Q&A

Diabetes and kidney disease. Part 2: management

Robert Lewis

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Q How should we manage a very high ACR? The NICE CKD guideline advises referral if ACR is ≥70 mg/mmol (unless the person has diabetes), but might this result in clinical inertia for people with diabetes?

NICE recommends referral of patients with heavy proteinuria (albumin:creatinine ratio [ACR] ≥70 mg/mmol) who do not have diabetes because a significant number of these may have treatable primary glomerular diseases. Early diagnosis and intervention is critical.

The development of heavy proteinuria is not unusual in diabetes. If the diagnosis of diabetic kidney disease (DKD) is fairly secure and is regularly reassessed (see answer to first question in part 1 of this article; Lewis, 2019), patients with this level of proteinuria can be managed in primary care without risk of clinical inertia. Management of cardiovascular (CV) risk in DKD is no different in the presence of heavy proteinuria, except when it is sufficient to cause hypoalbuminaemia and swelling (nephrotic syndrome). This unusual complication of DKD may require specialist referral.

Q What is the best dietary advice to give to people with CKD and diabetes?

Advice for maintaining a healthy diet whilst optimising glycaemic control, which is standard practice for patients with diabetes, should be continued when DKD develops. In early DKD, there are no specific additional dietary restrictions, except perhaps avoidance of excessive salt intake as an aid to BP control.

In advanced DKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), dietary restriction of potassium and phosphate (and sometimes protein) may be required, but this should be overseen by renal dietitians in the context of specialist chronic kidney disease (CKD) management.

Q What are the optimum levels of blood pressure and lipids in those with established DKD? Which statin should be used when eGFR is <30?

As stated in part 1 of this article (Lewis, 2019), the optimum blood pressure (BP) in DKD is 130/80 mmHg, where this can be achieved without causing symptoms (NICE, 2014).

A current NICE quality standard for the management of CKD is that patients with renal impairment (of any aetiology) should be offered atorvastatin 20 mg (NICE, 2017). The Association of British Clinical Diabetologists (ABCD)/Renal Association (RA) guidelines 2019 recommend that atorvastatin 20 mg should be started in all patients with type 2 diabetes and DKD irrespective of their lipid profile (Mark et al, 2017). This calls into question the value of using QRISK3 for deciding on lipid management in patients with an eGFR <60 mL/min/1.73 m^2 or proteinuria.

Higher doses of atorvastatin (40–80 mg) may be considered in patients who are at especially high CV risk (e.g. >40 years, poor glycaemic control, poor BP control, etc.; Mark et al, 2017).

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The lipid profile should be measured annually in DKD. The lipid targets recommended by the ABCD/RA guidelines for patients with DKD are: total cholesterol, 4 mmol/L; low-density lipoprotein (LDL), 2 mmol/L; and non-high-density lipoprotein (non-HDL), 2.5 mmol/L.

Atorvastatin is the statin of choice in patients with DKD and an eGFR <30 mL/min/1.73 m^2. However, if it is not tolerated, simvastatin is a safe substitute. Simvastatin is less potent than atorvastatin and may need to be supplemented with ezetimibe to reach lipid targets. This combination has been shown to be effective in CKD (Baigent et al, 2011).

Rosuvastatin is effective at lipid-lowering, but it should be avoided in those with DKD (proteinuria or renal impairment) as it may adversely affect renal function (de Zeeuw et al, 2015). Fibrates may be added to statins if required to attain targets, but only in patients who have an eGFR >45 mL/min/1.73 m^2.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor drugs, such as evolocumab or alirocumab, have been approved by for specialist management of patients with high CV risk who remain hypercholesterolaemic despite maximal oral lipid-lowering therapy. These monoclonal antibodies are administrated by self-injection and reduce blood cholesterol by reducing degradation of hepatocyte LDL receptors, thereby increasing LDL clearance from the circulation. Presently, it is not clear how these agents fit into lipid management for patients with renal impairment, although small studies indicate that they are effective in lipid-lowering and are well tolerated in these people (Mafham and Haynes, 2018).

Q If DKD is diagnosed, should we consider initiating an SGLT2 inhibitor for potential renal benefits in slowing further decline or should we wait for licensing changes?

Large trials (EMPA-REG, CANVAS and DECLARE-TIMI) have shown that sodium–glucose cotransporter-2 (SGLT2) inhibitors improve major CV outcomes, especially heart failure, when added to standard care (which includes optimal renin–angiotensin–aldosterone system [RAAS blockade]; Zelniker et al, 2019). Secondary outcomes from these trials showed additional beneficial effects on DKD. This prompted a number of studies looking specifically at renal outcomes. Only one has reported so far: the CREDENCE study showed that in patients with established DKD (eGFR 30–90 mL/min/1.73 m^2 and proteinuria) receiving optimal RAAS inhibition, canagliflozin significantly slowed progression of renal impairment and reduced the risk of renal failure (Perkovic et al, 2019). These findings have caused quite a sensation in nephrology; they are not explained by the glucose-lowering effects of these agents, so studies are now in progress to see if SGLT2 inhibitors may have similar benefits in non-diabetic CKD.

