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ORIGINAL RESEARCH

Glycemic Control and Long-Acting Insulin Analog Utilization in Patients with Type 2 Diabetes

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ABSTRACT

Introduction: The objective was to compare glycemic control, insulin utilization, and body weight in patients with type 2 diabetes (T2D) initiated on insulin detemir (IDet) or insulin glargine (IGlar) in a real-life setting in the Netherlands. ***Methods:*** Insulin-naïve patients with T2D, starting treatment with IDet or IGlar between January 1, 2004 and June 30, 2008, were selected from the PHARMO data network. Glycemic control (hemoglobin A1c [HbA1c]), target rates (HbA1c <7%), daily insulin dose, and weight gain were analyzed comparing IDet and IGlar for patients with available HbA1c levels both at baseline and at 1-year follow-up. Analysis of all eligible patients (AEP) and a subgroup of patients without treatment changes (WOTC) in the follow-up period were adjusted for patient characteristics, propensity scores, and baseline HbA1c. ***Results:*** A total of 127 IDet users and 292 IGlar users were included in the WOTC analyses. The mean HbA1c dropped from 8.4%-8.6% at baseline to 7.4% after 1 year. Patients at HbA1c goal increased from 9% at baseline to 32% for IDet and 11% to 35% for IGlar, which was not significantly different (OR 0.75, 95% CI 0.46, 1.24). Weight gain (n=90) was less among IDet users (+0.4kg) than among IGlar users (+1.1kg), albeit not significant. The AEP analysis (252 IDet + 468 IGlar users) showed similar results with 33%-36% at goal (OR 0.81, 95% CI 0.57, 1.16), and median daily insulin doses of 25 IU/day (P=0.70). ***Conclusion:*** There was no significant difference between users of IDet and IGlar with respect to glycemic control and insulin dose in a real-life setting. The low proportion of patients on target at baseline may indicate that insulin therapy is initiated too late. Moreover, the observation that one-third of the patients reached HbA1c target at follow-up may indicate that basal insulin analogs are not titrated intensively enough.

Keywords: dose; glycemic control; HbA1c; insulin detemir, insulin glargine; retrospective cohort study; type 2 diabetes; utilization

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INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease, which is characterized by increased blood glucose levels. Glycemic control is important for the prevention of cardiovascular, renal, and neurological complications.[1-5] To obtain glycemic control, patients are initially treated with oral antidiabetics (OAD), along with diet and exercise management. In the course of the disease progression, most patients will require exogenous insulin to maintain hemoglobin A1c (HbA1c) at target levels. The purpose of insulin therapy is to mimic the natural insulin secretion and reduce HbA1c in patients with elevated levels. In order to delay or prevent diabetes-related complications, the goal for therapy is "near-normal" glycemia. The Dutch general practitioners (GPs) guidelines,[6] and the new American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus algorithm,[7,8] which was developed in 2009, set the general glycemic treatment goal to HbA1c <7%.

The two long-acting insulin analogs insulin detemir (IDet) and insulin glargine (IGlar) offer a prolonged duration of action compared to intermediate-acting basal insulin (NPH). In patients with T2D, basal insulin can be used either as an add-on to OADs, or as part of a basal-bolus regimen.[9,10] The advantage of long-acting insulin analogs compared to NPH is reduced risk of hypoglycemic events, while providing similar HbA1c levels.[11-17] Studies have shown that IDet and IGlar provide similar glycemic control at similar doses.[18-20] IDet has demonstrated less weight gain compared to both NPH[12,16,21] and IGlar.[19,20,22,23]

Most of the above-mentioned results are obtained in randomized controlled trials (RCT), which demonstrate the efficacy of basal insulin. However, clinical trials are limited by low generalizability of the findings due to the controlled study settings. Consequently, there may be a discrepancy between the efficacy (outcome in RCTs) and effectiveness (outcome in real life). Retrospective data analysis using real-world healthcare utilization and laboratory data can provide additional insights into the effectiveness in terms of utilization pattern, glycemic outcome, and body weight for IDet and IGlar.[13,24-26]

The objective of this study was twofold. Firstly, to compare glycemic control, insulin utilization, and body weight in patients with T2D initiated on IDet or IGlar in a Dutch real-life setting. Secondly, to examine how these real-life results correspond with treatment guidelines.

