

# Association of British Clinical Diabetologists - Renal Association (ABCD-RA) Clinical Practice Guidelines for Management of Lipids in Adults with Diabetes Mellitus and Nephropathy and/or Chronic Kidney Disease

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**on behalf of the ABCD - RA Diabetes CKD guidelines writing group**



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## Introduction

Cardiovascular disease is a key contributor to excess morbidity and premature mortality in diabetes and chronic kidney disease is an independent and major risk factor for cardiovascular disease. Lipids are a modifiable risk factor and good lipid management offers improved outcomes for diabetic patients with concomitant renal disease. Herein a detailed rationale is presented in association with the guidelines, as well as recommendations for clinical audit and outstanding questions for further research.

### Box 1. Differentiating renal disease in diabetes

<b>Diabetic Nephropathy (DN)</b>	Damage to glomerular capillaries in patients with diabetes mellitus resulting in albuminuria in the absence of other causes of albuminuria.
<b>Diabetes Mellitus Chronic Kidney Disease (DM CKD)</b>	Presence of structural renal abnormalities with reduced glomerular filtration, present for >3 months in patients with diabetes mellitus.

The primary purpose of these guidelines is to provide practical recommendations for UK diabetologists, nephrologists, general practitioners and other members of the multidisciplinary team involved in the care of adults with diabetes who also have nephropathy (DN) and/or chronic kidney disease (DM CKD), (Box 1).

**Figure 1.** Glomerular filtration rates (GFR) and albumin:creatinine ratio (ACR) categories and risk of adverse outcomes

eGFR (ml/min/1.73m <sup>2</sup> )	Urinary albumin:creatinine ratio			CKD grade Previously CKD stage 1-5
	<3mg/mmol <30mg/g	3-29mg/mmol 30-299mg/g	≥30mg/mmol ≥300mg/g	
>90	No CKD in the absence of markers of kidney damage			G1 Normal or high GFR
60-89				G2 Slight ↓ in GFR
45-59				G3a Mild-moderate ↓ in GFR
30-44				G3b Moderate-severe ↓ in GFR
15-29				G4 Severe ↓ in GFR
<15				G5 Renal failure
	A1 Normal or slight	A2 Micro-albuminuria	A3 Macro-albuminuria	

INCREASING RISK

INCREASING RISK

Based on Renal Association <http://www.renal.org/information-resources/the-uk-eckd-guide/about-gfr#sthash.mQ76je8d.dpbs> and KDIGO 2012 [http://www.kdigo.org/clinical\\_practice\\_guidelines/pdf/CKD/KDIGO\\_2012\\_CKD\\_GL.pdf](http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf)  
As simultaneously published in Br J Diabetes 2017;17:64-72.<sup>124</sup>

The presence and extent of renal disease is generally defined by measurement of serum creatinine from which an estimated glomerular filtration rate (eGFR) is generated, and a urinary albumin:creatinine ratio test – the latter being more sensitive for detection of diabetic nephropathy (Figure 1).

## Methodology

These clinical practice guidelines are based upon systematic literature searches conducted between October 2013 and March 2016. We searched Pubmed/MEDLINE (search terms used were 'diabetes' AND 'nephropathy/chronic kidney disease/nephropathy'), the Cochrane database of systematic reviews and hand searched reference lists and articles identified by the writing group members up till March 2016. We also reviewed all related guidelines from the National Institute for health and Clinical 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.

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).<sup>1,2</sup> (Box 2).

### Box 2. Evidence grades for recommendation

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

## Why do we need these guidelines?

Type 2 diabetes mellitus is associated with 2-4 fold excess risk of cardiovascular disease (CVD) in adults aged >40 years, and similar risks are present in those with type 1 diabetes of the same age, especially where renal disease has intervened<sup>3-14</sup>. Regardless of aetiology, CKD is associated with a 20% cumulative risk of CVD over 10 yrs but this risk is magnified when there is comorbid diabetes, and markedly magnified if proteinuria is also present<sup>5,8,11-13,15,16</sup>. The risk of CVD in CKD with reduced glomerular filtration rate (eGFR) and proteinuria is additive, and more so with co-existent diabetes<sup>15,16</sup>. Standard CVD risk factors apply and operate to increase CVD risk in both type 1 and type 2 diabetes with CKD<sup>3-16</sup>. CKD is defined by eGFR calculated using the 4 variable MDRD formula, although over the life of this guideline the formula used by laboratories in the UK is likely to change to the CKD-EPI formula (see Appendix 1).

Standard CVD risk factors may apply to a different degree in patients with ESRD requiring haemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation. Thus, with advanced diabetic kidney disease established CVD lipid risk factors may be of less importance in reducing risk, thus their modification may be less likely to reduce vascular events. However the weak association between LDL cholesterol and risk of acute coronary syndromes when eGFR < 30ml/min remains<sup>17</sup>.

These guidelines will offer best practice guidance with evidence base grading for the management of lipids and use of hypolipidaemic agents in type 1 and type 2 diabetes, through the spectrum of DN-DM CKD.

The principle of multiple risk factor management is important throughout this portfolio of recommendations so lipid management must be considered alongside managing blood pressure, glycaemia and thrombotic risk.

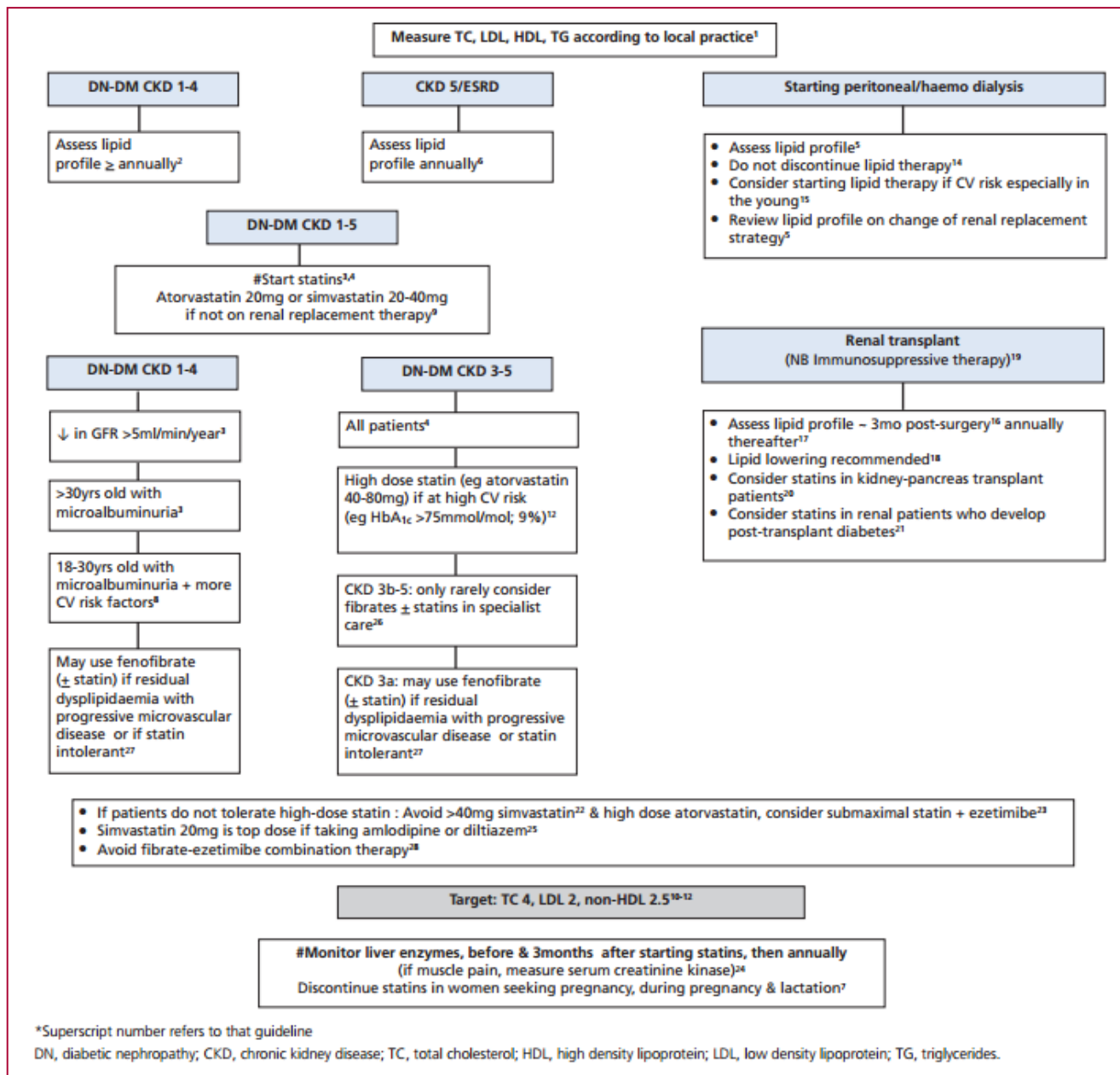
The patient cohorts with DN-DM CKD managed by general practitioners, diabetologists and nephrologists will differ, albeit with degrees of overlap, which may colour perspectives on treatment. The issue as to what constitutes an appropriate level of risk to justify introduction of lipid-lowering therapy in patients with diabetes has been considered in several national guidelines<sup>4,18-20</sup>.

