Improved glycaemic control and lower hypoglycaemia risk with reduced prior oral antidiabetes drug therapy in patients with type 2 diabetes treated with insulin glargine 300 U/mL

George Dailey1 | Timothy Reid2 | John White3 | Jason Chao4 | Fang L. Zhou5 | Sachin Paranjape5 | Paulos Berhanu5

1Scripps Whittier Diabetes Institute, San Diego, California
2Mercyhealth Diabetes Center, Janesville, Wisconsin
3Washington State University College of Pharmacy, Spokane, Washington
4Xinyi, Inc., Bridgewater, New Jersey
5Sanofi US, Inc., Bridgewater, New Jersey

Correspondence
George Dailey, Scripps Whittier Diabetes Institute, San Diego, CA.
Email: Dailey.George@scrippshealth.org

Funding information
This study was funded by Sanofi US, Inc. The authors received writing/editorial support in the preparation of this manuscript provided by Grace Richmond, PhD, of Excerpta Medica, funded by Sanofi US, Inc.

Summary

Aims: Data from the EDITION 3 randomized study and the Clinformatics claims database were analysed to determine whether insulin glargine 300 U/mL (Gla-300) could provide insulin-naive patients with type 2 diabetes (T2D) on oral antidiabetes drugs (OADs) with reductions in prior OAD therapy without compromising glycaemic control, and while preserving its known low incidence of hypoglycaemia compared with insulin glargine 100 U/mL (Gla-100).

Methods: Patient-level data from EDITION 3 and de-identified data from the Clinformatics real-world claims database were analysed.

Results: At baseline, 70% of patients in EDITION 3 were on a background of ≥2 OADs. Among the 435 and 437 patients who initiated basal insulin with Gla-300 and Gla-100, respectively, at Month 6, 336 (77%) and 338 (77%) were using ≤1 OAD. Adding Gla-300 or Gla-100 similarly allowed for a reduction in background OAD medication in the Clinformatics dataset (N = 6430), such that, at 6 months postbasal insulin initiation, 14% of patients were no longer taking any OADs. In the analysis of the EDITION 3 study, reduction in OAD burden did not compromise glycaemic benefit, and the low incidence of hypoglycaemia associated with Gla-300 compared with Gla-100 was also preserved. Documented symptomatic hypoglycaemia (blood glucose ≤70 mg/dL) occurred in 30.5% vs 41.0% of patients treated with Gla-300 and Gla-100, respectively (P = 0.0442).

Conclusion: Patients with T2D who initiate basal insulin with Gla-300 could potentially reduce their prior OAD use without compromising glycaemic control and with less hypoglycaemia than with Gla-100.

Keywords
antidiabetic drug, basal insulin, diabetes, insulin therapy, type 2 diabetes
1 | INTRODUCTION

Despite advances in our understanding of the pathophysiology of type 2 diabetes (T2D) and its treatment, approximately half of patients fail to achieve accepted blood glucose targets, placing them at increased risk of diabetes-related complications and increased long-term healthcare costs. Treatment with a single glucose-lowering agent will only address limited pathophysiological defects, necessitating the use of multiple medications in most patients to achieve adequate glycaemic control. The resulting polypharmacotherapy typical of many daily anti-hyperglycaemic drug regimens carries a high burden of treatment resulting from treatment-related effects and self-care duties that are seldom adequately explored during clinical encounters.

Polypharmacotherapy may result in poor treatment adherence, suboptimal glucose control and increased costs, particularly when patients perceive a high medication burden. In older patients in particular, polypharmacotherapy associated with intensive treatment increases the risk of hypoglycaemia, which can be severe, especially when insulin secretagogues are used. Polypharmacotherapy in older people is also associated with an increased risk of adverse drug reactions, medication nonadherence, falls, confusion and medication errors.

