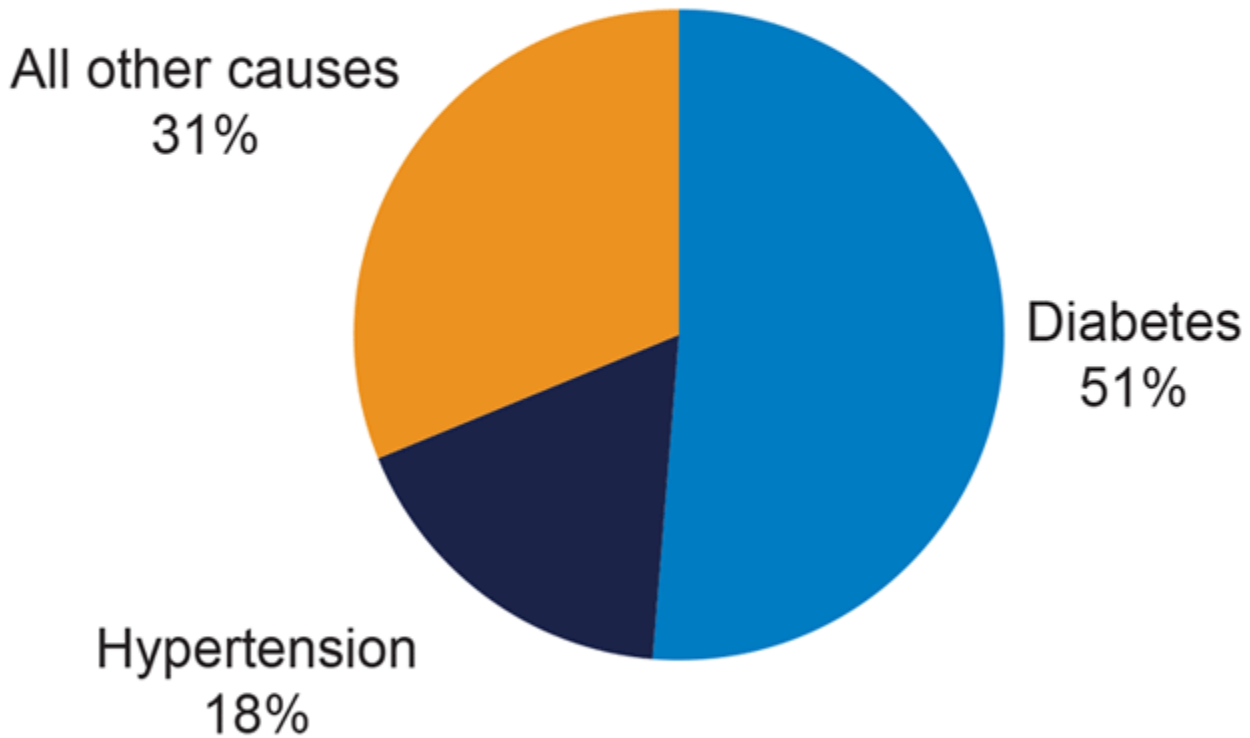
Diabetic Nephropathy

Diabetic nephropathy is a serious complication of type 1 diabetes and type 2 diabetes. It's also called diabetic kidney disease

Importance of DKD

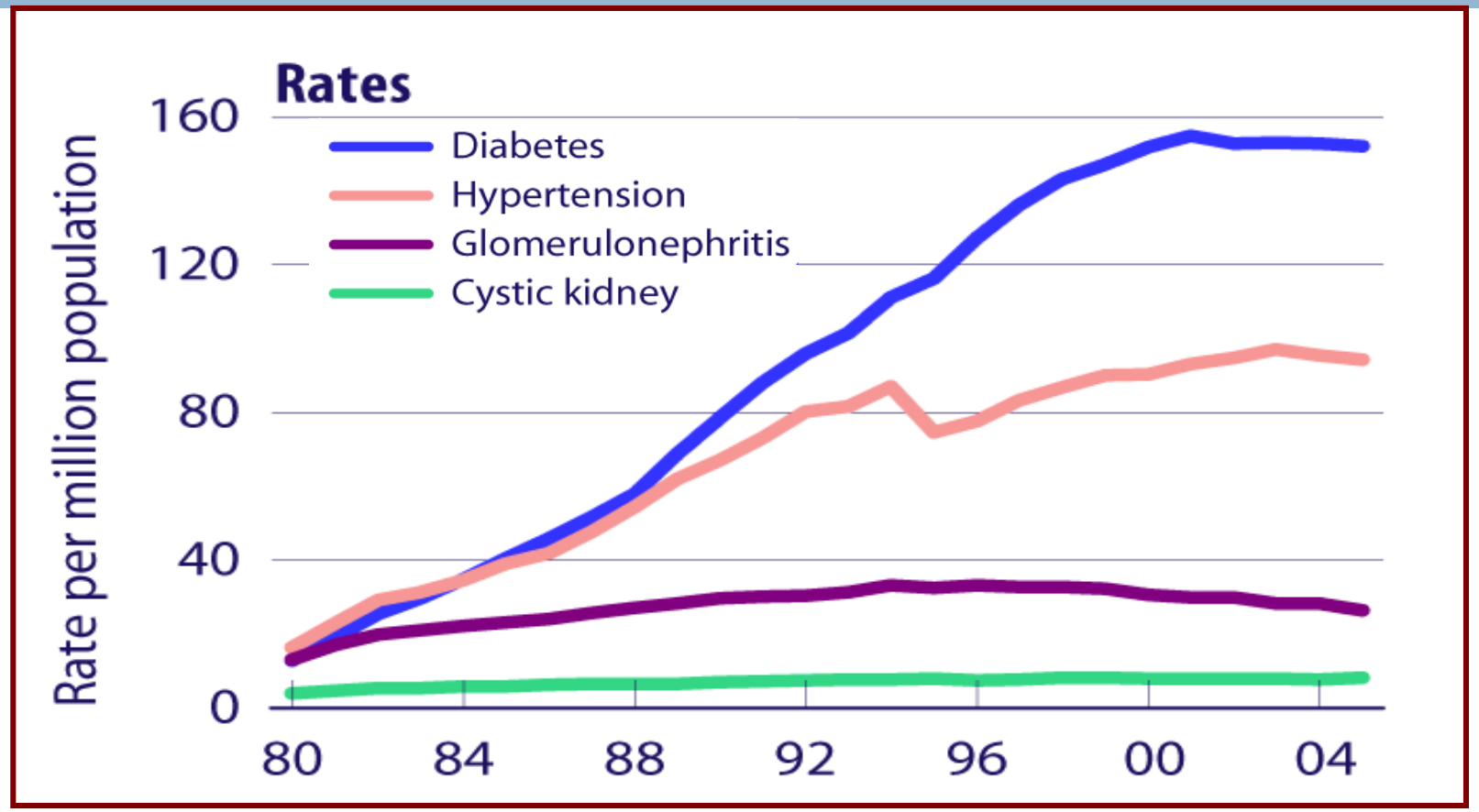
- Individuals with diabetes are at risk of CKD
- Diabetes is the leading cause of ESRD
- Patients with T2DM and CKD are at greatly increased risk of mortality
- These risks can be reduced but not eliminated with multifactorial traditional cardiovascular risk factor management (eg, controlling A1C, blood pressure, and cholesterol levels, and smoking cessation)

Diabetes Is the Leading Cause of ESRD[1]



1. https://www.usrds.org/2018/view/Default.aspx. Accessed April 30, 2019.

