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Cost-effectiveness of Initiating an Insulin Pump in T1D Adults Using Continuous Glucose Monitoring Compared with Multiple Daily Insulin Injections: The DIAMOND Randomized Trial

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Abstract

Background. The economic impact of both continuous glucose monitoring (CGM) and insulin pumps (continuous subcutaneous insulin infusion [CSII]) in type 1 diabetes (T1D) have been evaluated separately. However, the cost-effectiveness of adding CSII to existing CGM users has not yet been assessed. **Objective.** The aim of this study was to evaluate the societal cost-effectiveness of CSII versus continuing multiple daily injections (MDI) in adults with T1D already using CGM. **Methods.** In the second phase of the DIAMOND trial, 75 adults using CGM were randomized to either CGM + CSII or CGM + MDI (control) and surveyed at baseline and 28 weeks. We performed within-trial and lifetime cost-effectiveness analyses (CEAs) and estimated lifetime costs and quality-adjusted life-years (QALYs) via a modified Sheffield T1D model. **Results.** Within the trial, the CGM + CSII group had a significant reduction in quality of life from baseline (−0.02 ± 0.05 difference in difference [DiD]) compared with controls. Total per-person 28-week costs were $8,272 (CGM + CSII) versus $5,623 (CGM + MDI); the difference in costs was primarily attributable to pump use ($2,644). Pump users reduced insulin intake (−12.8 units DiD) but increased the use of daily number of test strips (+1.2 DiD). Pump users also increased time with glucose in range of 70 to 180 mg/dL but had a higher HbA1c (+0.13 DiD) and more nonsevere hypoglycemic events. In the lifetime CEA, CGM + CSII would increase total costs by $112,045 DiD, decrease QALYs by 0.71, and decrease life expectancy by 0.48 years. **Conclusions.** Based on this single trial, initiating an insulin pump in adults with T1D already using CGM was associated with higher costs and reduced quality of life. Additional evidence regarding the clinical effects of adopting combinations of new technologies from trials and real-world populations is needed to confirm these findings.

Keywords

continuous glucose monitoring, cost-effectiveness, insulin pump, randomized clinical trial, type 1 diabetes

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For patients with type 1 diabetes (T1D), intensive glucose control with insulin is critical to reduce the risk of developing future complications.[1,2] Despite evidence of the benefits of intensive glucose control, many patients with T1D continue to have suboptimal glycemic control.[3,4] More than 70% of U.S. adults with T1D who are older

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than 30 years do not achieve a target HbA1c of $<7.0\%$.[4] Persistent hyperglycemia increases the risk of developing acute and chronic diabetic complications[1,3] and thus increases the economic burden of diabetes. Inappropriate insulin dosing has been found to be one of the key driving factors of suboptimal glycemic control.[5]

Intensive insulin therapy can be delivered by multiple daily injection (MDI) or an insulin pump with continuous subcutaneous insulin infusion (CSII).[6,7] Accompanying blood glucose monitoring can be achieved with self-monitoring of blood glucose (SMBG) or real-time continuous glucose monitoring (CGM).[6,8] The availability of these options creates four possible comprehensive glucose control methods by combining one insulin-delivering method with one glucose-monitoring method: CSII + CGM, MDI + CGM, CSII + SMBG, and MDI + SMBG.[6] Prior studies have explored the clinical benefits and/or cost-effectiveness of pump use versus MDI in patients using SMBG[9] (i.e., comparing CSII + SMBG v. MDI + SMBG), of CGM use versus SMBG in patients using MDI[10] (i.e., MDI + CGM v. MDI + SMBG), and of CGM use versus SMBG in patients using an insulin pump[11] (i.e., CSII + CGM v. CSII + SMBG). The economic impact of initiating insulin pump use versus MDI in patients already using CGM, however, has not been addressed.

More than 65% of patients with T1D use MDI,[3,12] and many of these patients are adopting newer CGM technology, which has significant improvements in data accuracy compared with older technology.[13,14] In the recently completed substudy of the DIAMOND trial, patients using MDI and CGM were randomly assigned to continue using CGM with either CSII or MDI for 28 weeks.[15] The purpose of this study was to evaluate the cost-effectiveness of CSII versus continuing MDI among adults with T1D already using CGM, based on the results of the DIAMOND trial.[15]

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Methods

The study protocol was reviewed by the University of Chicago Institutional Review Board and determined to be nonhuman subject research.

