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ORIGINAL RESEARCH

Clinical Effects and Safety of Direct-Acting Insulin Analogs in Patients with Type 1 Diabetes: A Nation-Wide Observational Cohort Study

Vincent Lak · Ann-Marie Svensson · Mervete Miftaraj · Stefan Franzén · Björn Eliasson

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ABSTRACT

Introduction: Studies comparing direct-acting insulin analogs (DAIs) in terms of effectiveness and long-term safety are scarce. Our aim was to explore these variables in clinical practice among patients with type 1 diabetes, including the elderly and those with renal impairment.

Methods: We linked four national registers in a population-based cohort study. Patients with type 1 diabetes and continuous use of all currently available DAIs (lispro, aspart, or glulisine) in 2005–2013 were monitored for up to 7.5 years. Inverse probability of treatment weighting was used to adjust for differences in baseline characteristics between treatment groups. Unadjusted mean HbA1c and weights were plotted. Hazard ratios and 95% confidence intervals of cardiovascular events (CVEs) and mortality were estimated using Cox proportional hazards regression models.

Results: We included 41,165 patients—14,047 lispro, 26,813 aspart, and 305 glulisine users. At baseline, the mean age was highest among glulisine users (49.4 years), followed by 41.0 years for lispro users and 40.1 years for aspart users. A total of 9.2% of the patients were 65 years or older. Diabetes duration was shortest among glulisine users (11.6 years), followed by 15.4 years for aspart users and 19.5 years for lispro users. The mean HbA1c and weights during the follow-up period were similar. The numerical differences at baseline were subsequently adjusted for. There were no significant differences between groups regarding hyperglycemia requiring hospitalization, CVE, or mortality, while Cox regression suggested lower rates of hypoglycemia among glulisine users. Severe hypoglycemia was more common, and severe hyperglycemia was less common among patients aged 65 years or older, while severe hypoglycemia and hyperglycemia were more common in patients with low renal function (estimated glomerular filtration rate).

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Conclusion: There were no pronounced differences in effectiveness and long-term cardiovascular safety and mortality between the DAIs, although there were some differences in clinical characteristics between patients using the three types of insulin. Severe hypoglycemia was more common among older patients, while severe hypoglycemia and hyperglycemia were more common among patients with impaired renal function.
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Keywords: Cohort study; Effectiveness; Elderly; Insulin analogs; Insulin aspart; Insulin glulisine; Insulin lispro; Renal failure; Safety; Type 1 diabetes

INTRODUCTION

Direct-acting insulin analogs (DAIs) are a cornerstone of contemporary type 1 diabetes treatment [1]. Insulin lispro was approved for use in the mid-1990s, making it the first DAI to enter the market. Insulin aspart became available in 1999 and insulin glulisine in 2004. Both before and after approval of each DAI, many clinical trials and studies have shown non-inferiority and some clinical advantages over ordinary human insulin, including fewer doses, increased flexibility, less hypoglycemia, and greater cost-effectiveness [2, 3]. Only a few studies have directly compared the clinical efficacy of various DAIs [4, 5] and none have addressed cardiovascular safety.

Long-term, real-life safety data concerning the impact of DAIs on hard endpoints, such as cardiovascular events (CVEs) and mortality are lacking, particularly among elderly patients and those with renal impairment. The aim of this study was to explore the long-term effectiveness on glycemic control, weight, and safety of DAIs in routine clinical practice among patients with type 1 diabetes, particularly elderly patients and those with renal impairment. We conducted a population-based longitudinal cohort study linking data from the Swedish National Diabetes Register (NDR) with other databases to capture information about hospitalization and cause of death.

METHODS

The Regional Ethical Review Board in Gothenburg approved the study, which was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. All patients gave their informed consent prior to inclusion.

Databases

The NDR was launched in 1996 to enable local quality control and regional benchmarking against national treatment guidelines [6]. Physicians and nurses from hospitals and primary healthcare centers nationwide report annually to the NDR. Body mass index (BMI), HbA1c, type of diabetes, age at onset, and other clinical data were obtained from the NDR. The Prescribed Drug Register (PDR) fully covers all drug prescriptions (pharmaceutical agents and amounts) filled at Swedish pharmacies. The Cause of Death Register contains information about mortality and date of death. The National Patient Register focuses on diagnoses. Data concerning place of birth and educational level were obtained from the Longitudinal Integration Database for Health Insurance and the Labor Market Studies register. These databases have recently been reviewed and validated [7].

