Management of lipids in adults with diabetes mellitus and nephropathy and/or chronic kidney disease: summary of joint guidance from the Association of British Clinical Diabetologists (ABCD) and the Renal Association (RA)

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Abstract

In diabetes, nephropathy and chronic kidney disease are independent and co-existent harbingers of end stage renal failure as well as increased morbidity and premature mortality due to cardiovascular disease. Whilst lipid management is beneficial in reducing cardiovascular risk in populations with and without diabetes, there is a paucity of national guidance on the utility of this approach in diabetes patients with renal disease. This joint guidance collates the best available evidence and expert opinion (in the absence of clear evidence) to provide 28 guidelines to empower clinicians to deliver optimal lipid management according to renal status in these patients at high cardiovascular risk. The abridged guideline herein provides a practical overview of the full document. The full guidance with detailed rationale is available online.

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Key words: diabetes, nephropathy, chronic kidney disease, cardiovascular disease, lipids, statins, guidelines

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.

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).

Box 1 Differentiating renal disease in diabetes

Nephropathy (DN)	Damage to glomerular capillaries in patients with diabetes mellitus resulting in albuminuria in the absence of other causes of albuminuria
Diabetes mellitus chronic kidney disease (DM CKD)	Presence of structural or functional renal abnormalities, present for >3 months in patients with diabetes mellitus

The abridged guidelines herein provide a practical overview of the full document which should be consulted when designing treatment strategies. The full guidelines are available online.* The full guidance can also be accessed via the ABCD and Renal Association websites.

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

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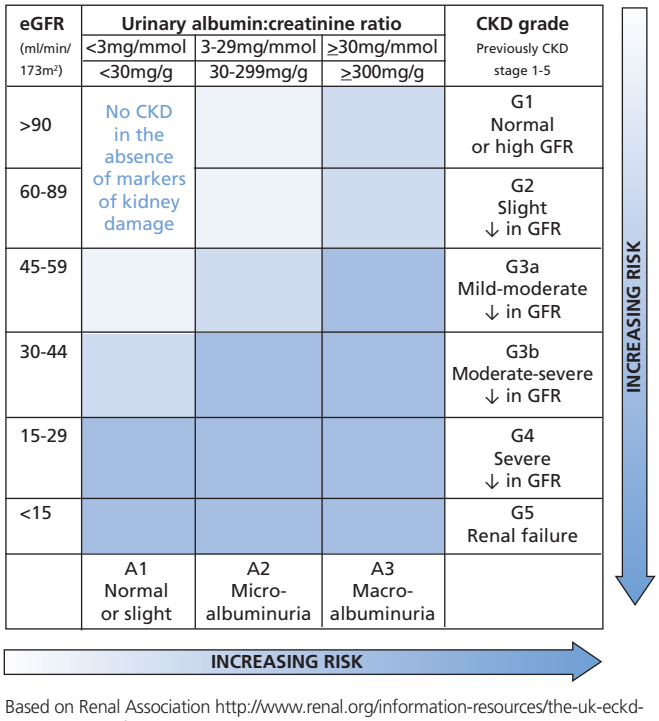
Figure 1. Glomerular filtration rates (GFR) and albumin:creatinine ratio categories and risk of adverse outcomes



Based on Renal Association http://www.renal.org/information-resources/the-uk-eckd-guide/about-egfr#sthash.mQ76je8d.dpbs and KDIGO 2012 http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf

up to March 2016. We also reviewed all related guidelines from the National Institute for Clinical Excellence, 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).[1,2] (See full guidance online).*

Guideline summary

The evidence grading has determined the strength of recommendations (ranging from 1A to 2D), suggested standards for clinical audit and the outstanding questions for future research.

The guidelines are listed here with diagrams to summarise their utility in type 1 diabetes (Figure 2) and type 2 diabetes (Figure 3) and suggested audit measures are noted. It is recommended that the unabridged guidance is viewed online.*

Guidelines

A detailed rationale for these guidelines can be viewed online.*

To support rapid access to evidence from this abbreviated publication, the references used to inform these guidelines (Box 2) are listed at the end of this document.

The following standard lipid abbreviations are used in these guidelines: total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG).