Study Design

The DIAMOND trial was done at 20 US endocrinology practices. In the second phase of the trial,[15] 75 patients with T1D using CGM who completed the first phase were randomly assigned in a 1:1 ratio to either CSII (CGM + CSII, pump) or MDI (CGM + MDI, control). Similar to the first phase of the DIAMOND trial, all patients were surveyed at baseline (the beginning of the second phase) and at 28 weeks (about 6 months) to collect health-related quality of life (QoL) and all potential costs (detailed below) for the prior 6 months. Primary outcomes were total costs and quality-adjusted life-years (QALYs). Clinical outcomes of interest included time with glucose concentrations in the range of 70 to 180 mg/dL (denoted by "time-in-range"), HbA1c, nonsevere hypoglycemic events (NSHEs), body mass index (BMI), insulin dosing, daily strip use, and numbers of hypoglycemic and hyperglycemic events. Details on the second phase of the DIAMOND trial, including its study design, populations, and clinical results, can be found in Beck et al.[15]

We conducted a 6-month within-trial cost-effectiveness analysis (CEA), as well as a life-time CEA based on the results of the trial.[15] We adopted the societal perspectives for both analyses. We analyzed all trial data to determine the clinical factors that would have a potential impact on CEAs. We chose and modified the patient-level Sheffield model to simulate the T1D complications. We also conducted subgroup CEAs and one-way sensitivity analyses. Per the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine[16] and the Consolidated Health Economic Reporting Standards,[17] we have provided an impact inventory table and reporting checklist in Supplementary Tables 1 and 2.

Costs

The 28-week within-trial total costs included 1) all direct costs associated with health care utilization that occurred outside of the study, device use (CGM and/or CSII), glucose-lowering medications, and test strip use and 2) all indirect costs associated with reduced work productivity if employed and number of hours per day devoted to self-management diabetes care. Due to poor data quality for

the reported daily hours of self-management (high kurtosis and missing data), we calculated total costs with and without considering the self-management costs. All cost assumptions are provided in Supplementary Table 3.

We calculated each cost by multiplying median hourly wages (or prices per service) by hours spent (or number of services used) in the 6-month time period.

Direct clinical personnel costs. We included all staff time devoted to CSII/CGM training and counseling and excluded research time.

Device costs. A tubeless, nondurable insulin pump was used. CSII cost was estimated to be $13.49/day, based on its first annual costs, and includes costs from its two components (i.e., personal diabetes manager starter kit and pod; Supplementary Table 4). CGM cost was estimated to be $15.20/day, including costs from its three components (i.e., G4 sensor, receiver, and transmitter; Supplementary Table 5). These prices are estimated average allowable prices in the US marketplace.

Nondevice medical care costs. Health care service utilization costs included routine office visits, after-hour clinic visits (urgent care), 911 calls, ambulance use, emergency department visits and hospitalizations, as well daily test strip use and glucose-lowering medications for the 6-month period.

Indirect costs. In addition to health service utilization, patients were also surveyed at baseline and 6 months on daily hours of self-management diabetes care, the number of days missed from work due to their diabetes, and the number of workdays with underperformance (defined as $<50\%$ productivity). All costs are expressed in 2015 US dollars.

QoL

The EuroQol 5-level 5-dimension questionnaire (EQ-5D-5L) used to assess health-related QoL and was converted into a health-state utility scale ranging from 0.0 (death) to 1.0 (perfect life).[18] For the long-term CEA, we used previously published utilities for microvascular and cardiovascular complications, as well as severe and nonsevere hypoglycemia. We then incorporated the utilities into a simulation model of long-term outcomes.

Cost-effectiveness Outcomes

QALYs, a measure of health outcomes and disease burden, were calculated by multiplying the utility value associated with a given health state by the years lived in that state (i.e., area under the curve of utilities). We calculated the incremental cost effectiveness ratio (ICER; i.e., costs per QALY gained) as the ratio of the difference in costs to the difference in QALYs between the two treatment groups.

Nonsevere Hypoglycemic Events and Time with Glucose in Range of 70–180 mg/dL

Based on CGM-collected glucose data, we developed two measures. The first measure captured time (minutes/day) with glucose concentrations in the range of 70 to 180 mg/dL (denoted as "time-in-range"). The second measure was a daily rate of NSHEs. We defined an NSHE as the detection of a glucose value <3.0 mmol/L (<54 mg/dL) for at least 20 consecutive minutes and considered to be clinically significant biochemical hypoglycemia, per the recommendations of the International Hypoglycemia Study Group.[19] The first 4 weeks of CGM-available data were for baseline, and the data after the first 4 weeks were pooled for the following 5 months.

Within-Trial CEAs

We applied the intent-to-treat principle to all within-trial analyses. Costs, utility, QALYs, and other outcomes were summarized per study group at baseline and 28 weeks. The Wilcoxon rank-sum test was used to compare the two groups in terms of QALYs, utility, and other continuous outcomes. The Fisher's exact test was used for each categorical outcome. As suggested by Manca et al.,[20] to compare the two groups in QALYs, we used the analysis of covariance analysis (ANCOVA) method to adjust for their baseline utility values. To model repeatedly measured utility and the continuous clinical outcomes over time, we used linear mixed models (LMMs) to test effects of treatment, time, and their interaction, respectively. In the ANCOVA and LMMs, clinic site was considered a random effect, and its baseline outcome (measured at either the end of the phase 1 study or the beginning of the phase 2 study), along with potential covariates (age, gender, and duration of T1D), were adjusted. To assess the homogeneity of the treatment effect, we conducted a test of the interaction between the baseline outcome and treatment arm through an LMM. Backward model selection was performed to achieve an LMM with the smallest Bayesian information criterion. We considered the

treatment effect to be significant if either the *P* value for the treatment effect or the *P* value for the interaction effect between treatment and time were significant. Subgroup analyses were performed per baseline HbA1c level of 7.5% as a cutoff for sensitivity analyses.

