Renal / Metabolic control

PCDS Wales 2025

Dr David Millar-Jones

Renal Function

Consider what is the role of the kidneys

It is generally assumed that the kidney serves as a fluid regulator of the body and some may be aware that it helps to “clean “the blood

The kidneys have a wider role in maintaining balance than is normally appreciated

The role of the healthy kidney

Sodium and water balance | Potassium balance | Elimination of Nitrogenous waste | Erythropoetin production | Acid Base balance | Activation Vitamin D | Phosphate elimination | Glucose Regulation

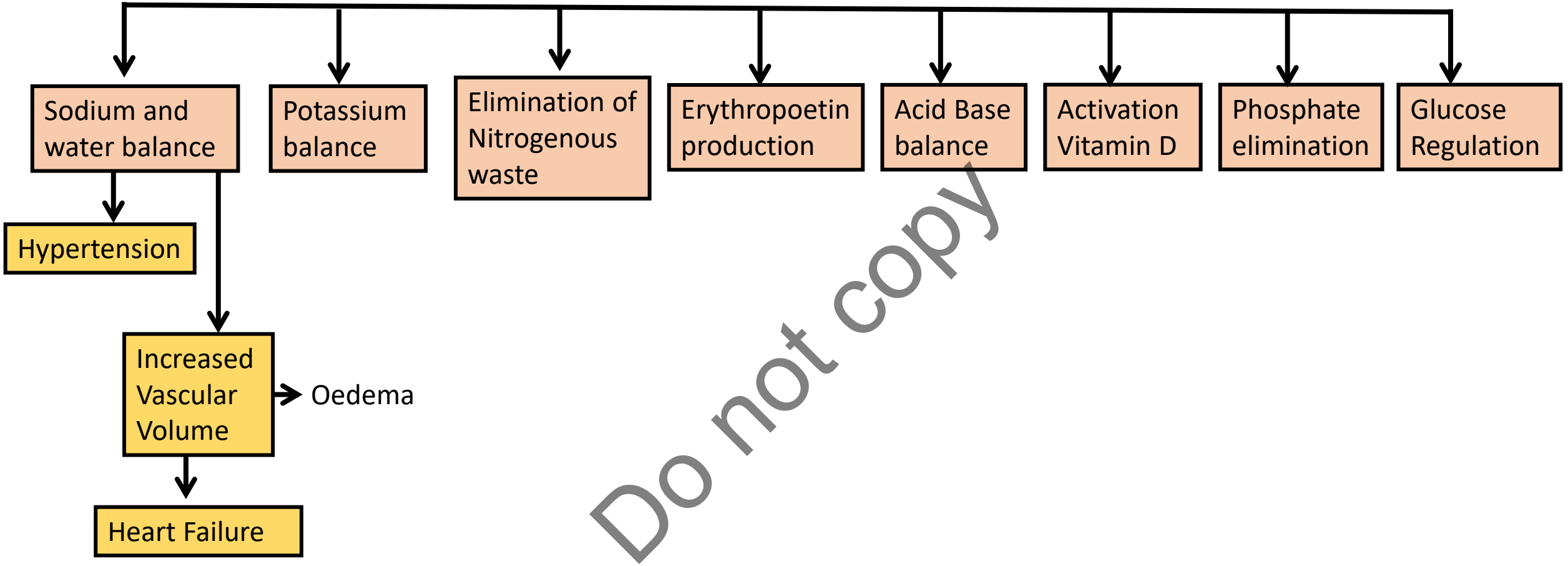
- The kidney is involved in
  - Waste elimination
  - Salt balance
  - Stimulation of red blood cell production by the bone marrow
  - Bone health
  - Glucose control
    - Storage of glucose as glycogen
    - Excretion of excess glucose

The role of the healthy kidney

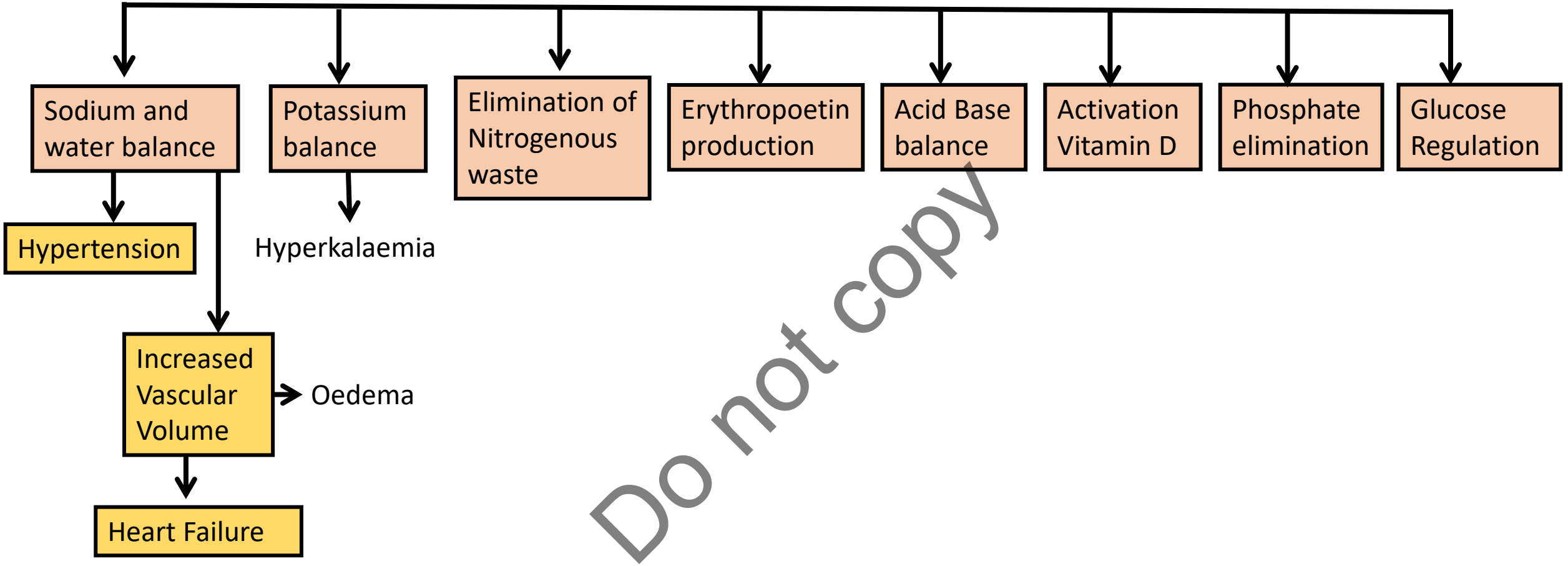
- Sodium and water balance
- Potassium balance
- Elimination of Nitrogenous waste
- Erythropoetin production
- Acid Base balance
- Activation Vitamin D
- Phosphate elimination
- Glucose Regulation

Consider what can happen if things go wrong.

