Diabetes and Chronic Kidney Disease

Why the fuss and what should you know?

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Speaker Disclosure

Advisor board attendance

- Aspen
- AZ
- BI
- Medtronic
- Merk Serono
- MSD
- Novartis
- Servier
- Sanofi
- Novo Nordisk

Speaking fees

- Abbot
- Aspen
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- Cipla
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- Novo Nordisk
- Pfizer
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Research support

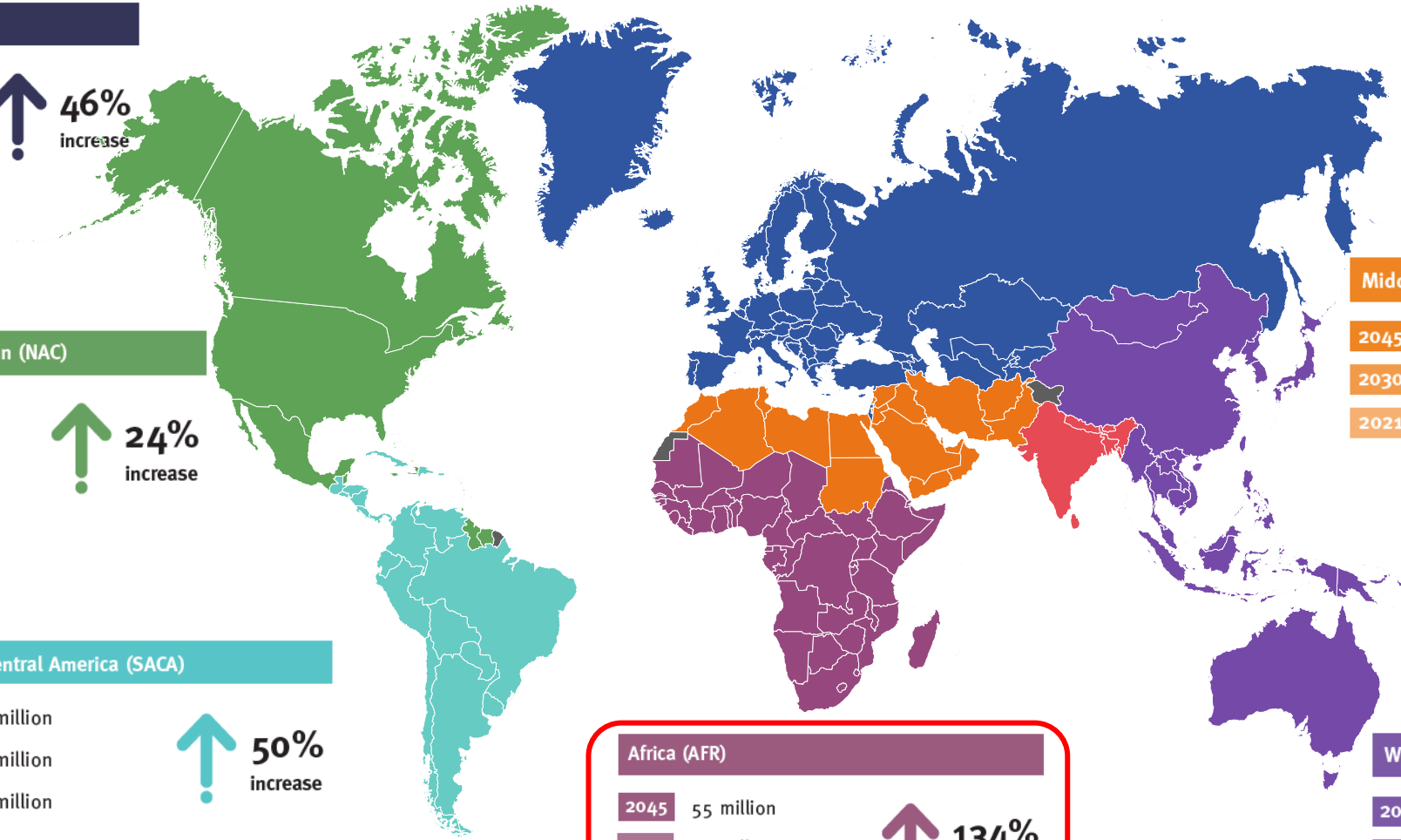
- Abbot
- Aspen
- AZ
- Sanofi
- Novartis

Overview

- Diabetes in 2023
- CKD
- Diabetes and CKD
- Screening
- Management
- Take Home Messages

Diabetes in 2023

Diabetes has reached pandemic proportions



World

2045	784 million
2030	643 million
2021	537 million

46% increase

Europe (EUR)

2045	69 million
2030	67 million
2021	61 million

13% increase

Middle East & North Africa (MENA)

2045	136 million
2030	95 million
2021	73 million

87% increase

North America & Caribbean (NAC)

2045	63 million
2030	57 million
2021	51 million

24% increase

South-East Asia (SEA)

2045	152 million
2030	113 million
2021	90 million

68% increase

South & Central America (SACA)

2045	49 million
2030	40 million
2021	32 million

50% increase

Africa (AFR)

2045	55 million
2030	33 million
2021	24 million

134% increase

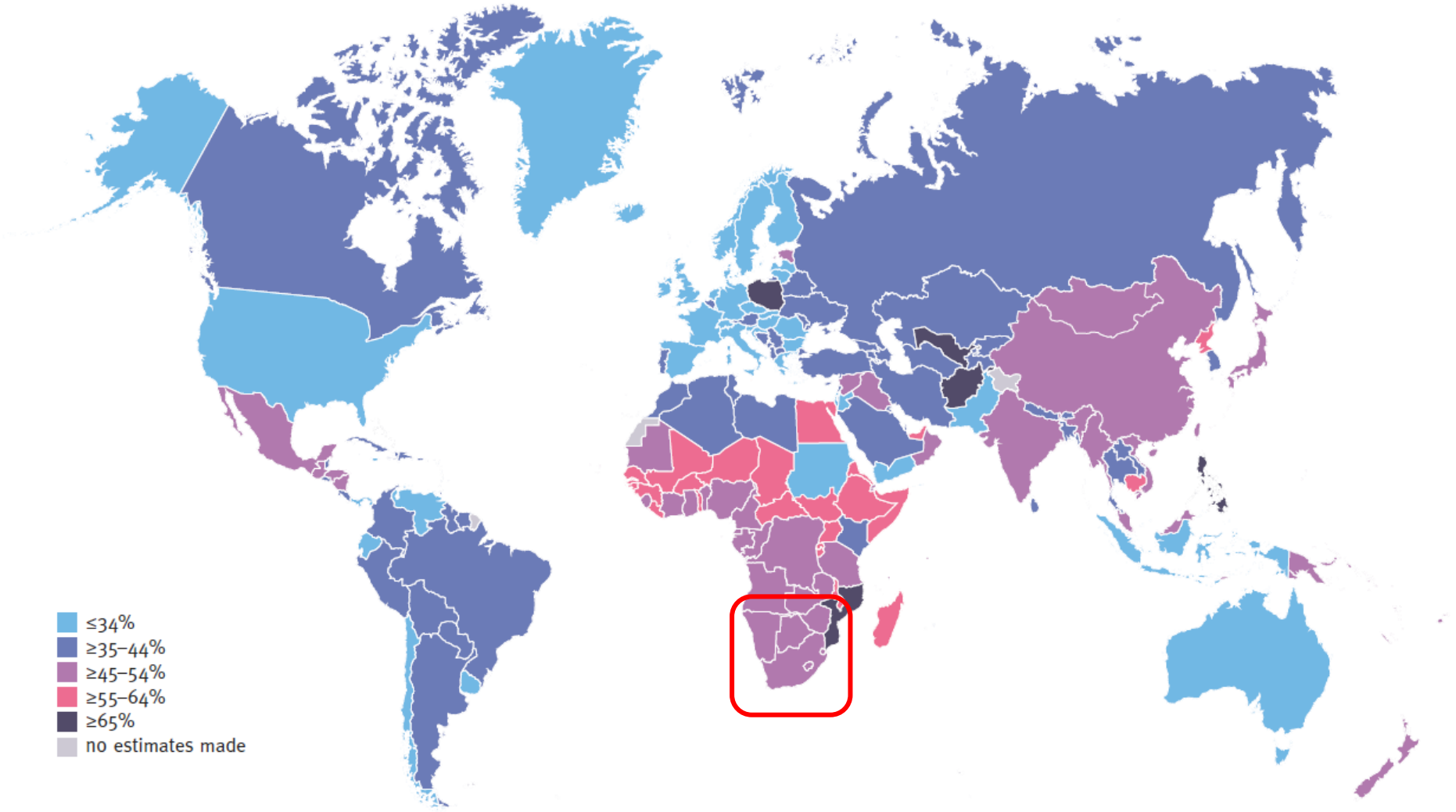
Western Pacific (WP)

2045	260 million
2030	238 million
2021	206 million

27% increase

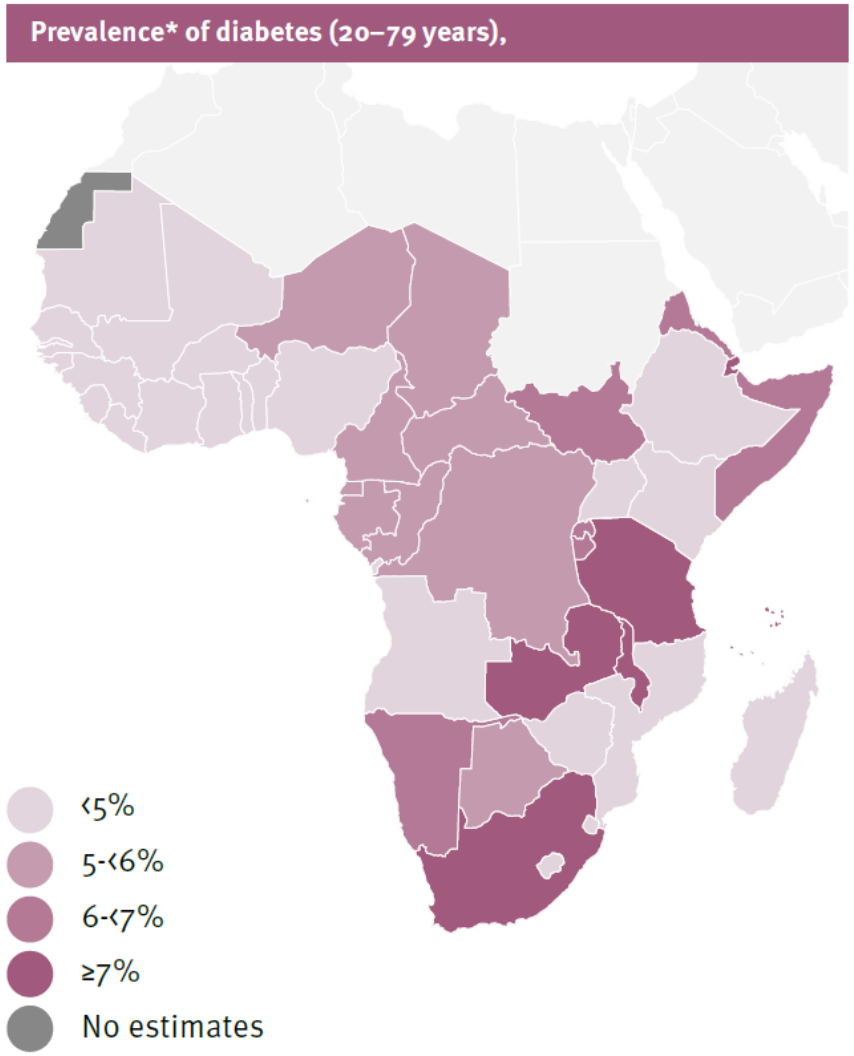
International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021

Many people are unaware of their diagnosis



International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021

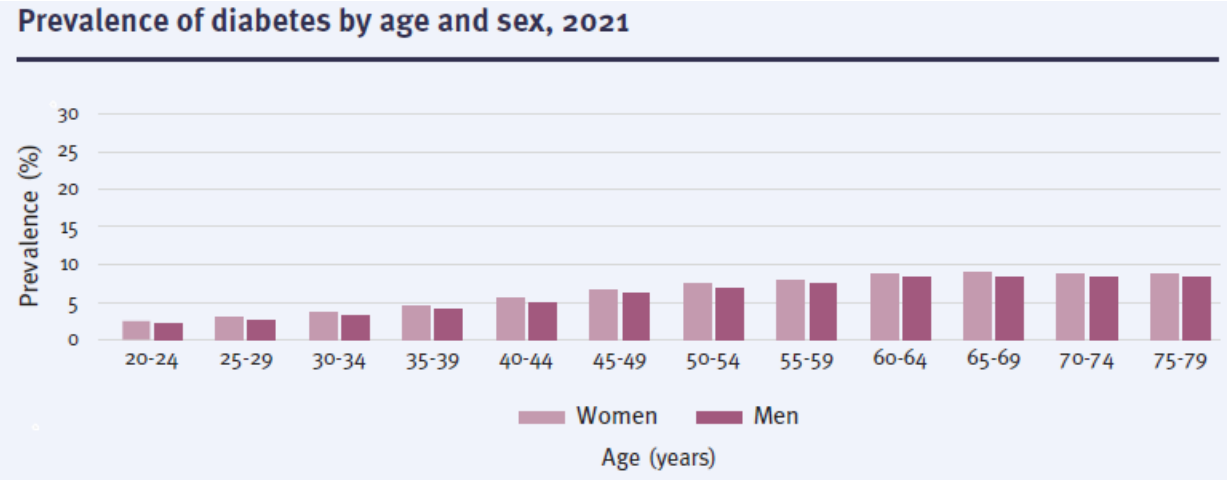
Lets look deeper into Africa



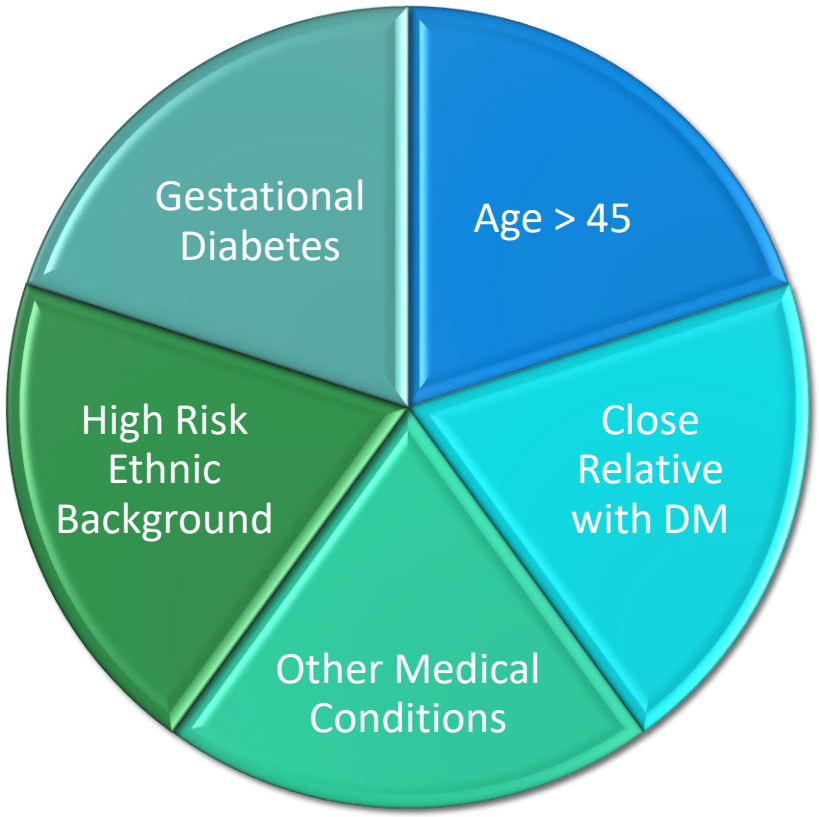
Top 5 countries for number of people with diabetes (20–79 years)	2011	2021
South Africa	1.9m	4.2m
Nigeria	3.1m	3.6m
United Republic of Tanzania	472,900	2.9m
Ethiopia	1.4m	1.9m
Democratic Republic of the Congo[i]	730,700	1.9m

