Clinical practice guidelines for management of lipids in adults with diabetic kidney disease

2021 update

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Contents

Summary of changes

1. The guidelines have been reordered and simplified into the following sections:
    a. Measurement of the lipid profile
    b. Lipid management in type 1 diabetes
    c. Lipid management in type 2 diabetes
    d. Lipid management in end-stage kidney disease, dialysis and following transplantation
    e. Choice of hypolipidaemic agent, dose and treatment targets
    f. Safety and monitoring
    g. Appropriate cessation of lipid monitoring and therapy
2. There has been a change in vocabulary: diabetic nephropathy – diabetes related chronic kidney disease (DN-DM CKD) has been abbreviated to diabetic kidney disease (DKD)
3. They recommend the use of CKD-EPI formula to estimate GFR
4. They suggest the use of non-HDL cholesterol and non-fasting lipid profile measurements
5. They recommend atorvastatin 20 mg in place of other generic statins (e.g. simvastatin) as first-line therapy
6. They include discussion of PCSK9 inhibitors and omega 3 fatty acids
7. There are updated sections on national and international guidelines including NICE, ESC/EAS, ADA

Introduction

Chronic kidney disease (CKD), regardless of aetiology, is a risk factor for cardiovascular disease (CVD). This risk is magnified when there is comorbid type 1 or type 2 diabetes which contributes to excess morbidity and premature mortality.[1-13]

Lipids are a modifiable risk factor and good lipid management offers improved outcomes for people with diabetes and concomitant renal disease. The principle of multiple risk factor management is important, and lipid management must be considered alongside managing blood pressure, weight, glycaemia, smoking cessation and thrombotic risk. This should be in conjunction with lifestyle measures and appropriate counselling and education on the risks and benefits of the various hypolipidaemic agents.

The primary purpose of these guidelines is to provide practical recommendations on lipid management for diabetologists, nephrologists, general practitioners and other members of the multidisciplinary team involved in the care of adults with diabetic kidney disease (DKD).

DKD is an umbrella term encompassing pathology both within the glomerulus (diabetic nephropathy – DN) and outside of the glomerulus (diabetes-related chronic kidney disease – DM CKD) **(Table 1)**. The advice for lipid management is currently equivalent for DN and DM CKD, hereafter referred to as DKD.

Table 1 Differentiating kidney disease in diabetes

Diabetic nephropathy	Damage to the glomerular capillaries in people with diabetes mellitus resulting in albuminuria in the absence of other causes of albuminuria.
Diabetes mellitus and chronic kidney disease	The presence for more than 3 months of structural renal abnormalities with reduced glomerular filtration in people with diabetes mellitus.

The presence and extent of renal disease is generally defined by two factors. Firstly, the measurement of serum creatinine from which an estimated glomerular filtration rate (eGFR) is generated, calculated using the CKD-EPI formula and secondly, a urinary albumin: creatinine ratio (UACR) – the latter being more sensitive for the detection of DN **(Figure 1).** Five stages of eGFR (G1 to G5) and three stages of albuminuria (A1 to A3) are defined. The diagnosis of CKD requires two measurements of renal function at least 3 months apart. Of note, many of the studies referenced within these guidelines use alternate equations to calculate GFR such as the Modification of Diet in Renal Disease (MDRD) equation. This equation can overestimate renal function at higher levels of GFR and may not discriminate between hyperfiltration and normal function.

It is recognised that as kidney function deteriorates, cardiovascular risk increases. However, it is important to consider that standard CVD risk factors may apply to different degrees in people with end-stage kidney disease (ESKD) requiring haemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation. The pathology of CVD in the absence of renal impairment is largely attributed to atherosclerotic coronary artery disease, whereas in CKD the pathology may be due to arteriosclerosis, arrhythmia or cardiomyopathy. Inflammation, uraemia, oxidative stress and endothelial dysfunction are just a few of the processes thought to contribute to the overall risk profile in CKD. Thus, with advanced DKD, established CVD lipid risk factors may be of less importance in reducing risk, and their modification may be less likely to reduce vascular events.

While many guidelines exist for the management of CKD, diabetes and lipids individually, this guideline looks specifically at the management of lipids within the spectrum of DKD. The cohorts of people with DKD managed by diabetologists, nephrologists and general practitioners will differ,

albeit with degrees of overlap, which may colour perspectives on treatment. The issue as to what constitutes an appropriate level of risk to justify introduction of lipid-lowering therapy in people with diabetes has been considered in several national and international guidelines.[14-16]

There is marked variation between these guidelines in terms of monitoring, treatment and treatment targets **(Appendix)**. In some guidelines, recent trials of newer hypolipidaemic agents, described in later sections, have led to the recommendation of lower treatment targets. Target attainment should take into account the levels achieved in the controlled prospective outcome studies, discussed later, where it appears that >50% of trial participants fail to reach the LDL or non-HDL cholesterol targets on combination statin–ezetimibe or high intensity statin therapy.

There is still a dearth of evidence regarding lipid management in type 1 diabetes and in younger adults with diabetes (type 1 or 2) and DKD. In many cases, general population guidelines are extrapolated to cover these populations which may not reflect lifetime accumulated CVD risk.

A detailed rationale for lipid modification is presented with the guidelines, as well as recommendations for clinical audit and outstanding questions for further research. These guidelines offer best practice guidance with evidence base grading for the management of lipids and use of hypolipidaemic agents in DKD.

eGFR and ACR categories

Fig 1 Renal Association classification of estimated glomerular filtration rates (eGFRs) and albumin:creatinine ratio (ACR) categories. Figure from Renal Association and KDIGO 2012

¹ Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Methodology

The 2017 ABCD-RA clinical practice guidelines were based upon systematic literature searches conducted between October 2013 and March 2016. This updated guideline is based on searches conducted between April 2016 and January 2020. We searched PubMed, the Cochrane database of systematic reviews and hand searched reference lists and articles identified by ABCD-RA writing group members. Search terms used were 'diabetes', 'lipids' AND 'chronic kidney disease/nephropathy'. We also reviewed all related guidelines from the National Institute for Health and Care Excellence (NICE), the Renal Association, Kidney Disease Improving Global Outcomes (KDIGO), the European Renal Association Best Practice Guidelines, and the American and European Diabetes Associations.

Evidence grades for the recommendations

This grading system classifies expert recommendations as 'strong' (Grade 1) or 'weak' (Grade 2) and the quality or level of evidence is designated as high (Grade A) to very low (D).[17]

1A	Strong recommendation: high-quality evidence
1B	Strong recommendation: moderate-quality evidence
1C	Strong recommendation: low-quality evidence
1D	Strong recommendation: very low-quality evidence
2A	Weak recommendation: high-quality evidence
2B	Weak recommendation: moderate-quality evidence
2C	Weak recommendation: low-quality evidence
2D	Weak recommendation: very low-quality evidence

Guideline rationale

The rationale behind the recommendations may be presented for an individual aspect of guidance, or to avoid repetition several recommendations may be considered collectively.

Abbreviations

Standard lipid abbreviations are used in these guidelines: total cholesterol (TC), chylomicron (CM), high density lipoprotein (HDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL), lipoprotein (a) (Lp(a)) and triglycerides (TG). Study acronyms are listed in **Box 1**.

Box 1 List of study acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ALERT	Assessment of LEscol in Renal Transplantation
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events
BANTING	evolocumaB efficAcy aNd safeTy IN type 2 diabetes mellitus on backGround statin therapy study
BERSON	evolocumaB Efficacy for LDL-C Reduction in subjectS with T2DM On background statiN
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events
CTT	Cholesterol Treatment Trialists
4D	Deutsche Diabetes Dialyse Studie
DAIS	Diabetes Atherosclerosis Intervention Study
DOPPS	Dialysis Outcomes and Practice Patterns Study

EBBINGHAUS	Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FinnDiane	Finnish Diabetic Nephropathy study
FOURIER	Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
JBS	Joint British Societies
JUPITER	Justification for the Use of Statin in Prevention: An interventional Trial Evaluating Rosuvastatin
LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
PANDA	Protection Against Nephropathy in Diabetes with Atorvastatin
PLANET	Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease
PROFICIO	Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 in Different Populations
SHARP	Study of Heart and Renal Protection
TNT	Treating to New Targets
WOSCOPS	West of Scotland Coronary Prevention Study

1 Lipid measurement in DKD

Recommendations

1   We recommend that evaluation of a non-fasting full lipid profile (TC, non-HDL, HDL, LDL cholesterol and TG) is performed at least annually in DKD, including in ESKD, dialysis or post renal transplantation. In hypertriglyceridaemia (>4.5 mmol/L), we would recommend 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 renal transplantation, we suggest that lipid status be assessed once the immediate post-operative period has passed (typically 3 months post transplantation) (Grade 2D).

Lipid metabolism in diabetes

Lipid metabolism fundamentally differs between type 1 and type 2 diabetes and there are qualitative and quantitative compositional changes.[18-20]

People with well-controlled type 1 diabetes without complications have similar total cholesterol, LDL cholesterol and triglyceride (TG) levels to the general population. HDL cholesterol levels are often similar or higher than the general population. In poorly controlled type 1 diabetes, insulin deficiency and poor glycaemic control lead to reductions in HDL cholesterol and elevations of total cholesterol, LDL cholesterol and TG. In this scenario, reduction in HbA1c by insulin repletion is associated with a more beneficial impact on TG and HDL cholesterol compared with LDL cholesterol.

Type 2 diabetes is characterised by insulin resistance and the atherogenic lipoprotein phenotype is well described with hypertriglyceridaemia, reduced HDL cholesterol and normal LDL cholesterol. There is a preponderance of smaller, denser, more atherogenic TG-enriched IDL and LDL particles based on increased apolipoprotein B (apo B) levels. These smaller LDL particles breach the endothelial wall and then become trapped and oxidised.

These compositional changes in all lipoprotein classes enhance oxidative potential and atherogenicity.[18,19,21] Whereas poor glycaemic control will exacerbate this pattern, this dyslipidaemia is less amenable to correction with improved HbA1c compared with type 1 diabetes.

Lipid metabolism in renal disease

CKD is associated with an atherogenic lipid profile. Qualitative and functional changes in lipoprotein particles are affected by the degree of albuminuria and progressive reductions in eGFR.

CKD is most commonly associated with elevated TG levels. Within the spectrum of CKD, LDL levels may be low, normal or raised and LDL particle morphology varies. TG enrichment of LDL leads to smaller, denser, more atherogenic particles. Reduced lipoprotein lipase (LPL) seen in CKD leads to increased VLDL and VLDL remnants which are also atherogenic.

Lecithin cholesterol acyltransferase (LCAT) esterifies cholesterol, allowing expansion and maturation of HDL from a discoid to spherical form. In CKD, reduced LCAT leads to lower levels of HDL cholesterol, which is dysfunctional, and a corresponding impairment of the reverse cholesterol transport pathway.