Diabetes and hypertension are leading causes of kidney failure

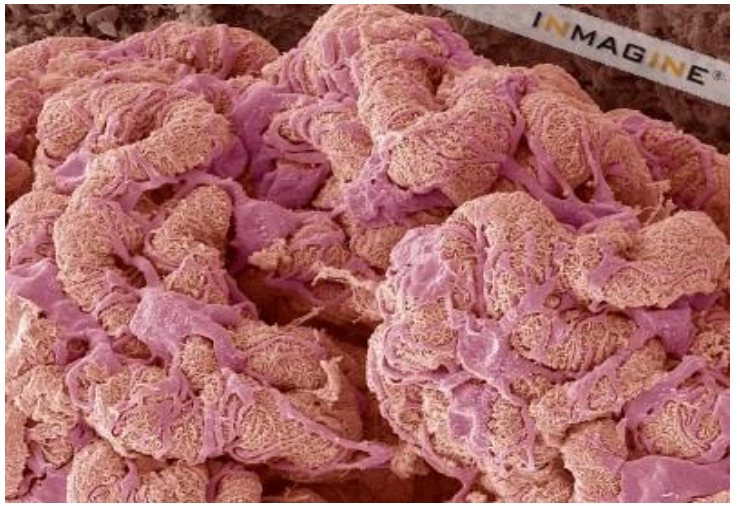


Incident ESRD rates, by primary diagnosis, adjusted for age, gender, & race.

ESRD, end stage renal disease
USRDS ADR, 2007

DEFINITION

Diabetic Nephropathy is a progressive kidney disease characterised by:



- Histopathologically:
  - Angiopathy of glomerular capillaries
  - Diffused glomerulosclerosis

- **Late** clinical stages associated with
  - Persistent albuminuria
  - Progressive decline in the glomerular function
  - Elevated blood pressure

EPIDEMIOLOGY

Most common cause of ESKD

- Common microvascular complication of diabetes
- **Early DN is reversible, and probably preventable**

- More common in T1DM patients
  - Well defined clinical course regarding progression

- Accounts for ~40% of patients starting DIALYSIS
- Male > Female

RISK FACTORS

- Duration of diabetes
- Poor control of diabetes
- Smoking
- Metabolic syndrome: Overweight, Hypertension, dyslipidemia
- Associated micro-vascular complications as retinopathy, neuropathy
- Genetic susceptibility
- Gender M>F

CHARACTERISTICS OF DN

Diabetic milieu → hyperglycaemia→ AGEs

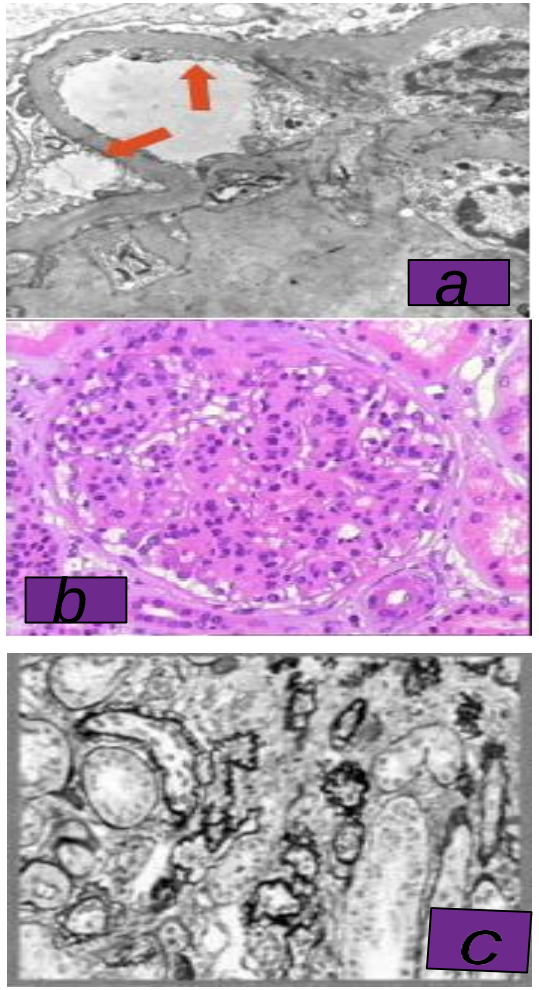
(mediators for functional and structural abnormalities of DN)

Structural

- hypertrophy of the kidney
- increased GBM thickness (*a*)
- Nodular and diffuse glomerulosclerosis (*b*)
- Tubular atrophy
- Interstitial fibrosis (*c*)

Functional

- Early increase in glomerular filtration rate
- Intraglomerular hypertension
- Subsequent proteinuria
- Eventual loss of renal function



5 STAGES OF DN

Stage 1 – **early hypertrophy** increase in renal plasma flow and GFR

Stage 2 – **silent stage**Subtle morphological changes Thickening of GBM Glomerular hypertrophy mesangial and tubulointerstitial expansion

Stage 3 – **incipient DN (+/- Abnormal Creatinine/ BP)**Microalbuminuria (U ACR: 5-25 mg/mmol)

Stage 4 – **Overt DN (High BP +/- Abnormal Creatinine)**Macroalbuminuria (U ACR >25 mg/mmol)

Stage 5 – **ESRD with uraemia**

Natural History of DN and classifications of CKD stages

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300	Type 1 normal Type 2 normal	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

Classifications of CKD stages

Table 3. Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73m²)	Action*
	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
1.	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3.	Moderate ↓ GFR	30-59	Evaluating and treating complications
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5.	Kidney Failure	<15 (or dialysis)	Replacement (if uremia present

Classification of CKD Based on GFR and Albuminuria Categories: "Heat Map"

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	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppls*. 2013;3:1-150.

Diabetes Is the Most Likely Cause of CKD IF:

- Albuminuria is present.
- Diabetic retinopathy is present.
- The patient has diabetes of at least 10 years duration.

However, kidney disease in diabetes may manifest differently in different people. In the future, individualized treatment may be guided by kidney biopsy and advanced biochemical or genetic testing.

Am J Kidney Dis. 2012;60(5):850-886
Clin J Am Soc Nephrol. 2017;12(9):1544-1547

Clinical evidence of DN

Earliest biochemistry abnormality –albuminuria

- **Without interventions,** 80% with T1DM have urinary albumin excretion increase at 10-20% per year to **overt nephropathy** over a period of 6-15 yrs

- Once overt nephropathy occurs , **with/ without interventions,** GFR falls over a period of several years.

- Eventually,
  - 50% of T1DM individuals develop ESRD within 10 yrs
  - 75% of T1DM individuals develops ESRD by 20 years

What about T2DM ?

