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Association of insulin regimens with severe hypoglycemia in people with Type 1 diabetes - a Danish case-control study

Running title: Insulin regimens and severe hypoglycemia

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The authors confirm that the PI for this paper is Peter Vestergaard and that he had direct clinical responsibility for patients.

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Abstract

***Aims*:** To evaluate the risk of severe hypoglycemia for people with Type 1 diabetes (T1D) when exposed to insulin regimens including human insulin only or insulin analogues.

***Methods*:** A total of 19,896 people with T1D were extracted from the Danish National Patient Register. 6,379 T1D people experiencing one of more severe hypoglycemic episodes (total of 17,242 episodes) were matched 1:1 with T1D people without severe hypoglycemia. A logistic regression model with last insulin regimen used as exposure was constructed to analyse the effect on severe hypoglycemia.

***Results*:** People on a basal-bolus regimen with insulin analogues had a reduced risk of severe hypoglycemia of 39% (OR: 0.61, 95% CI: 0.54-0.68) compared to people on a basal-bolus human insulin only regimen. Furthermore, people on a pre-mixed regimen containing an insulin analogue had a 58% (OR: 0.42, 95% CI: 0.36-0.49) reduced risk of severe hypoglycemia compared to people on a pre-mixed human insulin only.

Conclusions: This study indicates that use of a basal-bolus insulin regimen with an insulin analogue is safer with respect to severe hypoglycemia in people with T1D than the use of a basal-bolus human insulin only regimen.

1: What is already known about this subject:

- Meta-analysis of randomised controlled trials indicate that insulin analogues reduce the risk of devastating severe hypoglycemic episodes compared to human insulin.
- Real-world evidence confirming these results is very sparse but necessary because population selections in randomized controlled trials are typically unnatural leading to less generalisable results.

2: What this study adds:

- From investigation of more than 6,000 people suffering from severe hypoglycemic episodes, insulin analogues in a treatment regimen do reduce the risk of severe hypoglycemia with up to 30%.
- These real-world results suggest that clinicians should consider treating their patients with insulin analogues as compared to human insulin.

Introduction

Late-complications in diabetes mellitus is a major cause of morbidity and premature mortality[1]. The late-diabetic complications include retinopathy, nephropathy, neuropathy and macrovascular diseases and are a consequence of the abnormal hyperglycemic stage[2]. To obtain euglycemia, tight glycemic control is thus necessary, and major studies have shown that intensive insulin therapy aiming at near-normal glucose levels reduces risk of both micro- and macrovascular late-complications[3,4]. However, the reduction in glucose levels increases the risk of severe hypoglycemia[5]. Severe hypoglycemia is a major challenge for people with diabetes and reduces quality of life[3,6]. Furthermore, severe hypoglycemia is associated with the risk of major microvascular events[5] and has been associated with the dead-in-bed syndrome [7,8]. Severe hypoglycemic episodes lead to therapeutic incompliance and expensive hospital-admissions confirmed by a study where 7% of the severe episodes for people with type 1 and 2 diabetes led to hospital admissions > 24 hours[9]. Lastly, the recurrent hypoglycemic episodes impair the hypoglycemic counterregulatory hormonal response, which, in turn increases the risk of subsequent episodes[10,11], i.e. a vicious circle. The risk factors for severe hypoglycemia include diabetes duration, hypoglycemia unawareness, loss of endogenous insulin secretion, inappropriate exogenous insulin use[12]. In older T1D people, the risk of severe hypoglycemia increases, which is linked to the risk factors of unawareness and glucose variability[13]. Human insulins have been the standard basal, basal-bolus and pre-mixed insulin treatment for insulin-dependent people with diabetes for many years, but recent clinical trials have paved the way for approval of a variety of insulin analogues with insulin lispro as the first analogue introduced to the US market in 1996. The different properties of insulin analogues enable once daily administrations and better glycemic control including less severe hypoglycemic episodes[14–17]. One study[18] showed that an insulin analogue increases the risk of severe hypoglycemia, but confounding by indication could not be ruled out. Real-world evidence on change in frequency of severe hypoglycemia remains sparse. Real-world evidence is important to include in the evaluation of insulin analogues, because the results from the clinical trials might be biased due to unrealistic titration procedures and exclusion of people with recurrent hypoglycemia. Some real-world studies have showed that insulin analogues are associated with a lower risk of severe hypoglycemia compared to human insulins[14,19,20] with varying population under

investigation (T2D, T1D, T1D+T2D, respectively). Typically, the studies only compare basal regimens and single products although basal-bolus is the most widely used regimen[21].

