Diabetes, Obesity and Metabolism 18: 500–507, 2016.

ORIGINAL ARTICLE

Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpT2mise randomized trial

R. Aronson[1,†], Y. Reznik[2,†], I. Conget[3], J. A. Castañeda[4], S. Runzis[5], S. W. Lee[6], O. Cohen[7] & for the OpT2mise Study Group

[1] *LMC Diabetes and Endocrinology, Toronto, ON, Canada*
[2] *Department of Endocrinology, University of Caen Côte de Nacre Regional Hospital Center, Caen, France*
[3] *Diabetes Unit, Endocrinology and Nutrition Department, University Hospital Clinic, Barcelona, Spain*
[4] *Medtronic Bakken Research Center, Maastricht, The Netherlands*
[5] *Medtronic International Trading Sàrl, Tolochenaz, Switzerland*
[6] *Medtronic Diabetes, Northridge, CA, USA*
[7] *Institute of Endocrinology, Chaim Sheba Medical Center, Tel Hashomer, Israel*

Aims: To compare insulin pump therapy and multiple daily injections (MDI) in patients with type 2 diabetes receiving basal and prandial insulin analogues.
Methods: After a 2-month dose-optimization period, 331 patients with glycated haemoglobin (HbA1c) levels ≥8.0% and ≤12% were randomized to pump therapy or continued MDI for 6 months [randomization phase (RP)]. The MDI group was subsequently switched to pump therapy during a 6-month continuation phase (CP). The primary endpoint was the between-group difference in change in mean HbA1c from baseline to the end of the RP.
Results: The mean HbA1c at baseline was 9% in both groups. At the end of the RP, the reduction in HbA1c was significantly greater with pump therapy than with MDI (−1.1 ± 1.2% vs −0.4 ± 1.1%; $p < 0.001$). The pump therapy group maintained this improvement to 12 months while the MDI group, which was switched to pump therapy, showed a 0.8% reduction: the final HbA1c level was identical in both arms. In the RP, total daily insulin dose (TDD) was 20.4% lower with pump therapy than with MDI and remained stable in the CP. The MDI–pump group showed a 19% decline in TDD, such that by 12 months TDD was equivalent in both groups. There were no differences in weight gain or ketoacidosis between groups. In the CP, one patient in each group experienced severe hypoglycaemia.
Conclusions: Pump therapy has a sustained durable effect on glycaemic control in uncontrolled type 2 diabetes.
Keywords: continuous subcutaneous insulin infusion, insulin pump, multiple daily injections, type 2 diabetes

Date submitted 23 October 2015; date of first decision 20 November 2015; date of final acceptance 8 February 2016

Introduction

Early initiation of basal insulin, with or without oral antidiabetic therapies, is becoming increasingly common in patients with type 2 diabetes. Approximately 40% of patients require further intensification [1], but even a basal-bolus regimen providing rapid-acting insulin at meals, responsibly titrated, will only achieve glycated haemoglobin (HbA1c) targets in approximately half of these patients, and incurs associated risks of hypoglycaemia and weight gain [2].

The option of insulin pump therapy in type 2 diabetes has been previously explored in case series [3,4], which suggested possible stable long-term improvements in glycaemia and lower insulin dose requirements, and an acceptable safety profile. Randomized controlled trials have followed, with inconclusive findings. While two small but well-designed crossover studies [5,6] resulted in gains in glycaemic control with pump therapy versus multiple daily injections (MDI) with basal and prandial insulin, three parallel-group studies found equal improvements in HbA1c both in subjects assigned to pump therapy and those continuing MDI [7–9].

The OpT2mise trial (ClinicalTrials.gov number: NCT01182493) was designed to evaluate the efficacy and safety of pump therapy in type 2 diabetes by comparing pump therapy and MDI therapy in patients with diabetes who were already receiving basal and prandial therapy with insulin analogues, and who remained uncontrolled despite a period of insulin dose optimization [10]. Results of the initial 6-month randomization phase (RP) showed significant improvement in HbA1c with pump therapy compared with MDI, and a 20% reduction in total daily insulin dose (TDD) in the pump therapy group [11,12]. In the present paper, we report the results of the full 12-month study period, including the continuation phase (CP), during which pump therapy was provided to all

Correspondence to: R. Aronson, LMC Diabetes and Endocrinology, Suite 106, 1929 Bayview Avenue, Toronto, ON, M4G 3E8, Canada.
E-mail: ronnie.aronson@lmc.ca

[†] R. A. and Y. R. contributed equally to this manuscript.

enrolled patients, which show the sustained and durable nature of these improvements in glycaemic control.

Materials and Methods

Study Design

The OpT2mise study was an international, multicentre, randomized, parallel-group study consisting of a run-in period, a 6-month RP and a 6-month CP.

