ΚΛΙΝΙΚΟ ΦΡΟΝΤΙΣΤΗΡΙΟ

Θεραπευτικές επιλογές/ διλήμματα στον ασθενή με ΣΔτ2

Ο ασθενής με Χρόνια Νεφρική Νόσο

Παπαδοκωστάκη Ελένη MSc, PhD (c)
Παθολόγος με εξειδίκευση στον Σακχαρώδη Διαβήτη,
Επιμ. Β’ Παθολογική κλινική ΠΑΓΝΗ

ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ

Ασθενής 62 ετών έχει ιστορικό ΣΔτ2 από 10 ετίας υπο αγωγή με μετφορμίνη/σιταγλιπτίνη 1000/50 mg/dl 1x2, Αρτηριακή Υπέρταση υπό Ιρμπερσαρτάνη 150 mg 1x1, Δυσλιπιδαιμία υπό Ατορβαστατίνη 40 mg

Κλινική εξέταση

Παχυσαρκία ΔΜΣ 31kg/m^2

ΑΠ 145/94 mmHg σφ 75

Εργαστηριακός έλεγχος: Hct 41, HbA1c 8% κρεατινίνη 1,5 mg/dl, LDL 65 mg/dl, γενική ούρων ερυθρά (-),πυοσφαίρια (-), λεύκωμα (+)

Ερώτηση: Έχει ο ασθενής Χρόνια νεφρική νόσο?

1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (*Not Graded*)

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

The American Society of Nephrology and National Kidney Foundation advocate using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate glomerular filtration rate (GFR) from creatinine, age, and sex

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m^2) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Εκτίμηση λευκωματουρίας

Δεν είναι απαραίτητη η 24ωρη συλλογή ούρων

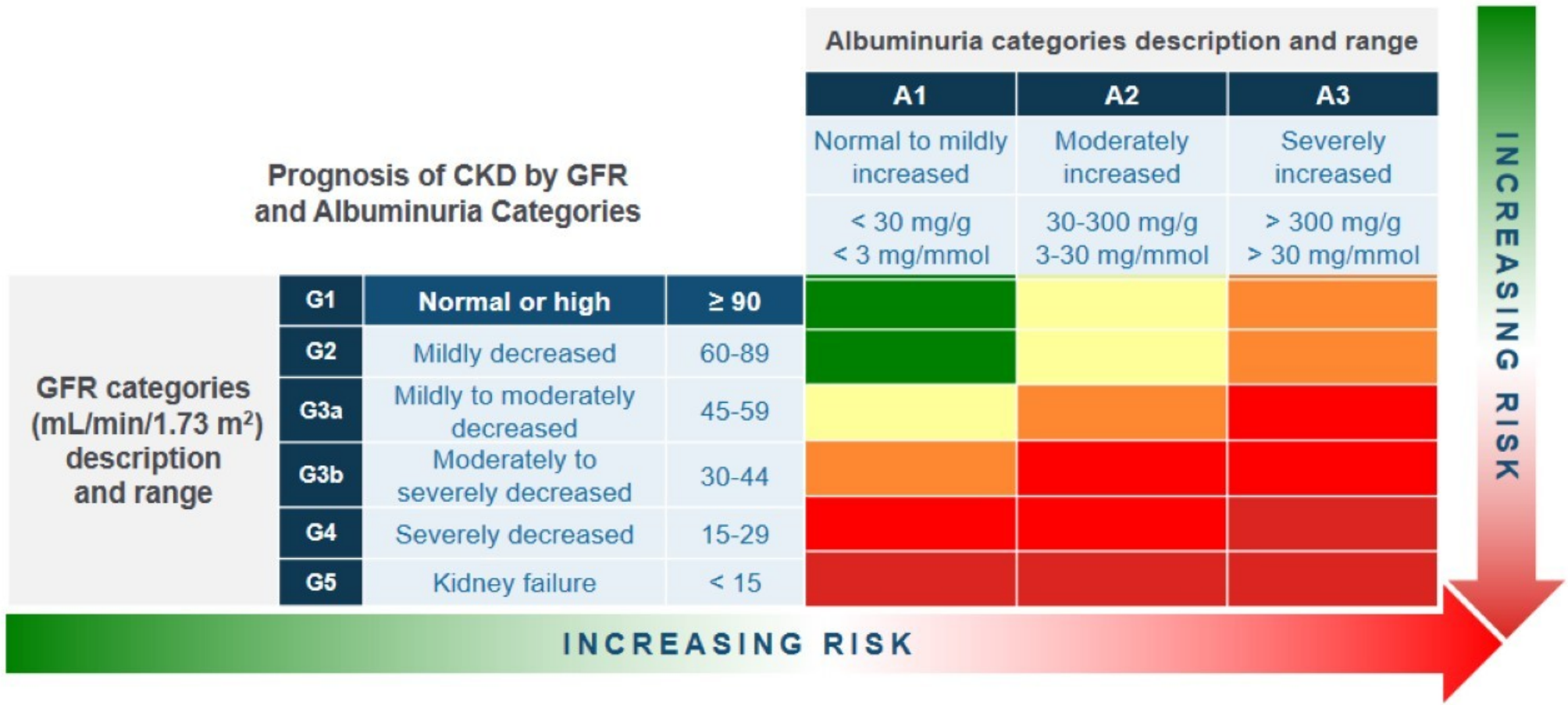
Σε τυχαίο δείγμα ούρων προσδιορίζεται ο λόγος αλβουμίνη προς κρεατινίνη (Albumin to creatinine ratio, ACR)

Για να τεκμηριωθεί η διάγνωση της λευκωματουρίας θα πρέπει να υπάρχουν δυο θετικά δείγματα σε διάστημα 3-6 μηνών.

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased

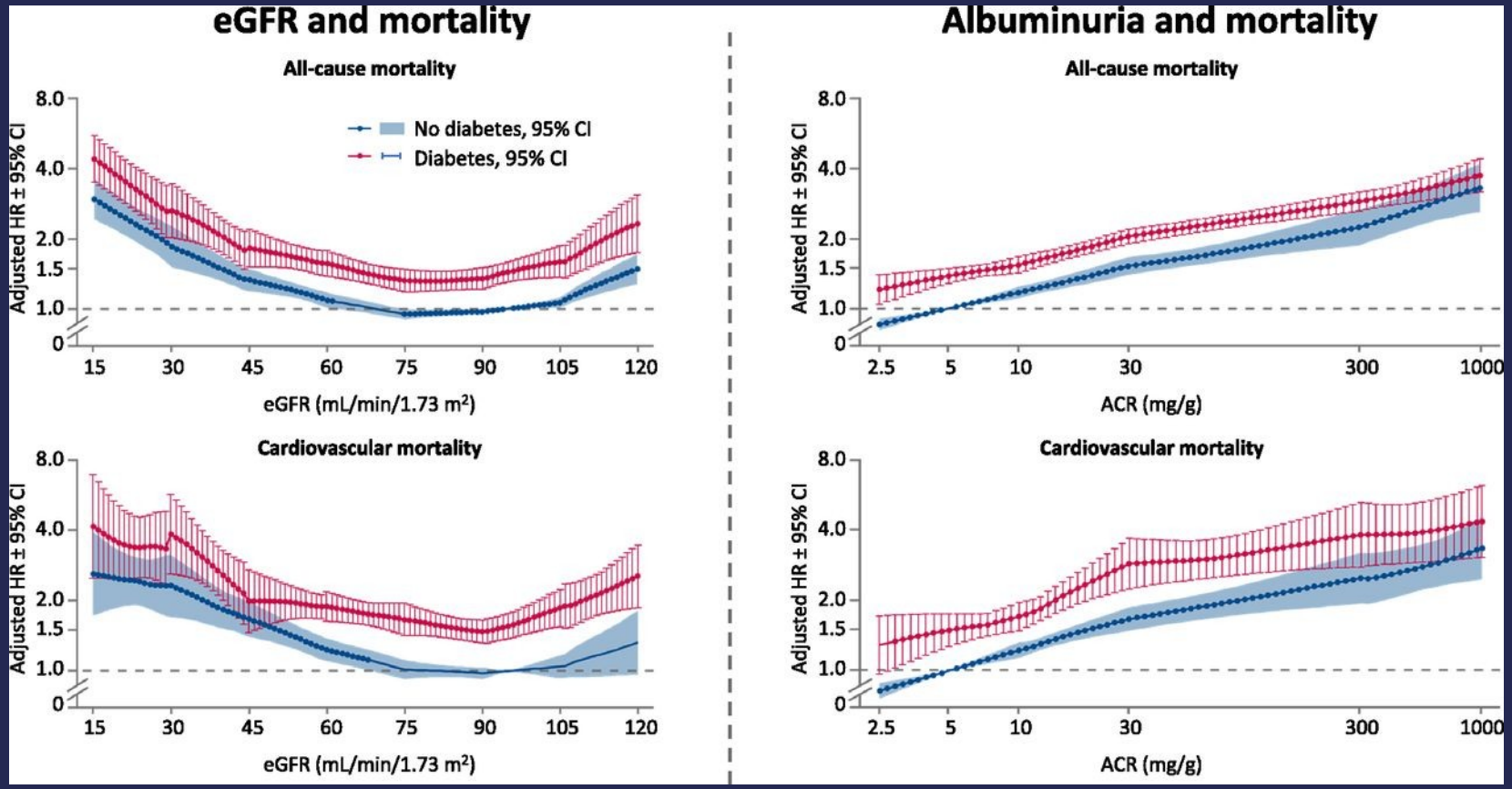
*Relative to young adult level
ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease

Prognosis of CKD by GFR and Albuminuria Categories



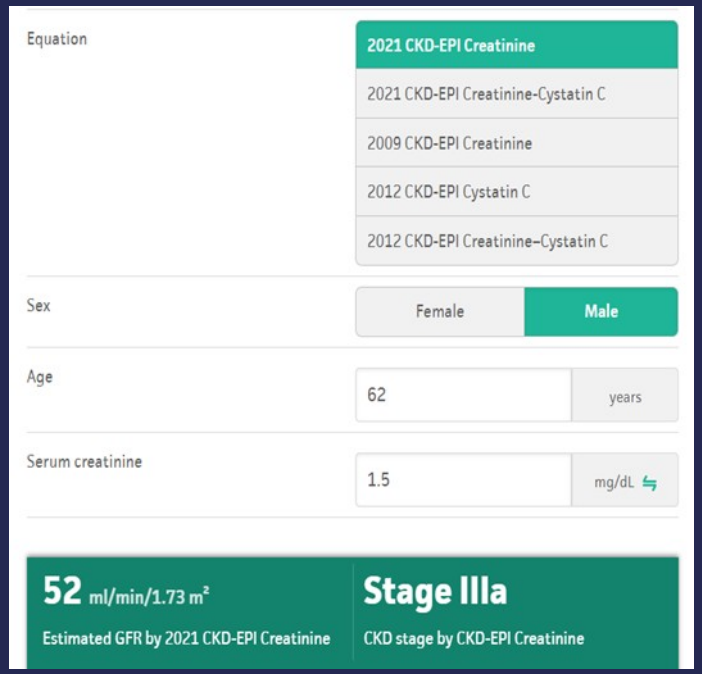
A, albuminuria; G, grade.
GFR and albuminuria grid to reflect the progression by intensity of coloring (green, yellow, red, deep red).
KDIGO. Kidney Int Suppl. 2013;3:1-150.

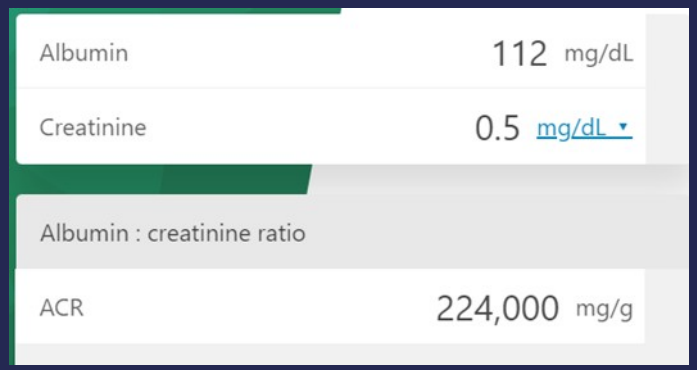
Declining eGFR and increasing albuminuria are associated with mortality in individuals with diabetes.



Peter Rossing et al. Diabetes 2021;70:39-50

Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria.





CKD is classified based on:
- **Cause (C)**
- **GFR (G)**
- **Albuminuria (A)**

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
	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

Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S191-S202

ΔΙΑΒΗΤΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ

Η διαβητική νεφροπάθεια είναι μια μικροαγγειοπαθητική επιπλοκή του διαβήτη που χαρακτηρίζεται από

- σταδιακή αύξηση του ρυθμού αποβολής λευκωματίνης στα ούρα και/ή
- από σταδιακή μείωση του ρυθμού σπειραματικής διήθησης επί απουσίας άλλης νεφρικής νόσου

Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023

ΔΙΑΒΗΤΙΚΗ ΝΕΦΡΟΠΑΘΕΙΑ

Η διαβητική νεφροπάθεια (ΔΝΦ) προσβάλλει περίπου το 20-40% των ασθενών με ΣΔ.

