Real-World Costs of Continuous Insulin Pump Therapy and Multiple Daily Injections for Type 1 Diabetes: A Population-Based and Propensity-Matched Cohort From the Swedish National Diabetes Register

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OBJECTIVE

To investigate real-world costs of continuous insulin pump therapy compared with multiple daily injection (MDI) therapy for type 1 diabetes.

RESEARCH DESIGN AND METHODS

Individuals with type 1 diabetes and pump therapy in the Swedish National Diabetes Register (NDR) since 2002 were eligible. Control subjects on MDI were matched 2:1 using time-varying propensity scores. Longitudinal data on health care resource use, antidiabetes treatment, sickness absence, and early retirement were taken from national registers for 2005–2013. Mean annual costs were analyzed using univariate analysis. Regression analyses explored the role of sociodemographic factors. Subgroup and sensitivity analyses were performed.

RESULTS

A total of 14,238 individuals with type 1 diabetes entered in the NDR between 2005 and 2013 (insulin pump *n* = 4,991, MDI *n* = 9,247, with switches allowed during the study) were included. Mean age at baseline was 34 years, with 21 years of diabetes duration and a mean HbA_{1c} of 8.1% (65 mmol/mol). We had 73,920 person-years of observation with a mean follow-up of 5 years per participant. Mean annual costs were higher for pump therapy than for MDI therapy ($12,928 vs. $9,005, respectively; $P < 0.001$; mean difference $3,923 [95% CI $3,703–$4,143]). Health care costs, including medications and disposables, accounted for 73% of the costs for pump therapy and 63% of the costs for MDI therapy. Regression analyses showed higher costs for low education, low disposable income, women, and older age.

CONCLUSIONS

Nine years of real-world data on all measurable diabetes-related resource use show robust results for additional costs of insulin pump therapy in adults by subgroup and alternative propensity score specifications. Identification of tangible and intangible benefits of pump therapy over time remain important to support resource allocation decisions.

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Continuous subcutaneous insulin infusion, or insulin pump, therapy for individuals with type 1 diabetes has increased gradually since the 1980s. Yet, a Cochrane review concluded in 2010 that although some evidence indicates that insulin pumps improve glycemic control compared with standard multiple daily injection (MDI) therapy, insufficient evidence exists regarding mortality, morbidity, and costs (1). A systematic review of cost-effectiveness studies summarized comparisons of insulin pump and MDI therapy using model analyses to describe the expected impact on long-term costs, development of complications, and quality of life (2). Five of the studies reported long-term discounted incremental costs of insulin pumps of $20,000–$40,000, whereas two studies reported lower and one higher additional costs for insulin pump therapy. However, real-world data on health care and societal costs of insulin pump therapy compared with MDI therapy are scarce.

In principle, optimal glycemic control may be achieved by either MDI or insulin pump therapy. If that were the case, the incidence of diabetic complications would not differ between the two treatment alternatives, at least not those associated with maintaining adequate glycemic control. In practice, where individuals with type 1 diabetes face challenges of the disease in daily management, the two modes of insulin administration could differ in effectiveness, ease of use, and association with adverse events and, therefore, be associated with differences in patient outcomes (1,3,4).

Data from the Swedish National Diabetes Register (NDR) have shown a lower incidence of some cardiovascular events and all-cause mortality for individuals with type 1 diabetes on insulin pump therapy in 2005–2012 (5). Registration of insulin pump therapy started in 2002 in the NDR, and use of pump therapy among individuals with type 1 diabetes increased from 10% in 2002 to 22% in 2015 (6). A relevant research question from a health care planning perspective is whether real-world data match earlier model-based predictions for differences in resource use and costs. We investigated from a societal perspective costs of continuous insulin pump and MDI therapy in clinical practice for individuals with type 1 diabetes using the NDR and a 9-year observational panel from national health and socioeconomic data registers.

RESEARCH DESIGN AND METHODS

Population

The NDR includes ~97% of all Swedish individuals with type 1 diabetes age 18 years and older. Each individual provides informed consent. The register includes risk factors, diabetic complications, and medications. Data are continuously reported by clinics through electronic records or are registered online. Type 1 diabetes is defined as treatment with insulin and diagnosis at age 30 years or younger. Between 1,000 and 1,500 new individuals were entered yearly in the NDR in 2002–2012. A total of 35,921 individuals with type 1 diabetes had at least one entry in 2002–2012 and were eligible for this study.

