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

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Lead authors
Sagen Zac-Varghese PhD FRCP
Patrick Mark FRCP
Peter Winocour MD FRCP

ABDC UKKA writing group additional members
Stephen Bain MD FRCP
Debasish Banerjee MD FRCP
Tahseen A Chowdhury MD FRCP
Indranil Dasgupta DM FRCP
Parijat De MD FRCP
Damian Fogarty MD FRCP
Andrew Frankel MD FRCP
Gabrielle Goldet MRCP
Janaka Karalliede MD FRCP
Ritwika Mallik MRCP
Rosa Montero MD MRCP
Adnan Sharif MD FRCP
Mona Wahba MA FRCP

Authors

Sagen Zac-Varghese, Consultant Diabetologist, East and North Herts NHS Trust
Patrick Mark, Professor of Renal Medicine, University of Glasgow
Peter Winocour, Consultant Diabetologist, East and North Herts NHS Trust
Steve Bain, Professor of Medicine (Diabetes), Swansea University, Swansea
Debasish Banerjee, Consultant Nephrologist, St George's Hospital, London
Tahseen A Chowdhury, Consultant Diabetologist, Royal London Hospital, London
Indranil Dasgupta, Consultant Nephrologist, Heartlands Hospital, Birmingham
Parijat De, Consultant Diabetologist, City Hospital, Birmingham
Damian Fogarty, Consultant Nephrologist, Belfast Health and Social Care Trust, Belfast
Andrew Frankel, Consultant Nephrologist, Imperial College Healthcare NHS Trust, London
Gabrielle Goldet, Renal Specialist Registrar, Imperial College London NHS Trust
Janaka Karalliede, Consultant Diabetologist, Guy's and St Thomas' Hospital London
Ritwika Mallik, Endocrinology Specialist Registrar - Barts Health NHS Trust
Rosa M Montero, Consultant Nephrologist, St George's Hospital, London
Adnan Sharif, Consultant Nephrologist, University of Birmingham
Mona Wahba, Consultant Nephrologist, St Helier Hospital, Carshalton

Correspondence

Sagen Zac-Varghese
East and North Herts Institute of Diabetes and Endocrinology (ENHIDE),
Lister Hospital, Stevenage SG1 4AB, UK
Tel +44 (0) 1438 284090
Email: sagen.zac-varghese@nhs.net

Peter Winocour
East and North Herts Institute of Diabetes and Endocrinology (ENHIDE),
Queen Elizabeth II Hospital, Welwyn Garden City, Herts AL7 4HQ, UK
Tel +44 (0)1438 288324
Email: peter.winocour@nhs.net

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Contents

Summary of changes

1. We have updated the treatment target level
    - LDL cholesterol ≤ 1.8 mmol/L (from previous target of ≤ 2 mmol/L)

2. We have updated Section 6 - *Choice of hypolipidaemic agent* and included discussion of inclisiran, Bempedoic acid and icosapent ethyl.

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 on the risks and benefits of 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 (urine ACR) – 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]