### Guideline rationale

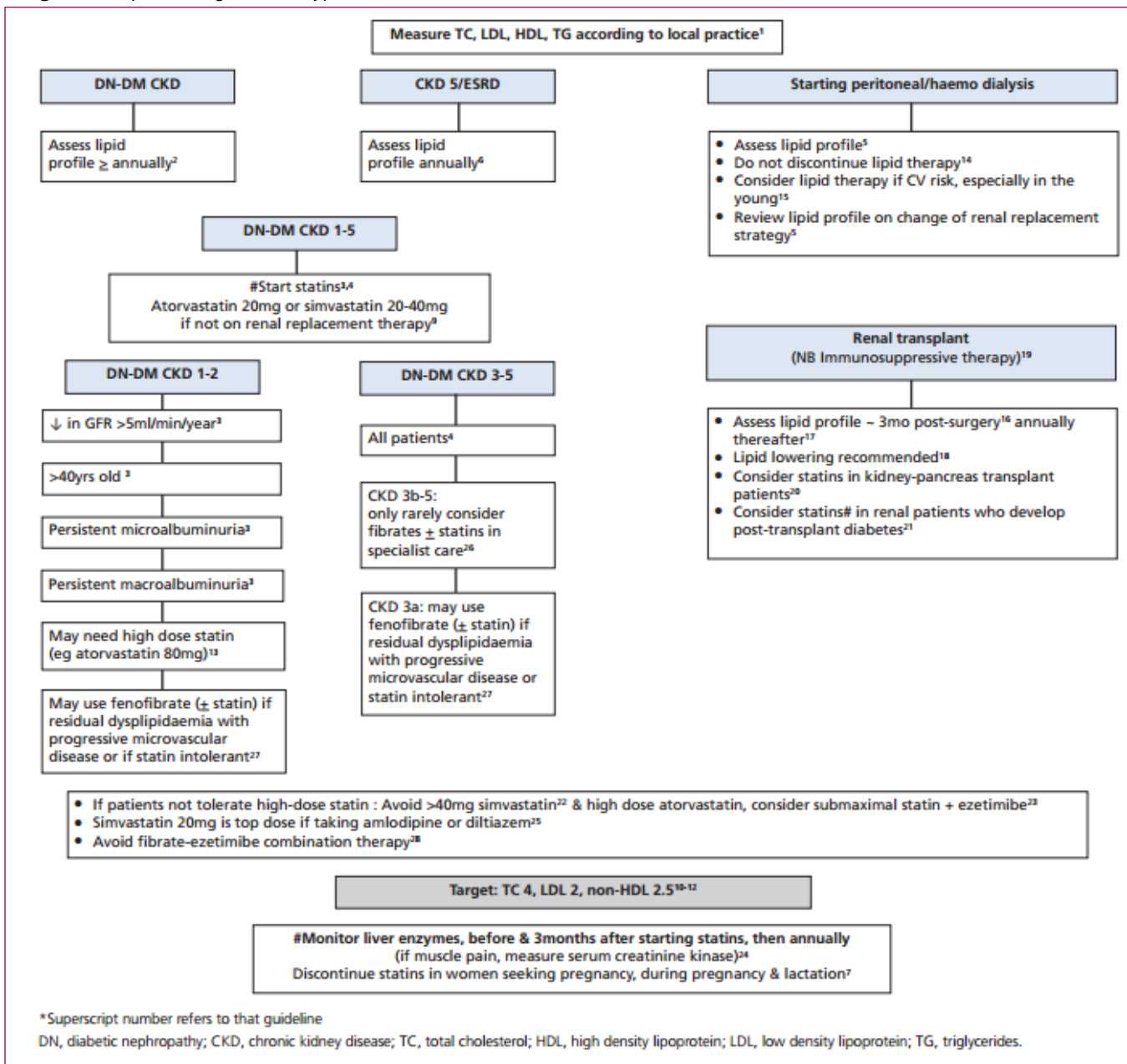
The rationale behind the guidelines may be presented for an individual aspect of guidance (eg guideline 8) or to avoid repetition several guidelines may be considered collectively (eg guidelines 1-7). Following exposition of the rationale the guideline(s) is noted. Flow chart summaries of the guidelines in type 1 and type 2 diabetes are presented in Figure 2 and Figure 3 respectively.

Standard lipid abbreviations are used in these guidelines: total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG); study acronyms are listed in Box 3.

**Figure 2.** Lipid management in type 1 diabetes\*



**Figure 3.** Lipid management in type 2 diabetes\*



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**Box 3.** Trial acronyms

<b>ACCORD</b>	Action to Control Cardiovascular Risk in Diabetes
<b>ALERT</b>	Assessment of LEscal in Renal Transplantation
<b>AURORA</b>	A study to evaluate the Use of ROsuvastatin in subjects on Regular hemodialysis: An assessment of survival and cardiovascular events
<b>CARDS</b>	Collaborative Atorvastatin Diabetes Study
<b>CARE</b>	Cholesterol And Recurrent Events
<b>CTT</b>	Cholesterol Treatment Trialists
<b>4D</b>	Deutsche Diabetes Dialyse Studie
<b>DOPPS</b>	Dialysis Outcomes and Practice Patterns Study
<b>FIELD</b>	Fenofibrate Intervention and Event Lowering in Diabetes
<b>IMPROVE-IT</b>	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
<b>JBS</b>	Joint British Societies
<b>JUPITER</b>	Justification for the Use of statin in Prevention: an Intervention Trial Evaluating Rosuvastatin
<b>LIPID</b>	Long-term Intervention with Pravastatin in Ischaemic Disease
<b>PANDA</b>	Protection Against Nephropathy in Diabetes with Atorvastatin
<b>PLANET</b>	Prospective evaluation of proteinuria and renal function in diabetic patients with progressive renal disease
<b>SHARP</b>	Study of Heart And Renal Protection
<b>TNT</b>	Treating to New Targets
<b>WOSCOPS</b>	West Of Scotland COronary Prevention Study

## Rationale for guidelines 1-7

In observational studies of CVD risk in type 1 diabetes, major coronary heart disease (CHD) events ranged from 0.98% per annum in the Pittsburgh Epidemiology Study, of a small cohort of patients (n <800) aged 30–40 years with a duration of diabetes of 20–30 years<sup>21</sup>, to 0.69% per annum in almost 7500 UK patients aged 35–45 years<sup>11</sup>. A similar incidence of macrovascular disease (5% over 6–9 years follow up) was noted overall in over 21000 adults with type 1 diabetes in Scotland<sup>8,9</sup>. By contrast, the incidence of CVD was at least 20% in 10 yr risk in studies of proteinuric type 1 diabetes<sup>15,22</sup>.

Whereas younger type 1 diabetes patients with persistent albuminuria may not have a 10-year 10% CVD risk (which is the threshold suggested for statin initiation in the recent NICE lipid lowering guidelines<sup>23</sup>), lifetime CVD risk is substantially elevated 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. The variable reversible nature of albuminuria in adolescents and adults with type 1 diabetes is important to consider. Without outcome data on the benefit of statins in this age group, a clear benefit should be evident to justify statin therapy at this stage. In AddIT, a statin intervention trial in adolescents with type 1 diabetes, endothelial dysfunction and modest dyslipidaemia were noted at baseline in subjects with high normal albuminuria. In these subjects the outcome of statin intervention on indirect measures of atherosclerosis, such as arterial intimal medial thickness (aIMT), should be reported within 1-2 years<sup>24</sup>.

The only major study CVD outcome data with statins in type 1 diabetes is the Heart Protection Study, in which subjects benefited in line with the much larger type 2 diabetes cohort<sup>25</sup>, but 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, only 1466 had type 1 diabetes,<sup>26</sup> their mean age was 55 years, 56% had established vascular disease, and there was a high evident incidence of hypertension (48%) and nephropathy (although mean serum creatinine was 101µmol/l).

Consequently, the basis for intervention in different guidelines has been variably set depending on age, presence of additional vascular risk factors or diabetes microvascular complications, levels of HbA1c and family history. The focus has been on statin initiation when advocating therapeutic intervention for CVD risk reduction in type 1 diabetes. 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 risk factors. Women with albuminuria who are on statins and planning a pregnancy should stop this therapy.

In keeping with most previous national guidance<sup>4,18,23</sup>, simvastatin 40 mg has been recommended by NICE, with additional therapy with ezetimibe or alternative statins to achieve TC and LDL-cholesterol targets of 4 and 2 mmol/L respectively. More recently, a starting dose of atorvastatin 20 mg has been recommended for type 1 diabetes in cases aged >40 years, those with

Nephropathy and those with diabetes duration of >10 years. High intensity statin (up to 80 mg atorvastatin) has been recommended for those at highest CVD risk, inevitably the majority of diabetic patients with CKD<sup>4,23</sup>.

## Lipid Metabolism in diabetes and in renal disease

Lipid metabolism fundamentally differs between type 1 and type 2 diabetes without complications. There are qualitative compositional and quantitative changes in lipid metabolism in both types of diabetes<sup>27-29</sup>. Microalbuminuria and persistent higher level proteinuria affect lipid metabolism mainly - manifest as increased LDL cholesterol, which is further altered when GFR falls <30 ml/min, when reduced HDL cholesterol and TG elevation may be noted<sup>17</sup>. The compositional changes at this stage further increase atherogenicity.

These are impacted by poor glycaemic control, insulin resistance and obesity, all of which increase TGs and reduce HDL cholesterol. Insulin deficiency in uncontrolled type 1 diabetes leads to similar changes in lipids and lipoproteins. The dyslipidaemia from poor glycaemic control will be more amenable to correction by insulin repletion in type 1 diabetes. These abnormalities may also be affected in part by the degree of albuminuria and progressive reductions in eGFR in both type 1 and type 2 diabetes. More marked proteinuria is associated with increased LDL cholesterol. When eGFR is reduced below 30 ml/min, there is a tendency for higher TG and reduced HDL cholesterol concentrations, partly reflecting reduced lipase activity<sup>30-37</sup>.

In addition to the role of lipids in CVD, there is some evidence in type 1 and type 2 diabetes that dyslipidaemia independently may be linked with progression of DM CKD<sup>38-41</sup>. However as marked familial cholesterol elevation (Familial Hypercholesterolaemia) does not itself cause CKD and to date evidence suggests that lipid lowering therapy is not nephroprotective *per se*, it is difficult to consider elevated LDL cholesterol as being directly nephrotoxic. Nevertheless, it may still conceivably interact with the glycaemic nephrotoxic effects, potentially through glycation of LDL cholesterol.

It is worth considering the relative risk attributable to non-HDL cholesterol compared to that purely due to LDL cholesterol, as a sub fraction of non-HDL cholesterol. A recent meta-analysis of statin treated patients has suggested non-HDL cholesterol may be a better predictor of coronary artery disease (CAD) risk than LDL cholesterol – possibly reflecting the additional impact of larger triglyceride rich molecules and loss of the benefit of higher HDL cholesterol levels<sup>42</sup>. It may therefore be preferable to use non-HDL cholesterol targets of < 2 or < 2.5 mmol/L to best assess the response to hypolipidaemic therapy in DM CKD.

## Previous lipid lowering guidelines in diabetes and renal disease

Several guidelines have been published in the past 2 years but with the exception of JBS3 they do not specifically refer to the management of lipids in diabetes

with nephropathy and at different stages of CKD (Table 1). There is inconsistency as to statin choice and dosage, use of ezetimibe and fibrates, and whether or not to employ lipid targets. The joint EASD and ESC 2013 guidelines<sup>19</sup> recommend intensive statin therapy in type 2 diabetes, with the highest CVD risk using simvastatin-ezetimibe in DM CKD based on the SHARP study<sup>19</sup>. The guidance makes reference to the similar relative risk reduction but greater absolute risk reduction in DM CKD. Type 1 diabetes with renal impairment was also stated to justify statin therapy regardless of LDL cholesterol concentrations. Fibrates were stated to

reduce major CVD events in meta-analysis and to be safe in combination with statins. The guidance mentioned fibrates may reduce kidney function, but went on to state that fenofibrate reduced albuminuria and slowed eGFR loss over 5 years, despite initially and reversibly increasing plasma creatinine in type 2 diabetes. There was no explicit guidance as to whether to use fenofibrate in DN-DM CKD. In respect of target levels LDL cholesterol < 1.8mmol/L and non-HDL cholesterol < 2.6mmol/L in highest risk category which would include DN-DM CKD.

