Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial

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Summary

Background Many patients with type 2 diabetes do not meet their glycated haemoglobin targets and randomised controlled studies comparing the efficacy of pump treatment and multiple daily injections for lowering glucose in insulin-treated patients have yielded inconclusive results. We aimed to resolve this uncertainty with a randomised controlled trial (OpT2mise).

Methods We did this multicentre, controlled trial at 36 hospitals, tertiary care centres, and referral centres in Canada, Europe, Israel, South Africa, and the USA. Patients with type 2 diabetes who had poor glycaemic control despite multiple daily injections with insulin analogues were enrolled into a 2-month dose-optimisation run-in period. After the run-in period, patients with glycated haemoglobin of 8.0–12.0% (64–108 mmol/mol) were randomly assigned (1:1) by a computer-generated randomisation sequence (block size 2 with probability 0.75 and size 4 with probability 0.25) to pump treatment or to continue with multiple daily injections. Neither patients nor investigators were masked to treatment allocation. The primary endpoint was change in mean glycated haemoglobin between baseline and end of the randomised phase for the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01182493.

Findings 495 of 590 screened patients entered the run-in phase and 331 were randomised (168 to pump treatment, 163 to multiple daily injections). Mean glycated haemoglobin at baseline was 9% (75 mmol/mol) in both groups. At 6 months, mean glycated haemoglobin had decreased by 1.1% (SD 1.2; 12 mmol/mol, SD 13) in the pump treatment group and 0.4% (SD 1.1; 4 mmol/mol, SD 12) in the multiple daily injection group, resulting in a between-group treatment difference of −0.7% (95% CI −0.9 to −0.4; −8 mmol/mol, 95% CI −10 to −4, p<0·0001). At the end of the study, the mean total daily insulin dose was 97 units (SD 56) with pump treatment versus 122 units (SD 68) for multiple daily injections (p<0·0001), with no significant difference in bodyweight change between the two groups (1.5 kg [SD 3.5] vs 1.1 kg [3.6], p=0.322). Two diabetes-related serious adverse events (hyperglycaemia or ketosis without acidosis) resulting in hospital admission occurred in the pump treatment group compared with one in the multiple daily injection group. No ketoacidosis occurred in either group and one episode of severe hypoglycaemia occurred in the multiple daily injection group.

Interpretation In patients with poorly controlled type 2 diabetes despite using multiple daily injections of insulin, pump treatment can be considered as a safe and valuable treatment option.

Funding Medtronic.

Introduction Type 2 diabetes is characterised by insulin resistance and progressive β-cell failure, which results in increasing hyperglycaemia.1 Many patients with advanced disease require treatment with insulin, and in most cases the addition of basal insulin is sufficient to achieve glycated haemoglobin targets.2 3 If these targets are not met after active dose titration of basal insulin, a multiple daily injection regimen combining a long-acting and a rapid-acting insulin in a basal-bolus fashion can be offered to patients; however, such intensified regimens do not meet glycated haemoglobin targets in about 30% of patients, and are associated with increased risks of hypoglycaemia and weight gain.4 These limitations of multiple daily injection treatment show the need for new treatments for this group of patients.

Only four randomised controlled studies have compared pump treatment and multiple daily injection treatment for lowering glycated haemoglobin in patients with type 2 diabetes. Two parallel-group studies5 6 included 132 and 107 moderately obese, insulin-using patients with a baseline glycated haemoglobin of 8.0–8.4%. The studies lasted 6 months and 12 months respectively and reported similar benefit from treatment intensification. By contrast, two randomised crossover studies7 8 showed that pump treatment was superior to multiple daily injections. Uncontrolled longitudinal studies9 10 have also shown that pump treatment can help to achieve and maintain good metabolic control.

To further assess the potential benefits of pump treatment for type 2 diabetes, we did a randomised, controlled trial (OpT2mise) to compare the efficacy and
safety of pump treatment and multiple daily injection treatment for patients with type 2 diabetes who had not responded to a basal-bolus regimen after active insulin titration.

Methods
Study design and participants
Opt2mise was a randomised, parallel-group study consisting of a run-in period, a 6-month randomised phase, and a 6-month continuation phase. 36 hospitals, tertiary care centres, and referral centres participated: eight in Canada, 23 in Europe and Israel, two in South Africa, and three in the USA. The study started in December 2010, and the final data collection date for the primary outcome measure was in February 2014. The study methods have been reported in full elsewhere.11 Only the results of the randomised phase are reported here; the results of the continuation phase will be presented separately.

