Diabetes Ther (2020) 11:561–567
https://doi.org/10.1007/s13300-019-00755-3

COMMENTARY

Commentary to "Differential Effect of Hypoalbuminemia on Hypoglycemia on Type 2 Diabetes Patients Treated with Insulin Glargine 300 U/ml and Insulin Degludec" by Kawaguchi et al. Diabetes Therapy 2019

Thomas R. Pieber · Lars Bardtrum · Joakim Isendahl · Lily Wagner · Rimei Nishimura

Received: November 18, 2019 / Published online: January 10, 2020

Keywords: Albumin; Hypoglycaemia; Insulin degludec; Insulin glargine U300

Key Summary Points

Two publications from a small-scale cross-over study comparing insulin glargine 300 units/mL (glargine U300) with insulin degludec (degludec) in 30 patients with type 2 diabetes have been published recently.

The results from these studies indicate that glargine U300 was associated with a lower percentage of time in hypoglycaemia and that this lower risk of hypoglycaemia was in patients with low albumin concentrations.

However, this study was limited by the lack of adjustment in starting insulin dose, the short study period to assess continuous glucose monitoring and the heterogeneous background therapies of the patient group.

A post hoc analysis of the DEVOTE cardiovascular outcomes trial did not indicate an increased relative risk of hypoglycaemia for degludec versus insulin glargine 100 units/mL (glargine U100) and did not show any albumin-related safety signal concerning degludec.

We acknowledge that glargine U100 and U300 have different pharmacokinetic profiles that likely explain the higher hypoglycaemia risk of glargine U100 compared with glargine U300 and degludec.

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.11417859.

T. R. Pieber (✉)
Medical University of Graz, Graz, Austria
e-mail: thomas.pieber@medunigraz.at

L. Bardtrum · J. Isendahl · L. Wagner
Novo Nordisk A/S, Søborg, Denmark

R. Nishimura
The Jikei University School of Medicine, Tokyo, Japan

Kawaguchi et al. have produced two publications of data from a small-scale cross-over study comparing insulin glargine 300 units/mL (glargine U300) with insulin degludec (degludec) in 30 patients with type 2 diabetes [1, 2]. This cross-over study was approved by the ethics committee of Minami Osaka Hospital and executed in accordance with the Declaration of

Helsinki, with all patients providing informed consent. In the first of the two publications, the glargine U300 treatment period was associated with an overall lower percentage of time in a predefined hypoglycaemic range of < 70 mg/dL (1.3% ± 2.7% [glargine U300] vs. 5.5% ± 6.4% [degludec]; $p = 0.002$) assessed by continuous glucose monitoring (CGM) over a 3-day period, with the authors concluding that glargine U300 carries a lower risk of hypoglycaemia [1]. It should be noted that recently published recommendations suggest longer CGM data collection periods for individuals with variable glycaemic control—for example, 4 weeks of data to investigate hypoglycaemia exposure [3]. In a secondary analysis, the authors hypothesised that this apparent risk difference might derive from differences in the pharmacokinetic properties of the two basal insulins [2]. As degludec forms a circulating depot by reversibly binding to albumin after absorption from the subcutaneous depot, they hypothesised that patients with low albumin concentrations might be subject to greater exposure to unbound degludec. The authors therefore assessed the relationship between time in hypoglycaemia and albumin concentration and found that the risk difference between the insulins was confined to the 15 patients with serum albumin levels of < 3.8 g/dL when the cohort was stratified above or below this concentration [2].

If the findings of Kawaguchi et al. [1, 2] are genuine, they raise important considerations about the use of degludec with regard to patients' serum albumin level. We contend, however, that these findings are likely to be anomalous and actually reflect methodological flaws in the original cross-over study that relate to the well-documented lower unit potency of glargine U300 [4–6]. We therefore offer commentary on this methodology and present some relevant and previously unpublished data from the DEVOTE cardiovascular outcomes trial that concern albumin concentration and hypoglycaemia risk.

Firstly, we would like to stress that in any comparative study of two insulins in which hypoglycaemia is evaluated as an outcome, it is essential to achieve parity in another parameter of glucose control. Conventionally, this would be glycated haemoglobin (HbA_{1c}), a marker of overall glucose exposure and the standard reference point when comparing other outcomes in diabetes. A disadvantage of HbA_{1c}, however, is that it is retrospective (reflecting glucose exposure over a period of a few weeks) and slow to change in response to interventions; hence, most diabetes trials using this endpoint tend to be run for a minimum of 26 weeks. Presumably, this is why HbA_{1c} was not evaluated in the Kawaguchi et al. cross-over study. The duration of the treatment periods in this study is not clearly explained, but the authors state that the first treatment period ran for a period of > 10 days for titration (every 3–4 days) followed by 5 days of CGM; this duration is clearly insufficient for meaningful HbA_{1c} assessment.

