

CLINICAL COMMENTARY

FULL TEXT ARTICLE

Initial combination therapy for patients with type 2 diabetes mellitus: considerations for metformin plus linagliptin

Jeffrey S Freeman

Division of Endocrinology and Metabolism, Philadelphia College of Osteopathic Medicine, Philadelphia, PA 19131-1633, USA

Summary

For patients with type 2 diabetes mellitus, management of hyperglycemia is typically complex, and few patients successfully achieve and maintain recommended targets for glycated hemoglobin (HbA1c). Increasingly, combination therapy is recommended early in the disease course, or even directly at diagnosis in patients with relatively high HbA1c levels. A recent randomized, placebo-controlled, Phase III trial investigated the initial combination of linagliptin and metformin in patients with inadequate glycemic control to assess the benefits of initial combination compared with monotherapy. Linagliptin and metformin act in complementary ways, and the combination treatment showed superior efficacy compared with either monotherapy. Notably, responses were largest in patients with higher baseline HbA1c levels compared with moderate levels, suggesting this combination could be considered in these patients. This may be particularly relevant for those unwilling to start insulin because they prefer oral therapy or need to avoid body weight gain. Neither metformin nor linagliptin is associated with weight gain, and in this trial the combination was also weight neutral. As this combination therapy was well tolerated, with a low frequency of hypoglycemia, these findings suggest that initial combination of linagliptin plus metformin may have advantages for a large proportion of patients in clinical practice.

Keywords: biguanides, diabetes mellitus, dipeptidyl peptidase-IV inhibitors, drug therapy, combination, hyperglycemia, incretins, linagliptin, metformin

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Correspondence address	Jeffrey S Freeman DO, Division of Endocrinology and Metabolism, Philadelphia College of Osteopathic Medicine, Philadelphia, PA 19131-1633, USA
Email address	jeffreymando@aol.com
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Abbreviations	AE, adverse event; BID, twice daily; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; HbA1c, glycated hemoglobin; QD, once daily; SD, standard deviation; SGLT, sodium-glucose co-transport; T2DM, type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is a disease all general practitioners are familiar with, since it is one of the most common reasons for patient visits to their primary care physician [1]. Despite being common, treatment is not always straightforward. For every patient, there are many aspects of care to be considered, including weight, smoking, lipids, blood pressure, foot care, and so on [2]. Raised blood glucose – hyperglycemia – is the defining feature of T2DM, and managing this aspect alone can require a substantial investment of time by the healthcare provider and the patient. While the importance of reducing hyperglycemia is not controversial, the target goal needs to be personalized for each individual, with less stringent targets for some patients [3]. Choosing the most appropriate therapy for hyperglycemia can

be particularly time-consuming, because antidiabetic drugs have been the focus of intensive research, with hundreds of clinical studies published every year.

This mass of information is synthesized yearly by the American Diabetes Association, and other societies also release clinical practice guidelines and treatment algorithms. These make recommendations for a 'typical' patient, but patients seen in day-to-day clinical practice will not likely fit so neatly into these guidelines. Indeed, over the past few years, it has been widely recognized that the management approach for each individual needs to be personalized based on their clinical characteristics (for example, the likelihood of weight gain in patients already overweight) and comorbidities (such as the risk of hypoglycemia in patients at high risk of bone fracture from falls), as well as their lifestyle and other personal preferences (many patients may be reluctant to use injections) [3]. Therapies for hyperglycemia will also need to be reviewed regularly, because most patients do not maintain long-term glycemic control, probably due to the progressive nature of T2DM [4]. Based on data from the National Health and Nutrition Examination Survey in 2007–2010, it is estimated that

glycated hemoglobin (HbA1c) is not appropriately controlled in about one-third of patients, even using less stringent targets [5].

