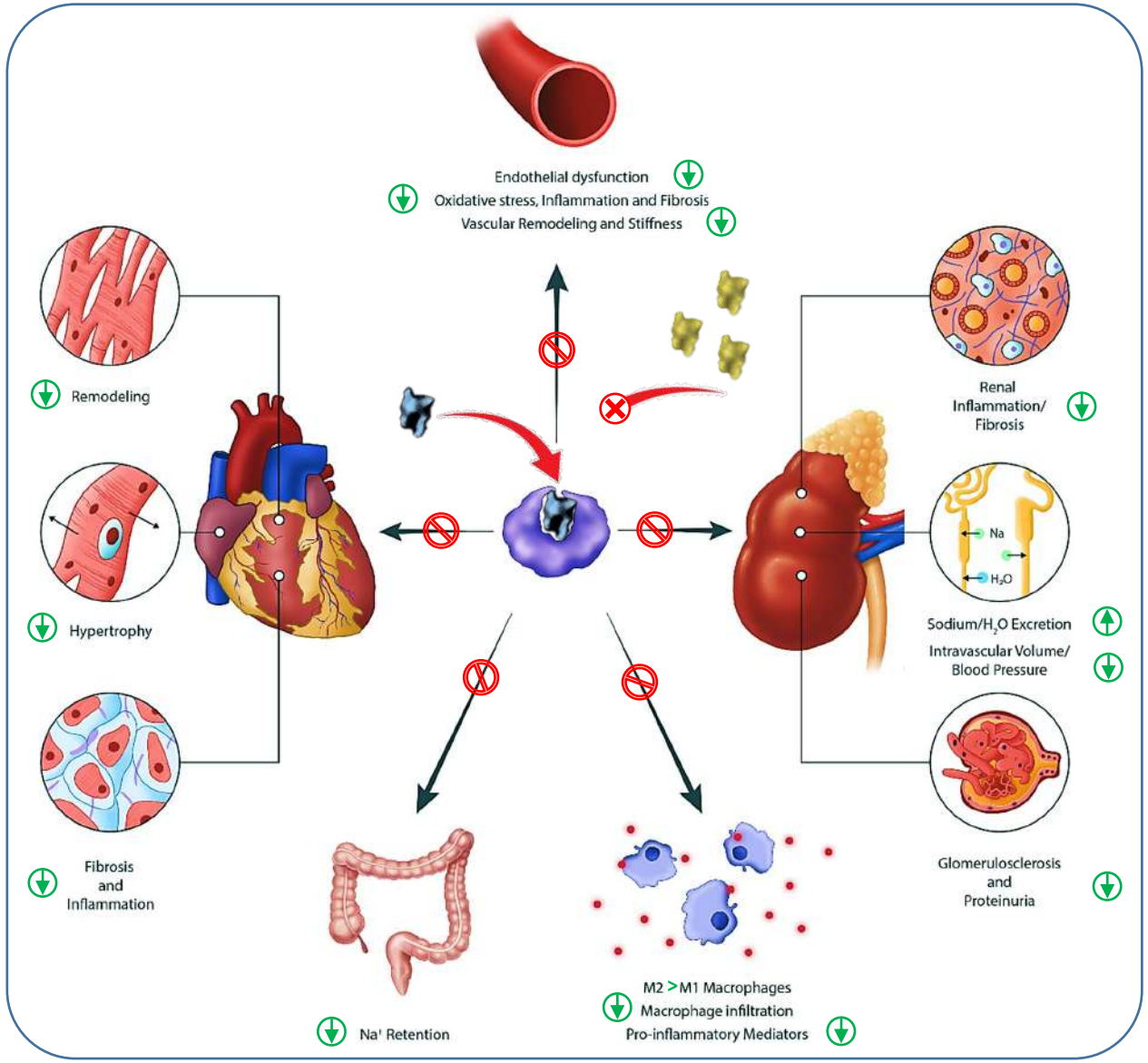


Aldosterone / cortisol

Mineralocorticoid receptor

Modified from: Pandey AK et al., *Eur Heart J* 2022; 43(31):2931-2945

Finerenone, a novel, selective, non-steroidal MRA, blocks MR overactivation



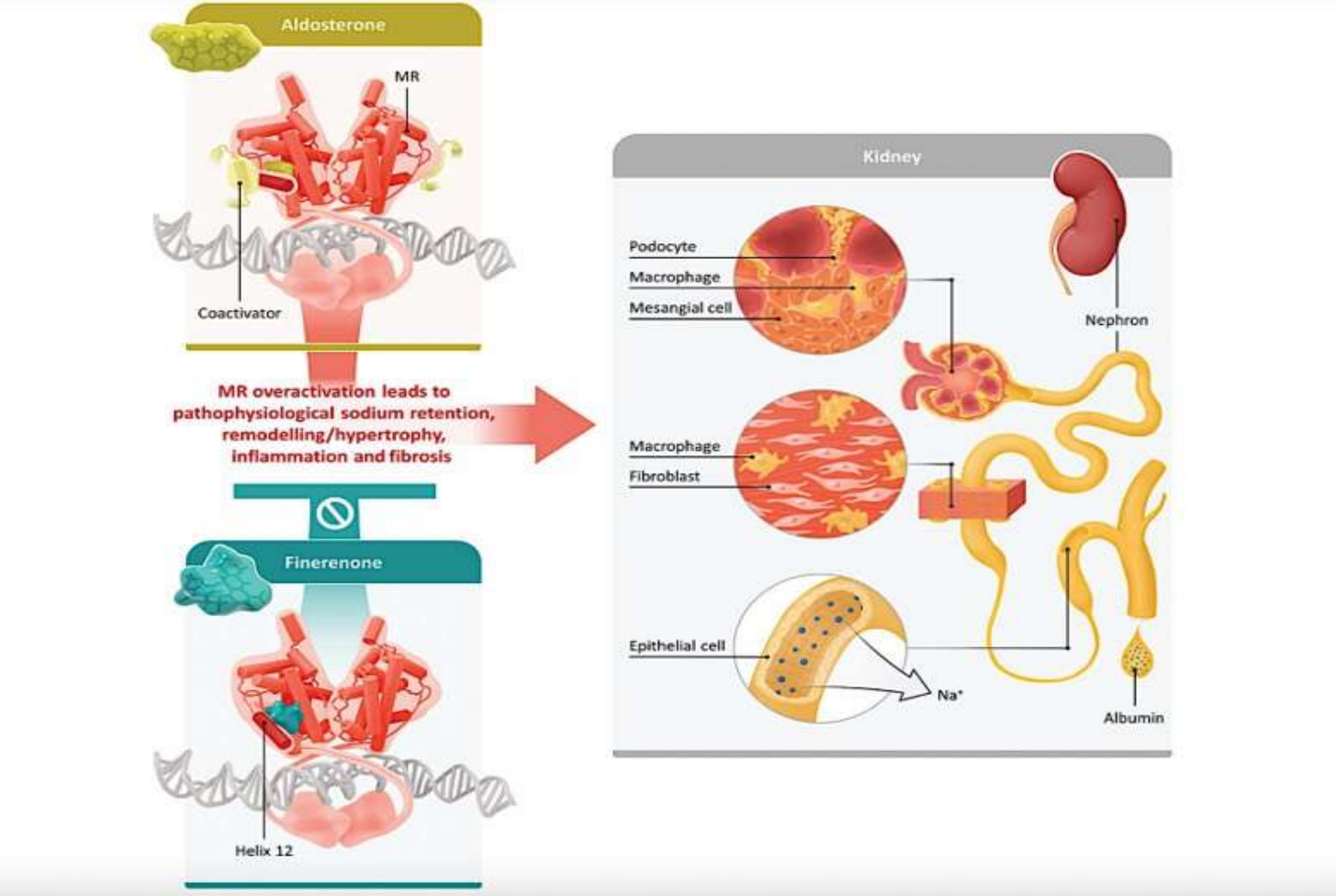
Aldosterone / cortisol

Mineralocorticoid receptor

Finerenone

Modified from: Pandey AK et al., *Eur Heart J* 2022; 43(31):2931-2945

Mechanism of action of the non steroidal mineralcorticoid receptor antagonist: FINERENONE



Kintscher U, et al., Br J Pharmacol. 2022; 179: 3220-3234

The phase III study programme is investigating renal and CV outcomes with finerenone in patients with CKD and T2D

