

# A 26-Week, Randomized, Parallel, Treat-to-Target Trial Comparing Insulin Detemir With NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin-Naïve People With Type 2 Diabetes

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ON BEHALF OF THE LEVEMIR TREAT-TO-TARGET STUDY GROUP

**OBJECTIVE** — To assess efficacy and tolerability of insulin detemir or NPH insulin added to oral therapy for type 2 diabetes in a treat-to-target titration protocol.

**RESEARCH DESIGN AND METHODS** — Individuals ( $n = 476$ ) with HbA<sub>1c</sub> (A1C) 7.5–10.0% were randomized to addition of twice-daily insulin detemir or NPH insulin in a parallel-group, multicenter trial. Over 24 weeks, insulin doses were titrated toward prebreakfast and predinner plasma glucose targets of  $\leq 6.0$  mmol/l ( $\leq 108$  mg/dl). Outcomes assessed included A1C, percentage achieving A1C  $\leq 7.0\%$ , risk of hypoglycemia, and body weight.

**RESULTS** — At 24 weeks, A1C had decreased by 1.8 and 1.9% (from 8.6 to 6.8 and from 8.5 to 6.6%) for detemir and NPH, respectively (NS). In both groups, 70% of participants achieved an A1C  $\leq 7.0\%$ , but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26 vs. 16%,  $P = 0.008$ ). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% ( $P < 0.001$ ) and nocturnal hypoglycemia by 55% ( $P < 0.001$ ). Mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin ( $P < 0.001$ ), and the difference in baseline-adjusted final weight was  $-1.58$  ( $P < 0.001$ ).

**CONCLUSIONS** — Addition of basal insulin to oral drug therapy in people with suboptimal control of type 2 diabetes achieves guideline-recommended A1C values in most people with aggressive titration. Insulin detemir compared with NPH insulin achieves this with reduced hypoglycemia and less weight gain.

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Improved glycemic control reduces incidence and delays progression of complications in type 2 diabetes (1–4). Treatment guidelines generally advocate HbA<sub>1c</sub> (A1C) targets of 6.5% (5), but clin-

ical audits/studies suggest that many have difficulty achieving and maintaining such goals (6–8). An important contributory factor is a resistance to initiate insulin on the part of people with diabetes and care-

givers. Insulin is usually added only after oral glucose-lowering drugs (OGLDs) fail to curtail hyperglycemia over extended periods, often when A1C exceeds 9.0% (9).

Delays in insulin initiation arise from fear of injections, psychological issues such as nonacceptance of treatment failure, and concerns about hypoglycemia and weight gain (10–12). However, blood glucose control is improved by introduction of insulin therapy (13). Insulin analogs have favorably shifted the achievable balance between glucose control and tolerability. In a recent study in which insulin glargine or NPH insulin was added to OGLDs with intensive titration, mean A1C was reduced from  $\sim 8.6\%$  to just under 7.0% during 24 weeks, with 60% of patients achieving A1C  $< 7.0\%$  (14). The analog recipients benefited from reduced hypoglycemia, but there was no between-treatment difference in weight gain.

The present study used a similar treat-to-target design. Insulin detemir is an acylated insulin analog achieving extended action through self-association and reversible albumin binding (15). This and its solubility underpin a greater within-patient consistency in glucose-lowering time-action profile compared with other basal insulins (16,17). In clinical comparisons with NPH insulin in meal + time + basal therapy, insulin detemir was repeatedly associated with a reduced risk for nocturnal hypoglycemia (18–23) and with less or absent weight gain (18–25) at equivalent glycemic control.

These findings suggest that insulin detemir could be successfully added to OGLDs in people with inadequately controlled type 2 diabetes. We tested this hypothesis using active dose titration and glucose monitoring to determine the proportion of participants who could safely reach glycemic targets.