Importantly, for the first period of the cross-over study, both insulin-naïve patients started on the same unit dose for each insulin (glargine U300 or degludec) and previously insulin-treated patients were switched unit-for-unit to the study insulins. For the second treatment period, the basal insulin was also switched (from glargine U300 to degludec, or vice versa) unit for unit (after a 3–4-day wash-out period) and then left unchanged. This approach presupposes parity in the glucose-lowering potency of the two insulins, but the potency of glargine U300 is known to be reduced compared with insulin glargine 100 units/mL (glargine U100) and degludec. Indeed, the prescribing information for glargine U300 (TOUJEO®; Sanofi S.A., Paris, France) states [4]:

> "For patients controlled on LANTUS (insulin glargine, 100 units/mL) expect that a higher daily dose of TOUJEO will be needed to maintain the same level of glycemic control."

> "At steady state, the 24 h glucose lowering effect (GIR-$AUC_{0–24}$) of TOUJEO 0.4 U/kg was approximately 27% lower with a different distribution profile than that of an equivalent dose of LANTUS."

Given that degludec and glargine U100 have been shown to produce parity in HbA_{1c} in numerous trials at equivalent unit doses, it

follows that degludec will have a greater unit potency than glargine U300. This has indeed been confirmed in glucose clamp studies [5, 6]. Assuming that the disparity between glargine U300 and degludec is similar to that between glargine U300 and U100, insulin-naïve patients who commenced the cross-over study on the same unit dose of glargine U300 as of degludec would have effectively commenced on a dose with approximately 27% less glucose-lowering potency. Similarly, previous insulin users switching unit-for-unit from, for example, NPH insulin or glargine U100 to degludec would have maintained an equivalent dose, whereas those switching to glargine U300 would, in effect, have received a substantial dose reduction by 27%. Admittedly, the minimum 10-day titration period would have gone some way to mitigating this dose difference, but this interval is short and would have allowed only a few titration steps. In the second period of the study, patients were crossed over unit-for-unit and the dose left unchanged, so those switching from degludec to glargine U300 would have, in effect, had a 27% dose reduction, whereas those switching from glargine U300 to degludec would have had a substantial dose increase, in effect by 37%.

Since the insulin doses were not adequately controlled, we contend that no meaningful comparisons can be drawn from the hypoglycaemia data as the protocol would have resulted in a more potent overall glucose-lowering dose of degludec being used. This is further supported by the CGM data, which show not only a shorter period of time in hypoglycaemia with glargine U300 (1.3% ± 2.7% [glargine U300] vs. 5.5% ± 6.4% [degludec]; $p = 0.002$), but also a non-significant tendency toward a longer period of time in hyperglycaemia ≥ 180 mg/dL (20.9% ± 19.0% [glargine U300] vs. 17.7% ± 18.3% [degludec]; $p = 0.505$) and non-significantly higher mean 24-h glucose concentrations of 144.4 ± 36.3 mg/dL (glargine U300) versus 134.3 ± 26.5 mg/dL (degludec) ($p = 0.141$) [1] . Furthermore, there was a non-significantly higher mean pre-breakfast glucose concentration reported for glargine U300 (122.2 ± 22.2 mg/dL [glargine U300] vs. 111.1 ± 30.5 mg/dL [degludec]; $p = 0.1$) [1]. This is especially pertinent as the majority of 'time in hypoglycaemia' occurred in the nocturnal interval, and if patients were titrated to a lower pre-breakfast glucose level, then this would directly impact nocturnal glycaemia. Finally, in the secondary publication stratifying patients by albumin concentration, in which the hypoglycaemia difference was reported to be confined to 15 patients with serum albumin levels < 3.8 g/dL, there was a significantly higher mean 24-h glucose level with glargine U300 (143.0 ± 20.7 mg/dL [glargine U300] vs. 124.0 ± 25.3 mg/dL [degludec]; $p = 0.033$) [2]. In short, these data are all consistent with the glargine U300 treatment periods having less glucose-lowering potency on average—especially in the subset of patients with low albumin.