We enrolled patients (age 30–75 years) with investigator-diagnosed type 2 diabetes. We excluded pregnant patients. The required daily dose of insulin at screening was 0·5–1·8 units per kg or a maximum daily dose of 220 units, and to be eligible for randomisation, the total dose required at randomisation was 0·7–1·8 units per kg or a maximum dose of 220 units. Exclusion criteria included having had two or more hypoglycaemia-related seizures or comas within the past 6 months, or significant diabetic complications. We used these criteria to target patients with type 2 diabetes with insulin resistance. Baseline assessments included laboratory testing of anti-glutamic acid decarboxylase antibodies and C-peptide, which will be reported in a separate analysis.

Before randomisation, patients underwent a 2-month run-in phase consisting of three visits, designed to achieve optimum injection treatment. During this period, insulin treatment was intensified with a standardised titration protocol to achieve preprandial and postprandial glycaemic target ranges. This titration protocol allowed for adjustments of both basal and bolus insulin (appendix). Depending on the initial insulin dose, the total dosage increase was targeted at 10–40% above baseline. Patients were treated with both long-acting analogues (glargine or detemir) and rapid-acting analogues (lispro, aspart, or glulisine). Patients were allowed to use pens during the study for the administration of either rapid-acting or long-acting analogues (lispro, aspart, or glulisine). Patients were instructed to stop all other antidiabetes drugs other than metformin.

Patients were encouraged to regularly monitor their blood glucose with a minimum of three measurements per day. Participants were excluded if they checked their glucose fewer than 2·5 times per day. We provided guidelines for assessment of blood glucose results and titrating insulin doses as appropriate, and we supplied worksheets to encourage dose titration and adherence to the protocol with guidance from the steering committee. Patients were given nutritional counselling and diabetes education throughout the run-in period.

All patients provided written informed consent. The protocol was approved by institutional ethics committees at each centre, and the study was done in accordance with ISO 14155 guidelines and applicable country regulations. An independent data and safety monitoring board monitored the study and guaranteed its safety and validity. A steering committee supervised the overall conduct of the study (appendix).

Randomisation and masking
On completing the run-in phase, patients whose glycated haemoglobin was between 8·0% and 12·0% (64 to 108 mmol/mol), who had done at least 2·5 blood glucose self-assessments per day, and had daily insulin requirements of 0·7–1·8 units per kg (maximum 220 units per day), were randomly assigned (1:1) to continue injection treatment or to receive pump treatment (Medtronic MiniMed Paradigm Veo system; Medtronic). The randomisation sequence was prepared by the study statistician with block randomisation (block size 2 with probability 0·75 and size 4 with probability 0·25) and was implemented electronically via a case report form at each study site. The randomisation scheme was applied per site and study sites were not aware of the size and number of blocks. Neither patients nor investigators were masked to treatment allocation.

Procedures
Patients assigned to pump treatment underwent training after randomisation and up to 3 weeks after the end of the run-in phase, while injection treatment with ongoing titration to target was continued in the comparator group. Pumps were initially set to deliver half of patients’ total daily dose of insulin as a continuous basal flow. Bolus dosing was left to investigators’ discretion in both treatment groups. Bolus dosing ranged from set bolus doses at meals to dosing based on insulin:carbohydrate ratios or variable scales. Both treatment groups received identical continuing scheduled support from health-care providers (ie, seven visits for both groups), with continued encouragement to self-monitor, maintain a healthy lifestyle, and titrate to target. Carbohydrate counting was not required.

Glycated haemoglobin was assessed at baseline, at the start of pump treatment, and at 3 months and 6 months after randomisation; standard clinical chemistry tests were done at baseline, at the start of pump treatment, and at 6 months. A Montreal Cognitive Assessment test11 was done during the screening visit. Further study visits were planned for each group during the study phase at 1 month, 2 months, 3 months, and 6 months after randomisation.

On completing the randomised phase, patients receiving
multiple daily injections were switched to pump treatment and follow-up was continued for a further 6 months.

Data from the pump and blood glucose meter were uploaded with Medtronic CareLink Therapy Management Software, which was used to optimise treatment. Masked continuous glucose monitoring data were obtained with Medtronic iPro2, with glucose data recorded over 6 days before randomisation and on completion of 6 months’ randomised treatment.