Progression of Diabetic Nephropathy in Type 2 DM

Type 2 DM — **950,000 (1)**

30% ↓

Microalbuminuria — **225,000 (2)**

30% ↓

Proteinuria — **32,000 (2)**

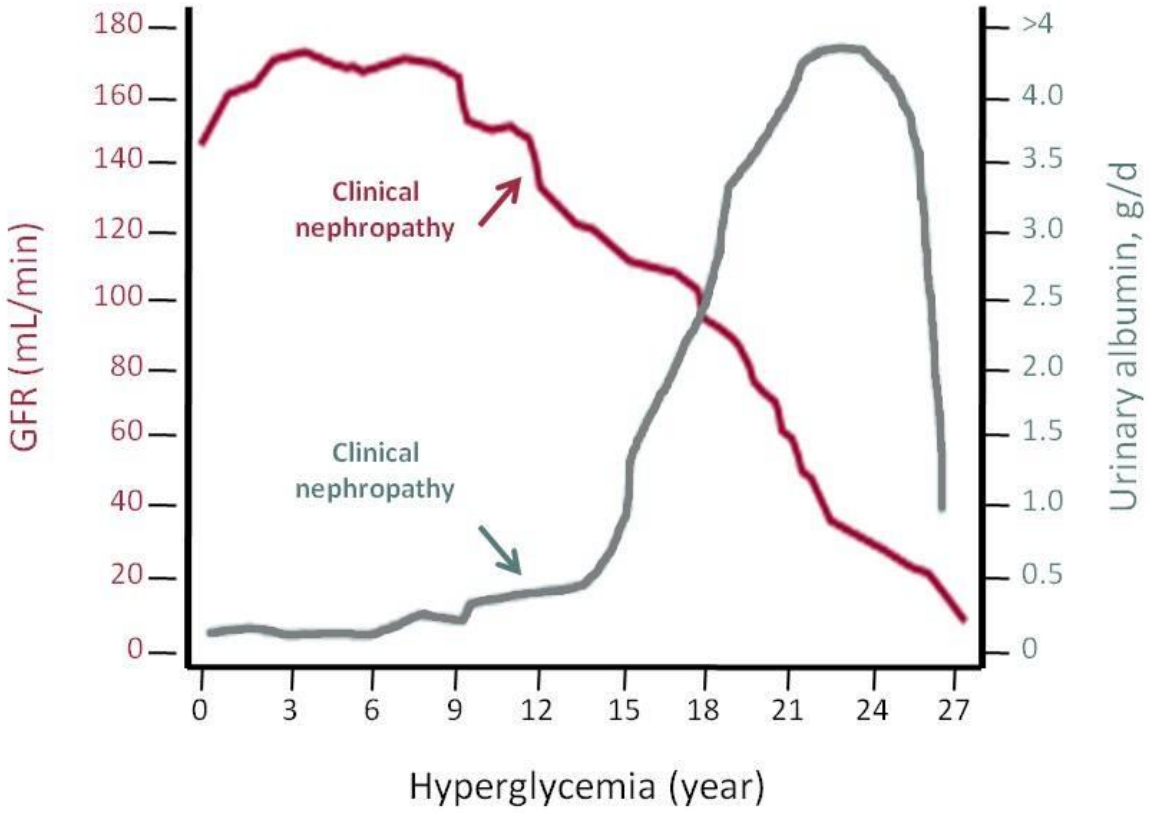
30% ↓

(but 70% have CV death first) End

Stage Renal Disease — **2,000 (3)**

Dunston et al Diabets Care 2002
Atkins R KI 2004 ANZDATA 2004

Natural History of Diabetic Nephropathy: Hyperglycemia Causes Hyperfiltration, Followed by Albuminuria and Decreased GFR



Reference: Adapted from Friedman, 1999

DIAGNOSIS

- Patients history
- Physical examination
- Laboratory evaluations
- Imaging of the kidneys
- Positive microalbuminuria:
  - Spot urine, confirmed 2 out of 3, 3-6 mths
- Elevated creatinine urea
  (as kidney damage progress)
- Diabetic retinopathy
  - Long term T1D > 10yrs
  - Proteinuric T2D

DIAGNOSIS CONT…

Proteinuria is the hallmark of DN Although characteristics of DN are :

- Thickening of GBM
- Mesangial expansion

These changes do not explain development of proteinuria Recent advances in **podocytes** cell biology may be early markers of DN

Hyperglycemia → AGEs → podocytes cell deaths → protein leakage

Dead podocytes cells excreted in the urine

Strong evidence of podocytes injury very early in the course of DN → ??
Podocyte numbers : early marker

Wolf, G (2007). Nephron Physiology, 106(2): 26-31

Urine Albumin is a Marker for Kidney Damage

- An abnormal urine albumin level is a marker for glomerular disease, including diabetes.
- Urine albumin is a marker for cardiovascular disease and is a hypothesized marker of generalized endothelial dysfunction.
- May be associated with increased mortality.

Risk Factors for Albuminuria

Known risks	Possible risks	Transient increases may be due to:
• Diabetes • Hypertension • Smoking • Obesity	• High sodium intake • High protein intake • Inflammation	• Episodic hyperglycemia • Exercise within 24 hrs. • Fever • Urinary tract infection

References: De Jong et al. *Kidney International*. 2004;66:2109–2118;
Tuttle et al. *Diabetes Care*; 2014: 37:2864–2883

Damaged Kidneys Allow More Albumin to Cross the Filtration Barrier into the Urine

- Increased glomerular permeability allows albumin and other proteins to cross the glomerulus into the urine.
- Higher levels of protein which exceed the tubule's capacity to reabsorb that protein may exacerbate kidney damage through injury to the tubules.

Use Urine Albumin-to-Creatinine Ratio (UACR) for Urine Albumin Assessment

- UACR uses a spot urine sample.
- In adults, ratio of urine albumin to creatinine is used to estimate 24 hour albumin excretion.
- Ratio is between two measured substances (not dipstick).

$$\frac{\text{Urine albumin (mg/dL)}}{\text{Urine creatinine (g/dL)}} = \text{UACR (mg/g)} \cong \text{Albumin excretion in mg/day}$$

- UACR $\leq$ 30 mg/g is generally the most widely used cutoff for "normal."

https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-education-outreach/quick-reference-uacr-gfr

Which Urine Test to Use?

- Dipstick
  - Semi-quantitative, screening only
    - Affected by urine concentration, highly variable
  - Detection of urine albumin ≥ 300 mg/day
    (1+ approximates albumin excretion of 30 mg/day)
- Urine protein/creatinine ratio
  - All proteins, not just albumin
- **Urine albumin-to-creatinine ratio (UACR)**
  - Other common names for UACR include microalbumin, urine albumin, albumin-to-creatinine ratio or microalbumin/creatinine ratio.