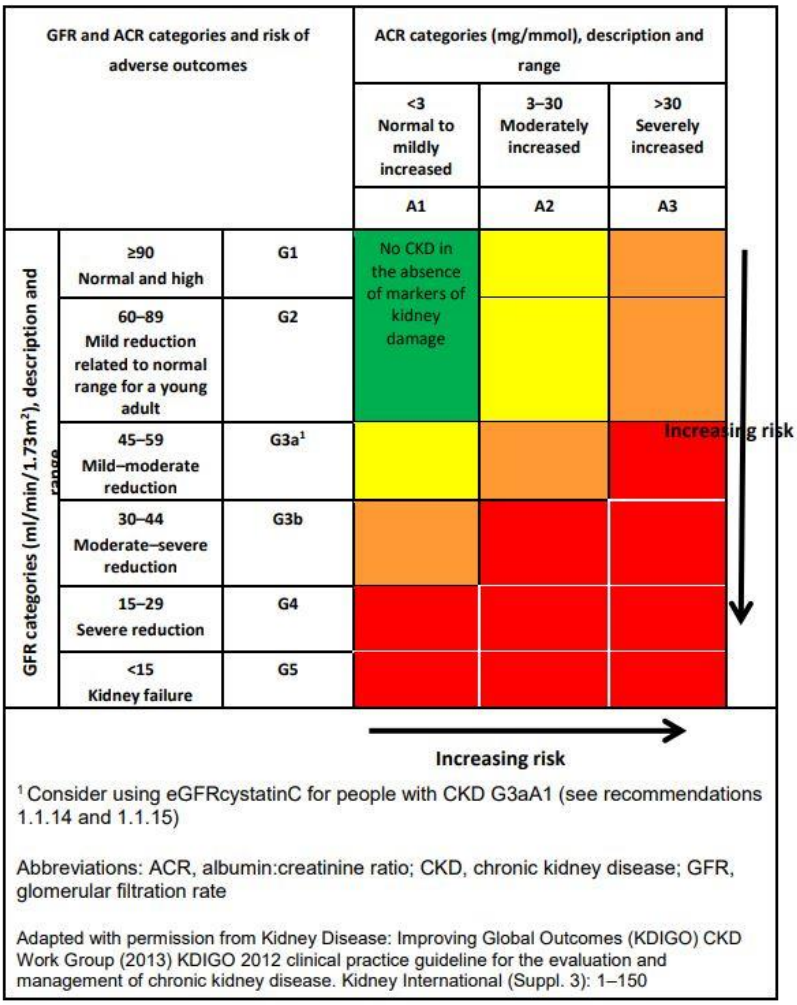
There is marked variation between these guidelines in terms of monitoring, treatment, and treatment targets. In some guidelines, recent trials of newer hypolipidaemic agents, described in later sections, have led to the recommendation of lower treatment targets. Target attainment should consider the 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 a dearth of evidence regarding lipid management in people with 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



Methodology

The 2017 ABCD-RA clinical practice guidelines were based upon systematic literature searches conducted between October 2013 and March 2016.
The 2021 updated guideline was based on searches conducted between April 2016 and January 2020.
This 2024 update is based on searches conducted between January 2020 and March 2023.

We searched PubMed, the Cochrane database of systematic reviews and hand searched reference lists and articles identified by ABCD-UKKA 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 (TC), 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 TC, 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 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), a single LDL particle linked to an apo (a) protein, is an independent CVD risk factor which is highly genetically determined. CKD is related to changes in Lp(a) catabolism and metabolism. Several studies have shown that Lp(a) is elevated in CKD, possibly related to reduced clearance.[22,23] It has also been hypothesised that the prolonged duration of elevated Lp(a) in people on dialysis may contribute towards CVD.[24] 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.

Marked proteinuria with nephrotic syndrome (urine ACR >220 mg/mmol, hypoalbuminaemia and oedema) leads to more evident dyslipidaemia that is associated with premature CVD and progressive kidney disease.[25] 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.[25] In nephrotic syndrome, LCAT activity is reduced and cholesterol ester transfer protein (CETP) is activated leading to production of immature HDL.[20,25-35]

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.

Kidney transplant recipients have a high prevalence of dyslipidaemia, including raised TC, HDL and LDL cholesterol and hypertriglyceridaemia.[36] Dyslipidaemia is a consequence of immunosuppressive therapy, specifically corticosteroids, ciclosporin (more so than tacrolimus), sirolimus and everolimus.[37] 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.

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.[38] This was first proposed as the lipid nephrotoxicity hypothesis in 1982.[38] 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.[39]

In type 1 and type 2 diabetes, dyslipidaemia may be independently linked with the progression of DKD.[35,40-42] A range of lipoprotein measures including hypertriglyceridaemia, apobetalipoproteinaemia, elevated Lp(a) and apo E have been related to progression of DKD.[19,26,34,43]

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.[32,34,35]

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 TG levels to be <4.5 mmol/L.

Non-HDL cholesterol is calculated as TC 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, TG rich molecules and the loss of benefit of higher HDL cholesterol levels.[44] 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.[16,45] 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 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 regarding monitoring lipid profiles.

The **KDIGO guidelines** recommend lipid measurement initially at all stages of CKD; however, do not recommend follow up measures.[46] There is also debate regarding the value of measuring lipids in people on dialysis.[47] 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 to monitor response to treatment and to assess compliance.[14]

The **ESC/EAS** guidelines advise assessment of response to therapy at 6–8 weeks and monitoring at 6–12 months.

