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BRIEF REPORT

Efficacy and Safety of Treatment with New Basal Insulin Analogues in Type 1 Diabetes: Nation-Wide Survey

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ABSTRACT

Introduction: To date, only a few studies have addressed the long-term safety of basal insulins. We have therefore investigated the efficacy and safety of all available basal insulins used in the treatment of type 1 diabetes, using data from national databases in Sweden.

Methods: We assessed patients with type 1 diabetes who were using insulin glargine 100 U/mL (IG100) and who either continued using IG100 or switched to insulin glargine 300 U/mL (IG300) or insulin degludec (ID) for differences in clinical characteristics at baseline (index date) and subsequent changes in glycated haemoglobin (HbA1c), weight and hospitalizations caused by hypoglycaemia, cardiovascular disease or death.

Results: The mean follow-up time was 1.1 years for patients who switched to IG300 and ID and 1.6 years for those remaining on IG100. There were no marked differences in clinical characteristics between the groups, but patients on IG100 were slightly older and had used insulin pumps or continuous glucose monitors more seldom. The mean HbA1c levels were similar, and 4% of the patients had a history of cardiovascular disease. HbA1c decreased in all groups during follow-up, while the body mass index remained virtually unchanged. Rates of severe hypo- or hyperglycaemia were low and similar between the groups. Sixteen patients (0.7%) treated with IG300 and 13 patients (0.8%) treated with ID died during follow-up, while 221 patients (1.95%) on IG100 therapy died. All other severe adverse events were numerically more frequent in those patients receiving IG100, while there were no apparent differences between those receiving IG300 and those on ID.

Conclusion: The long-term effects and safety of IG300 and ID appear to be very similar in adult patients with type 1 diabetes. The results of this study suggest that these basal insulin analogues may provide benefits compared with the established reference IG100.

Keywords: Basal insulin; Drug safety; Insulin degludec; Insulin glargine; Type 1 diabetes

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Key Summary Points

Only a few studies have addressed the long-term safety of basal insulins.

We assessed baseline differences in clinical characteristics and subsequent changes in glycated haemoglobin (HbA1c), weight, hospitalizations caused by hypoglycaemia, cardiovascular disease or death In patients with type 1 diabetes who used insulin glargine 100 U/mL (IG100) and switched to insulin glargine 300 U/mL (IG300) or insulin degludec (ID).

Patients on IG100 were slightly older and had used insulin pumps or continuous glucose monitors more seldom.

HbA1c decreased in all groups during follow-up, while the body mass index remained virtually unchanged. Rates of severe hypo- or hyperglycaemia were low and similar between the groups; 0.7% of patients treated with IG300, 0.8% of those treated with ID and 1.95% of those on IG100 died.

The long-term effects and safety of IG300 and ID seem to be very similar in adult patients with type 1 diabetes, suggesting that these basal insulin analogues may provide benefits compared with the established reference, IG100.

INTRODUCTION

Four basal insulin analogues (insulin glargine 100 U/mL, insulin detemir, insulin degludec and insulin glargine 300 U/mL) have been introduced since the turn of the last century, challenging neutral protamine Hagedorn (NPH) insulin as the most widely used basal insulin, particularly in people with type 1 diabetes. Randomized trials have shown that the positive effects of these new treatment options are principally lower frequencies of hypoglycaemia and less weight gain, but the debate on the roles of these basal insulin analogues in clinical treatment guidelines remains ongoing [1–3].

The only long-term prospective safety studies involving these basal insulin analogues have been conducted in persons with type 2 diabetes at an elevated cardiovascular risk. In the ORIGIN trial, insulin glargine 100 U/mL (IG100) was compared with conventional treatment and shown to have noninferior cardiovascular safety as well as a neutral effect on cardiovascular outcomes and cancers compared with standard care in people with high cardiovascular risk, impaired fasting glucose or impaired glucose tolerance or type 2 diabetes [4]. IG100 also reduced the frequency of new-onset diabetes, and there was an increased rate of hypoglycaemia and a modest weight gain. The DEVOTE trial, which compared IG100 with insulin degludec (ID), demonstrated a similar cardiovascular safety between the two insulin analogues, but the results suggested that ID was associated with a lower frequency of hypoglycaemia [5].