The real-world findings of a large managed-care claims database in the USA reported that ~33% of adult patients with T2D were receiving three or more oral antidiabetes drugs (OADs) at the time of basal insulin initiation; another ~40% of patients were on two OADs. Consistent with the difficulties shown in this study in not only achieving glycaemic control, but also with maintenance of euglycaemia in T2D, a similar study reported that the addition of a third OAD to background therapy of 2 OADs did not translate into improved glycaemic control compared with patients adding insulin as a third agent, the higher treatment persistence. Regimen complexity in addition to hypoglycaemia risk may therefore be a barrier to the successful management of T2D.

The aim of this study was to determine whether the use of insulin glargine 300 U/mL (Gla-300) compared with insulin glargine 100 U/mL (Gla-100) in insulin-naive patients enables a reduction in prior OAD burden without compromising glycaemic control and while preserving the lower incidence of hypoglycaemia events associated with Gla-300, compared with Gla-100. To this end, we conducted an analysis of patient-level data from the randomized controlled EDITION 3 trial that evaluated Gla-300 compared with Gla-100 in an insulin-naive T2D population, and further assessed, in a real-world setting, the impact of initiating basal insulin with Gla-300 and Gla-100 on OAD use.

2 | METHODS

2.1 | Study design and patients

This was a post hoc analysis of patient-level data from the randomized controlled EDITION 3 clinical trial (NCT01676220), and de-identified data from the Clinformatics real-world claims database.

EDITION 3 was a multicentre, randomized, open-label, two-arm, parallel-group phase 3a study conducted from August 2012 to September 2013, involving 878 participants with T2D. The study comprised a 2-week screening phase and a 6-month treatment period followed by a 6-month safety-extension period. To be considered eligible for inclusion in EDITION 3, patients had to be insulin-naïve, ≥18 years of age, with a diabetes duration of ≥1 year and having used OADs for ≥6 months before screening. Exclusion criteria were a glycated haemoglobin (HbA1c) level <7% or >11% at screening. Participants were required to have been on noninsulin anti-hyperglycaemic treatment for at least 6 months prior to screening and to discontinue any OADs not approved for use in combination with insulin, and/or sulfonylureas or glinides. Otherwise, participants continued their previous OAD therapies at stable doses. Patients received once-daily evening injections of Gla-300 or Gla-100 administered via a modified TactiPen® (Sanofi-Aventis, Frankfurt, Germany) or SoloSTAR® (Sanofi-Aventis, Frankfurt, Germany) pen injector, respectively. Insulin dose was titrated to a fasting self-monitored plasma glucose (SMPG) level of 80-100 mg/dL (4.4-5.6 mmol/L) in the absence of hypoglycaemia.

For the Clinformatics database component, the study period was from the fourth quarter of 2014 to the first quarter of 2016, with a basal insulin initiation period occurring during the second and third quarters of 2015. To be considered eligible for inclusion in the Clinformatics database study, patients had to be ≥18 years of age at index date, with a diagnosis of T2D during the study period, continuous enrolment for at least 6 months pre- and postbasal insulin initiation, and a record of at least 1 OAD/glucagon-like peptide-1 receptor agonist (GLP-1 RA) prescription during the baseline period. Patients who had any insulin pharmacy claims during the baseline period were excluded.

2.2 | End-points

Study end-points for patients from EDITION 3 treated with Gla-300 compared with Gla-100 were reduction in prior OAD burden, glycaemic control, and hypoglycaemia (≤70 mg/dL and ≤54 mg/dL) incidence. The Clinformatics database was used to address the research questions of whether there is a reduction in OAD use after initiation of Gla-300 or Gla-100 in the real world, and which OADs are impacted.

