



Intensifying Insulin Monotherapy with Oral Agents



Volume 3 Issue 3

In this Issue...

Despite the increasing number of new diabetes medications currently available, almost one-third of US patients with type 2 diabetes remain in inadequate glycemic control. Many of these individuals are on insulin monotherapy and may benefit by intensifying their glucose control with adjunctive oral agents. But which agents are likely to provide the best outcomes with which patients?

In this issue, Dr. Clare Lee from the Johns Hopkins University School of Medicine reviews the latest evidence evaluating the use of oral diabetes medications as adjunct to insulin monotherapy in patients with poorly controlled type 2 diabetes.

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[Accreditation](#)
[Credit Designations](#)
[Intended Audience](#)
[Statement of Need](#)
[Internet CME/CE Policy](#)
[Faculty Disclosure](#)
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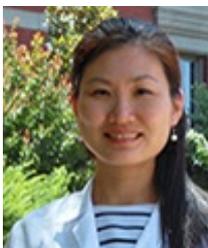
January 18, 2020

LEARNING OBJECTIVES

- Differentiate between the oral agent options to intensify treatment in patients receiving insulin monotherapy.
- Evaluate the efficacy, tolerability, and benefits beyond glucose reduction related to oral medications used to intensify insulin monotherapy.
- Discuss the cautions and advantages in combining specific oral agents with insulin to maximize clinical benefit while minimizing risks in specific populations.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews



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Guest Faculty Disclosure

Dr. Lee has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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IN THIS ISSUE

[COMMENTARY](#)

[Add-On of Oral Agents to Insulin Monotherapy](#)

Program Directors

Nestoras Mathioudakis, MD,

[Review of Current Insulin + Oral Strategies](#)

[SGLT2 Inhibitors vs DPP-4 Inhibitors as Add-On to Insulin](#)

[Linagliptin as Add-On to Insulin](#)

[Saxagliptin as Add-On to Insulin](#)

[KEY TAKEAWAYS](#)

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COMMENTARY

The diabetes epidemic has fueled the development of new diabetes medications over the past several decades. Currently, oral diabetes medications include metformin, sulfonylureas, pioglitazones, alpha glucosidase inhibitors, DPP-4i (dipeptidyl peptidase-4 inhibitors), and SGLT2i (sodium glucose cotransporter-2 inhibitors). The latter two are the latest additions to the type 2 diabetes treatment armamentarium, with sitagliptin as the first DPP-4 inhibitor approved in the United States (2006) and canagliflozin as the first approved SGLT2 inhibitor (2013). Despite the availability of these additional medications, less than a third of adults with type 2 diabetes achieve adequate glycemic control.¹ This failure may be due to both patient factors (progressive disease, lifestyle, and medication adherence) as well as clinician factors, namely clinical inertia.²

Because of the progressive failure of the pancreatic beta cells in patients with type 2 diabetes, many patients may eventually require insulin to achieve adequate glycemic control. At that stage, insulin may be initiated alone (insulin monotherapy) or in combination with oral diabetes medication. In cases where the treatment needs further intensification, it is unclear whether increasing the insulin dose or adding additional oral medications would lead to better clinical outcomes. This knowledge gap served as the rationale for the studies reviewed in this issue.

The recent Cochrane review (Vos et al) examined the efficacy of adding oral diabetes medications to insulin monotherapy. This work is by far the largest and most comprehensive review on this topic, with combined results from 37 trials involving 3227 participants. The results of this review showed strong evidence for adding oral diabetes medications (e.g, sulfonylurea, metformin, pioglitazone, DPP-4 inhibitors, and alpha glucosidase inhibitors) to insulin therapy to improve glycemic control while reducing insulin requirements. Of note, the oral medications differ in their glucose-lowering efficacy, with metformin and sulfonylurea reducing the HbA1c by about 1% compared to approximately 0.5% with DPP-4 inhibitors and SGLT2 inhibitors. Most oral therapies led to a reduction in total daily insulin dose; the reduction was smallest with DPP-4 inhibitors. Sulfonylureas led to weight gain and more frequent hypoglycemic episodes when added to insulin than insulin monotherapy. Metformin was the only oral medication examined that caused weight loss. Therefore, a careful consideration favoring metformin over other oral diabetes medications is needed, unless the patient has a significant renal dysfunction or is unable to tolerate metformin because of gastrointestinal or other side effects. Of note, this review did not include SGLT2 inhibitors, a drug also associated with weight loss, because of lack of related data at the time the review was completed.