To compare the mean costs, we also performed the bootstrap method. We ran 10 000 bootstrap replications and calculated the 95% confidence interval (CI) of mean difference in costs between the two groups.

Missing data analyses. The primary analysis was based on the complete data set, due to only 6.7% to 9.3% missing information across main outcomes. We used the approximate Bayesian bootstrap method,[21] a multiple imputation approach, to impute missing values of utility, QALYs, and costs for a sensitivity analysis. Age, sex, duration of T1D, five EQ-5D-5L questions, and baseline utility were used as variables in the imputation model. The imputations were conducted separately for each study group. We generated 10 imputed data sets and applied the same methods in the primary analysis to each data set. Since costs data were nonnormally distributed, we used the bootstrap method to calculate their CIs per imputed data set. Then, we combined all the results into one by a confidence interval of a mean difference between the 2 groups using a formula from Rubin.[21]

All *P* values are 2-sided, and *P* values <0.05 were considered significant. Analyses were conducted with SAS version 9.4.

Lifetime CEAs

To evaluate the cost-effectiveness of CGM + CSII versus CGM + MDI, we used a modified version of the Sheffield T1D policy model,[22] one of the most rigorous and thoroughly reported T1D models.[23] The Sheffield model simulates the patient-level natural history of T1D over the projected lifetime of patients, including progression through major microvascular and macrovascular complications, as well as short-term complications (hypo- and hyperglycemia) and their associated costs and health utilities. Among the existing 15 T1D simulation models,[22,24–37] we selected the Sheffield model based on the following features: the model was constructed solely using T1D studies and trials; it includes HbA1c, a risk factor, in most risk equations; it was validated against major T1D trial studies; and it is completely transparent and hence reproducible.

Following the same approach as the lifetime CEA conducted for phase 1 of the DIAMOND trial, we modified the original Sheffield model due to the relationship between HbA1c level and hypoglycemic events. The original hypoglycemia module assumed that the risk of severe hypoglycemic events rises as HbA1c level decreases. This relationship did not occur in the DIAMOND trial (phase 1 and phase 2). The same finding of improved glucose control with concurrent reduction of hypoglycemia in CGM users was also described in a systematic review and meta-analysis conducted on behalf of the Agency for Healthcare Research and Quality.[7] Therefore, we replaced this module with the observed hypoglycemia event rates. All base-case model parameters, including clinical inputs, cost, and health utility, are described in Supplementary Tables 6 to 8. We applied a 3% annual discount rate to both costs and health utilities and calculated the 95% CI for the key outcomes by using bootstrapping of simulation samples.

Projected CSII effects. Because of the different patterns in the clinical and QoL outcomes found between the 2 HbA1c subgroups, the simulation model carried forward the CSII effects found in the within-trial subgroup analyses through the lifetime of patients. The CSII treatment effects at 6 months were estimated through LMMs and assumed to be maintained over time. The simulation results from the 2 subgroups were then combined and summarized for the base-case model.

Subgroup and sensitivity CEA analyses. We performed 2 separate CEAs for the HbA1c subgroups. We also conducted a 1-way sensitivity analysis under the assumption of no utility difference between the 2 treatment groups while holding other variables constant at their base-case estimates.

Role of the Funding Source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article.

Results

Thirty-seven participants were randomly assigned to the CGM + CSII group and 38 to the CGM + MDI group. The EQ-5D-5L surveys were completed at 6 months by 36 (97%) participants in the pump group and 35 (92%) in the control group. We found no significant differences in baseline characteristics between the 2 treatment groups (Table 1). The mean (± standard deviation [SD]) utility value at baseline was 0.93 ± 0.09, indicating that the

