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Association of Insulin Pump Therapy vs Insulin Injection Therapy With Severe Hypoglycemia, Ketoacidosis, and Glycemic Control Among Children, Adolescents, and Young Adults With Type 1 Diabetes

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IMPORTANCE Insulin pump therapy may improve metabolic control in young patients with type 1 diabetes, but the association with short-term diabetes complications is unclear.

OBJECTIVE To determine whether rates of severe hypoglycemia and diabetic ketoacidosis are lower with insulin pump therapy compared with insulin injection therapy in children, adolescents, and young adults with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study conducted between January 2011 and December 2015 in 446 diabetes centers participating in the Diabetes Prospective Follow-up Initiative in Germany, Austria, and Luxembourg. Patients with type 1 diabetes younger than 20 years and diabetes duration of more than 1 year were identified. Propensity score matching and inverse probability of treatment weighting analyses with age, sex, diabetes duration, migration background (defined as place of birth outside of Germany or Austria), body mass index, and glycated hemoglobin as covariates were used to account for relevant confounders.

EXPOSURES Type 1 diabetes treated with insulin pump therapy or with multiple (≥4) daily insulin injections.

MAIN OUTCOMES AND MEASURES Primary outcomes were rates of severe hypoglycemia and diabetic ketoacidosis during the most recent treatment year. Secondary outcomes included glycated hemoglobin levels, insulin dose, and body mass index.

RESULTS Of 30 579 patients (mean age, 14.1 years [SD, 4.0]; 53% male), 14 119 used pump therapy (median duration, 3.7 years) and 16 460 used insulin injections (median duration, 3.6 years). Patients using pump therapy (n = 9814) were matched with 9814 patients using injection therapy. Pump therapy, compared with injection therapy, was associated with lower rates of severe hypoglycemia (9.55 vs 13.97 per 100 patient-years; difference, −4.42 [95% CI, −6.15 to −2.69]; $P < .001$) and diabetic ketoacidosis (3.64 vs 4.26 per 100 patient-years; difference, −0.63 [95% CI, −1.24 to −0.02]; $P = .04$). Glycated hemoglobin levels were lower with pump therapy than with injection therapy (8.04% vs 8.22%; difference, −0.18 [95% CI, −0.22 to −0.13], $P < .001$). Total daily insulin doses were lower for pump therapy compared with injection therapy (0.84 U/kg vs 0.98 U/kg; difference, −0.14 [−0.15 to −0.13], $P < .001$). There was no significant difference in body mass index between both treatment regimens. Similar results were obtained after propensity score inverse probability of treatment weighting analyses in the entire cohort.

CONCLUSIONS AND RELEVANCE Among young patients with type 1 diabetes, insulin pump therapy, compared with insulin injection therapy, was associated with lower risks of severe hypoglycemia and diabetic ketoacidosis and with better glycemic control during the most recent year of therapy. These findings provide evidence for improved clinical outcomes associated with insulin pump therapy compared with injection therapy in children, adolescents, and young adults with type 1 diabetes.

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Supplemental content

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The use of insulin pumps for intensive insulin therapy among patients with type 1 diabetes has substantially increased from 0.6% to 1.3% in 1995 to 44% to 47% between 2012 and 2016.[1-4] Pump therapy with rapid-acting insulin allows for a more physiologic insulin replacement and may thus contribute to improved metabolic control, thereby reducing the risk of long-term complications.[5,6] Randomized clinical trials[7] and observational studies[3,4,8,9] have shown lower levels of glycated hemoglobin (HbA_{1c}) with insulin pump therapy than with multiple daily insulin injections. Insulin pumps have also become an integral part of closed-loop treatment systems ("artificial beta cell" systems) in which subcutaneous insulin infusion and continuous glucose monitoring devices are linked to automatically deliver insulin in response to current and predicted glucose levels.[10-12]

Several studies reported an increased risk of ketoacidosis associated with insulin pump therapy in pediatric patients with diabetes,[8,9,13]raising concerns about the safety of pump therapy. A decline in the frequency of severe hypoglycemia during recent years along with an increase in insulin pump use has been observed,[1,14] but a causal relationship between insulin regimen and outcome remains controversial.[15] The association of pump therapy with the risk of acute diabetes complications has not been comprehensively studied in direct comparison to injection therapy, because evaluating rare events such as severe hypoglycemia and ketoacidosis requires adequately sized large datasets.

The aim of this study was to investigate the outcomes of current insulin pump therapy, compared with injection therapy, in young patients with type 1 diabetes using a large population-based clinical practice database to identify participants. We hypothesized that insulin pump therapy, compared with injection therapy, would be associated with reduced rates of acute diabetes complications and lower HbA_{1c} levels.