The data are also potentially confounded by very heterogeneous background therapy, with 13 patients being previously insulin-naïve, four having been on only basal insulin and five and eight patients having used basal-bolus and premixed insulin, respectively, and hence using bolus insulin during the cross-over study [1]. This heterogeneous background therapy is of particular concern when it comes to the stratification of patients by albumin level because the baseline characteristics of the two groups were not reported [2].

That time in hypoglycaemia in the cross-over study was linked to albumin level nevertheless merits further attention. The authors note a diurnal change in serum albumin, with serum abumin levels rising in the daytime and decreasing at night; and suggest that this diurnal change might lead to increases in free degludec concentrations at night-time raising the risk of nocturnal hypoglycaemia [1]. In fact, most of the time in hypoglycaemia was nocturnal with both insulins, and in patients with average albumin levels both above and below 3.8 g/dL. The dynamic mean glucose levels of eight patients by insulin were plotted in Fig. 2 of one of their publications [2] (reproduced in the present publication as Fig. 1). These patients were selected for having comparable pre-breakfast glucose levels of approximately 100 mg/dL; it was noted that they had a mean serum albumin level of 3.6 g/dL. The traces in the

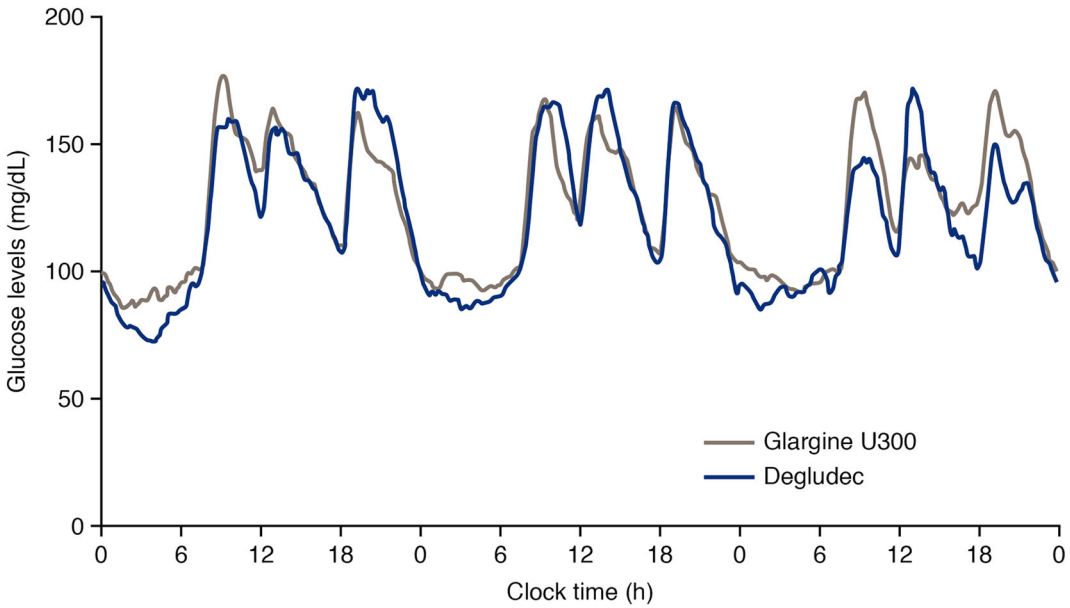

Fig. 1 Figure 2 of Kawaguchi et al. [2], showing mean glucose profiles obtained by continuous glucose monitoring during 3 days of treatment with insulin degludec (*Degludec*) and insulin glargine 300 units/mL (*Glargine U300*) in eight patients selected from a cross-over study. Use of this figure is licensed under CC BY 4.0

figure show the nocturnal fall in mean glucose with both insulins following three daytime peaks that are presumably associated with meals. The degludec glucose curve could be interpreted as showing a greater peak:trough ratio across 24 h, but few data were presented in the original article to support this, and no information was given about the use in these patients of bolus insulins, which would greatly impact the daytime profiles. It cannot be excluded, therefore, that this is a chance finding or a non-causal association.

The present authors would like to note that the principle of albumin binding as a protraction mechanism was originally developed for insulin detemir in the expectation that it would be safe due to the vast ratio of albumin binding sites to insulin molecules. In the case of degludec, the plasma concentration is very low (typically < 0.01 μmol/L) at anticipated clinical doses [7] compared with the normal serum albumin concentration of approximately 600 μmol/L [8]. Therefore, degludec will occupy $< 0.01\%$ of total albumin molecules, and the fraction occupied would remain negligible even in patients with hypoalbuminaemia. Furthermore, it should be remembered that degludec, like any insulin, is individually titrated to the patient's glycaemic response. For the free degludec fraction to increase significantly in an individual, therefore, would require that there be very significant changes in that person's albumin concentration.

