KSA Kantonsspital Aarau

Diabetic Kidney Disease (DKD)

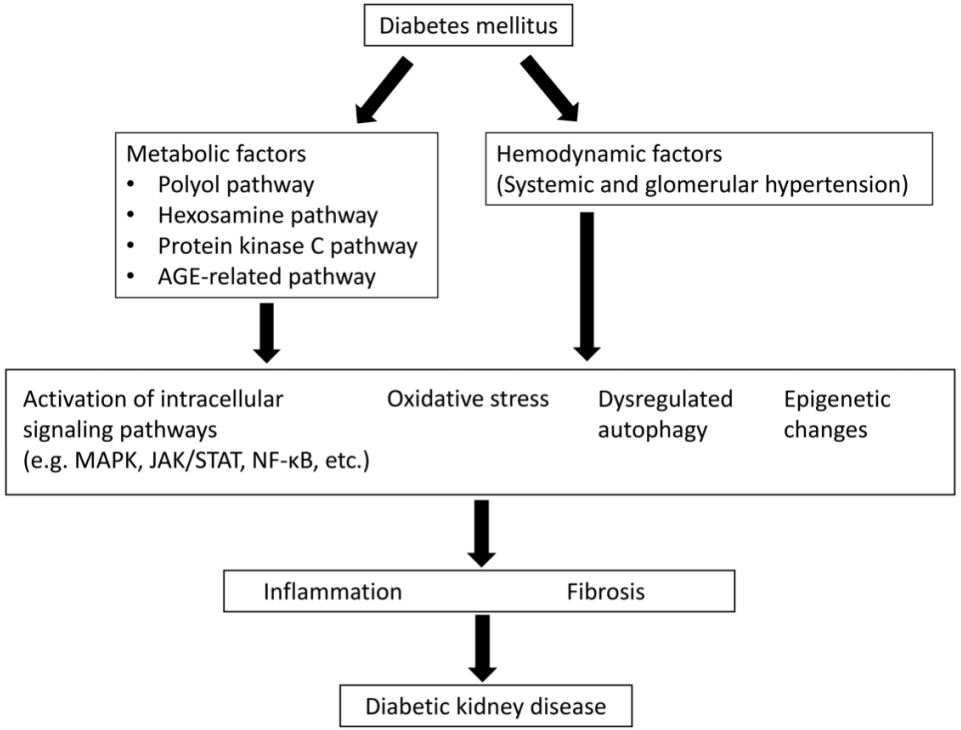
Natasha Müller
Swiss Endo Grand Rounds, 12.04.2023
Pocket Guide - Chapter 11

Epidemiology

- 2021: worldwide 537 million people living with diabetes
- Prevalence of CKD among people with diabetes: > 25% → 135 millions
- Life-time risk of developing CKD in people with diabetes ist estimated to be 40%

Pathophysiology

FIGURE 1 The pathogenesis of DKD. Diabetic milieu induces metabolic and haemodynamic abnormalities that trigger a complex network of pathological events. AGE, advanced glycation end-product; DKD, diabetic kidney disease; JAK/STAT, Janus kinase-signal transducers and activators of transcription; MAPK, mitogen-activated kinase; NF-κB, nuclear factor kappa-B



Screening and Diagnosis

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

Screening and Diagnosis

Who and when to screen?

T1D Yearly starting 5 years after diagnosis

T2D Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

Screening and Diagnosis

Who and when to screen?

- **T1D** Yearly starting 5 years after diagnosis
- **T2D** Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