Key Points

Question Are the rates of severe hypoglycemia and diabetic ketoacidosis lower with insulin pump therapy than with insulin injection therapy in young patients with type 1 diabetes?

Findings In this population-based observational study including 30 579 young patients with type 1 diabetes, pump therapy, compared with injection therapy, was associated with significantly lower rates of severe hypoglycemia (9.55 vs 13.97 per 100 patient-years) and ketoacidosis (3.64 vs 4.26 per 100 patient-years), and with lower hemoglobin A_{1c} levels (8.04% vs 8.22%) in a propensity score–matched cohort.

Meaning Insulin pump therapy was associated with reduced risks of short-term diabetes complications and with better glycemic control compared with injection therapy.

Methods

Study Design and Oversight

This was a population-based cohort study comparing patients with type 1 diabetes mellitus who used insulin pump therapy and patients who used insulin injection therapy between January 1, 2011, and December 31, 2015. Patients included in the study were identified from the Diabetes Prospective Follow-up (DPV) Initiative database at the University of Ulm, Germany. As of December 31, 2015, 446 diabetes centers (hospitals and practices) in Germany, Austria, Luxembourg, and Switzerland have documented treatment and outcome of diabetes care using the DPV Diabetes Documentation System.[1,16,17] Parameters collected in the DPV system have been described previously.[17] Twice a year, locally collected longitudinal data are transmitted anonymously for central analysis, and inconsistent data are reported back to participating centers. The DPV database covers an estimated proportion of more than 80% of all pediatric patients with diabetes in Germany, Austria, and Luxembourg.

Informed consent for participation in the DPV Initiative was obtained from patients or their parents by verbal or written procedure, as approved by the responsible administrators for data protection of each center. The analysis of anonymized data was approved by the ethics committee of the University of Ulm.

Study Population

Patients were eligible for inclusion in the study if they had a clinical diagnosis of type 1 diabetes and were treated with intensive insulin therapy administered by either pump or injection, defined as 4 or more insulin injections per day. Exclusion criteria were younger than 6 months at diagnosis; 20 years or older; diabetes duration less than 1 year; use of 3 or fewer daily insulin injections; and use of continuous glucose monitoring. All patients continuously used either pump therapy or injection therapy during the entire observation period of 12 months, thus excluding treatment crossover. For each patient, clinical data including HbA_{1c} level, total daily insulin dose, prandial to total insulin ratio, frequency of self-monitoring of blood glucose level, and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of the most recent treatment year were aggregated as medians, and hypoglycemic and ketoacidosis events were summed and related to the individual time at risk, as described previously.[16]

Propensity Score Analyses

Propensity score matching was used to ensure that both the pump therapy group and injection therapy group had similar baseline characteristics, because patients who are presented with the option of using pump therapy may have different baseline characteristics, affording them the opportunity to use this technology. Propensity score for pump therapy was estimated applying a multivariable logistic regression model, with age, sex, duration of diabetes, migration background, BMI, and HbA_{1c} level as covariates. Migration background was defined as birthplace outside of Germany or Austria for the patient or of 1 or both parents. For each patient, the probability (propensity score) for pump therapy was estimated from the logistic model based on the patient's specific covariate values. Matching was conducted with a one-to-one

matching process (greedy-matching algorithm).[18,19] Standardized differences were assessed to evaluate balancing of covariates between treatment groups. A standardized difference of less than 10% for a baseline covariate reveals a negligible imbalance.[18] Treatment effects were estimated by directly comparing outcomes between an equal number of pump-treated and injection-treated individuals with the same propensity score (matched cohort).

Since a considerable proportion of eligible patients were lost during the matching process, we performed additional exploratory analyses with inverse probability of treatment weighting using the propensity score[19,20] to estimate the association between treatment and outcomes including all eligible patients (entire cohort).

Outcomes

The primary outcomes were the rates of severe hypoglycemia and diabetic ketoacidosis during the most recent year of treatment. Severe hypoglycemia was defined as requiring assistance from another person to actively administer carbohydrates, glucagon, or intravenous glucose consistent with guidelines from the International Society of Pediatric and Adolescent Diabetes (ISPAD)[21] and the American Diabetes Association.[22] Hypoglycemic coma was defined as loss of consciousness or occurrence of seizures according to ISPAD classification.[23] In preschool children, severe hypoglycemia was defined as the presence of altered mental status and the inability to assist in their care, and coma as unconsciousness or occurrence of convulsions, requiring parenteral treatment.[23] Hypoglycemic events and other parameters were actively enquired and recorded at each medical visit using the standardized DPV questionnaire across all participating centers during the whole study period.[1,17] Diabetic ketoacidosis was defined as pH less than 7.3 or bicarbonate concentration less than 15 mmol/L (all events) and as severe ketoacidosis if pH was less than 7.1 or bicarbonate concentration was less than 5 mmol/L.[24]