Table 1 Baseline Characteristics of the Study Population

	CGM + MDI (n = 38)	CGM + CSII (n = 37)	P Value
Demographic characteristics			
Gender, female (%)	19 (50)	16 (43)	0.65
Race, %			1.00
White	34 (89)	33 (89)	
Black	3 (8)	2 (5)	
Other	1 (3)	2 (5)	
Age, years			0.82
Mean ± SD	44.9 ± 12.1	45.8 ± 15.4	
Range	26–67	25–72	
T1D duration, years			0.19
Mean ± SD	17.9 ± 13.5	21.5 ± 13.5	
Range	2–48	2–56	
Clinical outcomes at baseline			
Time in range 70–180 mg/dL			0.14
Mean ± SD	762.1 ± 223.5	708.3 ± 162.2	
Range	158.4–1252.8	417.6–993.6	
HbA1c			0.59
Mean ± SD	7.6 ± 0.9	7.6 ± 0.7	
Range	6.0–10.1	6.4–9.8	
Number of daily strip tests			0.44
Mean ± SD	3.5 ± 1.2	3.3 ± 1.3	
Range	1–7	2–7	
Insulin (unit)			0.11
Mean ± SD	54.9 ± 19.6	62.9 ± 22.6	
Range	25–95	24–101	
Daily event rate of NSHEs			0.31
Mean ± SD	0.22 ± 0.26	0.19 ± 0.23	
Range	0–1.15	0–0.87	
BMI			0.11
Mean ± SD	27.7 ± 5.4	28.7 ± 3.4	
Range	19.2–43.0	23.6–39.4	
No. of patients using noninsulin glucose-lowering medication n (%)	1 (2.6)	2 (5.4)	0.61
No. of patients with severe hypoglycemia in previous 6 mo n (%)	2 (5)	0	0.49
No. of patients with severe hyperglycemia in previous 6 mo n (%)	0	0	1.00
Quality of life at baseline			
Utility			0.26
Mean ± SD	0.91 ± 0.11	0.95 ± 0.06	
Range	0.57–1.0	0.78–1.0	

BMI, body mass index; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; NSHE, nonsevere hypoglycemic event; T1D, type 1 diabetes mellitus.

study patients had high QoL. The baseline HbA1c was 7.6% ± 0.8%, and time-in-range was 735.6 ± 196.3 minutes/day (i.e., 51% time-in-range per day).

Within-Trial CEA

During the 28-week trial, the mean utility values decreased by −0.01 ± 0.05 from baseline in the CGM + CSII group, while they increased by +0.01 ± 0.05 in the CGM + MDI group (P = 0.10 by the Wilcoxon rank sum test; Table 2). The within-trial QALYs were quite similar for the groups: 0.46 ± 0.05 years (mean ± SD: CGM + MDI) versus 0.47 ± 0.03 years (CGM + CSII; P = 0.99). However, after adjusting for baseline utility values, the adjusted QALY means (± SE) became 0.475 ± 0.002 (CGM + MDI) versus 0.465 ± 0.002 (CGM + CSII; P = 0.06), and the treatment effect on utilities became significant (P = 0.032 from the