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In a more recent review of strategies to improve glycemic control in patients with type 2 diabetes on insulin monotherapy, Umpierrez and colleagues discuss the efficacy and safety profile of oral diabetes medications including DPP-4 inhibitors, SGLT2 inhibitors, and alpha glucosidase inhibitors. The authors conclude that current data support adding a DPP-4 inhibitor or an SGLT2 inhibitor to insulin monotherapy, and DPP-4 inhibitors may be of particular value in elderly patients at risk of hypoglycemia. The recent interest in the cardioprotective effects of the SGLT2 inhibitors empagliflozin and canagliflozin makes these agents attractive options in insulin-requiring patients with type 2 diabetes, who are more likely to have advanced disease and be at higher risk for CVD. Since these reviews were published, additional studies of SGLT2 inhibitors became available that further confirm cardiovascular and renal benefits: canagliflozin led to a reduction in cardiovascular mortality (HR 0.86, 95% CI 0.75 to 0.97, $P < .001$) while risk of lower extremity amputation tended to increase, albeit not significantly (HR 2.07, 95% CI 1.43 to 3.00, $P = .63$).³ The use of alpha glucosidase inhibitors remains low because of their gastrointestinal side effects and modest HbA1c reduction.

Many clinicians will face the choice of whether to add an SGLT2 inhibitor or a DPP-4 inhibitor as an adjunct therapy to their patients whose diabetes is uncontrolled on insulin monotherapy. In the (reviewed) article by Min et al, the authors showed that SGLT2 inhibitors may be more efficacious than DPP-4 inhibitors; they provide a similarly low risk of hypoglycemia, with the added benefits of weight loss and reduction in fasting blood glucose. On the other hand, patients receiving insulin monotherapy with renal dysfunction may be good candidates for linagliptin, a DPP-4 inhibitor, which does require renal dose adjustment. Of note, some of the authors received pharmaceutical funding for this study.

There is also the question of which DPP-4 inhibitor to select as add-on therapy to insulin. Zinman and colleagues, in a detailed review of linagliptin as adjunct therapy to insulin monotherapy, reported linagliptin was shown to improve glycemic control when added to insulin, while avoiding hypoglycemia, weight gain, or worsening of cardiovascular risk factors. Similar to the cardiovascular outcomes study results of saxagliptin, there was a slight increase in hospitalization due to heart failure in linagliptin users; thus caution is warranted in using any DPP-4 inhibitor in patients with heart failure. Another recent study by Chen and colleagues (reviewed herein) examined the efficacy of saxagliptin as adjunct to insulin monotherapy. In this randomized controlled trial involving 953 patients, the authors confirmed that saxagliptin is a useful adjunct to insulin monotherapy in Chinese patients with type 2 diabetes who had minimal risk of hypoglycemia.

