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ACCREDITED MODULE FOR LEARNING AND CPD

Managing glycaemia in people with type 2 diabetes and renal impairment:

An update for clinical practice

Stephen Bain, Richard Brice, Gwen Hall

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Prescribing information and adverse event reporting information for Victoza® (liraglutide) can be found on page 14

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Richard Brice
GP with a Special Interest in Diabetes, Whitstable

Welcome to this module entitled *Managing glycaemia in people with type 2 diabetes and renal impairment: An update for clinical practice*. Many people with type 2 diabetes either have, or are at risk of developing, chronic kidney disease (CKD). It is essential that healthcare professionals can detect this comorbidity and appropriately tailor glucose-lowering treatment approaches to take account of CKD, particularly with respect to the reduction in renal function (referred to as renal impairment) that can develop. Over the past few years, we have seen new guidance on CKD from NICE, the introduction of several oral and injectable glucose-lowering agents for use in type 2 diabetes and updates to the summaries of product characteristics for other such agents in relation to their use in renal impairment. As a result, this module is designed to provide a short overview of CKD in people with type 2 diabetes and to help you when choosing appropriate therapies for improving glycaemic control in this group. The content of this module has been accredited as relevant to continuing professional development (CPD), and you can find more details on this below. My co-authors and I hope that you find this a useful resource for keeping up to date with developments in type 2 diabetes and renal impairment.

Sections in this module

Learning objectives

After reading this module, you should be able to:

- Detect, classify and monitor chronic kidney disease in people with type 2 diabetes
- Provide examples of glucose-lowering therapies that are contraindicated, require dose adjustment or require caution when used in people with type 2 diabetes and renal impairment
- Implement individualised glucose-lowering strategies for people with type 2 diabetes that take account of renal impairment

How to use this module

- All GPs and nurses working in the UK are required to undertake continuing professional development (CPD) activities relevant to their practice, as part of their revalidation processes
- After reading the module, you can claim applicable CPD credits and request a certificate of completion for your CPD portfolio. Instructions on how to do this are given at the bottom of page 14
- On pages 15 and 16, CPD worksheets are provided to assist you in applying what you have learnt after reading Sections 1 to 7 of this module. The worksheets will help you to demonstrate the impact of your learning and to think about how to implement CPD initiatives or other actions in your practice
- This module has been accredited by the Royal College of Nursing (RCN) Centre for Professional Accreditation until 26 May 2016. The RCN has awarded 3 study hours. Accreditation applies only to the educational content of the module and does not apply to any product

Authors

- **Stephen Bain** is Professor of Medicine (Diabetes) at Swansea University. He is the Assistant Medical Director for Research & Development for ABM University Health Board
- **Richard Brice** is a GP with a Special Interest in Diabetes based in Whitstable, Kent. He chairs Whitstable Medical Practice, one of the largest general practice partnerships in the UK
- **Gwen Hall** is an independent Diabetes Specialist Nurse based in Surrey. She is also an Associate Clinical Teacher for the University of Warwick

Chronic kidney disease in type 2 diabetes: Epidemiology and impact

Richard Brice

Epidemiology of CKD in type 2 diabetes

Chronic kidney disease (CKD) can be defined as "abnormalities of kidney function or structure present for more than 3 months, with implications for health".[1] Diabetes is a major risk factor for the development of CKD,[1] and diabetic renal disease is the most common cause of renal failure in the UK.[2] Furthermore, for women and men with type 2 diabetes, the risk of developing advanced CKD (stages G3b or worse; see Section 2 for a summary of CKD stages) is 4.5- and 6.1-times higher, respectively, than for those who do not have type 2 diabetes.[3]

Depending on age, duration of diabetes and glycaemic control, it is estimated that up to 40% of people with type 2 diabetes will develop moderate or severe impairment of kidney function (defined as an estimated glomerular filtration rate of <60 or <30 mL/min/1.73 m^2, respectively) during their lifetime.[4] Consistent with this, in the UK Prospective Diabetes Study, over a median of 15 years from diagnosis, 29% of people with type 2 diabetes developed renal impairment (defined as a creatinine clearance of <60 mL/min or doubling of plasma creatinine).[5] In the same study, 38% of people with type 2 diabetes developed albuminuria, a marker of kidney damage.[5]

Modifiable factors that increase the risk of developing CKD in people with type 2 diabetes include hypertension, hyperglycaemia, smoking,[6] and having a BMI >25 kg/m^2.[7,8] Non-modifiable factors are also relevant, as certain groups of people may be at greater risk of CKD development or progression. For example, people with diabetes from South Asian and Black ethnic groups are more than twice as likely to require renal replacement therapy (RRT) than those from White ethnic groups.[9]

Impact of CKD in type 2 diabetes

Having CKD has negative effects for people with type 2 diabetes, their healthcare professionals and the NHS. For the person with type 2 diabetes, the presence of CKD increases cardiovascular disease morbidity and mortality,[10] risk of hypoglycaemia,[11] risk of hospitalisation,[12] and the duration of hospital stays.[12] Health-related quality of life scores in people with CKD are also reduced in proportion to the CKD severity.[13]

For healthcare professionals, the management of a person with type 2 diabetes who develops CKD becomes more complex because additional monitoring (see Section 2) and adjustment of therapy, including glucose-lowering drugs (see Section 3), may be needed.