**Table 1.** Summary of lipid lowering guidance for patients with diabetes and renal disease

Guidelines	Diabetes	Age	Guidelines	Proteinuria	Cholesterol Target			Agents (1)	Intensity of statin therapy
					TC	LDL	Non LDL		
JBS3	Type 1	>30	All	-	-	2.0	-		
Advice is regardless of other CV risk factors which may also justify lipid lowering therapy		40-50	3-5	-	-	2.0	-		
		18-40	All	>30 mg/day Albuminuria	-	2.0	-		
	Type 2	40+	All*	-	-	2.0	-	All should receive a statin regardless of cholesterol	
		18-40	G1-2	>30 mg/day Albuminuria	-	2.0	-	Statin	Intensive
		18-40	Non dialysis G3-5		-	2.0	-	All should receive a statin regardless of cholesterol	Intensive for stage CKD 3
KDIGO	All	18-49	Non dialysis CKD G1-5	-	-	-	-	Statin or statin ezetimibe	
	Any	50+	Non dialysis CKD G1-2	-	-	-	-	Statin	-
	Any	18+	Dialysis		-	-	-	Do not initiate statin. If already taking don't stop	Normal
	Any	18+	Kidney transplant		-	-	-	Statin for all	Normal
ABCD-RA	Type 1	>40	All		4.0	2.0	2.5	Statin	Normal-high
	Type 1	30-40	All		4.0	2.0	2.5	Statin	Normal-high
	Type 1	<30	All	>30 mg/day Albuminuria	4.0	2.0	2.5	Statin	Normal-high
	Type 2	Any	CKD stage G1-2		4.0	2.0	2.5		Intensive if albuminuria (ACR> 30µg/mg)
	Type 2	Any	Non-dialysis CKD G3		4.0	2.0	2.5	Statin or statin-ezetimibe	Intensive
		Any	Non dialysis CKD G4-5		-	-	-	Statin or statin-ezetimibe	Normal, Intensive if CAD
		Any	Haemodialysis/peritoneal dialysis		-	-	-	Do not routinely initiate for 1yr prevention	Normal
	All (includes PTDM)	18+	Kidney transplant					Statin	Normal

\* JBS3 makes no specific mention if CKD patients receiving dialysis should be treated any differently from those not on dialysis



The 2013 KDIGO guideline for Lipid Management in CKD does not distinguish between diabetic and non-diabetic CKD based on eGFR and does not specifically advise on albuminuria as a separate criteria or basis for lipid lowering therapy<sup>20</sup>. Although lipid measurement was recommended initially at all grades of CKD including dialysis or transplantation, follow up measures were not recommended for the majority of patients. Statin or statin-ezetimibe combination was recommended for adults ≥50 years old with eGFR <60 ml/min if not on dialysis or with a renal transplant. Statin alone was suggested if aged >50 years with eGFR > 60ml/min and CKD, or if aged 18-49 years with CKD and diabetes. Statins +/- ezetimibe were not to be initiated in dialysis patients, but could be continued, whilst statins were suggested for adult renal transplant patients. Medication for hypertriglyceridaemia was not recommended at any stage of CKD. Fibrates were not recommended concomitantly with statins in CKD. The guidance stated there was insufficient evidence to justify specific LDL cholesterol targets or statin dose adjustment and recommended fixed doses at all stages of CKD including dialysis or transplantation (e.g. simvastatin 40 mg, or simvastatin 20 mg with 10 mg ezetimibe, atorvastatin 20 mg, or rosuvastatin 10 mg). The relative effects of various statins and dosing are shown in Table 2.

**Table 2.** Effect of statin dose on LDL cholesterol

Classification of statin intensity by reduction in LDL-C:

Low intensity: ↓20%–30%	Medium intensity: ↓31%–40%	High intensity ↓>40%
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Dose	Reduction in low density lipoprotein cholesterol				
	5mg	10mg	20mg	40mg	80mg
<b>Statin</b>					
<b>Fluvastatin</b>	-	-	21%	27%	33%
<b>Pravastatin</b>	-	20%	24%	29%	-
<b>Simvastatin</b>	-	27%	32%	37%	*42%
<b>Atorvastatin</b>	-	37%	43%	49%	55%
<b>Rosuvastatin</b>	38%	43%	48%	53%	-

\* do NOT use in CKD. Adapted from NICE guidelines using data from Wald et al<sup>23,63</sup>

The ADA 2014-15 Clinical Practice Recommendations do not distinguish the issue of lipid lowering treatment in DN-DM CKD by the type of diabetes<sup>18</sup>. The target LDL cholesterol was stated as 2.6 mmol/L if no CVD, although 1.8 mmol/L for overt CVD where high dose statin was stated as an option. Statin treatment was recommended if >40years old and albuminuria was present regardless of the level of LDL Cholesterol, and for those aged < 40years if LDL Cholesterol was > 2.6mmol/L in the presence of multiple CVD risk factors (by implication persistent albuminuria and CKD). Target LDL cholesterol, in the absence of overt CVD, was set at 2.6mmol/L or 30-40% reduction from baseline. There was no specific mention of lipid lowering strategies at different stages of CKD. There

There was no mention of the role of ezetimibe. Combination statin therapy with fibrates were considered to pose a greater risk of muscle or hepatic side effects in those with 'renal insufficiency', and by implication not recommended. However, the risk of rhabdomyolysis was suggested to be lower with fenofibrate and statin than with gemfibrozil added to statins. Fibrates were indicated for severe hypertriglyceridaemia (TG >12 mmol/L) to reduce the risk of pancreatitis.

The JBS3 consensus recommendations for the prevention of cardiovascular disease suggested a separate approach to lipid lowering in type 1 and type 2 diabetes. The majority of patients aged ≥40 years (unless short duration type 1 diabetes and otherwise fit) would be considered for statin therapy regardless of renal status, without any need to utilise a CVD risk assessment tool<sup>4</sup>. Persistent proteinuria and/or eGFR < 60ml/min in younger adults, aged 18-40years, should also be considered for statin therapy. Intensive statin therapy (e.g. atorvastatin 80 mg) was recommended for those with pre-existing CVD as well as those with persistent albuminuria and/or eGFR < 60ml/min, or if not achieving non-HDL cholesterol target of 2.5 mmol/L. Fibrates were not recommended routinely for CVD risk reduction but could still have a role in reducing the progression of retinopathy and progression to persistent proteinuria when eGFR was >60ml/min. The separate renal section in JBS3 restated the KDIGO guidance of statin alone or statin-ezetimibe combination for all patients with CKD.

The NICE Lipid Modification 2014 guidance<sup>23</sup> stated that there was no need to use a CVD risk assessment tool if eGFR was < 60ml/min and/or there was albuminuria (level not defined). Plant stanols or fibrates were not recommended for either CKD or diabetes patients. As with JBS3, statins were recommended for all type 1 diabetes patients aged ≥40years and/or with established nephropathy, but extended recommend inclusion of those with other CVD risk factors or those with >10 years duration of diabetes without any age restriction. NICE still advocated use of CVD risk tables for type 2 diabetes, suggesting a 10% 10-year CVD risk would justify using statins. Atorvastatin 20 mg was suggested in these situations and in those with CKD, although a dose increase was suggested if a >40% reduction in non-HDL cholesterol was not achieved with eGFR > 30ml/min. Where eGFR was <30ml/min, further consultation with a nephrologist was suggested prior to considering higher dose statin. High intensity statin (atorvastatin 80 mg) was recommended for those at high CVD risk (by implication CKD and persistent proteinuria) who do not achieve a >40% reduction in non-HDL cholesterol.

There appears to be a clear consensus that DM CKD and persistent proteinuria conveys a high CVD risk and statin therapy should be initiated. However, there is wide inconsistency on the entry point for initiation, the dosage of statins, consideration of additional therapy with ezetimibe and fibrates, and the use of (or not) of different total, LDL and non-HDL cholesterol targets to guide statin dosing. With the exception of the KDIGO guidance all other guidelines use target-based approach

for lipid therapy in DN-DM CKD. Patients with end stage renal disease requiring dialysis or renal transplantation are a separate group with differing risk factors and levels of evidence for lipid-lowering therapy and are discussed later.

Target attainment needs to take account of the levels attained in the controlled prospective outcome studies discussed later, where it appears that >50% of trial patients would fail to reach the LDL or non-HDL cholesterol targets on other combination statin–ezetimibe or high intensity statin therapy.

#### Guideline 1

We recommend that evaluation of a full lipid profile (TC, LDL cholesterol, HDL cholesterol, TGs) is performed in patients with DN-DM CKD as is current practice. (Grade 1A)

#### Guideline 2

We suggest that the lipid profile is assessed at least annually in patients with DN-DM CKD. (Grade 1C)

#### Guideline 3

We advise that the major goal of commencing lipid-lowering therapy in adult patients with DN-DM CKD is to reduce risk of cardiovascular events. (Grade 2A)

We suggest that in patients with stage 1-2 DN-DM CKD, lipid-lowering therapy with statins is commenced in the following categories:

- Patients with type 1 diabetes and persistent microalbuminuria aged > 30 years
- Patients type 2 diabetes with rapidly progressing early CKD (loss of GFR >5ml/min/year) irrespective of albuminuria status
- Patients with type 2 diabetes aged >40 years irrespective of cholesterol levels
- All patients with type 2 diabetes and persistent microalbuminuria or macroalbuminuria

#### Guideline 4

We recommend that lipid lowering therapy with statins should be considered for all patients with stage 3-5 DN-DM CKD. (Grade 1B)

#### Guideline 5

We recommend review of the lipid profile on commencement or change of modality of renal replacement therapy (dialysis or kidney transplantation).(Grade 1D)

#### Guideline 6

We suggest that in patients with end stage renal disease (ESRD) measurement of the lipid profile should be performed annually to assess compliance and need for continuing therapy. (Grade 2D)

#### Guideline 7

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

## Rationale for guideline 8

### **Type 1 diabetes with persistent microalbuminuria and/or reduced glomerular filtration rate (60-90ml/min) – Stage 2 CKD**

Well-controlled insulin replete type 1 diabetes patients without complications have similar total and LDL cholesterol and TG levels to the general population. HDL cholesterol levels in this situation often are similar or higher than the general population. Insulin deficiency and poor glycaemic control lead to reductions in HDL cholesterol and elevations of total and LDL cholesterol and TGs, with reductions in HbA1c associated with more beneficial impact on TGs and HDL cholesterol than on LDL cholesterol. Qualitative changes in lipoprotein particles are evident in association with persistent microalbuminuria and moderate proteinuria, initially with increases in intermediate density lipoproteins and TG enrichment of LDL leading to smaller denser more atherogenic particles, partly reflecting elevated hepatic lipase activity. LDL particle number increases based on increased levels of apolipoprotein B with microalbuminuria and proteinuria. HDL cholesterol levels have been reported to be reduced with increased proteinuria. Marked proteinuria with nephrotic syndrome leads to more evident LDL cholesterol elevation, whilst reducing filtration function with advancing CKD has been linked with further reductions in HDL cholesterol and TG elevation, reflecting reduced endothelial lipoprotein lipase activity<sup>22,29,31,35,37,41</sup>.

An increased risk of CVD in type 1 diabetes was observed over 30 years ago<sup>5</sup>. Whilst earlier reports indicated a 4-10 fold relative risk compared with a younger control population without diabetes<sup>11-13,43-46</sup>, a more contemporary large study in Scotland observed a lower relative risk of CVD of 2.3 in men and 3 in women<sup>9</sup>. The risk of CVD is highest amongst those with diabetic nephropathy. A reduced incidence of nephropathy has been observed over this period<sup>9,21,47</sup> so it appears that there has been a reduction in CVD incidence in the last 10–20 years.

