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Title: 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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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: 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 to controls. Total per-person 28-week costs were $8,272 (CGM+CSII) vs $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 use of daily number of test strips (+1.2 DiD). Pump users also increased time with glucose in range 70-180 mg/dL, but had higher HbA1c (+0.13 DiD) and more non-severe hypoglycemic events. In the lifetime CEA, CGM+CSII would increase total costs by $112,045 DiD, decrease QALYs by 0.71, and 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 are needed to confirm these findings.

INTRODUCTION

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 over 30 years of age 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 vs MDI+SMBG), of CGM use versus SMBG in patients using MDI[10] (i.e., MDI+CGM vs MDI+ SMBG), and of CGM use versus SMBG in patients using an insulin pump[11] (i.e., CSII+CGM vs CSII+SMBG). The economic impact of initiating insulin pump use versus MDI in patients already using CGM, however, has not been addressed.

Over 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 to older technology.[13,14] In the recently completed sub-study 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]

METHODS

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

Study design

The DIAMOND trial was done at US 20 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 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 range of 70-180 mg/dL (denoted by "time-in-range"), HbA1c, non-severe 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 (CHEERS),[17] we have provided an impact inventory table and reporting checklist in eTables 1 and 2 in the Supplement.

Costs

The 28-week within-trial total costs included 1) all direct costs associated with healthcare 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 eTable 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, non-durable 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 (PDM) starter kit and pods (eTable 4)). CGM cost was estimated to be $15.20/day, including costs from its three components (i.e., G4 sensor, receiver, and transmitter (eTable 5)). These prices are estimated average allowable prices in the U.S. marketplace. **Non-device medical care costs:** Healthcare service utilization costs included routine office visits, after-hour clinic visits (urgent care), 911 calls, ambulance use, emergency room visits and hospitalizations, as well as 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 U.S. dollars.

Quality of life

The EuroQol 5-level 5-dimension questionnaire (EQ-5D-5L), used to assess health-related QoL, 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 non-severe 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.

Non-severe 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 range of 70-180 mg/dL (denoted as "time-in-range"). The second measure was a daily rate of non-severe hypoglycemic events (NSHEs). We defined a 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 Hypoglycaemia 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 cost-effectiveness analyses

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 in 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 (LMM) 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 homogeneity of the treatment effect, we conducted a test of the interaction between the baseline outcome and treatment arm through a LMM. Backward model selection was performed to achieve a LMM with the smallest Bayesian information criterion (BIC). We considered 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 10000 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 dataset, due to only 6.7% - 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 datasets and applied the same methods in the primary analysis to each dataset. Since costs data were non-normally distributed, we used the bootstrap method to calculate their CIs per imputed dataset. Then, we combined all the results into one by a confidence interval of a mean difference between the two groups using a formula from Rubin (1987).[21]

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

Life-time cost-effectiveness analyses (CEA)

To evaluate the cost-effectiveness of CGM+CSII vs 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 life-time of patients including progression through major micro-vascular and macro-vascular complications, as well as short-term complications (hypo- and hyper-glycaemia) 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 (AHRQ).[7] Therefore, we replaced this module with the observed hypoglycemia event rates. All the base-case model parameters, including clinical inputs, cost, and health-utility, are described in eTables 6-8. 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: Due to different patterns in the clinical and quality of life outcomes found between the two 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 two subgroups were then combined and summarized for the base-case model.

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

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

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 two treatment groups (Table 1). The mean (± standard deviation (SD)) utility value at baseline was 0.93 ± 0.09, indicating that the 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 cost-effectiveness analysis

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) vs 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) vs 0.465 ± 0.002 (CGM+CSII) ($p = 0.06$), and the treatment effect on utilities became significant ($p = 0.032$ from interaction between treatment and time). These results indicate that adding a pump significantly lowered quality of life.

