Management of type 1 diabetes

Insulin degludec: A significant advance?

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I have long argued that we set people with type 1 diabetes impossible goals to achieve using very inadequate tools. Whilst affordable, closed-loop insulin-delivery systems (integrated pumps with sensors) that automatically adjust insulin infusion rates according to blood glucose level are the holy grail, their time has not yet come. Until then, the hunt goes on for the perfect background insulin. Through the years, many "peakless" long-acting insulins have been brought to market, only for the promise to lead to disappointment. Although the analogues, insulin detemir (Levemir®; Novo Nordisk) and insulin glargine (Lantus®; Sanofi-Aventis), have demonstrably flatter profiles than the human isophanes, the benefits in the real world have been less impressive than expected (Monami et al, 2008; 2009). Nevertheless, a reduction in nocturnal hypoglycaemia has been a consistent finding in both type 1 and type 2 diabetes.

Insulin degludec (Tresiba®; Novo Nordisk) is an altogether novel basal insulin with an ultra-long, flat and stable action profile. Upon subcutaneous injection, degludec forms soluble multihexamers that slowly and steadily dissociate and release insulin monomers into the circulation. This results in a stable and consistent glucose-lowering effect for >42 hours at steady state and lower rates of hypoglycaemia compared with insulin glargine (Bode et al, 2013).

In the 26-week, open-label study by Davies and colleagues (summarised alongside), insulin degludec was compared to insulin detemir in people with type 1 diabetes. Insulin doses were titrated individually once per week to a blood glucose level of 3.9–4.9 mmol/L using a titration algorithm. As would be expected in a treat-to-target study, the two insulins resulted in similar reductions in HbA_{1c}, although the reduction in fasting plasma glucose level was significantly greater with degludec than with detemir. Despite this, there was a significant 34% reduction in the rate of nocturnal hypoglycaemia with degludec.

So is insulin degludec a significant advance? I think so. For people with type 1 diabetes wanting to achieve tight glycaemic control, degludec probably represents the most predictable basal insulin on the market. However, there are unanswered questions about its use in exercise or in people with hypoglycaemic unawareness. ■

Bode BW, Buse JB, Fisher M et al (2013) Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(®) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. *Diabet Med* **30**: 1293–7

Monami M, Marchionni N, Mannucci E (2008) Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* **81**: 184–9

Monami M, Marchionni N, Mannucci E (2009) Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. *Diabetes Obes Metab* **11**: 372–8

Diabetes Obes Metab

Insulin degludec for T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this multinational, 26-week, open-label, phase IIIa trial, the efficacy and safety of insulin degludec was compared with insulin detemir, both administered in conjunction with meal-time rapid-acting insulin aspart.

2 Adults with T1D were randomised in a 2:1 ratio to receive degludec (n=301) or detemir (n=152).

3 The primary end-point, mean change in HbA_{1c} level, was similar in the two groups (0.73% [8.0 mmol/mol] vs 0.65% [7.1 mmol/mol]), although fasting plasma glucose levels were lower in the degludec group.

4 The rates of confirmed and severe hypoglycaemia were similar between the two groups; however, degludec resulted in a 34% reduction in the rate of nocturnal hypoglycaemia compared with detemir (P=0.005).

5 There were slight increases in body weight in both groups, but degludec was associated with a greater increase.

6 The rate of adverse events was similar in the two groups, the most common events being nasopharyngitis, headache and hypoglycaemia, and the majority being mild or moderate.

7 The authors conclude that, notwithstanding the limitations of the open-label design, these results show that insulin degludec was non-inferior to insulin detemir. The lower rate of nocturnal hypoglycaemia observed with degludec could be a result of the agent's longer duration of action and lower pharmacodynamic variability.

Davies MJ, Gross JL, Ono Y et al (2014) Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes Metab* **16**: 922–30

Diabetes Care

Improving awareness of hypoglycaemia in long-standing T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The aim of this 24-week study was to determine whether impaired awareness of hypoglycaemia (IAH) could be improved through rigorous prevention of biochemical hypoglycaemia without reducing overall glycaemic control.