For the NHS overall, patients with advancing CKD require increasingly specialised care, which raises treatment costs. In the NHS in England, providing RRT for the 2% of CKD patients who have renal failure was estimated to account for >50% of the £1.44 billion cost of treating patients with CKD stages G3a to G5 in 2009–10.[14] Across the UK, the estimated costs of treating kidney failure and other renal complications in people with type 2 diabetes in 2010–11 were >£750 million, with £379 million of this due to RRT.[15] Limiting the progression of CKD in people with type 2 diabetes is therefore a high priority.[5]

Learning points

- Type 2 diabetes is a significant risk factor for the development of chronic kidney disease
- Diabetes is a major risk factor for renal failure in the UK
- The presence of chronic kidney disease is associated with increased morbidity and mortality in people with type 2 diabetes
- For a person with type 2 diabetes, having chronic kidney disease impairs quality of life

Learning objectives

After reading this section, you should be able to:

1. Describe the epidemiology of chronic kidney disease in type 2 diabetes
2. Outline key modifiable and non-modifiable risk factors for chronic kidney disease development in people with type 2 diabetes
3. Summarise ways in which chronic kidney disease impacts people with type 2 diabetes, their healthcare professionals and the NHS

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Classifying and monitoring chronic kidney disease in type 2 diabetes

Richard Brice

Learning objectives

After reading this section, you should be able to:

1. Describe the tests that are typically used to identify chronic kidney disease in clinical practice, and use them with appropriate frequency
2. Classify chronic kidney disease based on a person's glomerular filtration rate and albumin:creatinine ratio
3. Explain why chronic kidney disease imposes limitations for medicines that may be used by people with type 2 diabetes

Detection and classification

Chronic kidney disease (CKD) is generally asymptomatic, so regular screening of people who are at risk enables early detection of this condition and, where indicated, treatment to limit its progression.[1]

National guidelines for the management of type 2 diabetes advise that all people with this condition should be screened annually for CKD.[2,3] In clinical practice, two tests are commonly used:[1]

- A blood sample is taken to estimate the glomerular filtration rate (GFR); the estimate is often made on the basis of the serum creatinine level.
- An early morning urine sample is used to measure the albumin:creatinine ratio (ACR).

Updated classification system for chronic kidney disease

In 2014, NICE issued a new guideline for CKD, which replaced an earlier document from 2008.[1] The 2014 guideline reflects recent global recommendations[4] in classifying the condition according to both the level of reduction in GFR and the level of increase in ACR (*Table 1*).[1] Decreased GFR and increased ACR are each associated with increased risk of adverse outcomes; however, when both are found in combination, the risk of adverse outcomes is multiplied.[1]

Ongoing monitoring

In general, the frequency of monitoring should be increased in relation to the severity of CKD, because the condition can be progressive.[1,5] NICE recommends testing GFR at a frequency ranging from annually (where GFR is >60 mL/min/1.73 m^2 and ACR is <3 mg/mmol) to four or more times per year (where GFR is <15 mL/min/1.73 m^2 and ACR is ≥3 mg/mmol).[1]

Ongoing monitoring helps identify when referral for specialist assessment is needed, for example when GFR falls to <30 mL/min/1.73 m^2 (i.e. there is severe renal impairment or kidney failure) or when accelerated progression of CKD is detected.[1]

Assessing progression

The NICE guideline defines accelerated progression of CKD as a sustained decrease in GFR of ≥25% and a change in GFR category within 12 months, or a sustained decrease in GFR of 15 mL/min/1.73 m^2 per year.[1] The guideline provides related recommendations for clinical practice, including:

- That at least three eGFR results should be obtained over a period of ≥90 days to identify the rate of progression of CKD;
- That the progression of CKD can be extrapolated from the current rate of decline of GFR; and
- That the progression should be taken into account when planning intervention strategies, particularly if it suggests that the person might need renal replacement therapy in their lifetime.[1]

Importance of monitoring renal function in people with type 2 diabetes

For people with type 2 diabetes, declining renal function has an impact on the glucose-lowering medication options available. Some of these medications are not licensed, require additional caution or dose adjustment at certain levels of renal impairment, or are associated with a higher risk of hypoglycaemia (see Section 3).[5]

Furthermore, other medicines prescribed for people with type 2 diabetes may require caution when used by people with CKD. For example, continued use of non-steroidal anti-inflammatory drugs increases the risk for CKD progression;[1] and renin–angiotensin–aldosterone system blockers and diuretics should be temporarily discontinued when GFR is <60 mL/min/1.73 m^2 in people with serious intercurrent illness that increases the risk of acute kidney injury.[4]

Table 1. Classification of CKD (adapted by permission from Macmillan Publishers Ltd: *Kidney Int Supp* 3:1–150[4]).

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (mL/min/1.73 m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal for a young adult	G2			
	45–59 Mild–moderate reduction	G3a*			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk and more frequent monitoring needed →

Increasing risk and more frequent monitoring needed→

*In the table, a "G" denotes the GFR category (G1–G5), and an "A" denotes the ACR category (A1–A3), so each individual is defined using both markers. For example, a person with an eGFR of 25 mL/min/1.73 m² and an ACR of 15 mg/mmol has CKD G4A2. *Consider using serum cystatin C rather than serum creatinine for calculating eGFR in people who have had CKD G3aA1 for at least 90 days. Estimates of GFR based on serum cystatin C have a higher specificity for significant disease outcomes than those based on serum creatinine.[1] Shading refers to risk for adverse outcomes, e.g. CKD progression, acute kidney injury, and cardiovascular mortality. Green=low risk (if no other markers of kidney disease, no CKD); Yellow=moderately increased risk; Orange=high risk; Red=very high risk.[4]*

ACR=albumin:creatinine ratio; CKD=chronic kidney disease; GFR=glomerular filtration rate.

Learning points

- Chronic kidney disease (CKD) in type 2 diabetes is typically an insidious complication, so regular proactive screening is essential to detect it as early as possible to try to minimise the likelihood of adverse outcomes, such as end stage renal disease
- Determining the CKD stage for a person with type 2 diabetes helps identify his or her risk level and whether treatment, referral or more frequent follow-up monitoring is needed
- Decreased glomerular filtration rate and increased albumin:creatinine ratio both increase the risk of adverse outcomes in people with CKD
- In people with type 2 diabetes and CKD, the degree of renal impairment should be taken into account when making medicine choices

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Current options for managing hyperglycaemia in people with type 2 diabetes and renal impairment

Stephen Bain

Learning objectives

After reading this section, you should be able to:

1. Describe dose adjustment requirements for glucose-lowering therapies when used in people with type 2 diabetes and chronic kidney disease manifested as renal impairment (RI)
2. List glucose-lowering therapies that are contraindicated due to moderate and severe RI in people with type 2 diabetes
3. Explain why the risk of hypoglycaemic episodes is an important consideration when choosing from glucose-lowering therapy options for people with type 2 diabetes and RI

In type 2 diabetes, intensive control of blood glucose levels has been associated with a reduced risk of complications, particularly those relating to the microvasculature, such as kidney-related disease.[1–3] Glycaemic control is therefore a key focus for people with type 2 diabetes, including those with chronic kidney disease (CKD), for whom intensive glycaemic control has been shown to improve albuminuria.[3]

However, glucose control in this group is challenging, not least because a number of the available glucose-lowering medications for type 2 diabetes have restrictions relating to their use in people with renal impairment.[4,5] These cautions are summarised in *Table 1* and discussed further in this section below.