PATIENTS AND METHODS

Data

This retrospective study used the PHARMO data network in the Netherlands, which contains linked community pharmacy and hospitalization data for approximately 3.1 million patients. Community pharmacies dispense all outpatient drug prescriptions from both GPs and hospital specialists. Clinical laboratory data from tests ordered by both GPs and hospital specialists were available from central, eastern, and southern parts of the Netherlands. The overlapping catchment areas for the community pharmacies and the clinical laboratories result in a geographically defined subset of around 1 million patients. The PHARMO data network has been shown to be representative for the Dutch population.[27-29]

In the Netherlands, basic health insurance is mandatory for all residents, independent of age or employment status. Health insurance companies require clients to register with a community pharmacy, allowing for follow-up of medication history for each patient. Basic health

insurance fully reimburses most antidiabetic treatment options and covers diabetes-monitoring programs implemented throughout the Netherlands, starting in 2001. Regular check-ups are part of these monitoring programs. Since this is a retrospective study using anonymous data from the PHARMO network, approval by an ethics committee was not required.

Patient Selection

Patients were identified as users of either IDet (ATC A10AE05) or IGlar (ATC A10AE04). The first dispensing of long-acting insulin in the period January 1, 2004 to June 30, 2008 was defined as the cohort entry date, and the type of insulin treatment at this date was defined as the index treatment. Patients with an index treatment other than long-acting insulin as monotherapy were excluded, along with patients with missing HbA1c data (see Glycemic Control, below). A history of OADs dispensed at any time during the available history of patients was used to identify patients with T2D, since patients with T1D normally do not use OADs. Patients with T2D starting the use of IDet or IGlar were eligible for inclusion in the study if: they had been recorded in the database at least 1 year before cohort entry date; no insulin was dispensed to them in the year prior to cohort entry date; and they were followed up for at least 1 year. All patients fulfilling the above eligibility criteria were included in the "all eligible patients" (AEP) group. The "without treatment change" (WOTC) group consisted of a subgroup with no changes in insulin therapy prior to the HbA1c measurement at 1-year follow-up. Treatment changes included switches from basal to basal-bolus, changes in type of basal insulin, switches to premixed insulin, and cessation of insulin therapy before the 1-year follow-up HbA1c measurement. If more than 6 months elapsed between two dispensings of insulin, insulin treatment was assumed to have ceased. Dose titrations and changes in concomitant OAD use were not viewed as changes in treatment. The treatment goal used for comparison was HbA1c <7%, in line with both Dutch GPs guidelines[6] and the new ADA/EASD consensus algorithm.[7,8] The WOTC group was included to enable a "clean" analysis without possible noise arising from treatment changes.

Glycemic Control

Baseline HbA1c was based on the measurement closest to the cohort entry date, but limited to a time window of 1 year before cohort entry date. Follow-up HbA1c at 12 months was obtained in the period between 9 and 15 months after cohort entry date using the HbA1c measurement closest to 12 months after cohort entry date. HbA1c goal attainment was defined as <7%, in line with ADA/EASD consensus and Dutch guidelines,[6-8] and was determined both at baseline and at 12 months.

Daily Insulin Dose

To estimate the average daily insulin dose per type of insulin during the follow-up period, the total amount of insulin dispensed in the time interval from cohort entry date to the follow-up measurement of HbA1c was divided by the number of days between the cohort entry date and follow-up HbA1c measurements. Insulin dose measurements were excluded if there was only one insulin dispensing before the follow-up measurement or if there were more than 6 months (183 days) between the insulin dispensings before and after the follow-up measurement (assumed cessation of insulin therapy within these 6 months). For the AEP analysis all dispensed long-acting insulin up to

the point of treatment change was included in the calculation.

Body Weight

Changes in body weight were determined for the subset of patients for which weight assessments were registered both at baseline and at follow-up. These data were routinely collected during the diabetes-monitoring programs in primary care, but can only be accessed in one laboratory in the PHARMO network, limiting the number of patients for which these data were available.