Endpoints
The primary endpoint was the between-group difference in change in mean glycated haemoglobin from baseline to the end of the randomised phase. Secondary endpoints included changes from baseline to 6 months of continuous glucose monitoring data, including mean 24-h glucose concentrations, the area under the curve (AUC) for hypoglycaemia (defined as sensor glucose values <3.9 mmol/L) and hyperglycaemia (sensor glucose values >10 mmol/L), and the time spent in hypoglycaemia and hyperglycaemia. Glycated haemoglobin and blood glucose measurement results were unmasked for ethical reasons because these data are commonly used in diabetes management. Continuous glucose monitoring data was a study-related measure and was masked.

Safety endpoints included the number of severe hypoglycaemic events, defined as episodes requiring assistance from another person and preferably accompanied by a confirmatory finger-prick blood glucose measurement less than 2.8 mmol/L, and the number of ketoacidosis events. The appendix shows the other endpoints.

Statistical analysis
We calculated the sample size with the standard formula for a two-sided, two-sample t test. A total sample size of 284 would provide 80% power to detect a 0.5% (6 mmol/mol) between-group difference in the mean reduction in glycated haemoglobin from baseline to 6 months at a 95% confidence level, assuming a standard deviation of 1.5% (16 mmol/mol). A failure rate of 20% was expected during screening. We adjusted the planned sample size to be a minimum of 320 participants allowing for 10% of patients to drop out during the 6 months of the study phase.

However, because of uncertainty about the magnitude of the standard deviation and the effect of treatment, we allowed for reassessment of the sample size based on an interim analysis to be done by the data and safety monitoring board after 114 patients had completed the 6-month visit. We used the O’Brien-Fleming rule with one interim look to preserve the overall two-sided type 1 error of 0.05. After this interim analysis, the data and safety monitoring board recommended no change to the sample size.

We assessed efficacy on an intention-to-treat basis, including all randomised patients. We imputed missing data with the multiple imputation method. We analysed the primary endpoint with a two-sided, two-sample t test. We calculated the final p value with East (version 5), using the method of Chen and colleagues, which incorporates a p value penalty for the interim analysis and an adaptive design to preserve the overall type 1 error. We also analysed the primary endpoint with an ANCOVA model, with study group as categorical variable and baseline glycated haemoglobin as continuous variable. We analysed the proportion of patients who reached glycated haemoglobin targets by logistic regression with adjustment for baseline glycated haemoglobin. We assessed associations between baseline factors and decreases in glycated haemoglobin by multivariate regression with only factors that were significant in univariate model evaluation (at α=0.20). We calculated AUCs as the product of the magnitude and duration of sensor-measured glucose values above or below specified cutoffs; the normalised AUC was the average glucose excursion for each sensor value (ie, AUC/total number of sensor values).

We did the analyses with SAS (version 9.3). All p values were two-sided, and we deemed those below 0.05 as statistically significant.

This study is registered with ClinicalTrials.gov, number NCT01182493.

590 patients assessed for eligibility
95 screen failure
495 entered run-in phase
164 excluded
134 ineligible
26 withdrawn
1 lost to follow-up
1 other
331 randomly assigned
168 allocated to pump treatment group
16 dropped out
11 withdrawn
3 adverse event
2 lost to follow-up
168 included in intention-to-treat analysis
161 allocated to multiple daily injection group
16 dropped out
11 withdrawn
3 adverse event
2 lost to follow-up
163 included in intention-to-treat analysis

Figure 1: Trial profile
Role of the funding source

The study was designed and sponsored by Medtronic, and amended with input from a data and safety monitoring committee. Medtronic had no role in data collection. Medtronic statisticians analysed the data according to a pre-specified analysis plan. Medtronic paid for the development and publishing of the manuscript, including writing assistance. All authors had complete access to the analysed data, participated in the drafting and reviewing of the report, and vouch for the accuracy and completeness of this report. YR, OC, IC, RA, SR, JC, and SL had final responsibility for the decision to submit for publication. Covance Central Laboratory Services was a central laboratory for the study.