Ο Σακχαρώδης Διαβήτης αποτελεί την πρώτη αιτία τελικού σταδίου νεφρικής ανεπάρκειας.

Η ΔΝΦ τυπικά αναπτύσσεται σε ασθενείς με ΣΔΤ1 μετά από 10 χρόνια διάρκειας της νόσου ενώ μπορεί να είναι παρούσα κατά τη διάγνωση του ΣΔΤ2.

ΟΡΙΣΜΟΣ

Διαβητική νεφροπάθεια: νεφρική νόσος οφειλόμενη στον σακχαρώδη διαβήτη αποδεδειγμένη με βιοψία

Διαβητική νεφρική νόσος (Diabetic kidney disease): πιθανή διάγνωση νεφρικής νόσου που οφείλεται στον σακχαρώδη διαβήτη (κλινικά και εργαστηριακά κριτήρια)

Am J Kidney Dis. 2007 Feb;49(2 Suppl 2):S12-154.

Διάγνωση Διαβητικής Νεφρικής Νόσου

Η διαβητική νεφρική νόσος συνήθως διαγιγνώσκεται κλινικά με βάση την παρουσία αλβουμινουρίας και/ή μειωμένου GFR, απουσία σημείων και συμπτωμάτων άλλης κύριας νεφρικής νόσου.

Η διάγνωση της διαβητικής νεφρικής νόσου τίθεται τυπικά σε έναν ασθενή με μεγάλη διάρκεια της νόσου, συνυπάρχουσα αμφιβληστροειδοπάθεια ,αλβουμινουρία χωρίς αιματουρία και προοδευτική μείωση του ρυθμού σπειραματικής διήθησης.

Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2023

Στοιχεία υπέρ ΜΗ διαβητικής νεφροπάθειας

Παθολογικό ίζημα ούρων (αιματουρία, δύσμορφα ερυθρά, ερυθροκυτταρικοί κύλινδροι)

Απουσία διαβητικής αμφιβληστροειδοπάθειας (ιδίως στον ΣΔΤ1)

Διάρκεια διαβήτη τύπου 1 λιγότερο από 5 έτη

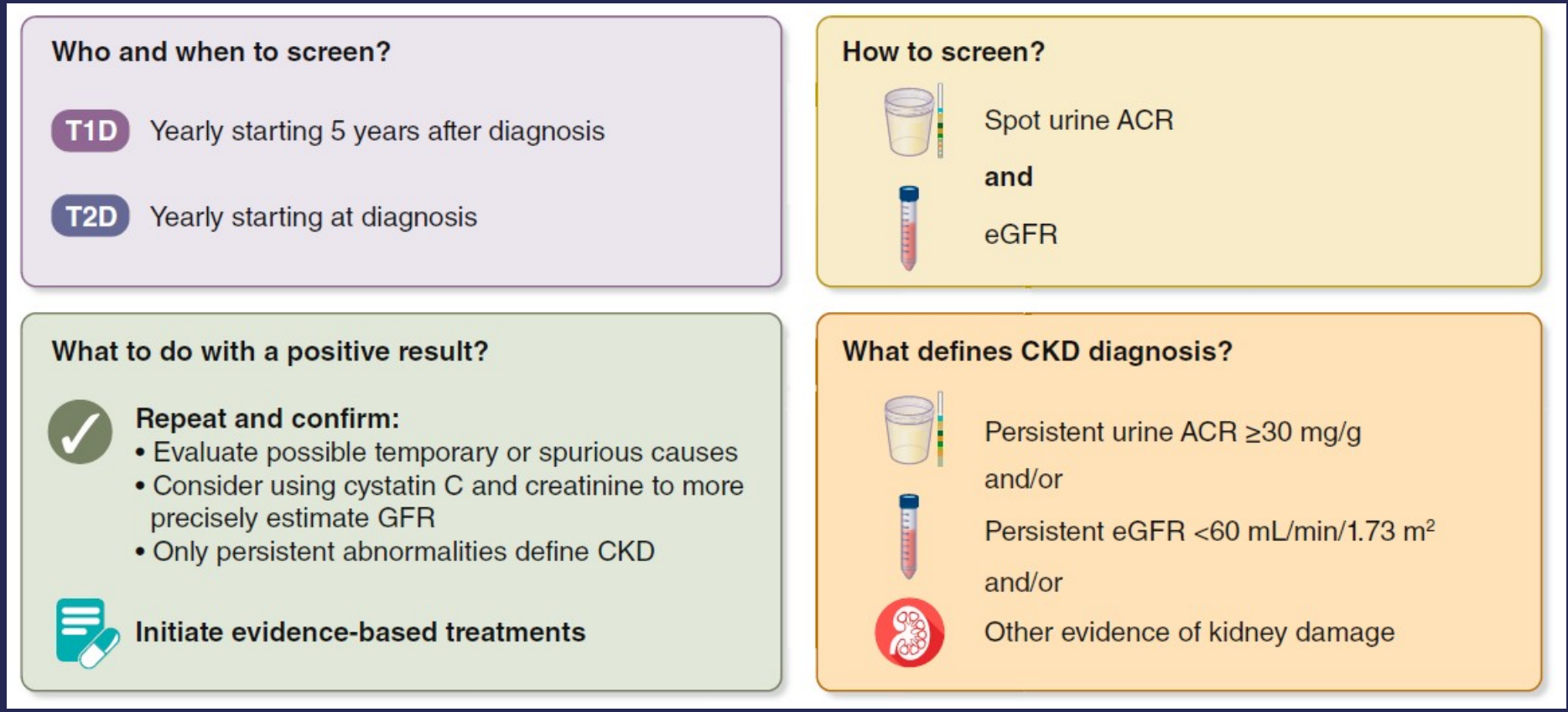
Ταχεία επιδείνωση πρωτεϊνουρίας

Ταχεία άνοδος κρεατινίνης ορού

Αιφνίδια εμφάνιση νεφρωσικού συνδρόμου χωρίς να έχει προηγηθεί το στάδιο της μικρολευκωματινουρίας

Κλινικές εκδηλώσεις συστηματικού νοσήματος

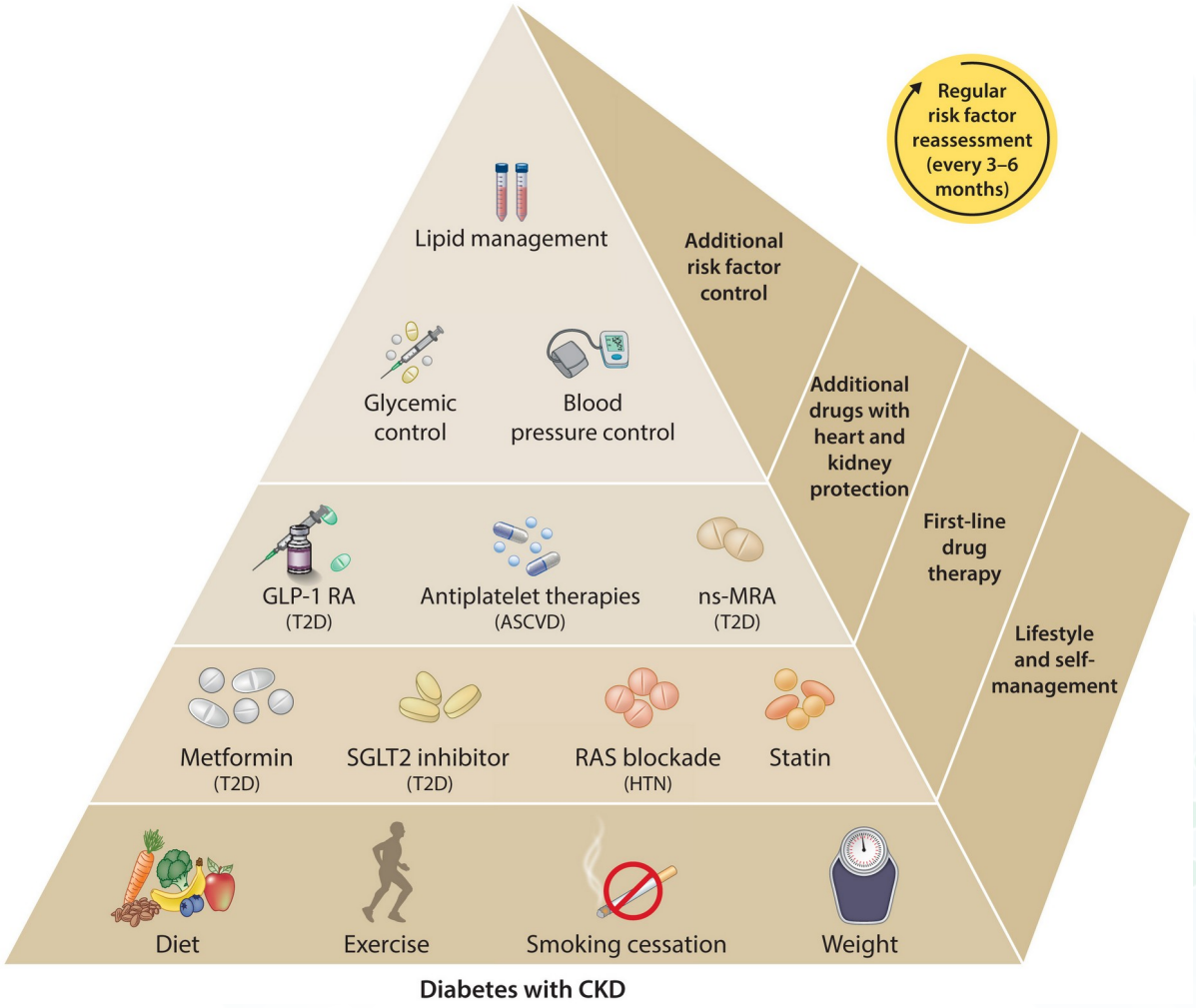
Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO)



doi.org/10.2337/dci22-0027

COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figure 1 and 2).



Chronic Kidney Disease—Treatment

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. A

11.3 Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of chronic kidney disease. A

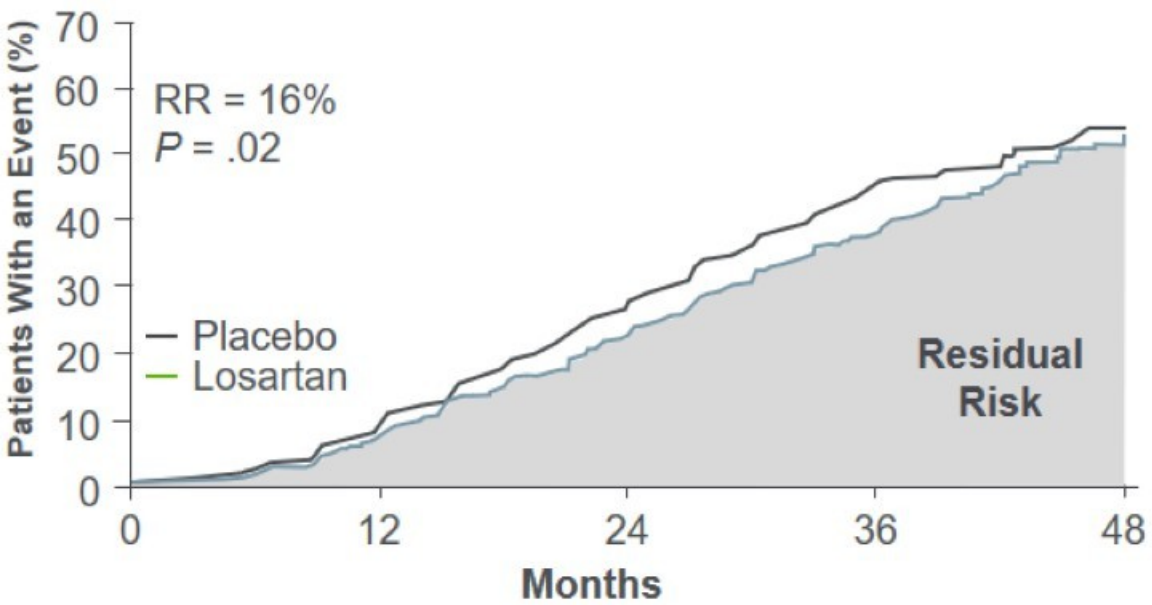
A blood pressure level <130/80 mmHg is recommended to reduce CVD mortality and slow CKD progression among all people with diabetes.

COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated *(1B)*.