Table 2. Within-trial CEA Results

	CGM + MDI (n = 38)		CGM + CSII (n = 37)		
	Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**	***P* Value[b]**
Utility and QALYs					
Utility change from baseline	0.01 (0.05)	0 (–0.08, 0.13)	–0.01 (0.05)	0 (–0.13, 0.06)	0.10
QALYs	0.46 (0.05)	0.48 (0.28, 0.50)	0.47 (0.03)	0.47 (0.38, 0.50)	0.99
	Mean (SD)	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	***P* Value[b]**
Costs (in 2015 U.S. dollars)					
Total direct costs	5,550 (770)	5,405 (4911, 5998)	8,203 (667)	8,326 (7620, 8616)	**<0.01**
Direct trial personnel	40 (51)	0 (0, 65)	58 (106)	47 (0, 65)	0.39
Medical care	2,534 (753)	2,411 (1910, 2924)	2,519 (648)	2,618 (1995, 2927)	0.79
CSII	0 (0)	0	2,644 (0)	2644	**<0.01**
CGM	2,979 (0)	2979	2,979 (0)	2979	1.00
Total indirect costs[a]	48 (146)	0 (0, 0)	47 (157)	0 (0, 0)	0.84
Missed work	34 (136)	0 (0, 0)	38 (162)	0 (0, 0)	0.97
Poor performance	34 (153)	0 (0, 0)	28 (155)	0 (0, 0)	0.28
Self-management	7,250 (10.8k)	3,301 (3208, 6636)	11.0k (18.0k)	3,301 (2636, 9818)	0.79
Total costs	12.8k (10.9k)	8723 (8042, 12.8k)	19.6k (18.1k)	11.9k (10.9k, 18.3k)	**<0.01**
Total costs[a]	5,623 (834)	5,405 (4911, 6224)	8,272 (639)	8,340 (7740, 8729)	**<0.01**
	Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**	***P* Value[c]**
Clinical Outcomes: Change from Baseline					
Time in range 70 - 180 mg/dL	–18.00 (104.90)	–14.4 (–201.6, 374.4)	77.20 (186.17)	86.4 (–446.4, 432.0)	**<0.01**
HbA1c	0.15 (0.43)	0.10 (–0.80, 1.30)	0.28 (0.88)	0.20 (–1.60, 3.30)	**<0.01**
Daily rate of NSHEs	–0.03 (0.09)	–0.03 (–0.26, 0.17)	0.09 (0.17)	0.09 (–0.26, 0.55)	**<0.01**
Insulin dose	-5.38 (22.72)	0.0 (–95.0, 23.0)	–18.19 (18.23)	–17.0 (–90.0, 11.0)	**<0.01**
Daily strip tests	–0.31 (1.00)	0.0 (–2.0, 2.0)	0.89 (1.47)	1.0 (–2.0, 4.0)	**<0.01**
BMI	0.24 (1.29)	0.23 (–3.90, 4.42)	0.04 (1.33)	0.02 (–2.66, 3.25)	0.44
# of patients having severe hyper events (%)	0 (0)	2 (5.4)		0.24	
# of patients having severe hypo events (%)	1 (2.6)	0 (0)		1.00	
Subgroup analyses: change from baseline					
In the subgroup with high baseline HbA1c (≥7.5%) (n = 42)					
Utility	0.017 (0.05)	0 (–0.05, 0.11)	–0.017 (0.05)	0 (–0.13, 0.06)	**0.03** [d]
Time in range 70 - 180 mg/dL	10.61 (113.37)	14.4 (–129.6, 374.4)	153.60 (151.40)	158.4 (–86.4, 432.0)	**<0.01**
HbA1c	0.06 (0.54)	0 (–0.80, 1.30)	–0.09 (0.66)	0 (–1.60, 0.80)	**0.03**
Daily rate of NSHEs	–0.04 (0.09)	–0.08 (–0.17, 0.13)	0.15 (0.17)	0.12 (–0.14, 0.55)	**<0.01**
Insulin dose	–8.28 (26.36)	0.50 (–95.0, 21.0)	–16.80 (19.47)	–16.50 (–90.0, 11.0)	0.93
Daily strip test	0.0 (0.91)	0.0 (–2.0, 2.0)	1.25 (1.55)	1.0 (–1.0, 4.0)	**<0.01**
In the subgroup with low baseline HbA1c (<7.5%) (n = 32)					
Utility	0.006 (0.05)	0 (–0.08, 0.13)	–0.002 (0.04)	0 (–0.08, 0.06)	0.79
Time in range 70 - 180 mg/dL	-49.98 (87.02)	–28.8 (–201.6, 86.4)	–47.31 (174.49)	–14.4 (–446.4, 216.0)	0.49
HbA1c	0.24 (0.26)	0.20 (–0.10, 0.80)	0.82 (0.91)	0.90 (–0.40, 3.30)	**0.02**
Daily rate of NSHEs	–0.02 (0.09)	–0.01 (–0.26, 0.17)	–0.00 (0.15)	–0.03 (–0.26, 0.28)	**0.03**
Insulin dose	-2.16 (18.06)	0.0 (–48.0, 23.0)	–19.13 (16.74)	–18.65 (–50.80, 5.70)	**<0.01**[d]
Daily strip test	–0.65 (1.0)	–1.0 (–2.0, 1.0)	0.42 (1.16)	0.50 ((–2.0, 2.0)	**0.01**

BMI, body mass index; CEA, cost-effectiveness analysis; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; NSHE, nonsevere hypoglycemic event; QALY, quality-adjusted life-year.

[a]Both total indirect costs and total costs did not include the costs from diabetes self-management, due to high kurtosis and 19% missing data. That is, about 19% of patients reported unknown daily number of hours of self-management. 7 patients reported ≥12 hours/day (2 in MDI and 5 in CSII), while the majority reported 1 hour/day.

[b]The Wilcoxon rank-sum test was used to compare the two groups.

[c]A linear mixed model was used to compare the two groups, adjusting its baseline outcome and clinical site as a random effect. The *P* Value is for group comparison across all visits.

[d]*P* values are for the interaction between treatment and time.

interaction between treatment and time). These results indicate that adding a pump significantly lowered QoL.

From the societal perspective, the average 28-week total costs were $19,649 in the CSII group and $12,833 in the control group ($P < 0.01$; Table 2). After excluding self-management costs, which had 19% missing data and were highly skewed (due to 7 patients who reported ≥12 hours/day, detailed in the footnote in Table 2), the total costs became $8,272 in the CSII group and $5,623 in the control group. The major difference in costs between the 2 groups was attributable to CSII use ($2,644). We found no significant differences between the 2 groups in terms of other major cost categories, such as direct personnel costs, nondevice medical care costs, and indirect costs of reduced work productivity and self-management diabetes care (all P values ≥0.28). The 95% CIs of mean differences in costs between the groups by the bootstrap method (in Supplementary Table 9) were consistent with the results by the Wilcoxon's test. CSII users had reduced insulin intake (−12.8 ± 20.6 difference in difference [DiD], $P < 0.01$) but increased daily strip use (+1.2 ± 1.2 DiD, $P < 0.01$) compared with controls. Besides the 2 kinds of medical care, no other differences were found in health care utilization (Supplementary Table 10). No within-trial ICER was calculated because of the lack of difference in QALYs. The CSII was dominated by MDI in the within-trial CEA.