Screening and Diagnosis

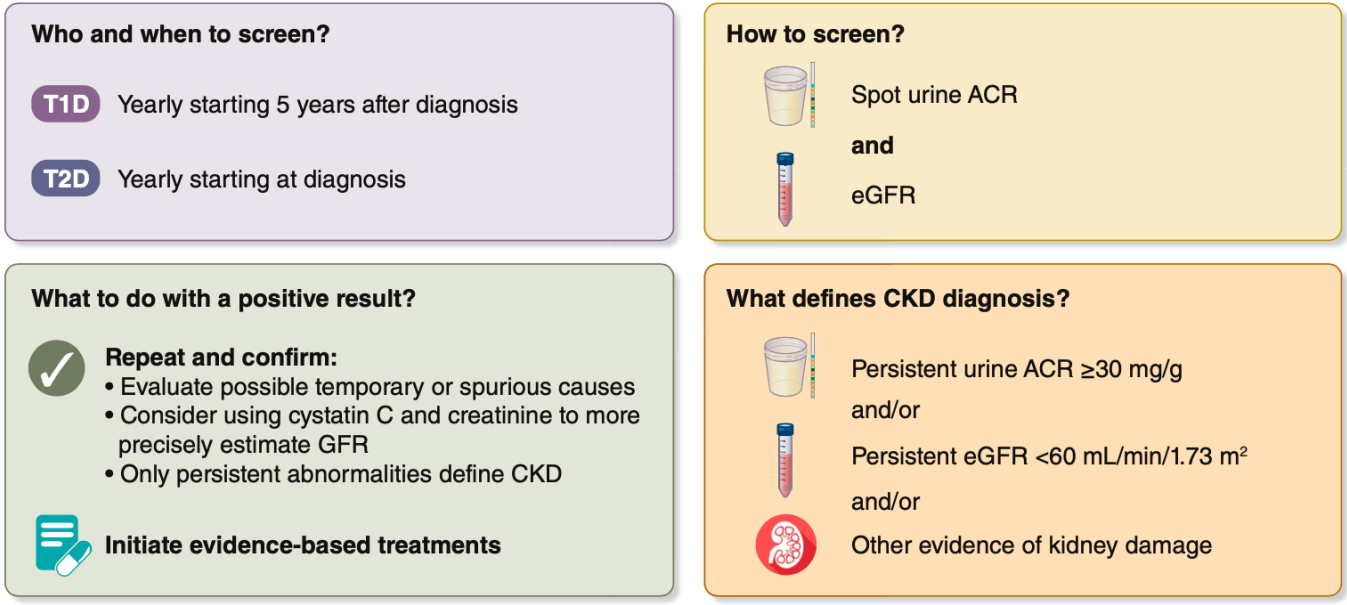


Figure 1—CKD screening and diagnosis for people living with diabetes. Screening includes measurement of both urine albumin and eGFR. Abnormalities should be confirmed. Persistent abnormalities in either urine ACR or eGFR (or both) diagnose CKD and should lead to immediate initiation of evidence-based treatments. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes.

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CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 2—Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by eGFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months, [deep red]) according to risks of CKD progression and CKD complications. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate.

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Red Flags

A cause of CKD other than diabetes should be considered:

- presence of other systemic diseases that cause CKD →
  - Arterial Hypertension
  - Cardiovascular disease
  - History of acute kidney injury
  - Familiy history of kidney disease
  - Viral infection
  - Rheumatological disease
  - Nephrotoxic drugs
  - Obesity
- No retinopathy
- With CKD signs not common with diabetes
  - Glomerular hematuria or active urine sediment
  - Large and abrupt changes in eGFR or in albuminuria
  - Presence of Nephrotic syndrome
  - Abnormal blood serology tests
  - Resistent Hypertension (BD > 140/90 mmHg despite RAAS-inhibitor, diuretic agent & Ca-antagonist)
  - ≥ 30% decrease in eGFR after start with RAAS-inhibition

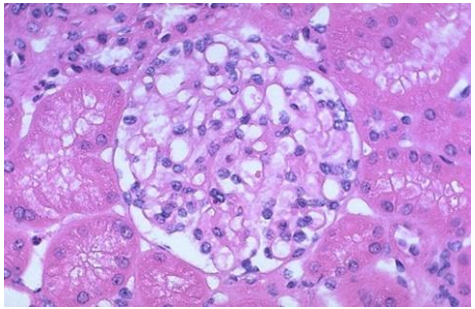
→ In the absence of these red flags, CKD is usually attributed to diabetes and treated accordingly

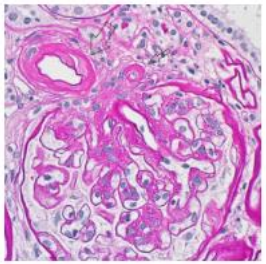
Red Flags & when to refer to a nephrologist

Refer to a nephrologist if

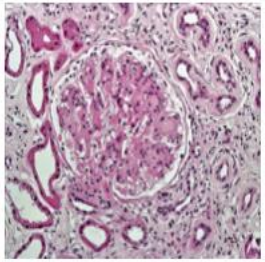
- AKI or abrupt sustained fall in eGFR
- CKD of unknown origin
- eGFR <30 ml/min/1.73 m^2
- ACR consistently >300 mg/g (30 mg/mmol)
- Progression of CKD/deterioration of eGFR
- Glomerular microhematuria
- CKD + resistant hypertension
- Persistent abnormalities of serum K+
- Hereditary kidney disease
- Recurrent or extensive nephrolithiasis

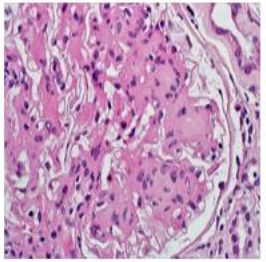
Biopsy &
Diabetic Glomerulopathy



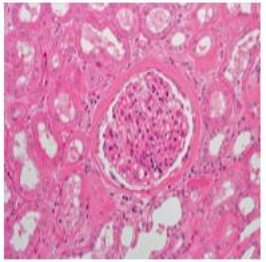


Afferent and efferent hyalinosis, PAS

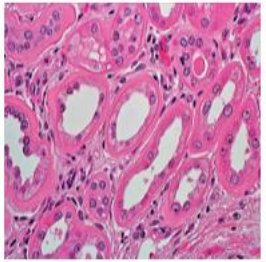




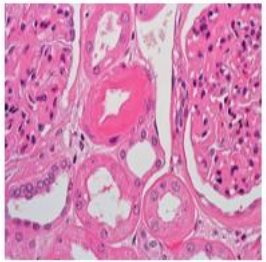
Diffuse and nodular mesangial expansion



Thickening of Bowman capsule



Thickening of basement membrane



Vascular hyalinosis

Literature:
02.04.2023; https://www.pathologyoutlines.com/topic/kidneydiabetes html
08.04.2023; https://webpath.med.utah.edu/RENAHTML/RENAL101.html

