ORIGINAL ARTICLE

Multicenter, open-label, nonrandomized, observational safety study in subjects using insulin aspart in basal-bolus regimen for the treatment of diabetes

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KEY WORDS

basal-bolus regimen, diabetes, glycemic control, insulin aspart, observational study

ABSTRACT

INTRODUCTION Basal-bolus insulin therapy is a standard method of intensifying diabetes treatment. A common adverse effect of such treatment is hypoglycemia. Data on frequency of hypoglycemia when fast-acting insulin analogue is used in everyday clinical practice is scarce.

OBJECTIVES The aim of the study was to investigate the risk of hypoglycemia after the use of insulin aspart in basal-bolus therapy in patients with type 1 and 2 diabetes.

PATIENTS AND METHODS It was a multicenter, open-label, noninterventional study. It involved 950 patients with type 1 and 1332 patients with type 2 diabetes who started preprandial insulin aspart in basal-bolus regimen. Patients were followed for 13 weeks. The primary endpoint was the incidence of major daytime and nocturnal hypoglycemic events assessed on the basis of patients' self-reports during follow-up compared with a 4-week period before the baseline visit. Secondary endpoints were: incidence of minor daytime and nocturnal hypoglycemia, hemoglobin A_{1c} (HbA_{1c}), fasting and postprandial glycemia.

RESULTS The rate of major hypoglycemia decreased in patients with type 1 diabetes – the incidence rate ratio (IRR) was 0.14 for daytime and 0.03 for nocturnal episodes (P <0.0001) and did not change in patients with type 2 diabetes. The rate of minor episodes decreased in patients with type 1 diabetes (IRR = 0.44 for daytime and IRR = 0.24 for nocturnal episodes, P <0.0001) and in patients with type 2 diabetes (IRR= 0.57, P <0.0001 for daytime and IRR = 0.89, P <0.05 for nocturnal episodes). HbA_{1c} decreased by 1.28 ±1.64% in type 1 and 1.25 ±1.10% in type 2 diabetes (both P <0.0001). Self-measured fasting and postprandial blood glucose levels were significantly lower at the final visit compared with baseline, irrespective of diabetes type.

CONCLUSIONS In clinical practice, treatment with insulin aspart in basal-bolus regimen is associated with low risk of hypoglycemia and leads to a significant improvement in glucose control, irrespective of diabetes type.

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INTRODUCTION An ultimate goal of diabetes management, regardless of the type, is to maintain glycemic control, which is essential for reducing the incidence and progression of long-term diabetes complications.[1-4] Based on the evidence from a number of recent studies (mainly the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes Study), the leading organizations such as the American Diabetes Association, the American Association of Clinical Endocrinologists, and the International Diabetes Federation currently recommend

hemoglobin A_{1c} (HbA_{1c}) levels of <7%, ≤6.5%, and ≤6.5%, respectively.[1-7] The Polish Diabetes Society recommends HbA_{1c} values <7% in patients with type 2 diabetes and <6.5% in patients with type 1 or newly diagnosed type 2 diabetes.[8] Patients with type 1 diabetes are dependent on exogenous insulin replacement therapy due to absolute insulin deficiency from the onset of the disease. Patients with type 2 diabetes may be initially treated mainly by lifestyle interventions alone, but due to the natural history of type 2 diabetes characterized by progressive loss of β-cell function, they will later require numerous pharmacological agents to maintain glycemic control, and eventually many patients will need insulin treatment.[9,10] Unfortunately, insulin therapy is underutilized in this most common type of diabetes.[11] Despite substantial literature data supporting the benefits of glucose lowering, mean HbA_{1c} levels are still high in this patient group.[12]