As described in Section 2, CKD staging is now established on the basis of both the estimated glomerular filtration rate (eGFR) and the albumin:creatinine ratio. However, readers should note that the summaries of product characteristics (SPCs) for type 2 diabetes drugs commonly refer only to "renal impairment" and categorise its severity according to creatinine clearance (CrCl) thresholds. Interpretation of these restrictions is complicated by the fact that renal function is typically estimated in routine practice using eGFR (rather than CrCl) values.[5]

Oral agents

Metformin

Metformin is currently first-line in type 2 diabetes management algorithms and is the initial treatment of choice for most people.[4,29,30] However, metformin has numerous cautions and contraindications, including some relating to renal impairment.[4,6,29] In addition, there is disparity between national guidance for using metformin in renal impairment[29] and the various metformin SPCs. Specifically, NICE suggests reviewing the dose, and withdrawal of metformin if the eGFR falls <45, and <30 mL/min/1.73 m^2, respectively.[29] In contrast, the SPC for the standard-release formulation of Glucophage® (metformin) advises discontinuation if the eGFR falls <45 mL/min/1.73 m^2,[6] while the SPCs for certain generic metformin preparations advise that a CrCl of <60 mL/min is a contraindication for use.[31,32] Furthermore, SPC cautions are not always adhered to:[33] for example, a survey in Scotland found that of 88 subjects with type 2 diabetes who developed the contraindication of renal impairment, only 22 (25%) were taken off their metformin.[34]

Sulphonylureas

The sulphonylureas (SUs) can be used at all stages of mild and moderate renal impairment, although they are associated with weight gain and hypoglycaemia, which may limit their utility for some individuals.[4] The risk of hypoglycaemia is increased in people with type 2 diabetes who also have renal impairment, and hypoglycaemic episodes may be greatly prolonged in these individuals.[7] For this reason, the SPC for gliclazide, which has been reported to be the most commonly used SU in the UK,[35] states that severe renal insufficiency is a contraindication to its use.[7]

Meglitinides

Repaglinide is primarily excreted in bile[12] and is, therefore, not generally affected by renal disorders.[5] However, 8% of a dose of repaglinide is excreted through the kidneys and total plasma clearance of the product is decreased in individuals with renal impairment. As insulin sensitivity is increased in people who have type 2 diabetes with renal impairment, "caution is advised when titrating these patients".[12] Nateglinide is primarily excreted in the urine and may require dose adjustment in people with moderate to severe renal impairment (defined in the SPC as CrCl 15–50 mL/min).[11]

Table 1. Cautions related to renal impairment for glucose-lowering therapies for type 2 diabetes. Details based on summaries of product characteristics.

Class	Compound(s)	Renal impairment category (eGFR values in mL/min/1.73 m²)*			
		Mild (60–89)	Moderate (30–59)	Severe (15–29)	Kidney failure (<15)
Biguanides	Metformin[6]	No dose adjustment	Reduce dose and use caution when eGFR is 45–59; avoid use if eGFR is <45 mL/min/1.73 m²†	Avoid use	
Sulphonylureas	Gliclazide[7] Glimepiride[8] Glipizide[9]	No dose adjustment		Avoid use	
	Tolbutamide[10]	Lower initial dose		Avoid use	
Meglitinides	Nateglinide[11]	No dose adjustment		May need to adjust dose if CrCl is 15–50 mL/min	
	Repaglinide[12]	Titrate dose with caution			
Alpha-glucosidase inhibitors	Acarbose[13]	No dose adjustment		Avoid use if CrCl is <25 mL/min	
Thiazolidine-diones	Pioglitazone[14]	No dose adjustment if CrCl is >4 mL/min			Avoid use in dialysis patients
Dipeptidyl peptidase-4 inhibitors	Alogliptin ▼[15] Saxagliptin[16] Sitagliptin[17] Vildagliptin[18]	No dose adjustment if CrCl is ≥50 mL/min	Lower dose if CrCl is <50 mL/min. Sitagliptin can be used in haemodialysis and peritoneal dialysis patients; for other drugs, see individual SPCs for dialysis restrictions		
	Linagliptin ▼[19]	No dose adjustment. Can be used in haemodialysis and peritoneal dialysis patients			
Sodium–glucose co-transporter 2 inhibitors	Dapagliflozin ▼[20]	No dose adjustment	Avoid use if GFR is <60 mL/min/1.73 m²		
	Canagliflozin ▼[21] Empagliflozin ▼[22]	No dose adjustment if eGFR is ≥60 mL/min/1.73m²	Do not initiate; use lower dose when eGFR is 45–59; discontinue if eGFR is <45 mL/min/1.73 m²	Avoid use	
Glucagon-like peptide receptor-1 agonists	Dulaglutide ▼[23]	No dose adjustment		Avoid use if eGFR is <30 mL/min/1.73 m²	
	Exenatide twice-daily[24]	No dose adjustment if CrCl is 50–80 mL/min	Escalate dose cautiously if CrCl is 30–50 mL/min	Avoid use if CrCl is <30 mL/min	
	Exenatide once-weekly[25]	No dose adjustment if CrCl is 50–80 mL/min	Avoid use if CrCl is <50 mL/min		
	Liraglutide[26]	No dose adjustment if CrCl is 30–90 mL/min		Avoid use if CrCl is <30 mL/min	
	Lixisenatide ▼[27]	No dose adjustment	Use caution if CrCl is 30–50 mL/min	Avoid use if CrCl is <30 mL/min	
Insulins	Various formulations	Intensify glucose monitoring, adjust dose to patient's needs[28]			