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**Abbreviations:** FPG, fasting plasma glucose; ITT, intention-to-treat; OGLD, oral glucose-lowering drug.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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## RESEARCH DESIGN AND METHODS

In this parallel-group trial, 475 insulin-naïve people with type 2 diabetes were randomized and treated (with informed consent) to twice-daily subcutaneous insulin detemir (Levemir; Novo Nordisk, Bagsvaerd, Denmark) or human NPH insulin (Insulatard; Novo Nordisk) added to current OGLD therapy (metformin, insulin secretagogues, and  $\alpha$ -glucosidase inhibitors). The study (carried out between March 2003 and January 2004) was conducted in accordance with the Declaration of Helsinki, Good Clinical Research Practice, and local regulatory ethics approval in 58 centers from 10 European countries. Individual investigators are listed in the online appendix (available at <http://care.diabetesjournals.org>). Participants were recruited at investigational sites or referred from general practitioners with randomization carried out via a telephone system.

Participants were required to be aged  $\geq 18$  years, have a BMI  $\leq 35$  kg/m<sup>2</sup>, an A1C of 7.5–10.0%, and type 2 diabetes for at least 12 months. The definition of inadequate control required at least 4 months' treatment with one or two OGLDs at doses at least half the recommended maximum or highest tolerated.

People using thiazolidinediones were excluded due to licensing restrictions. Other exclusion criteria included secondary diabetes, maturity-onset diabetes of the young, proliferative retinopathy/maculopathy requiring treatment, hypoglycemia unawareness or recurrent major hypoglycemia, use of drugs likely to affect glycemia, impaired hepatic (alanine aminotransferase more than twice the upper local reference limit) or renal function (serum creatinine  $\geq 150$   $\mu$ mol/l [1.7 mg/dl]), significant cardiovascular disease, pregnancy, and breast-feeding.

### Insulin dose titration

Dose titration lasted 24 weeks, during which OGLD doses remained unchanged. An open-label protocol was used because insulin detemir is a clear solution and NPH insulin a cloudy suspension. Insulin was used twice daily throughout: before breakfast and in the evening (within 1 h before dinner until bedtime) via a pen injector (NovoPen 3; Novo Nordisk). Participants were advised to keep evening injection time constant and to inject in the subcutaneous tissue of the thigh or abdomen.

Based on self-measured plasma glucose levels (average records from 3 con-

Table 1—Summary of insulin titration algorithm used for both insulins

Criteria for titration	Insulin dose adjustment (units or IU)	
	Responders	Nonresponders
If average prebreakfast/predinner plasma glucose:		
>10.0 mmol/l (>180 mg/dl)	+10	+10
9.1–10.0 mmol/l (163–180 mg/dl)	+6	+8
8.1–9.0 mmol/l (145–162 mg/dl)	+4	+6
7.1–8.0 mmol/l (127–144 mg/dl)	+2	+4
6.1–7.0 mmol/l (109–126 mg/dl)	+2	+2
If one prebreakfast plasma glucose:		
3.1–4.0 mmol/l (56–72 mg/dl)		–2
<3.1 mmol/l (<56 mg/dl)		–4

Plasma glucose categories are based on the average of three consecutive self-measurements immediately preceding each contact. Responders: people in whom the average plasma glucose value was reduced to a lower category following the previous adjustment. Nonresponders: people in whom the average plasma glucose value remained in the same category or increased following the last adjustment.

secutive days), insulin doses were titrated throughout the trial, aiming at prebreakfast and predinner concentrations of  $\leq 6.0$  mmol/l ( $\leq 108$  mg/dl). Starting doses were 10 units/IU per injection. If initial prebreakfast or predinner plasma glucose was  $<7.0$  mmol/l (126 mg/dl) or BMI was  $<26.0$  kg/m<sup>2</sup>, starting doses were reduced to 6 units/IU. Thereafter, doses were titrated individually using an algorithm (Table 1) by clinic or telephone contacts made at least weekly for 12 weeks and then at least fortnightly thereafter.

Participants measured capillary blood glucose (plasma calibrated) with a Precision Xtra meter (Medisense; Abbott Laboratories, Abbott Park, IL) and were advised to make additional measurements whenever hypoglycemia was suspected.