There is uncertainty as to whether type 1 diabetes, acquired in childhood, accelerates CVD in all cases<sup>47,48</sup>. Studies demonstrate that the most consistent predictors of CVD risk are age and markers of nephropathy, primarily albuminuria, as well as chronically poor glycaemic control<sup>9,21,43</sup>. The presence of proteinuria conveys a 10-fold greater risk of CVD compared to type 1 diabetes without proteinuria<sup>15,21,44</sup>. Measures of dyslipidaemia, such as reduced HDL-cholesterol and hypertriglyceridaemia and, to a lesser extent, central adiposity, independently predict higher CVD risk<sup>11,45,46</sup>.

A recent 10 year follow up of the Finn Diane study found the predictive ability of lipid variables differed depending on age, renal status and glycaemic control<sup>22</sup>. It appeared that apolipoprotein B levels (effectively the number of LDL particles) was an independent predictor of coronary artery disease (CAD) in men whilst the triglyceride:HDL cholesterol and apolipoprotein B:A-1 ratios were more highly predictive of CAD in women. These relationships appeared more evident with poor



control and proteinuria; with traditional lipid risk predictors, such as TC and LDL cholesterol, less predictive without persistent proteinuria. Although albuminuria has primacy in CVD risk prediction, the presence of proliferative retinopathy and autonomic neuropathy also independently added to the risk<sup>45,46</sup>.

Although the vast majority of patients 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<sup>49</sup>. The risk of end stage CKD and CVD is sufficiently high to justify the same approach to CVD prevention as those with persistent albuminuria at all levels of GFR. There is a need to develop CVD risk scores specifically for patients with type 1 diabetes.

#### **Evidence base for lipid reduction and reduced CVD outcome in type 1 diabetes**

The Heart Protection Study type 1 diabetes cohort appeared to have a sizeable minority with CKD based on available renal measures and benefited from simvastatin 40mg<sup>25</sup> so it would appear that there is CVD benefit from the use of statins in type 1 diabetes with a degree of CKD<sup>26</sup>. The meta-analysis of statin trials in diabetes fewer than 10% had type 1 diabetes, and amongst them 56% had known vascular disease. The mean serum creatinine in the group was 101 micromol/L, so a sizeable proportion had CKD but there was no information provided on albuminuric status in the analyses<sup>26</sup>. There are in fact currently no other CVD outcome studies with statins in type 1 diabetes. The evident magnified CVD risk in the presence of proteinuria and/or reduced GFR remains the justification for statin initiation.

#### **Areas of uncertainty**

The predominant recommendations regarding lipid lowering in type 1 diabetes and early nephropathy aim to achieve the optimal lipid profile. It is unclear whether there is a role for additional non-statin lipid-lowering therapy when these targets are not attained, and indeed there is a dearth of information on levels of lipid attainment using statins in this category. The observation in one study of type 1 diabetes with varying renal function<sup>36</sup> 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. 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 in the highest risk group with type 1 diabetes and nephropathy. Any beneficial role of statins in adolescents below the age of 18 with persistent microalbuminuria has yet to be clarified<sup>24</sup>.

#### **Guideline 8**

We suggest that in patients with type 1 diabetes with CKD stage 1-2, lipid-lowering therapy with statins is commenced in patients aged 18-30years with persistent albuminuria and additional CVD risk factors evident. (Grade 1B)

## **Rationale for guidelines 9-13**

### **Specific groups - Type 2 diabetes with microalbuminuria-macroalbuminuria and GFR 30- 59ml/min (Stage 3 CKD)**

#### Lipid metabolism in type 2 diabetes

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 but a preponderance of smaller denser more atherogenic TG enriched intermediate density lipoprotein (IDL) and LDL particles based on increased apolipoprotein B levels along with compositional changes in all lipoprotein classes that may enhance oxidative potential and atherogenicity<sup>27,28,51</sup>. Whereas poor glycaemic control will exacerbate this pattern, this dyslipidaemia is less amenable to correction with improved HbA1c than in type 1 diabetes. These changes evidently increase CVD risk in type 2 diabetes with microalbuminuria<sup>32,33 52</sup>.

These features are closely related with diabetic nephropathy and the changes accentuated with albuminuria and progressive CKD. A range of lipoprotein measures including hypertriglyceridaemic apobetalipoproteinaemia and raised levels of apolipoprotein E have been related to progression of DN in both type 1 and type 2 diabetes<sup>22,28,30,51</sup>. It is unclear whether these changes better predict CVD events in type 2 diabetes with or without nephropathy in comparison to standard lipid measures such as non-HDL cholesterol or TC:HDL cholesterol ratios which should currently still be the mainstay of lipid CVD risk management in type 2 diabetes with kidney disease.

#### Evidence base for risk in type 2 diabetes

Until relatively recently type 2 diabetes has been considered as a CHD risk equivalent (i.e. equivalent risk to that of a person without diabetes who has had a myocardial infarction (MI)) in terms of future risk of a CHD event<sup>52</sup>, it is now clear that at diagnosis, diabetes is not a CHD risk equivalent condition<sup>4,10,53</sup>. Rather, certain characteristics are required to escalate CHD risk in diabetes patients towards a CHD risk equivalence level, most notably longer duration of diabetes and/or the presence of proteinuria<sup>3,6,7,9,10,14,16</sup>.

The frequent occurrence of stage 3 CKD as defined by GFR in older people with coincident type 2 diabetes, rather than classical DN with increasing albuminuria as the primary cause makes the classification more challenging. However it is clear that type 2 diabetes with albuminuria enhances CVD risk<sup>10</sup> and CKD based on reduced GFR also enhances risk<sup>16,53</sup>. The combination of type 2 diabetes with proteinuria, stage 3 CKD or worse substantially increases the risk of CVD events<sup>53</sup>. In the Emerging Risk Factor meta-analysis the prevalence of diabetes was 10%, but diabetes accounted for 11% of vascular deaths<sup>6</sup>. Diabetes, independent of other conventional risk factors, doubles the risk of macrovascular disease.

Statins are clearly the lipid modifying agent of choice for patients with diabetes. In the CTT meta-analysis of outcomes in over 18,000 patients 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. Similarly, coronary revascularization was reduced by 25% and stroke by 21%<sup>26</sup>.

The recent UK JBS3 and NICE guidelines<sup>4,23</sup> recommend that all patients with type 2 diabetes >40years old be prescribed statins (unless there are specific contra-indications). Whilst 10-year cardiovascular risk in newly diagnosed patients with diabetes at age 40years is on average well below the 20% risk threshold, lifetime cardiovascular risk in diabetes is clearly escalated<sup>4</sup>.

The CVD risk in type 2 diabetes with either persistent albuminuria and/or reduced GFR (< 60ml/min) is high enough to consider higher intensity statin therapy, i.e. atorvastatin 80 mg, alongside those with existing CVD, and those who fail to meet current cholesterol targets on 40 mg simvastatin or atorvastatin, as proteinuria and/or reduced GFR confers high vascular and mortality risks, near equivalent to those with existing CVD<sup>4,10,23</sup>.

***Evidence base for lipids reduction and reduced CVD outcome in type 2 diabetes with (eGFR >60ml/min) or 30-60ml/min, taking account of albuminuria (ie CKD Stage G1-2 A2-A3, and G3 A1-3)***

There have been several large-scale prospective CVD outcome studies involving type 2 diabetes with CKD, although none specifically evaluating type 2 diabetes and CKD. Earlier placebo controlled studies with pravastatin 40 mg (WOSCOPS, LIPID and CARE) included subjects with both diabetes and CKD but only 571 of over 20,000 patients studied were in this category and this included those with eGFR 30-60ml/min as well as those with albuminuria and eGFR >60ml/min. The combined data from these studies in DM CKD suggested a 25% relative risk reduction in major CVD events<sup>54-56</sup>. CARDS, SHARP and TNT evaluated lipid lowering strategies in type 2 diabetes patients who were characterised by the degree of glomerular filtration and albuminuria<sup>57-59</sup>.

The CTT collaborators meta-analysis of over 18000 diabetes patients also investigated the impact of renal dysfunction on outcomes but did not distinguish between patients with eGFR<30ml/min and < 60ml/min<sup>26</sup>. Although not seen in all studies, the incidence of CVD events was usually increased in patients with eGFR <60ml/min and persistent albuminuria. The relative risk reduction in CVD events was stated to be at least equivalent amongst those with eGFR 30-60ml/min compared to those with eGFR >60ml/min, and likewise amongst 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 <60ml/min or where there was albuminuria.

The CARDS trial investigated the utility of 10mg atorvastatin/day in type 2 diabetes patients with at least one additional CVD risk factor. Of these 2,838 subjects, 970 (33.4%) had an eGFR of 30-60ml/min. To prevent 1 CVD event in this CKD subgroup the estimated number needed to treat (NNT) was 26 patients for 4 years<sup>59</sup>. The TNT study in >10,000 patients 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 CKD patients with atorvastatin 80mg/day compared to 10mg/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. The NNT with 80mg atorvastatin to prevent 1 major CVD event over 5 years was 24<sup>60</sup>.

The SHARP study evaluated >9000 patients with CKD of whom 23% (2094 subjects) had type 2 diabetes. In this placebo controlled study patients were randomised 1:1 to receive once daily simvastatin 20 mg plus ezetimibe 10 mg or placebo. At baseline 80% of subjects had increased albuminuria, 37% had eGFR 30-60ml/min, but the majority had stage G4 CKD or worse, with 33% of patients requiring dialysis<sup>58</sup>. The type 2 diabetes cohort benefited similarly to the overall group and those with increased albuminuria benefited at least as much as those without albuminuria. There was no differential benefit amongst those with eGFR 30-60ml/min as opposed to those with eGFR < 30ml/min. There was a clear differential benefit amongst those with baseline TC >5.5 mmol/L. Overall in SHARP, to prevent a major CVD event the estimated NNT was 25-33 over 5 years.

The relative risk reduction in CVD events was 17% in SHARP and in the CTT meta-analysis of subjects with CKD and eGFR < 60ml/min<sup>26,58</sup>. There appeared to be a greater CVD risk reduction of 42% in the CARDS CKD cohort<sup>59</sup> and of 32% in the TNT CKD higher dose atorvastatin cohort<sup>60</sup>. Attained mean levels of LDL cholesterol in the TNT study were 2 mmol/L with 80 mg atorvastatin compared to 2.6 mmol/L with 10 mg atorvastatin<sup>60</sup>. In CARDS the mean attained LDL cholesterol was 1.8 mmol/L, whereas in SHARP it was 2 mmol/L<sup>58,59</sup>.

The recent IMPROVE-IT trial confirmed the benefit of attainment of LDL cholesterol <1.8 mmol/L, particularly in the cohort with diabetes and CVD. It appears that even with high intensity statin use or statin-ezetimibe combination therapy in DM CKD patients, over 50% would fail to attain the optimal reduction in LDL or non-HDL cholesterol<sup>61</sup>. Patients in IMPROVE-IT had median creatinine levels of 84 µmol/L and there was no information on proteinuria status provided, so it appears there were few with clinically important DN-DM CKD.