NICE recommend annual lipid profile screening and at 3 months following initiation of a statin.[45]

We feel that annual screening is a reasonable approach. It is also acceptable to monitor more frequently if this influences management. Post-transplantation, 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.

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 albuminuria 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.[8-10,48-51] 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,[52] to 0.69% per annum in UK adults aged 35–45 years (n≈7500).[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.[53,54] Studies demonstrate that the most consistent predictors of CVD risk are age, chronically poor glycaemic control and markers of nephropathy, primarily albuminuria.[6,48,52] The presence of albuminuria conveys a 10-fold greater risk of CVD compared with type 1 diabetes without albuminuria.[12,49,52]

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.[12,34] 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.[55] 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.[8,50,51] 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.[34] It appeared that apo B was an independent predictor of coronary artery disease (CAD) in men while the TG: 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 urine ACR 11 mg albumin/ g creatinine). In these individuals, the primary outcome for both statins and ACE inhibitors was urine ACR. Secondary outcomes were changes in GFR, retinopathy, lipid levels, CRP, and arterial intimal medial thickness (aIMT).[56] The primary outcome was not affected by ACE inhibitors or statins. Statins were associated with reductions in TC, LDL and non-HDL cholesterol. However, no change was noted in carotid intima-media thickness, cardiovascular markers, GFR or retinopathy.[57] 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 urine ACR 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.[58] 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.[58] 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.[59]

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.[60] 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 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. [32] 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 albuminuria 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.[7,60,61] 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.[7,13,61] Thus, the combination of type 2 diabetes with albuminuria, stage G3 CKD or higher substantially increases the risk of CVD.[61]

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.[62-64]

CARDS, SHARP and TNT evaluated lipid-lowering strategies in people with type 2 diabetes characterised by the degree of glomerular filtration and albuminuria.[65-67]

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.[67]

The SHARP study evaluated >9,000 people with CKD of whom 23% (2,094 people) had type 2 diabetes.[66] 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.[66] 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.[68]

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%.[59] In the 2008 meta-analysis, the CTT collaborators investigated the impact of renal dysfunction on outcomes.[59] 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.[69] 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.[69]

A 2014 Cochrane review of statins in people with CKD (not requiring dialysis) found that mortality and major coronary events were reduced by 20%.[70]

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.[71] 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.[71,72] 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.[71]

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.[73] 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.[73]

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.[74]

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.[75] However, as with larger studies, failure to achieve tight cholesterol targets was seen, 30% of the participants still had TC 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.[68,76] This effect was not observed in the CARDS, PANDA or SHARP studies with between 2 to 4 years follow up.[67,77,78] 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.[79]

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)).[80,81]

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.[80,82] The 2014 updated Cochrane analysis for people with CKD not requiring dialysis confirmed the lack of beneficial effect on statins on creatinine clearance.[70]

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 hypolipidaemic agents be continued in those commencing dialysis, (Grade 2D).

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

3 Where indicated, we recommend that hypolipidaemic agents should be commenced post kidney transplantation or combined kidney-pancreas transplantation and that the choice and dose of hypolipidaemic agent 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 with a 'J' or 'U'-shaped relationship between cholesterol and mortality, possibly driven by malnutrition or inflammation being associated with lower serum cholesterol levels.[83]

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. For some, continuation of hypolipidaemic agents may be inappropriate. 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.[84] Therefore, it is important to lower cardiovascular risk. Lipid-lowering therapy is likely to be beneficial for many renal transplant recipients.[85]

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. [86] 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.[87] 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.[88]

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. [66]

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.[69]

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.[69] However, smaller effects were seen as eGFR declined with little evidence of benefit seen in dialysis.[69] 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.

There are no direct data to inform whether to continue lipid-lowering therapy once dialysis has commenced.

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.[89]

A retrospective cohort study in people on dialysis with peripheral arterial disease and dyslipidaemia, identified from the Taiwanese national health insurance research database (NHIRD), found that people on statins had a reduced risk of cardiovascular disease and all cause death at 3 years follow up, hazard ratio 0.86 [95% CI 0.77-0.96] and reduced risk of adverse limb events.[90] This study included 6470 people who were 1:1 propensity score matched, 83.3-84.1% with diabetes.[90]

Conversely, a study looking at 20–40-year-olds on dialysis, identified from the Taiwanese NHIRD, comparing people who had received statin therapy for > 90 days or had never received statins, balanced with propensity score weighting, found that the statin group (n = 771) had a higher risk of MACE, hazard ratio 1.44% (95% CI 1.43-2.45).[91] The authors included a discussion on whether statin therapy contributed to atherosclerotic plaque calcification in the context of possible vitamin K deficiency amongst people on dialysis.