2.3 | Statistical analyses

Efficacy and safety end-points were summarized using descriptive statistics. P values were calculated using a two-sample t test for continuous variables and the Pearson chi-square test for proportions. A generalized linear model with repeated-measures was used to test for the statistical significance of reduction of OAD usage by visit. Statistical analyses were performed using SAS® software version 9.2 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Baseline characteristics and disposition

From the EDITION 3 data set, a total of 435 patients treated with Gla-300 and 437 patients treated with Gla-100 were included in the present analysis. At baseline, most patients treated with Gla-300 or Gla-100...
were receiving 2 OADs as background therapy (Gla-300: n = 226 [52%];
Gla-100: n = 206 [47%]). In the Gla-300 group, 129 (30%) and 73 (17%)
patients were receiving 1 and 3 OADs, respectively, as background
therapy; in the Gla-100 group, 134 (31%) and 84 (19%) patients were
receiving 1 and 3 OADs, respectively, as background therapy. For pa-
tients assigned to Gla-300 vs Gla-100 in EDITION 3, baseline HbA1c and
fasting plasma glucose (FPG) values are summarized by number of OADs
at baseline and at Month 6 (Table 1). Mean HbA1c values at baseline
were similar for patients treated with Gla-300 or Gla-100.

Figure 1 summarizes the disposition of patients from the Clinformatics
data set who were treated with either Gla-300 or Gla-100. During the
basal insulin initiation period of the study, 7715 patients initiated basal
insulin with Gla-300 and 83885 initiated Gla-100. Of these, 267 and
6163 patients, respectively, met eligibility criteria and were included in
the analyses.

### 3.2 | Change in OAD use

In the EDITION 3 data set, adding basal insulin allowed for a reduction
in background OAD medication use at Month 6 among patients treated
with Gla-300 (P < 0.0001), with an increase in patients receiving 0 or
1 OADs and a decrease in patients receiving 2 or 3 OADs (Figure 2A).
Adding Gla-100 also allowed for a reduction in background OAD use
at Month 6 (Figure 2B). In both Gla-300- and Gla-100-treated patients,
there were notable decreases in the numbers of patients using 2 or 3
OADs from baseline to Month 6 (3 OADs [Gla-300: n = 73 to n = 6;
Gla-100: n = 84 to n = 9]; and 2 OADs [Gla-300: n = 226 to n = 95;
Gla-100: n = 206 to n = 90]). Compared with baseline, where most
patients (70%) were on a background therapy of 2 or more OADs, at
Month 6 a total of 314 (72%) and 22.5% Gla-300-treated patients
were using 1 and 0 OADs, respectively. Similarly, in the Gla-100 arm, 312
(72%) and 26 (6%) patients were receiving 1 or 0 OADs at Month
6, respectively. Most of the reduction in OAD burden occurred in the
first month after starting Gla-300 and was maintained throughout the
duration of the study (data not shown).

Similar to the observations in the clinical trial setting, in the
Clinformatics data set adding Gla-300 or Gla-100 allowed for a reduc-
tion in background OAD medication. Again, notable decreases from
baseline were observed in the number of patients at Month 6 using 3
OADs (Gla-300: n = 50 to n = 31; Gla-100: n = 914 to n = 619), 2 OADs
(Gla-300: n = 119 to n = 97; Gla-100: n = 2364 to n = 1911) and, in the
case of Gla-100, 1 OAD (Gla-100: n = 2607 to n = 2486). Compared
with baseline where most patients (70%) treated with Gla-300 were on

### Table 1 Baseline characteristics of EDITION 3 patients

| Characteristic | Gla-300 | Gla-100 |
|----------------|---------|---------|
| Patients with 1 OAD at baseline and 1 OAD at Month 6 | | |
| Age, y | | |
| n | 177 | 161 |
| Mean (SD) | 58.97 (9.90) | 57.47 (9.80) |
| Duration of diabetes, y | | |
| n | 174 | 160 |
| Mean (SD) | 10.22 (6.08) | 9.35 (5.86) |
| BMI, kg/m² | | |
| n | 177 | 161 |
| Mean (SD) | 33.45 (7.25) | 33.04 (5.86) |
| HbA1c, % | | |
| n | 115 | 116 |
| Mean (SD) | 8.53 (1.01) | 8.61 (1.09) |
| FPG, mg/dL | | |
| n | 115 | 115 |
| Mean (SD) | 180 (53.8) | 189 (52.6) |