Initially, patients (aged 30–75 years) were enrolled if they had type 2 diabetes, used at least three daily injections of long-acting and rapid-acting insulin analogues (0.5–1.8 U/kg, maximum daily dose 220 U) for ≥3 months, and had HbA1c levels ≥8.0% and ≤12.0%. After an 8-week optimization phase using a standardized titration protocol, patients with persistently uncontrolled diabetes (HbA1c ≥8.0%), using at least 0.7 U/kg of insulin, and who had performed at least 2.5 blood glucose self-assessments per day, were randomized to continue injection therapy or to receive pump therapy (Medtronic MiniMed Paradigm Veo system; Medtronic, Inc).

At pump initiation, the TDD was kept constant and split evenly between basal and prandial dosing. The approach to bolus dosing included set meal doses, dosing based on insulin:carbohydrate ratios, or variable scales, at the discretion of the investigators. Thereafter, pump therapy management, including basal and bolus dose changes, was largely at investigators' discretion. Patients initiating pump therapy typically received pump training over two visits, within the first 2 weeks of pump initiation. Both groups otherwise had similar contact with their healthcare providers, and maintained efforts at lifestyle and dietary management, but carbohydrate counting was not required. After the RP, patients receiving injection therapy were switched to pump therapy and both groups were followed up during the 6-month CP, making a total study period of 12 months.

Data from the pump and blood glucose meter were uploaded using Medtronic CareLink Therapy Management Software, which was used for treatment optimization. Patient assessments, including the Diabetes Treatment Satisfaction Questionnaire [13] and blinded continuous glucose monitoring data (obtained using the Medtronic *i*Pro2), were performed at baseline, 6 and 12 months.

Endpoints

The primary endpoint (previously reported) was the between-group difference in change in mean HbA1c from baseline to 6 months (end of the RP) [11]. Secondary endpoints included between-group difference in mean HbA1c only at 12 months (end of the CP), as well as in lipids, blood pressure and continuous glucose monitoring variables, including mean 24-h glucose levels, 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 time spent with hypoglycaemia and hyperglycaemia. Secondary endpoints also included within-group changes in HbA1c and continuous glucose monitoring variables from baseline to 12 months in the pump–pump arm, and from 6 to 12 months in the MDI–pump arm. Safety endpoints included the numbers of hospitalizations, ketoacidosis episodes and severe hypoglycaemic events (defined as events requiring third party assistance). HbA1c was analysed using a Diabetes Control and Complications Trial-standard assay at Covance Central Laboratory.

Study Oversight

The study was sponsored by Medtronic International Trading Sàrl, Tolochenaz, Switzerland. The protocol was approved by institutional ethics committees at each centre, and the study was performed in accordance with ISO 14155 guidelines and applicable country regulations. Medtronic representatives, with study investigators, performed the data collection and analysis. An independent Data Safety Monitoring Board monitored the study and guaranteed its safety and validity. A steering committee supervised the overall conduct of the study.

Statistical Methods

The statistical analyses have been described in detail elsewhere [11]. Efficacy analyses of the primary endpoint were performed on an intention-to-treat basis, including all randomized patients. Missing data were imputed using the multiple imputation method [14]. Given the descriptive nature of the CP of the protocol, available data from this period were analysed without imputation of missing values.

Analyses of secondary endpoints accounted for the fact that at the month 12 study visit, the duration of pump therapy differed between the two groups. In order to assess the effects of long-term (12 months) pump therapy in the pump–pump arm, the mean change from baseline (at the beginning of the RP) to 12 months was tested using a *t*-test. A *t*-test was also used to assess the short-term pump therapy effect in the MDI–pump arm (6 months from end of RP to the end of CP). Median, interquartile range and the Wilcoxon signed-rank test were used in cases of skewed data.

Secondary endpoints comparing the 12-month outcomes in both arms were assessed with *t*-tests for two independent samples. All reported p values are two-sided, and p values < 0.05 were taken to indicate statistical significance. Analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). The final adjusted p value for the primary endpoint was calculated using East software, version 5.4 (Cytel, Cambridge, MA, USA).

Results

Study Recruitment and Baseline Characteristics

As previously reported [10–12], between December 2010 and May 2013, 590 patients were assessed for eligibility, of whom 495 entered the 8-week run-in phase. At randomization, 331 were assigned to either pump therapy (n = 168) or the control group which continued using MDI (n = 163). In all, 308 patients completed the RP. Of the 152 patients in the pump therapy group who completed the RP (pump–pump arm), 146 completed the CP. Of the 156 patients initially assigned to MDI