Phase II studies

ARTS[1] (N=457)
Patients with HF (LVEF ≤40%) and mild CKD

Well tolerated with **less hyperkalaemia** vs spironolactone

ARTS-DN[2] (N=823)
Patients with T2D and albuminuria

Dose-dependent **reduction in albuminuria** with similar adverse events to placebo

ARTS-HF[3] (N=1066)
Patients with HFrEF and CKD and/or T2D

Well tolerated with **comparable safety** to eplerenone

Phase III trial programme

Patients with CKD and T2D (persistent high or very high albuminuria)

N≈13,000

FIDELIO-DKD[4]

Finerenone reducing **kidney failure and disease progression** in patients with CKD and T2D

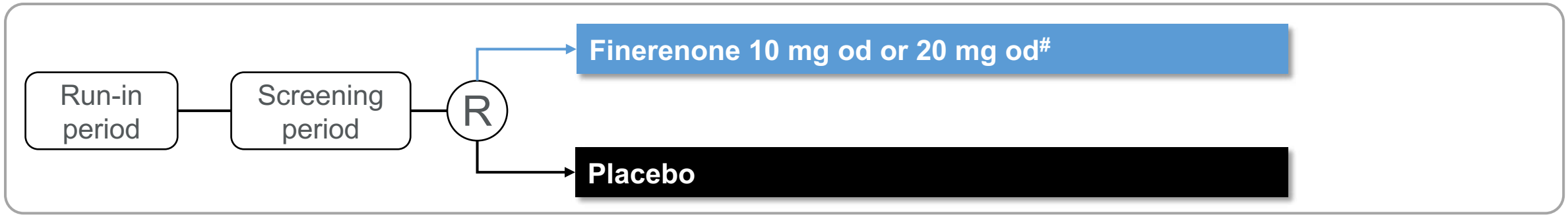
FIGARO-DKD[5]

Finerenone reducing **cardiovascular mortality and morbidity** in patients with CKD and T2D

CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; T2D, type 2 diabetes

1. Pitt B, *et al. Eur Heart J* 2013;34:2453–2463; 2. Bakris GL, *et al. JAMA* 2015;314:884–894; 3. Filippatos G, *et al. Eur Heart J* 2016;37:2105–2114; 4. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 5. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356

FIDELIO-DKD and FIGARO-DKD are investigating effects of finerenone on kidney and CV outcomes in patients with CKD and T2D

