The easy-to-do audit series

Drug management in people with type 2 diabetes and renal impairment: Incretin-based agents

Undertaking simple audits and reflecting and acting on our findings can be a powerful way to change practice and improve the care we deliver. In this series, Dr Sam Seidu introduces simple, easy-to-run audits. The following audit is on the management of people with type 2 diabetes and chronic kidney disease, specifically ensuring that individuals are on appropriate medication and dosage of incretin-based agents. The PCDS hopes these hands-on "how to" audit guides will provide the practical guidance and motivation we all need to take action in the limited time available.

Effective glycaemic control in type 2 diabetes reduces the risk of microvascular complications; however, healthcare professionals need to remember that there are

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Table 1. Recommendations for dose adjustments for dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists with increasing renal impairment.

	DPP-4 inhibitors					GLP-1 receptor agonists				
	Sitagliptin	Alogliptin	Saxagliptin	Vildagliptin	Linagliptin	Exenatide BD	Exenatide QW	Lixisenatide	Dulaglutide	Liraglutide
Mild renal impairment CKD stage 2 (eGFR 60–89 mL/min/1.73 m²)	100 mg od	25 mg od	5 mg od	50 mg bd	5 mg bd	◆	◆	◆	◆	◆
Moderate renal impairment* CKD stage 3 (eGFR 30–59 mL/min/1.73 m²)	50 mg od	12.5 mg od	2.5 mg od	50 mg **od**	5 mg od	◇	◇ ǂ	◇	◆	◆
Severe renal impairment CKD stage 4 (eGFR 15–29 mL/min/1.73 m²)	25 mg od	6.25 mg od	Caution	50 mg **od**	5 mg od	◆	◆	◆	◆	◆
End-stage renal impairment CKD stage 5 (eGFR <15 mL/min/1.73 m²)	25 mg od	6.25 mg od	◆	50 mg **od**	5 mg od	◆	◆	◆	◆	◆

◆=No dose adjustment required; ◇=Dose adjustment/caution required; ◆=Contraindicated/not recommended; BD=twice daily; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; QW=once weekly.

*** eGFR <50 mL/min/1.73 m² should trigger dose change for sitagliptin, alogliptin and vildagliptin if following the licence recommendations.**

ǂ If eGFR is <50 mL/min/1.73 m², Exenatide QW should be stopped.

Information taken from the electronic Medicines Compendium available at: http://www.medicines.org.uk (accessed on 27.07.2016).

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"Incretin-based agents occupy a growing place in the armamentarium of drugs for the management of hyperglycaemia in type 2 diabetes, but their widespread use is often limited by renal impairment."

risks to very tight glycaemic control, which are dependent on individual risk factors. Kidney disease is one such factor that can often limit the use of some anti-diabetes treatments. It is estimated that a third of people with type 2 diabetes have chronic kidney disease (CKD) in some stage of severity (Middleton et al, 2006). In a study using observed and modelled data from the UK, researchers measured the annual probability of transitioning through the stages of CKD, death and other long-term measures. The authors estimated that each year, people with microalbuminuria had a 2.8% chance of progressing to macroalbuminuria and a 3% risk of mortality. Those with macroalbuminuria had a 2.3% chance of progressing to elevated plasma creatinine or requiring renal replacement therapy, and a 4.6% risk of mortality. Those who received renal replacement therapy were estimated to have a death rate of 19.2% (Adler et al, 2003).

Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists occupy a growing place in the armamentarium of treatments for the management of hyperglycaemia in type 2 diabetes, and renal function must be considered and monitored when these treatments are in use.

Most DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin) undergo extensive renal clearance (Scheen, 2010). Therefore, in deteriorating renal function, the total exposure to these drugs is increased so dosage reductions are required. The DPP-4 inhibitor linagliptin is eliminated predominantly through the hepatobiliary route and renal excretion represents only a minor elimination pathway (Blech et al, 2010), so dose adjustments are not a requirement in CKD (Graefe-Mody et al, 2011).

In the case of the GLP-1 receptor agonist class, and according to their respective summary of product characteristics (SPCs), exenatide BID and QW are eliminated by renal mechanisms. It is not possible to measure creatinine clearance in primary care, so eGFR values are used as a surrogate in deciding when to stop exenatide BID and QW. The SPCs recommend caution in increasing the dose of exenatide BID if eGFR is 30–50 mL/min/1.73 m^2 and that once-weekly versions should not be recommended if eGFR is <50 mL/min/1.73 m^2 (electronic Medicines Consortium [eMC], 2016a; 2016b). No specific organ has been identified as the major route of elimination of liraglutide but it should be stopped if eGFR is <30 mL/min/1.73 m^2 (eMC, 2016c). Only limited pharmacokinetic data are available for dulaglutide, lixisenatide and lixisenatide, so their use at eGFR <30 mL/min/1.73 m^2 is not currently recommended.

The audit

Many individuals with type 2 diabetes and reduced renal function continue on full doses of incretin-based anti-diabetic medicines, despite their respective product licences. The aims of this audit are to assess the prevalence of inappropriate prescribing of incretin-based agents in people with renal impairment and explore how to reduce inappropriate prescribing.

Top tips

Top tips for carrying out the audit from Jane Diggle, Practice Nurse, West Yorkshire:

- When searching, ensure you include the brand and generic names for the drugs, and include DPP-4 inhibitor/metformin combinations.
- Search in current medication only.
- If your lab has changed methods for calculating eGFR (e.g. MDRD, CKD-EPI) then these will have different codes – ensure you include both.
- Undertaking the eGFR search on your population with type 2 diabetes, then combining it with your search of those on each type of incretin therapy simplifies the data collection.
- You will then need to manually review the records of the small number of patients flagged up to ensure appropriate therapy changes have been made.