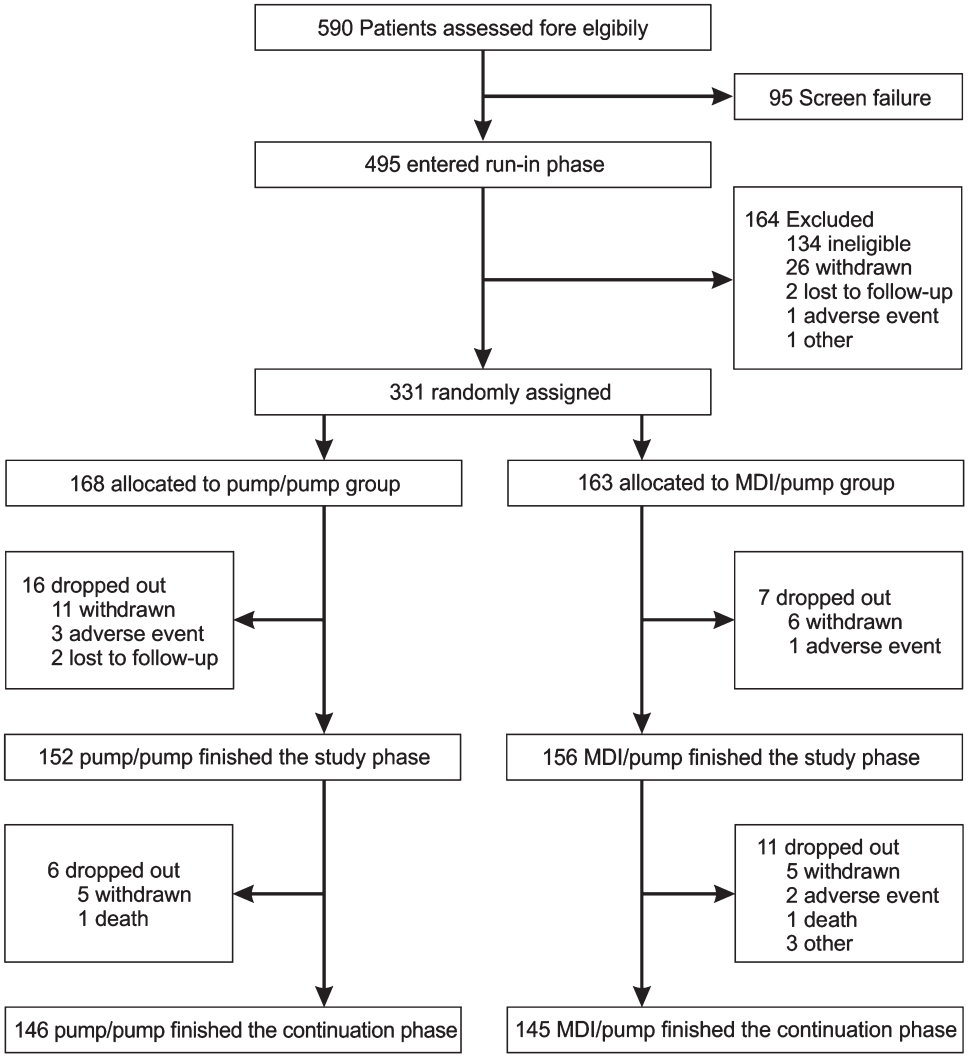

Figure 1. Enrolment, randomization and inclusion in the randomization phase and the continuation phase. MDI, multiple daily injections.

therapy who completed the RP, 145 were switched to pump therapy and completed the CP (MDI–pump arm; Figure 1). Table 1 shows the baseline characteristics of the randomized patients.

The mean baseline HbA1c level was 9.0% in both groups, and at 6 months (end of the RP), this had improved to 8.6% in the MDI group (−0.4 ± 1.1% reduction) and 7.9% in the pump group (−1.1 ± 1.2% reduction); the between-group difference in favour of pump therapy was −0.7% [95% confidence interval (CI) −0.9 to −0.4, adjusted (16) $p < 0.001$). At the 12-month visit occurring at the end of the CP, the pump–pump group had a HbA1c level of 7.8%, maintaining the improvement achieved at the end of the RP (change from baseline to 12 months = −1.2 ± 1.14%; $p < 0.0001$). After the switch to pump therapy in the CP, the MDI–pump group showed a significant reduction in HbA1c of −0.8 ± 1.2% ($p < 0.0001$), to reach an identical final HbA1c level of 7.8% (Figure 2A).

At 6 months, as previously reported [11], the proportion of responders (defined as patients reaching HbA1c ≤8%) was 55% in the pump therapy group and 28% in the injection group (odds ratio 1.9; 95% CI 1.5–2.5). At 12 months, the response rate was similar in both groups, at 57.2% in the pump–pump group and 56.9% in the MDI–pump group. Both groups achieved similar success at each target HbA1c level defined (Figure 2B).

Secondary Endpoints

As a result of additional measures undertaken to preserve continuous glucose monitoring data blinding, the completion rates were consistently low (41.7% overall) across both arms, individual sites and geographic regions. At 12 months, the 24-h mean glucose level decreased by 12.5% ($p = 0.0009$) in the pump–pump group [baseline = 10.4 (2.04) mmol/l, median (25th quartile, 75th quartile) 10.3 (9.2, 11.5) mmol/l and 12-month change = −1.3 (2.96), median (25th quartile, 75th quartile) −1.1 (−2.6, 0.7) mmol/l)] and by 8.9% ($p = 0.0021$) in the MDI–pump group [baseline = 10.1 (1.97), median (25th quartile, 75th quartile) 9.9 (8.7, 11.2) mmol/l and 12-month change = −0.9 (2.28), median (25th quartile, 75th quartile) 1.0

Table 1. Baseline demographic characteristics of randomized patients.