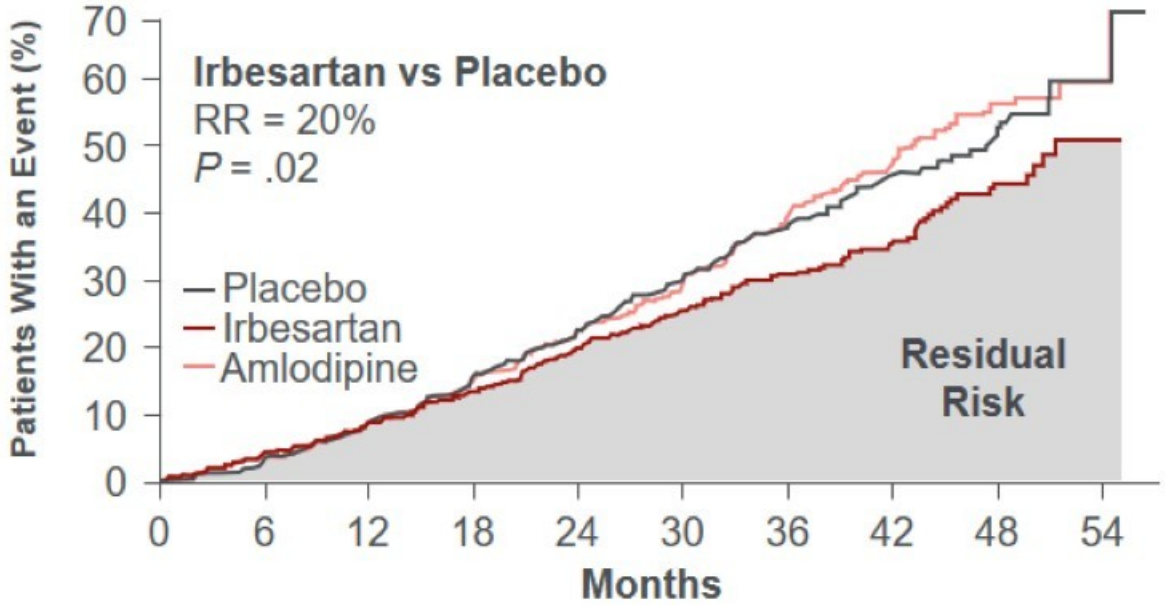
ACEis or ARBs for the Treatment of CKD in T2D

RENAAL: Losartan vs Placebo[a]



Primary composite endpoint:
Doubling of SCr, kidney failure, or death

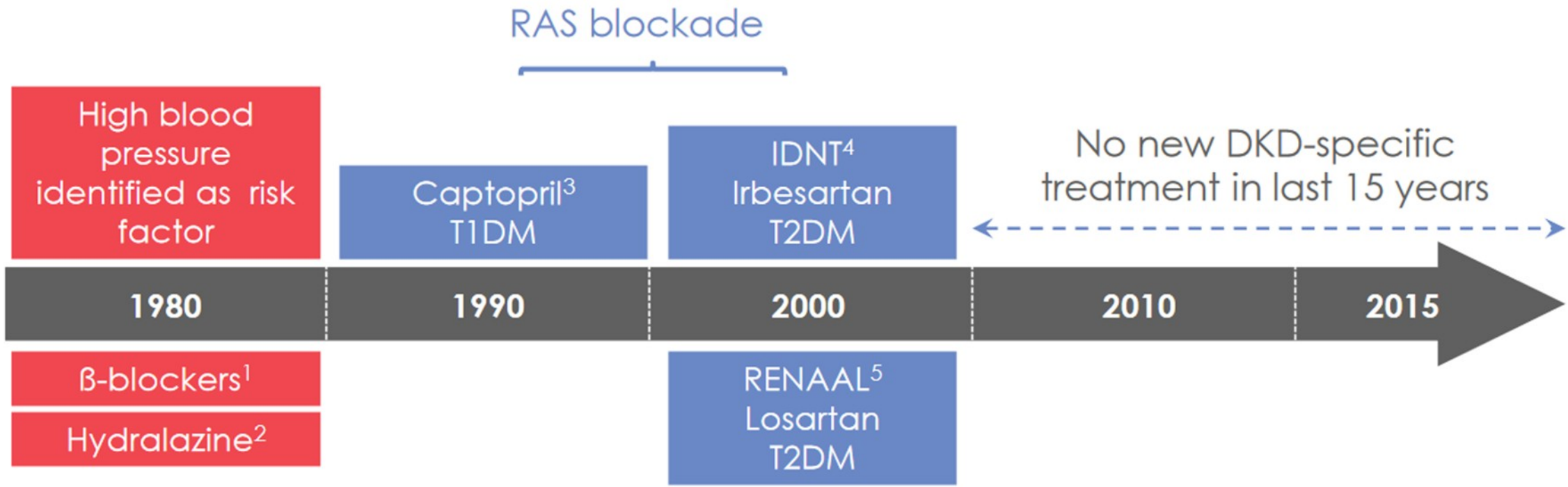
IDNT: Irbesartan vs Amlodipine vs Placebo[b]



Primary composite endpoint:
Doubling of SCr, kidney failure, or death

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; SCr, serum creatine.
a. Brenner BM, et al. N Engl J Med. 2001;345:861-869; b. Lewis EJ, et al. N Engl J Med. 2001;345:851-860.

Medical need in diabetic kidney disease remains high



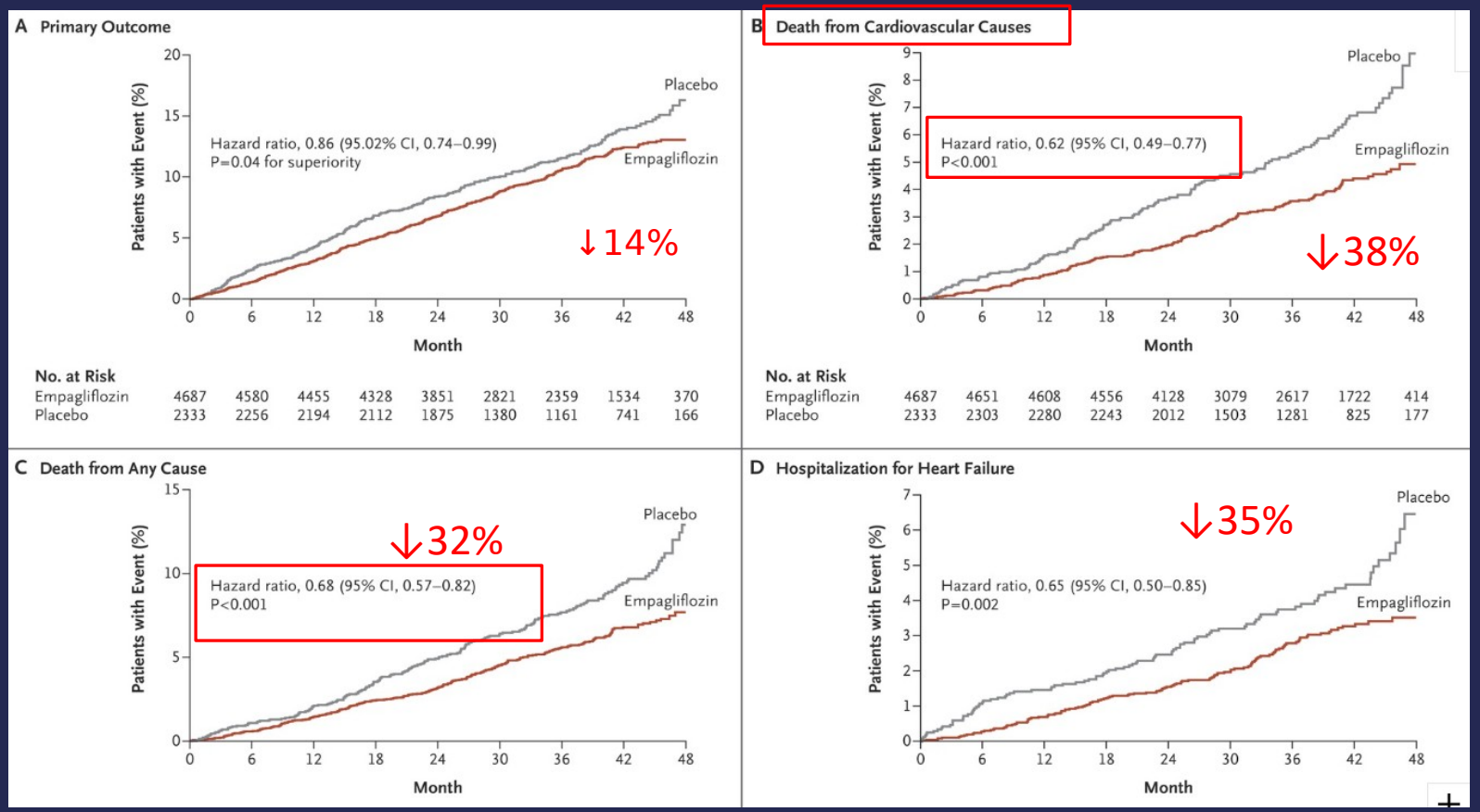
DKD, diabetic kidney disease; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAS, renin-angiotensin system; RENAAL,Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

1. Mogensen CE et al. Br Med J (Clin Res Ed)1982;285:685-8; 2. Parving HH et al. Lancet 1983;1:1175-9;
3. Lewis EJ et al. N Engl J Med 1993;329:1456-62; 4. Lewis EJ et al. N Engl J Med 2001;345:851-60;
5. Brenner BM et al. N Engl J Med 2001;345:861-9.

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D. for the EMPA-REG OUTCOME Investigators

7020 patients, 99% of patients had established cardiovascular disease, median of 3.1 years.



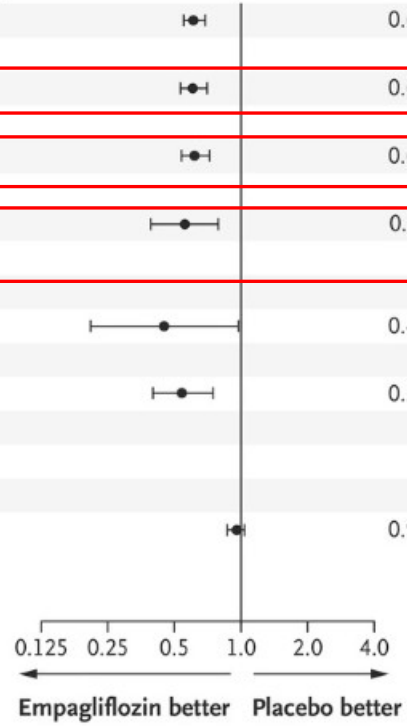
N Engl J Med 2015; 373:2117-2128

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D. for the EMPA-REG OUTCOME Investigators*

the mean GFR 74ml/min, 24% had GFR 30-60ml/min, 28.7% had microalbuminuria, and 11.0% had macroalbuminuria

Renal Outcome Measure	Empagliflozin: *no. with event/ no. analyzed (%)*	Empagliflozin: *rate/1000 patient-yr*	Placebo: *no. with event/ no. analyzed (%)*	Placebo: *rate/1000 patient-yr*	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



N Engl J Med 2016; 375:323-334

CVOTs of SGLT2 Inhibitors *Exploratory Renal Outcomes*

Study	Patient Population	Mean eGFR, mL/min/1.73 m^2	Median UACR, mg/g	Renal Composite	Results
EMPA-REG OUTCOME[a,b]	4124 patients with T2D and established CVD	74	18	Progression to macro-albuminuria; doubling of sCr and eGFR ≤ 45 mL/min/1.73 m^2; ESRD; renal death	46% renal composite reduction 38% reduced progression to macro-albuminuria
CANVAS Program[c,d]	10,142 patients with T2D; ~2/3 with established CVD	76	12.3; 27% with micro-albuminuria	Doubling of sCr; ESRD; renal death	47% renal risk reduction 27% lower albumin progression 42% lower new-onset macro-albuminuria
DECLARE-TIMI 58[e]	17,160 patients with T2D; ~40% with CVD	85	13	≥ 40% loss of eGFR to < 60 mL/min; ESRD; death from CV or renal causes	24% renal risk reduction

- a. Wanner C, et al. *N Engl J Med*. 2016;375:323-334; b. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; c. Perkovic V, et al. *Lancet Diabetes Endocrinol*. 2018;6:691-704; d. Neal B, et al. *N Engl J Med*. 2017;377:644-657; e. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357.

Effects of SGLT2i in people with chronic kidney disease

	CREDENCE[a-c]	DAPA-CKD[d-f]	EMPA-KIDNEY[g-h]
Population	**DIABETIC KIDNEY DISEASE** ✓ T2D x Non-DM x Non-Albuminuric	**PROTEINURIC CHRONIC KIDNEY DISEASE** ✓ T2D ✓ Non-DM x Non-Albuminuric	**CHRONIC KIDNEY DISEASE** ✓ T2D ✓ Non-DM ✓ Non-Albuminuric
No. of patients	4401[b,c]	4304	~6000
Key inclusion criteria	eGFR ≥30 to <90 **and** UACR >300 mg/g	eGFR ≥25 to ≤75 **and** UACR ≥200 mg/g	eGFR ≥20 to <45 **or** eGFR ≥45 to <90 and UACR ≥200 mg/g
Primary composite outcome	ESKD, doubling of creatinine, or renal/ CV death	ESKD, ≥50% sustained eGFR decline, or renal/CV death	ESKD, or ≥40% sustained eGFR decline, or renal/CV death
Study start and stop date (announced or planned)	February 2014 [b] July 2018	February 2017 [d] March 2020	November 2018 [g] ~June 2022*
Results	+ [c] ↓30%	+ [f] ↓39%	+ [g-i] ↓28%

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy- the CREDENCE Trial

4401 patients with t2DM with GFR 30 to <90 ml and ACR >300 to 5000 and were treated with renin–angiotensin system blockage. a median follow-up of 2.62 years

The mean estimated GFR was 56.2 ml per minute per 1.73 m2, and the median ACR was 927

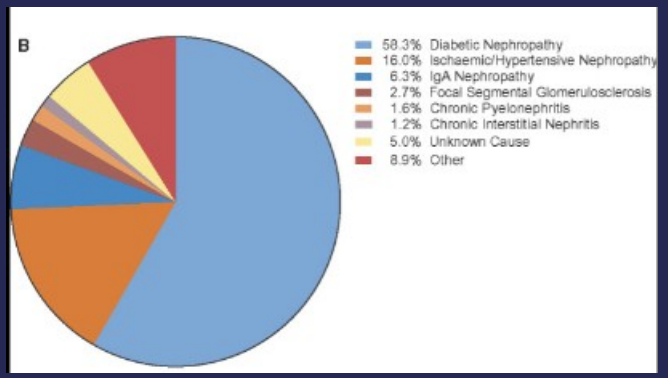
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m^2	78/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05
Secondary outcomes						
Cardiovascular death or hospitalization for heart failure	179/2202	253/2199	31.5	45.4	0.69 (0.57–0.83)	<0.001
Cardiovascular death, myocardial infarction, or stroke	217/2202	269/2199	38.7	48.7	0.80 (0.67–0.95)	0.01
Hospitalization for heart failure	89/2202	141/2199	15.7	25.3	0.61 (0.47–0.80)	<0.001
End-stage kidney disease, doubling of serum creatinine level, or renal death	153/2202	224/2199	27.0	40.4	0.66 (0.53–0.81)	<0.001

N Engl J Med 2019; 380:2295-2306

Dapagliflozin in Patients with Chronic Kidney Disease- the DAPA-CKD Trial

4304 participants with GFR of 25 to 75 ml per minute and a ACR 200 to 5000.