The NDR documents insulin treatment regimens since entry in the register, and the start date of insulin pump therapy is available for individuals who initiate treatment while entered in the NDR. We considered observations with $\leq$24 months between multiple entries in the NDR as valid for analysis of continuous treatment. Exclusion criteria were filled prescription of implantable insulin pump or extemporaneous insulin, intermittent use of insulin pump therapy, one or more insulin pumps in the Swedish Prescribed Drug Register $>$1 year before entry as a pump user in the NDR, or entry in the NDR after the date of death.

For each individual with insulin pump therapy, we matched two control subjects and allowed treatment switches from MDI to insulin pump. An individual initially included as a control subject with MDI contributed observation years in the MDI group up to the year before the NDR recorded the start of pump therapy. The remaining study years, including the year of switch, contributed to the insulin pump group for this individual.

Matching Strategy

We accounted for nonrandom selection into type of insulin treatment by propensity score matching conditioned on clinical, individual, and socioeconomic factors. Cox proportional hazard functions were used to account for time-variant covariates in the matching equations and to model the time since last measurement for control subjects (7).

We selected two control subjects for each insulin pump user, defining the index date as the date of entry in the NDR for those with ongoing insulin pump therapy since childhood/adolescence or the first registration of insulin pump therapy in the NDR. Time-invariant covariates included sex, education, and country of origin, and time-variant covariates were age, marital status, diabetes duration, HbA_{1c}, systolic and diastolic blood pressure, BMI, LDL and HDL cholesterol, estimated glomerular filtration rate, microalbuminuria, macroalbuminuria, smoking status, preventive treatment (use of statins for hyperlipidemia, antihypertensive drugs, acetylsalicylic acid for platelet inhibition, use of other anticoagulants), previous disease (cancer, atrial fibrillation, myocardial infarction, coronary heart disease, cardiovascular disease, heart failure, hyperglycemia, liver disease, mental disease, renal failure, stroke), and yearly disposable income.

Using the often high within-patient correlation in clinical and socioeconomic data between years, missing data were imputed in three steps starting with the *1*) last value carried forward, *2*) first value carried backward, and *3*) single stochastic imputation on the basis of a multivariate normal distribution. Imputation, matching, and construction of cohorts were performed with SAS 9.3 software (SAS Institute, Cary, NC). Further description of the matching strategy is provided in the Supplementary Data.

Data Sources

We obtained longitudinal health and socioeconomic data for 2005–2013 from the National Patient Register, National Prescribed Drug Register, National Cause of Death Register, and National Integrated Database for Labor Market Research. The cost analysis estimated health care costs and costs of lost production. The ethical review board at the University of Gothenburg approved the study.

Variables

The main study variables were number of inpatient and outpatient events; costs of inpatient care, outpatient care, medication, and disposables; sickness benefit, early retirement benefits, and unemployment benefits; and all data summarized annually. Production loss was approximated as the sum of sickness benefit,

early retirement benefits, and unemployment benefits.

Health care events were categorized using ICD-10 on the basis of the main diagnosis entered for the appointment (Supplementary Table 1). In line with previous studies from the NDR, a cardiovascular event included any subsequent admissions or appointments within 28 days.

We used diagnosis-related group (DRG) codes and the main diagnosis to assign costs to inpatient and outpatient specialist appointments. The DRG code was linked with the corresponding yearly DRG weight (Swedish National Board of Health and Welfare [8,9]). Cost of medications and disposables by Swedish pharmacy official retail prices were taken from the Swedish Prescribed Drug Register. Data on sickness benefits, unemployment benefits, and early retirement benefits were taken from the National Integrated Database for Labor Market Research (10). The Supplementary Data further describes the costing strategy and variables (Supplementary Table 2).

All prices are at the 2013 level, using the Consumer Price Index to adjust costs of medications, disposables, and income and the Län (County) Price Index to adjust prices of appointments. Costs in dollars were calculated using $1 = 6.514 SEK (annual exchange rate for 2013 from the Swedish Central Bank).

Data Analysis

The univariate analysis of mean values used the *t* test for differences between the therapy groups on the basis of the central limit theorem, guaranteeing near normality of sample means (11). Semilogarithmic population-averaged panel data regression analysis was used to investigate the correlation between total costs and explanatory variables with and without a time trend. Explanatory variables included an indicator for insulin treatment therapy, demographics (sex, marital status), and socioeconomic characteristics (logarithm of disposable income, level of education). The Supplementary Data presents additional panel data regressions on the risk of at least some inpatient care, sickness episodes, and use of unemployment benefits.

Individuals were included in the analyses up to 31 December 2012, and each observation was followed until 31 December 2013 for all outcomes. Attrition of the panel was a result of death. Years for which individuals had no available data in population registers, for instance, because of migration, were excluded together with those of matched control subjects, unless the control subject had switched to pump therapy and thus had been censored as a control. The economic analyses were performed with Stata 14 software (StataCorp, College Station, TX).