	Pump therapy N = 168	MDI therapy N = 163
Age, years	55.5 (9.70)	56.4 (9.50)
Gender: Men/Women, n (%)	94 (56.0)/74 (44.0)	86 (52.8)/77 (47.2)
Ethnic origin, n (%)		
White	162 (96.4)	156 (95.7)
Black	6 (3.6)	7 (4.3)
Duration of diabetes, years	14.9 (7.99)	15.3 (7.96)
HbA1c, %	9.0 (0.75)	9.0 (0.76)
Weight, kg	97.3 (22.60)	94.9 (22.04)
Body mass index, kg/m^2	33.5 (7.50)	33.2 (6.99)
Systolic blood pressure, mm Hg	132.3 (15.17)	131.9 (14.82)
Diastolic blood pressure, mm Hg	75.6 (9.38)	76.0 (10.55)
Total cholesterol, mmol/l	4.5 (1.40)	4.4 (1.03)
HDL cholesterol, mmol/l	1.2 (0.35)	1.4 (0.44)*
LDL cholesterol, mmol/l	2.2 (0.81)	2.2 (0.76)
Triglycerides, mmol/l	2.3 (2.41)	1.9 (1.60)
Smokers, n (%)	24 (14.3)	25 (15.3)
Metformin use, n (%)	120 (71.4)	112 (68.7)
Metformin dose, mg	1810 (679.8)	1788 (636.1)
Total daily insulin dose, U/kg/day	1.1 (0.4)	1.1 (0.4)
Total daily insulin dose, U/day	112.3 (53.9)	106.2 (49.2)
Total long-acting insulin dose, U/day	57.4 (30.3)	52.4 (27.7)
Total rapid-acting insulin dose, U/day	55.6 (31.7)	53.8 (30.8)
History of diabetic complications and comorbidities, n (%)		
Dyslipidaemia	26 (15.5)	16 (9.8)
Cardiac-related diseases	142 (84.5)	137 (84.0)
Peripheral vascular disease	12 (7.1)	7 (4.3)
Retinopathy	6 (3.6)	3 (1.8)
Diabetic nephropathy	22 (13.1)	12 (7.4)
Peripheral neuropathy	0 (0.0)	0 (0.0)

Results are presented as mean (standard deviation), unless otherwise indicated. HbA1c, glycated haemoglobin; MDI, multiple daily injection.
*$p < 0.01$.

(−2.0, 0.7) mmol/l]; this difference was not statistically significant (P = 0.34). Similarly, the AUCs for hyperglycaemia (>10 mmol/l) were significantly decreased [pump–pump group 39.1% (p = 0.0078); MDI–pump group 36.2% (p = 0.002)] and similar in both groups (p = 0.86). The AUC for hypoglycaemia (<3.9 mmol/l) was very low and did not differ between the two treatment groups (p = 0.054) and there was no significant change in either arm (pump–pump arm, p = 0.06; MDI–pump arm, p = 0.19).

At 12 months, the pump–pump group TDD was 98.3 ± 57.9 U (0.95 ± 0.44 U/kg), maintaining the reduction observed during the RP (Figure 3). The MDI–pump group showed a 19% decline in TDD after initiation of pump therapy (total decline from baseline: 0.11 ± 0.33 U/kg; $P < 0.0001$). Both groups showed similar TDD; a similar number of bolus injections (pump–pump 3.5 ± 1.5 and MDI–pump 3.4 ± 1.1 injections/day); and a similar frequency of self-monitoring of blood glucose at 12 months (3.6 ± 1.3 vs 3.4 ± 1.3; p = 0.34).

The ratio of basal and bolus daily dose was similar in both groups at baseline, and increased significantly in each group after pump therapy. The basal:bolus ratio in the pump–pump therapy group was 51 : 49% at baseline and 56 : 44% at 6 months; by 12 months, it had increased to 58 : 42%. Similarly, the MDI–pump group showed a basal:bolus ratio of 50 : 50% at baseline and 51 : 49% at 6 months, but the 12-month ratio, after pump use, was higher at 57 : 43%. The change in ratio in both cases was related to a reduction in the daily bolus dose, with no significant change in the daily basal dose requirement. Bolus dose declined by 10.8 ± 26.7 U in the pump–pump group after 12 months of pump therapy, and by 14.5 ± 22.7 U from month 6 to month 12 in the MDI–pump group. Patients in the pump therapy group had access to the pump bolus wizard, but used it inconsistently, with 58% of patients using it <25% of the time. Use of the bolus calculator was not itself associated with reductions in mean HbA1c level.

Blood pressure and lipid variables did not change significantly during the study. At 12 months, no significant differences were seen in any of the lipid variables.

No episodes of ketoacidosis occurred in either group during the study. During the RP, one episode of severe hypoglycaemia occurred in the MDI group. In the CP, one episode of severe hypoglycaemia occurred in the pump–pump group, and two occurred in the same patient in the MDI–pump group after transition to pump therapy.