In the absence of prospective trials, real-world data can provide additional information on the effects of insulin treatment, comparing short- and long-term effects over a wide spectrum of patients treated in clinical practice. Therefore, the overall aim of this study was to investigate the efficacy and safety of all available basal insulins used to treat type 1 diabetes, using data from National Diabetes Register of Sweden (NDR) linked to information available in other national health registries in Sweden.

METHODS

Research Objective

Patients with type 1 diabetes who were using IG100 but switched to insulin glargine 300 U/mL (IG300) or ID at baseline were assessed for differences in clinical characteristics and subsequent changes in glycated haemoglobin (HbA1c), weight, hospitalizations caused by hypoglycaemia, cardiovascular disease or death, as well as persistence to treatment. Patients who continued to use IG100 were used in the analysis as a comparator group.

Datasets

The study database was created by using the unique personal identity number assigned to every Swedish resident as the identifier to cross-link nationwide healthcare registries [6]. NDR is a national quality register and has played an essential role in diabetes care since 1996 by providing information on risk factors and complications of diabetes that is reported directly online or continuously by physicians and nurses in hospitals and primary care clinics nationwide via electronic medical records [7]. It has been estimated that the NDR includes data on almost 95% of all patients with type 1 diabetes aged ≥ 18 years in Sweden. For the present study, we extracted data on clinical characteristics, blood pressure- and lipid-lowering medications and the use of an insulin pump from the NDR.

Information was collected on hospitalizations due to pre-existing conditions (codes from the International Classification of Diseases, 10th revision [ICD-10]) from 1997 to the index date, including cardiovascular disease, atrial fibrillation, congestive heart failure, peripheral arterial disease, amputations and severe renal disease. Information on conditions occurring during the study period, including severe hypoglycaemia, hyperglycaemia, ketoacidosis or unclear coma, were obtained from the National Patient Register.

The Swedish prescribed drug register is a nationwide register that contains information on all prescriptions that have been filled at a pharmacy. The Cause of Death Registry holds information on mortality (date and diagnosis). Data on country of birth were retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies.

The linkage of databases as well as the anonymization of the data was performed at the National Board of Health and Welfare. All patients had consented to being reported in the registry; however, the consent of each patient was not required to be included in this study according to Swedish law.

Inclusion and Exclusion Criteria

Male and female patients with type 1 diabetes who were aged ≥ 18 years, had no previous treatment with other long-acting insulins than IG100 during the 6 months immediately preceding the index date and had at least one filled prescription of a basal insulin during the 6 months immediately following the index date were included in the study. All patients using an insulin pump were excluded from the analysis.

Definitions

Glycated haemoglobin was reported in millimoles per mole (mmol/mol). The clinical definition of microalbuminuria used was two positive tests from three samples taken within 1 year, with an albumin/creatinine ratio of 3–30 mg/mmol (approx. 30–300 mg/g) or urine albumin (U-albumin) measurement of 20–200 μg/min (20–300 mg/L). Macro-albuminuria wass defined as an albumin/creatinine ratio of > 30 mg/mmol (approx. > 300 mg/g) or U-albumin > 200 μg/min (> 300 mg/L).

