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Title	In search of the ideal basal insulin: Does the new-generation ultra-long-acting insulin, degludec, provide the answer?
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In search of the ideal basal insulin: Does the new-generation ultra-long-acting insulin, degludec, provide the answer?

Improving glycemic control without increasing the risk of hypoglycemia has been the main crux of the management of patients with both type 1 and type 2 diabetes mellitus. Nocturnal hypoglycemia and hypoglycemic unawareness has long been a well-recognised contributor to morbidity and mortality in type 1 diabetes. Hypoglycemia becomes a progressively frequent clinical problem as patients approach the insulin deficient end of the spectrum in advanced type 2 diabetes. Recent multicenter studies on the benefits of intensive glycemic control, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[1] studies, showed that hypoglycemia was an independent predictor of mortality and an increased risk of adverse clinical outcomes in patients with type 2 diabetes.

The challenges of new subcutaneous insulin therapies to achieve normoglycemia would be to reduce the incidence of iatrogenic hypoglycemia, minimize excessive weight gain and maintain a good long-term safety profile, as recent suggestions that insulin might promote cancers, though not proven, have raised concerns regarding the safety of exogenous insulin use.

In *The Lancet*, two phase 3, open-label, treat-to-target, non-inferiority studies examined the use of a new ultra-long-acting basal insulin, degludec, as part of a basal–bolus insulin regimen, in the treatment of patients with type 1[2]

and type 2[3] diabetes. Insulin degludec, on subcutaneous injection, forms a depot of soluble multihexamers from which monomers are slowly and continuously absorbed into the circulation by attachment to albumin, giving a long duration of action of more than 40 h. Pharmacokinetic data showed a flat and stable profile at steady state and a terminal half-life of more than 25 h, which is five times longer than that of insulin detemir (5–7 h) and twice that of insulin glargine (13 h).

The BEGIN Basal–Bolus Type 1[2] and Type 2[3] trials confirmed non-inferiority of insulin degludec to insulin glargine in efficacy and safety. In type 1 diabetes, glycated hemoglobin (HbA_{1c}) had fallen by 0.40% points in both degludec and glargine at 1 year (estimated treatment difference −0.01, 95% confidence interval [CI] −0.14 to 0.11). A total of 188 (40%) and 67 (43%) participants achieved a target HbA_{1c} of less than 7% (<53 mmols/mol) from mean baseline values of 7.7 ± 1.0% standard deviation (60.7 ± 11.0 mmols/mol). A 3:1 randomization ratio was used to ensure adequate exposure to degludec, as required by regulatory guidelines. In type 2 diabetes, the primary end-point of HbA_{1c} reduction at 1 year was 1.1% with degludec and 1.2% with glargine (estimated treatment difference 0.08, 95% CI −0.05 to 0.21). The mean reductions in laboratory-reported fasting plasma glucose and the nine-point self-measured plasma glucose were also similar between treatments, providing further support of non-inferiority.

The rates of overall confirmed hypoglycemia (plasma glucose <3.1 mmol/L or severe episodes requiring assistance) were significantly lower with degludec than glargine in type 2 diabetes, as were the rates of nocturnal confirmed

hypoglycemia in both type 1 and type 2 diabetes (Table 1).

The lower rates of nocturnal hypoglycemia can be explained by an evenly-distributed exposure (approximately 50:50) to degludec in the first and second 12-h period after once-daily administration. In contrast, 60% of exposure to glargine occurs in the first 12 h, which can lead to more nocturnal hypoglycemia after bedtime dosing compared with morning administration. The timing of insulin glargine dosing was not recorded in both studies, which might have affected the estimated risk of nocturnal hypoglycemia. However, the authors[3] dismissed the timing effect, as the administration of glargine was adherent to its product labelling (any time, but the same time each day at the investigator's discretion). A second explanation for the lower hypoglycemic rates in these trials lies in the variability of insulin absorption from subcutaneous tissue. Subcutaneous administration of currently available exogenous insulin does not always result in a uniformly reproducible metabolic effect, even when injected at the same dose under comparable conditions. Insulin degludec has a significantly more predictable glucose-lowering effect than glargine, with a four-times less day-to-day variability compared with glargine at steady state (using euglycemic glucose clamps) in type 1 diabetes[4]. It remains to be seen if this translates into clinical benefit and whether the lowered variability extends to patients with type 2 diabetes.