To improve glycemic control, expert groups have increasingly suggested making use of combination therapy early after diagnosis [3,6]. Many of the commonly available antidiabetes therapies can be used together, and each combination needs careful consideration of the advantages and disadvantages for the patient. The recent publication of a study showing that initial combination of metformin and linagliptin provides greater HbA1c lowering than either metformin monotherapy or linagliptin monotherapy is of particular interest, since this combination offers theoretical advantages based on the mechanism of action of the two drugs. Here, I review the study (ClinicalTrials.gov Identifier: NCT00798161) published by Haak et al [7], and the possible implications of the results in the context of clinical practice.

Compatibility of metformin (biguanide) and linagliptin (DPP-4 inhibitor)

For a useful combination therapy, the individual components need to have mechanisms of action that are complementary; for an optimal combination therapy, the drugs should also target the core pathophysiologies of T2DM, namely insulin resistance and loss of pancreatic beta-cell function [8]. The combination of metformin and a dipeptidyl peptidase (DPP)-4 inhibitor, such as linagliptin, would appear to meet these requirements based on their mechanisms of action. DPP-4 inhibitors inhibit cleavage of the incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). By raising levels of endogenous GLP-1, DPP-4 inhibitors stimulate post-prandial glucose-dependent insulin secretion from beta cells and suppress gluconeogenesis. Metformin chiefly acts by decreasing

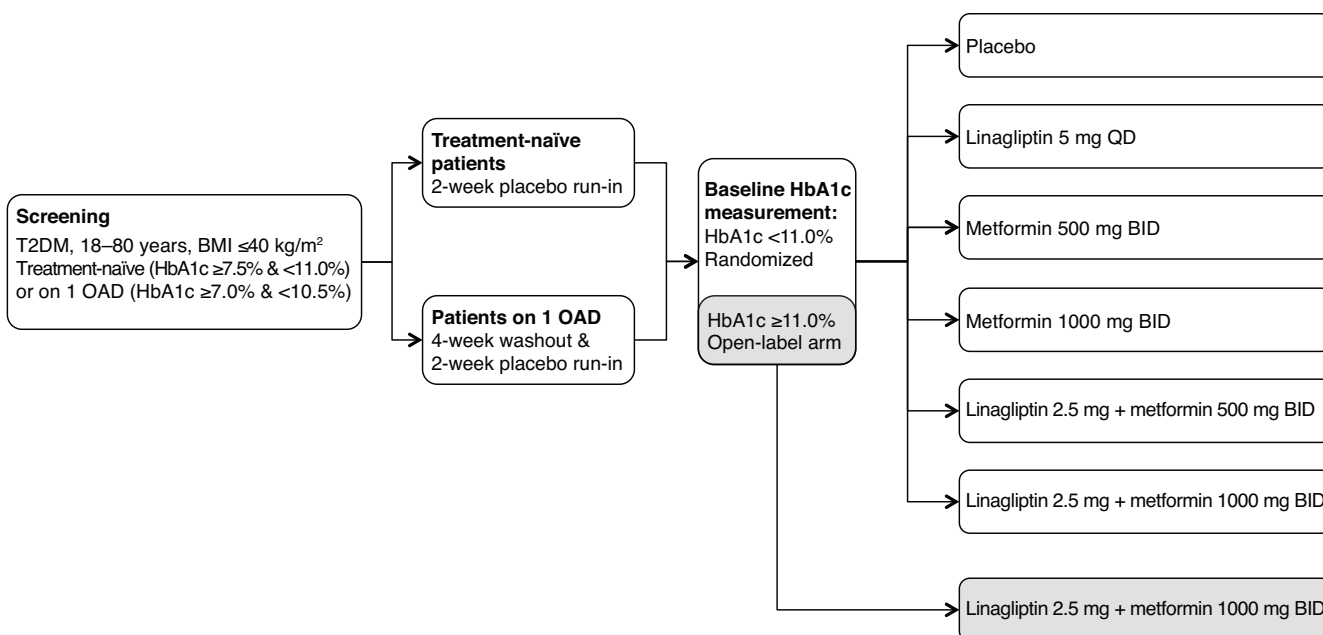
hepatic glucose production and increasing insulin sensitivity; in addition, it also increases GLP-1 levels after glucose load, which may give metformin an additive effect when used with DPP-4 inhibitors [9].

