Clinical Overview : Chronic Kidney disease and Diabetic Kidney disease

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Clinical overview : CKD and DKD - outline

- Epidemiology of CKD and DKD
- eGFR and proteinuria
- Basic principles of management
  - Slowing progression
  - CVS risk reduction
  - Reducing complications (anaemia, metabolic bone disease)
- Exciting new data regarding SGLT-2 inhibitors

What do your kidneys do?

Make urine

Regulate salt and water in your body, making about 3-4 pints of urine each day

Remove waste products from your blood into your urine

Produce hormones

Regulate your blood pressure

Create erythropoietin to control the production of red blood cells

Activate Vitamin D

Keep bones healthy

Clean your blood

Remove many drugs that some people take for other conditions

Classification of kidney function (NICE)

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

GFR categories, description and range (ml/min/1.73 m²)			Albuminuria stages, description and range		
			A1 Normal to mildly increased <30 mg/g (<3 mg/mmol)	A2 Moderately increased 30–300 mg/g (3–30 mg/mmol)	A3 Severely increased >300 mg/g (>30 mg/mmol)
G1	Normal or high	≥90			
G2	Mild	60–89			
G3a	Mild – moderate	45–59			
G3b	Moderate – severe	30–44			
G4	Severe	15–29			
G5	Kidney failure	<15			

Increasing risk

Increasing risk

Adapted from: NICE. Chronic kidney disease in adults: assessment and management (CG182). 2014. Available at: www.nice.org.uk/CG182 (accessed October 2018).

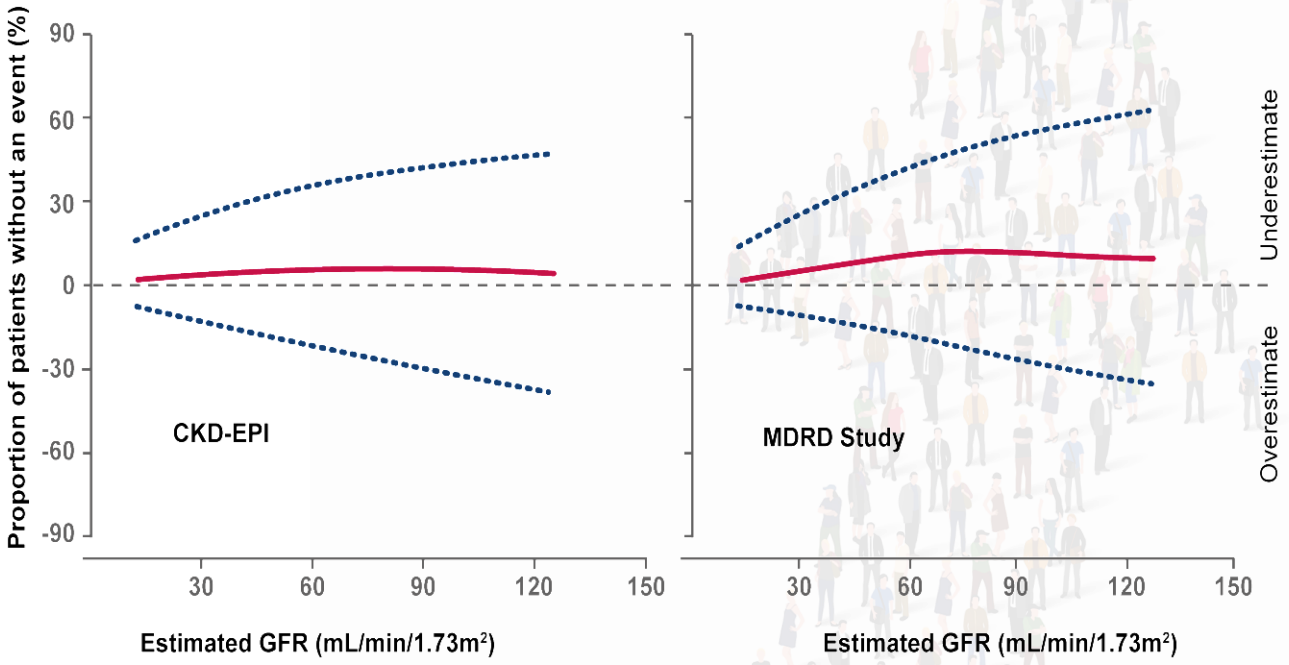
CKD, chronic kidney disease; GFR, glomerular filtration rate; NICE, National Institute for Health and Care Excellence.

UK/INV-18021o; October 2018

How to estimate GFR

1. **Modification of Diet in Renal Disease (MDRD)**
   - GFR (mL/min/1.73m^2) = 175 x $(S_{Cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if black)

2. **Chronic kidney disease (CKD) Epidemiology Collaboration (CKD-EPI)**
   - GFR = 141 x min $(S_{Cr}/K,1)^{-\alpha}$ x max $(S_{Cr}/K,1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black]



CKD, chronic kidney disease; GFR, glomerular filtration rate; S_{Cr}, serum creatinine.
NIDDK. Glomerular Filtration Rate (GFR) Calculators. Available from: www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators. Accessed July 2019.

Causes of progressive CKD in the UK

Diabetes	20 %
Hypertension/ renovascular	18 %
Glomerulonephritis	15 %
Pyelonephritis/ reflux	12 %
Polycystic/ other familial	10 %
Other	10 %
Unknown	15 %

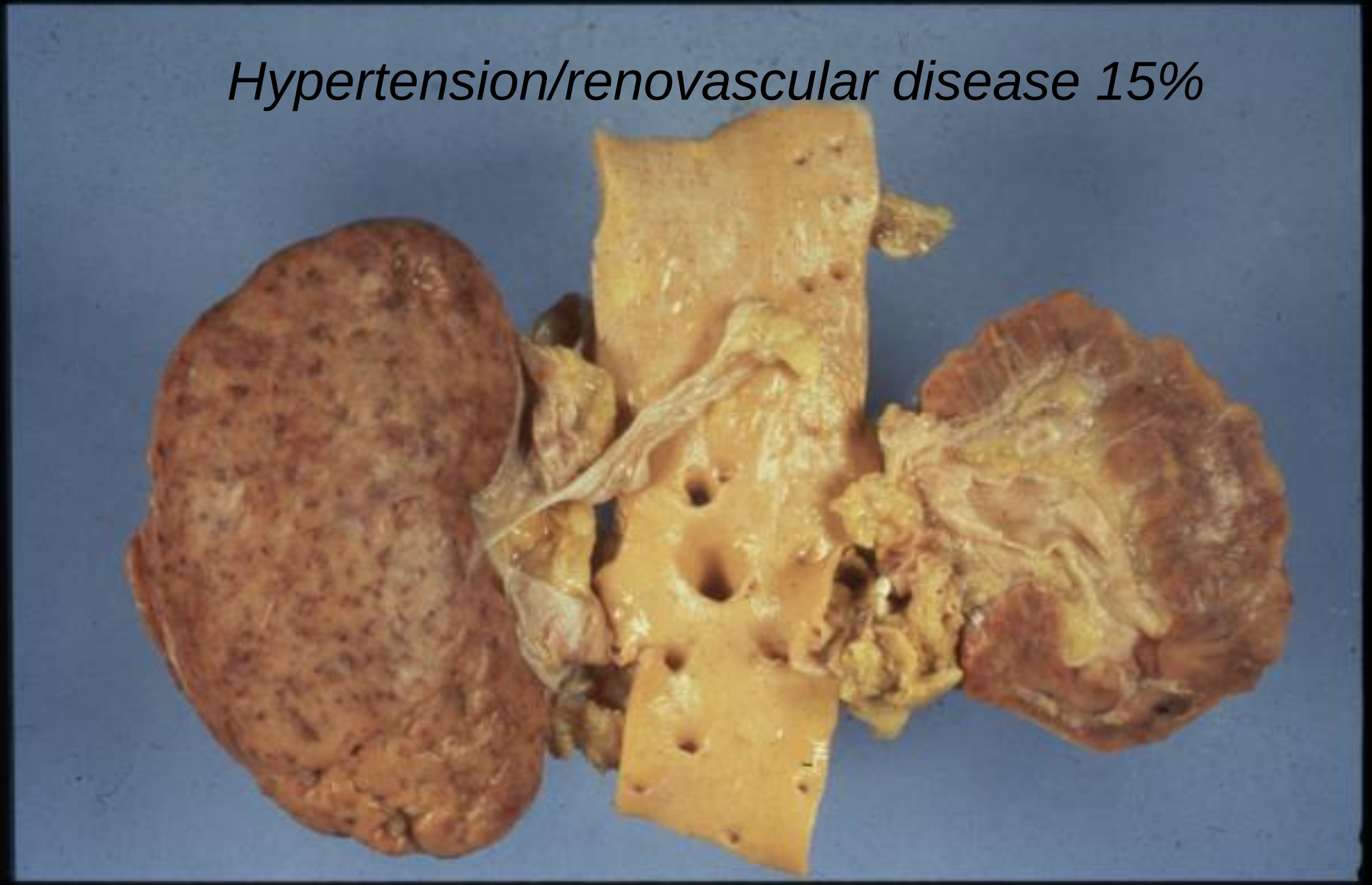
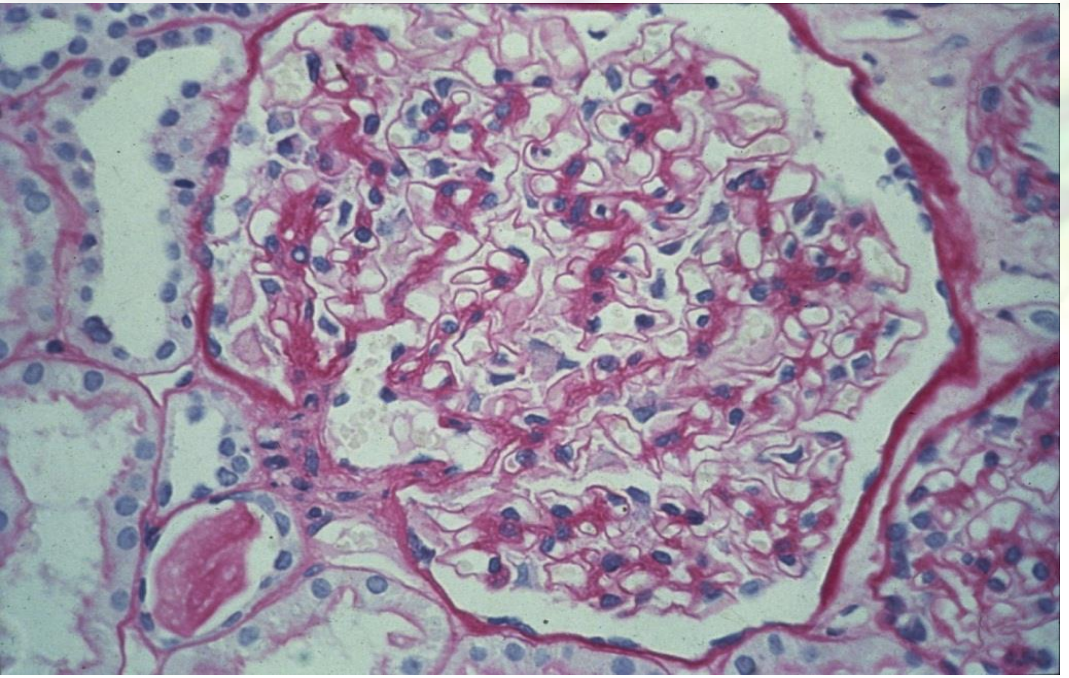

Hypertension/renovascular disease 15%

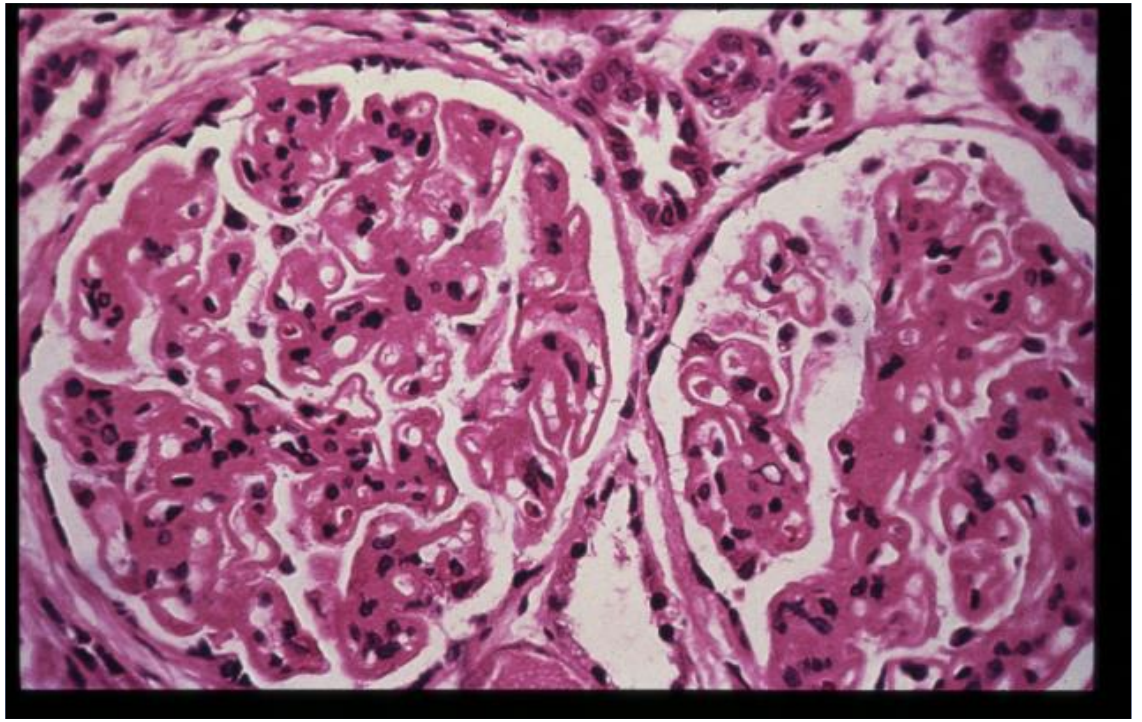
Fig. 101 Macroscopic appearance of a polycystic kidney. (Courtesy of Dr D Peat.)