Tolerability

Diabetes-, device- or study-related adverse events are listed in Tables S1 and S2, Supporting Information. Weight gain

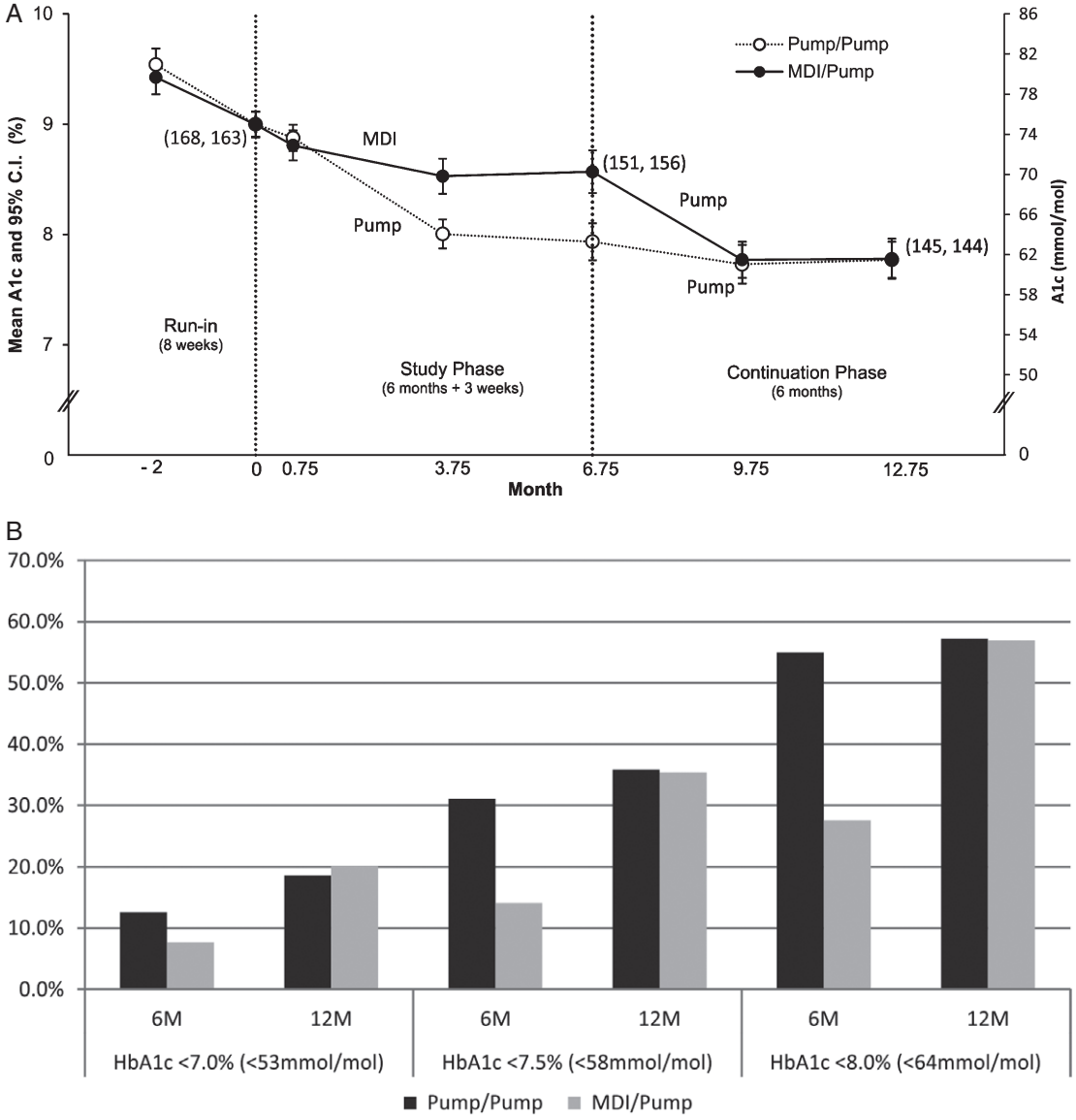

Figure 2. (A) Mean glycated haemoglobin (HbA1c) levels and 95% confidence intervals at baseline, randomization and 1, 3, 6, 9 and 12 months in both treatment groups. (B) Responder analysis: proportion reaching HbA1c targets at 6 and 12 months (numbers in brackets are n for pump–pump group and n for multiple daily injection (MDI)–pump group, respectively). CI, confidence interval.

was observed at the end of the CP but did not differ significantly between the two groups (2.1 ± 5.2 and 2.3 ± 4.9 kg, pump–pump and MDI–pump groups, respectively).

