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ORIGINAL RESEARCH

Effect of Insulin Detemir Dose Frequency on Clinical Outcomes in Patients with Diabetes in PREDICTIVE

Pierre Fontaine · Henri Gin · Michel Pinget · Charles Thivolet · Hélène Hanaire · Jean-Jacques Robert · Michel Marre · Srishyla Venkatanarasimhachar

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ABSTRACT

Introduction: The aim was to compare clinical outcomes by different dosing frequencies of insulin detemir (detemir) used over 52 weeks in various regimens. ***Methods:*** This analysis involved French patients enrolled in PREDICTIVE (a large-scale, multinational, observational study of empirical use of detemir in everyday clinical practice) for whom data have been collected over 52 weeks. Three cohorts were considered: patients with type 1 diabetes; patients with type 2 diabetes using detemir in a basal insulin plus oral antidiabetic drug (OAD) regimen; patients with type 2 diabetes using detemir as part of basal–bolus insulin therapy. In each cohort, data were stratified according to detemir dosing frequency at the beginning and end of 52 weeks: once daily (o.d.) at the beginning and end; twice daily (b.i.d.) at the beginning and end; o.d. at the beginning, but b.i.d. at the end. Endpoints assessed included glycated hemoglobin, fasting plasma glucose, hypoglycemia, weight, and insulin dose. ***Results:*** There were improvements in glycemic control and tolerability in all subgroups. Patients completing on o.d. dosing tended to have better outcomes than those completing on b.i.d. dosing in all cohorts, and o.d. administration was associated with lower insulin dosing. There was little evidence that switching from o.d. to b.i.d. dosing influenced outcomes other than insulin dose. However, there were some baseline differences between subgroups selected for o.d. and b.i.d. dosing that might have influenced outcomes: many patients appeared to have been continued on

Pierre Fontaine (✉)
Department of Endocrinology-Diabetes, CHRU, Lille, France. Email: p-fontaine@chru-lille.fr

Henri Gin
Unit of Standard Care, C.H.U. Hauts Levêque Hospital, Pessac, France

Michel Pinget
Department of Medicine E, Civil Hospital, Leriche House, Strasbourg, France

Charles Thivolet
Department of Endocrinology-Diabetes, Edouard Herriot Hospital, Lyon, France

Hélène Hanaire
Department of Diabetes, Rangueil Hospital, Toulouse, France

Jean-Jacques Robert
Department of Diabetes, Necker Hospital for Ill Children, Paris, France

Michel Marre
Department of Endocrinology-Diabetes, Bichat Hospital, Paris, France

Srishyla Venkatanarasimhachar
Senior International Medical Advisor, International Medical Affairs, Novo Nordisk AS, Virum, Denmark

previous basal dosing frequencies; for others, b.i.d. detemir dosing seemed to be used to intensify previous therapy. ***Conclusions:*** With the caveat that empirical choices of dose frequency were made, this analysis shows that empirical use of o.d. detemir produces results at least as good as empirical use of b.i.d. detemir in basal–bolus-treated type 1 and type 2 diabetes, and in basal plus OAD-treated type 2 diabetes.

Keywords: detemir; insulin analog; once daily; PREDICTIVE; twice daily; type 1 diabetes; type 2 diabetes

INTRODUCTION

Insulin detemir (detemir) is a basal insulin analog developed to produce a prolonged and reproducible time-action profile through a unique mechanism of protracted absorption involving self-association of detemir molecules and reversible albumin binding.[1] Detemir has a more prolonged and less peaked pharmacodynamic profile in comparison to neutral protamine Hagedorn (NPH) insulin,[2] and has reduced intrasubject variability in this profile in comparison with both NPH insulin[3,4] and insulin glargine (glargine).[3,5] These properties likely contribute to a well-documented relative risk reduction for nocturnal hypoglycemia in clinical trial comparisons with NPH insulin.[6,7] Despite its relatively prolonged duration of action, many of the earlier clinical trials of detemir involved twice-daily (b.i.d.) dosing regimens, fostering a view that this is the most appropriate dosing schedule. Yet some recent clamp study analyses[5,8] suggest that detemir has a mean duration of action of approximately 24 hours and a very similar pharmacodynamic profile to that of glargine, a basal insulin that is routinely injected once daily (o.d.). Moreover, good results have been reported when detemir has been used o.d. in clinical trials,[9,10] and in observational studies.[11] This is of potential therapeutic and economic importance because not only might an o.d. schedule be regarded as more convenient by patients, but there is also evidence that b.i.d. dosing tends to escalate the basal insulin dose without achieving a proportional benefit in glycemic control.[12]

A controlled study (Assessment of Detemir Administration in a Progressive treat-to-target Trial: ADAPT) has recently been reported that compared o.d. with b.i.d. dosing of detemir used as the basal component of basal–bolus therapy for 520 patients with type 1 diabetes.[10] ADAPT comprised a 4-month randomized period comparing o.d. to b.i.d. detemir followed by an additional nonrandomized 3-month follow-up period during which time a change of basal dosing frequency (from o.d. to b.i.d. or vice versa) was permitted. The ADAPT study showed noninferiority with regard to glycemic control for o.d. versus b.i.d. dosing at the end of the 4-month randomized period, while at 7 months, patients who switched from o.d. to b.i.d. detemir did not show clinically significant improvement in glycated hemoglobin (HbA_{1c}). In short, the study suggested that o.d. dosing is the most appropriate routine dosing schedule with which to introduce detemir, although there was some evidence of a subset that would benefit from a change to b.i.d. dosing.