For many years, pharmacokinetic limitations of conventional insulin made treatment goals difficult to achieve, and intensive regimens often resulted in frequent hypoglycemia and weight gain.[1,3] Optimal metabolic control requires treatment that mimics the physiological basal and prandial insulin secretion of healthy individuals as closely as possible.[13] Because absorption time of human insulin is short and poorly reproductible, postprandial glucose (PPG) excursions are difficult to reduce. It is particularly important because PPG correlates more closely with the progression of cardiovascular disease than with either fasting glucose or HbA_{1c} levels.[14-16] Modification of the insulin molecule with recombinant DNA technology led to synthesis of insulin analogues characterized by more physiologic time-action profiles.[17] Rapid-acting insulin analogues, such as insulin aspart, are chemically engineered variants of human insulin that were developed to match mealtime physiological insulin secretion more closely. As an alternative to regular human insulin, insulin aspart injected before meals is more rapidly absorbed, has faster onset and shorter duration of action, as well as higher peak concentrations, mimicking the postprandial spike. A rapid-acting insulin analogue allows patients to "inject-and-eat", or even inject after meals, with no need for a 30-minute injection-meal interval necessary in the case of short-acting human insulin.[18]

Of note, outcome measures of the studies assessing new insulin therapies and regimens evaluate not only near-normalization of blood glucose but also reduction of hypoglycemia risk. Evaluation of hypoglycemia is particularly important because it is common in insulin-treated diabetes and remains the major barrier for optimal glycemic control. What is even more important according to the recent data is that intensive glycemic control, which targets HbA_{1c} <6%, may be associated with worse clinical outcomes compared with standard glycemic control.[19,20]

There have been a number of randomized controlled trials (RCTs) showing that insulin aspart leads to improved glycemic control without increasing the risk of hypoglycemia.[21-30] Although RCTs are of great value, they may not be fully representative of the general, heterogeneous patient population with complex chronic diseases, due to patient selection criteria. It has been proved that observational studies, which do not require controlled conditions and restrictive inclusion and exclusion criteria, are useful in validating clinical trial data on adverse events and efficiency of treatment in a large number of diverse patients, in the actual clinical practice.[31-33] Because patients with type 1 and some patients with type 2 diabetes use mealtime insulin every day, there is a need for an observational study to assess how glycemic control has been affected in routine clinical practice, which may complement data from RCTs and support evidence-based medicine. That is why we considered it important to evaluate the safety and efficacy of insulin aspart as mealtime insulin added to different basal insulin preparations in real clinical setting.

PATIENTS AND METHODS

Study design It was an open-label, nonrandomized, noninterventional, 13-week observational study involving 2388 patients with type 1 or type 2 diabetes and conducted in the setting of routine clinical practice. Patients were recruited from primary and secondary care settings and 1000 researchers were involved in data collection. The study was conducted between November 2006 and April 2007. Physicians made decisions about the dosage and duration of insulin therapy as well as the use of any other medications in individual cases.

The aim of the study was to evaluate the incidence rate of major hypoglycemic episodes in patients with any type of diabetes treated with insulin aspart in basal-bolus regimen in normal clinical conditions. The effectiveness of insulin aspart was considered a secondary endpoint.

Because it was an observational study, the decision to administer insulin aspart to a patient was made prior to inclusion in the study. In other words, whether a patient received insulin did not depend on whether he or she was included in the study; therefore, there was no need to obtain informed consent from patients or the approval of an ethics committee.

Study population Any patient with type 1 or 2 diabetes was eligible for the study if a physician decided to start intensive insulin therapy (basal-bolus regimen) with insulin aspart (NovoRapid®, Novo Nordisk AS, Denmark) in addition to basal insulin therapy with neutral protamine Hagedor (NPH) insulin (Insulatard®, Novo Nordisk AS, Denmark) or long-acting insulin analogue detemir (Levemir®, Novo Nordisk AS, Denmark). There were no limitations concerning previous diabetes treatment; insulin aspart had to be started not earlier than 14 days before inclusion in

the study. In order to minimize selection bias, patients were enrolled on consecutive basis, until the quota of 5 patients for each participating physician was reached.