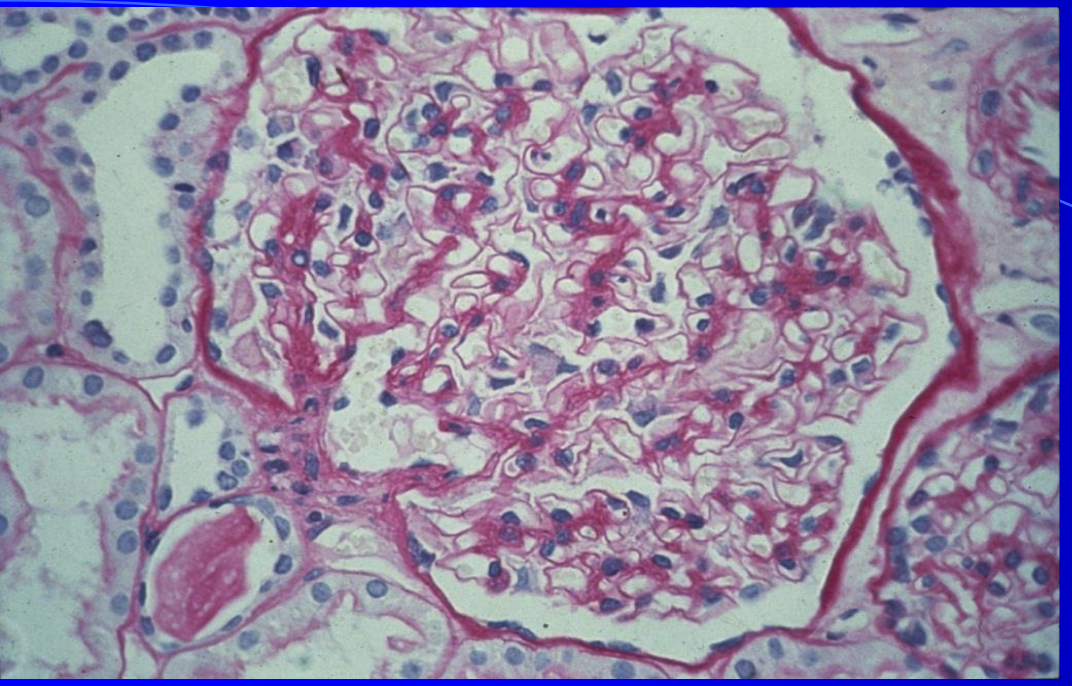
Polycystic kidney disease 10%

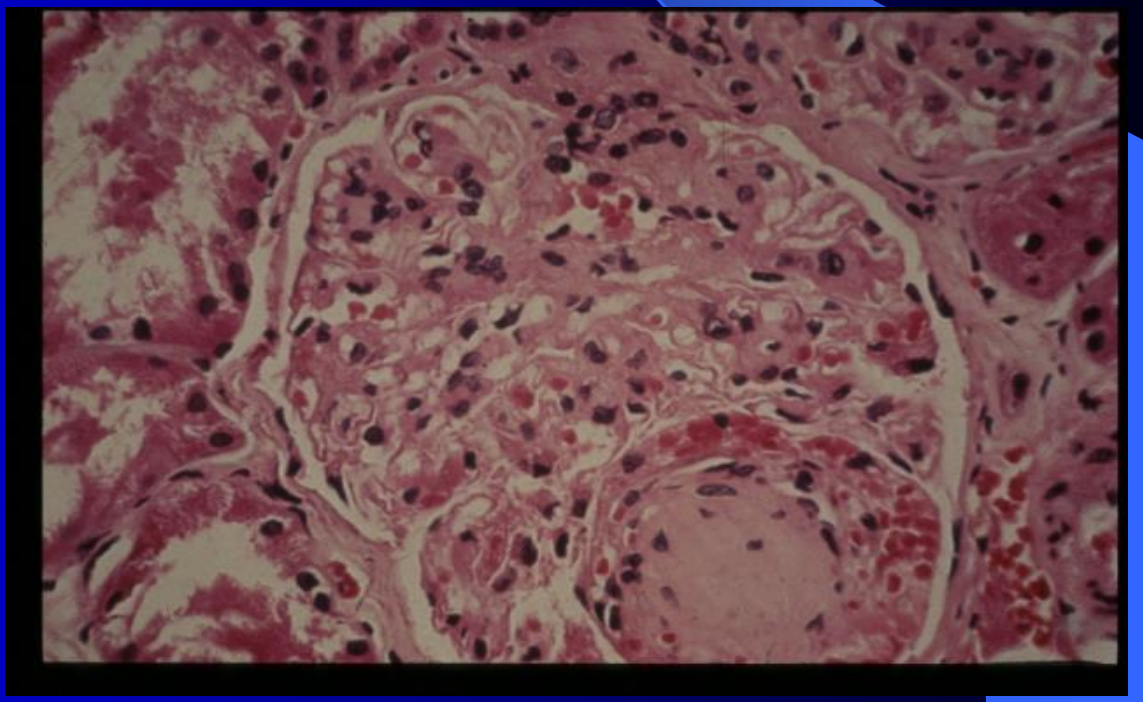


Normal glomerulus

Membranous Glomerulonephritis

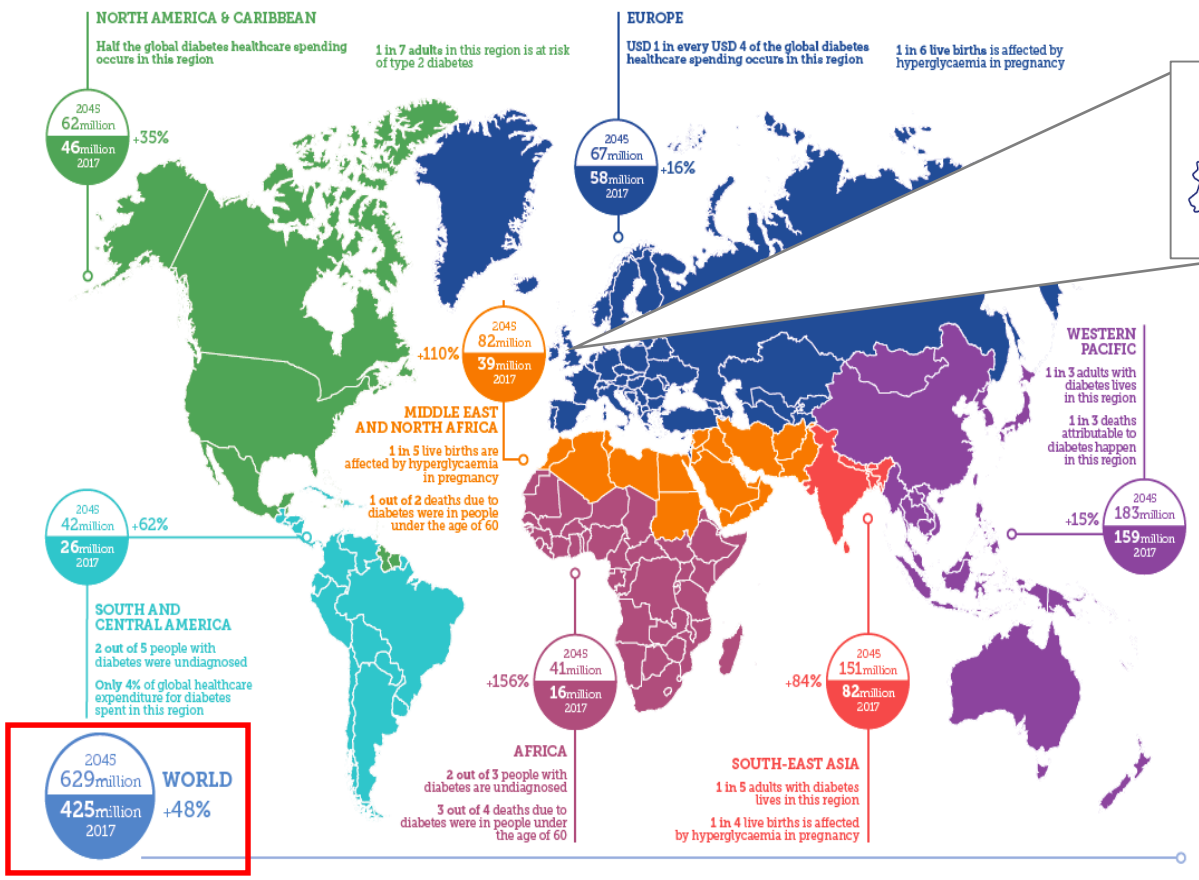






Diabetic nephropathy

Global estimates of diabetes



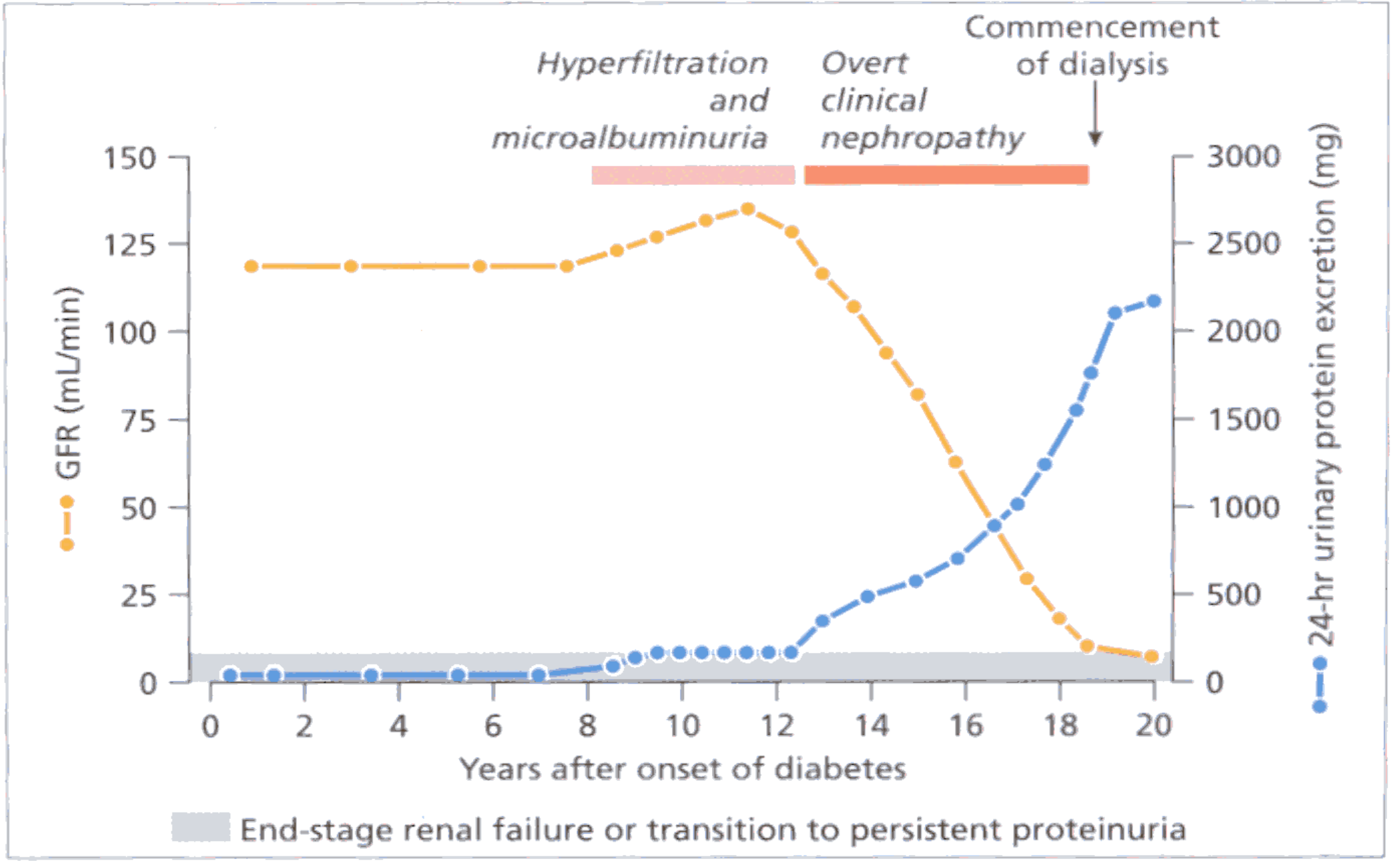
The UK picture

Almost 3.7 million people have been diagnosed with diabetes in the UK

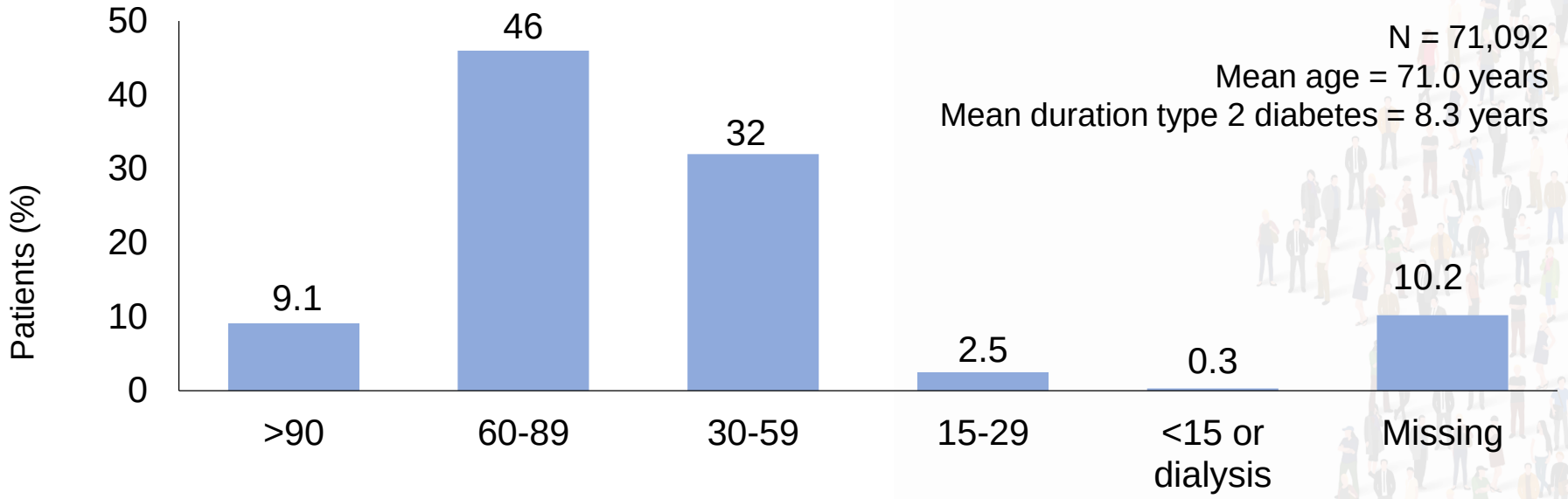
- Diabetes diagnosis has almost doubled in the past 20 years
- 90% of these cases are T2DM

T2DM, type 2 diabetes mellitus.

International Diabetes Federation. Diabetes Atlas, 8th edition. 2017. Available from: http://diabetesatlas.org/resources/2017-atlas.html. Accessed July 2019.
Diabetes UK. Number of people living with diabetes in twenty years (2018). Available from: https://www.diabetes.org.uk/about_us/news/diabetes-prevalence-statistics. Accessed July 2019.


Hyperfiltration and microalbuminuria
Overt clinical nephropathy
Commencement of dialysis
GFR (mL/min)
150
125
100
75
50
25
0
3000
2500
2000
1500
1000
500
0
24-hr urinary protein excretion (mg)
0
2
4
6
8
10
12
14
16
18
20
Years after onset of diabetes
End-stage renal failure or transition to persistent proteinuria

Stages of chronic kidney disease in people with type 2 diabetes