| Patients with 2 OADs at baseline and 1 OAD at Month 6 | | |
| Age, y | | |
| n | 177 | 161 |
| Mean (SD) | 58.97 (9.90) | 57.47 (9.80) |
| Duration of diabetes, y | | |
| n | 174 | 160 |
| Mean (SD) | 10.22 (6.08) | 9.35 (5.86) |
| BMI, kg/m² | | |
| n | 177 | 161 |
| Mean (SD) | 33.45 (7.25) | 33.04 (5.86) |
| HbA1c, % | | |
| n | 177 | 161 |
| Mean (SD) | 8.59 (1.10) | 8.73 (1.08) |
| FPG, mg/dL | | |
| n | 174 | 158 |
| Mean (SD) | 183 (47.7) | 185 (51.3) |

| Patients with 2 OADs at baseline and 2 OADs at Month 6 | | |
| Age, y | | |
| n | 40 | 31 |
| Mean (SD) | 56.48 (9.09) | 59.13 (9.97) |
| Duration of diabetes, y | | |
| n | 40 | 31 |
| Mean (SD) | 9.31 (5.37) | 9.40 (4.74) |
| BMI, kg/m² | | |
| n | 40 | 31 |
| Mean (SD) | 34.00 (6.49) | 34.15 (8.62) |
| HbA1c, % | | |
| n | 40 | 31 |
| Mean (SD) | 8.23 (0.92) | 8.30 (0.74) |

(Continues)
a background therapy of 2 or more OADs, at Month 6 a total of 98 (37%) and 32 (12%) Gla-300 patients were using 1 or 0 OADs, respectively. At Month 6, 32 of 267 (12%) Gla-300-treated patients and 853 of 6163 (14%) Gla-100-treated patients were no longer taking any OADs.

3.3 | Reduction in OAD use by class of OAD

Percentage of reduction in background OAD medications is summarized by class of OAD among patients treated with Gla-300/Gla-100...
in EDITION 3 (Figure 3A) and Gla-300/Gla-100 in the Clinformatics database (Figure 3B).

In EDITION 3, consistent with the protocol-mandated cessation of OADs that are incompatible for use with insulin, the largest reduction in OAD use was for sulfonylureas (96% reduction). However, the use of combination OADs was reduced by 49%, thiazolidinediones by 28% and dipeptidyl peptidase-4 (DPP-4) inhibitors by 22% (Figure 3A).

Among patients in the Clinformatics real-world database where there was no specifically mandated reduction of OADs, sulfonylurea use was reduced by 22%, with notable reductions also observed for thiazolidinediones (27%), DPP-4 inhibitors (22%) and meglitinide (20%) (Figure 3B). The only drug class to show an increase following initiation of basal insulin was the GLP-1 RA class for which a 12% increase in use was observed for Gla-300 (data not shown), compared with an overall slight decrease for the combined Gla-300/Gla-100 Clinformatics cohort.

### 3.4 Glycaemic benefit and hypoglycaemia in EDITION 3

In EDITION 3, the reduced number of OADs taken by patients treated with Gla-300 or Gla-100 did not compromise glycaemic benefit or the reduced risk of hypoglycaemia that Gla-300 offers in comparison to Gla-100 (Figure 4). The mean (±SD) reductions in HbA1c were as follows: 2 OADs at baseline to 1 OAD at 6 months (Gla-300, n = 177: −1.5% [1.01]; Gla-100, n = 161: −1.5% [1.17]; P = 0.9933); 2 OADs to 2 OADs (Gla-300, n = 40: −1.5% [0.78]; Gla-100, n = 31: −1.8% [0.80]; P = 0.1981); 1 OAD to 1 OAD (Gla-300, n = 115: −1.3% [1.36]; Gla-100, n = 116: −1.6% [1.42]; P = 0.3867). The changes in HbA1c did not differ significantly between OAD baseline and follow-up categories.