Although clear evidence of benefit has not been demonstrated in trials of lipid-lowering therapy in people with diabetes on dialysis, currently, there are no convincing data to suggest harm in using lipid-lowering therapy.

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.[85] In the 2-year extension trial, fluvastatin led to a significant 35% relative reduction in the risk of cardiac death or non-fatal MI.[92] In a post-hoc analysis of ALERT, 18.7% of participants had diabetes at baseline and diabetes was a risk factor for cardiac death.[93] 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).[94] However, the effects were imprecise and included the possibility of no effect.[94] The adverse effect of statins, including on liver enzymes and creatine kinase, was uncertain.[94] 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.[95] This risk appears to be greatest with simvastatin and is lowest with fluvastatin or pravastatin.

A retrospective study looked at renal transplant recipients, comparing those on statins (n=250) to those without.[96] In this study, 48% were on atorvastatin, 15% on simvastatin, 4% on fluvastatin, 4% on rosuvastatin, and 3% of statin on pravastatin.[96] Whilst overall statins did not reduce the risk of the primary outcome of compound cardiovascular events (ischaemic cardiovascular events or death) there was a significant positive association of statin use in a subgroup of those on cyclosporin, hazard ratio 6.60 (95% CI 1.75-24.9) and correlation of statins with cyclosporin trough levels.[96] This study found that statin use is potentially harmful in those on cyclosporin.

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.[97,98]

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.[99] 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.[100] 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 the following treatment targets
- TC ≤ 4.0 mmol/L,
- non-HDL cholesterol ≤ 2.5 mmol/L,
- LDL cholesterol ≤ 1.8 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.[101] A lower LDL cholesterol (≤1.8 mmol/L) was associated with a further 15% reduction in major vascular events.[101] There was no evidence of a threshold LDL cholesterol level or 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.[70] Paradoxically, however, many guidelines suggest tighter targets for people with a greater severity of CKD.

National and international guidelines all recommend different target LDL and non-HDL cholesterol levels.[14,45,102] In addition, some recommend target attainment levels, whereas others, e.g. NICE, recommend a percentage reduction from baseline.

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 ≤1.8 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

Where indicated and to achieve lipid treatment targets:

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

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

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

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

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

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

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

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

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

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

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

Introduction

Role for statins

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.[103,104] 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.

Table 3 Examples of high intensity and moderate intensity statins in the USA. Adapted from ADA guidelines[102]

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
	Pitavastatin 1-4

Table 4 Effect of statin dose on LDL cholesterol. Statins are grouped into different intensity categories according to the percentage reduction in LDL 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 LDL 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.[105] 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.[106]

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.[66]

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 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.[107]

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 Bempedoic acid

Bempedoic acid is a once daily, oral medication used at a dose of 180 mg. It is a prodrug converted to bempedoyl-CoA by very-long-chain acyl-CoA synthetase-1, an enzyme present within the liver but absent in skeletal muscle, thus eliciting a liver specific action.[108] The active substrate, bempedoyl Co-A, inhibits ATP citrate lyase, an enzyme up stream of HMG-CoA reductase, thus suppressing cholesterol synthesis. This leads to increased membrane LDL receptors and LDL cholesterol clearance.[108]

CLEAR trials
The CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) trials are phase 3 double blind, randomised controlled trials.

Clear Tranquility was a 12 week study involving 269 people with a history of statin intolerance and LDL cholesterol > 2.6 mmol/L.[109] Following a 4-week run in with ezetimibe, Bempedoic acid or placebo was initiated.[109] The primary endpoint was change in LDL cholesterol at week 12. The combination of Bempedoic acid and ezetimibe reduced LDL cholesterol by 28.5 % (95 % confidence interval -34.4 to -22.5 %).[109] Non-HDL cholesterol was reduced by 23.6 % (±2.8 %) and hsCRP reduced by 31 %.[109]