### End points

The primary end point was A1C. Other efficacy end points included laboratory-measured fasting plasma glucose (FPG), proportion of participants achieving A1C  $\leq 7.0\%$ , proportion achieving this without hypoglycemia ("responders," with hypoglycemia defined as symptomatic episodes confirmed by a plasma glucose value  $<4.0$  mmol/l [ $<72$  mg/dl] or any single plasma glucose value  $<3.1$  mmol/l [ $<56$  mg/dl] in the last 12 weeks of treatment), within-participant variation in self-measured prebreakfast and predinner plasma glucose, and self-measured 10-point plasma glucose profile.

A1C was measured in a central laboratory by ion-exchange high-performance liquid chromatography on a Bio-Rad Diamat (Munich, Germany), reference range 4.3–6.1%. FPG was measured centrally using the Gluco-quant system (Roche, Mannheim, Germany).

Hypoglycemia was classified for all analyses other than the responder analysis as major (third-party assistance required), minor (self-managed, plasma glucose confirmed  $\leq 3.0$  mmol/l), symptoms only (self-managed but without a plasma glucose measurement or with a level  $\geq 3.1$  mmol/l), and nocturnal (2300–0600). Body weight was measured using calibrated scales.

Safety assessments included adverse events, standard laboratory analyses, and physical examination. Laboratory analyses were performed at Laboratorium für Klinische Forschung (Raisdorf, Germany).

### Statistical analyses

A noninferiority criterion, defined as a  $<0.4\%$  difference in A1C, was calculated to require 198 completers per arm for 95% power with a 5% significance level and with a maximum baseline-adjusted SD of 1.1%.

Statistical analyses of efficacy and safety presented were based on the intention-to-treat (ITT) population (all randomized and treated participants). A per-protocol analysis was also performed for the noninferiority criterion of the primary end point. The result was very similar to the ITT analysis, so data are not given. Analyses of A1C and FPG were based on the last observation carried forward for patients completing at least 12 weeks. A1C and FPG after 24 weeks were analyzed by baseline-adjusted ANOVA with treatment, country, and OGLD therapy as fixed effects. The percentage of patients achieving A1C  $\leq 7.0\%$  with/without hypoglycemia was analyzed using Fisher's exact test. Within-subject variation in prebreakfast and predinner plasma glucose and 10-point plasma glu-

cose profiles were analyzed by ANOVA with treatment, country, OGLD therapy, day or time, and treatment by day or time interaction as fixed effects and participant as random effect.

Analyses of hypoglycemia were based on all registered events in the ITT cohort unless otherwise stated. Incidence of hypoglycemia was evaluated by relative risk. Hypoglycemic episodes were analyzed as recurrent events in a Cox regression analysis (with treatment and OGLD therapy as covariates) using a  $\gamma$ -frailty model. Explorative analyses of hypoglycemia were performed adjusting for A1C. To evaluate the relative risk of hypoglycemia by end point A1C, hypoglycemia rate was modeled using a negative-binomial distribution with a log-link function, using hypoglycemic events in the last 12 weeks of study.

Body weight at the end of the study (and the change in body weight) was compared by baseline-adjusted ANOVA including treatment group, country, and OGLD therapy as fixed effects. A similar exploratory analysis of change in body weight was performed with change in A1C as a covariate, and regression analyses were performed for change in weight as a function of baseline BMI.

Treatment-emergent adverse events, laboratory measurements, and vital signs were compared using descriptive statistics. All analyses were performed using SAS version 8.0 (Cary, NC) on a UNIX platform except for the  $\gamma$ -frailty model on hypoglycemic episodes, which was performed using S-plus 2000 (MathSoft, Seattle, WA). The study database was validated and locked before data analysis commenced. Patient numbers are given throughout, as recommended in the Consolidated Standards of Reporting Trials guidelines (26).