Patients, Study Period, Follow-Up, and Censoring

We included patients with type 1 diabetes who were at least 18 years old and had used DAIs continuously for at least 1 year (Fig. 1). Latent autoimmune diabetes of adults (LADA) is also reported as type 1 diabetes in the NDR. The first pick up of a DAI in the PDR was defined as the index date. Continuous use was defined as having filled at least three ordinary or 19 multi-dose prescriptions during the first year after the index date. This multi-dose, which is called ApoDos® (Apoteket AB), is a parallel system dispensed at shorter intervals (usually twice per month), and has been a source of confusion when used together with ordinary prescriptions [8]. Thus, we excluded patients who had picked up both ordinary DAI and ApoDos prescriptions. The study period was July 1, 2005 to December 31, 2014. Patients were monitored until the end of the study period or the occurrence of a censoring event. Start of follow-up was defined as the date that the third insulin prescription was picked up. Censoring events included picking up a new type of DAI, death, emigration, and the occurrence of a safety outcome (see below).

Patient Characteristics

Variables measured at baseline (index date) included age, gender, diabetes duration, smoking, physical inactivity (exercising less than once a week), higher (post-secondary) education, history of hyperglycemia or hypoglycemia, history of cardiovascular disease (CVD), and type of basal insulin. The latest values for HbA1c, BMI, weight, blood pressure, blood lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and estimated glomerular filtration rate (eGFR) up to 12 months before the index date were used. The Modification of Diet in Renal Disease (MDRD) study equation [9] was used to calculate eGFR. Renal impairment was defined as eGFR <60 mL/min/1.73 m^2. HbA1c analyses and other laboratory tests were performed locally. During the study period, HbA1c analyses were quality assured nationwide by means of regular calibration with the high-performance liquid chromatography Mono-S® (GE Healthcare) method.

History of coronary heart disease (CHD) was defined as diagnosis of ischemic heart disease (I20–I25), treatment with percutaneous coronary intervention (PCI) or treatment with coronary artery bypass graft (CABG) prior to the index date. History of CVD was defined as diagnosis of stroke or peripheral vascular disease prior to the index date, or history of CHD. History of atrial fibrillation, congestive heart failure, stroke, kidney failure, hyperglycemia, and hypoglycemia was defined in a similar manner using International Classification of Diseases (ICD) 10 codes (Table 1).

Outcomes

We examined annual changes in mean HbA1c and weight. The safety outcomes were hospitalization due to hyperglycemia or hypoglycemia, kidney failure, CVEs (CHD, CVD, stroke, atrial fibrillation, or congestive heart failure) or death. Except for death, these outcomes are defined using the same ICD codes as described in the section on patient characteristics (Table 1).

Statistical Methods

Missing baseline data were assigned values by means of multiple imputations from a multivariate normal model using a Monte