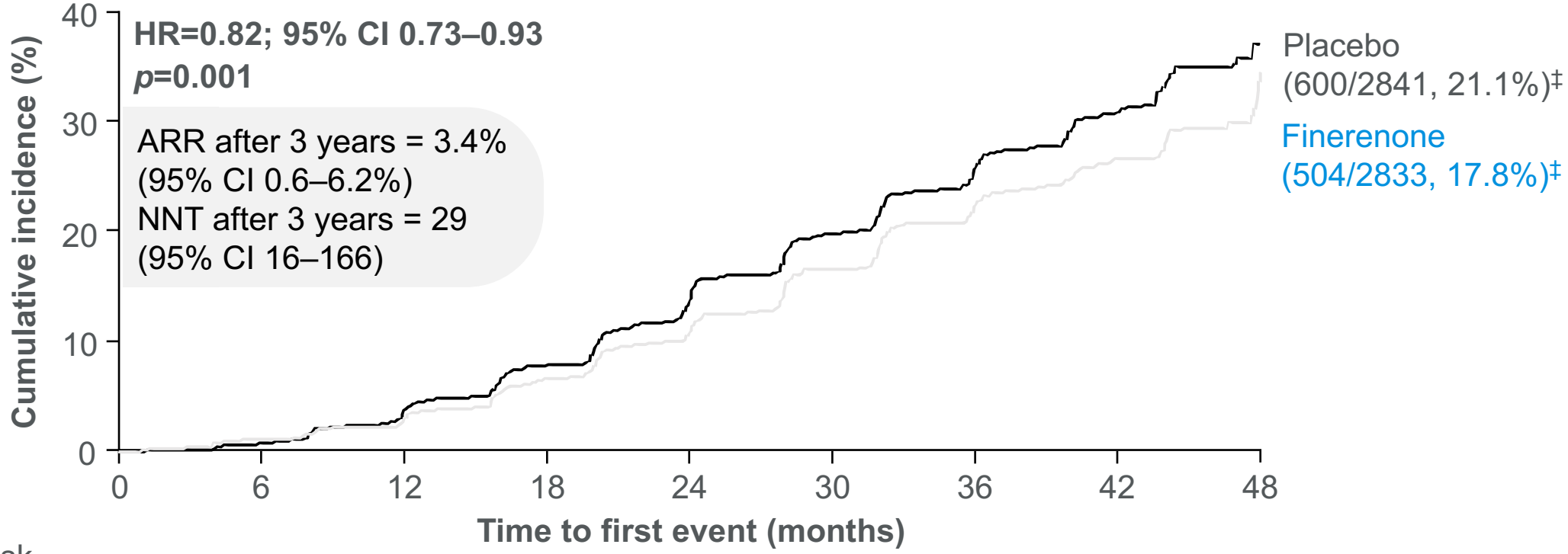


	FIDELIO-DKD[1]	FIGARO-DKD[2]
Clinical efficacy primary endpoint	**Composite endpoint**: time to onset of kidney failure* or decrease of eGFR ≥40% from baseline or death due to kidney disease	**Composite endpoint**: time to CV death, non-fatal MI, non-fatal stroke or hospitalisation for HF

1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356

Finerenone significantly reduced the risk of the primary composite kidney endpoint vs placebo

Time to kidney failure*, sustained ≥40% decrease in eGFR from baseline#, or renal death



No. at risk					
Finerenone	2833	2607	1808	787	83
Placebo	2841	2586	1758	792	82

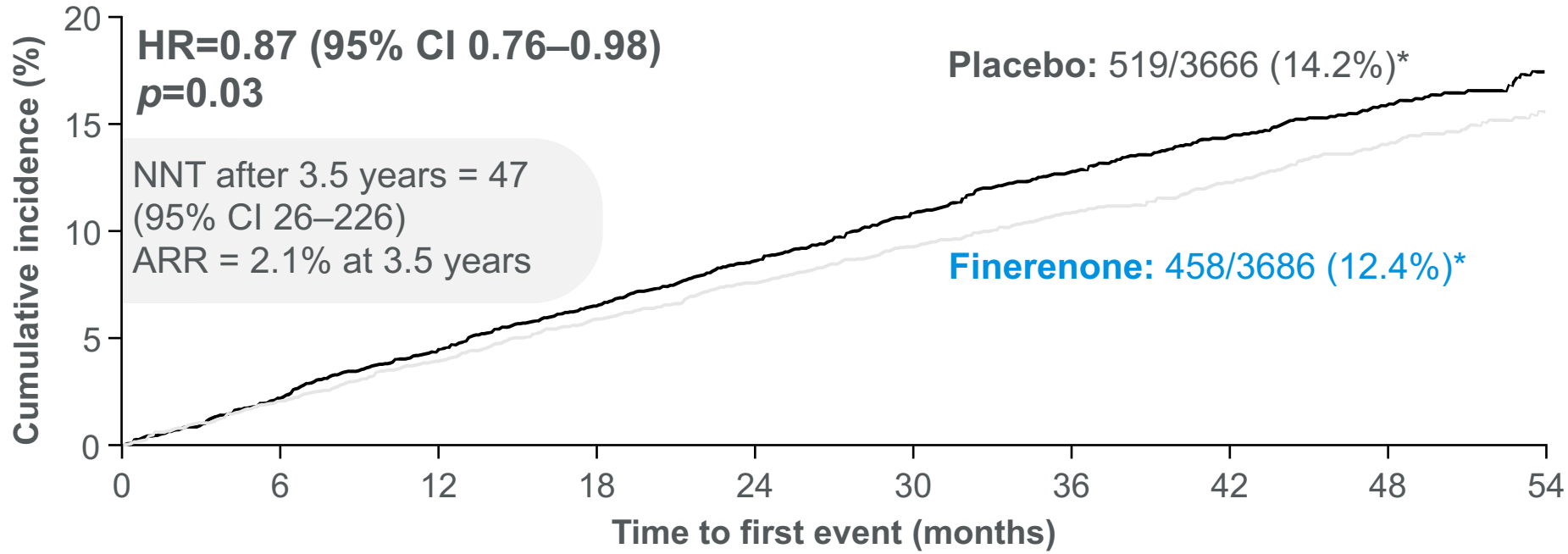
*ESKD or an eGFR <15 ml/min/1.73 m^2; #sustained over ≥4 weeks; ‡over a median follow-up of 2.6 years