**The eGFR values at the top of this table for each renal impairment category are included to assist readers; however, the measures of renal function and cut-offs for different categories of renal impairment differ between SPCs. Prescribers should therefore always check individual SPCs carefully. †The SPC for Glucophage® standard release[6] advises that this formulation should be used with dose adjustment and caution when eGFR is <59 and should not be used if eGFR is <45 mL/min/1.73 m²; NICE recommends reviewing the dose of metformin if eGFR is <45 and stopping its use if eGFR is <30 mL/min/1.73 m².[29] Oral drugs in the table are listed by order of class introduction. Green=no dose adjustment; Orange=dose adjustment or caution; Red=avoid use.CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; SPC=summary of product characteristics.*

Alpha-glucosidase inhibitors

Acarbose has limited trial data in people with renal impairment but since only 1–2% of the active agent is absorbed from the gastrointestinal tract,[13] it is unlikely to cause significant issues in these individuals. However, given the lack of experience, the SPC recommends that it should not be used in patients when their CrCl is <25 mL/min.[13]

Thiazolidinediones

Pioglitazone does not have any warnings related to renal dysfunction up to the point of end-stage renal failure (ESRF; defined in the SPC as a CrCl >4 mL/min).[14] However, tolerability and safety concerns regarding oedema, heart failure, bone fractures and bladder cancer may limit the use of this agent for some people with type 2 diabetes.[4]

Dipeptidyl peptidase-4 inhibitors

The dipeptidyl peptidase-4 inhibitors alogliptin, saxagliptin, sitagliptin and vildagliptin all require dose reduction in people with type 2 diabetes who have moderate or worse renal impairment (the equivalent of eGFR <60 mL/min/1.73 m^2) due to their renal mode of elimination leading to drug accumulation.[15–18] Only linagliptin is licensed for use at its standard dose irrespective of renal impairment since it is predominantly excreted in bile.[19]

Sodium–glucose co-transporter 2 inhibitors

The mode of action of sodium–glucose co-transporter 2 inhibitors is dependent upon adequate filtration of glucose by the kidneys and so their efficacy wanes as renal function declines.[4] For this reason, these agents[20–22] are not licensed for initiation when the eGFR is <60 mL/min/1.73m^2. The SPCs for canagliflozin[21] and empagliflozin[22] recommend reducing their doses in people with eGFR 45–60 mL/min/1.73 m^2 (CKD stage G3a).[21,22]

Oral fixed-dose combinations

Several fixed-dose combinations (FDCs) of oral glucose-lowering agents are now available, with further products in the pipeline. Renal cautions and contraindications for these FDCs reflect those of their components: this is of particular importance for those containing metformin.

Injectable agents

Glucagon-like peptide-1 receptor agonists

The glucagon-like peptide-1 receptor agonists lixisenatide[27] and exenatide twice-daily[24] require caution when used in people with type 2 diabetes and moderate renal impairment (defined in their SPCs as CrCl 30–50 mL/min) and should not be used in severe renal impairment (CrCl <30 mL/min) or ESRF. Exenatide once-weekly should not be used if CrCl is <50 mL/min (i.e. in moderate or worse renal impairment).[25] In contrast, liraglutide[26] and dulaglutide[23] can both be used in mild and moderate renal impairment (defined by SPCs as a CrCl of 30–90 mL/min for liraglutide, and eGFR of ≥30 mL/min/1.73 m^2 for dulaglutide) without dose adjustment or other restrictions. Liraglutide and dulaglutide should not be used in severe renal impairment or ESRF.[23,26]

These agents are discussed in more detail in Section 4.

Insulins

As the kidney is a principal site for the removal of circulating insulin, renal impairment can reduce the rate of insulin disposal, and a dose reduction is typically needed due to the increased risk of hypoglycaemia.[5,28] Furthermore, the compensatory response to hypoglycaemia may also be impaired in renal impairment.[36]

Learning points

- The presence of renal impairment in a person with type 2 diabetes reduces the number of oral and injectable glucose-lowering therapies that can be prescribed
- There are marked differences in the restrictions related to renal impairment for agents within the same class of glucose-lowering therapies
- The risk of hypoglycaemia is increased and hypoglycaemic episodes may be greatly prolonged in people with renal impairment
- Cautions concerning renal impairment may be due to safety concerns regarding drug accumulation, a lack of experience in people with renal impairment, or because the drug class mode of action relies on renal function for efficacy

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GLP-1 receptor agonists in type 2 diabetes and renal impairment: Focus on liraglutide

Stephen Bain

Glucagon-like peptide-1 receptor agonists

Injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of glucose-lowering therapies for people with type 2 diabetes.[1,2] In the UK, current guidance tends to position these agents as a third-line option for glucose lowering in type 2 diabetes, particularly for those who are overweight,[1,3] while the American Diabetes Association/European Association for the Study of Diabetes position statement proposes GLP-1RAs as options for second- and third-line treatment and as add-on to basal insulin.[2]

A meta-analysis of 17 randomised clinical trials (RCTs) (mostly of 26 weeks' duration) for GLP-1RAs in type 2 diabetes reported that they provide HbA_{1c} reductions of approximately 11 mmol/mol (1%).[4] Another meta-analysis of 51 RCTs (mean duration 31 weeks) in type 2 diabetes reported that weight loss on a GLP-1RA ranged from 1.22 to 3.31 kg.[5] In addition, GLP-1RAs are typically associated with a low risk of hypoglycaemia when used in combination with other glucose-lowering therapies, with the exception of sulphonylureas or basal insulin.[6–10]