## RESULTS

### Participants and characteristics

The disposition of participants during the trial is shown in online appendix Fig. A. A total of 475 people were randomized and treated (ITT cohort), with 227 (96%) on insulin detemir and 225 (95%) on NPH insulin completing the study. In each group, 90% completed the study per protocol. Most protocol violations involved OGLDs; 12 patients did not receive a constant OGLD regimen in the 4 months before randomization, while 8 changed OGLD or dose during the study.

Participant characteristic data at ran-

domization are given in online appendix Table A. The groups were well matched. Respective means  $\pm$  SD for the insulin detemir and NPH insulin groups were age  $61.3 \pm 9.1$  and  $60.4 \pm 9.3$  years, BMI  $28.9 \pm 3.6$  and  $29.0 \pm 3.6$  kg/m<sup>2</sup>, and duration of diabetes  $9.6 \pm 6.6$  and  $9.8 \pm 6.2$  years. Possible imbalances include the inclusion of more women than men (50.6 vs. 43.3%) and slightly higher mean A1C levels in the insulin detemir group (8.61 vs. 8.51%).

In each group, ~65% received combination OGLD therapy (mostly metformin plus secretagogue). Respective use of monotherapy in the insulin detemir and NPH insulin groups was 28.7 and 26.5% for secretagogues and 5.9 and 8.0% for metformin. Concurrent medical conditions were similarly frequent in the two groups, the most common including hypertension (69%) and ischemic heart disease (14%). At the end of the trial, the doses of insulin detemir ( $n = 227$ ) were  $36.1 \pm 27.1$  units in the morning and  $29.5 \pm 21.8$  units in the evening; corresponding doses of NPH insulin ( $n = 225$ ) were  $25.3 \pm 18.9$  IU in the morning and  $19.7 \pm 13.8$  IU in the evening. Total mean dose over time is shown in online appendix Fig. B.

### Measures of glycemia

The main improvements in efficacy measures occurred during the first 12 weeks (online appendix Fig. B). With insulin detemir, A1C decreased by 1.8%, from 8.6% ( $n = 237$ ) to 6.8% ( $n = 230$ ) by 24 weeks. For NPH insulin, the decrease was 1.9%, from 8.5% ( $n = 237$ ) to 6.6% ( $n = 232$ ). This gave baseline-, country-, and OGLD-adjusted means of  $6.58 \pm 0.06$  and  $6.46 \pm 0.06\%$ , fulfilling criteria for noninferiority (mean difference 0.13 [95% CI 0.00–0.25]). The proportion of participants reaching A1C  $\leq 7.0\%$  without hypoglycemia during the last 12 weeks of treatment was higher with insulin detemir (26%, 59 of 230) than NPH insulin (16%, 36 of 233;  $P = 0.008$ ). Regardless of hypoglycemia, these proportions were 70 and 74%, respectively (NS).

Clinic FPG decreased from 11.1 mmol/l ( $n = 236$ ) to 6.9 mmol/l ( $n = 227$ ) with insulin detemir and from 10.8 ( $n = 236$ ) to 6.6 mmol/l ( $n = 224$ ) with NPH insulin (between-treatment difference 0.32 mmol/l [95% CI  $-0.02$  to 0.66], NS).

The self-monitored prebreakfast glycemic target of  $<6.0$  mmol/l ( $<108$  mg/dl) was reached by 63% (145 of 231) and

68% (158 of 232) of participants on insulin detemir and NPH insulin, respectively (NS). Predinner target was reached by 49 and 52%, respectively (NS). Although the within-participant SD in prebreakfast plasma glucose was lower after 12 weeks for insulin detemir than for NPH insulin (0.88 mmol/l [ $n = 229$ ] vs. 0.99 mmol/l [ $n = 230$ ],  $P = 0.003$ ), it was not different after 24 weeks (0.88 mmol/l [ $n = 230$ ] vs. 0.90 mmol/l [ $n = 228$ ]). Within-participant variation in predinner plasma glucose was lower with insulin detemir after 24 weeks (1.38 vs. 1.53 mmol/l,  $P = 0.008$ ), as was the pooled prebreakfast and predinner estimate (1.32 vs. 1.44 mmol/l,  $P < 0.001$ ).