In conclusion, current evidence supports the use of oral diabetes medications as adjunct to insulin monotherapy because they can improve glycemic control while reducing insulin requirement. By reducing insulin requirements, one can reduce the risk of hypoglycemia — except with the sulfonylurea and insulin combination. Metformin and SGLT2 inhibitors bring added benefits of modest weight loss, in addition to improving the glycemic control. Moreover, clinicians are encouraged to continue evaluating the efficacy of the patients' diabetes treatment, as the glucose-lowering efficacy of oral diabetes medications is limited and may not be sufficient in patients with severe hyperglycemia (eg, HbA1c > 10%). In such cases, short-acting insulin and/or glucagon-like peptide-1 (GLP-1) may be added to further intensify the diabetes regimen. As more studies become available discussing the long-term benefits, risks, and cost effectiveness of newer medications such as DPP-4 inhibitors and SGLT2 inhibitors, providers will be better equipped to individualize the appropriate oral diabetes medications to add to insulin monotherapy in any particular patient.

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3. Mahaffey KW, Neal B, Perkovic V, et al. [Canagliflozin for primary and secondary prevention of cardiovascular events: Results from the CANVAS program \(canagliflozin cardiovascular assessment study\)](#). *Circulation*. 2017; Nov 13. pii: CIRCULATIONAHA.117.032038. doi: 10.1161/CIRCULATIONAHA.117.032038.

Add-On of Oral Agents to Insulin Monotherapy

Vos RC, van Avendonk MJ, Jansen H, et al. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. *The Cochrane Library*. 2016.



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This article is a Cochrane systematic review on the benefits and risks of adding oral diabetes medications in adults with type 2 diabetes who have inadequate glycemic control on insulin monotherapy. The authors reasoned that there was a lack of consensus among health care providers on whether to continue insulin monotherapy or to add oral diabetes medications to treat inadequate type 2 diabetes control, and that knowledge gap served as the rationale for the systematic review.

The authors performed a comprehensive search up to November 2015 and found 37 randomized controlled trials comparing 40 treatments among 3227 participants lasting two to 12 months in study duration. The participants were adults ages 29-83 years from across the five continents who were treated in both inpatient and outpatient settings. The primary outcomes were all-cause mortality, diabetes-related morbidity, and adverse events. The secondary outcomes were HbA1c, fasting glucose, lipid levels, insulin dose, health-related quality of life, and patient satisfaction. Among the key findings:

- Sulfonylurea and Insulin:** The addition of sulfonylurea to insulin monotherapy was associated with a moderate reduction in HbA1c of -1% (95% confidence interval (CI) -1.6 to -0.5%, $P < .01$). The insulin and sulfonylurea combination resulted in a higher number of mild episodes of hypoglycemia (2.2-6.1 episodes per participant) compared to insulin monotherapy group (2-2.6 episodes per participant). The addition of sulfonylurea was associated with weight gain of 0.4 to 1.9 kg vs -0.8 to 2.1 kg in the insulin monotherapy group. All of the studies included a reduction or no change in insulin requirement with sulfonylurea/insulin combination therapy compared to insulin monotherapy.
- Metformin and Insulin:** The addition of metformin to insulin monotherapy was associated with a reduction in HbA1c of -0.9% (95% CI -1.2 to -0.5, $P < .01$) and weight loss of -2.1 kg (95% CI -2.2 to -1.1 kg, $P < .01$). Metformin users reported more gastrointestinal side effects than insulin monotherapy users (range 7%-67% vs 5% to 16%). All of the studies that reported on the change in the mean total daily insulin dose reported a reduction or no change in insulin requirement with metformin and insulin combination therapy compared to insulin monotherapy.
- TZD and Insulin:** HbA1c results for adding pioglitazone to insulin monotherapy could not be pooled. The insulin and pioglitazone combination resulted in a higher number of mild episodes of hypoglycemia than with insulin monotherapy group (15 to 90 episodes vs 9 to 75 episodes). Similarly to sulfonylurea, the addition of pioglitazone was associated with more weight gain than with insulin monotherapy: 3.8 kg (95% CI 3 to 4.6 kg, $P < .01$). All of the studies that reported on the change in the mean total daily insulin dose reported a reduction or no change in insulin requirement with pioglitazone and insulin combination therapy compared to insulin monotherapy.
- DPP-4i and Insulin:** When adding dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), HbA1c was reduced by -0.4% (95% CI -0.5 to -0.4, $P < .01$) compared to insulin monotherapy. DPP-4 inhibitor + insulin showed similar weight change compared to insulin monotherapy (-0.7 to 1.3 kg vs 0.6 to 1.1 kg). One study reported an increase in mean total daily insulin requirement with DPP-4 inhibitor and insulin combination therapy compared to insulin monotherapy, while other studies reported a decrease.
- Alpha Glucosidase Inhibitor and Insulin:** Adding alpha glucosidase inhibitors to insulin monotherapy, reduced HbA1c by -0.4% (95% CI -0.5 to -0.2, $P < .01$) compared to insulin monotherapy. Alpha glucosidase inhibitor combination therapy showed a tendency toward weight loss compared to insulin monotherapy (-0.5 kg, 95% CI -1.2 to 0.3 kg, $P = .26$). Similarly to metformin, alpha glucosidase inhibitor

