Multidisciplinary management of type 2 diabetes:
Practical considerations in diagnosis, care planning and treatment selection

Case study*

Managing type 2 diabetes in a person whose glycaemic control is sub-optimal and who has declining renal function

Overview Click any of the options below to go to that section:

***Fictitious case, created for illustrative purposes only by a healthcare professional**

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Prescribing information and adverse event reporting information can be found at the end of the case study.
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Presentation details

- JB* is a retired 74-year-old African-Caribbean man
- 3 years ago he was diagnosed with type 2 diabetes (T2D)
- He regularly takes an over-the-counter non-steroidal anti-inflammatory drug (NSAID) for arthritis, and plays a round of golf twice a week
  - He gave up smoking in his 40s and drinks alcohol in moderation
  - He has a BMI of 32 kg/m^2, with abdominal obesity, which increases risks for T2D, CVD and metabolic syndrome[1]
- His current medication is:
  - metformin 500 mg twice daily (the maximum he has been able to tolerate)
  - ramipril 10 mg once daily for hypertension
- He has declined a statin despite a total cholesterol of 5.2 mmol/mol[2]

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Go to **Initial assessment (i)**

BMI, body mass index; CVD, cardiovascular disease

Initial assessment (i)

- At his annual diabetes review, JB has checks for HbA_{1c}, non-fasting lipids, thyroid, liver and renal function, albumin to creatinine ratio (ACR) and an FBC
  - JB was advised to avoid eating meat for 12 hours before providing a blood sample for serum creatinine measurement and, once his sample was taken, the practice nurse dispatched this promptly to the lab[3]
- JB's results show that:
  - His HbA_{1c} and total cholesterol have remained stable for the last 2 years
  - However, over this time, his renal function has deteriorated (see table below)

	At diagnosis	2 years ago	1 year ago	Latest
HbA_{1c} (mmol/mol) [%]	74 [8.9]	62 [7.8]	64 [8.0]	64 [8.0]
Total cholesterol (mmol/mol)	Static at around 5 →			
eGFR (mL/min/1.73m²)*		>60	47	42
ACR (mg/mmol)				7

*JB's eGFR values were corrected for African-Caribbean family origin[3]

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Go to **Initial assessment (ii)**

eGFR, estimated glomerular filtration rate; FBC, full blood count

Initial assessment (ii)

- JB has moderate–severe renal impairment and is classified as having chronic kidney disease (CKD) G3bA2[3]
- His blood pressure is at target and results for his thyroid and liver function, and FBC are all within normal parameters

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Go to **Considerations for management (i)**

FBC, full blood count;
GFR, glomerular filtration rate

Considerations for management (i)

- JB is at risk for CKD progression due to his obesity[4], type 2 diabetes[3,4], hypertension[3,4], African American family origin[3] and regular NSAID use[3]
- NICE advises that:
  - if eGFR falls to <45 mL/min/1.73 m^2 in a person with T2D taking metformin, the dose should be reviewed[5]
  - if eGFR is <30 mL/min/1.73 m^2, metformin should be stopped[5]
  - when eGFR is <45 mL/min/1.73 m^2 and ACR is ≥3 mg/mmol, renal function should be monitored 2 to ≥4 times per year[3]
- JB's CKD results over the past 2 years show a sustained decrease in GFR of 25% or more, and a change in GFR category in the past year − he is therefore referred for specialist renal assessment[3]

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Go to **Considerations for management (ii)**

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug

Considerations for management (ii)

- After discussing his results with the practice nurse, JB agreed to continue on metformin, with his renal function monitored every 3 months[6]
- Despite taking metformin at the maximum dose recommended for his current renal impairment (1000 mg OD in two to three divided doses)[6], JB's HbA_{1c} has remained above the target which NICE suggests:
  - i.e. 48 mmol/mol [6.5%] for a person with T2D who is on metformin monotherapy[5]
  - His HbA_{1c} is also above his individualised HbA_{1c} target of 58 mmol/mol [7.5%] (which took account of his comorbidities and age)[5]
- The practice nurse discussed options for adding-on an additional glucose-lowering therapy with JB

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Go to **Considerations for management (iii)**

T2D, type 2 diabetes

Considerations for management (iii)

A dipeptidyl peptidase 4 (DPP-4) inhibitor	• Impedes the enzyme DPP-4, which is involved in the inactivation of the incretin hormones GLP-1 and GIP that play important roles in the physiological regulation of glucose homeostasis[7] • Low risk of hypoglycaemia when used with metformin[8] • Weight neutral[8] • With the exception of Trajenta® (linagliptin), dosage adjustments are required when moderate-severe renal impairment is present[9–13]
A thiazolidinedione	• Reduces insulin resistance and improves insulin sensitivity by activating peroxisome proliferator-activated receptor gamma (PPARg) and promoting differentiation of fat cells[7] • Low risk of hypoglycaemia when used with metformin[8] • Risk of weight gain[8] • May cause fluid retention, which may exacerbate or precipitate heart failure[14] • JB is at higher risk of heart failure due to his T2D and history of hypertension[15]

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Go to **Considerations for management (iv)**

GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; T2D, type 2 diabetes

Considerations for management (iv)