Secondary outcomes were HbA_{1c} level, total daily insulin dose, prandial to total insulin ratio, frequency of self-monitoring of blood glucose level, and BMI during the most recent year of treatment. HbA_{1c} values were mathematically standardized to the Diabetes Control and Complications Trial reference range (4.05%-6.05%) using the multiple-of-the-mean transformation method.[1] BMI values were transformed to SD scores based on German reference values by applying the 3 parameter-based lambda-mu-sigma method.[16]

Statistical Analyses

Event rates of severe hypoglycemia, hypoglycemic coma, diabetic ketoacidosis, and severe ketoacidosis were evaluated in pump therapy and injection therapy by negative binomial regression analyses including matched pairs (in the matched cohort) or treatment center (in the entire cohort) as a random factor. Individuals with no available information on severe hypoglycemia or coma events were not included in these regression analyses. In additional analyses, event rates of severe hypoglycemia, coma, diabetic ketoacidosis, and severe ketoacidosis were estimated by age groups from negative binomial regression models including a therapy × age group interaction term in the matched cohort. Age groups were defined as 1.5 to 5 years; 6 to 10 years; 11 to 15 years; or 16 to 19 years.

HbA_{1c} levels, total daily insulin dose, prandial to total insulin ratio, frequency of self-monitoring of blood glucose level, and BMI were compared between pump therapy and injection therapy by linear regression analyses, and use of rapid-acting insulin analogues by logistic regression analysis, including matched pairs (in the matched cohort) or treatment center (in the entire cohort) as a random factor. In additional analyses, HbA_{1c} levels and the insulin treatment-related parameters were estimated stratified by age groups from linear regression models including a therapy × age group interaction term in the matched cohort.

Results from regression analyses are presented as means, event rates per 100 patient-years, absolute between-group differences, and incidence rate ratios (IRRs), with 95% CIs. Adjustment for multiple comparisons was performed separately for the matched cohort and the entire cohort considering primary and secondary outcomes by controlling the false discovery rate according to the method of Benjamini and Hochberg.[25] Because the percentage of missing data was small (0%-6%), no imputation was performed.

$P < .05$ (2-sided) was considered statistically significant. All analyses were performed using SAS for Windows, version 9.4 (SAS Institute).

Results

Study Population

Of the 446 diabetes centers, 350 treated 30 579 individuals with type 1 diabetes (mean age, 14.1 years [SD, 4.0]; 53% male) meeting the inclusion criteria (**Figure 1**), with a mean number of 4.8 visits (SD, 2.5) per patient during the most recent treatment year. Among the treated patients, 14 119 used insulin pump therapy, with a median duration of 3.7 years; 16 460 used multiple (≥4) daily insulin injections, with a median duration of 3.6 years. In the propensity score–matched cohort, 9814 patients using insulin pump therapy were matched with 9814 patients using injection therapy from 328 diabetes centers. In this matched cohort the standardized differences were 1.8% or less for all baseline characteristics, demonstrating only minor differences between both treatment groups (**Table 1**). The median duration of insulin pump therapy was 3.6 years and of insulin injection therapy was 4.4 years in the matched cohort. Since 10 951 individuals were lost during the matching process, we additionally conducted an analysis for the entire cohort with inverse probability of treatment weighting using propensity scores (Figure 1).

Primary Outcomes

Severe Hypoglycemia

In the matched cohort, a total of 2371 events of severe hypoglycemia in 1251 patients (6.4% of patients), including 520 events of hypoglycemic coma in 406 patients (2.1%), were recorded at 97 451 medical visits during the most recent

treatment year. Data on severe hypoglycemia and coma events were available for 94% of individuals.

Event rates for severe hypoglycemia were significantly lower with pump therapy compared with injection therapy (9.55 vs 13.97 per 100 patient-years; difference per 100 patient-years, −4.42 [95% CI, −6.15 to −2.69]; IRR, 0.68 [95% CI, 0.59 to 0.79]) (**Table 2**, **Figure 2**). Event rates for hypoglycemic coma were also significantly lower with pump therapy compared with injection therapy (2.30 vs 2.96 per 100 patient-years; difference per 100 patient-years, −0.66 [95% CI, −1.24 to −0.08]; IRR, 0.78 [95% CI, 0.62 to 0.97]) (Table 2, Figure 2). These differences remained significant after adjusting for multiple comparisons ($P < .001$ for severe hypoglycemia, $P = .03$ for hypoglycemic coma). Age-group analyses showed significantly lower rates of severe hypoglycemia with pump therapy vs injection therapy in all age groups except for preschool children aged 1.5 to 5 years (eFigure 1A in the Supplement). Significantly lower rates of hypoglycemic coma with pump therapy compared with injection therapy were observed in children aged 6 to 10 years and 11 to 15 years but not in other age groups (eFigure 1B in the Supplement).