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was associated with more gastrointestinal side effects than with insulin monotherapy (14%-75% vs 4%-35%). All of the studies that reported on the change in the mean total daily insulin dose reported a reduction in insulin requirement with alpha glucosidase and insulin combination therapy compared to insulin monotherapy.

In conclusion, the addition of sulfonylurea, metformin, pioglitazone, DPP-4 inhibitors, and alpha glucosidase inhibitors led to improvement in glycemic control, with some agents providing reduced insulin requirements. The addition of a sulfonylurea to insulin increased hypoglycemic episodes, while metformin was shown to be the only oral medication that caused weight loss when combined with insulin. However, this review did not include SGLT2 inhibitors (sodium glucose cotransporter-2 inhibitors), a drug also associated with weight loss, because of lack of related data at the time the review was completed.

[Back to top](#)

Review of Current Insulin + Oral Strategies

Umpierrez GE, Bailey TS, Carcia D, Shaefer C, Shubrook JH, Skolnik N. Improving postprandial hyperglycemia in patients with type 2 diabetes already on basal insulin therapy: A review of current strategies. *J Diabetes*. 2017 Jun 5

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Less than a third of adults treated with insulin monotherapy achieve target HbA1c of less than 7%, according to recent National Health and Nutrition Examinations Surveys.¹ In this article, the authors present efficacy, safety, and cost-effectiveness analyses of several oral diabetes medications to add to insulin monotherapy to intensify glycemic control.

Dipeptidyl peptidase-4 inhibitors (DPP-4i) increase glucose-dependent insulin secretion by prolonging the half-life of glucagon-like peptide-1. Trials of DPP-4i added to insulin monotherapy decreased HbA1c by -0.65% to -0.37% and decreased both postprandial and fasting glucose compared with placebo, while not causing weight gain or hypoglycemia. DPP-4 inhibitor safety profiles show they are generally well tolerated, with minimal gastrointestinal side effects. In 2016, the FDA added a warning about severe and potentially disabling joint pain for this class of drugs. Although postmarketing reports noted acute pancreatitis related to glucagon-like peptide-1 receptor agonists, the FDA concluded the current data do not confirm causative association between incretin therapy and pancreatic safety.² Saxagliptin was associated with an increased risk of hospitalization for heart failure, but several subsequent studies of other DPP-4i inhibitors (eg, sitagliptin, alogliptin) did not show significantly increased cardiovascular disease (CVD) risk compared with placebo. Adding a DPP-4i to insulin is generally considered cost-effective, although there is a lack of high quality cost analysis data over the long term.