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 under 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 two groups was attributable to CSII use ($2,644). We found no significant differences between the two groups in terms of other major cost categories such as direct personnel costs, non-device 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 eTable 9) were consistent with the results by the Wilcoxon's test. CSII users had reduced insulin intake (-12.8 ± 20.6 DiD, $p < 0.01$), but increased daily strip use (+1.2 ± 1.2 DiD, $p < 0.01$) compared to controls. Beside the two kinds of medical care, no other differences were found in healthcare utilization (in eTable 10). No within-trial ICER was calculated due to 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 vs 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 non-insulin glucose-lowering medicines (two CGM+MDI patients increased medicine during the trial: one added Victoza and the other added Farxiga).

We also conducted HbA1c subgroup analyses (Table 2) and found different patterns of clinical outcomes for the two subgroups (eFigures 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 (eFigure 1). The p-value for the interaction effect between treatment and time is 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 (eFigure 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 datasets (in eTable 11) were consistent with the main analyses.

Long-term cost-effectiveness analysis

Base-case CEA analyses. We incorporated the within-trial results from the sub-group analyses at week 28 for HbA1c, NSHEs, insulin, daily strip test, and utility into the base-case lifetime modified Sheffield model (eTable 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 multiple daily injections (Table 3). In particular, adding CSII would lead to increased life-time risks of end-stage micro-vascular complications and macro-vascular complications. CGM+CSII would increase lifetime total costs by $112,045, mainly due to pump use (annual price: $4,426, in eTable 4). Compared with controls, life-expectancy would decline from 26.08 to 25.60, an average 0.48 years, with the addition of CSII. The reduction in quality-adjusted life expectancy

was -0.71 QALYs with its 95% confidence interval [-0.87, 0.56]. CSII was dominated by MDI in the lifetime CEA.

Sub-group and sensitivity CEA analyses. The results of the sub-group and sensitivity analyses were consistent with the results of the base-case (Table 3). 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 quality of life 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 is 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 to 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 quality of life, 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 to 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 (≥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 quality of life.[39,40] These findings in HbA1c in the high baseline HbA1c subgroup are consistent with those of three meta-analyses of numerous studies comparing CSII to 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 ± 0.40% (ranged: 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 (≥7.5%).

The two DIAMOND trials (CGM+MDI vs. SMBG+MDI[43]; CSII+CGM vs. 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 four glucose monitoring and insulin delivery combinations (CSII+CGM, MDI+CGM, CSII+SMBG, and MDI+SMBG), and found that the CSII+CGM and MDI+CGM groups both had very similar improvements in glucose control over a 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 where 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 healthcare 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 healthcare expenditures by $6856.[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 to 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% ± 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 continuous glucose monitoring. 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 where a majority of 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 future work should explore. Finally, an appropriate disutility value of a NSHE was difficult to ascertain due to 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 (<54mg/dL for ≥ 20 successive minutes)[19], derived from CGM, that 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 quality of life. 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 are needed to confirm these findings.

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Table 1. Baseline characteristics of the study populations

	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			0.82
mean ± SD	44.9 ± 12.1	45.8 ± 15.4	
range	26 - 67	25 - 72	
T1D Duration (year)			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	
# of patients using non-insulin glucose-lowering medication			
n (%)	1 (2.6)	2 (5.4)	0.61
# of patients having severe hypoglycemia in previous 6 m			
n (%)	2 (5)	0	0.49
# of patients having severe hyperglycemia in previous 6 m			
n (%)	0	0	1
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	

Table 2. Within-trial CEA results

	CGM+MDI (n=38)		CGM+CSII (n=37)		p-value[b]
	mean (SD)	**median (IQR)**	**mean (SD)**	**median (IQR)**	
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
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
	mean (SD)	**median (range)**	**mean (SD)**	**median (range)**	**p-value[c]**
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**

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.