Mean 10-point glucose profiles at 24 weeks are shown in online appendix Fig. B. The overall profiles were comparable by group ( $P = 0.19$ ) and were similar to those obtained at 12 weeks (data not shown). There was no evidence of glucose levels rising during the daytime with the twice-daily injection regimen, and this might have contributed to the low mean A1C values.

Insulin detemir was associated with a 47% lower risk for any hypoglycemic event ( $P < 0.001$ ) and a 55% lower risk for nocturnal events ( $P < 0.001$ ). With adjustment for A1C, these risk reductions were 44 and 54%, respectively. This pattern of risk reduction was seen in each month of the study, but the difference was most marked during weeks 4–8 (Fig. 1A). Further hypoglycemia data are available in online appendix Table B.

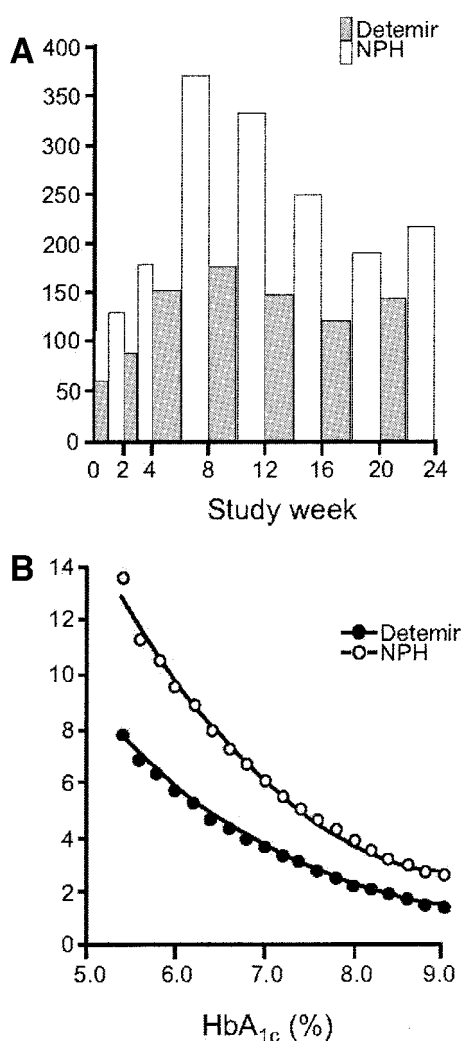
The modeled relationship of frequency of hypoglycemia in the final 12 weeks with A1C at end point is shown in Fig. 1B. Consistent with the event rates, the model predicts an approximate halving of hypoglycemia at an A1C of  $\sim 7.0\%$ , with greater absolute reductions at 6.0% and lesser reductions at 8.0%.

### Body weight

Mean body weight data are shown in online appendix Fig. C. Less weight was gained with insulin detemir, baseline-adjusted weight being statistically significantly lower than with NPH insulin after 24 weeks (83.6 kg [ $n = 226$ ] vs. 85.1 kg [ $n = 223$ ], difference  $-1.58$  kg [95% CI  $-2.18$  to  $-0.98$ ],  $P < 0.001$ ). On average, insulin detemir recipients gained 1.2 kg, while NPH insulin recipients gained 2.8 kg. Adjustment for  $\Delta$ A1C did not affect this finding ( $-1.55$  kg [ $-2.15$  to  $-0.95$ ],  $P < 0.001$ ).