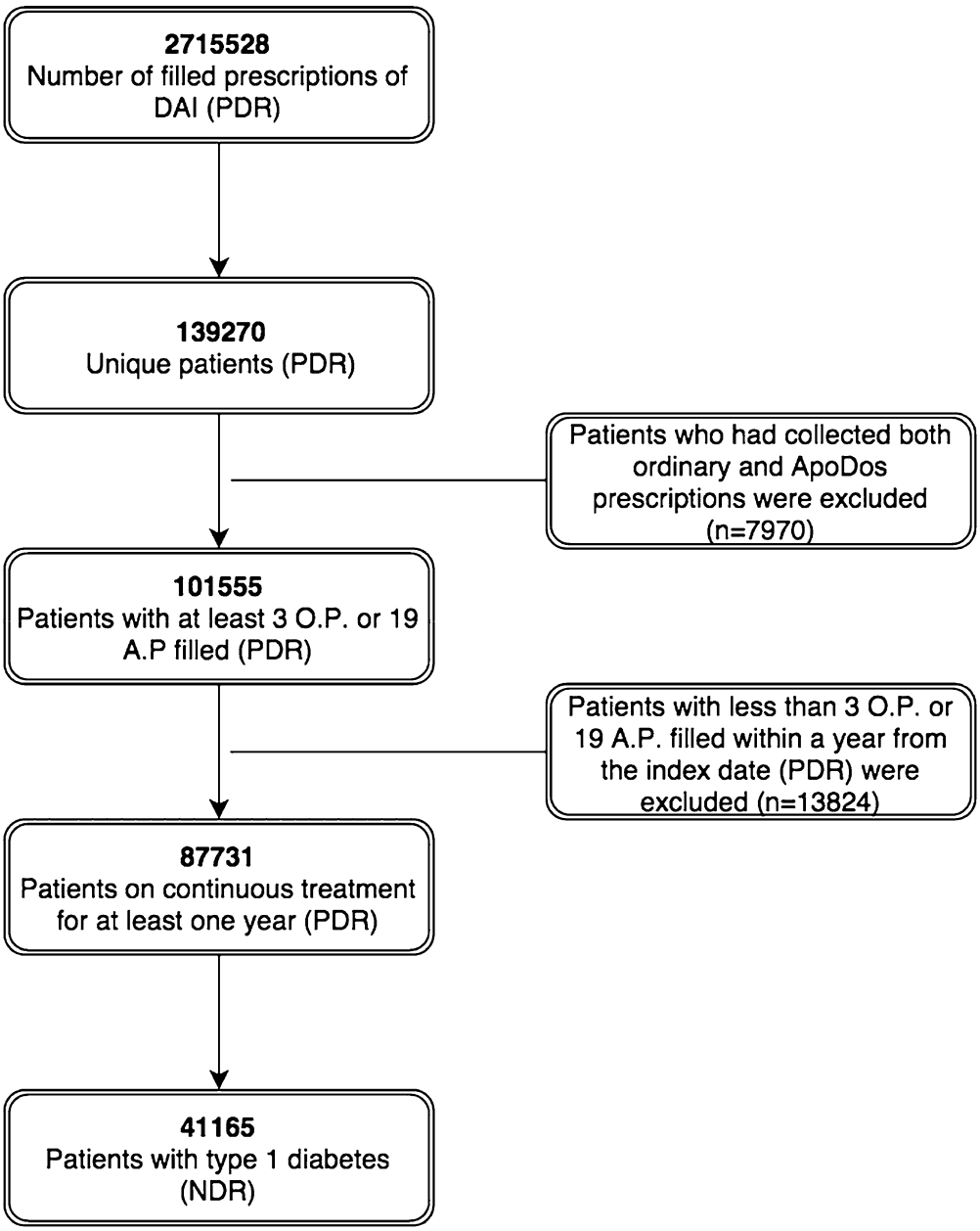

Fig. 1 Patient selection flow chart. Stages of inclusion and exclusion, used databases used. *A.P.* ApoDos prescription, *DAI* direct-acting insulin analogs, *NDR* National Diabetes Register, *O.P.* ordinary prescription, *PDR* Prescribed Drug Register

Carlo Markov chain approach, creating ten data sets. The percentage of missing data ranged from zero (age, gender, treatment, and prior conditions) to 76% (physical activity).

Propensity scores [10] were estimated using a multinomial generalized boosted regression model [11], including all variables in Table 2 for each imputed data set. The inverse of the average propensity score was used for inverse probability of treatment weighting to adjust for differences in baseline characteristics between treatment groups.

Patient characteristics at baseline were evaluated by means of standard descriptive

Table 1 ICD groups and corresponding codes

Group number and name	ICD10 diagnosis or treatment codes
0. Ischemic heart disease	I20–25
1. PCI	FNG0, FNG00, FNG02, FNG05, FNG06, FNG10, FNG30, FNG96
2. CABG	FNA0, FNA00, FNA10, FNA20, FNA96, FNB00, FNB20, FNB96, FNC10, FNC20, FNC30, FNC40, FNC50, FNC60, FNC96, FND10, FND20, FND96, FNE00, FNE10, FNE20, FNE96, FNF00, FNF10, FNF20, FNF30, FNF96
3. Stroke	I61, I63, I64, I67.9
4. Peripheral vascular disease	I70.2, I73.1, I73.9, I79.2, E10.5, E11.5, E14.5. NHQ09, NHQ11, NGQ09, NGQ11, NGQ99, NFQ09, NFQ19, NFQ99, NEQ19, NEQ99
5. Atrial fibrillation	I46–48
6. Congestive heart failure	I50
7. Kidney failure	N18, N19
8. Hypoglycemia	E100, E106A, E110, E110C, E110X, E116A, E120, E130, E140, E159, E160, E161 W, E162, R402
9. Hyperglycemia	E100A, E100B, E100D, E100X, E101, E101A, E101B, E101D, E101X, E110, E110A, E110B, E110D, E110X, E111, E111A, E111B, E111D, E111X, R739

A. CHD = groups 0–2
B. CVD = groups 0–4
CABG coronary artery bypass graft, *CHD* coronary heart disease, *CVD* cardiovascular disease, *ICD10* International Classification of Diseases 10, *PCI* percutaneous coronary intervention

statistics. Variations between the treatment groups were evaluated graphically using the maximal pairwise standardized difference. Unadjusted mean HbA1c and weights were plotted by means of penalized B-splines with 95% confidence intervals (CIs). The treatment groups were compared with respect to CVEs and mortality by fitting a weighted Cox proportional hazards model with standard errors that were deemed to reflect the weighted analysis. We used SAS® version 9.4 (SAS Institute Inc.) and R version 3.1.0 (The R Foundation) to perform the statistical calculations.