Moreover, the lower incidence of hypoglycaemia previously observed with Gla-300 when compared with Gla-100 was also maintained following the reduction of OAD burden, as shown. In patients who were able to reduce OAD utilization from baseline, the percentage of patients with any documented symptomatic hypoglycaemia (blood glucose ≤70 mg/dL) was 30.5% with Gla-300 compared with 41.0% with Gla-100 (P = 0.0442; Figure 4A); the percentage with any nocturnal documented symptomatic hypoglycaemia (≤70 mg/dL) was 11.9% with Gla-300 compared with 16.8% with Gla-100 (P = 0.1969; Figure 4C). Documented symptomatic hypoglycaemia and nocturnal documented symptomatic hypoglycaemia (≤54 mg/dL) also occurred significantly less frequently for patients treated with Gla-300 compared with Gla-100: the percentage of patients with documented symptomatic hypoglycaemia (≤54 mg/dL) was 8.5% with Gla-300 compared with 18.6% with Gla-100 (P = 0.0060; Figure 4B); the percentage of patients with nocturnal documented symptomatic hypoglycaemia (≤54 mg/dL) was 2.3% with Gla-300 compared with 7.5% with Gla-100 (P = 0.0247; Figure 4D).

### 4 DISCUSSION

The findings of this post hoc analysis of data from EDITION 3 and from the Clinformatics real-world database demonstrate that the use of basal insulin in patients with T2D currently uncontrolled on OADs allows the reduction of prior OAD therapy without compromising...
Indeed, in EDITION 3, the initiation of basal insulin either with Gla-300 or Gla-100 resulted in a similar improvement in HbA1c from baseline. The reductions in HbA1c were comparable in patients both with and without a decrease in the number of OADs used during 6 months postbasal insulin initiation, indicating that a reduction in OAD burden did not compromise glycemic control. In addition, compared with Gla-100 treatment, the risk of any hypoglycemia (≤70 mg/dL or ≤54 mg/dL) and nocturnal hypoglycemia (≤54 mg/dL) was significantly reduced with Gla-300 despite the achieved reduction in OAD burden. Consistent with the study protocol which mandated the discontinuation of OADs not compatible with insulin use, the reduction in OAD burden in EDITION 3 occurred within the first month after initiating basal insulin. The observed benefits of Gla-300 and Gla-100 treatment at Month 6 despite this early withdrawal of OADs favor a reduction in OAD use in some patients initiating therapy with basal insulin. The findings from the Clininformatics database support the EDITION 3 clinical study observations by demonstrating that in a real-world clinical setting there was a similar reduction in OAD burden after initiating either Gla-300 or Gla-100. Collectively, these observations suggest that when adding basal insulin, some patients with T2D can safely reduce their prior OAD burden while achieving an improvement in glycemic control and at the same time preserving the known lower incidence of hypoglycemia associated with Gla-300 compared with Gla-100.

The finding that patients with T2D who initiate or intensify therapy with insulin may benefit from reduced OAD usage is not unique. Analysis of data from a large US managed-care database showed that in patients already receiving basal insulin, the addition of insulin aspart led to a reduction in OAD usage. However, there is a surprising shortage of relevant data regarding this phenomenon, perhaps because it may be considered counterintuitive to reduce the overall therapeutic burden in a disease that is complex and progressive. On the one hand, for those patients initiating insulin therapy, it would make sense to discontinue insulin secretagogues (such as sulfonylureas). On the other hand, however, discontinuing other classes of OAD with different mechanisms of action may reduce the possibilities to further decrease HbA1c levels and modify noninsulin-dependent physiological targets. For example, discontinuing an OAD with a pronounced postprandial glucose-lowering effect would potentially be counterproductive due to a loss in potential synergy with the FPG-lowering effects of insulin glargine. Speculation concerning the suboptimal treatment effects of an insulin-based regimen in the context of reduced OAD burden needs