With increasing baseline BMI, pa-





**Figure 1**—A: Hypoglycemia event number (all reported events including symptoms only) during intervals of time (bars). B: Relationship between incidence of hypoglycemia (confirmed minor and major events, excluding “symptoms only”) in the previous 12 weeks of the study and A1C at end point, as modeled using a negative-binomial distribution with a log-link function.

tients gained less weight with insulin detemir (weight gain  $5.37 - 0.15 \times \text{BMI}$ ,  $P = 0.01$ ), whereas no relationship was found for NPH insulin. This pattern was also apparent with stratification by BMI (online appendix Fig. C). Exploratory analysis of A1C,  $\Delta\text{A1C}$ , and hypoglycemia by baseline BMI did not show any differences indicating that differences in weight outcome are not explained by differences in glycemic control.

### Safety monitoring

Both insulins were well tolerated with no major safety issues arising. There was no evidence of any trends for change in lipid profile or blood pressure with either treat-

ment. The adverse event profiles of the two insulins were similar, with most adverse events mild or moderate and considered unlikely related to trial products. The only between-treatment difference with a probable relation to trial medication concerned injection site reports, which were more frequent with insulin detemir (14 events, 13 participants) than with NPH insulin (6 events, 6 participants). Nine people on insulin detemir and six on NPH insulin suffered injection-site reactions. The other injection-site events in the detemir group were two reports of pain and two of hematoma.

Seven participants were withdrawn because of adverse events (three insulin detemir treated, four NPH insulin treated). One case in each group was considered related to trial product: mild allergy with insulin detemir, mild injection-site reaction with NPH insulin.

**CONCLUSIONS**— This study was nonblinded by necessity due to visibly different properties of the comparators and must therefore be interpreted with some caution. Nevertheless, this study confirms the feasibility of adding basal insulin to OGLDs, with intensive dose titration, as a strategy for achieving recommended glycemic targets in previously poorly controlled type 2 diabetes. End-point mean A1C level was 6.5–6.6%, with >70% of people attaining A1C  $\leq 7.0\%$ . The improvement in A1C (1.8–1.9%) is larger than generally reported in people starting insulin in other studies (3,4,27,28), and the benefit in mean level and improvement of glycemic control even exceeded that achieved in the earlier study applying the treat-to-target concept, in which once daily NPH insulin or insulin glargine were used (14). While caution is advisable in making comparisons between studies, this latter difference may reflect the use of twice-daily basal insulin dosing (which may exert a more constant effect and also permit more rapid dose titration) or greater acceptance of the treat-to-target concept. Another key difference between the present and original treat-to-target study is that the latter permitted use of thiazolidinediones, which are potentially insulin sparing. Results of the U.K. Prospective Diabetes Study suggest that people achieving A1C levels of  $\leq 7.0\%$  may benefit from reductions in diabetes complications (27).

In the original treat-to-target study (14) and in the LanMet study (29), basal blood glucose rose during the day by

$\sim 2.0$  mmol/l from excellent prebreakfast levels. In the present study, the effect was much smaller ( $\sim 0.5$  mmol/l) with both insulins (online appendix Fig. B) and may be at least partly attributable to the use of twice-daily injections.

In the current trial, a similar proportion in both groups achieved glycemic targets, but significantly more recipients of insulin detemir did so without hypoglycemia. This is of clinical importance because the A1C levels achieved in the treat-to-target studies are associated with relatively frequent hypoglycemia:  $\sim 64$  and  $\sim 80\%$  of insulin detemir- and NPH insulin-treated participants in the present study experienced at least one episode. However, at comparable levels of glycemic control, the risks for overall and nocturnal hypoglycemia were reduced with insulin detemir by 47 and 55%, respectively.

A problem with treat-to-target studies is that, by design, glucose control converges on the target measure over a relatively short period. In clinical practice, hypoglycemia plays a larger part in limiting achieved blood glucose control. A study (which would have to be of much longer duration) targeted on hypoglycemia rates rather than glycemic values would result in quite large differences in achieved A1C, in the order of 1.0–1.8% (Fig. 1B).

