General

1 in 10 adults has CKD

All causes of ESKD

- 44 % DM
- 28 % HTN
- 11 % GN
- 15 % unknown

CVD is the major cause of premature death in DKD

DKD leads to

- RAAS activation
- Sympathetic drive
- Insulin resistance
- Arterial calcification
- LV hypertrophy
- High BP

Structural heart disease is identified in half of patients with CKD stage 4-5.
CKD often co-exists with heart failure and this is usually HFpEF.

Albuminuria is an important independent risk factor for CVD.

Finn Diane Study

Type 1 DM and microalbuminuria (A2) – 3 x risk of premature mortality
Type 1 DM and macroalbuminuria (A3) – 9 x risk premature mortality
Type 1 DM and ESKD – 18 x risk of premature mortality

For type 2 DM you see the same (Advance study)

T1 DM and DKD have a 12-year shorter life expectancy
T2 DM and DKD have a 5-year shorter life expectancy

Definition of CKD

CKD is a sustained reduction in eGFR and/or urinary abnormalities or structural abnormality of the renal tract.

eGFR

- 2 x abnormal eGFR (< 60 ml/min) 3 months apart +/- 2 x abnormal Urine ACR (> 3mg/mmol)
- 60 is used as a cutoff as it is 2 SD below the average for healthy individuals aged 20-35 years
- The Cockcroft Gault is not recommended. It was created by testing people with normal kidney function and does not work in people with abnormal function.
- Current guidelines are to use CKD-EPI without adjustments for ethnicity.

- eGFR is only an estimate, it is affected by
    - Extremes of body habitus
    - limb amputations
    - severe malnourishment
    - body builders.

- Adults should be advised not to eat meat 12 hours before the test.

If a significant decline in kidney function is noted, it should be repeated in 2 weeks.

Albuminuria

Urine ACR 3- 69 mg/mmol should be rechecked within 3 months (NICE recommendation) on an early morning urine sample, some patients have orthostatic proteinuria which can be excluded by an early morning sample. This also obviates the effect of exercise on urine albumin excretion.

Urine ACR > 70 mg/mmol does not need retesting.

If there is frank haematuria, referral fast track to urology.

300 mg/g = 30 mg/mmol

A1 < 3 mg/mmol	
A2 3-30 mg/mmol	previously microalbuminuria
A3 > 30 mg/mmol	previously macroalbuminuria

HbA1c

This is the amount of glucose bound to the Hb in a red blood cell, irreversible, non-enzymatic glycation of β haemoglobin. Therefore, it is dependent on the life of the Hb molecule and the RBC.

RBC turnover is abnormal in CKD (even if the patient is on EPO).

- In dialysis, RBC are damaged, this leads to a shortened RBC span. This leads to a falsely low HbA1c.
- Treatment with iron/EPO leads to increased RBC production and can falsely lower HbA1c.
- Iron deficiency is associated with higher HbA1c as it reduces RBC turnover.

HbA1c does not reflect glycaemic variability.

There is inadequate data on the use of alternative glycated proteins such as glycated albumin or fructosamine (haemoglobin and albumin). Fructosamine estimates glycated control over 14 days. Its value should be corrected for serum albumin. Glycated albumin is affected by conditions that affect serum albumin e.g. nephrotic syndrome or malnutrition. In small studies, GA is superior to HbA1c.

Diagnosis

In type 1 DM, there is usually diabetic nephropathy. This is thickening of the basement membrane, mesangial expansion, Kimmelstiel Wilson nodules and podocyte change and loss.

Classic DN is a clinical diagnosis. There is increased urine albumin, reduced GFR and usually HTN and diabetic retinopathy.

Excessive albuminuria or proteinuria suggests an underlying glomerular disease.

In type 2 DM, different aetiologies contribute to kidney disease such as ageing, HTN and obesity.

Renal referral

Rapidly declining renal function
> 25% and change in eGFR category or
> 15 % within 12 months

KFRE

5-year risk of kidney failure > 5 % refer to specialist

Five finger rule

BMJ 2024 study in Sweden – underuse of statins, RAASi, SGLT2i

Therapeutic inertia -failure to advance therapy and failure to de-intensify therapy

1. **Glucose control**
    a. DM-1 DCCT and EDIC (improved glycaemic control leads to a reduction in retinopathy and nephropathy)
    b. DM-2 UKPDS, ADVANCE ON (reduced retinopathy, nephropathy, and neuropathy). Meta-analysis- shows reduced microvascular complications with intense therapy.
2. **BP control**
    a. 140/90 at least
    b. 130/80 if proteinuria
    c. BP < 125/75 increases the risk of adverse events and is not recommended

    SPRINT trial excluded people with DM but showed a clear benefit with a lower target systolic BP.

    ACCORD was primarily a glycaemic trial but had a BP and lipid arm. The Primary outcome was MACE (CV death, non-fatal MI and non-fatal stroke). There was no improvement with intensive treatment.
3. **ACEi/ARB**
    a. Reduces constrictions in efferent arterioles → reduced pressure in glomerulus
    b. ARBs maybe have fewer side effects
    c. If A2/3 albuminuria should be offered regardless of BP
4. **Stop smoking**
5. **Lipid lowering**

Aspirin for existing CVD. Uncertainty for primary prevention, no studies show benefit.

Steno 2 – started in 1992 – multifactorial intervention – glucose, BP, lipids – 50 % RRR in nephropathy progression and increased lifespan by 8 years with multiple risk factor reduction.

Lifestyle intervention

Type 2 DM is caused by excess fat in the liver and pancreas in genetically susceptible individuals.

Twin cycle hypothesis – excess liver fat is transported via VLDL to the pancreas – excess pancreatic fat leads to beta cell dysfunction.

Counterpoint study 2011 – 800 kcal/day – reduced liver fat – normalises glucose
Counterbalance study – longer – 6 months
DIRECT study – primary care nurses

They found that responders and non-responders differed by the duration of diabetes.
If you lose 15 kg weight you have a 70 % chance of going into remission.

Personal fat threshold.

Kings staging criteria – complications of obesity or Edmonton

A airway – OSA, oximetry
B BMI
C cardiovascular
D DM
E economic – can they work – return to work
F Flight of stairs
G gonadal – sexual health
H- how is their mental health – screen for anxiety and binge eating
I – body image, hair low effects, skin fold effects – e.g. no mirrors,
J – junction – reflux
K – kidneys
L – liver NAFLD

GLP-1

Incretin hormones were discovered 100 years ago
GLP-1 has been in use for diabetes for 20 years (since 2006) and for obesity for 10 years.