In both trials, nocturnal hypoglycemia only contributed to 10–15% of all confirmed hypoglycemic events. Most of the hypoglycemic episodes occurred during daytime hours, probably attributed to the bolus mealtime insulin aspart. Furthermore, there was no uniform dose

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Table 1 | Hypoglycemic rates per patient-year of exposure in the insulin degludec and insulin glargine groups

	Type 1 diabetes				P-value	Type 2 diabetes				P-value
	Insulin degludec (n = 472)		Insulin glargine (n = 154)			Insulin degludec (n = 753)		Insulin glargine (n = 251)		
	Participants (%)	Rate per PYE	Participants (%)	Rate per PYE		Participants (%)	Rate per PYE	Participants (%)	Rate per PYE	
Severe hypo	58 (12)	0.21	16 (10)	0.16	0.34	34 (5)	0.06	11 (4)	0.05	*
Overall hypo	451 (96)	42.54	147 (95)	40.18	0.48	609 (81)	11.09	206 (82)	13.63	0.0359
Nocturnal hypo	341 (72)	4.41	114 (74)	5.86	0.021	298 (40)	1.39	119 (47)	1.84	0.0399

Data are n (%). Adapted from Heller et al.[2] and Garber et al.[3]. *Insufficient episodes for statistical assessment. Hypo, hypoglycemia; PYE, patient-year of exposure.

titration algorithm for the bolus insulin aspart, as it did for the basal insulins degludec and glargine. The open-label design also contributes to the risk of reporting bias, which might affect the subjective outcomes, such as symptomatic hypoglycemia and quality of life. Greater caution might also be preferentially given to the dose adjustment of the new drug, degludec. However, full masking of treatments was not achievable because of differences in the delivery devices.

One of the common patient barriers to insulin intensification is weight gain. The present studies showed similar mean weight gain in both treatment groups in patients with type 1 diabetes (1.8 kg [standard error 0.2] with degludec and 1.6 kg [0.3] with glargine, P = 0.62); and with type 2 diabetes (3.6 kg [standard deviation 4.9] with degludec and 4.0 [4.6] with glargine). The weight gain in patients with type 2 diabetes might be partly ascribed to the increase in total daily insulin doses, including both basal and bolus insulins, throughout the trial. However, total daily insulin doses decreased in those with type 1 diabetes, suggesting other contributing factors to the weight gain. Insulin-related weight gain might result from a conservation of ingested calories as improved glycemic control returns patients to glycemic levels that are below the renal threshold. Furthermore, insulin exerts an anabolic effect by inhibiting muscle protein breakdown and free fatty acid metabolism, inhibiting

lipolysis and promoting lipogenesis. The defensive increase in caloric intake because of the fear of or avoidance of genuine hypoglycemia might also contribute to insulin-related weight gain.

Can insulin degludec become the ideal basal insulin? The answer will depend on its long-term efficacy and safety profile. In both trials, the adverse event rates did not differ between insulin degludec and glargine. Most adverse events were mild or moderate. The rate of injection site reactions was low (3–5%) in both treatment groups. A low insulin-like growth factor-1 receptor binding affinity and low mitogenic activity of insulin degludec *in vitro* suggested a molecular safety similar to that of human insulin.

Four major adverse cardiovascular events were reported in the type 1 diabetes trial[2], of which three were fatal. One sudden death was attributed to the treatment of insulin glargine and aspart, whereas two reported fatal myocardial infarctions in the degludec group were deemed to be causally unrelated to treatment. Nonetheless, hypoglycemia-induced prolonged QT interval is a potential risk factor for sudden death in diabetes and should not be overlooked.

Insulin degludec is the first basal analog insulin that can be co-formulated with the prandial analog insulin aspart[5]. The novel premixed insulin (IDegAsp: 70% degludec and 30% aspart) confers a similar reduction in HbA_{1c} and hypoglycemic risk compared with insulin glargine, with the additional advantage of

targeting the fasting and postprandial glucose increase simultaneously. IDegAsp would be a promising treatment option for initiating insulin therapy in patients with type 2 diabetes inadequately controlled with oral antidiabetic agents.

In summary, the results of two phase 3 basal–bolus studies in patients with long-standing type 1 and type 2 diabetes showed that insulin degludec achieved glycemic control that was similar to insulin glargine, with reduced nocturnal hypoglycemia in both type 1 and type 2 diabetes, in addition to a reduction in overall hypoglycemia in type 2 diabetes. The long-acting and flat profile of insulin degludec potentially offers a more physiological insulin response akin to the basal secretory pattern of endogenous β-cells, thus potentially providing an improved basal insulin in the management of type 1 and type 2 diabetes.

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