Bakris GL, *et al. N Engl J Med* 2020; doi: 10.1056/NEJMoa2025845

FIDELIO-DKD

On top of maximum tolerated RAS therapy, finerenone significantly reduced the risk of the primary CV outcome by 13%

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



No. at risk

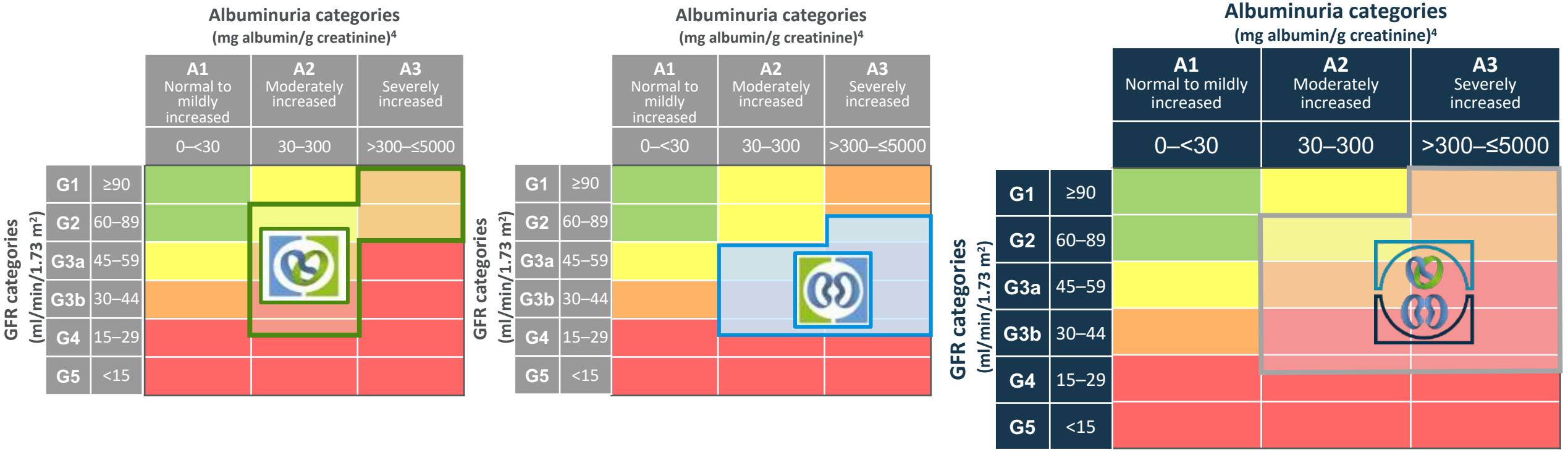
Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598
Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585

*Number of patients with an event over a median of 3.4 years of follow-up
[FIGARO primary-placeholder]

FIGARO-DKD
FInerenone in reducinG cArdiovascular moRtality and mOrbidity in DKD

FIDELIO-DKD and FIGARO-DKD assessed prespecified kidney outcomes in patients across the spectrum of CKD severity

FIGARO-DKD[1,*] + FIDELIO-DKD[2,*] = FIDELITY (FIDELIO-DKD + FIGARO-DKD pooled)[3]



*Please see slide notes for recruitment caps and eGFR/UACR cut-off details

1. KDIGO. *Kidney Int* 2020;98:S1–S115; 2. Ruilope LM, *et al*. *Am J Nephrol* 2019;50:345–356; 3. Bakris GL, *et al*. *Am J Nephrol* 2019;50:333–344; 4. Filippatos G, *et al. ESC* 2021; abstract 7161

FIDELITY is a large prespecified individual patient-data meta-analysis of the FIDELIO-DKD and FIGARO-DKD phase III trials[1–3] including CV- and kidney-specific composite outcomes across the spectrum of CKD stages

FIDELIO-DKD[1]
N=5734

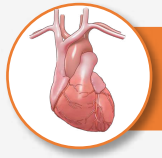
+

FIGARO-DKD[2]
N=7437

FIDELITY

prespecified pooled analysis[3]

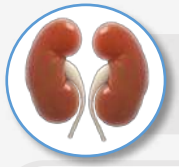
Total N=13,171



CV composite outcome

Time to first occurrence of:

- CV death*
- Non-fatal MI
- Non-fatal stroke
- Hospitalisation for HF



Kidney composite outcome

Time to first occurrence of:

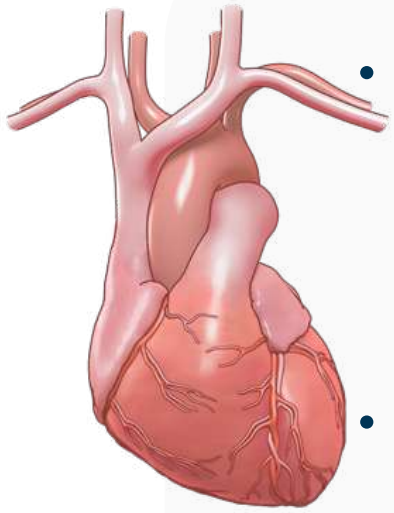
- Onset of kidney failure:
  - ESKD (initiation of chronic dialysis for ≥90 days or kidney transplantation)
  - Sustained eGFR <15 ml/min/1.73 m$^{2\#}$
- A sustained ≥57% decrease of eGFR from baseline*
- Renal death‡

*Please refer to the slide notes section for footnotes

1. Bakris GL, *et al. Am J Nephrol* 2019;50:333–344; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356; 3. Filippatos G, *et al. ESC* 2021; abstract 7161

CV composite outcome: Summary

- In patients with CKD stage 1–4 with moderate-to-severely elevated albuminuria and T2D, with well-controlled blood pressure and HbA1c, and treated with optimised RAS therapy:

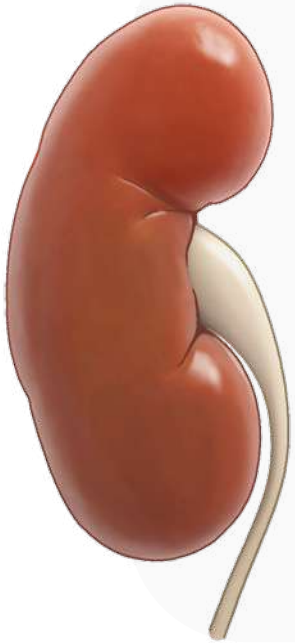


- **Finerenone significantly reduced** the **risk of CV morbidity and mortality** by **14% (equivalent to an HR of 0.86)** vs placebo
  - With consistent effects irrespective of region, baseline CKD severity, blood pressure, HbA1c and serum [K^+]
  - Absolute risk reduction = **2.2%** at 3 years
- **CV benefits of finerenone were clinically relevant**
  - NNT to prevent one CV outcome event over 3 years = 46

Filippatos G, *et al. ESC* 2021; abstract 7161

Kidney composite outcome*: Summary

- In patients with CKD stage 1–4 with moderate-to-severely elevated albuminuria and T2D, with well-controlled blood pressure and HbA1c, and treated with optimised RAS therapy:



- **Finerenone significantly reduced the risk** of the **≥57% eGFR kidney composite outcome*** by **23% (equivalent to an HR of 0.77)** vs placebo
  - With consistent effects on the components of the ≥57% eGFR kidney outcome
  - Absolute risk reduction = **1.7%** at 3 years
- **Kidney benefits of finerenone were clinically relevant**
  - NNT to prevent one kidney outcome event over 3 years = **60**