GLP-1 has no effect on insulin or glucagon secretion when glucose is in the normal range.

Should GLP-1 be used for Type 1 DM? Beneficial for overweight and obesity and possibly for heart and kidney patients.

LEADER and Sustain demonstrate renoprotective effects of GLP-1

GLP-1 reduce inflammation and increase plaque stability in arteries (due to effect on macrophages).
GLP-1 receptors in the juxtaglomerular apparatus,
GLP-1 suppresses Na-H exchange and leads to natriuresis
GLP-1 can also reduce TG

Semaglutide has the greatest impact on weight 5 to 6 kg

SGLT2 inhibitors

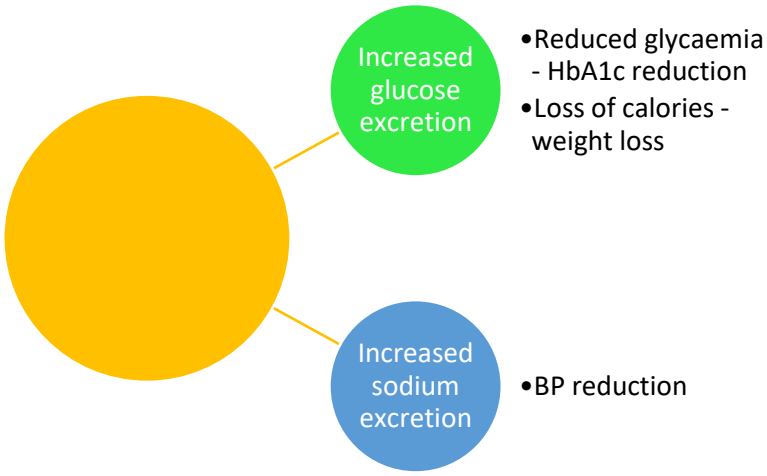
Everyone has a threshold of renal tubular glucose concentration above which glucose appears in the urine.

SGLT2i block 90 % of glucose absorption
SGLT1i block 10 % of glucose absorption

When these are blocked you get glucose loss in the urine.

- 100g/day glucose loss
- 400 calories/day loss
- 4 kg weight loss
- 5 mm Hg loss in systolic BP
- HbA1c reduces by 1 %

SGLT2i block sodium reabsorption in the proximal convoluted tubule so more sodium is delivered to the macula densa in the distal tubule. This causes afferent arteriole constriction and normalises GFR.



Canagliflozin was launched in 2013
Empa and dapa launched in 2014

EMPA-REG
CANVAS
DECLARE TIMI

In the kidney outcome trials, SGLT2i was continued until the initiation of kidney replacement therapy (dialysis or transplant) providing indirect evidence for eGFR < 20.
Licences do not encourage initiation below 25 but you can continue beyond this even up to dialysis if passing good volumes of urine, e.g. peritoneal dialysis. There is no mandate to stop them. There is no evidence that the benefits of SGLT2i attenuate in lower eGFR. There is no evidence for an eGFR threshold below which kidney benefits attenuate, down to stage 5 kidney disease.
There is currently insufficient evidence to make recommendations on SGLT2i in people receiving maintenance dialysis.

The effect of SGLT2i on kidneys and heart is likely to be a class effect.
Recommend single agent RAASi with SGLT2i.

When eGFR is < 30, SGLT2i do not affect glucose excretion so will not influence HbA1c.
If the eGFR is > 30 and on insulin reduce this by 20 %, if on gliclazide, reduce this by 50 %.

Kidney outcomes

1. > 50 % decline in eGFR from randomization
2. Kidney failure
3. Death from kidney failure

SGLT2i actually reduce the risk of AKI

Kidney transplant

There is an increased risk of graft loss with ascending UTIs and genital mycotic infections

CREDENCE

4400 people
All with type 2 diabetes
All on ACEi/ARB
Urine ACR 30-500 mg/mmol and eGFR 30-90
eGFR 30 lowest
All patients have albuminuria
Reduced risk of progression to ESKD by 30 %

DAPA-CKD

4300 patients
eGFR 25-75 and urine ACR 20-500 mg/mmol
Patients with and without DM
All patients have albuminuria
40 % RRR in renal outcome

EMPA-KIDNEY

eGFR down to 20
Included patients without albuminuria
Within and without DM and some Type 1 DM
28 % RRR

The effect on primary outcome was larger in people with a higher baseline urine ACR. People without albuminuria were at substantially lower risk of the primary outcome.

Finerenone

3rd generation
Bulky inverse agonist
Mineralocorticoid receptor
Equally distributed between heart and kidney

TABLE 1. Differences Among Spironolactone, Eplerenone, and Finerenone

	Spironolactone	Eplerenone	Finerenone
Structural aspects	Flat (steroidal)[66]		Bulky, passive antagonist (nonsteroidal)[59,66]
MRA structure	Steroidal	Steroidal	Nonsteroidal
Metabolites	Multiple, active metabolites[48]	No active metabolites[48]	No active metabolites[57]
Half-life	Spironolactone: <2 hours Active metabolites: >12-24 hours[48,50]	4 hours[55]	2-3 hours[57,58]
Tissue distribution	Heart < kidney[51]	Heart < kidney[51]	Heart ≈ kidney[61]
Affinity to MR	Finerenone > spironolactone >> eplerenone[54,56]		
Affinity to AR, GR, and PR	Spironolactone >> eplerenone ≈ finerenone[54]		
Inhibitory effect on aldosterone-dependent gene activation	Finerenone > spironolactone[60]		
Sexual side effects	Observed[51-53]	Low frequency[67]	Not observed or rare[64,65]
Effect on SBP	Spironolactone > finerenone[49] Spironolactone > eplerenone[68] Eplerenone ≈ finerenone[62]		
Effect on inflammation and fibrosis in animals	Eplerenone < finerenone[61,63]		
Risk of hyperkalemia	Eplerenone ≈ finerenone[62] Spironolactone > finerenone[49]		

AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; PR, progesterone receptor; SBP, systolic blood pressure.

FIDELIO DKD and FIGARO DKD are complementary studies in patients with type 2 diabetes and CKD. The studies had overlapping populations.

FIDELITY – combined data from FIDELIO and FIGARO and showed that finerenone reduced both cardiovascular and renal outcomes when added to maximally tolerated RAASi.

