Clinical Experience of Insulin Detemir in Turkey: Efficacy and Safety Data From the PREDICTIVE™ Study

Türkiye'de İnsulin Detemir ile Klinik Deneyim: PREDICTIVE™ Çalışması Etkililik ve Güvenlilik Verileri

Mustafa Yenigün, Gonca Oruk*, Akın Dayan**, Gaye Akoz***, Sevil Emek****

Haseki Education and Research Hospital, 4. Internal Medicine Clinic, Istanbul, Turkey
*Izmir Ataturk Education and Research Hospital, Endocrinology Clinic, Izmir, Turkey
**Haydarpasa Numune Hospital, Diabetes Outpatient Clinic, Istanbul, Turkey
***Sait Ciftci Public Health Center, Istanbul, Turkey
****Novo Nordisk, Medical Department, Istanbul, Turkey

Abstract

Objective: To assess outcomes in Turkish type 1 and 2 diabetic patients given insulin detemir in the multinational PREDICTIVE™ study.

Materials and Methods: PREDICTIVE™ was a large, open-label, prospective, observational study examining the efficacy and safety of insulin detemir in routine clinical practice. Data from the Turkish cohort (2786 patients) were analysed following a 12-week treatment period.

Results: Following treatment, HbA_{1c} significantly decreased by-1.81% (from 9.66%) in type 1 diabetics and by-1.77% (from 9.54%) in type 2 diabetics (P<0.0001). Mean fasting blood glucose (FBG) reduced from 12.35 mmol/L (222.3 mg/dL) to 8.10 mmol/L (145.8 mg/dL) in type 1 diabetics and from 13.46 mmol/L (242.3 mg/dL) to 8.05 mmol/L (144.9 mg/dL) in type 2 diabetics (P<0.0001). Mean within-patient variability of FBG was also reduced (P<0.0001). Serious adverse drug reactions occurred in four patients, 38 if including major hypoglycaemia. Total, major and nocturnal hypoglycaemic events all reduced in frequency after 12 weeks (P<0.0001).

Conclusions: Insulin detemir treatment for 12 weeks resulted in improved, more predictable glycaemic control, modest weight loss or minimal weight gain, and reduced incidence of hypoglycaemia in a large cohort of Turkish patients with diabetes treated according to local clinical practice. *Turk Jem 2008; 12: 91-6*

Key words: Insulin detemir, insulin glargine, NPH insulin, type 1 diabetes, type 2 diabetes

Özet

Amaç: Bu çalışma, uluslararası bir çalışma olan PREDICTIVE™ çalışmasına Türkiye'den katılan Tip 1 veya Tip 2 diyabetli hastaların insülin detemir tedavisine başlamalarının sonuçlarını değerlendirmektedir.

Gereç ve Yöntemler: PREDICTIVE™, insülin detemirin rutin klinik uygulamadaki güvenilirlik ve etkinliğini gözleyen, büyük çaplı, açık etiketli, prospektif bir gözlemsel çalışmadır. 12 haftalık bir tedavi döneminden sonra, Türkiye kohortundan (2786 hasta) elde edilen verilerin analizi yapılmıştır.

Bulgular: Tedavi döneminin sonunda HbA_{1c}, Tip 1 diyabetli hastalarda belirgin olarak %1.81 oranında (%9.66'dan), Tip 2 diyabetli hastalarda ise %1.77 (%9.54'den) olacak şekilde belirgin olarak düşmüştür (her iki grup için de P<0.0001). Ortalama açlık kan glukozu (AKG) Tip 1 diyabetli hastalarda 12.35 mmol/L (222.3 mg/dL)'den 8.10 mmol/L (145.8 mg/dL)'ye; Tip 2 diyabetli hastalarda 13.46 mmol/L (242.3 mg/dL)'den 8.05 mmol/L (144.9 mg/dL)'ye düşmüştür (her iki grup için de P<0.0001). Bununla birlikte, hastaların kendi içinde görülen AKG değişkenliği de azalmıştır (her iki grup için de P<0.0001). Tip 2 diyabetli hastaların vücut ağırlığında az miktarda (0.2 kg) düşüş görülmüştür. Hastaların dördünde (majör hipoglisemiler de dahil olduğunda otuzsekizinde) ciddi advers ilaç reaksiyonu görülmüştür. Total, majör ve noktürnal hipoglisemik olaylar, detemir tedavisine başlandıktan sonra düşüş göstermiştir (P<0.0001): Majör hipoglisemik olaylar Tip 1 diyabetli hastalarda, 3.9'dan 0.6 olay/hasta-yılı'na; Tip 2 diyabetlilerde ise 1.2'den 0.1 olay/hasta yılı'na düşmüştür (her iki grup için de P<0.0001).