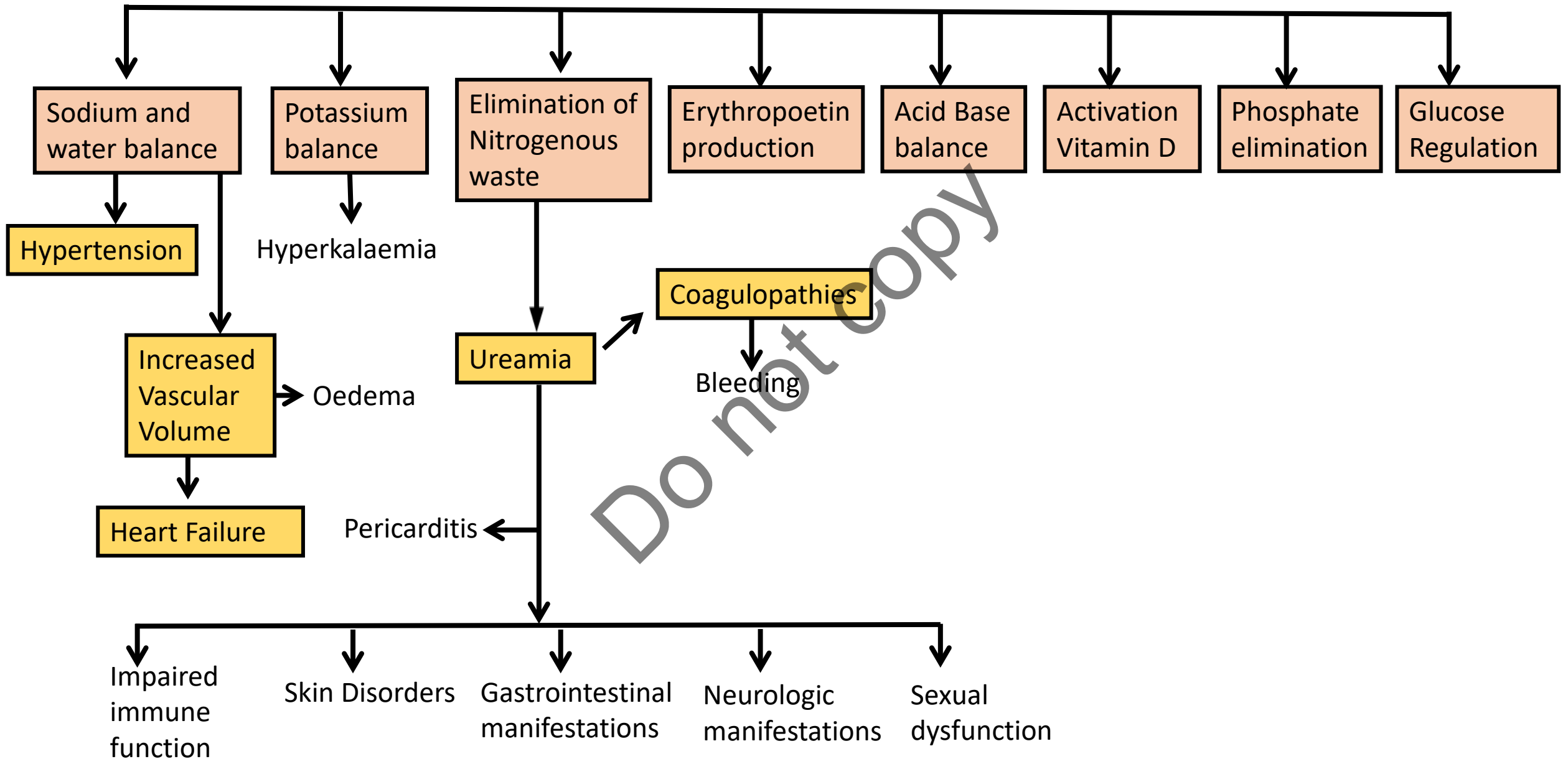
Chronic Kidney Disease



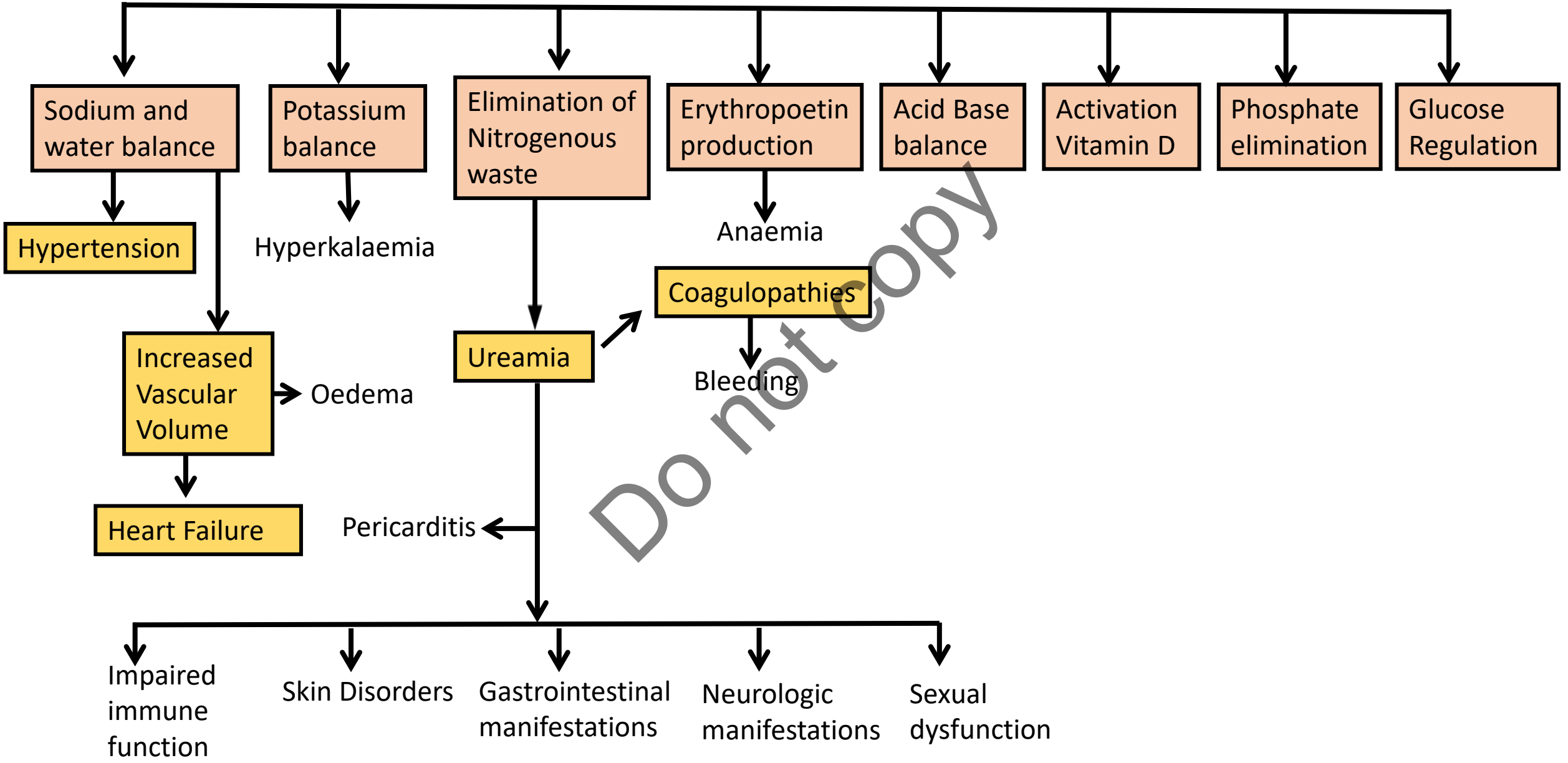
Chronic Kidney Disease



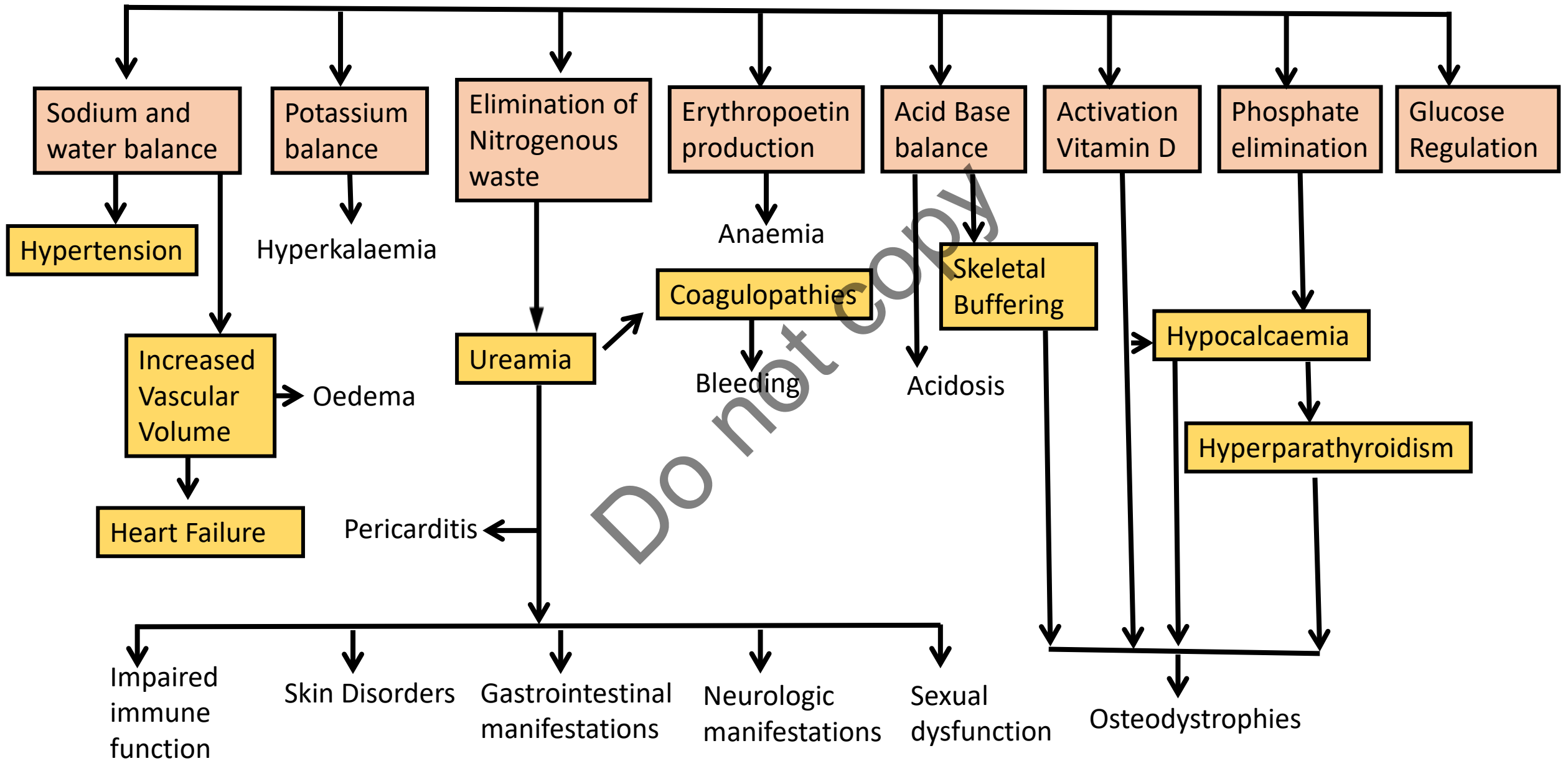
Chronic Kidney Disease



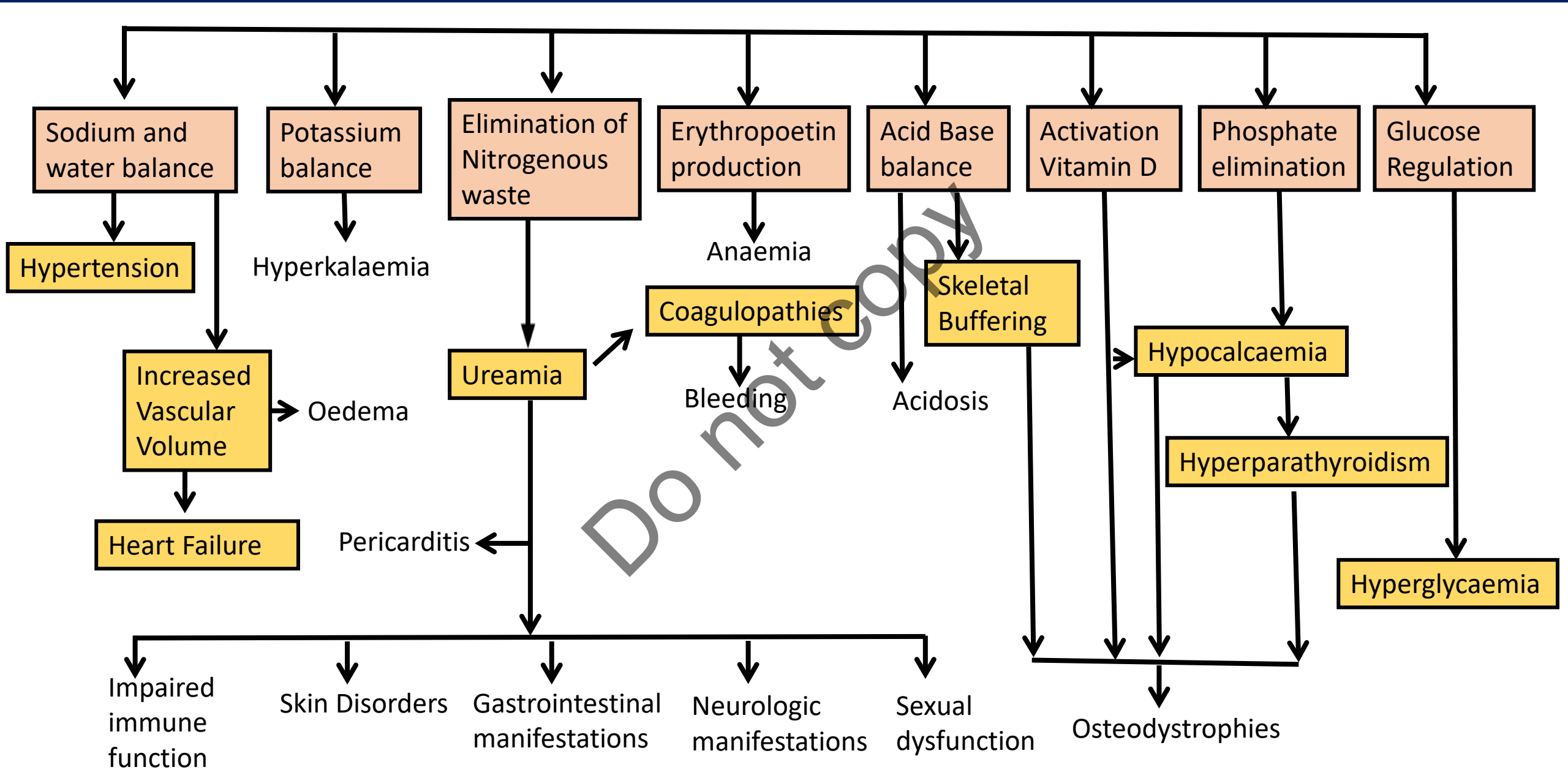
Chronic Kidney Disease



Chronic Kidney Disease



Chronic Kidney Disease



Diabetes and renal Disease

Diabetes is the commonest cause of chronic kidney disease (CKD) globally accounting for 42% cases (1).

- Half of the cases of CKD and one third of end stage kidney disease (ESKD) starting kidney replacement therapy (KRT) are attributed to diabetes(1, 2).

Type-2 diabetes (T2D) is one the fastest growing health challenges of the 21st Century globally and contributes to high economic costs of diabetes (approximately £10 billion per year).

- Of these costs 80% is spent on treating complications of diabetes (3).

Currently, there are 5 million people with diabetes in the UK, 40% of whom will develop CKD in their lifetime (3- 5)

1. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int. 2018;94(3):567- 81.
2. UK Renal Registry (2022) UK Renal Registry 24th Annual Report – data to 31/12/2020, Bristol, UK. Available from https://ukkidney.org/audit-research/annualreport
3. Diabetes statistics. DIABETES UK. https://www.diabetes.org.uk/professionals/position-statements-reports/statistics. Accessed 19/07/2024
4. Kidney Research UK Kidney Disease : A UK Public Health Emergency. 2023.
5. Kidney Research UK Time To Act: A New Review of Kidney Health Inequalities 2024

Other management considerations

Anaemia may occur in CKD3+

- Hb<110 check iron levels; falsely high HbA1c (may fall 6mmol/mol)
- Anaemia chronic disease - falsely low HbA1c

Retinopathy

- Albuminuria/CKD/retinopathy - progress more rapidly
- Poor view of feet – ulceration and amputation increased

Foot ulceration and amputation

- Increased in those with CKD even in CKD3; care with SGLT2i

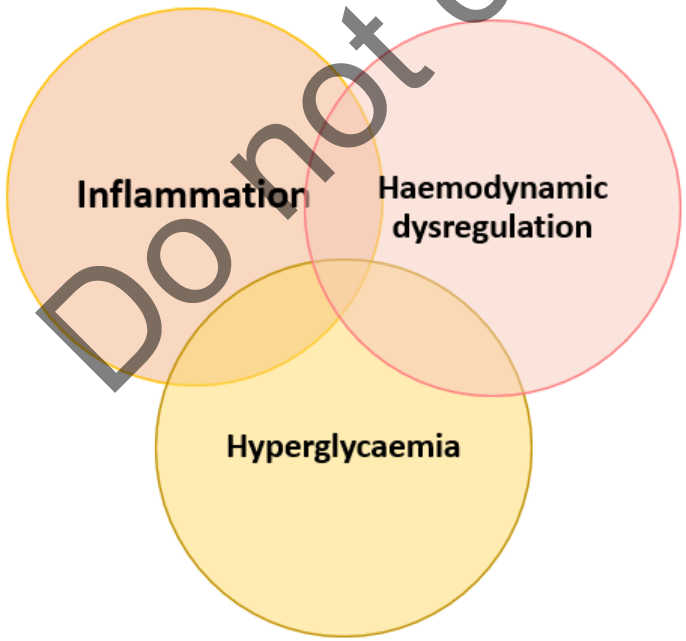
Bone health

- Metabolic abnormalities from CKD3b – measure PTH, calcium and vitamin D annually

Winocour Diabet Med 2018 35 300-305

Drivers of DKD progression

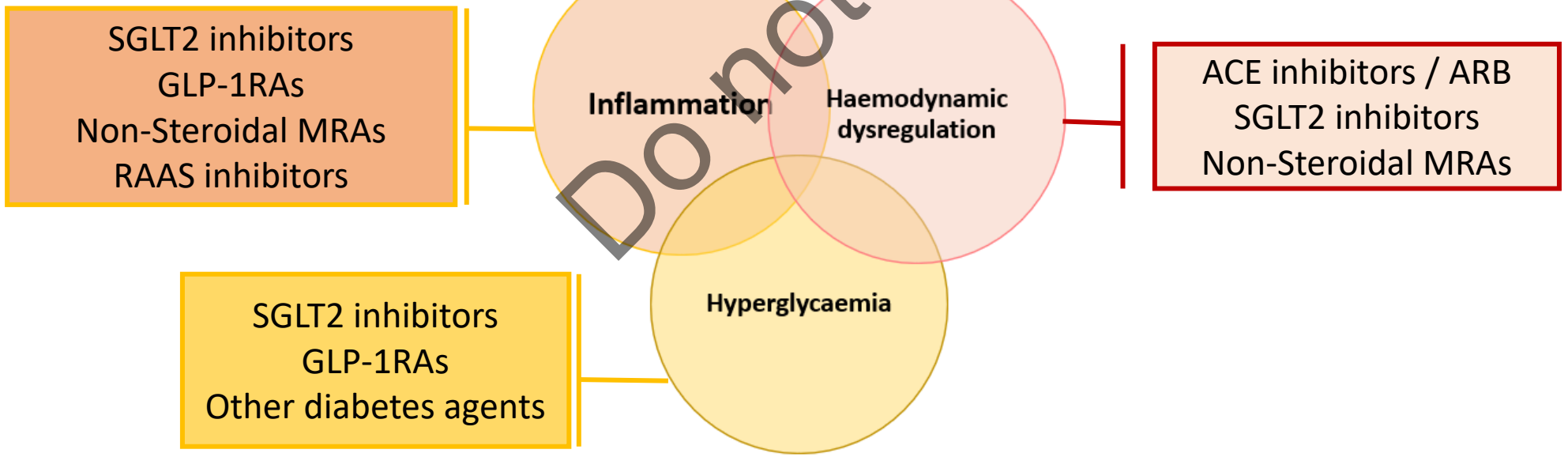
- The pathogenesis of CKD involves a complex interplay of multiple mechanisms including haemodynamic, metabolic and inflammatory processes leading to progressive kidney damage and fibrosis (1).



1. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022;102(2):248-60.

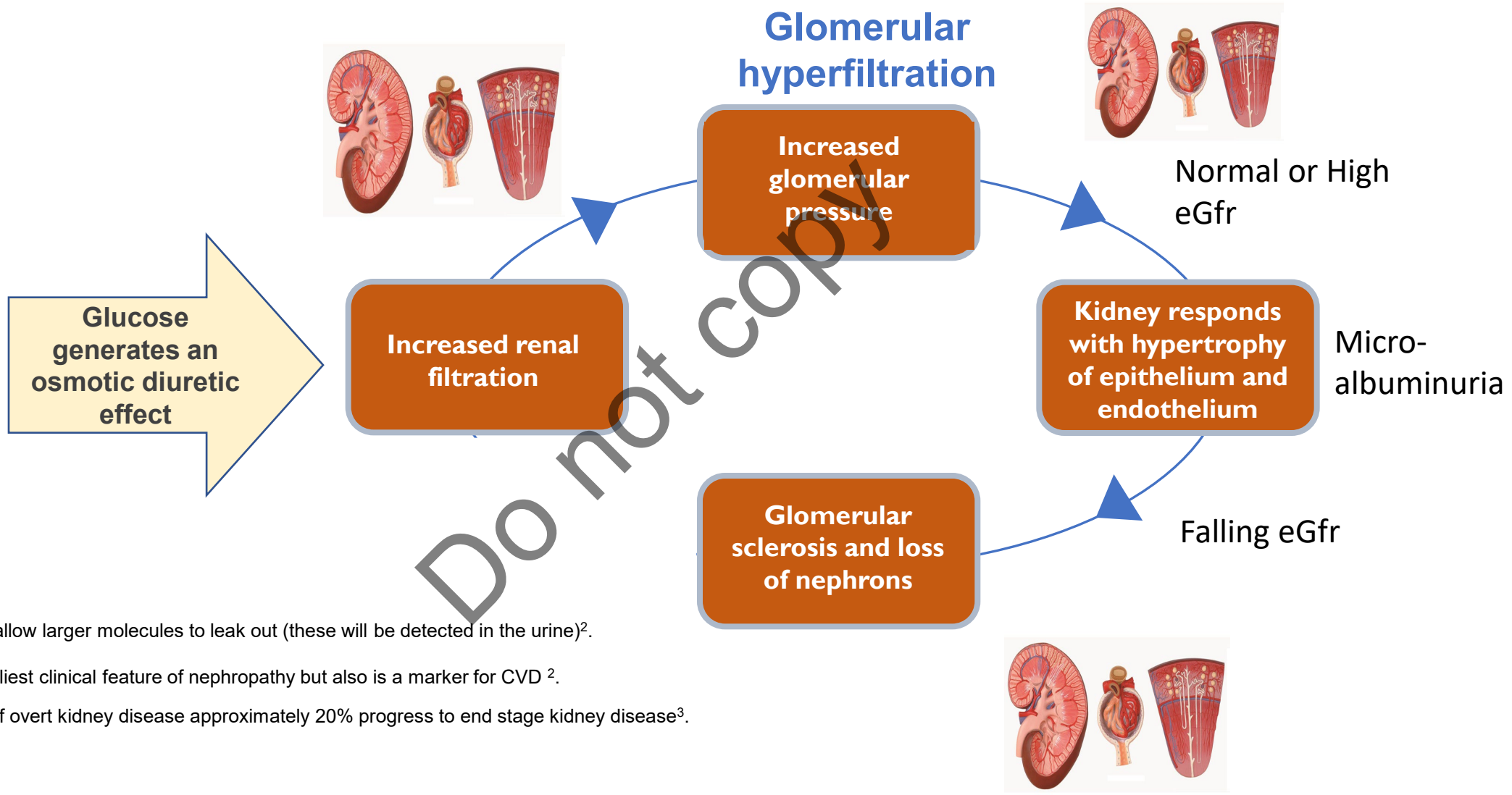
Drivers of DKD progression

- Multiple risk factor interventions are necessary to stem the progression of CKD.



1. Tuttle KR, Agarwal R, Alpers CE, Bakris GL, Brosius FC, Kolkhof P, et al. Molecular mechanisms and therapeutic targets for diabetic kidney disease. Kidney Int. 2022;102(2):248-60.

What is diabetic kidney disease?[1]



- Damaged capillaries allow larger molecules to leak out (these will be detected in the urine)[2].
- Albuminuria is the earliest clinical feature of nephropathy but also is a marker for CVD [2].
- 20 years after onset of overt kidney disease approximately 20% progress to end stage kidney disease[3].

1. Adapted from: Dronavalli S, Duka I, GL Bakris. *Nat Clin Pract Endocrinol Metab* 2008;4:444-45
2. Bilous R (2016) Diabetic nephropathy: Diagnosis, screening and management. Diabetes & Primary Care **18**: 38–46
3. American Diabetes Association. Diabetes Care 2004;27(suppl 1):s79-s83.

Defining CKD

CKD is defined as abnormalities of kidney function or structure present for >3 months. This includes people with markers of kidney damage and those with a GFR<60ml/min/1.73m² on at least 2 occasions separated by a period of at least 90 days (with or without markers of kidney damage).

It is detected and monitored by two tests:

Estimated glomerular filtration rate (eGFR)

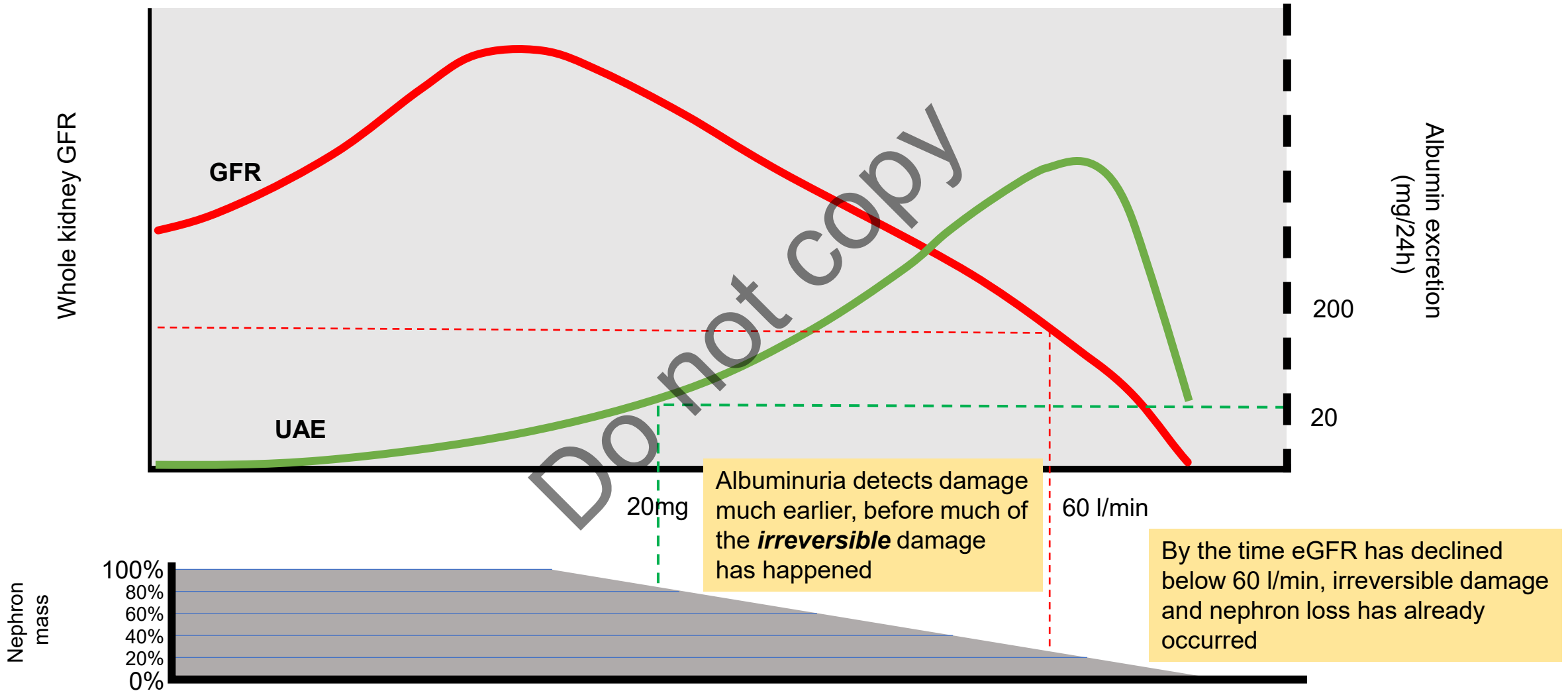
- (Function)

Urine albumin-to-creatinine ratio (ACR)

- (Damage)

NICE clinical guideline 182. July 2014. Available at http://www.nice.org.uk/guidance/cg182/resources/guidance-chronic-kidney-disease-pdf

Albuminuria is a better marker for renal damage



eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; UAE, urinary albumin excretion.

Tonneijck L, et al. J Am Soc Nephrol 2017; 28(4): 1023–1039.

Diagnosing CKD and Albuminuria

There are many factors that can influence renal function (eGFR).

- Do not rely on just one result

To diagnose CKD Stages 3 to 5 requires **two** consecutive eGFR readings <60ml/min/1.73m^2 **more than three months apart** (with no readings of ≥60ml/min/1.73m^2 in between)

- **Do not add people to the CKD register after a single reduced eGFR.**

To confirm persistent albuminuria (ACR >3mg/mmol) requires at least **two positive tests**.

Be aware that Raised albuminuria is an independent risk factor for CKD progression and a marker for CVD & mortality in those with hypertension.

NICE clinical guideline 182. Chronic kidney disease early identification and management of chronic kidney disease in adults in primary and secondary care. July 2014. Available at http://www.nice.org.uk/guidance/cg182/resources/guidance-chronic-kidney-disease-pdf

Interpret eGFr with caution

Falsely high (low Creatinine)

- Reduced muscle mass (e.g. muscle wasting, amputations) will lead to overestimation
- Hypothyroidism

Falsely low (High Creatinine)

- Increased muscle mass (e.g. body builders)
- Hyperthyroidism
- Dehydration may lead to underestimation
- Eating meat during the 12 hours before testing
- Sample processed more than 12 hours after drawn

NICE clinical guideline 182. July 2014. Available at http://www.nice.org.uk/guidance/cg182/resources/guidance-chronic-kidney-disease-pdf

Cardio – Renal – Metabolic issues

CKD is associated with a very high risk of cardiovascular disease (CVD), which increases steeply with the progression of CKD (1,2).

Most people with CKD are likely to die of CVD rather than need kidney replacement therapy (KRT)(7).