Study Design

The index date was defined as the date of the first filled prescription of IG300 or ID, and the index period lasted between 29 March 2016 and 30 June 2017; the end of follow-up was 30 December 2017. The patients should have had at least one filled prescription of IG100 (and no other basal insulin) during the 6 months immediately preceding the index date and at least one filled prescription of basal insulin within the 6 months immediately following the index date. A third group of patients that remained on IG100 (continuous users) and satisfied the inclusion criteria were also included in the study, comprising the comparator group. Patients fulfilling the requirements for inclusion in both the IG300 and ID groups were only included in the group where the criteria were first met. The Regional Ethical Review Board of the University of Gothenburg approved the study, which conformed to the Helsinki Declaration of 1964, as revised in 2013, concerning

Table 1 Clinical characteristics of patients participating in the study

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
Age (years)	47.8 (16.5)	46.1 (17.2)	49.2 (17.1)
Sex			
Male	1411 (58.84%)	955 (55.56%)	7227 (63.73%)
Female	987 (41.16%)	764 (44.44%)	4113 (36.27%)
Diabetes duration (years)	23.1 (14.6)	23.6 (14.5)	23.5 (15.7)
Weight (kg)	83.2 (17.4)	80.0 (15.6)	81.4 (16.1)
BMI (kg/m^2)	27.2 (4.8)	26.3 (4.4)	26.6 (4.6)
HbA1c (mmol/mol)	64.4 (13.5)	65.7 (14.6)	62.4 (12.9)
Systolic blood pressure (mmHg)	127.7 (14.0)	127.4 (14.8)	128.9 (14.8)
Diastolic blood pressure (mmHg)	74.4 (9.2)	74.0 (9.2)	74.1 (9.3)
Total cholesterol (mmol/L)	4.6 (1.0)	4.6 (1.0)	4.6 (0.9)
Low-density lipoprotein (mmol/L)	2.5 (0.8)	2.5 (0.9)	2.5 (0.8)
High-density lipoprotein (mmol/L)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)
Triglycerides(mmol/L)	1.2 (1.0)	1.1 (0.8)	1.2 (0.8)
Creatinine (μmol/L)	77.8 (35.2)	77.1 (37.8)	79.5 (43.4)
eGFR (ml/min/1.73 m^2)	91.8 (25.0)	93.1 (25.4)	91.2 (25.5)
Insulins and anlogues for injection, fast-acting	2236 (93.24%)	1578 (91.80%)	10186 (89.82%)
Continuous glucose monitoring (assuming that missing means mean no)	817 (34.07%)	564 (32.81%)	495 (4.37%)
Antihypertensive treatment	880 (42.33%)	558 (39.13%)	4182 (47.32%)
Lipid-lowering treatment	992 (47.56%)	624 (43.85%)	4304 (48.72%)
Micro-albuminuria	239 (12.55%)	178 (14.37%)	1210 (15.19%)
Macro-albuminuria	75 (4.26%)	55 (4.84%)	365 (4.96%)
Physical activity			
Never	163 (8.46%)	109 (8.33%)	648 (7.86%)
< 1 time/week	285 (14.79%)	192 (14.68%)	1213 (14.71%)
1–2 times/week	457 (23.72%)	278 (21.25%)	1902 (23.06%)
3–5 times/week	543 (28.18%)	370 (28.29%)	2472 (29.97%)
Daily	479 (24.86%)	359 (27.45%)	2013 (24.41%)
Smoking	237 (11.69%)	167 (12.51%)	1033 (11.88%)

Table 1 continued

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
Born in Sweden	2233 (93.12%)	1596 (92.84%)	10313 (90.94%)

Values in table are presented as means with the standard deviation (SD) or as counts with the proportion (%)
BMI Body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated haemoglobin