In the entire cohort, 3572 episodes of severe hypoglycemia in 1875 patients (6.1%), including 786 episodes of coma in

Figure 1. Selection of Study Population

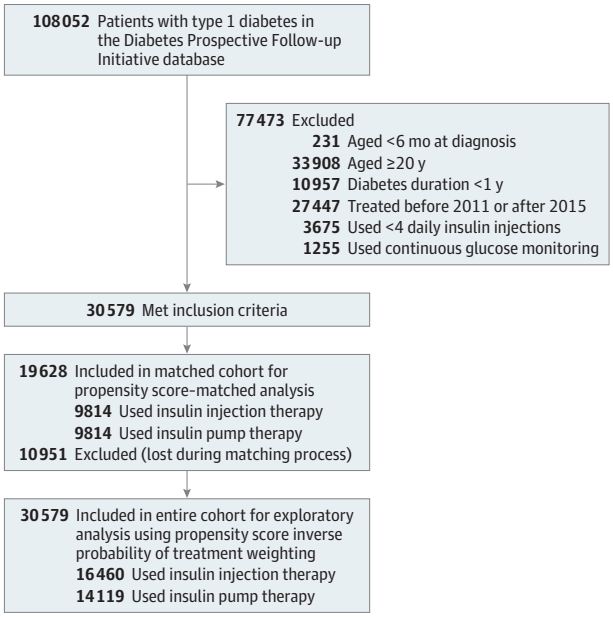


Table 1. Baseline Characteristics of the Study Population

Characteristic	Matched Cohort (n = 19 628)[a]			Entire Cohort (N = 30 579)[b]		
	Injection Therapy (n = 9814)	Pump Therapy (n = 9814)	Standardized Difference, %[c]	Injection Therapy (n = 16 460)	Pump Therapy (n = 14 119)	Standardized Difference, %[c]
Age						
Mean (SD), y	14.6 (3.6)	14.6 (3.6)	0.02	15.1 (3.3)	13.1 (4.4)	-50.6
No. (%)						
1.5 to 5 y	156 (2)	172 (2)	1.3	174 (1)	1125 (8)	33.8
6 to 10 y	1594 (16)	1578 (16)	-0.4	2071 (13)	3329 (24)	28.9
11 to 15 y	3801 (39)	3773 (38)	-0.6	6218 (38)	4934 (35)	-5.9
16 to 19 y	4263 (43)	4291 (44)	0.6	7997 (49)	4731 (34)	-31.0
Sex, No. (%)						
Female	4754 (48)	4764 (49)	0.2	7076 (43)	7204 (51)	16.2
Male	5060 (52)	5050 (51)	-0.2	9384 (57)	6915 (49)	-16.2
Duration of diabetes						
Mean (SD), y	7.0 (3.9)	7.0 (3.9)	-0.7	5.9 (4.0)	6.6 (3.9)	20.2
No. (%)						
1 to <5 y	3543 (36)	3582 (36)	0.8	8258 (50)	5538 (39)	-22.2
≥5 y	6271 (64)	6232 (64)	-0.8	8202 (50)	8581 (61)	22.2
Migration background, No. (%)[d]	1890 (19)	1913 (19)	0.6	3680 (22)	2556 (18)	-10.6
BMI SD score, mean (SD)[e]	0.30 (0.89)	0.32 (0.87)	1.8	0.29 (0.91)	0.34 (0.87)	5.0
HbA_{1c}, mean (SD), %	8.1 (1.5)	8.1 (1.4)	0.3	8.2 (1.7)	7.9 (1.3)	-15.2

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin.

[a] Propensity score–matched cohort.

[b] Before propensity score matching.

[c] The standardized differences (pump therapy vs injection therapy) are reported as percentages; a difference of less than 10% reveals a negligible imbalance.[18]

[d] Migration background was defined as birthplace outside of Germany or Austria for the patient or of 1 or both parents.

[e] Calculated as weight in kilograms divided by height in meters squared and reported as SD score based on German normative data. An SD score of zero corresponds to the 50th percentile (median), and an SD score of +2 corresponds to the 97.7th percentile of an age- and sex-specific reference group.