Currently, in the UK, CKD accounts for 45,000 premature deaths and over 100,000 hospital admissions a year, mainly for cardiovascular events (1).

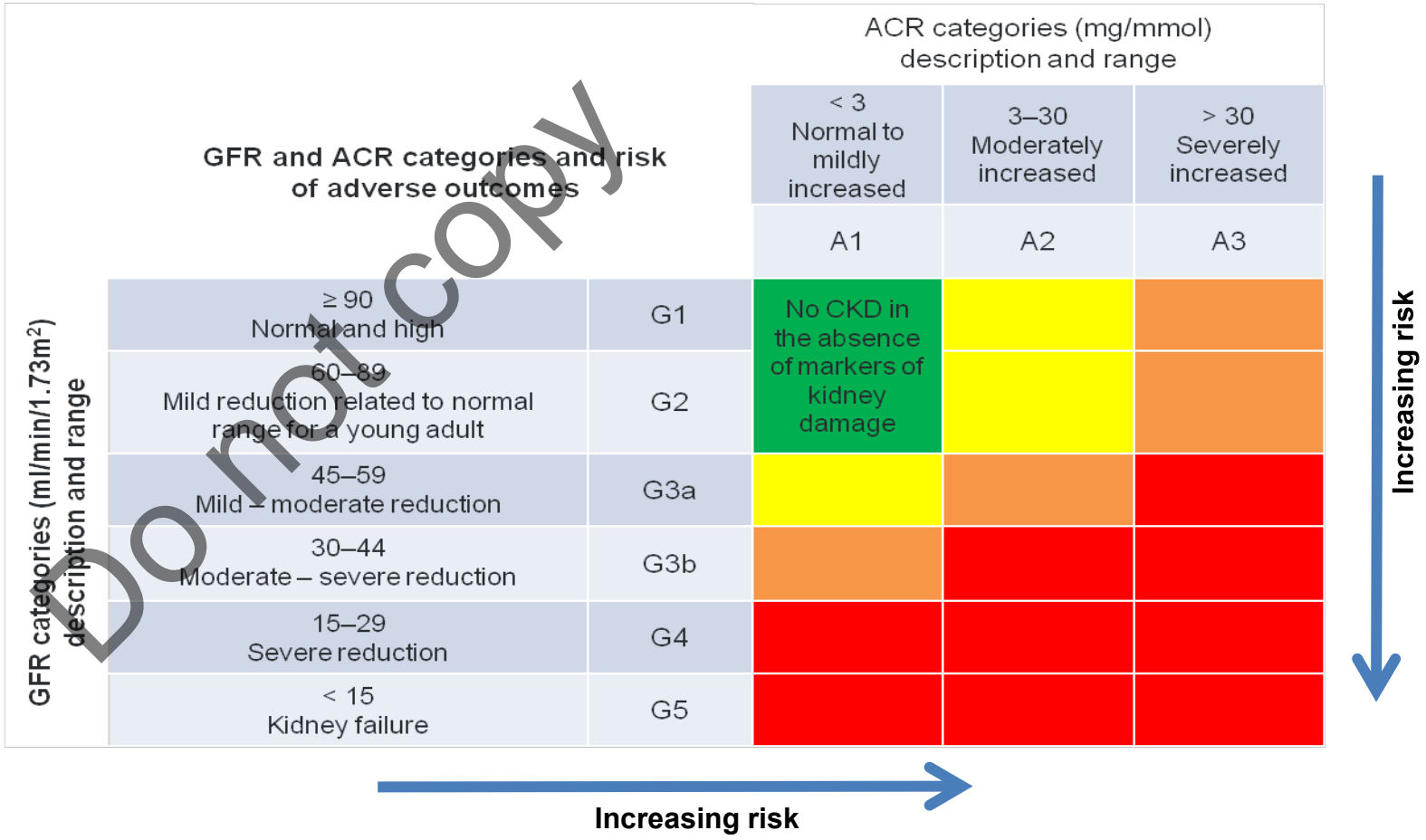
1. Kidney Research UK Kidney Disease : A UK Public Health Emergency. 2023.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

Classification of chronic kidney disease using GFR and ACR categories

Renal health is determined by the measurement of kidney function (eGFR) and damage (ACR)

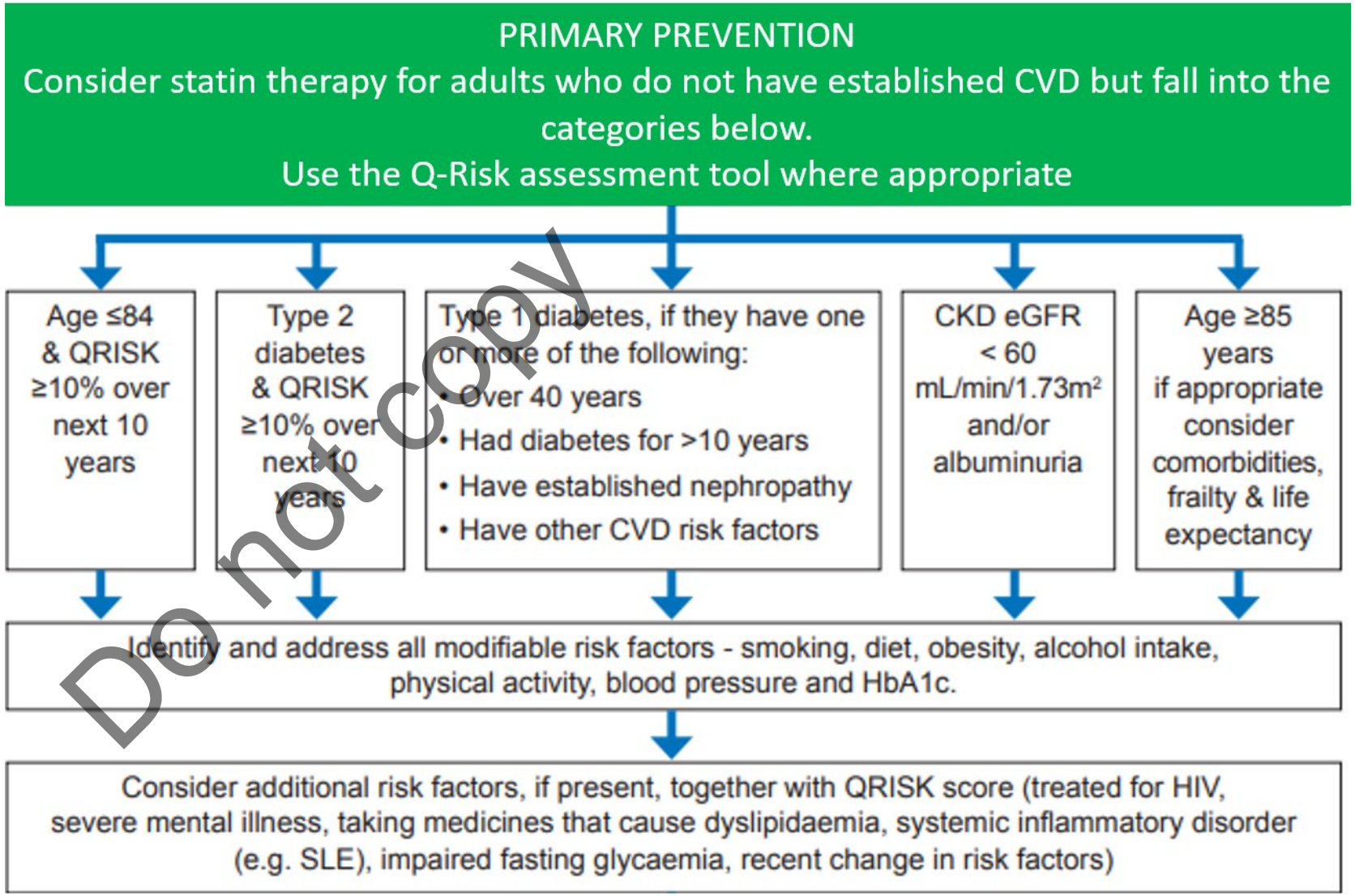
Function is categorised G1-G5
Damage is categorised A1- A3

Increasing risk accounts for chances of developing renal failure but also other risks that include cardiovascular , bone and retinal disease.



ACR: albumin to creatinine ratio; GFR: glomerular filtration rate.

Primary Prevention

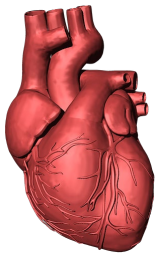


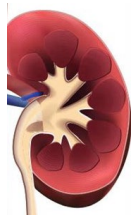
Cardiorenal Syndrome
The mechanism of renal disease progression

FIBROSIS is a disease mediator in the cardiorenal syndrome

Systemic Factors

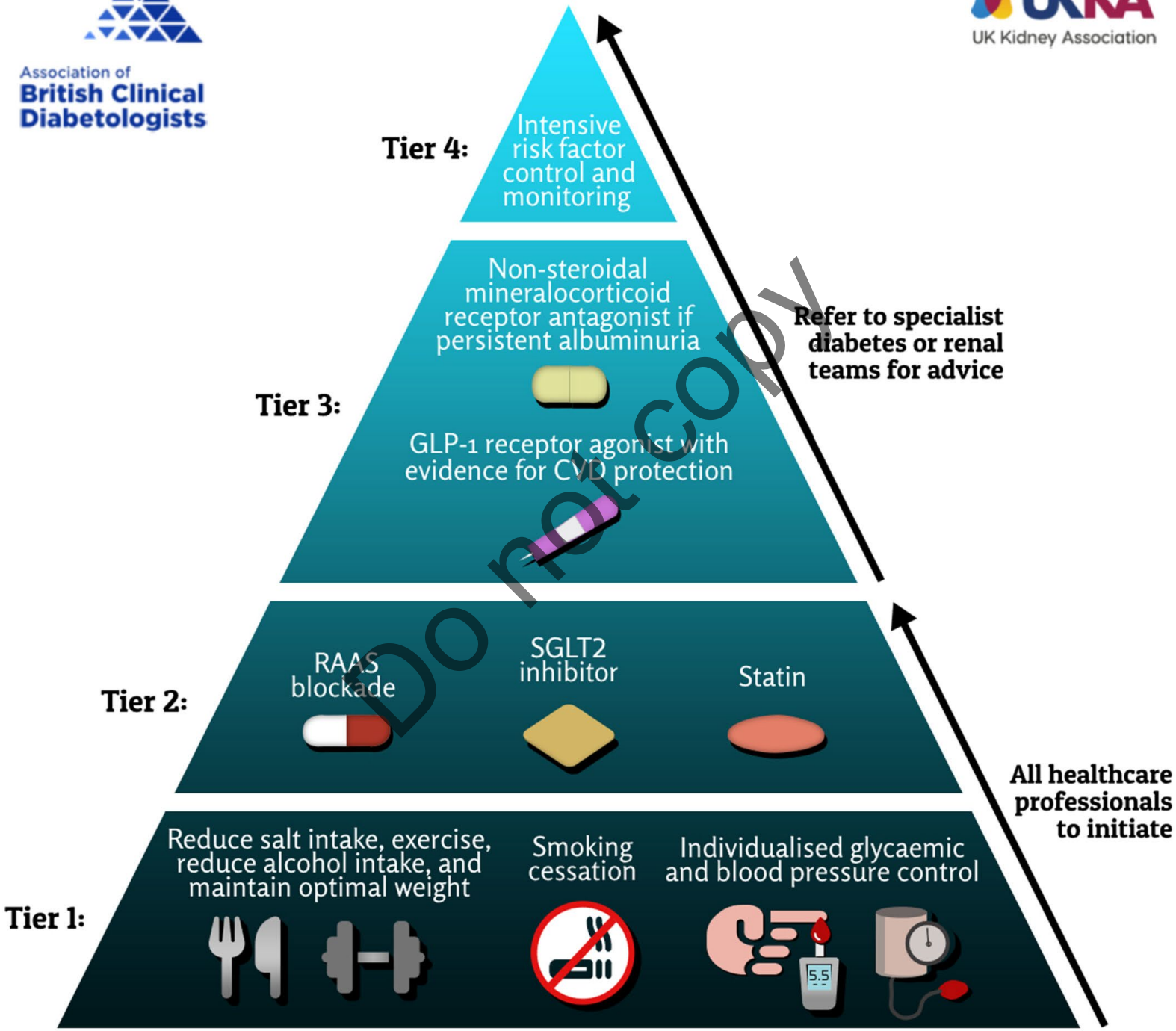
- Diabetes
- Obesity
- Metabolic syndrome
- Hypertension
- Amyloidosis





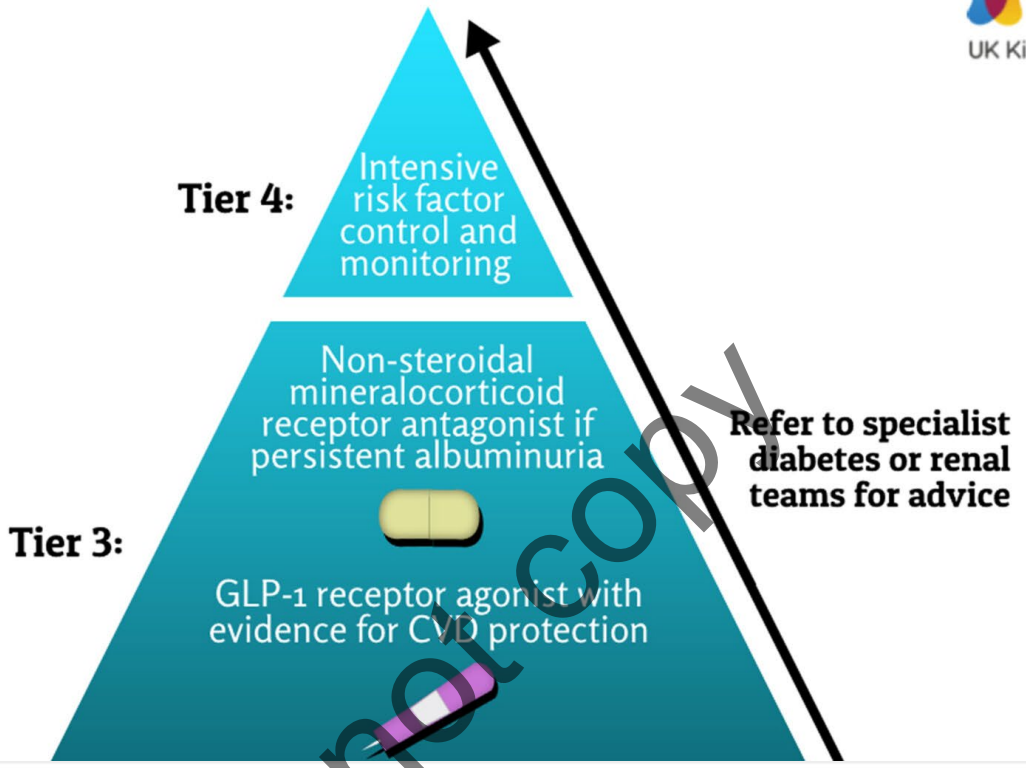
Association of British Clinical Diabetologists

UKKA
UK Kidney Association



Association of British Clinical Diabetologists

UKKA
UK Kidney Association



Tier 1 - lifestyle change

The five main elements of lifestyle advice are:-

Salt

- reduced salt intake <90 mmol of sodium daily (<2 g of sodium or <5 g of sodium chloride daily),

Alcohol

- alcohol <14 units per week,

Smoking

- smoking cessation,

Exercise

- regular exercise at least 30 minutes daily for 5 days a week,

Weight

- maintain a body mass index between 20 and 25 kg/m2(12).

SADMANS – the therapies

S	**S**ulphonylurea
A	**A**CEi
D	**D**iuretics
M	**M**etformin
A	**A**RB
N	**N**SAID
S	**S**GLT2i

SADMANS – the evidence

two thirds of patients admitted to hospital due to AKI were taking at least one SADMANS medication and over half of them took two or more of these medications.

Large pharmacovigilance studies reflect the significant consequences of the SADMANS drug classes

- diuretics were the second most implicated medication (18.5%), followed by renin–angiotensin system inhibitors (16.3%), for causing drug-induced AKI .

Pierson-Marchandise M., Gras V., Moragny J., Micallef J., Gaboriau L., Picard S., Choukroun G., Masmoudi K., Laibeuf S. The Drugs That Mostly Frequently Induce Acute Kidney Injury: A Case – Noncase Study of a Pharmacovigilance Database. *Br. J. Clin. Pharmacol.* 2017;83:1341–1349. doi: 10.1111/bcp.13216

Glycaemic management

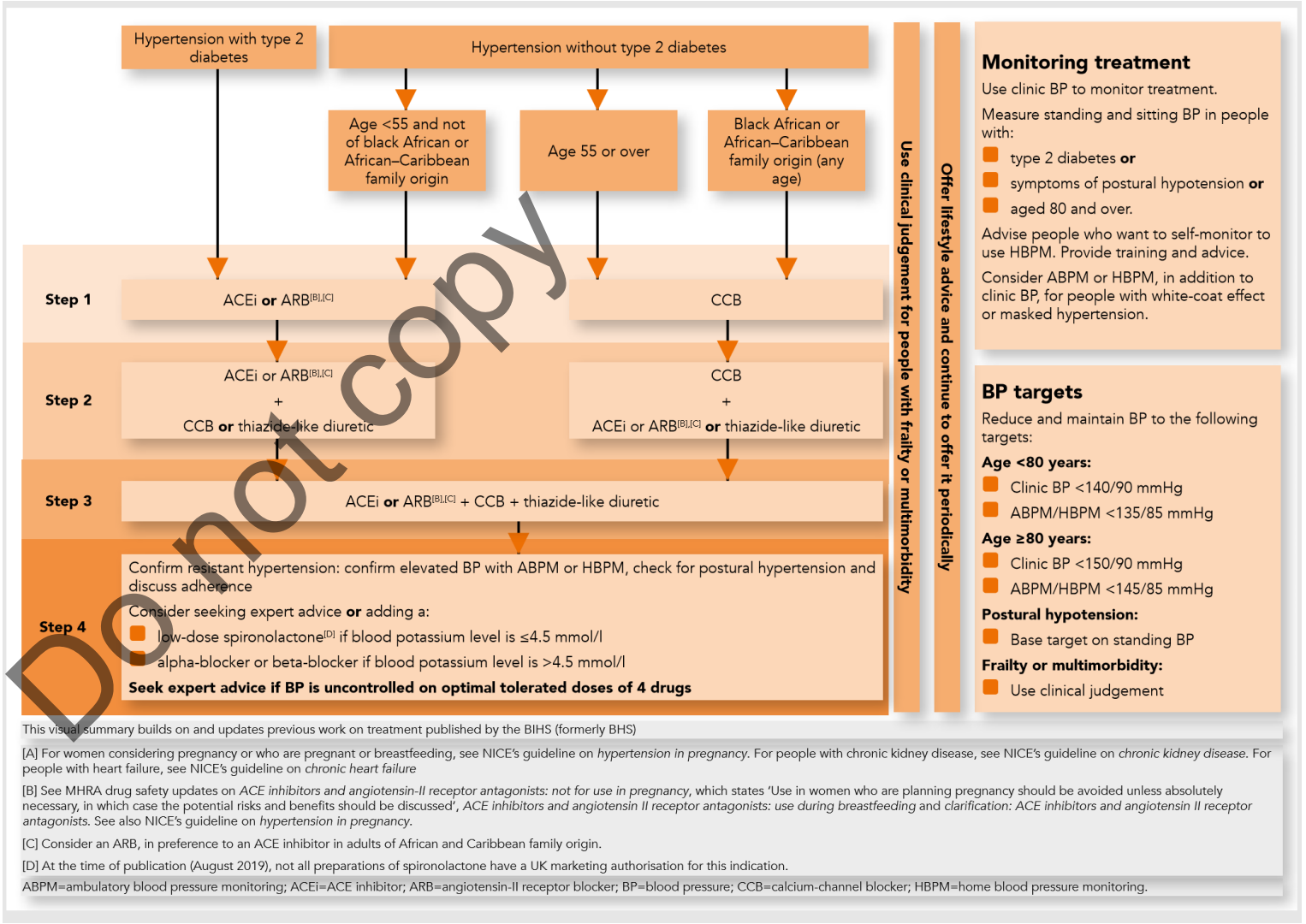
Reduce hyperglycaemia to improve osmotic symptoms and prevent the onset, and slow down progression, of kidney and vascular complications over time.