RRR

- Endpoint cardiovascular composite 14 %
- HHF 22 %
- Kidney composite 23 %
- Dialysis 20 %

FIDELIO- DKD

Composite end point –
time to onset of kidney failure ESKD,
sustained decrease of eGFR > 40 % from baseline,
renal death
CKD 3-4 with moderate or severe albuminuria

eGFR 25-60 with urine ACR of 3-30 mg/mmol or eGFR 25-75 with urine ACR 30-500 mg/mmol

FIGARO- DKD

Composite endpoint
Time to CVD death
Nonfatal MI
Nonfatal stroke
Hospitalization for heart failure

CKD stage 2-4 with urine ACR 3 to 30 mg/mmol or CKD 1-2 with urine ACR 30 to 500 mg/mmol

Hyperkalaemia

Mild K^+	5.5 to 5.9	Recheck in 3 days
Moderate	6 to 6.4	Recheck in 1 day
Severe	≥ 6.5	Admit

5 step approach

1. Protect the heart – assess risk of arrhythmia
2. Shift K^+
3. Remove K^+
4. Monitor K^+ and glucose
5. Prevent reoccurrence

3 tier approach

1. Correct correctable factors
    a. Optimise bicarb, glucose
    b. Consider loop diuretics, SGLT2i
    c. Treat constipation, this reduces K excretion in the gut.
        i. Lactulose is an osmotic laxative
        ii. AVOID Macrogol (laxido or movicol) as they contain potassium
2. Diet
    a. In persistent hyperK (> 5.5), dietary restriction < 3 g daily is recommended
3. Adjuncts
    a. Adjust K elevating drugs
    b. Initiate K binders

RAASi

Check U&E prior to starting
Use with caution if K^+ > 5 mmol/L
Monitor U&E 1-2 weeks after starting
Stop in patients with K^+ > 6 who don't meet criteria for patiromer or lokelma (NICE)
Stop RAASi if Cr increases > 30 % (NICE)

Lokelma is an option for adults to manage persistent hyperK ≥ 6 in CKD stage 3b to 5 (not on dialysis) or heart failure receiving suboptimal RAASi.

MRA

If K^+ 5.5 to 5.9 halve the MRA and monitor
If K^+ > 6 start K binder

Finerenone can be used in T2 DM with eGFR > 25, urine ACR > 3 mg/mmol and normal K^+.

Calcium

Give IV calcium to patients with life-threatening ECG changes (absent P waves, wide QRS, sine wave pattern, arrhythmia, and cardiac arrest, also isolated tented T waves as these are early indicators).

Do not give in moderate hyperK^+ without ECG changes.

IV calcium antagonises the cardiac membrane excitability provoked by excess K.
It is effective within 5 minutes.
Duration of action is 30-60 minutes.
10 ml 10 % calcium chloride over 5 minutes RESUS
30 ml 10 % calcium gluconate over 10 minutes – ALL OTHER PATIENTS

Insulin

Following insulin, K^+ falls within 15 minutes, it is sustained at 2 hours, then rebounds.

Give 10 units insulin in 25 g glucose (this can be 50 ml of 50%, 125 ml of 20 % or 250 ml of 10 %).
This should be administered over 5-15 minutes into a large vein.

Then 10 % glucose at 50 ml/hour for 5 hours (i.e. 10 % 250 ml which is 25 g)
Recheck BG at 30-minute intervals for the first 2 hours then hourly intervals for the next 4 hours – so 6 hours in total.

Salbutamol

B2 receptor agonist → stimulates Na^+ K^+ ATP pump
10 mg salbutamol nebuliser
Onset of action within 30 minutes
Peak effect seen at 120 minutes
Variable degree of K^+ lowering

Sodium bicarbonate

Use in CKD patients with bicarb < 22

Metabolic acidosis is present in 20 % of people with CKD stage 3-5.
It is associated with muscle wasting, bone disease, hyperK and rapid progression of CKD
Systemic review (2022) no benefit of bicarb replacement
Risk of worsening HTN and oedema

Sodium zirconium cyclosilicate (lokelma)

A non-absorbed K binder that exchanges Na^+ and H^+ for K^+ and ammonia
Unlike patiromer does not affect magnesium levels.
Adverse effects include oedema, heart failure, HTN, hypoK
The onset of action is within 1 hour of ingestion and the median time to normalisation is 2.2 hours.

10 mg TDS for maximum 72 hours if $K^+ > 6.5$, consider if K^+ 6 to 6.4 mmol/L
If normalisation of potassium does not occur by 72 hours, the lokelma should be discontinued.
After this, the maintenance dose is 5 mg daily. This can be increased to 10 mg daily or reduced to 5 mg on alternate days.
It complements rather than replaces a low K diet.

The duration of treatment in practice is lifelong unless RAASi is discontinued.

Patiromer

Non absorbed, sodium free K^+ binding polymer
Calcium is used, rather than sodium, as the counter ion for K^+ exchange. This avoids the potential for excessive sodium absorption and volume overload.
It can also bind oral medications – metformin, thyroxine, ciprofloxacin and needs to be separated from these medications by 3 hours.

The onset of action is slower than lokelma, it is 4-7 hours. So it is not too useful in the acute setting.

Starting dose is 8.4 g and the maximum dose is 25.2 g.

Can be used if heart failure or CKD stage 3b to 5 (not on dialysis) and $K^+ \geq 6$ mmol/L and suboptimal RAASi.

A rebound in K^+ occurs when the patiromer is stopped.

Calcium resonium is no longer given

Dialysis is a definitive treatment for hyperK.

It removes around 100 mmol of K.
You still need IV calcium to protect from arrhythmias.

Hypoglycaemia

Increased risk in DKD

50 % of insulin secreted by the pancreas is extracted by the liver and the majority of the rest is excreted via the kidney so patients with renal impairment have more insulin circulating in their blood.

During fasting, 30 % of gluconeogenesis comes from the kidneys.

BG 3.8	Counter-regulatory hormones glucagon, adrenaline
BG 3.2 to 2.8	Symptoms – autonomic and neuroglycopaenic.
BG 2.8	Cognitive dysfunction, inability to complete tasks
BG < 1.5	Reduced GCS, convulsions, coma

Take 15 g of carbs and recheck after 15 minutes

Mild	**Moderate**	**Severe**
15 g and recheck in 15 minutes Repeat x 3	15 g and recheck in 15 minutes Repeat x 3	15 g and recheck in 15 minutes Repeat x 3
5 tablets of dextrosol Lift glucotabs	2 tubes of 40 % glucogel	100 ml of 20 % dextrose 200 ml of 10 % dextrose 1 mg IM glucagon

When glucose > 4 give 20 g of long-acting carbohydrate

Do not omit insulin if due. The insulin that is about to be given is unlikely to be the insulin dose that was active at the time.