PREDICTIVE (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation) is a very large-scale, international, open observational study assessing the empirical use of detemir in the everyday clinical setting.[13] Data have been collected for patients with type 1 or type 2 diabetes and these can be stratified by current and previous regimens. Most patients in PREDICTIVE have been given detemir o.d., achieving clinically

important improvements in glycemic control,[11,14-17] but some have received detemir b.i.d. from the start of therapy, or after commencing on o.d. detemir. PREDICTIVE therefore provides an opportunity to verify the conclusions of the ADAPT study in a variety of different patient groups and over longer time periods. In France, the study has continued for 52 weeks so useful longitudinal assessments can now be made. We therefore sought to compare outcomes after 52 weeks of treatment for patients who had begun and completed this study period on o.d. detemir to those of patients beginning and completing on b.i.d. dosing, or switching from o.d. to b.i.d. dosing. We also had the opportunity to stratify results by diabetes type and treatment regimen to answer the question of whether clinical outcomes are affected by the dose frequency of detemir.

MATERIALS AND METHODS

Study Design

PREDICTIVE is an observational, multicenter, open-label, prospective study of the empirical use of detemir in type 1 and type 2 diabetes. The present analysis included patients from the French cohort of PREDICTIVE who had received 52 weeks of treatment with detemir injected subcutaneously and prescribed according to product labeling at the discretion of participating diabetologists/endocrinologists in a routine clinical practice setting. Data for the full French PREDICTIVE cohort of 1772 patients will be published separately. The present post-hoc analysis considered three separate and identifiable cohorts within this full cohort for whom baseline and 52-week data were available:

1. Patients with type 1 diabetes receiving detemir in basal–bolus insulin therapy
2. Patients with type 2 diabetes receiving detemir in basal insulin plus oral antidiabetic drug (OAD) therapy
3. Patients with type 2 diabetes receiving detemir in basal–bolus insulin therapy.

For each of these cohorts we attempted to stratify outcomes according to the frequency of basal insulin dosing. Therefore, three subgroups were specified according to basal insulin dose frequency:

- Patients commencing and completing the study on o.d. detemir. This cohort (hereafter termed the "o.d. group") is likely to include mostly individuals who were on o.d. detemir throughout, although it is possible that some patients may have used different regimens at some interim stage of the study.
- Patients commencing and completing the study on b.i.d. detemir. This cohort (hereafter termed the "b.i.d. group") is likely to include mostly individuals who were on b.i.d. detemir throughout, but it is again possible that some may have used different regimens at some interim stage of the study.
- Patients commencing the study on o.d. detemir, but subsequently switching and hence completing the study on b.i.d. dosing (hereafter termed the "o.d.-b.i.d. switch group").

As this was an observational study, there were few inclusion and exclusion criteria, with the selection of patients being at the discretion of each participating physician. The minimum age for inclusion in France, however, was 18 years. No study-specific procedures outside normal clinical practice were conducted except for the collection of data at clinic visits held at baseline and at 12, 26, and 52 weeks.

The study was performed in accordance with the regulatory requirements for observational studies in France. Informed, verbal consent

was given by patients prior to enrollment in the study.

Clinical Endpoints

The primary endpoint of PREDICTIVE is the occurrence of serious adverse drug reactions, but for the purposes of the current analysis we considered the efficacy endpoints of insulin dose, HbA_{1c}, fasting plasma glucose (FPG), and FPG variability (defined as the standard deviation of the mean FPG value taken from immediate pre-visit patient records), and the safety endpoints of body weight and the number of hypoglycemic episodes occurring within the 4-week period immediately preceding each visit.

Hypoglycemic episodes were categorized according to severity and time of occurrence and incidences extrapolated into events per patient per year. A major hypoglycemic episode was defined as an episode with severe central nervous system symptoms consistent with hypoglycemia, in which the patient was unable to perform self-treatment and had either a blood glucose measurement of <2.8 mmol/L or a reversal of symptoms after food, glucagon, or intravenous glucose was administered. Nonmajor episodes were defined as symptoms of hypoglycemia that resolved with oral carbohydrate intake, glucagon, or intravenous glucose, and any symptomatic or asymptomatic glucose reading of <2.8 mmol/L. A nocturnal hypoglycemic episode was defined as an episode occurring while the subject was asleep and/or in bed between their evening retirement and morning waking. Data concerning hypoglycemia and FPG variability were based on patients' notes, self-monitored blood glucose diaries, and their general recollection. Therefore, signed informed consent forms were not required.

Statistical Analysis

Variables were presented using descriptive statistics (number of events, number of patients, mean±SD, or mean±%). Changes between baseline and 52 weeks were analyzed for statistical significance for the main efficacy and safety endpoints, but differences between the cohorts and the dose-frequency groups within the cohorts were not compared statistically due to confounding factors; the groups were not randomized and baseline differences were present. In an attempt to show longitudinal changes in endpoints, data were also collected at the 12- and 26-week visits.

Changes in the number of hypoglycemic events from baseline to 52 weeks were tested using the Wilcoxon rank-sum test. Changes in mean HbA_{1c}, FPG, FPG variability, and weight were analyzed by paired *t* test. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Demographics

Baseline demographic data for all patients included in the present analysis are presented in Table 1.

From the cohort of patients with type 1 diabetes, 157 began and completed the study on a regimen of o.d. detemir, while 132 began and completed on b.i.d. detemir. There were 57 patients identified who began on o.d. detemir and completed on b.i.d. detemir. Therefore, approximately 73% of patients beginning on o.d. detemir dosing remained on this regimen after 52 weeks. As the combined percentages of patients at baseline recorded as taking NPH insulin or glargine were often considerably less than 100%, as were the percentages recorded as taking bolus insulin, it is likely

Table 1. Baseline demographic data stratified by regimen and insulin detemir dosing frequency.