Results

Between Dec 26, 2010 to May 17, 2013, 590 patients were assessed for eligibility, of whom 495 entered the 2-month run-in phase. Of these, 164 were excluded (figure 1) and 331 entered the study phase and were randomly assigned to either the pump treatment group (n=168) or the multiple daily injection group (n=163). This small imbalance is a result of the random block sizes for each centre and also by the different number of patients recruited at each centre. Centres stopped recruitment when the total enrolment number was reached. Following randomisation, 23 patients withdrew from the study, and 308 completed the study (figure 1). Participation of one centre was terminated on the advice of the data and safety monitoring board and steering committee because of repeated protocol violations.

Baseline characteristics were much the same in each group except for a higher HDL-cholesterol concentration in the multiple daily injections group (table 1). At baseline, 64 (38%) patients in the pump treatment group and 64 (39%) in the multiple daily injection group had abnormal scores on the Montreal Cognitive Assessment test, indicative of mild cognitive impairment. Both groups had a similar fall in glycated haemoglobin (figure 2) and a similar increase in total daily insulin dose (figure 3B) during the run-in period.

At baseline, mean glycated haemoglobin was 9.0% (75 mmol/mol) in both groups. At 6 months, mean glycated haemoglobin had decreased to 7.9% (63 mmol/mol) in the pump treatment group (mean change −1.1%, SD 1.8; −12 mmol/mol, SD 13), compared with 8.6% (70 mmol/mol) in the multiple daily injection group (−0.4%, SD 1.1; −4 mmol/mol, SD 12).

Table 2: Baseline characteristics
shown). The decrease in glycated haemoglobin did not differ significantly between patients treated with metformin and those who were not (appendix).

Comparison of 6-day masked continuous glucose monitoring data at baseline and 6 months showed a significantly greater decrease in 24-h mean glucose concentration in the pump treatment group (10·4 mmol/L, SD 2·0 at baseline, 9·3 mmol/L, SD 2·0 at 6 months) than in the multiple daily injection group (10·1 mmol/L, 2·0 at baseline, 9·6 mmol/L, 2·1 at 6 months) with a mean change during treatment favouring pump treatment (p=0·0062). We also recorded significant differences favouring pump treatment for the duration of hyperglycaemic events (mean difference 169 min, p=0·0007) and the AUC for hyperglycaemia change (p=0·0047; table 2).

We noted no significant difference between groups for glycaemic variability using SD (appendix). At the end of the study, the total daily dose of insulin was significantly lower in the pump treatment group than in the multiple daily injection group (mean 97 units [SD 56] vs 122 units [SD 68], p=0·0001; figure 3B). At 6 months, the mean basal daily dose in the multiple daily injection group was larger than that in the pump treatment group (61 vs 52 units per day, p=0·0159).

Data for the number of insulin bolus with pump treatment compared with multiple daily injections were not available. Furthermore, because of the nature of both treatments, we could not fully and equally assess the actual insulin dose used. The ratio of basal and bolus daily doses was similar in each group at baseline (1·2, 95% CI 1·1 to 1·4 in the pump treatment group vs 1·4, 1·0 to 1·9 in the multiple daily injection group). They were unchanged at 6 months in the multiple daily injection group (mean 1·2, SD 0·8) but increased in the pump treatment group (1·7, 1·2). Patients in the pump treatment group had access to the pump bolus calculator and it was used inconsistently, with 93 (59%) of 158 patients using it less than 25% of the time. Use of the bolus calculator was not associated with a reduction of mean glycated haemoglobin. Lipid parameters did not change significantly (appendix), with the exception of HDL-cholesterol concentration, which increased by 8% in the pump treatment group and decreased by 7% in the multiple daily injection group (p=0·01).

By the end of the run-in phase, the mean number of blood glucose tests done was 3·7 per day with no difference between the treatment groups (data not shown). Thereafter, it remained stable at 3·8 tests per day in the pump treatment group while falling to 3·1 tests per day in the multiple daily injection group during the last 3 months of the study.

Five episodes of hyperglycaemia related to device or study procedure occurred in the pump treatment group, which did not result in hospital admission. Three diabetes-related serious adverse events (hyperglycaemia or ketosis without acidosis) resulting in admission to hospital occurred (two in the pump treatment group, one in the

![Figure 2: Changes in glycated haemoglobin](http://dx.doi.org/10.1016/S0140-6736(14)61037-0)

**Figure 2:** Changes in glycated haemoglobin

Error bars are 95% CIs. MDI = multiple daily injection.