Sensitivity and Subgroup Analyses

Use of real-world data implied imperfect entry over time for treatment and missing data among the clinical variables in the NDR. Sensitivity analyses were used to explore two alternative definitions of continuous insulin pump therapy (liberal = 1, strict = 2) and four strategies (A–D) for imputing missing variable information (last value carried forward, first value carried backward, model-based single imputation, no imputation), which generated eight different and overlapping cohorts (A1–D2) (Supplementary Table 3). The main analysis used cohort A1, combining a liberal definition that allowed for single information gaps and the most extensive imputation strategy. This cohort contained the highest number of individuals.

We performed 13 subgroup analyses to evaluate the robustness of the estimates of level of costs and differences between treatment groups. The subgroup analyses explored duration of continuous pump therapy (≥6 study years), individuals with an observed switch to pump therapy (at least one entry of MDI in the NDR before switching to insulin pump), three levels of HbA_{1c} at the index date (Diabetes Control and Complications Trial [DCCT] <6.5%, 6.5–8.5%, ≥8.6%; International Federation of Clinical Chemistry and Laboratory Medicine <48 mmol/mol, 48–69 mmol/mol, ≥70 mmol/mol), four age-groups, and sex.

RESULTS

Table 1 shows baseline characteristics for 15,030 individuals with type 1 diabetes (pump *n* = 5,010, MDI *n* = 10,020). A total of 748 individuals switched from MDI to pump therapy after inclusion as a control subject and contributed data in each group. The study cohort was younger than the average individual with type 1 diabetes in the NDR (34 vs. 46 years), had a shorter duration of diabetes (21 vs. 24 years), and had a higher HbA_{1c} (8.1 vs. 7.8% [65 vs. 62 mmol/mol]) at baseline. Supplementary Figure 2*A–C* shows the distribution of age, diabetes duration, and HbA_{1c} level at baseline (index date).

The final analysis set included data in 2005–2013 for 14,238 individuals with type 1 diabetes, of whom 4,991 had insulin pump therapy (598 individuals switched to pump therapy in 2005 or later after original inclusion as control subjects with MDI). We had 73,920 person-years of observation with a mean follow-up of 5 years per subject. Supplementary Fig. 1 shows a flowchart of study inclusion and exclusion.

The distribution of annual costs was left-skewed with a tail of observations with high costs, although the most person-years incurred costs corresponding to typical insulin therapy and up to two regular follow-up appointments (Supplementary Fig. 3*A–C*). The difference in the annual total cost between the therapy groups was $3,923 (95% CI $3,703–$4,143). Table 2 shows univariate estimates of mean annual resource use and costs by type, and Supplementary Table 4 presents median statistics. The difference in annual medication costs, including disposables, was $3,600, indicating that they contributed significantly to overall annual cost differences. Pump users had more outpatient appointments (3.8 vs. 3.5 per year; $P < 0.001$) and were less likely to have person-years without use of outpatient or inpatient care (9% vs. 12% of person-years). Even with a median duration of diabetes of 21 years at baseline, the mean cost per patient-year of cardiovascular comorbidities and diabetic complications was low because of the overall low rates of events.

Analyses of the number of health care events related to specific complications defined by the main diagnosis showed limited need overall in terms of events per 1,000 person-years (Supplementary Table 5). Three exceptions were type 1 diabetes as the main diagnosis (1,376 vs. 1,210 events per 1,000 person-years for pump vs. MDI, respectively; $P < 0.001$); eye disease, including diabetic retinopathy (749 vs. 670 events per person-year; $P < 0.001$); and kidney disease (764 vs. 633 events per person-year; $P < 0.001$), where the two former types included preventive care and regular follow-up of risk factors. The number of events related to kidney disease was driven by a few individuals with manifest kidney disease and frequent appointments. Pump users also had relatively more events

Table 1—Descriptive statistics of preindex date individual, clinical, disease, and socioeconomic characteristics