Statistical Analyses

Data processing and statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA). Treatment changes were reported descriptively (numbers of patients and proportions). Patient characteristics were compared between IDet and IGlar users using descriptive statistics, Chi-squared tests, and two-sample Student's *t* tests. Propensity scores were constructed using multivariate logistic models with the index treatment as the dependent variable and baseline characteristics as independent variables. Only relevant characteristics were included in the propensity scores (ie, only characteristics that were associated with the choice of treatment). Characteristics with a strong association to goal attainment were introduced as separate covariates in the multivariate models comparing outcomes, and were therefore excluded from the propensity scores. Characteristics that were evaluated as possible covariates were demographic characteristics, baseline HbA1c levels, and all known baseline comorbid conditions, based on medication use and hospitalizations, that were present in at least 5% of the population. HbA1c goal attainment rates at follow-up were eventually compared between users of IDet and IGlar using logistic regression modeling, adjusted for age, gender, baseline HbA1c level, concomitant OAD use, and propensity score. The propensity score included prescriber initiating insulin therapy, year of starting insulin therapy, and prior OAD use. The validity of the propensity scores was checked by determining if the characteristics were similarly distributed in each of the quintiles of the propensity scores.

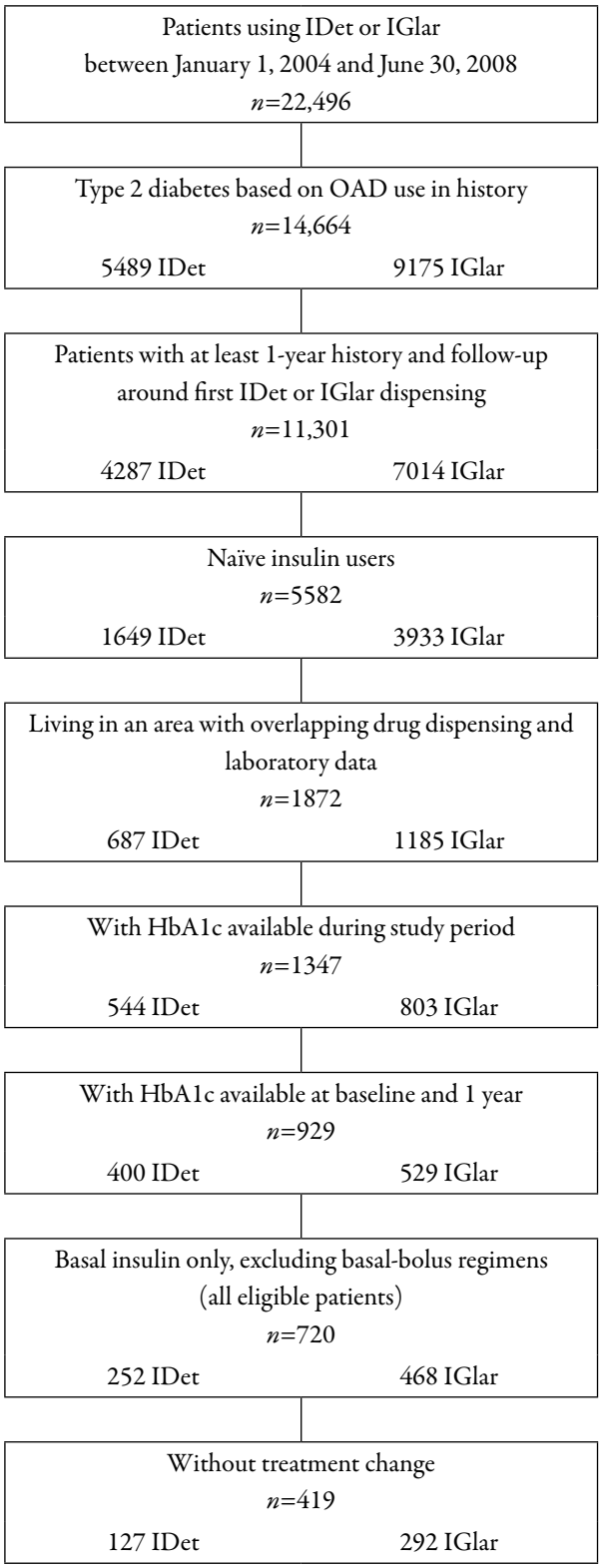
Daily average insulin dose was compared using linear regression of log-transformed data adjusting for age, gender, baseline HbA1c level, concomitant OAD use, and propensity score. Weight changes were compared using two-sample Student's *t* tests.