[i] *based on extrapolation from similar countries*

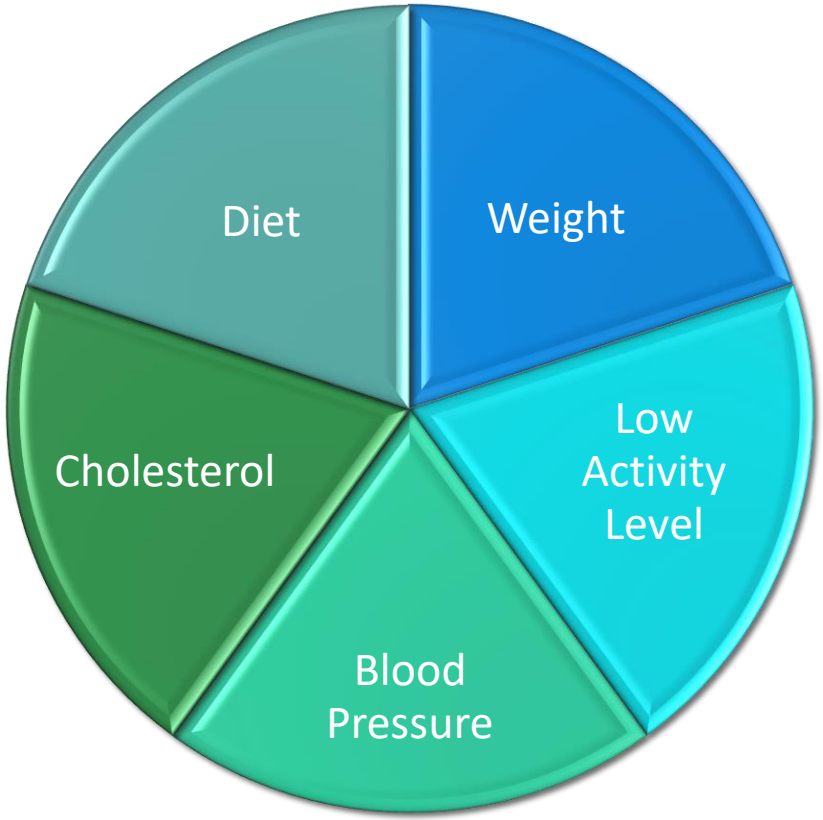
m=million b = billion



Risk Factors

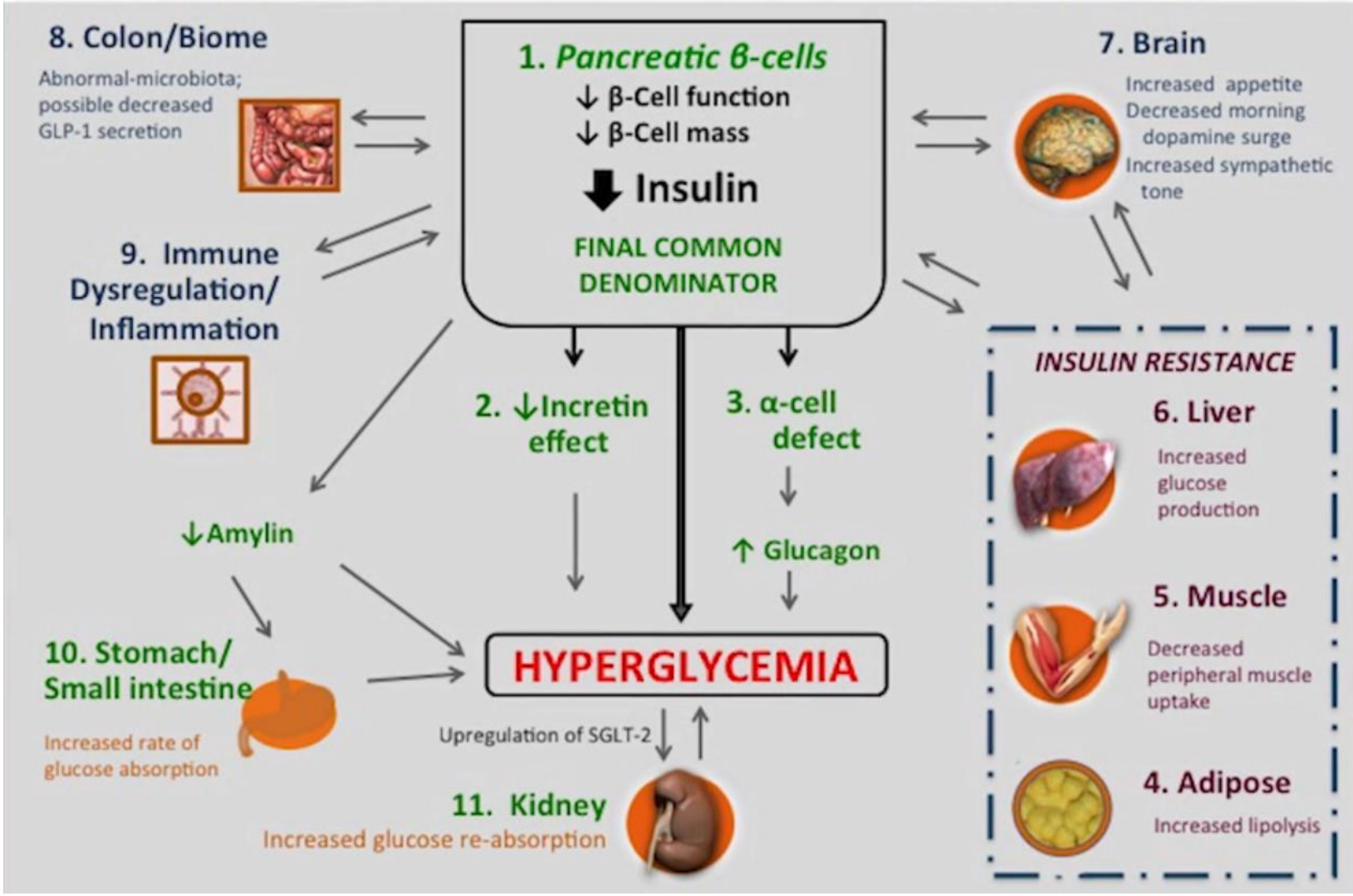


Non Modifiable Risk Factors

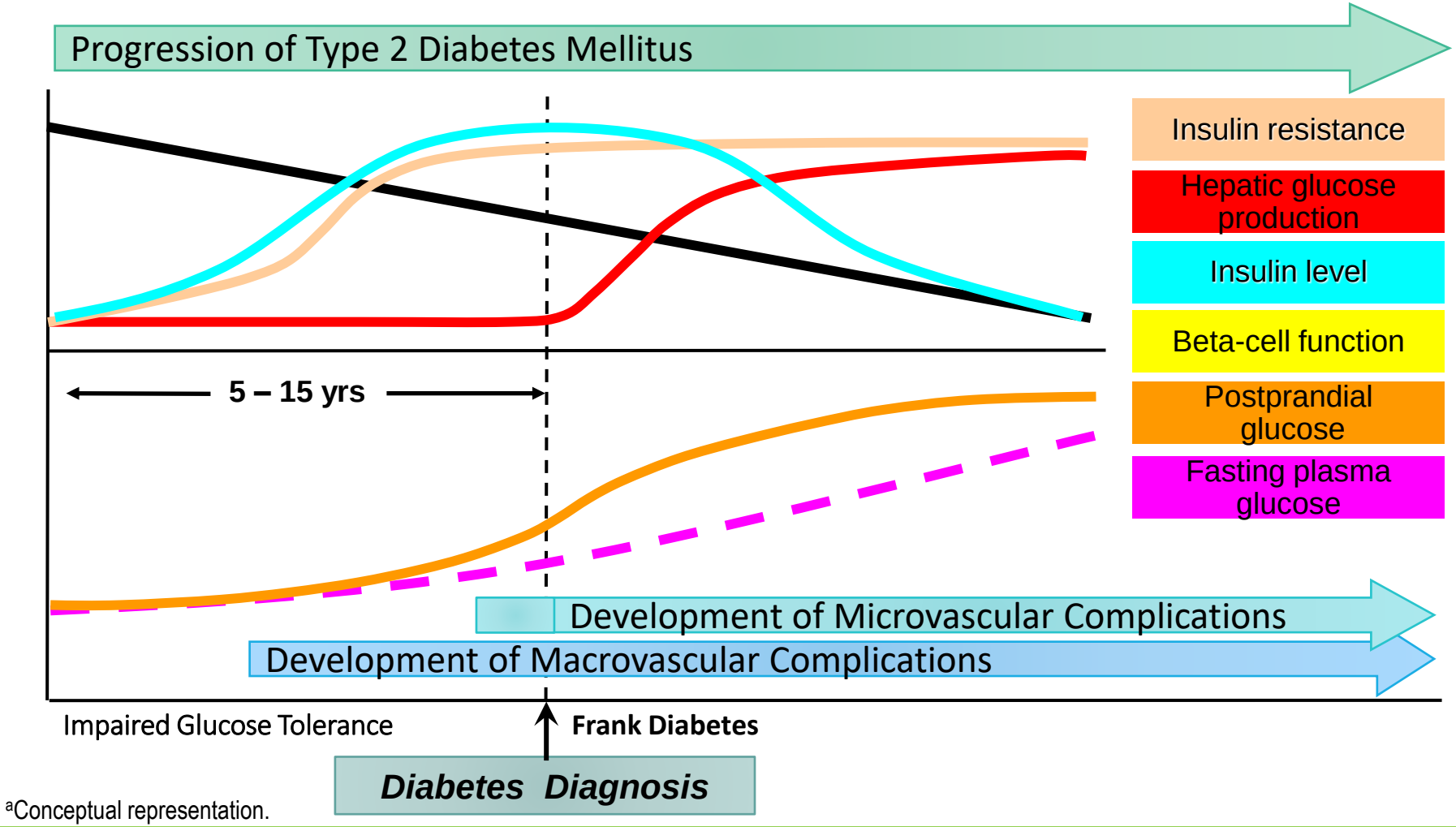


Modifiable Risk Factors

Our understanding of Diabetes has improved



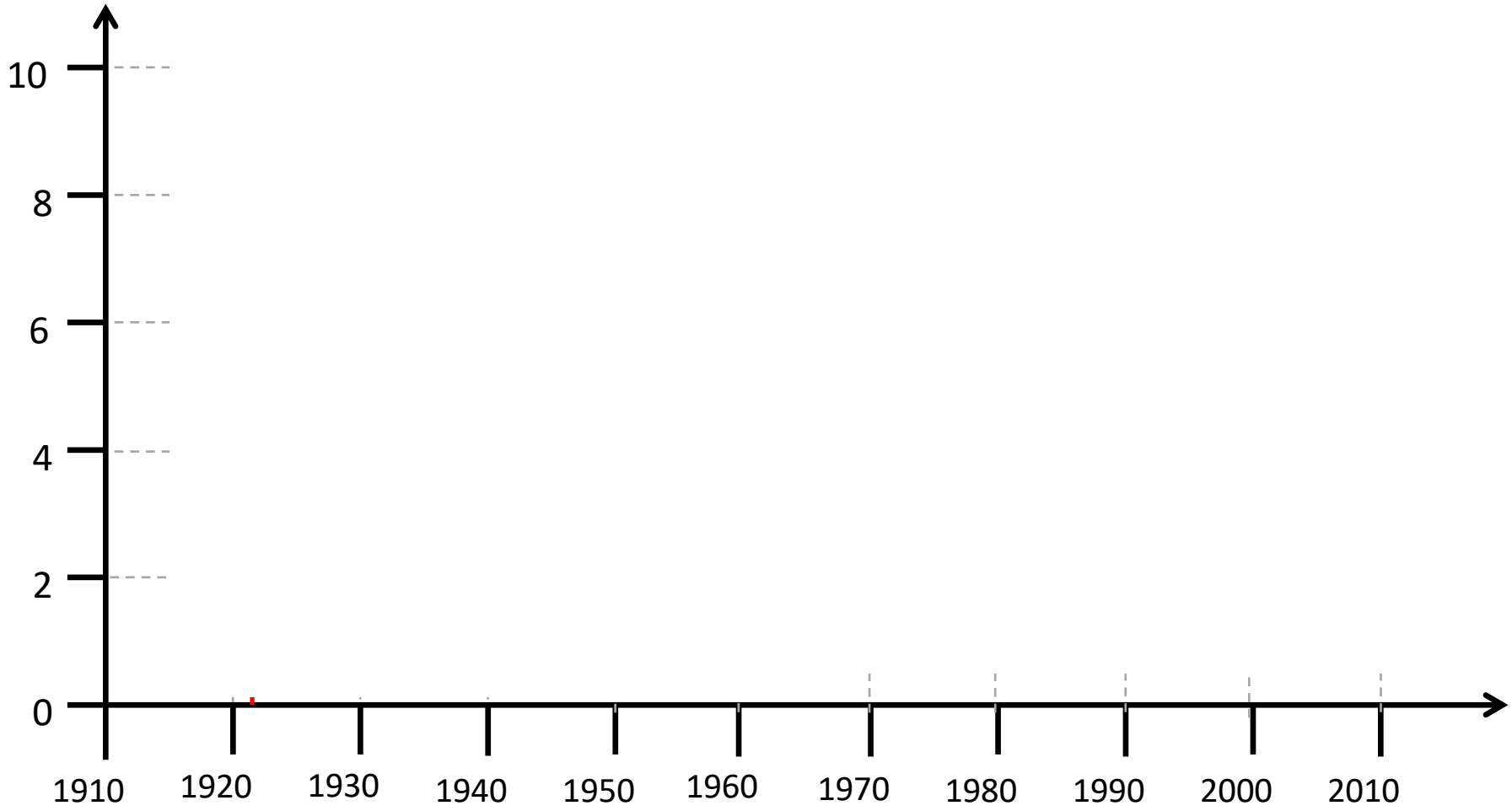
Natural history of T2DM



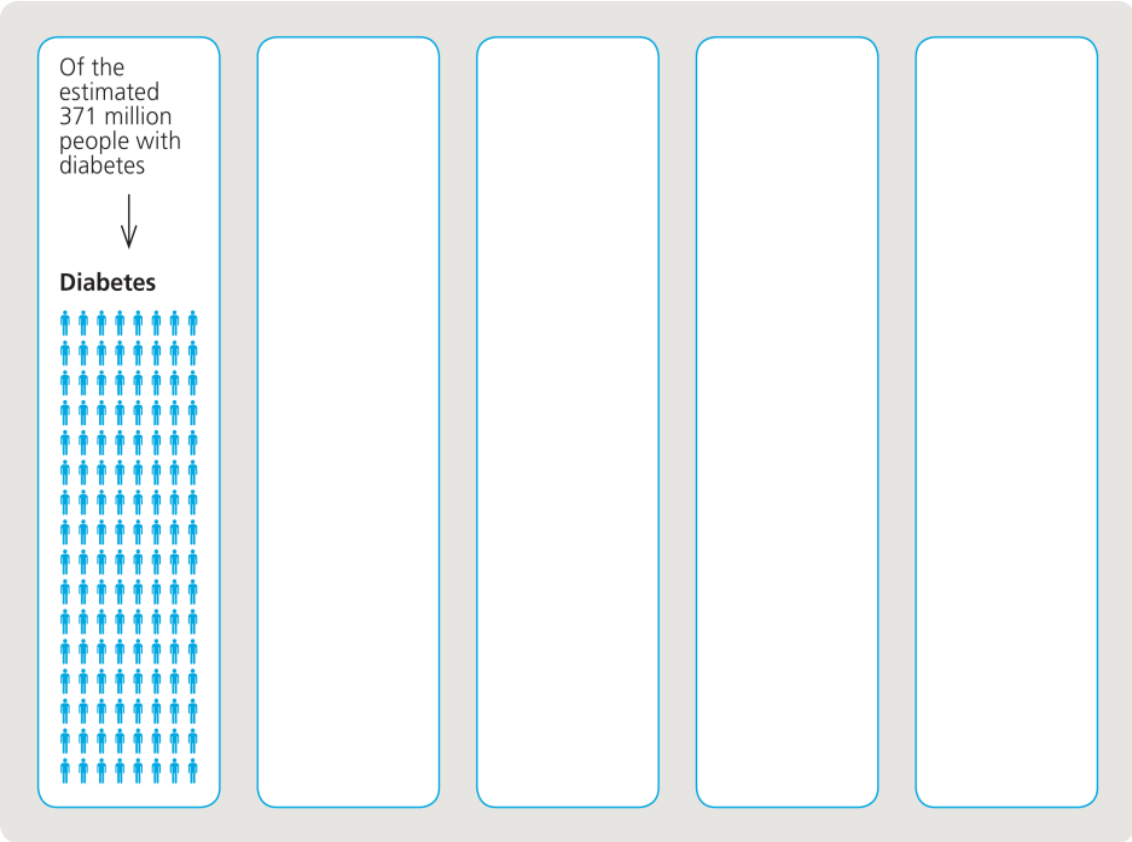
[a]Conceptual representation.

1. Reproduced with permission of Elsevier from Ramlo-Halsted et al. *Primary Care.* 1999; 26(4):771–789.

We now have more treatment options



Rules of Halves

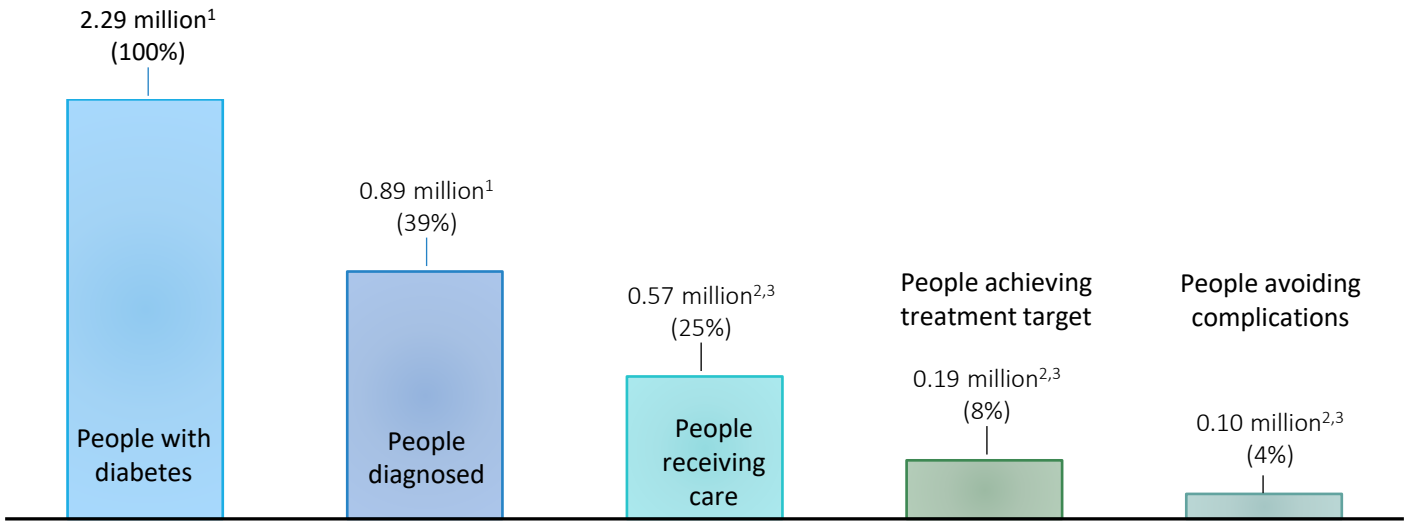


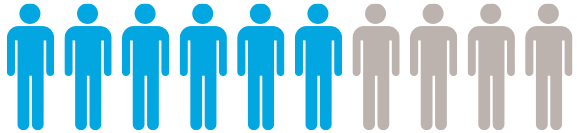
The ‘rule of halves’ states that only around **6% of people** with diabetes are estimated to achieve well-managed diabetes and desired health outcomes.

Actual rates of diagnosis treatment, targets and outcomes vary from country to country.[1]

* Hart J.T., Rule of Halves: implications of increasing diagnosis and reducing dropout for future workload and prescribing costs in primary care, Br J Gen Pract 1992, March; 42(356):116–119, and W.C.S. Smith, A.J. Lee, I.K. Coombie, H. Tunstall-Pedoe, Control of blood pressure in Scotland: The rule of halves, Br. Med. J, 300 (1990): 981–983.

Rules of Halves in South Africa





OVER **SIX** OUT OF **TEN**

people with diabetes **do not** know they have diabetes[1]

LESS THAN **ONE** IN **TWELVE**

people with diabetes are expected to reach treatment targets[2,3]

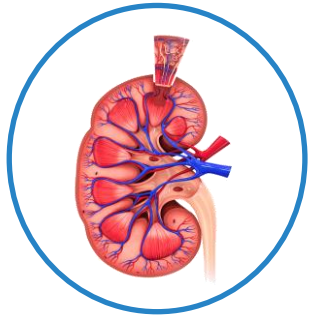
Diabetes is responsible for major complications such as stroke, heart attack, blindness, kidney failure and lower limb amputation. The **RULE OF HALVES** outlines five hurdles to overcome to get diabetes successfully under control.

References: 1. IDF. Diabetes Atlas, Seventh Edition, 2015. Available at:http://www.diabetesatlas.org/component/attachments/?task=download&id=116. 2. Hart JT. Rule of Halves: implications of increasing diagnosis and reducing dropout for future workload and prescribing costs in primary care, *Br J Gen Pract*, 1992; 42(356):116–119. 3. Statistics South Africa. 2015 Mid-year statistics. http://statssa/gov/za/publications/P0302/P03022015 accessed 06 April 2016.

Complications of Diabetes

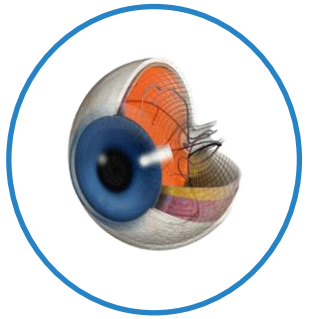
50–80% of people with diabetes die of cardiovascular disease[2]

44% of new kidney failure cases are observed in patients with diabetes[3]



60% of non-traumatic lower-limb amputations occur in diabetes patients ≥20 years old[3]

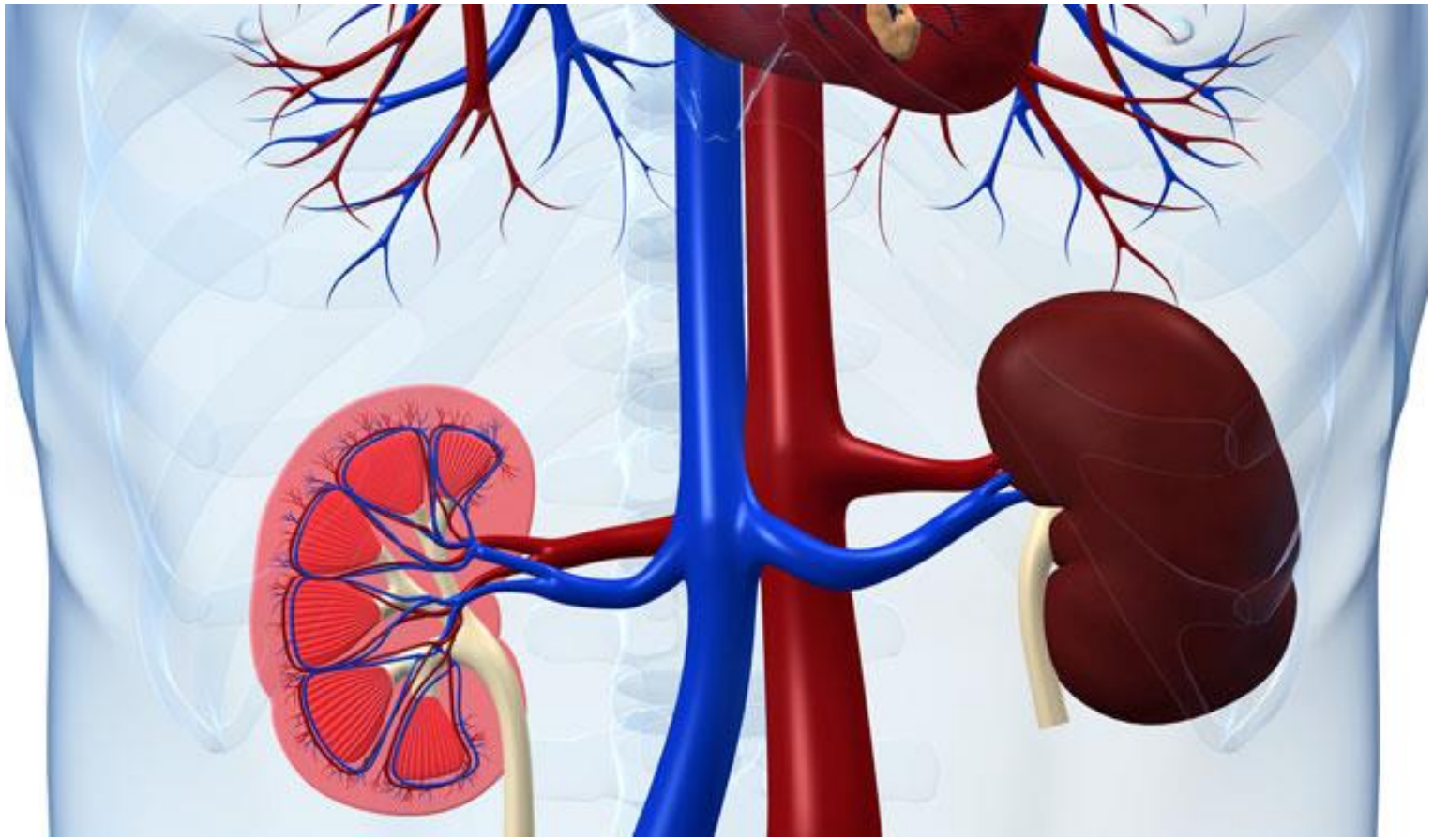
16% of people aged >65 years with diabetes die of stroke[4]



29% of people with diabetes aged ≥40 years have diabetic retinopathy[3]

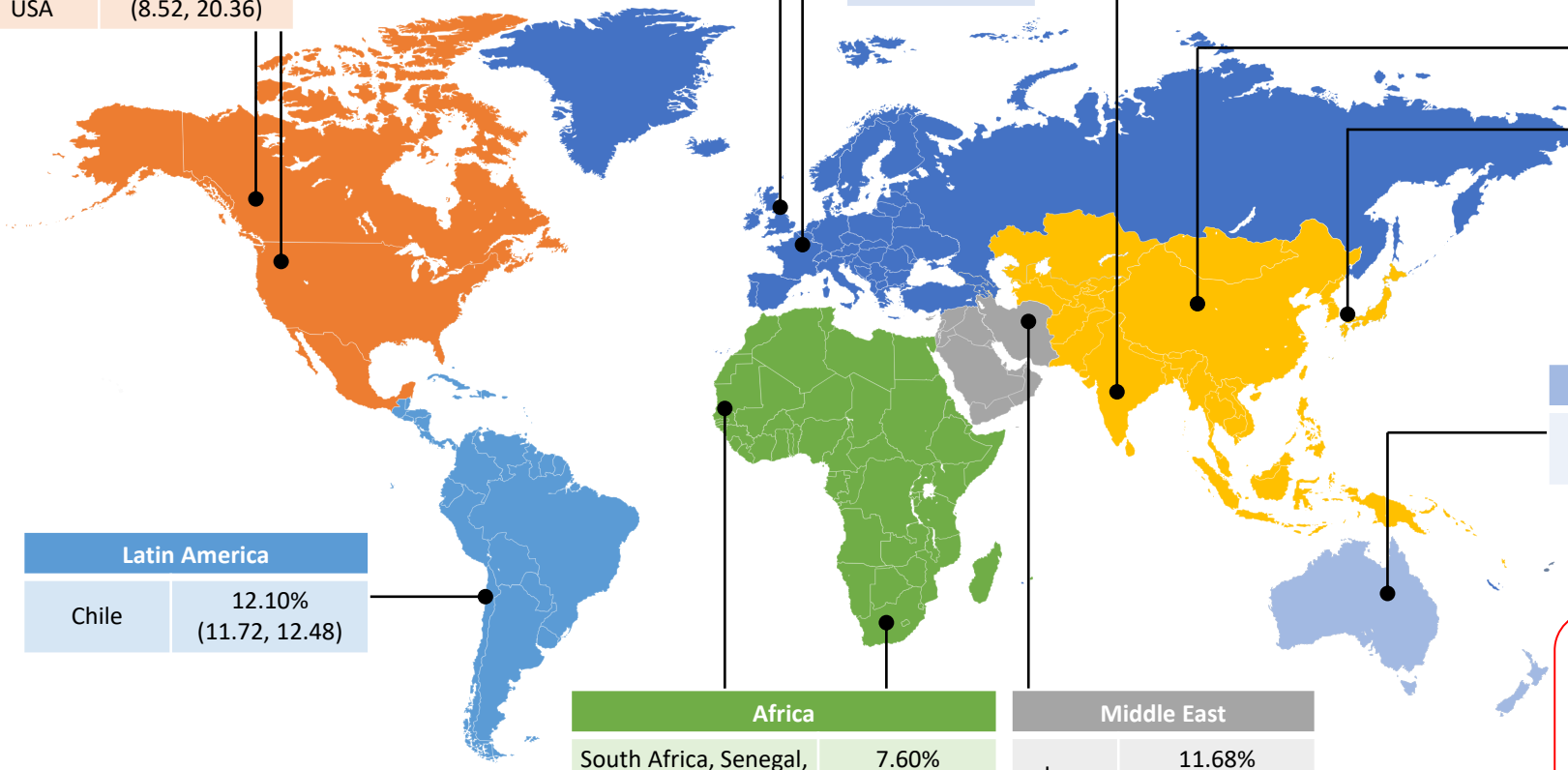
1. International Diabetes Federation. *IDF Diabetes Atlas*. 7th edn. 2015. www.idf.org/diabetesatlas (accessed 22 Feb 2016); 2. WHO. 10 Facts about Diabetes: www.who.int/features/factfiles/diabetes/facts/en/index5.html (accessed 22 Feb 2016); 3. Adapted from: CDC 2014 National Diabetes Fact Sheet: www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf (accessed 22 Feb 2016); 4. American Heart Association. Statistical Fact Sheet. 2014 www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_462019.pdf (accessed 22 Feb 2016)

Chronic Kidney Disease



Global Prevalence of CKD[1]

Meta-analysis estimating the global prevalence of CKD (stages 3–5)[2,a]



North America	
Canada, USA	14.44% (8.52, 20.36)

Europe
11.86% (9.93, 13.79)

Asia	
India, Bangladesh	6.76% (3.68, 9.85)
China, Taiwan, Mongolia	10.06% (6.63, 13.49)
Japan, South Korea, Oceania	11.73% (5.36, 18.10)

Australasia	
Australia	8.14% (4.48, 11.79)

Latin America	
Chile	12.10% (11.72, 12.48)

Africa	
South Africa, Senegal, Congo	7.60% (6.10, 9.10)

Middle East	
Iran	11.68% (4.51, 18.84)

A staggering ~840 million people worldwide are affected

[a]Global prevalence reported as percentage with 95% confidence intervals. CKD = chronic kidney

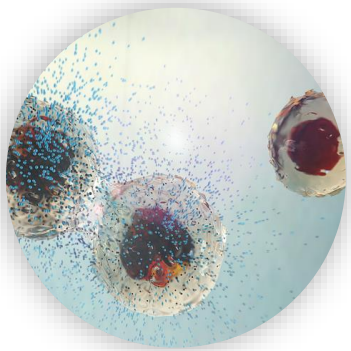
1. Jager KJ et al. *Nephrol Dial Transplant.* 2019;34:1803-1805; 2. Hill NR et al. *PLoS One.* 2016;11:e0158765.