Sonuç: Sonuç olarak, lokal klinik uygulamalara uygun olarak Türk hastalardan oluşan büyük bir kohorta uygulanan insülin detemir tedavisi, 12 hafta sonunda iyileşmiş ve daha öngörülebilir glisemik kontrol, az miktarda kilo kaybı ve hipoglisemi insidansında düşüş ile sonuçlanmıştır. *Turk Jem 2008; 12: 91-6*

Anahtar kelimeler: İnsülin detemir, insülin glargin, NPH insülin, tip 1 diyabet, tip 2 diyabet

Address for Correspondence: Mustafa Yenigün, Haseki Education and Research Hospital, 4. Internal Medicine Clinic, Istanbul, Turkey
Phone.: 0212 529 44 73 Fax: 0212 586 95 57 E-mail: dryenigun@hotmail.com **Recevied:** 26.08.2008 **Accepted:** 31.12.2008

Introduction

The therapeutic goal in diabetes is to achieve and maintain blood glucose levels as close to normal as possible. Glycated haemoglobin (HbA_{1c}) provides a measure of long-term glucose control and individuals with normal glycaemic control would be expected to have HbA_{1c} values <6.0% (1). Current treatment goals from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend that individuals with diabetes should strive to achieve an HbA_{1c} of ≤7.0%, while the American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) recommend a lower HbA_{1c} target of ≤6.5% (1,2). Achieving target HbA_{1c} levels are important because poorly controlled diabetes is associated with a greater incidence and a faster rate of progression of complications such as retinopathy, circulatory problems and cardiovascular disease (3-6). While maintenance of strict glycaemic control is important to minimize diabetic complications, it also increases the risk of hypoglycaemic events. This risk may be increased because of the pharmacokinetic limitations of human insulins, such as neutral protamine Hagedorn (NPH), making insulin dosing more difficult. NPH exhibits peak activity 5-7 h after administration, which can raise the risk of nocturnal hypoglycaemic events following evening administration (7,8). The absorption kinetics of NPH are also variable (9), which can make it difficult to accurately predict the duration of action (7). In addition, insulin treatment can induce pronounced weight gain, which means that patients often resist insulin initiation and may fail to comply with treatment (10).

Insulin analogues were developed to provide a more 'physiological' pharmacokinetic profile than that achieved with subcutaneously injected human insulin. Basal insulin analogues, such as insulin detemir and glargine, offer more prolonged activity than NPH insulin, potentially reducing the risk of hypoglycaemia (11). In isoglycaemic clamp studies, insulin detemir has demonstrated improved pharmacokinetic and pharmacodynamic activity combined with improved within-patient variability compared with NPH insulin (11-13), or insulin glargine (11,14). Clinical trials have shown that insulin detemir provides effective glycaemic control with reduced weight gain compared with NPH or insulin glargine (15-22), and a reduced risk of hypoglycaemic events compared with NPH insulin (15,16,19,20,23,24).

Approximately 2.6-2.9 million Turkish people have diabetes and 300,000 individuals develop the disease each year (25,26). Moreover, an additional 2.4 million are estimated to have impaired glucose tolerance (26), placing them at increased risk of developing diabetes and cardiovascular disease. Insulin analogues are being increasingly used in the treatment of diabetes in Turkey, hence the importance of insights into their everyday clinical performance from studies such as PREDICTIVE™ (Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation). PREDICTIVE was an open-label, prospective, observational study to evaluate the safety and efficacy of insulin detemir in a large cohort of diabetic patients in primary and secondary care settings (27,28). In this report, the safety and efficacy of insulin detemir treatment was examined in the Turkish cohort of the PREDICTIVE study.

Materials and Methods

Study design and objectives

PREDICTIVE is an open-label, prospective, observational study evaluating the safety and efficacy of insulin detemir treatment in patients with type 1 or type 2 diabetes.

Patient population

PREDICTIVE has recruited more than 35,000 patients from 25 nations worldwide, including more than 20,500 patients from 11 European countries. This study reports on the 12-week follow-up data from 2786 patients in the Turkish cohort with type 1 diabetes (627 patients, 23%) or type 2 diabetes (2150 patients, 77%). Disease classification was missing for nine patients in the cohort. The trial was performed in accordance with Turkish regulatory requirements, with recruited patients giving informed consent.

Treatment regimen

Patients were prescribed insulin detemir by their physician as part of their standard clinical care and followed up after 12 weeks. The choice of insulin dosing regimen, and any decision to discontinue or modify any element of the treatment at the time of commencing insulin detemir (or subsequently), were based on clinical evaluation and were at the discretion of the physician. The inclusion and exclusion criteria have been reported previously (27).