CLEAR Harmony, involving 2230 people (1488 on Bempedoic acid), assessed safety (primary end point) and efficacy (secondary end point) over a 52-week period.[110] Participants had ASCVD, heterozygous familial hypercholesterolaemia or both with an LDL cholesterol of at least 1.8 mmol/ L and were on maximally tolerated statins with or without additional lipid lowering medications. 28.6 % of people in each group had diabetes. People on simvastatin > 40 mg or gemfibrozil were excluded. Bempedoic acid led to a 0.5 mmol/ L reduction in LDL cholesterol at week 12 and a 13.3 %

reduction in non-HDL cholesterol. These effects slightly waned but were still evident at 52 weeks. There was a minor increase in serum creatinine in the Bempedoic acid group which was purported to be related to renal transporter competition. There was a significant increase in uric acid and gout. The incidence of new-onset diabetes or worsening of glycaemic control was lower in the Bempedoic acid group, 3.3 % versus 5.4 %.[110]

CLEAR Wisdom was similarly designed to CLEAR Harmony.[111] In this study, the primary endpoint was LDL cholesterol change. The secondary endpoint was changes in other lipid parameters including non-HDL cholesterol. Participants had ASCVD, heterozygous familial hypercholesterolaemia or both on maximum tolerated statins (however, not all were on a statin or alternate lipid lowering medication).[111] 5 people on PCSK9 inhibitors were included in the study, 2 in the Bempedoic acid group. The screening LDL cholesterol threshold was 2.6 mmol/ L.

The study included participants with CKD; 338 people in the Bempedoic acid group had eGFR 60-90 mL/ min/ 1.73 m^2, and 77 people had eGFR < 60 mL/ min/ 1.73 m^2. People with eGFR < 30 mL/ min/ 1.73 m^2 were excluded. 30.3 % of participants had diabetes.

At 12 weeks, the mean LDL cholesterol was 2.52 mmol/L in the Bempedoic acid group and 3.18 mmol/ L in the placebo group.[111] Non-HDL cholesterol reduced by 10.8 % in the Bempedoic acid group and increased 2.3 % in the placebo group. Gout was more prevalent in the Bempedoic acid group compared to placebo (2.1 % versus 0.8 %). HbA1c slightly improved in the Bempedoic acid group, a reduction of 0.08 % versus an increase of 0.13 % in the placebo group. Creatinine increased by 0.05 mg/dL (4.42 micromol/L) in the Bempedoic acid group. A subgroup analysis of the effects of Bempedoic acid within the subcategories of CKD was not performed.

CLEAR Serenity looked at the effect of Bempedoic acid on people requiring lipid lowering for primary or secondary prevention, with statin intolerance, over 24 weeks.[112] People were allowed to continue lipid lowering therapy including what the study investigators defined as very low-dose statin therapy (rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg).[112] The primary outcome was change in LDL cholesterol at 12 weeks. People with LDL cholesterol > 3.36 mmol/ L were included or LDL cholesterol > 2.6 mmol/ L if they had a confirmed history of heterozygous familial hypercholesterolaemia. Diabetes was present in 26.9 % and 23.4 % of the Bempedoic acid and placebo group respectively. The mean cholesterol was 4.1 mmol/ L. People with eGFR < 30 mL/ min/ 1.73 m^2 were excluded.[112]

At 12 weeks, there was a 21.4 % reduction (95 % confidence interval -25.1 to -17.7%) in LDL cholesterol and a 17.9 % reduction (95 % confidence interval -21.1 % to -14.8 %) in non-HDL cholesterol.[112]

Myalgia occurred in 4.7 % of the group on Bempedoic acid and 7.2 % on placebo.[112] As with the other CLEAR studies, new-onset or worsening diabetes mellitus was less frequent in the Bempedoic acid group, 2.1 %, compared to placebo, 4.5 %. Gout was more common in the Bempedoic acid group, 1.7 %, compared to the placebo group, 0.9 %.[112]

Cardiovascular benefit

A meta-analysis, 11 trials (4391 people), looked at composite cardiac outcomes: cardiovascular death, myocardial infarction, non-fatal stroke, hospitalization for unstable angina and coronary revascularization.[113] This meta-analysis found a reduced risk ratio of 0.75 (95 % confidence interval 0.56–0.99).[113]