RESULTS

Population Size

Of the 22,496 patients using IDet or IGlar between January 1, 2004 and June 30, 2008 there were 1872 insulin-naïve patients with T2D living in an area for which laboratory results were available (see Figure 1). For 929 of those, HbA1c measurements at baseline and after 1 year were available. In all, 209 patients were excluded because they used a basal-bolus regimen. Of all eligible patients (AEP group, n=720) 252 started IDet use and 468 started IGlar use. At the time of the 1-year follow-up HbA1c measurement, 127 IDet users and 292 IGlar users were without treatment change (WOTC group). During the patient selection process the proportion of IDet and IGlar users remained more or less the same, indicating that exclusion criteria affected users of both insulin types in a similar way. Moreover, most patients were excluded due

Figure 1. Patient selection. HbA1c=hemoglobin A1c; IDet=insulin detemir; IGlar=insulin glargine; OAD=oral antidiabetics.



to the geographic area (living in an area without data capture). Thus, the potential selection bias is minimal and mainly affected by geography rather than access to care or different treatment paradigms.

Patient Characteristics

There were no significant differences between patient characteristics for IDet and IGlar users, either in the AEP analysis or the WOTC subgroup analysis, except for the higher proportion of male IGlar users in the AEP analysis and the significantly higher proportion of IDet users with heart failure (Table 1). However, the proportion of patients with heart failure was too small to be clinically relevant. Any differences in combinations of patient characteristics were balanced out in the following analyses using the propensity scores.

Glycemic Control

There was no difference in glycemic control (HbA1c levels) between IDet and IGlar users in both the AEP and the WOTC group, both at baseline (8.4%-8.6%) and after 1 year (7.4%-7.5%) (Table 2). Further, there was no difference in goal attainment rates between IDet and IGlar in the AEP analysis at baseline (12.7% and 11.3%) and at follow-up (33.3% and 35.7%). There was also no difference in goal attainment rates between IDet and IGlar in the WOTC analysis at baseline (8.7% and 11.0%) and at follow-up (31.5% and 35.3%). Multivariate comparison of IDet vs. IGlar users adjusting for age, gender, baseline HbA1c, concomitant OAD use, and propensity score showed no significant differences between goal attainment rates at follow-up, either in the AEP analysis (OR 0.81, 95% CI: 0.57, 1.16) or in the WOTC analysis (OR 0.75, 95% CI: 0.46, 1.24).

Table 1. Baseline characteristics.

Characteristics	All eligible patients			Without treatment changes		
	IDet (*n*=252), *n* (%)	IGlar (*n*=468), *n* (%)	Chi-square test, *P* value	IDet (*n*=127), *n* (%)	IGlar (*n*=292), *n* (%)	Chi-square test, *P* value
Male gender	117 (46.4)	263 (56.2)	0.01	63 (49.6)	163 (55.8)	0.24
Age in years, mean (SD)	64.8 (12.1)	63.2 (12.8)	0.10*	65.7 (11.0)	63.4 (12.1)	0.06*
Prescriber:						
GP	143 (56.7)	237 (50.6)	0.28	81 (±63.8)	162 (±55.5)	0.21
Internist	99 (39.3)	207 (44.2)		41 (32.3)	121 (41.4)	
Other specialist	10 (4.0)	24 (5.1)		5 (3.9)	9 (3.1)	
Concomitant OAD use:†						
None	21 (8.3)	32 (6.8)	0.76	11 (8.7)	9 (3.1)	0.11
Metformin	44 (17.5)	102 (21.8)		21 (16.5)	76 (26.0)	
Metformin + SU	137 (54.4)	240 (51.3)		76 (59.8)	155 (53.1)	
Metformin + SU + TZD	6 (2.4)	15 (3.2)		2 (1.6)	11 (3.8)	
Metformin + TZD	6 (2.4)	14 (3.0)		4 (3.1)	9 (3.1)	
SU	36 (14.3)	58 (12.4)		12 (9.4)	29 (9.9)	
SU + TZD	2 (0.8)	4 (0.9)		1 (0.8)	2 (0.7)	
TZD	0 (0)	2 (0.4)		0 (0)	1 (0.3)	
Other	0 (0)	1 (0.2)		0 (0)	0 (0)	
Prior OAD use:‡						
Any	246 (97.6)	454 (97.0)	0.63	126 (99.2)	286 (97.9)	0.35
Metformin	216 (85.7)	405 (86.5)	0.76	110 (86.6)	261 (89.4)	0.41
SU	216 (85.7)	408 (87.2)	0.58	109 (85.8)	250 (85.6)	0.95
TZD	64 (25.4)	137 (29.3)	0.27	34 (26.8)	90 (30.8)	0.40
Comedications:§						
Antihypertensives	174 (69.0)	322 (68.8)	0.95	90 (70.9)	202 (69.2)	0.73
Platelet inhibitors	100 (39.7)	187 (40.0)	0.94	53 (41.7)	125 (42.8)	0.84
Nitrates	35 (13.9)	55 (11.8)	0.41	17 (13.4)	32 (11.0)	0.48
Digoxin	11 (4.4)	21 (4.5)	0.94	5 (3.9)	13 (4.5)	0.81
Comorbidities:◊						
Ischemic heart disease	7 (2.8)	21 (4.5)	0.26	4 (3.1)	10 (3.4)	0.89
Heart failure	5 (2.0)	2 (0.4)	0.04	3 (2.4)	1 (0.3)	0.05
Cerebral vascular disease	4 (1.6)	2 (0.4)	0.10	2 (1.6)	1 (0.3)	0.17
Peripheral vascular disease	0 (0)	1 (0.2)	0.46	0 (0)	1 (0.3)	0.51
Number of hospitalizations:¶						
None	179 (71.0)	362 (77.4)	0.16	94 (74.0)	235 (80.5)	0.33
1	42 (16.7)	64 (13.7)		19 (15.0)	32 (11.0)	
≥2	31 (12.3)	42 (9.0)		14 (11.0)	25 (8.6)	