Primary and secondary endpoints

The primary endpoint was serious adverse drug reactions (SADRs), including major hypoglycaemic events. Secondary endpoints included rates of total and nocturnal hypoglycaemia, HbA_{1c}, mean self-monitored fasting blood glucose (FBG) or fasting plasma glucose, within-patient FBG variability and body weight change. Safety and efficacy endpoints were assessed from patient records, recall and diaries. Hypoglycaemic events were recorded over the 4 weeks preceding the initiation of insulin detemir and again during the 4 weeks preceding follow-up. Major hypoglycaemic events were defined as an episode in which the patient was unable to self-treat and third-party intervention was required. The patient also had to have one of the following for this classification: (i) blood glucose <2.8 mmol/L (<50 mg/dL); or (ii) reversal of symptoms after food intake, glucagon or intravenous glucose administration. Nocturnal events were defined as those occurring in the interval between bedtime and normal morning waking.

FBG variability was defined as the standard deviation (SD) calculated from FBG measurements made within the 4-week intervals preceding the baseline and follow-up visits. Up to 6 values were included wherever possible with a minimum of 2 values required.

Statistical analysis

Efficacy analyses included all patients with at least one efficacy measurement at baseline and during the follow-up period. Descriptive statistics, including means and SD, were used to describe demographic parameters, HbA_{1c}, mean FBG, body weight, body mass index and hypoglycaemic events. Changes from baseline were analysed using paired *t*-tests for HbA_{1c}, body weight change, and mean FBG. The Wilcoxon paired sign rank sum test was used for discrete variables such as rate of hypoglycaemic events. A P-value of <0.05 was considered statistically significant.

Results

Demographics

Table 1 shows basic demographic data and recorded reasons for initiating insulin detemir in the type 1 and type 2 diabetic patients. The most common reasons for physicians initiating insulin detemir at baseline were: to improve glycaemic control; to reduce blood glucose variability; and to reduce the risk of hypoglycaemia (Table 1).

SADRs and hypoglycaemia

A total of 11 SADRs, other than major hypoglycaemia, were experienced by 4 of 2786 (0.14%) patients (Table 2). One patient with type 1 diabetes experienced generalised oedema, while three patients with type 2 diabetes experienced the remaining SADRs (Table 2). When major hypoglycaemic events were included as SADRs, the number of individuals experiencing SADRs increased to 38 of 2786 (1.36%). SADRs including major hypoglycaemic events were more common in patients with type 1 than in those with type 2 diabetes (19 of 627 [3.0%] compared to 19 of 2150 [0.9%]). After 12 weeks of insulin detemir therapy, the mean rate of total hypoglycaemic events was significantly decreased compared with baseline in patients with type 1 diabetes (10.0 fewer hypoglycaemic events/patient-year; P<0.0001) and in type 2 diabetes (3.5 fewer hypoglycaemic events/patient-year; P<0.0001; Figure 1). Significant decreases in major and nocturnal hypoglycaemic events were also observed following 12 weeks of insulin detemir treatment. The mean rate of major hypoglycaemic events decreased by 3.3 events/patient-year (P<0.0001) and 1.1 episode/patient-year (P<0.0001) in type 1 and type 2 diabetes, respectively. Nocturnal hypoglycaemic events were reduced by 2.9 events/patient-year in patients with type 1 diabetes and by 1.2 events/patient-year in the patients with type 2 diabetes (P<0.0001).

Glycaemic control

Insulin detemir treatment resulted in significant improvements in all of the measures of glycaemic control (mean HbA_{1c}, mean FBG and mean within-patient FBG variability) in both type 1 and type 2 diabetes patients (P<0.0001, all endpoints; Figure 1). Insulin detemir reduced HbA_{1c} by 1.81% and 1.77% in patients with type 1 and type 2 diabetes, respectively (P<0.0001; Figure 2a). Mean FBG was reduced by 76.5 mg/dL (4.25 mmol/L) in patients with type 1 diabetes and by 97.4 mg/dL (5.41 mmol/L) in patients with type 2 diabetes (P<0.0001, Fig. 2b). Mean within-patient FBG variability was reduced by 24.9 mg/dL (1.38 mmol/L) and 18.9 mg/dL (1.05 mmol/L) in patients with type 1 and type 2 diabetes, respectively (P<0.0001; Figure 2c).