Discussion

The results of the full treatment period of OpT2mise show that pump therapy provides sustained glycaemic control, as manifested by decreases in HbA1c and insulin dosage, in patients with type 2 diabetes. In the patients who had initially been assigned to pump therapy, the attained benefit in HbA1c was stable and persistent over a further 6 months. Moreover, patients initially assigned to continue MDI therapy were subsequently able to achieve similar improvements in HbA1c after crossover to pump therapy, confirming the original finding of improved HbA1c with pump therapy. Furthermore, the magnitude of the HbA1c improvement observed in the group who switched from MDI to pump therapy (0.8%) was very similar to the 0.7% benefit observed during the RP in the group initially assigned to pump therapy. This observed benefit of glucose control in the group who switched from MDI to pump therapy occurred, despite the fact that patients received intensive support, counselling and dose adjustment guidance for 6 months beyond the initial 2-month optimization run-in period. Potential explanations of the improvements in glycaemic control achieved with pump therapy include a more physiological method of delivery, improved absorption of smaller subcutaneous insulin depots with continuous insulin infusion, prevention of the hyperglycaemia of the dawn phenomenon, and improved adherence to insulin dosing. The

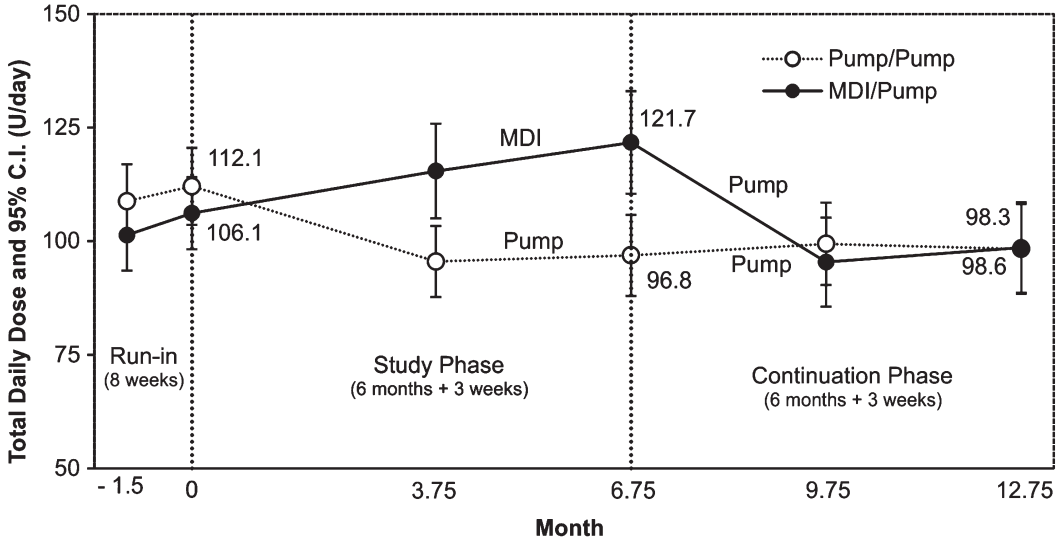

Figure 3. Daily insulin doses at baseline, randomization and 1, 3, 6, 9 and 12 months in both treatment groups. CI, confidence interval; MDI, multiple daily injections.

finding that gains of similar magnitude were seen even after an extended 8-month period of well-supported MDI therapy intensification, however, suggests that the improved glycaemic control is not solely attributable to better adherence.

The demonstration in a randomized controlled trial of the durability of the glycaemic control obtained with pump therapy should be emphasized. Earlier randomized controlled trials were too brief to offer insights into durability of response, although observational studies have consistently shown a durable response lasting up to 1 year and more. Three large French observational surveys of patients with poorly controlled type 2 diabetes each showed a significant improvement in HbA1c (1.2–1.7%), which was subsequently maintained during long-term follow-up [3,15,16]. The OpT2mise study complements and extends these findings by showing the sustained superiority of pump therapy over MDI treatment in a similar patient population.

Previous randomized controlled studies of pump therapy, with similar parallel-group designs, performed in small samples of patients with type 2 diabetes, found significant benefits in terms of reduction in HbA1c levels, but both pump therapy and intensification of MDI therapy produced similar effects over 6 or 12 months [7–9]. These studies included patients at different stages of diabetes, who were using a range of diabetes therapies, including basal insulin therapy alone or with oral antidiabetic agents. Moreover, these studies did not require the use of analogue insulins, nor did they include a run-in period dedicated to the active titration of MDI dosing. In contrast, the OpT2mise trial has shown that the most appropriate potential candidates for pump therapy were patients who had already been using established MDI therapy and remained far from achieving target glycaemic control, despite intensive dose titration of both long-acting and rapid-acting insulin analogues. The study has therefore provided useful information to inform treatment decisions when considering pump therapy for patients with type 2 diabetes.

Pump therapy is generally perceived as requiring a high level of technical skill and learning aptitude on the part of the patient; however, the present trial shows that pump therapy in type 2 diabetes can be successful without requiring use of a bolus calculator and without the need for carbohydrate ratio determination at each meal. Reduction of SMBG frequency was observed in both treatment arms but did not limit the efficacy of pump therapy.