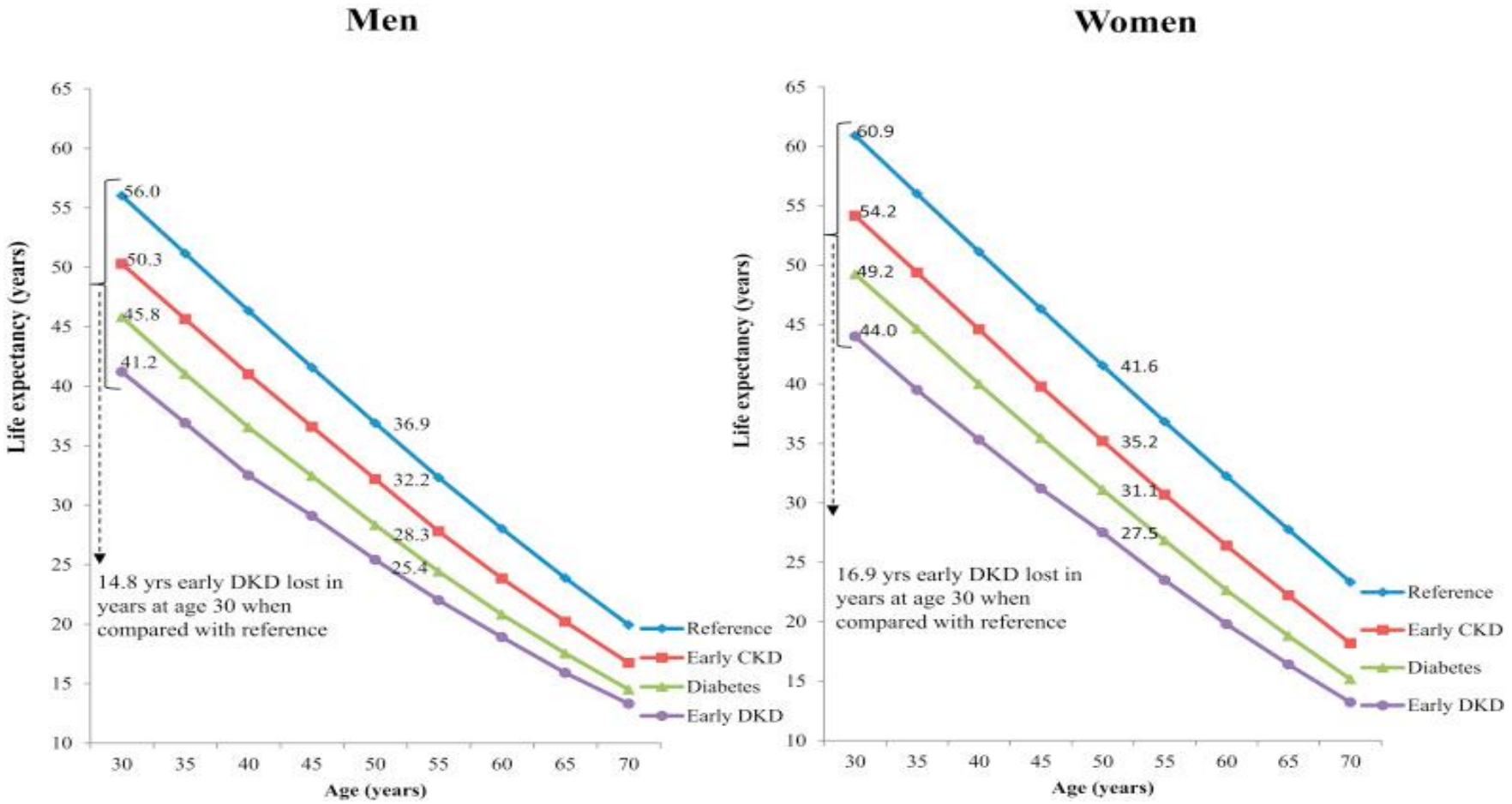


No. patients	**6444**	**32,674**	**22,754**	**1770**	**194**	**7256**

- In this large cohort of elderly patients, the vast majority of patients had stage 2–3 chronic kidney disease

Huang ES, et al. Diabetes Care 2011; 34: 1329–1336.

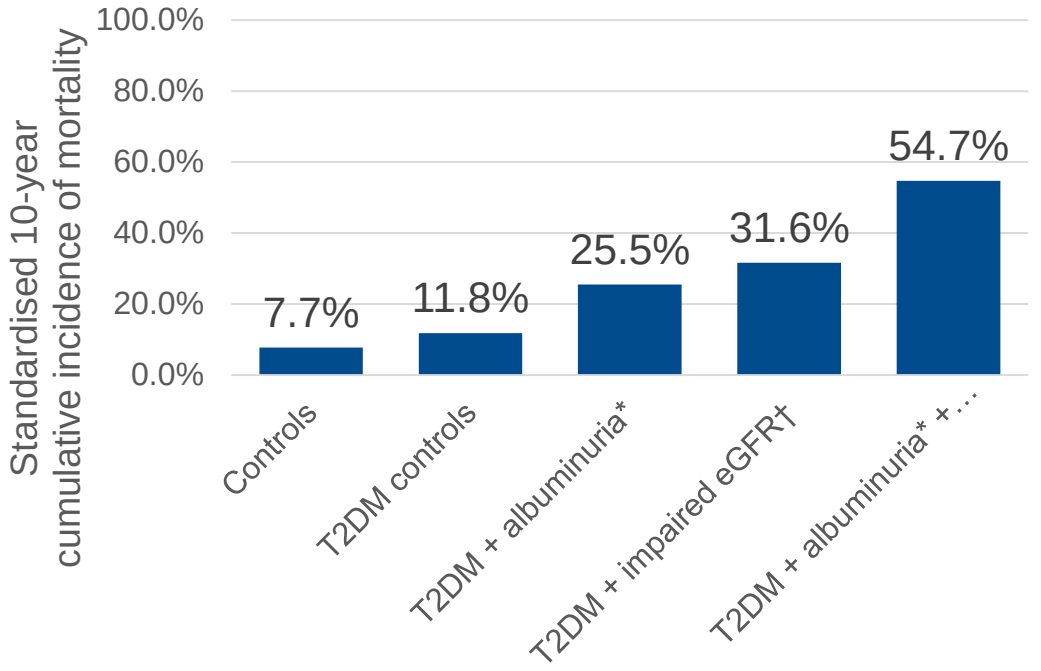
Diabetic Nephropathy reduces life expectancy



Wen et al KI 2017

Kidney disease and mortality in type 2 diabetes

All-cause and cardiovascular mortality risk associated with type 2 diabetes is concentrated in a subgroup of people with diabetes and kidney disease (defined by albuminuria, impaired GFR or both)



Kidney disease powerfully predicts increased mortality in people with diabetes

*Albuminuria was defined as >30mg/g (equivalent to >3mg/mmol, or microalbuminuria); †Impaired GFR was defined as a GFR ≤60mL/min/1.73m^2.
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; T2D, type 2 diabetes.
Afkarian M, et al. J Am Soc Nephrol 2013; 24: 302–308.

CKD - Management strategy

A

ACE inhibitor/angiotensin receptor blockade

B

BP targeting

C

CV risk reduction

(D)

Diabetes management:

- Glycaemia
- Kidney protective agents

ACE, angiotensin-converting enzyme; BP, blood pressure; CV, cardiovascular.