This study sought to evaluate the risk of severe hypoglycemia for people with T1D when exposed to basal, bolus, basal-bolus and pre-mixed insulin (mix insulin) regimens including either human insulin, insulin analogues or a combination hereof.

Methods

2.0 Ethics

This was an observational study, and ethics committee approval was according to local regulations thus not required.

2.1 Study design

The investigation was carried out using a case-control study of adults admitted to hospitals in Denmark from 1st of January 1996 to 31st of December 2017. The people enrolled in this study can be seen in Figure 1. Cases experienced hypoglycemic episodes leading to hospital admission and controls did not. Controls were matched to cases 1:1 by age and gender.

People with T1D were identified using the International Classification of Diseases 10 (ICD-10) system and the Anatomical Therapeutical Chemical (ATC) classification system. T1D people (n=19,896) should have at least one DE10 (Type 1 diabetes mellitus) ICD-code and at least one A10A (insulins and analogues) ATC code and no A10B (blood glucose lowering drugs, excl. insulins) ATC code.

2.2 Source of data

Diagnosis of diabetes, hypoglycemia and concomitant illnesses were extracted from the Danish National Patient Register. The Danish National Patient Register was established in 1977 and initially covered information on inpatient in somatic wards. Since then it has been expanded and now includes information on all patients in Danish hospitals. The validity of registrations are in general very high.[22–24] Insulin use and concomitant medications were extracted from the National Pharmacological Database by the Danish Medicines Agency. The National Pharmacological Database is a nationwide register of medicines sold after 1996.

2.3 Endpoint and exposure

The endpoint (outcome) in the study was hypoglycemia leading to hospital admission. In a study by Heller et al.[9] of people with type 1 and type 2 diabetes, only 19% of severe hypoglycemic episodes led to emergency room attendance/hospital admission (64 "Hospital or emergency room ≤ 24 h" and 36 "Hospital > 24 h" of 536 events), and the episodes investigated in this study are thus of high severity and from now on referred to as severe hypoglycemia. The episodes (n_{obs}=17,242) were identified via the ICD-10 codes DE159 (hypoglycemic coma, unspecified), DE160 (drug-induced hypoglycemia without coma), DE161 (other hypoglycemia), DE161B (encephalopathy following hypoglycemic coma) and DE162 (Hypoglycemia, unspecified). Only the last hypoglycemic episode experienced by each person was included in the investigation. The control people inherited this hypoglycemia date of their matched cases as a dummy date. Exposure was last insulin regimen used in the period from the hypoglycemia date/dummy date and 180 days prior. Insulin use was defined as prescriptions of insulin, and the 6 months interval was thus chosen to ensure that prescriptions exist. Only cases with the same regimen throughout the period were kept. Both bolus, basal and pre-mixed insulins were categorised into being an analogue or not as seen in Table 1.

The different insulin regimens can be seen in Table 2. "Mix insulin" is pre-mixed insulin containing only human insulin products whereas "Mix insulin analogue" is pre-mixed insulin with either one or two insulin analogues. Insulin dose was calculated as the sum of the units of dispensed insulin in the defined exposure period before the hypoglycemic episode/dummy date divided by the exposure period duration.

2.4 Statistical analyses

Descriptive statistics will be presented with mean and standard deviation (SD) or percentage of people. T-tests, Chi-square tests and Mann-Whitney U tests will be used to present statistical differences in person characteristics. Age and diabetes duration are calculated from date of birth and date of diagnosis, respectively, to hypoglycemia date/dummy date. Late-diabetic complications is presented in the following categories: Nephropathy (ICD-10: DE102), retinopathy (ICD-10: DE103), neuropathy (ICD-10: DE104-5), multiple (ICD-10: DE107 or >1 of the mentioned complications) and other (ICD-10: DE106, DE108).