The mean age was 61. The mean estimated GFR was 43.1±12.4 ml per minute per 1.73 m2, the median ACR was 949, and 67.5% of participants had type 2 diabetes. median follow-up was 2.4 years



Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004

N Engl J Med 2020; 383:1436-1446

Empagliflozin in Patients with Chronic Kidney Disease- The EMPA-KIDNEY Collaborative Group

6609 patients with eGFR of at least 20 but less than 45 ml per minute or eGFR of at least 45 but less than 90 ml per minute per 1.73 m2 with ACR at least 200 Median duration of 2.0 years. 54.0% did not have diabetes The eGFR was 37.3±14., and 34.5% of the patients had an eGFR of less than 30 . The median ACR 329, and 48.3% of the patients had a ACR 300 or less

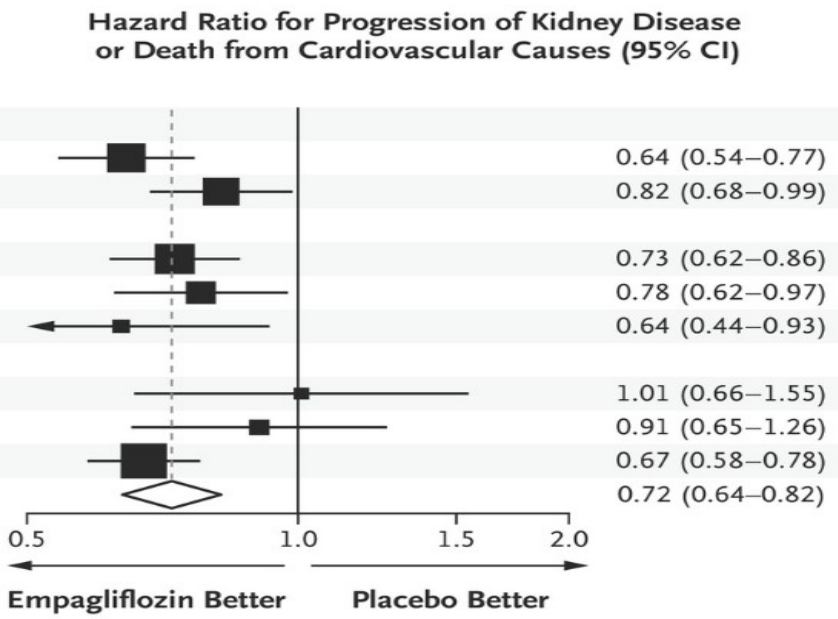
progression of kidney disease defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21
Other secondary outcomes						
Progression of kidney disease	384 (11.6)	6.09	504 (15.2)	8.09	0.71 (0.62–0.81)	
Death from cardiovascular causes	59 (1.8)	0.91	69 (2.1)	1.06	0.84 (0.60–1.19)	
End-stage kidney disease or death from cardiovascular causes§	163 (4.9)	2.54	217 (6.6)	3.40	0.73 (0.59–0.89)	

N Engl J Med 2023; 388:117-127

Empagliflozin in Patients with Chronic Kidney Disease- The EMPA-KIDNEY Collaborative Group

Subgroup	Empagliflozin	Placebo
	no. of patients with event/total no.	
Diabetes mellitus		
Present	218/1525	306/1515
Absent	214/1779	252/1790
Estimated GFR		
<30 ml/min/1.73 m^2	247/1131	317/1151
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461
≥45 ml/min/1.73 m^2	45/706	66/693
Urinary albumin-to-creatinine ratio		
<30	42/665	42/663
≥30 to ≤300	67/927	78/937
>300	323/1712	438/1705
All patients	432/3304	558/3305

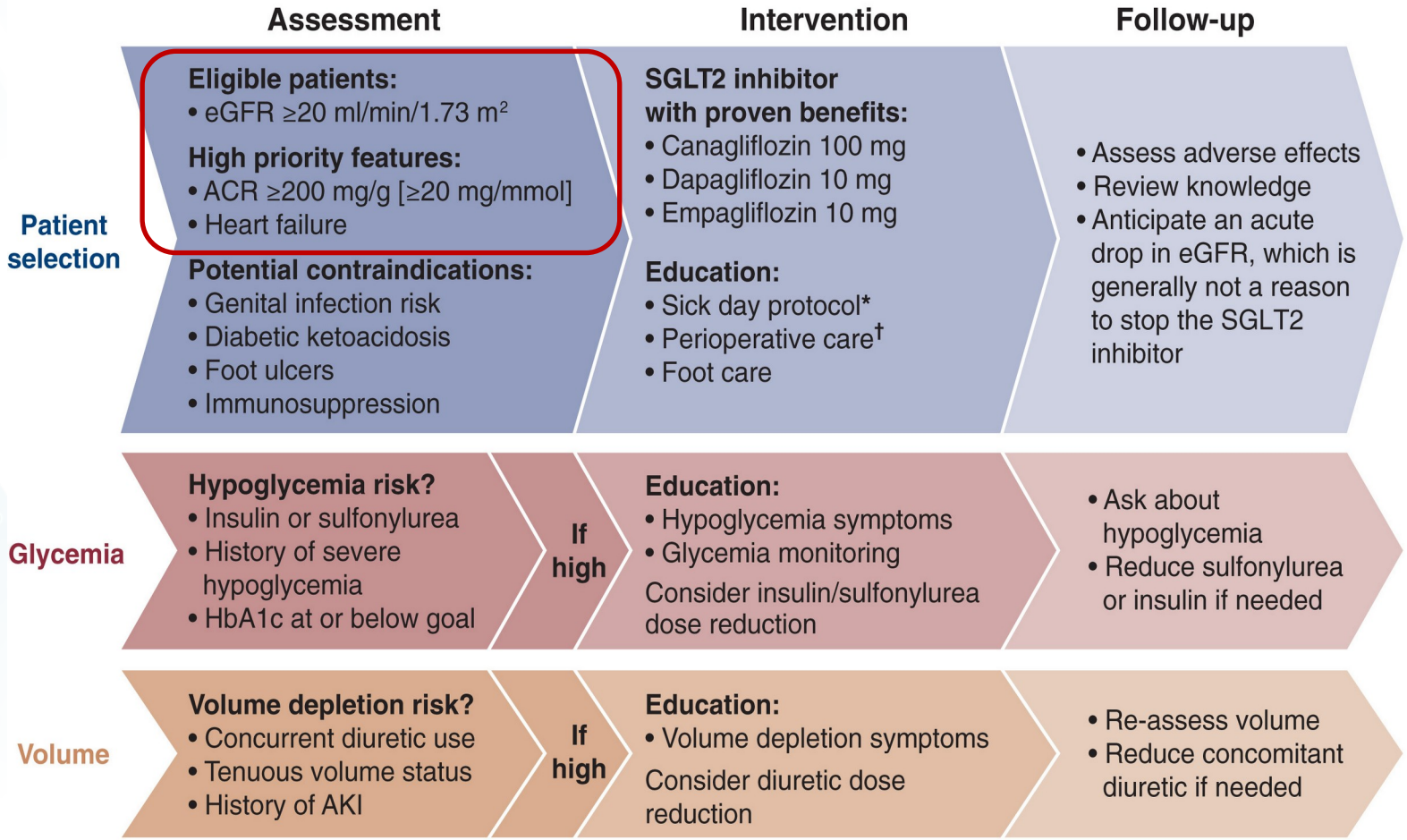


Prespecified exploratory analyses in subgroups showed that the rate of decline after the initial decrease was slower in the empagliflozin group than in the placebo group in all key subgroups, including in the subgroup of patients with a low urinary albumin-to-creatinine ratio.

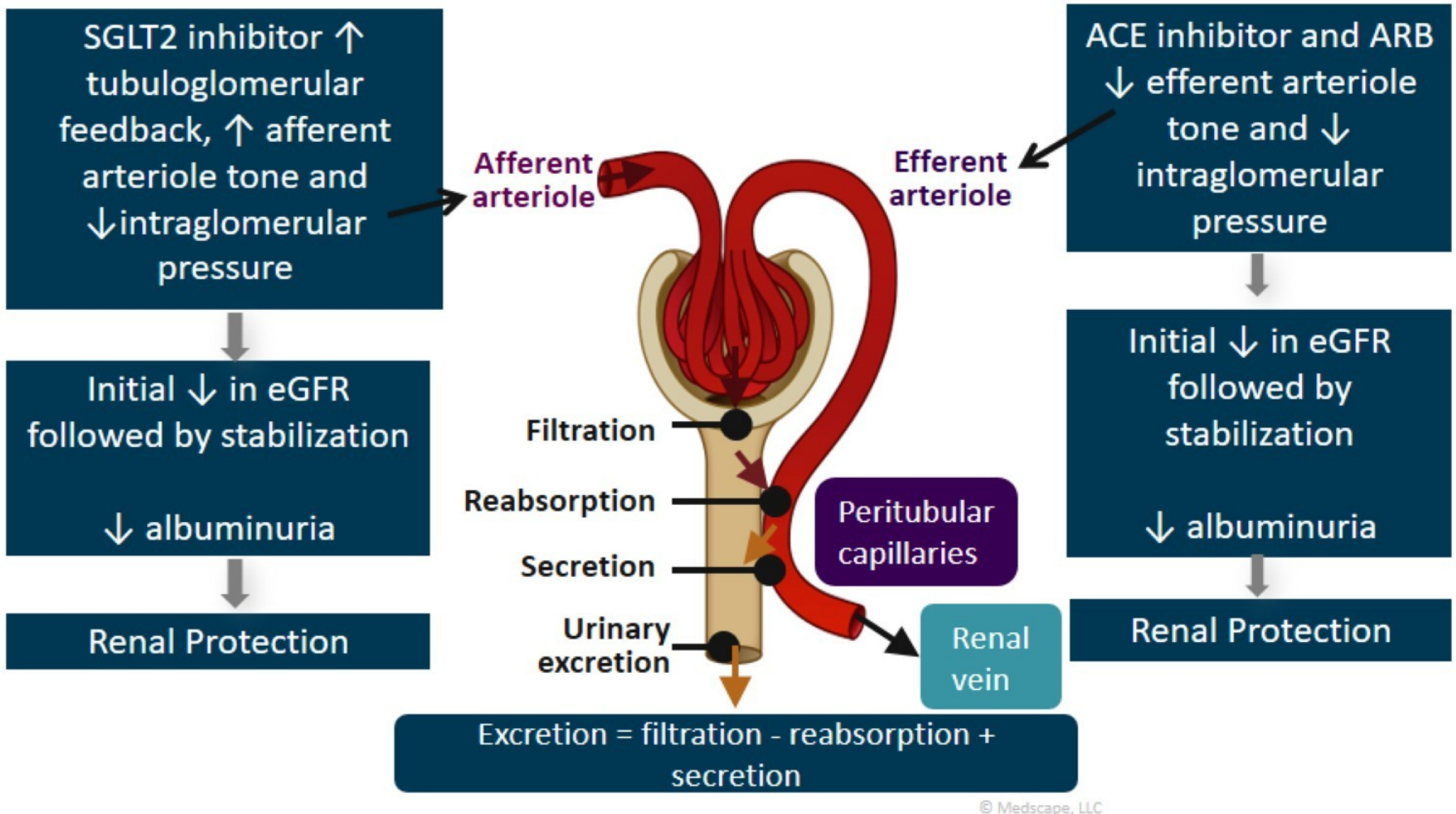
COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i *(1A)*.

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



SGLT2 Inhibition and ACE Inhibition/ARBs Reduce Intraglomerular Pressure



Cherney DZ, et al. *Circulation*. 2014;129:587-597; Perkovic V, et al. *Curr Med Res Opin*. 2015;31:2219-2231.