Patients were excluded from the study if they were unable to follow the protocol requirements such as assessment at the final visit, had hypersensitivity to insulin aspart or any of the excipients, or were included to the study previously. The decision to discontinue insulin aspart was at the discretion of individual physicians and was based on clinical evaluation of the patient's condition.

We recruited 5000 eligible patients; 2388 individuals actually participated in the study. It was conducted by 1000 primary and secondary care physicians.

In 31 patients a discrepancy between the diagnosis (type 1 diabetes) and administered treatment (oral antidiabetic drugs) was found. This group was classified as "unconfirmed diagnosis" and was excluded from further efficacy and safety analysis.

Assessments and outcome measures Data were collected from medical records, patient reports and diaries at baseline (first visit) and during the final visit after a 13-week follow-up. Physicians recorded the following information: demographics, medical history (type and duration of diabetes, micro- and macrovascular complications, the number of minor daytime and nocturnal hypoglycemic events during 4 weeks prior to the study, the number of all major daytime and nocturnal hypoglycemic events during the study), and measures of glycemic control: HbA_{1c}, fasting blood glucose (FBG), postprandial blood glucose (PPBG).

The primary endpoint was the incidence rate of major hypoglycemic events reported as serious adverse drug reactions during a 13-week treatment.

The secondary outcome measure during a 13-week treatment was safety: the number of all major (daytime and nocturnal) hypoglycemic events reported as serious adverse drug reactions, the number of all minor (daytime and nocturnal) hypoglycemic events during 4 weeks preceding the study, and changes in the body mass index (BMI) at the end of the study.

Another secondary outcome measure during a 13-week treatment was effectiveness: changes in HbA_{1c} at the end of the study, the proportion of patients who reached target HbA_{1c} $\leq$6.5% and <7% as well as the targets set by physicians, mean FBG and PPBG after main meals.

Major hypoglycemia was defined as an episode with severe central nervous system symptoms consistent with hypoglycemia that could not be self-treated by a patient and was associated with either a confirmed blood glucose reading <56 mg/dl (3.1 mmol/l) or prompt recovery after glucagon or intravenous glucose administration. Minor hypoglycemia was defined as an episode with either symptoms of hypoglycemia with blood glucose measurement <3.1 mmol/l that was self-treated by a patient, or any asymptomatic blood glucose measurement <3.1 mmol/l. Nocturnal hypoglycemia was defined as a symptomatic hypoglycemic episode occurring during sleep, between the evening insulin injection and morning wake up. Data concerning hypoglycemia was obtained mainly from patient diaries. If a diary was not available, the data was based on patient recollection obtained during medical interview and a physician decided about its credibility.

Statistical analysis The sample size was based on the primary objective of the study, namely evaluation of the incidence of major hypoglycemia reported as a serious adverse drug reaction. A sample of 4000 patients was needed to detect the incidence of serious adverse drug reactions of at least 0.025% with probability of at least 95%. It means that a total of 4000 patients were required to detect at least 1 serious adverse drug reaction occurring in 25 of 100,000 patients with 95% probability. To provide at least 4000 individuals for the final statistical analysis, we had to recruit 5000 patients given the fact that some patients might withdraw from the study and be lost to follow-up. Descriptive statistics were used to present baseline data from the full analysis set (FAS). Continuous variables were presented using descriptive statistics (mean, standard deviation [SD]). For categorical variables frequencies were computed (n,%). The primary endpoint (major hypoglycemia) was presented as a number of events and a number and proportion of patients suffering from a major hypoglycemic event. The total incidence of major hypoglycemia was summarized for 1 patient count-up and presented concomitantly.