STOP ACE

411 patients with advanced CKD, eGFR < 30 (median 18) at baseline were randomized to continue RAASi or stop. They were followed up 3 monthly for 3 years. The primary outcome was eGFR at 3 years.

At the end of the 3 years,
Continuation group eGFR was 13.3, ESKD/RRT 56 %
Discontinuation group eGFR was 12.6, ESKD/RRT 62 %

i.e. no significant difference between groups.
Adverse events were the same in both groups.

Glycaemic control on dialysis guideline

Glycaemic targets

There is a U-shaped curve for glycaemic control with the lowest mortality seen in people with HbA1c 53-63 mmol/mol. If HbA1c is > 69 there is a 30 % increase in mortality.

Aim for BG 6-12.

TIR - > 50%
Hypos < 1 %
Significant hyperglycaemia (BG > 13.9) < 10 %

Burnt out diabetes is a phenomenon where individuals with diabetes experience frequent hypos leading to temporary or permanent cessation of anti-diabetic medications. This does not occur in type 1 diabetes.

Dialysis and clearance of drugs

Dialysis clears both insulin and glucagon (endogenous and exogenous)

Dialysis can cause periodic improvements in uraemia/acidosis/hyperphosphataemia which leads to improved insulin secretion and reduced insulin resistance.

Oral agents in dialysis

Metformin, sulphonylureas, SGLT2i are not licenced for dialysis.
DPPIVi and pioglitazone are licenced for dialysis.

Sulphonylureas are metabolised by hepatic cytochrome P450 and the kidney. They accumulate in renal failure.
They are generally highly protein bound so unlikely to be dialysed and can cause post-dialysis hypoglycaemia.
They are not licenced when eGFR if < 30.

GLP-1 is licenced to 15.
Liraglutide – BNF – avoid if ESRF
Saxenda – BNF avoid if eGFR < 30
Semaglutide avoid if ESRF

Insulin

Insulin is partly metabolised in the kidney so progressive renal failure means that there is a decreased insulin requirement.
Insulin requirement falls by 50 % when the eGFR is < 10.

Reduce by 25% on dialysis days.

Euglycaemic clamp studies on HDx indicate that there is a 25 % reduction in basal insulin requirement following HDx. So reduce insulin 25% on dialysis days.

Hypoglycaemia on dialysis

During dialysis, glucose falls. The nadir is at hour 3. You can give 10-20 g of low GI carbohydrate at hour 2 to prevent hypos.

Assess BG pre and post dialysis
If BG is < 7 pre-dialysis, give 20-30 g of low GI carbohydrate.

If someone has a hypo, give 15 g of rapid acting carbohydrate, recheck BG after 15 minutes and recheck if necessary. Follow this with 10-20 g of complex carbs.

Individuals who have a large amount of food on dialysis have a risk of hypotension during hours 3-4, as blood flow is diverted to the gut.

Peritoneal dialysis

Continuous ambulatory peritoneal dialysis – 3 day exchanges and a longer night exchange
Automated PD – multiple shorter night exchanges and a longer day exchange

PD fluid can be glucose, icodextrin or amino acids.
Glucose is the most commonly used. The others can only be used 1-2 x in a day and maybe aren't as osmotic.

Glucose based dialysates may lead to systemic glucose absorption. Increased insulin is needed to counter this.
Non glucose containing dialysates were associated with improvements in glycaemic control.
There is also more potential for CGM interference in PD.

Islet cell transplant

1. Isolate islets from pancreas – collagenase digestion
2. Purify
3. Transplant into liver – islets embolize into small portal branches of the liver

2000 Edmonton Group protocol.

After 5 years only a minority of patients were insulin free. In the best centres 50 % at five years.

Pancreas transplant

1966 – the first pancreas transplant in the USA

Simultaneous pancreas kidney transplant has better survival compared to pancreas after kidney. This is because there the creatinine can be used to mirror monitoring of the pancreas.
Solitary pancreas transplants are more difficult to monitor and carry a higher risk of immunological rejection.

SPK – insulin dependence is better than islets – 80-90 % at five years.

Risk of early graft rejection in 8 %, i.e. having to take out the pancreas in the first week.

DKA

Absolute or relative insulin deficiency.
Leads to an increase in counter regulatory hormones

1. Increased gluconeogenic enzymes (liver and skeletal muscle) which leads to
    a. Increased gluconeogenesis
    b. Increased glycogenolysis
    c. Reduced glucose utilisation

    This all leads to hyperglycaemia and osmotic diuresis
2. Increased hormone sensitive lipase
    a. Increased FFA (from adipose tissue) to the liver
    b. Increased ketogenesis and Acidosis (FFA are substrates for the production of ketone bodies)

Anion gap (Na +K) – (bicarb + Cl) NORMAL is 8-16

Deficiencies in DKA

100 ml/kg	water
10 mmol/kg	Na
3-5 mmol/kg	Cl
3-5 mmol/kg	K

Resolution

Ketones reduce 0.5 mmol/hour
Bicarb increases 3 mmol/L/hour
Glucose increases 3 mmol/L/hour

Continue until pH 7.3 and ketone < 0.6

Add 10 % glucose at 125 ml/hour if BG < 14

DKA is less common in renal failure because

1. There is reduced renal gluconeogenesis
2. Reduced insulin clearance
3. No osmotic diuresis in oliguric/anuric patients – thus protecting them from dehydration

Check ketones if BG > 15 in type 1 (or if BG > 15 on two occasions 1 hour apart in type 2)

If there is a delay in moving the patient to e.g. ED or a ward, give them sc insulin at a dose of 0.05/kg.

In ESRF, give 250 ml aliquots of normal saline as needed for hypovolaemia
FRII 0.1 units/kg/hour

CGM

When you use CGM, you see more hypoglycaemia than before. Sensors tend to over-report hypoglycaemia.
A real hypo is defined with the added dimension of time.
Sensor glucose < 3 for at least 15 minutes.
The event ends when the BG is > 3 for 15 more minutes
Prolonged hypoglycaemia is when the BG is < 3 for 120 minutes.