American Diabetes Association.

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**

Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

USE OF GLUCOSE–LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

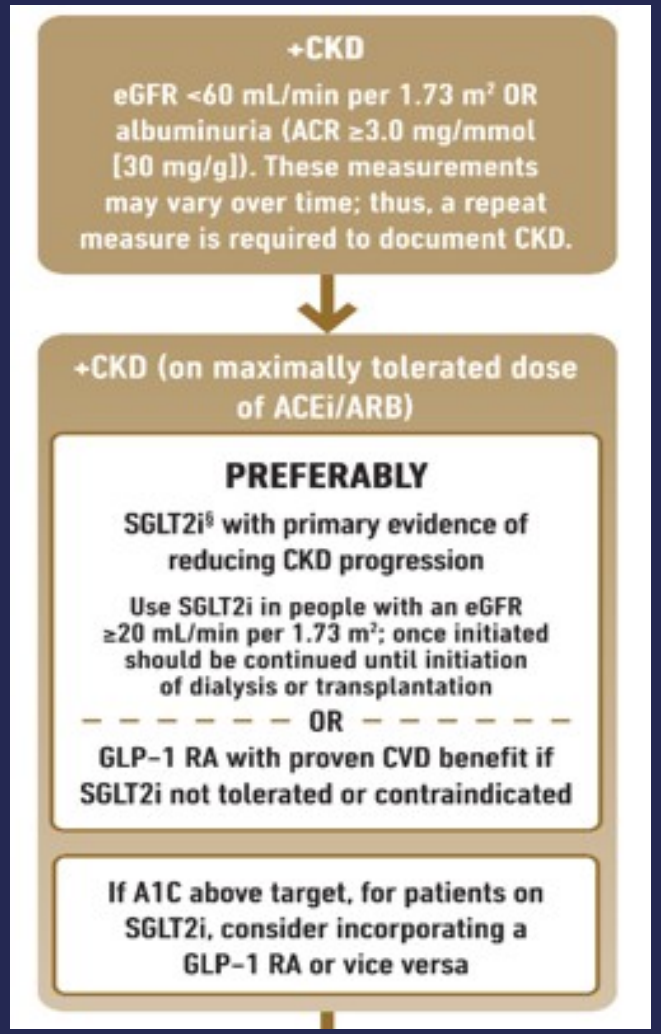
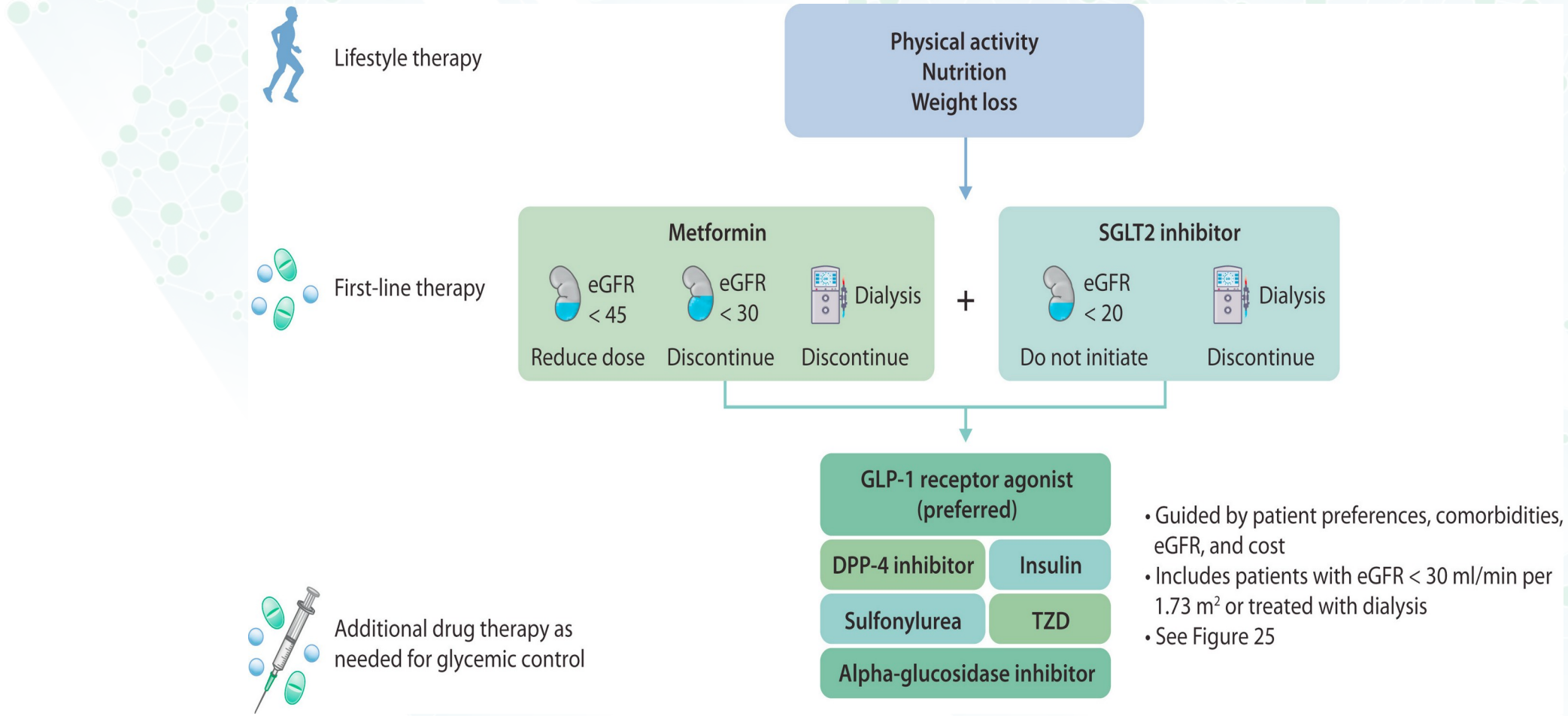


FIGURE 23. TREATMENT ALGORITHM FOR SELECTING GLUCOSE-LOWERING DRUGS FOR PATIENTS WITH T2D AND CKD



GLUCOSE-LOWERING THERAPIES IN PATIENTS WITH DIABETES AND CKD

Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA *(1B)*.

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

GLP-1 RAs and renal outcomes

Liraglutide reduced the risk of new or worsening nephropathy by 22%

N Engl J Med 2016; 375:311-322

Semaglutide reduced the risk of new or worsening nephropathy by 36%

N Engl J Med 2016; 375:1834-1844

Dulaglutide reduced the composite renal outcome by 15%

Lancet 2019; 394: 121–30

nephropathy defined as new onset of persistent macroalbuminuria (>300 mg/g/24hrs), or persistent doubling of serum creatinine level and creatinine clearance ≤45 mL/min/1.73m2, or the need for continuous renal-replacement therapy (in the absence of an acute reversible cause), or death due to renal disease

The renal benefit of GLP-1RA was almost entirely driven by reduction in albuminuria and not by hard renal endpoints such as decline in eGFR, ESRD or kidney-related death.

Ο ασθενής μας…

Τιτλοποίηση ιρμπεσαρτάνης σε 300mg x1, προσθήκη αμλοδιπίνης 5 mg x1

Διατήρηση μετφορμίνης

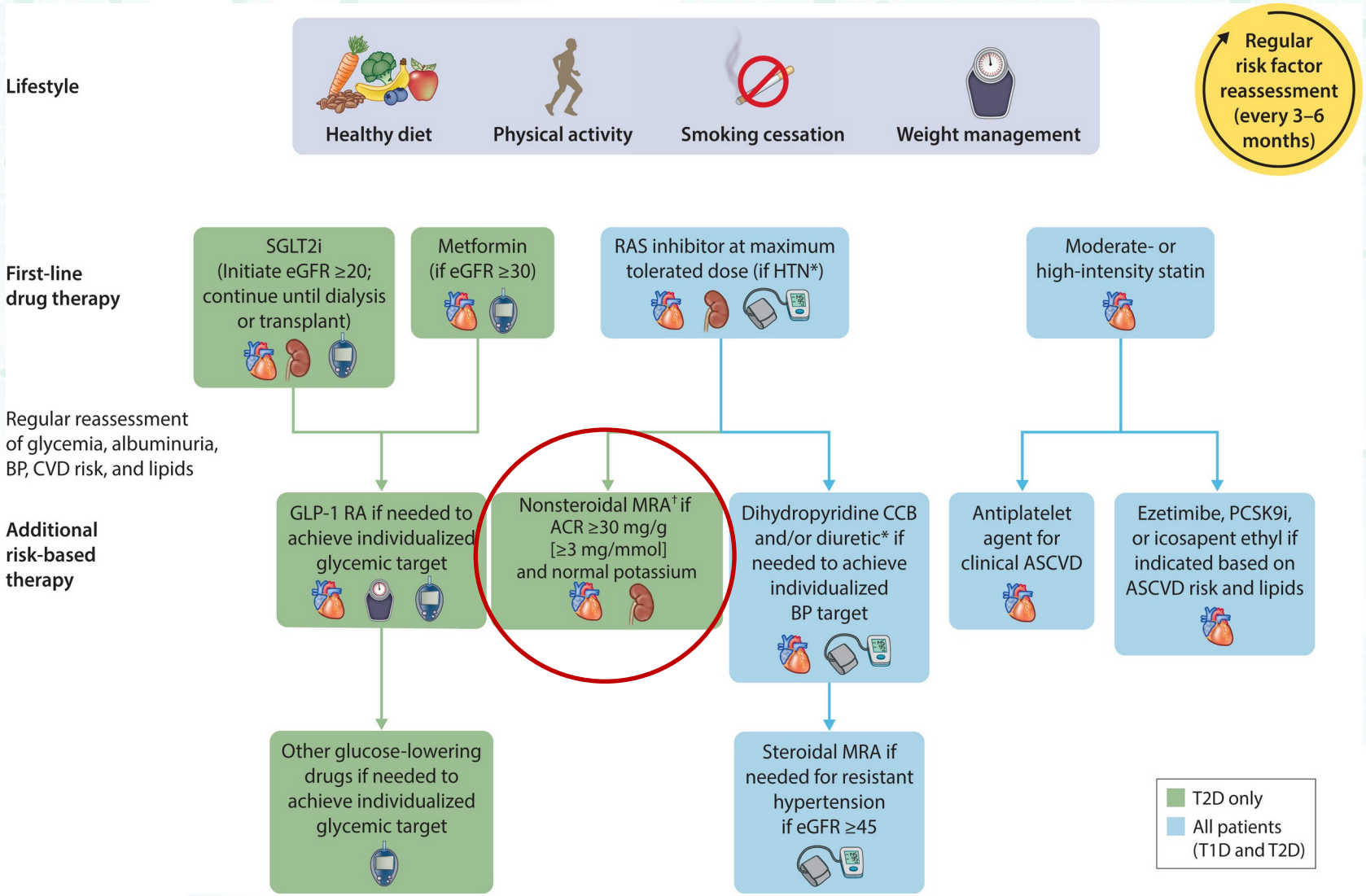
Διακοπή σιταγλιπτίνης

Έναρξη SGLT2i , Έναρξη GLP1 RA μακράς δράσης

Μετά από 6 μήνες

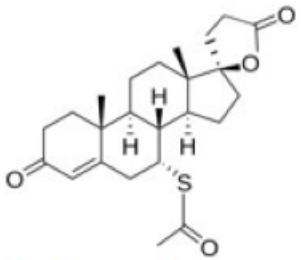
ΑΠ 125/75 mmHg ΣΦ 74 HbA1c 6,5% κρεατινίνη 1,5 mg/dl ACR 190 mg/gr, Να 140 mEq/L K 4 mEq/L

FIGURE 2. HOLISTIC APPROACH FOR IMPROVING OUTCOMES IN PATIENTS WITH DIABETES AND CHRONIC KIDNEY DISEASE

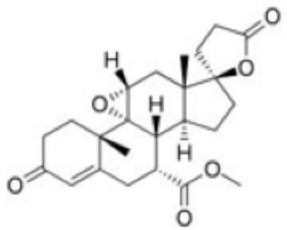


Steroidal vs Nonsteroidal MRAs

Steroidal MRAs

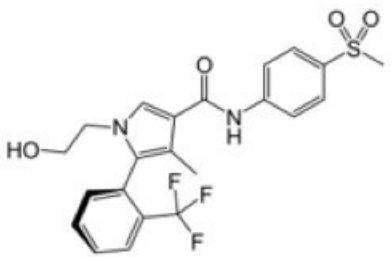


Spironolactone

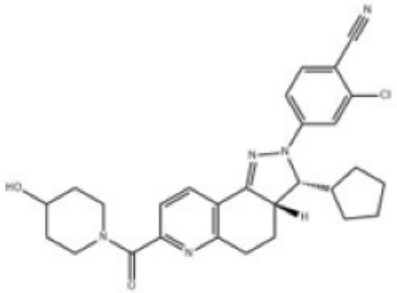


Eplerenone

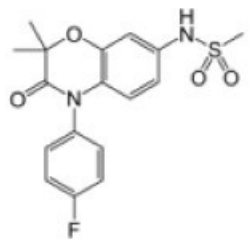
Nonsteroidal MRAs



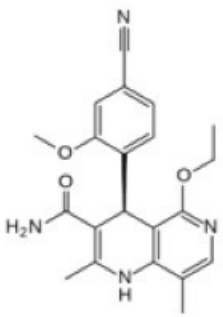
Ocedurenone*



Esaxerenone‡



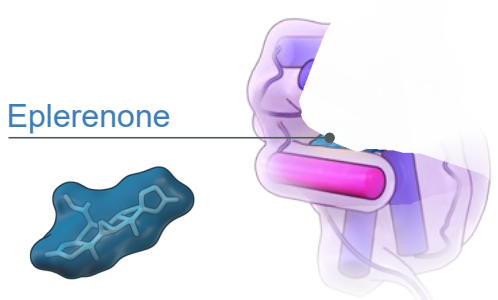
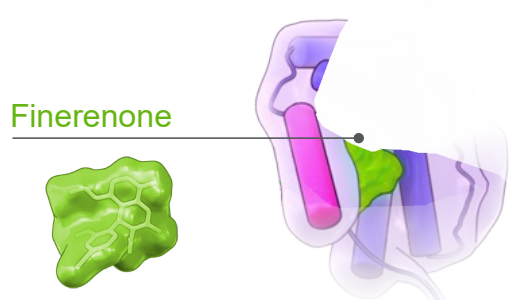
Apararenone†



Finerenone

*Ocedurenone is being investigated for uncontrolled hypertension in advanced CKD.
†Apararenone has been discontinued for the treatment of hypertension.
‡Esaxerenone is available only in Japan and approved for treatment of hypertension.
Kintscher U, et al. Br J Pharmacol. 2022;179:3220-3234.