Insulin dosing

The subgroup of patients receiving basal-bolus insulin therapy at baseline and at Week 12 allowed a 'like with like' comparison of changes in insulin dosing to be made. In this group of patients with type 1 diabetes, the mean daily dose of basal insulin was 0.32 U/kg at baseline and 0.34 U/kg at Week 12 (respective total insulin doses were 0.88 U/kg at baseline and 0.95 U/kg at Week 12). In basal-bolus treated patients with type 2 diabetes, the mean daily basal insulin dose was 0.31 U/kg at baseline and 0.32 U/kg at Week 12 (respective total insulin doses were 0.76 U/kg at baseline and 0.81 U/kg at Week 12). At Week 12, 88% of all patients administered one daily basal insulin dose (90% of patients with type 1 diabetes and 87% of patients with type 2 diabetes).

Mean weight change

After 12 weeks of insulin detemir treatment, there was a modest increase in total body weight in patients with type 1 diabetes and a modest decrease in body weight in patients with type 2 diabetes (P=0.02; Fig. 3).

Discussion

These data from 2786 Turkish patients with type 1 and type 2 diabetes demonstrate that 12 weeks of insulin detemir treatment resulted in improved glycaemic control compared with baseline, without clinically significant weight gain and with a simultaneous reduction in hypoglycaemic events. All measures of glycaemic control (HbA_{1c}, mean FBG, and mean within-patient variability in

Table 1. Patient demographics

Demographic parameter	Type 1 patients N=627	Type 2 patients N=2150
Gender (male/female, %)	54/46	40/60
Age (years, mean±SD)	28.9±15.2	55.9±10.5
Weight (kg, mean±SD)	67.8±12.1	77.0±13.0
Body mass index (kg/m^2, mean±SD)	22.8±4.1	28.8±5.3
Duration of diabetes (years, mean±SD)	8.2±6.7	10.6±6.6
Physicians' reason(s) for initiating insulin detemir* (%)		
Improve glycaemic control	93.6	93.3
Reduce blood glucose variability	47.7	49.0
Reduce risk of hypoglycaemia	31.7	35.1
Unstable diabetes	29.9	30.3
Try new insulin	28.4	28.4
Improve weight control	28.5	27.8
Dissatisfied with current therapy	24.7	23.4
Change as a result of insulin pen	8.1	8.1
Side effects from current therapy	8.3	7.8

*Physicians could state more than one reason
SD = standard deviation

Table 2. Serious adverse drug reactions (SADR). A total of 11 adverse events were observed in 4 of 2786 patients (0.14%)

SADR*	Number of episodes
Nausea	1
Vomiting	1
General oedema	1
Injection site oedema	1
Injection site pain	1
Injection site rash	1
Malaise	1
Hypersensitivity	1
Dizziness	1
Erythema	1
Pruritis	1