SCREENING FOR MICROALBUMINURIA

- ✓ **Screening for microalbuminuria provides early intervention opportunity**
- ✓ **performed annually from the onset of T2DM , 5 yrs after onset of T1DM**
- ✓ **morning spot urine for albumin : creatinine ratio (ACR) is most reliable**

ACR Result	Test Results Range	Recommended Follow -up
Normal	*Females* <3.5 mg/mmol *Males* <2.5 mg/mmol	Re-test annually
Microalbuminuria	*Females* 3.5 – 35 mg/mmol *Males* 2.5 – 25 mg/mmol	Repeat 2 times over 3 months – confirm microalbuminuria if 2 out of 3 tests is positive
Macroalbuminuria (also called proteinuria)	*Females* >35 mg/mmol *Males* >25 mg/mmol	Do a protein :creatinine ratio (PCR) or 24 hour urine protein (to quantify protein excretion)

NHMRC Guidelines 2009

Interventions for Reducing Urine Albumin

- Control blood pressure
- Reduce sodium intake
- Achieve good control of diabetes early; may help prevent albuminuria
- Reduce weight, if obese
- Reduce protein intake, if excessive
- Achieve tobacco cessation

Hyperglycemia is Associated with Hyperfiltration

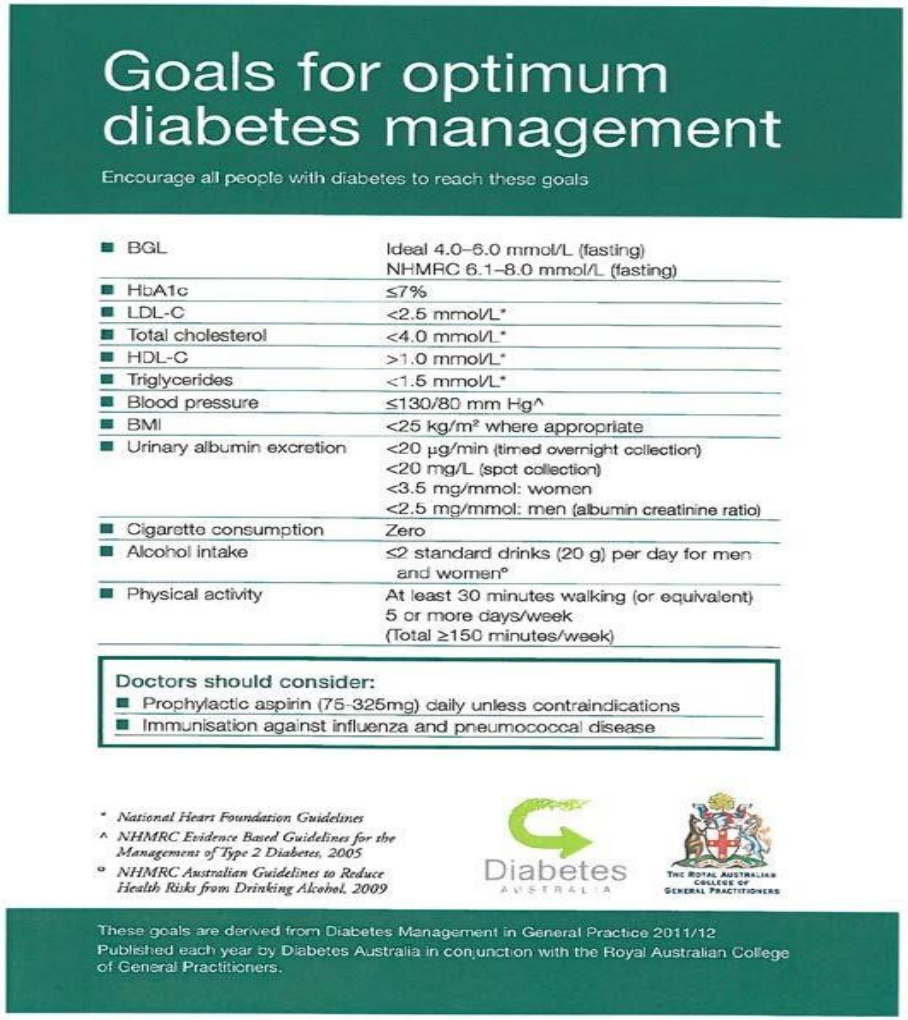
- The initial response to hyperglycemia is an increase in GFR, or hyperfiltration, followed by a slow decline.
- The increased pressure and flow within the glomerular capillary may damage the nephrons.
- Diabetic kidney disease (DKD) is generally, but not always, associated with progressive albuminuria.

References: Molitch et al. *Diabetes Care* 2010; 33(7):1536–1543; Retnakaran et al. *Diabetes* 2006; 55(6):1832–1839.

Much of the Necessary Care May be Managed in the Primary Care Setting

- Many CKD interventions are similar to those for diabetes care.
- Other key interventions include co-morbidity screening.
- Timing of nephrology referral varies depending on patient status and provider experience.
  - Lack of appropriate care is associated with more rapid progression, worse health status at time of dialysis initiation, higher mortality after starting dialysis, and decreased access to transplant.
- Refer to a Registered Dietitian who is familiar with CKD for Medical Nutrition Therapy.

MULTIFOCAL TREATMENT APPROACH



Goals for optimum diabetes management

Encourage all people with diabetes to reach these goals

BGL	Ideal 4.0–6.0 mmol/L (fasting) NHMRC 6.1–8.0 mmol/L (fasting)
HbA1c	≤7%
LDL-C	<2.5 mmol/L*
Total cholesterol	<4.0 mmol/L*
HDL-C	>1.0 mmol/L*
Triglycerides	<1.5 mmol/L*
Blood pressure	≤130/80 mm Hg^
BMI	<25 kg/m² where appropriate
Urinary albumin excretion	<20 µg/min (timed overnight collection) <20 mg/L (spot collection) <3.5 mg/mmol: women <2.5 mg/mmol: men (albumin creatinine ratio)
Cigarette consumption	Zero
Alcohol intake	≤2 standard drinks (20 g) per day for men and women°
Physical activity	At least 30 minutes walking (or equivalent) 5 or more days/week (Total ≥150 minutes/week)

Doctors should consider:
- Prophylactic aspirin (75-325mg) daily unless contraindications
- Immunisation against influenza and pneumococcal disease

* *National Heart Foundation Guidelines*
^ *NHMRC Evidence Based Guidelines for the Management of Type 2 Diabetes, 2005*
° *NHMRC Australian Guidelines to Reduce Health Risks from Drinking Alcohol, 2009*

Diabetes AUSTRALIA

THE ROYAL AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS

These goals are derived from Diabetes Management in General Practice 2011/12
Published each year by Diabetes Australia in conjunction with the Royal Australian College of General Practitioners.

SLOW DOWN PROGRESSION OF DN

A. Optimal glycemic control –

A. Hb A1c < 7%

B. Intensive antihypertensive control

A. BP <130/80 for people with Proteinuria < 1g/day

B. BP <120/75 for people with Proteinuria >=1g/day

C. Blockade of RAS

A. ACEi OR ARB

Goals of Care in CKD: Glucose Control

- Target HbA1c ~7.0%
- Can be extended above 7.0% with comorbidities or limited life expectancy, and risk of hypoglycemia
- Risk of hypoglycemia increases as kidney function becomes impaired
- Declining kidney function may necessitate changes to diabetes medications and renally-cleared drugs

NKF KDOQI. Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. 2012 60:850-856.