Lipoprotein(a) is a single LDL particle linked to an apo (a) protein. Lp(a) has been found to be highly genetically determined; however, CKD is related to changes in Lp(a) catabolism and metabolism. Several studies have shown that Lp(a) is elevated in CKD and is an independent CVD risk factor.[22] The ESC/EAS 2019 guidelines advise measuring Lp(a) at least once in a person's lifetime and that this information be used to assess cardiovascular risk. If the levels are >430 nmol/L, they advise that the lifetime cardiovascular risk is equivalent to that of heterozygous familial hypercholesterolaemia.[16] Lp(a) is currently unavailable in many district general hospitals. However, where it is available, this is a useful tool to further delineate risk, especially in younger people or in those who have type 1 diabetes. However, currently, there is a lack of clinical evidence in these populations with regard to lipid assessment and management.

Marked proteinuria with nephrotic syndrome (UACR >220 mg/mmol [1946.9 mg/g], hypoalbuminaemia and oedema) leads to more evident dyslipidaemia that is associated with premature CVD and progressive kidney disease.[23] Apo B containing lipoproteins (including LDL, VLDL, IDL and Lp(a)) increase and severe hypertriglyceridaemia occurs due to reduced clearance secondary to decreased LPL and hepatic lipase activity and overall increased hepatic lipoprotein synthesis. Increased expression of proprotein convertase subtilisin-kexin 9 (PCSK9) also results in reduced LDL clearance.[23] In nephrotic syndrome, LCAT activity is reduced and cholesterol ester transfer protein (CETP) is activated leading to production of immature HDL.[20,23-33]

People on peritoneal dialysis (PD) have increased LDL cholesterol due to mechanisms similar to those encountered in nephrotic syndrome due to significant losses of protein in the dialysate.

There has been considerable debate regarding the value of measuring lipids in people on dialysis, as reflected in the KDIGO guidelines.[34] Performing a baseline assessment of lipid status will establish diagnoses of severe hypercholesterolemia, and/or hypertriglyceridaemia. LDL cholesterol may not be elevated; however, Lp(a) is usually elevated, possibly due to reduced clearance.[35] It has been hypothesised that the prolonged duration of Lp(a) in people on dialysis may contribute towards CVD.[36] Measuring lipid status is inexpensive and will also identify a cohort where lipid-lowering therapy may not be indicated.

Kidney transplant recipients have a high prevalence of dyslipidaemia, including raised TC, HDL and LDL cholesterol and hypertriglyceridaemia.[37] Dyslipidaemia is a consequence of immunosuppressive therapy, specifically corticosteroids, ciclosporin (more so than tacrolimus), sirolimus and everolimus.[38] Corticosteroids increase VLDL directly through increased hepatic production and increased peripheral insulin resistance. Calcineurin inhibitors, especially ciclosporin, can contribute towards hyperlipidaemia through increased activity of hepatic lipase and reduced activity of LPL resulting in reduced clearance of atherogenic lipoproteins.

Performing a baseline assessment of lipid status allows compliance with therapy to be assessed and additionally allows estimation of the magnitude of any benefits of lipid-lowering therapy. Compliance with therapy is recognised to be challenging in renal transplant recipients as they are usually on multiple agents often including immunosuppression, antihypertensive therapy and antimicrobial prophylaxis.

Lipid assessment should be performed once immunosuppressive drug dosing has been stabilised and the risk of acute rejection requiring corticosteroid therapy has fallen. This period of stability is likely to be achieved 3 months post transplantation at the earliest.

The association between dyslipidaemia and CKD

In addition to the role of lipids in CVD, there is some evidence that dyslipidaemia contributes to the progression of kidney disease.[39] This was first proposed as the lipid nephrotoxicity hypothesis in 1982.[39] It was suggested that hyperlipidaemia led to glomerulosclerosis in a manner analogous to atherosclerosis causing CVD.

A prospective cohort study looking at the risk of CKD in familial hypercholesterolaemia (n=106,172 [7,109 with FH]), found that individuals with FH were at higher risk of CKD.[40]

In type 1 and type 2 diabetes, dyslipidaemia may be independently linked with the progression of DKD.[33,41-43] A range of lipoprotein measures including hypertriglyceridaemia, apobetalipoproteinaemia, elevated Lp(a) and apo E have been related to progression of DKD.[19,24,32,44]

The large prospective FinnDiane study recorded that lipid abnormalities in type 1 diabetes, particularly increases in TG, predicted progression to overt albuminuria. In addition, the FinnDiane study confirmed that features of metabolic syndrome linked to insulin resistance and worsening dyslipidaemia further increased CVD events and mortality, as well as progression of diabetic nephropathy.[30,32,33]

Measurement of non-HDL cholesterol

LDL cholesterol is usually not directly measured. It is calculated (using the Friedewald formula) and requires a fasting sample and for triglyceride levels to be <4.5 mmol/L.

Non-HDL cholesterol is calculated as total cholesterol minus HDL cholesterol and thus includes CM, VLDL, ILD, LDL cholesterol and Lp(a). It relates well to apo B levels. The measurement of non-HDL cholesterol does not require fasting. Considering the difficulties experienced in measuring fasting lipid profiles (delays in medication and disruption of glycaemic control), non-HDL cholesterol measurement is more convenient.

It is also worth considering the relative risk attributable to non-HDL cholesterol compared with that purely due to LDL cholesterol. In fact, measurement of LDL cholesterol alone may underestimate CVD risk. 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, triglyceride rich molecules and the loss of benefit of higher HDL cholesterol levels.[45] It may therefore be preferable to use non-HDL cholesterol targets to best assess the response to hypolipidaemic therapy in people with DKD.

National UK lipid guidelines (NICE) and European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines advocate the measurement of a non-fasting lipid profile including non-HDL cholesterol.[15,16] The ESC/EAS 2019 guidelines go a step further and recommend the use of non-fasting apo B levels, particularly in people with diabetes or obesity.[16] This recommendation is based on the fact that apo B is directly related to the quantity of atherogenic particles.

Despite the clear theoretical advantages to measuring either non-HDL cholesterol or apo B, these are surrogate markers for cardiovascular outcomes. These are only recently being routinely measured in large clinical trials and correlated with cardiovascular risk. Currently most of the available evidence and many risk calculators are based on LDL cholesterol. There is clear historic and current evidence relating LDL cholesterol levels to atherosclerotic CVD (ASCVD) risk and also evidence with regard to reducing LDL cholesterol levels and reducing ASCVD risk. Therefore, in

addition to measuring non-HDL cholesterol we would recommend the continued measurement of LDL cholesterol.

Frequency of lipid profile monitoring

There is marked variation between current guidelines with regard to monitoring lipid profiles. For example, in the KDIGO guidelines, lipid measurement is recommended initially at all stages of CKD including dialysis or transplantation; however, follow up measures are not recommended.[46] This is because at the time of writing of the KDIGO guidelines there was insufficient evidence to advocate treating to specific cholesterol targets. Thus, monitoring of lipid levels was considered to be unnecessary.

The 2020 American Diabetes Association (ADA) Standards of Care recommend monitoring lipid profiles (TC, LDL cholesterol, HDL cholesterol and TG) at diagnosis and every 5 years in people under the age of 40. Monitoring is also recommended at the time of initiation of a statin and 4–12 weeks after initiation or dose change. This is to help monitor response to treatment and to assess compliance.[14] The ESC/EAS guidelines advise assessment of response to therapy at 6–8 weeks with standard monitoring at 6–12 months. NICE recommend annual lipid profile screening and at 3 months following initiation of a statin.

Annual screening appears to be a reasonable approach, as this would coincide with an annual diabetes review. However, it is also acceptable to monitor more frequently if this would lead to changes in management.

2 Lipid management in type 1 diabetes and DKD

Recommendations

1   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 microalbuminuria (Grade 2D).
    - People aged between 18 to 30 years with persistent microalbuminuria and ≥1 additional CVD risk factor (Grade 2D).

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

Evidence base for CVD risk in people with type 1 diabetes and DKD

Forty years ago, the relative risk of CVD in people with type 1 diabetes was reported as being up to 10 times greater than in those without diabetes.[2] Subsequent reports over the past two decades demonstrate a reduction in this risk.[8-10,47-50] A study in Scotland (2012) observed a relative risk of CVD of 2.3 in men and 3 in women.[6]

In other observational studies, major coronary heart disease (CHD) events ranged from 0.98% per annum in the Pittsburgh Epidemiology Study of people with type 1 diabetes (n≈800), aged 30–40 years with diabetes duration of 20–30 years,[51] to 0.69% per annum in UK adults aged 35–45 years (n≈7,500).[8] A similar incidence of macrovascular disease (5% over 6–9 years follow up) was noted overall in over 21,000 adults with type 1 diabetes in Scotland.[5,6]

There is uncertainty as to whether type 1 diabetes acquired in childhood accelerates CVD in all cases.[52,53] Studies demonstrate that the most consistent predictors of CVD risk are age, chronically poor glycaemic control and markers of nephropathy, primarily albuminuria.[6,47,51] The presence of albuminuria conveys a 10-fold greater risk of CVD compared with type 1 diabetes without albuminuria.[12,48,51]

The incidence of CVD was significantly higher, at least 20% over 10 years, in the FinnDiane study (n=4,201) in people with albuminuric type 1 diabetes.[12,32] In this study, urine albumin status correlated with mortality. Individuals with microalbuminuria had 2.8 times higher standardised mortality ratio (SMR) and individuals with macroalbuminuria had 9.2 times higher SMR. Participants with ESKD had 18.3 times higher SMR compared with the general age and sex matched population. Individuals with normoalbuminuria had no excess mortality.[12]

Although the vast majority of people with type 1 diabetes who develop nephropathy first manifest persistent albuminuria before a decline in GFR, a cohort of 2–4% of those with progressively declining GFR (more usually women) have been defined without persistent albuminuria.[54] The risk of CVD is sufficiently high to justify the same approach to CVD prevention in this cohort. The variable reversible nature of albuminuria in adolescents and adults with type 1 diabetes is also important to consider.

Measures of dyslipidaemia, such as reduced HDL cholesterol and hypertriglyceridaemia, independently predict higher CVD risk.[8,49,50] A 10-year follow up of the FinnDiane study found that the predictive ability of lipid variables differed depending on age, renal status and glycaemic control.[32] It appeared that apo B was an independent predictor of coronary artery disease (CAD) in men while the triglyceride: HDL cholesterol and apo B: A-1 ratios were more highly predictive of CAD

in women. These relationships appeared more evident with poor glycaemic control and albuminuria. Traditional lipid risk predictors, such as TC and LDL cholesterol, were less predictive without persistent albuminuria.

