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Dipeptidyl peptidase-4 inhibitors—still a major player in type 2 diabetes care

The positioning of DPP-4 inhibitors within clinical guidelines and the evolving NHS landscape

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This supplement has been commissioned and funded by Boehringer Ingelheim Limited and developed in partnership with *Guidelines for Nurses*. Boehringer Ingelheim Limited suggested the topic and author, and carried out full medical approval on all materials to ensure compliance with regulations. The funding of the project included the honorarium for the author. The views and opinions of the author are not necessarily those of *Guidelines for Nurses*, its publisher, advisers, or advertisers.
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PC-GB-102714 December 2020

Dipeptidyl peptidase-4 (DPP-4) inhibitors—still a major player in type 2 diabetes care

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors retain an important position within current clinical guidelines for the management of type 2 diabetes and continue to be a main part of the overall treatment armamentarium. Most recently, they have come to the fore as a crucial treatment option for patients with type 2 diabetes and confirmed or suspected SARS-CoV-2 (COVID-19) infection, and look set to play a key role in the reshaped NHS landscape of the future.[1]

Key points

- DPP-4 inhibitors are recommended in leading clinical guidelines and are suitable for use across a broad spectrum of patients with type 2 diabetes
- Most can be prescribed as monotherapy or as part of combination therapy for type 2 diabetes
- As a class, DPP-4 inhibitors are generally well tolerated and weight neutral, with a low risk of hypoglycaemic episodes
- Not all DPP-4 inhibitors are equivalent and linagliptin is the only agent that requires no dose adjustment or additional routine monitoring in patients with renal impairment, however severe
- DPP-4 inhibitors have become the default class in suspected/diagnosed COVID-19 infection and are well-suited for use in the expanding primary care landscape of diabetes management.[1,2]

The current treatment landscape

A key benefit of DPP-4 inhibitors is their suitability for use across a wide spectrum of adult patients with type 2 diabetes, including elderly and frail patients and individuals in whom other drug classes may be contraindicated or poorly tolerated.[3–7] DPP-4 inhibitors benefit from a tolerable safety profile and relatively little additional renal monitoring.[3–7] The safety profile of DPP-4 inhibitors makes them suitable for prescribing in primary care, and this, in turn, makes them easier for physicians to prescribe and easy for patients to take, with little need for initial education or ongoing follow-up.

The broad therapeutic utility of DPP-4 inhibitors is underpinned by their current positioning within UK guidance from NICE and the Scottish Intercollegiate Guidelines Network (SIGN), and in leading international consensus reports and treatment guidelines from the American Diabetes Association/European Association for the Study of Diabetes and the European Society for Cardiology (ADA/ESC; see Box 1).[8–12] Primarily used as supplemental second-line agents, most DPP-4 inhibitors, such as linagliptin, can also be prescribed as monotherapy (when metformin is contraindicated or not tolerated), or as part of combination therapy for type 2 diabetes.[3]

Box 1: DPP-4 inhibitors are recommended in leading clinical guidelines:[8–12]

In adults with type 2 diabetes:

- as monotherapy if metformin is contraindicated or not tolerated
- as a dual therapy with metformin if initial metformin treatment has not continued to control HbA_{1c}
- as a dual therapy with pioglitazone OR a sulfonylurea if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c}
- as triple therapy with metformin and sulfonylurea if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification
- please refer to the relevant Summary of Product Characteristics for full details before prescribing.

One of the current challenges in management of type 2 diabetes is the tendency to adopt a 'one-size-fits-all' approach. However, in real-world clinical practice, the individualisation of treatment—choosing medication that best suits an individual patient or group of patients with similar clinical characteristics—remains critical. In this respect, not all DPP-4 inhibitors are equivalent, and it is important to consider comorbidities, such as renal impairment, when selecting treatment from within this drug class.

