Impact of kidney function on the safety and efficacy of insulin degludec versus insulin glargine U300 in people with type 2 diabetes: A post hoc analysis of the CONCLUDE trial

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Funding information
Novo Nordisk, Grant/Award Number: n/a

KEYWORDS: insulin analogues, insulin therapy, type 2 diabetes

Chronic kidney disease (CKD) is a common complication of type 2 diabetes (T2D) that, in insulin-treated people can result in decreased insulin clearance and increased risk of hypoglycaemia.1 Severe hypoglycaemia is associated with increased morbidity and mortality, particularly in relation to cardiovascular disease (CVD).2,3 CKD is associated with an increased risk of hypoglycaemic events in people with or without diabetes,1 and also independently increases the risk of CVD and death.4 Careful titration of insulin is therefore required in people with reduced kidney function, to minimize the risk of hypoglycaemia.5 Newer basal insulin analogues, such as insulin degludec 100 units/mL or 200 units/mL (degludec U100 or U200) and insulin glargine 300 units/mL (glargine U300), have more stable and prolonged pharmacokinetic/pharmacodynamic profiles than their first-generation predecessors6,7 resulting in reduced glycaemic variability and allowing for more flexible dosing and reduced risk of hypoglycaemia.8,9

A post hoc analysis of the BRIGHT trial showed a greater difference in reduction of glycated haemoglobin (HbA1c) levels with glargine U300 versus degludec U100 in participants with poor kidney function at baseline (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) than in subgroups with less impaired kidney function.10 The CONCLUDE trial (NCT03078478) investigated the effect of degludec U200 (degludec) and glargine U300 on hypoglycaemia in adults with basal insulin-treated T2D who had at least one risk criterion for hypoglycaemia,11 one of which was...
moderate CKD (eGFR 30–59 mL/min/1.73 m²). Participants with an eGFR lower than 30 mL/min/1.73 m² were excluded. The CONCLUDE study design and methods have previously been reported. In February 2018, a protocol amendment led to a trial extension to a total duration of up to 94 weeks with up to 88 weeks of active treatment, including a maintenance period of 36 weeks. The primary endpoint was not met, with the rate of symptomatic hypoglycaemia not significantly lower with degludec U200 versus glargine U300. Other, exploratory post hoc analyses demonstrated lower rates of nocturnal symptomatic hypoglycaemic events and severe hypoglycaemia during the maintenance period and a significantly greater, but not clinically meaningful, reduction in mean HbA1c from baseline to end of treatment (EOT) with degludec versus glargine U300 (−0.54 [−0.91] vs. −0.46 [−0.90], −0.10 [−0.18; −0.02] vs. −0.10 [−0.18; −0.02]). The mean (± standard deviation [SD]) dose of degludec was also lower than that for glargine U300 at the end of the trial (66.6 ± 48.5 U vs. 73.0 ± 48.5 U).

| Overall symptomatic hypoglycaemia | Degludec (N = 805) | Glargine U300 (N = 804) | Rate ratio [95% CI] | P value for interaction | Favours degludec | Favours glargine U300 |
|----------------------------------|------------------|------------------------|---------------------|------------------------|-----------------|---------------------|
| eGFR subgroup (mL/min/1.73 m²)   |                  |                        |                     |                        |                 |                     |
| 30–60 (n = 282)                 | 305.2            | 276.1                  | 0.89 [0.57; 1.39]   | 0.919                  |                 |                     |
| 60–<90 (n = 623)                | 203.2            | 243.4                  | 0.80 [0.59; 1.09]   |                        |                 |                     |
| ≥90 (n = 578)                   | 183.9            | 230.2                  | 0.80 [0.58; 1.09]   |                        |                 |                     |
| Primary analysis                | 216.8            | 243.9                  | 0.88 [0.73; 1.06]   |                        |                 |                     |