Use in type 2 diabetes with renal impairment

At the time of writing, there are five GLP-1RAs available for use in the UK: exenatide twice-daily (BD),[7] exenatide once-weekly (QW),[8] liraglutide once-daily (OD),[6] lixisenatide OD[9] and dulaglutide QW.[10] While all of these agents can be used in mild renal impairment (RI), there are differences within the class when moderate RI is considered. Exenatide BD and lixisenatide OD can be used with caution in people with moderate RI (defined by the summaries of product characteristics [SPCs] as a creatinine clearance [CrCl] of 30–50 mL/min).[7,9] Exenatide QW remains unlicensed for use in moderate RI (defined in the SPC as a CrCl of 30–50 mL/min).[8] Dulaglutide QW, first licensed in November 2014, was indicated for use in adults with type 2 diabetes and moderate RI (defined in the SPC as an estimated glomerular filtration rate [eGFR] of ≥30 mL/min/1.73 m^2) from the point of marketing authorisation.[10] In the same month, the Committee for Medicinal Products for Human Use issued a positive opinion for the use of liraglutide in adults with type 2 diabetes and moderate RI.[11] The liraglutide SPC was updated in December 2014 to allow its use without dose adjustment or additional caution in adults with type 2 diabetes and moderate RI (defined as a CrCl of 30–59 mL/min).[6] (Prior to this, liraglutide was already approved for use without dose adjustment in patients with mild RI, defined as a CrCl of 60–90 mL/min.)

The study data on which this recent update is based are described in further detail below.

Update to the liraglutide summary of product characteristics

LIRA-RENAL study

Findings from the LIRA-RENAL (Efficacy and Safety of Liraglutide versus Placebo as Add-on to Glucose Lowering Therapy in Patients with Type 2 Diabetes and Moderate Renal Impairment) study were first presented at the American Diabetes Association meeting in 2014.[12] This phase 3b trial was conducted to evaluate the efficacy and safety of liraglutide as an add-on to existing oral glucose-lowering medications and/or insulin therapy in people with inadequately controlled type 2 diabetes and moderate RI.

Adult participants with HbA_{1c} 53–86 mmol/mol (7–10%)*, BMI 20–45 kg/m^2 and eGFR 30–59 mL/min/1.73 m^2 were randomised (1:1) in a double-blind manner to receive either liraglutide 1.8 mg OD (n=140) or placebo (n=137) for 26 weeks.

The estimated treatment difference in HbA_{1c} change from baseline to week 26 was –7.2 mmol/mol (–0.66%) (95% confidence interval [CI]: –9.8 to –4.7 mmol/mol [–0.90 to –0.43%]; *P*<0.0001)

Learning objectives

After reading this section, you should be able to:

1. Describe key features of the glucagon-like peptide-1 receptor agonist class and current guidelines for their use in type 2 diabetes
2. Outline the main differences between the glucagon-like peptide-1 receptor agonists in terms of their use in people with type 2 diabetes and moderate renal impairment
3. Summarise the changes that were made to the summary of product characteristics for liraglutide based on the LIRA-RENAL study

* *The LIRA-RENAL posters cited report HbA_{1c} levels in % units only. The mmol/mol conversions for these values have been added to reflect current practice with regard to HbA_{1c} reporting*

Box 1. Liraglutide use in people with type 2 diabetes and renal impairment (wording from current summary of product characteristics)[6]

Patients with renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance 60–90 mL/min and 30–59 mL/min, respectively). There is no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 mL/min). Victoza® can currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (see section 5.2)

for liraglutide compared with placebo. There was a greater reduction in body weight with liraglutide (–2.41 kg) than with placebo (–1.09 kg) (*P*=0.0052 for treatment difference).

Importantly, no deterioration in renal function was observed (eGFR change from baseline: liraglutide, -1%; placebo, +1%; *P*=0.36) and the most common adverse events were gastrointestinal side effects (liraglutide, 35.7%; placebo, 17.5%). Overall, 5.7% of subjects in the liraglutide group and 10.9% of subjects in the placebo group experienced a hypoglycaemic episode (*P*=0.076), and there was no difference in confirmed hypoglycaemic episode event rates (event-rate/100 patient-years exposure: liraglutide 30.5; placebo 40.1; *P*=0.54).[13]

The LIRA-RENAL study investigators concluded that liraglutide treatment caused no change in renal function and was associated with a low risk of hypoglycaemia in patients with type 2 diabetes and moderate RI.[12,13] Superior glycaemic control with liraglutide compared with placebo was demonstrated in the patient cohort.

Implications for clinical practice

Based on the outcome of the LIRA-RENAL study the SPC for liraglutide was updated, allowing for its use in adults with type 2 diabetes and moderate RI without dose adjustment (see *Box 1*).[6] As a result of this change, liraglutide is currently the only once-daily GLP-1RA with no cautions in moderate RI.

In practice, where eGFR values are often used in categorising RI associated with CKD (see Section 2), this update means that liraglutide can be used in people with type 2 diabetes with an eGFR level down to 30 mL/min/1.73 m^2 without additional caution.

It should be noted that the 1.8 mg OD dose of liraglutide is the highest licensed dose for the treatment of adults with type 2 diabetes, and the results of this study should provide reassurance for both patients receiving and healthcare providers prescribing the lower 1.2 mg OD dose, as is currently recommended by NICE.[14] Furthermore, the mean HbA_{1c} reduction achieved during the 26 week study (–11.4 mmol/mol [–1.05%]) is consistent with one of the metabolic response "continuation rules" for GLP-1RAs advocated by NICE (i.e. a ≥11 mmol/mol [≥1%] fall in HbA_{1c} at 6 months).[14]

The change in licence for liraglutide relating to type 2 diabetes and RI provides healthcare professionals with more choice when individualising treatment based on a person's profile and goals. It also means that individuals who have achieved their HbA_{1c} target while taking liraglutide no longer have to have this treatment withdrawn on the basis of the often age-related decline in eGFR to <60 mL/min/1.73 m^2 (i.e. moderate RI).[15]

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Learning points

- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a glucose-lowering therapy option for people with type 2 diabetes
- The LIRA-RENAL study provided evidence that liraglutide is effective in improving glycaemic control in adults with type 2 diabetes and moderate renal impairment
- The summary of product characteristics for liraglutide has been updated based on the LIRA-RENAL study results, allowing use of this once-daily GLP-1RA in adults with type 2 diabetes and moderate renal impairment without dose adjustment or additional caution

Case 1: Type 2 diabetes with renal impairment in an older person

Gwen Hall

Freda Smith* is 87 years old and 2 years ago was diagnosed with type 2 diabetes. She self-cares and likes her independence. At diagnosis, her HbA_{1c} was 57 mmol/mol (7.4%), her BMI was 22 kg/m^2 and her estimated glomerular filtration rate (eGFR) was 45 mL/min/1.73 m^2.