Individualised approach to care and targets for glucose control.

- Greater risk for hypoglycaemia in CKD
  - especially with the use of insulin or sulfonylureas/ glinides as kidney function deteriorates.

Specific emphasis should be placed on selecting medications for their cardio-renal benefits independent of their glucose lowering effects for this high-risk cohort.

Hypertension management



This visual summary builds on and updates previous work on treatment published by the BIHS (formerly BHS)

[A] For women considering pregnancy or who are pregnant or breastfeeding, see NICE's guideline on *hypertension in pregnancy*. For people with chronic kidney disease, see NICE's guideline on *chronic kidney disease*. For people with heart failure, see NICE's guideline on *chronic heart failure*

[B] See MHRA drug safety updates on *ACE inhibitors and angiotensin-II receptor antagonists: not for use in pregnancy*, which states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed', *ACE inhibitors and angiotensin II receptor antagonists: use during breastfeeding* and *clarification: ACE inhibitors and angiotensin II receptor antagonists*. See also NICE's guideline on *hypertension in pregnancy*.

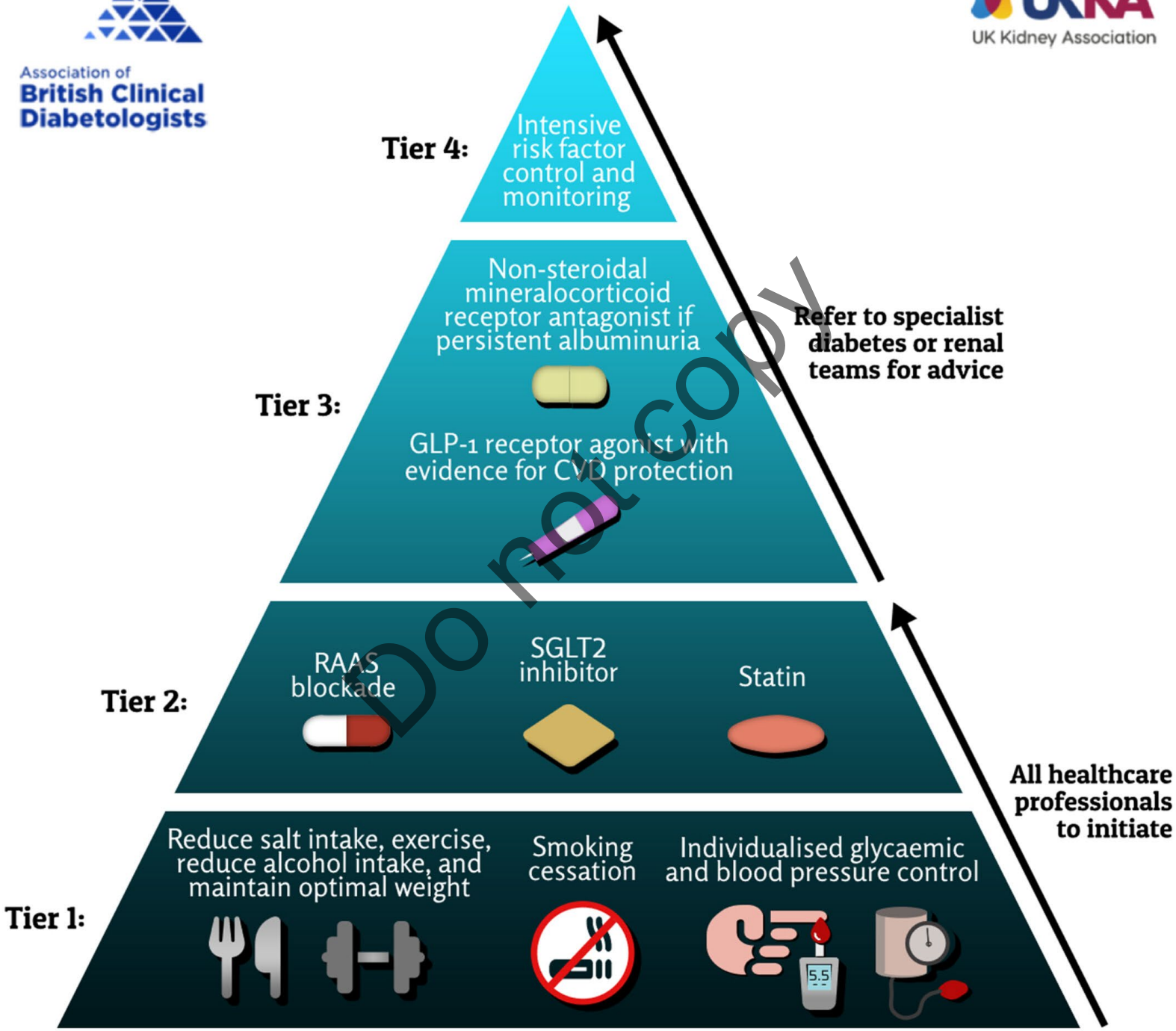
[C] Consider an ARB, in preference to an ACE inhibitor in adults of African and Caribbean family origin.

[D] At the time of publication (August 2019), not all preparations of spironolactone have a UK marketing authorisation for this indication.

ABPM=ambulatory blood pressure monitoring; ACEi=ACE inhibitor; ARB=angiotensin-II receptor blocker; BP=blood pressure; CCB=calcium-channel blocker; HBPM=home blood pressure monitoring.

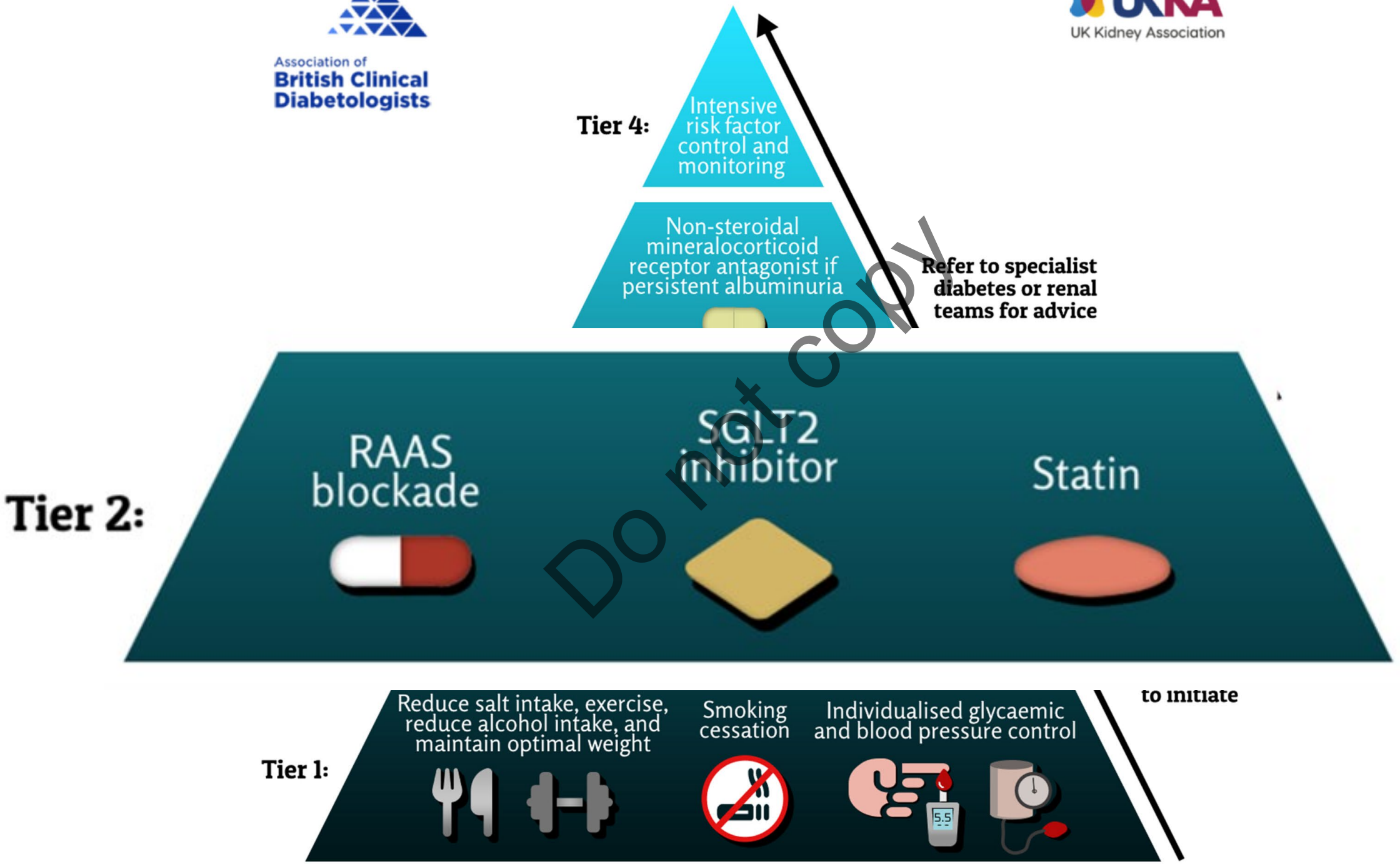
Association of British Clinical Diabetologists

UKKA
UK Kidney Association



Association of British Clinical Diabetologists

UKKA
UK Kidney Association



Tier 2 renin angiotensin blocking

Use of renin angiotensin blocking agents Over and above the BP lowering effect, reduce the risk of progression of CKD.

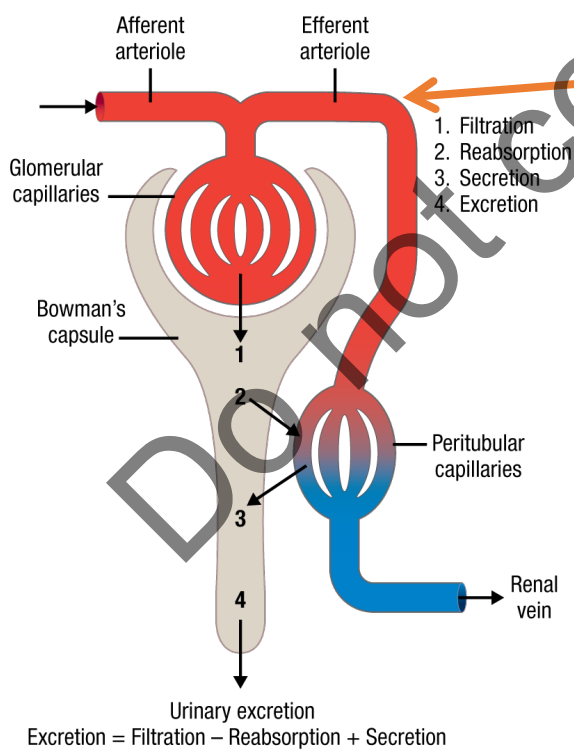
- In the landmark RENAAL and IDNT trials, there was 16 - 20% reduction in the risk of kidney disease progression (1, 2, 3).

For maximum kidney protection the dose of ACE inhibitor or ARB should be titrated up to the **maximum tolerated**,

- watching :- BP , serum potassium and creatinine

1. Chaudhry K, Karalliedde J. Chronic kidney disease in type 2 diabetes: The size of the problem, addressing residual renal risk and what we have learned from the CREDENCE trial. Diabetes Obes Metab. 2024.
2. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.
3. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345(12):851-60.

ACEi/ARB Reduce Intra-glomerular Pressure: Mechanism for Renal Protection



ACEi and ARB
↓ efferent arteriole tone and
↓ intraglomerular pressure

↓

Initial ↓ in eGFR
followed by stabilization

↓ albuminuria

↓

Renal protection

SGLT-2 inhibitors

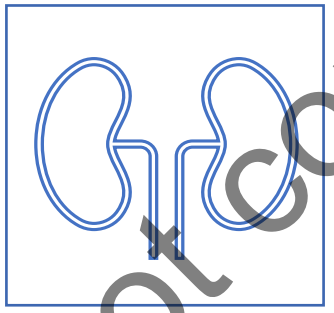
RAS blockade slows progression of CKD, in the trials around 40% patients still met the primary kidney endpoints.

SGLT2 inhibitor trials have shown further reduction in the risk of progression of kidney disease by around 30%.

- These trials have also demonstrated reduction in risk of CVD and mortality.
- The trials had different inclusion and exclusion criteria, but all showed significant renal benefit and thus no one agent can be recommended above the other.

SGLT2i in all patients with CKD in T2D eGFR >15 ml/min/1.73m2.

SGLT-2 inhibitors and diabetic Nephropathy



SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes:

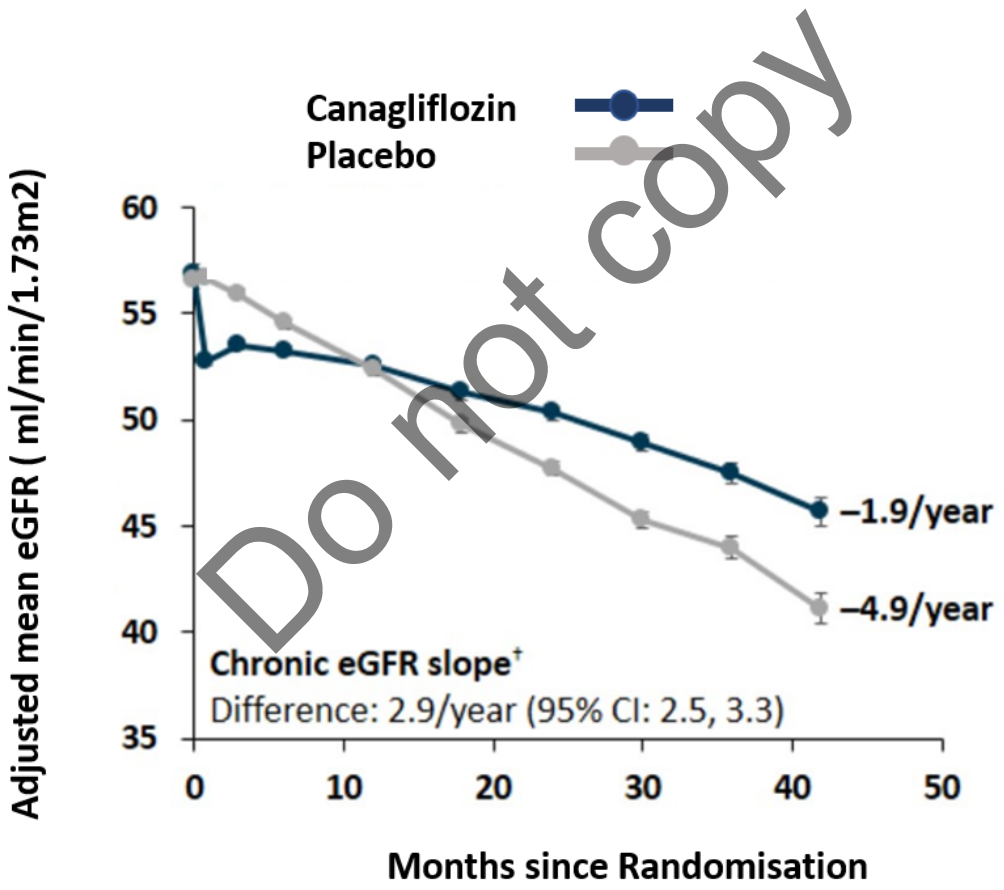
A systematic review and meta-analysis

SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease in individuals with type 2 diabetes and provided protection against acute kidney injury. These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent major kidney outcomes in people with type 2 diabetes

Neuen BL et al. *Lancet Diabetes Endocrinol* 2019;7:845–54

Credence

The effects of canagliflozin over time with eGFR

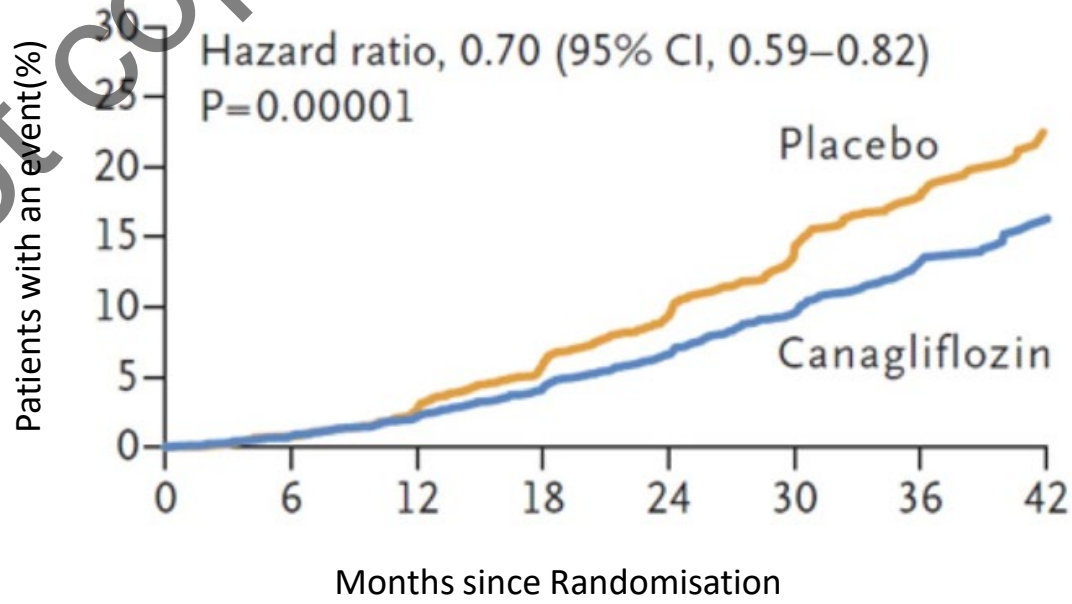


CREDENCE: Primary Composite Outcome

- ESKD
  - Dialysis
  - Transplantation
  - Sustained eGFR of <15ml/l/min/1.73m^2
- Doubling of serum creatinine
- Death from CV or renal cause