Sodium glucose cotransporter-2 inhibitors (SGLT2i) lower blood glucose by enhancing urinary glucose excretion. They also exert other beneficial effects, including promoting weight loss, reducing hypertension, and lowering CVD risks. Adding a SGLT2i to insulin monotherapy (compared with placebo) improved overall glycemic control while reducing weight. Since the effect of inducing urinary glucose excretion is greater with a higher HbA1c, SGLT2i may be particularly beneficial in those with HbA1c above 9%. Both SGLT2i + insulin and DPP-4i + insulin showed a greater reduction in the insulin dose than with placebo (WMD 6.40 IU/day, 95% CI 8.97 to 3.82 IU/day, $P < .001$ and WMD 1.86 IU/day, 95% CI 3.27 to 0.45 IU/day, $P = .010$, respectively).

Regarding safety, hypoglycemia risk was higher when canagliflozin was added to insulin, and thus caution is needed to lower the dose of insulin when used in combination with an SGLT2i. There is also a risk for postural hypotension, genitourinary infection, and bone fracture. In addition, the FDA issued a safety announcement regarding increased risk of ketoacidosis (hazard ratio of 1.6, 95% CI 0.7-3.5) and acute kidney injury associated with the use of SGLT2i. Empagliflozin was associated with a 38% reduction in relative CVD risk and a 32% reduction in mortality from any cause. Of note, a recent study on the cardiovascular effect of canagliflozin reported a similar reduction in cardiovascular mortality (HR 0.86, 95%

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CI 0.75 to 0.97, $P < .001$), albeit with possible increase in the risk of lower extremity amputation (HR 2.07, 95% CI 1.43 to 3.00, $P = .63$).³ No relevant studies cost studies were available at the time of this review.

Alpha glucosidase inhibitors (AGI) lower blood glucose by blocking the intestinal breakdown of oligosaccharides to monosaccharides. When added to insulin, AGIs lower HbA1c by approximately 0.6%. AGIs cause mild to moderate gastrointestinal side effects and rarely cause hypoglycemia or weight gain. Rare cases of hepatotoxicity were reported, although the causality was not established. There was a 49% reduction in the relative risk of CVD events associated with AGI (acarbose) use.

In summary, data are increasing to support adding a DPP-4i or SGLT2i to insulin monotherapy. DPP-4i may be particularly useful in the elderly population at risk of hypoglycemia. SGLT2i have attracted attention because of the CVD risk reduction association with empagliflozin, although whether it is a class-wide effect remains to be seen. The glucose-lowering effect of SGLT2i may be greater in those with relatively poor glycemic control (ie, HbA1c above 9%) by causing more urinary glucose excretion in this group than in those with better glycemic control. While AGIs are an option in combination with insulin, clinical use of those agents remains low because of their high risk of gastrointestinal side effects with only modest HbA1c reduction.

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[Back to top](#)

SGLT2 Inhibitors vs DPP-4 Inhibitors as Add-On to Insulin

Min SH, Yoon J, Hahn S, Cho YM. Comparison between SGLT2 inhibitors and DPP-4 inhibitors added to insulin therapy in type 2 diabetes: A systematic review with indirect comparison meta-analysis. *Diabetes Metab Res*. 2017;33(1). DOI: 0.1002/dmrr.2818



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In this systematic review, the investigators sought to compare the efficacy of SGLT2 inhibitors vs DPP-4 inhibitors when added to insulin monotherapy in patients with inadequately controlled type 2 diabetes. The authors found 14 randomized controlled trials by searching through journal databases up to June 2015. The primary outcome was the change in HbA1c, with secondary outcomes as change in fasting plasma glucose, body weight, insulin dose from baseline, proportion of patients achieving HbA1c < 7%, and incidence of hypoglycemia. Two reviewers independently extracted the data and the authors used the Cochrane collaboration's tool to assess risks of bias. Among the key findings:

- Efficacy: Both the SGLT2 inhibitors and DPP-4 inhibitors resulted in a greater reduction of HbA1c (weighted mean difference (WMD) -0.65%, 95% CI -0.74 to -0.55%, $P < .001$ for SGLT2 inhibitors and WMD -0.58%, 95% CI -0.70 to -0.45%, $P < .001$) for DPP-4i when combined with insulin compared to insulin monotherapy. When comparing the unadjusted efficacy between SGLT2i /insulin combination and DPP-4i/insulin combination, there was no significant difference between the two (WMD -0.07%, 95% CI -0.27 to 0.13%, $P = .474$). However, on adjusting for clinical factors including age, sex, BMI, and baseline insulin dosage, the SGLT2i/insulin combination led to a greater HbA1c reduction than the DPP-4i /insulin combination

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(WMD -0.24%, 95% CI -0.43 to -0.05%, $P = .02$). Fasting glucose results similarly favored the SGLT2i /insulin combination compared to a DPP-4i/insulin combination (WMD -18.0 mg/dl, 95% CI -28.5 to -7.6 mg/dl, $P = .003$).

- Body Weight: The SGLT2i /insulin combination caused weight loss compared to DPP-4i /insulin combination (WMD -2.07 kg, 95% CI -2.45 to -1.70 kg, $P < .001$).
- Change in insulin dose: Both the SGLT2i /insulin combination and DPP-4i /insulin combination led to a greater reduction in insulin dose compared to placebo/insulin (WMD -6.40 units/day, 95% CI -8.97 to -3.82 units/day, $P < .001$), although the difference between these combinations was not significant.
- Safety: No significant differences in hypoglycemia rates were found between the two combinations.

In conclusion, as adjunct to insulin monotherapy, SGLT2 inhibitors may be more efficacious than DPP-4 inhibitors, with a similarly lower risk of hypoglycemia, as well as the added benefits of weight loss and reduction in fasting blood glucose. The limitation of this study is in indirectly driven comparison, although the placebo groups of both SGLT2 inhibitor studies and DPP-4 inhibitor studies were similar in baseline characteristics.

[Back to top](#)

Linagliptin as Add-On to Insulin

Zinman B, Ahren B, Neubacher D, Patel S, Woerle HJ, Johansen OE. Efficacy and cardiovascular safety of linagliptin as an add-on to insulin in type 2 diabetes: A pooled comprehensive post hoc analysis. *Can J Diabetes*. 2016;40(1):50-57.



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The increasing number of oral diabetes agents available for treating type 2 diabetes provides a wider selection of medications for clinicians to consider for patients with inadequate glycemic control already on insulin. The authors of this paper aimed to evaluate the efficacy and cardiovascular (CV) safety of the DPP-4 inhibitor linagliptin as an add-on to insulin monotherapy in patients with type 2 diabetes at increased risk for CV events. They performed a post hoc analysis in which the data from four randomized, double blind, phase 3 clinical trials and CV events were adjudicated by an independent clinical event committee. These trials ranged in duration from 12 to > 52 weeks with patients in inadequate glycemic control (HbA1c 7% to 10%) and included a total of 1870 patients. The overall mean age was 61.6 years, body mass index 31.3 kg/m², baseline HbA1c 8.3%, baseline insulin dose 47 units per day; renal impairment was present in 72.8%. The primary outcome was change in HbA1c; secondary outcomes were changes in insulin dose, body weight, blood pressure, and CV risk factors.

Adding linagliptin to insulin significantly reduced A1c compared to placebo (-0.41 +/- 0.05%, 95% CI -0.50 to -0.32, $P < .001$). In addition, linagliptin provided relative weight benefit (-0.59 kg +/- 0.19, 95% CI -0.97 to -0.21 kg) and modestly reduced insulin requirements (-1.64 units +/- 0.70, 95% CI -3.01 to -0.27), with no significant increased risk of hypoglycemia. No significant changes in CV risk factors were observed. Adding linagliptin to insulin did not increase risk of CV events (hazard ratio (HR) 1.07, 95% CI 0.62 to 1.85). However, hospitalization incidence rates for CHF were higher with linagliptin than with placebo (HR 1.3, 95% CI 0.55 to 3.1).