Variable	Pump therapy (*n* = 5,010)	MDI (*n* = 10,020)	Standardized difference (%)
Individual characteristics			
Age (years), mean (SD)	33.8 (13.7)	33.8 (13.5)	0.3
Sex			
Male	2,075 (48.9)	4,863 (48.7)	0.7
Female	2,168 (51.1)	5,132 (51.3)	0.7
Marital status			
Married	1,294 (30.6)	2,967 (29.8)	2.2
Single	2,676 (63.3)	6,392 (64.1)	2.9
Divorced	260 (6.1)	614 (6.2)	0.0
Country of origin			
Sweden	4,055 (95.6)	9,539 (95.4)	3.0
Nordic except Sweden	72 (1.7)	176 (1.8)	0.5
Other countries	116 (2.7)	280 (2.8)	0.4
Diabetes duration (years)	20.8 (12.8)	20.7 (13.8)	0.8
BMI (kg/m^2)	25.4 (4.1)	25.3 (4.2)	1.2
Smoker	356 (9.5)	864 (9.9)	1.4
Socioeconomic status			
Education			
<10 years	687 (16.2)	1,934 (19.3)	9.1
10–12 years	2,207 (52.0)	5,034 (50.4)	4.7
College/university	1,309 (30.9)	2,883 (28.8)	5.2
Disposable income ($)	1,559 (813–2,201)	1,493 (909–2,141)	2.0
Biomarkers			
HbA_{1c} (mmol/mol)	65.1 (13.4)	65.1 (15.2)	0.5
HbA_{1c} (%)	8.1 (1.23)	8.1 (1.39)	0.1
Systolic BP (mmHg)	122.5 (14.0)	122.5 (14.6)	0.6
Diastolic BP (mmHg)	72.0 (8.7)	71.8 (8.9)	1.8
HDL cholesterol (mmol/L)	1.6 (0.5)	1.6 (0.5)	1.9
LDL cholesterol (mmol/L)	2.6 (0.8)	2.6 (0.8)	1.3
eGFR (mL/min/1.73 m^2)	96.3 (35.5)	98.1 (29.1)	5.5
Previous disease/coexisting condition			
Macroalbuminuria	194 (5.5)	446 (5.7)	0.7
Microalbuminuria	407 (12.0)	920 (12.1)	0.3
Cancer	39 (0.9)	89 (0.9)	0.3
Atrial fibrillation	20 (0.5)	58 (0.6)	1.5
Myocardial infarction	73 (1.7)	174 (1.7)	0.2
Coronary heart disease	149 (3.5)	371 (3.7)	1.1
Cardiovascular disease	98 (2.3)	243 (2.4)	0.8
Heart failure	32 (0.8)	70 (0.7)	0.6
Hyperglycemia	853 (20.1)	2,107 (21.1)	2.4
Liver disease	8 (0.2)	15 (0.2)	0.9
Mental illness	76 (1.8)	183 (1.8)	0.3
Renal disease	42 (1.0)	99 (1.0)	0.0
Stroke	29 (0.7)	74 (0.7)	0.7
Physical activity			
Never	151 (3.6)	429 (4.3)	3.9
<1 time per week	347 (8.2)	787 (7.9)	1.2
1–2 times per week	659 (15.5)	1,495 (15.0)	1.7
3–5 times per week	790 (18.6)	1,828 (18.3)	0.9
Daily	585 (13.8)	1,393 (13.9)	0.5

Data are *n* (%) or median (interquartile range) unless otherwise indicated. BP, blood pressure; eGFR, estimated glomerular filtration rate.

related to ketoacidosis, hyperglycemia, and atrial fibrillation, but all those rates were <50 per 1,000 person-years. In three cases, pump users had fewer events (peripheral vascular disease [*P* = 0.004]) and, with borderline significance, fewer events of angina pectoris (*P* = 0.052) and liver disease (*P* = 0.057).

The median cost of lost production and all its components was $0 in both groups (Supplementary Table 4). A small difference was found in mean sickness benefits between the treatment groups but no significant difference in early retirement benefits. Including unemployment benefits, a small difference was found in total production loss, with higher costs in the pump users (*P* = 0.041).

Results from regression analyses of the annual risk of having an inpatient admission (15% of person-years), a period of sick leave (12% of person-years), and a period of unemployment (6% of person-years) are shown in Supplementary Table 6. Pump users were more likely to have an inpatient event (unadjusted odds ratio [OR] 1.072 [95% CI 1.013–1.135]), and this changed marginally when controlling for demographic and socioeconomic variables

Table 2—Annual resource use and annual costs in 2005–2013 for individuals with type 1 diabetes on insulin pump or MDI therapy