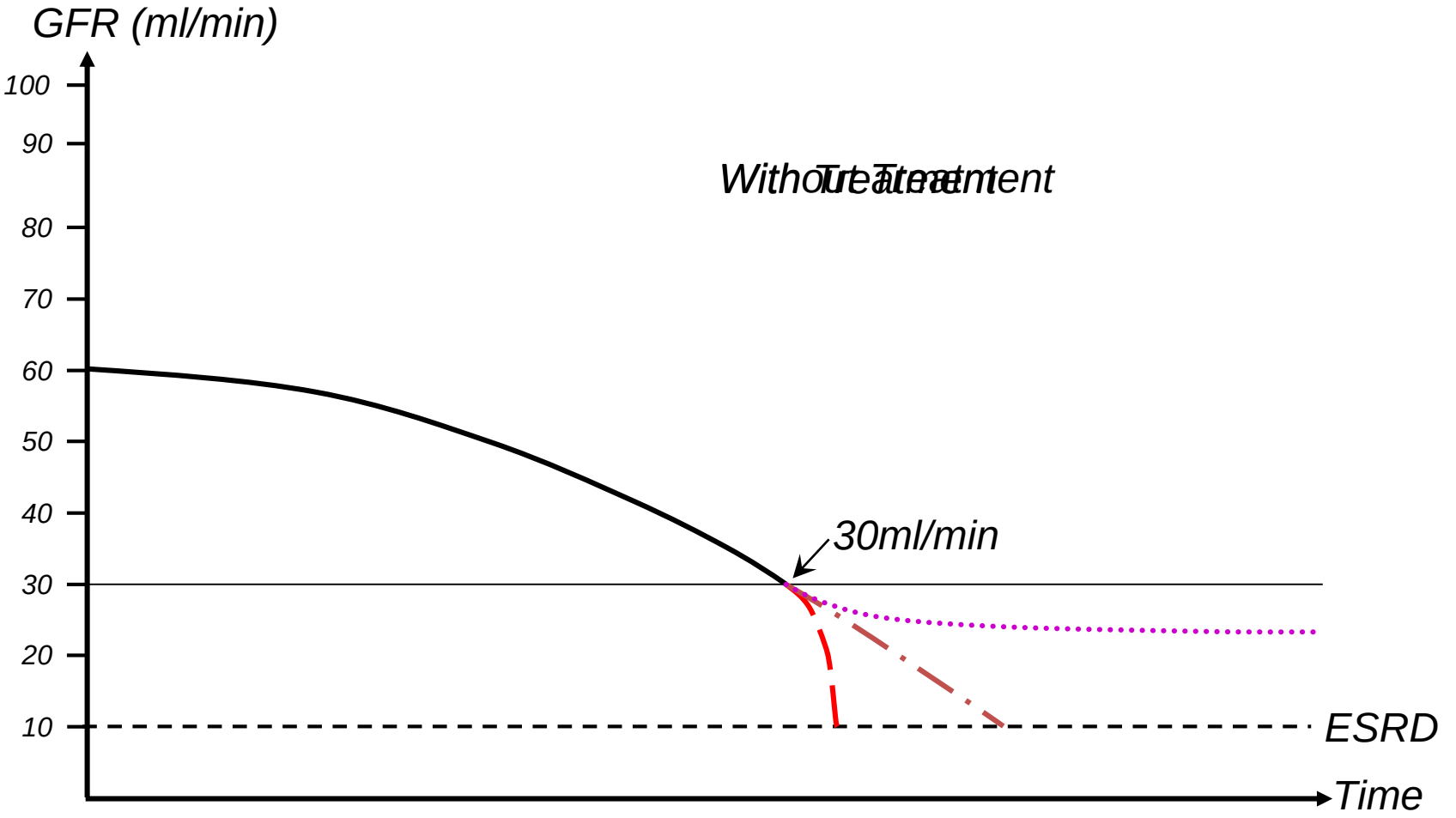
Goals of treatment in CKD (ABCD)

- **Slowing or preventing nephropathy and ESKD**
  - Glycaemic control (D)
  - Blood pressure control (A, B)
  - Control of proteinuria (A, B)
- **Improving quality of life**
  - Weight loss (B, C, D)
  - Life style change with regular exercise (B, C, D)
  - Anaemia management (C)
- **Improving survival**
  - All of the above
  - CVS risk management (C)

Targets for treatment

- Glycaemic control : HbA1C < 48 mmol/mol (< 7.5%)
- Blood pressure : < 130/80
- Proteinuria : to be reduced (eg < 70 mg/mmol = < 700 mg/g; approx 700 mg/day)
- Haemoglobin : > 120 g/l (if no ESA); 100-120 g/l with ESA
- Cholesterol : total < 4 mmol/l, LDL-C < 2 mmol/l
- Obesity : reduce BMI (eg < 30)
- Exercise : 30 mins aerobic exercise x 3-4/week

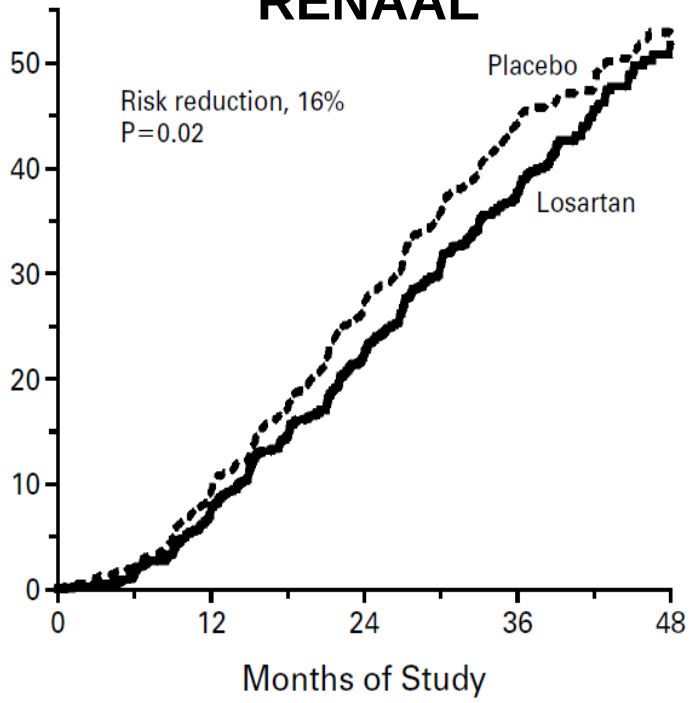
Progression of CKD



RENAAL & IDNT: Supporting the backbone of therapy for 18 years

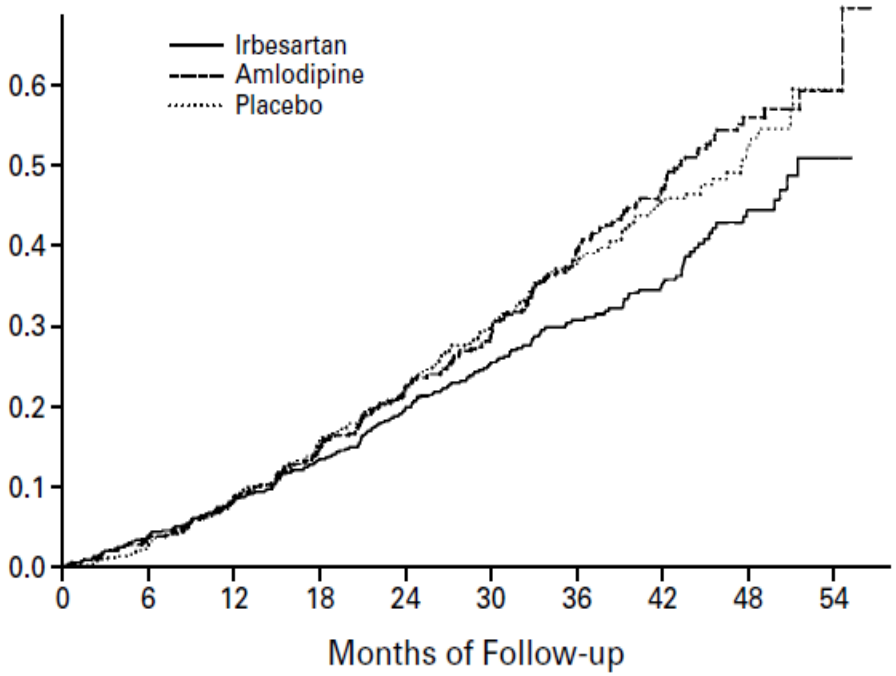
Doubling of serum creatinine, ESKD, or death

RENAAL



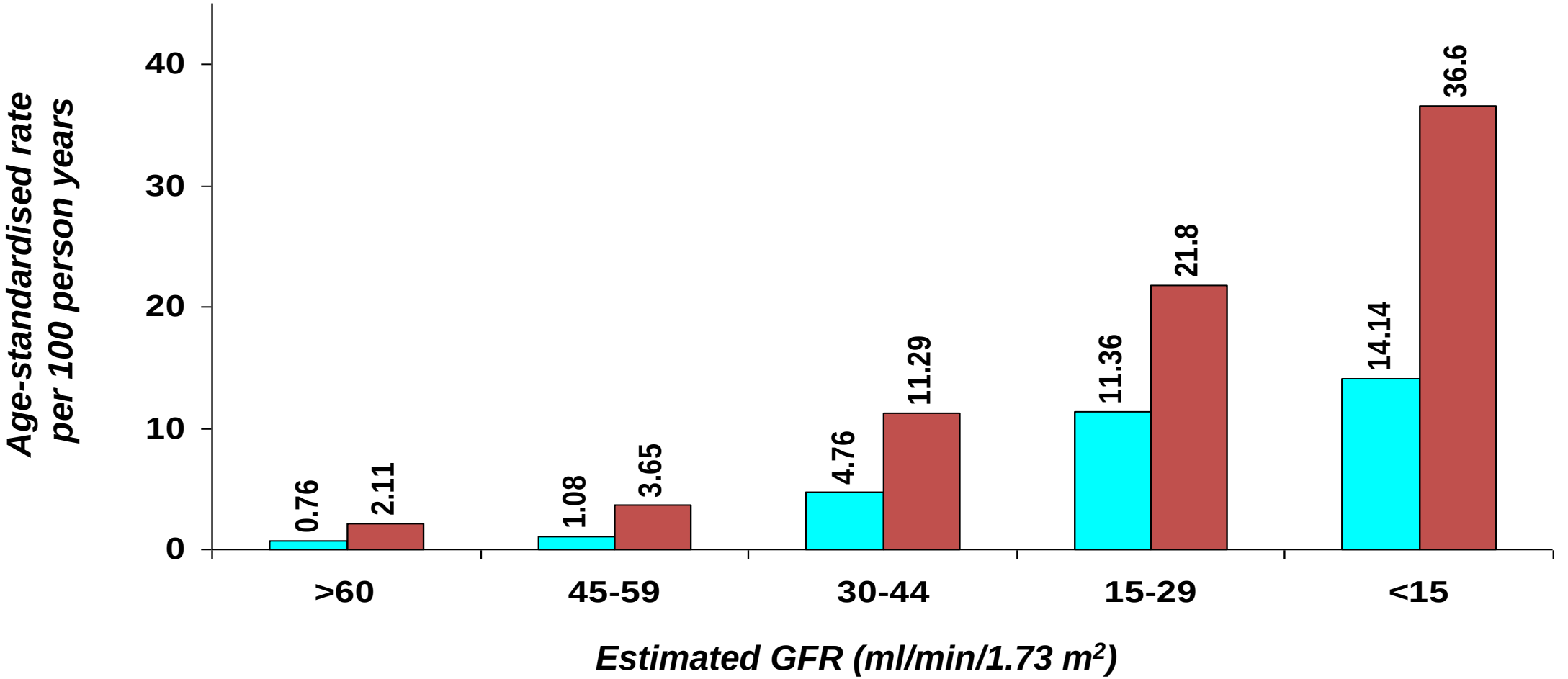
ESKD, end-stage kidney disease.
Brenner B, et al. N Engl J Med 2001; 345(12): 861–869.

IDNT



Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860.