Predicted hypo alert – recommend if BG < 6 and ↓ - take 5 to 10 g of carbohydrate and recheck in 10 minutes.
↑ arrow straight up means BG increases by 1 mmol in 7 minutes
↗ arrow half up means BG increases by 1 mmol in 15 minutes
↓ arrow down means BG decreases 1 mmol in 7 minutes
↘ arrow half down means BG decreases 1 mmol in 15 minutes

If you have an arrow half up ↗ before your bolus, you can take 10-20 % more
If you have an arrow half down ↘ before your bolus you can take 10-20 % less.

The rate of rise alert can be used as a missed bolus alert.

The 1 hour glucose tells you if you bolus pre-meal was early enough.
The 2 hour glucose tells you if you took enough insulin
The 3 hour glucose – if still high – could mean presence of fat/protein in meal (or could be stress).

Hybrid closed loop (HCL) Medtronic mini med 670G – regulates to a fixed glucose level. It is not fully automated and needs to be calibrated.

Lipids (ABCD UKKA guideline)

Introduction

People with diabetes and chronic kidney disease (CKD) are at increased risk of developing cardiovascular disease (CVD). Lipids are a modifiable risk factor and good lipid management offers improved outcomes for people with diabetic kidney disease (DKD).

Lipid management should be considered alongside lifestyle measures and management of blood pressure, weight, glycaemia, smoking cessation, and thrombotic risk. Attention should also be paid to the newer pillars of care for those with DKD, including sodium glucose co-transporter 2 inhibitors and non-steroidal selective mineralocorticoid receptor antagonists. These other aspects of DKD management are addressed in the Joint Association of British Clinical Diabetologists (ABCD) and UK Kidney Association (UKKA) guidelines.[1,2]

The primary purpose of this guideline is to provide practical recommendations on lipid management for members of the multidisciplinary team involved in the care of adults with DKD. This guideline covers: what to measure, frequency of monitoring, who to treat, treatment targets, what to use and, when to stop treatment.

Recommendations for lipid measurement and frequency of monitoring

There is clear evidence relating LDL cholesterol levels to atherosclerotic CVD (ASCVD) risk and evidence with regard to reducing LDL cholesterol levels and reducing ASCVD risk.[3,4] There is also a relative risk attributable to non-HDL cholesterol (calculated as TC minus HDL cholesterol). A meta-analysis of people treated with statins suggested that non–HDL cholesterol may be a better predictor of coronary artery disease (CAD) risk than LDL cholesterol, possibly reflecting the additional impact of larger, atherogenic, TG rich molecules and the loss of benefit of higher HDL cholesterol levels.[5]

In the past, fasting lipid profiles were recommended. However, obtaining fasting samples can be problematic and inconvenient, leading to delays in medication and disruption of glycaemic control. Large population studies show that there are only minor differences between fasting and non-fasting LDL and TG levels. In addition, non-fasting lipid levels correlate well with cardiovascular outcomes. National UK lipid guidelines (NICE) and European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines also advocate the measurement of a non-fasting lipid profile.

Kidney transplant recipients have a high prevalence of dyslipidaemia. Immunosuppressive therapy, specifically corticosteroids, ciclosporin, sirolimus and everolimus, contributes to this.[6] Lipid assessment should be performed once immunosuppressive drug dosing is stable and the risk of acute rejection requiring corticosteroids has fallen. This is likely to be achieved 3 months post transplantation at the earliest.

People on dialysis represent a diverse group. Within this group, there are people who are continued on lipid-lowering agents and others where this is inappropriate. In addition, some people on dialysis will progress to receive a kidney transplant. Where is it of benefit, i.e. where it would change management, annual screening can be continued within this group.

There is marked variation between current guidelines regarding monitoring lipid profiles in DKD. We feel that annual screening is a reasonable approach. It is also acceptable to monitor more frequently if this influences management.

We recommend that a non-fasting full lipid profile (TC, non-HDL, HDL, LDL cholesterol and TG) is performed at least annually in stage G1-5 DKD, including post kidney transplantation and, where appropriate, in dialysis, stage G5d.

LDL cholesterol is calculated (using the Friedewald formula) and requires a fasting sample if TG levels are >4.5 mmol/L. In hypertriglyceridaemia (>4.5 mmol/L), we recommend measuring fasting profiles (Grade 1B).

We suggest review of the lipid profile on commencement or change of modality of renal replacement therapy (dialysis or kidney transplantation) (Grade 2D).

Following kidney transplantation, we suggest that lipid status be assessed once the immediate post-operative period has passed (typically 3 months post transplantation) (Grade 2D).

Recommendations for lipid management in type 1 diabetes

Outcome studies of lipid lowering in people with type 1 diabetes and DKD are lacking. However, younger people with type 1 diabetes and persistent albuminuria have a substantially elevated lifetime CVD risk and this would be the basis for statin initiation. The principle of identifying exaggerated lifetime risk beyond the initial decade of treatment was clearly outlined in the Joint British Societies (JBS) 3 guidelines.[7] While the absolute risk for young people (aged 18 to 30 years) with DKD may be low, there is a high relative risk. There is no evidence base to support initiation of statins in type 1 diabetes aged < 18 years, or in newly diagnosed type 1 diabetes aged ≤ 30 years without any additional risk factors.

Where trials of people with type 1 diabetes and DKD are lacking, it is reasonable to extrapolate general population data and use CKD stage **(Figure 2)** as a CVD risk equivalent. In CKD stages G3–5, the elevated risk of CVD justifies the initiation of lipid-lowering agents, notwithstanding the additional impact of type 1 diabetes in elevating this risk.

Where the question arises whether or not to start those on dialysis, CKD stage G5d, on lipid-lowering agents, consideration should be placed on the likelihood of transplantation, life expectancy and the risk benefit ratio. In most cases, we do not recommend initiating lipid-lowering therapy in those on dialysis.

GFR category	eGFR (ml/min/1.73m^2)
G1	≥ 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	< 15
Albuminuria category	**Albumin to creatinine ratio (ACR) mg/mmol**
A1	< 3
A2	3-30
A3	> 30

Figure 2 Nomenture and categories of estimated glomerular filtration rates (eGFRs) and albuminuria. Adapted from KDIGO. [8]

We suggest that in type 1 diabetes and stage G1–2 DKD, lipid-lowering therapy is commenced in the following categories:

- **People aged >30 years with persistent albuminuria, category A2-3 (Grade 2D).**
- **People aged between 18 to 30 years with persistent albuminuria, category A2-3, and ≥1 additional CVD risk factor (Grade 2D).**

We recommend that in type 1 diabetes and stage G3–5 DKD, regardless of albuminuric status, lipid-lowering therapy is commenced (Grade 1C).