| Nocturnal symptomatic hypoglycaemia | Degludec (N = 805) | Glargine U300 (N = 804) | Rate ratio [95% CI] | P value for interaction | Favours degludec | Favours glargine U300 |
|-----------------------------------|------------------|------------------------|---------------------|------------------------|-----------------|---------------------|
| eGFR subgroup (mL/min/1.73 m²)   |                  |                        |                     |                        |                 |                     |
| 30–60 (n = 282)                 | 50.9             | 93.9                   | 0.44 [0.23; 0.87]   | 0.299                  |                 |                     |
| 60–<90 (n = 623)                | 62.9             | 102.8                  | 0.57 [0.37; 0.89]   |                        |                 |                     |
| ≥90 (n = 578)                   | 67.8             | 83.7                   | 0.81 [0.52; 1.28]   |                        |                 |                     |
| Primary analysis                | 62.3             | 93.8                   | 0.63 [0.48; 0.84]   |                        |                 |                     |

| Severe hypoglycaemia | Degludec (N = 805) | Glargine U300 (N = 804) | Treatment difference [95% CI] | P value for interaction | Favours degludec | Favours glargine U300 |
|----------------------|------------------|------------------------|-------------------------------|------------------------|-----------------|---------------------|
| eGFR subgroup (mL/min/1.73 m²) |                  |                        |                               |                        |                 |                     |
| 30–60 (n = 261)      | −0.49 [0.94]     | −0.36 [0.85]           | −0.05 [−0.23; 0.14]           | 0.842                  |                 |                     |
| 60–<90 (n = 579)     | −0.49 [0.85]     | −0.41 [0.83]           | −0.11 [−0.23; 0.02]           |                        |                 |                     |
| ≥90 (n = 554)        | −0.62 [0.95]     | −0.56 [0.98]           | −0.11 [−0.24; 0.02]           |                        |                 |                     |
| Primary analysis     | −0.54 [0.91]     | −0.46 [0.90]           | −0.10 [−0.18; −0.02]          |                        |                 |                     |

FIGURE 1 Hypoglycaemia endpoints, by baseline estimated glomerular filtration rate (eGFR) subgroup. Overall symptomatic hypoglycaemic events were defined as severe (requiring third-party assistance) or confirmed blood glucose <3.1 mmol/L [with symptoms]. Nocturnal symptomatic hypoglycaemic events were defined as severe or blood-glucose confirmed with symptoms, occurring between 00:01 and 05:59 AM. The number of hypoglycaemic events was analysed using a negative binomial regression model (log link) with the logarithm of the time period in which a hypoglycaemic event was considered treatment emergent as offset. The model included treatment, number of oral antidiabetic drugs, region, gender, dosing time and interaction of kidney function group with treatment as fixed factors, and age as a covariate. Because of a very low number of events, severe hypoglycaemia was analysed using a simplified model. CI, confidence interval; degludec, insulin degludec; glargine U300, insulin glargine 300 units/mL.

FIGURE 2 Change from baseline to end of treatment (EOT) in glycated haemoglobin (HbA1c), by baseline estimated glomerular filtration rate (eGFR) subgroup. Mean change in HbA1c from baseline to EOT was analysed using a mixed model for repeated measures with an unstructured residual covariance matrix. Treatment, number of oral antidiabetic drugs, region, sex, dosing time, and interaction between treatment and eGFR category were included as fixed factors. Age and baseline HbA1c were included as covariates. The model included the interaction between visit number and all explanatory variables. CI, confidence interval; degludec, insulin degludec; glargine U300, insulin glargine 300 units/mL; SD, standard deviation.
As the risk criteria for hypoglycaemia in CONCLUDE included moderate CKD, the study allowed additional analyses on the impact of renal function on the safety and efficacy of degludec versus glargine U300. Therefore, in a post hoc analysis, we assessed mean change in rates of overall symptomatic, nocturnal symptomatic and severe hypoglycaemia during the 36-week maintenance period (during which the data would not be confounded by effective differences in titration of two insulins with different unit potencies). HbA1c from baseline to EOT, and EOT total daily insulin dose, stratified by baseline eGFR (30-60, 60-90 or ≥90 mL/min/1.73 m²).