Initial combination of linagliptin and metformin: clinical trial results

The combination of linagliptin used as add-on to metformin therapy in patients with T2DM has been studied previously, but the use of an initial combination had not been directly examined. Therefore, to evaluate the efficacy and safety of initial combination therapy with linagliptin 5 mg/day plus metformin, Haak and colleagues randomized 791 adults with inadequate glycemic control (HbA1c $\geq 7.5\%$ to 11.0%) to one of six double-blind treatment arms for 24 weeks' treatment: placebo, linagliptin 5 mg once daily (QD), metformin 500 mg twice daily (BID), metformin 1000 mg BID, linagliptin 2.5 mg plus metformin 500 mg BID, or linagliptin 2.5 mg plus metformin 1000 mg BID (Figure 1) [7]. Patients with severe hyperglycemia (HbA1c $\geq 11.0\%$) were ineligible for randomization, since this could have resulted in placebo treatment. Instead, they received open-label linagliptin 2.5 mg plus metformin 1000 mg BID for 24 weeks.

About half the patients in the study were treatment-naïve (47.5%), and the other half had been treated with a maximum of one oral antidiabetic drug that was washed out for 6 weeks before starting the study drug. Among randomized patients, the mean age was 55.3 years, and 37% entered the trial less than 1 year after diagnosis of T2DM, 37% had diabetes for 1–5 years, and 26% had diabetes for more than 5 years. According to the study design, patients with moderate renal impairment (estimated glomerular

Figure 1. Comparing linagliptin and metformin combination regimens with monotherapy: 6-month randomized, double-blind, placebo-controlled study, with an open-label arm.



Abbreviations

BID, twice daily; BMI, body-mass index; HbA1c, glycated hemoglobin; OAD, oral antidiabetes drug; QD, once daily; T2DM, type 2 diabetes mellitus
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filtration rate [eGFR] <60 mL/min/1.73 m²) at screening were excluded; however, a small proportion of patients who subsequently had eGFR values in this range at the baseline measurement were included. Thus, the majority of patients (52%) had normal renal function (eGFR ≥90 mL/min/1.73 m²), while 42% had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m²); the remaining 8% had either eGFR 30–60 mL/min/1.73 m² or had no value recorded.

Figure 2 shows the improvements in hyperglycemia after 24 weeks of treatment. Both monotherapy arms demonstrated significant changes from baseline compared with placebo, but the mean change in HbA1c from baseline to week 24 was significantly greater for the two combination arms compared with their respective metformin monotherapy arms (*p*<0.0001). Subgroup analyses showed that the response to initial combination therapy was greater in patients with higher baseline HbA1c levels (8.5% to <11.0%) compared with moderate baseline HbA1c levels (≥7.5% to <8.5%). Furthermore, there was an HbA1c reduction of 3.7% (SD 1.7%) in those with baseline HbA1c ≥11.0%, who received open-label linagliptin 2.5 mg plus metformin 1000 mg, both BID.