Significantly lower risks for nocturnal hypoglycemia comparing insulin detemir with NPH insulin have also been reported in studies of meal-time bolus + basal insulin therapy in people with type 1 diabetes (18–23). In bolus + basal therapy in people with type 2 diabetes, a significant risk reduction of 46% for nocturnal hypoglycemia has been reported when insulin detemir + insulin aspart was compared with a human insulin-based regimen (30). The fact that the current study showed reduced hypoglycemia over the whole day probably relates to the use of only a basal insulin, without contamination of events due to meal-time insulin. This fits with the observation here that the risk reduction across the day was of similar magnitude to that for nocturnal hypoglycemia. Thus, the present study confirms previous reports suggesting that insulin detemir has an inherently lower propensity for causing hypoglycemia. The reduced risk of hypoglycemia might also have contributed to the dose discrepancy seen in the present study. There are two possible explanations for this observation that are not mutually exclusive. One is that insulin detemir was less potent

than NPH insulin; the other is that a lower incidence of hypoglycemia allowed more aggressive titration. Insulin detemir has relatively low molar potency compared with human insulin and is therefore formulated at a higher concentration (2,400 vs. 600 nmol/ml for NPH and most other insulin formulations). Thus, 1 unit of insulin detemir contains four times the insulin dose of 1 IU of NPH insulin on a molar basis, but in studies in people with type 1 diabetes these formulations have achieved unit dose equivalence in terms of overall blood glucose-lowering effect. It cannot be excluded that this unit dose parity did not apply to the present study population.

However, the average NPH dose increased by only 3.1 IU between weeks 12 and 24, while the detemir dose increased by 10.1 unit, yet glycemic control did not improve substantially during this time (online appendix Fig. C). This could imply that a limit of efficacy had been achieved with both insulins, the lower hypoglycemic incidence seen with insulin detemir allowing the dose to be titrated harder against this limit.

Such a limit likely reflects the fact that no prandial insulin was given and no postprandial glycemic targets set. As A1C decreases, postprandial glycemic excursions increasingly contribute to residual hyperglycemia (31,32). Therefore, a limit to the A1C achievable with a regimen that uses only a basal insulin (plus OGLD) might be expected. This hypothesis requires further testing; however, a similar effect was observed in the insulin glargine treat-to-target study, where the analog also incurred a lower hypoglycemic risk (14,33), with daily dosages at end point adjusted for body weight ~15% larger for insulin glargine than for NPH insulin ( $P < 0.001$ ).

Weight gain with insulin detemir in the present study was less than half of that for NPH insulin and was similar to that reported in the previous treat-to-target study (14) for NPH insulin and insulin glargine. A significant between-treatment difference in weight gain favoring insulin detemir was found consistently in clinical trials comparing insulin detemir with NPH insulin in people with type 1 (18–23) or type 2 (24,25) diabetes. In the present study, this advantage appeared to increase with baseline BMI. Weight gain with long-term insulin has been associated with dyslipidemia and hypertension (34–36) and is a cause of low self-esteem and psychological resistance to insulin

therapy (37). The mechanism underlying this weight-sparing effect of insulin detemir is unlikely to be wholly explained by reduced calorie intake arising from reduced hypoglycemic risk; this latter advantage was also seen for insulin glargine in the original treat-to-target study, but there was no concomitant advantage over NPH insulin for weight gain. Potential pharmacological explanations for the weight-sparing effect of insulin detemir are currently under investigation and include improved hypothalamic insulin signaling (37) and a relative reduction in peripheral lipogenesis (38).

In general, the safety profiles of insulin detemir and NPH insulin were comparable. Although there was a small relative increase in reported injection-site problems with insulin detemir, episodes were sufficiently mild, so as to not interfere with continuation.

In conclusion, treatment with twice-daily insulin detemir or NPH as an add-on to OGLD therapy, using tight dose titration, resulted in clinically important improvements in glycemic control, with A1C levels mostly  $<7.0\%$ . At all levels of control, insulin detemir incurred a lower risk of hypoglycemia and reduced weight gain compared with NPH insulin. Insulin detemir therefore appears to be a significant clinical advance over NPH insulin when used in active dose titration to achieve target glycemic control.

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