Evidence base for lipid-lowering therapy and CVD outcome

In AdDIT, a statin and angiotensin-converting enzyme (ACE) inhibitor intervention trial in 443 adolescents with type 1 diabetes, endothelial dysfunction and modest dyslipidaemia were noted at baseline in participants with high normal albuminuria (median UACR 1.24 mg/mmol [11 mg/g]). In these individuals, the primary outcome for both statins and ACE inhibitors was UACR. Secondary outcomes were changes in GFR, retinopathy, lipid levels, CRP and arterial intimal medial thickness (aIMT).[55] The primary outcome was not affected by ACE inhibitors or statins. Statins were associated with reductions in total cholesterol, LDL and non-HDL cholesterol. However, no change was noted in carotid intima-media thickness, cardiovascular markers, GFR or retinopathy.[56] It is not clear if this lack of effect was due to the relatively short period of follow up of 2–4 years, or if the lack of effect was due to the relatively modest baseline increased UACR and dyslipidaemia. It is not currently known if a legacy effect would occur if the study participants were followed up for a longer period.

The Heart Protection Study investigated statins in high risk individuals.[57] A sizeable minority had CKD. In this study, people with type 1 diabetes benefited from simvastatin 40 mg in line with the much larger type 2 diabetes cohort.[57] However, all were >40 years old, and there was no information on albuminuric status to better define baseline risk.

In a meta-analysis demonstrating the benefit of cholesterol-lowering therapy in 18,686 people with diabetes, fewer than 10% had type 1 diabetes, their mean age was 55 years, and among them 56% had known vascular disease. The mean serum creatinine was 101 µmol/L and there was no information on albuminuric status in the analyses.[58]

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.[59] 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 a need to develop CVD risk scores specifically for people with type 1 diabetes. A recent update to NICE guidelines (CG181) suggests that the use of the QRISK3 assessment tool in type 1 diabetes or CKD may help people make an informed decision about whether or not to take a statin. ESC/EAS suggest using relative risk tables, lifetime risk or a risk age to discuss the risks with younger adults.[16]

The basis for intervention in different guidelines has been variably set depending on age, presence of additional vascular risk factors, diabetes related microvascular complications, levels of HbA1c and family history. There is no evidence base to currently 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.

The observation in one study of type 1 diabetes with varying renal function that no more than 43% of individuals attained an LDL cholesterol level of <2.6 mmol/ L reflected an overall low use of lipid-lowering agents.[30] Importantly, despite more frequent use of lipid-lowering agents with reduced GFR or macroalbuminuria, there was progressively lower attainment of lipid targets. This raises the possibility that more aggressive lipid-lowering strategies may be required. It is unclear whether there is a role for additional non-statin based lipid-lowering therapy when targets are not attained, and indeed there is a dearth of information on levels of lipid attainment using statins in this category.

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

3 Lipid management in type 2 diabetes and DKD

Recommendations

1   We recommend that in 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 microalbuminuria (Grade 1C)
    - People aged between 18 to 30 years with persistent microalbuminuria and ≥1 additional CVD risk factor (Grade 1D)

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

Introduction

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.[7,59,60] Rather, certain characteristics are required to escalate CVD risk, most notably longer duration of diabetes and/ or the presence of albuminuria.[1,3,4,7,11,13] In addition, CKD, based on reduced GFR, also enhances CVD risk.[7,13,60] Thus, the combination of type 2 diabetes with albuminuria, stage G3 CKD or higher substantially increases the risk of CVD.[60]

Use of cardiovascular risk calculators

The use of cardiovascular risk calculators is not recommended in people with established CVD or who are at high risk of developing CVD, e.g. people with familial hyperlipidaemia. In addition, risk assessment tools are not necessary in people with an eGFR <60 mL/min/1.73 m^2 and/or albuminuria (due to the already elevated risk of CVD).

The ESC/EAS 2019 guidelines discuss the issue in younger adults and recommend the use of risk age or lifetime risk. Specifically, the SCORE (Systematic Coronary Risk Estimation) risk stratification tool is discussed which can be calibrated for different populations and different European countries (see www.heartscore.org).[16]

Evidence base for lipid-lowering therapy and CVD outcome

There have been several large-scale prospective CVD outcome studies involving people with type 2 diabetes and CKD, although none specifically evaluating type 2 diabetes and CKD.

Earlier placebo-controlled studies with pravastatin 40 mg (WOSCOPS, LIPID and CARE) included participants with both diabetes and CKD. However, only 571 out of over 20,000 participants studied were in this category and included those with eGFR 30–59 mL/min/1.73 m^2 as well as those with albuminuria and eGFR >60 mL/min/1.73 m^2. The combined data from these studies suggested a 25% relative risk reduction in major CVD events.[61-63]

CARDS, SHARP and TNT evaluated lipid-lowering strategies in people with type 2 diabetes characterised by the degree of glomerular filtration and albuminuria.[64-66]

The CARDS trial (n=2,838) investigated 10 mg atorvastatin/day in people with type 2 diabetes with at least one additional CVD risk factor. A total of 970 (33.4%) had an eGFR of 30–60 mL/min/1.73 m^2. To prevent one CVD event in this CKD subgroup the estimated number needed to treat (NNT) was 26 people for 4 years.[66]

The SHARP study evaluated >9,000 people with CKD of whom 23% (2,094 people) had type 2 diabetes.[65] In this placebo-controlled study, participants were randomised 1:1 to receive once daily simvastatin 20 mg plus ezetimibe 10 mg or placebo. At baseline, 80% of participants had albuminuria, 37% had eGFR 30–60 mL/min/1.73 m^2, but the majority had stage G4 CKD or higher, with 33% requiring dialysis.[65] The type 2 diabetes cohort benefited similarly to the overall group and those with albuminuria benefited at least as much as those without albuminuria. There was no differential benefit among those with eGFR 30–60 mL/min/1.73 m^2 as opposed to those with eGFR <30 mL/min/1.73 m^2. There was a clear differential benefit among those with baseline TC >5.5 mmol/L. Overall in the SHARP study, to prevent a major CVD event the estimated NNT was 25–33 over 5 years.

The TNT study in >10,000 people with coronary heart disease included >30% with CKD, of whom 560 (18%) also had type 2 diabetes. This study reported a greater reduction in CVD events in people with CKD when treated with atorvastatin 80 mg/day compared with 10 mg/day, without additional safety concerns and no evidence of myositis, which suggests there is benefit in using high intensity statins in this highest risk group. However, the number of participants with eGFR <30 mL/min/1.73 m^2 was small (13–16 participants in the 10 mg versus 80 mg groups). The NNT with 80 mg atorvastatin to prevent 1 major CVD event over 5 years was 24.[67]

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%, with no effect on non-vascular deaths. Coronary revascularisation was reduced by 25% and stroke by 21%.[58] In the 2008 meta-analysis, the CTT collaborators investigated the impact of renal dysfunction on outcomes.[58] Although not seen in all studies, the incidence of CVD events was usually increased in people with eGFR <60 mL/min/1.73 m^2 and persistent albuminuria. The relative risk reduction in CVD events was stated to be at least equivalent among those with eGFR <60 mL/min/1.73 m^2 compared with those with eGFR ≥60 mL/min/1.73 m^2, and likewise among those with or without albuminuria. In general, given the higher relative risk in those with more overt renal dysfunction, the absolute quantitative benefit was greater where eGFR was <60 mL/min/1.73 m^2 or where there was albuminuria.

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.[68] This time the CTT looked at the 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.[68]

A 2014 Cochrane review of statins in people with CKD (not requiring dialysis) found that mortality and major coronary events were reduced by 20%.[69]

These studies and meta-analyses demonstrate the efficacy of statins as primary prevention.

Evidence base for impact of lipid lowering with statins on progression of albuminuria and CKD

There has been considerable interest in the possibility that statins may reduce deterioration in renal function. It has been suggested that statins have pleiotropic effects and that the benefits of statins may not be exclusively related to their lipid-lowering effects.

The JUPITER study of rosuvastatin 20 mg/day raised the possibility that the anti-inflammatory effects of statins may be related to renal outcomes.[70] The JUPITER study included 3,267 participants with eGFR <60 mL/min/1.73 m^2, none had diabetes and baseline TC was 4.9 mmol/L, LDL cholesterol <3.3 mmol/L and high sensitivity C-Reactive Protein (CRP) modestly raised. Virtually all participants with renal dysfunction had CKD stage G3 (median eGFR 56 mL/min/1.73 m^2). There was a higher incidence of CVD in people with CKD compared with the non-CKD group. The benefits were more evident in those with raised CRP as a marker of inflammation.[70,71] There was no impact of active treatment on GFR among those with baseline eGFR <60 mL/min/1.73 m^2, although at 12 months a marginal but significant preservation of eGFR was observed when eGFR was ≥60 mL/min/1.73 m^2 at baseline.[70]

In PLANET 1, a randomised, double-blind, parallel group trial of atorvastatin 80 mg and rosuvastatin 10 mg and 40 mg in participants with proteinuric (predominantly type 2) diabetes with eGFR >40 mL/min/1.73 m^2, a significant reduction in proteinuria was only observed with atorvastatin.[72] While 40 mg rosuvastatin was more effective in reducing cholesterol, eGFR and cystatin-based measures of glomerular filtration rate deteriorated significantly. The small sample size and absence of a placebo control group limited a firm conclusion being drawn regarding differential effects.[72]

A small study of people who have type 2 diabetes with nephropathy suggested that over 12 months pitavastatin reduced albuminuria to a greater extent than pravastatin.[73]

In type 2 diabetes, high dose statin (up to 80 mg atorvastatin) in 85% of participants with microalbuminuria led to reductions in CVD and progression of nephropathy in a small study of multiple risk factor reduction.[74] However, as with larger studies, failure to achieve tight cholesterol targets was seen, 30% of the participants still had total cholesterol levels >4.5 mmol/L. As the trial was multi-factorial, it is difficult to differentiate the benefit attributable to that purely from the statin.

The only study suggesting that statins could actually improve GFR was the TNT study over 5 years, where GFR improved by 10% with high dose atorvastatin among those with CKD.[67,75] This effect was not observed in the CARDS, PANDA or SHARP studies with between 2 to 4 years follow up.[66,76,77] Similarly, a retrospective cohort study in Taiwan suggested that atorvastatin and rosuvastatin were not associated with significant changes in renal function in type 2 diabetes.[78]

Meta-analyses that included all studies with diabetes cohorts found no evidence that renal failure events (defined as a 25% decrease in eGFR, doubling of serum creatinine or ESKD) were reduced by statins (RR 0.95 (CI 0.9–1.01) or 0.91 (0.78–1.06)).[79,80]

In 2009, the Cochrane Collaborative Meta-Analysis stated that in CKD in general, statins do not impact on the decline in renal function as measured by creatinine clearance, but may reduce proteinuria.[79,81] The 2014 updated Cochrane analysis for people with CKD not requiring dialysis confirmed the lack of beneficial effect on statins on creatinine clearance.[69]

It thus appears that although statins may reduce albuminuria in the short term, they do not lead to sustained improved measures of renal function, although it is conceivable that any benefit may only manifest after more extended statin use, or if statins were initiated at an earlier stage. It is plausible to believe that aggressive lipid-lowering might have some beneficial effect on progression of renal disease, perhaps in early DKD with albuminuria but relatively preserved eGFR. The optimal combination or regimen of lipid-lowering agents to be used in this setting has not been defined and further trials may clarify this issue.