Table 2 Previous medical events and diagnoses in patients

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
Hypoglycaemia	2 (0.08%)	3 (0.17%)	0 (0%)
Hyperglycaemia	33 (1.38%)	45 (2.62%)	123 (1.08%)
Ketoacidosis	32 (1.33%)	43 (2.50%)	120 (1.06%)
Unclear coma	1 (0.04%)	7 (0.41%)	11 (0.10%)
Cardiovascular disease	84 (3.50%)	66 (3.84%)	459 (4.05%)
Acute myocardial infarction	43 (1.79%)	35 (2.04%)	220 (1.94%)
Angina pectoris	73 (3.04%)	42 (2.44%)	313 (2.76%)
Coronary heart disease	150 (6.26%)	109 (6.34%)	770 (6.79%)
Stroke	42 (1.75%)	32 (1.86%)	251 (2.21%)
Atrial fibrillation	50 (2.09%)	45 (2.62%)	274 (2.42%)
Heart failure	46 (1.92%)	22 (1.28%)	200 (1.76%)
Amputation	15 (0.63%)	8 (0.47%)	106 (0.93%)
Peripheral arterial disease	36 (1.50%)	16 (0.93%)	245 (2.16%)
Severe renal disease	51 (2.13%)	46 (2.68%)	275 (2.43%)

Values in table are presented as counts with the proportion (%) in parenthesis

human and animal rights. Springer's policy concerning informed consent was followed.

Statistical Methods

Descriptive statistics are presented in terms of means with standard deviation or counts and percentages depending on the nature of the variable described. Changes in risk factors are presented as the change from baseline (except albuminuria). The number of events occurring during the study period are presented as rates per patient-year, and the proportion of patients with at least one event is reported. Hospitalizations are reported as the total number of days and as a rate (number of hospital days/patient-year). Mortality rates, overall and due to cardiovascular disease only, are presented by mean percentages and Kaplan–Meier curves. Due to the nature of the study, no statistical comparisons of the groups and effects were performed.

Table 3 Clinical variables before and after patients changed their basal insulin regimen

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
HbA1c (mmol/mol)			
n	1805	1196	8223
Pre-index	64.44 (13.52)	65.75 (14.24)	62.11 (12.76)
Post-index	63.36 (12.38)	64.49 (13.56)	60.93 (12.31)
Change	− 1.08 (10.45)	− 1.26 (10.57)	− 1.18 (9.97)
BMI (kg/m^2)			
n	1136	674	5003
Pre-index	27.20 (4.70)	26.36 (4.60)	26.63 (4.55)
Post-index	27.22 (4.73)	26.48 (4.73)	26.85 (4.63)
Change	0.02 (1.93)	0.13 (1.36)	0.21 (1.66)
Weight (kg)			
n	1213	769	5469
Pre-index	83.34 (17.28)	80.07 (16.11)	81.41 (16.08)
Post-index	83.20 (17.05)	80.37 (16.38)	82.06 (16.44)
Change	− 0.14 (6.97)	0.30 (4.32)	0.65 (5.04)
eGFR (ml/min/1.73 m^2)			
n	999	771	5257
Pre-index	90.75 (25.31)	92.44 (25.24)	90.44 (25.12)
Post-index	88.69 (25.17)	91.27 (25.05)	87.33 (24.76)
Change	− 2.07 (11.15)	− 1.16 (12.19)	− 3.11 (12.64)

Values in table are presented as means with SD. Summary of continuous endpoints for patients with data at both pre- and post-index, by treatment group

SAS version 9.4 software was used in all analyses (SAS Institute, Cary, NC, USA).

RESULTS

A total of 15,457 patients who were receiving IG100 during the 6 months immediately preceding the index date participated in the study. Of these, 2398 patients switched to IG300, 1719 switched to ID and 11,340 remained on IG100 (continuous users). The use of the basal insulins was quite stable during the follow-up period. Approximately 6% of all patients switching to IG300 or ID filled one prescription or more of IG100 after the index date (7.0 and 5.8%, respectively). Only 3.7% of the patients on IG300 filled at least one prescription for ID, and only 1.2% of patients on ID filled one prescription or more for IG300. Among the patients continuing on IG100 during the follow-up period, 5.0% filled one prescription or more of IG300 and 9.0% filled one prescription or more of ID. These proportions are low due to the design of the study.