Chronic Kidney Disease – A silent progressive killer

~840 MILLION

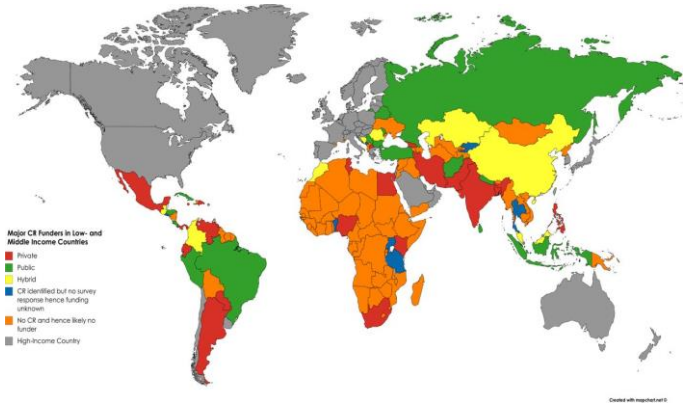
HAVE CKD[1]

>2.5 MILLION



On RRT, but expected to be **5.4 M by 2030[2]**

Up to 7 MILLION

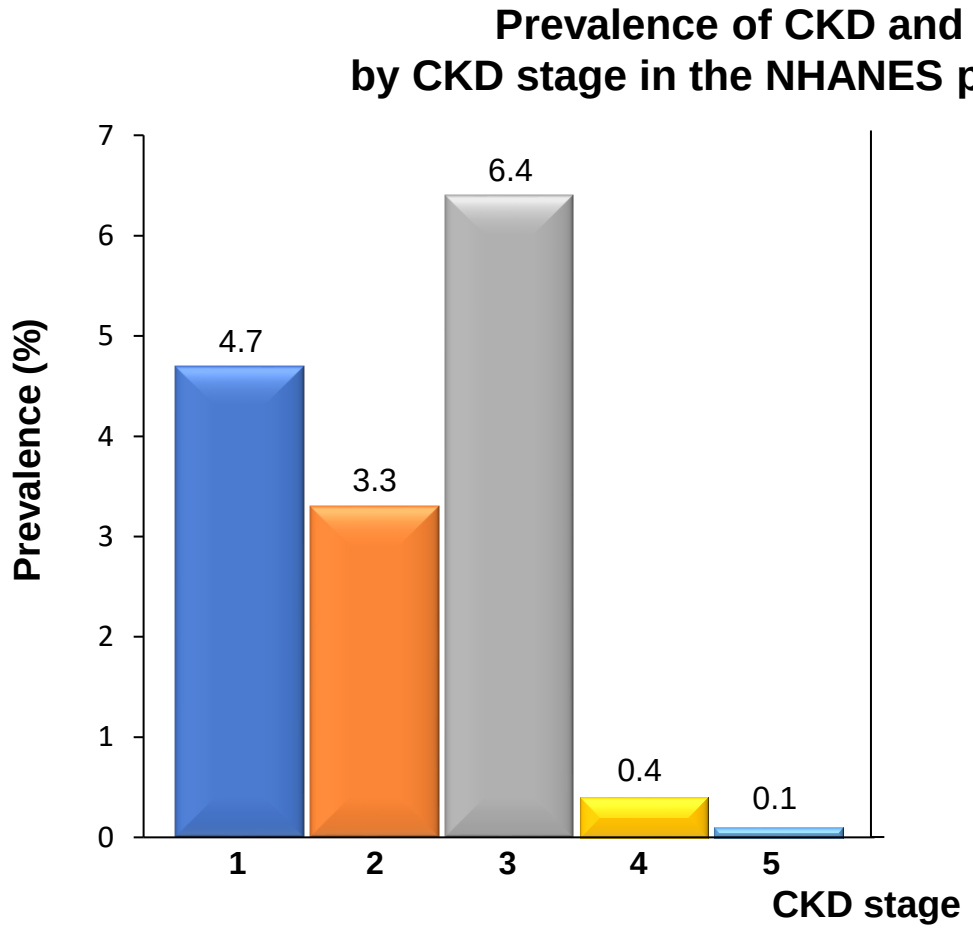


DIED prematurely from **lack of access to RRT[2]**

Chronic Kidney Disease remains UNDERDIAGNOSED.

1. Jager KJ et al. Nephrol Dial Transplant. 2019;34:1803-1805; 2. Hill NR et al. PLoS One. 2016;11:e0158765. 2..Global, regional, and national burden of chronic kidney disease , 1990-2017: a systemic analysis of the Global Burden of Disease Study 2017. Available at:https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30045-3/fulltext (Accessed June 2022)

Patient awareness of their diagnosis

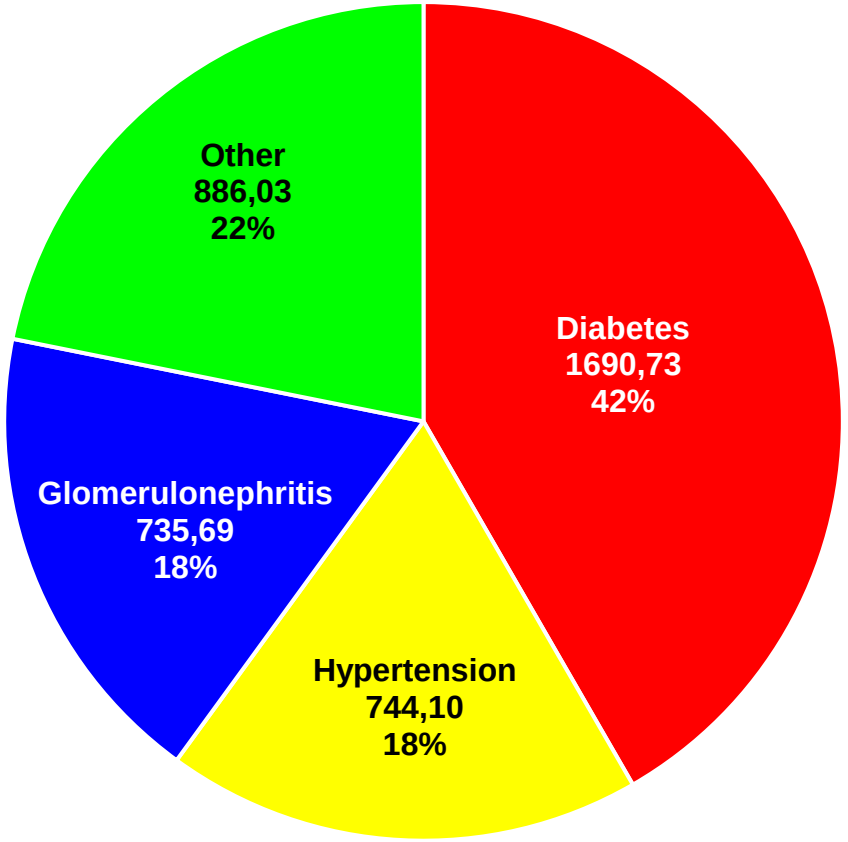


[a]Awareness was assessed as those who reported being told that they had kidney disease.

CKD = chronic kidney disease; NHANES = National Health and Nutrition Examination Survey.

Causes of CKD

Age-standardized global prevalence rate of CKD by cause per 100,000 persons in 2016

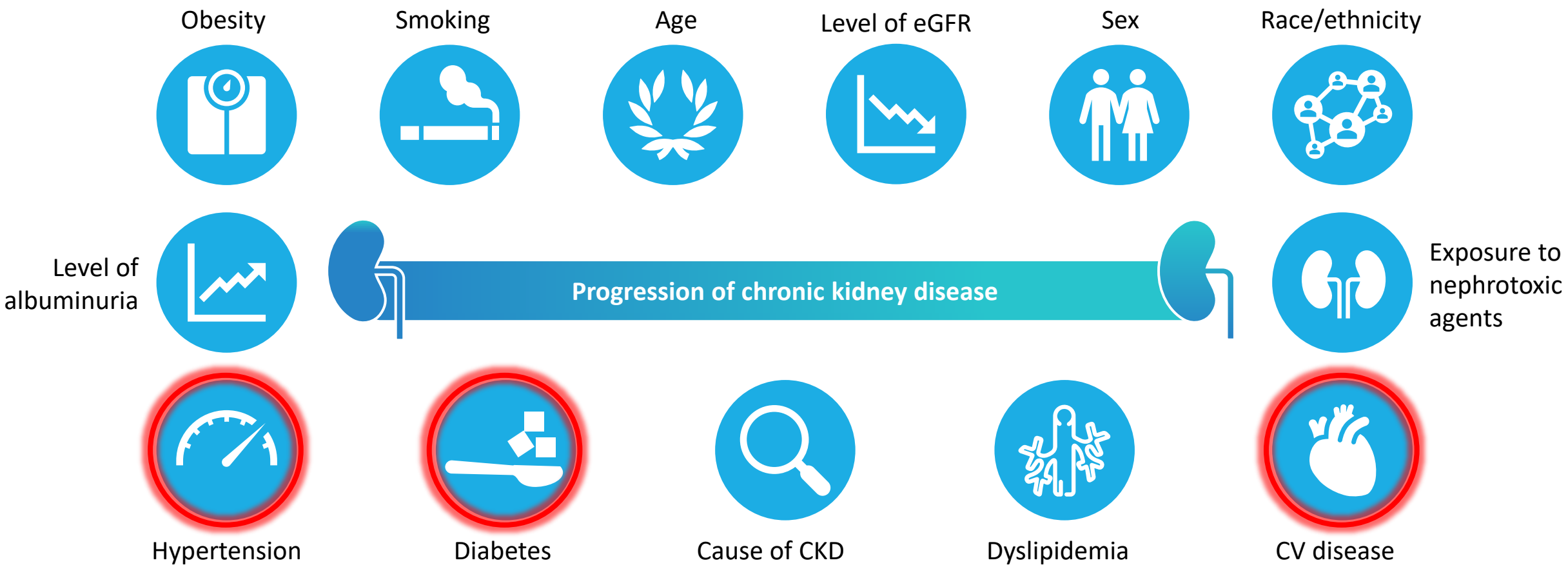


Diabetes and hypertension responsible for more than half of all cases

CKD = chronic kidney disease.

Xie Y et al. *Kidney Int.* 2018;94:567–581.

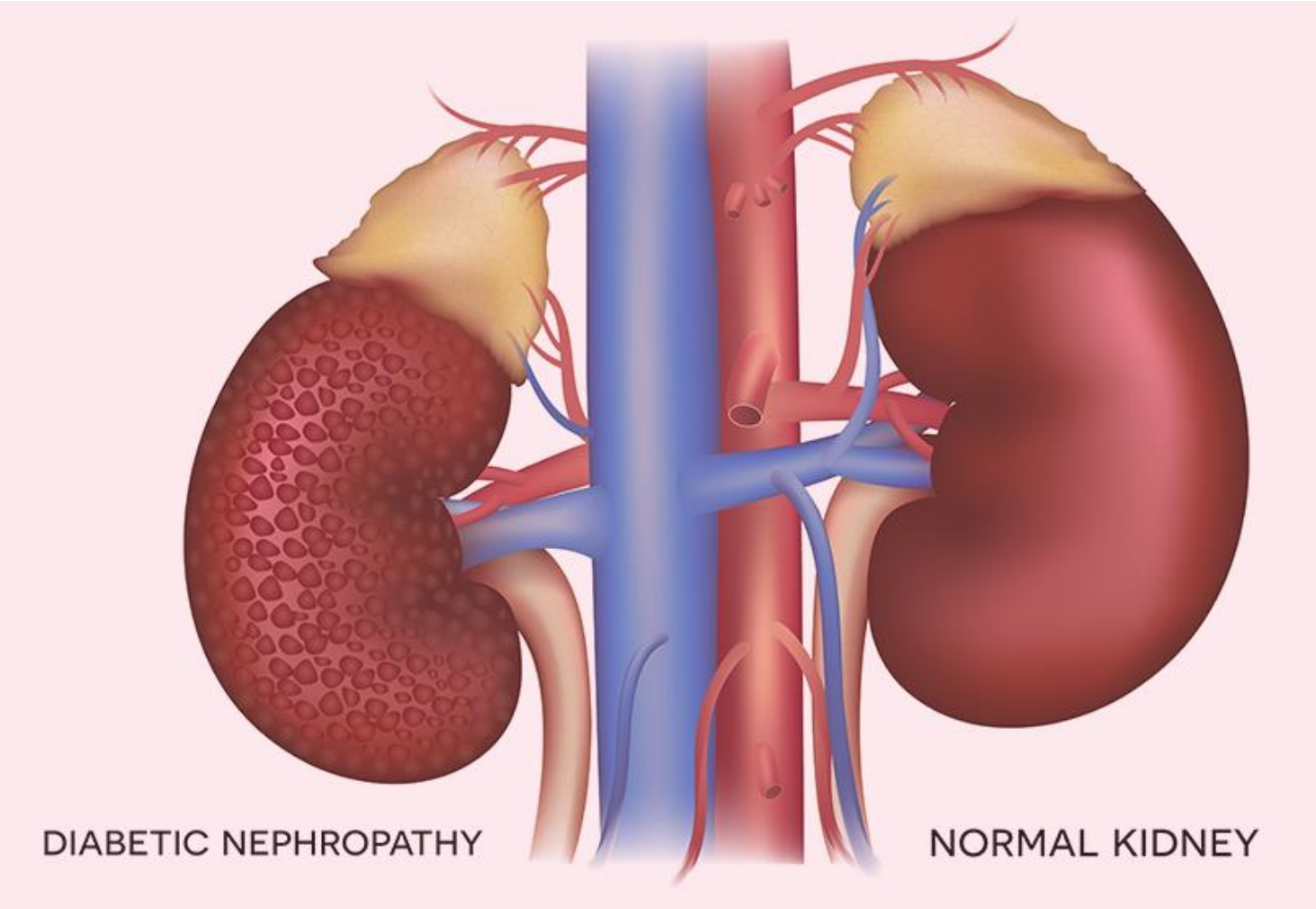
Factors affecting progression[1]



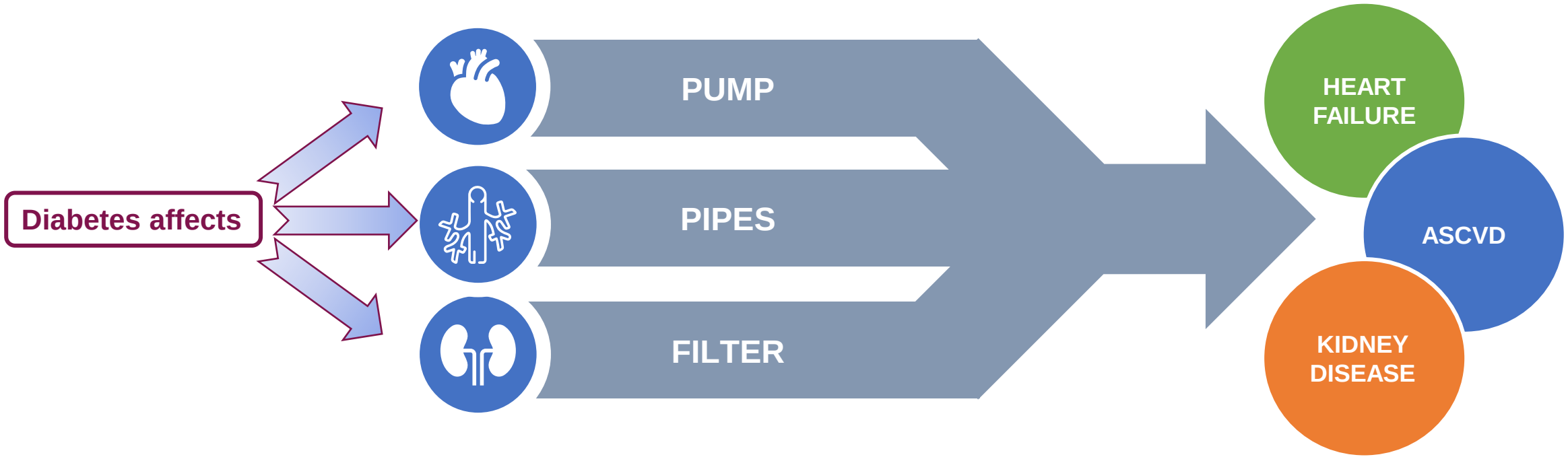
CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150; 2. Shlipak MG et al. *Kidney Int.* 2021;99:34–47.

Diabetes and CKD



Consequences of DM



Diabetes is complex disease involving multiple organ systems

ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes

CKD and DM share common risk factors

These risk factors are also associated with diabetes[2,3]

CKD, chronic kidney disease

1. Chronic Kidney Disease in the United States, 2019. Available from: https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf (Accessed 24 Jul 2019); 2. National Institute of Diabetes and Digestive and Kidney diseases (NIDDK) https://www.niddk.nih.gov/health-information/diabetes/overview/risk-factors-type-2-diabetes (Accessed 27 February 2020); 3. Federal Drug Agency (FDA). https://www.fda.gov/tobacco-products/health-information/cigarette-smoking-risk-factor-type-2-diabetes (Accessed 27 February 2020)

Diabetes is a strong risk factor for CKD

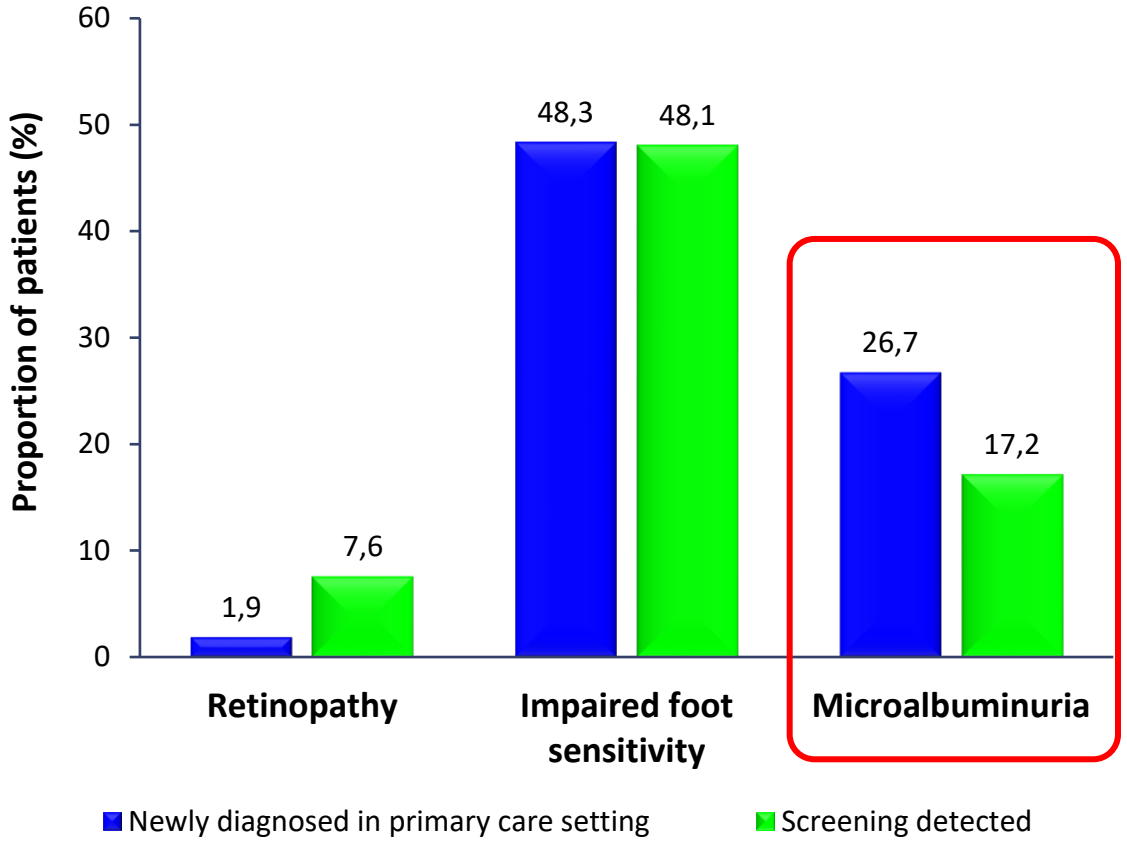
[a]CKD was defined as eGFR of 15–59 mL/min/1.73 m^2 (stages 3–4); [b]CKD stages were defined as: stage 1, eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g; stage 2, eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g; stage 3a, eGFR 45–59 mL/min/1.73 m^2; stage 3b, eGFR 30–44 mL/min/1.73 m^2; stage 4, eGFR 15–29 mL/min/1.73 m^2; stage 5, eGFR <15 mL/min/1.73 m^2.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes; UACR = urine albumin:creatinine ratio.

1. Murphy D et al. *Ann Intern Med.* 2016;165:473–481; 2. Wu B et al. *BMJ Open Diabetes Res Care.* 2016;4:e000154.

When does kidney disease occur in T2DM

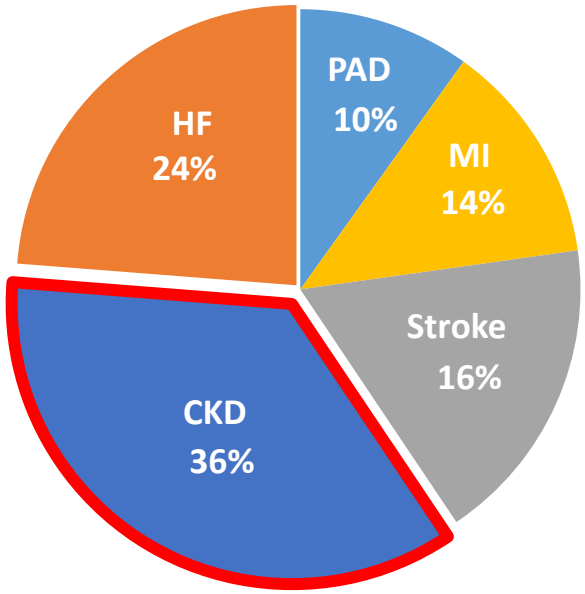
Prevalence of microvascular complications at time of T2DM diagnosis[1]



First comorbidity identified in CV-free patients with T2DM[2]

137,081 patients (18% of total CV-free patient population)[a]

Mean follow-up: 4.5 years



[a]Retrospective analysis of data from >1.1 million patients with T2D including population data from England and the Netherlands, claims data from Germany and Japan, and full population data from Norway and Sweden.

CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; MI = myocardial infarction; PAD = peripheral artery disease; T2D = type 2 diabetes.

1. Spijkerman AM et al. *Diabetes Care.* 2003;26:2604–2608; 2. Birkeland KI et al. *Diabetes Obes Metab.* 2020;22:1607–1618.

Nephropathy worsens CV outcome

Ischemic nephropathy

1.5×

Greater risk of mortality[1,2,a]

47% of patients received an ACE inhibitor/ARB[2]

Hypertensive nephropathy

>3×

Greater risk of CV events and mortality[3,b]

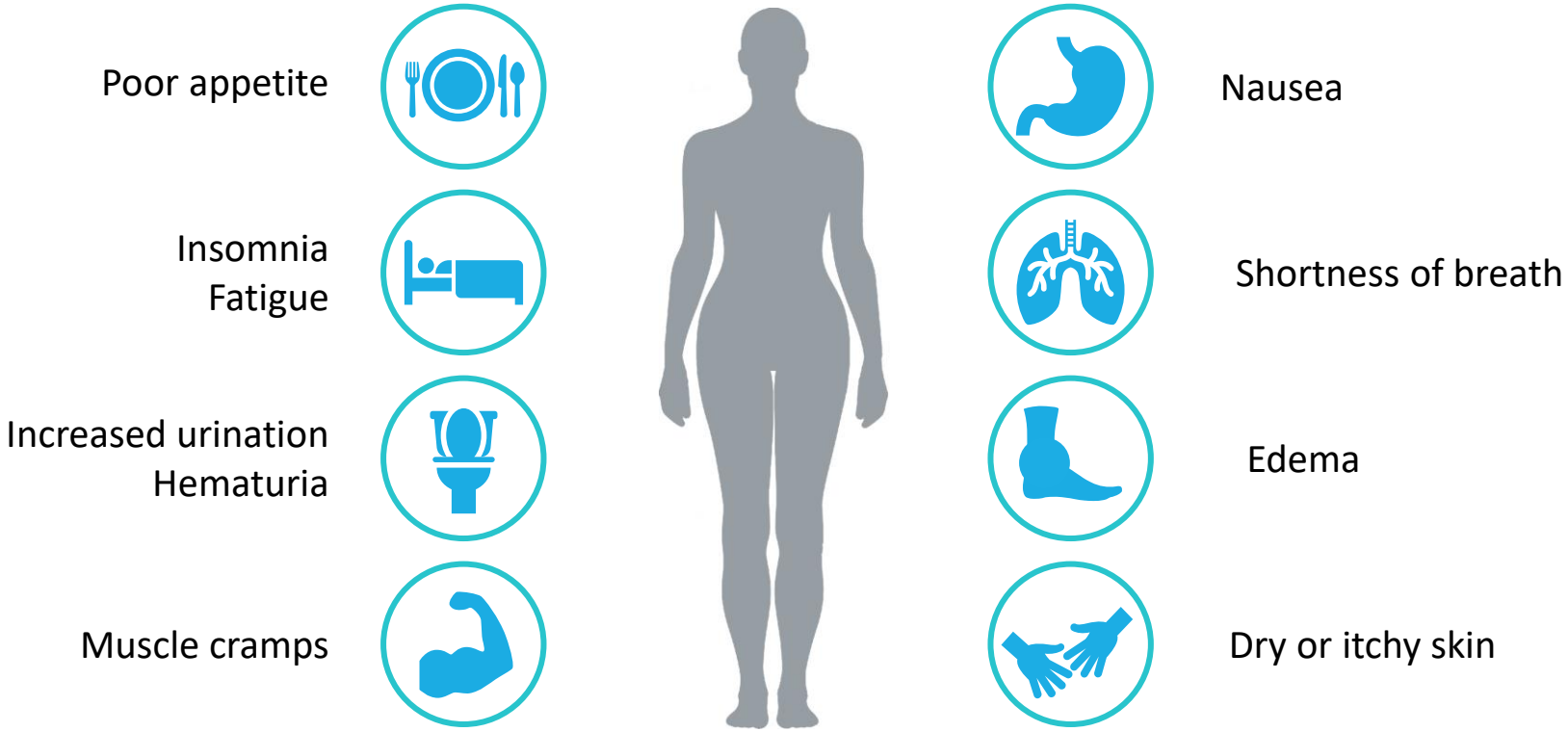
70% of patients received an ACE inhibitor/ARB

[a]Multivariate analysis comparing mortality for ARVD (often termed ischemic nephropathy and defined as >50% unilateral stenosis) with other causes of CKD; [b]Compared with primary renal disease defined by primary glomerulonephritis and tubulointerstitial nephritis.