For comparisons between the baseline and final visits, the paired t-test for normally distributed variables and the Wilcoxon's matched-pairs signed rank test for nonnormally distributed variables were used. The Shapiro-Wilk W test was used to verify normality assumptions. The main outcome variable was the incidence of major hypoglycemia events during a 13-week treatment with insulin aspart. Other outcome variables were secondary endpoints, i.e., safety and effectiveness. The incidence rate of severe hypoglycemia was calculated by dividing the total number of severe hypoglycemic events by the total number of patients. The differences in intensity of hypoglycemic events between the baseline and final visits were presented as incidence rate ratios (IRRs) and assessed using the general estimating equation for the Poisson panel data. IRR = 1 indicates that the intensity of hypoglycemic events did not differ between the 2 visits. IRR <1 when compared with the baseline visit indicates that the intensity of hypoglycemic events at the final visit was lower, and IRR >1 indicates that it was higher. Patients included in the FAS took part in the final study visit and had at least

TABLE 1 Demographic and disease characteristics at baseline

	Total population n = 2388	Type 1 diabetes n = 923	Type 2 diabetes n = 1332
women, n (%)	1259 (53.06)	486 (52.9)	715 (54)
men, n (%)	1114 (46.94)	433 (47.1)	609 (46)
age, y	48.1 ±18.8	31.1 ±15.2	60.3 ±10.1
body mass, kg	77.5 ±19.6	64.7 ±18.3	86.6 ±16.9
height, cm	166.69 ±12.50	165 ±16.5	167.7 ±8.6
BMI, kg/m^2	27.55 ±6.08	23.1 ±4.4	30.8 ±5.1
time from diagnosis, mo	117.30 ±87.98	105.9 ±100.6	115.1 ±68.4
macrovascular complications, n (%)	982 (41.12)	91 (9.9)	851 (63.9)
peripherial vascular disease, n (%)	424 (17.76)	41 (4.4)	363 (27.2)
coronary heart disease, n (%)	734 (30.74)	49 (5.3)	661 (49.6)
stroke, n (%)	108 (4.52)	8 (0.9)	96 (7.2)
other, n (%)	147 (6.16)	11 (1.2)	134 (10.1)
microvascular complications, n (%)	1 141 (47.78)	294 (31.9)	790 (59.3)
retinopathy, n (%)	898 (37.60)	239 (25.9)	616 (46.2)
nephropathy, n (%)	296 (12.40)	87 (9.4)	199 (14.9)
peripherial neuropathy, n (%)	578 (24.20)	142 (15.4)	402 (30.2)
autonomic neuropathy, n (%)	142 (5.95)	47 (5.1)	88 (6.6)
other complications, n (%)	9 (0.38)	3 (0.3)	5 (0.4)
oral diabetes medication, n (%)	833 (34.88)	0	784 (58.9)
previous insulin therapy, n (%)			
analogue premix	214 (9.36)	154 (16.14)	60 (4.5)
analogue rapid acting	111 (4.86)	18 (1.89)	93 (6.98)
basal	812(35.52)	509 (53.35)	303 (22.75)
biphasic human	972 (42.52)	313 (32.81)	659 (49.47)
human short acting	1035 (45.27)	648 (67.92)	387 (29.05)

Data are shown as absolute numbers and percentage; continuous variables are shown as mean ± SD

Abbreviations: BMI – body mass index, SD – standard deviation

TABLE 2 Rate of hypoglycemia (number of events per patient) and the incidence rate ratio [confidence interval] of hypoglycemic events in the Poisson model

		Type 1 diabetes	*P*	Type 2 diabetes	*P*
minor events					
day	baseline	2.52	<0.001	0.78	<0.001
	EOT	1.13		0.45	
	IRR	0.44 [0.42, 0.47]		0.57 [0.52, 0.64]	
night	baseline	1.3	<0.001	0.41	<0.05
	EOT	0.36		0.36	
	IRR	0.28 [0.24, 0.31]		0.89 [0.80, 0.99]	
major events					
day	baseline	0.33	<0.001	0.06	NS
	EOT	0.05		0.06	
	IRR	0.14 [0.10, 0.20]		0.94 [0.68, 1.31]	
night	baseline	0.25	<0.001	0.04	
	EOT	0.01		0.0	
	IRR	0.04 [0.02, 0.08]		NA	

Abbreviations: CI – confidence interval, EOT – end of trial, IRR – incidence rate ratio, NA – not applicable (analysis not performed), NS – nonsignificant

1 FBG and PPBG measurement done as well as the most recent HbA_{1c} outcome and body weight measured, and were asked about the occurrence of hypoglycemic events at baseline and at the final visit after a 13-week follow-up. All statistical tests were two-sided, with a significance level of 5%. Statistics were based on patients with complete data. The statistical analyses were performed using STATA 10.0.