CONCLUDE randomized 805 participants to degludec and 804 to glargine U300. The eGFR 30 to 60 mL/min/1.73 m², 60 to <90 mL/min/1.73 m² and ≥90 mL/min/1.73 m² subgroups included 174, 325 and 306 participants, respectively, in the degludec treatment arm, and 149, 345 and 310 participants in the glargine U300 treatment arm. Baseline characteristics were generally similar between insulin treatment groups within each of the eGFR subgroups (Table S1). Participants with CKD stage III (eGFR 30-60 mL/min/1.73 m²) tended to be older than those in the other eGFR subgroups, and to have had a longer duration of diabetes.

The rate of overall symptomatic hypoglycaemia increased progressively with declining eGFR in both treatment arms (Figure 1). The hypoglycaemia rate ratios in the eGFR subgroups were comparable with the primary analysis for all hypoglycaemia endpoints assessed, with numerically lower estimated rates of hypoglycaemia observed with degludec compared with glargine U300. No significant treatment-eGFR subgroup heterogeneity was observed for degludec and glargine U300 comparisons for any of the hypoglycaemia endpoints measured (overall symptomatic hypoglycaemia: P interaction = 0.919; nocturnal symptomatic hypoglycaemia: P interaction = 0.299; severe hypoglycaemia: P interaction = 0.957 [Figure 1]).

When comparing HbA1c change from baseline to EOT between the degludec and glargine U300 groups, the treatment difference was similar in the eGFR subgroups (P interaction = 0.842), and comparable to what was seen in the primary analysis: estimated treatment difference –1.07 (95% confidence interval [CI] –1.94, –0.20) mmol/mol (–0.10 [95% CI –0.18, –0.02%]), with a slightly greater, although not clinically significant, decrease in HbA1c with degludec versus glargine U300 (Figure 2). The HbA1c treatment differences for degludec versus glargine U300 were –0.52 (95% CI –2.53, 1.48) mmol/mol (–0.05 [95% CI –0.23, 0.14%]), –1.18 (95% CI –2.52, 0.17) mmol/mol (–0.11 [95% CI –0.23, 0.02%]) and –1.20 (95% CI –2.59, 0.19) mmol/mol (–0.11 [95% CI –0.24, 0.02%]) in the eGFR 30 to 60 mL/min/1.73 m², 60 to <90 mL/min/1.73 m² and ≥90 mL/min/1.73 m² subgroups, respectively.

The mean EOT total daily insulin dose was lower with degludec versus glargine U300 in all three eGFR subgroups, consistent with data reported in the primary analysis (Table S2). The mean (SD) dose ranged from 60.9 (40.6) U to 73.6 (56.5) U with degludec, and from 65.3 (43.3) U to 78.8 (52.5) U with glargine U300; higher doses of both insulins were used in patients in the higher eGFR subgroups. The treatment ratios for mean EOT total daily insulin dose ratios for degludec versus glargine U300 were 0.95 (95% CI 0.80, 1.12); 0.87 (95% CI 0.77, 0.97) and 0.90 (95% CI 0.80, 1.01) in the eGFR 30 to 60 mL/min/1.73 m², 60 to <90 mL/min/1.73 m² and ≥90 mL/min/1.73 m² subgroups, respectively, while the ratio was 0.88 (95% CI 0.83, 0.94) in the primary analysis. No significant interaction was seen between insulin type and eGFR subgroup in terms of the EOT daily insulin dose (interaction P = 0.688).

In this post hoc analysis of CONCLUDE trial data, rate ratios for overall symptomatic hypoglycaemia did not differ significantly between insulin treatments by eGFR subgroup and were consistent with the primary analysis. Further, irrespective of renal function, there was a small but consistent greater reduction in HbA1c from baseline to EOT, and a lower total daily insulin dose with degludec versus glargine U300.