	Pump (n = 4,991)	MDI (n = 9,247)	P value of difference
Person-years	25,610	48,310	
Resource use (number of events)			
Inpatient and outpatient events	3.79 (3.70–3.89)	3.51 (3.44–3.57)	<0.001
Inpatient event	0.28 (0.27–0.29)	0.28 (0.27–0.29)	0.649
Health care costs ($)			
Outpatient costs	1,665 (1,615–1,714)	1,507 (1,473–1,542)	<0.001
Type 1 diabetes main diagnosis	610 (600–621)	539 (532–546)	<0.001
Costs >0 (person-years: pump 20,446, MDI 36,150)	764 (752–775)	721 (712–729)	<0.001
Cardiovascular comorbidities	411 (363–458)	346 (315–377)	0.021
Costs >0 (person-years: pump 5,409, MDI 9,272)	1,945 (1,725–2,165)	1,802 (1,643–1,961)	0.296
Diabetic complications	323 (314–331)	288 (282–294)	<0.001
Costs >0 (person-years: pump 10,936, MDI 17,904)	795 (778–812)	776 (763–790)	0.092
Inpatient costs	1,972 (1,864–2,081)	1,897 (1,826–1,968)	0.241
Type 1 diabetes main diagnosis	393 (354–432)	310 (288–331)	<0.001
Costs >0 (person-years: pump 1,127, MDI 1,673)	8,928 (8,195–9,662)	8,941 (8,483–9,400)	0.975
Cardiovascular comorbidities	760 (643–876)	646 (578–715)	0.079
Costs >0 (person-years: pump 768, MDI 1,398)	25,332 (21,857–28,807)	22,337 (20,281–24,394)	0.121
Diabetic complications	349 (320–379)	303 (282–325)	0.012
Costs >0 (person-years: pump 833, MDI 1,308)	10,742 (10,206–11,279)	11,209 (10,715–11,704)	0.224
Medication costs, including disposables	5,861 (5,814–5,907)	2,285 (2,270–2,300)	<0.001
Medication costs, excluding disposables	1,305 (1,288–1,321)	1,415 (1,406–1,424)	<0.001
Lost production ($)			
Total lost production	3,431 (3,339–3,522)	3,316 (3,252–3,380)	0.041
Sickness benefits (all)	1,070 (1,019–1,120)	858 (825–891)	<0.001
Benefits >0 (person-years: pump 4,192, MDI 6,216)	6,534 (6,284–6,784)	6,669 (6,462–6,876)	0.416
Early retirement benefits (all)	1,997 (1,923–2,071)	2,005 (1,952–2,058)	0.854
Benefits >0 (person-years: pump 3,138, MDI 5,964)	16,295 (16,011–16,579)	16,242 (16,060–16,424)	0.749
Total costs ($)	12,928 (12,738–13,118)	9,005 (8,880–9,129)	<0.001

Data are mean (95% CI). The t test was used for differences between therapy groups.

(adjusted OR 1.087 [1.027–1.151]). The risk for inpatient admissions was higher for women, increased with age, and decreased with disposable income and years of education. Pump users were more likely to have at least one period of sick leave (unadjusted OR 1.308 [1.224–1.398], adjusted OR 1.265 [1.184–1.353]), as were women. The risk also increased with age and disposable income, which may relate to sickness benefits being contingent on having a certain level of income.

Pump users were less likely to have a period of unemployment (unadjusted OR 0.803 [95% CI 0.721–0.894], adjusted OR 0.821 [0.736–0.915]). The risk for unmarried individuals was higher and showed an inverted U shape for age and education, with the highest risk for those 28–37 years old and for those with 10–12 years of education.

Table 3 shows the adjusted results of the cost-regression analysis, controlling for time-varying demographic and socioeconomic factors. Total annual costs increased with age for both insulin therapies, and pump therapy was associated with higher costs across age-groups. However, the cost increments for insulin pump therapy decreased with age (differences ranging from 56% for those 18–27 years of age to 44% for those ≥48 years [reference: MDI 18–27 years]). Total costs were higher for women but decreased with years of education and disposable income. Supplementary Table 7 shows results by three alternative model specifications.

Subgroup and Sensitivity Analyses

Subgroup analyses revealed expected and substantial differences in average annual costs by diabetes duration and age (Fig. 1*A* and *B*). The difference in annual costs between the main analysis and the subgroup analyses was more pronounced for individuals with MDI versus pump therapy. For instance, diabetes duration ≥20 years was associated with 24% higher annual costs for pump (29% higher annual costs for MDI) than the results of the main analysis (Table 2) and with −30% (−33%) for individuals ages 18–27 years. Age-related cost differences were driven by an increasing impact of production loss with age from an increasing percentage of person-years with at least some production loss (18–27 years 17%, 28–37 years 29%, 38–47 years 37%, ≥48 years 42%).

Higher annual costs in individuals with insulin pump therapy ≥6 years during 2005–2013 (mean follow-up time 8 years) and in their matched control subjects, as well as a greater cost difference, were associated with costs of medications, disposables, and production loss. Mean cost for women and individuals starting insulin pump therapy while entered in the NDR were slightly higher, but the difference was lower between treatment groups than in the main analysis. Individuals with HbA_{1c} ≥8.6% (≥70 mmol/mol) at baseline had the smallest cost difference between treatment groups across all subgroups (pump $13,309 vs. MDI $10,966; $P < 0.001$). This subgroup had a slightly younger mean age and mean diabetes duration when entering the cost analysis than the cohort for the main analysis. The smaller difference was driven by lower health care costs and production loss in the pump group. The largest cost difference was found for individuals with middle HbA_{1c} levels (6.5–8.5% [48–69 mmol/mol], pump $12,824 vs. MDI $8,083; $P < 0.001$).