A logistic regression model was constructed to analyse the effect of the insulin regimens on severe hypoglycemia. The most widely used regimen "Basal insulin + bolus insulin" (cf. Table 2) was used as reference for the other regimens. The model included use of glucocorticoids (ATC: H02AB), use of agents acting on the renin-angiotensin system (ATC: C09) use of beta blocking agents (ATC: C07), use of antiepileptics (ATC: N03AX12, N03AX16), use of antidepressants (ATC: N06AA), history of alcohol abuse (ICD-10: DF10, DZ721) and history of liver disease (ICD-10: DK70, DK71, DK74) as dichotomous covariates. These covariates are judged as potential confounders as they all affect the glucose metabolism and may be associated with insulin regimens. Furthermore, the model was adjusted for diabetes duration and late-diabetic complications.

The descriptive and inferential analyses were conducted in SAS 9.4. The significance level was set at a p value of less than 0.05 for two-sided testing.

Results

Table 3 shows the person characteristics of the case-control. The control group has a lower diabetes duration and, therefore, in general less late-diabetic complications. Daily insulin use is slightly lower in the control group. Person characteristics for each insulin regimen can be seen in Table 4.

The results of the logistic regression can be seen in Table 5. Using a regimen with an insulin analogue resulted in an almost 40% lower risk of severe hypoglycemia as can be seen in all three basal-bolus regimens. Furthermore, there is a risk-reduction for people on a bolus insulin analogue. On the other hand, using a mix human insulin only and a basal human insulin regimen seem to increase the risk of severe hypoglycemia compared to using a basal-bolus human insulin only regimen. A model with mix human insulin only as reference showed an odds ratio of 0.42 with 95% CI of 0.36 to 0.49 for people on a mix insulin analogue regimen.

Discussion

Findings from this study indicate that the risk of severe hypoglycemic episodes is up to 39% lower for people on a basal-bolus insulin analogue regimen compared to people on a basal-bolus human insulin only regimen. Furthermore, people on a bolus insulin analogue regimen had a reduced risk of severe hypoglycemia. On the contrary, people on a mix human insulin

only regimen had a 2-fold increase in risk of severe hypoglycemia compared to people on a basal-bolus human only insulin regimen.

A register study by Strandberg et al.[20] including both people with T1D and type 2 diabetes (T2D) showed a similar risk-reduction of 30% and 24% in severe hypoglycemia for the insulin analogues of insulin glargine and insulin detemir, respectively, compared to the human insulin NPH (neutral protamine Hagedorn). In another register study, Ou et al.[19] investigated basal insulin analogues vs. basal human insulins on diabetes-related complications in T1D. They found a risk-reduction of approximately 35% in severe hypoglycemia for people on a basal insulin analogue compared to people on a basal human insulin. In a cross-over trial of 159 people with T1D suffering from recurrent severe hypoglycemia, Pedersen-Bjergaard et al.[17] found a comparable relative reduction in rate of severe hypoglycemia of 29% for people on a regimen with an insulin analogue compared to a human insulin. Other studies investigating the risk of hypoglycemia for people on insulin analogues compared to people on human insulins confirm the trend[25–27].

In this study, a statistically significant risk-reduction for people on a bolus insulin analogue. From the characteristics of people in the different regimens, it is evident that people on a bolus insulin analogue are much younger with shorter diabetes duration and with less late-diabetic complications. Although the model was adjusted for these confounders, other underlying comorbidities might be increasing the risk of severe hypoglycemia for people on a basal-bolus human insulin only regimen. Also, we observed that use of mix human insulin only, resulted in a pronounced increase in the risk of severe hypoglycemia compared to a basal-bolus human insulin only, and with mix human insulin only as reference, the risk of severe hypoglycemia was reduced by 58% for people on a mix insulin analogue, which is in line with a risk reduction in overall hypoglycemia for people on insulin glargine compared to mix human insulin in a study by Rys et al.[14]