CLEAR outcomes, a placebo-controlled, double blind study, randomized 13,970 people with established ASCVD or at high risk, with documented statin intolerance and a mean LDL cholesterol of 3.59 mmol/ L to placebo or Bempedoic acid.[114,115] The primary outcome was a composite of time to cardiovascular death, non-fatal MI, non-fatal stroke and coronary revascularization. 22.7 % of people in the study were on a statin. 45.6 % of people in the study had diabetes. 17.4 - 17.7 % had an eGFR > 90 mL/ min/ 1.73 m^2, 61.4 - 61.8 % had eGFR 60 – 90 mL/ min/ 1.73 m^2 and 20.6 - 20.7 % had eGFR 30-60 mL/ min/ 1.73 m^2.[115] In the Bempedoic acid group, the primary outcome was lower, 11.7 %, compared to the placebo group, 13.3 %, hazard ratio 0.87 [95 % confidence interval 0.79 – 0.96].[115]

Recommendations for use
NICE recommends Bempedoic acid for people with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed lipidaemia where statins are contraindicated or not tolerated and where ezetimibe alone is insufficient.[116] It is currently not recommended by NICE to be added where maximal statin therapy is insufficient.[116] The latest iteration of the ADA Standards of care, advises that Bempedoic acid be considered where other evidence based therapies are not tolerated or effective.[102]

The main adverse effects of Bempedoic acid are increased risk of gout and slight reduction in eGFR. Elimination is mainly through renal, 70 %, and hepatic clearance, 30 %. Bempedoic acid has not studied below eGFR 30 mL/ min/ 1.73 m^2 and should not be used in severe liver disease. Bempedoic acid increases the exposure of simvastatin and pravastatin. There is no data for use in pregnancy or lactation.

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.[117] 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.[118]

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.[119] 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.[119,120]

Both FIELD and ACCORD suggested that fenofibrate led to reductions in progression of retinopathy, albuminuria and foot amputations.[120,121]

Two other studies, the Diabetes Atherosclerosis Intervention Study (DAIS), and the Steno 2 study, 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.[122] 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.[75]

The PROMINENT study, a phase 3, double blind, placebo-controlled, randomised trial investigated pemafibrate (a selective PPAR α modulator). It recruited 10,497 participants with type 2 diabetes, TG 2.3-5.6 mmol/L and increased CVD risk. 33.1 % were from a primary prevention cohort and the rest secondary prevention. After a median 3.4 year follow up, there were reductions in TG of 26.2% and an increase in apolipoprotein B levels of 4.8%. Overall, there was no significant difference in the primary endpoint of non-fatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes, hazard ratio 1.03 (95% confidence interval 0.91 to 1.15).[123] There were increased adverse renal events in the pemafibrate group compared to placebo, hazard ratio 1.12 (95% CI, 1.04 to 1.20). However, the eGFR returned to baseline following pemafibrate discontinuation.[123]

A consistent finding from both ACCORD and FIELD was that fenofibrate increases serum creatinine 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.[120] 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.[124] It appeared that older males with established CVD and lower baseline creatinine were most likely to exhibit the fenofibrate associated rise in creatinine.[125] It is notable that the time-related decline in eGFR in the placebo group in both studies 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.[126] 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.[126] 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.[127-131] Whilst 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.[127,132] 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.

Role for Inclisiran

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

It has been approved by the EMA and FDA. NICE guidelines have placed it on the lipid lowing pathway for people with a history of ASCVD and raised cholesterol, above 2.6 mmol/ L. It is currently not recommended for primary prevention. It has a lower threshold for approval compared to PCSK9i. In Wales, the guidelines differ. Inclisiran is licensed for people with high risk of CVD due to previous events and LDL cholesterol ≥ 4.0 mmol/L, those with recurrent disease and LDL cholesterol ≥ 3.5 mmol/L and, people with heterozygous familial hypercholesterolaemia and LDL cholesterol ≥ 5.0 mmol/L for primary prevention.[133]

The side effects are site specific reactions and non-specific symptoms such as headache and fatigue.