*SADR in this table do not include major hypoglycaemic events

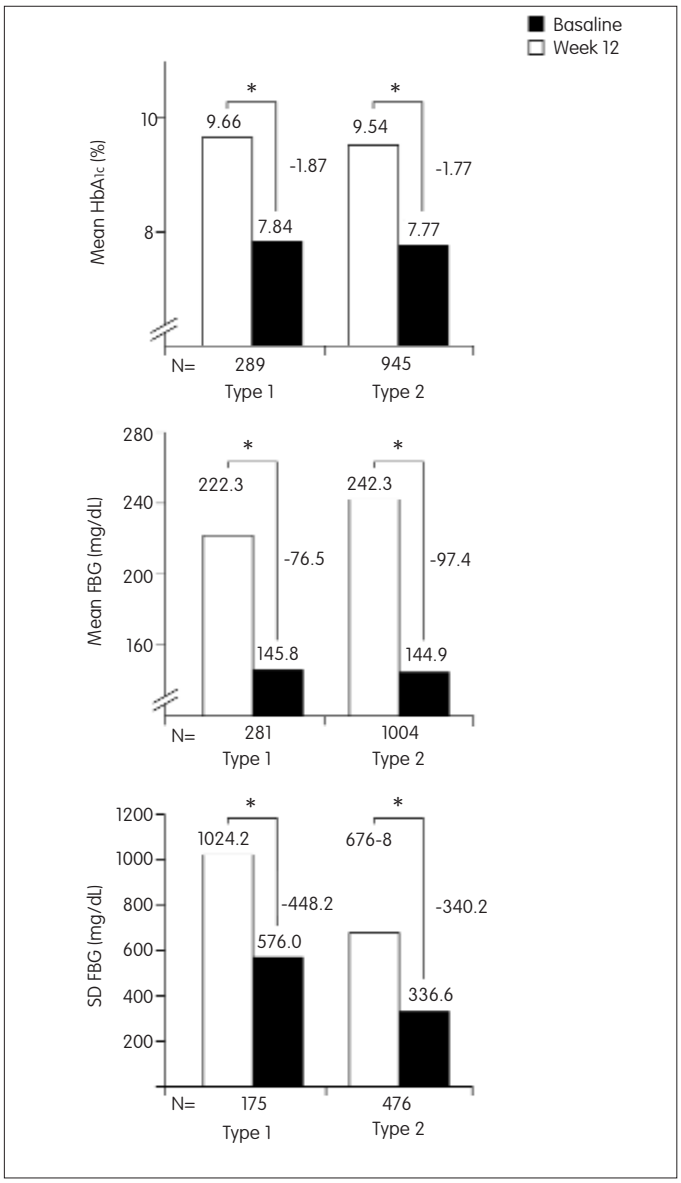

Figure 1. Mean rate of total, major and nocturnal hypoglycaemic events at baseline and after 12 weeks of insulin detemir treatment. *P<0.0001

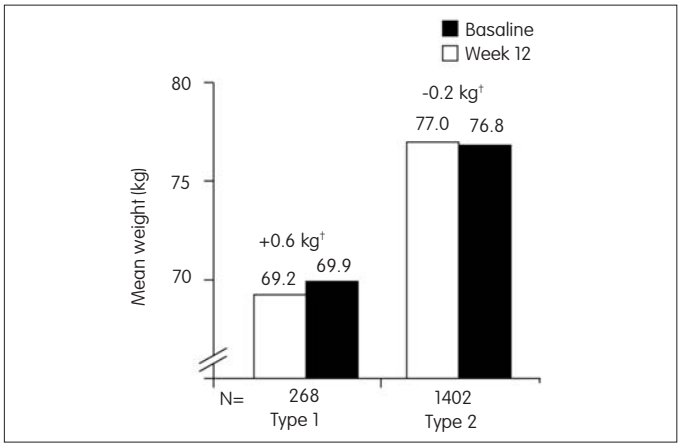

Figure 2. Mean HbA1c, fasting blood glucose (FBG) and within-patient FBG variability at baseline and after 12 weeks of insulin detemir treatment. *P< 0.0001

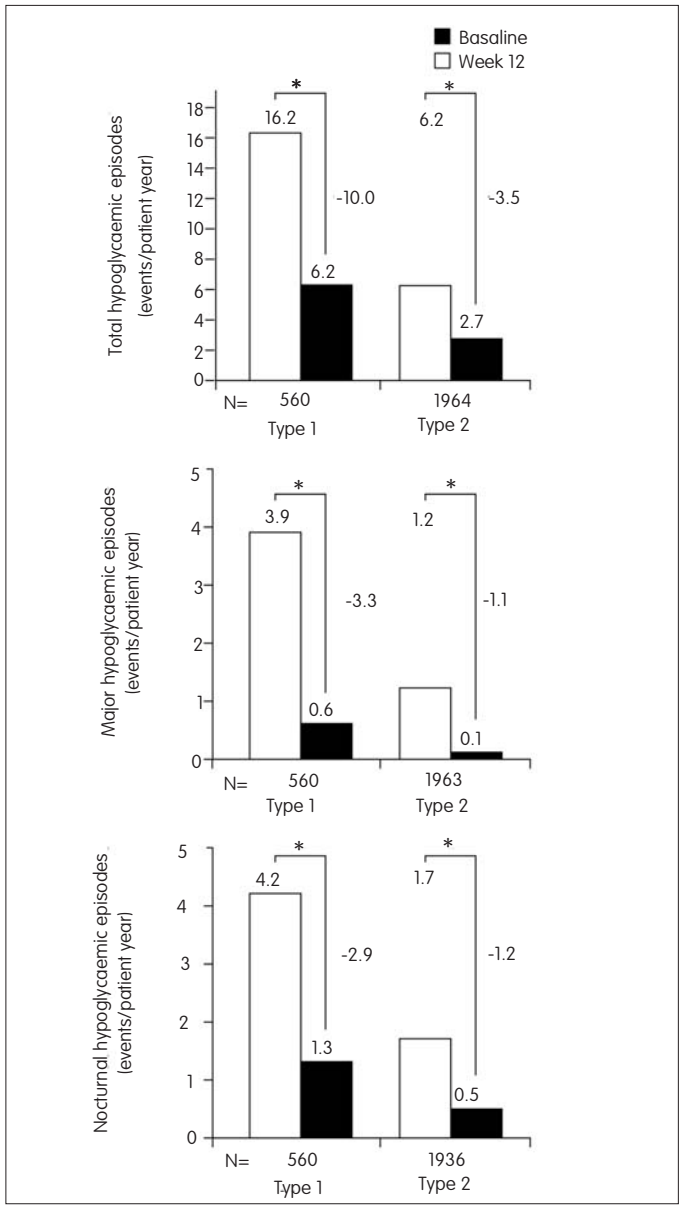

Figure 3. Mean body weight before and following 12 weeks of insulin detemir treatment. †P=0.02