Type 1 diabetes, basal–bolus therapy			
Parameter	**o.d.** ***n*=157**	**b.i.d.** ***n*=132**	**o.d.-b.i.d.** ***n*=57**
Gender (male/female), %	53.5/46.5	50.0/50.0	47.4/52.6
Age, years (mean±SD)	49.0±15.4	49.2±15.0	46.5±16.6
BMI, kg/m^2 (mean±SD)	24.7±4.0	24.9±3.8	24.0±3.3
Weight, kg (mean±SD)	69.7±12.6	70.7±12.7	69.0±13.9
Duration of diabetes, years (mean±SD)	15.9±12.0	17.9±12.3	18.5±12.7
Insulin-naïve, %	14.0	3.0	1.8
Basal dose frequency o.d./b.i.d., %	56.7/5.7	43.2/38.6	64.9/10.5
Prior use of NPH/glargine, %	19.7/40.1	31.8/50.0	15.8/56.1
Use of rapid-acting analog, %	50.3	70.5	73.7
Type 2 diabetes, basal insulin plus OAD therapy			
Parameter	**o.d.** ***n*=222**	**b.i.d.** ***n*=41**	**o.d.-b.i.d.** ***n*=0**
Gender, male/female, %	56.8/43.2	53.7/46.3	–
Age, years (mean±SD)	62.5±9.8	63.1±11.7	–
BMI, kg/m^2 (mean±SD)	29.3±5.4	31.5±5.8	–
Weight, kg (mean±SD)	82.0±15.4	88.2±19.8	–
Duration of diabetes, years (mean±SD)	13.4±7.9	14.2±8.4	–
Insulin-naïve, %	61.7	9.8	–
Basal dose frequency o.d./b.i.d., %	28.4/2.3	56.1/24.4	–
Prior use of NPH/glargine, %	17.1/12.6	36.6/43.9	–
Use of rapid-acting analog, %	0.9	4.9	–
Type 2 diabetes, basal–bolus therapy			
Parameter	**o.d.** ***n*=37**	**b.i.d.** ***n*=22**	**o.d.-b.i.d.** ***n*=7**
Gender, male/female, %	43.2/56.8	27.3/72.7	28.6/71.4
Age, years (mean±SD)	62.0±12.2	56.9±9.9	61.0±17.2
BMI, kg/m^2 (mean±SD)	32.2±5.3	32.9±6.3	32.2±4.6
Weight, kg (mean±SD)	87.1±19.2	90.2±18.7	86.2±12.5
Duration of diabetes, years (mean±SD)	17.6±10.5	15.5±9.3	22.0±12.5
Insulin-naïve, %	8.1	0.0	0.0
Basal dose frequency o.d./b.i.d., %	56.8/8.1	36.4/50.0	71.4/0.0
Prior use of NPH/glargine, %	27.0/37.8	27.3/59.1	14.3/57.1
Use of rapid-acting analog, %	75.7	63.6	74.1

b.i.d.=twice daily; BMI=body mass index; NPH=neutral protamine Hagedorn; OAD=oral antidiabetic drug; o.d.=once daily; o.d.-b.i.d.=once daily switched to twice daily.

that not all patients were previously treated with basal–bolus insulin therapy and that some patients were newly diagnosed upon enrollment into PREDICTIVE.

From the cohort of patients with basal plus OAD-treated type 2 diabetes, 222 commenced and completed on o.d., and 41 on b.i.d. detemir. Therefore, 84% of basal plus OAD-treated patients were put onto o.d. detemir. No patients could be identified who began on o.d. and who completed on b.i.d. detemir. It is noteworthy that a relatively high percentage of patients assigned to o.d. detemir were previously insulin-naïve (Table 1).

From the small cohort of patients on basal–bolus insulin-treated type 2 diabetes, 37 patients began and completed on o.d. and 22 on b.i.d. detemir, with just seven commencing on o.d. detemir and completing on b.i.d. detemir. Therefore, approximately 84% of patients started on o.d. were still on this frequency at 52 weeks.

Clinical and Insulin Dose Outcomes

Clinical outcomes across the cohorts and detemir dosing frequency subgroups are presented in Table 2. Data for HbA_{1c} and final insulin doses are shown graphically in Figure 1.

Basal–Bolus Insulin-Treated Type 1 Diabetes

Glycemic control improved significantly in all subgroups. The reductions in HbA_{1c} were particularly marked in the o.d. and b.i.d. detemir groups, but of a lesser extent in the subgroup switching from o.d. to b.i.d. detemir (Table 2A, Figure 1). Notwithstanding missing data from the interim (12 and 26 week) visits, and, for a few patients, missing data for certain measurements at baseline, the benefits tended to be either progressive or sustained from early improvement (eg, for hypoglycemia rate).

Weight remained stable across 52 weeks in all groups despite the improvements in glycemic control (Table 2A). The event rate for hypoglycemia decreased from baseline in all groups (Table 2A), with the difference between baseline and endpoint being statistically significant for all categories except for major events in the subgroup switching from o.d. to b.i.d. detemir (due to low patient and event numbers). The insulin dose, particularly for basal insulin, was higher in the b.i.d. detemir compared to the o.d. group, and was higher still in the switched patients (Figure 1).

Basal-Only Insulin Plus OAD-Treated Type 2 Diabetes

Improvement in glycemic control was seen in both o.d.- and b.i.d.-detemir-treated patients, but the overall control and the level of improvement were both numerically superior in the o.d. group (Table 2B, Figure 1).

Weight remained stable throughout the study despite the improvement in glycemic control, with patients receiving b.i.d. detemir tending to be heavier (Table 2B). Hypoglycemia rates also tended to decrease across the study despite the improved glycemic control (Table 2B). The reduction in total hypoglycemia was statistically significant in patients receiving detemir o.d., but there were too few patients receiving b.i.d. detemir and too few events to establish statistical significance in this subgroup.