RESULTS Demographic and disease characteristics of the study population as well as the occurrence of micro- and macrovascular complications are summarized in TABLE 1.

Safety **Hypoglycemic events** IRR in patients with type 1 diabetes was 0.04 for nocturnal and 0.14 for daytime major hypoglycemia (P <0.001) and 0.28 for nocturnal and 0.44 for daytime minor hypoglycemia (P <0.001) (TABLE 2). A decrease in the rate of mild hypoglycemia was observed also in patients with type 2 diabetes (IRR = 0.57 for daytime and 0.89 for nocturnal episodes, P <0.01 and P <0.05, respectively). Risk of severe daytime hypoglycemia in patients with type 2 diabetes did not change. Also in these patients, no severe nocturnal episodes were recorded during the study, so the analysis was unfeasible.

Changes in body mass and body mass index Body mass and BMI did not change significantly during 3 months of follow-up. Data are summarized in TABLE 3.

Efficacy Glycemic control at baseline was poor, with HbA_{1c} levels of 8.77 ±1.7% (mean ± SD) and improved to 7.54 ±0.93 (1.26 ±1.35%; P <0.0001) after a 13-week treatment. A similar effect was observed both in type 1 and 2 diabetic patients. Improvement in glycemic control included both

TABLE 3 Body mass and body mass index change at the end of a 13-week study

	n	Baseline visit	Final visit	Mean change	*P*
body mass					
type 1 diabetes	840	64.5 ±18.3	64.7 ±17.8	0.25 ±2.63	NS
type 2 diabetes	1224	86.1 ±16.9	85.6 ±14.5	–0.51 ±1.95	NS
BMI					
type 1 diabetes	821	23.1 ±4.4	23.2 ±3.2	0.12 ±1.0	NS
type 2 diabetes	1188	30.8 ±5.1	30.6 ±4.4	–0.17 ±1.1	NS

Data are shown as means ± SD

Abbreviations: see TABLES 1 and 2

TABLE 4 Efficacy at baseline and at final visit

	n	Baseline visit	Final visit	Mean change	*P*
HbA_{1c}, %					
type 1 diabetes	385	8.75 ±1.93	7.48 ±1.00	–1.27 ±1.63	<0.0001
type 2 diabetes	498	8.81 ±1.4	7.60 ±0.90	–1.25 ±1.10	<0.0001
FBG, mg/dl					
type 1 diabetes	845	161.70 ±53.66	118.22 ±27.60	–43.48 ±50.10	<0.0001
type 2 diabetes	1250	165.22 ±43.33	125.05 ±23.79	–39.72 ±40.82	<0.0001
PPBG at breakfast, mg/dl					
type 1 diabetes	784	173.26 ±57.55	138.36 ±26.05	–34.88 ±55.12	<0.0001
type 2 diabetes	1137	191.30 ±49.24	144.61 ±25.97	–46.38 ±46.13	<0.0001
PPBG at lunch, mg/dl					
type 1 diabetes	781	172.77 ±51.96	139.42 ±26.05	–33.37 ±49.64	<0.0001
type 2 diabetes	1143	199.64 ±49.54	150.41 ±25.94	–49.48 ±48.77	<0.0001
PPBG at dinner, mg/dl					
type 1 diabetes	771	168.15 ±48.40	137.24 ±28.04	–30.91 ±48.98	<0.0001
type 2 diabetes	1086	188.97 ±47.59	145.30 ±25.63	–43.43 ±46.38	<0.0001

Data are shown as means ± SD; statistical differences calculated with Wilcoxon's matched-pairs signed rank test