FBG) showed statistically significant improvements (P<0.0001). These data are consistent with the results of the wider European PREDICTIVE study, which included 20,531 patients from 11 European countries (28). Baseline HbA1c was somewhat higher in the Turkish patient population (9.7% for type 1 and 9.5% for type 2 diabetes) compared with the European cohort (8.3% for type 1 and 8.5% for type 2 diabetes) (28). However, following insulin detemir treatment, HbA1c levels in both type 1 and type 2 diabetes groups of the Turkish cohort were lowered to 7.8%, which was similar to the wider European data (HbA1c=7.6-7.8%). Similarly, mean FBG values and mean within-patient FBG variability were higher in the Turkish cohort at baseline compared with the European cohort, but following insulin detemir treatment these parameters were reduced to similar levels in both cohorts (28). These improvements in glycaemic control were achieved without major increases in total insulin dose, and 88% of all Turkish patients required only a once-daily basal insulin detemir injection.

Insulin treatment is often associated with weight gain, which may have health implications for patients and is an important reason for patient resistance to initiating insulin treatment and subsequent failure to adhere to insulin treatment (29). Clinical trials have shown that insulin detemir can provide effective glycaemic control with weight loss or with minimal weight gain in comparison to other basal insulins (29,30). Although randomized clinical trials provide the 'gold standard' for evaluating medicines, they do have certain drawbacks as they include relatively small numbers of highly selected patients who receive intensive clinical support in order to optimise clinical outcomes (31). Therefore, large observational studies, such as PREDICTIVE, can complement randomized clinical trials by providing valuable information about the efficacy and safety of drugs in the normal clinical setting, where patients do not receive such intensive support. Results from both the PREDICTIVE European cohort (28), and the Turkish cohort reported here, demonstrate that insulin detemir treatment can result in substantially improved glycaemic control without clinically significant weight gain in a real-life clinical setting. This study demonstrated that in predominantly adult patients with type 2 diabetes, insulin detemir treatment is associated with modest weight loss despite the improvement in glycaemic control. In the type 1 diabetic patient population, which includes a greater proportion of adolescents and children, insulin detemir was associated with modest weight gain, as would be expected in such a population.

The Turkish data were also consistent with the overall European PREDICTIVE data (28) in showing statistically significant and clinically significant reductions in total, major, and nocturnal hypoglycaemic events. The rates of major hypoglycaemia in the Turkish population at baseline (3.9 and 1.2 events/patient-year in patients with type 1 and type 2 diabetes, respectively) were similar to those reported in the larger European cohort (3.8 and 0.8 events/patient-year) (28). In the Turkish cohort, 12 weeks of insulin detemir treatment significantly reduced the rate of major hypoglycaemic events to 0.6 events/patient-year in patients with type 1 disease and to 0.1 events/patient-year in those with type 2 diabetes, which was consistent with the data from the wider European cohort (28). The reported rates of total and nocturnal hypoglycaemia in the Turkish cohort were lower than those reported by the larger European cohort. For example, the baseline rate of nocturnal hypoglycaemia in patients with type 1 disease was 4.2 events/patient-year in the Turkish cohort and 13.7 events/patient-year in the European cohort (28). However, in both cohorts, insulin detemir treatment significantly reduced the burden of nocturnal hypoglycaemia. Hypoglycaemic events are distressing for patients and can result in failure to adhere to insulin treatment, so any treatment that can reduce the rate of hypoglycaemia is likely to improve glycaemic control (32).

While the results of this analysis are broadly positive, they should be interpreted in light of some limitations of this study. PREDICTIVE is an open-label, prospective, observational non-comparative study that is likely to include patients for whom insulin detemir was considered to be well suited and/or patients who were not considered to be optimally responding to alternative previous therapies. In addition, the study cohorts do not exclude patients for whom additional changes of regimen (other than the use of insulin detemir) were made. Thus, the improvements in endpoints documented here cannot be unambiguously attributed to insulin detemir in every case and cannot be expected for every patient given insulin detemir in preference to alternative treatments. Another limitation of this study is that data concerning postprandial blood glucose control were not collected. Nevertheless, it is encouraging to observe that many of the objectives physicians gave as reasons for using insulin detemir and including patients in PREDICTIVE (Table 1) were achieved.

