A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs

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**Objective** To determine whether glargine was non-inferior to detemir regarding the percentage of patients reaching HbA1c <7% without symptomatic hypoglycemia ≤3.1 mmol/l.

**Research Design and Methods** In this 24-week trial, 973 insulin-naive type 2 diabetic patients on stable OGLDs and HbA1c 7.0-10.5% were randomized to glargine once-daily or detemir twice-daily. Insulin doses were systematically titrated.

**Results** 27.5 and 25.6% of patients reached the primary outcome with glargine and detemir, demonstrating non-inferiority of glargine. Improvements in HbA1c were -1.46±1.09% for glargine and -1.54±1.11% for detemir (P=0.149), with similar proportions of patients achieving HbA1c <7% (P=0.254), but more detemir-treated patients reaching HbA1c <6.5% (P=0.017). Hypoglycemia risk was similar. Weight gain was higher for glargine (difference: 0.77 kg, P<0.001). Glargine doses were lower than detemir doses: 43.5±29.0 versus 76.5±50.5 units/day (P<0.001).

**Conclusions** In insulin-naive type 2 diabetic patients, glargine reached similar control as detemir, with more weight gain, but requiring significantly lower doses.
The ‘treat-to-target’ clinical trials have demonstrated that the addition of systematically titrated basal insulin to existing oral therapy results in adequate glycemic control in the majority of patients with type 2 diabetes (1-3). The basal insulin analogues, insulin glargine and insulin detemir, achieve this with a reduced risk of hypoglycemia compared to the conventional NPH insulin (1,2). The aim of this study was to compare the efficacy, safety, and the effect on quality of life of once-daily glargine and twice-daily detemir in insulin-naive patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs (OGLDs), including metformin. The primary objective was to determine whether glargine was non-inferior to detemir regarding the percentage of patients reaching HbA1c <7% without symptomatic hypoglycemia with plasma glucose (PG) ≤3.1 mmol/l.

**RESEARCH DESIGN AND METHODS**

The rationale for dosing detemir twice-daily and the study methods have been detailed before (4). In brief, this multinational, open-label trial randomized insulin-naive type 2 diabetic subjects, treated for ≥3 months with stable OGLDs (including metformin ≥1 g/day) and with HbA1c of 7.0-10.5%, to 24-week treatment with glargine in the evening or detemir at breakfast and dinner. Glargine doses were increased every 2 days by 2 units until fasting PG <5.6 mmol/l, while the systematic titration of detemir involved three steps to obtain both fasting and pre-dinner PG <5.6 mmol/l (4).

The primary outcome was the percentage of patients reaching HbA1c <7% without symptomatic hypoglycemia ≤3.1 mmol/l. Secondary outcomes included proportions of patients achieving HbA1c <7% and <6.5%, hypoglycemia, weight, insulin doses, and quality of life (5-8).

Non-inferiority of glargine to detemir was accepted if the lower limit of the 2-sided 95% CI for the difference in the proportions of patients reaching the primary outcome was ≥-30% of the percentage of detemir-treated patients achieving this outcome (4).

**RESULTS**

Of 1230 patients screened, 973 were randomized, and 478 treated with glargine and 486 with detemir. More patients on glargine than on detemir completed the study (95.4 and 89.9%, respectively, \textit{P}=0.001). The main reason for study discontinuation was an adverse event: 7 patients on glargine (1 possibly related to study drug) and 22 on detemir (20 possibly related) dropped-out for this reason (\textit{P}=0.005) (Online Fig. A which is available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org)). Online Table A shows the population’s baseline characteristics. Of 865 patients using insulin secretagogues at study entry, 42.4% stopped these at randomization (43.5 and 41.4% in the glargine and detemir group).

In the glargine and detemir group, 27.5 and 25.6% of patients reached HbA1c <7% without symptomatic hypoglycemia ≤3.1 mmol/l (difference: 1.85% [95% CI: -3.78–7.48%]), demonstrating non-inferiority of glargine to detemir (non-inferiority margin: -7.68%).

**Secondary outcomes.** Fig. 1A illustrates that the mean improvements in HbA1c were similar: -1.46±1.09% for glargine and -1.54±1.11% for detemir (\textit{P}=0.149). The proportions of patients achieving HbA1c <7% were also similar (44.1 and 47.8%, \textit{P}=0.254), but significantly fewer glargine- than detemir-treated patients reached HbA1c <6.5% (16.5 and 22.7%, respectively, \textit{P}=0.017). The 8-point PG profiles at baseline and end-of-study show that while the decrease in fasting PG was significantly greater for glargine (\textit{P}<0.001), detemir resulted in significantly larger reductions in PG before and after
lunch, before and after dinner, and at bedtime (all $P<0.001$) (Online Fig. B).

Risk of hypoglycemia was comparable between treatments with ~30% of patients experiencing symptomatic hypoglycemia $\leq 3.1\text{mmol/l}$ in either group (Online Table B). Weight gain was significantly higher with glargine versus detemir: $1.4\pm 3.2$ and $0.6\pm 2.9$ kg ($P<0.001$). Insulin doses, however, were significantly lower for glargine: $43.5\pm 29.0$ versus $76.5\pm 50.5$ units/day ($P<0.001$) (Fig. 1B). Quality of life improved during the study with no differences between groups, except for a discrepancy in treatment satisfaction in favor of glargine (Online Table C).

**CONCLUSIONS**

This ‘treat-to-target’ comparison between glargine and detemir in insulin-naive patients with type 2 diabetes demonstrated that glargine and detemir result in similar improvements in HbA1c and similar risk of hypoglycemia. In addition, our study confirms the higher weight gain, lower daily insulin doses, and fewer drop-outs (because of adverse events) for glargine versus detemir, found in the previous comparison of the two basal analogues in this patient group (3). Finally, our findings suggest that initiating glargine or detemir in patients not achieving adequate control on OGLDs positively affects quality of life.

Our study indicates that higher detemir doses may be needed to obtain the same level of glycemic control as with other basal insulins. This difference has been attributed to the twice-daily dosing of detemir (9), but NPH dosed twice-daily does not lead to dose escalation (1). Moreover, trial data suggest that, although insulin doses are indeed higher in patients using detemir twice-versus once-daily, once-daily detemir doses are still higher than once-daily NPH and glargine doses (3,10,11). At present there is no clear explanation for the increased dose requirements for detemir (12).

A limitation of our study was its open-label design. This design was necessary, however, as detemir was dosed twice-daily with a separate titration target before dinner. As explained elsewhere (4), we deliberately chose to dose detemir twice-daily. Trial data available at the time of the current study’s design suggested that twice-daily detemir reached superior HbA1c compared with once-daily dosing (1,13). The difference in dosing schedule for the two insulins does, however, affect the interpretation of some of our findings. Advantages of glargine over detemir, such as the greater increase in treatment satisfaction, may be explained by its once-daily dosing and less complex titration. Also, since the design of our study, the current recommendation has become to initiate detemir once-daily (based on a more recent once-daily detemir versus NPH trial showing non-inferior HbA1c reductions for detemir (11)). Thus, with advancing knowledge, it is now clear that another ‘treat-to-target’ trial comparing both basal analogues using an identical, once-daily dosing regimen is desirable.

In conclusion, we demonstrated that in insulin-naive patients with type 2 diabetes glargine once-daily is non-inferior to detemir twice-daily regarding the percentage of patients reaching target HbA1c without hypoglycemia. Detemir-treated patients had less weight gain and more often achieved HbA1c $<6.5\%$, but the drop-out rate and daily insulin doses were lower in the glargine group.

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Figure

A

B

Glargine versus detemir in type 2 diabetes