- Add an alert to the records of those who need dose or therapy changes as well as contacting them, so this can be undertaken opportunistically if they attend. ■

Adler AI, Stevens RJ, Manley SE et al (2003) Development and progression of nephropathy in type 2 diabetes: The United Kingdom prospective diabetes study (UKPDS 64). *Kidney Int* **63**: 225–32

Blech S, Ludwig-Schwellinger E, Gräfe-Mody EU et al (2010) The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, in humans. *Drug Metab Dispos* **38**: 667–78

electronic Medicines Consortium (2016a) *Byetta 5 micrograms solution for injection, prefilled pen. Byetta 10 micrograms solution for injection, prefilled pen.* eMC, London. Available at: https://www.medicines.org.uk/emc/medicine/19257 (accessed 18.08.16)

electronic Medicines Consortium (2016b) *Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen.* eMC, London. Available at: https://www.medicines.org.uk/emc/medicine/29798 (accessed 18.08.16)

electronic Medicines Consortium (2016c) *Victoza 6 mg/ml solution for injection in pre-filled pen.* eMC, London. Available at: https://www.medicines.org.uk/emc/medicine/21986 (accessed 27.07.16)

Graefe-Mody U, Friedrich C, Port A et al (2011) Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin. *Diabetes Obes Metab* **13**: 939–46

Lee S, Spencer W, Bingham-Gardiner P et al (2016) *Use of dipeptidylpeptidase-4 inhibitor (DPP-4) in patients with type 2 diabetes and reduced renal function: a CPRD study.* Presented at: *Diabetes UK Professional Conference* (P340). Glasgow, UK, 2–4 March

Middleton RJ, Foley RN, Hegarty J et al (2006) The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant* **21**: 88–92

Scheen AJ (2010) Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab* **12**: 648–58

Your turn:

The instructions alongside explain how to complete the audit. You can download the full-size audit form at www.diabetesandprimarycare.co.uk/audits to fill in and retain. The audit should take no more than a few hours to complete.

After you have completed the first data collection, you can send in your top-line aggregated data to **dpc@omniamed.com**.

Instructions to complete the audit.

Aims

1. To assess the prevalence of inappropriate prescribing of incretin-based agents in people with type 2 diabetes and renal impairment.
2. To explore how to reduce inappropriate prescribing of incretin-based agents in people with type 2 diabetes and renal impairment through appropriate local implementation strategies.

Audit method

This will be a two-step audit completed in primary care centres in the UK. The first data collection will be done between 1st September and 31st October 2016 and follow-up data collection will be done 6 months later to allow for appropriate interventions to be put in place at the local or practice level in order to effect change.

Criteria

1. People with type 2 diabetes and a most recent estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 taking a dipeptidyl peptidase-4 (DPP-4) inhibitor should have a dosage review and dose modifications or drug stopped if appropriate.
2. People with type 2 diabetes and a most recent eGFR <50 mL/min/1.73 m^2 taking a glucagon-like peptide-1 (GLP-1) receptor agonist should have a dosage review and drug stopped if appropriate.

Standards

1. For criterion 1, 70% of people with type 2 diabetes and reduced renal function (a most recent eGFR <50 mL/min/1.73 m^2) should have had the doses of their DPP-4 inhibitor treatment modified or stopped if appropriate as per the product licence.
2. For criterion 2, 70% people with type 2 diabetes and reduced renal function (a most recent eGFR <50 mL/min/1.73 m^2) should have had their GLP-1 receptor agonist reviewed or stopped if appropriate as per the product licence.

A standard of 70% is selected as realistic as the authors of a recent audit noted that 30% of patients fitting the criteria did not have down titration of doses of DPP-4 inhibitors (Lee et al, 2016).

N.B. Set a reminder on the practice's electronic calendar to repeat the audit 6 months later.

Download the full-size audit form at www.diabetesandprimarycare.co.uk/audits

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Date of first data collection: __/__/__

Date of second data collection (6 months later): __/__/__

Criteria

1. People with type 2 diabetes and a most recent estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 taking a dipeptidyl peptidase-4 (DPP-4) inhibitor should have a dosage review and dose modifications or drug stopped if appropriate.
2. People with type 2 diabetes and a most recent eGFR <50 mL/min/1.73 m^2 taking a glucagon-like peptide-1 (GLP-1) receptor agonist should have a dosage review and drug stopped if appropriate.

Steps to complete the audit

1. Search computer system for all individuals who are taking a DPP-4 inhibitor or a GLP-1 receptor agonist with type 2 diabetes and eGFR <50 mL/min/1.73 m^2. Note the numbers in each search for the corresponding criterion in the "first data collection" column.
2. From the results from step 1, count how many peple have had a recent dosage review and are on the correct medication based on their renal function. These are your achievement numbers for criteria 1 and 2 respectively.
3. Note the numbers and percentages of the respective criteria in the appropriate columns in the results table below.

Criteria	First data collection Number with an eGFR <50 mL/min/1.73 m^2	Date one achievement Number of people meeting the criterion	Percentage	Second data collection Number with an eGFR <50 mL/min/1.73 m^2	Date two achievement Number of people meeting the criterion	Percentage	Standard
e.g. 1	*85*	*65*	*76%*	*87*	*80*	*92%*	*70%*
1							70%
2							70%

1. What change(s) will be implemented after the first data collection?

2. What are the conclusions and lessons learned following the first and second data collections?

3. Are any further steps required for change, such as repeating the audit next year?