A major limitation in this study is the lack of HbA1c measurements. We have no indication of whether the lower risk of severe hypoglycemia comes at the expense of an increased HbA1c, and thereby a higher risk of earlier onset and accelerated progression of late-diabetic complications. However, the lower risk of severe hypoglycemia does not seem to be associated with a decreased daily insulin dose. Neither does the prevalence of late-diabetic complications within each regimen indicate a relation between reduced risk of severe hypoglycemia and less effective glucose control. Also, lack of hypoglycemia unawareness

status is a limitation, because higher hypoglycemia unawareness significantly increases the risk of severe hypoglycemia[28]. Another limitation is the use of ICD-10 codes for classification of T1D and T2D, identification of hypoglycemic episodes and for concomitant illnesses. The codes are entered manually by clinicians, and human errors will thus be present. Due to the fact that the Danish National Patient Register is known for registrations of high validity, the detrimental effect is deemed minimal though. Cases and controls could have been matched by year of diabetes diagnosis, but due to the resulting lower sample size, we chose only to adjust for diabetes duration. More than 10% of the population were users of a basal regimen, which is not typical for T1D, but a few patients were in Denmark formerly only treated with basal insulin. Furthermore, some people with T2D might have been classified erroneously as T1D in the register, and some people with a very low bolus insulin need, might not have had bolus insulin dispensed in the 180 days period. These are two clear limitations. Finally, a limitation is that only a small subset of the severe hypoglycemic episodes has been investigated. Severe hypoglycemic episodes that do not lead to hospitalization are equally important to avoid, and the results from this study might not be generalizable to these episodes.

Use of an insulin analogue in a basal-bolus regimen compared to a basal-bolus human insulin only regimen is associated with a reduction in the risk of severe hypoglycemia in people with T1D. Moreover, use of a pre-mixed insulin regimen with an insulin analogue compared to a pre-mixed human insulin only regimen resulted in a lower risk of severe hypoglycemia. However, a limitation is that glucose control e.g. via HbA1c and hypoglycemia unawareness status is not available. These results do not reveal evidence on head-to-head investigations of different insulin analogues, which are also important, but they add to the sparse real-world evidence that insulin analogues are safer to use than human insulins with respect to severe hypoglycemia.

Conflicts of interests

There are no competing interests to declare.

Data availability

Data are available through Statistics Denmark[29] and all authorized research organizations can apply for access. Access for international researchers can only be gained if they are

affiliated to a Danish research organization.

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Table 1: Categoristation of insulin products into human basal/bolus/mix insulin or basal/bolus/mix insulin analogue.

Insulin type	Insulin product	Group
Bolus	Actrapid®	Bolus insulin
	Humulin® Regular	Bolus insulin
	Insuman® Rapid Solostar®	Bolus insulin
	Apidra®	Bolus insulin analogue
	Fiasp®	Bolus insulin analogue
	Humalog®	Bolus insulin analogue
	NovoRapid®	Bolus insulin analogue
Basal	Humulin® NPH (neutral protamine Hagedorn)	Basal insulin
	Insulatard®	Basal insulin
	Abasaglar KwikPen	Basal insulin analogue
	Lantus®	Basal insulin analogue
	Levemir®	Basal insulin
	Toujeo®	analogue
	Tresiba®	Basal insulin analogue
		Basal insulin analogue
Pre-mixed	Mixtard® 30	Mix insulin
	Humalog® Mix25 KwikPen	Mix insulin analogue
	NovoMix®	Mix insulin
	Ryzodeg®	analogue
		Mix insulin analogue

Table 2: Different insulin regimens based on categorisation of insulin products. Abbreviation is added and used for later reference in Table .

Abbreviation	Insulin regimen
Ba0	Basal insulin[a]
Ba1	Basal insulin analogue
Bo0	Bolus insulin[a]
Bo1	Bolus insulin analogue
Ba0Bo0	Basal insulin[a] + bolus insulin[a]
Ba1Bo0	Basal insulin analogue + bolus insulin
Ba0Bo1	Basal insulin[a] + bolus insulin analogue
Ba1Bo1	Basal insulin analogue + bolus insulin analogue
Mix0	Mix insulin[b]
Mix1	Mix insulin analogue[c]

[a] If ”analogue” is not mentioned then the insulin is human

[b] Zero analogue components

[c] One or two analogue components

Table 3: Person characteristics of cases and controls.