*Student's *t* test.
†OAD categories are mutually exclusive.
‡Metformin SU and TZD may have been used simultaneously.
§Based on drug dispensings in the year before start insulin.
◊Based on hospitalizations in the year before start insulin.
¶Hospitalizations for any cause in the year before start of insulin.
GP=general practitioner; IDet=insulin detemir; IGlar=insulin glargine; OAD=oral antidiabetics; SU=sulfonylurea; TZD=thiazolidinedione.

Table 2. Glycemic control.

	All eligible patients			Without treatment changes		
Patients	**IDet, (*n*=252)**	**IGlar, (*n*=468)**	***P* value***	**IDet, (*n*=127)**	**IGlar, (*n*=292)**	***P* value***
HbA1c at baseline, mean (SD)	8.4 (1.4)	8.5 (1.4)	0.27	8.4 (1.3)	8.6 (1.4)	0.22
HbA1c at follow-up, mean (SD)	7.5 (1.0)	7.4 (1.0)	0.56	7.4 (0.9)	7.4 (0.9)	0.60
No. at goal at baseline, % (*n*)	12.7 (32)	11.3 (53)	0.59	8.7 (11)	11.0 (32)	0.48
No. at goal at 1 year, % (*n*)	33.3 (84)	35.7 (167)	0.53	31.5 (40)	35.3 (103)	0.45
No. at goal at 1 year, unadjusted OR (95% CI)	0.90 (0.65, 1.24)		0.53	0.84 (0.54, 1.32)		0.45
No. at goal at 1 year adjusted OR (95% CI)†	0.81 (0.57, 1.16)		0.25	0.75 (0.46, 1.24)		0.26

Goal attainment = HbA1c <7%.
*Unadjusted Student's *t* test (HbA1c), or unadjusted Chi-square test (at goal), or logistic regression (OR).
†Logistic regression model adjusting for age, gender, baseline HbA1c, concomitant oral antidiabetics use, and propensity score.
CI=confidence interval; IDet=insulin detemir; IGlar=insulin glargine; OR=odds ratio.

Table 3. Median daily dose during follow-up.

	Daily IDet dose (IU/day)		Daily IGlar dose (IU/day)		
Patients	***n***	**Median (IQR)**	***n***	**Median (IQR)**	***P* value**
All eligible patients	190	26.8 (17.3-39.8)	389	27.4 (17.8-39.0)	0.76
Without treatment changes	127	24.7 (16.2-37.8)	292	25.3 (16.8-35.6)	0.70

Doses were compared using linear regression of log-transformed doses adjusting for age, gender, concomitant oral antidiabetic use, propensity score, and baseline HbA1c. Analysis of all eligible patients includes dispensings up to treatment change only.
IQR=interquartile range, encompassing 50% of all data (25%-75%); IDet=insulin detemir; IGlar=insulin glargine.
IU=International Unit.