Box 2 Listing of references used to support the guidelines

Guidelines	References
1–7	4,8,9,11,15,17–42
8	5, 9,11–13,15,21,22,24,25,29,31,35–37,41,43–49
9–13	3,4,6,7,9,10,14,16,22,23,27,28,30,32,33,49–73
14–21	58,65,74–90
22–24	23,55,58,65–67,70,72,76,91–95
25–28	4,23,58,61,63,94–119

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 with type 2 diabetes with progressing early CKD (loss of GFR >5 ml/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)

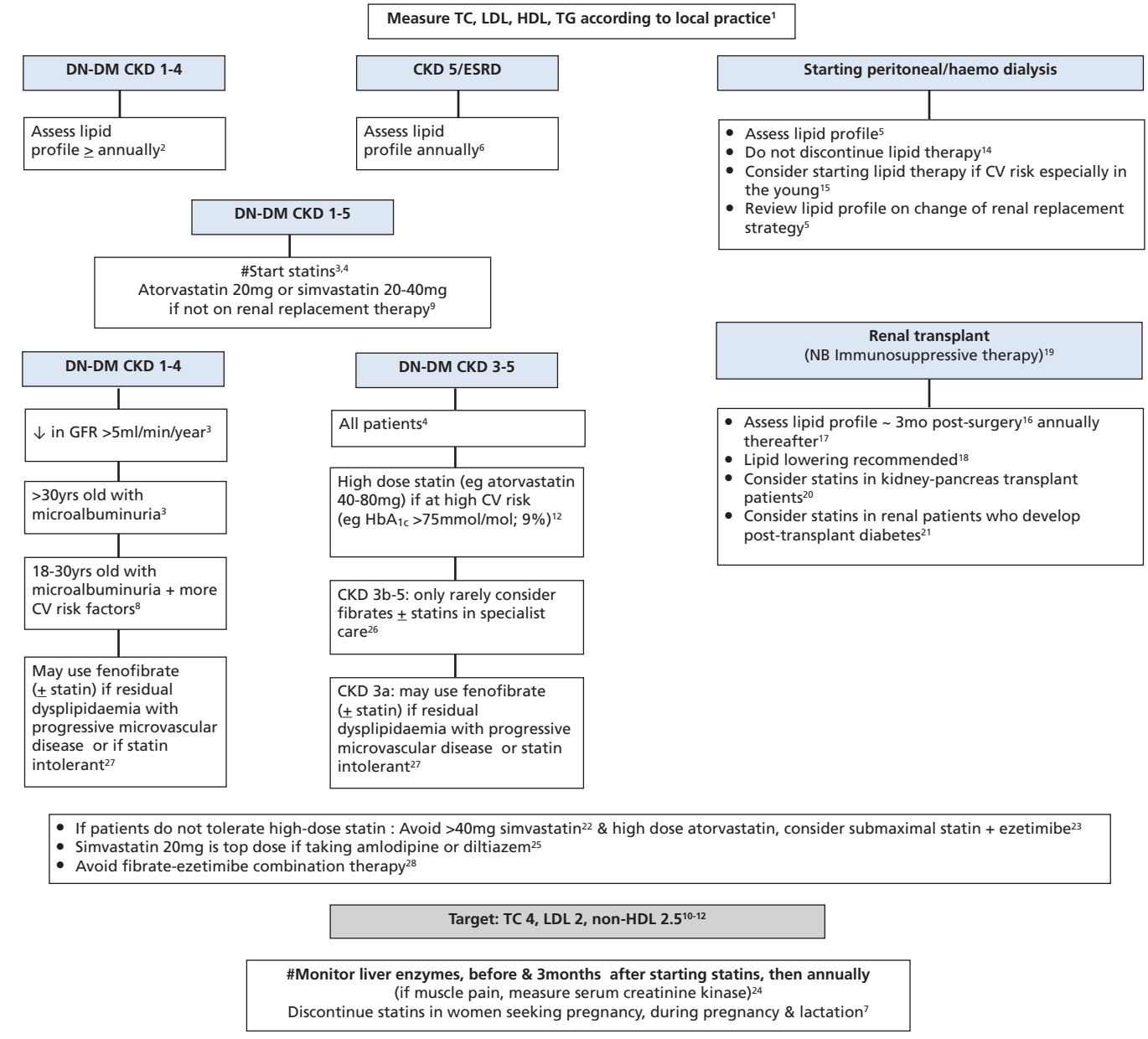
Guideline 6

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

Figure 2. Lipid management in type 1 diabetes*



*Superscript number refers to that guideline

DN, diabetic nephropathy; CKD, chronic kidney disease; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

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 18–30 years with persistent albuminuria and additional CVD risk factors evident. (Grade 1B)