A. Optimal glycemic control

Effects of Hyperglycaemia

- Acutely increases membrane permeability to macromolecules
- Raises BP by inducing sodium retention and extravascular sodium and fluid shift
- Generation of AGE leading to podocytes effacement
- leads to development and progression of DN

A. Optimal glycemic control

Tight glycaemia control delays onset /progression of DN

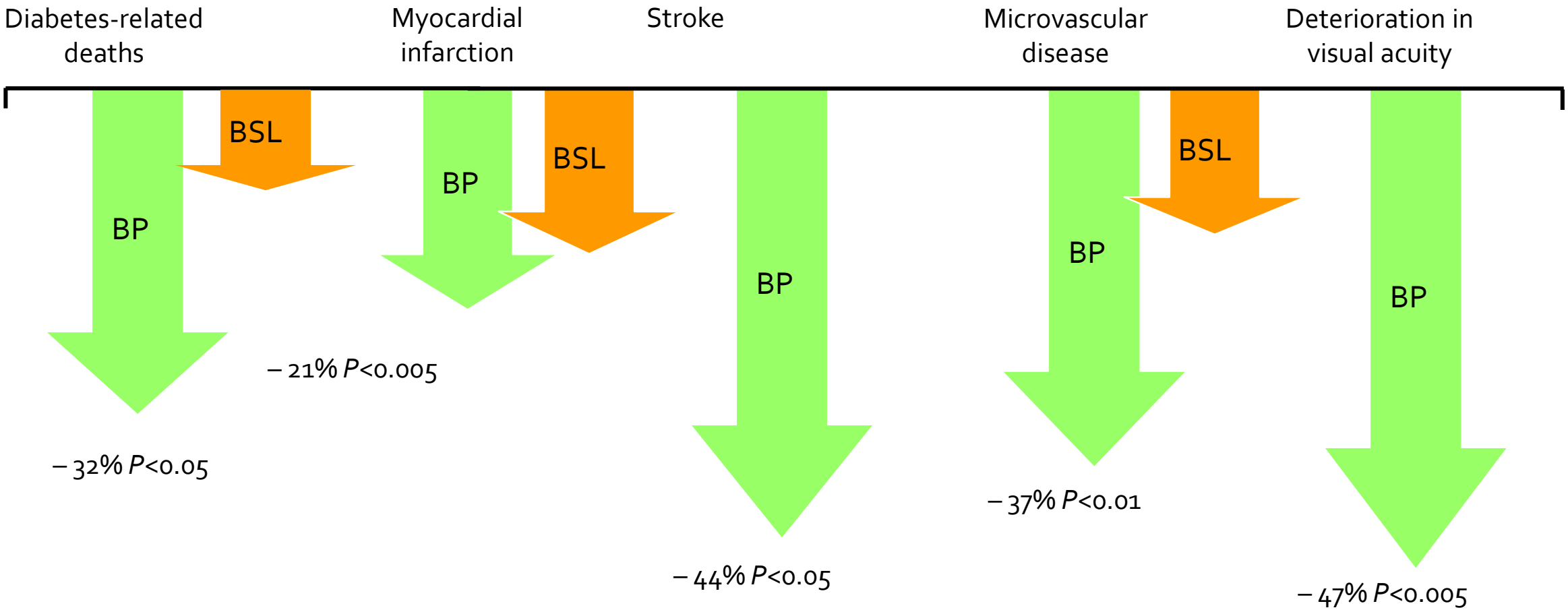
DCCT: 1441 IDDM , 1983-1993
Intensive (Insulin => tds)
Vs conventional (insulin 1 or 2 daily)

Intensive group outcome:

(no retinopathy) – DN progression reduced by 76%
-Microalbuminuria reduced by 34%
(mild retinopathy) –DN progression reduced by 54%
- Microalbuminuria reduced by 43% Albuminuria reduced by 54%
Neuropathy reduced by 60%

B. Intensive antihypertensive control

UKPDS 38: RR reduction with tight vs less tight BP control (T2DM pts)

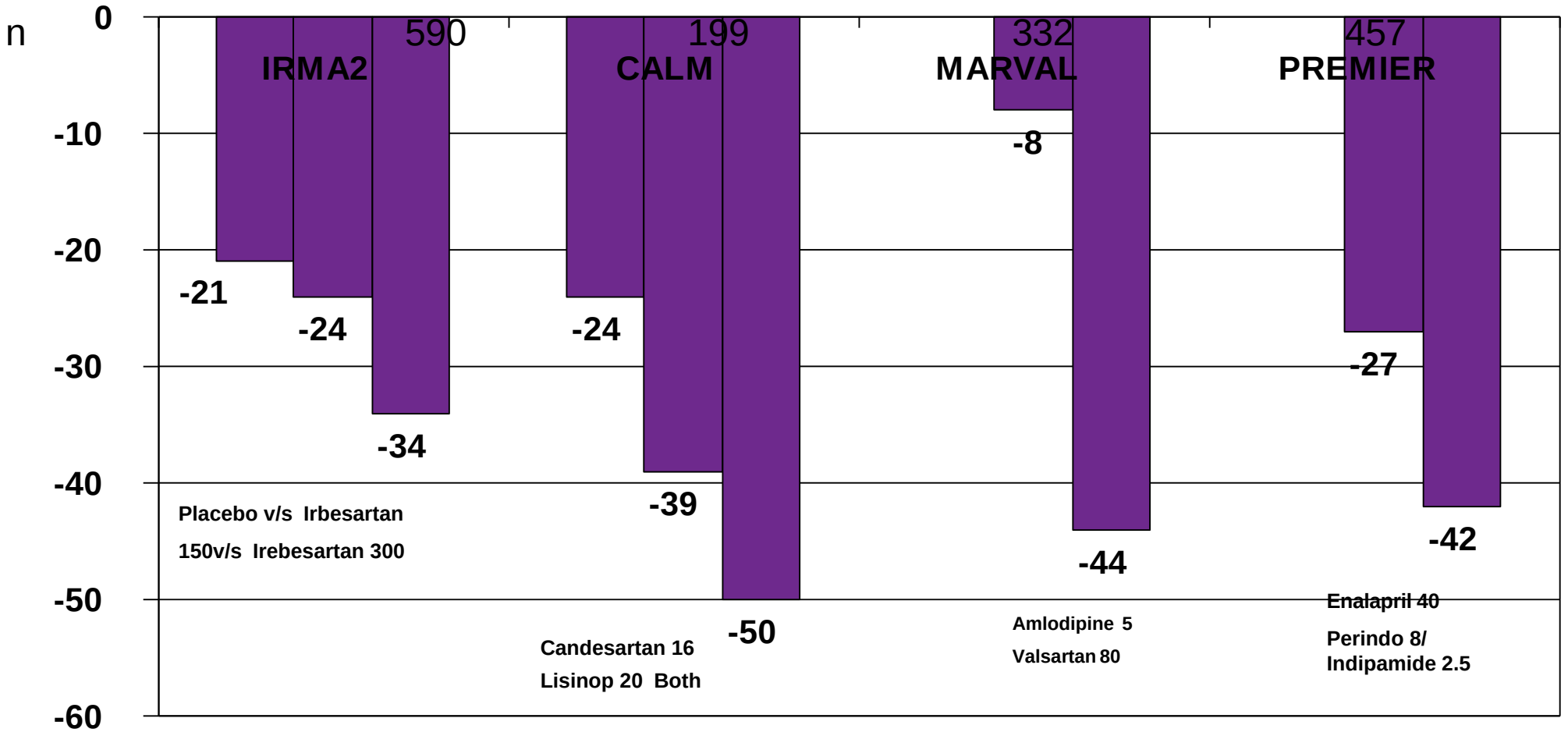


Tight BP (NOT BSL) control ↓ morbidity ,mortality in T2D patients

UKPDS Group. UKPDS 38. *BMJ* 1998;317:703–713.
UKPDS Group. UKPDS 33. *Lancet*. 1998;352:837-853.