Table 3. Lifetime cost-effectiveness analysis results

	CGM+MDI	CGM+CSII
BASE-CASE CEA		
Life-time 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) - (-0.04)]
Discounted QALYs (means)	12.65	11.94
Difference in QALYs (mean and [95% CI*])	(-0.71)	[(-0.87) - (-0.56)]
Discounted total costs (means)	494,571.02	606,625.04
Difference in costs (mean and [95% CI*])	112,054	[97,338 - 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) – 0.14]
Discounted QALYs (means)	13.08	12.17
Difference in QALYs (mean and [95% CI*])	(-0.91)	[(-0.96) – (-0.86)]
Discounted total costs (means)	467,991	569,473
Difference in costs (mean and [95% CI*])	101,482	[97,07 – 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) – (-1.14)]
Discounted QALYs (means)	13.3	12.80
Difference in QALYs (mean and [95% CI*])	(-0.51)	[(-0.52) – (-0.41)]
Discounted total costs (means)	450,158	553,944
Difference in costs (mean and [95% CI*])	103,785	[99,838 – 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) – (-0.44)]
Discounted QALYs (means)	12.69	12.19
Difference in QALYs (mean and [95% CI*])	(-0.48)	[(-0.53) – (-0.43)]
Discounted total costs (means)	493,619	594,728
Difference in costs (mean and [95% CI*])	101,109	[96,424 – 105,618]

*CI = confidence interval

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

Supplementary eTable 1. Impact inventory for cost-effectiveness analysis (CEA)[a]

Sector	Type of Impact	Included in this reference case analysis		Notes on sources of evidence
		Health Care Sector	Societal	
Formal health care sector				The within-trial CEA used the observed trial data and the cost assumptions provided in eTables 3-5. The lifetime CEA used the modified Sheffield T1D model (Thokala et al. 2013)[22] and cost, health-utility, and other input parameters provided in eTables 6-8.
health	**Health outcomes (effects)**			
	Utility	Yes	Yes	
	HbA1c	Yes	Yes	
	Time-in-range 70 – 180 mg/dL[b]	Yes	Yes	
	Daily rate of NSHEs	Yes	Yes	
	BMI	Yes	Yes	
	# of patients having severe hyper events	Yes	Yes	
	# of patients having severe hypo events	Yes	Yes	
	Medical costs			
	Direct trial personnel costs	Yes	Yes	
	Medical care costs including	Yes	Yes	
	healthcare services	Yes	Yes	
	test strip use	Yes	Yes	
	insulin	Yes	Yes	
	Device (CGM) costs	Yes	Yes	
Informal health care sector				
health	Self-management costs	NA	Yes	
Non-health care sectors				
productivity	Costs of unpaid lost productivity due to illness if employed	NA	Yes	
	Costs of underperformance due to illness if employed	NA	Yes	

a The impact inventory table was based on the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine.[16]

b Time-in-range refers to time with glucose concentrations in range of 70 – 180 mg/dL. Time-in-range was not taken into account in the simulation model, since no available simulation models account for its effect.

Supplementary eTable 2. Reporting checklist for cost-effectiveness analysis[a]

Element	Journal Article	Technical Appendix
INTRODUCTION		
Background and objectives	Yes	
RESEARCH DESIGN AND METHODS		
Study design	Yes	
Target populations and subgroups	Yes	
Setting and location	Yes	
Study perspective	Yes	
Comparator	Yes	
Time horizon	Yes	
Discount rate	Yes	
Type of analysis	Yes	
Choice of health outcomes	Yes	
Measurement of effectiveness	Yes	
Measurement and valuation of preference-based outcomes	Yes	Yes
Estimating resources and costs	Yes	Yes
Currency, price date, and conversion	Yes	Yes
Choice of model	Yes	
Assumptions		Yes
Analytic methods	Yes	
RESULTS		
Study parameters	Yes	Yes
Incremental costs and outcomes	Yes	Yes
Characterizing uncertainty	Yes	Yes
Characterizing heterogeneity	Yes	Yes
DISCUSSION		
Study findings, limitations, generalizability, and current knowledge	Yes	
OTHER		
Source of funding	Yes	
Conflicts of interest	Yes	