Selecting a DPP-4 inhibitor

The number of people over the age of 70 years with diabetes is growing worldwide and a high prevalence of comorbidities, polypharmacy, and frailty can make treatment in this population particularly challenging.[13,14] In elderly patients who do not require stringent HbA_{1c} control but often suffer with complex comorbidities, DPP-4 inhibitors represent an important treatment option. While some drugs for type 2 diabetes are contraindicated in the elderly, DPP-4 inhibitors have been shown to be well tolerated in older adults.[15] Some other classes are associated with an increased risk of side effects that may be particularly problematic in elderly patients—for example hypoglycaemia with sulfonylureas,[16] and thrush and other genital infections with sodium-glucose co-transporter-2 inhibitors (SGLT-2i).[17] Linagliptin should be used with caution in combination with a sulfonylurea and/or insulin (which are known to cause hypoglycaemia). A dose reduction of the sulfonylurea or insulin may be considered.[3] When used alone or in combination with non-hypoglycaemia-causing drugs (such as metformin), linagliptin shows an incidence of hypoglycaemia that is comparable to placebo.[3]

Renal impairment is a common comorbidity among patients with type 2 diabetes, especially the elderly. Linagliptin is particularly well suited for use in renal impairment as it can be prescribed at estimated glomerular filtration rates <30 ml/min and is also suitable without dose adjustment for patients with renal failure who are on dialysis.[3]

Unlike other DPP-4 inhibitors, linagliptin does not require dose adjustment based on renal function or additional renal function monitoring,[3] whereas sitagliptin, vildagliptin, saxagliptin, and alogliptin require both.[4–7] This makes linagliptin simple to prescribe at a single dose of 5 mg daily, irrespective of renal function. In clinical trials, linagliptin has demonstrated efficacy as an add-on therapy both for patients with severe renal impairment and elderly patients ≥70 years of age.[3]

Based on compelling evidence of renal and cardiovascular (CV) benefits from cardiovascular outcome trials (CVOT), recently published guidelines have placed SGLT-2i and glucagon-like peptide-1 receptor agonists (GLP-1 RA) as preferred second-line therapy choices for patients with underlying CV and renal disease;[10,11] although data suggest that the proportion of the total number of patients with type 2 diabetes who may benefit may be up to around 25–30%.[10,18,19]

The CV safety of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin and sitagliptin has been assessed across five CVOTs.[20–24] Across these trials, there was no increase in the risk of primary three- or four-point major adverse cardiac events outcomes (3P-MACE and 4P-MACE).

In the CARMELINA non-inferiority study, there was no difference in risk for linagliptin versus placebo for both CV and renal outcomes in patients with type 2 diabetes.[3,23] Similarly, in the CAROLINA study of adults with early type 2 diabetes and elevated CV risk, use of linagliptin demonstrated non-inferiority compared to glimepiride with regard to the risk of major CV events.[24]

DPP-4 inhibitors in the evolving NHS landscape

In addition to treatment individualisation, it is important for diabetes management to reflect the evolving NHS landscape. The NHS Long Term Plan sets out a number of key primary care goals, of which primary care networks are a central pillar.[25] As the prevalence of type 2 diabetes continues to rise, there will be an increasing focus on this primary care-led diabetes management, incorporating initiatives such as Structured Medication Reviews and Enhanced Health in Care Homes.[26] Upskilling primary care professionals will also be important for further improving diabetes patient care, as the management of type 2 diabetes is becoming more complex, with improvements in care. The increasing prevalence of type 2 diabetes makes it imperative that primary care physicians, pharmacists, and nurses have the necessary skills to manage these patients, and thereby avoid unnecessary referrals to specialist consultants. Clear, clinical pathways are needed, with dissemination and training of all healthcare teams.

Within the new primary care-focused landscape, DPP-4 inhibitors represent a good fit as a well-established drug class for the treatment of type 2 diabetes, and one that not only specialists but also generalist GPs will feel comfortable and confident in prescribing. With its suitability for use across a broad spectrum of patients, including those with renal failure, linagliptin has a lower burden of monitoring than many other antidiabetic drugs.[3] This may, in turn, lead to important clinical and cost benefits to the NHS resulting from fewer follow-up appointments with the practice nurse or GP, and reduced need for blood tests.