B. Intensive BP control - Clinical Trials

Decrease in % albumin excretion rate in microalbuminuric with type 2 diabetes



Parving et al.. NEJM 2001

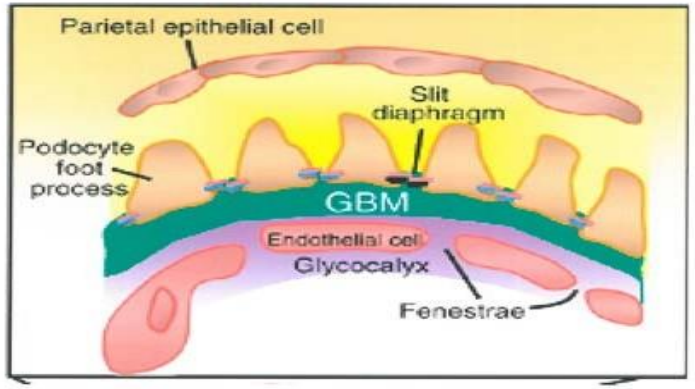
Mogenson BMJ 2000

Viberti Circulation 2002

Mogenson Hypertension 2003

C. BLOCKADE OF RAS

ACE converts Angiotensin I to Angiotensin II (ANGII)



ANGII stimulates podocyte-derived VEGF, suppress nephr induces podocytes apoptosis
→ glomerular damage.

ANG II reduces insulin sensitivity , impairs insulin secretion

- Short tem effect –interferes with glucose-mediated insulin secretion
- Long term effect – causes degeneration and fibrosis of islet cells

Blockade of RAS has antidiabetogenic, antiproteinuric effects:

- preventing progression of DN
- Reducing progression from micro to macroalbuminuria

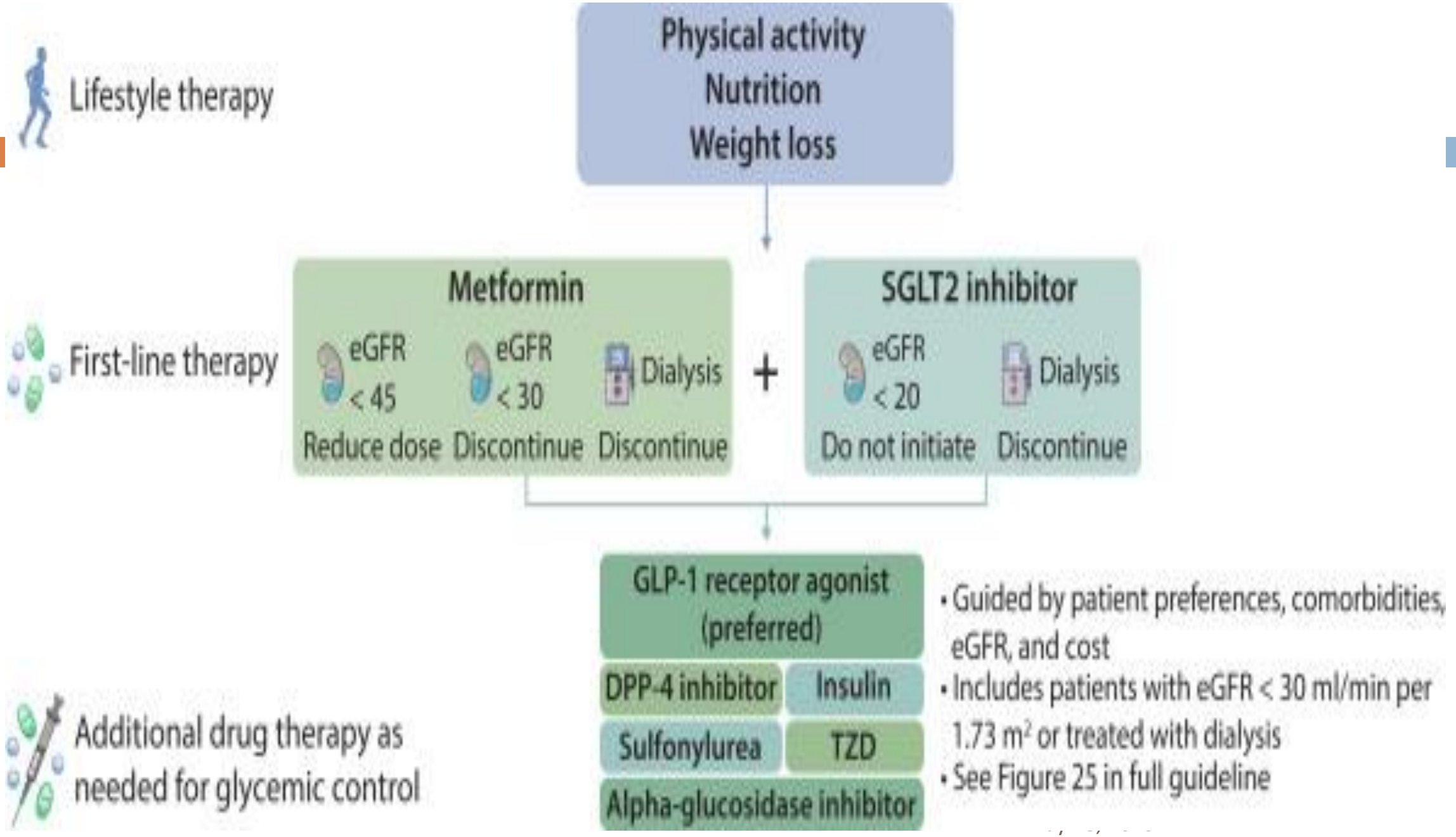
EARLY REFERRAL

Early specialist renal referral reduces rate of progression of CKD, better management of complications better preparation for eventual RRT