The risk of kidney failure and CV events was reduced with SGLT-2 inhibitors

Rate of renal failure reduced by 30%



Perkovic V et al. *N Engl J Med* 2019;380:2295–306

SGLT-2 inhibitors Reduce Intra-glomerular Pressure: Mechanism for Renal Protection

SGLT2i
Afferent vasomodulation
↓ intraglomerular pressure

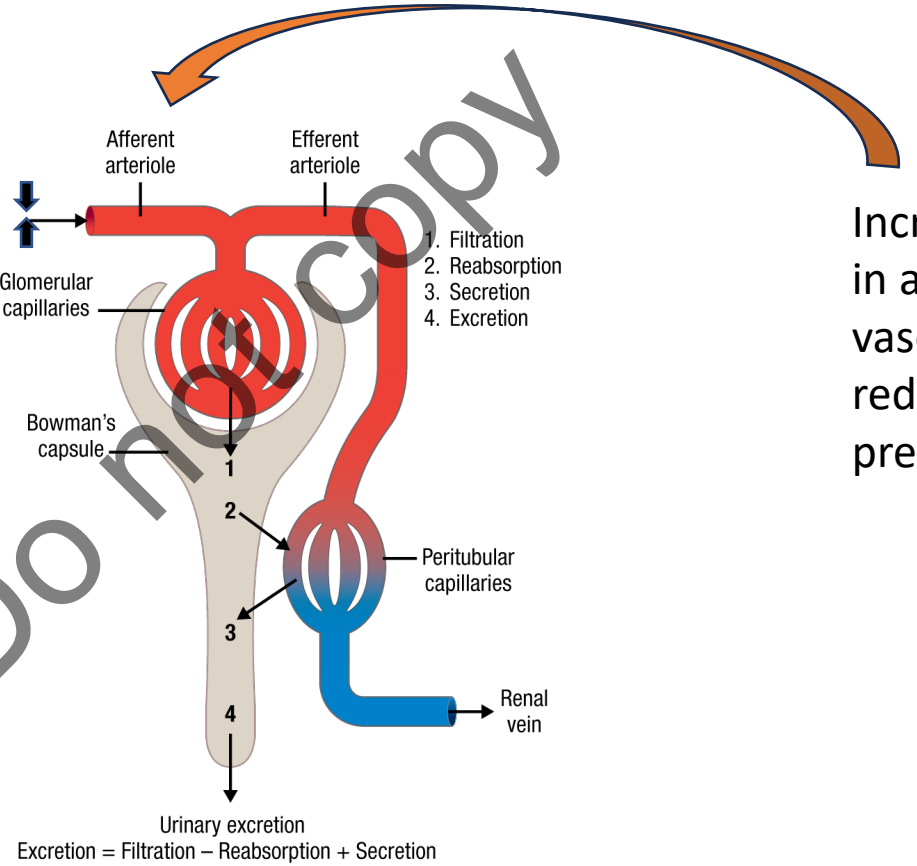
↓

Initial ↓ in eGFR
followed by stabilisation

↓ albuminuria

↓

Renal protection



Increase Na+ loss results in afferent arteriole vasoconstriction that reduces glomerular pressure

Sternlicht H, Bakris G. *Curr Hypertension Rep* 2019;21:12–8; Gilbert RE. *Kidney Int* 2014;86:693–700; Cherney DZ et al. *Circulation* 2014;129:587–97.

The Diabetic Kidney

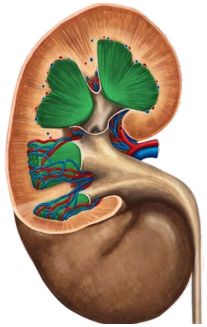
Increased fatty acid oxidation
Reduced glucose oxidation

Reduced fat oxidation
Reduced glucose oxidation
Increased beta hydroxybutyrate oxidation

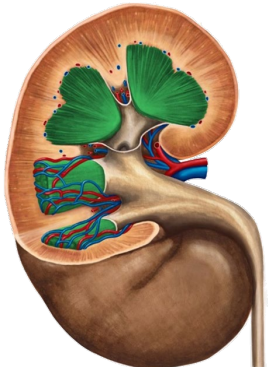
Increased energy expenditure

SGLT-2 inhibition

Improved energy expenditure



Renal hypoxia
causing progression
to renal failure



Improved
renal
oxygenation

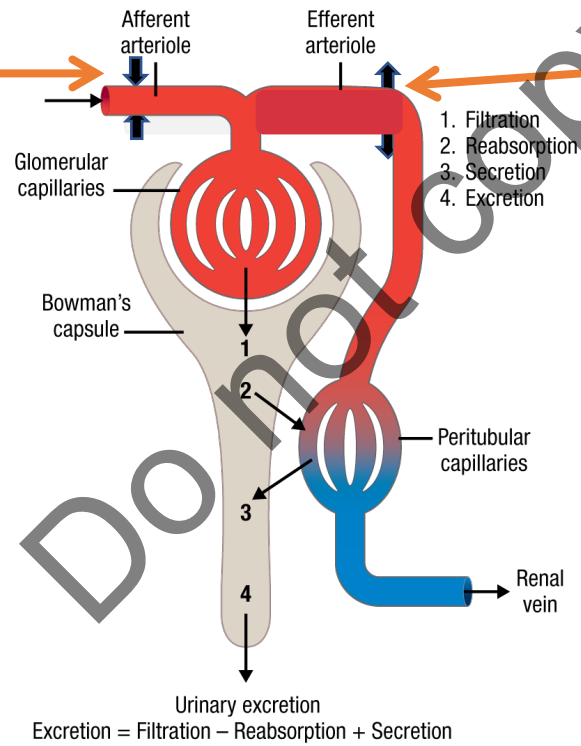
SGLT-2i + ACE-i Reduce Intra-glomerular Pressure: Mechanism for Renal Protection

SGLT2i
Afferent vasomodulation
↓ intraglomerular pressure

Initial ↓ in eGFR
followed by stabilisation

↓ albuminuria

Renal protection



ACEi and ARB
↓ efferent arteriole tone and
↓ intraglomerular pressure

Initial ↓ in eGFR
followed by stabilisation

↓ albuminuria

Renal protection

Sternlicht H, Bakris G. *Curr Hypertension Rep* 2019;21:12–18; Gilbert RE. *Kidney Int* 2014;86:693–700; Cherney DZ et al. *Circulation* 2014;129:587–97.

Lipid lowering therapy

People with type 2 diabetes and CKD should receive an optimum dose of a statin for primary prevention (1).

1 mmol/L reduction in low density lipoprotein (LDL) cholesterol reduces cardiovascular events by 21 % (2).

- These benefits are seen in people with diabetes and in CKD. However, smaller effects are evident as eGFR declines with no benefit seen in people on KRT with haemodialysis (3).
- Following kidney transplantation, lipid lowering reduces major adverse cardiovascular events (4).

Larger reductions in LDL cholesterol led to further reductions in major vascular events

- no evidence of adverse effects with more intensive LDL lowering treatment (5)

1. Zac-Varghese S, Mark P, Bain S, Banerjee D, Chowdhury TA, Dasgupta I, et al. Clinical practice guideline for the management of lipids in adults with diabetic kidney disease: abbreviated summary of the Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) Guideline 2024. Bmc Nephrol. 2024;25(1):216.
2. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25
3. Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin- 21 based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol. 2016;4(10):829-39.
4. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev. 2009(2):Cd005019.
5. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.

Lipid lowering therapy

Atorvastatin 20 mg is suggested as the first line

- with dose titration or use of higher intensity statins as required
- Specialist advice should be sought at eGFR < 30 mL/minute/1.73 m2.

If statin intolerance, ezetimibe alone or in combination with bempedoic acid can be used.

- Fibrates cause a reversible increase in creatinine and specialist advice is recommended when these are used in people with CKD (1).

There are newer agents, inclisiran, PSCK9 inhibitors and icosapent ethyl, available for people who do not meet treatment targets using statins or ezetimibe.

- evidence for benefit exists up to stage G3b CKD (1)

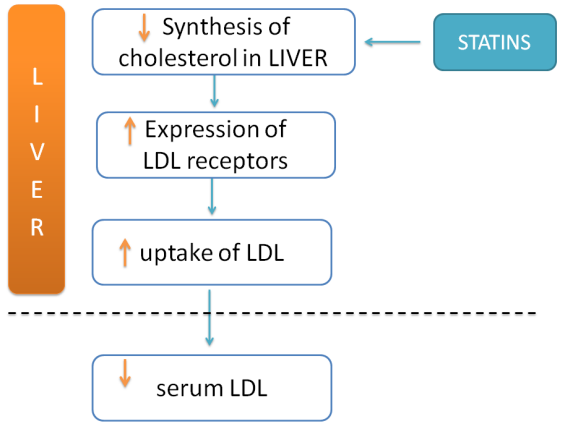
1. Zac-Varghese S, Mark P, Bain S, Banerjee D, Chowdhury TA, Dasgupta I, et al. Clinical practice guideline for the management of lipids in adults with diabetic kidney disease: abbreviated summary of the Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) Guideline 2024. Bmc Nephrol. 2024;25(1):216.

Statin

Main action is within the Liver

Statins work by lowering cholesterol by inhibiting the synthesis of cholesterol and also by causing the liver to upregulate the number of clearance receptors.

- Structural analogue of the HMG-CoA intermediate
- Increase high-affinity LDL receptors
- Increase catabolic rate of LDL and the liver's extraction of LDL precursors (reducing LDL)



Statins = inhibit synthesis of cholesterol and increase liver uptake of LDL

Statin Intolerance

Side effects may be reduced by change in dose or the type of statin used.

Dose related

- Conditions that increase serum / muscle concentrations increase incidence
  - (Hypothyroidism , smaller body size, female sex , old age , Asian ethnicity)

Lipophilic statins (Simvastatin / Atorvastatin) are more prone to cause myopathy than **Hydrophilic** (Pravastatin / Rosuvastatin)

- (likely due to different transport systems leading to increase intramuscular concentration of the former)

People who are more susceptible to statin side effects tend to be :

- Women
- Asian
- Hypothyroid
- Low in Vitamin D

Statin

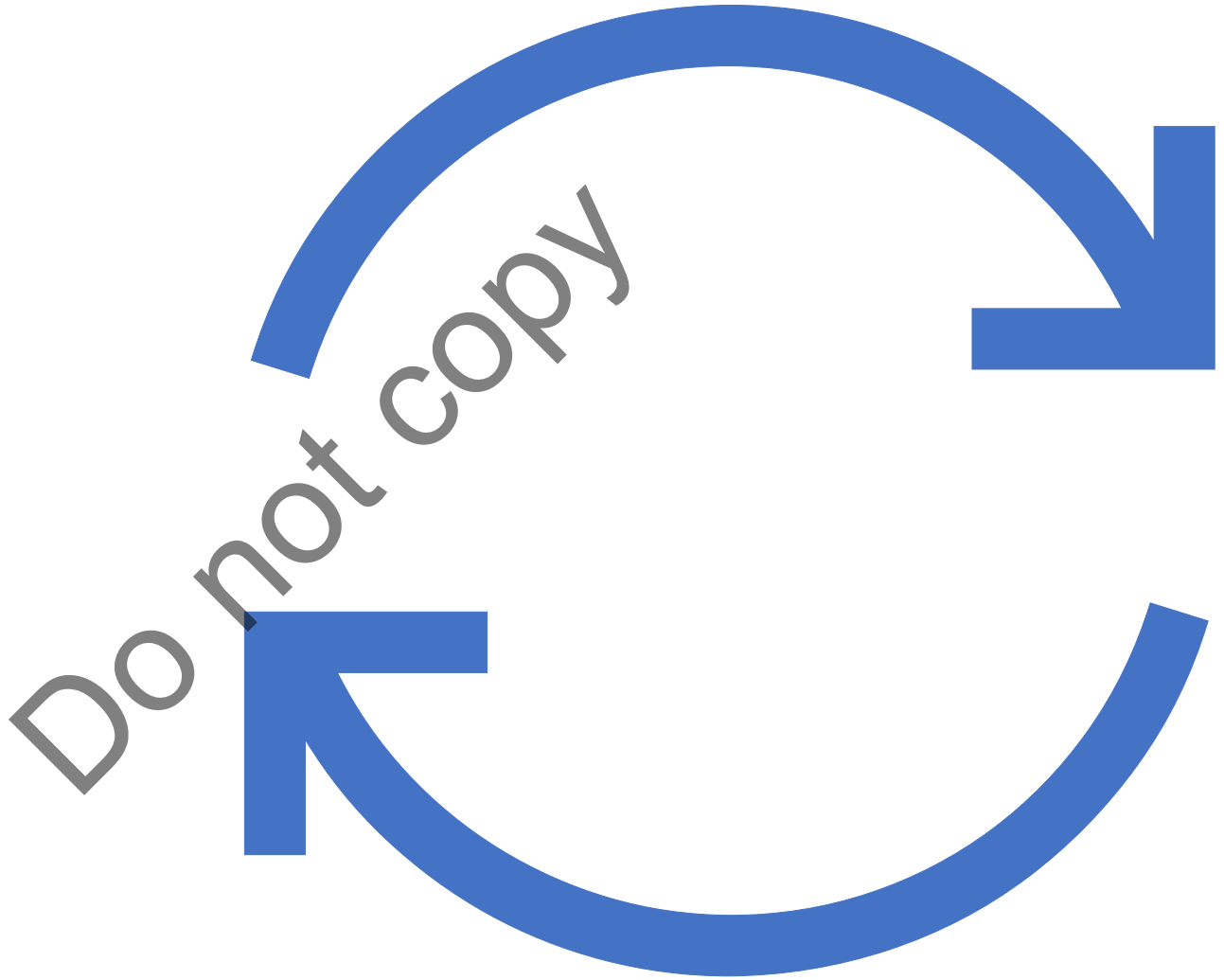
Not all the statins have the same potency

	Reduction in LDL- Cholesterol				
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	-	-	21%	27%	33%
Pravastatin	-	20%	24%	29%	-
Simvastatin	-	27%	37%	37%	42%
Atorvastatin	-	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	-

- 20-30% = low intensity
- 31-40% = medium intensity
- > 40% = High intensity

Advice from MHRA of the increased risk of myopathy with high dose simvastatin

Are there Alternatives to statin therapy ?



Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol.

- If used alone, it has a modest effect on lowering LDL-cholesterol, with little effect on other lipoproteins

It works in a different way to statins and so is often prescribed alongside a statin because of the added cholesterol lowering it offers

Ezetimibe = blocks absorption of cholesterol

Bempedoic Acid

Bempedoic Acid is an adenosine triphosphate citrate lyase (ACL) inhibitor which inhibits cholesterol synthesis in the liver, thereby lowering LDL-cholesterol

- is indicated as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia or existing atherosclerotic cardiovascular disease that warrants additional lowering of LDL-C.

B**empedoic Acid** can lower cardiovascular events

- Bempedoic acid was associated with a significant reduction in the risk of the secondary 3-component composite end point of time to cardiovascular death, nonfatal MI, or stroke, which occurred in 83 patients (4.0%) in the bempedoic acid group and 134 patients (6.4%) in the placebo group (HR, 0.64 [95% CI, 0.48-0.84]

Bempedoic Acid = inhibits synthesis of cholesterol

Nissen et.al. N Engl J Med 2023; 388:1353-1364
DOI: 10.1056/NEJMoa2215024

Fibrates

Mechanism of action

- Inhibit cholesterol synthesis
- Decrease Triglyceride synthesis
- Inhibit lipolysis in adipose tissue
- Decrease production of VLDL and aid its clearance
- Increase plasma and hepatic LPL (Lipoprotein Lipase) activity

- Reduce LDL
- Increase HDL
- Reduce Triglyceride +++

Studies have also suggested that Fibrates may have a role in preventing worsening of retinopathy

Fibrates = inhibit lipid synthesis

Icosapent ethyl

Icosapent ethyl is a stable ethyl ester of the omega 3 fatty acid eicosapentaenoic acid.

It improves the lipoprotein profile by suppressing cholesterol-, fatty acid-, and triglyceride-synthesising enzymes,

- increasing fatty acid β-oxidation, and reducing microsomal triglyceride transfer (MTP) protein, resulting in decreased hepatic triglyceride and very low-density lipoprotein (VLDL) synthesis and release.

It also increases the expression of lipoprotein lipase, leading to increased triglyceride removal from circulating VLDL and chylomicron particles.

- In people with elevated triglyceride levels, icosapent ethyl lowers triglyceride, VLDL, remnant lipoprotein cholesterol, and levels of inflammatory markers, such as C-reactive protein.

Icosapent ethyl is taken orally and is available as 998 mg soft capsules.

The recommended dosage is 1.996 g (2 capsules) twice daily.

Icosapent = inhibit lipid synthesis and aids removal of triglycerides

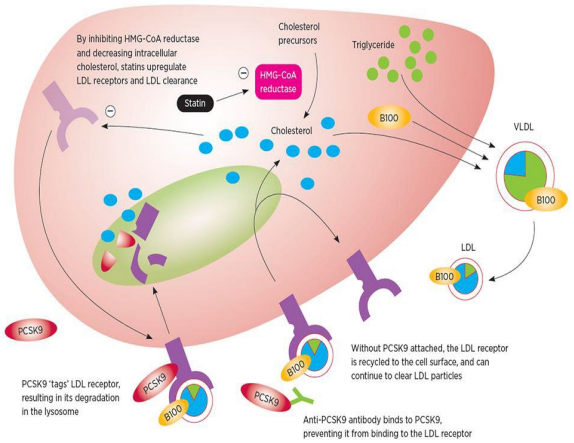
PCSK 9 inhibitors

These are a class of injectable therapies that have been shown to dramatically lower LDL by up to 60%when combined with a statin

PCSK9 inhibitors are monoclonal antibodies (MABs).

They inactivate a protein in the liver called proprotein convertase subtilisin kexin 9 (PCSK9).

- This protein would normally prevent the needed receptors on the liver cell surface that transport LDL into the liver for metabolism (break down) from working .
- Without these receptors, more LDL remains in the blood.



PCSK9 inhibitors = act on clearance of cholesterol

Seidah NG. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors in the treatment of hypercholesterolemia and other pathologies (abstract). Curr Pharm Des. 2013;19(17):3161-72.

Gouni-Berthold I, Berthold HK. PCSK9 Antibodies for the Treatment of Hypercholesterolemia. Nutrients. 2014 Dec; 6(12): 5517–5533.