The mean detemir dose was more than twice as high in the b.i.d. group as in the o.d. group throughout (Table 2B, Figure 1).

Basal–Bolus Insulin-Treated Type 2 Diabetes

The cohort size of this group was small, hence few changes between baseline and endpoint were found to be statistically significant, and interpretation of the data should be made with caution

Table 2. Clinical data by visit.

(**A**) Data stratified by insulin detemir dosing subgroup for type 1 diabetes cohort.

1. o.d. 2. b.i.d. 3. o.d.-b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
HbA_{1c}, % (mean±SD)					
1.	8.49±1.69 *n*=135	7.90±1.21 *n*=124	7.71±1.15 *n*=118	7.66±1.06 *n*=135	−0.83±1.76 *P*<0.0001
2.	8.40±1.55 *n*=112	7.91±1.29 *n*=98	7.80±1.23 *n*=98	7.83±1.16 *n*=112	−0.57±1.38 *P*<0.0001
3.	8.50±1.48 *n*=52	8.24±1.34 *n*=47	7.93±1.19 *n*=48	8.11±1.35 *n*=52	−0.39±1.20 *P*=0.023
FPG, mmol/L (mean±SD)					
1.	9.48±3.32 *n*=101	7.86±2.10 *n*=87	7.50±2.07 *n*=90	7.60±2.32 *n*=101	−1.89±3.48 *P*<0.0001
2.	9.35±3.01 *n*=92	8.46±2.34 *n*=83	8.34±2.84 *n*=80	8.43±2.65 *n*=92	−0.92±3.82 *P*=0.023
3.	8.97±2.41 *n*=37	8.31±2.99 *n*=32	9.05±2.96 *n*=31	8.57±2.75 *n*=37	−0.39±2.94 *P*=NS
FPG SD, mmol/L (mean±SD)					
1.	2.85±1.60 *n*=85	2.30±1.30 *n*=74	2.30±1.40 *n*=76	2.01±1.23 *n*=85	−0.84±1.59 *P*<0.0001
2.	3.01±1.59 *n*=86	2.50±1.48 *n*=76	2.58±1.18 *n*=73	2.35±1.30 *n*=86	−0.66±1.64 *P*<0.001
3.	3.06±1.26 *n*=35	2.55±1.29 *n*=31	2.87±1.62 *n*=28	2.28±1.56 *n*=35	−0.79±1.74 *P*=0.0116
% HbA_{1c} <7.0%					
1.	10 *n*=135	20 *n*=124	26 *n*=118	25 *n*=135	–
2.	12 *n*=112	19 *n*=98	24 *n*=98	21 *n*=112	–
3.	13 *n*=52	15 *n*=47	25 *n*=48	19 *n*=52	–
Weight, kg (mean±SD)					
1.	69.5±12.5 *n*=151	69.8±12.3 *n*=146	69.5±12.6 *n*=141	69.7±12.8 *n*=151	+0.1±4.6 *P*=NS
2.	70.6±12.8 *n*=123	70.0±12.0 *n*=110	70.8±12.9 *n*=114	70.0±13.4 *n*=123	−0.6±4.2 *P*=NS
3.	69.2±14.1 *n*=54	69.0±13.6 *n*=49	69.5±14.7 *n*=51	69.5±14.2 *n*=54	0.4±5.1 *P*=NS

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Table 2. (*Continued*)

1. o.d. 2. b.i.d. 3. o.d.-b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
Hypoglycemia					
(total e/pt/y)					
1.	70.46 *n*=155	37.05 *n*=154	30.29 *n*=147	27.3 *n*=155	–43.16 *P*<0.0001
2.	93.34 *n*=131	62.66 *n*=118	54.73 *n*=123	45.76 *n*=131	–47.58 *P*<0.0001
3.	116.74 *n*=57	78.52 *n*=53	77.74 *n*=53	67.34 *n*=57	–49.53 *P*=0.0028
(major e/pt/y)					
1.	4.94 *n*=155	0.52 *n*=154	1.17 *n*=147	1.04 *n*=155	–3.90 *P*=0.006
2.	8.84 *n*=131	0.39 *n*=118	0.26 *n*=123	0.39 *n*=131	–8.45 *P*<0.0001
3.	4.55 *n*=57	1.69 *n*=53	0 *n*=53	0.65 *n*=57	–3.90 *P*=NS
(nocturnal e/pt/y)					
1.	15.99 *n*=155	8.45 *n*=154	6.50 *n*=147	6.11 *n*=155	–9.88 *P*<0.0001
2.	21.45 *n*=131	11.09 *n*=118	10.79 *n*=123	10.40 *n*=131	–11.05 *P*=0.0002
3.	26.00 *n*=57	16.38 *n*=53	13.52 *n*=53	13.00 *n*=57	–13.00 *P*=0.0104
Insulin dose, Units/kg (mean±SD)					
1.	0.65±0.28 *n*=135	0.71±0.31 *n*=131	0.71±0.29 *n*=126	0.72±0.30 *n*=135	–
2.	0.65±0.23 *n*=124	0.74±0.30 *n*=110	0.76±0.28 *n*=115	0.77±0.29 *n*=124	–
3.	0.69±0.25 *n*=56	0.78±0.28 *n*=50	0.82±0.30 *n*=53	0.83±0.32 *n*=56	–
Insulin detemir, Units/kg (mean±SD)					
1.	0.30±0.13 *n*=157	0.34±0.17 *n*=152	0.34±0.17 *n*=146	0.34±0.18 *n*=157	–
2.	0.40±0.17 *n*=128	0.46±0.20 *n*=113	0.48±0.21 *n*=118	0.49±0.22 *n*=128	–
3.	0.34±0.13 *n*=57	0.45±0.22 *n*=51	0.48±0.23 *n*=54	0.52±0.23 *n*=57	–

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Table 2. (*Continued*)

(**B**) Data stratified by insulin detemir dosing subgroup for type 2 diabetes insulin plus oral antidiabetic drug cohort.