Table 3—Socioeconomic and demographic factors associated with annual cost, 2005–2013

Variable	Coefficient	95% CI	*P* value
Insulin therapy by age-group (reference MDI 18–27 years)			
MDI (years)			
28–37	0.229	0.196–0.262	<0.001
38–47	0.336	0.297–0.375	<0.001
≥48	0.619	0.576–0.663	<0.001
Pump therapy (years)			
18–27	0.563	0.528–0.598	<0.001
28–37	0.788	0.746–0.830	<0.001
38–47	0.866	0.823–0.908	<0.001
≥48	1.056	1.008–1.103	<0.001
Male sex (reference female)	−0.228	−0.252 to −0.203	<0.001
Married (reference single, divorced, or widowed)	−0.017	−0.0423 to 0.009	0.199
Disposable income	−0.053	−0.065 to −0.040	<0.001
Level of education (reference 10–12 years)			
<10 years	0.158	0.123–0.194	<0.001
College/university	−0.165	−0.189 to −0.142	<0.001
Constant	10.71	10.56–10.85	<0.001

Coefficients measure proportional change (higher [+] vs. lower [−]) in cost compared with the reference group. Population-averaged semi-logarithmic panel data regression analysis controlling for year fixed effects and with robust SEs. Based on 64,021 person-years for 13,942 unique individuals (pump therapy *n* = 4,935, MDI *n* = 9,007, with both including switchers).

The sensitivity analyses of cohort specifications and matching criteria indicated that average annual costs for individuals with type 1 diabetes were robust and similar to results from the main analysis (pump therapy range −0.6% to −8.5%, MDI range 0.5% to −10.5%) (full results in Supplementary Table 9). The greatest deviation (pump −8.5%, MDI −10.5%) was observed for the smallest cohort with a strict definition of continuous treatment and no imputation (complete cases cohort D2) (Supplementary Table 3 and Supplementary Fig. 4). The higher annual costs observed in the main analysis were driven by more health care resource use and loss of production in the broadest population, while cohort D2 included only very regular individuals with complete observations. However, cost differences between the study groups of the sensitivity analyses were stable at ∼$4,000 (range $3,600–$4,600).

CONCLUSIONS

This large nationwide study of 4,991 individuals with type 1 diabetes and insulin pump therapy and 9,247 propensity score–matched control subjects with MDI treatment showed higher annual total costs for pump therapy (∼$3,900). The results were robust to choice of matching and imputation strategy. Subgroup analyses indicated an expected variation in level of annual costs by age and duration of diabetes. The level of HbA_{1c} at baseline affected the differences in average annual cost between study groups: the smallest difference ($2,300) was observed for individuals with HbA_{1c} ≥8.6% (≥70 mmol/mol) and the greatest difference for individuals with HbA_{1c} 6.5–8.5% (48–69 mmol/mol) at baseline. Regression analyses controlling for demographic and socioeconomic factors underscored the robustness of results on cost differences related to pump therapy.

These data reflect real-world clinical decision making and use of insulin pump therapy in 2005–2013. The study cohort was young (mean baseline age 34 years) with relatively few diabetic complications in both study groups. For instance, 1.5% of person-years had a cardiovascular event, and 5% had at least one health care contact with a cardiovascular diagnosis.

Observational studies provide a better indication of what is achieved in daily medical practice than randomized controlled studies (12). The strength of this observational study is the size and completeness of the study population, with virtually all adults with type 1 diabetes in Sweden included, longitudinal national register data, and a matching technique that accounts for time-variant variables, including diabetes duration, diabetes-related conditions and comorbidities, and demographic and socioeconomic factors. With the use of time-varying propensity scores, we allowed selected MDI control subjects to switch to pump therapy rather than to condition their eligibility or noneligibility on a future therapeutic change. The plentiful data allowed us to match two control subjects to each pump user to account for the variance in cost variables and enabled extensive subgroup and sensitivity analyses.

The costs of production loss were somewhat underestimated. Periods of sick leave <14 days are not included in national registers, and some of the workforce may not yet be eligible for unemployment benefits (e.g., young people with short contracts). Social insurance payments underestimate the value of lost production because they are subject to floor and ceiling effects and are lower than wages.