Table 2. Primary Outcomes: Severe Hypoglycemia and Diabetic Ketoacidosis With Injection Therapy vs Pump Therapy[a]

Outcome	Matched Cohort (n = 19 628)[b]				Entire Cohort (N = 30 579)[c]			
	Injection Therapy (n = 9814)	Pump Therapy (n = 9814)	Between-Group Difference (95% CI)[d]	*P* Value	Injection Therapy (n = 16 460)	Pump Therapy (n = 14 119)	Between-Group Difference (95% CI)[d]	*P* Value
Severe Hypoglycemia								
No. of events	1371	1000			2135	1437		
No. of patients with events (%)	712 (7.3)	539 (5.5)			1091 (6.6)	784 (5.6)		
Rate per 100 patient-years (95% CI)	13.97 (12.47 to 15.48)	9.55 (8.49 to 10.62)	-4.42 (-6.15 to -2.69)	<.001	15.53 (13.22 to 17.84)	10.30 (8.73 to 11.86)	-5.23 (-6.93 to -3.53)	<.001
Hypoglycemic Coma								
No. of events	287	233			476	310		
No. of patients with events (%)	229 (2.3)	177 (1.8)			379 (2.3)	243 (1.7)		
Rate per 100 patient-years (95% CI)	2.96 (2.51 to 3.41)	2.30 (1.93 to 2.67)	-0.66 (-1.24 to -0.08)	.02	3.43 (2.78 to 4.08)	2.26 (1.81 to 2.72)	-1.16 (-1.72 to -0.60)	<.001
Diabetic Ketoacidosis (pH <7.3)								
No. of events	453	389			886	533		
No. of patients with events (%)	381 (3.9)	338 (3.4)			724 (4.4)	474 (3.4)		
Rate per 100 patient-years (95% CI)	4.26 (3.81 to 4.72)	3.64 (3.22 to 4.05)	-0.63 (-1.24 to -0.02)	.04	6.94 (5.58 to 8.31)	4.66 (3.70 to 5.61)	-2.29 (-3.12 to -1.46)	<.001
Severe Ketoacidosis (pH <7.1)								
No. of events	296	246			594	328		
No. of patients with events (%)	264 (2.7)	212 (2.2)			502 (3.0)	290 (2.1)		
Rate per 100 patient-years (95% CI)	2.80 (2.43 to 3.16)	2.29 (1.97 to 2.61)	-0.50 (−0.99 to -0.02)	.04	5.17 (3.87 to 6.47)	3.17 (2.34 to 4.01)	-2.00 (-2.79 to -1.21)	<.001

[a] Values are estimated from negative binomial regression analysis with matched pairs (matched cohort) or treatment center (entire cohort) as a random factor.

[b] The propensity score–matched cohort comprises 10 621 patient-years with injection therapy and 10 639 patient-years with pump therapy.

[c] The entire cohort was included in propensity score inverse probability of treatment weighting analysis and comprises 16 546 patient-years with injection therapy and 15 009 patient-years with pump therapy.

[d] Absolute differences between pump therapy and injection therapy.

622 patients (2.0%), were documented at 146 919 visits during the most recent treatment year. Data on these events were available for 94% of individuals. Event rates for severe hypoglycemia were significantly lower with pump therapy compared with injection therapy (10.30 vs 15.53 per 100 patient-years; difference per 100 patient-years, −5.23 [95% CI, −6.93 to −3.53]; IRR, 0.66 [95% CI, 0.59 to 0.75]) (Table 2, Figure 2). Event rates for hypoglycemic coma were also significantly lower with pump therapy compared with injection therapy (2.26 vs 3.43 per 100 patient-years; difference per 100 patient-years, −1.16 [95% CI, -1.72 to -0.60]; IRR, 0.66 [95% CI, 0.55 to 0.80]) (Table 2, Figure 2). These differences remained significant after adjusting for multiple comparisons ($P < .001$ for severe hypoglycemia, $P < .001$ for hypoglycemic coma).

Diabetic Ketoacidosis

In the matched cohort, a total of 842 events of diabetic ketoacidosis in 719 patients (3.7% of patients), including 542 events of severe ketoacidosis (pH <7.1) in 476 patients (2.4%), were noted during the most recent treatment year. Compared with injection therapy, pump therapy was associated with significantly lower event rates for ketoacidosis (3.64 vs 4.26 per 100 patient-years; difference per 100 patient-years, −0.63 [95% CI, −1.24 to −0.02]; IRR, 0.85 [95% CI, 0.73 to 0.995]) (Table 2, Figure 2). Event rates for severe ketoacidosis were significantly lower with pump therapy than with injection therapy (2.29 vs 2.80 per 100 patient-years; difference per 100 patient-years, −0.50 [95% CI, −0.99 to −0.02]; IRR, 0.82 [95% CI, 0.68 to 0.99]) (Table 2, Figure 2). These differences remained significant after adjusting for multiple comparisons ($P = .048$ for diabetic ketoacidosis, $P = .048$ for severe ketoacidosis). Age-group analyses showed significantly lower rates of diabetic ketoacidosis and severe ketoacidosis with pump therapy vs injection therapy in adolescents and young adults aged 16 to 19 years but not in other age groups (eFigure 1C and eFigure 1D in the Supplement).