1. o.d. 2. b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
HbA_{1c}, % (mean±SD)					
1.	8.73±1.45 *n*=208	7.90±1.13 *n*=192	7.77±1.14 *n*=194	7.73±1.07 *n*=208	−1.01±1.48 *P*<0.0001
2.	8.88±1.31 *n*=39	8.29±1.28 *n*=36	8.28±1.30 *n*=33	8.22±1.22 *n*=39	−0.66±1.51 *P*<0.01
FPG, mmol/L (mean±SD)					
1.	9.73±2.92 *n*=139	7.46±2.00 *n*=123	7.15±1.70 *n*=126	7.00±1.69 *n*=139	−2.73±3.07 *P*<0.0001
2.	8.28±2.27 *n*=25	8.26±2.19 *n*=23	8.57±2.12 *n*=21	8.18±1.72 *n*=25	−0.10±2.66 *P*=NS
FPG SD, mmol/L (mean±SD)					
1.	1.38±1.15 *n*=114	1.08±0.57 *n*=98	1.29±0.75 *n*=99	1.17±0.92 *n*=114	−0.21±1.29 *P*=0.083
2.	1.70±1.17 *n*=21	1.49±0.97 *n*=18	1.49±1.05 *n*=17	1.32±1.07 *n*=21	−0.39±1.26 *P*=NS
% HbA_{1c} <7.0%					
1.	5 *n*=208	18 *n*=192	20 *n*=194	21 *n*=208	–
2.	8 *n*=39	17 *n*=36	21 *n*=33	13 *n*=39	–
Weight, kg (mean±SD)					
1.	81.9±15.3 *n*=215	81.3±15.0 *n*=208	81.7±15.0 *n*=209	81.9±15.2 *n*=215	0.0±4.9 *P*=NS
2.	89.7±19.8 *n*=38	90.0±19.4 *n*=37	88.0±19.1 *n*=36	89.4±19.9 *n*=38	−0.2±3.9 *P*=NS
Hypoglycemia					
(total e/pt/y)					
1.	10.40 *n*=222	7.54 *n*=217	6.11 *n*=218	3.38 *n*=222	−7.02 *P*=0.0014
2.	12.09 *n*=41	0.65 *n*=40	4.03 *n*=39	3.51 *n*=41	−8.58 *P*=NS
(major e/pt/y)					
1.	0.52 *n*=222	0 *n*=217	0 *n*=218	0.13 *n*=222	−0.39 *P*=NS
2.	2.21 *n*=41	0 *n*=40	0 *n*=39	0.26 *n*=41	−1.95 *P*=NS

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Table 2. (*Continued*)

1. o.d. 2. b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
(nocturnal e/pt/y)					
1.	2.08 *n*=222	0.91 *n*=217	1.69 *n*=218	0.91 *n*=222	−1.17 *P*=NS
2.	2.21 *n*=41	0 *n*=40	1.04 *n*=39	2.60 *n*=41	+0.26 *P*=NS
Insulin detemir, Units/kg (mean±SD)					
1.	0.29±0.15 *n*=85	0.33±0.18 *n*=81	0.33±0.17 *n*=84	0.35±0.16 *n*=85	–
2.	0.54±0.28 *n*=34	0.69±0.32 *n*=33	0.71±0.28 *n*=32	0.74±0.30 *n*=34	–

(**C**) Data stratified by detemir dosing subgroup for type 2 diabetes basal–bolus cohort.

1. o.d. 2. b.i.d. 3. o.d.-b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
HbA_{1c}, % (mean±SD)					
1.	8.79±1.74 *n*=36	8.31±1.93 *n*=32	8.11±1.53 *n*=31	8.06±1.56 *n*=36	−0.73±1.78 *P*=0.0190
2.	8.37±1.38 *n*=19	8.35±1.31 *n*=19	7.83±0.84 *n*=17	8.15±1.12 *n*=19	−0.22±0.87 *P*=NS
3.	8.40±1.12 *n*=7	8.30±1.04 *n*=7	7.73±0.77 *n*=7	7.96±1.05 *n*=7	−0.44±1.29 *P*=NS
FPG, mmol/L (mean±SD)					
1.	9.95±3.66 *n*=25	8.31±2.76 *n*=22	7.22±2.40 *n*=22	8.07±3.34 *n*=25	−1.88±4.81 *P*=0.0624
2.	10.20±3.58 *n*=18	9.23±2.40 *n*=18	8.82±2.04 *n*=16	9.18±2.24 *n*=18	−1.02±2.44 *P*=NS
3.	9.24±3.67 *n*=7	8.89±3.75 *n*=7	8.99±3.05 *n*=7	8.26±2.49 *n*=7	−0.99±2.81 *P*=NS
FPG SD, mmol/L (mean±SD)					
1.	1.89±1.48 *n*=19	1.68±0.95 *n*=17	1.37±1.02 *n*=18	1.52±0.92 *n*=19	−0.37±1.20 *P*=NS
2.	2.54±1.75 *n*=15	1.24±0.61 *n*=15	1.43±0.79 *n*=13	1.66±1.02 *n*=15	−0.88±1.76 *P*=NS
3.	1.75±0.52 *n*=7	1.69±1.22 *n*=7	1.40±1.13 *n*=7	1.70±1.31 *n*=7	−0.06±1.19 *P*=NS

(continued on next page)

Table 2. (*Continued*)