In addition to the key CEA results, we evaluated a number of important clinical outcomes (Table 2). CSII helped to increase time-in-range of glucose concentration (CGM + CSII: +77 ± 186 v. CGM + MDI: −18 ± 105 minutes/day, $P < 0.01$) but increased the HbA1c level (+0.13 ± 0.70 DiD, $P < 0.01$ by LMM) and the daily rate of NSHEs (+0.125 ± 0.138 DiD, $P < 0.01$). There were no significant differences in changes to BMI, numbers of severe hypoglycemic and hyperglycemic events, and number of patients who changed noninsulin glucose-lowering medicines (2 CGM + MDI patients increased medicine during the trial: 1 added Victoza and the other added Farxiga).

We also conducted HbA1c subgroup analyses (Table 2) and found different patterns of clinical outcomes for the 2 subgroups (Supplementary Figures 1 and 2). Among patients with high baseline HbA1c (≥7.5%), compared with the MDI group, the CSII group experienced a reduction in utility ($P = 0.03$) and an increase in time-in-range ($P < 0.01$). CSII reduced HbA1c at 3 months, but this difference disappeared at 6 months (Supplementary Figure 1). The P value for the interaction effect between treatment and time was 0.03, indicating that CSII had an effect on HbA1c over the study period. The CSII users also experienced a higher frequency of NSHEs ($P < 0.01$), and they used more test strips ($P < 0.01$). Meanwhile, CSII users and controls had similar insulin dose reductions over time ($P = 0.93$).

We found a different pattern of clinical outcomes for patients with low baseline HbA1c (<7.5%; Table 2). Both groups maintained similar utility values over the study period ($P = 0.79$) and had similar reductions in time-in-range ($P = 0.48$). However, the CSII group had higher HbA1c levels ($P = 0.02$), a smaller reduction in NSHEs ($P = 0.03$), a greater reduction in insulin dose ($P < 0.01$), and greater use of test strips ($P = 0.01$) than the MDI group (Supplementary Figure 2).

Missing data. There were no patterns of missing values between the groups. With the exception of daily hours of self-management (a confusing question with poor quality), only 5 (13%) patients in the control group and 2 (5%) patients in the pump group had missing data. The overall results of the sensitivity analyses through the imputed data sets (in Supplementary Table 11) were consistent with the main analyses.

Long-term CEA

Base-case CEA analyses. We incorporated the within-trial results from the subgroup analyses at week 28 for HbA1c, NSHEs, insulin, daily strip test, and utility into the base-case lifetime modified Sheffield model (Supplementary Table 6). We did not account for time-in-range, since no available simulation models account for its effect.

The simulation results of the lifetime analysis suggest that adding CSII to CGM users is expected to increase the incidence of multiple complications, compared with CGM users with MDIs (Table 3). In particular, adding CSII would lead to increased lifetime risks of end-stage microvascular complications and macrovascular complications. CGM + CSII would increase lifetime total costs by $112,045, mainly due to pump use (annual price: $4,426; see Supplementary Table 4). Compared with controls, life expectancy would decline from 26.08 to 25.60, an average of 0.48 years, with the addition of CSII. The reduction in quality-adjusted life expectancy was −0.71 QALYs, with a 95% confidence interval [−0.87, 0.56]. CSII was dominated by MDI in the lifetime CEA.

Subgroup and sensitivity CEA analyses. The results of the subgroup and sensitivity analyses were consistent with the results of the base-case analysis (Table 3).

Table 3 Lifetime CEA Results

	CGM + MDI	CGM + CSII
Base-case CEA		
Lifetime probability of, %		
Background diabetic retinopathy	27.40	32.00
Proliferative diabetic retinopathy	24.60	28.60
Macular edema	6.90	8.60
Blindness	2.50	2.60
Macroalbuminuria	17.00	19.40
End-stage renal disease	10.20	12.20
Neuropathy	44.80	47.00
Amputation	14.60	15.20
Myocardial infarction	41	42
Stroke	14	14
Angina	27	28
Heart failure	17	17
Expected life-years	26.08	25.6
Difference in expected life-years (mean and [95% CI])	(−0.48) [(−0.90) to (−0.04)]	
Discounted QALYs (means)	12.65	11.94
Difference in QALYs (mean and [95% CI])	(−0.71) [(−0.87) to (−0.56)]	
Discounted total costs (means)	494,571.02	606,625.04
Difference in costs (mean and [95% CI])	112,054 [97,338 to 126,833]	
Subgroup CEAs		
Subgroup with high baseline HbA1c		
Expected life-years	25.97	25.97
Difference in expected life-years (mean and [95% CI])	0.0 [(−0.14) to 0.14]	
Discounted QALYs (means)	13.08	12.17
Difference in QALYs (mean and [95% CI])	(−0.91) [(−0.96) to (−0.86)]	
Discounted total costs (means)	467,991	569,473
Difference in costs (mean and [95% CI])	101,482 [97,07 to 105,975]	
Subgroup with low baseline HbA1c		
Expected life-years	27.42	26.14
Difference in expected life-years (mean and [95% CI])	(−1.28) [(−1.42) to (−1.14)]	
Discounted QALYs (means)	13.3	12.80
Difference in QALYs (mean and [95% CI])	(−0.51) [(−0.52) to (−0.41)]	
Discounted total costs (means)	450,158	553,944
Difference in costs (mean and [95% CI])	103,785 [99,838 to 107,954]	
Sensitivity CEA: No utility difference		
Expected life-years	26.26	25.67
Difference in expected life-years (mean and [95% CI])	(−0.58) [(−0.72) to (−0.44)]	
Discounted QALYs (means)	12.69	12.19
Difference in QALYs (mean and [95% CI])	(−0.48) [(−0.53) to (−0.43)]	
Discounted total costs (means)	493,619	594,728
Difference in costs (mean and [95% CI])	101,109 [96,424 to 105,618]	