ORION 9, a randomized, placebo-controlled phase 3 trial, involved 482 adults with heterozygous FH on maximum statin therapy with or without ezetimibe.[134] 10 % of the participants had diabetes. Inclisiran 300 mg given on day 1, 90, 270 and 450 led to a 39.7 % reduction in LDL cholesterol (CI -43.7 % to -35.7 %).[134] Inclisiran also reduced Lp(a) by 17.2 %.[134]

ORION 10 and ORION 11 are two double blind, placebo-controlled, parallel group phase 3 trials.[135] ORION 10 involved people with ASCVD and was run in the US. ORION 11 included people with CVD risk equivalents and was run in Europe and South Africa. The participants in both trials had elevated LDL cholesterol and were on maximum tolerated statins. People on PCSK9i were excluded. The primary endpoint was change in LDL cholesterol. In ORION 10, LDL cholesterol reduced by 52.3 % (CI 48.8 to 55.7 %), in ORION 11, LDL cholesterol reduced by 49.9 % (CI 46.6 to 53.1 %). [135]

Inclisiran is primarily renally excreted and a third of the total administered dose is detectable in the urine after 24 hours. **ORION 7**, a phase 1 pharmacokinetic pharmacodynamics study in 31 people with renal impairment, found no difference in safety profile across groups of people with mild, moderate or severe renal impairment.[136] This study included 8 people with normal renal function, defined as eGFR > 90 mL/ min/ 1.73 m^2, 8 people with mild renal impairment, eGFR 60 – 90 mL/ min/ 1.73 m^2, 8 people with moderate renal impairment, eGFR 30 – 59 mL/ min/ 1.73 m^2, and 7 people with severe renal impairment, eGFR 15 – 29 mL/ min/ 1.73 m^2. As the degree of renal impairment increased, the exposure to inclisiran increased. The maximal plasma concentration increased greater than 4-fold in people with severe renal impairment.[136] However, in all groups, inclisiran levels were undetectable after 48 hours.

ORION 7 found no difference in the effect of inclisiran on LDL cholesterol across the different groups with varying renal impairment.[136] A post-hoc analysis of the dose finding ORION 1 study, which included 247 people with eGFR > 30, found similarly, that the effect of inclisiran on LDL cholesterol levels was not influenced by renal impairment.[136]

Whether or not LDL cholesterol reductions through inclisiran translate into improved cardiovascular outcomes has been partially addressed in a pooled analysis looking at ORION 9, 10 and 11.[137] It will be more formally assessed in dedicated CV outcomes trials ORION-4 and VICTORION-2 Prevent.

The pooled ORION 9, 10, 11 analyses examined prespecified endpoints of MACE, including cardiovascular death, cardiac arrest, non-fatal myocardial infarction and fatal and non-fatal stroke, from 3655 participants over 18 months.[137] In this analysis, inclisiran was found to reduce composite

MACE [odds ratio 0.74 (CI 0.58–0.94)], but not fatal and non-fatal MIs or fatal and non-fatal stroke.[137]

Role for 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.[138] 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.[139] Out of the 27,564 participants in the study, 11,031 (40%) had diabetes, 10,344 had borderline diabetes and 6,189 had normoglycaemia. Further analysis found that evolocumab did not increase the risk of hyperglycaemia or new onset diabetes.[140] The PCKS9 inhibitor was similarly effective in people with diabetes, compared with people without diabetes.[140] 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).[141] 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.[141] 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.[142] 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.[142]

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.[143] 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.[143] 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.[144] Evolocumab decreased LDL cholesterol by 65.0% at the mean of weeks 10 and 12 compared with a 0.8% reduction with placebo.[144]

The efficacy and safety of evolocumab was assessed in CKD.[145] 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.[145] 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.[145]

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.[146]

The effect of alirocumab was assessed in individuals with CKD (eGFR 30–59 ml/min/1.73 m^2) pooled from ODYSSEY trials.[147] 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.[147] 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.[147]

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.[148] 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.[148]

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.[149] 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.[149] 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.[149]

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.[150] 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.[150]

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.[151] 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.[146]

Role for 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).[152]

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, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, or unstable angina. Primary end-point events occurred in 17.2% of the icosapent ethyl group, compared with 22.0% of the placebo group.[152] There was a 25% relative risk reduction in primary composite endpoint, NNT=21. These benefits were observed regardless of the presence 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%).[152]. In the summary of product characteristics, as icosapent ethyl is obtained from fish oil, caution is suggested in those with known fish and/or shellfish hypersensitivity.