Rates of death and cardiovascular events rise as renal function declines

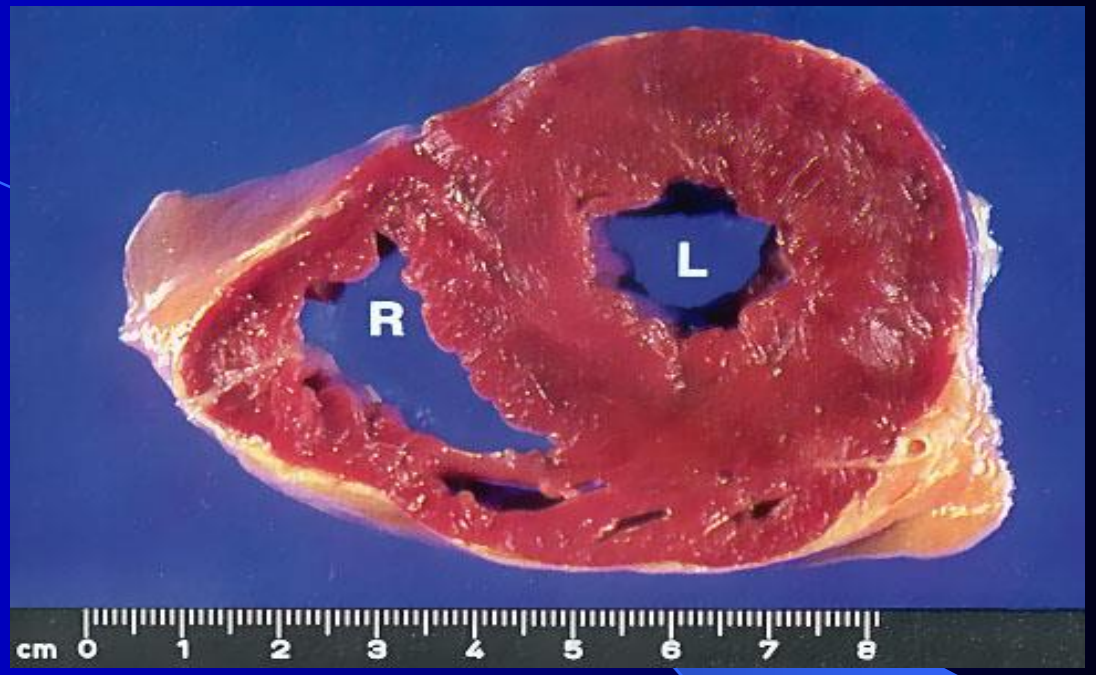


Go et al *et al. NEJM 2004 23: 351(13): 1296-1305*

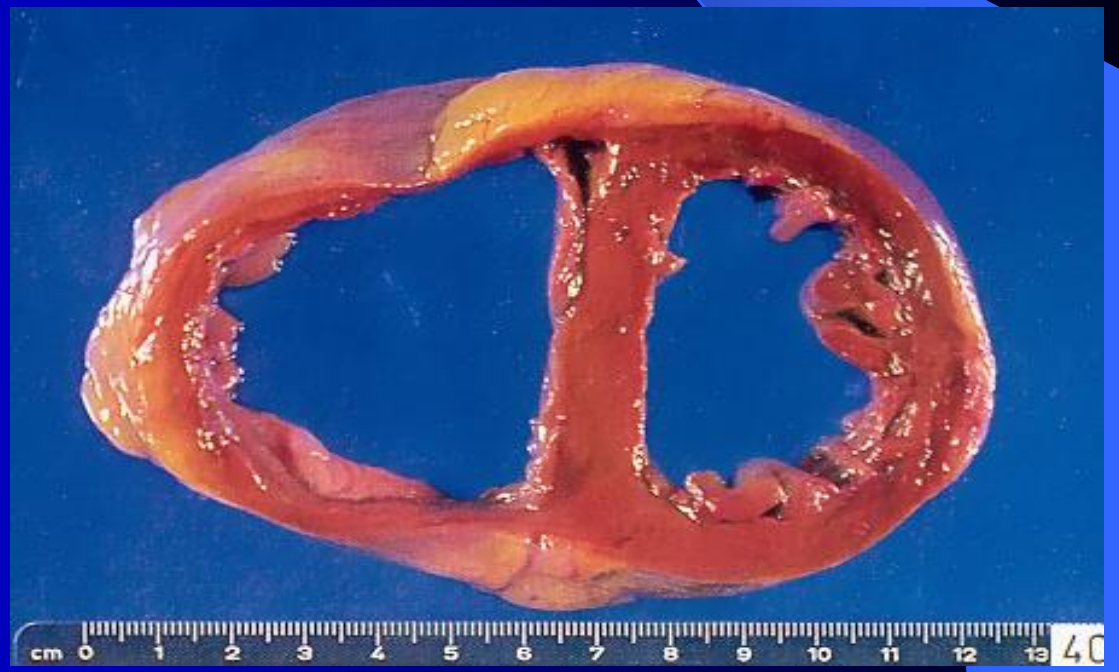
CVS risk factors in CKD

- Cardiac structural changes – LVH and CCF
- Atherosclerosis
- Vascular calcification/arterial stiffness
- Phosphate
- Vitamin D deficiency
- Anaemia
- Metabolic changes
- Inflammation

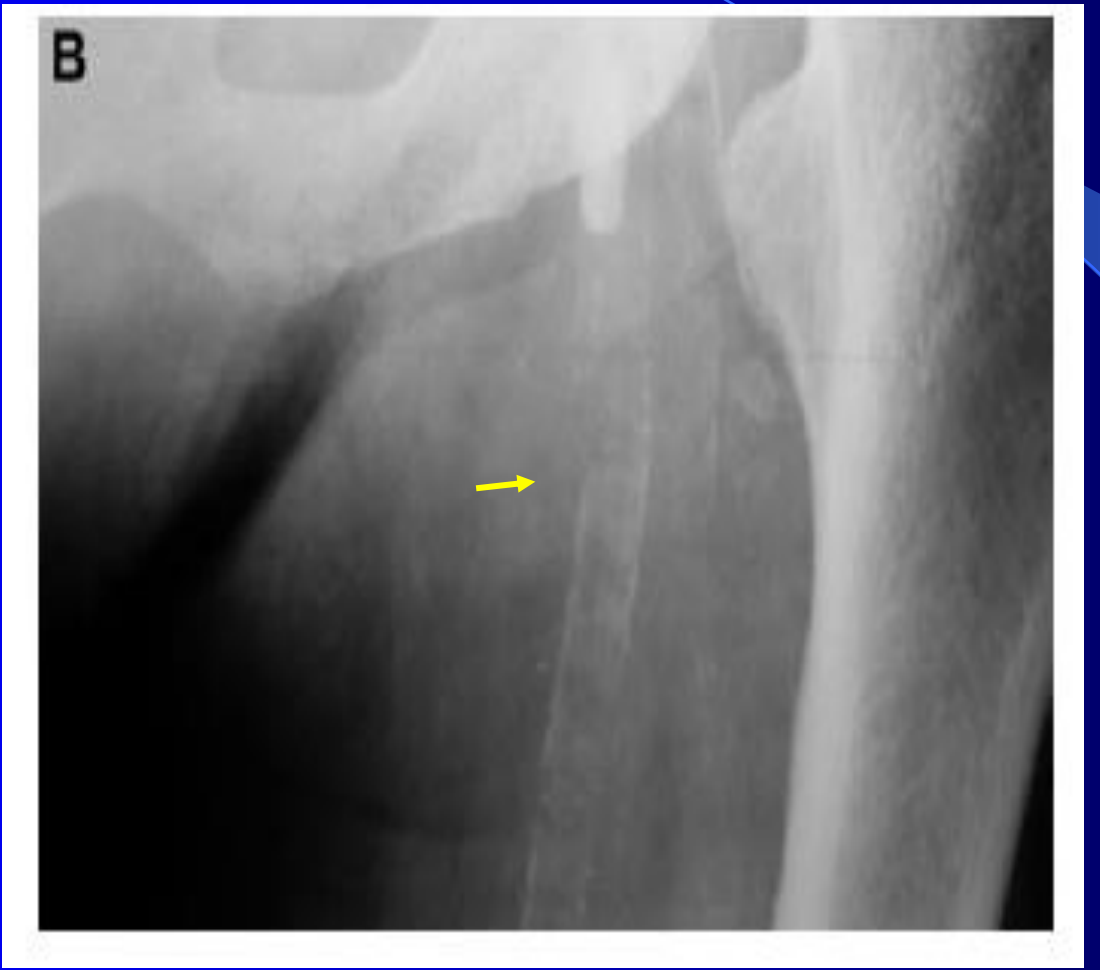
Concentric hypertrophy



Eccentric hypertrophy



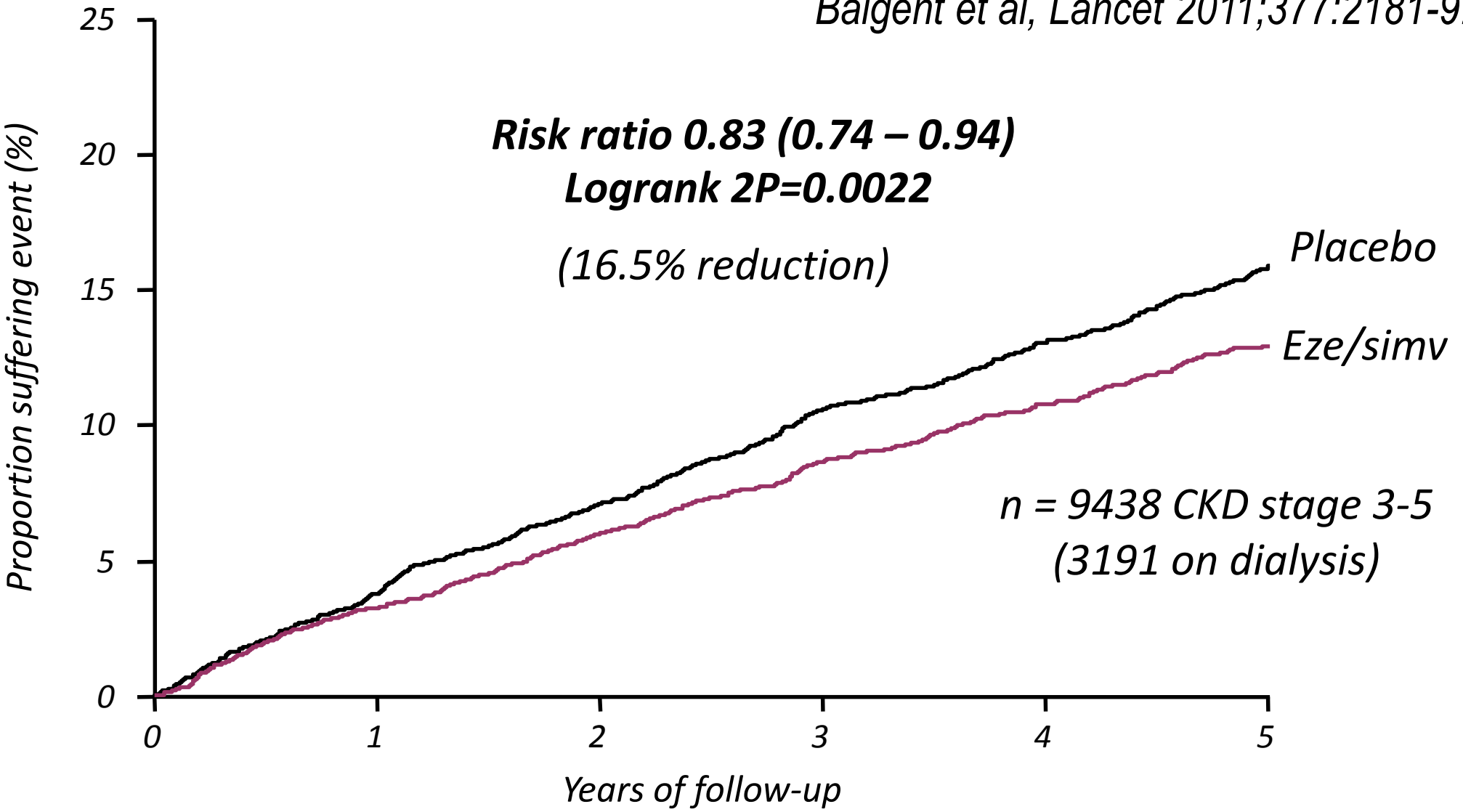
Arterial Medial Calcification in ESKD



London GM, et al. *Nephrol Dial Transplant*. 2003;18:1731-1740

SHARP: Major Atherosclerotic Events

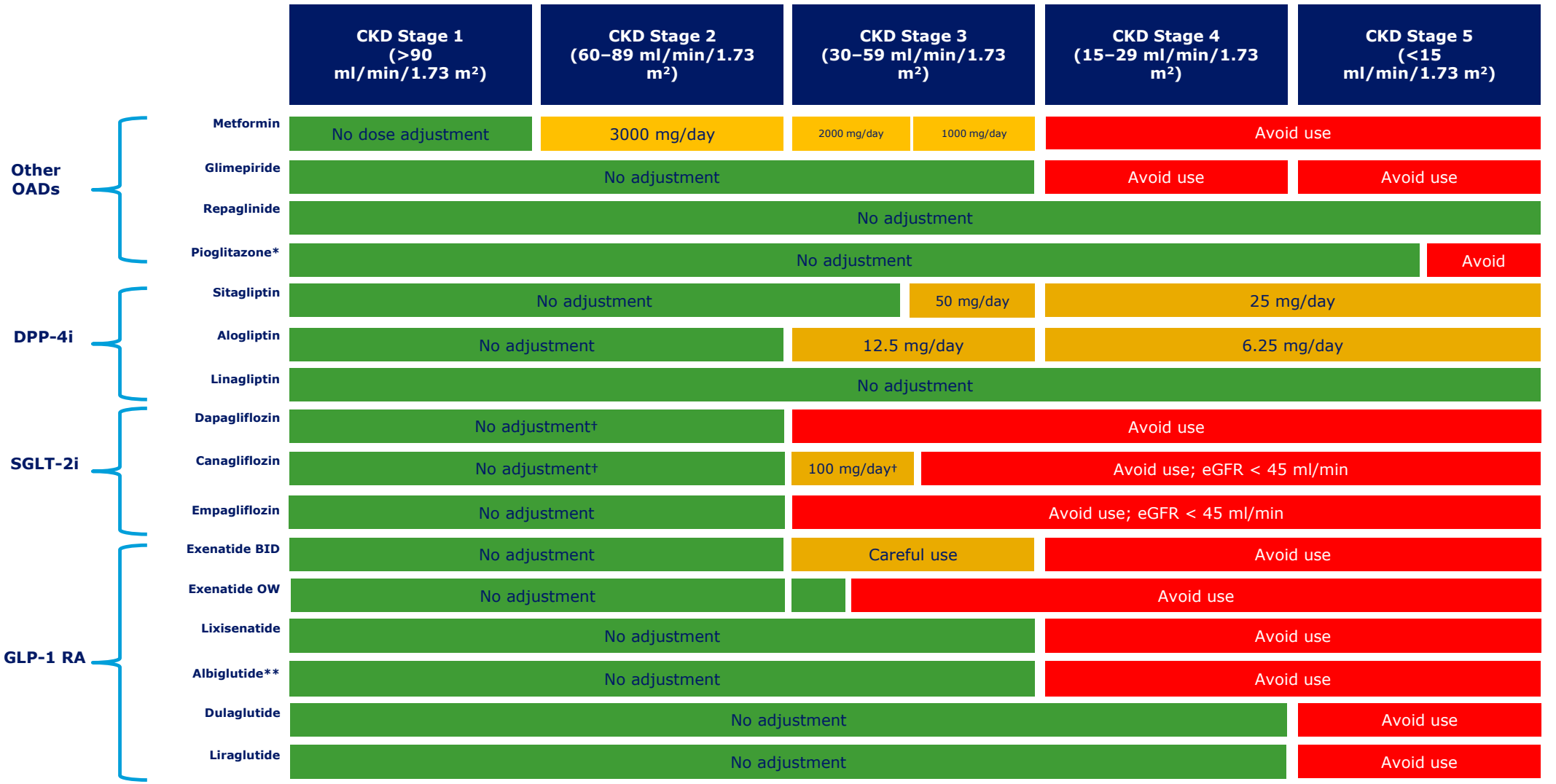
Baigent et al, Lancet 2011;377:2181-92.