Hypoglycaemia and anticipated weight gain are also generally perceived as barriers to pump therapy in type 2 diabetes. In the present study, the AUC for hypoglycaemia was low and severe hypoglycaemia was very infrequent, a reassuring finding that is consistent with previous reports [17,18]. Similar findings have been reported in previous studies that included continuous glucose monitoring with pump therapy [5,6]. In pump therapy studies, weight gain has been repeatedly shown to be neutral [8,11,19] or minimal (1–2 kg) [5,6,20].

Improvements in HbA1c were achieved in both groups, with significant declines in daily insulin requirements and constant or modestly declining frequency of self-monitoring. Reduced insulin dose requirements after pump initiation have been seen in a previous controlled trial [6] and in observational studies investigating the impact of pump therapy in very insulin-resistant patients [21–23]. The OpT2mise protocol also required the cessation of oral antidiabetic therapies (except metformin) that patients may have been using up to the time of screening: this requirement did not preclude improvements in glycaemic control. Each of these factors – better glycaemic control, reduced insulin dosing, and possibly reduced glucose testing strip costs – may potentially contribute to a favourable cost-effectiveness ratio, and this should be investigated further. Two retrospective studies of patients with type 2 diabetes moving to pump therapy within US managed-care organizations have identified cost savings through a 46% decrease in use of oral antidiabetic therapies and reduced emergency department visits and hospitalizations [24,25].

The present study has several limitations. Investigator blinding was not possible because of the nature of the interventions. Furthermore, although we intentionally targeted a group of insulin-resistant patients, the TDD ceiling of 220 U limited our ability to generalize the applicability of pump therapy to users of higher doses. Continuous glucose monitoring data were only available for a smaller portion of the total cohort; although the continuous glucose monitoring cohort did not differ from the total cohort in key baseline and key outcome criteria, the limited completion rate may have introduced selection or other biases which preclude extrapolation of the present data to the entire cohort. Finally, insulin dose was more readily assessed via pump downloads in the pump therapy group, whereas it may have been overestimated in the MDI group because of omitted injections.

In conclusion, the full 12-month findings of the OpT2mise study indicate that the improvement in glycaemic control observed after 6 months of pump therapy is maintained over 1 year, emphasizing the sustained and durable nature of the improvement in glycaemic control afforded by pump therapy [3,15,16]. Patients with refractory hyperglycaemia on a current basal-prandial injection regimen should be considered appropriate candidates for pump therapy, and may obtain sustained glycaemic control with a favourable safety profile and reduction of insulin dose.

Acknowledgements

We thank the OpT2mise study team at Medtronic for their support in this study, and the monitors, investigators, study coordinators and patients for having conducted this trial. We also thank John Shin and Severine Liabat, employees of Medtronic, for their assistance throughout the conduct of the study. Editorial assistance in the preparation of this paper, funded by Medtronic, was provided by Dr Michael Shaw (MScript Ltd, Hove, UK).

Conflict of Interest

Y. R. reports carrying out clinical trials as co-investigator for Medtronic, Eli Lilly and Novo Nordisk, providing advisory services to Medtronic, Abbott and Eli Lilly, attending conferences organized by Eli Lilly and Medtronic as a contributor, and receiving investigator's fees in relation to the OpT2mise protocol. I. C. reports receiving lecturing and consulting fees from Medtronic, Bayer, GSK, Eli Lilly, Novo Nordisk, Sanofi-Aventis, Novartis and MSD, and receiving investigator's fees in relation to the OpT2mise protocol. R. A. reports receiving speaker and consulting fees from Eli Lilly, Novo Nordisk, Sanofi, Becton Dickenson and Medtronic, and receiving investigator's fees in relation to the OpT2mise protocol. O. C. reports carrying out clinical trials as co-investigator for Medtronic, Eli Lilly, Novo Nordisk and Sanofi, providing advisory services and lectures to Medtronic, Eli Lilly and Sanofi, and receiving investigator's fees in relation to the OpT2mise protocol. S. R., J. C. and S. L. are full-time Medtronic employees.

Y. R., S. L., S. R. and J. C. conceived the trial. S. L., S. R. and J. C. designed the trial and obtained research funding. J. C. provided statistical advice on trial design and drafted the analysis plan. A steering committee was organized to provide guidance on the conduct of the study. All authors were members of the steering committee. Y. R., O. C., I. C. and R. A. contributed to data collection, as part of the OpT2mise study group. A Data Safety Monitoring Board reviewed the study performance, with the aim of protecting the safety of trial participants, the credibility of the study and the validity of study results. Covance carried out the laboratory testing of all blood samples. All authors contributed to the acquisition and review of the data. J. C. analysed the data. All authors contributed to the interpretation of data and the drafting of this report and approved the version to be published. R. A. and Y. R. had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. OpT2mise Steering Committee and Study Group, and role of the sponsor.

Appendix Table S1. Diabetes-, device- or study-related adverse events reported by subjects.

Appendix Table S2. Continued diabetes-, device- or study-related serious adverse events reported by subjects.