1. Hicks CW et al. *Am J Kidney Dis*. 2022;79(2):289-301; 2. Ritchie J et al. *Nephrology (Carlton)*. 2015;20(10):688-696; 3. Nakayama M et al. *Hypertens Res.* 2011;34(10):1106-1110.

Screening & Monitoring

Are there clinical signs?



Early CKD can be asymptomatic

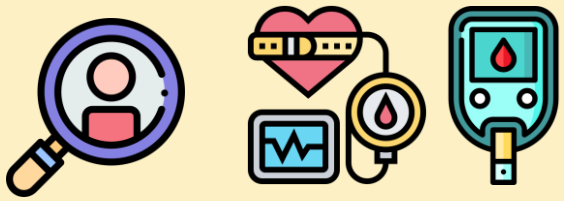
Identifying early stage CKD is often difficult

CKD = chronic kidney disease.

1. National Kidney Foundation. https://www.kidney.org/news/ekidney/august14/10_Signs_You_May_Have_Kidney_Disease; 2. Webster AC et al. *Lancet.* 2017;389:1238–1252.

Maintain a high index of suspicion

Determine at-risk individuals and populations



Screen for CKD in individuals with hypertension, diabetes and/or cardiovascular disease

Consider other factors including

- Demographics, older age, race/ethnicity
- Other systemic diseases that affect kidneys
- Genetic risk factors
- Environmental exposures

Every patient living with Diabetes

CKD, chronic kidney disease; UACR, urine albumin:creatinine ratio

ISN-KDIGO CKD Early Identification and Intervention Toolkit. Available at: https://www.theisn.org/wp-content/uploads/2021/03/KDIGO-CKD-EARLY-IDENT-INFOGRAPHIC.pdf (Accessed August 2022)

How do we screen?

Screening and diagnosis of CKD

Environmental exposures

Measure kidney function
Serum creatinine

Measure kidney injury
UACR
Urine dipstick if UACR not available

CKD, chronic kidney disease; UACR, urine albumin:creatinine ratio
ISN-KDIGO CKD Early Identification and Intervention Toolkit. Available at: https://www.theisn.org/wp-content/uploads/2021/03/KDIGO-CKD-EARLY-IDENT-INFOGRAPHIC.pdf (Accessed August 2022)

Urine testing - Albuminuria

- Moderate – old microalbuminuria – 3-30mg/mmol (**30-300mg/day**)
- Severe - > 30mg/mmol **(>300mg/day**)
- Moderate albuminuria has many causes and the link with progressive kidney disease is small (i.e most patients wont get ESRD)
- Moderate albuminuria has many associations
- Repeat if between 3-70mg/mmol
- Morning urine
- ACR preferred to PCR – more sensitive

Is it diabetic nephropathy?

Some clues that it may not be diabetic kidney disease

- Proteinuria < 5yrs after onset of diabetes
- Rapid rise in creatinine
- Active urine sediment
- Absent retinopathy in T1DM
- Features of another condition eg SLE , Vasculitis
- Rapid rise in creatinine with ACE inhibitor

Nephrosclerosis – related to age /HT may be indistinguishable

- Smaller kidneys
- Less proteinuria
- Rise in creatinine with ACE/ARB

How good are we at screening ?

Electronic health records from 39 US healthcare organizations[2]

976,299 patients with eGFR <60 mL/min/1.73 m^2

80.7%

received no UACR testing over three years

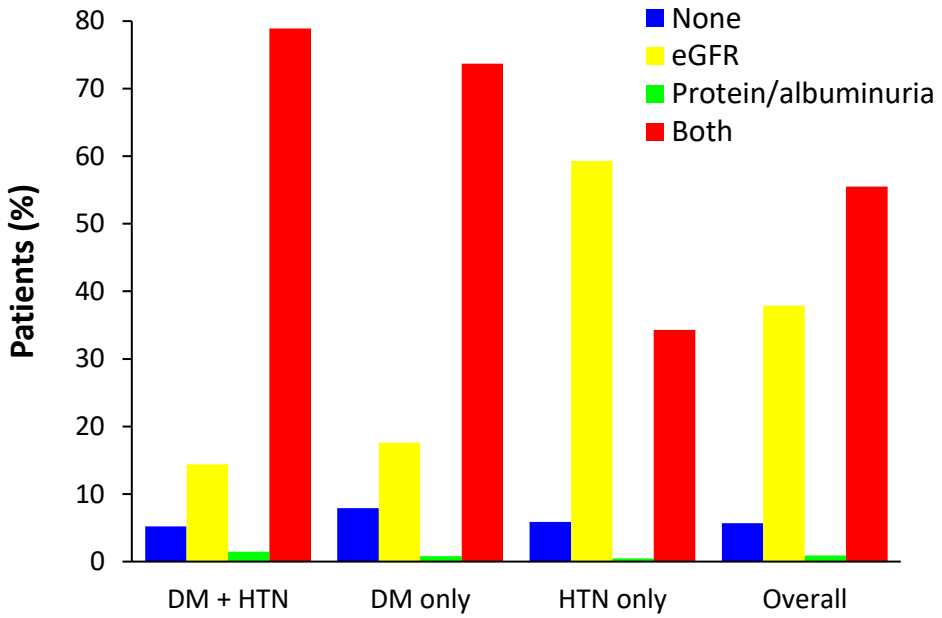
Primary care setting[3]

270,170 patients at risk of CKD due to DM, HTN, or both

Although **93.4%** of patients were tested for eGFR[a]

Only **56.4%** of patients were tested for protein/albuminuria[b]

Percentage of patients that received CKD testing by comorbidities[3]



Protein/albuminuria testing is lower in patients with hypertension compared with those with diabetes

[a]Patients tested for eGFR includes those tested for eGFR only and those tested for both eGFR and protein/albuminuria; [b]Patients tested for protein/albuminuria includes those tested for protein/albuminuria only and those tested for both protein/albuminuria and eGFR. CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; UACR = urine albumin:creatinine ratio.

1. Tuttle KR et al. *JAMA* Netw Open. 2019;2:e1918169; 2. Naranjo FS et al. *Kidney360*. 2021;2(3):415-424; 3. Bansal S et al. *Kidney360.* 2020;1:904–915.

Kidney Function vs Kidney Damage

Ideal CKD screening should consist of a dual assessment of eGFR and UACR[1]

Kidney function

- **Decreased eGFR**
  - eGFR <60 mL/min/1.73 m^2 (stage 3a–5)[2]
  - Addition of cystatin C measurement to creatinine measurement may enhance accuracy of eGFR assessment[1]
  - Diagnostic confirmation and staging should ideally include both creatinine and cystatin C for accurate eGFR measurements[1]

Kidney damage[2]

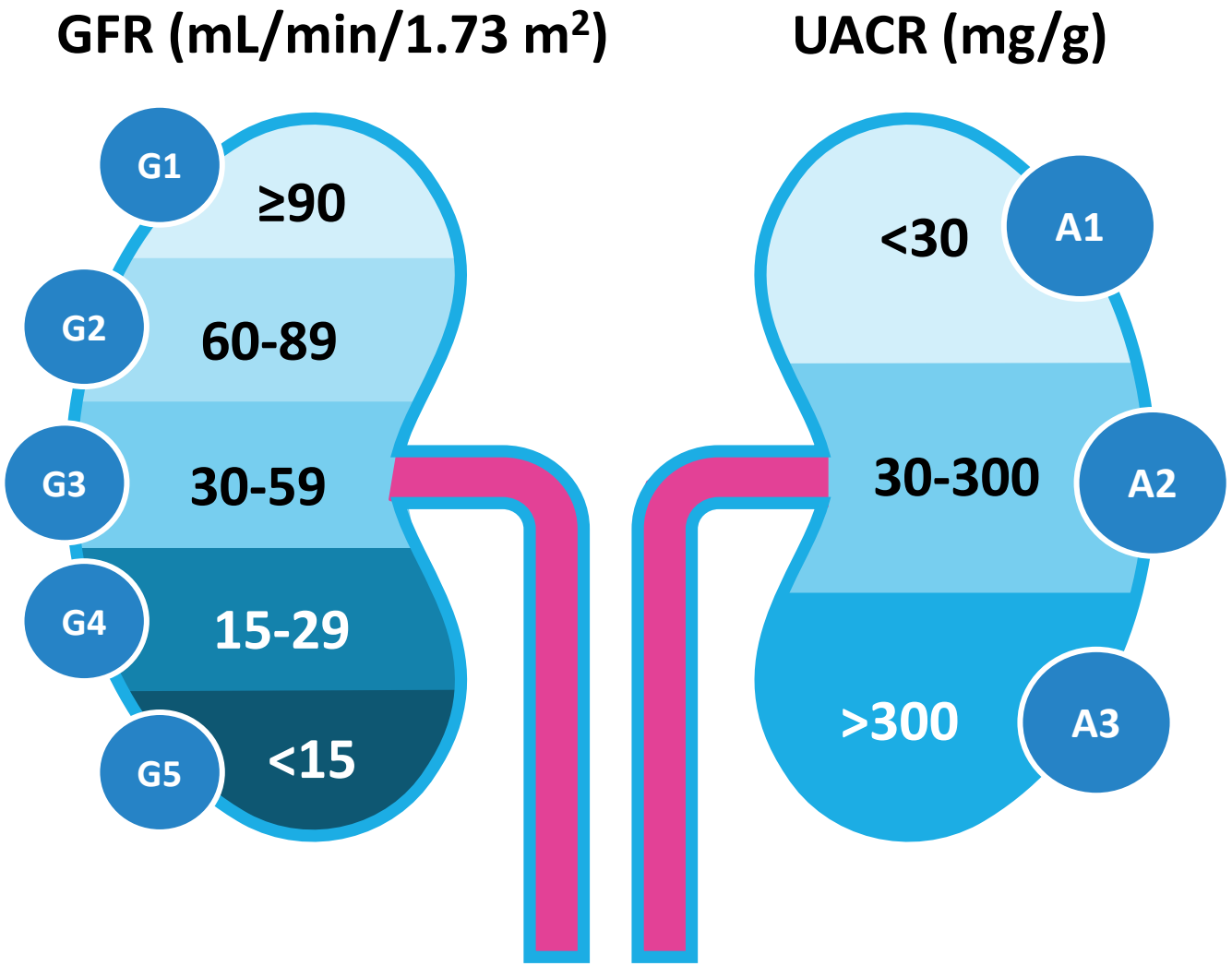
- **Albuminuria[2]**
  - AER ≥ 30 mg/24 h
  - UACR ≥ 30 mg/g [≥ 3 mg/mmol]
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Diagnosis of CKD requires two abnormal measurements at least 3 months apart

AER = albumin excretion rate; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urine albumin:creatinine ratio.

1. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

Stages of Kidney Function and Damage



CKD is **defined** as abnormalities of kidney structure or function, present for >3 months[1]

CKD is **classified** based on cause, GFR category, and albuminuria category[1]

CKD screening and risk stratification must consist of a **dual** assessment of eGFR and UACR[2]

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Working Group. *Kidney Int.* 2020;98(4S):S1-S115; 2. Shlipak MG et al. *Kidney Int.* 2021;99(1):34-47.

How often should you monitor ?

Recommended frequency of monitoring
(number of times per year)
by GFR and albuminuria category[1]

Green: low risk (if no other markers of kidney disease, no CKD)
Yellow: moderately increased risk
Orange: high risk
Red: very high risk

GFR categories (mL/min/1.73 m²) Description and range				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
	G1	Normal or high	>90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decrease	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Individuals with normal GFR, but with severely increased albuminuria (>300 mg/g), are still at risk for decline in renal function[2]

KDIGO recommends referral to a nephrologist for advanced CKD

Monitoring of CKD should increase as kidney function declines

CKD screening and risk stratification must consist of a dual assessment of eGFR and UACR[3]

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; UACR = urine albumin:creatinine ratio.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int Supp.l* 2013;3:1–150; 2. Perkins BA et al. *J Am Soc Nephrol.* 2007;18:1353–1361; 3. Shlipak MG et al. *Kidney Int.* 2021;99:34–47.

When should you refer?

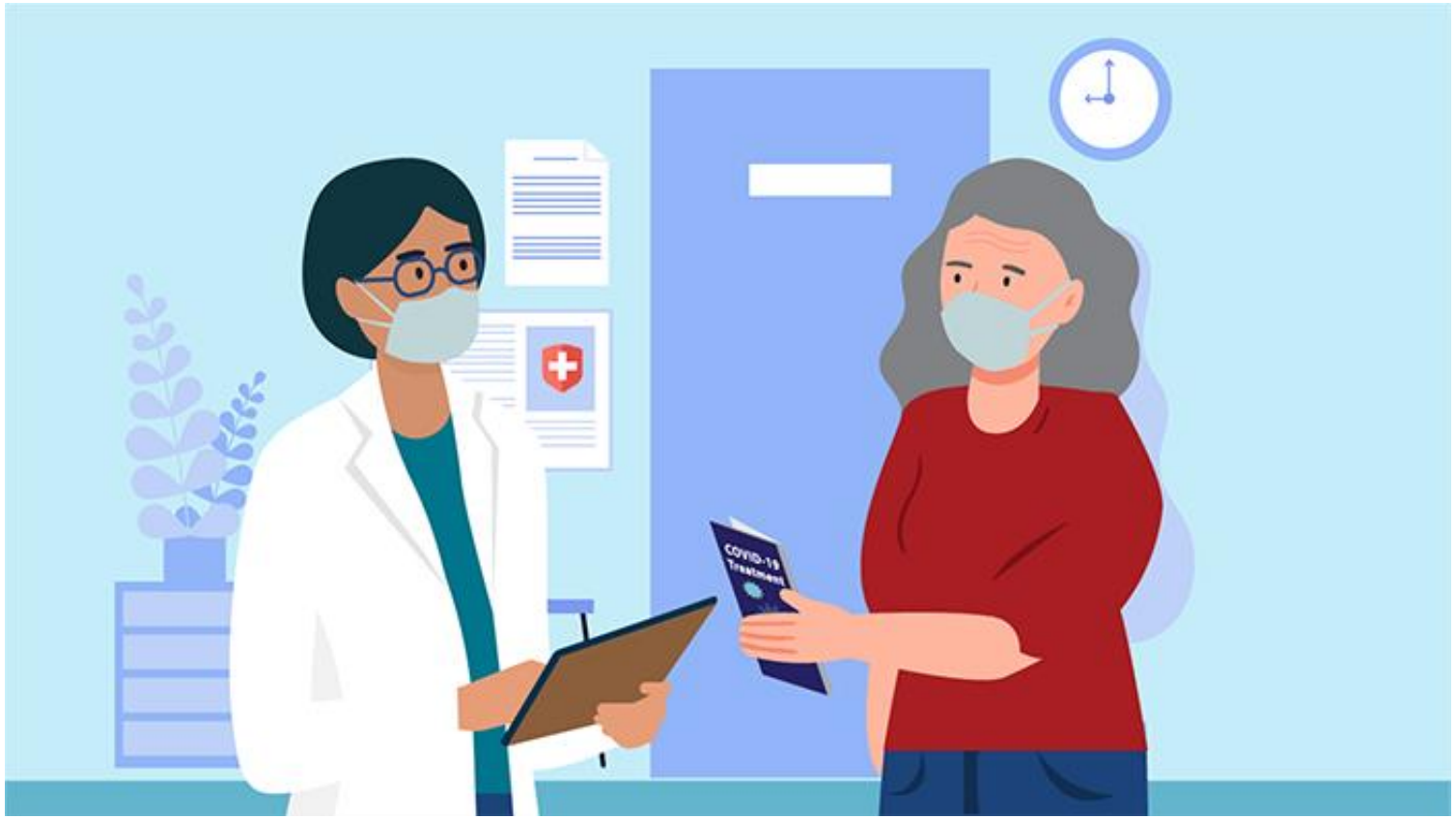
KDIGO 2012 prognosis of CKD by GFR and albuminuria categories

GFR categories (mL/min/1.73 m²) description and range				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
	G1	Normal or high	≥90		Monitor	Refer[a]
	G2	Mildly decreased	60–89		Monitor	Refer[a]
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Refer	Refer
	G4	Severely decreased	15–29	Refer[a]	Refer[a]	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk
[a]Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring
CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes

Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl* 2013;3:1–150

Management of CKD



Until recently- guidelines to slow progression

- Address underlying cause
- BP control (KDIGO SBP 120mmHg)- ACE/ARB especially if proteinuric
- Reduce proteinuria- ACE/ARB
- Control glucose (HbA1c < 7)
- Optimize weight
- Lipid control
- Reduce dietary protein/salt
- Stop smoking
- Avoid nephrotoxins
- *Replace Vit D*

Comparing Guidelines

KDIGO[1,2]

- Persons with hypertension, diabetes, or CVD should be screened for CKD
- CKD screening should also be implemented in other high-risk individuals and populations based on comorbidities, environmental exposures, and genetic risk factors
- Initiation, frequency, and cessation of CKD screening should be individualized based on kidney and CV risk profiles and individual preference
- Public health policies should include screening of these high-risk populations

NICE[3]

- Test for CKD using eGFRcreatinine[a] and ACR in people with:
  - Diabetes
  - Hypertension
  - Acute kidney injury
  - CVD (ischemic heart disease, chronic HF, peripheral or cerebral vascular disease)
  - Structural renal tract disease, recurrent renal calculi, or prostatic hypertrophy
  - Multisystem disease with possible kidney involvement, e.g. systemic lupus erythematosus
  - Family history of ESKD or hereditary kidney disease
  - Opportunistic detection of hematuria

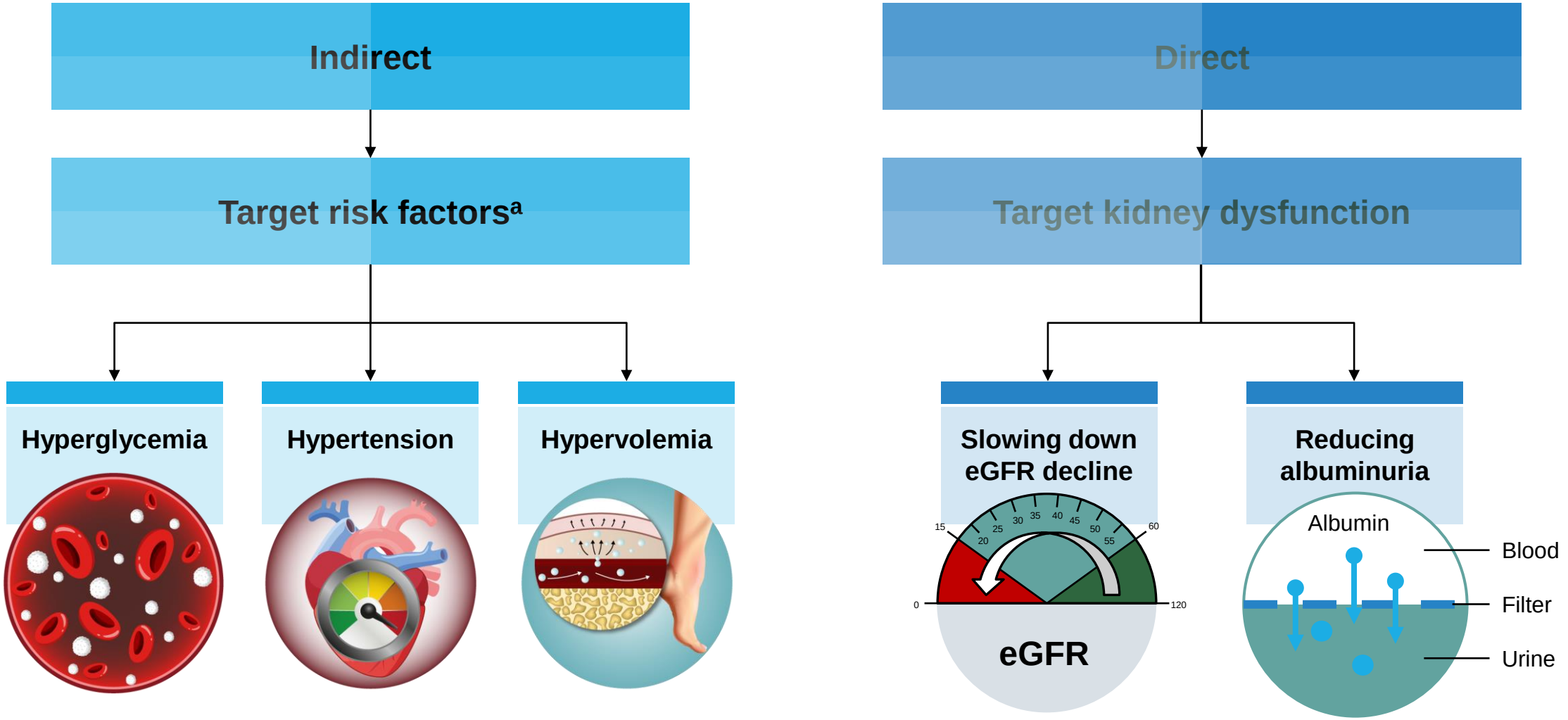
American Diabetes Association[4]

- At least once yearly, assess urinary albumin (spot urinary ACR) and eGFR in patients with:
  - T1D with duration of ≥5 years
  - T2D
  - Comorbid hypertension

[a]eGFRcreatinine refers to an eGFR calculated using the CKD-EPI creatinine equation, from a patients serum creatinine, age, sex and race.[5] ACR = albumin:creatinine ratio; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; KDIGO = Kidney Disease: Improving Global Outcomes;
NICE = UK National Institute for Health and Care Excellence; T1D = type 1 diabetes; T2D = type 2 diabetes.

1. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150; 3. UK National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management (CG182). 2014; 4. American Diabetes Association. *Clin Diabetes.* 2019;37:11–34; 5. Levey AS et al. *Ann Intern Med*. 2009;150:604–612.