1. o.d. 2. b.i.d. 3. o.d.-b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
% HbA_{1c} <7.0%					
1.	6 *n*=36	22 *n*=32	13 *n*=31	25 *n*=36	–
2.	0 *n*=19	16 *n*=19	12 *n*=17	11 *n*=19	–
3.	14 *n*=7	14 *n*=7	14 *n*=7	0 *n*=7	–
Weight, kg (mean±SD)					
1.	86.6±19.3 *n*=36	86.7±19.3 *n*=34	86.1±18.5 *n*=30	87.7±18.4 *n*=36	+1.0±4.8 *P*=NS
2.	90.5±19.1 *n*=21	88.3±17.4 *n*=20	90.9±17.1 *n*=20	90.6±18.2 *n*=21	+0.1±7.2 *P*=NS
3.	86.2±12.5 *n*=7	84.6±12.0 *n*=7	84.1±12.0 *n*=7	83.1±12.2 *n*=7	–3.1±5.9 *P*=NS
Hypoglycemia					
(total e/pt/y)					
1.	17.55 *n*=37	8.71 *n*=36	6.11 *n*=32	16.12 *n*=37	–1.43 *P*=NS
2.	28.99 *n*=22	10.66 *n*=22	16.51 *n*=22	13.00 *n*=22	–15.99 *P*=NS
3.	40.82 *n*=7	53.82 *n*=7	29.77 *n*=7	24.18 *n*=7	–16.77 *P*=NS
(major e/pt/y)					
1.	0 *n*=37	0 *n*=36	0 *n*=32	0 *n*=37	–
2.	0.65 *n*=22	0 *n*=22	0 *n*=22	0 *n*=22	–0.65 *P*=NS
3.	16.77 *n*=7	20.41 *n*=7	3.77 *n*=7	9.23 *n*=7	–7.41 *P*=NS
(nocturnal e/pt/y)					
1.	4.55 *n*=37	1.82 *n*=36	0.78 *n*=32	0.65 *n*=37	–3.90 *P*=NS
2.	2.99 *n*=22	1.17 *n*=22	2.34 *n*=22	3.51 *n*=22	+0.65 *P*=NS
3.	22.23 *n*=7	20.41 *n*=7	1.82 *n*=7	1.82 *n*=7	–20.41 *P*=NS

(continued on next page)

Table 2. (*Continued*)

1. o.d. 2. b.i.d. 3. o.d.-b.i.d.	Baseline	12 weeks	26 weeks	52 weeks	Change (baseline-52 weeks)
Insulin dose, Units/kg (mean±SD)					
1.	0.81±0.40 *n*=34	0.94±0.48 *n*=32	0.88±0.38 *n*=29	1.00±0.40 *n*=34	–
2.	1.02±0.56 *n*=22	1.17±0.55 *n*=21	1.30±0.60 *n*=21	1.31±0.63 *n*=22	–
3.	0.66±0.14 *n*=7	0.81±0.21 *n*=7	0.86±0.21 *n*=7	0.92±0.23 *n*=7	–
Insulin detemir, Units/kg (mean±SD)					
1.	0.39±0.16 *n*=37	0.43±0.19 *n*=35	0.43±0.20 *n*=30	0.45±0.22 *n*=37	–
2.	0.63±0.25 *n*=22	0.78±0.3 *n*=21	0.82±0.35 *n*=21	0.85±0.40 *n*=22	–
3.	0.36±0.14 *n*=7	0.48±0.20 *n*=7	0.54±0.20 *n*=7	0.58±0.18 *n*=7	–

P values refer to change between baseline and 52-week visit.
b.i.d.=twice daily; e/pt/y=episodes per patient per year; FPG=fasting plasma glucose; HbA_{1c}=glycated hemoglobin; NS=not significant; o.d.=once daily; o.d.-b.i.d.=once daily switched to twice daily.

(Table 2C). Glycemic control improved numerically in all groups with this being of the greatest magnitude in the o.d. group (Figure 1).