A sulphonylurea	• ⬇ Blood glucose by acting on pancreatic beta cells to ⬆ insulin secretion[7] • Can be used as rescue therapy in people with T2D who are symptomatically hyperglycaemic[5] • Risks of hypoglycaemia and weight gain[8] ▪ The risk of hypoglycaemia with sulphonylureas is ⬆ in severe renal impairment (eGFR <30 ml/min/1.73 m^2)[16] • As a frequent driver, JB preferred to avoid self-monitoring of blood glucose levels, and was concerned about the risk of hypoglycaemia[5]
A sodium–glucose co-transporter 2 (SGLT2) inhibitor*	• Improves glycaemic control by ⬇ renal glucose absorption, leading to ⬆ excretion of excess glucose in the urine[7] ▪ In addition, they ⬆ the excretion of sodium, resulting in osmotic diuresis and ⬇ intravascular volume[7] • Low risk of hypoglycaemia when used with metformin[8] • Can provide some weight loss[8*] ▪ Note: *SGLT2 inhibitors are not licensed for weight loss • Should not be initiated when eGFR is <60 mL/min/1.73 m^2 [17–19]

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Go to **Considerations for management (v)**

eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes

Considerations for management (v)

A glucagon-like peptide 1 (GLP-1) receptor agonist*	• Activates GLP-1 receptor, mimics action of GLP-1 to ⬆ prandial insulin secretion and ⬇ prandial glucagon secretion, also delays gastric emptying and exerts satiety effect[7] • Low risk of hypoglycaemia when used with metformin[8] • Can provide some weight loss[8*] ▪ Note: *GLP-1 receptor agonists are not licensed for weight loss • NICE does not recommend use of GLP-1 receptor agonists as a second-line blood-glucose lowering option for T2D[5]
Insulin	• Used as a direct substitute for the body's own insulin[20] ▪ Available in three injectable forms – animal, human and analogue – with a range of rates of action[20] • Risk of hypoglycaemia and weight gain[8] • NICE does not recommend use of insulin as a second-line blood-glucose lowering option for T2D[5]

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Go to **Considerations for management (vi)**

eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes

Considerations for management (vi)

- After considering the potential options, JB was started on Trajenta 5 mg once daily along with his current metformin dose
  - Linagliptin does not require a dose reduction based on renal function[9]
- The practice nurse encouraged JB to continue adhering to diet and lifestyle recommendations in his diabetes management plan[5] and counselled on potential side effects for his new medication, including pancreatitis[7]
- She advised JB that NSAIDs should not be used concomitantly with an ACE inhibitor[21] and that chronic use of NSAIDs increases risk for progression of CKD[3] , so alternative options for pain management should be discussed with his GP

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Go to **Follow-up**

ACE, angiotensin converting enzyme; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; NSAID, non-steroidal anti-inflammatory drug

Follow-up

- The practice nurse arranged repeat tests for HbA_{1c} and renal function in 3 months
  - In the interim, she liaised with JB by phone to support him with his new medication
  - He expressed no concerns
- After 3 months on his new regimen, his results were:
  - HbA_{1c} **57** mmol/mol [7.4%]
  - eGFR **42** mL/min/1.73m^2
- JB continued to feel well and had amended his diet to increase his intake of high-fibre, low-glycaemic-index sources of carbohydrate[5]
- He had lost 2 kg in weight and continued to play golf regularly

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Go to **Clinical implications**

eGFR, estimated glomerular filtration rate

Clinical implications

- CKD is usually asymptomatic, but it is detectable[3]
  - NICE advises that people with known CKD risk factors (e.g. those with T2D, hypertension or cardiovascular disease) should be screened for CKD using a creatinine-based estimate of GFR (from a blood sample) and ACR test for proteinuria (from a urine sample)[3]
  - NICE also advises that renal function should be assessed before starting treatment with metformin and at least annually thereafter (at least twice a year in patients with additional risk factors for renal impairment, or if deterioration is suspected)[22]
- When choosing a glucose-lowering therapy regimen for T2D:
  - Considerations for individual drugs can vary from patient to patient (e.g. if a patient has renal impairment, is overweight or obese, or has hypertension)[5,8]
  - Patient preferences should also be discussed during shared decision-making[5,8] (e.g. whether oral or injectable options are preferable, whether self-monitoring of blood glucose will be accepted)

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Go to **References**

ACR, albumin to creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate; T2D, type 2 diabetes

References

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Prescribing information PI

Prescribing information (i)

TRAJENTA® (linagliptin) 5 mg film-coated tablets

Film-coated tablets containing 5 mg linagliptin. **Indication:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily. If added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly. When used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia. Renal impairment: no dose adjustment required. Hepatic impairment: pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. Elderly: no dose adjustment is necessary based on age however, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population. Paediatric population: the safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. Take the tablets with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin; a dose reduction of the sulphonylurea or insulin may be considered. Acute pancreatitis: In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Bullous pemphigoid: If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interactions:** Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates. The risk for clinically meaningful interactions by other medicinal products on linagliptin is low and in clinical studies linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for linagliptin. **Undesirable effects:** Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies (frequencies identified from pooled analysis of placebo-controlled studies) in clinical trial and from post-marketing experience. The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Very common: hypoglycaemia (combination with/add-on to metformin and sulphonylurea). Common: lipase increased (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin; combination with/add-on to metformin and empagliflozin). Uncommon: nasopharyngitis (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); hypersensitivity e.g. bronchial hyperreactivity (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); cough (monotherapy; combination with/add-on to metformin; combination with/add-on to insulin); pancreatitis (combination with/add-on to insulin); constipation (combination with/add-on to insulin); rash (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin). Rare: angioedema (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); urticaria (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (monotherapy). Not known: nasopharyngitis (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); hypersensitivity e.g. bronchial hyperreactivity (combination with/add-on to metformin and empagliflozin); cough (combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); pancreatitis (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to metformin and empagliflozin); bullous pemphigoid (monotherapy; combination with/add-on to metformin; combination with/add-on to metformin and sulphonylurea; combination with/add-on to insulin); amylase increased (combination with/add-on to insulin). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 28 tablets £33.26. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** April 2017.

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 Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

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