In the entire cohort, 1419 episodes of ketoacidosis in 1198 patients (3.9%), including 922 episodes of severe ketoacidosis in 792 patients (2.6%), were reported during the most recent treatment year. Compared with injection therapy, pump therapy was associated with significantly lower event rates for ketoacidosis (4.66 vs 6.94 per 100 patient-years; difference per 100 patient-years, −2.29 [95% CI, −3.12 to −1.46]; IRR, 0.67 [95% CI, 0.59 to 0.76]) (Table 2, Figure 2). Event rates for severe

ketoacidosis were significantly lower with pump therapy than with injection therapy (3.17 vs 5.17 per 100 patient-years; difference per 100 patient-years, −2.00 [95% CI, −2.79 to −1.21]; IRR, 0.61 [95% CI, 0.52 to 0.72]) (Table 2, Figure 2). These differences remained significant after adjusting for multiple comparisons ($P < .001$ for diabetic ketoacidosis, $P < .001$ for severe ketoacidosis).

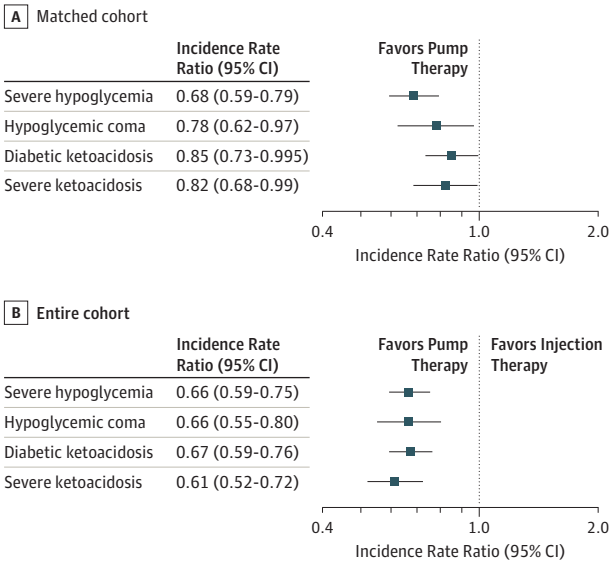
Secondary Outcomes: Metabolic Control and Insulin Treatment–Related Parameters

In the matched cohort, mean HbA_{1c} level was lower with pump therapy compared with injection therapy (8.04% vs 8.22%; difference, −0.18 [95% CI, −0.22 to −0.13]) (**Table 3**). In matched pairs aged 1.5 to 5 years, HbA_{1c} values were similar if treated with pump therapy or injection therapy, while HbA_{1c} levels were significantly lower with pump therapy in all other age groups (all $P \leq .02$) (eTable in the Supplement). In the entire cohort, mean HbA_{1c} level was lower with pump therapy compared with injection therapy (7.99% vs 8.17%; difference, −0.18 [95% CI, −0.21 to −0.15]) (Table 3).

Total daily insulin dose was lower and prandial to total insulin ratio was higher in pump therapy compared with injection therapy (Table 3), significant for all age groups of the matched cohort ($P < .001$ for all) (eFigure 2A and 2B in the Supplement). Rapid-acting insulin analogues were used in 96% of patients with pump therapy and 74% of patients with injection therapy (Table 3). The more frequent use of rapid-acting insulin analogues with pump therapy was observed in all age groups of the matched cohort ($P < .001$ for all) (eFigure 2C in the Supplement). Individuals with injection therapy used long-acting insulin analogues in 80% (matched cohort) and 77% (entire cohort), respectively.

Mean daily frequency of self-monitoring of blood glucose level was higher with pump therapy compared with injection therapy (Table 3), significant in all age groups ($P < .001$ for all) (eFigure 2D in the Supplement). There was no difference in BMI between treatment regimens (Table 3).

Figure 2. Incidence Rate Ratios of Severe Hypoglycemia and Diabetic Ketoacidosis for Pump Therapy vs Injection Therapy



Incidence rate ratios and 95% CIs are presented to show the risk of severe hypoglycemia, hypoglycemic coma, diabetic ketoacidosis (pH <7.3), and severe ketoacidosis (pH <7.1) in patients using insulin pump therapy compared with the risk in patients using insulin injection therapy. Error bars indicate 95% CIs. A, Analysis in the propensity score–matched cohort including 9814 patients using injection therapy and 9814 patients using pump therapy. B, Analysis with propensity score inverse probability of treatment weighting of the entire cohort (16 460 patients using injection therapy, 14 119 patients using pump therapy). Estimates are derived from negative binomial regression analyses.