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Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)

https://doi.org/10.2337/dci22-0027

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Consensus Statements

1. Treatment with a comprehensive plan
2. Glycemic control
3. Blood pressure control
4. Lipid control

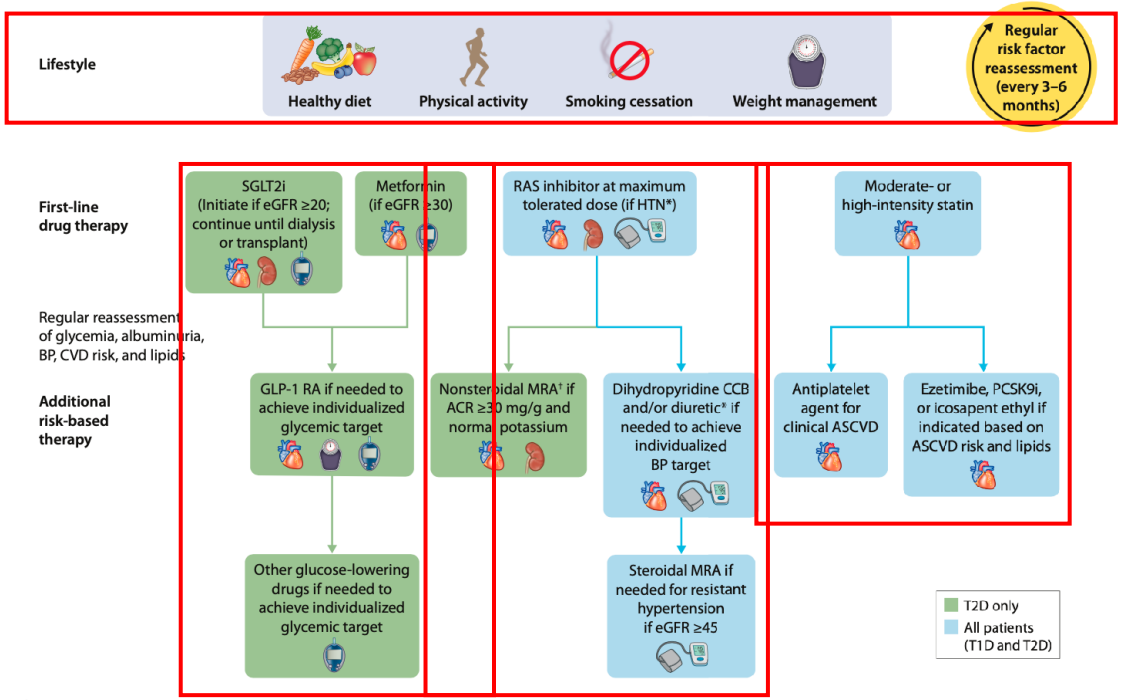

Figure 3—Holistic approach for improving outcomes in patients with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

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2. Gylcemic control

Metformin:

- In all type 2 Diabetes mellitus
- If eGFR ≥ 30 ml/min
- Dose reduction in patients with eGFR between 30 – 44 ml/min

SGLT2-inhibitor:

- In type 2 DM & CKD
- If eGFR ≥ 20 ml/min
- Independent of HbA1c

→ SGLT2-I lead to a reduction of:

- CKD-progression
- Heart failure
- Atherosclerotic cardiovascular disease

GLP-1-Analogon:

- Indicated if glycemic target is not reached despite Metformin & SGLT2-I
- Reduce albuminuria
- Slow eGFR decline

→ Individualised HbA1c-target of 6.5 – 8.0%

2. Glycemic control

Table 2—Considerations for selecting glucose-lowering agents in patients with T2D and CKD (2,17)

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

Potential risk or high cost to patient

Increased risk for adverse effects

[a]Benefit supported by primary and secondary outcome data. [b]Benefit supported by secondary outcome data. [c]Benefit or risk is agent specific. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

2. Glycemic control

- Possible side effects for oral antidiabetic drugs

Table 3—Key monitoring and risk mitigation strategies for preferred glucose-lowering agents

Medication	Consideration	Monitoring and/or risk mitigation strategies
Metformin	Metformin-associated lactic acidosis	• Monitor eGFR with increasing frequency as eGFR falls to <60 mL/min/1.73 m^2 • Adjust metformin dose as appropriate per eGFR (see Table 4) • Consider dose reduction in the presence of conditions that predispose patients to hypoperfusion and hypoxemia for eGFR 45–59 mL/min/1.73 m^2 • Discontinue for eGFR <30 mL/min/1.73 m^2 • Institute a sick day protocol
	B_{12} malabsorption	• Monitor patients for vitamin B_{12} deficiency when treated with metformin for >4 years
SGLT2i	Genital mycotic infections	• Counsel on genital hygiene
	Volume depletion	• Monitor for hypovolemia and consider proactive dose reduction of diuretics in patients at high risk • Hold SGLT2i during illness
	Diabetic ketoacidosis	• Educate about signs/symptoms to facilitate early recognition • Monitor blood or urine ketones in the case of very high risk • Institute a sick day protocol • Maintain at least low-dose insulin in insulin-requiring individuals
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate
GLP-1 receptor agonists	Nausea/vomiting/diarrhea	• Educate on tolerability and symptom recognition • Start at lowest recommended dose and titrate slowly
	Hypoglycemia	• Adjust background glucose-lowering agents (e.g., insulin or sulfonylureas) as appropriate

eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

2. Glycemic control

- Dose reduction of oral antidiabetic drugs according to eGFR

Table 4—Dose adjustments for eGFR <45 mL/min/1.73 m² (information presented reflects the package inserts rather than guidance from this consensus report)

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡		Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

*Glucose-lowering efficacy is reduced with SGLT2i as eGFR declines, but kidney and cardiovascular benefits are preserved. †Dapagliflozin is approved for use at 10 mg once daily with an eGFR of 25 to <45 mL/min/1.73 m². ‡Initiation not recommended with eGFR <30 mL/min/1.73 m² for glycemic control or <20 mL/min/1.73 m² for HF. Higher dose can be used but is not effective for glucose lowering and does not offer further clinical benefit in this range of eGFR. §Dulaglutide, liraglutide, and injectable semaglutide have demonstrated evidence of cardiovascular benefit in large cardiovascular outcome trials. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