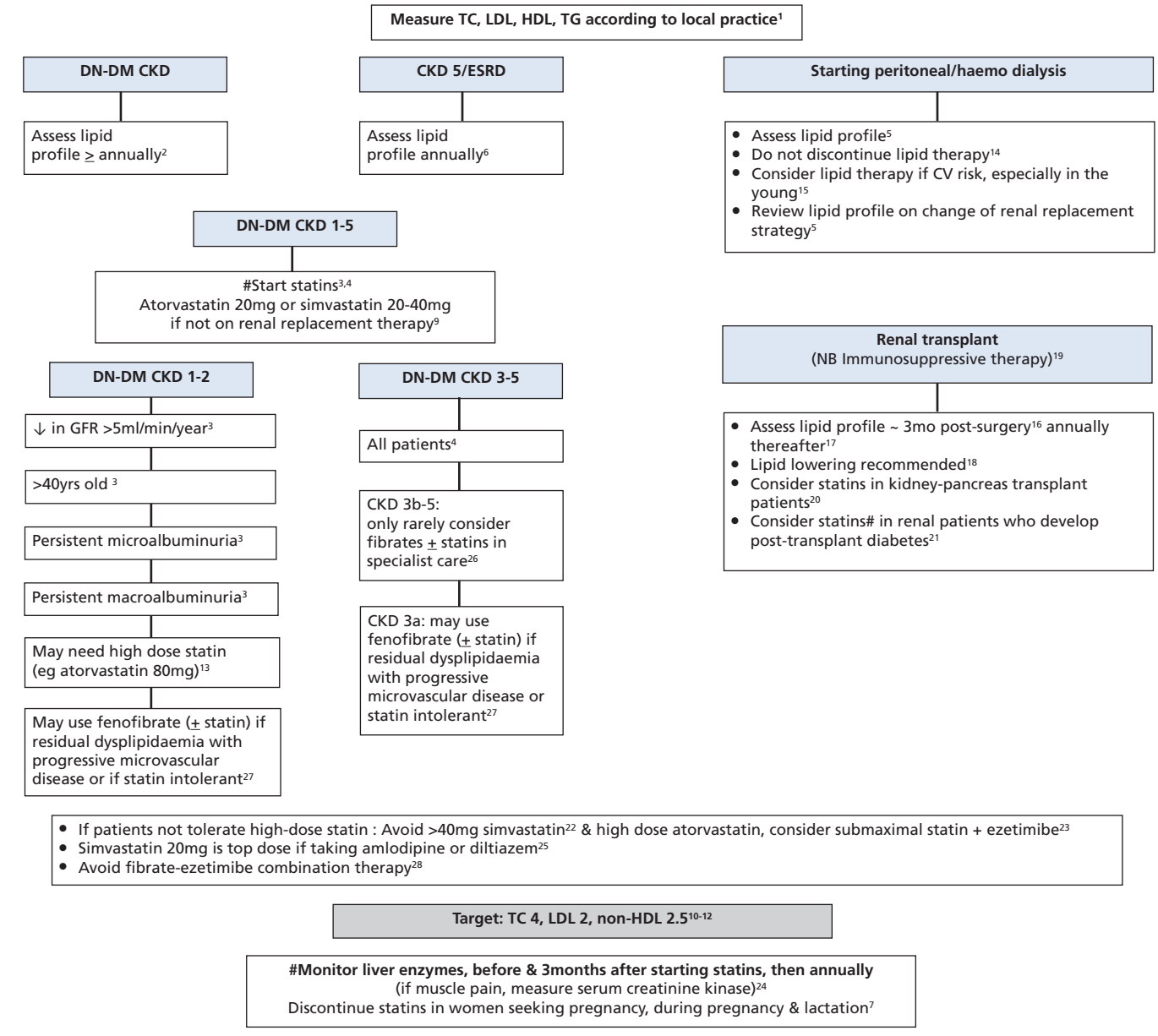
Guideline 9

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)

Figure 3. Lipid management in type 2 diabetes*



*Superscript number refers to that guideline

DN, diabetic nephropathy; CKD, chronic kidney disease; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides.

Guideline 11

We suggest that in patients with 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 (HbA_{1C} >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 postoperative 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 should 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 >40 mg/day simvastatin in DN-DM CKD due to the increased risk of muscular side effects. (Grade 1A)

Guideline 23
We suggest submaximal 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 20 mg. (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)

Clinical audit

Suggested audit measures for clinical practice guidelines for management of lipids in patients with DN-DM CKD (to assist data collection for audit a chart (Chart 1) is provided below. To enhance the utility of the audit for local circumstances this chart can be downloaded as a modifiable Excel document: Appendix 2 in reference*****).

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 <4 mmol/L), LDL cholesterol (<3 and <2 mmol/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 6 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. Data collection chart for audit of lipid management

Diabetes patients with DN-DM CKD	T1DM	T2DM	Total
Number of patients			
Patients not requiring dialysis			
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			
Patients on dialysis			
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			
Renal transplant patients			
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			

Is there more?

The full guidance also considers issues for further research as well as areas of therapeutic uncertainty.*

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The full guideline and links to this abridged guideline will be available via the ABCD (www.diabetologists-abcd.org.uk) and Renal Association (www.renal.org) websites.

Key messages

- Diabetic nephropathy and chronic kidney disease increase cardiovascular risk
- Lipid management, sensitive to renal status, reduces cardiovascular risk

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