	Cases	Controls	*P*
n	6,379	6,379	
Age, mean (SD)	50 (21)	50 (21)	-
Sex			
Women (%)	44.3	44.3	-
Men (%)	55.7	55.7	-
Hypoglycaemic episodes	17,242	0	-
Number of persons with 1 episode	3,199	0	-
Number of persons with 2 episodes	1,303	0	-
Number of persons with >2 episode	1,877	0	-
Hypoglycemic episodes per person, mean (SD)	2.7 (4.3)	0	-
Diabetes duration (yrs), mean (SD)	22 (9)	15 (10)	<.0001
Late-diabetic complications			
Nephropathy (%)	1.5	1.5	0.0003
Retinopathy (%)	6.7	7.9	<.0001
Neuropathy (%)	2.1	3.2	0.2855
Multiple (%)	46.5	23.7	<.0001
Other (%)	12.5	10.9	<.0001
Daily insulin dose (IU), mean (SD)	94 (57)	91 (56)	0.0025
Insulin Regimen[a]			
Basal insulin (%)	8.1	11.8	<.0001
Basal insulin analogue (%)	2.8	1.8	<.0001
Bolus insulin (%)	2.9	2.7	0.0977
Bolus insulin analogue (%)	7.7	8.4	<.0001
Basal insulin + bolus insulin (%)	22.7	21.5	0.1179
Basal insulin + bolus insulin analogue(%)	7.6	9.7	<.0001
Basal insulin analogue + bolus insulin (%)	3.0	2.3	<.0001
Basal insulin analogue + bolus insulin analogue (%)	25.3	23.8	0.0085
Mix insulin (%)	16.1	13.5	<.0001
Mix insulin analogue (%)	3.9	4.4	0.9046
Other covariates[a]			
Glucocorticoids (%)	3.9	3.0	0.0026
Renin-angiotensin agents (%)	42.1	34.8	<.0001

Beta blocking agents (%)	15.4	9.8	<.0001
Antiepileptics (%)	3.7	1.5	<.0001
Antidepressants (%)	3.4	2.1	<.0001
History of alcohol abuse (%)	5.9	3.1	<.0001
Previous liver disease (%)	0.2	0.5	0.0078

[a] Percentage of hypoglycemic/dummy episodes

Table 4: Person characteristics for each insulin regimen including people experiencing severe hypoglycemia and people without. The percentages are of people within regimen. Please refer to Table for explanation of insulin regimen abbreviations.

	Insulin regimens									
	Ba0	**Ba1**	**Bo0**	**Bo1**	**Ba0Bo 0**	**Ba0Bo 1**	**Ba1Bo 0**	**Ba1Bo 1**	**Mix0**	**Mix1**
n	1,268	298	356	1,024	2,820	1,105	335	3,134	1,887	531
Hypoglycemic/dummy episodes	3,431	677	1,172	1,908	10,465	2,997	840	6,233	5,564	1,248
Age, mean (SD)	68 (15)	54 (20)	51 (16)	32 (20)	49 (17)	43 (17)	56 (15)	44 (19)	59 (26)	57 (22)
Sex										
Women (%)	47.2	44.0	42.7	50.0	42.8	37.9	46.0	43.3	47.6	41.1
Men (%)	52.8	56.0	57.3	50.0	57.2	62.1	54.0	56.7	52.4	58.9
Diabetes duration (yrs), mean (SD)	15 (8)	24 (11)	20 (8)	16 (12)	19 (8)	18 (10)	26 (9)	21 (11)	15 (8)	19 (11)
Daily insulin dose (IU), mean (SD)	62 (40)	58 (41)	45 (40)	50 (33)	94 (51)	115 (54)	110 (59)	119 (61)	94 (65)	102 (63)
Late-diabetic complications										
Nephropathy (%)	2.7	0.0	2.2	0.6	1.8	1.8	0.9	1.0	1.6	2.1
Retinopathy (%)	5.0	5.4	8.1	7.1	10.0	7.0	8.7	8.4	3.8	5.5
Neuropathy (%)	4.5	2.0	2.0	0.7	3.1	2.4	3.0	1.8	3.2	4.3
Multiple (%)	30.4	59.1	42.7	22.9	34.6	26.5	52.5	36.8	37.9	40.9
Other (%)	11.7	10.1	9.3	13.8	9.4	11.0	9.3	12.3	14.3	12.6

Table 5: Logistic regression with episodes of hypoglycemia and episodes without as outcome and insulin regimens as exposure. The reference in the model was the most frequent regimen: Basal insulin + bolus insulin.