References

1. Riddle MC, Rosenstock J, Gerich J et al. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; **26**: 3080–3086.
2. Riddle M, Rosenstock J, Vlajnic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab 2014; **16**: 396–402.
3. Reznik Y, Morera J, Rod A et al. Efficacy of continuous subcutaneous insulin infusion in type 2 diabetes mellitus: a survey on a cohort of 102 patients with prolonged follow-up. Diabetes Technol Ther 2010; **12**: 931–936.
4. Kesavadev J, Balakrishnan S, Ahammed S, Jothydev S. Reduction of glycosylated hemoglobin following 6 months of continuous subcutaneous insulin infusion in an Indian population with type 2 diabetes. Diabetes Technol Ther 2009; **11**: 517–521.
5. Berthe E, Lireux B, Coffin C et al. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm Metab Res 2007; **39**: 224–229.
6. Wainstein J, Metzger M, Boaz M et al. Insulin pump therapy versusversus multiple daily injections in obese type 2 diabetic patients. Diabet Med 2005; **22**: 1037–1046.
7. Herman WH, Ilag LL, Johnson SL et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005; **28**: 1568–1573.
8. Raskin P, Bode BW, Marks JB et al. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. Diabetes Care 2003; **26**: 2598–2603.
9. Gao GQ, Heng XY, Wang YL et al. Comparison of continuous subcutaneous insulin infusion and insulin glargine-based multiple daily insulin aspart injections with preferential adjustment of basal insulin in patients with type 2 diabetes. Exp Ther Med 2014; **8**: 1191–1196.

10. Aronson R, Cohen O, Conget I et al. OpT2mise: a randomized controlled trial to compare insulin pump therapy with multiple daily Injections in the treatment of type 2 diabetes. Diabetes Technol Ther 2014; **16**: 414–420.
11. Reznik Y, Cohen O, Aronson R et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet 2014; **384**: 1265–1272.
12. Conget I, Castaneda J, Petroversuski G et al. The impact of insulin pump therapy on glycemic profiles in patients with type 2 diabetes: data from the OpT2mise study. Diabetes Technol Ther 2015; **17**: 1–7.
13. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: DTSQ. In: Bradley C, ed. Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice. Chur: Harwood Academic Publishers, 1994; 111–133.
14. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons, 1987.
15. Charras L, Sanz C, Labrousse-Lhermine F, Cazals L, Hanaire H. Traitement par pompe à insuline dans le diabète de type 2 (DT2): 12 ans de suivi d'une cohorte de 50 patients (Abstract). Diabetes Metab 2012; **38**: A11 [in French].
16. Courrèges JP, Donnet JP, Gouet D et al. Résultats métaboliques obtenus à 2 ans sous pompe à insuline ambulatoire chez des diabétiques de type 2 en échec d'insulinothérapie optimisée (Abstract). Diabetes Metab 2012; **38**: A98 [in French].
17. Pouwels MJ, Tack CJ, Hermust AR, Lutterman JA. Treatment with intravenous insulin followed by continuous subcutaneous insulin infusion improves glycaemic control in severely resistant type 2 diabetic patients. Diabet Med 2003; **20**: 76–79.
18. Wulffelé MG, Kooy A, Lehert P et al. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 2002; **12**: 2133–2140.
19. Reznik Y, Cohen O. Insulin pump for type 2 diabetes: use and misuse of continuous subcutaneous insulin infusion in type 2 diabetes. Diabetes Care 2013; **36**: S219–S225.
20. Kooy A, de Jager J, Lehert P et al. Long- term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009; **169**: 616–625.
21. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolterman OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985; **34**: 222–234.
22. Gormley MJ, Hadden DR, Woods R, Sheridan B, Andrews WJ. One month's insulin treatment of type II diabetes: the early and medium-term effects following insulin withdrawal. Metabolism 1986; **35**: 1029–1036.
23. Andrews WJ, Vasquez B, Nagulesparan M et al. Insulin therapy in obese, noninsulin-dependent diabetes induces improvements in insulin action and secretion that are maintained for two weeks after insulin withdrawal. Diabetes 1984; **33**: 634–642.
24. Lynch PM, Riedel AA, Samant N et al. Resource utilization with insulin pump therapy for type 2 diabetes mellitus. Am J Manag Care 2010; **16**: 892–896.
25. David G, Shafiroff J, Saulnier A, Gunnarsson C. Multiple daily injection (MDI) therapy versus durable insulin pump therapy in type 2 diabetics: a break-even analysis (Abstract). Value Health 2012; **15**: A65.
26. Nasreddine ZS, Phillips NA, Bédirian V et al. The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; **53**: 695–699.
27. Chen YH, DeMets DL, Lan KK. Increasing the sample size when the unblinded interim result is promising. Stat Med 2004; **23**: 1023–1038.
28. Edelman SV, Bode BW, Bailey TS et al. Insulin pump therapy in patients with type 2 diabetes safely improved glycemic control using a simple insulin dosing regimen. Diabetes Technol Ther 2010; **12**: 627–633.
29. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: hypoglycaemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab 2009; **94**: 729–740.