Finerenone is a novel, bulky, nonsteroidal and selective MR antagonist that is different from available steroidal drugs[1–3]

	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]
Sexual side effects	Yes (gynecomastia)[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 distribution (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

Selective Nonsteroidal MRAs Inhibit Inflammation and Fibrosis, Decreasing Progression of CKD

3 Drivers of CKD Progression in T2D

Inflammation and fibrosis

Not specifically targeted by treatments thus far[a-d]

Hemodynamic

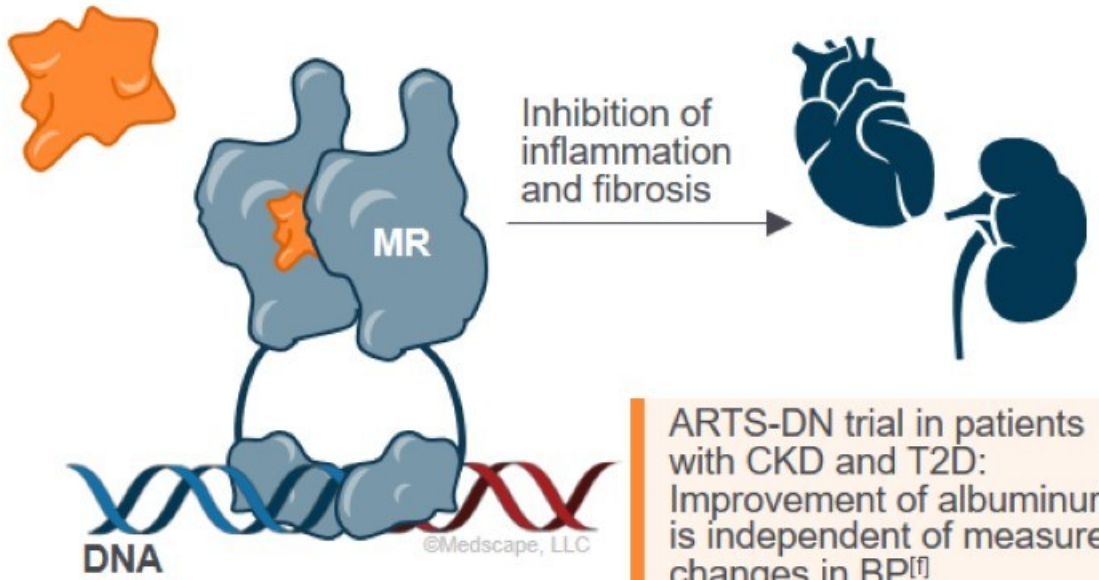
Elevated blood pressure and/or intraglomerular pressure

Metabolic

Poor glycemic control

Selective, nonsteroidal MRAs inhibit inflammation and fibrosis and protect against progressive renal and CV dysfunction in preclinical models[e]

Nonsteroidal MRA

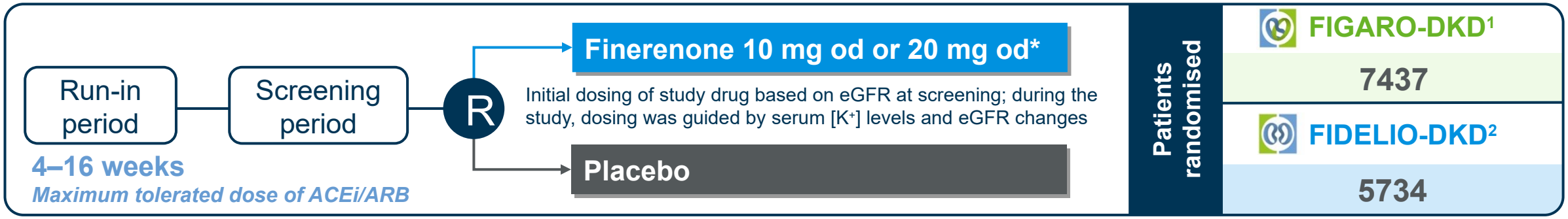


ARTS-DN trial in patients with CKD and T2D: Improvement of albuminuria is independent of measured changes in BP[f]

MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist.

a. Alicic RZ, et al. Clin J Am Soc Nephrol. 2017;12:2032-2045; b. Mora-Fernández C, et al. J Physiol. 2014;18:3997-4012; c. Bauersachs J, et al. Hypertension. 2015;65:257-263; d. Alicic RZ, et al. Adv Chronic Kidney Dis. 2018;25:181-191; e. Agarwal R, et al. Eur Heart J. 2021:42:152-161; f. Bakris GL, et al. JAMA. 2015;314:884-894; g. Bakris GL, et al. Am J Nephrol. 2019;50:333-344.

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]



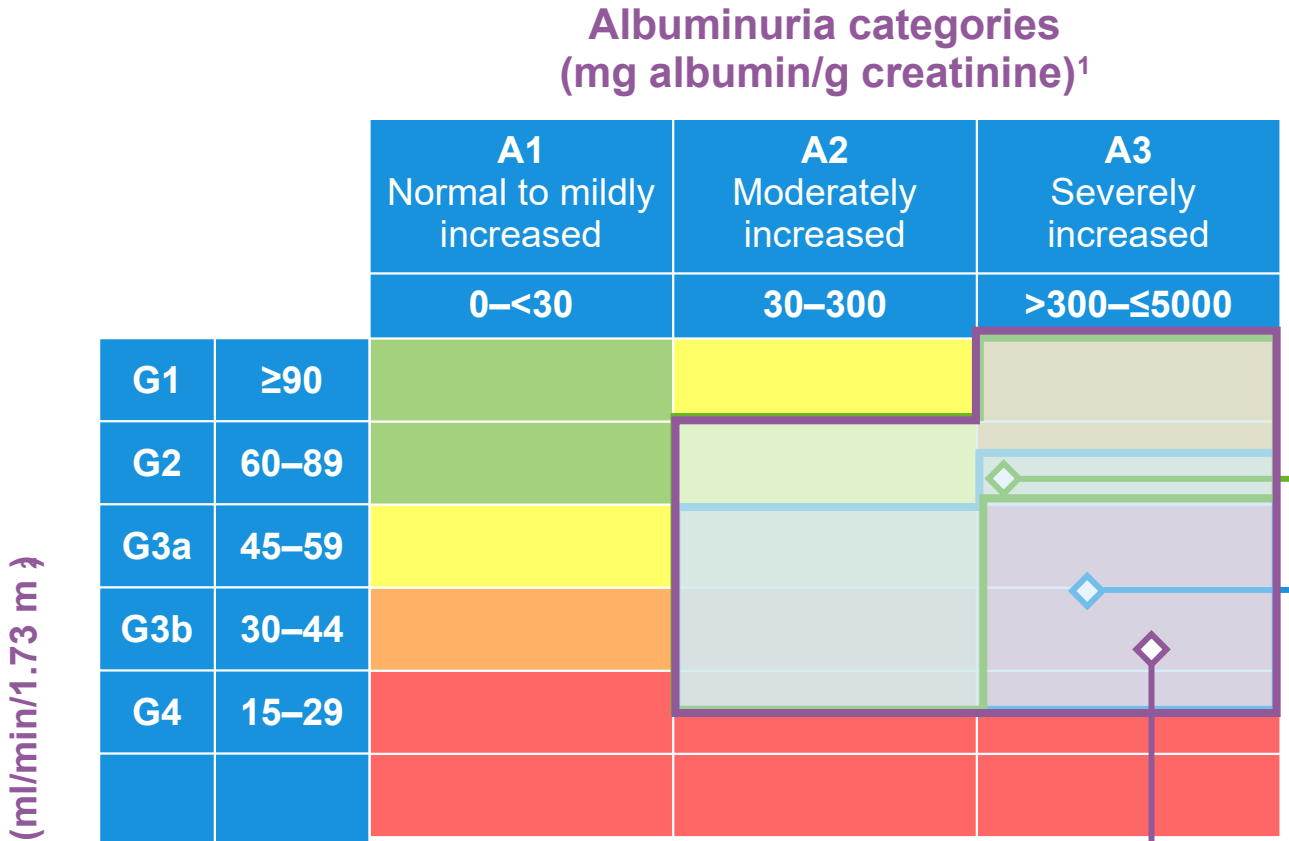
	FIGARO-DKD[1]	FIDELIO-DKD[2]	FIDELITY[3] Prespecified pooled analysis
Clinical efficacy primary endpoint	**Composite endpoint:** Time to CV death, non-fatal MI, non-fatal stroke or HHF	**Composite endpoint:** Time to kidney failure,# sustained ≥40% eGFR decline or renal death	**Key outcomes** **CV composite:** Time to CV death, non-fatal MI, non-fatal stroke or HHF
Key secondary endpoint	Same as primary endpoint in **FIDELIO-DKD**	Same as primary endpoint in **FIGARO-DKD**	**57% kidney composite:** Time to kidney failure,# sustained ≥57% eGFR decline or renal death

*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; #]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]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; [K+], potassium concentration; MI, myocardial infarction; od, once daily; R, randomisation

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

The finerenone phase III programme included patients across the spectrum of CKD severity



FIGARO-DKD (N=7437)[2]

Mean eGFR*: 67.8 ml/min/1.73 m²

Median UACR*: 312 mg/g

FIDELIO-DKD (N=5734)[3]

Mean eGFR*: 44.3 ml/min/1.73 m²

Median UACR*: 851 mg/g

FIDELITY (N=13,171)[4]

Prespecified pooled analysis

Mean eGFR*: 57.6 ml/min/1.73 m²

Median UACR*: 515 mg/g

In *rently indicated for the treatment of CKD (stage 3 and 4 with* *all* *h T2D in adults. EMA approval is based on FIDELIO-DKD data only*

*A

eC r filtration rate; UACR, urine albumin-to-creatinine ratio

1. ng Global Outcomes (KDIGO). *Kidney Int* 2020;98:S1–S115; 2. Ruilope LM, *et al. Am J Nephrol* 2019;50:345–356;
3. *phrol* 2019;50:333–344; 4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELIO-DKD was a randomised, double-blind, event-driven, placebo-controlled phase III trial

FIDELIO-DKD

13,911 patients enrolled

Run-in
4–16 weeks
Optimisation of ACEi or ARB therapy

Screening
≤2 weeks

R*

5734 patients randomised

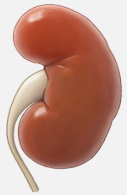
Finerenone (initial dose 10 or 20 mg od#) → Post-treatment follow-up