In summary, this post hoc pooled analysis supports adding linagliptin to insulin monotherapy for improved glycemic control without increasing the risk of hypoglycemia, weight gain, or cardiovascular risk factors. Caution is recommended in patients with heart failure, since a slight increase in hospitalization due to heart failure was seen with DPP-4 inhibitors, although further studies are needed to confirm this association.

[Back to top](#)



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Saxagliptin as Add-On to Insulin

Chen Y, Liu X, Li Q, et al. Saxagliptin add-on therapy in Chinese patients with type 2 diabetes inadequately controlled by insulin with or without metformin: results from the SUPER study, a randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2017 Nov 16. doi: 10.1111/dom.13161. [Epub ahead of print]

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The goal of this study was to evaluate the efficacy of saxagliptin as an add-on therapy to insulin with or without metformin in Chinese patients with type 2 diabetes. Prior to this study, there was a lack of evidence supporting the use of saxagliptin in Asian populations with type 2 diabetes; in an international study,¹ saxagliptin was shown to improve glycemic control up to 54 weeks of use, but only a small fraction of this population was Asian.

This prospective, randomized, double-blind, placebo-controlled phase 3 study was conducted over a 24-week period across 22 centers in China. Patients were randomized to 5 mg saxagliptin daily or placebo and stratified by metformin use, and their insulin regimen was maintained based on their usual total daily dose prior to randomization. Participants were adults with type 2 diabetes under inadequate glycemic control (HbA1c 7.5% to 10.5%) who did not have a history of cardiovascular event in the three months prior to screening or unstable angina or significantly abnormal renal or hepatic dysfunction. The primary outcome was change in HbA1c from baseline to week 24. Secondary outcomes were change in meal-stimulated postprandial glucose and total daily insulin dose.

Among the 953 enrolled patients, 466 patients were randomized to either saxagliptin or placebo as add-on therapy to insulin with or without metformin. A third of the patients were on insulin alone at baseline. Saxagliptin led to a greater reduction in HbA1c compared with placebo (-0.58% 95% CI -0.72 to -0.45, $P < .01$), regardless of metformin use. Furthermore, meal-stimulated postprandial glucose reduced with saxagliptin compared with placebo (postprandial glucose at 120 min -39.1 mg/dl 95% CI -49.4 to -28.8 mg/dl, $P < .01$), while total daily insulin dose did not change significantly (-0.13, 95% CI -0.44 to 0.19, $P = .43$). Fasting glucose was also reduced with saxagliptin compared with placebo (mean difference -15.88 mg/dl 95% CI -21.53 to -10.32 mg/dl, $P < .01$).

The most common adverse event was upper respiratory tract infection. Two patients died during the study: one patient on saxagliptin died due to cardiac failure, while the other patient on placebo died due to intestinal obstruction. The study investigators determined that these deaths were not related to saxagliptin. There was no increased risk of hypoglycemia with the use of saxagliptin.

In conclusion, saxagliptin improved glycemic control without causing hypoglycemia in Chinese patients with type 2 diabetes and was generally well tolerated. The findings of this study are in agreement with the prior larger international study.¹

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[Back to top](#)

KEY TAKEAWAYS

- Adding an oral diabetes medication to insulin monotherapy has been shown to improve glycemic control.
- The choice of oral diabetes medication to add must be tailored to the individual patient's needs, as each choice has pros and cons unique to the medication.
- Sulfonylureas and pioglitazones are potent glucose-lowering agents, but they may increase the risk of hypoglycemia when combined with insulin.

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- Newer agents such as DPP-4 inhibitors and SGLT2 inhibitors provide the added advantage of being weight neutral or weight loss-promoting in addition to glucose-lowering. However, these drugs only modestly lower HbA1c when added to insulin.
- SGLT2 inhibitors may be slightly more effective than DPP-4 inhibitors in lowering HbA1c when added onto insulin.

[Back to top](#)

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