Nevertheless, any safety concern must be taken seriously and investigated further. Therefore, we performed a post hoc analysis of the DEVOTE trial database to investigate whether there is a potential risk signal in patients with low albumin levels. DEVOTE was a large-scale, event-driven, randomised, double-blinded, parallel-group cardiovascular outcomes trial comparing degludec with glargine U100 in more than 7600 patients, with a mean follow-up time of just under 2 years [9]. DEVOTE was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines, was approved by all local independent ethics committees/institutional review boards and required written informed consent from each patient. As well as the primary composite endpoint of major adverse cardiovascular events (MACE), DEVOTE also assessed severe hypoglycaemia as a secondary endpoint. MACE

occurred in 8.5% of the degludec group and 9.3% of the glargine U100 group (hazard ratio 0.91; 95% confidence interval 0.78, 1.06), which confirmed non-inferiority for degludec. At a mean 24-month HbA_{1c} of 7.5% ± 1.2% in both groups, adjudicated severe hypoglycaemia had occurred in 4.9% of the degludec group and in 6.6% of the glargine U100 group (rate ratio 0.60; $p < 0.001$). Rates of other adverse events did not differ between the two groups.

We identified only 12 patients (6 in each insulin group) with serum albumin < 3.0 g/dL in DEVOTE, but there were 115 patients with serum albumin < 3.5 g/dL. Only one severe hypoglycaemic event was recorded among the 12 patients with serum albumin < 3.0 g/dL, and this patient was a recipient of degludec. In the subgroup of patients with albumin < 3.5 g/dL, 57 received degludec and 58 received glargine U100. There were three severe hypoglycaemic events reported by three patients in the degludec group, and seven events reported by four patients in the glargine U100 group, giving respective rates per 100 patient-years' exposure of 2.70 and 6.97, respectively.

We also modelled for each insulin, using Cox regression, the proportion of patients predicted to have a first severe hypoglycaemic event within a year of commencing DEVOTE according to baseline serum albumin concentration (Fig. 2). Interestingly, the modelling revealed an apparent inverse relationship between risk and albumin concentration with both insulins; however, the absolute risk was very small, and was lower with degludec than with glargine U100 across the entire range of albumin values available, albeit that confidence intervals widened at very low levels due to decreasing patient numbers. The Kawaguchi study also showed a higher risk of hypoglycaemia in the lower-albumin stratum of patients for both insulins, but it was in this stratum that there was a significant difference between the insulins in 24-h mean glucose levels [1].

We acknowledge that DEVOTE was a comparison involving glargine U100 rather than U300 and that the study only captured data on severe hypoglycaemia. However, while there may be a slight increase in hypoglycaemia risk with decreasing albumin level, the DEVOTE