**FIGURE 4** Percentage of patients on Gla-300 and Gla-100 with at least 1 hypoglycemia event during the 6-mo treatment period in EDITION 3 who reduced prior OAD use: **A**, all documented symptomatic hypoglycemia (≤70 mg/dL); **B**, all documented symptomatic hypoglycemia (≤54 mg/dL); **C**, nocturnal documented symptomatic hypoglycemia (≤70 mg/dL); **D**, nocturnal documented symptomatic hypoglycemia (≤54 mg/dL).
to be weighed against the potential benefits of regimen simplification in T2D, which include improved glycaemic control, medication adherence and reduced healthcare costs.17,18

In our study, we found a small increase in the use of GLP-1 RAs among patients who initiated treatment with Gla-300 in the Clinformatics database. This finding is somewhat surprising when compared to what we observed with regard to OADs. This might be due to the fact that these patients were more likely to be under the care of an endocrinologist,19 but this is purely speculative and the number of patients concerned is small.

This study has several limitations. The main limitation of the post hoc analysis of EDITION 3 data was the confounding aspect of investigating the effects of a reduction in background OADs when such a reduction was mandated by the study protocol. However, this did not extend to thiazolidinediones, DPP-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, GLP-1 RAs, biguanides and other drug classes that were compatible with insulin use, suggesting that the reduction in OAD use was determined by patient and physician factors that are relevant in a real-world setting. Indeed, the corroborating evidence of a reduction in background OAD use in patients from the Clinformatics database together with the observation that multiple classes of OADs were discontinued in EDITION 3 and not just OADs associated with a high risk of hypoglycaemia, support the notion that reductions in prior OADs can be implemented during initiation of basal insulin therapy without compromising the benefits of improved glycaemic control and lower hypoglycaemia risk, the latter dependent on the particular basal insulin used. The present study was not specifically intended to assess the type and magnitude of OAD reductions, any judgements around which should be left to the care provider based on individualized patient needs. The main limitation of the Clinformatics database analysis was that the difference in baseline characteristics of the two arms could have impacted the results. On the other hand, the strengths of the database include its real-world clinical setting and consequent capacity to assess effects that are determined by real-world clinical decision-making and not as a consequence of specific protocol mandates. The use of claims data from the Clinformatics database has the limitation that such data are potentially subject to coding errors, which can influence the study results. In addition, patient and other baseline factors not considered in the analysis may have influenced the results. However, it is relevant that despite the differences between the EDITION 3 and Clinformatics datasets, the data regarding OAD usage were consistent and lend credibility to the findings overall. As a retrospective analysis, the findings were exploratory in nature and, as such, cannot be used to establish causality of the observed outcomes. Finally, a limitation of the statistical analyses employed for this study include that two sample *t* tests assume normally distributed data in the EDITION 3 and Clinformatics populations, and the chi-square test is sensitive to small sample size and expected frequencies.

In conclusion, our findings suggest that T2D patients who initiate basal insulin therapy with Gla-300 could potentially reduce their use of OADs without compromising glycaemic control and with a lower risk of hypoglycaemia than with Gla-100. These findings have important ramifications for real-world clinical decision-making, particularly regarding regimen simplification, but require confirmation in prospective studies.

**CONFLICT OF INTEREST**

G. D. is a member of speakers’ bureaus for Sanofi, AstraZeneca, and Mannkind; an investigator for Eli Lilly, Lexicon, Mylan, and Sanofi; an occasional consultant for Sanofi, Novo Nordisk, and Eli Lilly. T. R. is a speaker/consultant for Novo Nordisk, Sanofi-Aventis, Janssen, Eli Lilly, and Intarcia, Inc. J. W. is an advisory board member for Sanofi US, Inc. and Novo Nordisk. J. C. is an employee of Xinyi, Inc.; under contract with Sanofi US, Inc. F. L. Z., S. P. and P. B. are employees and stock/shareholders of Sanofi US, Inc.