[a] The reporting checklist was based on the recommendations of the Consolidated Health Economic Reporting Standards (CHEERS) statement.[17]

Supplementary eTable 3. Within-trial cost assumptions

Within Trial Cost Assumptions		
Item	**Unit Cost (2015 USD) [a]**	**Source**
Direct CGM Personnel Costs: *Time of investigators/coordinators devoted to training/counseling patients on both RT-CGM and usual care*		
Primary care provider	$94.43/hour	Bureau of Labor Statistics 2016[59]
Advanced nurse practitioner	$47.21/hour	Bureau of Labor Statistics 2016
Registered nurse	$32.45/hour	Bureau of Labor Statistics 2016
Diabetes educator	$37.35/hour	Bureau of Labor Statistics 2016
Other provider	$35.92/hour	Bureau of Labor Statistics 2016
Direct Medical Care Costs		
Average daily insulin use over 6 months	$0.15/unit of insulin	Redbook 2016
Average daily fingerstick use over 6 months	$0.06/lancet $1.02/test strip	Redbook 2016
Event Complication Costs		
Outpatient diabetes care: primary care provider	$94.43/event	Bureau of Labor Statistics 2016
After-hours urgent care clinic visit	$180.23/event	Mehrotra et al 2005[60]
911 call	$0.86 surcharge/month	National Association of Emergency Numbers[61]
Outpatient care: emergency department	$476.06/event	Taubman et al 2014[62]
Ambulance use	$506.36/event	U.S. GAO Report to Congressional Committes, 2012[63]
Hospitalization (all causes)	$10,443.06/event	Healthcare Costs and Utilization Project[64]
Hospitalization due to hypoglycemic episode	$16,806.70/event	Ward et al 2014[65]
Hospitalization due to hyperglycemic episode	$15,657.00/event	St Charles et al 2009[48]
Hospitalization for other diabetic event	$10,107.70/event	Healthcare Costs and Utilization Project
Indirect Costs		
Days of work missed due to diabetes--patient	Age and sex specific median hourly wage	Bureau of Labor Statistics 2016
Days of underperformance at work with productivity <50%	Age and sex specific median hourly wage	Bureau of Labor Statistics 2016

[a] The annual inflation rate for a given year is the percent change from the previous year. Inflation rates were obtained from the Personal Consumption Expenditures: Chain-type Price Index (PCEPI), downloaded through the link: https://fred.stlouisfed.org/series/PCEPI. As an example, to convert a price expressed in 2010 dollars to 2015 dollars, one would use the following equation ((PCEPI(2015)/PCEPI(2010) x Price (2010)= Price (2015)).

Supplementary eTable 4. Itemized continuous subcutaneous insulin infusion (CSII) annual cost assumptions

Component	Annual price by ADW distributor	Annual price by Solara distributor	Unit	Annual usage	Total annual average price[c]	Annual price for the lifetime CEA[e]
PDM starter kit[a]	$660[66]	$669[67]	1 kit	1 kit	$664	$166
Omnipod[b]	$4320[68]	$4199[69]	10 pods/box	12 boxes	$4,260	$4,260
Total	$4,980	$4,868			$4,924[d]	$4,426

[a] Each PDM starter kit has a warranty of 4 years.

[b] A pod should be replaced every 3 days.

[c] Price was averaged of the two prices from ADW Inc and Solara Inc because the study patients randomly picked either one.

[d] The daily price in the within-trial of $13.49 was calculated by the total annual average price divided by 365.

e The annual price for the lifetime cost-effectiveness analysis was calculated to take into account the 4-year warranty of each PDM starter kit.

Supplementary eTable 5. Itemized blood glucose monitoring annual cost assumptions[e] used in base case and sensitivity analyses.