At follow-up 6 months ago, her HbA_{1c} was 58 mmol/mol (7.5%) and her eGFR was 34 mL/min/1.73 m^2. Today in clinic, her HbA_{1c} is 62 mmol/mol (7.8%), her eGFR is 33 mL/min/1.73 m^2 (i.e. she is approaching severe renal impairment [RI]), and her BMI is 22 kg/m^2. Freda has developed osmotic symptoms (polyuria and polydipsia), is not eating properly and does not feel well.

Considerations for treatment

Individuals who are slim when diagnosed with type 2 diabetes may be insulin deficient and should be investigated to exclude slow onset type 1 diabetes.[1] Freda's renal function is declining and her treatment goals should take account of her RI, her life expectancy, and the risk of drug-related adverse effects.[2]

Freda's healthcare team discussed the need to introduce medication to address her osmotic symptoms. Metformin was not appropriate because her eGFR is falling and is close to the cut-off at which NICE recommends stopping the use of this drug.[3†]

Sulphonylureas (SUs) should be used with care in people with mild to moderate RI, because of the risk of hypoglycaemia, and they should be avoided in severe RI.[4] It is estimated that >5,000 UK patients will experience a severe hypoglycaemic event caused by their SU therapy which will require emergency intervention annually.[5] SU-induced hypoglycaemia may persist for many hours and must always be treated in hospital.[4]

Basal neutral protamine Hagedorn (NPH) insulin was selected to improve Freda's hyperglycaemic symptoms, while not aiming for tight glycaemic control. Other glucose-lowering options were ruled out, even if these were licensed for use in people with type 2 diabetes and moderate to severe RI, as a rapid response was required to address symptoms and protect quality of life. Freda's structured care programme included training on symptoms and treatment of hypoglycaemia, and on self-monitoring of blood glucose, which enabled her to record her treatment response. The NICE type 2 diabetes guideline advises that if a person experiences significant hypoglycaemia on NPH insulin, they may be switched to a once-daily long-acting analogue insulin.[3]

Follow-up

For Freda it is more important to address osmotic symptoms and maintain quality of life than to strive for tight glycaemic control to prevent future complications of type 2 diabetes.[6] Ongoing support from her diabetes team or community staff will be required to ensure that she can maintain her independence and quality of life for as long as possible. Freda's renal function should be monitored regularly (at least twice per year at her current level of RI, see Section 2).[7]

Learning points

- Consider the possibility of adult onset type 1 diabetes in those of slim build who have rapid progression of diabetes with osmotic symptoms
- Maintaining quality of life in older people with type 2 diabetes may well be more important than focusing on tight glycaemic control
- Renal function declines with age and this can limit therapy options for people with type 2 diabetes

Learning objectives

After reading this section, you should be able to:

1. Advise your patients with type 2 diabetes and chronic kidney disease on the glucose-lowering therapy options that are appropriate, given their individual level of renal impairment
2. Recommend appropriate treatment goals based on the unique profile of the individual with type 2 diabetes
3. Implement strategies to minimise the risk of hypoglycaemic events in a person with type 2 diabetes initiating basal insulin

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* *Fictitious case, created for illustrative purposes only*

† *See Section 3 for discussion of differences between NICE guidance and the summaries of product characteristics for metformin formulations in relation to use of this medicine in people with type 2 diabetes and renal impairment*

Case 2: Second-line therapy in type 2 diabetes with renal impairment

Gwen Hall

Learning objectives

After reading this section, you should be able to:

1. Identify cardiovascular risk factors in people with type 2 diabetes
2. Recommend appropriate treatment goals for type 2 diabetes aligned to a person's lifestyle, cardiovascular risk profile and comorbidities including renal impairment
3. Explain why early improvement in glycaemic control is important for preventing future complications of type 2 diabetes

Alan Brown* was diagnosed with type 2 diabetes 5 years ago at age 51. He has features of the metabolic syndrome: hypertension, dyslipidaemia and type 2 diabetes with obesity.[1] His BMI is 32 kg/m^2 and his estimated glomerular filtration rate is 50 mL/min/1.73 m^2 (he has moderate renal impairment [RI]). He has early signs of cardiovascular disease (CVD), including chest pain on exertion. Alan takes little exercise and eats at irregular times. He drives and wants to lose weight. Alan's type 2 diabetes is currently treated with metformin, which has been titrated to 2 g daily,† and a dipeptidyl peptidase-4 (DPP-4) inhibitor, which initially lowered his HbA_{1c} from 69 to 64 mmol/mol (8.5% to 8.0%). His HbA_{1c} has since risen to 74 mmol/mol (8.9%). Diet and exercise advice has been reinforced.