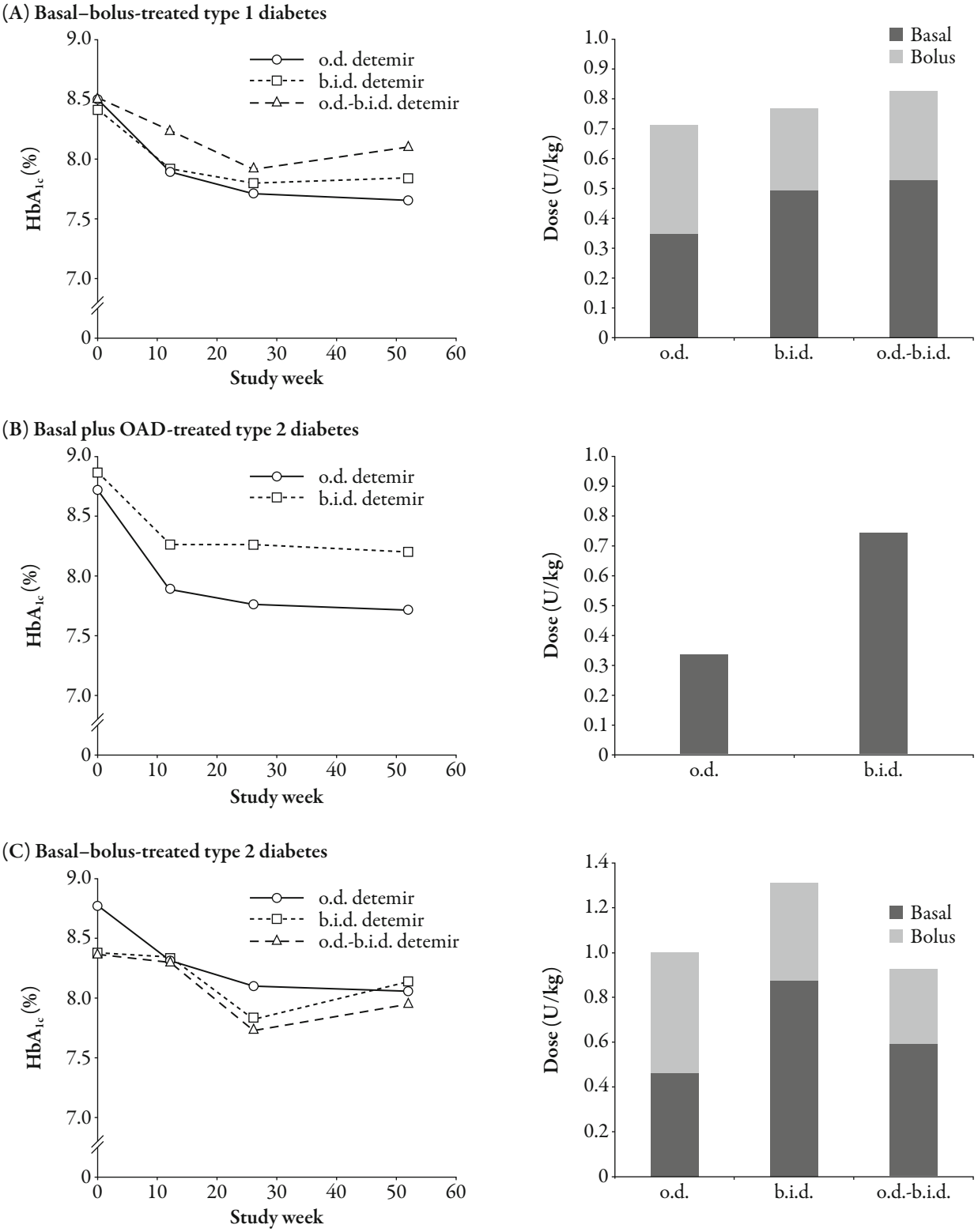
Weight was relatively stable in the o.d. and b.i.d. groups, but decreased steadily by a mean 3 kg in the seven patients switching from o.d. to b.i.d. detemir (Table 2C). Incidences of hypoglycemia tended to vary by visit in these small subgroups, but there was a clear trend towards a reduced incidence of hypoglycemia across the study (Table 2C). Hypoglycemic events tended to be most common throughout in the seven patients who switched from o.d. to b.i.d. detemir.

Insulin doses were lowest in the o.d. detemir group. In the seven patients switching to b.i.d. they did not reach such high values as in those patients on b.i.d. throughout, the latter commencing on a much higher starting dose.

DISCUSSION

The PREDICTIVE study provides a large database of clinical outcomes collected from a very wide range of detemir-treated patients (currently more than 35,000 worldwide), hence subgroups can be defined retrospectively by a variety of demographic or treatment criteria. The PREDICTIVE study therefore provides a resource with considerable potential to advance our knowledge about the clinical profile of detemir (as well as other practical issues of everyday diabetes management) through exploratory analyses. There are, however, important caveats and limitations to consider with such assessments due to PREDICTIVE being an open observational study, and these are discussed further below. Nevertheless, the present work has enabled us to make exploratory comparisons of clinical

Figure 1. HbA_{1c} by visit and final insulin doses, stratified by cohort and insulin detemir dosing subgroup. b.i.d.=twice daily; detemir=insulin detemir; HbA_{1c}=glycated hemoglobin; OAD=oral antidiabetic drug; o.d.=once daily; U=units.



outcomes associated with the empirical o.d. or b.i.d. use of detemir in three different cohorts defined by commonly used therapy regimens, i.e. basal–bolus insulin-treated type 1 diabetes, basal insulin plus OAD-treated type 2 diabetes, and basal–bolus insulin-treated type 2 diabetes.

There are some consistent findings that emerge from the present analyses when we compare outcomes according to detemir dosing frequency. These might be of importance in informing the clinical use of detemir. In all three cohorts, patients completing on o.d. detemir tended have numerically superior glycemic control than those on b.i.d. dosing or those switching from o.d. to b.i.d. dosing. Another consistency is that o.d. dosing tended to involve lower total and basal insulin doses. This latter observation supports the conclusion of DeVries et al.[12] (from an analysis of detemir and glargine clinical trial data) that increasing the dose frequency of a basal insulin analog (and then titrating the dose to two glycemic targets; fasting and pre-dinner) tends to escalate the basal insulin dose without a corresponding gain in glycemic control. Our findings are also consistent with those previously reported in the randomized ADAPT trial,[10] which compared o.d. to b.i.d. detemir in a cohort of basal–bolus insulin-treated adults with type 1 diabetes. Altogether, our data suggest there is no advantage to b.i.d. dosing over o.d. dosing since glycemic control was no better, hypoglycemia was often more frequent, and dose was invariably higher with b.i.d. dosing.

However, it must be remembered that the basal insulin injection frequency was not randomized in PREDICTIVE; rather, empirical choices for all clinical decisions were made by the practicing physician.[13] Clues about the factors driving such choices can be found in baseline differences between subgroups commencing on o.d. or b.i.d. detemir. In particular, it is striking that much higher percentages of previously insulin-treated patients commencing detemir twice daily were on b.i.d. prestudy basal insulin regimens and/or NPH insulin. Similarly, most previously basal insulin-treated patients initiated onto o.d. detemir were using an o.d. prestudy basal insulin regimen. This suggests that, in many cases, the initial choice of detemir dosing frequency was simply a continuation of previous regimens. Of course, the basal insulin dosing frequency of such previous regimens might have been determined by genuine clinical needs. Nevertheless, at the very least, we can conclude that the empirical use of o.d. detemir produces results at least as good as the empirical use of b.i.d. detemir in all three cohorts studied.