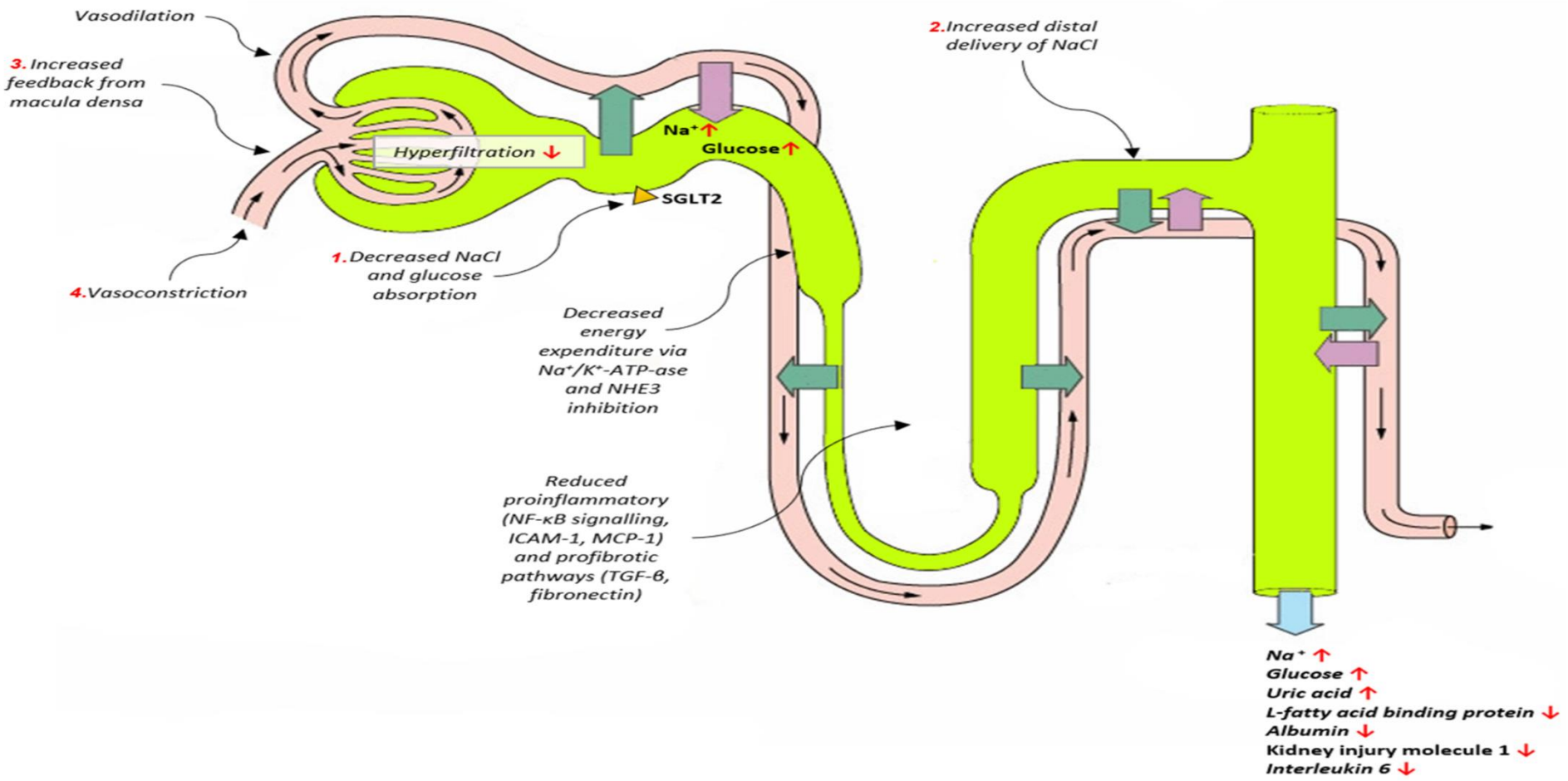
avoids complications related to LATE REFERRAL.

Consider referral when :

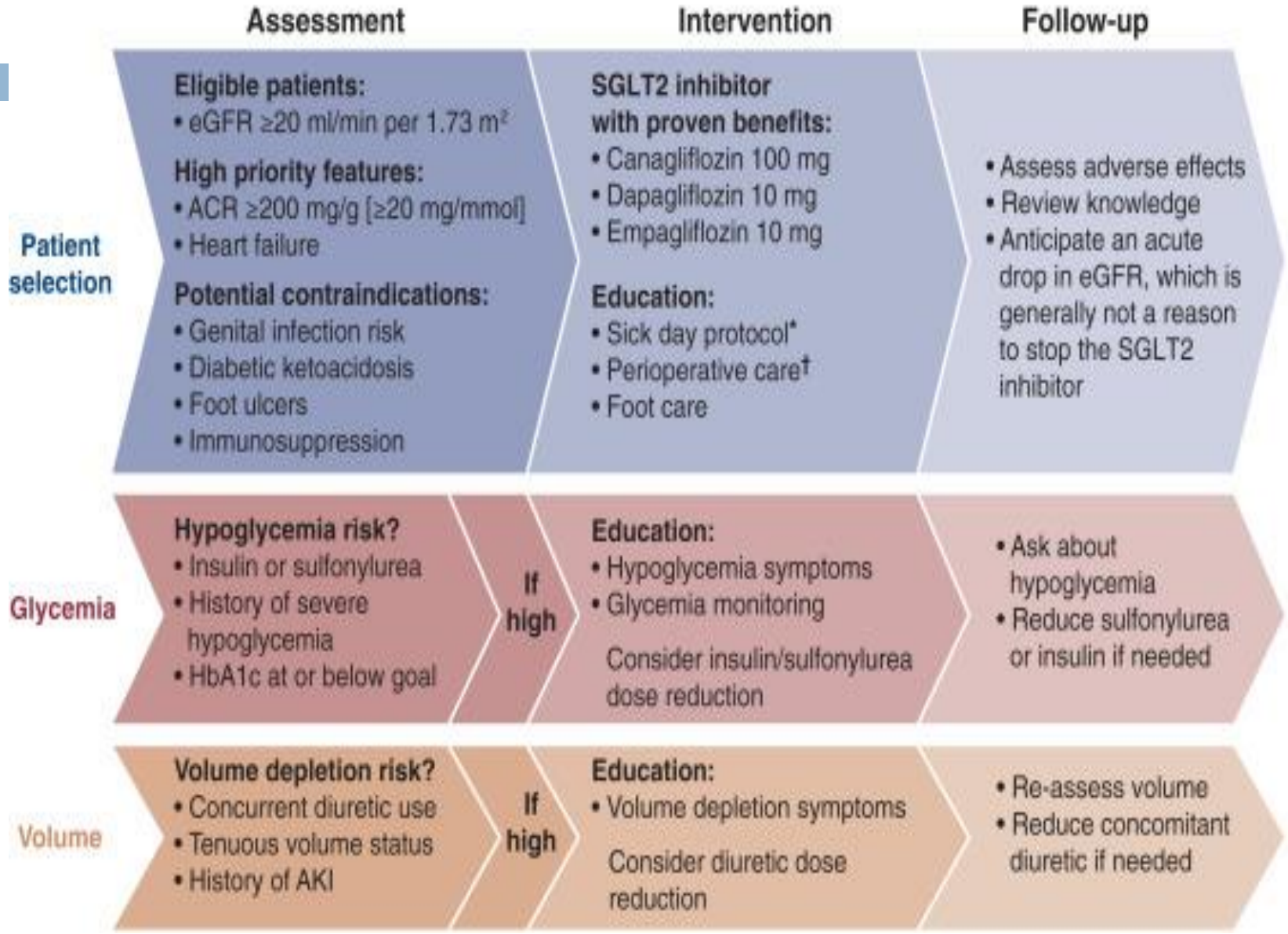
- Diabetes with eGFR < 60mL/min/1.73m
  - **Proteinuria > 1g/24hrs**
  - **difficult to control Hypertension**
  - **Other un-usual clinical findings**
    - **Haematuria, rapid progression**
- eGFR < 30mL/min/1.73m2
- Unexplained decline in kidney function
  - > 15% drop in eGFR over three months
- Abnormal findings:
  - Glomerular haematuria (particularly if proteinuria present)
  - Absence of albuminuria with abnormal creatinine
  - Resistant hypertension
  - Unexplained anaemia (Hb < 100 g/L)