Considerations for treatment

Alan is relatively young and his co-morbidities increase CVD risk.[1] In the UKPDS (UK Prospective Diabetes Study), intensive treatment of glycaemia early in type 2 diabetes was associated with a continued lower risk of micro- and macrovascular events relative to less intensive treatment, even after glycaemic control in the intensively treated group deteriorated later.[2] The UKPDS also showed that intensified control of both glycaemia and blood pressure limits chronic kidney disease progression in type 2 diabetes.[3] Weight loss in obese individuals with type 2 diabetes lowers CVD risk.[4]

The American Diabetes Association/European Association for the Study of Diabetes position statement on managing hyperglycaemia in type 2 diabetes is useful when agreeing HbA_{1c} goals and choosing therapies.[5] Alan's healthcare team discussed treatment options with him. Metformin was continued for now, with regular monitoring of RI planned due to the renal restrictions for this drug.[6] The DPP-4 inhibitor was stopped, as Alan's initial HbA_{1c} response on this drug had not been sustained. Several add-on options were discounted: a sulphonylurea (SU), due to Alan's irregular eating patterns, driving, and risk of hypoglycaemia;[5] pioglitazone, as any weight gain or fluid retention[5] could exacerbate his blood pressure and BMI; and a sodium–glucose co-transporter 2 inhibitor, as these agents should not be initiated at Alan's RI level.[7–9]

A glucagon-like peptide-1 receptor agonist (GLP-1RA), liraglutide, was instead selected as an add-on to metformin. Liraglutide typically lowers both HbA_{1c} and weight in people with type 2 diabetes,‡ and is licensed for use in people with moderate RI, without dose adjustment.[10] The use of metformin with a GLP-1RA has a low risk of hypoglycaemia[10–14] and does not require self-monitoring of blood glucose. If basal insulin is required in the future, liraglutide need not be withdrawn.[10]

Follow-up

Alan started on liraglutide 0.6 mg once daily, titrated to 1.2 mg after 2 weeks. He had minimal nausea, but felt well and admitted he felt full after taking his medicine and this put him off large meals. Over the next 8 months, his HbA_{1c} fell by 12 mmol/mol (1.1%) meeting NICE criteria to continue with his GLP-1RA therapy.[15] His weight also reduced by >3%. Alan was pleased with his weight loss,‡ although he understood liraglutide was prescribed to target his hyperglycaemia, not to reduce his weight. His renal function was unchanged.

Learning points

- The American Diabetes Association/European Association for the Study of Diabetes position statement provides up to date guidance on available glucose-lowering therapy options
- Avoiding weight gain is important for obese people with type 2 diabetes; this is particularly relevant for those with renal impairment, who have an elevated risk of cardiovascular disease

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* *Fictitious case, created for illustrative purposes only*

† *See Section 3 for discussion of differences between NICE guidance and the SPCs for metformin formulations in relation to use of this medicine in people with type 2 diabetes and renal impairment*

‡ *Liraglutide at doses of 1.2 and 1.8 mg is not licensed for weight loss management*

Case 3: Third-line therapy in type 2 diabetes with renal impairment

Gwen Hall

Bernard Crown*, aged 62, is a school bus driver who was diagnosed with type 2 diabetes 9 years ago. His estimated glomerular filtration rate is 52 mL/min/1.73 m^2 (i.e. he has moderate renal impairment [RI]) and his BMI is 35 kg/m^2. His HbA_{1c} has risen to 76 mmol/mol (9.1%) despite treatment with metformin 2 g daily† and a sulphonylurea (SU), gliclazide 160 mg twice daily. His 10-year cardiovascular (CV) risk score[1] is nearly 35%.

Bernard has had a couple of mild hypoglycaemic events (hypos), but declined insulin as he is due to retire in 3 years' time and worries he would lose his job. He frequently self-monitors his blood glucose (SMBG) as he fears future hypos. He attributes his weight gain to eating before driving and before bed to prevent possible hypos. He wants to understand what his therapeutic alternatives are.

Considerations for treatment

Bernard is obese and has inadequately controlled type 2 diabetes with RI; these conditions contribute to his high CV risk score.[1] It is important for him to avoid further weight gain and hypoglycaemia. Bernard's healthcare team discussed treatment options with him. Pioglitazone was not recommended due to its potential for weight gain.[2] Dipeptidyl peptidase-4 (DPP-4) inhibitors are weight neutral and provide HbA_{1c} reductions of around 9 mmol/mol (0.8%[3]). They have a low risk of hypoglycaemia, unless used with an SU or insulin.[4–8] DPP-4 inhibitors can be used in moderate RI but, with the exception of linagliptin, will require dose adjustment.[4–8] Glucagon-like peptide-1 receptor agonists (GLP-1RAs) typically reduce HbA_{1c}, by around 1.0% (11 mmol/mol),[9] and weight by 1.2–3.3 kg[10] and have a low risk of hypoglycaemia, unless combined with an SU or insulin.[11–15] For Bernard, liraglutide was selected as this once daily GLP-1RA can be used in moderate RI without dose adjustment.[11] Furthermore, in a head-to-head clinical trial in people with type 2 diabetes, liraglutide was associated with greater improvements in glycaemic control, and a reduction in body weight,‡ compared with the DPP-4 inhibitor sitagliptin.[16]

Follow-up

Bernard started liraglutide 0.6 mg once daily. The dose was titrated up to 1.2 mg once daily after 2 weeks, and his gliclazide dose was reduced by half. During this time he was encouraged to continue SMBG with the incentive that he might be able to stop gliclazide if his glycaemic control improved sufficiently. He was also advised of the NICE criteria for continuing the use of his GLP-1RA beyond an initial 6 month trial (i.e. a ≥11 mmol/mol [≥1%] reduction in HbA_{1c} and ≥3% reduction in body weight)[17] and encouraged to adhere to his glucose-lowering therapy regimen and diet and lifestyle plan.

After 8 months, Bernard had achieved an HbA_{1c} reduction of 14 mmol/mol (1.3%). The gliclazide was stopped. He and his care team were pleased to note a steady weight loss. He felt well and was more confident of being able to continue his job to age 65. He found no difficulties in performing his injections, and this helped him to feel less concerned about the practicalities of injecting insulin, should this become necessary in the future.