Inclisiran

Inclisiran works by limiting the production of PCSK9, which in turn boosts the liver's ability to remove harmful cholesterol (LDL) from the blood

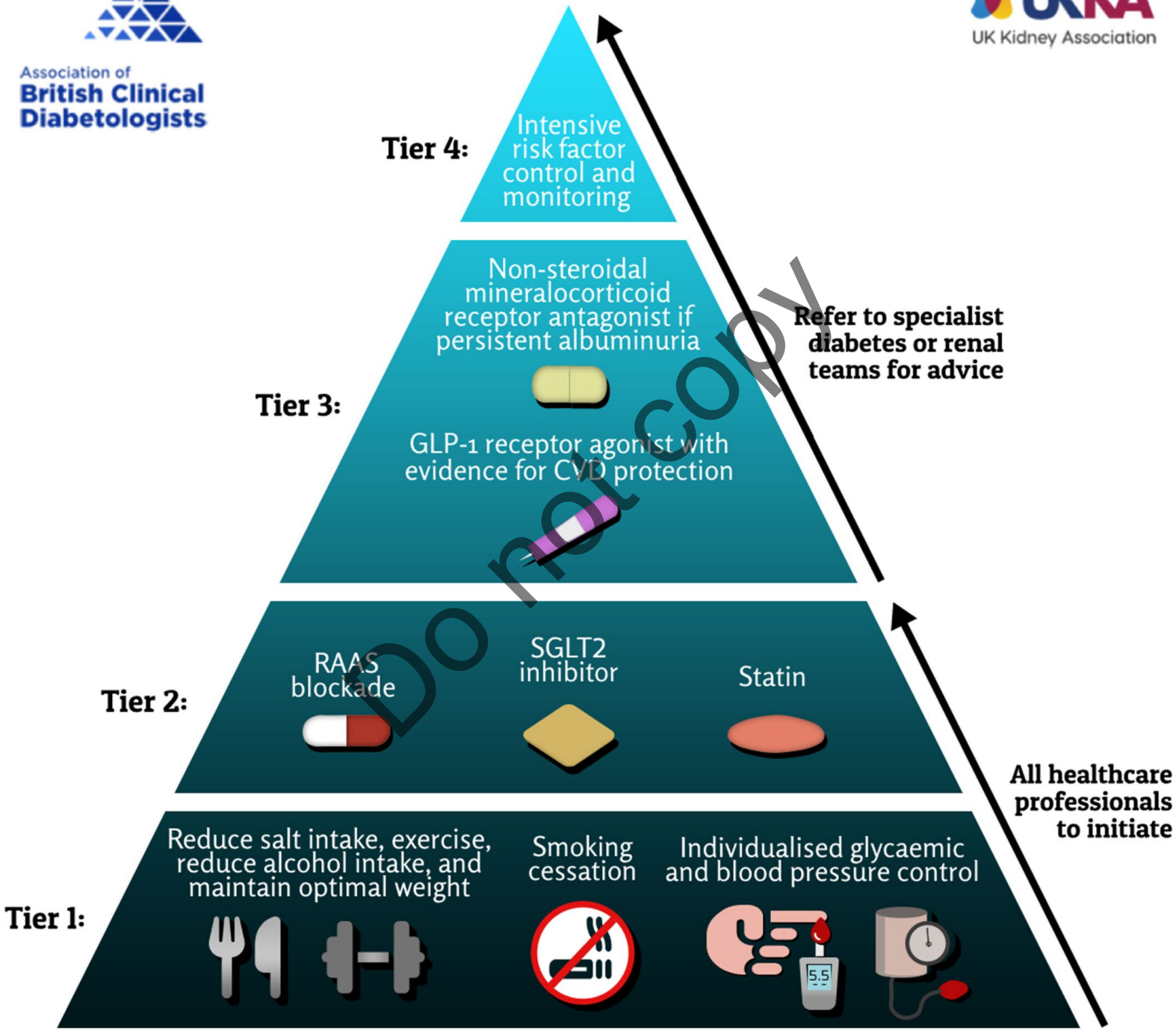
- Inclisiran is the first-in-class small interfering RNA (siRNA) proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor.

Injectable therapy given twice yearly

Inclisiran = increases liver uptake of LDL-Cholesterol

Association of British Clinical Diabetologists

UKKA
UK Kidney Association

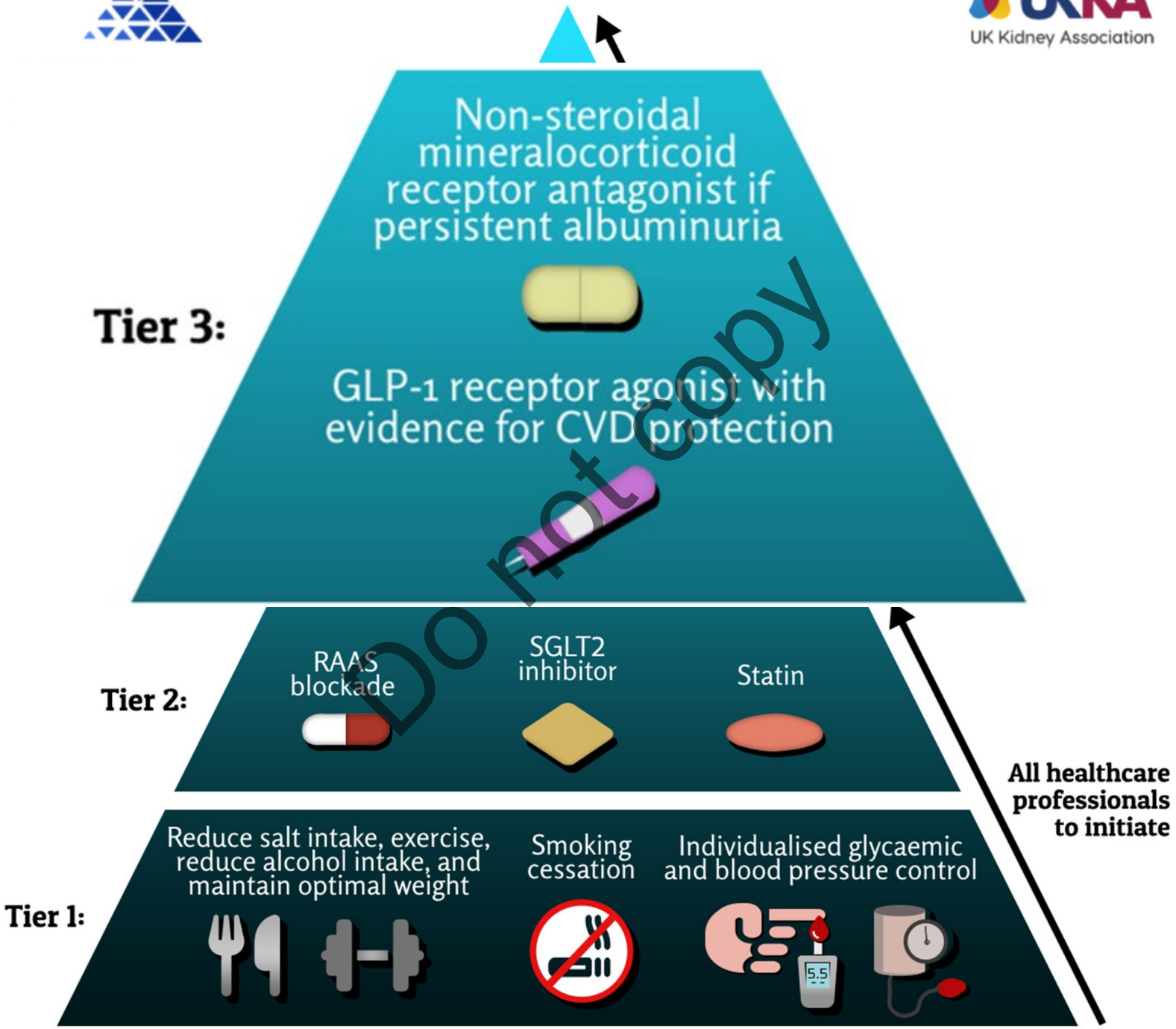


Tier 3

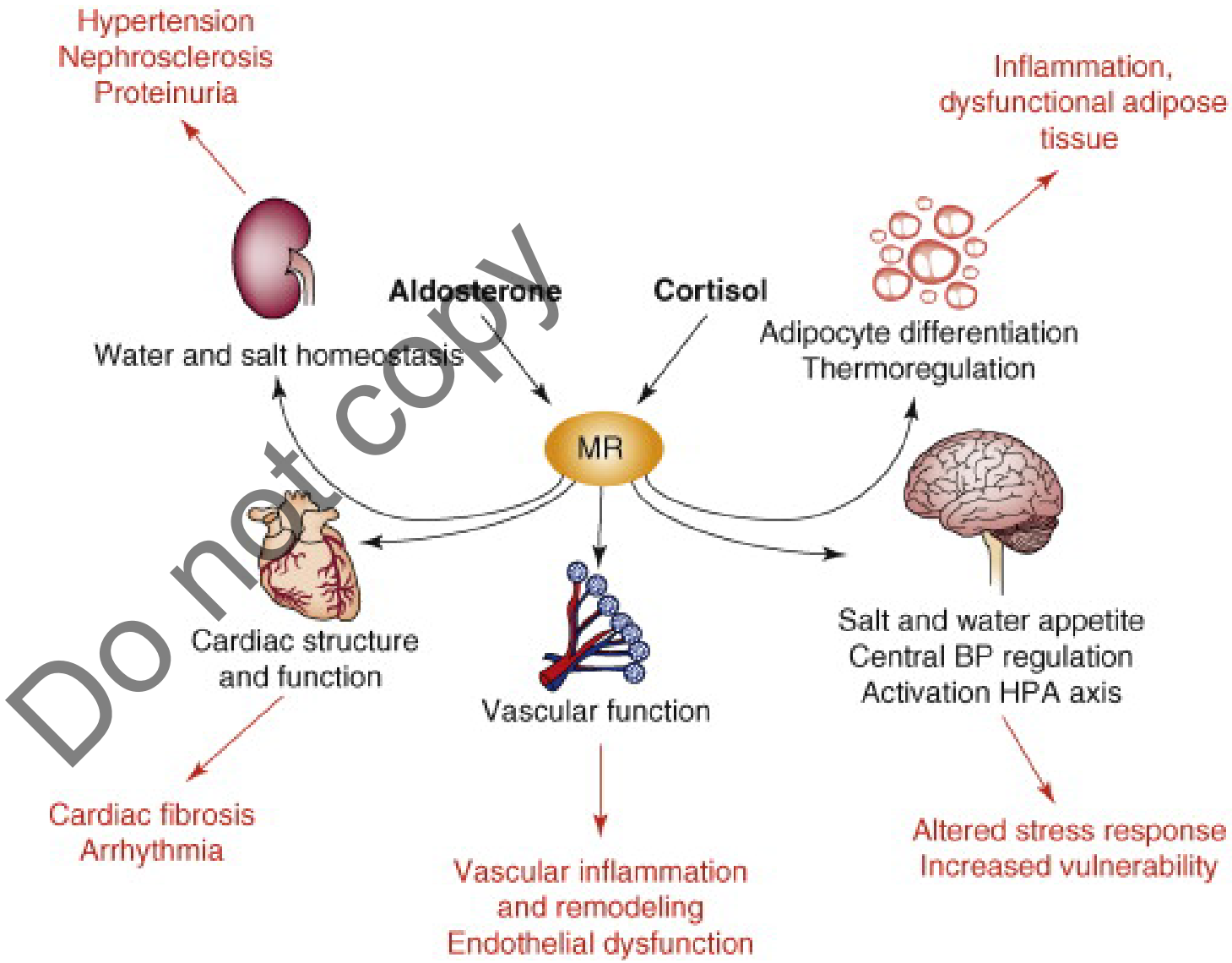
The use of SGLT2 inhibitors over and above the standard of care treatment, which included BP and glycaemic control and optimum RASi, around 10% patients reached primary kidney endpoints and around 7% reached CVD endpoints.(1 ,2) .

This suggests despite optimum Tier-2 treatment there remains residual risk of kidney disease progression and CVD in a significant number of patients

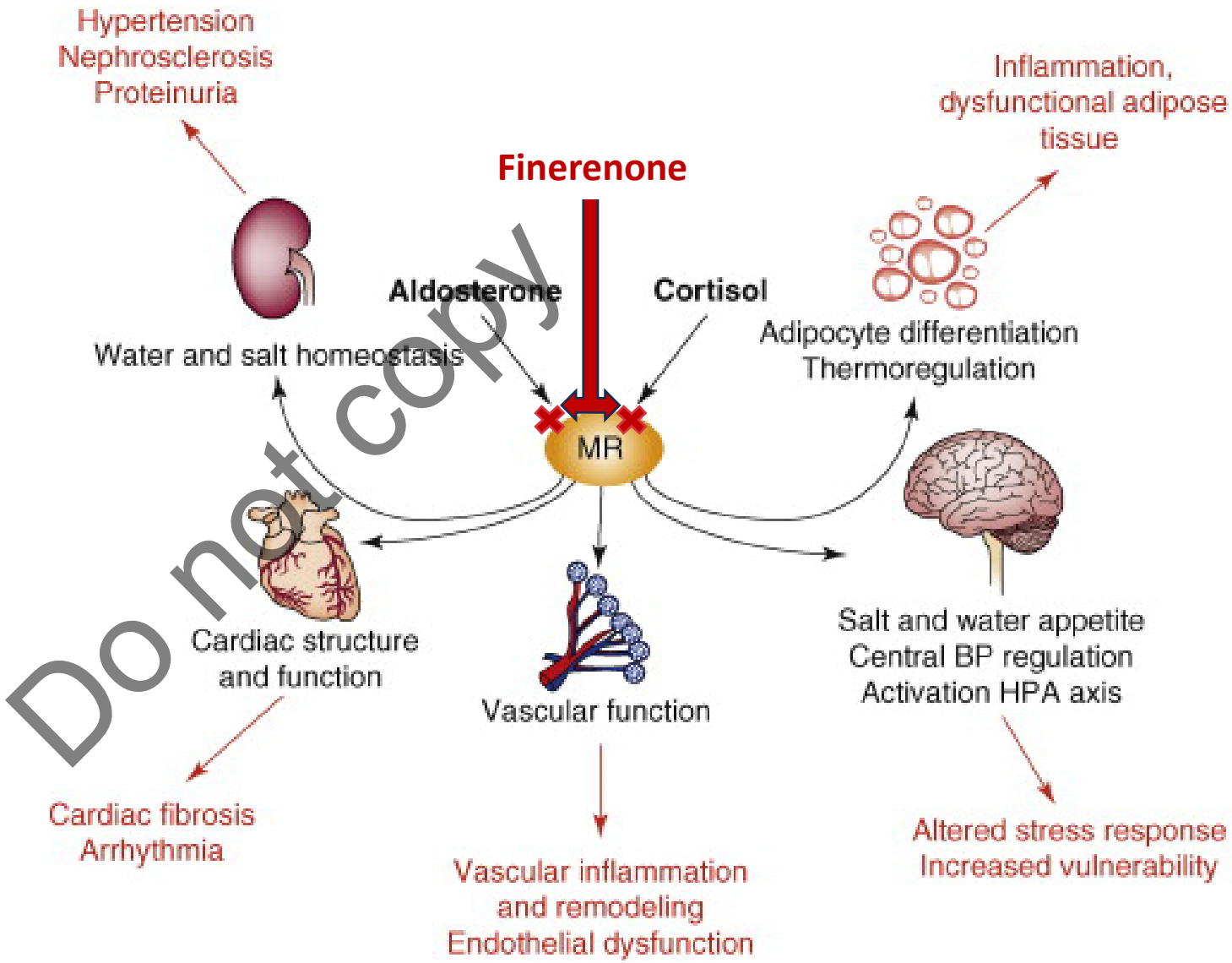
1. Chaudhry K, Karalliedde J. Chronic kidney disease in type 2 diabetes: The size of the problem, addressing residual renal risk and what we have learned from the CREDENCE trial. Diabetes Obes Metab. 2024.
2. Chaudhuri A, Ghanim H, Arora P. Improving the residual risk of renal and cardiovascular outcomes in diabetic kidney disease: A review of pathophysiology, mechanisms, and evidence from recent trials. Diabetes Obes Metab. 2022;24(3):365-76


UKKA
UK Kidney Association
Tier 3:
Non-steroidal mineralocorticoid receptor antagonist if persistent albuminuria
GLP-1 receptor agonist with evidence for CVD protection
Tier 2:
RAAS blockade
SGLT2 inhibitor
Statin
Tier 1:
Reduce salt intake, exercise, reduce alcohol intake, and maintain optimal weight
Smoking cessation
Individualised glycaemic and blood pressure control
5.5
All healthcare professionals to initiate
Do not copy

Mineralocorticoid Receptors - a new target for inflammation reduction



Mineralocorticoid Receptors - a new target for inflammation reduction



Finerenone for CKD

Finerenone (Kerendia) is a mineralocorticoid receptor antagonist

- like spironolactone and eplerenone has been demonstrated to improve blood pressure control, reduce proteinuria, and slow progression of CKD and reduce mortality in heart failure (1-4).

Licensed for the treatment of CKD stages 3-4 with albuminuria and type 2 diabetes

NICE recommends adding to ACE and SGLT2i

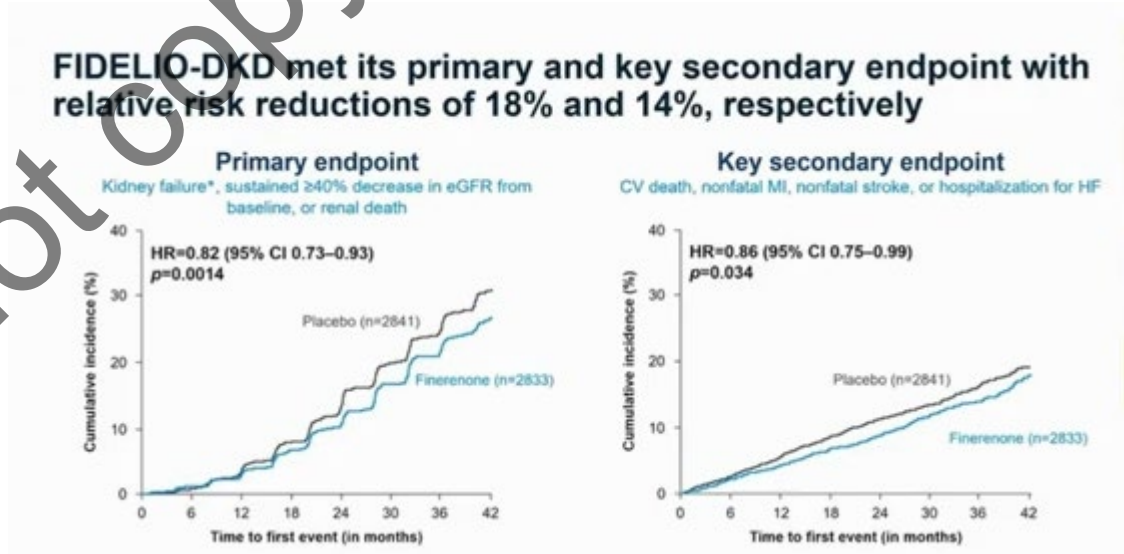
Action

- **- inhibits the overactivation of mineralocorticoid receptors by aldosterone and cortisol – reducing inflammation and fibrosis**

1. Chaudhuri A, Ghanim H, Arora P. Improving the residual risk of renal and cardiovascular outcomes in diabetic kidney disease: A review of pathophysiology, mechanisms, and evidence from recent trials. Diabetes Obes Metab. 2022;24(3):365-76.
2. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2016 Sep 8;17(1):127. doi: 10.1186/s12882-016-0337-0. PMID: 27609359; PMCID: PMC5015203.
3. Yang CT, Kor CT, Hsieh YP. Long-Term Effects of Spironolactone on Kidney Function and Hyperkalemia-Associated Hospitalization in Patients with Chronic Kidney Disease. J Clin Med. 2018 Nov 21;7(11):459. doi: 10.3390/jcm7110459. PMID: 30469400; PMCID: PMC6262621.
4. Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341(10):709–17.DOI:10.1056/NEJM199909023411001.