Daily Insulin Dose

There were no significant differences in insulin utilization, measured by median daily insulin dose, between IDet and IGlar users in the WOTC analysis; 24.7 IU/day for IDet and 25.3 IU/day for IGlar, which was not significantly different (*P*=0.70) (Table 3). Dose calculations in the AEP analysis were limited to the period leading up to the treatment change. Since not all patients had at least two dispensings of the initial basal insulin within 6 months of each other before the treatment change, the number of patients with a dose calculation in the AEP group was limited to 75% of IDet users, and 83% of IGlar users. The doses of patients that switched treatment were marginally higher than those of patients that had no treatment changes, but ultimately the daily dose was not significantly different between IDet and IGlar users in the AEP analysis.

Weight Change

Weight measurements at baseline and follow-up were available for approximately 20% of all patients. Weight changes show slightly higher weight gain among IGlar users than among IDet users, but these differences were not significant (Table 4).

DISCUSSION

RCTs have very high internal validity; however, RCTs may have low external validity (generalizabilty) due to strict inclusion and exclusion criteria (selected subpopulations), specialized treatment settings, frequent visits, and monitoring. The strength of this study is that it reflects insulin use in patients with T2D in daily routine clinical practice, without the strict inclusion criteria and controlled environment of clinical trials.

This study shows that in daily clinical practice in the Netherlands, IDet and IGlar provide similar glycemic control at similar daily insulin dose after adjustment for differences in patient characteristics. This is hardly surprising as RCTs previously have demonstrated no differences in glycemic control.[19,20,22,24,30,31] However, it is interesting to go beyond the "efficacy" results obtained in RCTs and examine the "effectiveness" observed in a real-life setting as these outcomes are essentially what physicians are dealing with on a daily basis.

A baseline HbA1c at 8.4%-8.5% and a corresponding baseline target rate as low as 11%-13% when initiating insulin treatment (Table 2) may indicate that insulin therapy in the study population was initiated too late. This hypothesis is consistent with the results from a US retrospective study which found that patients with T2D with inadequate glycemic control (HbA1c ≥8%) waited for approximately 5 years before insulin therapy was initiated.[32] A similar study based on UK data demonstrated that 50% of patients with T2D delayed insulin for almost 5 years after failure of glycemic control (HbA1c ≥8%).[33] A delay in timely insulin initiation is not trivial and has been documented to reduce life expectancy and compromise quality of life.[34]

A mean HbA1c at 7.4% and a corresponding target rate of 32%-35% after 1 year in the WOTC analysis may indicate the basal insulin analogs were not titrated aggressively enough (Table 2). The AEP analysis shows similar results with a follow-up HbA1c at 7.4%-7.5% and 33%-36% reaching HbA1c target after 1 year. This suggests

Table 4. Weight assessments.

	IDet		IGlar		
Patients	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***P* value**
All eligible patients:					
Baseline, kg	50	81.3 (13.3)	90	86.4 (±8.1)	
1 year, kg	50	81.5 (14.6)	90	87.6 (18.2)	
Weight change, kg	50	0.2 (4.7)	90	1.2 (4.4)	0.20
Without treatment changes:					
Baseline, kg	25	84.0 (14.3)	65	87.5 (19.7)	
1 year, kg	25	84.5 (51.3)	65	88.6 (19.4)	
Weight change, kg	25	0.4 (3.7)	65	1.1 (4.5)	0.50

Weight changes were compared using Student's *t* test.
IDet=insulin detemir; IGlar=insulin glargine.

that observed changes in treatment do not necessarily result in increased goal attainment. Similar trends have been documented in a UK-based real-life study.[35] In this study the mean HbA1c prior to therapy was 9.9%. Although the patients experienced a significant reduction of 1.3 percentage points in HbA1c, 73% still had HbA1c ≥7.5% 6 months after insulin initiation, which could indicate a suboptimal insulin dose. The hypothesis that insulin doses may be too low is supported by the finding that the basal insulin doses (see Table 4) were well below the 40 units as recommended by World Health Organization (WHO) to be defined as the defined daily dose (DDD). However, as insulin dose is dependent on individual patient characteristics such as weight, this value has to be used as a proxy.