Learning points

- Addressing patient concerns is important when agreeing a diabetes management plan
- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) may have a greater potential to lower HbA_{1c} than dipeptidyl peptidase-4 inhibitors, and some GLP-1RAs can be used in people with type 2 diabetes who also have moderate renal impairment

Learning objectives

After reading this section, you should be able to:

1. Ensure that an individual's medium- and longer-term goals are addressed when agreeing his or her diabetes management plan
2. Appropriately tailor the choice of glucose-lowering treatment for inadequately controlled type 2 diabetes based on cardiovascular risk
3. Identify opportunities to harness the motivation of the person with type 2 diabetes when agreeing his or her management plan and goals

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* *Fictitious case, created for illustrative purposes only*

† *See Section 3 for discussion of differences between NICE guidance and the SPCs for metformin formulations in relation to use of this medicine in people with type 2 diabetes and RI*

‡ *Liraglutide at doses of 1.2 and 1.8 mg is not licensed for weight loss management*

Victoza®
Liraglutide.

Victoza® 6 mg/ml pre-filled pen
1 ml of solution contains 6 mg of liraglutide. One pre-filled pen contains 18 mg liraglutide in 3 ml.
Indication: Treatment of adults with type 2 diabetes mellitus in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise do not provide adequate glycaemic control.
Posology and administration: Victoza® is administered once daily by subcutaneous injection and at any time independent of meals however it is preferable to inject around the same time of day. Victoza® should not be administered intravenously or intramuscularly. Recommended starting dose is 0.6 mg daily, after at least one week, the dose should be increased to a maintenance dose of 1.2 mg. Based on clinical response, after at least one week the dose can be increased to 1.8 mg. Daily doses higher than 1.8 mg are not recommended. When Victoza® is added to sulfonylurea or basal insulin, a reduction in dose of sulfonylurea or basal insulin should be considered to reduce the risk of hypoglycaemia. Victoza® can be used in the elderly (>65 years) without dose adjustment but therapeutic experience in patients ≥75 years is limited. No dose adjustment for patients with mild or moderate renal impairment (creatinine clearance (CrCl) 60-90 ml/min and 30–59 ml/min, respectively). There is no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 ml/min). Victoza® can currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (or patients with hepatic impairment or children and adolescents <18 years.
Contraindications: Hypersensitivity to the active substance or any of the excipients.
Special warnings and Precautions for use: Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. Limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and Victoza® should be used with caution. No experience in patients with NYHA III-IV and Victoza® is not recommended. Due to limited experience Victoza® is not recommended in patients with inflammatory bowel disease and diabetic gastroparesis since it is associated with transient gastrointestinal (GI) adverse reactions, including nausea, vomiting and diarrhoea. GLP-1 receptor agonists have been associated with a risk of developing acute pancreatitis; patients should be informed of symptoms of acute pancreatitis. If pancreatitis is suspected, Victoza® should be discontinued. If acute pancreatitis is confirmed, Victoza® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm reported in clinical trials particularly in patients with pre-existing thyroid disease and Victoza® should be used with caution. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. No studies on effects on ability to drive and use machinery. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulfonylurea or basal insulin. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products.
Fertility, pregnancy and lactation: If a patient wishes to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed.
Undesirable effects: The most frequently observed adverse reactions from long term phase 3 controlled studies and spontaneous (post-marketing) reports were: Very common (≥1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulfonylureas. Common (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, increased heart rate, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue, pyrexia and rash; GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of: angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Allergic reactions (including urticaria, rash and pruritus) and a few cases of anaphylactic reactions (with additional symptoms such as hypotension, palpitations, dyspnoea and oedema) have been reported from marketed use of Victoza®. The Summary of Product Characteristics should be consulted for a full list of side effects.

MA numbers and Basic NHS Price:
2 x 3 ml pre-filled pens EU/1/09/529/002 £78.48;
3 x 3 ml pre-filled pens EU/1/09/529/003 £117.72.

Legal Category: POM.

Further prescribing information can be obtained from: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. **Marketing Authorisation Holder**: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised**: December 2014.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.

Continuing professional development worksheets: Instructions for use

The worksheets on pages 15 and 16 have been designed to help you to record the key learning points from this module and, subsequently, to apply these appropriately to your clinical practice.

You will see that a template has been provided for you to fill in. Do make use of the space to note down any key learning points from the module, as well as to record each step of the four-stage "CPD cycle": reflection, planning, action and evaluation. Feel free to cut out these sheets and to add them to your portfolio, and if you require further sheets for yourself or for colleagues who have read the module then do make photocopies.

Claiming a certificate for your CPD portfolio

A certificate of completion is available which includes the details of the accreditation awarded. You can add this certificate to your CPD portfolio as a record of your participation in this module. To receive your certificate, please email: info@sbcommunicationsgroup.com and include the wording "Renal impairment in type 2 diabetes module CPD certificate" in the subject line of your email. In return, you will receive your certificate as a PDF to print.

Name:

Module title: Managing glycaemia in people with type 2 diabetes and renal impairment: An update for clinical practice

1. Identify key learning points

What were the key learning points from this module?

2. Reflect: Self-appraisal or assessment

What are your personal and organisational needs related to this module?
What could be changed or improved in your practice as a result of what you have learnt?
For example, organising an awareness training session for colleagues on managing people with type 2 diabetes and chronic kidney disease, undertaking an audit of patient records to ensure that people with type 2 diabetes are receiving appropriate treatment(s) if they also have impaired renal function, or reviewing the local referral pathway criteria for chronic kidney disease to ensure that this is aligned with current national guidance.

3. Plan and act

Record a stepped action plan below for implementing potential changes within your practice, based on what you have identified in box 2. (Please photocopy this sheet if you need more space to record your action plan)

Next steps to take	Date of implementation

4. Evaluate: Review the results and assess their impact

What you have done as a result of this process? What was successful? Did you encounter any problems? Would you do anything differently if you repeated the activity?

How has the initiative impacted on patient care?

5. Claim credits for the activity

Use the form below to record the number of hours spent on this CPD activity and to indicate whether or not the impact factor can be applied.

Time taken for this activity (hours). Each hour equates to one CPD credit	
Can you demonstrate the impact of this activity on patient care? (If yes, multiply the number of hours spent by two)	
Total number of credits claimed	
Signature	
Date	

Job code: UK/VT/0315/0226. Date of preparation: June 2015