RESULTS

We included 41,165 patients: 14,047 lispro, 26,813 aspart, and 305 glulisine users. We used inverse probability of treatment weighting to adjust for differences in baseline characteristics between the treatment groups. Prior to the adjustment, there were numerical differences between the groups. Mean age was highest among glulisine users (49.4 years), followed by 41.0 years among lispro users and 40.1 years among aspart users. A total of 9.2% of the patients were 65 years or older. Diabetes duration was shortest among glulisine users

Table 2 Baseline characteristics of patients treated with lispro, aspart, and glulisine

Characteristics	Lispro (*n* = 14,047)	Aspart (*n* = 26,813)	Glulisine (*n* = 305)
Age, years	41.0 (15.7)	40.1 (18.3)	49.4 (18.3)
Aged 65 years or older, *n*	1002 (7.1)	2694 (10.0)	75 (24.6)
Female, *n*	6323 (45.0)	11,210 (41.8)	127 (41.6)
Diabetes duration, years	19.5 (12.7)	15.4 (14.8)	11.6 (14.7)
Total cholesterol, mmol/L	4.8 (0.9)	4.8 (0.9)	4.8 (1.0)
Triglycerides, mmol/L	1.1 (0.7)	1.2 (0.9)	1.4 (1.1)
HDL, mmol/L	1.7 (0.5)	1.6 (0.5)	1.5 (0.5)
HbA1c, mmol/mol	63.6 (13.4)	64.1 (14.6)	70.3 (17.9)
BMI, kg/m^2	25.7 (3.7)	25.6 (3.9)	26.3 (4.9)
Systolic BP, mmHg	128.4 (15.8)	130.0 (16.7)	132.3 (17.0)
Diastolic BP, mmHg	74.4 (9.0)	74.3 (9.1)	75.2 (9.3)
eGFR, mL/min/1.73 m^2	86.7 (23.4)	86.7 (28.4)	90.2 (26.2)
Renal impairment, *n*	5986 (42.6)	9268 (34.6)	135 (44.3)
Smoker, *n*	875 (12.7)	1559 (14.3)	24 (15.1)
Higher education, *n*	4969 (35.6)	7605 (28.7)	78 (26.0)
Physical inactivity, *n*	776 (20.8)	1344 (22.0)	20 (16.9)
Insulin pump (CSII), *n*	1144 (18.3)	761 (8.1)	3 (2.4)
Long-acting insulin, *n*			
Human (NPH)	3793 (27)	7619 (28.4)	63 (20.7)
Glargine	7757 (55.2)	12,886 (48.1)	137 (44.9)
Detemir	720 (5.1)	2964 (11.1)	7 (2.3)
Other	1777 (12.7)	3344 (12.5)	98 (32.1)
History of …, *n*			
Ischemic heart disease	296 (2.1)	625 (2.3)	9 (3.0)
Atrial fibrillation	159 (1.1)	389 (1.5)	12 (3.9)
Myocardial infarction	266 (1.9)	590 (2.2)	11 (3.6)
Unstable angina	477 (3.4)	964 (3.6)	17 (5.6)
PCI	189 (1.3)	427 (1.6)	13 (4.3)
CABG	198 (1.4)	413 (1.5)	6 (2.0)
Peripheral vascular disease	304 (2.2)	646 (2.4)	7 (2.3)
Stroke	144 (1.0)	382 (1.4)	7 (2.3)
Congestive heart failure	151 (1.1)	365 (1.4)	9 (3.0)

Table 2 continued

Characteristics	Lispro (n = 14,047)	Aspart (n = 26,813)	Glulisine (n = 305)
Hypoglycemia	1093 (7.8)	1671 (6.2)	13 (4.3)
Hyperglycemia	1203 (8.6)	2289 (8.5)	17 (5.6)

Data are presented as means (standard deviations) unless otherwise stated
BMI body mass index, *BP* blood pressure, *CABG* coronary artery bypass graft, *CSII* continuous subcutaneous insulin infusion, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *NPH* neutral protamine Hagedorn, *PCI* percutaneous coronary intervention