In people with type 1 diabetes on dialysis, stage G5d DKD, we do not recommend initiation of lipid lowering therapy. However, we suggest that in certain cases, e.g. in those where transplantation is a likely outcome and where dialysis is temporary, initiation might be beneficial and may be considered (Grade 2D).

Recommendations for lipid management in type 2 diabetes

Until relatively recently, type 2 diabetes has been considered a CVD risk equivalent. It is now clear that diabetes per se is not a CVD risk equivalent.[9] Rather, certain characteristics are required to escalate CVD risk, most notably longer duration of diabetes and/ or the presence of albuminuria.[10-12] In addition, CKD, based on reduced GFR, also enhances CVD risk.[9,12] Thus, the combination of type 2 diabetes with albuminuria, stage G3 CKD or higher substantially increases the risk of CVD.[9]

There have been several large-scale prospective CVD outcome studies involving people with type 2 diabetes and CKD. The Cholesterol Treatment Trialists' (CTT) Collaboration database, established in 1994, includes individual participant data from statin trials with at least 1,000 participants with ≥2 years of follow up. In the 2008 CTT meta-analysis of outcomes in over 18,000 people with diabetes from 14 randomised trials of statin therapy, a 1 mmol/L reduction in LDL cholesterol reduced the combined endpoint of CHD death and non-fatal MI by 22 %, CVD events by 21 %, vascular death by 13 % and all-cause death by 9 %. Coronary revascularisation was reduced by 25 % and stroke by 21 %.[4]

A further CTT meta-analysis (2016) of data from 28 trials (n=183,419; 35,781 with diabetes), confirmed that statins reduce the risk of a first major vascular event by 21 % per mmol/L reduction in LDL cholesterol.[13] The CTT looked at risk ratios in sub-divisions of participants stratified by eGFR (≥60, 45–

<60, 30–<45, <30 and dialysis). Smaller effects were seen as eGFR declined with little evidence of benefit seen in dialysis.[13]

These meta-analyses demonstrate the efficacy of statins as primary prevention. There is limited data in young people with type 2 diabetes. However, considering the elevated lifetime risk within this cohort, we have suggested that this younger cohort receives treatment.

We recommend that in people with type 2 diabetes with stage G1–2 DKD, lipid-lowering therapy is commenced in the following categories:
- People aged >30 years with persistent albuminuria, category A2-3 (Grade 1C)
- People aged between 18 to 30 years with persistent albuminuria, category A2-3, and ≥1 additional CVD risk factor (Grade 1D)

We recommend that lipid-lowering therapy with statins should be considered in people with stage G3–5 DKD regardless of albuminuric status (Grade 1B).

In people with type 2 diabetes on dialysis, stage G5d DKD, we do not recommend initiation of lipid lowering therapy. However, we suggest that in certain cases, e.g. in those where transplantation is a likely outcome, initiation might be beneficial and may be considered (Grade 2D).

Recommendations for lipid management in ESKD and dialysis

People with ESKD are at dramatically increased risk of premature CVD, 5–20 times that of the general population. However, the relationship between cholesterol and CVD risk is not clear and there is a 'J' shaped relationship between cholesterol and mortality, possibly driven by malnutrition or inflammation being associated with lower serum cholesterol levels.

Commencement of renal replacement therapy (dialysis or transplantation) for ESKD is associated with the need for major lifestyle changes including dietary and fluid restrictions, hospital attendance and medication. For some, continuation of lipid-lowering therapy may be inappropriate.

As discussed earlier, the 2016 CTT meta-analysis confirmed that overall, statins reduce the risk of a first major vascular event; however, smaller effects were seen as eGFR declined with little evidence of benefit seen in dialysis.[13] It is not clear if the reduced efficacy of statins in ESKD is due to the reduced proportion of people with atherosclerotic coronary heart disease or, due to a misclassification of deaths partly based on the difficult of interpreting raised troponins in this group.[13]

Although clear evidence of benefit has not been demonstrated in trials of lipid-lowering therapy in people with diabetes on dialysis, currently, there are no convincing data to suggest harm in using lipid-lowering therapy. Many physicians continue lipid-lowering therapy in people on dialysis. However, it is uncommon for lipid-lowering therapy to be initiated in this group.

Recommendations for lipid management post-transplantation

The Assessment of LEscol in Renal Transplantation (ALERT) study showed that long-term treatment (5–6 years) with fluvastatin (40 - 80 mg/day) non-significantly reduced the risk of coronary death or non-fatal MI, compared with placebo in ciclosporin treated kidney transplant recipients.[14] In the 2-year extension trial, fluvastatin led to a significant 35 % relative reduction in the risk of cardiac death or non-fatal MI.[15]

A Cochrane review looking at 22 studies in kidney transplant recipients found that statins may reduce major adverse cardiovascular events.[16] The adverse effect of statins, including on liver enzymes and creatine kinase, was uncertain.[16]

Most statins are metabolised by the cytochrome P450 microsomal enzyme system. Concurrent therapy with inhibitors of this system, such as ciclosporin or tacrolimus, can lead to greater statin exposure and higher risk of side effects, such as rhabdomyolysis.[17] This risk appears to be greatest with simvastatin and lowest with fluvastatin or pravastatin.

Ezetimibe appears to be safe in kidney transplant recipients. It has been reported to interfere with ciclosporin levels; however, more recent reports suggest that this is unlikely to be a major clinical problem.[18]

Fibrates have a high risk of side effects and are generally best avoided in kidney transplant recipients.

Post-transplant diabetes mellitus and lipid lowering

Post-transplant diabetes mellitus (PTDM) affects 7–25 % of people following kidney transplantation.[19] Conventional risk factors include age, obesity, and ethnicity. Transplant-related risk factors include corticosteroids, calcineurin inhibitors and acute rejection. There are no studies to guide lipid management in PTDM and, in the absence of specific evidence, it seems reasonable to use conventional lipid-lowering agents in combination with dietary and lifestyle advice to achieve lipid targets.

Combined kidney pancreas transplant and lipid lowering

For people with type 1 diabetes and advanced DKD, simultaneous pancreas kidney transplantation (SPK) or pancreas after kidney transplantation (PAK) allows people to become insulin independent and has been shown to improve multiple markers of CVD.[20] All those being considered for SPK or PAK will have had prior indication for lipid-lowering therapy due to a cumulative lifetime risk of CVD. Therefore, unless there is an indication for discontinuation of lipid-lowering therapy, it would seem sensible to continue treatment of dyslipidaemia in this group.