Possible explanations for lack of titration to target may be that the patients have a history of severe hypoglycemia and/or advanced microvascular or macrovascular complications, or extensive comorbid conditions. The ADA/EASD consensus algorithm acknowledge that the stringent HbA1c targets are not appropriate for all patients and that clinical judgment should be used to balance risk and benefits of intensified treatments.[8] Similarly, despite the target HbA1c level of 7% of the Dutch diabetes type 2 guideline from 1999,[36] HbA1c levels up to 8% were also called acceptable. Patients and physicians may therefore have been satisfied with the status quo, possibly because they were not fully aware of the potential long-term complications caused by elevated HbA1c. Unfortunately, data on hypoglycemic events were not available in the data. Furthermore, many patients might benefit from a basal-bolus regimen instead of a basal insulin-only regimen. The Dutch guidelines[6] recommend increasing the dosing frequency or the use of premixed insulin before considering basal-bolus therapy. The study period may have been too short to allow improved goal attainment rates as a result of such treatment changes to show a clear difference between the AEP and WOTC results.

Even though many patients are not treated to target using the general HbA1c goal of <7% as recommended by ADA/EASD, an even lower HbA1c goal of <6.5% has been suggested by other professional diabetes organizations such as International Diabetes Federation (IDF).[37] The key argument for ADA/EASD not decreasing the target HbA1c recommendation is the exaggerated risk of hypoglycemia. However, in recent years, this risk has been greatly reduced in patients with type 1 diabetes, and even in patients with T2D with availability of the new insulin analogs.[11,14,38] It might be unrealistic to expect healthcare providers to do better than what is achieved in a clinical trial setting. However, setting a lower target of 6.5% might mean that clinicians would perhaps intervene sooner.[39] Future clinical studies focusing on reasons for lack of treatment-to-target might help to improve glycemic control in clinical practice.

An inherent limitation of any observational study is the sensitivity to bias, and the possibility that not all confounders may be available for adjustments in multivariate models. For example, diet and exercise are known to influence both glycemic control and weight gain to a large extent,[40] but these data were not available in the database. Therefore the possibility of bias cannot be excluded. However, there are no compelling reasons to assume these factors differ between the treatment groups. The analyses were adjusted for the most important determinants of goal attainment, ie, baseline HbA1c, as well as age and gender. Furthermore, indication bias was eliminated by adjusting for propensity scores. Characteristics that were ultimately included in the propensity scores were prior use of metformin, sulfonylurea derivatives or thiazolidinediones, prescriber initiating insulin

therapy, and calendar year in which insulin treatment was initiated. As matching based on propensity scores would have resulted in a loss of patients and thus power, it was decided to adjust for the propensity scores instead. Within the quintiles of the propensity scores, characteristics were equally distributed in each of the treatment groups, showing that the propensity score was valid as a method of this adjustment.

Insulin dosing had to be estimated from the total amount of insulin dispensed during the period leading up to the follow-up HbA1c assessment, as insulin dosing is flexible and therefore not recorded in the pharmacy records. For some patients in the AEP analysis, the amount or frequency of dispensings was insufficient to allow dose calculations, because a change in therapy was made early on in the follow-up period. The AEP analyses should therefore be interpreted with caution. For the WOTC analyses it was assumed that errors in dose calculation resulting from the proportion of insulin that is not actually used but discarded (for example if exposed to high temperatures) is similar for both insulin types. All patients used prefilled pens and hence there were no differences in packaging or administration methods that might have caused differences in the proportion of dispensed insulin that was actually used, which in turn could have introduced differences in accuracy of dose calculations. Furthermore, insulin dose requirements are correlated with weight so weight differences are important for interpretation of dosing results. Observed weight differences at baseline were limited (WOTC IDet 84 kg, IGlar 88 kg), which makes it unlikely to be an important factor in the dose comparisons. Although weight data are limited to 20% of the population, they were gathered as part of a routine monitoring program in a specific geographical area within the PHARMO catchment area, which limits the possibility of bias in these data. Although the sample size was too small to show any significant difference, the data do support the trend observed in other studies,[14,20,23] that weight gain is less among patients using IDet than among patients using IGlar, the difference being around 1 kg.

CONCLUSIONS

As documented in previous RCTs there was no significant difference between users of IDet and IGlar with respect to glycemic control and insulin dose in a real-life setting in the Netherlands. However, the observation that as few as 11% were on target when initiating insulin treatment may indicate than insulin therapy is initiated too late. Moreover, the observation that only 32%-35% reach HbA1c target after 1 year may indicate the basal insulin analogs are not titrated intensively enough.

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