Placebo (initial dose 10 or 20 mg od#) → Post-treatment follow-up

Hierarchical endpoints

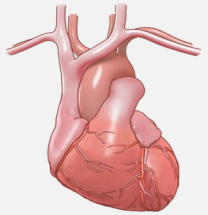
1. Kidney composite

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



2. CV composite

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



3. Death from any cause
4. Hospitalisation for any cause
5. Change in UACR
6. Second kidney composite

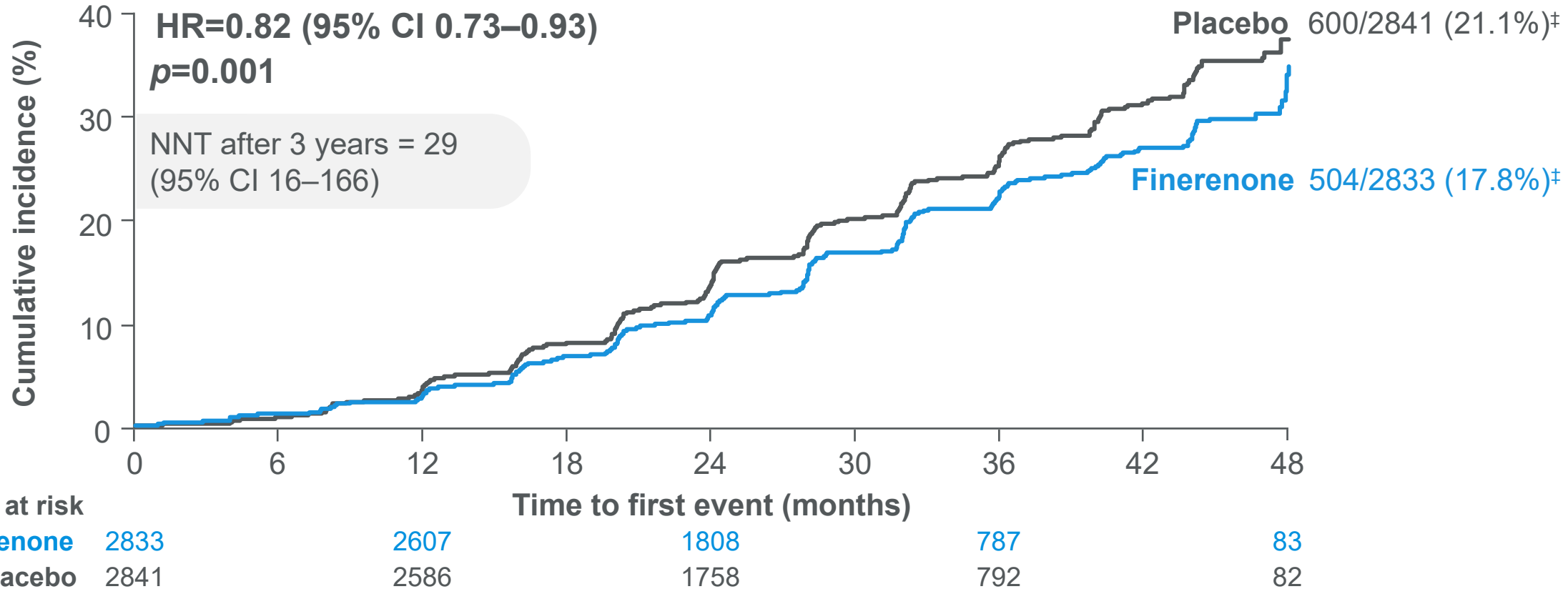
*Randomisation was stratified by region (North America, Latin America, Europe, Asia or Other), eGFR category at screening visit (25–<45, 45–<60, or ≥60 ml/min/1.73 m²) and albuminuria category at screening visit ('moderately increased' or 'severely increased'); #up-titration of study drug was encouraged after visit 2 provided potassium value was 4.8 mmol/l or less and eGFR was stable; down-titration was allowed any time after treatment initiation for safety reasons
HF, heart failure; UACR, urine albumin-to-creatinine ratio

Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229

In addition to maximum tolerated RAS therapy, finerenone significantly reduced the primary kidney outcome by 18%

FIDELIO-DKD

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



*ESKD or an eGFR <15 ml/min/1.73 m²; #events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated and (3) there was no other likely cause of death; ‡number of patients with an event over a median of 2.6 years of follow-up
CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio; NNT, number needed to treat; RAS, renin–angiotensin system

Bakris GL, *et al*. *N Engl J Med* 2020;383:2219–2229

FIGARO-DKD is the second phase III trial in the finerenone clinical programme

FIGARO-DKD

19,381 patients enrolled[1]

7437 patients randomised[1]

Run-in 4–16 weeks
Optimisation of ACEi or ARB therapy

Screening ≤2 weeks

R*

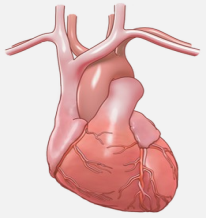
Finerenone (initial dose 10 or 20 mg od#) → Post-treatment follow-up

Placebo → Post-treatment follow-up

Hierarchical endpoints

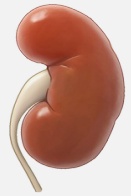
1. CV composite

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



2. Kidney composite

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



3. Hospitalisation for any cause
4. Death from any cause
5. Change in UACR
6. Second kidney composite

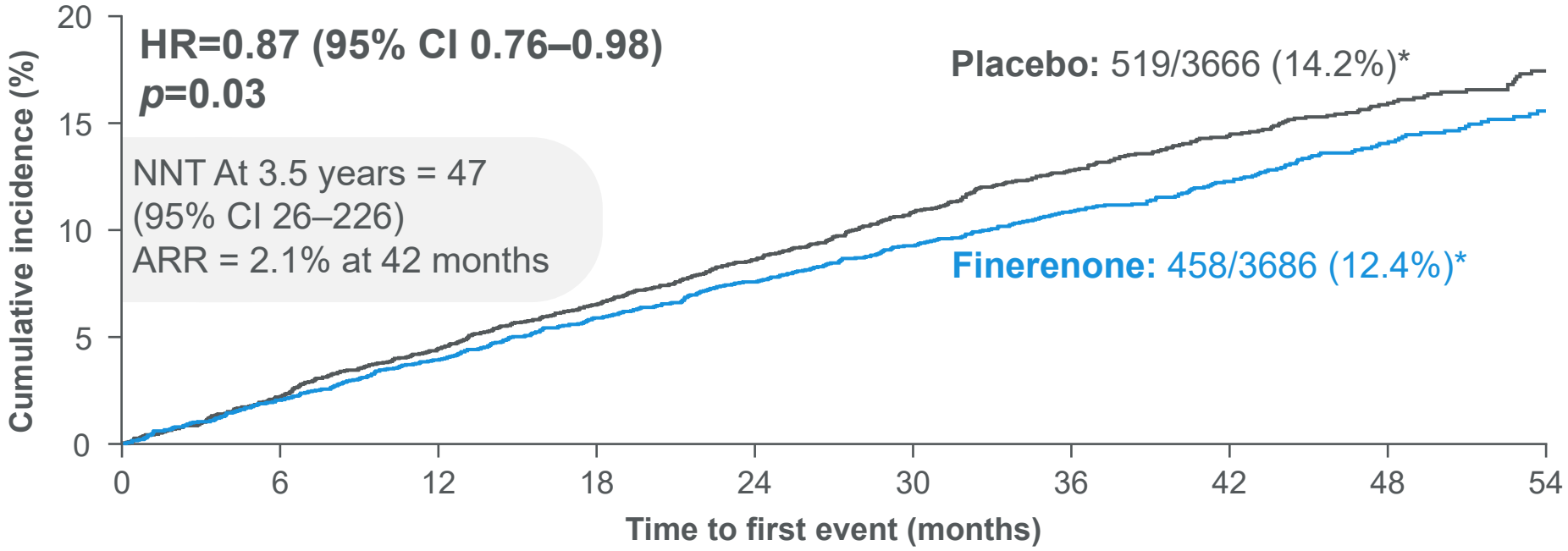
*Randomisation was stratified by region (North America, Latin America, Europe, Asia or other), eGFR category at screening visit (25–<45, 45–<60, or ≥60 ml/min/1.73 m²) and albuminuria category at screening visit ('moderately increased' or 'severely increased') and history of CV disease (present or absent)

Pitt B, *et al*. *N Engl J Med* 2021;385:2252–2263

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

FIGARO-DKD

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

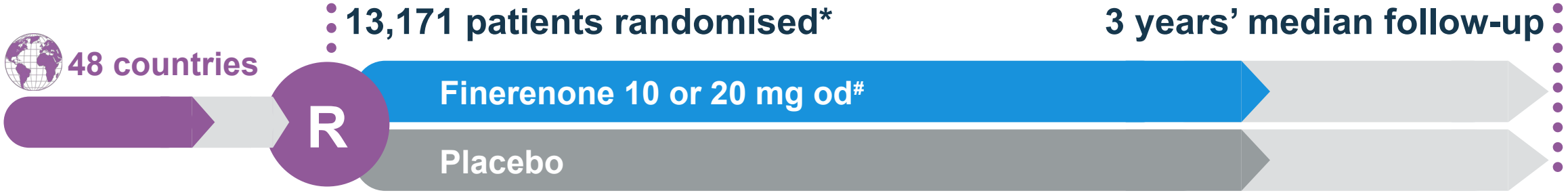


No. at risk										
Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598
Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585

*Number of patients with an event over a median of 3.4 years of follow-up
ARR, absolute risk reduction

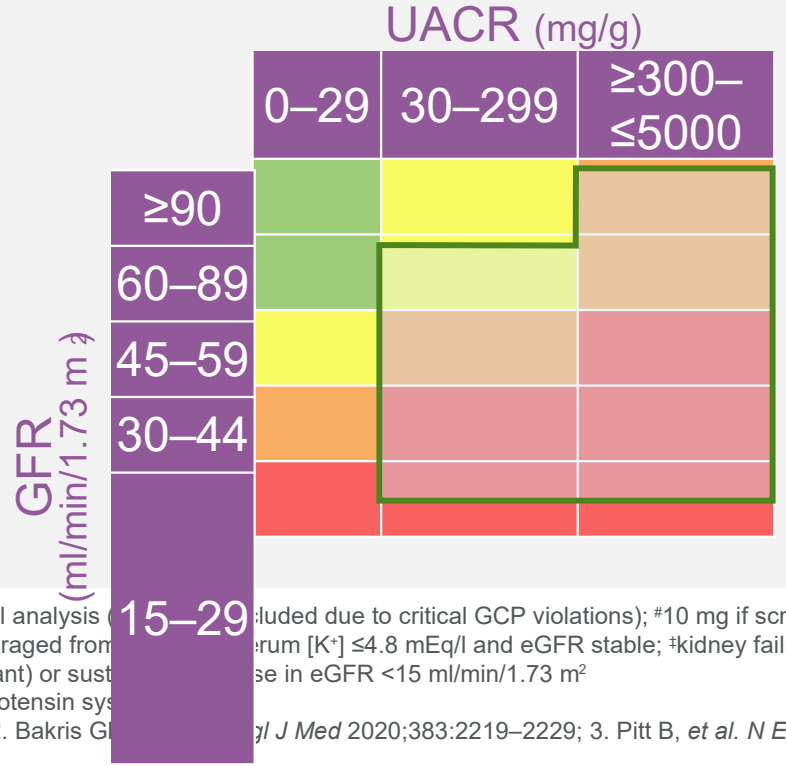
Pitt B, *et al. N Engl J Med* 2021;385:2252–2263

FIDELITY[1] is a large individual patient data meta-analysis of FIDELIO-DKD[2] and FIGARO-DKD[3]



Key eligibility criteria

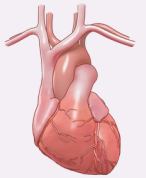
- ✓ T2D
- ✓ CKD
- ✓ On a single RASi
- ✓ Serum [K⁺] ≤4.8 mmol
- ✗ Symptomatic HFrEF



Key outcomes

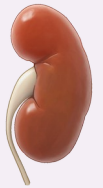
CV composite

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



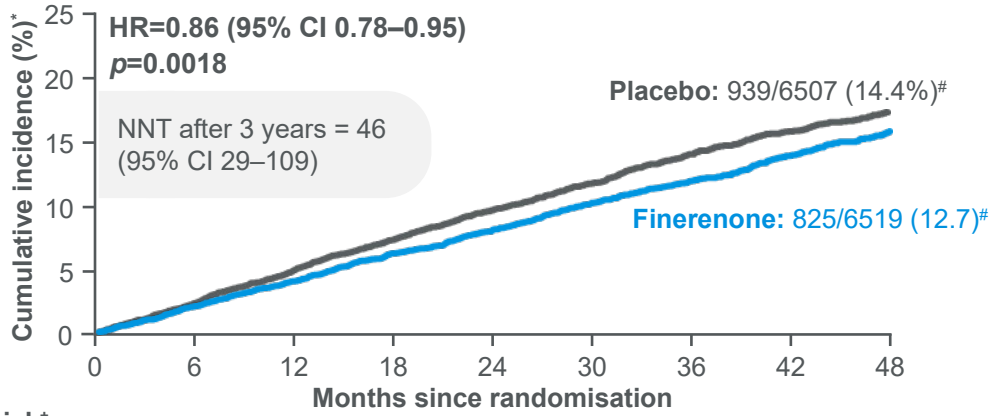
*13,026 patients were included in the statistical analysis (…luded due to critical GCP violations); #10 mg if screening eGFR 25–<60 ml/min/1.73 m²; 20 mg if ≥60 ml/min/1.73 m², up-titration encouraged from… …rum [K⁺] ≤4.8 mEq/l and eGFR stable; ‡kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sust… …se in eGFR <15 ml/min/1.73 m²
GCP, Good Clinical Practice; RASi, renin–angiotensin sys…

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

The FIDELITY primary analysis showed significant risk reductions in CV and kidney outcomes with finerenone