(11.6 years), followed by 15.4 years for aspart users and 19.5 years for lispro users (Table 2). Mean HbA1c was 70.3 mmol/mol among glulisine users, 63.6 mmol/mol among lispro users, and 64.1 mmol/mol among aspart users. A higher proportion of glulisine users had a history of CHD (8.2%), followed by 4.4% among lispro users and 4.2% among aspart users. A higher proportion of glulisine users had a history of CVD (10.5%), followed by 7.4% among aspart users and 6.5% among lispro users. A lower proportion of glulisine users, however, had a history of severe hypoglycemia (4.3%), followed by 6.2% among aspart users and 7.8% among lispro users. A lower proportion of glulisine users had a history of severe hyperglycemia (5.6%), followed by 8.5% among aspart users and 8.6% among lispro users. The differences between the groups were all adjusted for by means of weighting.

The mean follow-up period was shortest for glulisine (2.5 years), followed by 5.8 years for aspart users and 6.4 years for lispro users (Table 3). The absolute number of events was very low in the glulisine group, ranging from 0 to 13 (Table 3). The (unadjusted) mean HbA1c and weight during the follow-up period were similar (Figs. 2, 3). No significant differences emerged between the treatment groups regarding risk of hyperglycemia requiring hospitalization, CVD or mortality. Cox regression suggested lower risks among glulisine users for severe hypoglycemia (HR 0.16, CI: 0.04–0.64 vs. lispro users and HR 0.16, CI: 0.04–0.62 vs. aspart users). Cox regression suggested lower risks among glulisine users for heart failure (HR 0.08, CI: 0.02–0.31 vs. lispro users and HR 0.11, CI: 0.02–0.54 vs. aspart users; Table 4). Cox regression also suggested a lower risk of stroke (HR 0.80, CI: 0.68–0.93) but a higher risk of hyperglycemia (HR 1.13, CI: 1.03–1.23) among aspart users than lispro users.

For patients 65 years of age or older, the risk of CVD (HR 0.85, CI: 0.74–0.96), stroke (HR 0.61, CI: 0.46–0.81), and heart failure (HR 0.79, CI: 0.65–0.95) was lower among aspart users than lispro users (Table 5). Among these patients, the risk of heart failure remained significantly lower in the glulisine group compared with the lispro group. For elderly patients, Cox regression suggests that glulisine users were at lower risk of kidney failure (HR 0.12, CI: 0.02–0.88 vs. lispro and HR 0.12, CI: 0.01–0.79 vs. aspart). Overall, severe hypoglycemia was more common, and severe hyperglycemia was less common among patients age 65 year or older than among younger patients (HR 1.54, CI: 1.34–1.76 and HR 0.84, CI: 0.73–0.97). Adjusting for confounders did not change this result.

Among patients with renal impairment (Table 6), glulisine users had a lower risk of CVD (HR 0.14, CI: 0.03–0.68 vs. lispro; HR 0.13, CI: 0.03–0.66 vs. aspart) and CHD (HR 0.08, CI:

Table 3 Follow-up period, number of events and incidence per 1000 person years

Event	Lispro (n = 14,047)	Aspart (n = 26,813)	Glulisine (n = 305)
Deaths	563 (6.2)	1223 (7.9)	6 (7.7)
Fatal CHD	198 (2.2)	444 (2.9)	0 (0.0)
Fatal CVD	225 (2.5)	505 (3.2)	0 (0.0)
CHD	898 (10.3)	1676 (11.1)	9 (11.7)
CVD	1283 (14.9)	2352 (15.9)	13 (17)
Stroke	285 (3.2)	441 (2.9)	2 (2.6)
Heart failure	374 (4.2)	743 (4.8)	3 (3.9)
Kidney failure	385 (4.3)	724 (4.7)	3 (3.9)
Hypoglycemia	706 (8.0)	1299 (8.6)	3 (3.9)
Hyperglycemia	929 (10.7)	1946 (13.0)	3 (3.9)
Maximum follow-up time, years	7.5	7.5	7
Mean follow-up time, years	6.4	5.8	2.5
Median follow-up time, years	6.8	6.6	2.7

Values are presented as number of events (incidence per 1000 person-years) unless otherwise stated
CHD coronary heart disease, *CVD* cardiovascular disease