4 Lipid management in ESKD, dialysis and post-transplantation

Recommendations

1   We suggest that in people with DKD who commence dialysis, lipid-lowering therapy should be continued (Grade 2D).

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

3   Where indicated, we recommend that lipid-lowering therapy should be commenced in people with DKD who have undergone either kidney transplantation or combined kidney-pancreas transplantation and that the choice and dose of lipid-lowering therapy should take into account concurrent immunosuppressive therapy (Grade 1C).

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

CVD risk in ESKD

People with ESKD are at dramatically increased risk of premature CVD, 5–20 times that of the general population. However, while CVD risk is greatly increased, the prominent mode of death in most ESKD registries is sudden cardiac death, for example, due to arrhythmia. The relationship between cholesterol and CVD risk is not clear and the phenomenon of reverse epidemiology is well documented in ESKD with a 'J' or 'U'-shaped relationship between cholesterol and mortality, possibly driven by malnutrition or inflammation being associated with lower serum cholesterol levels.[82]

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. This is a time of increased vulnerability to various physical and psychological stresses, and the risk of cardiovascular events increases. During this period, it is appropriate to review medication regimens including management of lipid-lowering therapy. For some, continuation of lipid-lowering therapy may be inappropriate following commencement of dialysis. On the other hand, those on dialysis who have subsequently undergone renal transplantation are more likely to benefit from lipid-lowering therapy.

The leading cause of graft loss is death with a functioning graft, while the leading cause of death in renal transplant recipients is CVD.[83] Therefore, it is important to lower cardiovascular risk. Lipid-lowering therapy is likely to be beneficial for many renal transplant recipients.[84]

Evidence base for impact of lipid lowering on CVD risk in dialysis

There have been three large, randomised, placebo-controlled trials of lipid-lowering therapy in dialysis: The Die Deutsche Diabetes Dialyse (4D) study, AURORA and SHARP. The primary endpoints for these studies were cardiovascular death, stroke, myocardial infarction and revascularisation.

The 4D trial studied 1,255 people with type 2 diabetes, aged 18–80 years treated with haemodialysis for <2 years.[85] Participants were randomised to receive atorvastatin 20 mg or placebo. Exclusion

criteria were LDL cholesterol <2.1 mmol/L or >4.9 mmol/L and/or a vascular event in the 3 months prior to study entry. Atorvastatin failed to demonstrate any reduction in the primary endpoint compared with placebo.

In AURORA, 2,273 people on haemodialysis aged >50 years were randomised to receive rosuvastatin 10 mg or placebo. Of these, 26.3% had diabetes.[86] There was no reduction in the primary endpoint with rosuvastatin. In a pre-specified subgroup analysis, there was no difference in the incidence of the primary endpoint in diabetes. However, rosuvastatin led to a significant reduction in the incidence of cardiac events, at the expense of a non-significant increase in stroke.[87]

Finally, SHARP included 2,527 people on haemodialysis and 496 on peritoneal dialysis (23% had diabetes). A non-significant reduction in atherosclerotic events was observed in the simvastatin 20 mg – ezetimibe 10 mg combination group, compared with placebo. [65]

The CTT noted that AURORA attributed deaths of uncertain cause to CVD where there was previous history of CVD. This attribution differed from the SHARP and 4D trials. A re-adjudication of deaths from the AURORA trial led to the percentage of deaths initially attributed to CVD falling from 32% to 8% (which was more in line with 4D and SHARP data). 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.[68]

As discussed earlier, the 2016 CTT meta-analysis confirmed that overall, statins reduce the risk of a first major vascular event by 21% per mmol/L reduction in LDL cholesterol.[68] However, smaller effects were seen as eGFR declined with little evidence of benefit seen in dialysis.[68] There may be subgroups that benefit, such as people with higher LDL cholesterol levels or recent vascular events, but these groups were either excluded from or not randomised to these trials.

Although clear evidence of benefit has not been demonstrated in trials of lipid-lowering therapy in people with diabetes on dialysis, there are no data to suggest harm in using lipid-lowering therapy. Epidemiological data from DOPPS suggest that use of statins may be associated with better outcomes in haemodialysis, although this may represent effects unrelated to lipid-lowering therapy, such as treatment centre or person-related factors.[88] There are no direct data to inform whether or not to continue lipid-lowering therapy once dialysis has commenced.

Evidence base for impact of lipid lowering on CVD risk in renal transplant recipients

Statins have similar effects on the secondary dyslipidaemia seen in renal transplant recipients as demonstrated in primary dyslipidaemia in the general population. 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 renal transplant recipients.[84] In the 2-year extension trial, fluvastatin led to a significant 35% relative reduction in the risk of cardiac death or non-fatal MI.[89] In a post-hoc analysis of ALERT, 18.7% of participants had diabetes at baseline and diabetes was a risk factor for cardiac death.[90] However, in diabetic renal transplant recipients, there was no significant reduction in cardiac events with fluvastatin compared with placebo.

A Cochrane review looking at 22 studies in renal transplant recipients, 3,465 participants, found that statins may reduce major adverse cardiovascular events (1 study, 2,102 participants, RR 0.84, CI 0.66 to 10.6), cardiovascular mortality (RR 0.68, CI 0.45 to 1.01) and fatal or non-fatal myocardial infarction (RR 0.70, CI 0.48 to 1.01).[91] However, the effects were imprecise and included the

possibility of no effect.[91] The adverse effect of statins, including on liver enzymes and creatine kinase, was uncertain.[91] Most of the data from the meta-analysis was from ALERT. The median statin dose was low (equivalent to simvastatin 10 mg) and the median follow up 4 months (range 2 to 61 months). The risks or benefits of more intensive treatment are not currently known.

Risks of lipid-lowering therapy in renal transplant recipients

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.[92] This risk appears to be greatest with simvastatin and is lowest with fluvastatin or pravastatin. Ezetimibe appears to be safe in renal 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.[93,94] Fibrates have a high risk of side effects and are generally best avoided in renal transplant recipients.

Post-transplant diabetes mellitus and lipid lowering

Post-transplant diabetes mellitus (PTDM) affects 7–25% of people following renal transplantation.[95] Reporting varies depending on the method of definition of PTDM and how the diagnostic data were acquired (registries, prescription data, insurance data, clinical trial etc). Conventional risk factors include age, obesity and ethnicity. Transplant-related risk factors include corticosteroids, calcineurin inhibitors (particularly tacrolimus) 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 statins 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.[96] There are no data to inform strategies for lipid management in this population. All those with type 1 diabetes being considered for SPK or PAK will have had prior indication for lipid-lowering therapy and acquire 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 with statins in this group.

5 Treatment targets

Recommendation

1   We suggest that statin use should aim to reduce TC to ≤4.0 mmol/L, non-HDL cholesterol to ≤2.5 mmol/L, LDL cholesterol to ≤2 mmol/L (Grade 2D).

Target cholesterol levels

The 2010 CTT meta-analysis (including 26 eligible trials) demonstrated that larger reductions in LDL cholesterol led to further reductions in major vascular events.[97] A lower LDL cholesterol (≤1.8 mmol/L) was associated with a further 15% reduction in major vascular events.[97] They did not find evidence of a threshold LDL cholesterol level and they did not find evidence of adverse effects with more intensive therapy. The authors suggested that these results demonstrate the benefit of lowering LDL cholesterol levels below current suggested treatment targets (including below 1.8 mmol/L in high risk individuals).

A 2014 Cochrane review in CKD demonstrated that treatment effects varied according to severity of kidney disease. People with earlier stages of renal impairment had greater benefits.[69] Paradoxically, however, many guidelines suggest tighter targets for people with a greater severity of CKD.

Comparison of national and international guidelines

National and international guidelines all recommend different target LDL and non-HDL cholesterol levels **(Appendix)**.[14-16] In addition, some recommend target attainment levels, whereas others, e.g. NICE, recommend a percentage reduction from baseline.

The 2013 KDIGO guidance stated that there was insufficient evidence to justify specific LDL cholesterol targets.[46] This is understandable as this was published prior to convincing evidence of the benefit of lower cholesterol targets. In the 2013 KDIGO guidelines, fixed doses of lipid-lowering agents are recommended (e.g. atorvastatin 20 mg).[46] KDIGO guidelines advise against the use of high intensity statins in people with eGFR <60 mL/min/1.73 m^2; however, this appears to conflict with the need to use high intensity statins in those with increased CVD risk. Given the positive benefit of high intensity statin in the TNT study, it appears reasonable to use these to eGFR ≥30 mL/min/1.73 m^2 unless there are significant contraindications or drug interactions. Below eGFR 30 mL/min/1.73 m^2 it is reasonable to use lower doses and only to up titrate cautiously with monitoring and under specialist diabetologist or nephrologist care and guidance.

The ESC/EAS 2019 guidelines propose lower LDL cholesterol and non-HDL cholesterol targets and a revised cardiovascular risk stratification **(Table 2)**.[16] These guidelines state that people with type 1 diabetes, type 2 diabetes and CKD are at high or very high cardiovascular risk.[16] Initiation of a statin is advised in the high-risk group if the LDL cholesterol is ≥2.6 mmol/L and in the very high-risk group if the LDL cholesterol is ≥1.8 mmol/L.[16]

Table 2 ESC/EAS cardiovascular risk stratification

Cardiovascular risk category	Criteria	Treatment target
High risk	Diabetes with an additional risk factor Diabetes duration >10 years CKD stage 3	≥50% reduction in LDL cholesterol Goal LDL cholesterol <1.8 mmol/L Goal non-HDL cholesterol ≤2.6 mmol/L
Very high risk	Diabetes with target organ damage Type 1 diabetes of long duration, >20 years CKD stages 4, 5 Documented atherosclerotic cardiovascular disease	≥50% reduction in LDL cholesterol Goal LDL cholesterol <1.4 mmol/L Goal non-HDL cholesterol ≤2.2 mmol/L *For those at very high risk with recurrent ASCVD, a non-HDL cholesterol goal of <1.8 mmol/L is suggested.*

The 2020 ADA Standards of Care do not distinguish lipid-lowering treatment by type of diabetes or by stage of DKD.[14] While type 1 and type 2 diabetes are discussed separately, the recommendations are applied equally to both. For primary prevention in people with diabetes aged 40 to 75 years, a moderate intensity statin is recommended. For those aged 20 to 39 years with additional CVD risk factors, statin initiation is suggested. High intensity statins are recommended for people of all ages with diabetes and increased risk factors, including established ASCVD. For people with a 10-year ASCVD risk >20%, a statin/ezetimibe combination is recommended.[14] For secondary prevention, ezetimibe or PCSK9 inhibitors are recommended if LDL cholesterol levels are >1.8 mmol/L.