The effect of differing doses of statin on LDL-cholesterol has been described<sup>23,62</sup>. In type 2 diabetes high dose statin (up to 80 mg atorvastatin) in 85% of patients with microalbuminuria led to important reductions in CVD and progression of nephropathy in a small study of multiple risk factor reduction<sup>63</sup>. However as with larger studies failure to achieve tight cholesterol targets was seen, as 30% of the subjects still had total cholesterol levels >4.5 mmol/L.

***Evidence base for impact of lipid lowering with statins on progression of albuminuria and CKD in type 2 diabetes***

Given the unequivocal evidence that progressive albuminuria and declining glomerular filtration both accelerate major CVD outcomes and progression to ESRD, there has been considerable interest in the possibility that statins may reduce deterioration in renal function.

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 excretion<sup>64,65</sup>. More recent 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 ESRD) were reduced by statins (RR 0.95 (CI 0.9-1.01) or 0.91 (0.78-1.06))<sup>65,66</sup>. The only study suggesting that statins could improve GFR was the TNT study over 5 years, which suggested GFR improved by 10% with high dose atorvastatin amongst those with CKD<sup>60,67</sup>. This effect was not observed in CARDS or PANDA studies in type 2 diabetes with 2-4 years follow up, or in the SHARP study with 4 years follow up<sup>59,68,69</sup>. The PANDA study compared high and low dose atorvastatin as in the TNT study<sup>68</sup>.

The JUPITER trial investigated a high dose (20mg rosuvastatin/day) statin in CKD, but excluded patients with diabetes. There was no impact of active treatment on GFR amongst those with baseline eGFR <60ml/min, although at 12 months a marginal but significant preservation of eGFR was observed when eGFR was ≥60ml/min at baseline<sup>70</sup>. A small study in type 2 diabetes subjects with nephropathy suggested that over 12 months pitavastatin reduced albuminuria to a greater extent than pravastatin<sup>71</sup>. However, in neither the CARDS or PANDA studies was there any improvement in albuminuria with low or high dose atorvastatin<sup>59,68</sup>. Similarly, in SHARP, lipid lowering with simvastatin and ezetimibe in patients with established CKD (23% with diabetes) had no impact on progression of CKD compared to placebo<sup>69</sup>.

Most recently, a study over 34-52 weeks has examined the potential differential effects of statins on renal function in diabetes. In PLANET 1, a randomised double blind parallel group trial of atorvastatin 80 mg, and rosuvastatin 10mg and 40 mg in proteinuric (predominantly type 2) diabetes patients with eGFR > 40 ml/min, a significant reduction in proteinuria was only observed with atorvastatin. Although 40mg 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<sup>72</sup>. A retrospective cohort study suggested that atorvastatin and rosuvastatin were not associated with significant changes in renal function in type 2 diabetes, although very few patients were treated with atorvastatin 80 mg or rosuvastatin 40 mg<sup>73</sup>.

It thus appears that although statins may reduce albuminuria short term, they do not lead to sustained improved measures of renal function in DN-DM CKD after 4 years exposure, although it is conceivable that any benefit may only be manifest after more extended statin use, or if statins were initiated at an earlier stage of DN.

### Areas of uncertainty for lipid lowering therapy in type 2 diabetes

Does the attainment of lower LDL cholesterol levels <1.8mmol/L or non-HDL cholesterol levels <2mmol/L further improve CVD outcomes in type 2 diabetes with eGFR 30-60ml/min and or albuminuria?

Does addition of other agents, such as ezetimibe or fibrates, to high intensity statin improve attainment of lower LDL and non-HDL cholesterol levels in type 2 diabetes and stage G3 CKD and/or CKD with proteinuria?

Does addition of other agents, such as ezetimibe or fibrates, to high intensity statin improve CVD outcomes in type 2 diabetes and stage G3 CKD and/or CKD with proteinuria?

Do high dose atorvastatin or statin-ezetimibe combinations reduce progression in albuminuria and GFR decline in type 2 diabetes and in type 2 diabetes with stage G3 CKD and/or CKD with proteinuria with longer-term exposure over 5 years?

Does lipid-lowering impact on progression of DN DM-CKD as the previous studies are likely to have been underpowered to examine this specific question?

#### Guideline 9

We suggest that in DN-DM CKD patients not requiring renal replacement therapy it is appropriate to initiate statin therapy with either atorvastatin 20 mg or simvastatin 20-40 mg. (Grade 1D)

#### Guideline 10

We suggest that in patients with reduced GFR +/- persistent albuminuria the management of dyslipidaemia should be similar irrespective of whether the individual has type 1 or type 2 diabetes. (Grade 1B)

#### Guideline 11

We suggest that in type 1 diabetes with persistent albuminuria and/or reduced eGFR (60-90) statin use should aim to reduce TC to 4.0 mmol/l, LDL cholesterol to 2 mmol/l and non-HDL cholesterol to 2.5 mmol/l. (Grade 1D)

#### Guideline 12

We suggest that higher intensity statin use (atorvastatin 40-80 mg) can be considered for those with persistent albuminuria and or reduced eGFR (30-60) at highest CVD risk (e.g. aged >40 years; poor glycaemic control (HbA1c > 75 mmol/mol); additional CVD risk factors: smoking, hypertension, dyslipidaemia; proliferative retinopathy) who do not attain lipid targets in Guideline 11 on lower statin doses. (Grade 1D)

#### Guideline 13

We recommend that all type 2 diabetes patients with stage 1-2 CKD with albuminuria, who have the highest risk of CVD, should be considered for high intensity statins such as atorvastatin 80 mg. (Grade 1A)



## Rationale for guidelines 14-21

### **Evidence base for CVD risk in patients with diabetes requiring dialysis**

Patients with ESRD are at dramatically increased risk of premature CVD, approximately 5-20 times that of age-matched controls from the general population. However, this increased risk is incompletely explained by co-morbid disease such as diabetes and hypertension. Moreover, whilst CVD risk is greatly increased, the prominent mode of death in most ESRD registries is sudden cardiac death rather than atherosclerotic events. The relationship between cholesterol and CVD risk is not clear and the phenomenon of reverse epidemiology is well documented in ESRD, with a 'J' or 'U' shaped relationship between cholesterol and mortality, possibly driven by malnutrition or inflammation being associated with lower serum cholesterol levels<sup>74</sup>. Whilst CVD risk is high, and diabetes is the leading single cause of ESRD in the Western world, the relationship between lipids and CVD outcome in ESRD is not straightforward.

Commencement of renal replacement therapy (dialysis or transplantation) for ESRD is associated with the need for major changes in lifestyle, dietary and fluid intake restrictions, hospital attendance and medication. This is a time when patients are vulnerable to various physical and psychological stresses, and the risk of cardiovascular events increases. During this period, it is appropriate to review medication regimens and this should include management of lipid lowering therapy in patients with DM CKD. For some patients with a large pill burden and substantial co-morbid disease, continuation of lipid lowering therapy may be inappropriate following commencement of dialysis, especially after a prolonged period of CKD not requiring dialysis. On the other hand, dialysis patients not receiving lipid-lowering therapy who have subsequently undergone renal transplantation are more likely to benefit from lipid lowering therapy. There has been considerable debate regarding the value of measuring fasting lipids in patients on dialysis, as reflected in the comprehensive KDIGO guidelines<sup>75</sup>.

More detailed guidelines outlining potential scenarios where lipid management may be altered are discussed in the following section. Whilst, on balance, lipid lowering therapy with statins has not been shown to be of benefit in reducing cardiovascular events in dialysis patients, performing a baseline assessment of lipid status will establish diagnoses of severe hypercholesterolemia, and/or hypertriglyceridaemia and may rule out secondary causes of dyslipidaemia. Measuring lipid status is inexpensive and will also identify a group of patients where lipid-lowering therapy is not indicated (e.g. malnourished patients with LDL cholesterol <2.1 mmol/L).

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

There have been three large randomised placebo controlled trials of lipid lowering therapy in dialysis patients. The 4D trial studied 1255 patients with type 2 diabetes aged 18-80 years treated with haemodialysis for <2 years<sup>76</sup>. Patients were randomised to receive atorvastatin 20mg or placebo. Exclusion criteria were

LDL cholesterol <2.1 mmol/L or >4.9 mmol/L and/or a vascular event in the three months prior to study entry. Atorvastatin failed to demonstrate any reduction in the primary end point compared to placebo. The primary end point was a composite of cardiac death, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke. In AURORA 2273 haemodialysis patients aged >50years were randomised to receive rosuvastatin 10mg daily or placebo. Of these 26.3% (n=731) had diabetes<sup>77</sup>. There was no reduction in the primary end point (time to a major cardiovascular event: cardiovascular death, non-fatal MI or non-fatal stroke) with rosuvastatin. In a pre-specified subgroup analysis, there was no difference in the incidence of the primary end point in patients with diabetes, although rosuvastatin did lead to a significant reduction in the incidence of cardiac events, at the expense of a non-significant increase in the rate of stroke<sup>78</sup>.

Finally, SHARP included 2,527 haemodialysis patients and 496 peritoneal dialysis patients (23% patients in SHARP had diabetes)<sup>58</sup> and a non-significant reduction in atherosclerotic events was observed in dialysis patients treated with the simvastatin 20mg-ezetimibe 10mg combination, compared to placebo. This may be due to the sample size of the ESRD cohort in this study rather than due to the magnitude of effect.

Taken together, these trials suggest that lipid lowering therapy is not associated with reductions in cardiovascular events in DN-DM CKD patients with ESRD requiring dialysis. A recent Cochrane review<sup>65</sup> has confirmed this. There may be subgroups that may benefit such as patients with higher LDL levels or recent vascular events but these patients were either excluded from or not randomised to these trials.

Although clear evidence of benefit has not been demonstrated in trials of lipid lowering therapy in diabetes patients on dialysis, there are no data to suggest harm in using lipid-lowering therapy in this group of patients with appropriate monitoring. Epidemiological data from DOPPS suggest that use of statins may be associated with better outcomes in haemodialysis patients, although this may represent effects unrelated to lipid lowering therapy, such as treatment centre or patient related factors<sup>79</sup>. There are no direct data to inform whether to continue lipid-lowering therapy in the DN-DM CKD patients once dialysis has commenced. In the SHARP study, 34.2% of patients commenced treatment for ESRD (either dialysis or kidney transplantation)<sup>58</sup>. These patients continued in follow up after commencement of treatment for ESRD and therefore it is plausible to assume some benefit in these patients.

### **Evidence base for CVD risk in renal transplant patients with DM**

Patients with DN-DM CKD who have reached ESRD requiring transplantation are at high cardiovascular risk. The leading cause of graft loss is death with a functioning graft, whilst the leading cause of death in renal transplant recipients is cardiovascular di<sup>0</sup>. Therefore, it is imperative that cardiovascular risk is lowered aggressively to optimise patient and graft outcomes. Kidney transplant recipients have a high prevalence of dyslipidaemia, including raised TC,

HDL and LDL cholesterol and hypertriglyceridaemia<sup>81</sup>. Dyslipidaemia is a consequence of immunosuppressive therapy, specifically corticosteroids, ciclosporin (more so than tacrolimus), sirolimus and everolimus<sup>82</sup>. Lipid lowering therapy is likely to be beneficial for many renal transplant recipients<sup>83</sup>.