Component	Control (self-monitoring)	CGM			
		Dexcom G4 (base case)	Dexcom G4 (real-world use)	Dexcom G5	Dexcom G5 (real-world use)
Test strips [a]	$1,629.98	$1,330.84	$1,330.84	$1,104.52	$1,104.52
CGM sensor [b]	-	$4,066	$2,283.44	$4,066	$2,283.44
CGM receiver [c]	-	$476.63	$317.75	$482.17 ($241.085)	$482.17 ($241.085)
CGM transmitter [d]	-	$1,004.96	$669.97	$1,014.44	$1,014.44
Total	$1,629.98	$6,878.43	$4,602.00	$6,789.88 ($6,548.79)	$5,125.65 ($4,884.57)

[1] Test strip cost was calculated assuming a cost of $1.08 per test strip (see Supplementary eTable 3). For Dexcom CGM G5, the cost was calculated assuming 2.8 daily tests stated in the REPLACE-BG trial.[70]

[2] Dexcom sensors should be replaced every 7 days per label indication and cost $78.20 each. In real-world use, patients typically use one sensor per 10 days without comprising safety[71] and wear it 80% of the time.

[3] Dexcom CGM receivers have a warranty of 1 year. Numbers in parentheses indicate the cost associated with year 2+ of purchasing a CGM package, assuming 50% of patients would use their smart phone as the CGM receiver.

[4] Dexcom G4 transmitter costs $502.48 and has a warranty of 6 months, but typically lasts 9 months. Dexcom G5 transmitter costs $253.60 , has a warranty of 3 months, and shut off at 3 months.

[5] The prices of CGM components were the estimated average allowable prices in the U.S. marketplace and were provided by the Dexcom Pricing Department.

Supplementary eTable 6. Clinical input parameters for the long-term cost-effectiveness model

Cohort baseline characteristics			**Mean (SD)**	
Gender-female (%)			44%	
Race-white (%)			94%	
Smokes (%)			19%	
Age			47.59 (13.04)	
T1D duration (year)			20.75 (13.60)	
HbA1c			8.63 (0.64)	
Systolic blood pressure			118.45 (16.90)	
High-density lipoprotein			51.90 (21.75)	
Total cholesterol			176.15 (35.90)	
Clinical outcomes: reduction from baseline	**Control**		**CGM**	
	Low baseline HbA1c (<8.5%)	**High baseline HbA1c (≥8.5%)**	**Low baseline HbA1c (<8.5%)**	**High baseline HbA1c (≥8.5%)**
HbA1c reduction	0.22 (0.78)	0.53 (0.60)	0.63 (0.59)	1.29 (0.77)
Average annual rate of NSHE	131.4	100.6	85.9	100.6

Supplementary eTable 7. Cost assumptions of the long-term cost-effectiveness analysis

Definition	Base-Case Value (2015 USD)	References
Blood glucose monitoring[a] related costs		
Continuous subcutaneous insulin infusion (CSII)		See eTable 4
Daily blood glucose monitoring (CGM)		See eTable 5
Kidney related costs		
Microalbuminuria	21.75	St Charles et al, 2009
Macroalbuminuria	32.01	St Charles et al, 2009
End-stage renal disease	109,315.22	Beckwith et al, 2012[25]
Neuropathy related costs		
Neuropathy	1,443.79	Beckwith et al, 2012
Amputation, year of event	55,688.88	Beckwith et al, 2012
Amputation, year 2+ after event	1,959.42	Beckwith et al, 2012
Eye related costs		
Background diabetes retinopathy	9,551.63	Li et al, 2013[72]
Proliferative diabetes retinopathy	13,802.06	Li et al, 2013
Macular edema	8,640.82	Li et al, 2013
Blindness	4,716.18	St Charles et al, 2009
Cataract	3,275.50	Palmer et al, 2004[31]
Cardiovascular complication costs		
Myocardial infarction, year of event	43,711.23	St Charles et al, 2009
Myocardial infarction, year 2+ after event	2,416.25	St Charles et al, 2009
Fatal Myocardial infarction	3,329.18	Clarke et al, 2003 (UKPDS 65)[73]
Stroke, year of event	57,885.35	St Charles et al, 2009
Stroke, year 2+ after event	19,318.56	St. Charles et al, 2009
Fatal stroke	9,007.58	UKPDS 65
Heart failure, year of event	17,693.98	McQueen et al, 2011[26]
Heart failure, year 2+ after event	1,858.42	McQueen et al, 2011
Fatal heart failure	13,349.89	UKPDS 65
Angina, year of event	8,671.93	St Charles et al, 2009
Angina, year 2+ after event	3,754.94	St Charles et al, 2009
Glycemic control relate costs		
Severe hypoglycemia	1,391.14	St Charles et al, 2009
Non-severe hypoglycemia	20.32	Foos et al, 2015[74]
Hyperglycemia	15,657.10	St Charles et al, 2009