The American Heart Association and American College of Cardiology guidance recommends moderate intensity statins in people with diabetes mellitus, aged 40 to 75 years of age.[98] The presence of cardiovascular risk modifiers such as: long duration of diabetes (≥10 years for type 2 or ≥20 years for type 1), albuminuria ≥30 mcg albumin/ mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, ankle brachial pressure index <0.9 are listed as factors to consider when recommending high intensity statins.[98]

NICE recommends statin therapy in CKD but does not differentiate between the stages of CKD. Where the eGFR is <30 mL/min/1.73 m^2, further consultation with a nephrologist is suggested prior to consideration of higher intensity statins.[15]

The JBS3 consensus recommendations for the prevention of CVD suggest a separate approach to lipid lowering in type 1 and type 2 diabetes. The majority of people aged ≥40 years (unless short duration type 1 diabetes and otherwise fit) would be considered for statin therapy regardless of renal status, without any need to utilise a CVD risk assessment tool.[59] Persistent proteinuria and/or eGFR <60 mL/min/1.73 m^2 in younger adults, aged 18–40 years, were factors to be considered for statin initiation. Intensive statin therapy (e.g. atorvastatin 80 mg) was recommended for those with pre-existing CVD as well as those with persistent albuminuria and/or eGFR <60 mL/min/1.73 m^2, or if not achieving non-HDL cholesterol target of 2.5 mmol/L.

We suggest that statin use should aim to reduce TC to ≤4.0 mmol/L, non-HDL cholesterol to ≤2.5 mmol/L, LDL cholesterol to ≤2 mmol/L. 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.

6 Choice of hypolipidaemic agent

Recommendations

1   In DKD, where indicated, we recommend initiation with statin therapy, atorvastatin 20 mg (Grade 1D).

2   We recommend consideration of higher intensity statin therapy for those with persistent albuminuria and/ or reduced eGFR (≥30 mL/min/1.73 m^2), at highest CVD risk who do not attain lipid targets on lower statin doses (Grade 1D).

3   We suggest consideration of submaximal statin and ezetimibe combination therapy as an alternative in DKD at all stages in those unable to tolerate higher statin doses (Grade 2B).

4   We suggest that fenofibrate therapy alone or alongside statins should only be used in DKD stage G1–G3a, in statin intolerance or failure to achieve target levels despite statin ± ezetimibe therapy (Grade 2C).

5   We recommend that there is no role for fibrates in DKD stage G3b–5, either as monotherapy or in combination with statins – outside specialist care (Grade 1B).

6   We do not recommend fibrate ezetimibe combination therapy in DKD, without specialist advice (Grade 1D).

7   We suggest consideration of PCSK9 inhibitors in line with national guidelines in people with high or very high-risk CVD who fail to achieve target levels despite being on a maximum tolerated statin and ezetimibe (Grade 2C).

8   We suggest consideration of icosapent ethyl 2 g twice daily in people with TG 1.5 to 5.6 mmol/L at high or very high cardiovascular risk, already maximally treated with statins (Grade 2C).

Introduction

Statins are the lipid modifying agent of choice for people with diabetes. The effect of differing doses of statin on LDL cholesterol has been described.[99,100] There is a slight variation in the classification of high and moderate intensity statin regimes in the USA and UK **(Tables 3 and 4)**. Thus atorvastatin 20 mg is considered a high intensity statin in the UK and a moderate intensity statin in the USA. This difference can cause confusion when reading the various guidelines.

Table 3 Examples of high intensity and moderate intensity statins in the USA. Adapted from ADA guidelines[14]

High intensity statins (mg)	Moderate intensity statins (mg)
Atorvastatin 40–80	Atorvastatin 10–20
Rosuvastatin 20–40	Rosuvastatin 5–10
	Simvastatin 20–40
	Pravastatin 40–80
	Lovastatin 40
	Fluvastatin XL 80

Table 4 Effect of statin dose on LDL cholesterol. Statins are grouped into different intensity categories according to the percentage reduction in low density lipoprotein cholesterol they produce:[1] 20%–30%: low intensity,[2] 31%–40%: medium intensity,[3] Above 40%: high intensity,[4] MHRA advice, increased risk of myopathy. Adapted from NICE (UK) guidelines.

	Reduction in low density lipoprotein cholesterol				
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	–	–	21%[1]	27%[1]	33%[2]
Pravastatin	–	20%[1]	24%[1]	29%[1]	–
Simvastatin	–	27%[1]	32%[2]	37%[2]	42%[3,4]
Atorvastatin	–	37%[2]	43%[3]	49%[3]	55%[3]
Rosuvastatin	38%[2]	43%[3]	48%[3]	53%[3]	–

Statins are the primary lipid-modifying agent of choice for people with diabetes. The following sections discuss the role of other hypolipidaemic agents.

Role for ezetimibe

Ezetimibe blocks the intestinal absorption of cholesterol and upregulates hepatic LDL receptor expression, enabling reduction of atherogenic lipoproteins.[101] The main role for ezetimibe in DKD is as an adjunctive to statin use, or as single agent therapy in statin intolerant cases. A pooled analysis of statin and ezetimibe combination therapy in people with diabetes showed additive benefit and greater efficacy than sub maximal statin dosage without any untoward adverse effects. There was a marginal (0.6 versus 0.3%) excess of elevated liver transaminase enzymes in comparison to the statin monotherapy group. Renal status was not noted in the pooled meta-analysis.[102]

The SHARP study in CKD was a randomised, placebo-controlled trial of combination simvastatin 20 mg and 10 mg ezetimibe. The major rationale of adding ezetimibe to low dose simvastatin was to ensure a reduction in LDL cholesterol of >1 mmol/L without inducing a risk of rhabdomyolysis, which may occur with higher doses of simvastatin. There was a significant 17% reduction in major atherosclerotic events in the total study group, and non-significant improvements in cardiovascular outcomes. There was no excess of therapy discontinuation or hepatic enzyme elevation in the statin-ezetimibe cohort, although a marginal excess risk of myopathy was noted (0.2 versus 0.1%, equivalent to 1 case per 5,000 per year of treatment). There was no suggestion that the statin ezetimibe combination altered rates of ESKD or haemodialysis.[65]

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study, looking at ezetimibe add-on to 40 mg simvastatin, was the first clinical outcomes trial to demonstrate that ezetimibe reduces CVD risk. Compared with placebo (as in SHARP) the combination led to lower attained LDL cholesterol levels of 1.4 mmol/L (compared with 1.8 mmol/L with simvastatin alone). There was an overall absolute risk difference of 2% in the primary endpoint of combined fatal and non-fatal major CVD events, with the benefit particularly noted among the 25% of participants with diabetes. However, there appeared very few if any participants with diabetes and CKD, median creatinine levels were 84 µmol/L and there was no information on albuminuria status.[103]

In people with DKD not requiring dialysis it is unknown if it is more efficacious and safer to use a lower dose of a statin combined with ezetimibe, as used in SHARP, or to use a more potent statin such as atorvastatin 20–80 mg daily. It seems reasonable to use ezetimibe as a lipid-lowering agent

in people who are statin intolerant, although there is no specific evidence to support this in DKD. Ezetimibe can be used in mild to severe renal disease and co-administered with any dose of statin.

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.

Two CVD outcome trials, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD), have addressed the issue of fibrate therapy in diabetes.

In FIELD, a placebo-controlled trial of fenofibrate in 9,795 people with type 2 diabetes (of whom 519 had an eGFR <60 mL/min/1.73 m^2), a reduction in non-fatal MI was the only significant finding.[104] Over 5 years, the FIELD study suggested that longer-term fenofibrate therapy remained effective and safe in those with type 2 diabetes and renal impairment.[105]

The ACCORD study was a multifactorial interventional study (looking at intensive glycaemic control, blood pressure control and fibrates) in people with type 2 diabetes at high risk for CVD. A total of 5,518 people with type 2 diabetes being treated with open-label simvastatin were randomised to receive either masked fenofibrate or placebo. 37% of the participants had CKD with baseline eGFR <60 mL/min/1.73 m^2 ± albuminuria. It found that the annual rate of first occurrence of non-fatal MI, non-fatal stroke, or death from cardiovascular causes was 2.2% in the fenofibrate group and 2.4% in the placebo group.[106] In the overall ACCORD study group, fenofibrate only reduced CVD events in dyslipidaemic men with reduced HDL cholesterol. There was no increase in frequency of raised muscle enzyme activity with combination statin fibrate therapy in ACCORD.[106,107]

Both FIELD and ACCORD suggested that fenofibrate led to reductions in progression of retinopathy, albuminuria and foot amputations.[107,108] It was suggested that this was not purely attributable to lipid-lowering effects.

Two other studies, the Diabetes Atherosclerosis Intervention Study (DAIS), and the Steno 2 study, also demonstrated reduction in microvascular outcomes with fibrates. In DAIS (n=314), fenofibrate use over three years reduced the development of microalbuminuria in participants with diabetes.[109] In Steno 2, fenofibrate added to high dose statins alongside multiple risk factor reduction in microabuminuric type 2 diabetic participants led to reductions in all microvascular and macrovascular outcomes.[74]

The PROMINENT study, a phase 3, double blind, placebo-controlled, randomised trial investigating pemafibrate (a selective peroxisome proliferator activated receptor α modulator), is currently recruiting 10,000 participants with type 2 diabetes and increased CVD risk, already on moderate to high intensity statins or with specified LDL levels, to see if reducing TG rich lipoproteins reduces CVD risk.[110]

A consistent finding from both ACCORD and FIELD is confirmation that fenofibrate consistently leads to a rise in serum creatinine and decline in eGFR which is reversible 6–8 weeks after discontinuation. This appears to have a haemodynamic basis as cystatin C altered in a parallel fashion implying the effect was not due to muscle damage or altered creatinine secretion or synthesis. This was noted and maintained for 5 years in ACCORD.[107] In the ACCORD Follow-On Study (ACCORDION),

participants were followed up for an additional 6.5 years, fenofibrate was associated with a doubling of creatinine (hazard ratio 2.0).[111] It appeared that older males with established CVD and lower baseline creatinine were most likely to exhibit the fenofibrate associated rise in creatinine.[112] It is notable that the time-related decline in eGFR in the placebo group in both studies over the duration of the study was greater than in the fenofibrate group. Overall, there was a 2-fold greater discontinuation rate among those in the statin fibrate group due to reductions in GFR, and fenofibrate dose was reduced in 16%.

A study of fenofibrate with statins in 280 participants with stage G3 CKD (58% with diabetes) demonstrated lipid-lowering efficacy.[113] However, a clinically significant deterioration in hepatic function was observed in three of the 140 actively treated group. A decline in glomerular filtration (from 49 to 43 mL/min/1.73 m^2), that reversed on withdrawal of fenofibrate, was reported.[113] Nevertheless, a fibrate in combination with a statin led to greater lipid-lowering efficacy (TG reduction of 43% and HDL cholesterol increase of 17%), independent of diabetes status.