Exciting new results with SGLT-2 inhibitors : CREDENCE study

Job code: UK/VT/0118/0048a
Date of preparation: February 2018

Renal licences of commonly used antidiabetic drugs

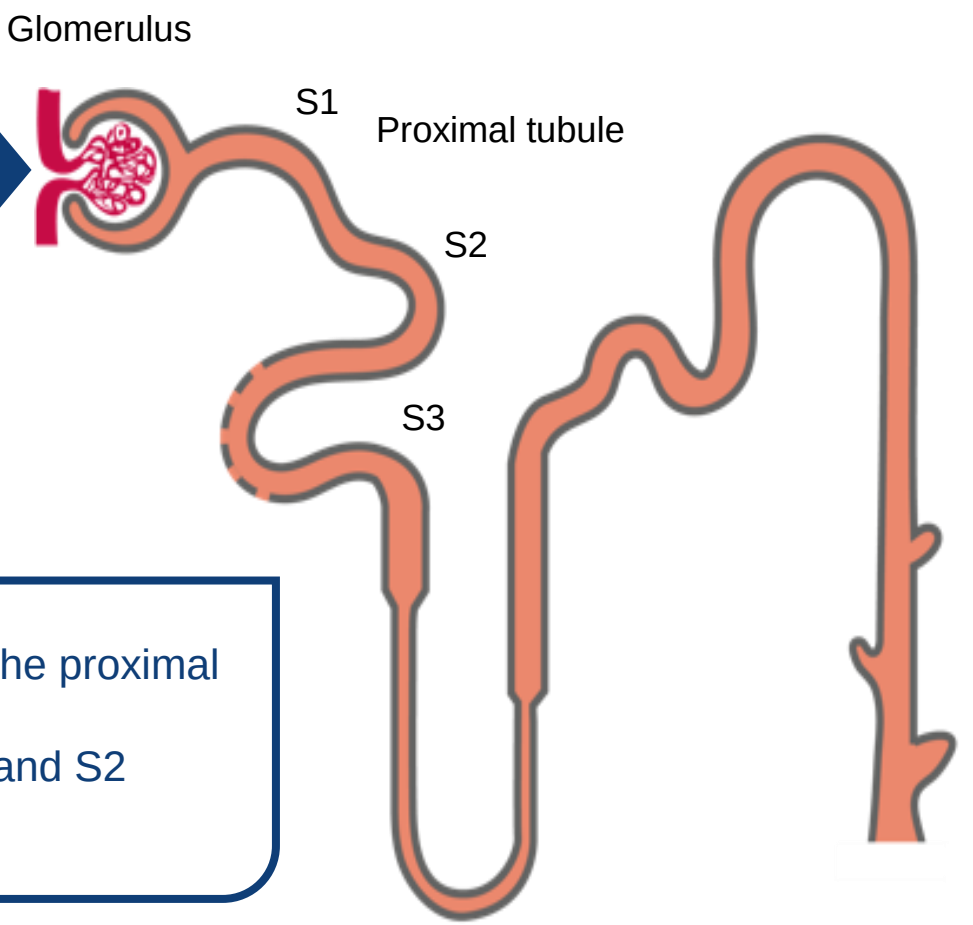


*Pioglitazone should be avoided in dialysed patients. No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min); †Additional licence precautions; **Not launched – Final licence precautions not confirmed. CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OADs, oral antidiabetics; SGLT-2i, sodium glucose co-transporter-2 inhibitor.

1. Product SmPCs. Available at: www.medicines.org.uk/EMC/medicine/

Most filtered glucose is reabsorbed by SGLT2 and SGLT1

180 g of glucose and 25,000 mmol sodium (Na^+) is filtered/day[1,2]



Urine output is 0.1–2 L/day[3]

40–220 mmol/day Na^+ secreted[4]

Very little or no glucose excreted in healthy people[5]

Glucose reabsorbed in the proximal tubule:[5]

- 90% by SGLT2 in S1 and S2
- 10% by SGLT1 in S3

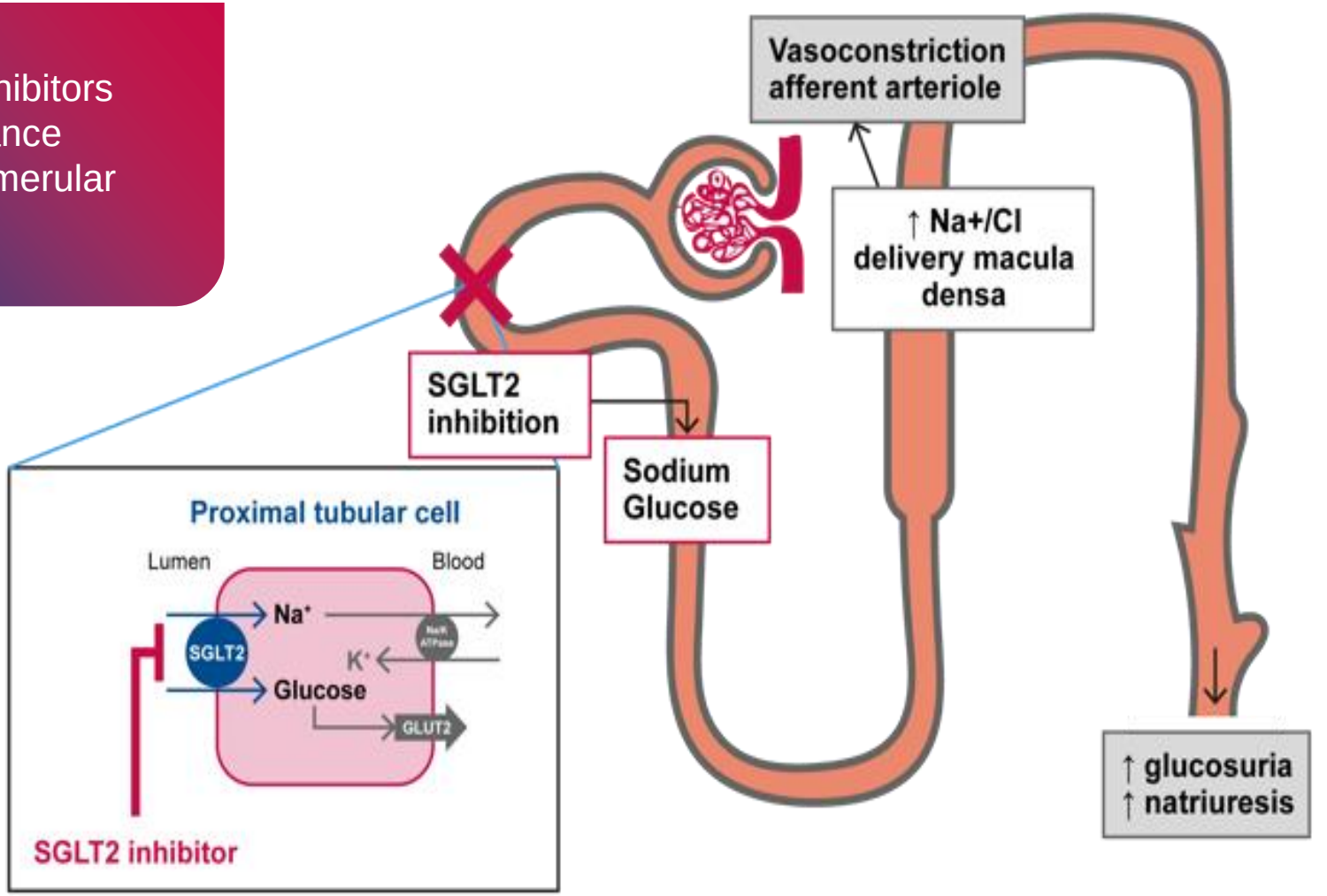
1. Wright EM, et al. J Int Med 2007;261:32–43; 2. Finkelstien FO, et al. Biol Med 1979;52:271–287; 3. MedlinePlus. Urine 24-hour volume. Available at: medlineplus.gov/ency/article/003425.htm (accessed October 2018); 4. Medscape. Urine Sodium: Reference Range, Interpretation, Collection and Panels. Available at: emedicine.medscape.com/article/2088449-overview (accessed October 2018). 5. Chao EC. Nat Rev Drug Discov 2010;9:551–559.

Na^+, sodium; SGLT, sodium–glucose co-transporter.

UK/INV-18021o; October 2018

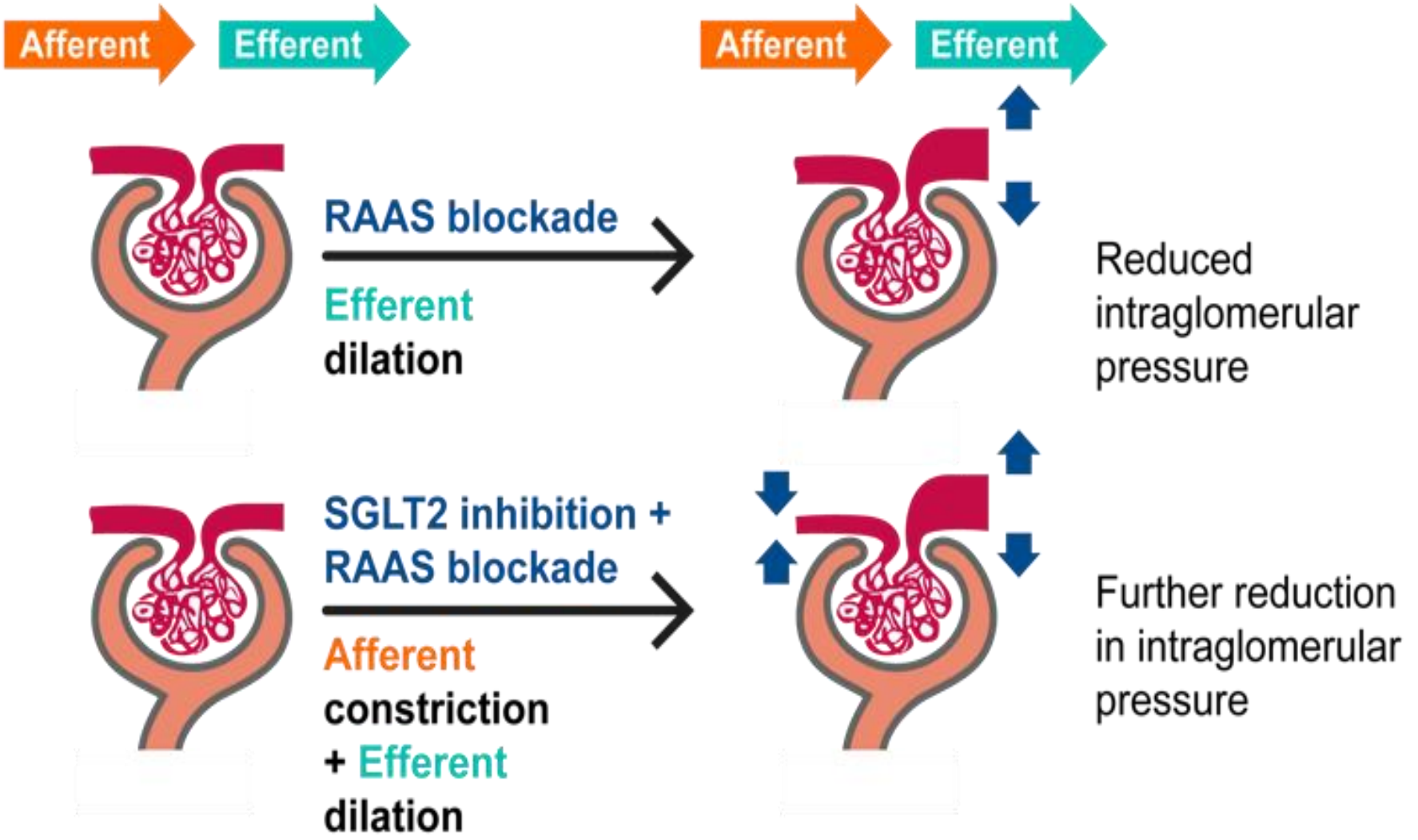
Tubuloglomerular feedback

SGLT2 inhibitors may enhance tubuloglomerular feedback



1. van Bommel EJ, et al. Clin J Am Soc Nephrol 2017;12:700-710.