The growing body of evidence that SGLT2 inhibitors slow CKD progression and improve CV outcomes in patients with DKD led the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) to recommend in their consensus statement that an SGLT2 inhibitor (or glucagon-like peptide-1 receptor agonist [GLP-1 RA]; see below) is the preferred option for patients who have DKD whose glycaemia is not controlled by metformin alone (Davies et al, 2018).

Licensing restrictions currently do not permit initiation of these drugs in patients with an eGFR <60 mL/min/1.73 m^2, but they are suitable for patients with DKD who have proteinuria. Those who subsequently develop renal impairment whilst already taking an SGLT2 inhibitor may stay on it until eGFR falls to 45 mL/min/1.73 m^2. At eGFRs <45 mL/min/1.73 m^2, the manufacturers recommend that they should be stopped.

So compelling is the recent trial evidence that some clinicians have advocated the use of SGLT2 inhibitors off licence in patients with an eGFR <45 mL/min/1.73 m^2. Although the evidence is persuasive, the results of ongoing studies are required to confirm the findings of CREDENCE in DKD, and one cannot recommend habitual off-licence use. Revision of the licences is anticipated soon and is likely to extend use of SGLT2 inhibitors to patients with more advanced renal impairment.

Q Are there any advantages in using GLP-1 RAs in people with CKD, given the favourable secondary renal outcomes seen in recent studies?

Large CV outcome trials have shown that the GLP-1 RAs liraglutide (Marso et al, 2016a), semaglutide (Marso et al, 2016b) and dulaglutide (Gerstein et al, 2019) reduce the risk of major CV events in people with diabetes, and may also reduce proteinuria and slow progression of DKD. The AWARD-7 study showed that dulaglutide slowed progression of renal impairment in people who already have moderate-to-severe CKD (Tuttle et al, 2018).

Longer-term studies with specific primary renal endpoints are required before it can be concluded that GLP-1 RAs are truly renoprotective, but early signs indicate that this is the case. Their CV and renal effects make them attractive in patients with DKD, and this has led the ADA and EASD to recommend GLP-1 RAs as one of the preferred classes for patients with DKD whose glycaemia is not controlled by metformin alone (Davies et al, 2018).

Unlike SGLT2 inhibitors, GLP-1 RAs are licensed for initiation in patients with established renal impairment. GLP-1 RAs derived from exendin-4 (e.g. exenatide) are largely renally excreted and so are not recommended in patients with eGFR <30 mL/min/1.73 m^2 (or <50 mL/min/1.73 m^2 for prolonged-release exenatide). In contrast, non-exendin-derived GLP-1 RAs, such as liraglutide, dulaglutide and semaglutide, can safely be used and are license for use to eGFR 15 mL/min/1.73 m^2 (CKD category G5). Although manufacturers advise against the use of these agents in patients receiving dialysis, their effectiveness and tolerability leads some clinicians to use them off licence in some of these patients.

Q People with DKD are at increased risk of CV disease. Should they receive aspirin?

Aspirin is recommended for secondary prevention of CV events in people with established CV disease. The presence of DKD does not alter this recommendation. However, there is no conclusive evidence that daily low-dose aspirin in patients with DKD is effective in primary CV risk reduction.

Given the particularly high CV risk associated with DKD, one might suppose that aspirin would be beneficial. But the changes in vascular and platelet function that occur in CKD, coupled with the possible effects of aspirin on renal function, make it unsafe to assume that aspirin should be given to all patients with DKD to reduce future CV disease.

This issue is the subject of ongoing clinical trials, but until they report, routine use of aspirin for primary CV risk reduction in DKD is not recommended.

Q What would be your recommendation for a woman trying to conceive who has a positive ACR or established CKD where an ACEi/ARB and statin are contraindicated?

The presence of DKD complicates pregnancy and pregnancy may worsen DKD (Bramham and Rajasingham, 2012). All women with DKD considering pregnancy should be counselled regarding these risks, which increase as DKD advances. In patients with renal impairment (eGFR <60 mL/min/1.73 m^2), pre-emptive specialist advice should be sought.

Whilst trying to conceive and for the duration of any subsequent pregnancy, angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) should be switched to safer alternatives (e.g. nifedipine, amlodipine or labetalol) and statins stopped. ACEis, ARBs and statins are all potentially damaging to the fetus.

Adequate BP control can usually be attained with the available safe drugs. Any effect on maternal DKD or CV risk of stopping statins and RAAS blockade for the duration of a pregnancy (which itself has such profound effects on vascular physiology) is likely to be minimal. ■

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