In summary, the results presented here show that the use of insulin detemir resulted in improved and more predictable glycaemic control without inappropriate weight gain, and reduced hypoglycaemic events in a Turkish patient population treated according to local clinical practice. The data are consistent with those reported from the wider European PREDICTIVE cohort and support the results of randomized clinical trials. In addition, our results support the clinical rationale behind the increasing use of insulin analogues in Turkey.

Declaration of Competing Interests

Authors have none to declare and full details can be supplied when requested.

Acknowledgement

The preparation of this article was supported by Novo Nordisk, Turkey. The assistance of Murray Edmunds is gratefully acknowledged.

References

1. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; 29: 1963-72.
2. American College of Endocrinology, American Association of Clinical Endocrinologists. American College of Endocrinology Consensus Statement on Guidelines for Glycemic Control. Endocr Pract 2002; 8: 5-11.
3. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005; 353: 2643-53.
4. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003; 290: 2159-67.
5. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002; 287: 2563-9.
6. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Wright AD, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
7. Peterson GE. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. Curr Med Res Opin 2006; 22: 2613-9.
8. Starke AA, Heinemann L, Hohmann A, Berger M. The action profiles of human NPH insulin preparations. Diabet Med 1989; 6: 239-44.
9. Kølendorf K, Bojsen J, Deckert T. Clinical factors influencing the absorption of 125I-NPH insulin in diabetic patients. Horm Metab Res 1983; 15: 274-8.
10. Farmer A, Kinmonth AL, Sutton S. Measuring beliefs about taking hypoglycaemic medication among people with type 2 diabetes. Diabet Med 2006; 23: 265-70.
11. Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C, Draeger E. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004; 53: 1614-20.

12. Plank J, Bodenlenz M, Sinner F, Magnes C, Gorzer E, Regittnig W, Endahl LA, Draeger E, Zdravkovic M, Pieber TR. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care 2005; 28: 1107-12.
13. Wutte A, Plank J, Bodenlenz M, Magnes C, Regittnig W, Sinner F, Rønn B, Zdravkovic M, Pieber TR. Proportional dose-response relationship and lower within-patient variability of insulin detemir and NPH insulin in subjects with type 1 diabetes mellitus. Exp Clin Endocrinol Diabetes 2007; 115: 461-7.
14. Klein O, Lynge J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes Metab 2007; 9: 290-9.
15. Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg J-E, Abrams P, Landin-Olsson M, Hylleberg B, Lang H, Draeger E; Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes; a randomised clinical trial. Diabetes Care 2004; 27: 1081-7.
16. De Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E, Elte JW. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005; 7: 73-82.
17. Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med 2005; 22: 850-7.
18. Pieber TR, Treichel HC, Hompesch B, Philotheou A, Mordhorst L, Gall MA, Robertson LI. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabet Med 2007; 24: 635-42.
19. Hermansen K, Davies M, Derezinski T, Martinez RG, Clauson P, Home P. 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-naive people with type 2 diabetes. Diabetes Care 2006; 29: 1269-74.
20. Philis-Tsimikas A, Charpentier G, Clauson P, Martinez Ravn G, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006; 28: 1569-81.
21. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008; 51: 408-16.
22. Raslová K, Tamer SC, Clauson P, Karl D. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. Clin Drug Investig 2007; 27: 279-85.
23. Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H, Kristensen A, Draeger E. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 2003; 26: 590-6.
24. Kølendorf K, Ross GP, Pavlic-Renar I, Perriello G, Philotheou A, Jendle J, Gall MA, Heller SR. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabet Med 2006; 23: 729-35.
25. Satman I, Yilmaz T, Sengul A, Salman S, Salman F, Uygur S, Bastar I, Tütüncü Y, Sargin M, Dinççag N, Karsidag K, Kalaça S, Ozcan C, King H. Population-based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). Diabetes Care 2002; 25: 1551-6.
26. Onat A, Hergenc G, Uyarel H, Can G, Ozhan H. Prevalence, incidence, predictors and outcome of type 2 diabetes in Turkey. Anadolu Kardiyol Derg 2006; 6: 314-21.
27 Luddeke HJ, Sreenan S, Aczel S, Maxeiner S, Yenigun M, Kozlovski P, Gydesen H, Dornhorst A; PREDICTIVE Study Group. PREDICTIVE: a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. Diabetes Obes Metab 2007; 9: 428-34.
28. Dornhorst A, Luddeke HJ, Sreenan S, Koenen C, Hansen JB, Tsur A, Landstedt-Hallin L. Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. Int J Clin Pract 2007; 61: 523-8.
29. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes-causes, effects and coping strategies. Diabetes Obes Metab 2007; 9: 799-812.
30. Hermansen K, Davies M. Does insulin detemir have a role in reducing risk of insulin-associated weight gain? Diabetes Obes Metab 2007; 9: 209-17.
31. Ligthelm RJ, Borzì V, Gumprecht J, Kawamori R, Wenying Y, Valensi P. Importance of observational studies in clinical practice. Clin Ther 2007; 29: 1284-92.
32. Jacqueminet S, Masseboeuf N, Rolland M, Grimaldi A, Sachon C. Limitations of the so-called 'intensified' insulin therapy in type 1 diabetes mellitus. Diabetes Metab 2005; 31: 445-50.