Performing a baseline assessment of lipid status allows compliance with therapy to be assessed and additionally allows estimation the magnitude of any benefits of lipid lowering therapy. Compliance with therapy is recognised to be challenging in renal transplant recipients as they are usually on multiple agents often including immunosuppression, antihypertensive therapy and antimicrobial prophylaxis. Lipid assessment should be performed once immunosuppressive drug dosing has been stabilised and the risk of acute rejection requiring corticosteroid therapy has fallen. This period of stability is likely to be achieved three months post transplantation at the earliest, although this will vary with individual patients.

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

Statins have similar effects on the secondary dyslipidaemia seen in renal transplant recipients as is demonstrated in primary dyslipidaemia in the general population. The ALERT, a large scale randomised controlled trial, study showed that long-term treatment with fluvastatin (40-80mg/day) non-significantly reduced the risk of coronary death or non-fatal MI, compared with placebo in ciclosporin treated renal transplant recipients<sup>83,84</sup>. Fluvastatin did lead to a significant 35% relative reduction in the risk of cardiac death or non-fatal MI. In ALERT 18.7% patients had diabetes at baseline and diabetes was a risk factor for cardiac death in this study<sup>85</sup>. However, in diabetic renal transplant patients there was not a significant reduction in cardiac events with fluvastatin compared to placebo.

Statins are metabolised by the cytochrome P450 microsomal enzyme system and 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<sup>86</sup>. This risk appears to be greater with simvastatin and is lowest with fluvastatin or pravastatin. Ezetimibe appears to be safe in renal transplant recipients, although it has been reported to interfere with ciclosporin levels, more recent reports suggest this is unlikely to be a major clinical problem<sup>87,88</sup>. Fibrates have a high risk of side effects and are generally best avoided in renal transplant recipients.

Post transplant diabetes mellitus (PTDM) affects 7-25% of patients following renal transplantation<sup>89</sup>. 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, ethnicity, and transplant-related risk factors include corticosteroids, calcineurin inhibitors (particularly tacrolimus) and acute rejection. There are no studies to guide lipid management in patients with 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.

For patients with type 1 diabetes and advanced CKD, simultaneous kidney pancreas transplantation (SPK) or less commonly pancreas after kidney transplantation (PAK) allows patients to become insulin independent and has been shown to improve multiple markers of CVD<sup>90</sup>. There are no data to inform strategies for lipid management in this population. All patients 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.

#### **Guideline 14**

We recommend that in patients with DN-DM CKD already treated with lipid lowering therapy who commence dialysis, lipid lowering therapy should be continued. (Grade 2C)

#### **Guideline 15**

We suggest that the decision to commence lipid lowering therapy *de novo* in DN-DM CKD patients requiring either haemodialysis or peritoneal dialysis should take into account risk of future atherosclerotic vascular events, life expectancy on dialysis and other co-morbid disease. In the absence of compelling evidence, it seems that any benefits of statin therapy in dialysis patients are likely to be greatest in younger patients with a longer projected treatment period, with the probability of renal replacement therapy. (Grade 2C)

#### **Guideline 16**

We recommend that all patients with DN-DM CKD who have undergone renal transplantation should have lipid status assessed once the immediate post operative period has passed (typically 3 months post transplantation). (Grade 2C)

#### **Guideline 17**

We suggest that in renal transplant recipients with DN-DM CKD lipid status is assessed annually. (Grade 2C)

#### **Guideline 18**

We recommend that lipid lowering therapy should be commenced in patients with DN-DM CKD who have undergone renal transplantation. (Grade 1B)

#### **Guideline 19**

We suggest that in patients with DN-DM CKD who have undergone kidney transplantation or kidney-pancreas transplantation the choice and dose of lipid lowering therapy should take into account concurrent immunosuppressive therapy. (Grade 2D)

#### **Guideline 20**

We suggest that all patients with DN-DM CKD who have undergone kidney-pancreas transplantation receive statin treatment. (Grade 2D)

#### **Guideline 21**

We suggest that all patients who develop post transplant diabetes mellitus are treated with statins. (Grade 2D)



## Rationale for guidelines 22-24

### **Statin side effects and safety in CKD**

The overall safety of statins has been exhaustively evaluated. In general use, serious side effects are considered remarkably uncommon, although controversy remains as to the frequency of muscular symptoms in the absence of raised muscle enzyme levels. This would appear to be more frequently encountered in routine clinical practice than was reported in the randomised clinical studies. A meta-analysis suggested a reduced risk of pancreatitis with statins in patients with normal or mildly elevated TG levels and no significant increased rate of pancreatitis with fibrates<sup>91</sup>. 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 amongst older patients with diabetes, although this was predominantly amongst patients using cerivastatin, which is not in use in the UK<sup>92</sup>.

When specifically examining the safety of statins in CKD, a Cochrane meta-analysis recorded no significant increase in the risk of rhabdomyolysis (defined as creatine kinase >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<sup>93</sup>. Other recent meta-analyses of statins in CKD also found no difference in the frequency of hepatic or muscular disorders in comparison to placebo<sup>65,66</sup>.

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 20mg daily. Combinations of simvastatin and ciclosporin, danazol and gemfibrozil should be avoided (<https://www.gov.uk/drug-safety-update/simvastatin-updated-advice-on-drug-interactions>).

In the TNT study comparing high (80 mg) versus low (10 mg) atorvastatin dosage 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 patients respectively<sup>67</sup>. In the SHARP study where simvastatin was combined with ezetimibe, there was no evidence of muscular or hepatic toxicity in comparison to placebo<sup>58</sup>. With active therapy, reduced pancreatitis episodes were observed although a similarly significant increase in withdrawal for muscle pain was noted.

In dialysis patients 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<sup>76,94</sup>. The recent NICE guidance routinely suggests measurement of liver enzymes before, 3 and 12 months after introduction of a statin<sup>23</sup>.

Whilst the link between a small increased risk of developing diabetes in non-diabetic subjects treated with statins is well described, JUPITER was the only study to suggest adverse glycaemic effects. In JUPITER non diabetic subjects 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<sup>70</sup>.

### **Effect and role of different statins studied in CKD (with and without diabetes)**

The JUPITER study of rosuvastatin 20mg/day raised the potential that different anti-inflammatory effects of statins may be relevant to renal outcomes<sup>70</sup>. Whereas pravastatin in WOSCOPS showed no effect on renal outcomes, the Pravastatin Pooling project (WOSCOPS combined with LIPID and CARE) showed pravastatin reduced CVD in CKD<sup>55</sup>. There were 3267 subjects in Jupiter with eGFR < 60ml/min. None had diabetes and baseline TC was 4.9mmol/L. LDL Cholesterol was < 3.3mmol/L with a modestly raised high sensitivity C-Reactive Protein (CRP). Virtually all subjects with renal dysfunction had stage 3 CKD, as the median eGFR was 56ml/min. There was a higher CVD incidence in subjects with CKD compared to the non-CKD group. The benefits were more evident in those with raised CRP, as a marker of inflammation<sup>70,95</sup>.

Whereas there may be differential efficacy, outcome and safety data with several statins used in DM CKD it appears that simvastatin, pravastatin, fluvastatin and atorvastatin have all been effective in reducing CVD events. PLANET1 was a head-to-head trial which compared rosuvastatin 10mg or 40mg to atorvastatin 80mg in patients with proteinuria<sup>72</sup>. Overall atorvastatin had a more impressive impact on reducing proteinuria, suggesting that it may be more nephroprotective than rosuvastatin. In summary, all statins have evidence for their use in CKD but if there is a need to use the most efficacious high intensity statins in DM CKD, then existing data would suggest that atorvastatin is preferable.

#### **Guideline 22**

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

#### **Guideline 23**

We suggest sub maximal statin (in patients who are unable to tolerate higher statin doses) and ezetimibe combination therapy should be considered as an alternative to high intensity atorvastatin in DN-DM CKD at all stages. (Grade 1B)

#### **Guideline 24**

We recommend routine measurement of liver enzymes before statin initiation in DN-DM CKD and at 3 months after commencement and annually thereafter. Routine measurement of serum creatinine kinase is unnecessary in the absence of muscle pain (consistent with NICE guideline CG181). (Grade 1A)

## Rationale for guidelines 25-28

Two CVD outcome trials (FIELD and ACCORD) have addressed the issue of fibrate therapy in diabetes. In FIELD, a placebo-controlled trial of fenofibrate in 9795 type 2 diabetes patients (of whom 519 had an eGFR <60ml/min) a reduction in non-fatal MI was the only significant finding<sup>96</sup>. The ACCORD study, which randomised 5518 type 2 diabetes patients being treated with open-label simvastatin to receive either masked fenofibrate or placebo, 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<sup>97</sup>. Only 2.5% had eGFR 30-49ml/min and of the vast majority, only a small number had eGFR 50-60ml/min. In the overall ACCORD study group fenofibrate only reduced CVD events in dyslipidaemic men with reduced HDL cholesterol.

Both FIELD and ACCORD suggested fenofibrate led to reductions in progression of retinopathy, albuminuria<sup>94,95</sup> and in foot amputations<sup>98,99</sup>. It was suggested this was not a lipid-mediated benefit. An earlier study had also suggested that development of microalbuminuria could be reduced by fenofibrate in diabetes<sup>100</sup>.

A consistent finding from both ACCORD and FIELD is confirmation that fenofibrate consistently leads to a rise in serum creatinine and decline in eGFR which is reversible 6-8 weeks after discontinuation and which 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<sup>99</sup>. It is notable that the time-related decline in eGFR in the placebo group in both studies over the duration of the study was greater than in the fenofibrate group.

There was no increase in frequency of raised muscle enzyme activity with combination statin fibrate therapy in ACCORD<sup>97,99</sup>. It appeared that older males with established CVD and lower baseline creatinine were most likely to exhibit the fenofibrate associated rise in creatinine<sup>101</sup>. Overall there was a 2-fold greater discontinuation rate amongst those in the statin-fibrate group due to reductions in GFR, and fenofibrate dose was reduced in 16%.

The FIELD study more recently suggested longer-term fenofibrate therapy remained effective and safe over a longer period in those with type 2 diabetes and renal impairment<sup>102</sup>. Fenofibrate was also added to high dose statins in hypertriglyceridaemic patients alongside multiple risk factor reduction in microalbuminuric type 2 diabetic patients in the well-designed Steno 2 study of 160 patients, who achieved marked reductions in all microvascular and macrovascular outcomes<sup>63</sup>.

A study of fenofibrate with statins in 280 patients with stage 3 CKD (58% with diabetes) demonstrated lipid-lowering efficacy but clinically significant hepatic dysfunction in three of the 140 actively treated group was observed and again a decline in glomerular filtration (from 49 to 43ml/min), that reversed on withdrawal of fenofibrate, was reported<sup>103</sup>. 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.