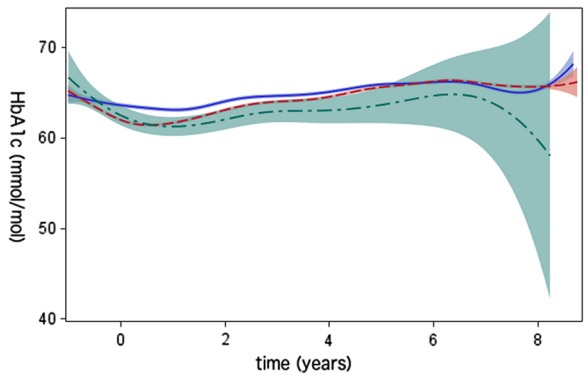

Fig. 2 Average HbA1c during follow-up period among patients treated with lispro, aspart, and glulisine. HbA1c in mmol/mol. *Blue* lispro; *red* aspart; *green* glulisine. *Shaded areas* represent 95% confidence intervals

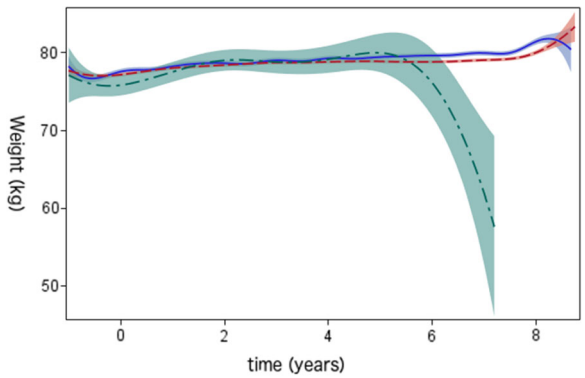

Fig. 3 Average weight during follow-up period among patients treated with lispro, aspart, and glulisine. Weight in kilograms. *Blue* lispro; *red* aspart; *green* glulisine. *Shaded areas* represent 95% confidence intervals

0.01–0.70 vs. lispro; HR 0.09, CI: 0.01–0.72 vs. aspart). For the three treatment groups taken together, the risk of severe hypoglycemia and hyperglycemia was higher among patients with low renal function than those with normal renal function (HR 1.30, CI: 1.18–1.42 and HR 1.92, CI: 1.76–2.09, respectively). Adjusting for confounders eliminated any significant difference in the risk of hypoglycemia between patients with low renal function and those with normal renal function (HR 1.12, CI: 1.00–1.25). The risk of hyperglycemia, however, remained higher among patients with low renal function (HR 1.77, CI: 1.59–1.98).

Table 4 Risks of death and hospitalization

Event	Aspart vs. lispro	Glulisine vs. lispro	Glulisine vs. aspart
Total mortality	1.04 (0.94, 1.16)	0.56 (0.19, 1.66)	0.54 (0.18, 1.58)
CHD	0.95 (0.87, 1.03)	0.49 (0.19, 1.27)	0.52 (0.20, 1.34)
Fatal CHD	1.06 (0.90, 1.25)	N/A	N/A
CVD	0.94 (0.88, 1.01)	0.56 (0.26, 1.24)	0.60 (0.28, 1.31)
Fatal CVD	1.04 (0.89, 1.23)	N/A	N/A
Stroke	0.80 (0.68, 0.93)[a]	0.50 (0.12, 2.08)	0.62 (0.14, 2.59)
Heart failure	0.93 (0.82, 1.05)	0.08 (0.02, 0.31)[a]	0.11 (0.02, 0.54)[a]
Kidney failure	1.07 (0.95, 1.22)	0.69 (0.11, 4.30)	0.57 (0.09, 3.49)
Hypoglycemia	1.03 (0.93, 1.15)	0.16 (0.04, 0.64)[a]	0.16 (0.04, 0.62)[a]
Hyperglycemia	1.13 (1.03, 1.23)[a]	0.69 (0.17, 2.73)	0.61 (0.15, 2.42)

Values are presented as estimated hazard ratios (95% confidence intervals)
CHD coronary heart disease, *CVD* cardiovascular disease, *N/A* not available
[a] *P* value <0.05

Table 5 Risks of death and hospitalization: subgroup analysis among patients age 65 or older