A study from the NDR investigated the association between insulin pump therapy and cardiovascular disease (5). The main findings included a lower adjusted hazard ratio of fatal coronary heart disease and fatal cardiovascular disease as well as lower all-cause mortality. The difference in research questions between this study and the NDR study required alternative estimation methods. The previous study investigated the relative risks of complications on the basis of time to the first event, whereas the current study summarized costs of all events of complications and regular health care use, medications, and production loss, given that all contribute to total annual costs.

The difference in study design and construction of cohorts suggests that cohort characteristics may differ. At baseline, the proportion of previous cardiovascular disease in the NDR study (5) was 5% versus 8% of the pump versus MDI groups, respectively, whereas it was ∼2.5% in both groups of the current study. The overall incidence rate of first events with cardiovascular disease for this study cohort was 9 per 1,000 person-years, whereas the corresponding figure for the previous study was 12.5 per 1,000 person-years.

We observed only a few deaths (*n* = 353 [2.5% main analysis sample], no difference pump vs. MDI [OR 0.98 (95% CI

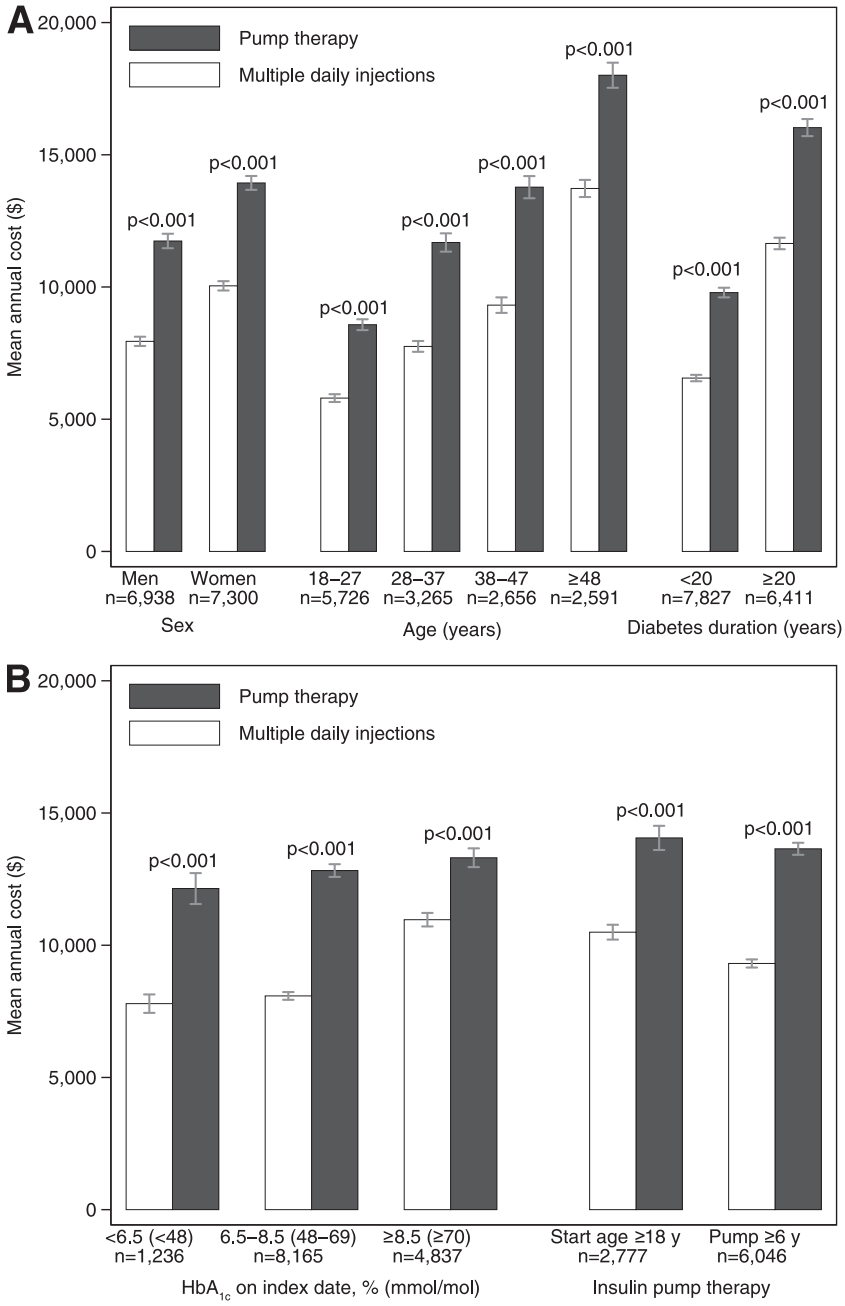

Figure 1—Mean annual costs in 2005–2013 for people with type 1 diabetes on insulin pump or MDI therapy by subgroup. *A*: By sex, age, and diabetes duration in year of observation. *B*: By HbA_{1c} on the index date, among people whose insulin pump therapy started after NDR entry, and among insulin pump users observed for at least 6 years in NDR. All costs are indexed to 2013 values. y, years.