Discussion

In this contemporary cohort of young patients with type 1 diabetes, the risk of severe hypoglycemia and diabetic ketoacidosis associated with insulin pump therapy was lower than that associated with insulin injection therapy. Pump therapy was associated with a lower rate of severe hypoglycemia and of hypoglycemic coma compared with injection therapy, particularly in school-aged children. Similarly, pump therapy was associated with a lower rate of diabetic ketoacidosis and severe ketoacidosis vs injection therapy, especially in adolescents and young adults. These results favor pump therapy, with lower rates of acute complications and, at the same time, lower HbA_{1c} levels reflecting improved metabolic control. There was no difference in BMI between treatment regimens.

Single randomized clinical trials comparing pump therapy with injection therapy have not been sufficiently powered to assess differences in the rates of severe hypoglycemia or ketoacidosis.[26,27] In a previous meta-analysis including 23 trials (with 976 randomized participants),[7] the data suggested that pump therapy may be better than injection therapy for reducing the incidence of severe hypoglycemia.[7] However, using the same meta-analysis methodology, the rate ratio for severe hypoglycemia in randomized clinical trials of injection therapy vs pump therapy varied from 1.56 to 3.91, according to the trial selection.[28,29]

Another approach to study rare but clinically relevant outcomes of pump therapy and injection therapy is to analyze observational data from registry-based documentation of routine diabetes care. In an analysis from 2015 involving pediatric patients from 3 diabetes registries,[30] bivariable analyses showed lower ketoacidosis frequency with pump therapy than with injection therapy. However, in multivariable analysis, pump therapy was associated with elevated ketoacidosis risk in children younger than 12 years but with reduced ketoacidosis risk in adolescents aged 13 to 18 years.[30] These studies included patients from different health care systems, with pump use varying between 11.5% and 56.1% of respective patients,[30] as well as lowest or highest rates of pump therapy in the youngest patients.[3]

The strengths of the present study include the large sample size of a population-based cohort of more than 30 000 patients with type 1 diabetes, with stringent prospective data collection and a nationwide capture rate of more than 80% of pediatric patients in Germany, Austria, and Luxembourg. Using

Table 3. Secondary Outcomes: Metabolic Control and Insulin Treatment–Related Parameters With Injection Therapy vs Pump Therapy[a]

Outcome	Matched Cohort (n = 19 628)[b]				Entire Cohort (N = 30 579)[c]			
	Injection Therapy (n = 9814)	Pump Therapy (n = 9814)	Between-Group Difference (95% CI)[d]	*P* Value[e]	Injection Therapy (n = 16 460)	Pump Therapy (n = 14 119)	Between-Group Difference (95% CI)[d]	*P* Value[e]
HbA_{1c}				<.001				.001
% (95% CI)	8.22 (8.18 to 8.25)	8.04 (8.00 to 8.07)	-0.18 (-0.22 to -0.13)		8.17 (8.14 to 8.19)	7.99 (7.96 to 8.01)	-0.18 (-0.21 to -0.15)	
mmol/mol (95% CI)	66.30 (65.95 to 66.66)	64.38 (64.02 to 64.73)	-1.93 (-2.38 to -1.47)		65.74 (65.43 to 66.04)	63.78 (63.47 to 64.09)	-1.96 (-2.32 to -1.59)	
Total daily insulin dose, U/kg/d (95% CI)	0.979 (0.973 to 0.985)	0.838 (0.832 to 0.844)	-0.14 (-0.15 to -0.13)	<.001	0.960 (0.955 to 0.965)	0.822 (0.816 to 0.827)	-0.14 (-0.15 to -0.13)	<.001
Prandial to total insulin ratio, % (95% CI)	54.90 (54.66 to 55.14)	59.89 (59.65 to 60.13)	4.99 (4.65 to 5.33)	<.001	55.58 (55.36 to 55.80)	60.55 (60.33 to 60.77)	4.97 (4.70 to 5.25)	<.001
Use of rapid-acting insulin analogues, No. (%) [95% CI]	7294 (74.32) [73.45 to 75.18]	9372 (95.50) [95.07 to 95.89]	21.18 (19.97 to 22.23) OR, 7.30 (6.58 to 8.13)	<.001	12 108 (74.15) [73.26 to 75.03]	13 464 (95.50) [95.13 to 95.85]	21.35 (20.10 to 22.59) OR, 7.41 (6.76 to 8.13)	<.001
Frequency per day of self-monitoring of blood glucose level, No. (95% CI)	5.89 (5.83 to 5.95)	6.57 (6.51 to 6.63)	0.68 (0.59 to 0.76)	<.001	5.95 (5.90 to 6.01)	6.76 (6.70 to 6.81)	0.80 (0.73 to 0.87)	<.001
BMI, SD score (95% CI)[f]	0.30 (0.28 to 0.32)	0.32 (0.30 to 0.34)	0.02 (-0.004 to 0.05)	.10	0.31 (0.30 to 0.33)	0.31 (0.30 to 0.33)	-0.001 (-0.02 to 0.02)	.95

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin; OR, odds ratio.