STRENGTH (Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) was a randomized double blind study looking at an omega-3 fatty acid preparation (EPA and DHA) versus corn oil.[153] This study was terminated early due to a null effect. It was initially suggested that the mixed preparation of EPA and DHA was responsible for the difference in outcome seen compared to REDUCE-IT. However, it was later suggested that the mineral oil comparator used in REDUCE-IT had an adverse effect on cardiovascular risk.

Whilst icosapent ethyl is licenced for primary prevention for people with diabetes and at least one additional cardiovascular risk factor, NICE have only recommended its use for secondary prevention. NICE have approved the use of icosapent ethyl in people with established cardiovascular disease taking a statin with TG > 1.7 mmol/L and LDL cholesterol between 1.04 and 2.60 mmol/L.[154]

Role for 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.

Role for Phytosterols

An intake of 2 g daily of phytosterols leads to a 10% reduction in 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]

Role for Nicotinic acid

Nicotinic acid and its derivatives were first recognised as lipid-lowering agents over 60 years ago.[155] Studies confirm that nicotinic acid reduces LDL cholesterol and TG while increasing HDL cholesterol in type 2 diabetes.[156] Studies in individuals with CKD, including those on dialysis, have confirmed that nicotinic acid improves dyslipidaemia and has a phosphate lowering effect.[157-159] However, based on current evidence, 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.

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 Regarding simvastatin,
   a. We do not recommend >40 mg/ day simvastatin in DKD due to the increased risk of muscular side effects (Grade 1A).
   b. We do not recommend >20 mg/ day simvastatin when prescribed in combination with amlodipine or diltiazem (Grade 1B).

4 We recommend caution with all hypolipidaemic agents in women of child-bearing potential and appropriate counselling and discontinuation of these agents if pregnancy is contemplated. Hypolipidaemic agents 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 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.[160]

A meta-analysis suggested a reduced risk of pancreatitis with statins in people with normal or mildly elevated TG levels.[161]

When 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.[162] The 2014 Cochrane analysis recorded increased withdrawal from treatment in those with reduced kidney function and with diabetes. It is not clear if this was due to side effects of treatment.[70]

Other meta-analyses of statins in CKD also found no difference in the frequency of hepatic or muscular disorders in comparison to placebo.[80,81]

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.[76]

In the SHARP study where simvastatin was combined with ezetimibe, there was no evidence of muscular or hepatic toxicity in comparison to placebo.[66] 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.[86,163]

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 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 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.[164]

Haemorrhagic stroke

The CTT reported a non-statistically significant increased risk of haemorrhagic stroke with statins.[101] 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.[165]

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.[141,166] 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.[167,168] The mechanism may be through an increase in body weight, increased insulin resistance and decreased beta cell function.[168] 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.[71] 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.[169] The hazard ratio after adjusting for potential confounding factors was 1.48; 95% CI, 1.38–1.59.[169]

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.[170] 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.[171]

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.

The side effects of other hypolipidaemic agents are discussed in the relevant sections in Section 6 – *Choice of hypolipidaemic agent* and are not repeated in this section.

8 When to stop hypolipidaemic agents

Recommendation

We recommend that initiation and continuation of hypolipidaemic agents in people aged >75 years be considered on a case-by-case basis, reflecting on relevant 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. 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.[172] 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.[173] The prevalence of diabetes ranged from 6.9% – 14.7%.[173] CVD outcomes were reduced in the statin group (hazard ratio 0.80) but there was no reduction seen for stroke or all-cause mortality.[173]

In the SAGE trial (Studies Assessing Goals in the Elderly) (n=893), pravastatin 40 mg was compared with atorvastatin 80 mg.[174] 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.[174]

A CTT analysis of statin therapy at different ages found evidence of benefit in those aged >75 years.[175] 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 be an inherent bias in this meta-analysis, and indeed in most studies and other post-hoc analyses, as people with frailty would be unlikely to be recruited. The participants included may represent the healthier and more engaged cohorts. In support of this theory, the meta-analysis found that older participants included in the studies were less likely to be smokers and had lower baseline LDL cholesterol levels.[175]

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.

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 and efficacy of hypolipidaemic agents in the following contexts:***
    - ***eGFR <15 ml/min/1.73 m^2***
    - ***ESKD***
    - ***Dialysis***
    - ***Post transplantation***

Currently clinicians are cautious in using higher intensity statins and other agents in these contexts. Definite evidence regarding safety and efficacy is needed in this cohort.

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