0.79–1.23)]) and similar rates of cardiovascular disease for pump and MDI in this study, except for borderline significantly fewer events with angina in the pump group. A heterogeneous distribution of events was found across nontreatment characteristics: ~70% of all cardiovascular events occurred among individuals 48 years of age or older, and >90% of the events occurred among individuals with diabetes duration ≥20 years at baseline.

A lack of comparable calculations of total costs of diabetes treatment has been published to date, but cost-effectiveness studies of pump and MDI therapy have predicted long-term costs for the two treatment methods. Roze et al. (2) performed a meta-review of model-based studies that compared pump therapy and MDI, concluding that pump therapy can be cost effective. Published models have identified change in HbA_{1c} and reduction in number of hypoglycemic events as important drivers of costs. A Swedish health technology assessment review in 2013 did not find evidence for differences in severe hypoglycemia between pump therapy and MDI but identified indications of lower HbA_{1c} (13).

With the use of propensity score matching, a real-world study of German-Austrian registry data (age up to 20 years) on type 1 diabetes found lower rates of severe hypoglycemia and diabetic ketoacidosis associated with pump therapy than with MDI and for the unmatched entire cohort (14). However, only 70% of individuals with pump therapy could be matched, and baseline characteristics indicated high standardized differences in age, diabetes duration, and HbA_{1c} between treatment groups in the entire cohort. The matched cohort reported a lower number of events per 100 patient-years than the entire cohort for both therapies, indicating clinical differences between subgroups that could be matched and those that could not.

The current data represent real-world use of insulin pumps in 2005–2013, with significant proportions of young adults and other individuals who had <20 years of diabetes duration. We found lower rates of events in our adult population than the German-Austrian study (14). Our low observed frequencies of severe hypoglycemia and ketoacidosis may be related to the structure of diabetes care, including educational programs that do not differ with respect to insulin therapy (15). Overall, we found similar results for both study groups in terms of health care resource use other than medications and disposables. Nevertheless, type 1 diabetes is associated with an increased risk of cardiovascular disease compared with the general population (16–18), and available effective means in diabetes care should be used to further increase the proportion meeting therapeutic targets.

Subgroup analyses by age indicated that the value of improved prevention may take time to manifest. Approximately one-quarter of additional annual costs for individuals with type 1 diabetes age ≥48 years (~25% of the cohort) could be prevented with insulin pump therapy.

Whether insulin pump therapy is cost efficient ultimately depends on therapeutic effects beyond resource use and costs as well as on how much the payer is

prepared to invest in additional quality-adjusted life-years (QALYs). If the payer's cost-effectiveness threshold is $50,000 per QALY gained, treatment needs to provide an average annual additional 0.1 QALY or, on the basis of the subgroup analyses, gains in the range of 0.06–0.12 QALY. Similarly, with a threshold of $100,000, the required gain in annual QALYs would have to be between 0.03 and 0.06. The average cost difference between insulin therapies in this study and a 20-year time horizon roughly correspond to a discounted (3%) lifetime cost difference of $62,000. The corresponding cost for a 40-year time horizon is $95,000. Previous model-based cost-effectiveness analyses have reported expected discounted QALY gains for a lifetime in the range of 0.46–1.06 QALYs, whereas the estimates of the increase in discounted lifetime costs varied (2).

This observational study calculated costs of insulin pump therapy and MDI in individuals with type 1 diabetes using real-world data with 9 years of follow-up. However, the time frame may need to be even longer to detect differences in treatment effects that have consequences for total costs exceeding those in this study. Some questions cannot be answered yet. What will be the outcome for today's generation with type 1 diabetes onset in the post–DCCT era once intensive glucose-lowering therapy with MDI and pumps has been established as the standard for >20 years and patients have access to a wide range of modern devices for glucose control and medications? The oldest age-group in this study experienced diabetes onset in the 1960s–1980s, when treatment options differed from today's standard care.

Our national real-world longitudinal data show additional costs for insulin pump therapy. Differences in these Swedish data were greater than previous cost-effectiveness analyses would indicate, but recent structural changes that include decentralized procurement of insulin pumps and disposables suggest that current expected costs reflect those of previous cost-effectiveness studies. Identification of tangible and intangible patient benefits from insulin pump therapy over time remain important to the valuation of technology and support of resource allocation decisions.

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