Appendix 1. Members of the PREDICTIVE Turkey Study Group

M. Acar, G. Acarturk, M. Adas, M. Adıguzel, M. Akbas, A. Akcay, G. Akcay, S. Akcurin, H. Akdeniz, T. Akdere, C. Akdogan, G. Akoz, E. Aktunc, E. Algun, N. Altıner, Y. Altunoglu, M. Araz, C. Arılar, Y. Arman, M. Arslan, M. Asik, A. Aslan, I. Aslan, E. Atabek, M. Atasoy, H. Atmaca, N. Aydin, M. Aydın, I. Aykanat, Y. Bahceci, I. Bahceci, K. Balci, H. Balkanci, K. Basak, M. Bastemir, S. Baysal, S. Baysoy, O. Bektasyıldırım, A. Bereket, O. Berker, N. Bilal, O. Bilgir, I. Bircan, F. Bulduk, A. Büyükbese, A. Buyukgediz, S. Caglayan, S. Cakir, H. Cakir, H. Calikusu, S. Can, N. Caneroglu, A. Catan, T. Cavuşoğlu, M. Cebi, T. Cecen, A. Celebi, O. Celik, M. Cesur, S. Cetin, B. Cetinarslan, S. Cetinkalp, M. Cevik, E. Cevizci, A. Cokay, Y. Colakoglu, H. Comert, R. Conkar , M. Davutoglu, A. Dayan, S. Demirel, R. Demirtunc, Z. Deniz, D. Dereli, S. Dileklen, I. Dinc, S. Dinc, C. Dizdarer, M. Dogan, S. Dokmetas, M. Donmez, B. Dundar, C. Duygulu , M. Ecer, I. Emir, C. Emiroglu, E. Emrullah Demirel, F. Erdemir, M. Ergoz, T. Erkenez, A. Erol, E. Ererer , R. Ersoy, C. Erten, Y. Eryilmaz, U. Eryilmaz, I. Etikan, D. Gezdirici, Y. Gokden, G. Goker, S. Gonen, S. Gunaydın , A. Gunbeyaz, E. Güney, F. Guven , N. Guvener, N. Haksever, A. Harmandag, S. Hatun, O. Hersek, H. Hikmet Yuce, B. Ilhan, S. İlhan , P. Isguven, B. Isik, I. Kahraman, Z. Kalaycioglu, S. Kanberoglu, C. Kara, E. Karabiyik, Y. Karabulut, A. Karacam, F. Karakurt, A. Karaman, A. Kaya, D. Kaya, S. Kayıhan, M. Kendirci, A. Kilavuz, F. Kılıclı, E. Kilinc, U. Kocak, T. Korukoglu, A. Kosekli, B. Kumbasar, S. Kurtoglu, S. Kurtoglu, N. Kurtulus, M. Kurtulus, Z. Mocan, B. Moral, N. Mungan, S. Nalbant, A. Okten, S. Onal, T. Onat, E. Orbay, G. Oruk, A. Ozaydın, O. Ozbag, K. Ozenc, U. Ozensoy, B. Ozgur, B. Ozturk, C. Peru, M. Polat, T. Sabuncu, A. Saglam, H. Saglam, G. Sagun, I. Sahin, N. Sahin, H. Sahin, C. Salman, Y. Sarac, I. Satman, S. Sayınalp, M. Seker, D. Sendag, A. Sengul, B. Silan, S. Sonmez, G. Sop, Y. Suleymanoglu, F. Sutcu, N. Tanaci, I. Tanyeri, S. Tanyolac, I. Tarkun, S. Tatliagac, M. Temelli, M. Temizel, F. Terzioglu, M. Tokgoz, A. Tomakin, O. Topaloglu, N. Tuncay, M. Turgut, C. Turkay, C. Turker, I. Uslu, A. Uyanıkoglu, A. Uykac, H. Uzunel, O. Uzunlar, S. Yalın, D. Yavuz, M. Yenigun, S. Yesil, A. Yesilaltay, T. Yigit, G. Yildiz, Y. Yilmaz, M. Yılmaz, A. Zengi.