2 In a 2×2 factorial design, 96 people with long-standing T1D and IAH were randomised to one of four groups: multiple daily injections (MDI) with self-monitoring of blood glucose (SMBG), MDI with SMBG and real-time continous glucose monitoring (RT-CGM), continuous subcutaneous insulin infusion (CSII) with SMBG, or CSII with SMBG and RT-CGM. Crucially, all participants received comparable education, support and congruent therapeutic targets.

3 In all groups, biochemical hypoglycaemia was significantly reduced, and the annualised rate of severe hypoglycaemia decreased more than ten-fold; however, overall glycaemic control did not worsen.

4 Multivariate analysis revealed no significant difference in hypoglycaemia awareness between MDI and CSII, or between SMBG alone and SMBG plus RT-CGM. The only noteworthy difference was that patients in the CSII groups reported higher treatment satisfaction than those in the MDI groups.

5 A follow-up study to determine the 2-year benefits of these regimens following return to routine clinical care is in progress.

Little SA, Leelarathna L, Walkinshaw E et al (2014) Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care* **37**: 2114–22

Diabetologia

Systolic and diastolic dysfunction in T1D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 The prevalence of subclinical systolic and diastolic dysfunction in people with T1D was investigated.

2 A total of 1093 people with T1D and without known heart disease (mean age, 49.6 years; 53% male) were evaluated.

3 Overall, 169 participants (15.5%) had abnormal systolic or diastolic function.

4 In the multivariate model, age (odds ratio [OR] for each 10-year increase, 2.1), female gender (OR, 1.9) and macroalbuminuria (OR, 5.2) were associated with abnormal myocardial function.

5 Subclinical myocardial dysfunction is common in T1D, and people with macroalbuminuria should undergo echocardiographical screening.

Jensen MT, Sogaard P, Andersen HU et al (2014) Prevalence of systolic and diastolic dysfunction in patients with type 1 diabetes without known heart disease: the Thousand & 1 Study. *Diabetologia* **57**: 672–80

Diabet Med

DAFNE education leads to reductions in diabetic ketoacidosis

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 The DAFNE (Dose Adjustment For Normal Eating) education programme, originally designed to improve blood glucose control, has now been delivered to >28 000 adults with T1D in the UK.

2 These authors evaluated the effect of DAFNE training on the incidence of diabetic ketoacidosis in 939 people with T1D.

3 In the 12 months after DAFNE training, the relative risk of ketoacidosis was 0.39 compared with the 12 months before the programme.

4 The number of patients requiring hospital admission with hypoglycaemia, paramedic assistance, or A&E attendance also decreased, and there was a 64% reduction in costs for emergency treatment.

Elliott J, Jacques RM, Kruger J et al (2014) Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with type 1 diabetes. *Diabet Med* **31**: 847–53

Diabet Med

Residual C-peptide response in people with long-standing T1D

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 In this small pilot study, the authors administered mixed-meal tolerance tests in a small subset (n=58) of the DCCT (Diabetes Control and Complications Trial) in order to determine whether a C-peptide response (an indicator of beta-cell activity) could be detected even after a diabetes duration of almost 30 years.

2 Overall, 17% had a post-meal C-peptide level of >0.03 nmol/L.

3 A stimulated C-peptide response can be detected in a small proportion of people with long-term T1D. While the prevalence of this response will probably be lower in the general T1D population, these results warrant investigation in the whole DCCT cohort to examine the clinical relevance of this spared beta-cell activity.

McGee P, Steffes M, Nowicki M et al (2014) Insulin secretion measured by stimulated C-peptide in long-established type 1 diabetes in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort: a pilot study. *Diabet Med* 16 May [Epub ahead of print]

> *"Subclinical myocardial dysfunction is common in type 1 diabetes, and people with macroalbuminuria should undergo echocardiographical screening."*