Abbreviations: FBG – fasting blood glucose; HbA_{1c} – hemoglobin A_{1c}, PPBG – postprandial blood glucose, others – see TABLE 1

TABLE 5 Proportion of patients reaching therapeutic goals at the final visit. Data shown as absolute numbers and percentage

Therapeutic target	Type 1 diabetes	Type 2 diabetes	Total population
HbA_{1c} ≤6.5%, n (%)	71/482 (14.7)	38/655 (5.8)	117/1195 (9.8)
HbA_{1c} <7%, n (%)	190/482 (39.4)	158/655 (24.1)	375/1195 (31.4)
HbA_{1c} (set by physicians), n (%)	79/479 (16.8)	82/631 (17)	171/1157 (14.8)

Abbreviations: see TABLE 4

TABLE 6 Reasons for starting basal-bolus treatment with aspart as the bolus insulin

	Total population n = 2388	Type 1 diabetes n = 923	Type 2 diabetes n = 1332
unsatisfactory HbA_{1c}, n (%)	1404 (62.3)	578 (62.6)	826 (62)
unsatisfactory FPG, n (%)	1795 (79.6)	660 (71.5)	1135 (85.2)
unsatisfactory PPBG, n (%)	1916 (85)	711 (77)	1205 (90.5)
risk of hypoglycemia, n (%)	1034 (45.8)	518 (56.1)	516 (38.7)
patient disappointment with previous therapy, n (%)	686 (30.4)	274 (29.7)	412 (30.9)
previous therapy adverse effects	217 (9.6)	62 (6.7)	155 (11.6)
injection device, n (%)	162 (7.2)	51 (5.5)	111 (8.3)
injection directly before or after the meal, n (%)	1284 (56.9)	528 (57.2)	756 (56.8)
other reasons, n (%)	156 (6.9)	99 (10.7)	57 (4.3)

Data are shown as absolute numbers and percentage

Abbreviations: see TABLE 4

FBG and PPBG measured after all main meals (TABLE 4).

At the end of follow-up, 9.8% of patients reached the target HbA_{1c} ≤6.5%, 31.4% reached the target HbA_{1c} <7%, and 14.8% reached the target set by individual physicians (TABLE 4). When patients were analyzed according to diabetes type, similar effects were observed for basically all parameters, except that more patients with type 1 diabetes reached target HbA_{1c} targets of 6.5% and 7% compared with patients with type 2 diabetes (TABLE 5).

Rationale for starting basal-bolus treatment with aspart as the bolus insulin The reasons for changing previous therapy to basal-bolus therapy with insulin aspart are presented in TABLE 6. The main reason for the change was glycemic control (mainly postprandial but a substantial number of physicians also indicated fasting glucose and HbA_{1c}).

DISCUSSION All patients with type 1 and many patients with type 2 diabetes require intensive insulin therapy to achieve HbA_{1c} treatment goals. In diabetes management, it is important to maintain the balance between optimal glycemic control and hypoglycemia caused by too intensive glucose-lowering treatment. Hypoglycemia is the main barrier in initiating and continuing insulin therapy, and, according to recent data, it is associated with poorer clinical outcomes.[19]

Our primary objective was to assess the incidence rates of severe hypoglycemic events in a large population-based cohort in everyday setting because it is different from representative samples observed so far under optimal conditions in many RCTs.[34]

Data from a 13-week follow-up of type 1 and 2 diabetic patients, treated with basal-bolus regimen of insulin aspart as mealtime insulin and either insulin detemir or NPH insulin as a basal component, showed low incidence of major hypoglycemic events. This was especially true for patients with type 2 diabetes. Apart from a marked improvement in glycemic control parameters, the results showed that intensive regimen with multiple insulin-aspart injections may be an efficient and safe option for treatment intensification in patients with type 2 diabetes. Compared with baseline, there was a significant reduction in the incidence of total daytime and nocturnal major hypoglycemic events. Our results are consistent with those obtained in clinical trials that showed improvement in glycemic control and a low risk of hypoglycemia, although it must be stressed that because it was an observational study, the recording and efficiency data were based on patient reports and diaries.[21,27,35-36]

Conclusions Our results indicate that in patients with types 1 and 2 diabetes, introduction of insulin aspart as part of basal-bolus regimen leads to a clinically significant decrease in the number of hypoglycemic events along an improvement in blood glucose control. We proved that the beneficial results observed in clinical trials can also be achieved in routine clinical practice.