Table 4 Hospitalizations and hypo- and hypoglycaemic events after patients changed their basal insulin regimen

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
Hospitalization (days)			
Total	1038	801	10.571
Days/patient-year	0.398	0.421	0.584
Hypoglycaemic episodes			
Total no. events	9	9	47
Events/patient-year	0.003	0.005	0.003
Hyperglycaemic episodes			
Total no. events	20	18	156
Events/patient-year	0.008	0.009	0.009
Episodes of ketoacidosis			
Total no. events	21	18	155
Events/patient-year	0.008	0.009	0.009
Episodes of unclear coma			
Total no. events	1	1	15
Events/patient-year	0.000	0.001	0.001

Clinical characteristics and previous events and diagnoses are presented in Tables 1 and 2. Overall, there were no marked differences in clinical characteristics between the three treatment groups. The patients in the IG100 group were numerically slightly older than those in the other two groups. In the IG300 and ID groups, the proportion of males was similar (59 and 56%, respectively), but there were more men in the IG100 (64%). The use of continuous glucose monitors before the index date was clearly lower among patients continuing on IG100 (38% vs. 47% of those on IG300 and 52% of those on ID). The mean HbA1c levels were similar pre-index date for all groups, ranging from 62.4 mmol/mol (IG100 group) to 65.7 mmol/mol (ID group). The incidence of severe hypo- or hyperglycaemia during the year prior to the index date was low and fairly similar across the groups, although the incidence of hyperglycaemia or ketoacidosis in the ID was roughly twofold higher than that seen in the other two groups. Overall, 4% of the patients had a history of cardiovascular disease.

The mean follow-up time differed (by study design) between the groups (1.1 years for both the IG300 and ID groups; 1.6 years for the IG100 group). During the study period, HbA1c decreased slightly in all treatment groups (Table 3), while the body mass index and estimated glomerular filtration rates remained virtually unchanged. The rates of hypo- and hyperglycaemic events were low and similar for all three groups, but the number of days hospitalized was numerically higher for the patients on IG100 than for those of the other treatment groups (Table 4).

Mortality and severe adverse events occurring in those patients who changed the basal insulin regimen are given in Fig. 1 and Table 5. Sixteen patients (0.7%) treated with IG300 and 13 patients (0.8%) treated with ID died during the follow-up period. In total, 221 patients (1.95%) treated with IG100 died during the study period. All other severe adverse events