Insulin regimen	Odds ratio, 95% CI	P value
Basal insulin	*1.53 (1.31-1.80)	<.0001
Basal insulin analogue	0.88 (0.66-1.16)	0.6899
Bolus insulin	0.96 (0.75-1.23)	0.7002
Bolus insulin analogue	*0.78 (0.66-0.92)	0.0235
Basal insulin + bolus insulin analogue	*0.64 (0.55-0.75)	<.0001
Basal insulin analogue + bolus insulin	*0.62 (0.48-0.80)	0.0006
Basal insulin analogue + bolus insulin analogue	*0.61 (0.54-0.68)	<.0001
Mix insulin	*2.10 (1.83-2.40)	<.0001
Mix insulin analogue	0.87 (0.71-1.08)	0.5729

The model was adjusted for age, sex, diabetes duration, daily insulin dose, late-diabetic complications, glucocorticoids, renin-angiotensin agents, beta blocking agents, antiepileptics, antidepressives, history of alcohol abuse and previous liver diseases.

* Statistically significant result

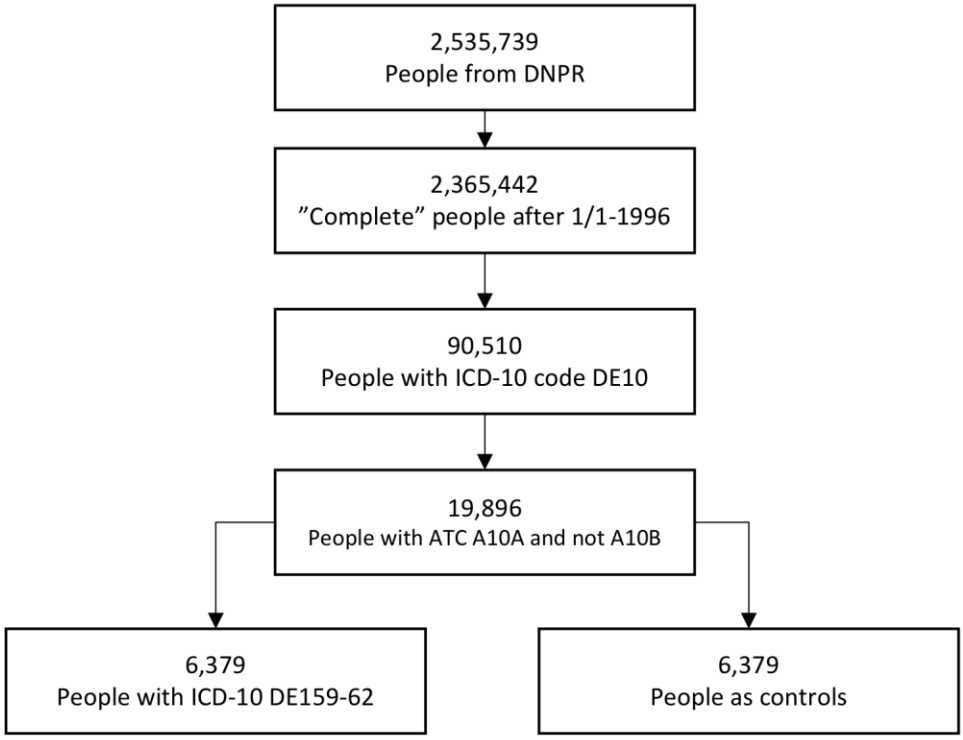

Figure 1: Number of people in the case-control study. From the available people from the Danish National Patient Register, 19,896 were identified as having Type 1 diabetes (T1D). 6,379 T1D people experiencing hypoglycemic episodes leading to hospital admission were matched 1:1 by age and gender with people without hypoglycemic episodes leading to hospital admission.

Word count
2,182