We suggest that lipid-lowering agents be continued in those commencing dialysis, (Grade 2D).

We suggest that the decision to commence lipid-lowering agents de novo in those requiring dialysis (haemodialysis or peritoneal) should take into account risk of future atherosclerotic vascular events, life expectancy and, other comorbid disease (Grade 2D).

Where indicated, we recommend that lipid-lowering agents should be commenced post kidney transplantation or combined kidney-pancreas transplantation and that the choice and dose of lipid-lowering agent should take into account concurrent immunosuppressive therapy (Grade 1C).

Where indicated, we suggest that people who develop post-transplant diabetes mellitus are treated with lipid-lowering agents (Grade 2D).

Recommendations for treatment targets

The 2010 CTT meta-analysis demonstrated that larger reductions in LDL cholesterol led to further reductions in major vascular events.[3] A lower LDL cholesterol (≤ 1.8 mmol/ L) was associated with a further 15 % reduction in major vascular events.[3] There was no evidence of a threshold LDL cholesterol level or evidence of adverse effects with more intensive therapy.

We suggest the following treatment targets
- TC ≤ 4.0 mmol/L
- non-HDL cholesterol ≤ 2.5 mmol/L
- LDL cholesterol ≤ 1.8 mmol/L (Grade 2D)

We have not suggested a percentage reduction for pragmatic reasons. Similarly, we have not suggested a graded approach to therapy with respect to risk stratification as we consider all those with diabetes (type 1 or 2) and DKD to be at high risk for CVD.

Choice of lipid-lowering agent

Role for statins

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and are the lipid modifying agent of choice for people with diabetes. Simvastatin is associated with a number of side effects and drug interactions with other agents (such as diltiazem and amlodipine). Thus, atorvastatin 20 mg is suggested as the first line lipid-lowering agent. Dose titration up to a maximum dose of 80 mg should be done with care, especially at lower eGFR < 30 mL/minute/1.73 m^2.

Rosuvastatin is a high intensity statin. In CKD stage 1-2, there is no dose adjustment. In CKD stage 3 or below, the starting dose is 5 mg. The US Food and Drug Administration (FDA) advises that the maximum dose below eGFR < 30 mL/minute/1.73 m^2 is 10 mg. However, European and SPC guidance is to avoid rosuvastatin at eGFR < 30 mL/minute/1.73 m^2.

Where statin intolerance is an issue, consider switching to an alternate statin, reducing the dose or, alternate day dosage.

Role for ezetimibe

Ezetimibe blocks the intestinal absorption of cholesterol and upregulates hepatic LDL receptor expression, enabling reduction of atherogenic lipoproteins.[21] The main role for ezetimibe in DKD is as an adjunctive to statin use, or in statin intolerance. Ezetimibe can be used in mild to severe kidney disease and co-administered with any dose of statin.

Role for Bempedoic acid

Bempedoic acid is a once daily, oral medication used at a dose of 180 mg. It is a prodrug converted to bempedoyl-CoA by very-long-chain acyl-CoA synthetase-1, an enzyme present within the liver but absent in skeletal muscle, thus eliciting a liver specific action.[22] The active substrate, bempedoyl Co-A, inhibits ATP citrate lyase, an enzyme up stream of HMG-CoA reductase, thus suppressing cholesterol synthesis. This leads to increased membrane LDL receptors and LDL cholesterol clearance.[22] Elimination is mainly through renal, 70 %, and hepatic clearance, 30 %. Bempedoic acid has not been studied below eGFR 30 mL/min/1.73 m^2.

NICE recommends Bempedoic acid for people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed lipidaemia where statins are contraindicated or not tolerated and where ezetimibe alone is insufficient.[26] It is currently not recommended by NICE to be added where maximal statin therapy is insufficient.[26]

Role for fibrates

Fibrates, peroxisome proliferator-activated receptor-α (PPAR-α) agonists, lower TG levels and TG rich particles. It has been proposed that TG rich particles participate in atherosclerosis. While CM and VLDL are too large to penetrate the arterial intima, the remnant particles are able to penetrate the intima and appear to reside for a longer period in the sub-intimal space. Thus, it would be reasonable to hypothesise that reducing TG levels would improve CVD risk.

Whilst there is no clear increase in progression to ESKD with fibrates, the reversible rise in creatinine which is reported consistently may in practice offset any perceived short-term advantage on albuminuria reduction. Addition of fibrates might be best restricted to younger people with fewer advanced complications and preserved GFR.[27,28] Lower doses of fibrates, including fenofibrate and gemfibrozil, are recommended below eGFR 60 ml/min/1.73 m^2. Fibrates should be withdrawn if eGFR falls below 30 ml/min/1.73 m^2.

Role for PCSK9 inhibitors

Proprotein convertase subtilisin-kexin type 9 (PCSK9) is an endogenous hepatic LDL receptor ligand. Binding of PCSK9 to the LDL receptor leads to receptor degradation which prevents LDL receptor recycling. This leads to an increase in LDL.

PCSK9 monoclonal antibodies are administered by subcutaneous injection fortnightly or monthly. Inhibition of the binding of PCSK9 to the LDL receptor reduces LDL receptor degradation, and leads to significant reductions in LDL cholesterol.

Two PCSK9 inhibitors, alirocumab and evolocumab, have been approved by the European Medicines Agency (EMA) and FDA. Both drugs reduce LDL and non-HDL cholesterol in people with diabetes and may be useful for those unable to reach their cholesterol targets in combination with a statin or in people who are intolerant of statins.

The current recommendations for the use of PCSK9i set by NICE are set out in **Figure 3**.

PCSK9i indications	**Without CVD**	**With CVD**	
		High risk[1]	Very high risk[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia		LDL ≥ 4.0 mmol/L	LDL ≥ 3.5 mmol/L
Primary heterozygous-familial hypercholesterolaemia	LDL ≥ 5.0 mmol/L	LDL ≥ 3.5 mmol/L	LDL ≥ 3.5 mmol/L

Figure 3 Recommendations for use of PSCK9i (adapted from NICE)[42]

[1]ACS, CHD, PVD, ischaemic stroke, revascularisation

[2]Recurrent events in more than 1 vascular bed

Role for Inclisiran

Inclisiran is a small interfering RNA that prevents hepatic PCSK9 translation thus reducing LDL receptor degradation and increasing surface LDL receptors. It is injected subcutaneously at 0 months, 3 months and then every 6 months.

Inclisiran is primarily renally excreted and a third of the total administered dose is detectable in the urine after 24 hours.