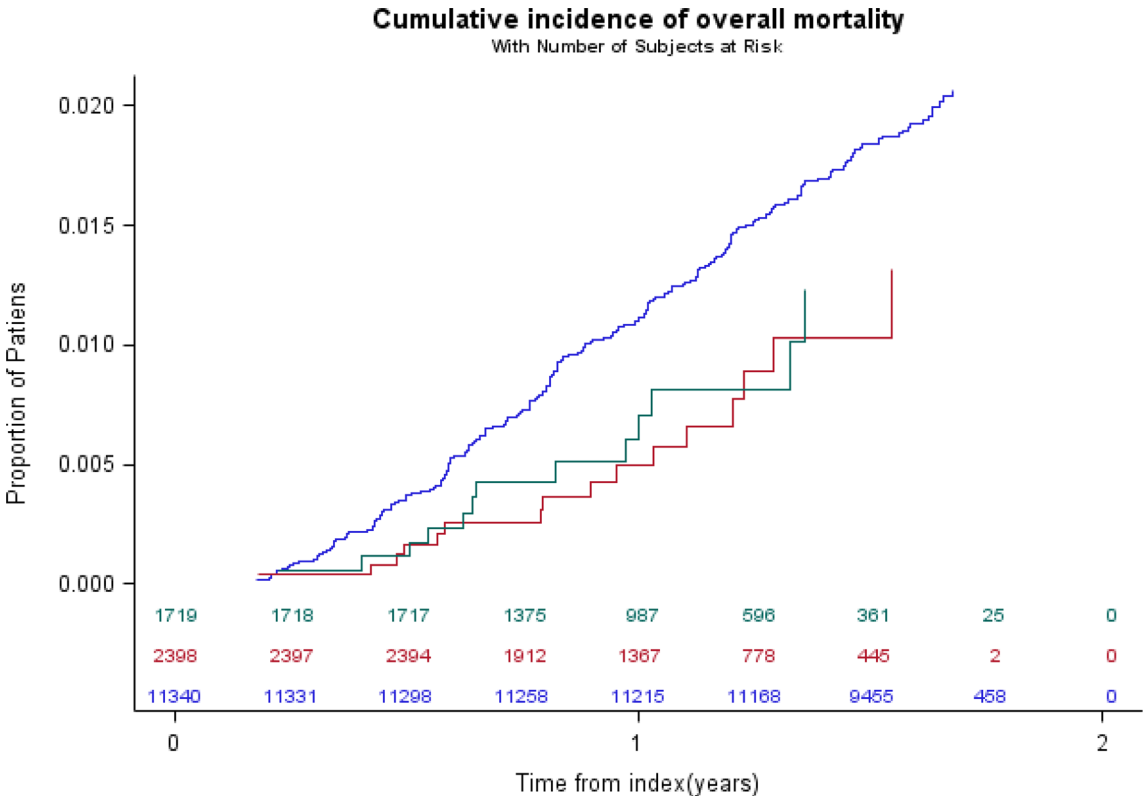

Fig. 1 Time to death after changes in the basal insulin regimen (cumulative incidence). Red line represents insulin glargine 300 U/mL, green line represents insulin degludec and blue line represents insulin glargine 100 U/mL

were also numerically higher in the group of patients treated with IG100, while there were no apparent differences between patients treated with IG300 and those receiving ID.

DISCUSSION

The results of this nationwide observational study in clinical practice suggest that IG300 and ID have similar effects on glycaemic control and body weight, severe hypo- and hyperglycemia events, cardiovascular events and all-cause mortality in people with type 1 diabetes. These findings are in line with the overall results of prospective safety trials that were exclusively performed in persons with type 2 diabetes that have been published to date [4, 5, 8] and are most likely due to the improved pharmacokinetic and pharmacodynamic properties of second-generation basal insulin analogues, especially regarding the prolonged and stable effect of these drugs [9]. Retrospective studies on the clinical effects of ID and IG300 in type 2 diabetes in clinical practice have shown diverging results [10, 11]. The results of a recent study suggest a lower mortality risk with ID compared with IG100 in a mixed population [12]. The DEVOTE prospective randomized trial, however, established noninferior safety in people with type 2 diabetes at high cardiovascular risk with ID compared with IG300 [5].

The major strengths of our study are its nation-wide scope and the high validity of data collected from nation-wide databases. The very recent and relatively short follow-up period, however, limit the number of patients with complete data, thereby preventing us from using more sophisticated statistical analyses, such as propensity score-based matching or statistical comparisons and multivariate analyses. We also have no reliable data on doses of the basal or the meal-time insulins. Furthermore, the design of the study, which required a

Table 5 Mortality and severe adverse events after patients changed their basal insulin regimen

Variable	Insulin glargine 300 U/mL (*n* = 2398)	Insulin degludec (*n* = 1719)	Insulin glargine 100 U/mL (*n* = 11,340)
Overall mortality	16 (0.67%)	13 (0.76%)	221 (1.95%)
Fatal cardiovascular disease	0 (0%)	1 (0.06%)	14 (0.12%)
Cardiovascular disease	20 (0.83%)	10 (0.58%)	138 (1.22%)
Acute myocardial infarction	12 (0.50%)	5 (0.29%)	77 (0.68%)
Angina pectoris	9 (0.38%)	6 (0.35%)	78 (0.69%)
Coronary heart disease	36 (1.50%)	27 (1.57%)	296 (2.61%)
Stroke	9 (0.38%)	5 (0.29%)	65 (0.57%)
Atrial fibrillation	14 (0.58%)	11 (0.64%)	133 (1.17%)
Heart failure	18 (0.75%)	8 (0.47%)	130 (1.15%)
Peripheral arterial disease	14 (0.58%)	9 (0.52%)	110 (0.97%)
Severe renal disease	24 (1.00%)	18 (1.05%)	205 (1.81%)