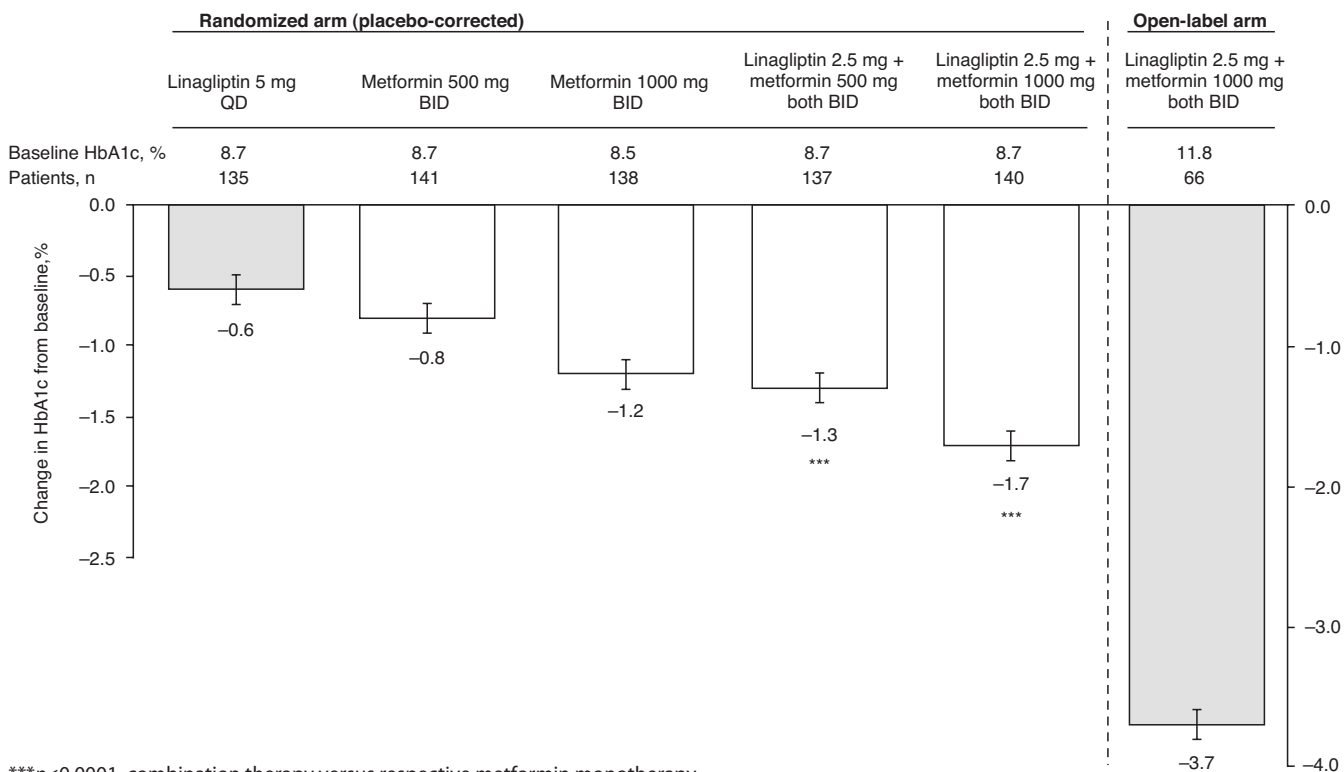
During the study, the combination of linagliptin plus metformin was well tolerated, with a similar proportion of patients in the placebo and treatment groups experiencing any adverse event

(AE), drug-related AEs, serious AEs, or discontinuations due to AEs. The incidence of gastrointestinal AEs, always a concern with metformin, was similar for combination therapies compared with their corresponding metformin monotherapy. In addition, there was a low rate of hypoglycemic events (any adverse event described as hypoglycemia by the treating investigator), and no patients in either of the combination arms had a serious hypoglycemic event (defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions). No clinically meaningful changes in body weight were noted in any of the treatment groups, nor were there any notable changes in waist circumference.

Implications for clinical practice

Based on the study results, Haak and colleagues concluded that initial combination therapy with linagliptin plus metformin was superior to either linagliptin or metformin monotherapy for improving glycemic control in patients with T2DM. However, simply providing better glycemic improvements than either agent individually does not make the combination suitable for all patients. In the rest of this paper, the key characteristics that would likely determine the use of this combination are considered in turn.

Figure 2. Placebo-adjusted change in glycated hemoglobin (HbA1c) from baseline to week 24.