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1. Treatment with a comprehensive plan
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4. Lipid control

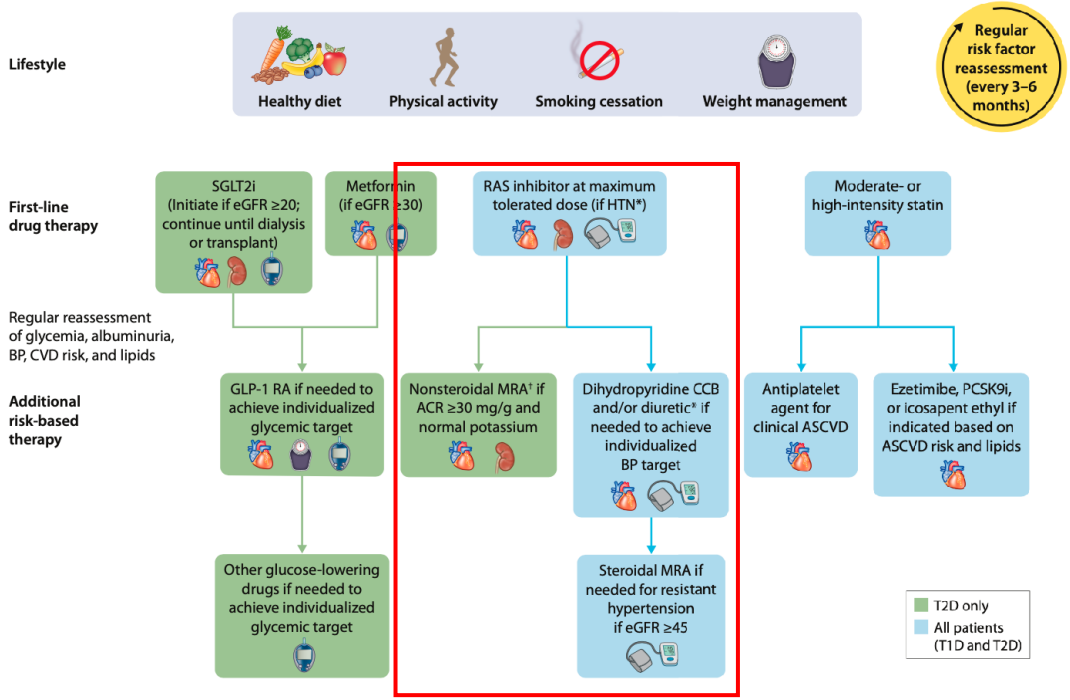

Figure 3—Holistic approach for improving outcomes in patients with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

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3. Blood pressure control

RAAS-Inhibitor (ACE-I / ARB):

In patients with:
- hypertension &
- DM (type 1 or 2) &
- Albuminuria
  - ≥ 300mg/g

    → Prevention of CKD progression
  - < 300 mg/g

    → Reduce progression to more pronounced albuminuria

    → Reduction of cardiovascular events

    →But NO reduction of progression to kidney failure

Ca-Antagonist / Diuretic agent:

In combination with RAAS-inhibition

Mineralcorticoid receptor antagonist:

A) Steroidal MRA:
- In resistant hypertension
- Primary hyperaldosteronism
- HF with reduced EF

B) Non-steroidal MRA:
- In patients with CKD & DM type 2 & RAAS-Inhibition

  → Slows CKD progression

  → Reduces cardiovascular events

Blood pressure target:
- Diabetes, hypertension & high cv risk: < 130/80 mmHg
- Diabetes, hypertension & low cv risk: < 140/90 mmHg
- KDIGO 2021: all patients < 120 mmHg systolic if tolerated

3. Blood pressure control - Finerenone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bakris at the Department of Medicine, University of Chicago, 5841 S. Maryland Ave., MC 1027, Chicago, IL 60637, or at gbakris@gmail.com.

*A complete list of the FIDELIO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2025845

= FIDELIO-DKD

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3. Blood pressure control - Finerenone

Reduction of:

- Progression of CKD
- Cardiovascular endpoints

- RRR: 18%
- ARR: 3.3%
- NNT: 30

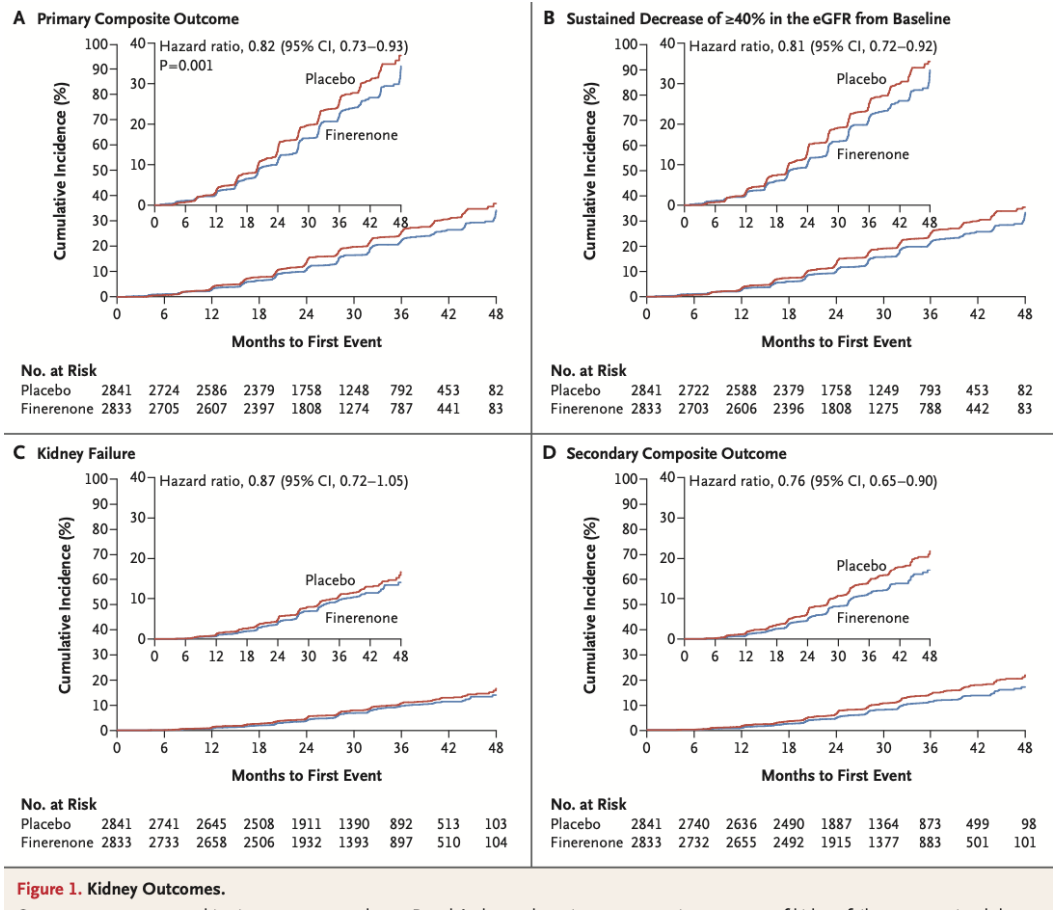

Figure 1. Kidney Outcomes.

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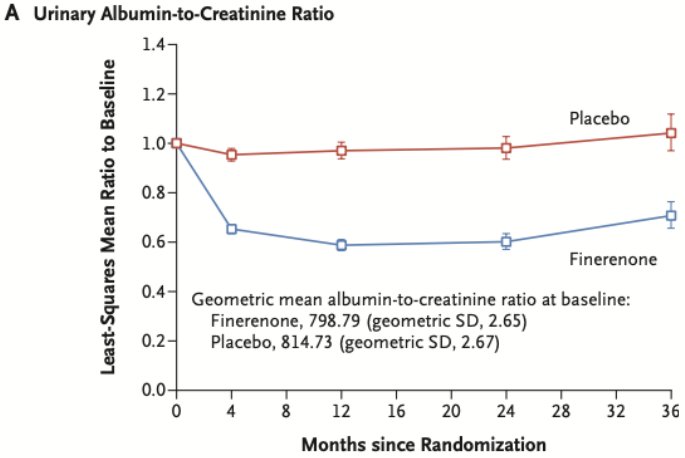
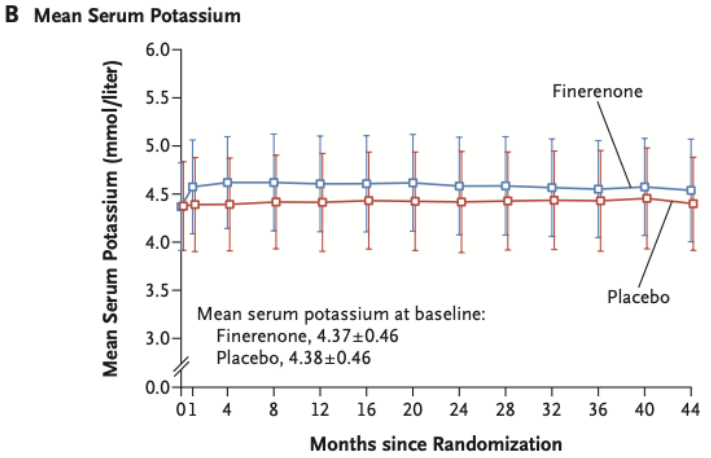
3. Blood pressure control - Finerenone



No. of Patients						
Finerenone	2831	2725	2582	1841	85(	
Placebo	2840	2726	2598	1825	83-	
Mean Change from Baseline (percent)						
Finerenone	Ref.	−34.7	−41.3	−39.9	−29	
Placebo	Ref.	−4.7	−3.0	−2.0	4	



No. of Patients						
Finerenone	2827	2708	2600	1872	882	344
Placebo	2831	2709	2596	1865	862	348
Mean Change from Baseline (mmol/liter)						
Finerenone	Ref.	0.25	0.24	0.21	0.21	0.20
Placebo	Ref.	0.02	0.04	0.05	0.07	0.07

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3. Blood pressure control - Finerenone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Pitt at the Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI 48109, or at bpitt@med.umich.edu.

*A complete list of the FIGARO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Pitt and Filippatos contributed equally to this article.