CEA, cost-effectiveness analysis; CI, confidence interval; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; QALY, quality-adjusted life-year.

Adding CSII would increase total costs by about $100,000, while QALYs would be reduced by 0.91 and 0.51 in the high and low baseline HbA1c subgroups, respectively. Adding CSII would have no effect on life expectancy in the high baseline HbA1c subgroup but would shorten life expectancy (−1.28 years) in the low HbA1c subgroup. In sensitivity analyses, the results were not significantly altered with the removal of the negative QoL effect of CSII.

Discussion

In the past decade, diabetes management for many patients with T1D has been transformed by new technologies such as CGM and CSII, but the high costs of these devices are a barrier to adoption. Although many patients may adopt CGM and CSII individually, together, or in different sequences, economic evaluations of innovations in CGM and insulin pumps have been

limited to studies of individual devices compared with usual care. Our study is the first to examine the economic value of a particular sequence of adoption of technologies in adults with T1D, namely, the adoption of CSII after the adoption of CGM. The within-trial CEA found that adding CSII to CGM users increased costs, reduced QoL, worsened glucose control (higher HbA1c), and increased NSHEs. Extrapolating these results, the lifetime CEA found that adding CSII would increase costs and cause overall clinical harm.

In this trial, CSII did not improve glucose control compared with MDI for the overall trial population as one would expect from pump use. One possible explanation for this finding is that the overall trial results mask the distinct and complex experiences of patients with high and low baseline HbA1c.[15] In the high baseline HbA1c group ($\geq$7.5%), pump use appeared to improve glucose control by increasing time-in-range and reducing HbA1c modestly over time (about 0.3% DiD at 3 months, not significant at 6 months). However, the addition of pump use did concurrently increase NSHEs,[38] which are associated with reduced QoL.[39,40] These findings in HbA1c in the high baseline HbA1c subgroup are consistent with those of 3 meta-analyses of numerous studies comparing CSII with MDI in adults with T1D without use of CGM (mean HbA1c difference of 0.30%, 0.37%, and 0.30%, respectively).[6,9,41] On the other hand, in CGM users with low baseline HbA1c ($<$7.5%), adding a pump worsened glycemic control. In this subgroup, the mean baseline HbA1c was 6.94% $\pm$ 0.40% (range, 6.0% to 7.4%), with at least 50% having an HbA1c $<$7.0%. As a result, the opportunity to improve glycemic control was far smaller, and the burdens of adding a pump might have been more prominent. The second potential reason for the overall trial findings is that the trial lacked a standardized and solid training method for introduction of CSII for the multicenter study. As the American Diabetes Association recommends, pump use requires care by skilled professionals, careful selection of patients, meticulous patient monitoring, and thorough patient education.[42] More rigorous pump training could have resulted in greater benefit for the CGM + CSII group.[15] The third possible reason is that the trial was not powered to assess HbA1c effect, especially in the small subgroup with high baseline HbA1c ($\geq$7.5%).

The 2 DIAMOND trials (CGM + MDI v. SMBG + MDI[43]; CSII + CGM v. MDI + CGM[15]) suggest that the decision to adopt CGM has a greater clinical benefit than the decision to adopt CSII. This is consistent with recent studies of glucose monitoring and/or insulin delivery methods in patients with T1D.[44,45] The COMISAIR study[45] compared the 4 glucose-monitoring and insulin-delivery combinations (CSII + CGM, MDI + CGM, CSII + SMBG, and MDI + SMBG) and found that both the CSII + CGM and MDI + CGM groups had very similar improvements in glucose control over 1 year from a mean baseline HbA1c of 8.3%. Both CGM groups had improvements in glucose control and reductions in hypoglycemia that were greater than those with CSII + SMBG. The SWITCH study[44] found that in patients already using CSII, adding CGM led to an improvement in glucose control, while removal of CGM resulted in a loss of the benefit. Overall, CGM is the primary driver of improved clinical outcomes.[15,44,45]