Event	Aspart vs. lispro	Glulisine vs. lispro	Glulisine vs. aspart
Total mortality	0.46 (0.80, 1.18)	0.82 (0.26, 2.60)	0.87 (0.28, 2.73)
CHD	0.88 (0.76, 1.03)	0.67 (0.28, 1.61)	0.76 (0.32, 1.81)
Fatal CHD	0.91 (0.70, 1.20)	N/A	N/A
CVD	0.85 (0.74, 0.96)[a]	0.68 (0.33, 1.43)	0.81 (0.39, 1.68)
Fatal CVD	0.89 (0.69, 1.15)	N/A	N/A
Stroke	0.61 (0.46, 0.81)[a]	0.82 (0.20, 3.49)	1.35 (0.32, 5.64)
Heart failure	0.79 (0.65, 0.95)[a]	0.22 (0.06, 0.82)[a]	0.28 (0.08, 1.03)
Kidney failure	1.11 (0.85, 1.46)	0.12 (0.02, 0.88)[a]	0.12 (0.01, 0.79)[a]
Hypoglycemia	1.12 (0.83, 1.50)	1.24 (0.33, 4.71)	1.11 (0.30, 4.14)
Hyperglycemia	0.94 (0.68, 1.29)	N/A	N/A

Values are presented as estimated hazard ratios (95% confidence intervals)
CHD coronary heart disease, *CVD* cardiovascular disease, *N/A* not available
[a] *P* value <0.05

DISCUSSION

This observational study of 41,165 patients with type 1 diabetes who were monitored up to 7.5 years provides information about the long-term effectiveness and safety of DAIs. The results confirm that there are no differences in mean HbA1c or weight between the three DAI groups during the follow-up period. The DAIs are equally safe in terms of CVD and all-cause

Table 6 Risks of death and hospitalization: subgroup analysis among patients with renal impairment

Event	Aspart vs. lispro	Glulisine vs. lispro	Glulisine vs. aspart
Total Mortality	1.24 (0.97, 1.59)	0.77 (0.15, 4.12)	0.62 (0.12, 3.29)
CHD	0.98 (0.80, 1.20)	0.08 (0.01, 0.70)[a]	0.09 (0.01, 0.72)[a]
Fatal CHD	1.23 (0.84, 1.80)	N/A	N/A
CVD	1.04 (0.87, 1.23)	0.14 (0.03, 0.68)[a]	0.13 (0.03, 0.66)[a]
Fatal CVD	1.16 (0.82, 1.65)	N/A	N/A
Stroke	0.93 (0.62, 1.38)	N/A	N/A
Heart failure	0.97 (0.74, 1.28)	0.20 (0.02, 1.71)	0.21 (0.02, 1.73)
Kidney failure	1.19 (0.96, 1.47)	2.17 (0.37, 12.57)	1.82 (0.32, 10.54)
Hypoglycemia	1.16 (0.79, 1.69)	0.57 (0.07, 4.99)	0.49 (0.06, 4.27)
Hyperglycemia	1.15 (0.81, 1.64)	N/A	N/A

Values are presented as estimated hazard ratios (95% confidence intervals)
CHD coronary heart disease, *CVD* cardiovascular disease, *N/A* not available
[a] *P* value <0.05

mortality. However, for the population with renal impairment, glulisine was associated with a lower risk of CVD. The risk of glulisine treatment for severe hypoglycemia and heart failure may have been lower in both the overall and elderly population. The sub-analysis of the elderly population also found that treatment with glulisine was associated with a lower risk of kidney failure. The results suggested a lower risk of stroke and a higher risk of hyperglycemia among aspart than lispro users, as well as a lower risk of CVD, stroke, and heart failure in the elderly cohort. Hypoglycemia requiring hospitalization was more common, and severe hyperglycemia was less common among patients aged 65 years or older than among younger patients. Both severe hypoglycemia and severe hyperglycemia were more common among patients with low renal function than those with normal renal function.

All new treatment for hyperglycemia must be evaluated with respect to cardiovascular safety and mortality [12]. To the best of our knowledge, no cardiovascular outcome trials have been conducted with DAIs, and no prospective studies have addressed differences in long-term safety between the three available options. The main reasons are no doubt their appearance in the 1990s and the early 2000s before Sweden adopted a new policy for introduction of pharmaceutical treatment. The NDR, additional quality registers, and similar databases should be used to evaluate insulin and other treatment as a way of verifying safety and detecting phenomena for more detailed exploration in future studies. Another objective of such surveys is to establish a basis for discussion of indications, reimbursement and price.