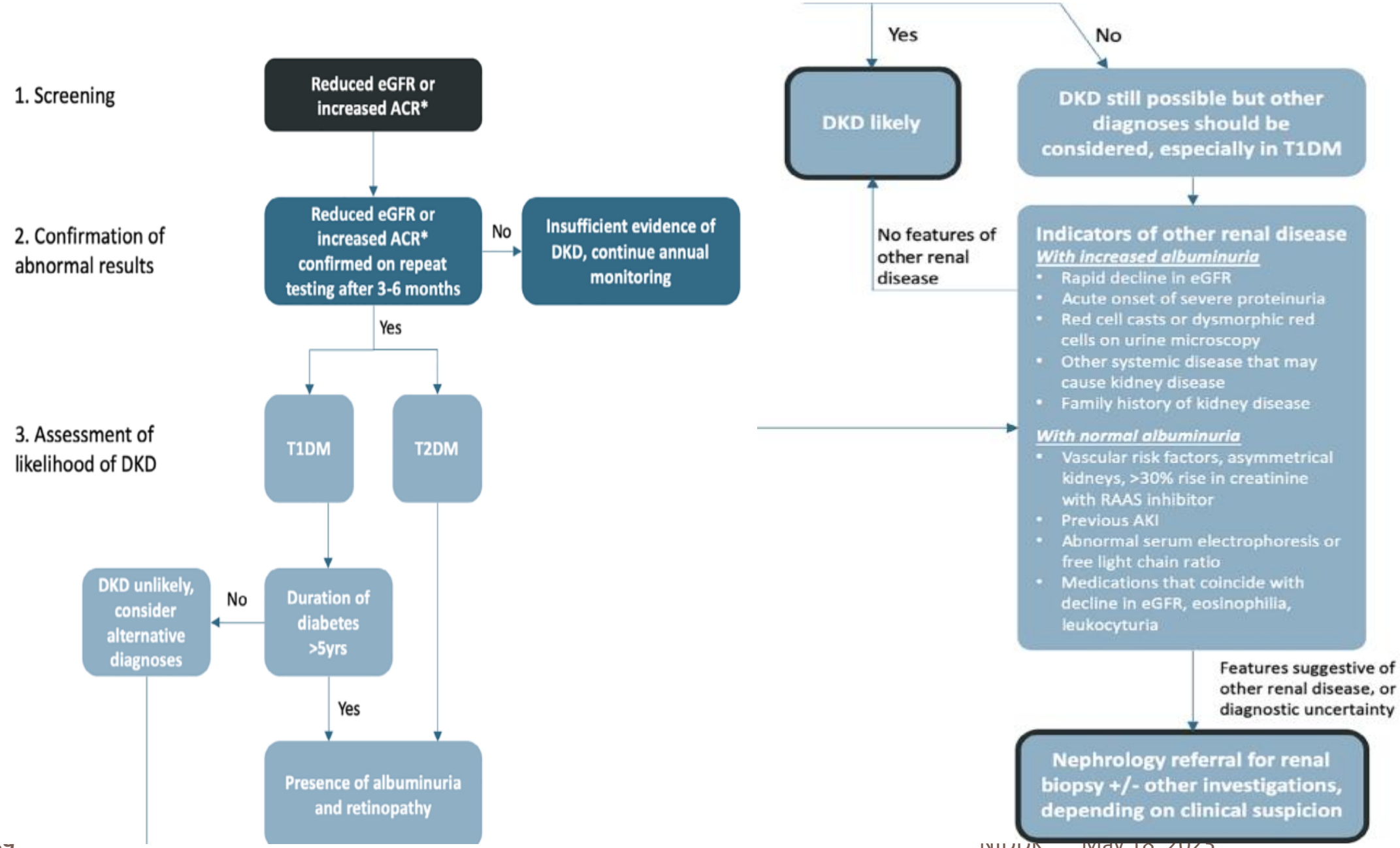

Lifestyle therapy
Physical activity
Nutrition
Weight loss
First-line therapy
Metformin
eGFR < 45
Reduce dose
eGFR < 30
Discontinue
Dialysis
Discontinue
+
SGLT2 inhibitor
eGFR < 20
Do not initiate
Dialysis
Discontinue
Additional drug therapy as needed for glycemic control
GLP-1 receptor agonist (preferred)
DPP-4 inhibitor
Insulin
Sulfonylurea
TZD
Alpha-glucosidase inhibitor
• Guided by patient preferences, comorbidities, eGFR, and cost
• Includes patients with eGFR < 30 ml/min per 1.73 m² or treated with dialysis
• See Figure 25 in full guideline

Inhibition of SGLT2 prevents renal sodium and glucose reabsorption, thus increasing sodium delivery to macula densa, which in turn restores tubuloglomerular feedback by causing afferent arteriolar vasoconstriction through increased adenosine production and intracellular calcium levels



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




1. Screening
Reduced eGFR or increased ACR*
2. Confirmation of abnormal results
Reduced eGFR or increased ACR* confirmed on repeat testing after 3-6 months
No
Insufficient evidence of DKD, continue annual monitoring
Yes
3. Assessment of likelihood of DKD
T1DM
T2DM
DKD unlikely, consider alternative diagnoses
No
Duration of diabetes >5yrs
Yes
Presence of albuminuria and retinopathy
Yes
No
DKD likely
DKD still possible but other diagnoses should be considered, especially in T1DM
No features of other renal disease
Indicators of other renal disease
With increased albuminuria
Rapid decline in eGFR
Acute onset of severe proteinuria
Red cell casts or dysmorphic red cells on urine microscopy
Other systemic disease that may cause kidney disease
Family history of kidney disease
With normal albuminuria
Vascular risk factors, asymmetrical kidneys, >30% rise in creatinine with RAAS inhibitor
Previous AKI
Abnormal serum electrophoresis or free light chain ratio
Medications that coincide with decline in eGFR, eosinophilia, leukocyturia
Features suggestive of other renal disease, or diagnostic uncertainty
Nephrology referral for renal biopsy +/- other investigations, depending on clinical suspicion

SUMMARY

- DN is the leading cause of ESRD
- ESRD treatment is a costly health burden
- DN is potentially reversible with intense early treatment
- Intensive management of hyperglycaemia, hypertension and proteinuria is important to slow progression
- Blockade of RAS has beneficial effects on DN and other microvascular complications
- Annual screening for microalbuminuria is essential
- Timely specialist Nephrology referral has important role in multidisciplinary team approach to slow down DN