[a] Blood glucose monitoring costs include costs of test strips and CGM sensor, transmitter, and receiver initial purchase and replacements. The cost of insulin was excluded since CGM did not modify insulin intake.

Supplementary eTable 8. Health-utility assumptions of the long-term cost-effectiveness analysis

Event/state	Utility/disutility[a,b]	References
Diabetes no complication	0.916	Trial data
Kidney related events/states		
End-stage renal disease	0.552	Lee et al, 2011[75]
Neuropathy related events/states		
Neuropathy	0.703	Begg et al, 2007
Amputation, year of event[2]	-0.109	Palmer et al, 2004
Amputation, year 2+ after event	0.766	Clarke et al, 2002
Eye related costs		
Proliferative diabetes retinopathy	0.894	Begg et al, 2007[76]
Macular edema	0.89	Begg et al, 2007
Blindness	0.826	Clarke et al, 2002
Cardiovascular complication events/states		
Myocardial infarction, year of event	-0.129	Clarke et al, 2002
Myocardial infarction, year 2+ after event	0.82	Clarke et al, 2002
Stroke, year of event	-0.181	Clarke et al, 2002
Stroke, year 2+ after event	0.614	Clarke et al, 2002
Heart failure, year of event	-0.129	Clarke et al, 2002
Heart failure, year 2+ after event	0.829	Clarke et al, 2002
Angina	0.768	Clarke et al, 2002
Glycemic control related events		
Severe hypoglycemia event	-0.0052	N.I.C.E., 2002[77]
Non-severe hypoglycemia event[c]	-0.00045	N.I.C.E., 2002 and Harris et al, 2014[56]
Hyperglycemia event	-0.001	Walters, 2006[78]

[a] Negative values indicate *per episode disutilities* of events, and positive values indicate *annual utilities of health-states*. For events that may happen more than once per year (e.g., glycemic control related events), the disutilites were multiplied by the event count.

[b] Literature based utilities were adjusted to reflect health-utilities observed in the trial.

[c] Harris et al (2014) reported disutilities of -.0056 and -0.003 for day-time and nocturnal non-severe hypoglycemia, and -0.0592 and -.0277 for day-time and nocturnal severe hypoglycemia, respectively. We calculated the disutility of an episode of non-severe hypoglycemia by multiplying the severe hypoglycemia disutility in N.I.C.E. (2002) by the ratio of severe and non-severe hypoglycemia disutilities reported in Harris et al (2014) (approximately 10%).

Supplementary eTable 9. Comparison of within-trial mean costs by the bootstrap method

Costs	Mean difference (CSII - MDI)		CSII - MDI (95% CI)[b]	
	by original data	by bootstrapped replications	Lower	Upper
Total direct costs	2653	2630	2319	2931
direct trial personnel	19	20	-13	64
medical care	-15	-39	-409	250
CSII	2644	-	-	-
CGM	0	-	-	-
Total indirect costs[a]	-2	-2	-90	146
missed work	4	4	-88	88
poor performance	-6	-6	-109	70
self-management	3826	3945	-2686	12687
Total costs	2649	2627	2243	2954
Total costs[a]	6816	6936	1046	14130

a. Both total indirect costs and total costs did not include the costs from diabetes self-management, due to poor data quality.

b. The confidence interval was calculated based on the percentile method.