However meta-analyses have demonstrated CVD outcome benefit, reduced risk of albuminuria progression and safety with fibrate and statin combination therapy in patients with combined dyslipidaemia and mild to moderate CKD<sup>104,105</sup>. However, both NICE and JBS3 state fibrates should not routinely be offered for CVD prevention in type 2 diabetes and CKD<sup>4,23</sup>. The ADA only suggests a role for fibrates in marked hypertriglyceridaemia and the potentially beneficial impact on microvascular disease is not fully explored outside the JBS3 guidelines.

The impact of fenofibrate on vascular outcomes balanced with consistent changes in eGFR suggest that any role for fibrates in DN-DM CKD would only be at a stage when there were anticipated microvascular (retinal-foot-albuminuria) benefit, and most notably amongst patients with dyslipidaemia. The recognition of adverse renal outcomes with fenofibrate amongst the elderly and particularly in combination with statins suggests that access might be best restricted to younger patients with less advanced complications and preserved GFR<sup>106,107</sup>. Use of fibrates usually in combination with statins may be considered in patients with albuminuria (or those with retinopathy-risk of adverse microvascular foot disease outcomes) with eGFR  $\geq$ 45ml/min, but only with regular monitoring of eGFR, liver enzymes and muscle enzyme activity. Fibrate dose reduction or withdrawal should be implemented if eGFR falls by more than 20% and/or below 45 ml/min. Fibrate dose reduction may need to be considered if continued in DN-DM CKD where eGFR > 45ml/min.

The meta-analyses suggest that albuminuria is reduced through the combination of statin and some fibrates in CKD<sup>3,107,108</sup>. Whereas there is no clear increase in progression to ESRD 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.

There are several unanswered questions, which have yet to be addressed when considering optimal lipid lowering strategies for patients with diabetes and CKD. Many of these will require future research, either from further clinical trials of with intelligent use of prescribing and laboratory data in these patients. Many of these questions revolve around the use of non-statin lipid lowering therapy.

- What is the role for fibrates in DN-DM CKD either as monotherapy or in addition to statins?
- What is the role for combination of a statin and a fibrate in CKD stages 3 or 4 and does this influence renal or CVD outcomes?

### What is the role for ezetimibe as a lipid-lowering agent in DM CKD?

Ezetimibe blocks intestinal absorption of cholesterol but has additional hepatic effects that enable reduction of atherogenic lipoproteins<sup>109</sup>. The main role in DN-DM CKD would be adjunctive to statin use, or as single agent therapy in statin intolerant cases. A pooled analysis of statin and ezetimibe combination therapy in diabetes patients showed additive benefit and greater

efficacy than sub maximal statin dosage without any untoward adverse muscle effects and greater reductions in total LDL and non-HDL cholesterol in comparison to non-diabetes patients on the combination statin-ezetimibe regime. There was a marginal (0.6 vs. 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<sup>110</sup>.

The SHARP study in CKD was a randomised placebo controlled trial of simvastatin 20 mg and 10 mg ezetimibe in combination. The major rationale of adding ezetimibe to low dose simvastatin was to ensure a reduction in LDL cholesterol of >1mmol/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 vs. 0.1%, equivalent to 1 case per 5000 patients per year of treatment). There was no suggestion that statin ezetimibe combination altered rates of end stage renal failure or rates of haemodialysis<sup>58</sup>. In patients with DN-DM CKD 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 use a more potent statin such as atorvastatin 20-80mg daily, as now suggested in the JBS3 guidelines. It seems reasonable to use ezetimibe as a lipid-lowering agent in statin intolerant patients, although there is no specific evidence to support this in DM CKD.

The most recent study with ezetimibe add-on was to 40 mg simvastatin the IMPROVE-IT study, although compared to placebo (as in SHARP) the combination led to lower attained LDL cholesterol levels of 1.4 mmol/L and an overall absolute risk difference of 2% in the primary end point of combined fatal and non fatal major CVD events, with the benefit particularly noted amongst the 25% of patients with diabetes. However there appeared very few if any patients with diabetes and CKD<sup>61</sup>. Nevertheless, the concept patients at highest CVD risk benefiting more from intensive LDL lowering was upheld, albeit in those without clear DN-DM CKD.

#### Other lipid lowering agents in DM CKD – Nicotinic acid

Nicotinic acid and its derivatives were first recognised as lipid lowering agents over 60 years ago<sup>111</sup>. Most recent studies confirm that nicotinic acid reduces LDL cholesterol and TG whilst increasing HDL cholesterol in type 2 diabetes<sup>112</sup>. Studies in patients with CKD, including those on dialysis, have confirmed that nicotinic acid improves dyslipidaemia and has a phosphate lowering effect<sup>113-115</sup>. Furthermore, pharmacokinetic studies with extended release nicotinic acid in CKD and dialysis patients showed no drug accumulation or need for dose adjustment<sup>114,115</sup>. As dyslipidaemic benefits have also been demonstrated in studies with type 2 diabetes it is logical to consider whether this class of drugs could have a role in the management of dyslipidaemic diabetes with CKD. There are no specific

outcome trials of niacin/nicotinate in CKD, but in the 505 patients with stage 3 CKD (41% with diabetes) in the AIM-HIGH study, there was no demonstrable cardiovascular benefit of niacin compared to placebo when added to statin in patients with coronary artery disease, and an increased mortality risk in the niacin treated patients. In the main AIM-HIGH study (34% of the 3414 patients had diabetes), there was no beneficial additive effect of using nicotinic acid compared to placebo in patients treated with simvastatin +/-ezetimibe to maintain LDL-cholesterol <2.07 mmol/L<sup>116</sup>.

A consistent finding with niacin in diabetes has been an elevation of HbA1c and modest worsening of fasting hyperglycaemia through excess fatty acid release<sup>117</sup>. In studies in dialysis patients the risk of thrombocytopenia is significantly increased<sup>114,115</sup>. In addition, the long recognised side effect of prostaglandin mediated flushing has remained a basis for high withdrawal rates, although laropiprant, a prostaglandin D2 receptor antagonist, can reduce the flushing. This combination therapy was utilised in 2 large cardiovascular endpoint trials, which included around 10,000 patients with type 2 diabetes<sup>118,119</sup>. Overall and within the diabetes subgroup there was no cardiovascular benefit despite consistent increased HDL cholesterol. Patients with creatinine >200micromol/L were excluded from the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2 THRIVE) trial. Based on current evidence, we cannot recommend nicotinic acid as a lipid-lowering agent in DM CKD for reduction of CVD risk, notwithstanding that this medication is no longer available in the UK as it has been withdrawn from the market.

#### Guideline 25

We recommend that when prescribed in combination with amlodipine or diltiazem the maximum dose of simvastatin should not exceed 20mg. (Grade 1B)

#### Guideline 26

We suggest that there is no role for fibrates in advanced DM CKD (3b-5) - either as monotherapy or in combination with statins - outside specialist care. (Grade 1A)

#### Guideline 27

We suggest that fenofibrate therapy alone or alongside statins should only be used in DN-DM CKD 3a or earlier stages - primarily to reduce risks of progressive microvascular events in patients with statin intolerance or residual dyslipidaemia despite statin therapy. (Grade 2C)

#### Guideline 28

We do not recommend fibrate-ezetimibe combination therapy in DN-DM CKD, out with specialist lipid clinic advice. (Grade 2D)

All 28 guidelines can be viewed sequentially in **Appendix 2**



### Clinical Audit

Suggested audit measures for clinical practice guidelines for management of lipids in patients with DN-DM CKD are noted below. To assist data collection for audit (**Chart 1**), and permit customisation to enhance local utility, a lipid audit chart can be downloaded as a modifiable Excel document (**Appendix 3**).

- i. Proportion of DN-DM CKD patients not requiring dialysis taking statins for primary and secondary prevention of cardiovascular disease
- ii. Level of achieved total cholesterol (<5 and <4mmol/L), LDL-cholesterol (<3 and <2mmol/L), non-HDL cholesterol (< 3 and <2.5 mmol/L) in patients not requiring dialysis
- iii. Proportion of DN-DM CKD on dialysis with measure of fasting lipids measured during first six months of commencement of dialysis
- iv. Proportion of DN-DM CKD on dialysis taking statins for primary and secondary prevention of cardiovascular disease
- v. Proportion of DN-DM CKD renal transplant patients with annual measure of fasting lipids
- vi. Proportion of DN-DM CKD renal transplant patients taking statins for primary and secondary prevention of cardiovascular disease
- vii. Attained levels of total cholesterol, LDL-cholesterol, non-HDL-cholesterol as stated previously
- viii. Proportion of DN-DM CKD renal transplant patients achieving dyslipidaemia targets (see ii above)

**Chart 1.** Lipid audit chart

Diabetes patients with DN-DM CKD	T1DM	T2DM	Total
Number of patients			
<b>Patients not requiring dialysis</b>			
Fasting lipids measured annually			
Taking statins for primary or secondary prevention of CV disease			
Achieving total cholesterol <5 mmol/L			
<4 mmol/L			
Achieving LDL cholesterol <3 mmol/L			
<2 mmol/L			
Achieving non HDL cholesterol <3 mmol/L			
<2.5 mmol/L			
<b>Patients on dialysis</b>			
Fasting lipids measured during first 6 months of starting dialysis			
Taking statins for primary or secondary prevention of CV disease			
Achieving total cholesterol <5 mmol/L			
<4 mmol/L			
Achieving LDL cholesterol <3 mmol/L			
<2 mmol/L			
Achieving non HDL cholesterol <3 mmol/L			
<2.5 mmol/L			
<b>Renal transplant patients</b>			
Fasting lipids measured annually			
Taking statins for primary or secondary prevention of CV disease			
Achieving total cholesterol <5 mmol/L			
<4 mmol/L			
Achieving LDL cholesterol <3 mmol/L			
<2 mmol/L			
Achieving non HDL cholesterol <3 mmol/L			
<2.5 mmol/L			

### Areas for consideration

#### Research question

Does addition of nicotinic acid to statin therapy confer CVD benefit in diabetes patients with albuminuria or low HDL-cholesterol?

#### Further areas of

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

It is widely documented in a number of clinical trials or observational epidemiological studies that elevated levels of inflammatory markers such as CRP are predictive of CVD. Statins have been shown to reduce C-reactive protein. It is unknown in CKD whether specific subtypes of patient such as those with elevated CRP may derive relatively greater benefit from lipid lowering therapy with statins. Whilst this is somewhat speculative, and overall there has been limited benefit from lipid lowering therapy in dialysis despite significant reduction in CRP with statins, one analysis has shown that once correction is made for inflammation, there is a linear relationship between TC and CVD risk in dialysis<sup>120</sup>. This notion suggests that levels of inflammation may confound any relationship between cholesterol and outcome and either patients with high grade inflammation are malnourished and do not need cholesterol lowered, or alternatively these patients are at highest risk and may have most to gain from statin therapy. Further study of the relationship between inflammation, CVD risk and lipid profile is required.

- What is the safety profile of high intensity safety and efficacy of lipid lowering therapies when eGFR < 30ml/min?