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ARTYKUŁ ORYGINALNY

Wieloośrodkowe, otwarte, nierandomizowane, obserwacyjne badanie bezpieczeństwa u pacjentów z cukrzycą stosujących insulinę aspart w schemacie *basal-bolus*

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SŁOWA KLUCZOWE

badanie obserwacyjne, *basal-bolus*, cukrzyca, insulina aspart, kontrola glikemii

STRESZCZENIE

WPROWADZENIE Schemat insulinoterapii *basal-bolus* jest standardową metodą intensyfikacji leczenia cukrzycy. Częstym niepożądanym efektem takiej intensyfikacji są epizody hipoglikemii. Mało jest jednak danych opisujących częstość epizodów hipoglikemii po zastosowaniu szybko działającego analogu insuliny w codziennej praktyce klinicznej.

CELE Celem badania było określenie częstości epizodów hipoglikemii po zastosowaniu insuliny aspart w schemacie *basal-bolus* u pacjentów z cukrzycą typu 1 i 2.

PACJENCI I METODY Badanie miało charakter wieloośrodkowy, otwarty, nieinterwencyjny. Objęło 950 pacjentów z cukrzycą typu 1 i 1332 z cukrzycą typu 2, rozpoczynających leczenie insuliną aspart jako doposiłkową insuliną w schemacie *basal-bolus*. Chorzy byli obserwowani przez 13 tygodni. Głównym punktem końcowym obserwacji była częstość ciężkich epizodów hipoglikemii w ciągu dnia i w ciągu nocy określana na podstawie samodzielnie zgłaszanych incydentów z okresu obserwacji w porównaniu z częstością w ciągu 4 tygodni przed rozpoczęciem obserwacji. Dodatkowymi punktami końcowymi były częstość łagodnych epizodów hipoglikemii w ciągu dnia i w ciągu nocy, hemoglobina A_{1c} (HbA_{1c}) oraz glikemia na czczo i po posiłkach.

WYNIKI Częstość występowania ciężkich hipoglikemii zmniejszyła się u pacjentów z cukrzycą typu 1 (*incidence rate ratio* [IRR] wynosił 0,14 i 0,03 odpowiednio dla epizodów dziennych i nocnych [$P < 0{,}0001$] oraz nie zmienił się u pacjentów z cukrzycą typu 2). Łagodne epizody hipoglikemii były rzadsze u pacjentów z cukrzycą typu 1 (IRR 0,44 dla epizodów dziennych i 0,24 dla epizodów nocnych, $P < 0{,}0001$) oraz z cukrzycą typu 2 (IRR 0,57; $P < 0{,}0001$ dla epizodów dziennych i 0,89; $P < 0{,}05$ dla epizodów nocnych). Odsetek HbA_{1c} zmniejszył się średnio o 1,28 ±1,64% u pacjentów z cukrzycą typu 1 i o 1,25 ±1,10% u pacjentów cukrzycą typu 2 (w obu przypadkach $P < 0{,}0001$). Samodzielnie mierzona glikemia na czczo i po posiłkach także była mniejsza pod koniec obserwacji w porównaniu z obserwowaną początkowo, niezależnie od typu cukrzycy.

WNIOSKI Leczenie insuliną aspart w schemacie *basal-bolus* jest związane z małym ryzykiem hipoglikemii i pozwala uzyskać poprawę wyrównania glikemii niezależnie od typu cukrzycy w praktyce klinicznej.

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