Direct vs Indirect Approach



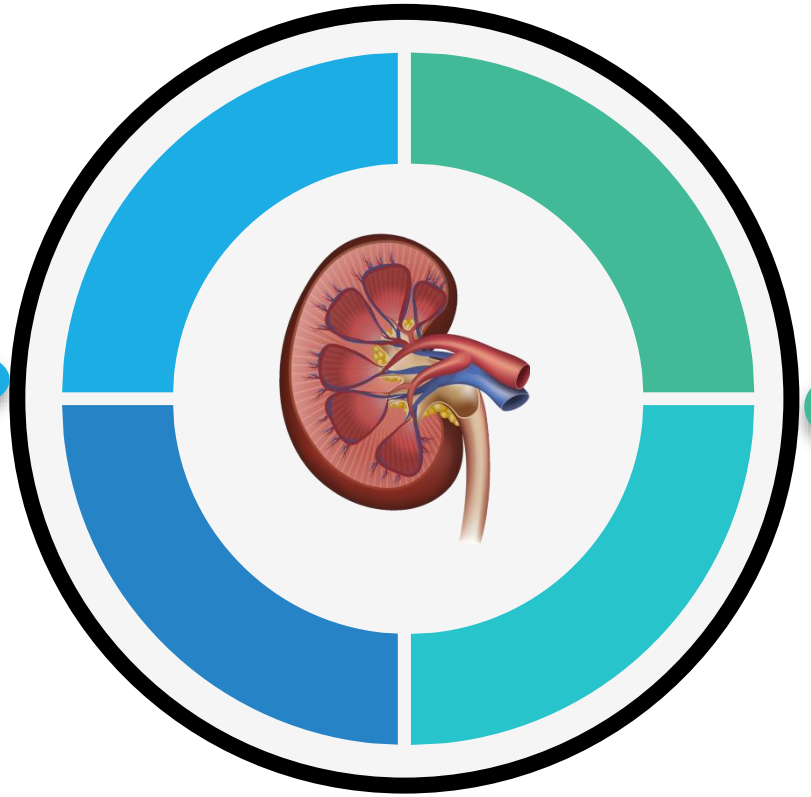
[a]This is not an exhaustive list of treatable risk factors. CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

Lifestyle modifications as per KDIGO

KDIGO recommend the following lifestyle modifications for those with CKD:

Protein intake

- Lower protein intake to 0.8 g/kg/day in adults with diabetes or without diabetes and eGFR <30 mL/min/1.73m^2 with appropriate education
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression



Lifestyle

Should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20–25, according to country-specific demographics) and stop smoking

Salt intake

Lower salt intake to less than 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated

Additional dietary advice

Should receive dietary advice and information in th context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated

BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease:

Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

KDIGO Guidelines

Use of an ACE inhibitor or ARB
for the treatment of CKD patients (all patients with albuminuria)

When to initiate ACE inhibitor / ARB therapy

Consider use of an ARB or ACE inhibitor in **normotensive patients with diabetes** and **albuminuria levels ≥30 mg/g** who are at high risk of DKD or its progression[1]

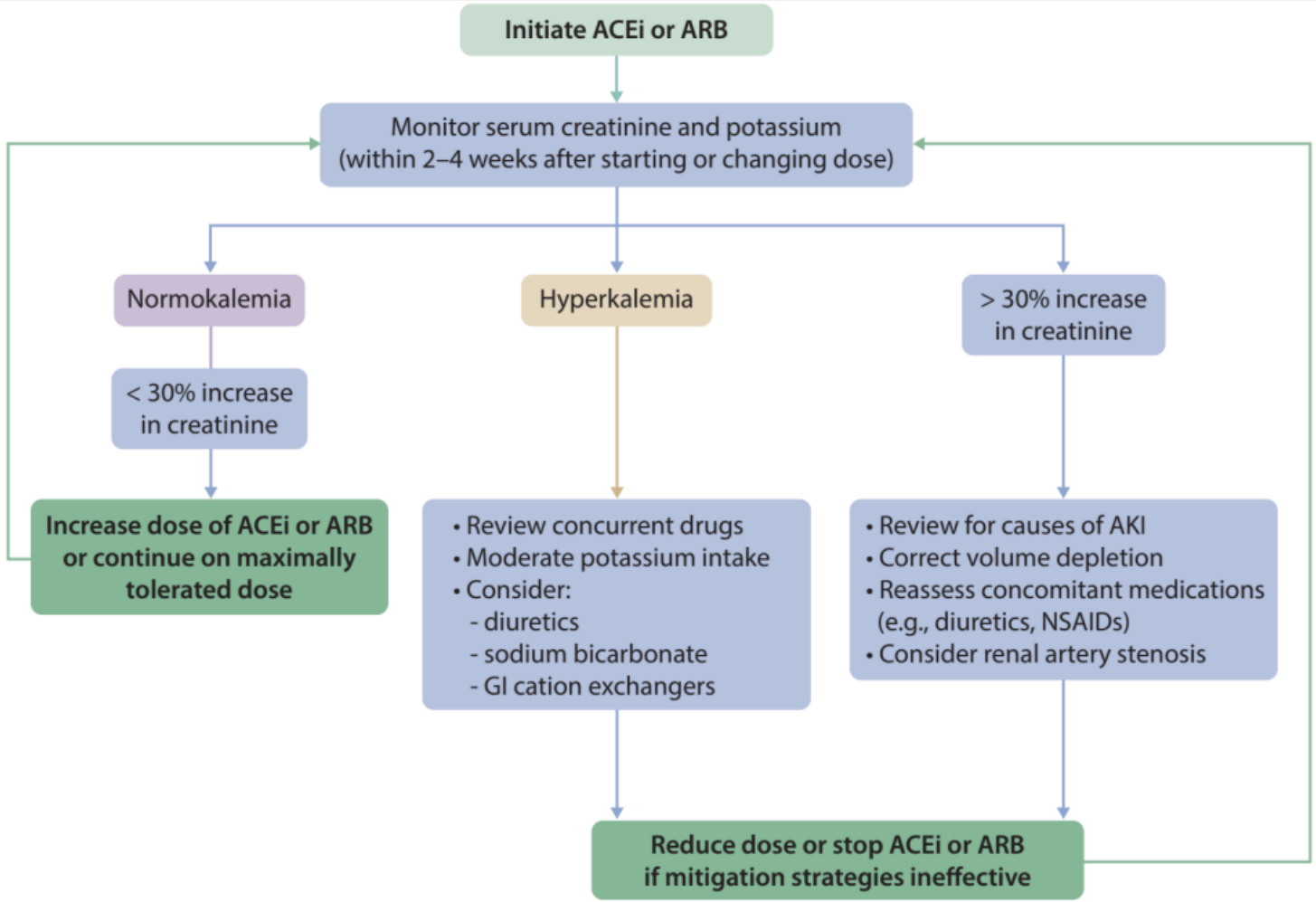
Suggest use of an ARB or ACE inhibitor in adults **with diabetes and CKD** with **urine albumin excretion 30–300 mg per 24 hours** (or equivalent)[2]

Recommend use of an ARB or ACE inhibitor in **adults with or without diabetes and with CKD** and **urine albumin excretion >300 mg per 24 hours** (or equivalent)[2]

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; DKD = diabetic kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes.

1. Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115; 2. Kidney Disease: Improving Global Outcomes. *Kidney Int Suppl.* 2013;3:1–150.

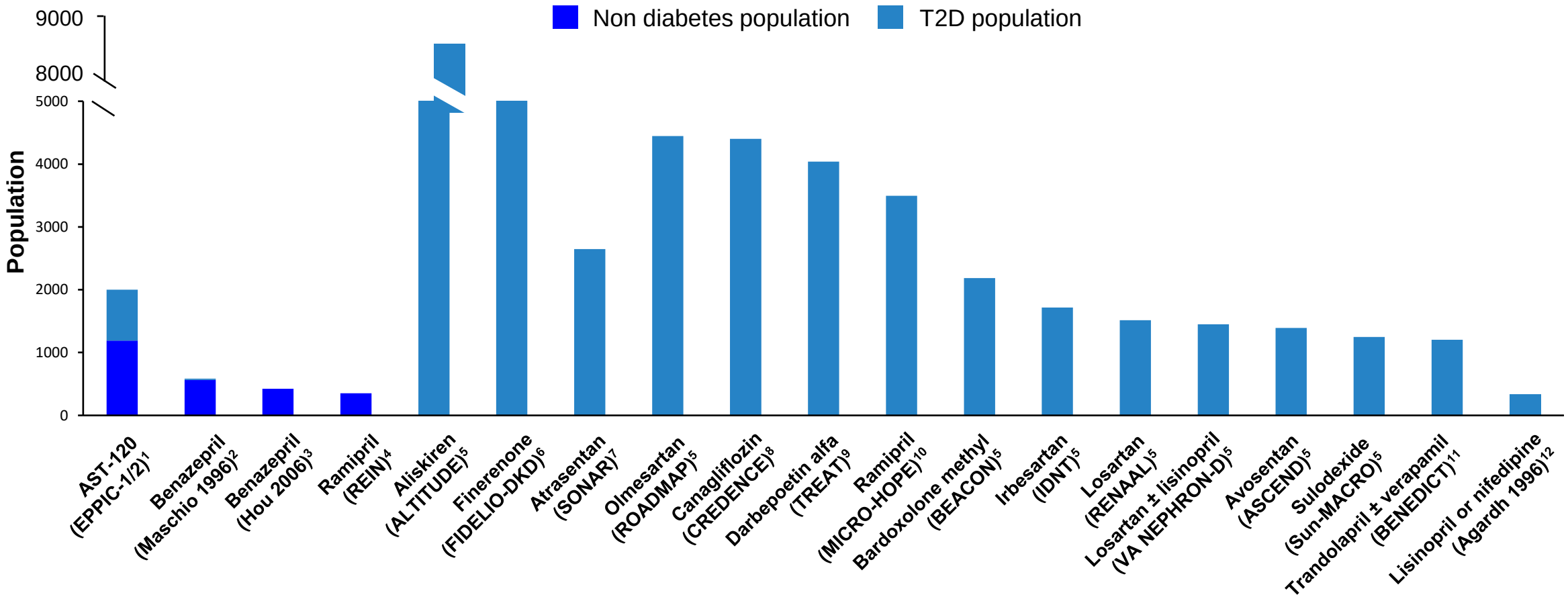
KDIGO Guidelines – Monitoring on ACE/ARB



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; DKD = diabetic kidney disease; KDIGO = Kidney Disease: Improving Global Outcomes.

CKD Clinical Trials

The Vast Majority of Larger-Scale Trials in CKD Have Focused on T2D Populations



CKD = chronic kidney disease; T1D = Type 1 diabetes; T2D = Type 2 diabetes.

1. Schulman G et al. *J Am Soc Nephrol.* 2015;26:1732–1746; 2. Maschio G et al. *N Engl J Med.* 1996;334:939–945; 3. Hou FF et al. *N Engl J Med.* 2006;354:131–140; 4. GISEN Group. *Lance.t* 1997;349:1857–1863; 5. Chan GC et al. *Nephrol Dial Transplant.* 2016;31:359–368; 6. Bakris JL et al. *Am J Nephrol.* 2019;50:333–344; 7. Heerspink HJL et al. *Lancet*. 2019;393:1937-1947; 8. Perkovic V et al. *N Engl J Med.* 2019;380:2295–2306; 9. Pfeffer MA et al *N Engl J Med.* 2009;361:2019–2032; 10. HOPE Study Investigators. *Lancet.* 2000;355:253–259; 11. Ruggenenti P et al. *N Engl J Med.* 2004;351:1941–1951; 12. Agardh CD et al. *J Hum Hypertens.* 1996;10:185–192.

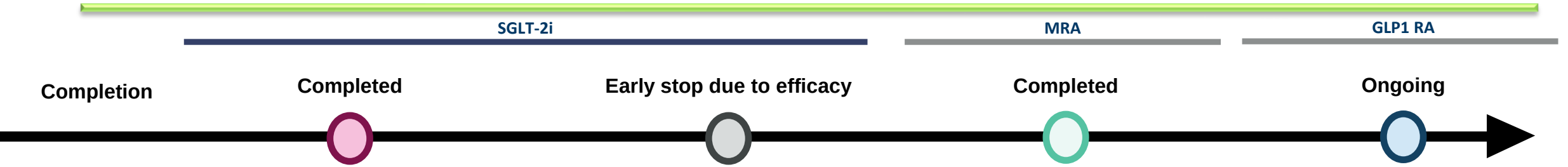
Until recently……

Therapeutic Innovation to Prevent New Onset or Worsening Renal Function Has Been Limited[1]

Drug/Class	Study Name	Patient Population	Year	Effect on CKD progression
ACEi				
Ramipril	REIN[2]	Non-DM Nephropathy (eGFR 20-70 mL/min/1.73 m^2 ; UPE >1g/24h)	1997	✓
ARBs				
Irbesartan	IDNT[3]	T2D; CKD (UPE ≥900mg/24h; SCr 1-3 mg/dL)	2001	✓
Losartan	RENAAL[4]	T2D; CKD (UACR ≥300; SCr 1.3-3 mg/dL)	2001	
Olmesartan	ROADMAP[5]	T2D; normoalbuminuria	2011	
ACEi/ARB Combo				
Telmisartan/ramipril	ONTARGET[6]	ASCVD or diabetes with end-organ damage	2008	–
Losartan/lisinopril	VA NEPHRON-D[7]	T2D; CKD (eGFR ≥30 to <90mL/min/1.73 m^2; UACR ≥300)	2013	
DRI				
Aliskiren	ALTITUDE[8]	T2D; CKD (eGFR ≥30 and <60mL/min/1.73 m^2) or CVD	2012	–
Glycosaminoglycan				
Sulodexide	Sun MACRO[9,10]	T2D; CKD (UPE >900mg/24h)	2012	–
Anti-inflammatory				
Bardoxolone methyl	BEACON[11]	T2D; CKD (eGFR 15 to <30 mL/min/1.73 m^2)	2013	–

ACEi = angiotensin-converting enzyme inhibitor; ALTITUDE = Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BEACON = Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; DRI = direct renin inhibitor; eGFR = estimated glomerular filtration rate; IDNT = Irbesartan Diabetic Nephropathy Trial; ONTARGET = Ongoing Telmisartan Along and in Combination with Ramipril Global Endpoint Trial; REIN = Ramipril Efficacy in Nephropathy; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; ROADMAP = Randomized Olmesartan and Diabetes Microalbuminuria Prevention trial; SCr = serum creatinine; SGLT2i = sodium-glucose cotransporter 2 inhibitor; Sun-MACRO = Sulodexide macro-albuminuria; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urine albumin to creatinine ratio; UPE = urinary protein excretion; VA NEPHRON-D = Veterans Affairs Nephropathy in Diabetes.

Have to Look beyond RAASi



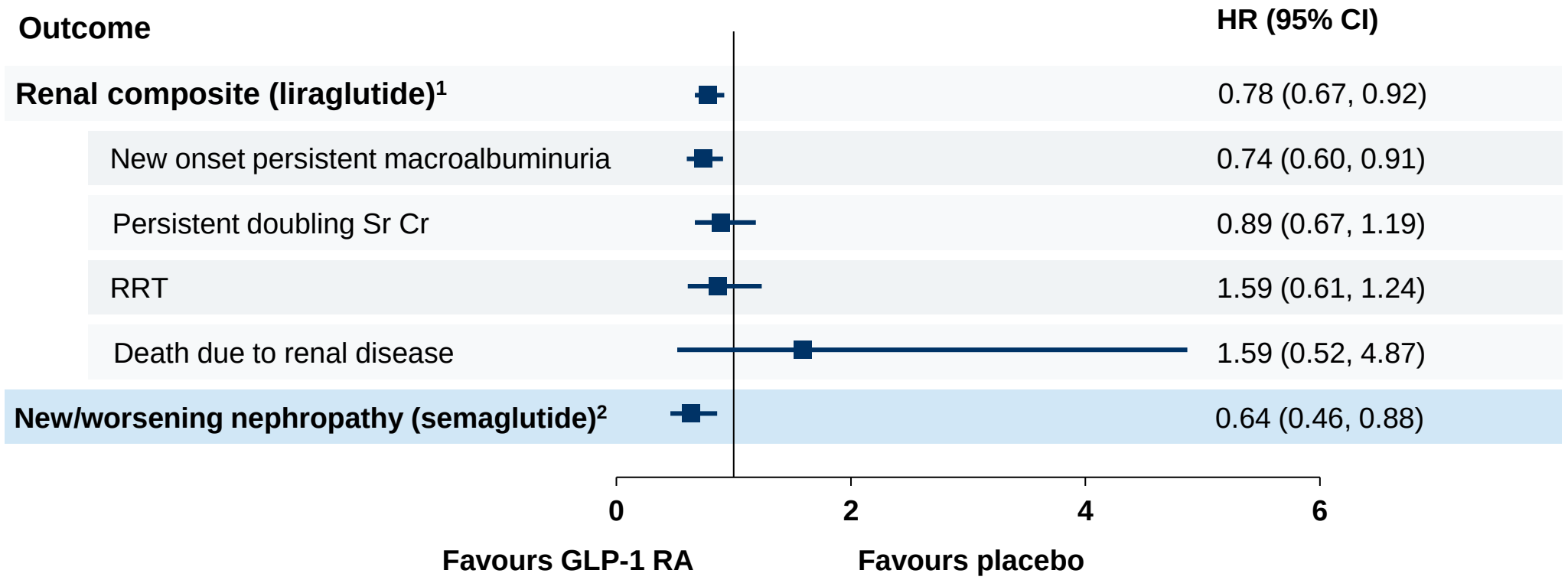
	DAPA CKD[2]	EMPA-KIDNEY[3]	FIDELIO-DKD[4]	FLOW[5]
Study				
Population	eGFR 25–75 mL/min/1.73m^2 Increased albuminuria and UACR 200–5000 mg/g	eGFR 20–44 mL/min/1.73m^2 or eGFR 45–89 mL/min/1.73m^2 with UACR ≥200 mg/g	eGFR ≥25 to <60 mL/min/1.73m^2 and UACR ≥ 30 to <300 mg/g and presence of diabetic retinopathy or eGFR ≥25 to <75 mL/min/1.73m^2 and UACR ≥300 mg/g	eGFR ≤75 to ≥50mL/min/1.73m^2 and UACR >300 to <5000mg/g or eGFR <50 to ≥25mL/min/1.73m^2 and UACR >100 to <5000mg/g
Primary endpoint	**Composite of: ≥50% sustained decline in eGFR, ESRD[b], CV death or renal death**	**Composite of: ESRD[c], a sustained decline in eGFR <10mL/min**	**Composite of: Kidney failure, ≥40% sustained decline in eGFR, renal death**	**Composite of: >50% sustained decline in eGFR, ESRD, renal or CV death**
Key secondary endpoints	≥50% sustained decline in eGFR, ESRD or renal death; CV death or hHF; all-cause death	hHF or CV death; kidney disease progression; CV death; CV death or ESRD	Stroke or hHF; All-cause death; All-cause hospitalizations; ≥57% sustained eGFR decline, kidney failure or renal death; UACR change from baseline	Annual rate of change in eGFR; Composite of MACE; All-cause death; Time to occurrence of individual primary endpoint and secondary MACE endpoint
Glycemic status	**With or *without* T2D**	**With or *without* T2D**	**With T2D**	**With T2D**

[a] ESRD defined as: sustained eGFR <15 mL/min/1.73m^2, initiation of maintenance dialysis for at least 30 days, or renal transplantation; [b] ESRD defined as: sustained eGFR <15 mL/min/1.73m^2, or chronic dialysis treatment or receiving a renal transplant; [c] ESRD defined as: initiation of maintenance dialysis or receipt of a kidney transplant CKD, chronic kidney disease; CV, cardiovascular; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; GLP1 RA, Glucagon-like Peptide-1 Receptor Agonists; ESRD, end-stage renal disease; hHF, hospitalization for heart failure; MACE, major adverse cardiac event; MI, myocardial infarction; MRA, mineralocorticoid antagonist; T2D, Type 2 diabetes; UACR, urine albumin:creatinine ratio

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02065791 (Accessed June 2022); 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03036150 (Accessed June 2022); 3. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03594110 (Accessed June 2022); 4. Bakris GL et al. Am J Nephrol. 2019;50:333-344; 5. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03819153 (Accessed June 2022).

GLP1-RA and CKD

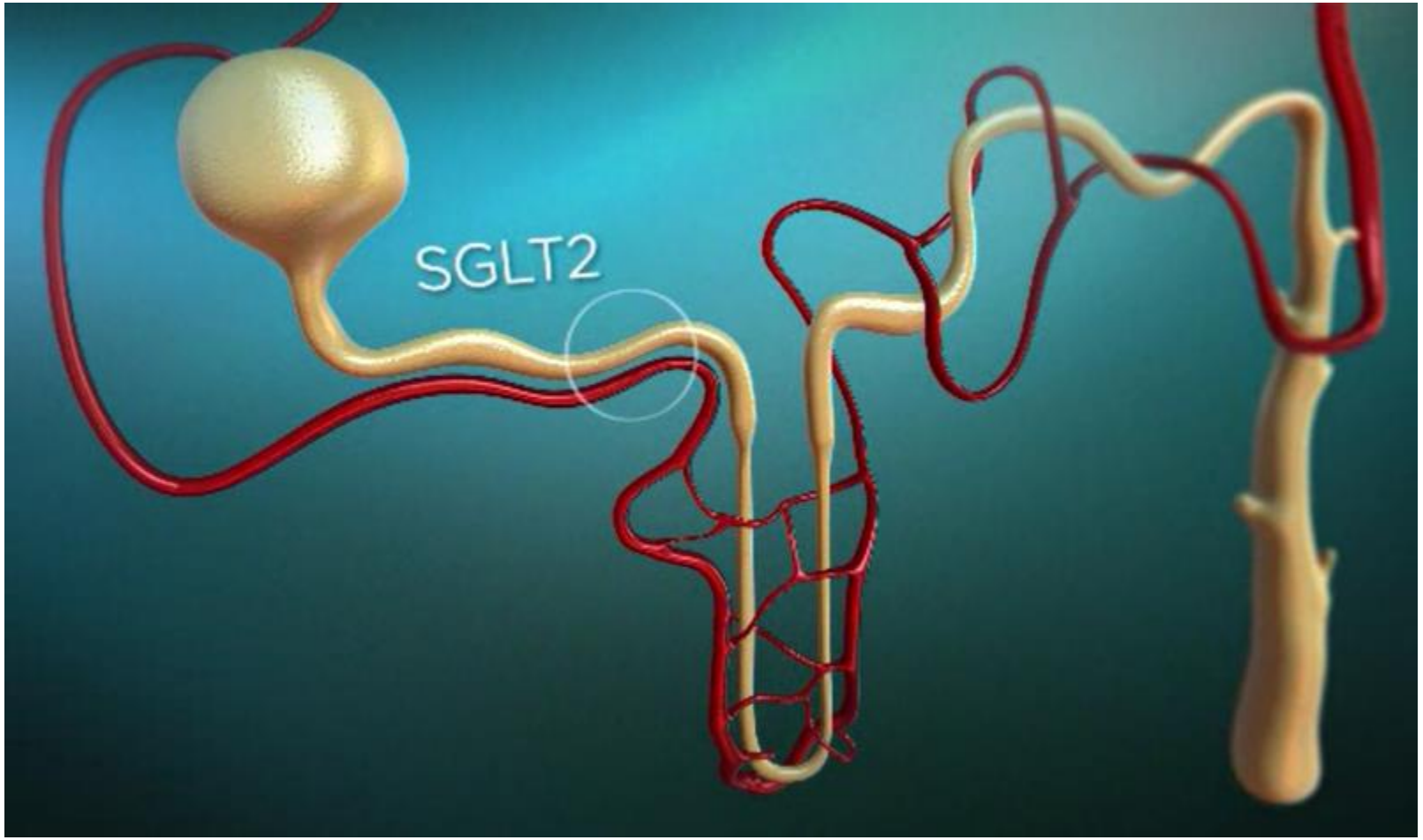
GLP-1 RA impact on renal outcomes due largely to effects on macro-albuminuria



- In LEADER (**liraglutide**) the mean eGFR in the liraglutide arm was 80 mL/min per 1.73 m^2
- In SUSTAIN-6 (**semaglutide**) ~30% of patients has a eGFR <60 mL/min per 1.73 m^2

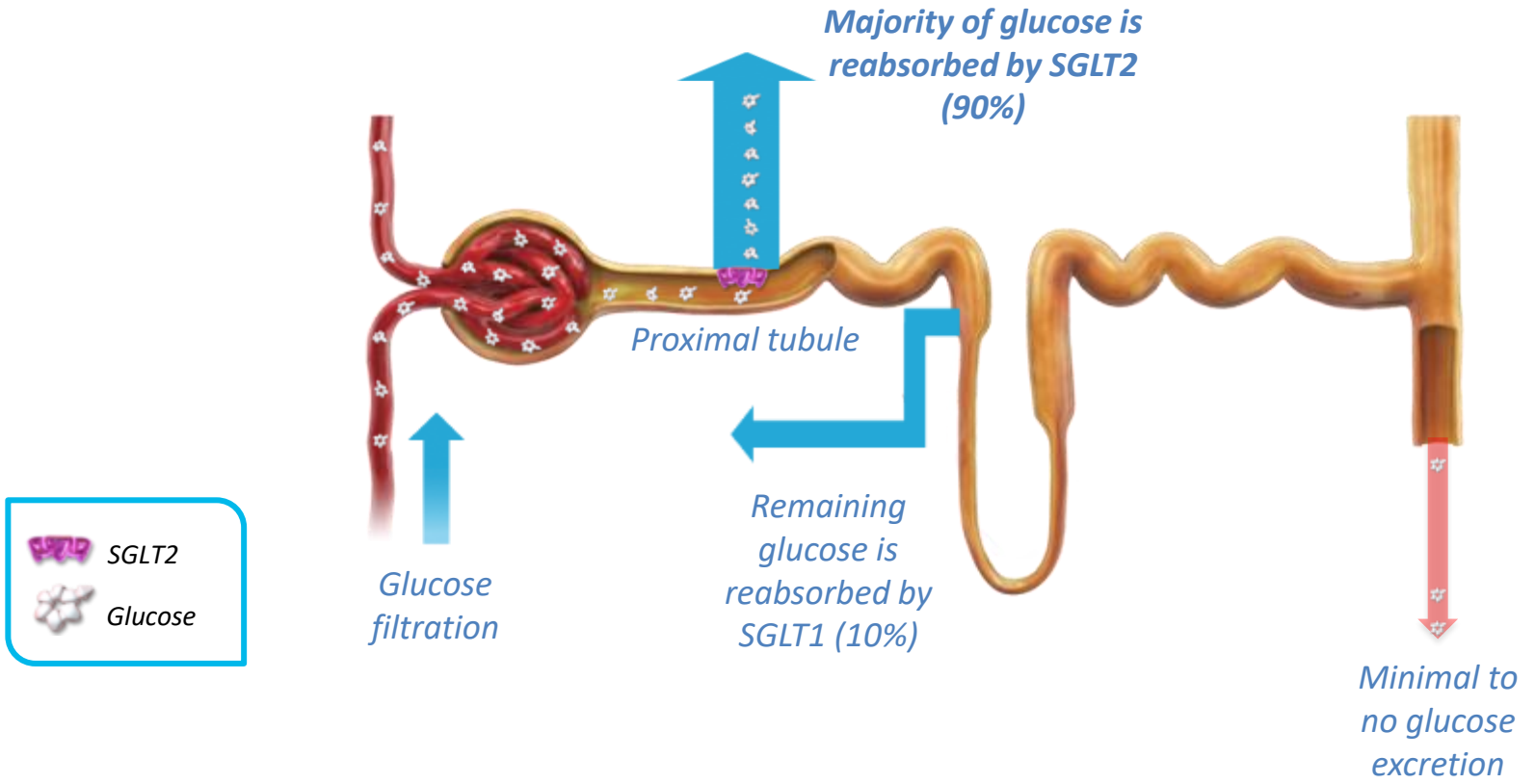
1. Mann, J. *N Engl J Med* 2017;377:839-848. **2.** Marso, S. *N Engl J Med* 2016;375:1834-1844.