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= FIGARO-DKD

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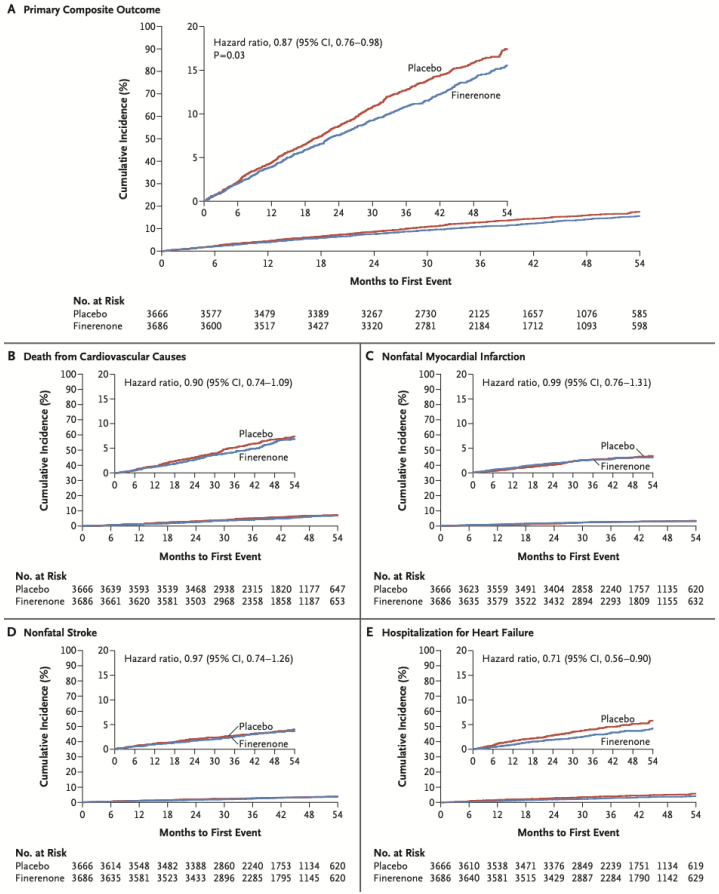
3. Blood pressure control - Finerenone

Reduction of:

- Progression of CKD
- Cardiovascular endpoints

- RRR: 13%
- ARR: 1.8%
- NNT: 56



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3. Blood pressure control - Finerenone

In summary, FIDELIO-DKD & FIGARO-DKD demonstrated:

- Cardiovascular and kidney benefits for finerenone among people with DM type 2
- Who were treated with standard of care
- Who were at high risk based on albuminuria ≥ 30 mg/g

Indication of Finerenone:

- eGFR ≥ 25 ml/min
- Serum potassium ≤ 5 mmol/l
- Albuminuria ≥ 30 mg/g
- Despite maximum tolerated RAAS-inhibitor

Consensus Statements

1. Treatment with a comprehensive plan

2. Glycemic control

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4. Lipid control

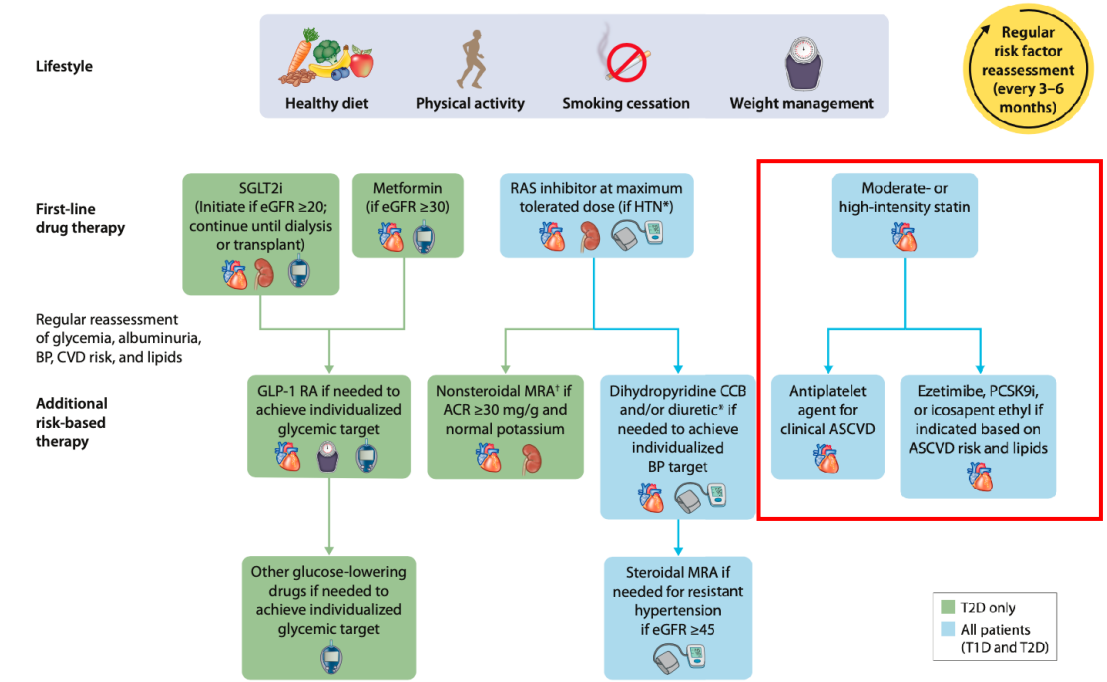

Figure 3—Holistic approach for improving outcomes in patients with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucometer, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. *ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only ns-MRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, GLP-1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

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4. Lipid control

Statin:

Primary prevention:
- All patients with DM (type 1& 2) & aged 40 – 75 years
- Patients aged 20– 39 years and additional ASCVD risk factors

Secondary prevention:
- All patients with known ASCVD

Ezetimibe:

Primary prevention:
- High ASCVD risk and LDL cholesterol above target despite statin therapy

PCSK-9-inhibitor:

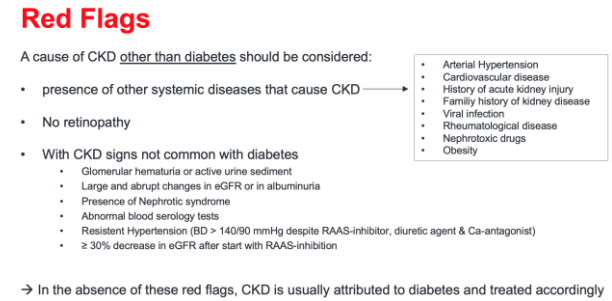
Primary prevention:
- High ASCVD risk and LDL cholesterol above target despite statin therapy

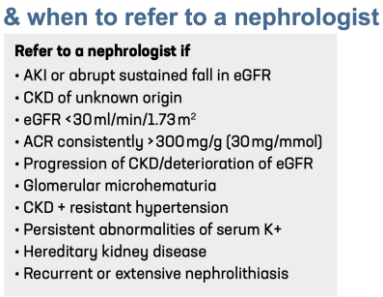
Summary & Pocket Guide (page 7)

Spätkomplik: **„Legacy“ d (initial) guten HbA1c! Labor Krea** (Clearance), **Lipide, Leberenzyme** (NAFLD / NASH, p9), Harnsäure
- Mikroangiop.: Retinop.: Ophtalmologe (privat, Konsil) n 20J 90% Dm1 (prolif) & 70% Dm2 (exsudativ) ⇒Makulaödem:**Lucentis (VGEF)**
Nephrop.: Alb/Krea iU 2. Morgenurin, falls 2x ↑ ⇒ **ACEH**, GFR_{calc}<40ml/'⇒ad Nephro (cvRF behandeln va optimale BD-Th, Nahrungseiweiss <0.8g/kg/d, Hkt 34-36%, Harnsre <300uM; keine NSAID), **Ko:** Dm 2 Ko 6mtl, Dm 1 Ko ab 5j;
Alb/krea↑ ohne Dm va b adip. M >50j, rauchen ⇒ unabh. cvRF; DD: HWI, Orthostase, Arbeit, Amyloidose

Diabetic Kidney Disease (DKD):

- urinary ACR 2x elevated OR GFR < 60 ml/min over 3 months
- RAAS-I & SGLT2-I (& Finerenone)
- link „Red Flags for other causes“
- link „when to refer to Nephrologist“
- link the ADA/KDIGO consensus statements





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Comparison between

SGLT2-Inhibitor:

Canagliflozin (CREDENCE-trial):
- RRR: 30%
- ARR: 4.4%
- NNT: 22

Dapagliflozin (DAPA-CKD):
- RRR: 39%
- ARR: 5.3%
- NNT: 19

Empagliflozin (EMPA-KIDNEY):
- RRR: 28%
- ARR: 3.8%
- NNT: 26

&

Finerenone:

FIDELIO-DKD:
- RRR: 18%
- ARR: 3.3%
- NNT: 30

regarding kidney endpoints

Figure S3. Primary composite renal outcome according to key prespecified subgroups