Supplementary eTable 10. Within-trial results in healthcare utilization

Outcomes in utilization	CGM + MDI (N=38)			CGM+CSII (N=37)			p-value[a]
	Mean	SD	Median (range)	Mean	SD	Median (range)	
Diabetes self-care costs during the trial							
N of daily strip tests	3.2	1.1	3 (1, 5)	4.3	1.7	4 (1, 8)	**<0.01**
Insulin dosing	49.5	24	48 (0, 100)	44.7	20.3	41.4 (0, 94.8)	0.26
Clinical trial staff encounters within the trial							
Physician	0.6	0.8	0 (0, 3)	1.1	2.1	1 (0, 12)	0.38
Advanced	0	0	0 (0, 0)	0	0	0 (0, 0)	1.00
Nurse	0.2	0.8	0 (0, 5)	0.1	0.4	0 (0, 2)	0.31
Educator	0.3	1.1	0 (0, 6)	0.1	0.4	0 (0, 2)	0.95
Other	0.2	0.8	0 (0, 5)	0.3	0.8	0 (0, 3)	0.29
Number of overall healthcare uses during the trial							
ER visits	0.0	0.2	0 (0, 1)	0.0	0.0	0 (0, 0)	0.32
911 call	0.0	0.2	0 (0, 1)	0.0	0.0	0 (0, 0)	0.32
Ambulance	0.0	0.2	0 (0, 1)	0.0	0.0	0 (0, 0)	0.32
Urgent care	0.1	0.3	0 (0, 2)	0.0	0.2	0 (0, 1)	1.00
Length of stay in hospital	0.0	0.0	0 (0, 0)	0.0	0.0	0 (0, 0)	1.00
Hospitalization	0.0	0.0	0 (0, 0)	0.0	0.0	0 (0, 0)	1.00
Healthcare provider	1.7	1.9	1 (0, 6)	1.9	2.2	1 (0, 7)	0.69
HbA1c test requested by health provider	0.6	0.7	0 (0, 2)	0.7	0.8	1 (0, 3)	0.48
Dietician use	0.3	1.0	0 (0, 6)	0.2	0.6	0 (0, 2)	0.92
Patients work costs if they were employed during the trial							
N of missed workdays	0.2	0.7	0 (0, 4)	0.2	0.9	0 (0, 5)	0.96
N of workdays with < 50% productivity	0.4	1.6	0 (0, 10)	0.3	1.6	0 (0, 10)	0.27