Meta-analyses have demonstrated CVD outcome benefit, reduced risk of albuminuria progression and safety with fibrate and statin combination therapy in combined dyslipidaemia and mild to moderate CKD.[114-117] Whereas there is no clear increase in progression to ESKD with this combination, the reversible rise in creatinine which is reported consistently with fibrate use may in practice offset any perceived short-term advantage on albuminuria reduction.

The impact of fenofibrate on vascular outcomes balanced with consistent changes in eGFR suggest that any role for fibrates in DKD would only be at a stage when there were anticipated microvascular (retinal-foot-albuminuria) benefit. Addition of fibrates might be best restricted to younger people with fewer advanced complications and preserved GFR.[114,118] Fibrate dose reduction or withdrawal should be implemented if eGFR falls by more than 20% and/ or below <45 mL/min/1.73 m^2.

PCSK9 inhibitors

Proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies are a new class of lipid-lowering agent. They are administered by subcutaneous injection fortnightly or monthly.

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. Inhibition of the binding of PCSK9 to the LDL receptor by monoclonal antibodies 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 the US Food and Drug Administration (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.

Trials of evolocumab
The PROFICIO study assessed the safety of evolocumab. This was a pooled safety analysis from 12 phase 2 or 3 trials and open-label extension trials.[119] It included adverse event data from 6,026 participants with a median exposure of 2.8 months, and, of those, from 4465 participants, median follow-up 11.1 months. Adverse event rates were similar between evolocumab and control in the parent trials (51.1% versus 49.6%) and in year 1 of open label extension trials (70.0% versus 66.0%). In addition, adverse event rates did not increase in participants with very low LDL cholesterol, including no increase in neurocognitive or muscle related adverse events. The most common adverse event noted was nasopharyngitis.

The FOURIER trial (Findings from the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk), a randomised, double blind, placebo-controlled trial, demonstrated that in a study population aged 40–85 years with stable atherosclerotic CVD, the addition of evolocumab to statin therapy lowered LDL cholesterol to a median of 0·8 mmol/L (IQR 0·5 – 1·2) and significantly reduced the risk of cardiovascular events in participants with stable CVD over 2·2 years.[120] Out of the 27,564 participants in the study, 11,031 (40%) had diabetes, 10,344 had prediabetes and 6,189 had normoglycaemia. Further analysis found that evolocumab did not increase the risk of hyperglycaemia or new onset diabetes.[121] The PCKS9 inhibitor was similarly effective in people with diabetes, compared with people without diabetes.[121] In this study, people with eGFR <20 mL/min/1·73 m² were excluded. A prespecified secondary analysis of the FOURIER trial categorised the participants into 5 groups (LDL <0.5, 0.5–<1.3, 1.3–<1.8, 1.8–<2.6, ≥2.6 mmol/L).[122] The group with the lowest LDL had the lowest risk of cardiovascular death (adjusted hazard ratio 0.69) compared with the group with LDL ≥2.6 mmol/L.[122] No significant association between LDL and prespecified adverse outcomes was observed.

A meta-analysis of 12-week, phase three, randomised controlled trials published between 2012 and 2015 compared the effects of evolocumab in participants with or without type 2 diabetes.[123] This included three trials, LAPLACE-2, RUTHERFORD-2 and GAUSS-2, with a total of 413 participants with type 2 diabetes and 2,119 without diabetes. The trials compared evolocumab to placebo or ezetimibe. The reduction seen in LDL, non-HDL cholesterol and Lp(a) in participants with diabetes was comparable to that seen in participants without diabetes. In the diabetes cohort, evolocumab reduced LDL cholesterol by 60% versus placebo and 39% versus ezetimibe.[123]

BERSON and BANTING were two dedicated trials in participants with type 2 diabetes. The BERSON trial, an international, randomised, double-blind, phase 3 trial in 981 people with type 2 diabetes and dyslipidaemia on background atorvastatin 20 mg, was conducted in 10 countries including Argentina, Brazil, Canada, China, Columbia, France and South Korea. Half of the participants were from China.[124] In addition to atorvastatin 20 mg, participants were randomised to 12 weeks of evolocumab 140 mg every 2 weeks or 420 mg monthly or placebo (2 weeks or monthly). Primary endpoints were the change in LDL cholesterol, atherogenic lipids, glycaemic measures and adverse events (AEs). A mean absolute reduction in LDL cholesterol of 1.62, 1.64 mmol/L (2-weekly, monthly evolocumab versus placebo) was observed.[124] No effect on glycaemia was observed, however, the study duration was relatively short.

The BANTING study, a 12 week randomised, placebo-controlled study, looked at monthly evolocumab or placebo in 421 participants with type 2 diabetes and hypercholesterolaemia or mixed dyslipidaemia on a maximum-tolerated statin of at least moderate intensity.[125] Evolocumab decreased LDL cholesterol by 65.0% at the mean of weeks 10 and 12 compared with a 0.8% reduction with placebo.[125]

The efficacy and safety of evolocumab was assessed in CKD.[126] In a subgroup analysis of the Fourier trial, participants were categorised into normal renal function (n=8,077), stage 2 CKD (n=15,034) and ≥stage 3 CKD (n=4,443). In this last group, 1064 were stage 3b CKD, 208 were stage 4 CKD and there were no participants with eGFR <20 mL/min/1·73 m². There was no classification in terms of albuminuric status. LDL cholesterol reduction was similar across CKD groups and primary and secondary outcomes were similar across groups.[126] However, absolute reduction in composite endpoints (cardiovascular death, MI, stroke) was increased with evolocumab in participants with more advanced CKD (up to stage 4). Of note, adverse events leading to cessation of therapy, serious adverse events, new onset diabetes and neurocognitive changes occurred more frequently in more severe CKD. But there was no increased risk in adverse events compared with placebo. In terms of

the effect of evolocumab on renal function, there was no significant effect; however, the follow up was short, 2.2 years.[126]

Trials of alirocumab – ODYSSEY trials

The safety of alirocumab was assessed from a pooled analysis of data from 14 ODYSSEY trials. Out of 5,234 participants, 1,524 had type 2 diabetes, 28 had type 1 diabetes and 2 had unspecified diabetes. There was no increase in adverse effects in participants with diabetes compared with the participants without diabetes. There was also no increase seen in HbA1c or fasting plasma glucose, regardless of baseline diabetes status.[127]

The effect of alirocumab was assessed in individuals with CKD (eGFR 30–59 mL/min/1.73 m^2) pooled from ODYSSEY trials.[128] The individuals with CKD were older and had a higher baseline incidence of diabetes (46.3% of the alirocumab group and 52% of the control group). These trials included comparisons of alirocumab versus placebo and alirocumab versus ezetimibe.[128] 10.5% of individuals (315/3,010) receiving alirocumab and 9.4% of controls (152/1,619) had CKD. Baseline levels of LDL cholesterol, non-HDL cholesterol and apo B were lower in the CKD study population and they had higher Lp(a) and TG. The reduction in LDL cholesterol, Lp(a) and non-HLD cholesterol at week 24 was comparable in populations with CKD and without. Safety data was similar; however, serious adverse events occurred at a higher rate in the CKD population. Of note, renal function did not change in response to alirocumab and cardiovascular outcomes were not mentioned.[128]

The ODYSSEY COMBO II trial was a 104-week, ezetimibe controlled, double blind study in 720 participants with documented atherosclerotic cardiovascular disease or high cardiovascular risk at baseline already receiving maximally tolerated statin therapy.[129] It included 148 participants with diabetes treated with alirocumab. Participants with eGFR <30 mL/min/1.73 m^2 were excluded. At 24 weeks, there was a reduction in LDL cholesterol by 49%, non-HDL cholesterol by 41%, Lp(a) by 20% and TG by 15% from baseline. HDL increased by 8%. In this trial, alirocumab treatment did not affect fasting glucose or HbA1c.[129]

The ODYSSEY DM-INSULIN trial was a phase IIIb, randomised, double blind, placebo-controlled, parallel group trial assessing the effect of alirocumab versus placebo over 24 weeks.[130] It looked at 441 participants with type 2 diabetes and 76 with type 1 diabetes treated with insulin, all with high CVD risk (established CVD or with micro/ macroalbuminuria ± retinopathy) and LDL >1.8 mmol/L despite maximally tolerated statin therapy.[130] A significant reduction in LDL cholesterol, non-HDL cholesterol and apo B levels was seen in both participants with insulin treated type 1 and type 2 diabetes. In type 2 diabetes, the percentage difference in LDL reduction in alirocumab versus placebo was 49%. In type 1 diabetes, the percentage difference was 47.8%. There was no significant increase in HbA1c or fasting glucose after 24 weeks.[130]

The ODYSSEY-DM-DYSLIPIDAEMIA trial was a phase IIIb/IV randomised, open-label, parallel group, multi-centre trial comparing alirocumab versus statins and usual care in participants with type 2 diabetes with documented atherosclerotic cardiovascular disease or at least one CVD risk factor and mixed dyslipidaemia.[131] Mixed dyslipidaemia was defined as non-HDL cholesterol ≥2.59 mmol/L and TG 1.70–5.65 mmol/L. Usual care included maximally tolerated statins alone or with added fenofibrate, ezetimibe, omega 3 fatty acids or nicotinic acid. The primary endpoint was a reduction in non-HDL cholesterol. A total of 413 participants were studied over a 24-week period. 14.9% of participants in the alirocumab group had CKD defined as eGFR 15–60 mL/min/1.73 m^2. Alirocumab led to significant reductions in non-HDL cholesterol (32.5% reduction), apo B (32.3%), Lp(a) (27.4%), TC (24.6%) and LDL cholesterol (43.0%) versus usual care.[131]

Adverse effects of alirocumab include nasopharyngitis, upper respiratory tract infection and injection site reaction. Adverse effects of evolocumab include injection site reactions and myalgia. A Mendelian randomised study found an association between PCKS9 genetic variants (that mimic PCSK9 inhibition) and an increased risk of diabetes.[132] While initial studies do not show an increased risk of new onset diabetes or worsened glycaemic control, it is not yet known if there is a longer term effect of PCSK9 inhibition.[127]

Omega 3 fatty acids

The Reduction of Cardiovascular Events with EPA - Intervention Trial (REDUCE-IT) was a phase 3b, double blind, placebo-controlled trial where participants were randomised to 2 g icosapent ethyl twice daily or placebo and were followed for 4.9 years (median).[133]

The trial included 8,179 people on statins with established ASCVD or diabetes (57.9% of the participants had type 2 diabetes and 0.7% had type 1 diabetes) with raised TG 1.52 to 5.63 mmol/L. Baseline eGFR was <60 mL/min/1.73 m^2 in 21.8% of the icosapent ethyl group and 28.8% of the placebo group.

The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal 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.[133] There was a 25% relative risk reduction in primary composite endpoint, NNT=21. These benefits were observed regardless of the presence or absence of diabetes or level of eGFR.