Inclisiran has been approved by the EMA and the FDA. NICE guidelines have placed it on the lipid lowering pathway for people with a history of ASCVD and raised cholesterol, above 2.6 mmol/ L. It is currently not recommended for primary prevention. It has a lower threshold for approval compared to PCSK9i. In Wales, the guidelines differ. Inclisiran is licensed for people with high risk of CVD due to previous events and LDL cholesterol ≥ 4.0 mmol/L, those with recurrent disease and LDL cholesterol ≥ 3.5 mmol/L and, people with heterozygous familial hypercholesterolaemia and LDL cholesterol ≥ 5.0 mmol/L for primary prevention.[33]

Role for Omega 3 fatty acids

Omega 3 fatty acids found in oily fish have been associated with reduced CVD risk in observational studies. However, formal randomised control trial evidence is mixed. Dietary fish oil supplements are poorly regulated and other low dose mixed preparations have failed to demonstrate cardiovascular benefit.

The Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT) was a phase 3b, double blind, placebo-controlled trial investigating 2g icosapent ethyl twice daily in people on statins with established ASCVD or diabetes.[43] The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, or unstable angina. Primary end-point events occurred in 17.2 % of the icosapent ethyl group, compared with 22.0 % of the placebo group.[43] This was observed regardless of the presence of diabetes or level of eGFR. The possible mechanism of action may be related to reduced TG levels, reduced VLDL, plaque stability and anti-inflammatory effects.

Whilst icosapent ethyl is licenced for primary prevention for people with diabetes and at least one additional cardiovascular risk factor, NICE have only recommended its use for secondary prevention in people with established cardiovascular disease, taking a statin, and with TG > 1.7 mmol/L and LDL cholesterol between 1.04 and 2.60 mmol/L.[45]

Role for Bile acid sequestrants

Bile acids sequestrants bind to bile acids in the gut and prevent their reabsorption. As bile acids are synthesized from cholesterol, this has a net effect of reducing cholesterol levels.

At the maximum dose, these reduce LDL cholesterol by up to 25 %. However, they have adverse gastrointestinal effects and drug interactions limiting their use. They may also reduce the absorption of fat-soluble vitamins and other drugs. Colesevelam can be used in conjunction with statins.

Recommendations

1 **At all stages of DKD, we recommend initiation with statin therapy, atorvastatin 20 mg (Grade 1D).**

2 **In stage G1-G3a DKD, we recommend consideration of higher dose/intensity statin therapy for those who do not attain treatment targets on lower statin doses and recommend seeking specialist advice if eGFR < 30 ml/min/1.73 m^2 (Grade 1D).**

3 **At all stages of DKD, we suggest consideration of submaximal statin and ezetimibe 10 mg combination therapy in those unable to tolerate higher statin doses (Grade 2B).**

4 **At all stages of DKD, in those with statin intolerance, we suggest ezetimibe 10 mg alone (Grade 2D).**

5 **In stage G1-G3a DKD, in those with statin intolerance, we suggest ezetimibe 10 mg in combination with Bempedoic acid 180 mg where treatment targets are not met (Grade 2D).**

6 **In stage G1–G3a DKD, we suggest that fenofibrate therapy (alone or in combination with statins) should only be used with specialist advice (Grade 2C).**

7 **In stage G3b–5 DKD, we recommend that there is no role for fibrates outside specialist care (Grade 1B).**

8 **We do not recommend fibrate ezetimibe combination therapy without specialist advice (Grade 1D).**

9 **We suggest consideration of inclisiran, in line with licensing and national guidelines, for secondary prevention in people who fail to achieve treatment targets. Currently there is limited data for use of inclisiran in severe DKD or ESKD; however, evidence exists for benefit up to stage G3b DKD (Grade 2C).**

10 **We suggest consideration of PCSK9 inhibitors, in line with licensing guidelines, in people who fail to achieve treatment targets. Currently there is limited data for use in severe DKD or ESKD; however, evidence exists for benefit up to stage G3b DKD (Grade 2C).**

11 **We suggest consideration of icosapent ethyl for secondary prevention, in line with licensing guidelines, in people with elevated fasted TG > 1.7 mmol/L and LDL cholesterol between 1.04 and 2.60 mmol/L. Currently there is limited data for use in severe DKD or ESKD (Grade 2C).**

Recommendations for the monitoring and safety of lipid-lowering agents

The overall safety of statins has been exhaustively evaluated. In general use, serious side effects are considered uncommon. Regarding the safety of statins in CKD, the 2009 Cochrane meta-analysis recorded no significant increase in the risk of rhabdomyolysis (defined as >10 times the upper limit of normal (ULN)), nor in liver function abnormalities (defined as >3 times the ULN).[46]

Women of childbearing potential should be advised about the teratogenic risks of statins. Women on statins and planning a pregnancy should stop this therapy three months before they attempt to conceive and should not restart until completion of breastfeeding.[47]

The main side effects noted in RCTs for ezetimibe, fibrates, Bempedoic acid, inclisiran, PCKS9i and icosapent ethyl are listed in **Figure 4**. For more extensive recommendations, please refer to the individual summary of product characteristics.

Drug	Side effect
Ezetimibe	• Tiredness • Joint pain • Upper respiratory tract infection • Diarrhoea
Fibrate	• Abdominal pain • Diarrhoea, constipation • Nausea and vomiting
Bempedoic acid	• Increased risk of gout • Slight reduction in eGFR • Should not be used in severe liver disease.
Inclisiran	• Site specific reactions • Non-specific symptoms such as headache and fatigue
PCSK9i	• Nasopharyngitis • Myalgia • Upper respiratory tract infection
Icosapent ethyl	• Allergy warnings listed to fish, shellfish, soya, and peanuts • Atrial fibrillation • Serious bleeding events • Peripheral oedema

Figure 4: Side effects of lipid-lowering agents

Recommendation for when to stop lipid-lowering agents

CVD is prevalent in older people; however, evidence for risk reduction by lipid management is limited. Subgroup analysis of major statin trials have been performed to determine if there is a differential outcome among different age groups. A CTT analysis of statin therapy at different ages found evidence of benefit in those aged >75 years.[48] There may, however, be an inherent bias in this meta-analysis and indeed other studies and post-hoc analyses as people with frailty, for example those with dementia or multiple comorbidities, would be unlikely to be recruited to these trials. The older group of participants included may therefore represent the healthier and possibly more engaged cohorts. A case-by-case approach is recommended for cessation of therapy in the elderly.