****p*<0.0001, combination therapy versus respective metformin monotherapy.

1. Randomized arm: values are mean with standard error; full analysis set, last observation carried forward.

2. Open-label arm in patients with poor glycemic control: values are mean with standard error; full analysis set, observed cases (n=48).

Abbreviations

BID, twice daily; HbA1c, glycated hemoglobin; QD, once daily

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Patients with moderate or high HbA1c values

For patients newly diagnosed with T2DM, general guidelines recommend lifestyle counseling and metformin monotherapy, with further therapies added as needed to help patients achieve their goal [3]. For patients with HbA1c $\geq 9.0\%$ at diagnosis, it may be worth initiating treatment with a combination regimen, since patients are unlikely to meet goals on monotherapy. Initiation of treatment with insulin can even be considered for these patients, and insulin is likely to offer the greatest HbA1c reduction, but a combination of metformin with insulin or any of a DPP-4 inhibitor, GLP-1 receptor agonist, sulfonylurea, or a thiazolidinedione are all recommended as possible initial combination therapies in patients with HbA1c $\geq 9.0\%$ at diagnosis [3]. If a combination oral therapy is being considered, a DPP-4 inhibitor plus metformin offers clear advantages: effective reductions in HbA1c with no weight gain, no increased risk of hypoglycemia compared with placebo, and convenient oral dosing with the option of fixed-dose combinations in a single pill.

For patients with high HbA1c, there is a common perception that addition of a DPP-4 inhibitor to metformin will likely provide only intermediate HbA1c improvements compared with addition of agents such as sulfonylureas [3]. However, larger reductions may be expected in this group, as seen in a pooled analysis of three linagliptin studies that showed an adjusted mean change from baseline to week 24 of 1.2% in patients with HbA1c $\geq 9.0\%$ [10]. When considered in addition to the improvement expected with metformin, reductions of this magnitude would be expected to enable a large proportion of patients to achieve target levels. Furthermore, a recent study of linagliptin added to metformin showed linagliptin was non-inferior to the sulfonylurea glimepiride in lowering HbA1c over 2 years [11], suggesting that the combination of metformin with a DPP-4 inhibitor can provide similar glucose lowering to metformin plus a sulfonylurea. In addition, the combination of linagliptin and metformin was associated with significantly less hypoglycemia and fewer cardiovascular events, and with a small weight loss compared with weight gain for metformin plus sulfonylurea [11].

The higher a patient's HbA1c level, the more likely we are to consider insulin. However, based on their study, Haak and colleagues concluded that linagliptin plus metformin may offer a plausible alternative to insulin as a first-line treatment option even for patients with severe hyperglycemia [7]. This was based partly on the subgroup analysis that showed that the efficacy of linagliptin plus metformin was greater in patients with higher baseline HbA1c levels, but partly on the combination having no increased risk of AEs compared with metformin alone, as well as the advantages of a low risk of hypoglycemia and no clinically significant changes in body weight – both significant problems with insulin [3]. In the study by Haak et al, patients with a baseline HbA1c level $\geq 11.0\%$ who were assigned linagliptin 2.5 mg plus metformin 1000 mg BID had a mean reduction in HbA1c of 3.7%, suggesting that this option may be worth consideration even in patients with very high baseline HbA1c, particularly when therapy choices are affected by other factors, as discussed in more detail below. However, it must be borne in mind that the study included a relatively small group of patients with very high HbA1c (n=48), and that they received open-label

treatment. Hence, we cannot place the same confidence in the results that we can in those of the randomized, double-blind portion of the trial.