SGLT2i in CKD



Normal Glucose Handling in patients with T2DM

In normal renal glucose handling, 90% of glucose is reabsorbed by SGLT2[1–4]

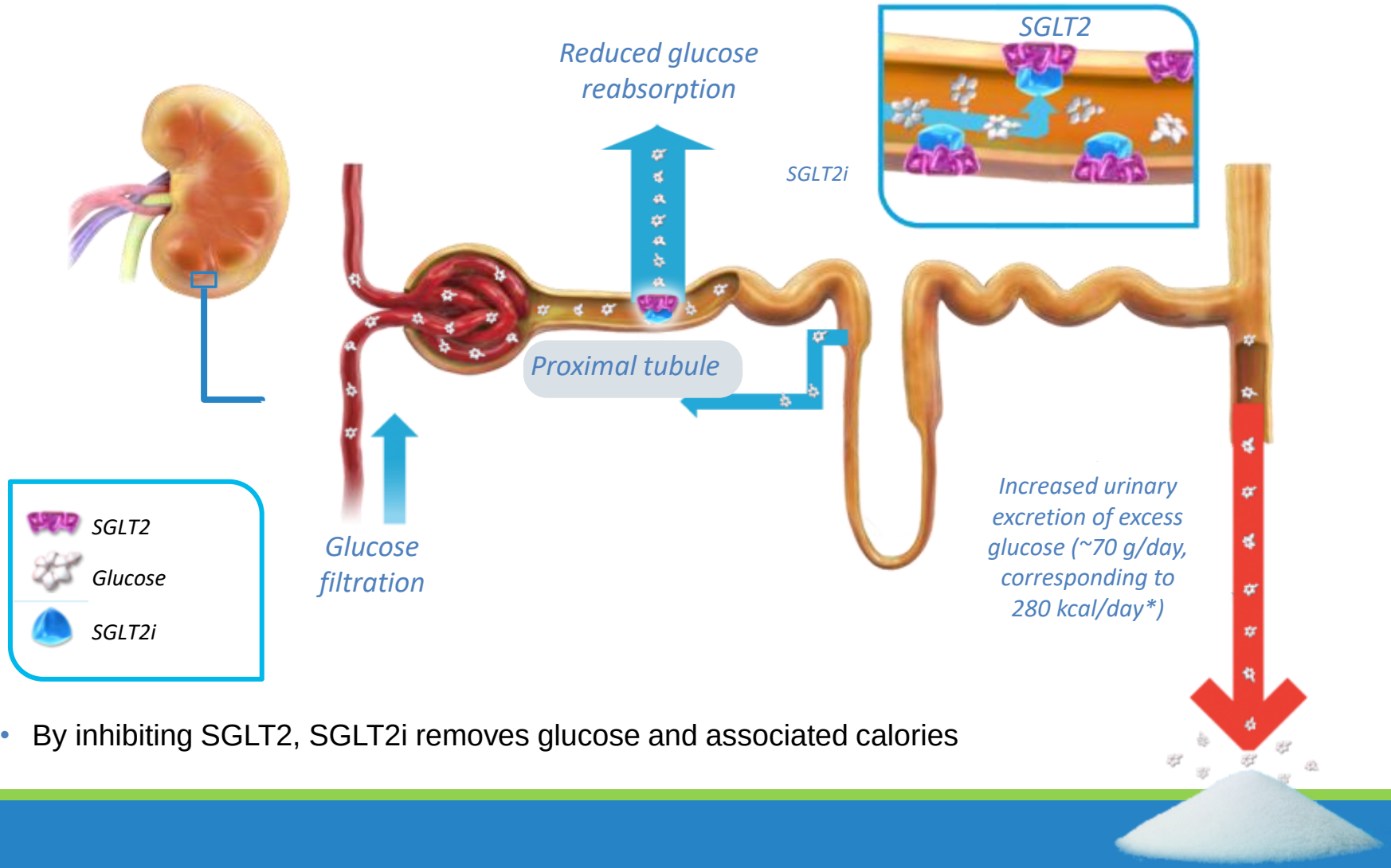


SGLT, sodium-glucose co-transporter.

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35;
3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. Marsenic O. *Am J Kidney Dis* 2009;**53**:875–83.

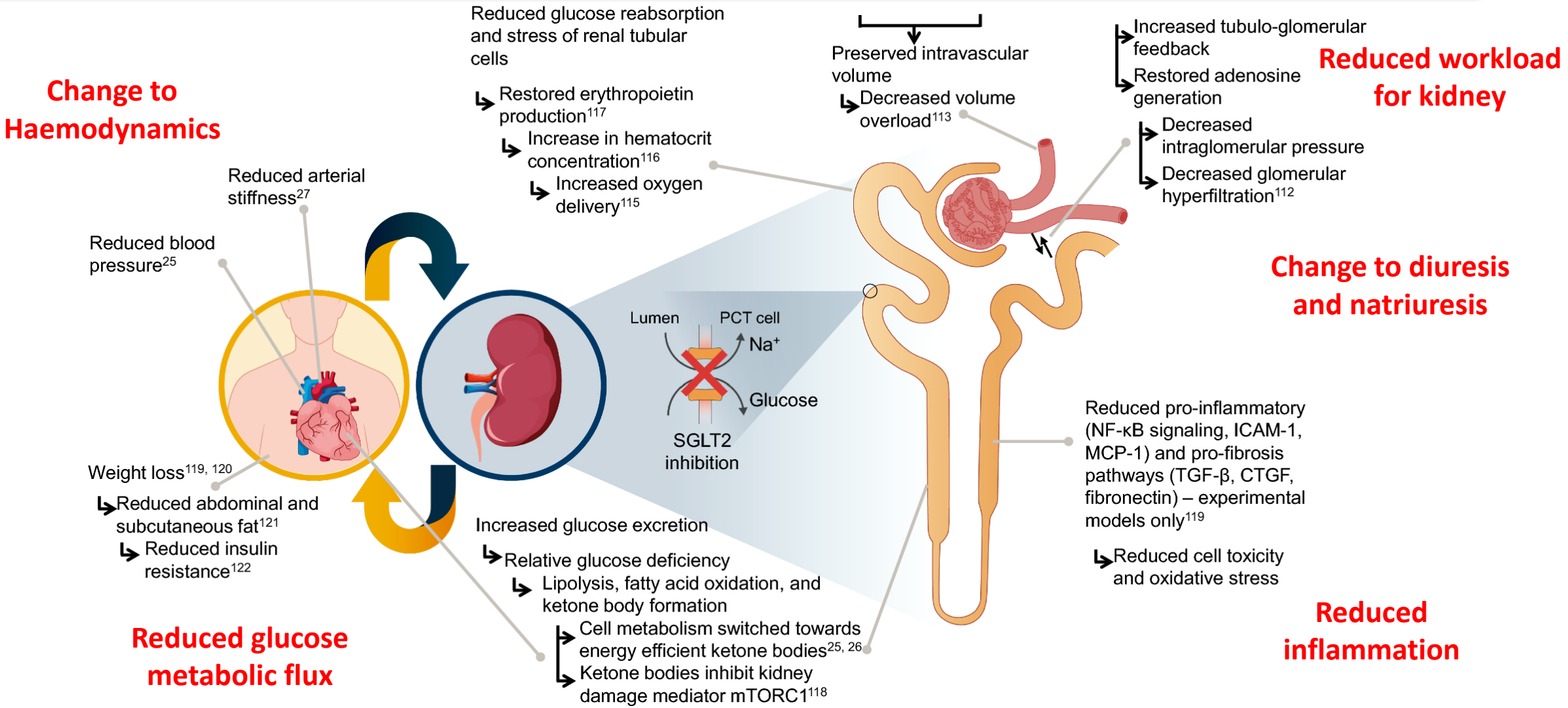
How do SGLT2i work?

Inhibition of SGLT2 removes excess glucose in the urine independently of insulin



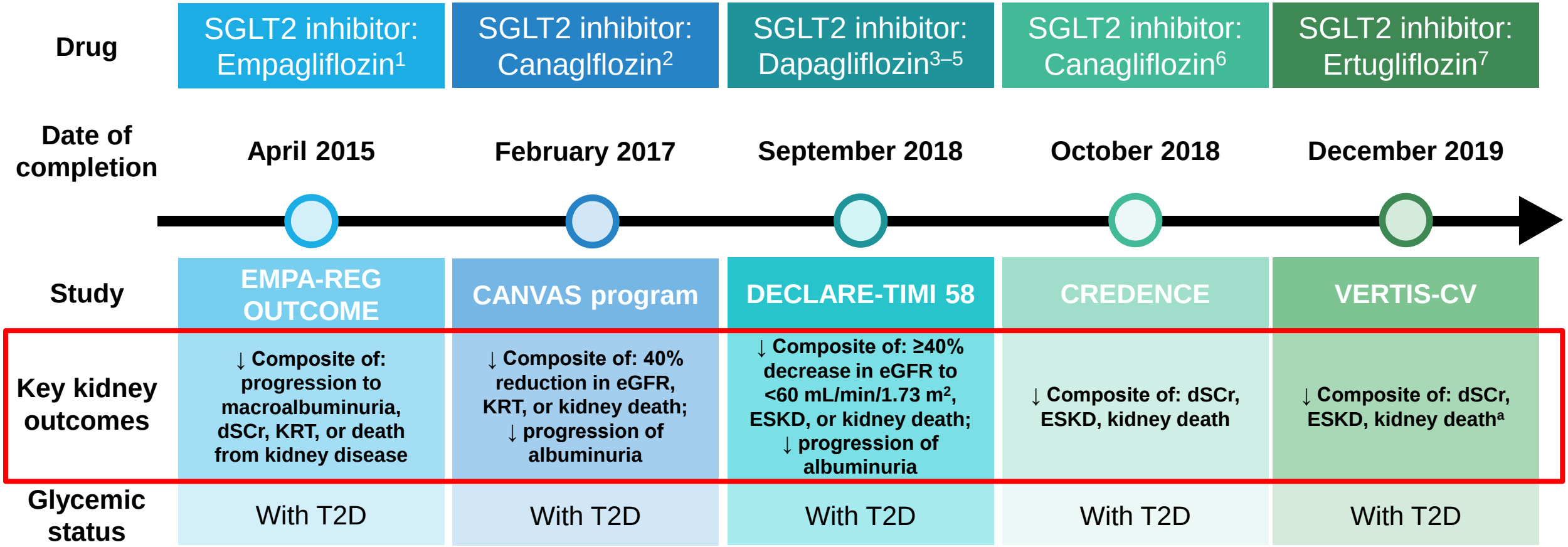
- By inhibiting SGLT2, SGLT2i removes glucose and associated calories

Proposed Reno-protective Pathways



Giorgino, F., Vora, J., Fenici, P. *et al.* Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol* **19**, 196 (2020). https://doi.org/10.1186/s12933-020-01163-9

SGLT2i and CVOT Trials

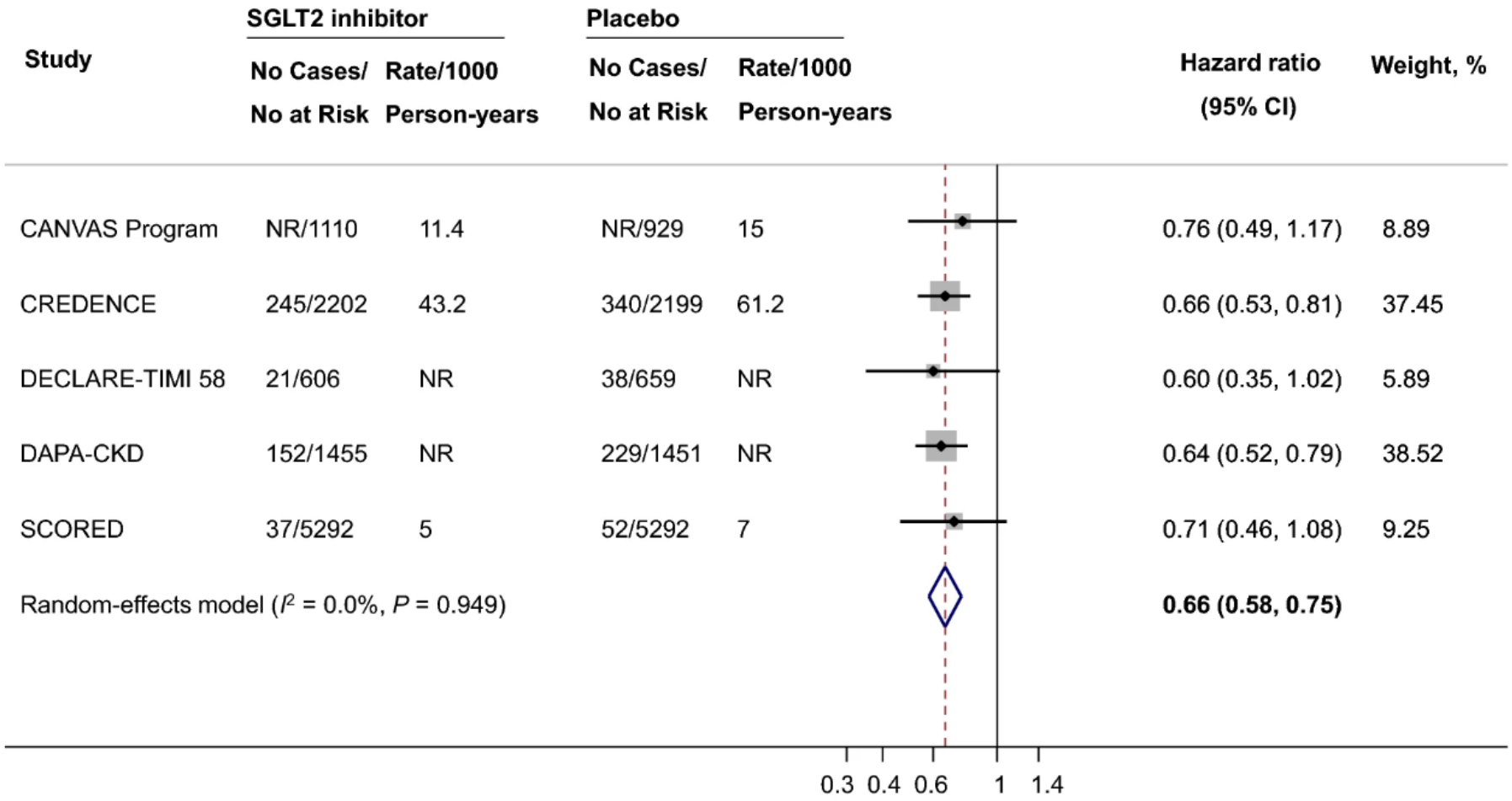


[a]The composite kidney outcome in VERTIS-CV was not considered to be statistically significant (*P*=0.081)
CV, cardiovascular; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KRT, kidney replacement therapy; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01131676 (Accessed January 2021); 2. Neal B, et al. *N Engl J Med* 2017;377:644–657; 3. Wiviott SD, et al. *N Engl J Med* 2019;380:347–357; 4. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01730534 (Accessed January 2021); 5. Raz I, et al. Presented at 79th Scientific Sessions of the American Diabetes Association; June 7th–11th, 2019; San Francisco, CA, USA; 244-OR; 6. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306; 7. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01986881 (Accessed January 2021)

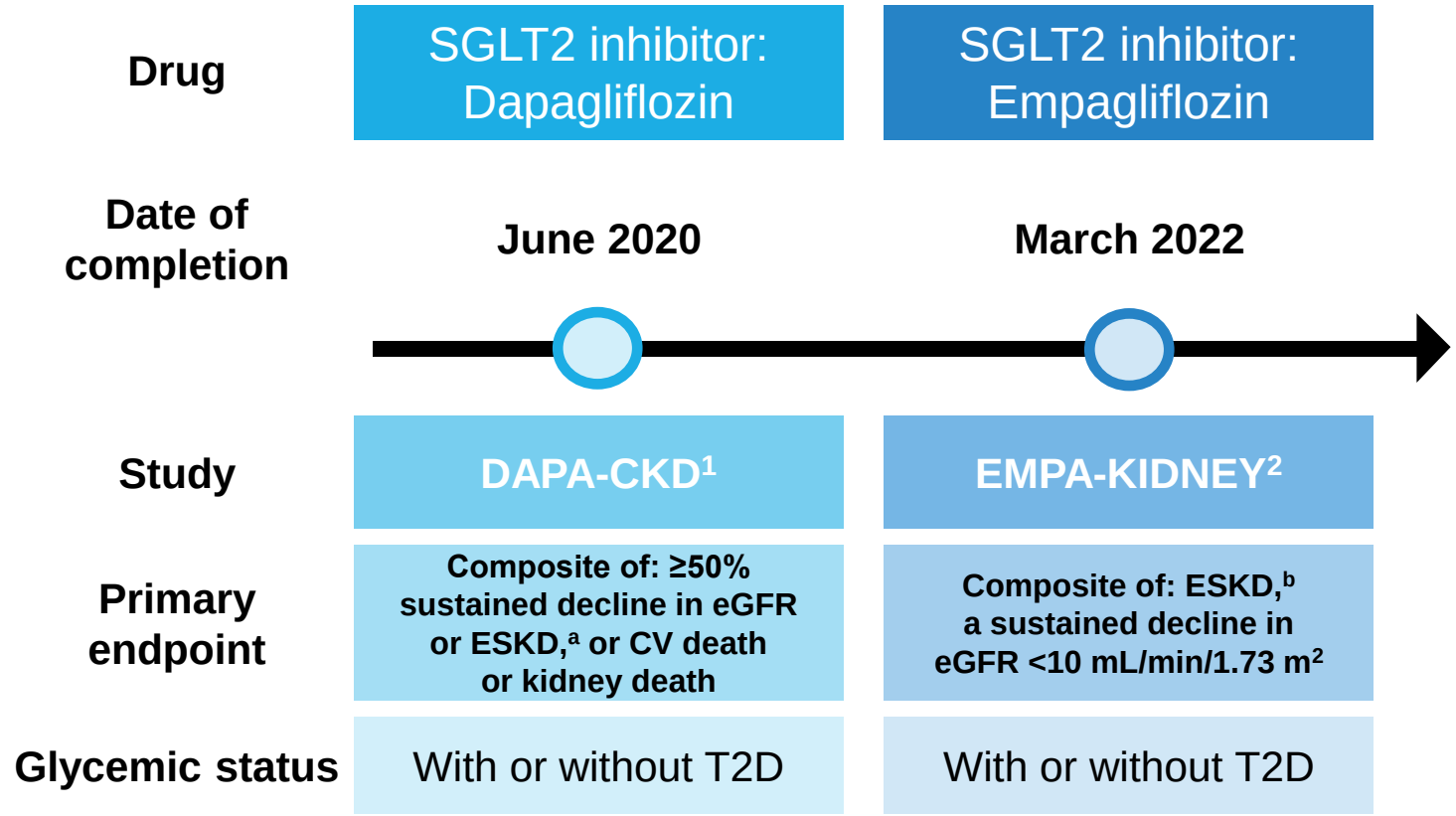
Meta Analysis

Effect of SGLT2i on ESKD, worsening kidney function, or death because of kidney disease



Kaze, A.D., Zhuo, M., Kim, S.C. *et al.* Association of SGLT2 inhibitors with cardiovascular, kidney, and safety outcomes among patients with diabetic kidney disease: a meta-analysis. *Cardiovasc Diabetol* **21**, 47 (2022). https://doi.org/10.1186/s12933-022-01476-x

Dedicated SGLT2 trials in patient with CKD



[a]ESKD defined as sustained eGFR <15 mL/min/1.73 m^2, chronic dialysis, or receiving kidney transplant; [b]ESKD defined as initiation of maintenance dialysis or receiving a kidney transplant

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03036150 (Accessed January 2022); 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03594110 (Accessed January 2022)

DAPA-CKD

Objective

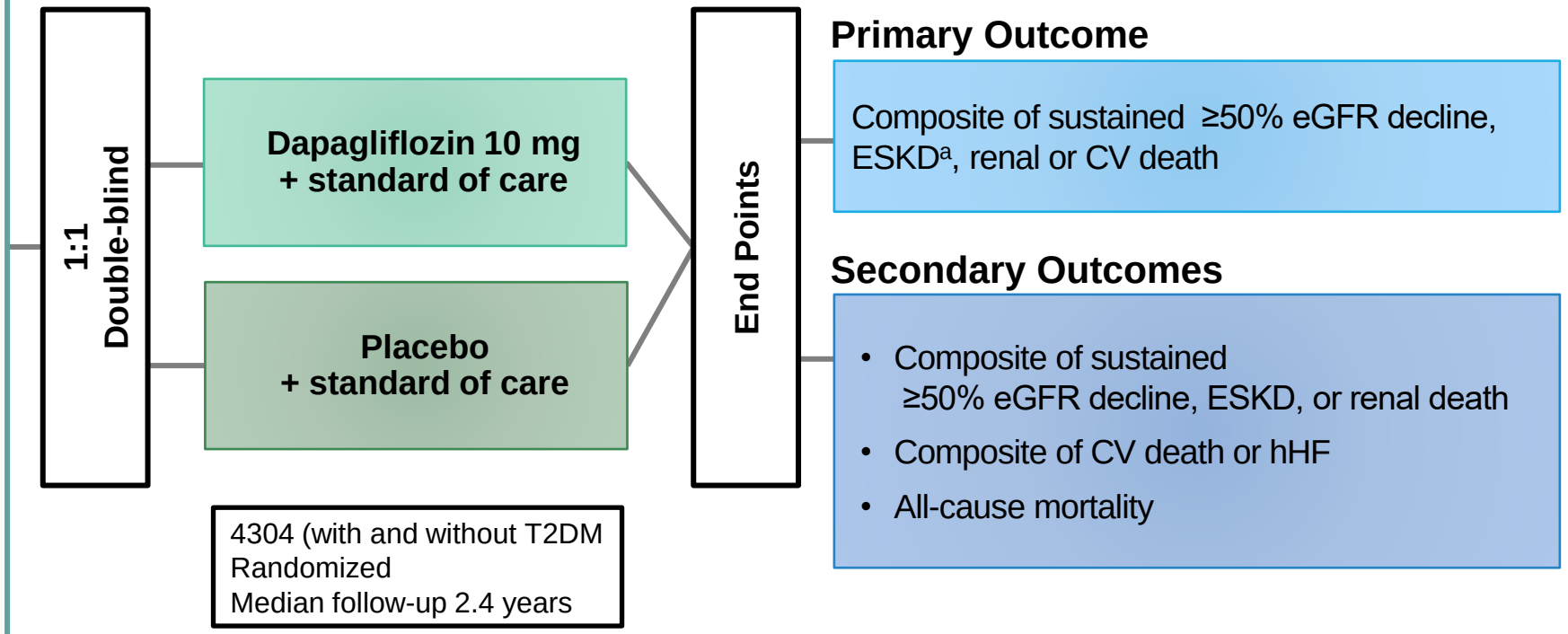
To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment

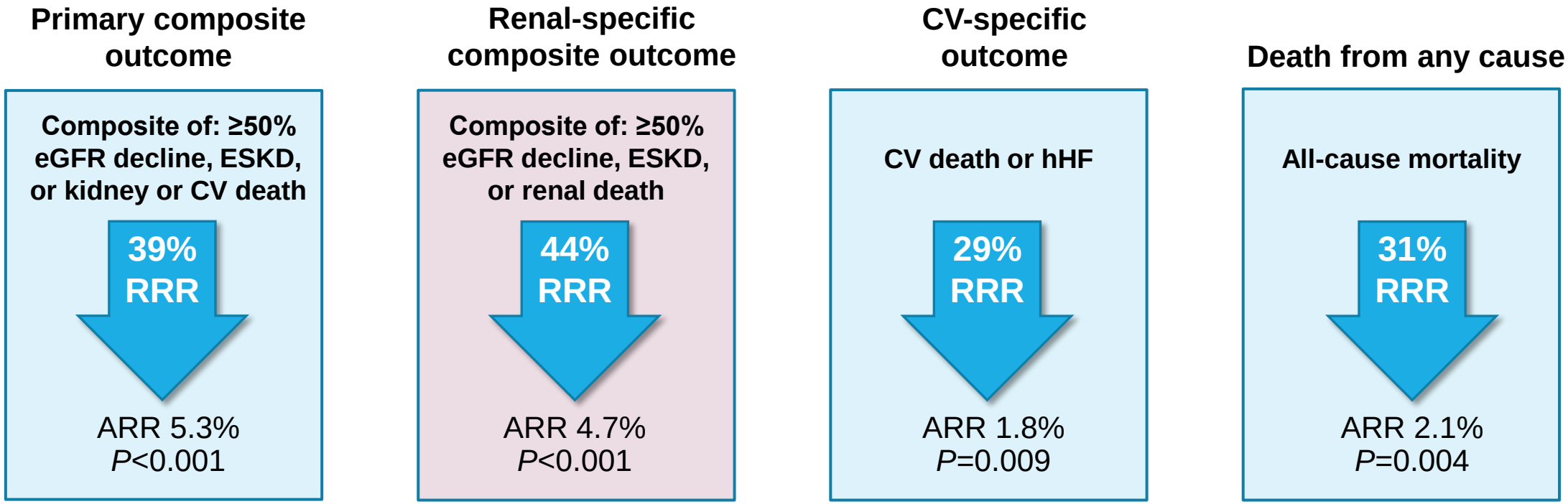


[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

DAKA-CKD Results

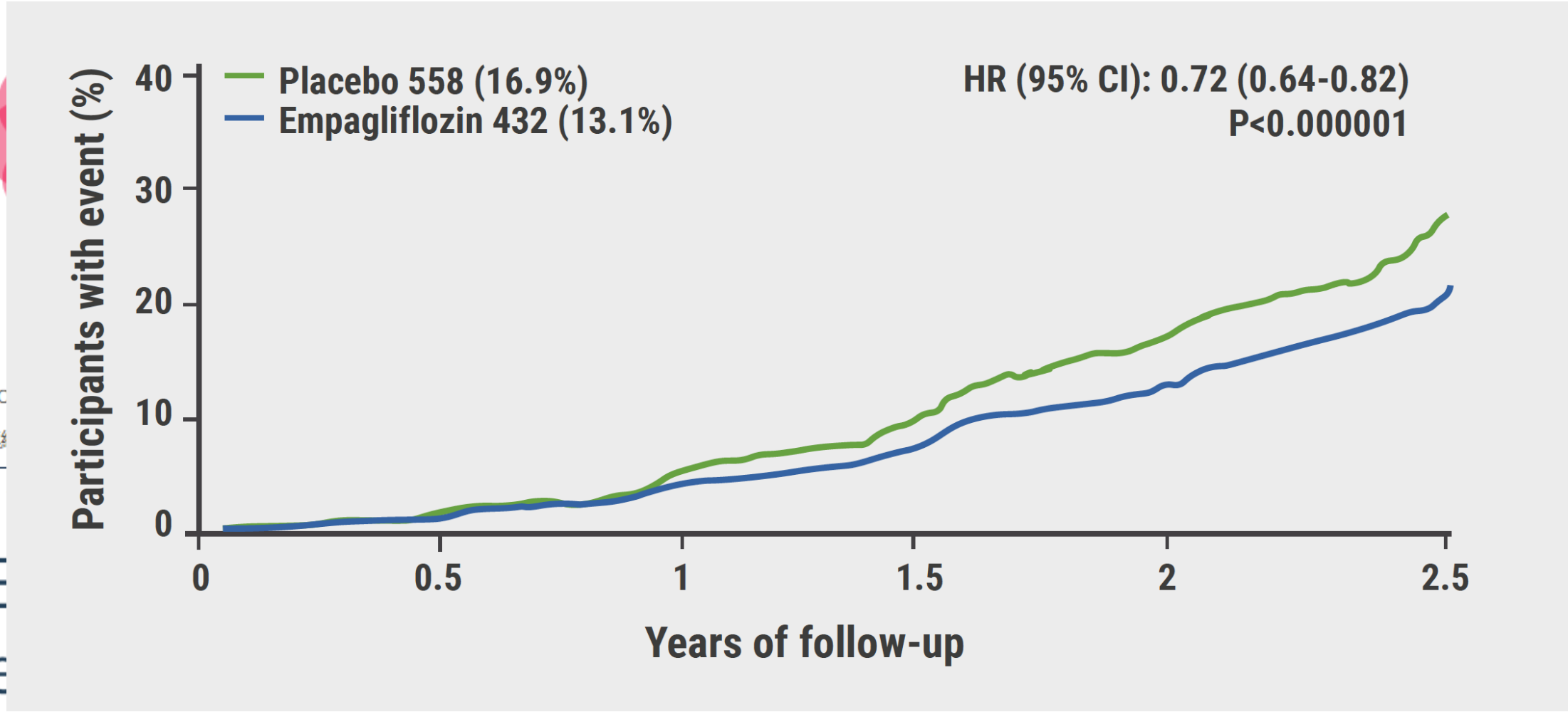
Dapa-CKD is the first SGLT2 inhibitor trial for patients with CKD, with and without T2D, to improve cardiorenal outcomes and reduce mortality



ARR = absolute risk reduction; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF, hospitalization for heart failure; RRR = relative risk reduction; SGLT2 = sodium–glucose co-transporter 2; T2D = Type 2 diabetes.

Heerspink HJL et al. *N Engl J Med.* 2020;383:1436-1446.

EMPA-KIDNEY



16 March 2022

Clinical Case Study

Case Study

Meet John

Seen Pre-Covid

Personal history

Age 54 years

Accountant

Married, has 3 children

Non smoker, occasional social drinking

Parents have DM, Mum on dialysis

Other medical problems

Hypertension for 3 years on amlodipine 10 mg

Routine Medical

Weight 107 kg	Pulse 92 bpm
Height 1.76 m	BP 136/84
BMI 34.5 kg/m^2	Systems normal
Waist 110 cm	Resting ECG normal

Lab Investigations

FBC	normal
FPG	7.8 mmol/l
HbA1c	6.9%
sCreat	88 umol/L
eGFR	92 ml/min
Cholesterol	5.2 mmol/L
HDL	1.1mmol/L
LDL-C	2.9 mmol/L
Trigs	2.7 mmol/L
UACR	1.8 mg/mmol
Urate	0.45 mmol/L

What are the issues ?

Meet John

Seen Pre-Covid

ASSESSMENT

Central obesity

Newly diagnosed T2DM

Essential hypertension

Diabetic dyslipidaemia

What are the issues ?

Meet John

Seen Pre-Covid

ASSESSMENT

Central obesity

Newly diagnosed T2DM

Essential hypertension

Diabetic dyslipidaemia

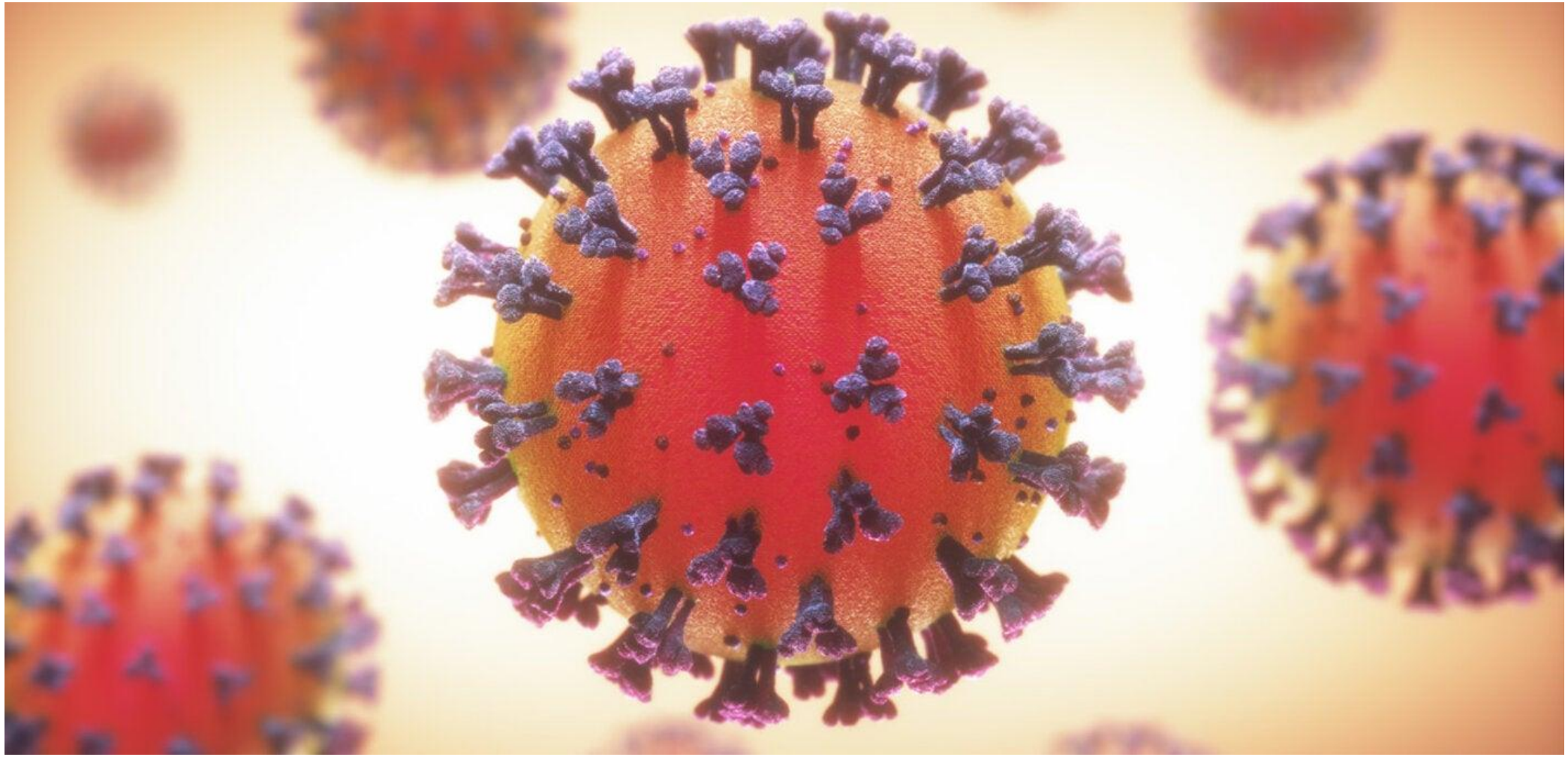
Diet and lifestyle

Metformin titrate to 1g bd

Continue Amlodipine

Atorvastatin 20mg added

Then came COVID



What are the issues ?

John

Seen Post Covid

ASSESSMENT

Worsening Central obesity

Worsening T2DM control

Essential hypertension

Diabetic dyslipidaemia

? Diabetes Kidney Disease

Glycaemic Management in patients with CKD

Management – HbA1c target

Patient features	< 6.5 %	< 7 %	7 - 8 %
Risks of hypoglycaemia / drug interactions	Low	⟷	High
Disease duration	Newly diagnosed	⟷	Long Standing
Life expectancy	Long	⟷	Short
Major comorbidities	Absent	⟷	Severe
Established macrovascular disease	Absent	⟷	Severe
Patient attitude	Highly motivated Adherent Good self-care capacity	⟷	Not motivated Non-adherent Poor self-care capability
Resources and support	Readily available	⟷	Limited

SEMDSA
Society for Endocrinology, Metabolism and Diabetes of South Africa

Recommendation 2.2.1: We recommend an individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis (Figure 9) *(1C)*.

< 6.5%	HbA1c	< 8.0%
CKD G1	Severity of CKD	CKD G5
Absent/minor	Macrovascular complications	Present/severe
Few	Comorbidities	Many
Long	Life expectancy	Short
Present	Hypoglycemia awareness	Impaired
Available	Resources for hypoglycemia management	Scarce
Low	Propensity of treatment to cause hypoglycemia	High

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.

Glucose lowering agents - overview

INSULIN	Sensitizers	Biguanides	Metformin	
		TZDs/Glitazones	Rosiglitazone, Pioglitazone	
	Secretagogues	K+ ATP	SUs	1st gen
				2nd gen: Glipizide, Glibencamide, Glimepiride, Gliclazide , etc
			Meglitinides	Nateglinide, Repaglinide, Mitiglinide
		GLP-1 agonists	Exenitide, Liraglutide, Lixenatide, Dulaglutide, Semaglutide, Albiglutide	
		DPP-4 inhibitors	Vildagliptan, Saxagliptan, Linagliptan, Sitagliptan, etc	
	Analogues		Fast acting, short acting, long acting , ultra long acting, mixed	
OTHER	Alpha-glucosidase inhibitors		Acarbose,	
	SGLT2 inhibitors		Empaglifozin, Canaglifozin, Dapaglifozin, Sotagliflozin	
	Amylin analog		Pramlintide	

Metformin: Recommendations

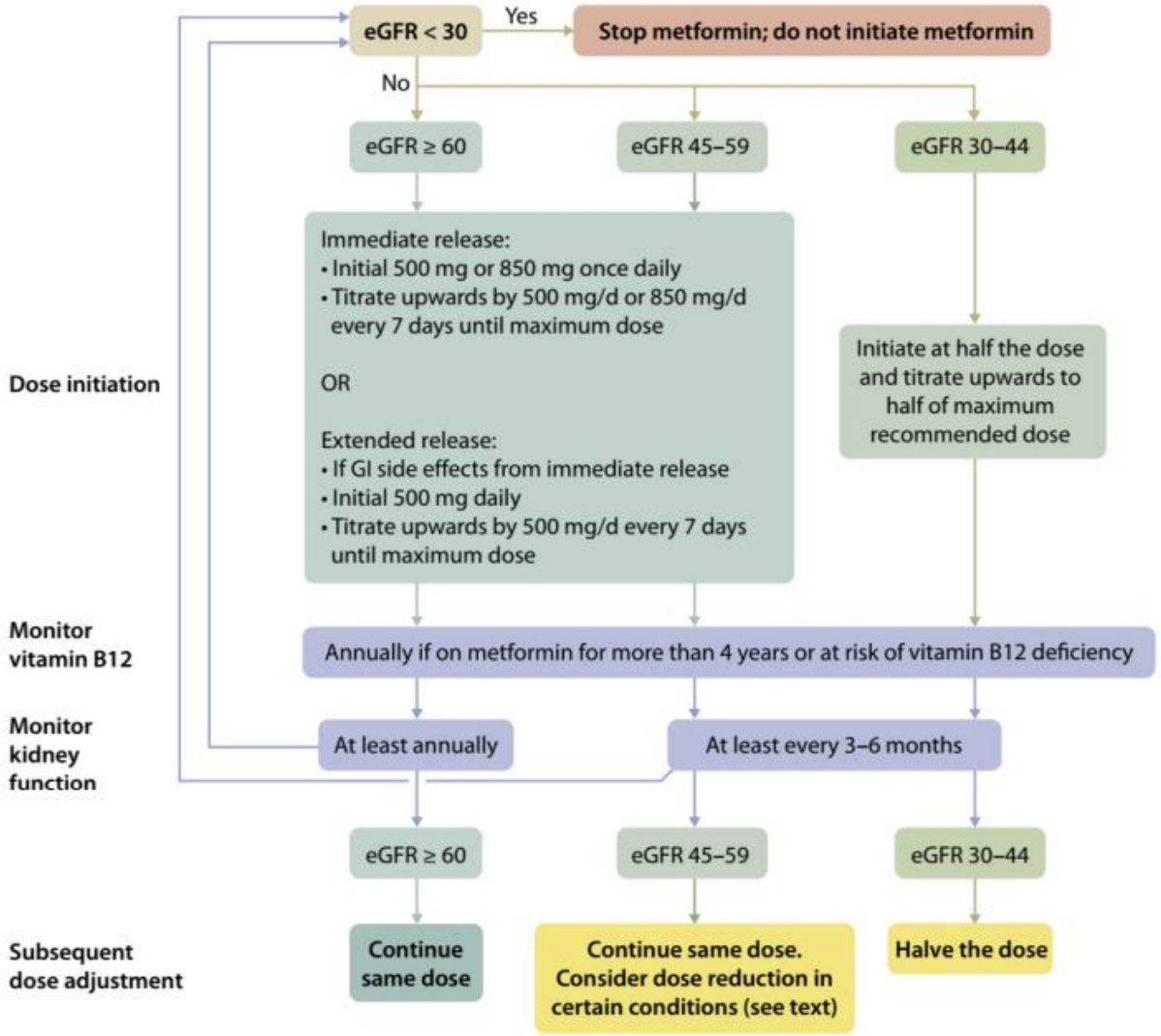


Table 1 Use of metformin in chronic kidney disease

eGFR (mL/min per 1.73 m^2)	Use of metformin
> 60 (CKD 1 and 2)	No contraindication Check of renal function annually
45-60 (CKD 3a)	Use of metformin-reduce dose (no more than 1.5-2 g daily) Frequent check of renal function (every 3-6 mo)
30-45 (CKD 3b)	Reduce dose (no more than 1-1.5 g daily) No new cases Frequent check of renal function (every 3-6 mo)
< 30 (CKD 4 and 5)	Stop metformin

CKD: Chronic kidney disease; eGFR: Estimate Glomerular Filtration Rate.

Sulfonylureas

Traditionally 2nd generation SUs were the most commonly used anti-DM meds in advanced CKD

Glipizide

- ✓ Recommended SU in advanced stage CKD
- ✓ Not renally excreted, therefore does not require dose adjustment

Gliclazide

- ✓ Metabolized by the liver to inactive metabolites which are then excreted by the kidney
- ✓ CKD 1-3: safe
- ✓ CKD 4 and 5: can theoretically be used at a lower dose, but no clinical data

Glimeperide

- ✓ Metabolized by the liver to 2 active metabolites which are excreted via the kidneys
- ✓ CKD 1-3: safe
- ✓ CKD 4: use reduced dosage
- ✓ CKD 5: contraindicated

Glibencamide

- ✓ Metabolized by the liver and excreted via kidneys and bowel
- ✓ Active metabolites may accumulate
- ✓ CI if eGFR< 60 Ml/min

DPP4- inhibitors

eGFR	Saxagliptin	Sitagliptin	Vildagliptin
≥50 ml/min	5 mg daily	100 mg daily	50 mg twice a day
30-50 ml/min	2.5 mg daily	50 mg daily	50 mg daily
<30 ml/min	2.5 mg daily	25 mg daily	50 mg daily

	CKD			
	CKD 1, 2 and 3a (Cl_{cr} > 50 mL/min)	CKD 3b (Cl_{cr} 30-50 mL/min)	CKD stage 4 (Cl_{cr} 15-30 mL/min)	CKD stage 5 (ESRD)
Sitagliptin	√ (100 mg × 1)	1/2 dose (50 mg × 1)	1/4 dose (25 mg × 1)	1/4 dose (25 mg × 1)
Vildagliptin	√ (50 mg × 2)	50 mg × 1		50 mg (no experience)
Saxagliptin	√ (5 mg × 1)	1/2 dose (2.5 mg × 1)	1/2 dose (2.5 mg × 1)	1/2 dose (2.5 mg × 1)
Linagliptin	√ (5 mg × 1)	√ (5 mg × 1)	√ (5 mg × 1)	P (5 mg × 1)
Alogliptin	√ (25 mg × 1)	1/2 dose (12.5 mg × 1)	1/4 dose (6.25 mg × 1)	1/4 dose (6.25 mg × 1)

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196., *Ioannidis I. Diabetes treatment in renal disease patients. 2014*

GLP-1 RA

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 CrCl >30 ml/min
Liraglutide	0.6 mg, 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
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

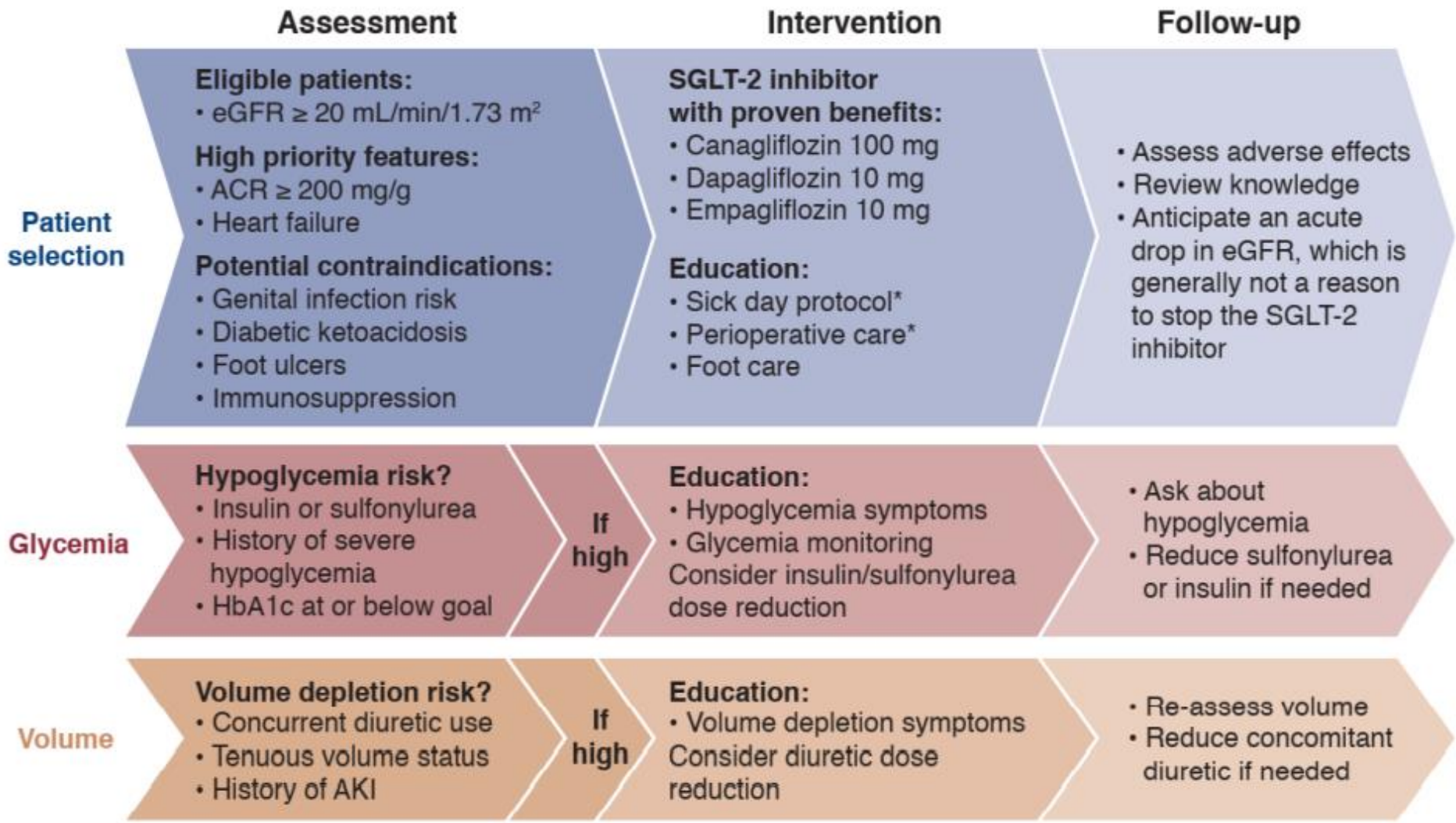
SGLT2i

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal	Dosing approved by the US FDA
Dapagliflozin			per 1.73 m^2
Empagliflozin	if needed for glucose control)	eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	per 1.73 m^2 for r glucose control eGFR ≥20 ml/min per 1.73m^2 for HFrEF

eGFR	**Dapagliflozin**	**Empagliflozin**
≥60 ml/min	5 mg or 10 mg	10 mg or 25 mg
45-60 ml/min	Contraindicated	Continue 25 mg but do not initiate therapy
<45 ml/min	Contraindicated	Contraindicated

KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf. . The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.,

Practice Points



KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf

Clinical practice points for SGLT2 use

It is reasonable to withhold SGLT2i therapy during times of prolonged fasting or critical medical illness (where patients may be at greater risk for ketosis)

If a patient is at risk for hypovolemia, consider decreasing diuretic (thiazide or loop) dosage before starting SGLT2i. Also advise patients about symptoms of dehydration and low blood pressure. Volume status should be assess at follow up.

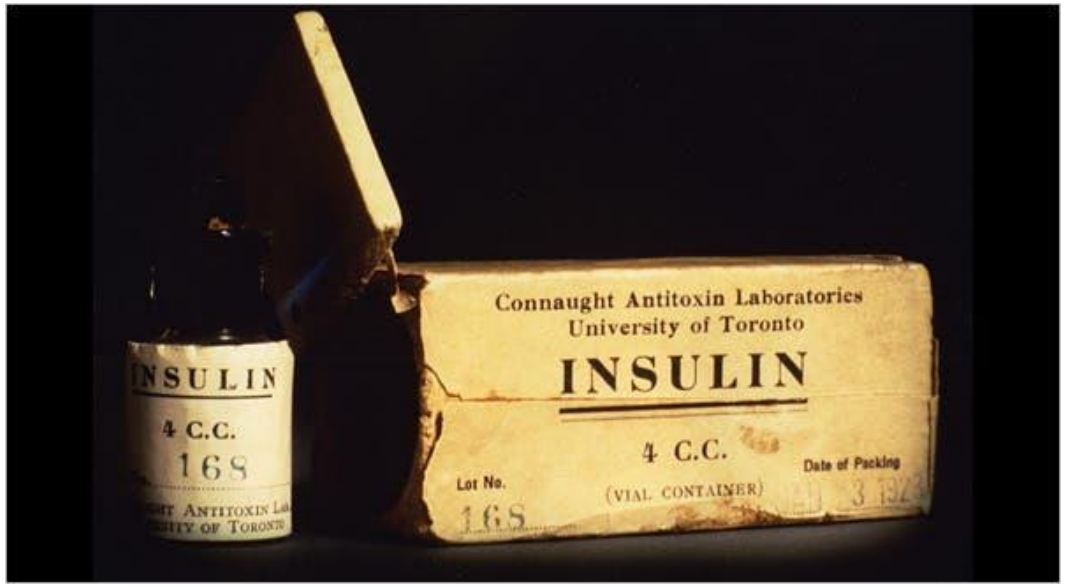
Once an SGLT2i is initiated it is reasonable to continue the drug even in the event of a decline in eGFR unless changes in eGFR are precipitating uremic symptoms or other complications of CKD

SGLT2i have not been adequately studied in kidney transplant patients, as such recommendations for their use does not apply to transplant recipients.

KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf. . The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196.,

Insulin

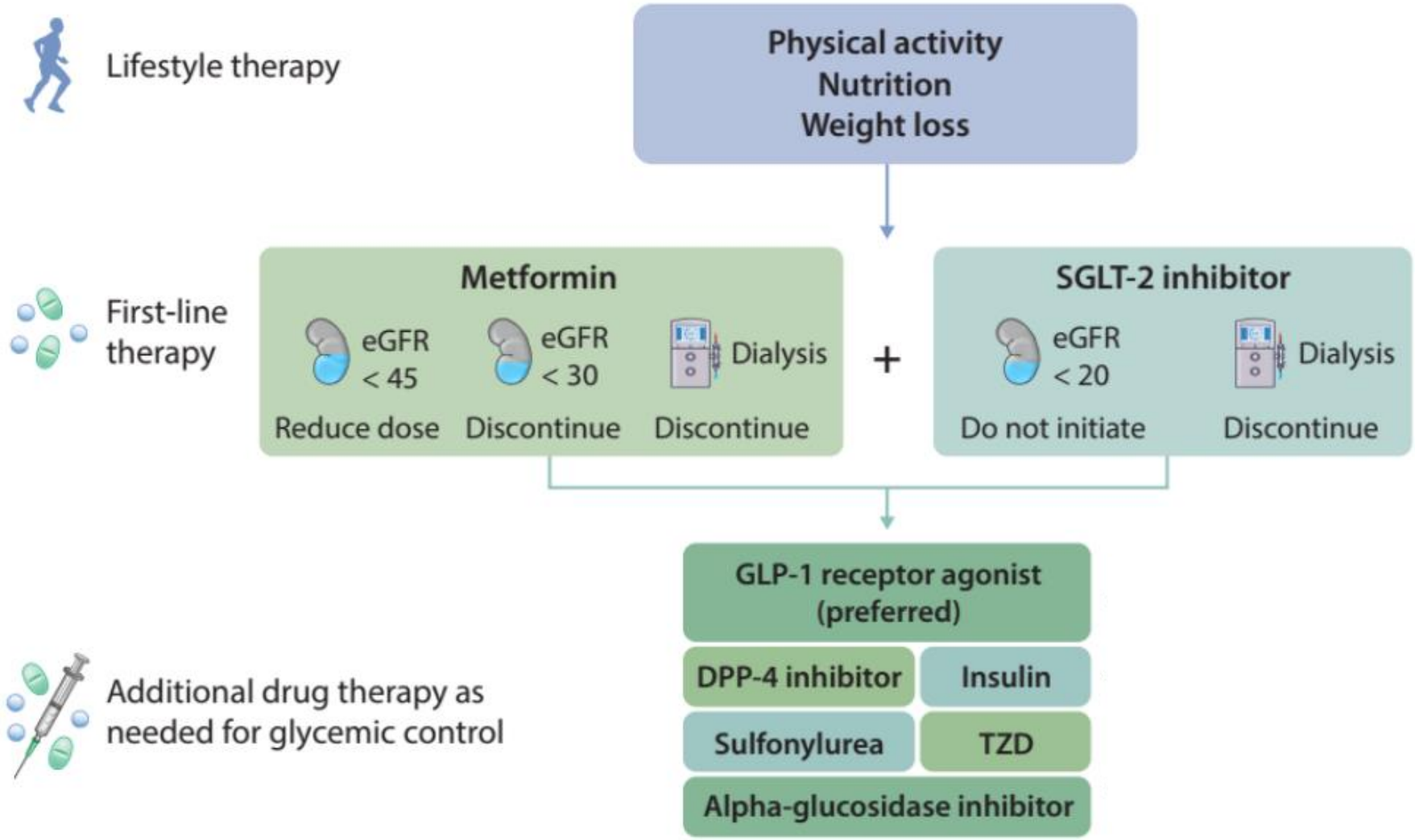
- Conventionally the mainstay of treatment for patients with advanced kidney disease
- High risk of hypoglycaemia
- Newer insulins – degludec, glargine 300 pharmacokinetics seem similar in normal and end stage renal patient, small reports –may be safer?



- **All insulin preparations are metabolised by the kidneys and will therefore require a dose reduction in patients with renal impairment[1] or as renal function worsens.**

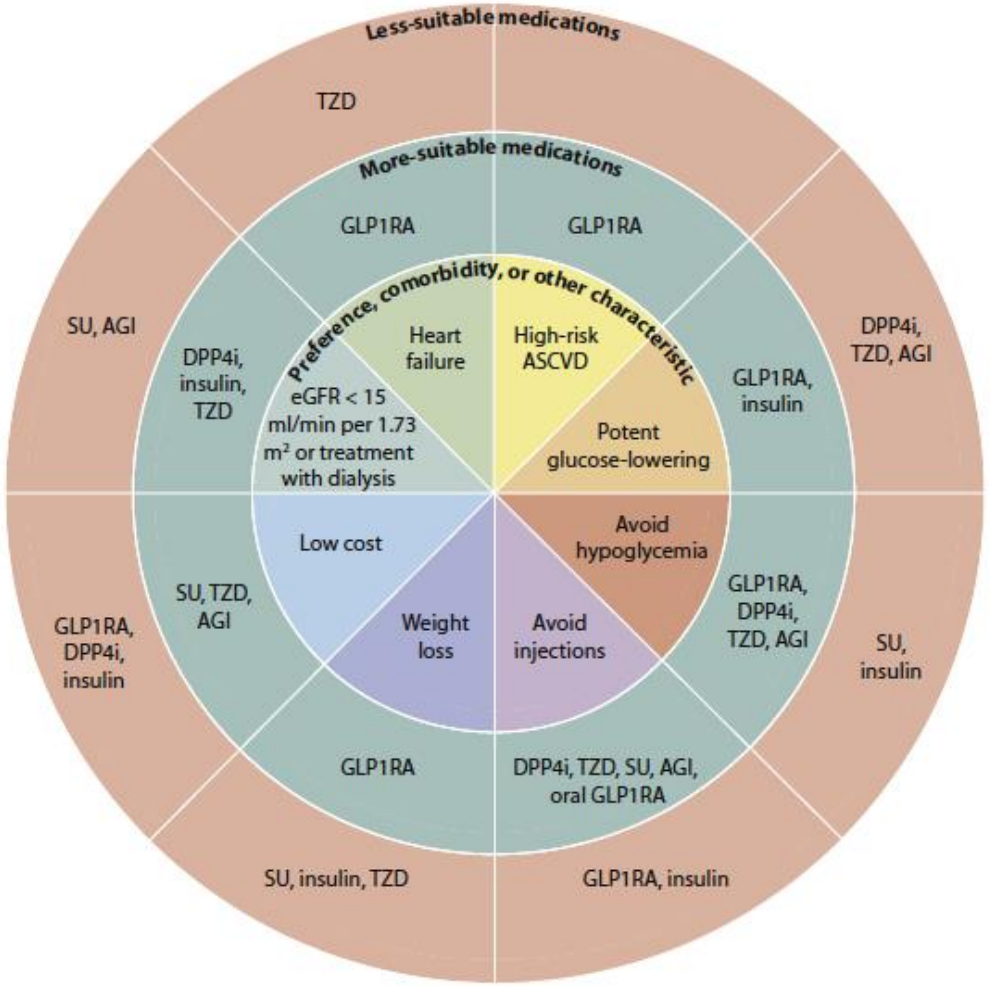
The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S1-S196

KDIGO Glycaemic Executive Summary



KDIGO Overall Executive Summary

What next after metformin and SGLT2i?



Medication options for John

John

Lab Investigations

HbA1c	**7.9%**
eGFR	**47 ml/min**
UACR	**4.8 mg/mmol**

Metformin	Maximum Dose 1.5g per day
SU	Gliclazide: safe but no additional benefit
DPP 4 inhibitor	DPP4i: safe but no additional benefit
SGLT2 inhibitor	Has CKD Benefit
GLP-1 RA	Has mild CKD benefit Severe Needle Phobia

Take home messages

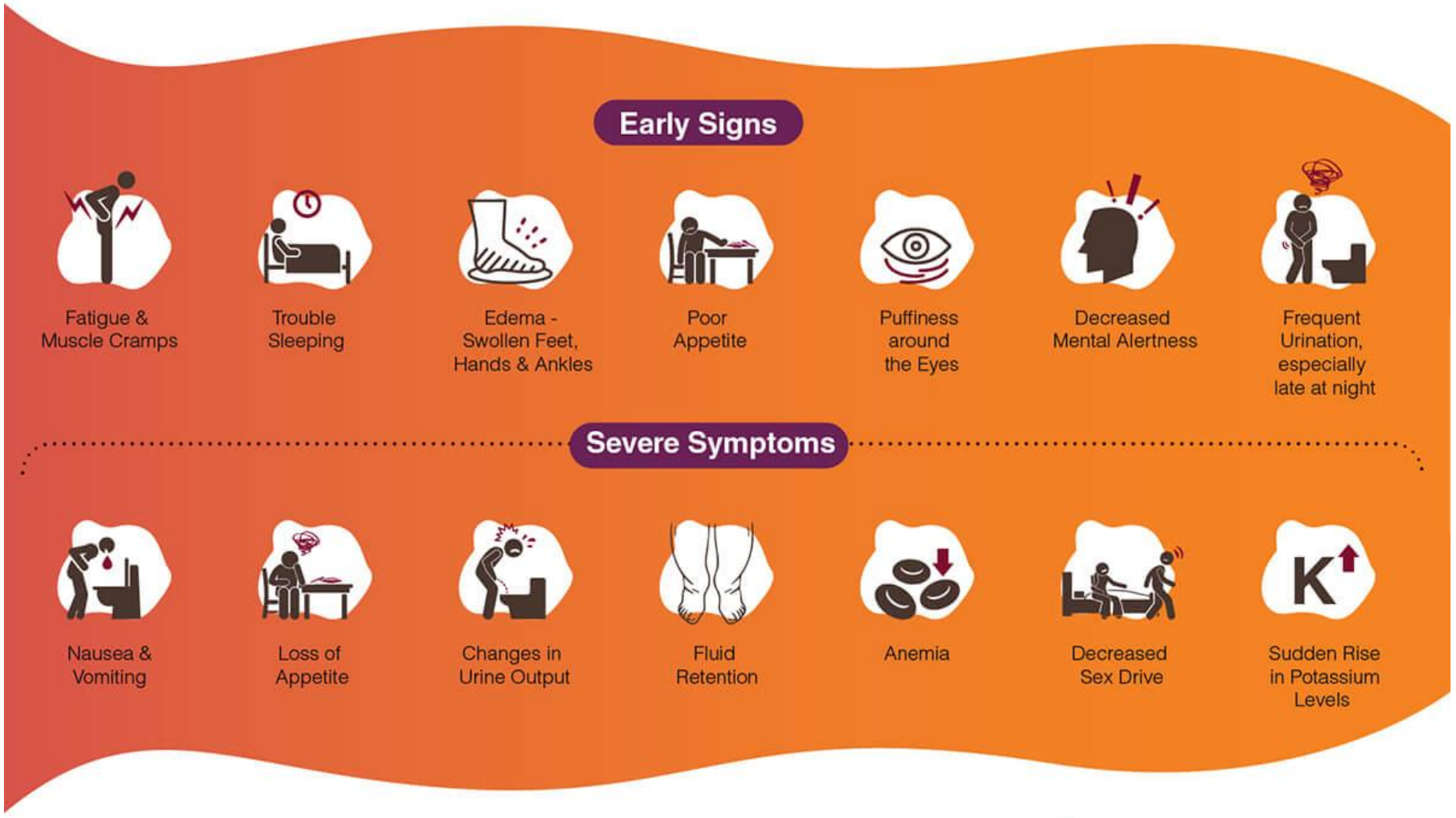
Take home messages

- The global burden of CKD continues to rise while diagnosis and patient awareness of the disease remains low[1–2]
- Diabetes, hypertension, and glomerulonephritis are the most common singular causes of CKD[3]
- Patients with hypertension, diabetes, and CVD are considered to be high risk for CKD and should be screened using eGFR and UACR[4]
- Risk of CV events and mortality are elevated in patients with CKD, independent of diabetes status or CKD etiology[5-7]
- The risk of mortality increases as CKD progresses, and is more likely than progression to ESKD[7,8]
- Guidelines recommend multifactorial interventional approaches for the management of CKD patients, including glycemic, blood pressure, and lipid management[9]

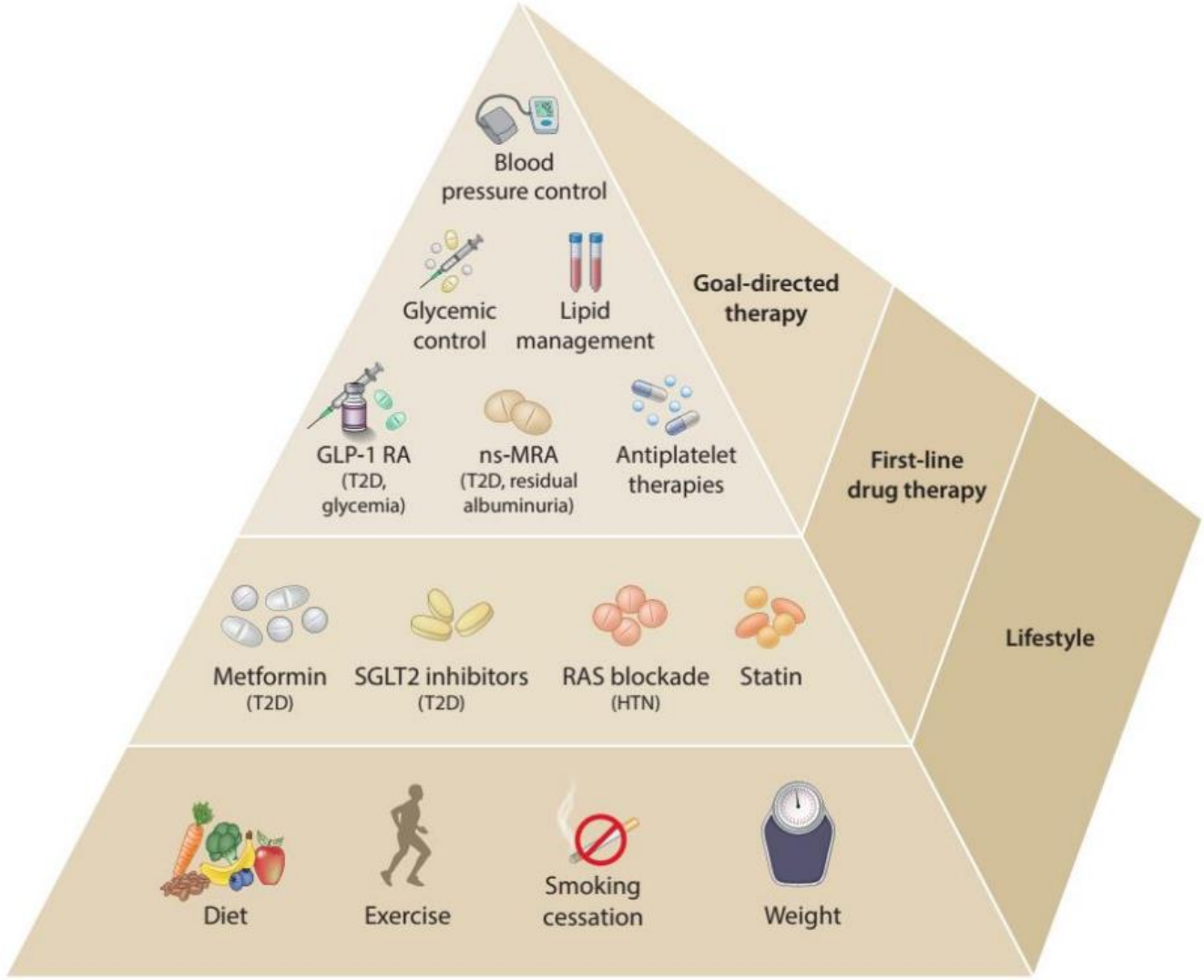
CKD = chronic kidney disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

1. Foreman KJ et al. *Lancet.* 2018;392:2052–2090; 2. USRDS. 2020 Annual data report: CKD in the general population. https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population; 3. Xie Y et al. *Kidney Int.* 2018;94:567–581; 4. Shlipak MG et al. *Kidney Int.* 2021;99:34–47; 5. Nakayama M et al. *Hypertens Res.* 2011;34(10):1106-1110; 6. Jarrick S et al. Article and online supplemental material. *J Am Soc Nephrol*. 2019;30(5):866-876; 7. Fox CS et al. *Lancet*. 2012;380:1662–1673; 8. Dalrymple LS et al. *J Gen Intern Med*. 2010;26:379–385; 9. Kidney Disease: Improving Global Outcomes. *Kidney Int.* 2020;98:S1–S115.

Maintain a High Index of Suspicion



Comprehensive Approach



de Boer, Ian H., et al. "Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment." *Kidney international* 98.4 (2020): 839-848.

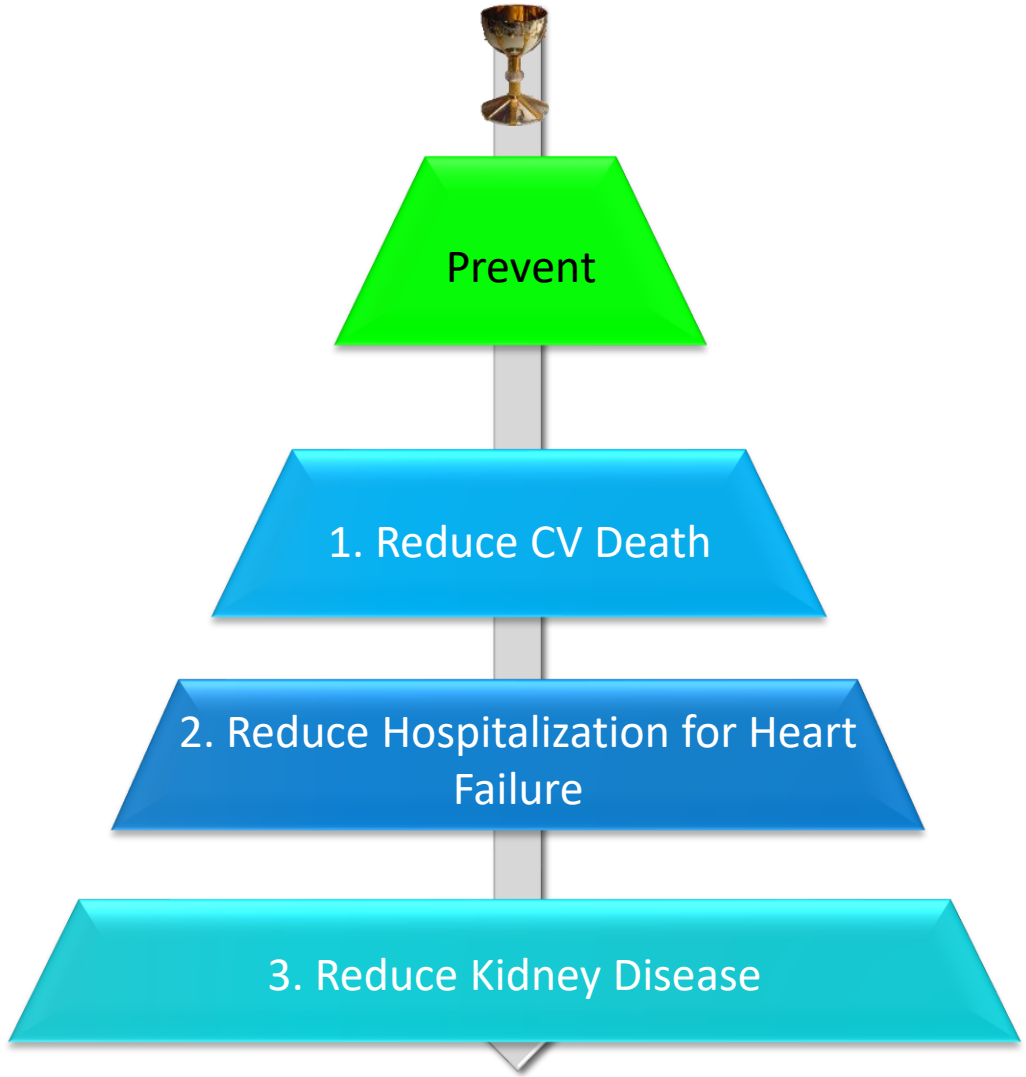
Individualize Treatment

SAFETY
- Bone Disease
- Amputations
- Euglycaemic DKA
- Eye Damage
- Pancreatitis

Reduced CV Death
- SGLT2 Inhibitor
- GLP1 R Agonist

Reduced Heart Failure Hospitalization
- SGLT2 Inhibitor

Improvement in Kidney Disease
- SGLT2 Inhibitor >>> GLP 1 RA



Adapted from Robert Chilton

When to use an SGLT2i

Healthy lifestyle behaviours; diabetes self-management education and support; social determinants of health

To avoid therapeutic inertia, re-assess and modify treatment regularly (3-6 months)

Goal

To reduce cardiorenal risk in high-risk people with T2D (in addition to comprehensive CV risk management)[a]

+ASCVD[b]

CVOTs included participants with established CVD (e.g., MI, stroke or any revascularisation procedure), but the definition of ASCVD differed between them. Variably included were TIA, unstable angina, amputation, symptomatic or asymptomatic CAD.

+High-risk indicators

Definition of ASCVD may vary across CVOTs; however, most patients are ≥55 years of age with ≥2 additional risk factors (including obesity, hypertension, smoking dyslipidaemia or albuminuria)

+ASCVD/High-risk indicators

GLP-1 RA[c] with proven CVD benefit

Either/ Or

SGLT-2i[d] with proven CVD benefit

If HbA1c above target levels

- Consider the addition of SGLT-2i with proven CVD benefit or vice versa in people using GLP-1 RA
- TZD[e]

+HF

HF symptoms, currently or earlier, with documented HFrEF or HFpEF

+HF

SGLT-2i[d] with proven HF benefit

+CKD

eGFR <60 mL/min/1.73 m^2 or albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may differ over time, needing a repeat measure to document CKD

+CKD (on MTD of ACEi/ARB)

SGLT-2i[d] with primary evidence of reducing CKD progression

Use SGLT-2i in people with eGFR ≥20 mL/min/1.73 m^2; once initiated, continue until initiation of dialysis or transplantation

Or

GLP-1 RA with proven CVD benefit if SGLT-2i not tolerated or contraindicated

If HbA1c above target levels, for people on SGLT-2i, consider including a GLP-1 RA or vice versa

If additional reduction of cardiorenal risk or lowering of glycaemia required

Goal

To achieve and maintain glycaemic and weight management goals

Managing glycaemia: Choose approaches that provide the efficacy to achieve goals:

Metformin **or** medicines including **combination** treatment that provide adequate **efficacy** to achieve and maintain treatment goals

In high-risk individuals, consider avoidance of hypoglycaemia a priority

Generally, higher efficacy approaches have increased the possibility to achieve glycaemic goals
Efficacy for lowering glucose levels

Very High

Dulaglutide (high dose), semaglutide, tirzepatide
Insulin

Combination oral, combination injectable (GLP-1 RA/insulin)

High

GLP-1 RA (not listed above), metformin, SGLT-2i, sulphonylurea, TZD

Intermediate

DPP-4i

Achieving and maintaining weight management goals:

Setting individualised weight management goals

Lifestyle advice: MNT/ healthy eating patterns/ physical activity

Intensive evidence-based structured weight management programme

Weight-loss medication to be considered

Metabolic surgery to be considered

When choosing antihyperglycaemic medications:
Consider regimen with high-to-very-high dual glucose and weight efficacies

Efficacy for weight loss

Very High

Semaglutide, tirzepatide

High

Dulaglutide, liraglutide

Intermediate

GLP-1RA (not listed above), SGLT-2i

Neutral

DPP-4i, metformin

If HbA1c above target levels

Note: Explanation for footnote indicators and abbreviations are available in the speaker notes.

1. Data from Davies MJ, et al. *Diabetes Care*. 2022;45(11):2753-2786. 2. Data from Davies MJ, et al. *Diabetologia*. 2022;65(12):1925-1966.

Identify barriers:

- Consider DSMES referral to support self-efficacy in goal achievement
- Identify and address social determinants of health that affect goal achievement
- Consider technology (e.g., diagnostic CGM) to identify therapeutic lacuna and individualise therapy

To Summarise

SEMDSA 2023 Guidelines

Thank you for listening