Based on these results, insulin glulisine would seem to be superior to the other DAIs in terms of safety, especially in view of the impressive hazard ratios, all of which imply a fivefold-to-tenfold reduction in risk for the outcomes. Are the differences found by the present study accurate? The answer is "maybe,"

but caution needs to be exercised not to conclude that any such differences definitely reflect effects of glulisine. For example, the results suggest a more than fivefold reduction of the risk for heart failure among the glulisine group compared to the lispro and aspart groups, even though the effect on HbA1c is the same. If such a reduction in risk is to be attributed to properties of insulin glulisine, there should be evidence of differences in the pharmacological properties of the DAIs. Pharmacological effects and their clinical consequences were reviewed just recently [3]. The general view is that the effects of the three DAIs are highly comparable, with rapid pharmacokinetic (PK) and time-action profiles, although glulisine has been suggested to have a slightly faster onset of action [13]. A trial with insulin lispro and the co-administration of hyaluronidase, which accelerates onset, indicated that a more rapid PK profile could improve control of postprandial hyperglycemia without increasing the risk of hypoglycemia [14]. In other words, faster onset could reduce glucose variability. However, it is still unclear whether glucose variability increases the risk for diabetic vascular complications [15]. Furthermore, it is unlikely that minor differences in PKs would translate into a pronounced reduction in the risk of heart failure.

The number and the mean follow-up time for glulisine users were also very limited and relatively short compared with those among the other two groups of DAI users. As a result, only three patients in the glulisine group had a heart failure outcome, as opposed to 374 in the lispro group and 743 in the aspart group. There were even fewer events for the sub-analyses. Thus, it is very difficult to objectively compare the risks of outcomes such as heart failure between the three treatment groups. In other words, the observed reduction in risk is more likely to have been a result of unobserved confounding than simply an effect of glulisine. The same line of reasoning holds for the other outcomes where Cox regression suggested that glulisine was safer than the remaining DAIs.

A confounding factor that may be of some importance is the probability that many insulin lispro and aspart users who were included at baseline in 2005 had already been taking DAIs for many years. Insulin glulisine, on the other hand, had just been made commercially available. Thus, users were generally glulisine-naive at baseline. Most glulisine users, however, had previously taken human insulin or another DAI.

Aspart was associated with more favorable outcomes than lispro regarding stroke among the overall cohort and regarding CVD, stroke, and heart failure among the elderly cohort. On the other hand, a higher risk of hyperglycemia was associated with aspart than lispro. As mentioned earlier, there is no known difference in pharmacological effect between these two types of insulin [3]. Thus, these differences are likely due to unobserved confounding.

The only way to confirm whether the observed differences between the safeties of the three DAIs are due to confounding is to conduct a randomized clinical trial (RCT). However, the number of patients and the duration of exposure needed for such a study in order to assess cardiovascular endpoints would probably deter most sponsors. As a result, an RCT of this type is improbable any time soon. Future observational studies are more likely to provide additional data about cardiovascular safety with the types of insulin that are currently available.

Well performed observational studies have been shown to generate results that are comparable to an RCT [16], although not

everyone agrees [17]. The most important limitation of an RCT is the possible lack of external validity. Pharmaceutical agents are frequently used outside of the characteristics of the populations treated in phase 3 programs before registration—hence, our rationale for the sub-analyses in this study of elderly patients and those with reduced renal function.

The major strengths of this study are its nationwide scope, the large number of patients with type 1 diabetes, the relatively long follow-up period, and the many covariates used in the multivariate analyses. As mentioned earlier, the relatively small number and mean follow-up period of insulin glulisine users were limiting factors. The possible influence of other unknown confounding factors that we were unable to account for was also limitations. For example, doses of the various types of insulin, the number of injections, titration algorithms for basal insulin, plasma glucose levels, and other pharmaceutical treatments was not taken into consideration. Such factors could certainly influence the occurrence of severe hypoglycemia, especially nocturnal, potentially leading to CVD and sudden death.

Swedish patients with type 1 diabetes are encouraged to titrate doses of insulin on a daily basis, based on their individual requirements, diet, physical activity, and self-monitored plasma glucose measurements. Furthermore, more insulin than needed is frequently prescribed to avoid running out. Thus, the PDR does not fully reflect the insulin doses that have actually been taken. For this reason, we refrained from using crude measures such as dispensed daily doses in this study. Nevertheless, the most important determinants of insulin requirement—HbA1c, BMI, and renal function—were quite comparable and were adjusted for.

CONCLUSIONS

In conclusion, we did not find any pronounced differences in effectiveness, long-term cardiovascular safety or mortality between the three available DAIs. Future studies should address the observed differences in the risk of hospitalization for hypoglycemia, hyperglycemia, stroke, and heart failure. The safety profile was also similar in the various subgroups, although the risk of severe hypoglycemia was more common and severe hyperglycemia was less common among elderly patients. Both severe hypoglycemia and severe hyperglycemia were observed more frequently among patients with low renal function.

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Compliance with Ethics Guidelines. The Regional Ethics Review Board in Gothenburg approved the study, which was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. All patients gave their informed consent prior to inclusion.

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