Overweight and obese patients

Obesity is strongly linked with T2DM, and so it is not surprising that the majority of patients we see day-to-day are overweight. Metformin is widely used in overweight patients because it is not associated with weight gain, making the combination with linagliptin attractive because it is also weight neutral. This was further confirmed by the study by Haak et al, with no significant changes in weight seen in any group. Furthermore, overweight patients are expected to have both insulin resistance and beta-cell dysfunction, and the combination of linagliptin and metformin is again worth considering here, since it tackles both aspects. Where weight loss is considered the highest priority, two of the other currently available agents for glucose control in T2DM can be considered: the sodium-glucose co-transport (SGLT)-2 inhibitors are oral agents that provide significant weight loss or, if injectable agents are being considered, GLP-1 receptor agonists are also associated with significant weight loss. As with the DPP-4 inhibitors, both GLP-1 receptor agonists and SGLT-2 inhibitors can be used in combination with metformin.

Older patients

Today, classifying patients as 'older' is problematic, since there is significant heterogeneity among the older population. Overall, however, the group is more likely to have renal impairment and atherosclerotic disease, and to be receiving multiple medications, and a patient's age should be a prompt to consider these and other important factors when choosing therapies. For example, in frail patients, hypoglycemia is a particular concern because of the risk of fractures resulting from falls.

In patients with a shorter life expectancy, strict glycemic control is a lower priority, since the reduction in the risk of microvascular events is seen over the longer term. Therefore, selected older patients have less stringent HbA1c targets than younger adults, making linagliptin plus metformin combination therapy an option where insulin might otherwise be the first choice. In the study by Haak et al, approximately one-fifth of patients were aged ≥ 65 years, but these patients were not analyzed separately. In other analyses of older patients, linagliptin has been effective and well tolerated. For example, in a pooled analysis of patients aged ≥ 65 years participating in seven clinical trials, linagliptin monotherapy, add-on therapy, and initial combination therapy regimens were effective at improving glycemic control with no additional risk of hypoglycemia [12]. Many factors will need to be taken into account when selecting therapies for individual patients, and for some older patients, particularly US patients affected by the Medicare Part D prescription coverage gap (the 'doughnut hole'), the clinical advantages of DPP-4 inhibitors will need to be weighed against the costs, since these agents are more expensive than older drugs such as sulfonylureas.

Chronic kidney disease

Chronic kidney disease is common in patients with T2DM, and all patients should be tested for renal impairment before begin-

ning therapy. Metformin is excreted renally, and is contraindicated in patients with moderate or severe renal impairment. This restriction of metformin use was added to reduce the risk of lactic acidosis, a serious adverse event but one that occurs very rarely when metformin is used appropriately. Linagliptin is not excreted renally, and can be used without dose adjustment in patients with renal impairment [13]. However, in this group of patients, if additional HbA1c lowering is required, linagliptin should be used in combination with an agent other than metformin.

Other DPP-4 inhibitors

The results of the clinical trial conducted by Haak and colleagues are in agreement with results of other studies investigating initial therapy with DPP-4 inhibitors in combination with metformin. For example, studies investigating initial therapy with sitagliptin and metformin demonstrated significantly greater improvements in glycemic control compared with individual monotherapies or active-comparators [14–18]. Furthermore, initial therapy with sitagliptin and metformin also resulted in larger improvements in beta-cell function (measured by the disposition index, the C-peptide minimal model, and the Matsuda index) than either treatment alone [18]. Similarly, saxagliptin given in combination with metformin as initial therapy led to statistically significant improvements in glycemic control compared with either treatment alone [19]. In the study by Haak and colleagues, linagliptin plus metformin provided similar HbA1c reductions to those seen with other DPP-4 inhibitors. However, in the absence of head-to-head studies, it is difficult to draw conclusions as to the benefits of the linagliptin plus metformin combination compared with other DPP-4 inhibitors plus metformin, and all combinations are available in combined tablets.

Conclusion

In their large clinical trial, Haak and colleagues demonstrated that initial combination therapy with linagliptin plus metformin was well tolerated, and provided improved glycemic control compared with monotherapy. This combination is not suitable for every patient but; based on these results, the linagliptin plus metformin combination can be considered as initial therapy in many patients with T2DM.

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