[a] Values estimated from linear regression analysis (for outcomes HbA_{1c} level, total daily insulin dose, prandial to total insulin ratio, frequency of self-monitoring of blood glucose level, BMI) or logistic regression analysis (for use of rapid-acting insulin analogues) with matched pairs (matched cohort) or treatment center (entire cohort) as a random factor.

[b] The propensity score–matched cohort included 9814 patients for each therapy, except for analysis of HbA_{1c} level (9999 patients each) and BMI (9873 patients each).

[c] The entire cohort was included in propensity score inverse probability of treatment weighting analysis.

[d] Absolute differences between pump therapy and injection therapy.

[e] Identical *P* values were obtained after adjusting for multiple comparisons.

[f] An SD score of zero corresponds to the 50th percentile (median), and an SD score of +2 corresponds to the 97.7th percentile of an age- and sex-specific reference group.

robust statistical methodology including a matched pair approach, a direct comparison of hypoglycemia and ketoacidosis frequencies in pump users and injection users was performed. Sample size and data collection at the time of adverse event allowed for further categorizing the severity of hypoglycemia and ketoacidosis, consistently showing lower event rates with pump therapy. Whereas previous randomized clinical trials have been too small to assess the risk of these short-term diabetes complications, this study provides outcome data in clinical use that are likely representative of patients with type 1 diabetes across the pediatric age spectrum and with a disease duration longer than 1 year.

This study has several limitations. This was a nonrandomized, observational study and thus was prone to residual selection bias despite effective propensity score matching. Intensity of diabetes education, motivation, family support, and mental health factors were not addressed, all relevant to hypoglycemia and ketoacidosis risk[15,31-33] but difficult to measure quantitatively in a large population. Another potential limitation is that the individual duration of insulin pump use was not considered in the analyses, and a patient adopting this technology might have a higher frequency of short-term complications. In addition, the use of continuous glucose monitoring, which has been shown to improve glycemic control and reduce HbA_{1c} levels and hypoglycemic events,[12,15,26] was not analyzed in this study. Moreover, the treatment discontinuation rate for insulin pump therapy was not examined in the present study, but previous studies in the DPV population have shown a low discontinuation rate of only 4%.[34]

In the present study, the reduced risk of severe hypoglycemia with pump therapy was associated with lower total daily insulin dose and a higher proportion of bolus insulin. These findings are in accordance with those from previous studies[4,14,35,36] reporting smaller but more frequent single insulin doses with pump therapy than with injection therapy. The more common use of rapid-acting insulin analogues with pump therapy in this and other studies allows for more flexible therapy with lower glycemic variability,[37] leading to lower rates of acute and long-term diabetes complications,[5,6] including severe hypoglycemia.[6] The lower risk of ketoacidosis with pump therapy in the present study was associated with more frequent self-monitoring of blood glucose level in patients receiving pump therapy, as observed in other studies.[2,8,35] Prevention of ketoacidosis is an integral part of diabetes education and may be trained more intensively in patients receiving pump therapy, thereby reducing the incidence of ketoacidosis.[38,39] Lower HbA_{1c} levels with pump therapy in this study were associated with reduced ketoacidosis risk, in line with previous observations showing lower risk of diabetic ketoacidosis in patients with lower HbA_{1c} levels.[40]

The data from the present study may have implications for the future care of patients with type 1 diabetes. Pump therapy

is rapidly moving toward semi-independent closed-loop systems that combine sensor-based continuous glucose monitoring and automatic subcutaneous insulin infusion ("artificial beta cell" systems).[10-12] Recent clinical trials have shown that sensor-responsive insulin delivery may optimize glycemic control by increasing time within target range of glucose concentrations.[15] Results of this study provide further evidence that insulin pump therapy, which is a core element of artificial beta cell technology, is safe and effective, even in routine diabetes care for unselected patients at a population-based level.

Conclusions

Among young patients with type 1 diabetes, insulin pump therapy, compared with insulin injection therapy, was associated with lower risks of severe hypoglycemia and diabetic ketoacidosis and with better glycemic control during the most recent year of therapy. These findings provide evidence for improved clinical outcomes associated with insulin pump therapy compared with injection therapy in children, adolescents, and young adults with type 1 diabetes.

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