Mechanism of action

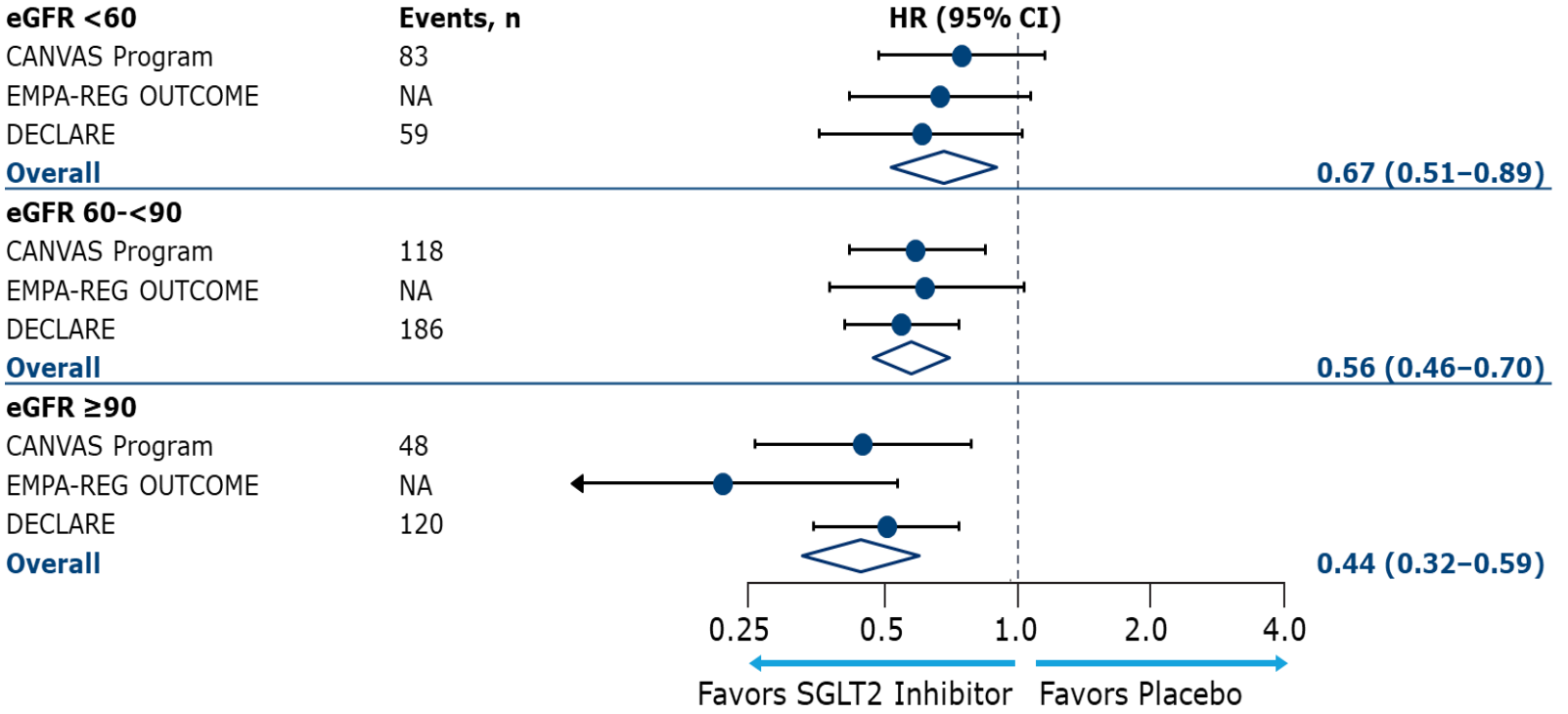


1. Cherney DZ, et al. Circulation 2014;129:587-97.

Why Is CREDENCE Important?

- CV outcomes trial results suggested possible attenuation of renal effects in patients with reduced kidney function

Composite of worsening of renal function, ESKD, or renal death

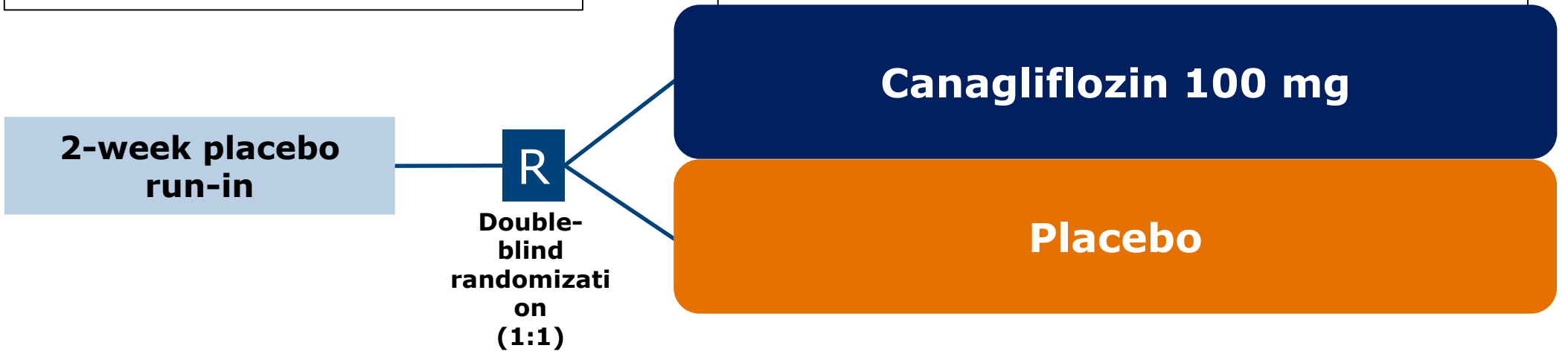


Interaction
P value = 0.0258

Study Design

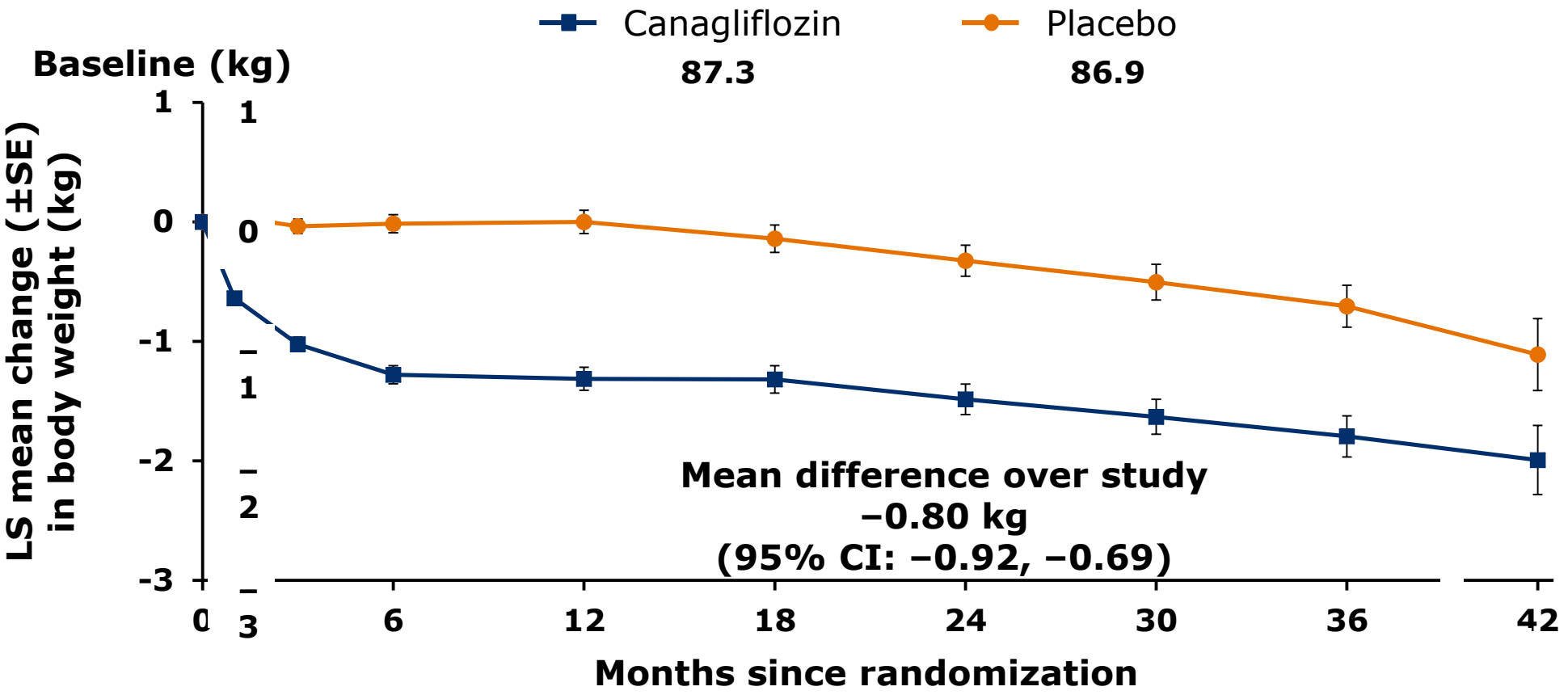
Key inclusion criteria
- ≥30 years of age
- T2DM and HbA1c 6.5% to 12.0%
- eGFR 30 to 90 mL/min/1.73 m^2
- UACR 300 to 5000 mg/g
- Stable max tolerated labelled dose of ACEi or ARB for ≥4 weeks

Key exclusion criteria
- Other kidney diseases, dialysis, or kidney transplant
- Dual ACEi and ARB; direct renin inhibitor; MRA
- Serum K^+ >5.5 mmol/L
- CV events within 12 weeks of screening
- NYHA class IV heart failure
- Diabetic ketoacidosis or T1DM



Participants continued treatment if eGFR was <30 mL/min/1.73 m^2 until chronic dialysis was initiated or kidney transplant occurred.

Effects on Body Weight



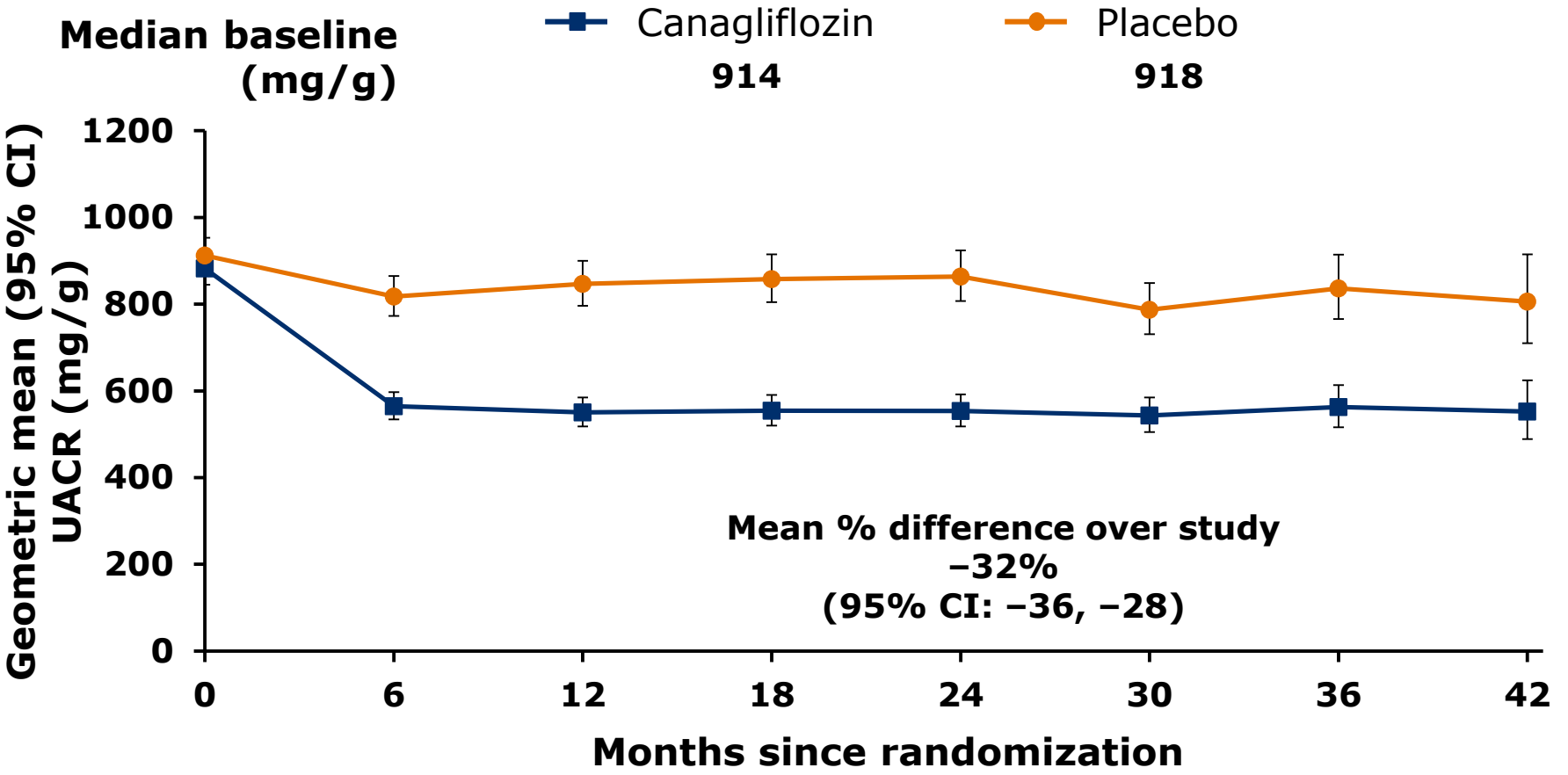
No. of participants

Placebo	2187	2126	2092	2005	1917	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1957	1830	1256	731	263