Finerenone for CKD

- FIDELIO – DKD study
- significantly reduced
  - risk of composite end point (time to cardiovascular death , non- fatal MI , non- fatal stroke or hospitalisation for HF) – HR 0.86
  - Reduced composite end point (onset kidney failure or renal death) HR 0.77



1. Chaudhuri A, Ghanim H, Arora P. Improving the residual risk of renal and cardiovascular outcomes in diabetic kidney disease: A review of pathophysiology, mechanisms, and evidence from recent trials. Diabetes Obes Metab. 2022;24(3):365-76.
2. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2016 Sep 8;17(1):127. doi: 10.1186/s12882-016-0337-0. PMID: 27609359; PMCID: PMC5015203.
3. Yang CT, Kor CT, Hsieh YP. Long-Term Effects of Spironolactone on Kidney Function and Hyperkalemia-Associated Hospitalization in Patients with Chronic Kidney Disease. J Clin Med. 2018 Nov 21;7(11):459. doi: 10.3390/jcm7110459. PMID: 30469400; PMCID: PMC6262621.
4. Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341(10):709–17.DOI:10.1056/NEJM199909023411001.

CKD and GLP

GLP-1 receptor agonists

GLP-1 RA have clinical trials demonstrating CVD benefits in those at risk of CVD or with established CVD.

GLP-1 receptor agonists (Semaglutide) in addition to RASi has shown -kidney benefits and CVD mortality benefits as compared to standard of care (RASi-only).

- combination treatment GLP-1 RA and SGLT-2 inhibitors should also be considered early in the management people with T2D and CKD to address residual cardio-renal risk (Tier 1 or 2) (1, 2, 3)

1. Neuen BL, Heerspink HJL, Vart P, Claggett BL, Fletcher RA, Arnott C, et al. Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA 18 Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria. Circulation. 2024;149(6):450-62.
2. Chaudhry K, Karalliedde J. Chronic kidney disease in type 2 diabetes: The size of the problem, addressing residual renal risk and what we have learned from the CREDENCE trial. Diabetes Obes Metab. 2024
3. Marsico F, Paolillo S, Gargiulo P, Bruzzese D, Dell'Aversana S, Esposito I, et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with Type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. Eur Heart J. 2020;41(35):3346-58

GLP-1 receptor agonists and CKD

Liraglutide and Semaglutide are approved to reduce CVD risk in patients with CVD and T2DM.

- Semaglutide is also approved to reduce CVD risk in patients with CVD and either obesity or overweight

Semaglutide , in phase 3 clinical trials has shown Renal and CVD protection in patients with T2DM and albuminuric CKD **(FLOW trial)**

as well as

without diabetes that had CVD and overweight/obesity **(SELECT trial).**

GLP-1 receptor agonists in patients with chronic kidney disease and either overweight or obesity
Daria Abasheva , Alberto Ortiz , Beatriz Fernandez-Fernandez *Clinical Kidney Journal*, Volume 17, Issue Supplement_2, December 2024, Pages ii19–ii35,

GLP-1 receptor agonists and CKD

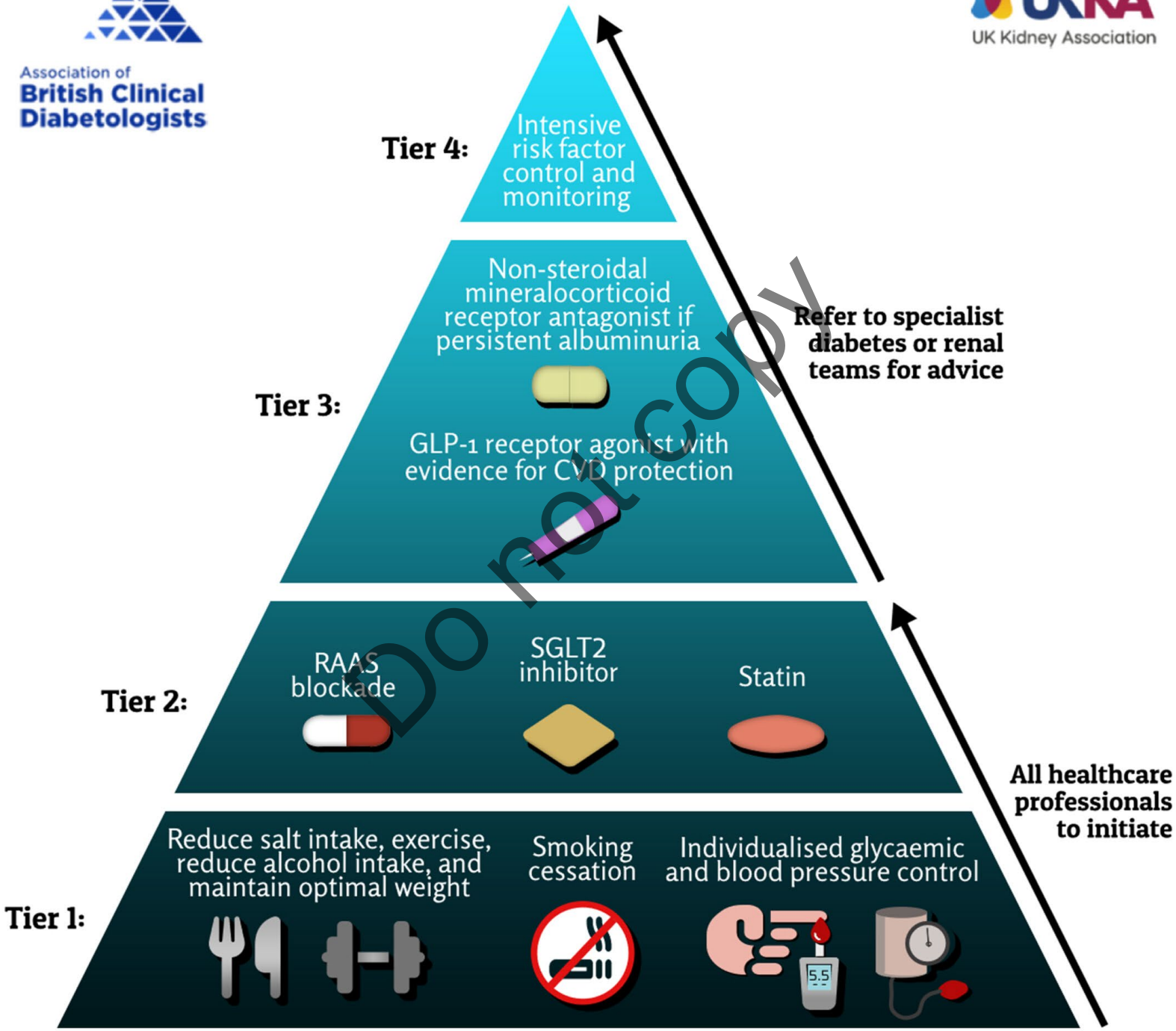
Thus, nephrologists should consider prescribing GLP-1 RAs to improve metabolic control, reduce CVD risk or improve kidney outcomes in three scenarios:

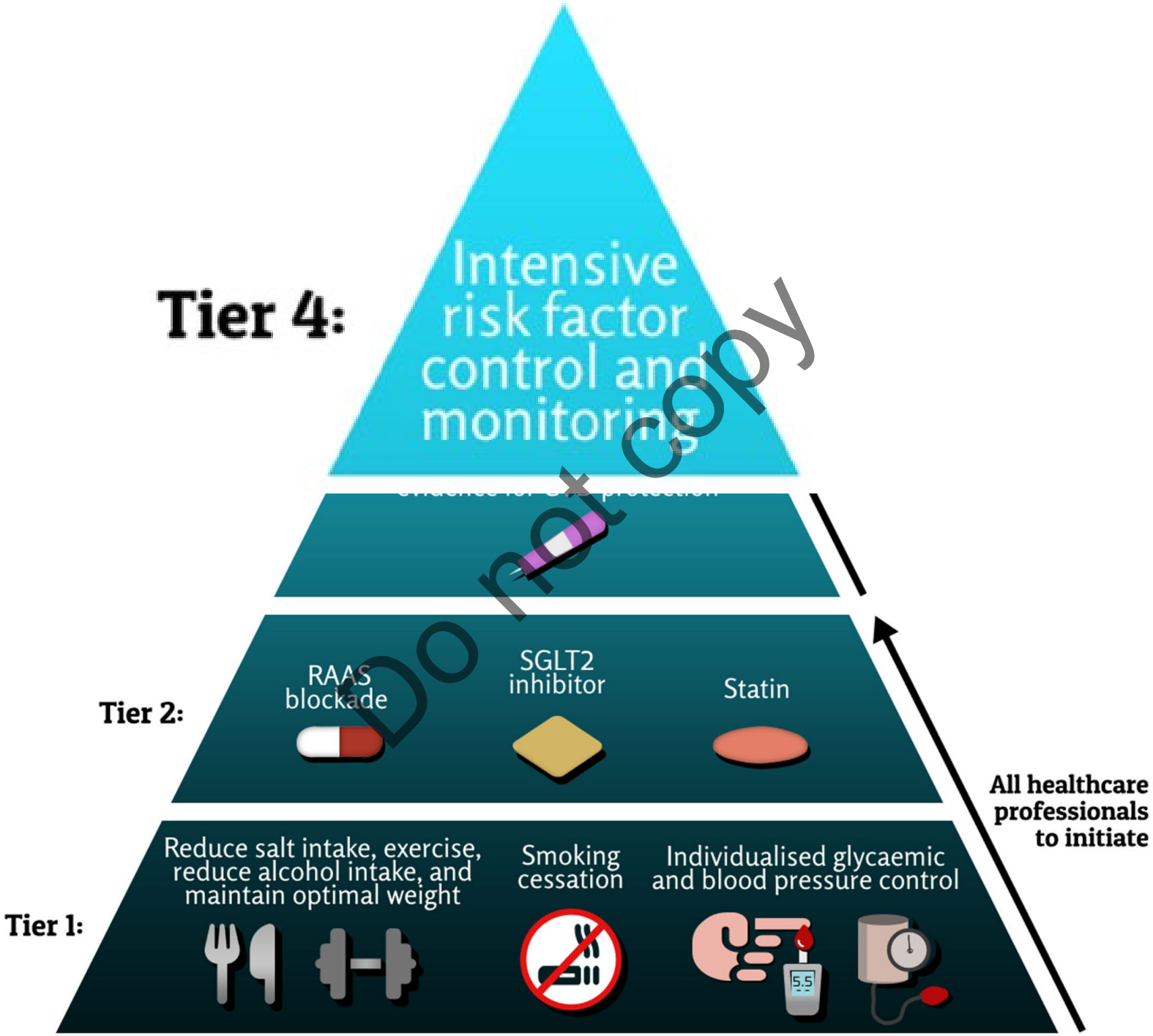
1) patients with overweight and a related comorbid condition such as hypertension, dyslipidaemia or CVD,
2) patients with obesity
3) patients with T2DM

GLP-1 receptor agonists in patients with chronic kidney disease and either overweight or obesity
Daria Abasheva , Alberto Ortiz , Beatriz Fernandez-Fernandez *Clinical Kidney Journal*, Volume 17, Issue Supplement_2, December 2024, Pages ii19–ii35,

Association of British Clinical Diabetologists

UKKA
UK Kidney Association




Tier 4:
Intensive risk factor control and monitoring
Tier 2:
RAAS blockade
SGLT2 inhibitor
Statin
Tier 1:
Reduce salt intake, exercise, reduce alcohol intake, and maintain optimal weight
Smoking cessation
Individualised glycaemic and blood pressure control
5.5
All healthcare professionals to initiate

Tier 4

Most people with CKD die of CVD before needing KRT.

A critical assessment of peoples' relative risk of CVD and kidney failure should inform further intensification of treatment.

- Kidney Failure Risk Equation (KFRE, UK version) and
- QRISK3 are established risk calculators for CKD progression and CVD risks (1,2).

If the person's QRISK3 is high with a low KFRE despite optimum Tier-3 management, BP control and lipid management may be tightened further (4-6).

dose of RAS blocking drug maximised and GLP-1 RA added to afford further protection to the kidney.

1. Bhachu HK, Fenton A, Cockwell P, Aiyegbusi O, Kyte D, Calvert M. Use of the kidney failure risk equation to inform clinical care of patients with chronic kidney disease: a mixed-methods systematic review. BMJ Open. 2022;12(1):e055572.
2. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. Bmj. 2017;357:j2099.
3. Karalliedde J, Winocour P, Chowdhury TA, De P, Frankel AH, Montero RM, et al. Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease. Diabet Med. 2022;39(4):e14769.
4. Banerjee D, Winocour P, Chowdhury TA, De P, Wahba M, Montero R, et al. Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. Bmc Nephrol. 2022;23(1).
5. Zac-Varghese S, Mark P, Bain S, Banerjee D, Chowdhury TA, Dasgupta I, et al. Clinical practice guideline for the management of lipids in adults with diabetic kidney disease: abbreviated summary of the Joint Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) Guideline 2024. Bmc Nephrol. 2024;25(1):216.
6. ABCD and UKKA Joint Finerenone consensus statement: https://ukkidneyorg/renal-association/news/abcd-ukka-joint-finerenone-consensusstatement. Accessed 29/07/2024.
7. Matsushita K, Jassal SK, Sang Y, Ballew SH, Grams ME, et al. Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EClinicalMedicine. 2020 Oct 14;27:100552. doi: 10.1016/j.eclinm.2020.100552. PMID: 33150324; PMCID: PMC7599294.

Summary

CKD occurs in more than 40% of patients with T2DM[1]

Guidelines support early diagnosis, management and monitoring of CKD in T2DM[2–5]

Earliest sign is albuminuria (ACR >3.0 mg/mmol); persistent reductions in eGFR <60 mL/min/1.73 m^2 confirm the diagnosis

CKD in T2DM is associated with an increased risk of CVD, increased mortality, and is the leading cause of ESRD

It is possible to slow progression but early intervention is key

CKD is an important consideration when choosing glucose lowering therapy[6]

Some glucose lowering drugs may reduce the risk of CKD progression[7,8,9,10,]

Remember other drugs also need dose reductions in CKD

Sick day rules and SADMAN therapies

1. http://patientsafety.health.org.uk/sites/default/files/resources/diabetes-kidney-disease-key-facts . 2.ADA. *Diabetes Care*. 2017;40(suppl 1):S1–S135. **3.** National Kidney Foundation. *Am J Kidney Dis*. 2007;49(suppl 2):S1-S160. **4.** IDF Global Guideline for Type 2 Diabetes 2012. Available at http://www.idf.org/guideline-type-2-diabetes. Accessed December 4, 2016. **5.** National Institute for Health and Care Excellence. Chronic Kidney Disease Guidelines. http://www.nice.org.uk/guidance/cg182/evidence/update-full-guideline-191905165. Accessed December 4, 2016. **6.** Inzucchi SE et al. *Diabetes Care*. 2015;38:140–149. 7. Zinman B, Wanner C, Lachin JM et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28. 8.Neal B, Perkovic V, Mahaffey KW et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* **377**: 644–57. 9. Marso SP, Daniels GH, Brown-Frandsen K *et al.* (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **375**: 311–22. 10. Marso SP, Bain SC, Consoli A *et al.* (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* **375**: 1834–44.

Diagnosing and monitoring CKD

About this series
The aim of the "How to" series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What and why

- CKD describes abnormal kidney function or structure, present for more than 3 months.
- CKD is diagnosed and monitored using eGFR, which measures kidney function, and ACR, which measures kidney damage (see *How to test for microalbuminuria*[1]).
- To diagnose CKD: an eGFR of <60 is required on at least 2 occasions over a period of at least 90 days, with or without markers of kidney damage.
- Laboratories use CKD-EPI or MDRD to estimate GFR.

! **It is important to remember, a raised ACR indicates risk even when the eGFR is normal.**

Send a non-fasting venous blood sample to the lab within 12 hours of venepuncture.

If the person is of African or African–Caribbean origin, apply a correction factor (**multiply eGFR by 1.159**)

Has the person been previously tested?

- Yes
- No

If eGFR >60:
eGFR 60–89: Code G2
eGFR ≥90: Code G1
Do not diagnose CKD (in the absence of markers of kidney damage *see blue box overleaf*
REPEAT ANNUALLY
eGFR values of ≥60 become less accurate as true GFR increases, which is why many labs do not report an exact figure for eGFR >60.

If eGFR <60:
Repeat test within 2 weeks to exclude AKI *see purple box overleaf*
If remains <60, repeat after at least 90 days. If <60, code and manage as below.

If eGFR <30
eGFR 15–29: Code G4
eGFR <15: Code G5
Diagnose CKD
Assess & code ACR[1]
Monitor as per *Table 1*
Consider referral

If eGFR 30–44
Code G3b
Diagnose CKD
Assess & code ACR[1]
Monitor as per *Table 1*

If eGFR 45–59 **
Code G3a
Diagnose CKD
Assess & code ACR[1]
Monitor as per *Table 1*

Consider referral as per local pathway or CG 182[3] if:

- eGFR <30 (G4 or G5).
- Sustained decrease in eGFR of ≥25%, and a change in eGFR category or sustained decrease in eGFR of ≥15 within 12 months.
- Hypertension poorly controlled on at least 4 agents.
- Suspected renal artery stenosis.

Involve the person with diabetes in the referral decision.

Table 1. Frequency of monitoring of eGFR for people with, or at risk of, CKD (adapted from CG 182[3]).

Frequency of monitoring of eGFR (number of times per year, by GFR and ACR category).	ACR categories (mg/mmol), description and range: A1 <3 Normal to mildly increased	A2 3–30 Moderately increased	A3 >30 Severely increased
G1 ≥90 Normal and high	≤1	1	≥1
G2 60–89 Mild reduction	≤1	1	≥1
G3a 45–59 Mild–moderate reduction	1	1	2
G3b 30–44 Moderate–severe reduction	≤2	2	≥2
G4 15–29 Severe reduction	2	2	3
G5 <15 Kidney failure	4	≥4	≥4

(eGFR categories, description and range)

**Consider using eGFR cystatinC[†] if available locally when an improved assessment of risk is needed and at initial diagnosis to confirm/exclude CKD in people with:

eGFR creatinine 45–59
sustained for at least 90 days
AND
no proteinuria or other marker of kidney disease

[†] When using eGFR cystatinC, hypothyroidism may lead to overestimation, hyperthyroidism to underestimation.

HOW TO DIAGNOSE AND MONITOR CKD

Author
Jane Diggle; Practice Nurse, West Yorkshire, Vice-Chair of PCDS, and Associate Member of TREND-UK.

Useful abbreviations
ACE-I: Angiotensin-converting enzyme inhibitor
ACR: Albumin:creatinine ratio
AKI: Acute kidney injury
ARB: Angiotensin receptor blocker
CKD: Chronic kidney disease
CVD: Cardiovascular disease
eGFR: estimated glomerular filtration rate
NSAIDs: Nonsteroidal anti-inflammatory drugs

Units
eGFR units are mL/min/1.73 m² throughout if not included.

NICE has not checked the use of its content in this article to confirm that it accurately reflects the NICE publication from which it is taken.