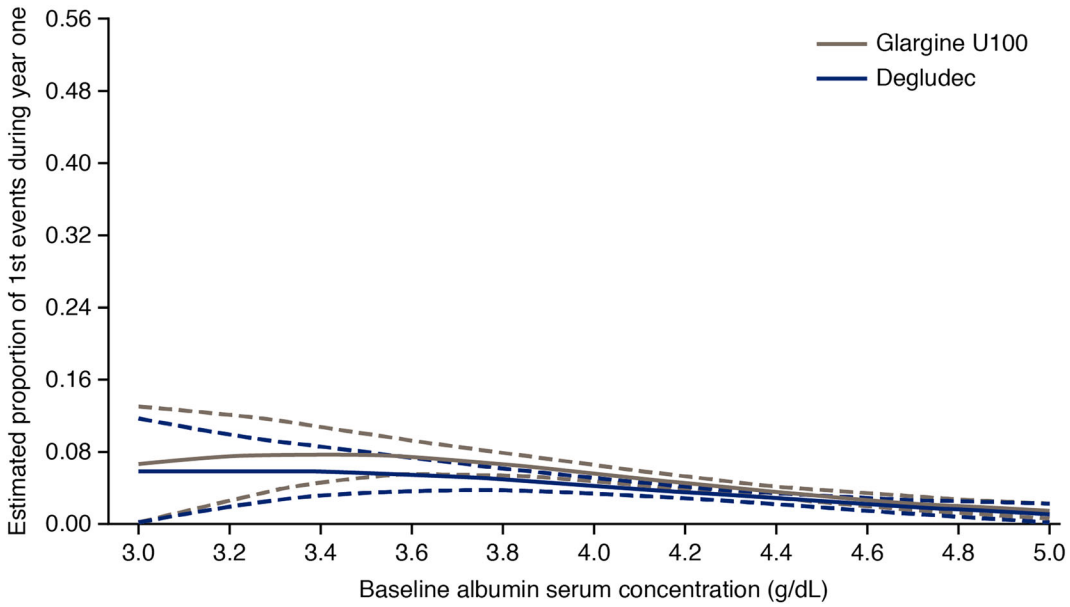

Fig. 2 Modelled proportion of patients having a first severe hypoglycaemic event within a year by baseline serum albumin concentration in the DEVOTE trial. Model is based on a Cox regression including treatment and baseline albumin serum concentration as effect. Dashed lines denote the confidence intervals; solid lines denote the estimates

data do not show an increased relative risk for degludec versus a comparator basal insulin and do not show any albumin-related safety signal concerning degludec.

ACKNOWLEDGEMENTS

Funding. The study was sponsored by Novo Nordisk, and the journal's Rapid Service Fee was funded by Novo Nordisk.

Medical Writing and Editorial Assistance. The authors thanks Yuiko Yamamoto (Novo Nordisk) for her review of and input to the manuscript. Medical writing and editorial support were provided by Murray Edmunds and Clare Lowe of Watermeadow Medical, an Ashfield Company, part of UDG Healthcare plc, funded by Novo Nordisk.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Thomas R. Pieber has received research support (paid to the University) from Novo Nordisk and AstraZeneca, and honoraria from Arecor, AstraZeneca, Boehringer Ingelheim, Convatec, Eli Lilly, Novo Nordisk and Sanofi. Lars Bardtrum is an employee and shareholder of Novo Nordisk. Joakim Isendahl and Lily Wagner are employees of Novo Nordisk. Rimei Nishimura has received honoraria from Sanofi Japan, Japan Medtronic, Boehringer Ingelheim Japan, Takeda, Kissei Pharmaceutical, Novartis Pharma Japan, Eli Lilly Japan, Novo Nordisk Pharma (Japan), MSD and Astellas; and scholarship grants from Boehringer Ingelheim Japan and Japan Diabetes Foundation.

Compliance with Ethics Guidance. This article is based on previously conducted studies that were conducted according to required ethical standards. The commentary concerns a cross-over study that was approved by the ethics committee of Minami Osaka Hospital (no. 2016-6), and was executed in accordance with the Declaration of Helsinki, with all patients providing informed consent before entering this study. Our commentary also presents new data from DEVOTE, which was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines, and had a protocol approved by independent ethics committees or institutional review boards for each centre, with written informed consent obtained from each patient before any trial-related activities.

REFERENCES

1. Kawaguchi Y, Sawa J, Sakuma N, Kumeda Y. Efficacy and safety of insulin glargine 300 U/mL vs insulin degludec in patients with type 2 diabetes: a randomized, open-label, cross-over study using continuous glucose monitoring profiles. J Diabetes Investig. 2019;10:343–51.

2. Kawaguchi Y, Sawa J, Hamai C, Kumeda Y. Differential effect of hypoalbuminemia on hypoglycemia on type 2 diabetes patients treated with insulin glargine 300 U/ml and insulin degludec. Diabetes Ther. 2019;10:1535–41.

3. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care. 2019;42:1593–603.

4. U.S. Food and Drug Administration. Toujeo prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206538lbl.pdf. Accessed 22 Oct 2019.

5. Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes Obes Metab. 2017;19:1032–9.

6. Bailey TS, Pettus J, Roussel R, et al. Morning administration of 0.4U/kg/day insulin glargine 300U/mL provides less fluctuating 24-h pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100U/mL in type 1 diabetes. Diabetes Metab. 2018;44:15–21.

7. Heise T, Hövelmann U, Nosek L, Hermanski L, Bøttcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. Expert Opin Drug Metab Toxicol. 2015;11:1193–201.

8. UNITSLAB.COM. Albumin. http://unitslab.com/node/31. Accessed 22 Oct 2019.

9. Marso SP, McGuire DK, Zinman B, DEVOTE Study Group, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377:723–32.