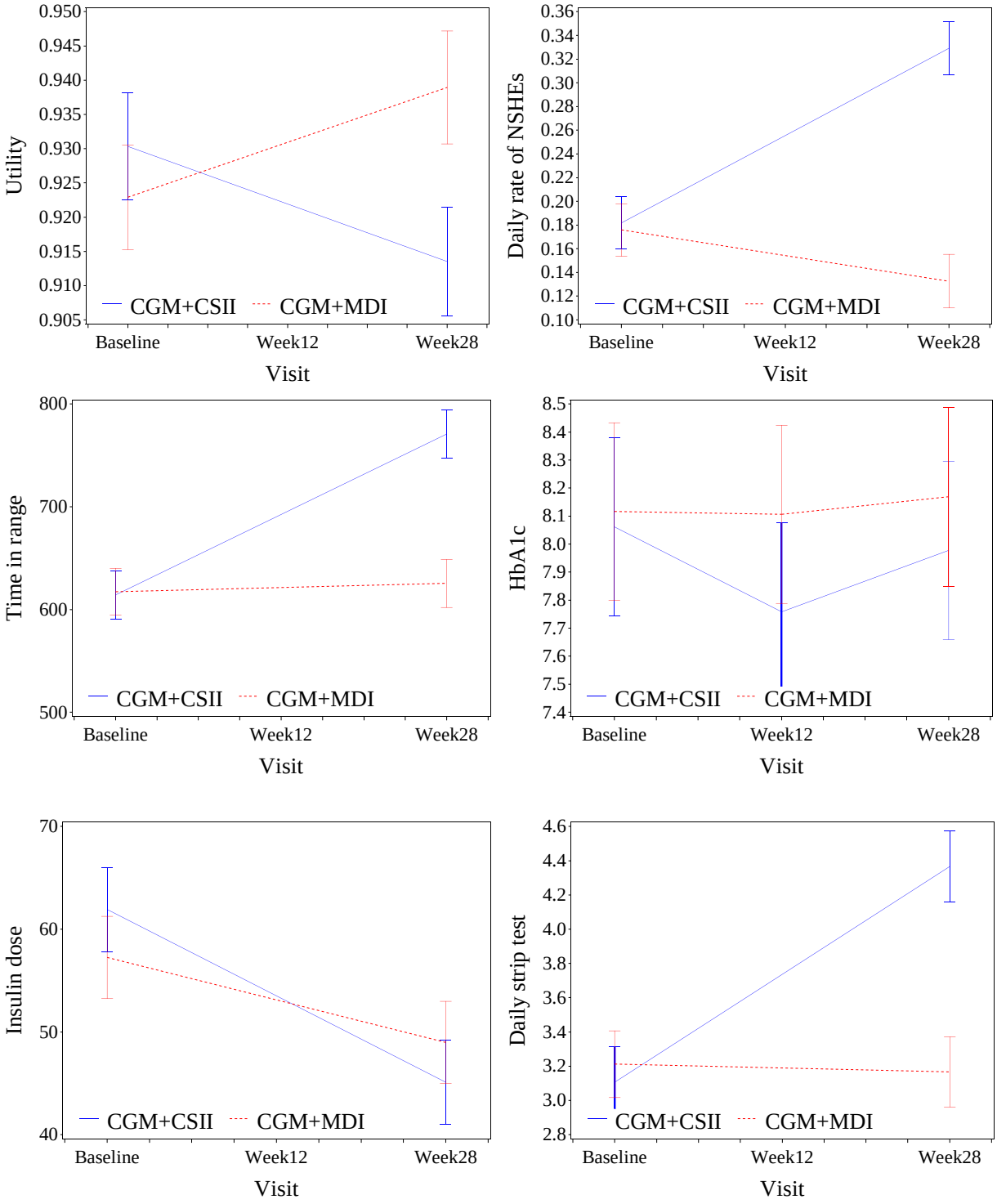
[a] Wilcoxon rank-sum test was used to compare the two groups.

Supplementary eTable 11. Comparison of within-trial means through imputed datasets

Outcomes		Mean Diff (CSII - MDI)	95% CI (CSII - MDI)	
			lower	upper
QALYs	Overall the populations (N=75)	-0.007	-0.018	0.003
	High baseline A1c subgroup (N = 43)	-0.012	-0.026	0.002
	Low baseline A1c subgroup (N= 32)	-0.001	-0.017	0.015
Utility	Overall the populations (N=75)	-0.025	-0.049	-0.001
	High baseline A1c subgroup (N = 43)	-0.035	-0.070	-0.001
	Low baseline A1c subgroup (N= 32)	-0.010	-0.039	0.020
total costs	Overall the populations (N=75)	2474	2050	2899
total costs[a]	Overall the populations (N=75)	5679	-2764	14121

a. The total costs did not include the costs from diabetes self-management, due to poor data quality.

Supplementary eFigure 1. Plots of adjusted means of the critical clinical outcomes with their standard error bars versus time in the high baseline HbA1c groups (HbA1c≥7.5%)



Supplementary eFigure 2. Plots of adjusted means of the critical clinical outcomes with their standard error bars versus time in the low baseline HbA1c groups (HbA1c<7.5%)