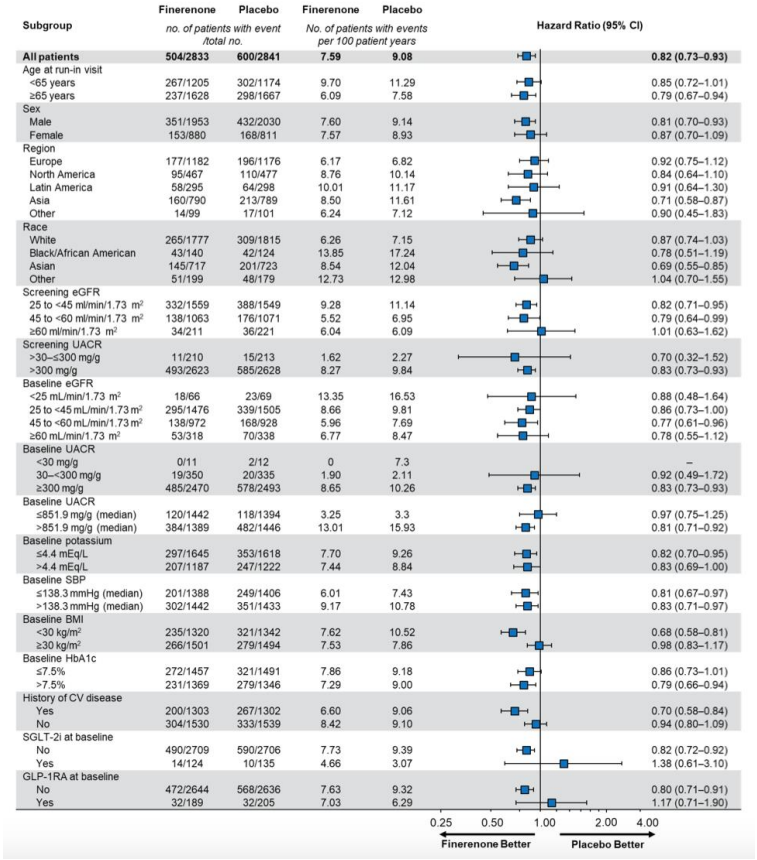

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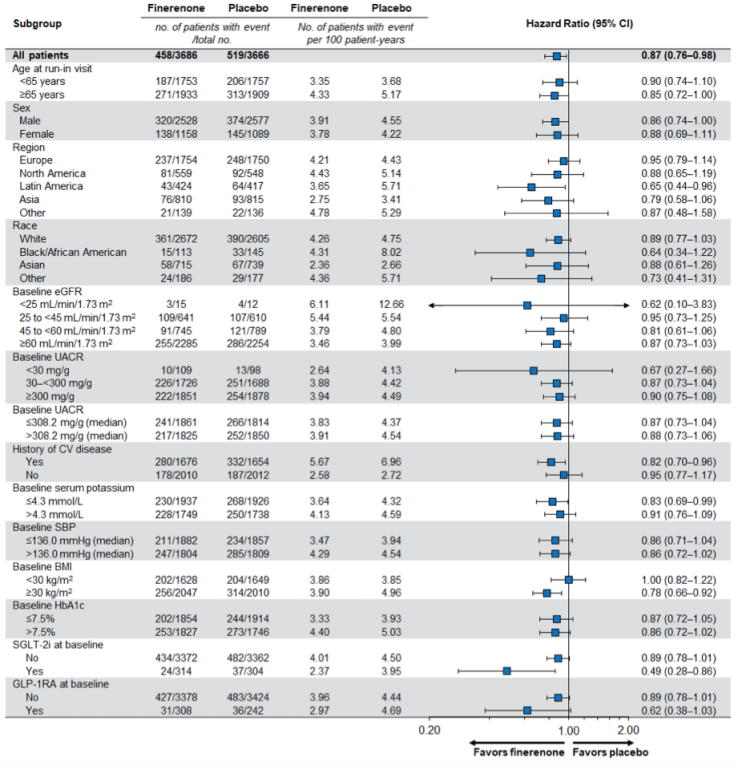
Figure S5. Primary Composite Cardiovascular Outcome According to Key Prespecified Subgroups



Subgroup	Finerenone no. of patients with event /total no.	Placebo no. of patients with event /total no.	Finerenone No. of patients with event per 100 patient-years	Placebo No. of patients with event per 100 patient-years	Hazard Ratio (95% CI)
All patients	**458/3686**	**519/3666**			**0.87 (0.76–0.98)**
Age at run-in visit					
<65 years	187/1753	206/1757	3.35	3.68	0.90 (0.74–1.10)
≥65 years	271/1933	313/1909	4.33	5.17	0.85 (0.72–1.00)
Sex					
Male	320/2528	374/2577	3.91	4.55	0.86 (0.74–1.00)
Female	138/1158	145/1089	3.78	4.22	0.88 (0.69–1.11)
Region					
Europe	237/1754	248/1750	4.21	4.43	0.95 (0.79–1.14)
North America	81/559	92/548	4.43	5.14	0.88 (0.65–1.19)
Latin America	43/424	64/417	3.65	5.71	0.65 (0.44–0.96)
Asia	76/810	93/815	2.75	3.41	0.79 (0.58–1.06)
Other	21/139	22/136	4.78	5.29	0.87 (0.48–1.58)
Race					
White	361/2672	390/2605	4.26	4.75	0.89 (0.77–1.03)
Black/African American	15/113	33/145	4.31	8.02	0.64 (0.34–1.22)
Asian	58/715	67/739	2.36	2.66	0.88 (0.61–1.26)
Other	24/186	29/177	4.36	5.71	0.73 (0.41–1.31)
Baseline eGFR					
<25 mL/min/1.73 m²	3/15	4/12	6.11	12.66	0.62 (0.10–3.83)
25 to <45 mL/min/1.73 m²	109/641	107/610	5.44	5.54	0.95 (0.73–1.25)
45 to <60 mL/min/1.73 m²	91/745	121/789	3.79	4.80	0.81 (0.61–1.06)
≥60 mL/min/1.73 m²	255/2285	286/2254	3.46	3.99	0.87 (0.73–1.03)
Baseline UACR					
<30 mg/g	10/109	13/98	2.64	4.13	0.67 (0.27–1.66)
30–<300 mg/g	226/1726	251/1688	3.88	4.42	0.87 (0.73–1.04)
≥300 mg/g	222/1851	254/1878	3.94	4.49	0.90 (0.75–1.08)
Baseline UACR					
≤308.2 mg/g (median)	241/1861	266/1814	3.83	4.37	0.87 (0.73–1.04)
>308.2 mg/g (median)	217/1825	252/1850	3.91	4.54	0.88 (0.73–1.06)
History of CV disease					
Yes	280/1676	332/1654	5.67	6.96	0.82 (0.70–0.96)
No	178/2010	187/2012	2.58	2.72	0.95 (0.77–1.17)
Baseline serum potassium					
≤4.3 mmol/L	230/1937	268/1926	3.64	4.32	0.83 (0.69–0.99)
>4.3 mmol/L	228/1749	250/1738	4.13	4.59	0.91 (0.76–1.09)
Baseline SBP					
≤136.0 mmHg (median)	211/1882	234/1857	3.47	3.94	0.86 (0.71–1.04)
>136.0 mmHg (median)	247/1804	285/1809	4.29	4.54	0.86 (0.72–1.02)
Baseline BMI					
<30 kg/m²	202/1628	204/1649	3.86	3.85	1.00 (0.82–1.22)
≥30 kg/m²	256/2047	314/2010	3.90	4.96	0.78 (0.66–0.92)
Baseline HbA1c					
≤7.5%	202/1854	244/1914	3.33	3.93	0.87 (0.72–1.05)
>7.5%	253/1827	273/1746	4.40	5.03	0.86 (0.72–1.02)
SGLT-2i at baseline					
No	434/3372	482/3362	4.01	4.50	0.89 (0.78–1.01)
Yes	24/314	37/304	2.37	3.95	0.49 (0.28–0.86)
GLP-1RA at baseline					
No	427/3378	483/3424	3.96	4.44	0.89 (0.78–1.01)
Yes	31/308	36/242	2.97	4.69	0.62 (0.38–1.03)

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