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

Filippatos G, *et al. ESC* 2021; abstract 7161

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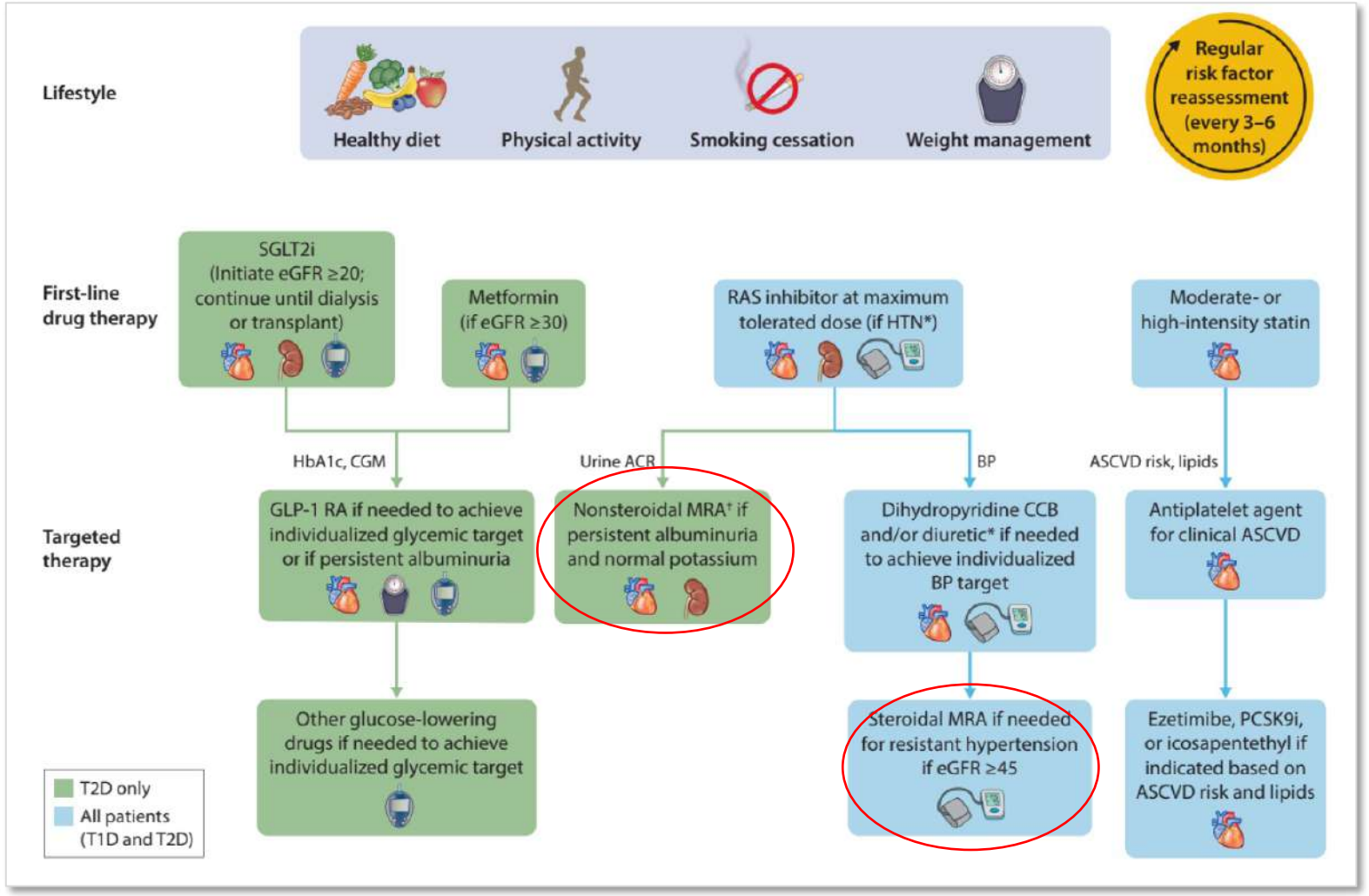
KDIGO Guidelines – Chapter 1. Comprehensive care in patients with diabetes and CKD

Therapeutical approach for improving outcomes in patients with diabetes and CKD



*ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or diuretic can also be considered; all three classes often needed to attain BP targets

†Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits

KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease – Public Review Draft – March 2022

Conclusions

Finerenone is a nonsteroidal MR antagonist that targets MR overactivation, a major driver in DKD, and has high affinity for MR and a unique binding mode

DKD increases the risk of cardiovascular disease and can shorten life expectancy, and patients often experience renal progression despite standard treatment

Finerenone has been studied in phase 2 clinical trials in patients with CHF and mild to moderate CKD, where it was found to be tolerable and associated with smaller increases in serum potassium vs spironolactone and a similar reduction in NT-proBNP and in UACR vs spironolactone

In a phase 2 clinical trial in patients with type 2 diabetes and persistent albuminuria (UACR ≥ 30 mg/g) who were receiving a RAS blocker, finerenone led to a dose-dependent reduction in albuminuria at day 90 with similar adverse events to placebo

Finerenone has also been studied in two phase 3 clinical trials in patients with DKD showing significant positive effects both on cardiac and renal outcomes
Finally, combination therapy with RAASi and/or SGLT2i (and GLP-1 agonists) could provide a 360° nephroprotection in diabetic and non – diabetic patients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