Further observations within each cohort are noteworthy, though must be considered with the caveat that analyses made using these smaller subgroups have limited statistical validity. In the cohort with type 1 diabetes, for example, glycemic control improved significantly in the subgroups beginning and completing on o.d. or b.i.d. dosing, but improvement was less marked in o.d.-b.i.d. switchers despite this subgroup having similar baseline HbA_{1c} values to the other two subgroups and subsequently using higher insulin doses. These observations might suggest that these "switchers" represent a self-selected "difficult" cohort, and could support a hypothesis that glycemic control is not a simple function of mean insulin dose. The biggest increase in insulin dosing in this "switch" group occurred between baseline and 12 weeks suggesting that for most patients switched from o.d. to b.i.d. dosing, the change was made early. It is therefore not possible to estimate the extent to which improved outcomes were due to an increased basal injection frequency rather than the change of basal insulin preparation. However, the observation that o.d. completers tended to do as well as b.i.d. completers implies that an increase in basal dose frequency does not necessarily bring

any benefit. On the other hand, it is impossible to know whether patients completing on b.i.d. detemir would have had less favorable outcomes if denied this dosing schedule.

For the cohort with type 2 diabetes treated with basal insulin only plus OADs, outcomes were clearly better in the subgroup completing on o.d. rather than b.i.d. detemir, since blood glucose control was numerically superior with half the insulin dose in the o.d. subgroup. There were, however, notable baseline differences between the o.d. and b.i.d. subgroups that are likely to be contributory factors in this. Firstly, the majority of the o.d. subgroup were previously insulin-naïve, whereas most individuals in the b.i.d. group were prior insulin users. Many of the latter were previously on glargine and/or a regimen involving o.d. basal insulin and some were even using rapid-acting analogs. These observations suggest that a major factor driving the choice to initiate detemir with b.i.d. dosing in this subgroup was the desire to "intensify" the basal insulin regimen with more frequent dosing, and this option is permitted by the labeling of detemir. It is not surprising that improvements in glycemic control were superior in the predominantly insulin-naïve o.d. subgroup than in the b.i.d. subgroup where many patients appear to have been intensifying their previous basal insulin therapy. It is nevertheless encouraging that HbA_{1c} improved in the b.i.d. subset, albeit with high insulin doses. The 4-T study[18] recently showed that superior glycemic control was achieved in patients with type 2 diabetes who initiated insulin with mealtime insulin aspart or twice-daily biphasic insulin aspart compared to those commencing insulin with detemir, but this difference only applied when baseline HbA_{1c} exceeded 8.5%. This might reflect the increasing importance of postprandial hyperglycemia in the progressive course of type 2 diabetes. Taking this finding into consideration, it could be speculated that many patients in our b.i.d. subset might have benefited more from the addition of mealtime bolus insulins than from a b.i.d. basal-only insulin regimen. The b.i.d. subgroup also differed from the o.d. group overall by being heavier, so it is possible that poorer outcomes in this group reflected greater insulin resistance. It could also be speculated that some overweight patients were selected for b.i.d. detemir to accommodate larger insulin doses. Hypoglycemia was infrequent and comparable between the o.d. and b.i.d. subgroups, so is unlikely to have influenced other results.

Few patients were identified for the analysis of basal–bolus insulin therapy in type 2 diabetes, so interpretations must be made with caution. Again, glycemic control tended to improve to the greatest extent in the o.d. subgroup in which insulin doses were, again, the lowest of the dosing subgroups. There is, again, evidence from the baseline data that intensification was being sought for the majority of patients in the b.i.d. subset. Hypoglycemia tended to be most problematical at baseline and thereafter in the seven patients who switched from o.d. to b.i.d. detemir. Although, as expected, the overall incidence of hypoglycemia was less common than in the type 1 diabetes cohort, the frequency of events (including major episodes) was perhaps sufficient in this small subgroup to have influenced the decision to switch to b.i.d. dosing, and there is some indication that hypoglycemia decreased markedly between the 12- and 26-week visits, perhaps as a response to a change in dosing frequency. The fact that insulin doses in these patients did not reach such high values as in the subgroup on b.i.d. detemir throughout might also relate to hypoglycemia, and presumably also reflects a much lower starting dose. Future research utilizing a continuous glucose monitoring system as a more accurate means of measurement could be used to explore further

the potential impact of dose frequency on frequency of hypoglycemia.

CONCLUSION

In conclusion, the present analysis has yielded observations that are entirely consistent with those made in the randomized ADAPT study,[10] but extending these into cohorts with type 2 diabetes. The data suggest no general advantage to b.i.d. dosing over o.d. dosing as glycemic control tends to be no better, whereas insulin doses tend to be higher. The data therefore tend to support o.d. dosing as the most appropriate starting regimen for detemir. However, basal injection frequency was not randomized and empirical choices were clearly made, as evidenced by some important baseline disparities between patients selected for b.i.d. and o.d. dosing. To some extent the choice of basal dosing frequency reflected prior regimens and (especially in type 2 diabetes) the choice of b.i.d. dosing appeared to reflect a desire to intensify therapy. In the latter case, even better improvements in glucose control might have been realized with a greater focus on the introduction or optimization of prandial insulin. At the very least, however, we can conclude that the empirical use of o.d. detemir produces results at least as good as the empirical use of b.i.d. detemir in both basal plus OAD and basal–bolus therapy, and in both type 1 and type 2 diabetes.

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The study is registered with ClinicalTrial.gov and has the following identifier: NCT00659295.

Clinical Trial Data Posting

No results have been posted.

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