Our findings for change in HbA1c (a similar treatment difference between degludec and glargine U300 across the eGFR subgroups) are in contrast to those of the recently published post hoc analysis of the BRIGHT trial, which suggested a greater reduction in HbA1c from baseline to week 24 in insulin-naïve patients (least squares mean difference –4.7 [95% CI –8.1, –1.4] mmol/mol [–0.43 [95% CI –0.74, –0.12%]) with glargine U300 versus degludec U100 in the lowest eGFR subgroup (<60 mL/min/1.73 m²). However, that result was based on a subgroup of only 47 (10.1%) participants in the glargine U300 arm and 49 (10.6%) participants in the degludec arm meeting the <60 mL/min/1.73 m² criterion. Our CONCLUDE analysis included more than three times the number of participants in the low eGFR 30 to 60 mL/min/1.73 m² subgroups (174 [21.6%] in the degludec arm and 149 [18.5%] in the glargine U300 arm), hence, in the absence of a dedicated trial comparing the two insulin analogues in moderate kidney insufficiency, this analysis may provide more accurate estimates. In addition, of the participants in BRIGHT who were treated with glargine U300, a greater proportion within the low eGFR <60 mL/min/1.73 m² subgroup were on a sulfonylurea medication at baseline (76.6%) than in the other subgroups (59.9% with eGFR 60 to <90 mL/min/1.73 m² and 65.4% with eGFR ≥90 mL/min/1.73 m²). This could have disproportionately impacted end-of-trial HbA1c. In contrast, patients treated with sulfonylureas were excluded from CONCLUDE.

Similarly to our analysis, the incidence of hypoglycaemia was found to increase with decreasing eGFR in the BRIGHT trial, with no heterogeneity by treatment effect observed across eGFR subgroups for the incidence of confirmed hypoglycaemia (<3.0 mmol/L and ≤3.9 mmol/L) over 24 weeks. In addition, similarly to our analysis, mean insulin doses were higher for glargine U300 (range 0.47-0.61 units/kg) compared with degludec (range 0.35-0.44 units/kg) at 24 weeks, irrespective of eGFR subgroup, in the BRIGHT trial.

It is possible that some differences in results between the BRIGHT analysis and the present analysis may be attributable to differences in the patient populations and trial design. BRIGHT (N = 929) was a smaller study than CONCLUDE (N = 1609) with a shorter treatment period (24 weeks, compared with up to 88 weeks in CONCLUDE). The BRIGHT trial included insulin-naïve people with T2D who were at lower risk of hypoglycaemia, whereas CONCLUDE included insulin-experienced individuals with T2D and additional hypoglycaemia risk factors. The mean duration of diabetes within the eGFR subgroups in
BRIGHT was also generally shorter than in CONCLUDE (range 9.3-15.4 years vs. 12.5-18.6 years, respectively). Moreover, the two trials had different titration algorithms, with an FBG target of 4.4 to 5.6 mmol/L in BRIGHT and 4.0 to 5.0 mmol/L in CONCLUDE.

Underlying mechanisms for any hypothetical differential effects of the two insulins based on kidney function are yet to be convincingly elucidated. Low serum albumin concentration has been associated with an increased risk of end-stage kidney disease.16 As degludec, and not glargine U300, is albumin-bound,17 it has been postulated that there could be a greater risk of hypoglycaemia with degludec in low albumin/eGFR conditions. Results from a small-scale crossover study suggested that degludec was associated with a higher risk of hypoglycaemia than glargine U300 in T2D participants with low albumin concentrations.18 However, these data were limited by the short study period, lack of adjustment in starting insulin dose and heterogeneous prior therapies in the study population.19 Of note, neither BRIGHT nor CONCLUDE measured albumin levels. A post hoc analysis of the DEVOTE trial did not indicate an increased relative risk of hypoglycaemia for degludec versus glargine U100 in people with low albumin levels (<3.0 g/dL; n = 12) and did not demonstrate any albumin-related safety signal concerning degludec.19 20 The hypothesis that degludec may have increased risk of hypoglycaemia in low albumin states appears improbable given that, at steady state, this insulin monomer occupies <0.01% of total albumin molecules, and the fraction occupied would remain negligible even in people with hypoalbuminaemia.19 Furthermore, degludec, like any insulin, is individually titrated to the patient’s glycaemic response. Therefore, for the free degludec fraction to increase significantly in an individual, there would need to be extreme acute changes in that person’s albumin concentration.