CV composite

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

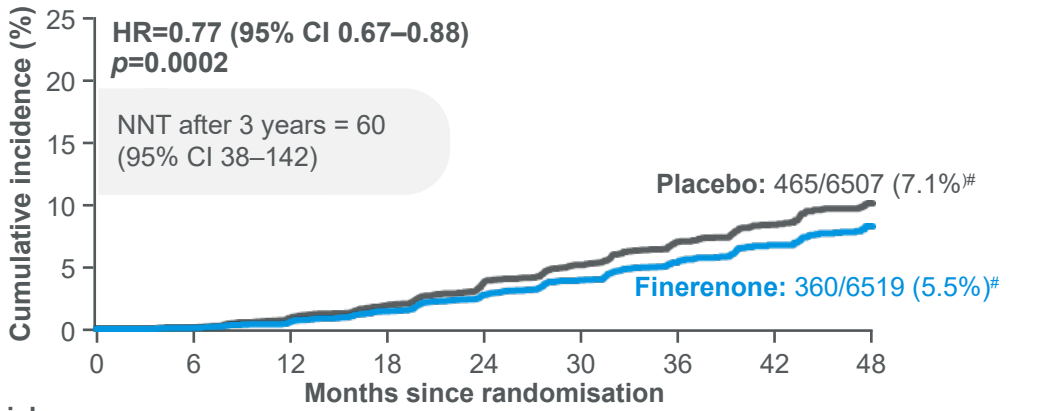


No. at risk‡									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** vs placebo (HR=0.86; 95% CI 0.78–0.95)

Kidney composite

Time to kidney failure§, sustained ≥57% decrease in eGFR from baseline or kidney-related death



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

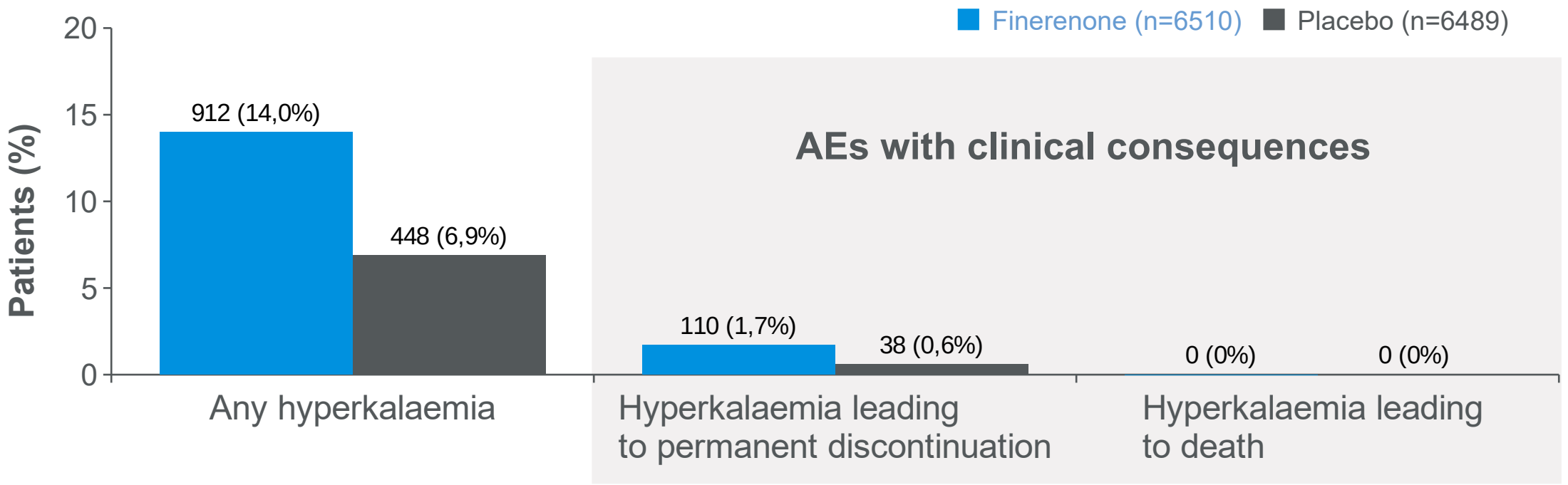
23% reduced **risk of CKD progression§** vs placebo (HR=0.77; 95% CI 0.67–0.88)

*cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; #number of patients with an event over a median of 3.0 years of follow-up; ‡at-risk subjects were calculated at start of time point;§ESKD or an eGFR <15 ml/min/1.73 m^2, events were classified as renal death if: (1) the patient died; (2) kidney replacement therapy had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death

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

In FIDELITY, finerenone increased hyperkalaemia, but the clinical impact was minimal

Investigator-reported hyperkalaemia AEs*[1]



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

*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalaemia' and 'blood potassium increased'
MedDRA, Medical Dictionary for Regulatory Activities
Agarwal R, et al. Eur Heart J 2022;43:474–484

COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (≥30 mg/g [≥ 3mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) *(2A)*.

K^+ ≤4.8 mmol/l

- Initiate finerenone
  - 10 mg daily if eGFR 25–59 ml/min per 1.73 m^2
  - 20 mg daily if eGFR ≥60 ml/min per 1.73 m^2
- Monitor K^+ at 1 month after initiation and then every 4 months
- Increase dose to 20 mg daily, if on 10 mg daily
- Restart 10 mg daily if previously held for hyperkalemia and K^+ now ≤5.0 mmol/l

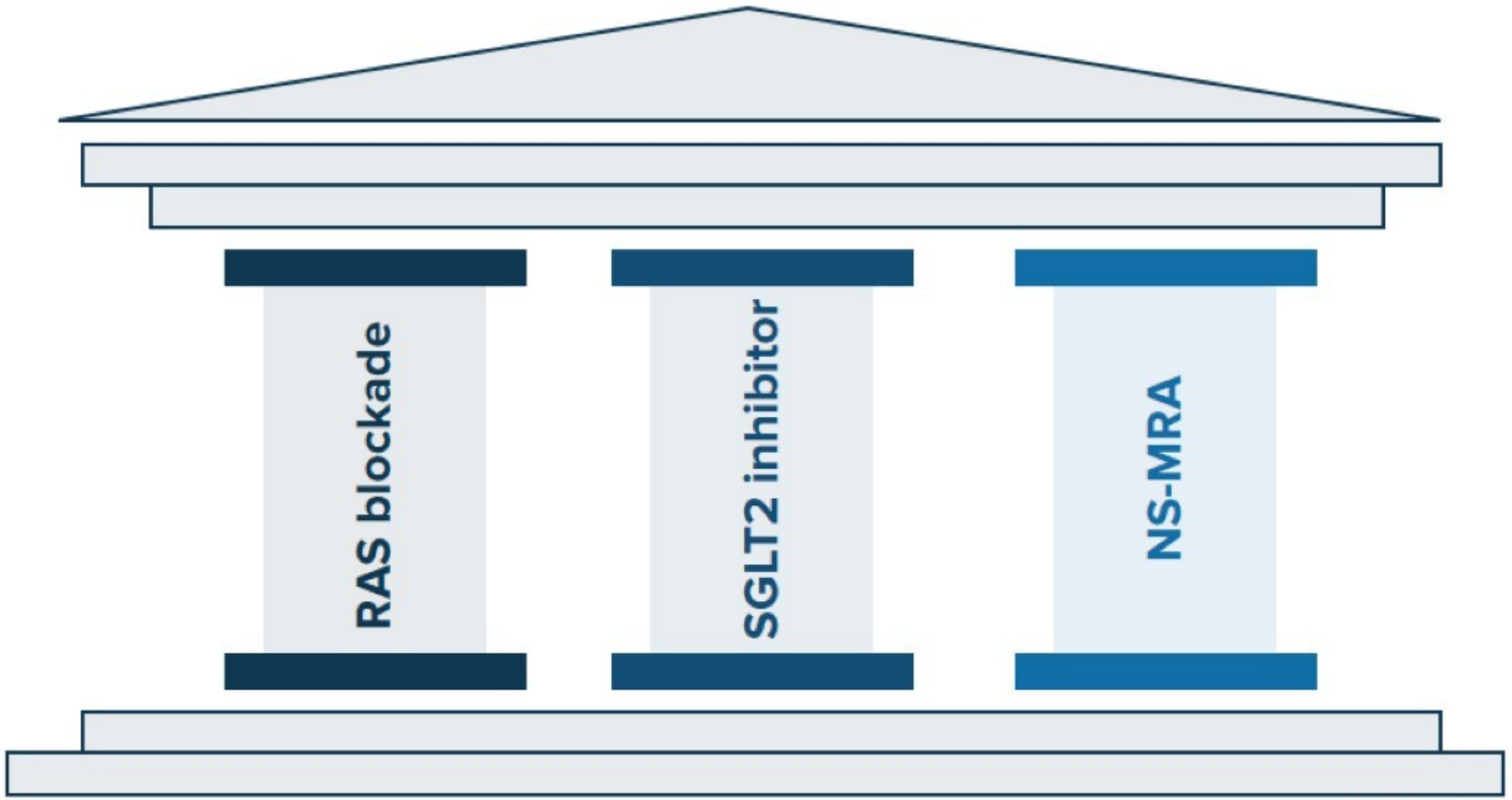
K^+ 4.9–5.5 mmol/l

- Continue finerenone 10 mg or 20 mg
- Monitor K^+ every 4 months

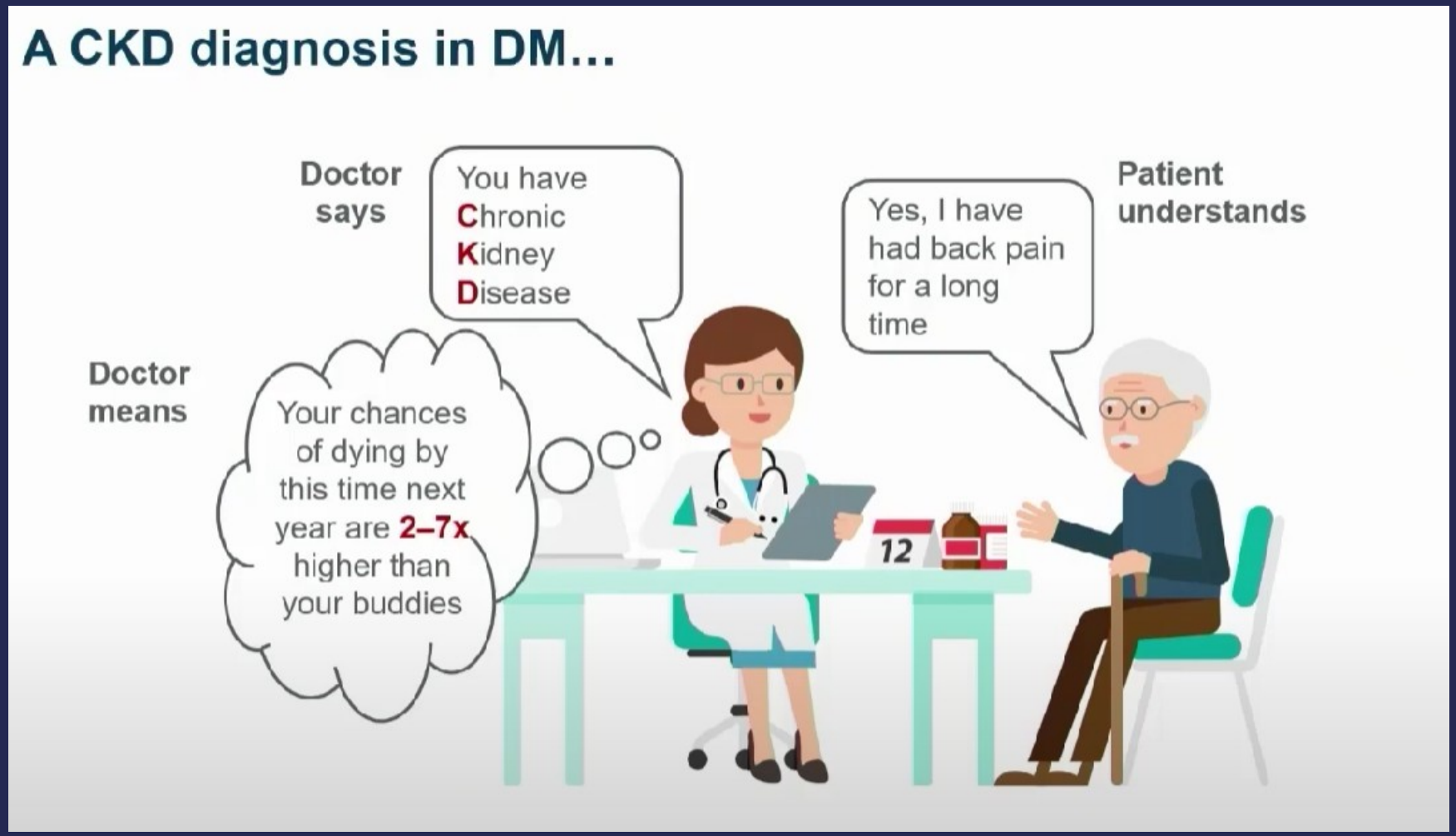
K^+ >5.5 mmol/l

- Hold finerenone
- Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
- Recheck K^+
- Consider reinitiation if/when K^+ ≤5.0 mmol/l

3 Pillars of Therapy to Reduce Cardiorenal Risk



NS-MRA, nonsteroidal mineralocorticoid antagonist.


A CKD diagnosis in DM…
Doctor says
You have Chronic Kidney Disease
Patient understands
Yes, I have had back pain for a long time
Doctor means
Your chances of dying by this time next year are 2–7x higher than your buddies
12

ΕΥΧΑΡΙΣΤΩ