<table>
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</table>

Data in parentheses are SD. Includes patients with at least 48 h of continuous measurement. AUC = area under the curve.

**Table 2: Glycaemic control in each treatment group**
multiple daily injection group). No episodes of ketoacidosis occurred in either group during the study. One episode of severe hypoglycaemia occurred in the multiple daily injection group, in a female patient who developed confusion and had a blood glucose concentration of 1.7 mmol/L. This episode resolved on administration of oral glucose. Non-severe hypoglycaemic episodes were quantified during the 6-day masked continuous glucose monitoring periods at baseline and at the end of randomised treatment. Data for self-reported mild hypoglycaemia and hyperglycaemia were not collected, nor were data for hyperglycaemia in the multiple daily injection group. However, hypoglycaemia AUC with continuous monitoring showed no significant differences between the two groups for duration of hypoglycaemic events or change of hypoglycaemic AUC (table 2). The appendix shows adverse events related to diabetes, device, or the study. 35 device-related adverse events occurred in the pump group versus three in the multiple daily injection group (appendix). Mean bodyweight increased during the randomised phase in both groups (1.5 kg [SD 3.5] in the pump treatment group and 1.1 kg [3.6] in the multiple daily injection group), but the between-group difference was not significant (p=0.250). Weight gain did not differ significantly between metformin users and non-users (data not shown).

Discussion
In this large multinational study, we report that treatment with an insulin pump is better at reducing glycated haemoglobin than multiple daily injections in patients with type 2 diabetes. Previous studies of the efficacy of pump treatment for patients with type 2 diabetes enrolled few participants and yielded inconclusive results (panel). Only four randomised controlled studies comparing the ability of pump treatment and multiple daily injection treatment to lower blood glucose have been done. Two parallel-group studies that included patients with moderate hyperglycaemia and insulin requirements have shown that benefits from pump treatment and multiple daily injection treatment were similar for glycaemic control. By contrast, results of two small crossover studies of patients with poorly controlled type 2 diabetes (glycated haemoglobin ≥9%), who were receiving insulin at doses of at least 1 unit/kg per day with at least two injections, showed that pump treatment was more efficacious than was treatment with multiple daily injections.

In view of these findings, the results from OpT2mise suggest that selection of patients who could most benefit from pump treatment is of paramount importance. The 2-month run-in period before randomisation, the dose adjustment schedule, and the guide for applying such adjustments, enabled us to identify patients who were good potential candidates for pump treatment because their glycated haemoglobin had not improved despite optimisation of multiple daily injection treatment. In these patients, improvements of overall glucose control—as manifested by decreases in glycated haemoglobin values—was confirmed by masked continuous glucose monitoring. More importantly, this monitoring also showed clinically significant reductions in the time spent in hyperglycaemia while using pump treatment, without an increase in the time spent in hypoglycaemia.

Furthermore, the finding that roughly 38% of patients in the pump treatment group had mild cognitive impairment suggests that pump treatment can be used effectively by such patients. Among pump users, the infrequent use of the bolus calculator and its lack of association with outcome also suggests that pump treatment can be effectively implemented in patients with type 2 diabetes. Although the study was not designed to assess the incidence of non-severe hypoglycaemia, the data from continuous glucose monitoring suggest that non-severe hypoglycaemia is not increased when switching from multiple daily injection treatment to pump treatment. Similar findings have been reported in other studies that included continuous glucose monitoring with pump treatment.

The absence of severe hypoglycaemia in the pump treatment group is reassuring. In previous randomised studies, severe hypoglycaemia was rare, and findings from randomised and observational studies also suggest that severe hypoglycaemia is not significantly increased when using pump treatment for type 2 diabetes. Our finding that pump treatment was not associated with significant weight gain are consistent with previous studies of 6–12 months’ duration, which found no weight change or only 1–2 kg weight gain. By contrast with previous studies of patients with type 2 diabetes receiving multiple daily injections, patients receiving pump treatment had no glycaemic improvement with the addition of oral metformin to insulin.