In terms of safety and serious adverse events, the rate of atrial fibrillation was higher in the icosapent ethyl group compared with placebo (5.3% vs 3.9%) as was the rate of peripheral oedema (6.5% vs 5%). Serious bleeding events also occurred more frequently in the icosapent ethyl group (2.7% vs 2.1%).[133]

The results from REDUCE-IT cannot be generalised across the board to other omega 3 fatty acids. There is a differential effect on lipoprotein composition with icosapent ethyl preparations compared with docosahexaenoic acid (DHA) preparations and indeed with dietary supplements with variable n-3 fatty acid content.

Inclisiran

Inclisiran is a small-interfering RNA which inhibits production of PCSK9 protein in the liver. This is delivered as a six-monthly injection. Inclisiran is due to be trialled in collaboration with Novartis and the National Institute for Health Research (NIHR) in the UK.

Bile acid sequestrants

At the maximum dose, these reduce LDL cholesterol by up to 25%. However, they have adverse gastrointestinal effects drug interactions limiting their use. Colesevelam can be used in conjunction with statins.

Phytosterols

An intake of 2 g daily of phytosterols leads to a 10% lowered TC and LDL cholesterol. It is not clear if this is associated with a reduced CVD risk. ESC/EAS and ADA guidelines recommend these in individuals who do not qualify for pharmacological therapy, as an adjunct where target cholesterol levels are not met, or as part of a healthy diet.[14,16] Plant stanols are not recommended for people with either CKD or diabetes in current NICE guidelines.[15]

Nicotinic acid

Nicotinic acid and its derivatives were first recognised as lipid-lowering agents over 60 years ago.[134] Studies confirm that nicotinic acid reduces LDL cholesterol and TG while increasing HDL cholesterol in type 2 diabetes.[135] Studies in individuals with CKD, including those on dialysis, have confirmed that nicotinic acid improves dyslipidaemia and has a phosphate lowering effect.[136-138] However, based on current evidence (discussed below), nicotinic acid is not recommended as a lipid-lowering agent in DKD for reduction of CVD risk, notwithstanding that this medication is no longer available in the UK or Europe as it has been withdrawn from the market.

In the AIM-HIGH study (34% of the 3,414 participants had diabetes), there was no beneficial additive effect of nicotinic acid compared with placebo in participants treated with simvastatin ± ezetimibe to maintain LDL cholesterol <2.07 mmol/L.[139]

A consistent finding with niacin in diabetes has been an elevation of HbA1c and modest worsening of fasting hyperglycaemia through excess fatty acid release.[140]

In studies in dialysis, the risk of thrombocytopenia is significantly increased.[137,138]

Laropiprant, a prostaglandin D2 receptor antagonist, can reduce the flushing associated with niacin. The HPS2-THRIVE trial using a niacin laropiprant combination therapy demonstrated both overall and within the diabetes subgroup that there was no cardiovascular benefit despite consistent increased HDL cholesterol.[141,142]

7 Monitoring and safety of hypolipidaemic agents

Recommendations

1   We recommend routine measurement of liver enzymes before statin initiation in DKD, at 3 months after commencement and annually thereafter (Grade 1C).

2   We recommend measurement of serum creatine kinase in people with muscle pain (Grade 1C).

3   We do not recommend >40 mg/ day simvastatin in DKD due to the increased risk of muscular side effects (Grade 1A).

4   We do not recommend >20 mg/ day simvastatin when prescribed in combination with amlodipine or diltiazem (Grade 1B).

5   We recommend caution with lipid-lowering therapy in women of child-bearing potential and appropriate counselling and discontinuation of these agents if pregnancy is contemplated. Lipid-lowering therapy should be discontinued during pregnancy and lactation (Grade 1B).

Statin side effects and safety in CKD

The overall safety of statins has been exhaustively evaluated. In general use, serious side effects are considered remarkably uncommon, although controversy remains as to the frequency of muscular symptoms in the absence of raised muscle enzyme levels. This would appear to be more frequently encountered in routine clinical practice than was reported in the randomised clinical studies.

A previous database of hospitalisation for rhabdomyolysis suggested no increased rates for any statins but did observe an increased rate of rhabdomyolysis with statin-fibrate combinations among older people with diabetes, although this was predominantly among those using cerivastatin, which is not in used in the UK.[143]

A meta-analysis suggested a reduced risk of pancreatitis with statins in people with normal or mildly elevated TG levels.[144]

When specifically examining 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), nor was there any change in withdrawal rates in comparison to placebo.[145] The 2014 Cochrane analysis recorded increased withdrawal from treatment in those with lower kidney function and with diabetes. It is not clear if this is due to side effects of treatment.[69]

Other meta-analyses of statins in CKD also found no difference in the frequency of hepatic or muscular disorders in comparison to placebo.[79,80]

In the TNT study comparing high (80 mg) versus low (10 mg) atorvastatin, in the cohort that had CKD, there was no evidence of muscular toxicity, although hepatic enzyme elevation >3 times the ULN was observed in 1.4 vs. 0.1%, of participants respectively.[75]

In the SHARP study where simvastatin was combined with ezetimibe, there was no evidence of muscular or hepatic toxicity in comparison to placebo.[65] With active therapy, reduced pancreatitis

episodes were observed although a similarly significant increase in withdrawal for muscle pain was noted.

In people on dialysis, there were no cases of rhabdomyolysis or severe hepatic dysfunction in the 4D study with 20 mg atorvastatin or in the AURORA study with 10 mg rosuvastatin.[85,146]

The interaction between simvastatin and a number of drugs leading to increased risk of rhabdomyolysis is well established. In keeping with MHRA advice, we recommend that the maximum dose of simvastatin prescribed with amlodipine or diltiazem should not exceed 20 mg daily. Combinations of simvastatin and ciclosporin, danazol and gemfibrozil should be avoided.

NICE guidance routinely suggests measurement of liver enzymes before, 3 and 12 months after introduction of a statin.[15]

NICE also suggests determining if someone has persistent muscle pain prior to initiating a statin. If so, then measurement of creatine kinase is advised. If the level is >5 times the upper limit of normal (ULN), the levels should be retested after 7 days, and if these are still elevated >5 times the ULN then statin treatment is not advocated. If the levels are elevated <5 times the ULN a lower dose of statin initiation is suggested.[15] In addition, in this situation, ACC guidelines suggest consideration of alternate dosing strategies, e.g. use of long half-life statins (e.g. atorvastatin, rosuvastatin) administered three times a week or once weekly.[147]

Haemorrhagic stroke

The CTT reported a non-statistically significant increased risk of haemorrhagic stroke with statins.[97] Statins lower the risk of ischaemic stroke and in many trials the type of stroke is not differentiated (haemorrhagic versus ischaemic) making it difficult to assess the effect of statins on stroke risk.

Pregnancy and breastfeeding

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.[15] Bile acid sequestrants have been used in pregnancy and this would be an appropriate alternative if required.

Neurocognitive dysfunction

Prolonged exposure to extremely low LDL cholesterol levels may lead to neurocognitive dysfunction. The FDA issued a warning related to statin therapy in 2012 with regard to reversible impairment in cognition. Systematic reviews and meta-analyses have shown conflicting evidence for this. The 2014 Statin Cognitive Safety Task Force concluded that statins are not associated with adverse cognitive effects.[148]

EBBINGHAUS, was a dedicated cognition study which enrolled >1,900 participants from FOURIER and used the Cambridge Neuropsychological Test Automated Battery to look at any effect on cognition.[122,149] A total of 1,204 participants were followed for a median of 19 months and no significant difference was found in cognitive function.

Statins and risk of diabetes

Statins increase the risk of developing type 2 diabetes.[150,151] The mechanism may be through an increase in body weight, increased insulin resistance and decreased beta cell function.[151] Mendelian randomisation studies looking at variants in the gene encoding HMGCoA reductase suggest a link between lower LDL cholesterol and increased risk of type 2 diabetes.

In JUPITER, non-diabetic participants with CKD receiving 20 mg rosuvastatin experienced a marginal but significant increase in HbA1c of 0.1% (p=0.001), although fasting glucose was unaltered.[70] In JUPITER, participants with ≥1 type 2 diabetes risk factor were at higher risk of developing type 2 diabetes than those without risk factors.

In the Women's Health Initiative, involving 161,808 postmenopausal women aged 50–79 years, statin use at baseline was associated with an increased risk of type 2 diabetes.[152] The hazard ratio after adjusting for potential confounding factors was 1.48; 95% CI, 1.38–1.59.[152]

It has been suggested that people of Asian ethnicity are at increased risk of the adverse glycaemic effects of statins due to the increased insulin resistance induced by statins. The Heart Outcomes Prevention Evaluation (HOPE)–3 trial evaluated the effects of 10 mg rosuvastatin among ethnically diverse participants across six continents.[153] HOPE-3 found no interaction between ethnicity and the benefit of statins on composite cardiovascular outcomes. Thus, the benefit of statin therapy seems equivalent based on ethnicity, although it has been suggested that optimal doses are lower in Asian populations. In MEGA, a randomised trial of low dose (10–20 mg pravastatin) in Japan, treatment with a low dose of pravastatin reduces the risk of coronary heart disease in Japan comparably to higher doses used in Europe and in the USA.[154]

Despite the reported adverse effect on glycaemia, the overall treatment benefit of statins in terms of reduced CVD risk and cardiac events outweighs the risk of adverse effects.

8 When to stop hypolipidaemic agents

Recommendation

1   We recommend initiation and continuation of statin therapy in people aged >75 years to be considered on a case by case basis, with consideration given to comorbidity, polypharmacy and life expectancy. Where statins are initiated in this age group, we suggest a lower starting dose and careful monitoring (Grade 1C).

Use of hypolipidaemic agents in older populations

While CVD is prevalent in older people, evidence for risk reduction by lipid management is limited in this group. It appears that the most important means to reduce CVD in older people would be through earlier risk reduction. Subgroup analysis of major statin trials have been performed to determine if there is a differential outcome among different age groups.

In JUPITER and in HOPE-3, post hoc analyses demonstrated equivalent CVD risk reduction in participants older or younger than 70 years.[155] In the 4S study, participants >65 years had a similar risk reduction to younger participants. In the HPS study, the risk reduction was similar in age groups <65 years, 65–70 and >70 years. Similar results were found in LIPID, CARE and TNT.

PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) included participants from Scotland, Ireland and the Netherlands, aged 70–82 years with CVD, or at high risk for CVD and compared pravastatin 40 mg versus placebo.[156] The prevalence of diabetes ranged from 6.9% – 14.7%.[156] CVD outcomes were reduced in the statin group (hazard ratio 0.80) but there was no reduction seen for stroke or in all-cause mortality.[156]

In the SAGE trial (Studies Assessing Goals in the Elderly) (n=893), pravastatin 40 mg was compared with atorvastatin 80 mg.[157] Participants had baseline ambulatory (Holter) ECG monitoring for 48 hours and were included in the study if they had ≥1 episode of myocardial ischaemia lasting ≥3 minutes. The primary outcome was an absolute change in the duration of myocardial ischaemia from baseline to 12 months. In both the pravastatin and atorvastatin groups a reduction in ischaemia was seen and both regimes were equally effective. In addition, the atorvastatin group had lower all-cause mortality (HR 0.33) and a non-significant trend towards reduction in CVD.[157]

A CTT analysis of statin therapy at different ages found evidence of benefit in those aged >75 years.[158] The benefit was greater in those with pre-existing vascular disease and there was a trend towards smaller proportional risk reduction in major vascular events with increasing age. This meta-analysis included 28 trials and 186,854 participants, 8% of whom were aged >75 years.