Diabetes management in care homes can be supported by use of DPP-4 inhibitors, which provide a treatment option well suited to elderly, frail patients. They may prove particularly valuable in this population as they are associated with a low risk of hypoglycaemic episodes, which contribute to falls and hospital admissions in elderly patients (reduction of which is a key NHS priority).[27]

Structured medication reviews are intended to eliminate issues with existing medication such as side-effects, and optimise overall treatment efficacy.[26] In cases where treatment needs to be escalated or changed, DPP-4 inhibitors have the flexibility for use as alternative or add-on therapies. Choosing linagliptin also eliminates the need for additional monitoring of renal function as it is the only DPP-4 inhibitor that does not require dose adjustment according to renal function.[3] Renal and other monitoring in patients with type 2 diabetes should be undertaken as per NICE guidelines.[8] Switching to or adding DPP-4 inhibitors during medication reviews is typically straightforward and requires minimal patient education or follow-up.

Impact of the COVID-19 pandemic

The COVID-19 pandemic has helped shine a spotlight on the important role that DPP-4 inhibitors still occupy within the type 2 diabetes treatment landscape. The pandemic has also highlighted glycaemic control and risk factor modification as key priorities, with patients with type 2 diabetes at twice the risk of dying in hospital with COVID-19 compared to the general population.[28]

During the pandemic, DPP-4 inhibitors have become the default drugs for the treatment of type 2 diabetes after NHS England issued guidance to halt treatment with metformin, sulfonylureas, GLP-1 RA, and SGLT-2i during concurrent COVID-19 infection.[2] Patients with type 2 diabetes hospitalised with COVID-19 will be prescribed insulin, with DPP-4 inhibitors as an addition or an option, although many patients will be restarted on their usual medications when they have recovered.

The DPP-4 inhibitors have proven to be well tolerated during coronavirus infection and provide a 'safety net' for prescribers and patients that avoids the need to switch medications if COVID-19 symptoms develop or are suspected.[1]

As a result, DPP-4 inhibitors look set to remain an important drug class in the post-COVID world. Coronavirus has caused patients with type 2 diabetes, particularly those who are vulnerable and shielding, to become more cautious about accessing diabetes care. Remote consultations have also complicated the logistics around accessing prescriptions. A degree of therapeutic inertia may therefore have crept in as patients stay at home and doctors delay treatment changes. Linagliptin appears particularly well suited to remote prescribing given its broad spectrum of patient suitability (including elderly/frail and renally impaired patients), simplicity of dosing, and established safety profile.[3] While other antidiabetic drugs (notably insulin and GLP-1 RA) may entail training in injection techniques and/or complex dosing protocols, DPP-4 inhibitors are administered orally and require limited patient education. Linagliptin also has lower need for the additional monitoring that may be required for other agents, both for glycaemic control and renal function.[3]

With the wider changes to the NHS resulting from the COVID-19 pandemic likely to remain in place over the longer term, DPP-4 inhibitors, like linagliptin, will continue to play an important role in ensuring good control in patients with type 2 diabetes in order to help optimise their clinical outcomes.

Summary

Dipeptidyl peptidase-4 inhibitors continue to be an important treatment option for type 2 diabetes and are recommended in many clinical guidelines. These well-established drugs are familiar to primary care prescribers and suitable for use across a broad spectrum of patients with type 2 diabetes. Linagliptin, in particular, benefits from simple, once-daily dosing at a dose of 5 mg, with no requirement for renal dose adjustment or additional monitoring, making it suitable for use in the elderly/frail and renally impaired. As a class, DPP-4 inhibitors have played a pivotal part in treatment of type 2 diabetes during the coronavirus pandemic and look set to retain a key role in the evolving NHS landscape of diabetes care post-COVID.

Conflicts of interest

Professor Wasim Hanif has received research funding, travel grants, and consultancy fees from Boehringer Ingelheim Ltd, as well as other companies. He has received an honorarium for his contribution to this supplement.

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Prescribing Information (UK) TRAJENTA® (Linagliptin)

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. 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 has been observed in patients taking linagliptin. 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 has been observed in patients taking Linagliptin. 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-glycoprotein 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 in clinical trials and from post-marketing experience. 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) or very rare (<1/10,000). *Adverse reactions with linagliptin 5 mg daily as monotherapy:* Common: lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough; rash; amylase increased. Rare: pancreatitis; angioedema; urticaria; bullous pemphigoid. *Adverse reaction with linagliptin in combination with metformin plus sulphonylurea:* Very common: hypoglycaemia. *Adverse reaction with linagliptin in combination with insulin:* Uncommon: constipation. 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** December 2019.

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