The TNT study suggested that high dose (80mg) atorvastatin in patients with stable CVD lead to significant benefits in terms of CVD risk, compared to 10mg atorvastatin, with no excess risk of myopathy. At study entry most patients had normal renal function and approximately 31% had stage 3 or 4 CKD, and, renal function appeared preserved and/or improved in the higher dose statin group. Therefore it is possible that further benefit for CVD risk and/or renal outcomes may be achieved with high dose atorvastatin compared to other agents. Similarly, a large retrospective study of high potency (n=651,000) versus low potency (n=1,360,000) statin use and Acute Kidney Injury (AKI) associated hospitalisations found a significant association between high potency statin use and AKI in the CKD cohort<sup>121</sup>. Outcomes with high intensity lipid lowering therapy require testing in further studies.

- What is the role for titrated lipid lowering therapy with regular testing of lipid profile, compared to 'fire and forget'?
- What is the need for specific lipid targets to direct intensity of therapy particularly in non-dialysis DN-DM CKD?

Existing guidelines follow two essentially contradictory dogmata. KDIGO suggest that repeat testing of lipid profile is not required in CKD patients as there are limited data to suggest that specific lipid targets are required in CKD. However, many trials of lipid lowering therapy would suggest that 'lower is better' in terms of the effect of reduction of LDL cholesterol and cardiovascular risk reduction, and at least in those without CKD this now appears to have been confirmed<sup>67</sup>. In early DM CKD where the CVD risk is high and patients are more likely to succumb to premature CVD rather than progress to ESRD, it seems likely that the major focus of lipid lowering therapy should be reduction of cardiovascular risk. As the patient edges towards needing dialysis, there may be a need to reconsider the intensity of lipid lowering therapy. As it stands further analysis of existing data from trials such as SHARP may inform whether achieving lower LDL cholesterol translates to reduced CVD risk. These data may inform whether repeated testing of lipid status in response to, or to inform changes in therapy is likely to improve patient outcomes.

- *What approach should be used for statin intolerant patients with DN-DM CKD?*

Despite statins being extensively studied and widely accepted as well tolerated, there is a small proportion of patients who are unable to tolerate statin therapy due to side effects, usually myalgia. A small proportion of patients experience genuine myopathy and/or rhabdomyolysis, but this is rare. However, there is ongoing debate about the relative incidence and severity of statin related side effects in real world clinical practice. Clinical evidence is somewhat lacking about strategies to address statin intolerance whilst aiming to reduce cardiovascular risk. Alternative options would include ezetimibe monotherapy, very low dose statin with additional ezetimibe, fibrates or niacin. The novel monoclonal antibodies for inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9) appear to be an extremely potent alternative to statins for reducing LDL cholesterol and this appears to translate to reduced cardiovascular events<sup>122,123</sup>. Further study is required to delineate the exact role for these agents for patients with DN-DM CKD.

- *Does high intensity atorvastatin or lower dose statin-ezetimibe combination therapy reduce progression or proteinuria and CKD stage 2 in DN?*

The PLANET studies suggest that some statins appear to have a more favourable nephroprotective profile than others, in this case atorvastatin led to an improvement in eGFR and reduction in proteinuria<sup>72</sup>. Whilst this effect was not seen in SHARP, it is plausible to believe that aggressive lipid lowering might have some beneficial effect on progression of renal disease, perhaps in early DN-DM CKD 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

## In summary.....

An abridged version of this guidance is published in the British Journal of Diabetes<sup>124</sup> and all 28 guidelines can be viewed sequentially in Appendix 2 .

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## APPENDIX 2

### Guideline listing

Listing of guidelines as presented in the summary of joint guidance and as reproduced in blue boxes within rationale sections of this document<sup>124</sup>.

#### Guideline 1

We recommend that evaluation of a full lipid profile (TC, LDL cholesterol, HDL cholesterol, TGs) is performed in patients with DN-DM CKD as is current practice. (Grade 1A)

#### Guideline 2

We suggest that the lipid profile is assessed at least annually in patients with DN-DM CKD. (Grade 1C)

#### Guideline 3

We advise that the major goal of commencing lipid-lowering therapy in adult patients with DN-DM CKD is to reduce risk of cardiovascular events. (Grade 2A)

We suggest that in patients with stage 1-2 DN-DM CKD, lipid-lowering therapy with statins is commenced in the following categories:

- Patients with type 1 diabetes and persistent microalbuminuria aged > 30 years
- Patients type 2 diabetes with rapidly progressing early CKD (loss of GFR >5ml/min/year) irrespective of albuminuria status
- Patients with type 2 diabetes aged >40 years irrespective of cholesterol levels
- All patients with type 2 diabetes and persistent microalbuminuria or macroalbuminuria

#### Guideline 4

We recommend that lipid lowering therapy with statins should be considered for all patients with stage 3-5 DN-DM CKD. (Grade 1B)

#### Guideline 5

We recommend review of the lipid profile on commencement or change of modality of renal replacement therapy (dialysis or kidney transplantation). (Grade 1D)

#### Guideline 6

We suggest that in patients with end stage renal disease (ESRD) measurement of the lipid profile should be performed annually to assess compliance and need for continuing therapy. (Grade 2D)

#### Guideline 7

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

#### Guideline 8

We suggest that in patients with type 1 diabetes with CKD stage 1-2, lipid-lowering therapy with statins is commenced in patients aged 18-30years with persistent albuminuria and additional CVD risk factors evident. (Grade 1B)

#### Guideline 9

We suggest that in DN-DM CKD patients not requiring renal replacement therapy it is appropriate to initiate statin therapy with either atorvastatin 20 mg or simvastatin 20-40 mg. (Grade 1D)

#### Guideline 10

We suggest that in patients with reduced GFR +/- persistent albuminuria the management of dyslipidaemia should be similar irrespective of whether the individual has type 1 or type 2 diabetes. (Grade 1B)

#### Guideline 11

We suggest that in type 1 diabetes with persistent albuminuria and/or reduced eGFR (60-90) statin use should aim to reduce TC to 4.0 mmol/l, LDL cholesterol to 2 mmol/l and non-HDL cholesterol to 2.5 mmol/l. (Grade 1D)

#### Guideline 12

We suggest that higher intensity statin use (atorvastatin 40-80 mg) can be considered for those with persistent albuminuria and or reduced eGFR (30-60) at highest CVD risk (e.g. aged >40 years; poor glycaemic control (HbA1c > 75 mmol/mol); additional CVD risk factors: smoking, hypertension, dyslipidaemia; proliferative retinopathy) who do not attain lipid targets in Guideline 11 on lower statin doses. (Grade 1D)

**Guideline 13**

We recommend that all type 2 diabetes patients with stage 1-2 CKD with albuminuria, who have the highest risk of CVD, should be considered for high intensity statins such as atorvastatin 80 mg. (Grade 1A)

**Guideline 14**

We recommend that in patients with DN-DM CKD already treated with lipid lowering therapy who commence dialysis, lipid lowering therapy should be continued. (Grade 2C)

**Guideline 15**

We suggest that the decision to commence lipid lowering therapy *de novo* in DN-DM CKD patients requiring either haemodialysis or peritoneal dialysis should take into account risk of future atherosclerotic vascular events, life expectancy on dialysis and other co-morbid disease. In the absence of compelling evidence, it seems that any benefits of statin therapy in dialysis patients are likely to be greatest in younger patients with a longer projected treatment period, with the probability of renal replacement therapy. (Grade 2C)

**Guideline 16**

We recommend that all patients with DN-DM CKD who have undergone renal transplantation should have lipid status assessed once the immediate post operative period has passed (typically 3 months post transplantation). (Grade 2C)

**Guideline 17**

We suggest that in renal transplant recipients with DN-DM CKD lipid status is assessed annually. (Grade 2C)

**Guideline 18**

We recommend that lipid lowering therapy should be commenced in patients with DN-DM CKD who have undergone renal transplantation. (Grade 1B)

**Guideline 19**

We suggest that in patients with DN-DM CKD who have undergone kidney transplantation or kidney-pancreas transplantation the choice and dose of lipid lowering therapy should take into account concurrent immunosuppressive therapy. (Grade 2D)

**Guideline 20**

We suggest that all patients with DN-DM CKD who have undergone kidney-pancreas transplantation receive statin treatment. (Grade 2D)

**Guideline 21**

We suggest that all patients who develop post transplant diabetes mellitus are treated with statins. (Grade 2D)

**Guideline 22**

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

**Guideline 23**

We suggest sub maximal statin (in patients who are unable to tolerate higher statin doses) and ezetimibe combination therapy should be considered as an alternative to high intensity atorvastatin in DN-DM CKD at all stages. (Grade 1B)

**Guideline 24**

We recommend routine measurement of liver enzymes before statin initiation in DN-DM CKD and at 3 months after commencement and annually thereafter. Routine measurement of serum creatinine kinase is unnecessary in the absence of muscle pain (consistent with NICE guideline CG181). (Grade 1A)

**Guideline 25**

We recommend that when prescribed in combination with amlodipine or diltiazem the maximum dose of simvastatin should not exceed 20mg. (Grade 1B)

**Guideline 26**

We suggest that there is no role for fibrates in advanced DM CKD (3b-5) - either as monotherapy or in combination with statins - outside specialist care. (Grade 1A)

**Guideline 27**

We suggest that fenofibrate therapy alone or alongside statins should only be used in DN-DM CKD 3a or earlier stages - primarily to reduce risks of progressive microvascular events in patients with statin intolerance or residual dyslipidaemia despite statin therapy. (Grade 2C)

**Guideline 28**

We do not recommend fibrate-ezetimibe combination therapy in DN-DM CKD, outwith specialist lipid clinic advice. (Grade 2D)

### APPENDIX 3

Copy of Excel version of Chart 1, which can be downloaded from this website

<b>Chart 1.</b>					
<b>Data collection chart for audit of lipid management</b>					
<b>Diabetes patients with DN-DM CKD</b>			<b>T1DM</b>	<b>T2DM</b>	<b>Total</b>
<b>Number of patients</b>					
<b>Patients not requiring dialysis</b>					
Fasting lipids measured annually					
Taking statins for primary or secondary prevention of CV disease					
Achieving total cholesterol			<5 mmol/L		
			<4 mmol/L		
Achieving LDL cholesterol			<3 mmol/L		
			<2 mmol/L		
Achieving non HDL cholesterol			<3 mmol/L		
			<2.5 mmol/L		
<b>Patients on dialysis</b>					
Fasting lipids measured during first 6 months of starting dialysis					
Taking statins for primary or secondary prevention of CV disease					
Achieving total cholesterol			<5 mmol/L		
			<4 mmol/L		
Achieving LDL cholesterol			<3 mmol/L		
			<2 mmol/L		
Achieving non HDL cholesterol			<3 mmol/L		
			<2.5 mmol/L		
<b>Renal transplant patients</b>					
Fasting lipids measured annually					
Taking statins for primary or secondary prevention of CV disease					
Achieving total cholesterol			<5 mmol/L		
			<4 mmol/L		
Achieving LDL cholesterol			<3 mmol/L		
			<2 mmol/L		
Achieving non HDL cholesterol			<3 mmol/L		
			<2.5 mmol/L		