There may however be an inherent bias in this meta-analysis and indeed in most studies and other post-hoc analyses as people with frailty, e.g. with dementia or multiple comorbidities, would be unlikely to be recruited to these trials in the first place. The older group of participants included may therefore represent the healthier and possibly more engaged cohorts. The meta-analysis found that the older participants included in the studies were less likely to be smokers and in the older participants, baseline LDL cholesterol levels were lower.[158]

Statin interactions are important to consider in this age group. The ESC/EAS guidelines advise initiation of statins in people older than 75 years if they are considered to be at high risk, starting at a low dose and titrating up cautiously.[16] The KDIGO guidelines do not have an upper age limit for treatment recommendations.[46] With regard to glycaemic management, ADA guidelines further

categorise older people into: stable elderly, those with organ failure and end of life. With regard to lipid management, they advise continuing statins in people aged >75 years and only to consider statin initiation following discussion of risk and benefit.[14]

Quality standard measures

Suggested quality measures for management of lipids in DKD are noted below.

    i.   Proportion of DKD (including those with ESKD, on dialysis or post-transplant) with annual measurement of lipid profile.

    ii.   Proportion of DKD achieving proposed lipid target levels.

    iii.   Proportion of DKD (including those with ESKD, on dialysis or post-transplant) taking statins for primary and secondary prevention of CVD.

    iv.   Proportion of DKD not on statins with documentation regarding discussion of lipid management.

    v.   Proportion of DKD on alternative hypolipidaemic agent e.g. ezetimibe, fibrate, PCKS9 inhibitor, icosapent ethyl.

Areas of uncertainty for lipid-lowering therapy

- *Is there a role for early intervention and lipid management in young people with type 1 or type 2 diabetes?*

Currently there is a dearth of evidence in younger people. Many large studies are comprised of participants with type 2 diabetes with average age 50 – 60 years. We currently do not have any evidence to suggest that early intervention reduces CVD risk. However, the heavy burden of CVD with diabetes and DKD validates the need to investigate and manage younger adults. In the absence of evidence of harm, we currently propose treatment of younger adults with DKD; however, larger studies in younger adults are needed, with prolonged duration of follow up.

- *What is the safety profile of high intensity safety and efficacy of lipid-lowering therapies when eGFR <30 mL/min/1.73 m^2 and when eGFR <15 mL/min/1.73 m^2?*

The TNT study suggested that high dose (80 mg) atorvastatin in people with stable CVD leads to significant benefits in terms of CVD risk, compared with 10 mg atorvastatin, with no excess risk of myopathy. However, the numbers of participants in the G5 CKD group were low.[64] Previous meta-analyses have not identified excess adverse events with statins in CKD.[79]

It is possible that further benefit for CVD risk and/or renal outcomes may be achieved with high dose atorvastatin compared with other agents. Currently clinicians are cautious in using higher intensity statins at lower eGFR and definite evidence regarding safety and efficacy is needed in this cohort.

- *What approach should be used for statin intolerant people with DKD?*

Despite statins being extensively studied and widely accepted as well tolerated, there is a small proportion of people who are unable to tolerate statin therapy due to side effects, usually myalgia. A small proportion experience genuine myopathy and/ or rhabdomyolysis, but this is rare. However, there is ongoing debate about the relative incidence and severity of statin related side effects in real world clinical practice. Clinical evidence is somewhat lacking about strategies to address statin intolerance while aiming to reduce cardiovascular risk. Alternative options would include ezetimibe monotherapy, very low dose statin with additional ezetimibe, fibrates or PCSK9 inhibitors. Further study is required to delineate the exact role for these agents for people with DKD.

- *Does the efficacy of different statins in high intensity doses depend on baseline levels of inflammation and/or absolute reductions in CRP?*

It is widely documented in a number of clinical trials or observational epidemiological studies that elevated levels of inflammatory markers such as CRP are predictive of CVD. Statins have been shown to reduce C-reactive protein. It is unknown in CKD whether specific subtypes of people such as those with elevated CRP may derive relatively greater benefit from lipid-lowering therapy with statins. While this is somewhat speculative, and overall there has been limited benefit from lipid-lowering therapy in dialysis despite significant reduction in CRP with statins, one analysis has shown that once correction is made for inflammation, there is a linear relationship between TC and CVD risk in dialysis.[159] This notion suggests that levels of inflammation may confound any relationship between cholesterol and outcome and either people with high grade inflammation are malnourished and do not need cholesterol lowered, or alternatively these people are at highest risk and may have most to gain from statin therapy. Further study of the relationship between inflammation, CVD risk and lipid profile is required.

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Appendix: Comparison of national and international lipid guidelines

Guideline	Stratification	Monitoring	Dose modification	Treatment targets	Hypertri-glyceridaemia	Dialysis	Transplant	PCSK9 inhibitors and ezetimibe	Older people and frailty
NICE 2018	Atorvastatin 20 mg recommended for type 1 diabetes aged >40 years, or with diabetes duration >10 years, with established nephropathy, or with other cardiovascular risk factors. Type 2 diabetes, statin recommended if 10 % 10-year CVD risk using QRISK2 Atorvastatin 20 mg recommended for people with CKD	Measure total, non-HDL, LDL at 3 months	Advise to use a high intensity statin, atorvastatin 20 mg eGFR <30 suggest consultation with a nephrologist prior to consideration of higher intensity statins	>40% reduction in non-HDL cholesterol	Plant stanols, omega 3 fatty acid compounds and fibrates not recommended			Ezetimibe recommended where statin therapy is contra-indicated Evolocumab or alirocumab recommended for primary prevention in familial hypercholesterolaemia and very high CVD risk, LDL >5.0 mmol/L or in those with known CVD and LDL cholesterol >3.5 or 4.0 mmol/L depending on further cardiovascular risk	Atorvastatin 20 mg may be considered for adults >85 years
JBS 2014				Non-HDL <2.5 mmol/L LDL <1.8 mmol/L	Fibrates not recommended routinely but possible role for fibrates if eGFR >60				
American Heart Association and American College of Cardiology 2019	Moderate intensity statins in adults aged 40 to 75 years with diabetes. The presence of cardiovascular risk modifiers: long duration of diabetes (≥10 years for type 2 or ≥20 years for type 1), albuminuria ≥30 mcg albumin/mg creatinine, eGFR <60, retinopathy, neuropathy, ankle brachial pressure index <0.9 are factors to consider when recommending high intensity statins				Fibrates were not recommended routinely for CVD risk reduction but could still have a role in reducing the progression of retinopathy and progression to persistent proteinuria when eGFR was >60				

Guideline	Stratification	Monitoring	Dose modification	Treatment targets	Hypertri-glyceridaemia	Dialysis	Transplant	PCSK9 inhibitors and ezetimibe	Older people and frailty
American Diabetes Association 2020	Adults with diabetes aged 40 to 75 years, moderate intensity statin is recommended. Adults aged 20-39 years with additional CVD risk factors, statin initiation is suggested. High intensity statins recommended for people of all ages with diabetes and increased risk factors, including established ASCVD.	In patients not taking statins, monitoring of lipid profiles (TC, LDL cholesterol, HDL cholesterol and TG) at diagnosis and every five years in adults <40 years. At statin initiation and 4-12 weeks after initiation or dose change			Fibrates not recommended Icosapent ethyl recommended			Adults with 10-year ASCVD risk >20 % statin/ezetimibe combination recommended For secondary prevention, ezetimibe or PCSK9 inhibitors recommended if LDL cholesterol levels >1.8 mmol/L	>75 years continuation of statins suggested
KDIGO 2013	Based on eGFR alone not on albuminuria status Regards type 1 and type 2 diabetes as equivalent Statin alone if ≥50 years with eGFR >60 or aged 18–49 years with CKD and diabetes Statin or statin-ezetimibe combination recommended for adults ≥50 years with eGFR <60 if not on dialysis or with a renal transplant.	Lipid measurement is recommended initially at all stages of CKD including dialysis or transplantation. Does not advise monitoring	eGFR <60 high intensity statins not recommended	No targets	Fibrates not recommended in CKD	Not to be initiated but can be continued	Statin recommended	Ezetimibe suggested for adults ≥50 years with eGFR <60 if not on dialysis or with a renal transplant	No upper age limit suggested
European Society of Cardiology/European Atherosclerosis Society 2019	High risk Diabetes with an additional risk factor Diabetes duration >10 years CKD stage 3	Non-fasting LDL, non-HDL cholesterol and apolipoprotein B (apo B) and advise measuring lipoprotein a		High risk ≥50 % reduction in LDL cholesterol Goal LDL cholesterol <1.8 mmol/L	If TG >2.3 mmol/L, fenofibrate or bezafibrate may be considered in combination with statin Omega-3 fatty acids		Low dose statin with up-titration recommended	Addition of ezetimibe is recommended. PCSK9 inhibitor is recommended in people with high or very high risk who fail to achieve target levels despite	Treatment is recommended ≤75 years >75 years, consideration of treatment in high risk groups

Guideline	Stratification	Monitoring	Dose modification	Treatment targets	Hypertri-glyceridaemia	Dialysis	Transplant	PCSK9 inhibitors and ezetimibe	Older people and frailty
	Very high risk Diabetes with target organ damage Type 1 diabetes of long duration, >20 years CKD stage 4,5 Documented atherosclerotic cardiovascular disease	(Lp(a)) at least once in a person's lifetime		Goal non-HDL cholesterol ≤2.6 mmol/L Very high risk ≥50 % reduction in LDL cholesterol Goal LDL cholesterol <1.4 mmol/L Goal non-HDL cholesterol ≤2.2 mmol/L For those at very high risk with recurrent ASCVD, a non-HDL cholesterol goal of <1.8 mmol/L is suggested.	(specifically icosapent ethyl 2 – 2g/day) are recommended in people with TG levels between 1.5–5.6 mmol/L, at high or very high cardiovascular risk, already treated with statins			being on a maximum tolerated statin and ezetimibe	suggested

The Renal Association

The Renal Association is the leading professional body for the UK renal community. From its foundation in 1950, the Renal Association has been active in promoting and disseminating research that may ultimately improve outcomes for patients with kidney disease.

www.renal.org

The Association of British Clinical Diabetologists

Established in 1997, the Association of British Clinical Diabetologists (ABCD) is the national organisation of consultant physicians in Britain who specialise in diabetes mellitus. Most are also acute general physicians, and many are also specialists in endocrinology and lipid metabolism.

www.diabetologists-abcd.org.uk