Our CEA findings are distinct from past economic evaluations of CSII because our analyses are based on a trial in which all patients used CGM, which likely altered the potential benefits of CSII. Our results are most similar to the recent CEA of CSII based on the REPOSE cluster randomized controlled trial[46] and the economic evaluation study of CSII using data from national member enrollment files and health care claims by Ackermann et al.[47] REPOSE compared insulin pump therapy to MDI, with both sets of patients using insulin analogues and receiving high-quality structured training. The REPOSE study concluded that insulin pump therapy did not provide significant improvement in glucose control compared with MDI and that extending the availability of pumps to adults with T1D is unlikely to be cost-effective. The long-term ICER in this study was £149,483/QALY. Ackermann's economic evaluation study found that adults with T1D, transitioning from MDI to CSII, had modest improvements in HbA1c (0.46% in 2 years and 0.32% in 3 years) but more hypoglycemia encounters, which increased total annual health care expenditures by $6,856.[47] The findings of our CEA, the REPOSE study, and the Ackermann study conflict with a number of earlier CEA studies that concluded that CSII compared with MDI may be beneficial and cost-effective in adults with T1D.[48–50] The ICERs from these studies ranged from $12,237 to $34,336/QALY. These studies used data from the clinical findings of a meta-analysis of CSII published in 2003[51]; the meta-analysis concluded that treatment with CSII for 1 year or greater was associated with a mean reduction in baseline HbA1c of 1.2% $\pm$ 0.2% and a mean increase in BMI of 1.03 kg/m^2 compared with MDI. A number of secular changes in diabetes care may explain why CSII in both the DIAMOND and REPOSE studies demonstrated negative or smaller clinical effects than the older trials included in this meta-analysis. The older studies

were all performed in an era that preceded the wide availability of insulin analogues and CGM. It is also likely that the baseline quality of diabetes care has improved over time[52] as physicians have more aggressively pursued intensive glucose control (HbA1c level of $<7.0\%$) following the publication of the Diabetes Control and Complications Trial in 1993.[2]

In contrast to studies of CSII, CGM consistently appears to be cost-effective in adults with T1D using MDI[26] (including a recent CEA study based on the recent DIAMOND trial)[53] or insulin pumps as found in the Juvenile Diabetes Research Foundation trial, in which most trial participants were pump users ($>80\%$).[11] The integrated CSII/CGM therapy (i.e., CGM + CSII) likely represents a cost-effective treatment option relative to CSII alone,[54] as well as a cost-effective alternative to MDI without CGM.[55]

Our study has limitations. First, as mentioned above, the main limitation of the DIAMOND trial is that the introduction of CSII was not accompanied by standardized methods for pump training, and individual clinical sites were allowed to introduce the pump as per their usual practice.[42] Second, the study was also not designed and powered to detect an effect for clinical outcomes (such as HbA1c) other than time-in-range. Larger, longer-term studies, especially among patients with HbA1c $\geq 7.5\%$ are needed. The third limitation relates to the survey question of time devoted to self-management: "How many hours per day do you currently devote to managing your glucose levels (i.e., looking at your glucose levels, modifying your meals and/or your insulin doses)?" Some trial patients considered CGM use as time devoted to managing their glucose levels and consequently answered more than 12 hours a day. This question may not have been specific enough to capture accurate information about self-management time. Fourth, we were not able to incorporate the clinical benefits of increased time-in-range in the lifetime model. None of the existing lifetime T1D models in the literature consider time-in-range, which should be explored by future work. Finally, an appropriate disutility value of an NSHE was difficult to ascertain because of diverse definitions of NSHEs within a limited literature. Prior studies of the QoL effects of NSHEs were based on either life with/without symptomatic hypoglycemia or the experience of a single symptomatic hypoglycemic event.[56–58] These patient-reported definitions are distinct from the new international definition (<54 mg/dL for ≥ 20 successive minutes),[19] derived from CGM, which has a higher frequency than past definitions and is frequently asymptomatic.

In conclusion, based on this trial, for adults with T1D already using CGM, initiating insulin pump use increased costs and reduced QoL. This suggests that the sequence of adoption of distinct technologies may have unexpected effects on the value of individual technologies. Additional evidence regarding the adoption of multiple technologies from trials and real-world populations is needed to confirm these findings.

Supplementary Material

Supplementary material for this article is available on the *Medical Decision Making* Web site at http://journals.sagepub.com/home/mdm.

Author Contributions

Dr. Wan, Dr. Skandari, and Dr. Huang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the article: Wan, Skandari, Huang. Critical revision of the article for important intellectual content: all authors. Statistical analysis: Wan, Skandari. Obtained funding: Huang. Administrative, technical, or material support: all authors. Study supervision: all authors.

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