Values in table are presented as counts with the proportion (%) in parenthesis

second filled prescription within 6 months of the index date, means that no patient in the study died before the date of the second withdrawal of insulin, which explains why the cumulative incidence of all-cause mortality was null during the first months of the follow-up period.

We used the results from patients continuing on IG100 as a comparator and reference, while being well aware of the numerous reasons for patients to remain on that treatment instead of switching to IG300 or ID. Patients in the group using IG100 were expected to differ from those in the other two groups with respect to demographic and other characteristics, and the differences in effects during the follow-up period may well be explained by similar factors, in addition to a longer observation time.

CONCLUSION

Future prospective trials and observational studies will hopefully be able to tell if there are distinct groups of patients who are likely to benefit from specific basal insulin and long-acting insulin analogues. At the present time the effects of IG300 and ID seem to be very similar in adult patients with type 1 diabetes, and the results of our study suggest that there may be advantages with these two insulin analogues compared with the established reference, IG100.

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Authorship. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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Compliance with Ethics Compliance. The Regional Ethical Review Board of the University of Gothenburg approved the study which conformed to the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. Springer's policy concerning informed consent has been followed.

Data Availability. The datasets generated during and/or analysed during the current study are not publicly available due to the nature of national quality registries but are available from the corresponding author on reasonable request.

REFERENCES

1. Bain S, Feher M, Fisher M, et al. A review of the NG17 recommendations for the use of basal insulin in type 1 diabetes. Diabet Med. 2019. https://doi.org/10.1111/dme.14180.

2. Madenidou AV, Paschos P, Karagiannis T, et al. Comparative benefits and harms of basal insulin analogues for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med. 2018;169(3):165–74.

3. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ. 2014;349:g5459. https://doi.org/10.1136/bmj.g5459.

4. Investigators OT, Gerstein HC, Bosch J, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319–28.

5. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017;377(8):723–32.

6. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish healthcare quality registries. J Intern Med. 2015;277(1):94–136.

7. Eliasson B, Gudbjornsdottir S. Diabetes care–improvement through measurement. Diabetes Res Clin Pract. 2014;106[Suppl 2]:S291–4.

8. Hernando VU, Pablo FJ. Efficacy and safety of the second generation basal insulin analogs in type 2 diabetes mellitus: a critical appraisal. Diabetes Metab Syndr. 2019;13(3):2126–41.

9. Owens DR, Bailey TS, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL)—a review of evidence and clinical interpretation. Diabetes Metab. 2019;45(4):330–40.

10. Knudsen ST, Lapolla A, Schultes B, et al. Clinical benefits of switching to insulin degludec irrespective of previous basal insulin therapy in people with Type 1 or Type 2 diabetes: evidence from a European, multicentre, retrospective, non-interventional study (EU-TREAT). Diabet Med. 2019;36(7):868–77.

11. Pettus J, Roussel R, Liz Zhou F, et al. Rates of hypoglycemia predicted in patients with type 2 diabetes on insulin glargine 300 U/ml Versus first- and second-generation basal insulin analogs: the real-world lightning study. Diabetes Ther. 2019;10(2):617–33.

12. Jensen MH, Hejlesen O, Vestergaard P. Risk of major cardiovascular events, severe hypoglycaemia, and all-cause mortality for users of insulin degludec versus insulin glargine U100-A Danish cohort study. Diabetes Metab Res Rev. 2019;2019:e3225. https://doi.org/10.1002/dmrr.3225.