Our study has several limitations. Because of the nature of the intervention, patients and investigators were aware of their individual group assignments. In addition, patients with daily insulin doses of more than 220 units were not included, and further evaluation of pump treatment might be warranted in such patients. The study did not include comparisons with new oral treatments for type 2 diabetes such as treatments SGLT2 inhibitors, other injectable drugs (eg, Glucagon-like peptide-1 receptor agonists), or concentrated basal insulin analogues that might be available soon (eg, U-200 and U-300). Finally, patients using multiple daily injections showed a decrease in their daily frequency of self-monitoring during the treatment phase, which did not occur in the pump treatment group. The difference does not appear to have led to higher insulin dosing in the pump treatment group (total daily dose fell by 20% in this group). We acknowledge that the average number of daily glucose self-monitoring tests in both groups was below the generally recommended standard of care. It may, however, be fully consistent with real-life patient
Our findings suggest that pump treatment might be considered a valuable therapeutic option for patients who are unable to reach glycated haemoglobin targets with multiple daily injection regimens. A further limitation of the study was that the actual dose of insulin could not be assessed equally in both groups because of the nature of the treatments.

There might be several reasons that pump treatment provides better glycaemic control with less insulin than does multiple daily injection treatment. The glycaemic advantage of pump treatment probably relies mainly on the basal component of insulin infusion, its better and less variable absorption from the subcutaneous tissue, and optimal flatness of insulin concentrations over 24 h compared with slow-acting insulin analogues. Apart from the more favourable pharmacokinetics and pharmacodynamics of the delivered dose, pump treatment might be more convenient for patients, lessening the burden associated with dose tracking and scheduling, and improving adherence to insulin injections. The relative contributions of these factors as well as other unknown factors should be assessed with an appropriate study design. Our findings suggest that pump treatment might be considered a valuable therapeutic option.

Panels

Panel: Research in context

Systematic review

We searched PubMed for reports published in English between Jan 1, 2000, and Sept 1, 2013. We used various combinations of the terms “type 2 diabetes”, “pump”, “insulin pump therapy”, “continuous subcutaneous insulin infusion”, and “multiple daily injection therapy”. We identified three observational studies and four randomised controlled trials. Two of these trials were parallel-group studies and showed that continuous subcutaneous insulin infusion and multiple daily injection both reduced glycated haemoglobin to a similar degree. By contrast, two randomised crossover studies have shown that continuous subcutaneous insulin infusion is superior to multiple daily injection. No conclusive findings can be drawn from these few studies. The crossover studies had small sample sizes and the parallel-group studies included populations that had not been adequately optimised on multiple daily injection regimens before randomisation. To date, no intervention study has included a large and homogeneous sample of patients with type 2 diabetes failing to respond to intensive multiple daily injection by a basal-bolus regimen to evaluate an advantage of continuous subcutaneous insulin infusion over multiple daily injection.

Interpretation

We report results from a randomised controlled trial of a large sample of patients with type 2 diabetes who had not responded to a basal-bolus regimen after active insulin analogue titration. Pump treatment significantly improved glycaemic control compared with multiple daily injection. Our findings suggest that pump treatment might be considered a valuable therapeutic option for patients who are unable to reach glycated haemoglobin targets with multiple daily injection regimens.

Contributors

SWL, SR, and JC had the idea for the trial, designed the trial, and obtained research funding. JC provided statistical advice on trial design and drafted the analysis plan. All authors are members of the steering committee. YR, OC, IC, RA collected data. Covance did the laboratory testing of all blood samples. All authors contributed to the acquisition and review of the data. JC analysed the data. All authors contributed to the interpretation of data and the drafting of the report. They critically revised the report for important intellectual content and approved the version to be published.

Declaration of interests

YR has done clinical trials as a co-investigator for Medtronic, Eli-Lilly, and Novo Nordisk. He has also provided advisory services to Medtronic, Abbott, and Eli-Lilly and attended conferences organised by Eli-Lilly and Medtronic as contributor. He has also received investigator’s fees in relation to OpT2mise. IC has received lecturing and consulting fees from Medtronic, Bayer AG, GlaxoSmithKline, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Novartis, and Merck Sharp-Dohme. He has also received investigator’s fees in relation to OpT2mise. RA has received speaker and consulting fees from Eli Lilly, Novo Nordisk, Sanofi, and Medtronic. He has also received investigator’s fees in relation to OpT2mise. OC has done clinical trials as co-investigator for Medtronic, Eli Lilly, Novo Nordisk, and Sanofi-Aventis and provided advisory services and lectures to Medtronic, Eli Lilly, and Sanofi-Aventis. He has also received investigator’s fees in relation to OpT2mise. SR, JC, and SWL are full time employees of Medtronic.

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References