**AUTHOR CONTRIBUTIONS**

F. L. Z., S. P. and P. B. contributed to the study design. All authors participated in critical reviewing and interpreting the data for the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**ORCID**

George Dailey [http://orcid.org/0000-0002-2906-445X](http://orcid.org/0000-0002-2906-445X)

Fang L. Zhou [http://orcid.org/0000-0003-1353-6376](http://orcid.org/0000-0003-1353-6376)

**REFERENCES**

1. Ross SA. Breaking down patient and physician barriers to optimize glycaemic control in type 2 diabetes. *Am J Med*. 2013;126(9 Suppl 1):S38-S48.

2. Lavernia F, Adkins SE, Shubrook JH. Use of oral combination therapy for type 2 diabetes in primary care: meeting individualized patient goals. *Postgrad Med*. 2015;127(8):808-817.

3. Bohlen K, Scoville E, Shippee ND, May CR, Montori VM. Overwhelmed patients: a videographic analysis of how patients with type 2 diabetes and clinicians articulate and address treatment burden during clinical encounters. *Diabetes Care*. 2012;35(1):47-49.

4. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med*. 2005;20(5):479-482.

5. Bluhr M, Kurz I, Dannenmaier S, Dworak M. Pill burden in patients with type 2 diabetes in Germany: subanalysis from the prospective, noninterventional PROVIL study. *Clin Diabetes*. 2015;33(2):55-61.

6. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. *JAMA*. 2016;315(10):1034-1045.

7. Ballentine NH. Polypharmacy in the elderly: maximizing benefit, minimizing harm. *Crit Care Nurs Q*. 2008;31(1):40-45.

8. Hubbard RE, O’Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69(3):319-326.

9. Levin PA, Zhou S, Gill J, Wei W. Health outcomes associated with initiation of basal insulin after 1, 2, or ≥3 oral antidiabetes drug(s) among managed care patients with type 2 diabetes. *J Manag Care Spec Pharm*. 2015;21(12):1172-1181.
10. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. J Manag Care Pharm. 2014;20(5):501-512.
11. Kruger DF. Intensifying insulin treatment: options, practical issues, and the role of the nurse practitioner. J Am Acad Nurse Pract. 2012;24(Suppl 1):260-269.
12. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab. 2015;17(9):859-867.
13. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/mL compared with glargine 100 U/mL in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015;17(4):386-394.
14. Aagren M, Luo W, Moes E. Healthcare utilization changes in relation to treatment intensification with insulin aspart in patients with type 2 diabetes. Data from a large US managed-care organization. J Med Econ. 2010;13(1):16-22.
15. Brunton SA. Hypoglycemic potential of current and emerging pharmacotherapies in type 2 diabetes mellitus. Postgrad Med. 2012;124(4):74-83.
16. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016;39(11):2026-2035.
17. Tikin M, Celik S, Berard L. Understanding adherence to medications in type 2 diabetes care and clinical trials to overcome barriers: a narrative review. Curr Med Res Opin. 2016;32(2):277-287.
18. Yeh A, Shah-Manek B, Lor KB. Medication regimen complexity and A1C goal attainment in underserved adults with type 2 diabetes. Ann Pharmacother. 2017;51(2):111-117.
19. Lin J, Zhou S, Wei W, Pan C, Lingohr-Smith M, Levin P. Does clinical inertia vary by personalized A1C goal? A study of predictors and prevalence of clinical inertia in a U.S. managed-care setting. Endocr Pract. 2016;22(2):151-161.

How to cite this article: Dailey G, Reid T, White J, et al. Improved glycaemic control and lower hypoglycaemia risk with reduced prior oral antidiabetes drug therapy in patients with type 2 diabetes treated with insulin glargine 300 U/mL. Endocrinol Diab Metab. 2018;1:e35. https://doi.org/10.1002/edm2.35