ITT analysis

CREDENCE

Effects on Albuminuria (UACR)

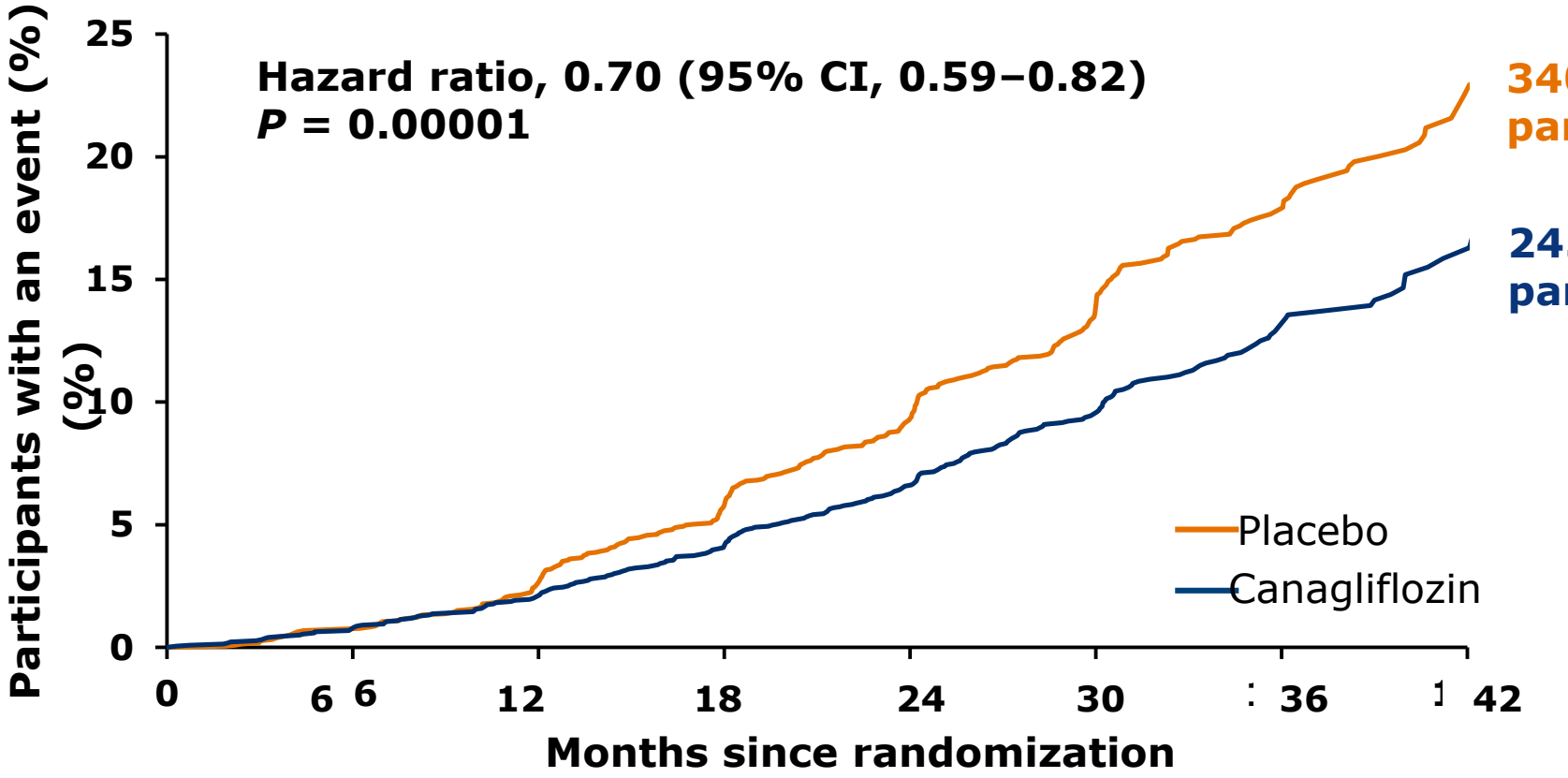


No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

ITT analysis

CREDENCE

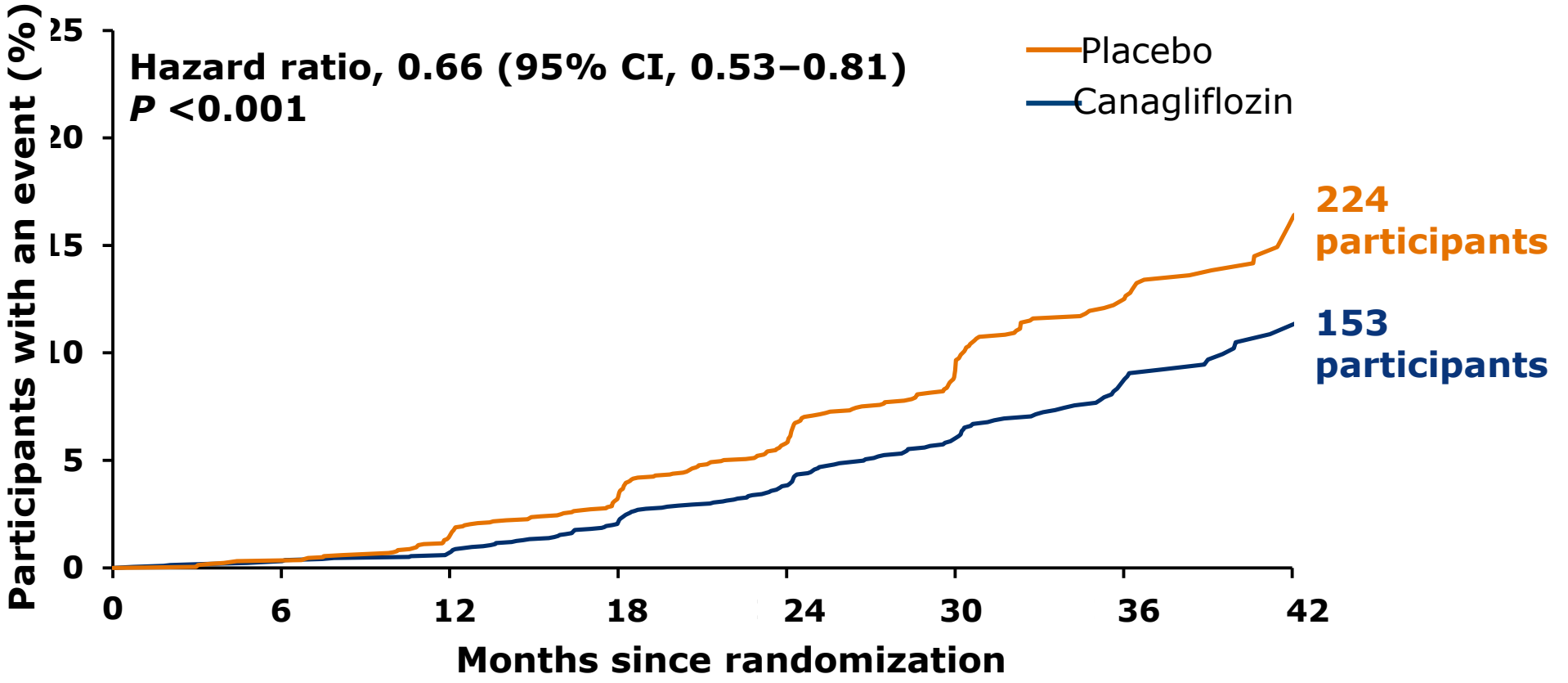
Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

CREDENCE

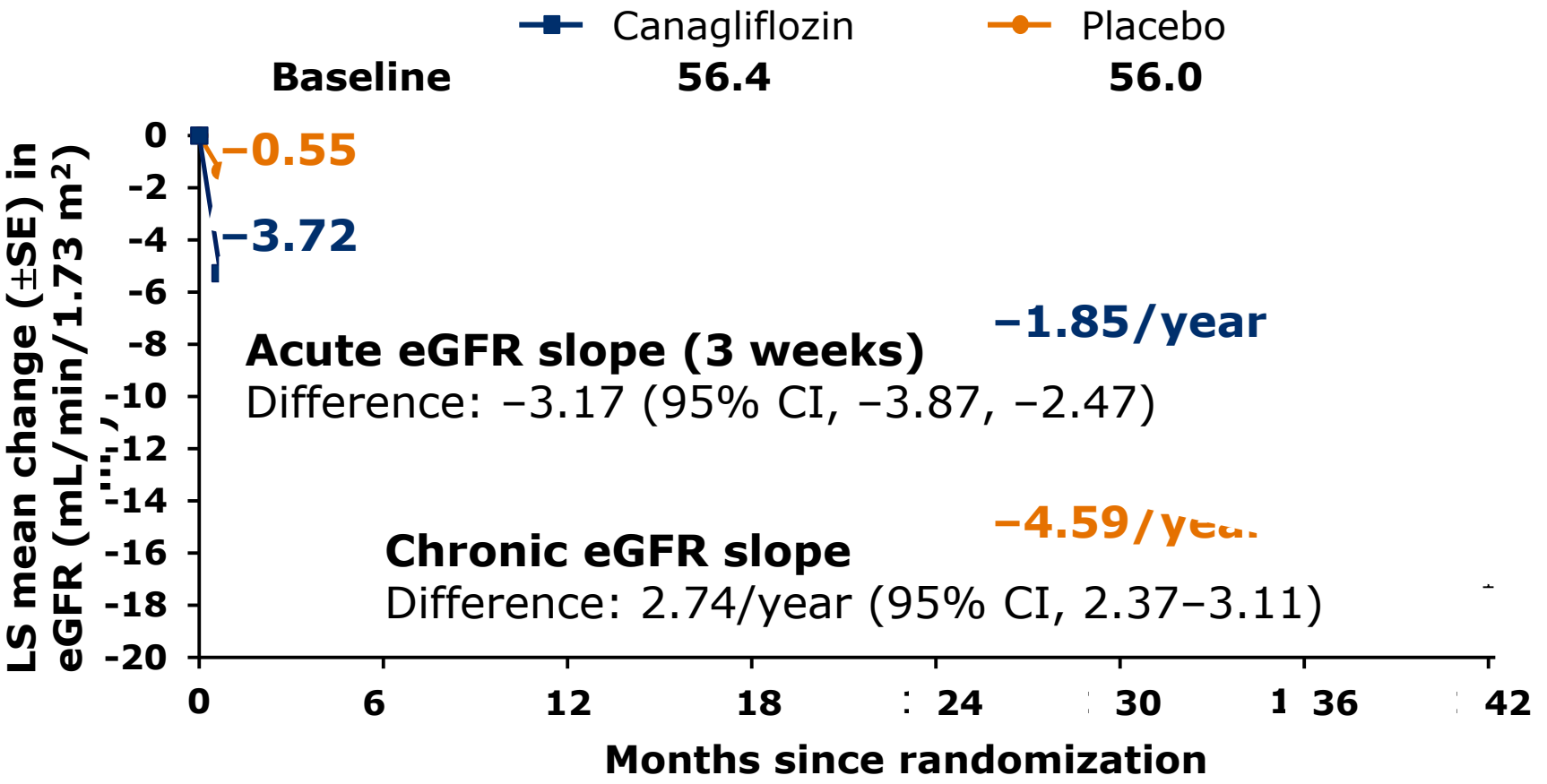
ESKD, Doubling of Serum Creatinine, or Renal Death



No. at risk								
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

CREDENCE

Effects on eGFR



No. of Participants

On treatment

Placebo 2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin 2179	2074	2005	1919	1782	1648	1116	652	241

CREDENCE

Summary : CKD and DKD

- CKD affects up to 10% of UK population
- DKD is commonest cause
- CKD associated with high CVS risk, greatest in DKD
- Clinical management is aimed at
  - Slowing progression (↓BP, ↓proteinuria)
  - CVS risk reduction
  - Managing complications (anaemia, metabolic bone disease)
- New class of anti-diabetic therapies shows great promise for future CKD management