In summary, this post hoc analysis of CONCLUDE found that rate ratios for hypoglycaemia were consistent with the primary analyses across kidney impairment subgroups. Furthermore, irrespective of kidney function, there was a small but consistent greater reduction in HbA1c from baseline and a lower total daily insulin dose with degludec versus glargine U300. It can therefore be concluded that degludec is a well-tolerated and efficacious treatment option for people with T2D and kidney impairment.

ACKNOWLEDGMENTS
The authors would like to thank the CONCLUDE study participants, investigators and coordinators. Medical writing support and editorial assistance for the development of this manuscript, under the direction of the authors, was provided by Jane Blackburn, PhD, and Beverly La Ferla, MA, MRes, of Ashfield MedComms, an Ashfield Health company, and funded by Novo Nordisk A/S. Novo Nordisk A/S participated in the study design, site selection, study coordination, data management, data analysis and study report preparation for this study. Analysis of the data for this manuscript was also funded by Novo Nordisk.

CONFLICTS OF INTEREST
T.R.P. has received research support from Novo Nordisk, AstraZeneca and Sanofi (paid directly to the Medical University of Graz) and personal fees as a consultant from Adocia, Arecon, AstraZeneca, Eli Lilly, Novo Nordisk and Sanofi. T.R.P. is also the Chief Scientific Officer of CBmed (Centre for Biomarker Research in Medicine), a public-funded biomarker research company. H.S.B. has received speaking honoraria from Eli Lilly and Novo Nordisk, and research funding paid to LMC Healthcare from Amgen, AstraZeneca, Boehringer Ingelheim, Ceaprio, Eli Lilly, Gilead, Janssen, Kowa Pharmaceuticals Co. Ltd, Madrical Pharmaceuticals, Merck, Pfizer, Novo Nordisk, Sanofi, and Tricida. S.R.H. has served on speaker panels for Novo Nordisk, for which he has received remuneration. He has served on advisory panels and as a consultant for Zealand, Novo Nordisk and Eli Lilly, for which his institution has received remuneration. K.K. has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi, and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi, and also acknowledges support from the National Institute for Health Research Applied Research Collaboration– East Midlands (NIHR ARC – EM), and the National Institute of Health Research (NIHR) Leicester Biomedical Research Centre. D.C.K. is a consultant for Eflow, Fractyl, Lifecare, Novo Nordisk, Roche, Samsung and Thirdwayv. L.A.L. has received research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Lexicon, Novo Nordisk and Sanofi, and has been on advisory panels and provided continuing medical education for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Pfizer, Sanofi and Servier. A.P.T. has served on advisory panels for Eli Lilly and Co., Dexcelom, Inc. and Voluntis, provided consultancy services for Novo Nordisk A/S and Sanofi US, and received research support from Merck & Co., Inc., Novo Nordisk A/S, Sanofi US, Eli Lilly and Co., AstraZeneca, Janssen Pharmaceuticals, Inc. and Genentech, Inc. A.P.T. does not receive any direct or indirect payment for these services. S.L., T.J. and L.W. and are full-time employees of, and hold stock in, Novo Nordisk A/S.

AUTHOR CONTRIBUTIONS
Thomas R. Pieber contributed to the initial design of this post hoc analysis and Thomas R. Pieber and Harpreet S. Bajaj contributed to the data collection. All authors contributed to the analysis and interpretation of results, and the drafting and critical review of the manuscript, and all read and approved the final version. Thomas R. Pieber is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14564.

DATA AVAILABILITY STATEMENT
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.
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SUPPORTING INFORMATION
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How to cite this article: Pieber TR, Bajaj HS, Heller SR, et al. Impact of kidney function on the safety and efficacy of insulin degludec versus insulin glargine U300 in people with type 2 diabetes: A post hoc analysis of the CONCLUDE trial. Diabetes Obes Metab. 2022;24(2):332-336. doi:10.1111/dom.14564