References
[1] Gaddam V (2017) How to test for microalbuminuria. *Diabetes & Primary Care* **19**: 13
[2] NICE (2013) *Acute kidney injury: prevention, detection and management* (CG 169). NICE, London
[3] NICE (2014) *Chronic kidney disease in adults: assessment and management* (CG 182). NICE, London
[4] NICE (2016) *Cardiovascular disease: risk assessment and reduction, including lipid modification* (CG 181). NICE, London
[5] Yenigun EC et al (2015) *Hippokratia* **19**: 148–2

What next

Interpret eGFR with caution

- eGFR values of ≥60 become less accurate as true GFR increases.
- Reduced muscle mass (e.g. muscle wasting, amputations) will lead to overestimation *(false high)*.
- Increased muscle mass (e.g. body builders) will lead to underestimation *(false low)*.
- Dehydration may lead to underestimation.

ACE-I/ARB monitoring

- ACE-Is/ARBs can cause a decline in eGFR. Check potassium and eGFR before starting therapy and within 1–2 weeks of starting and at every dose increase.
- If eGFR decreases by <25%, repeat eGFR in 1–2 weeks (no need to modify dose if result is the same).
- If eGFR decreases by ≥25% investigate other causes, if none found, reduce dose or consider stopping drug.

Markers of kidney disease[3]

- Albuminuria (ACR >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.

Be alert

- In people with a new finding of reduced eGFR, repeat the eGFR within 2 weeks to exclude causes of acute deterioration of eGFR (e.g. AKI or starting renin–angiotensin system antagonist therapy).
  - **If AKI suspected**, follow CG 169[2].
  - **If AKI not suspected** but eGFR remains <60, repeat eGFR after at least 90 days to confirm or refute diagnosis.
- Deterioration in eGFR in those with short duration of diabetes and the absence of retinopathy should raise suspicions of non-diabetic kidney disease and referral for renal biopsy may be appropriate[5].

How to assess rate of CKD progression

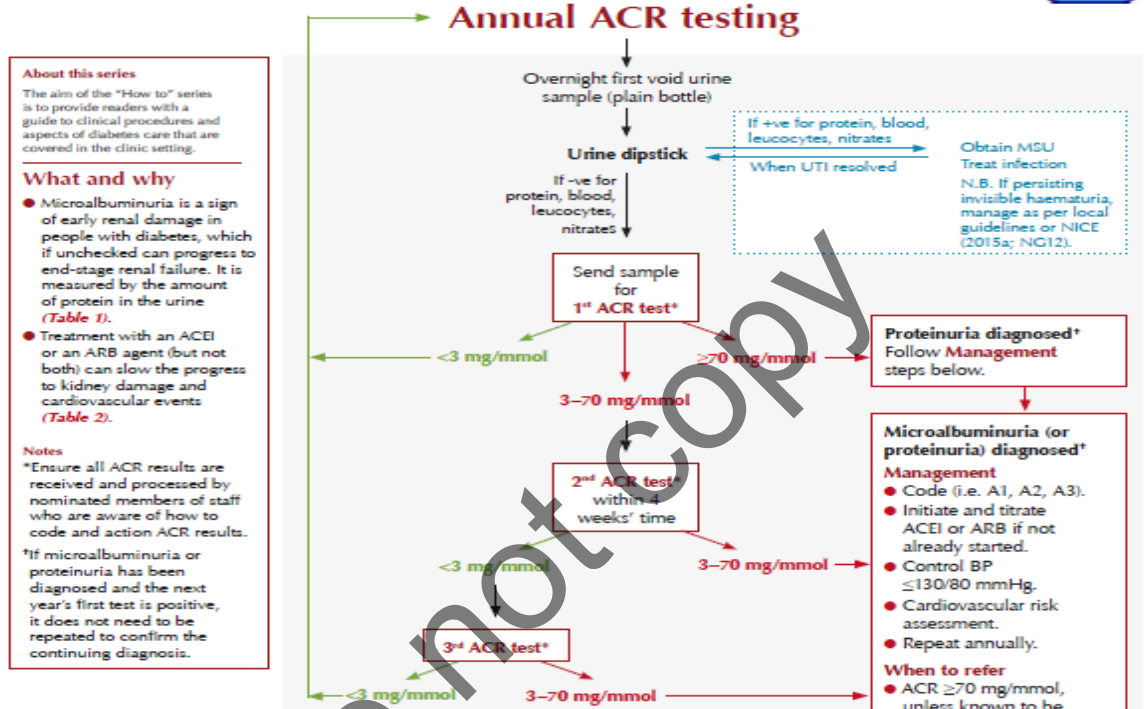
- Obtain minimum of 3 eGFR values over a period of not less than 90 days.
- **Accelerated progression** of CKD is:
  a sustained decrease in eGFR of ≥25% and a change in eGFR category within 12 months
  OR
  sustained decrease in eGFR of 15 mL/min/1.73 m² per year.

CKD management in primary care

- Lifestyle advice: exercise, smoking cessation, achieve healthy weight, dietary advice regarding potassium, phosphate and salt intake as appropriate.
- Aim for BP control <130/80 mmHg if diabetes and CKD.
- Offer ACE-I/ARB if they have CKD, diabetes and ACR ≥3 mg/mmol.
- Offer statins as per NICE CG 181[4].
- Offer antiplatelet drugs for secondary CVD prevention.
- Avoid NSAIDs if possible.

Local pathway notes

How to diagnose, manage and monitor microalbuminuria



About this series

The aim of the "How to" series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What and why

- Microalbuminuria is a sign of early renal damage in people with diabetes, which if unchecked can progress to end-stage renal failure. It is measured by the amount of protein in the urine *(Table 1)*.
- Treatment with an ACEI or an ARB agent (but not both) can slow the progress to kidney damage and cardiovascular events *(Table 2)*.

Notes

*Ensure all ACR results are received and processed by nominated members of staff who are aware of how to code and action ACR results.

†If microalbuminuria or proteinuria has been diagnosed and the next year's first test is positive, it does not need to be repeated to confirm the continuing diagnosis.

1. Classification of proteinuria (NICE, 2014).

ACR	Microalbuminuria diagnosis	NICE CKD classification
<3 mg/mmol	Normal	A1
3–30 mg/mmol	Microalbuminuria	A2
>30 mg/mmol	Proteinuria	A3

2. Target dose for renal protection (Weinberg et al, 2003)[1].

Drug	Initial dose	Target dose
Lisinopril	2.5 mg/day	20 mg/day[2]
Ramipril	1.25 mg/day	5 mg/day
Candesartan[3]	4 mg/day	16 mg/day
Irbesartan[4]	150 mg/day	300 mg/day
Losartan[5]	25–50 mg/day	100 mg/day

[1]Some studies of albuminuria/proteinuria reduction used both an ACEI and an ARB agent but this is no longer recommended.
[2]Some studies demonstrated increased benefit at higher than licensed doses of lisinopril. A dose over 20 mg must be managed in a specialist setting.
[3]Candesartan is not licensed for the treatment of albuminuria/proteinuria.
[4]Irbesartan is licensed for renal disease in hypertensive type 2 diabetes.
[5]Losartan is licensed for renal disease in people with hypertension and type 2 diabetes with proteinuria ≥0.5 g/day as part of hypertension treatment.
For up-to-date information on all drugs listed, including for special populations, see the relevant Summary of Product Characteristics (www.medicines.org.uk).

Useful abbreviations
ACEI: angiotensin-converting enzyme inhibitor
ACR: albumin: creatinine ratio
ARB: angiotensin receptor blockers
BP: blood pressure
MSU: mid-stream specimen of urine
UTI: urinary tract infection

References and further information
NICE (2014) *CKD in adults: assessment and management* (CG182). NICE, London
NICE (2015a) *Suspected cancer: recognition and referral* (NG12). NICE, London
NICE (2015b) *Type 2 diabetes in adults: management* (NG28). NICE, London
Weinberg MS et al (2003) *Current Hypertension Reports* 5: 418–25

Author
Prof Roger Gadsby MBE; Honorary Associate Clinical Professor, Warwick Medical School, University of Warwick; GP Clinical Lead for National Diabetes Audit

Diabetes & Primary Care Vol 19 No 1 2017

Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

ACCELERATED ACCESS COLLABORATIVE

NHS England

INITIAL CONSIDERATIONS:

- Measure non-fasting ***full lipid profile*** (Total cholesterol, HDL-C, non-HDL-C, LDL-C, triglycerides) and HbA1c as part of an initial baseline assessment.
- Consider secondary causes of hyperlipidaemia and manage as needed.
- Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI.
- Identify and exclude people with contraindications/drug interactions
- If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, *'Primary Prevention Risk Assessment'*)

- Age ≤84 & QRISK ≥10% over next 10 years
- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR < 60 mL/min/1.73m² and/or albuminuria
- Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors)

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer statin treatment.

Atorvastatin 20mg OD

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months;
  - discuss treatment adherence, timing of dose, diet and lifestyle
  - If at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 *'Additional Risk Factors'*) consider increasing the dose every 2-3 months up to a maximum dose of atorvastatin 80mg OD.
  - For how to increase in people with CKD see *'Special Patient Populations'* (page 2).

- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Statin Intensity Table'*)
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after 3 months consider adding Ezetimibe 10mg OD (NICE TA385)
- If recommended statin therapy is contraindicated or not tolerated;
  - Ezetimibe monotherapy may be considered. Assess response after 3 months
  - See local statin intolerance guidance / pathway where available

If non-HDL-C reduction remains < 40% of baseline despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic according to local arrangements

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and with no secondary causes: suspect Familial Hypercholesterolaemia (Possible Heterozygous FH)

Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.

Use the **Simon Broome** or **Dutch Lipid Clinic Network** (DLCN) criteria to make a **clinical diagnosis of FH**.

Refer to Lipid Clinic for further assessment if **clinical diagnosis of FH** or if TC>9.0mmol/L and/or LDL-C >6.5mmol/L and/or non-HDL-C >7.5mmol/L or Fasting triglycerides > 10mmol/L (regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH and/or other risk factors present follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, ***BUT***

Aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.

Consider specialist referral for further treatment and/or consideration of PCSK9i therapy IF

- they are assessed to be at very high risk of a coronary event**
- OR therapy is not tolerated
- OR LDL-C remains >5mmol/L (primary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

despite maximal tolerated statin and Ezetimibe therapy.

**defined as any of the following:

- Established coronary heart disease.
- Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes angina, previous MI, revascularisation,stroke or TIA or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours)

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors.
Prescibe a high intensity statin:
Atorvastatin 80mg OD

Use a lower dose of Atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference.

Offer Atorvastatin 20mg if CKD (people with GFR< 60 mL/min/1.73m²).

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months
  - discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 *'Additional Risk Factors'*), consider increasing to 80mg Atorvastatin. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If non-HDL-C baseline value is not available, use target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by JBS3 consensus statement - a ***'lower is better approach'***
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Statin Intensity Table'*)

- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value and/or non-HDL-C < 2.5mmol/L after 3 months consider adding Ezetimibe 10mg OD (NICE TA385)
- If recommended statin therapy is contraindicated or not tolerated
  - Ezetimibe monotherapy may be considered. Assess response after 3 months
  - See local statin intolerance guidance / pathway where available

If non-HDL-C > 4.0mmol/L despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications), arrange a **fasting blood test** for LDL-C measurement and if **PCSK9i eligibility criteria** (see page 2 *'Specialist Services'*) are met, refer for confirmation and initiation of PCSK9i (NICE TA 393, 394) according to local arrangements

MANAGEMENT

This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. If 40% reduction of non-HDL-C not achieved, offer high intensity statins. Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risk of side effects if changed to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.

If statin therapy is contraindicated, not tolerated or not effective, consider ezetimibe. Do not offer a fibrate, nicotinic acid, bile acid binder or omega-3 fatty acids alone or in combination with statin, for the prevention of CVD (Check NICE CG181 for exceptions).

PRIMARY PREVENTION RISK ASSESMENT

QRISK3 is the current version of the QRISK calculator. www.qrisk.org/three

- Do not use this risk assessment tool for people with established CVD or those who are at high risk of developing CVD because of FH or other inherited disorders of lipid metabolism.
- Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes, or eGFR less than 60 mL/min/1.73 m^2 and/or albuminuria.
- Consider people aged ≥ 85 at increased risk of CVD because of age alone particularly people who smoke or have raised BP.

Additional Risk Factors

Note, standard CVD risk scores including QRISK may underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include the following groups of people;

- severe obesity (BMI>40kg/m^2) increases CVD risk
- treated for HIV,
- serious mental health problems,
- taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders
- impaired fasting glycaemia
- significant hypertriglyceridaemia (fasting triglycerides 4.5-9.9mmol/L)
- recent risk factor changes e.g. quit smoking, BP or lipid treatment

Consider socio-economic status as an additional factor contributing to CVD risk.

If QRISK < 10% over the next 10 years - Give lifestyle advice and ensure regular review of CVD risk in line with guidance.

SPECIAL PATIENT POPULATIONS

Type 1 Diabetes

While NICE recommends offering statins to patients with Type 1 diabetes as detailed in the algorithm, it also states to consider statins in all adults with type 1 diabetes.

Chronic Kidney Disease

Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m^2 and/or albuminuria)

Increase the dose if a greater than 40% reduction in non-HDL-C is not achieved and eGFR is 30 mL/min/1.73m^2 or more.

Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m^2

ABBREVIATIONS

CVD: cardiovascular disease
FH: Familial Hypercholesterolaemia
ALT: alanine aminotransferase
non-HDL-C: non-high density lipoprotein cholesterol
LDL-C: low density lipoprotein cholesterol
PCSK9i: proprotein convertase subtilisin 9 inhibitor
CKD: chronic kidney disease
TC: total cholesterol
AST: aspartate aminotransferase
OD: once daily

STATIN INTENSITY TABLE

Approximate reduction in LDL-C					
Dose mg/day	5	10	20	**40**	**80**
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + Ezetimibe		52%	54%	57%	61%

Low/moderate intensity statins will produce an LDL-C reduction of 20-30%
Medium intensity statin will produce an LDL-C reduction of 31-40%
High intensity statins will produce an LDL-C reduction above 40%

- **Rosuvastatin** may be used as an alternative to Atorvastatin for primary or secondary prevention if compatible with other drug therapy. Lower starting dose maybe needed in some. See BNF.
- **Simvastatin** 80mg is not recommended (black) due to risk of muscle toxicity.
- Other statins should only be used in intolerance or drug interactions
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C/LDL-C than doubling the dose of the statin.
- **PCSK9i** (NICE TA393,394) alone or in combination with statins or Ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25-70%).

MONITORING

Baseline Measurements

In addition to full lipid profile, measure renal, thyroid and liver profiles (including albumin) and HbA1c to exclude secondary causes and co-morbidities.
Measure baseline liver transaminase (ALT or AST) before starting a statin.
Measure CK if unexplained muscle pain before starting a statin.
CK should not be measured routinely especially if a patient is asymptomatic.

	Primary Prevention		Secondary prevention	
	Lipid Profile	ALT or AST	Lipid Profile	ALT or AST
Baseline	✓	✓	✓	✓
3 months	✓	✓	✓	✓
6-9months	If <40% non-HDL-C reduction, up titration required. Repeat full lipid profile and ALT or AST within 3 months of each up-titration of statin dose or addition of Ezetimibe as required			
12 months	✓	✓	✓	✓
Yearly	✓ (where needed)		✓ (where needed)	

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, lifestyle modification and address CVD risk factors.

Consider an annual non-fasting **full lipid profile to inform the discussion around effectiveness of lipid lowering therapy and any medicines non-adherence.*

Monitoring

Repeat full lipid profile is non-fasting.
Measure liver transaminase within 3 months of starting treatment and then within 3 months of every additional up titration and then again at 12 months, but not again unless clinically indicated.

If ALT or AST are greater than 3 times the upper limit of normal then do not initiate a statin or discontinue statin therapy already prescribed and repeat the LFTs in a month.

If ALT or AST are elevated but are less than 3 times the upper limit of normal then:

- Continue the statin and repeat in a month.
- If they remain elevated but are less than 3 times the upper limit of normal then continue statin and repeat again in 6 months.

TITRATION THRESHOLD / TARGETS

	NICE titration threshold	JBS3
Primary prevention	Intensify lipid lowering therapy if: non-HDL-C reduction from baseline is less than 40%	non-HDL-C <2.5mmol/L (LDL-C <1.8mmol/L)
Secondary Prevention		
FH	Optimise lipid lowering therapy to achieve at least 50% reduction in LDL-C (or Non-HDL-cholesterol.)	

If baseline cholesterol is unknown in the setting of secondary prevention use the use Joint British Societies' JBS3 consensus recommendation.
Non-HDL-C = TC minus HDL-C
LDL-C = non-HDL-C minus (Fasting triglycerides[a]/2.2)
[a] valid only when fasting triglycerides are less than 4.5 mmol/L

SPECIALIST SERVICES

Scope of specialist service available locally may include; Lipid Clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH Genetic Diagnosis and Cascade testing, Lipoprotein Apheresis service. NICE eligibility criteria for PCSK9i and fasting LDL-C thresholds are summarised below

NICE TA393 Alirocumab NICE TA394 Evolocumab	Without CVD	With CVD	
		High risk [1]	Very high risk [2]
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmoL/L	LDL C > 3.5 mmoL/L
Primary heterozygous-FH	LDL C > 5.0 mmoL/L	LDL C > 3.5 mmoL/L	

[1] History of any of the following: ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD. [2] Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

TRIGLYCERIDES

Triglyceride concentration	Action
Greater than 20mmol/L	**Refer to lipid clinic for urgent specialist review** if not a result of excess alcohol or poor glycaemic control. At risk of acute pancreatitis.
10 - 20mmol/L	Repeat the TG measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and review for potential secondary causes of hyperlipidaemia. Seek specialist advice if the TG concentration remains > 10mmol/litre. At risk of acute pancreatitis
4.5 - 9.9mmol/L	If non-fasting triglycerides are greater than 4.5mmol/L, repeat with a fasting TG measurement Be aware that the CVD risk may be underestimated by risk assessment tools, optimise the management of other CVD risk factors present and seek specialist advice if non-HDL-C concentration is > 7.5 mmol/litre.

STATIN INTOLERANCE

Statin Intolerance is defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in adherence to therapy being compromised.

For people who are intolerant of the recommended statin treatment see the NHSE AAC statin intolerance algorithm which is available on the NHSE AAC page here: https://tinyurl.com/y9emrgy4.

References:
JBS3. 2014. www.jbs3risk.com/pages/6.htm
Kirsten *et al.* 2005. Hospital Pharmacy 40(8):687-692
Navarese *et al.* 2015. Annals of internal medicine 163(1):40-51
Soon Jun Hong *et al.* 2018. Clinical therapeutics 40(2): 226-241.e4
NICE. 2016. TA385 www.nice.org.uk/guidance/ta385
NICE. 2016. TA393 www.nice.org.uk/guidance/TA393
NICE. 2016. TA394 www.nice.org.uk/guidance/TA394
NICE. 2014. CG181 www.nice.org.uk/guidance/CG181
NICE. 2008. CG71 www.nice.org.uk/guidance/cg71

ACCELERATED ACCESS COLLABORATIVE

NHS England

Endorsed by the National Institute for Health and Care Excellence (NICE), April 2020.

Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. March 2020. Review date: March 2021. Pathway endorsed by NICE April 2020.