CHAPTER 5

# Intraperitoneal insulin infusion is non-inferior to subcutaneous insulin infusion in the treatment of type 1 diabetes: a prospective mached-control study

SUBMITTED AS

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# Abstract


### INTRODUCTION

Continuous intraperitoneal insulin infusion (CIPII) using an implantable pump is a last-resort treatment option for patients with type 1 diabetes mellitus (T1DM) who fail to reach glycaemic control with intensified subcutaneous (SC) insulin regimens. Aim of this study was to compare the effects of CIPII with SC insulin therapy in T1DM.

### PATIENTS AND METHODS

Prospective, observational matched-control study. Patients were eligible if they had been treated with either CIPII or SC insulin for > 4 years and had a HbA1c of ≥ 7.0%. CIPII treated cases were matched to SC treated controls regarding age and gender. Primary endpoint was a non-inferiority assessment (pre-defined margin of -0.5%) of the difference in HbA1c during a 26-week interval between both groups. Analysis were performed with ANCOVA, taking baseline differences into account.

### RESULTS

During study, one patient withdrew consent. Subsequently 183 patients with a mean age of 50 years (standard deviation (SD) 12) and a diabetes duration of 26 years (SD 13) were analysed. Of these, 39 were treated with CIPII and 144 with SC insulin therapy. Age and gender were well matched. HbA1c remained stable within the CIPII group while it decreased with -0.09% (95% confidence interval (CI) -0.17, -0.01) in the SC group. The difference between treatment groups was -0.27% (95% CI -0.46, -0.09) and met the predefined non-inferiority criterion. During continuous glucose sensor use, patients using SC insulin therapy spend less time in hyperglycaemia (-9.3%, 95% CI -15.8, -2.8%) and more in euglycaemia (6.9%, 95% CI 1.2, 12.5%) as compared to patients using CIPII. Besides a difference in alanine aminotransferase (ALT) concentrations between groups of 3.6 U/l (95% CI 1.2, 6.0), being lower in the CIPII group, no other biochemical or clinical differences were present.

### CONCLUSION

CIPII therapy is non-inferior to SC insulin therapy with respect to HbA1c in the treatment of poorly controlled T1DM patients. Besides a lower ALT among CIPII treated patients within the normal range, there are no differences in clinical and biochemical parameters. This study supports the long-term use of CIPII therapy as last-resort treatment in T1DM.

# Introduction

Treatment of type 1 diabetes mellitus (T1DM) consists of insulin administration or pancreas (islet cells) transplantation. In most patients, insulin is administered subcutaneously (SC) using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using an external pump. Although most patients achieve acceptable glycaemic control using SC insulin some patients fail to either reach adequate glycaemic control, some because of SC insulin resistance, or have frequent hypoglycaemic episodes [1]. Continuous intraperitoneal insulin infusion (CIPII) with an implantable pump is a treatment option for such patients.

With CIPII, the SC environment is bypassed and the physiological route of insulin is mimicked because intraperitoneal (IP) administered insulin diffuses into the portal vein catchment area. Compared to SC insulin therapy, IP administered insulin results in higher hepatic insulin uptake, alleviation of peripheral plasma insulin concentrations and a more rapid and predictable insulin action [2–5]. Of the three randomized clinical studies that compared CIPII with SC insulin treatment in T1DM patients, two reported HbA1c improvements of 0.76% to 1.28% without an increase in hypoglycaemic episodes and one did not find any differences between therapies [6–8].

Since CIPII with an implantable pump is an invasive and costly treatment for selected patients, there is a clear need for data regarding the long-term efficacy of CIPII as compared to SC insulin therapy in order to justify the use of CIPII. However, available randomized studies have a short duration and a small number of participants, and observational studies lack a control group [9,10]. Aim of this study was to compare the effects of long-term CIPII therapy with SC insulin therapy among patients with poorly controlled T1DM.

# Patients and methods

### STUDY DESIGN

We conducted an investigator initiated, prospective, observational matched-control study to compare the effects on glycaemic control of CIPII versus SC insulin therapy. Patient recruitment took place in two hospitals, the Isala (Zwolle, the Netherlands) and the Diaconessenhuis hospital (Meppel, the Netherlands).

Since CIPII is as a last-resort treatment option for T1DM, CIPII treated patients are a highly selected population with a rather complex background and disease history. In order to account for this inequality between both treatment groups (CIPII versus SC insulin therapy), the primary endpoint was a non-inferiority assessment of the difference in HbA1c during a 26-week period, taking possible baseline differences into account, between both groups.

#### PATIENT SELECTION

Cases were subjects on CIPII therapy using an implanted insulin pump (MIP 2007D, Medtronic/Minimed, Northridge, CA, USA) for the past 4 years without interruptions of >30 days, in order to avoid effects related to initiating therapy. Inclusion criteria for cases were identical to those of a prior study in our centre and have been described in detail previously [6]. In brief, patients with T1DM, aged 18 to 70 years with a HbA1c ≥ 7.5% and/or ≥ 5 incidents of hypoglycemia glucose (< 4.0 mmol/l) per week, were eligible.

Controls using SC insulin therapy were selected from the outpatient clinic population. Eligibility criteria were T1DM, MDI or CSII insulin as mode of insulin administration for the past 4 years without interruptions of >30 days, HbA1c ≥ 7.0% and proper knowledge of the Dutch language.

Exclusion criteria for both cases and controls were: impaired renal function (plasma creatinine ≥150 µmol/l or glomerular filtration rate as estimated by the Cockcroft-Gault formula ≤50 ml/min, cardiac problems (unstable angina or myocardial infarction within the previous 12 months or New York Heart Association class III or IV congestive heart failure, cognitive impairment, current or past psychiatric treatment for schizophrenia, cognitive or bipolar disorder, current use of oral corticosteroids or suffering from a condition which necessitated oral or systemic corticosteroids use more than once in the previous 12 months, substance abuse, other than nicotine, current gravidity or plans to become pregnant during the study, plans to engage in activities that require going >25 feet below sea level or any condition that the investigator and/or coordinating investigator feels would interfere with study participation or evaluation of results.

If patients were eligible to act as SC control, they were matched to the CIPII treated cases based on gender and age. The SC control group consisted of both MDI and CSII users. The ratio of participants on the different therapies (CIPII:MDI:CSII) was 1:2:2.

### STUDY PROCEDURES

There were four study visits. During the first visit, baseline characteristics were collected using a standardized case record form and a continuous glucose measurement (CGM) system was inserted for a period of six days. During the second visit (five to seven days later) the CGM system was removed and laboratory measurements were performed. During the third visit, 26 weeks after visit 1, clinical parameters were collected and again a CGM device was inserted for a period of six days. During the fourth visit, five to seven days after the third visit, laboratory measurements were performed and the CGM device was removed. During the study period all patients received usual care.

### MEASUREMENTS

Demographic and clinical parameters included: age, gender, weight, length, blood pressure, smoking and alcohol habits, co-morbidities, medication use, year of diagnosis of diabetes, presence of microvascular (nephropathy, neuropathy and/or retinopathy) or macrovascular complications (angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, stroke, transient ischemic attack, peripheral artery disease), previous day insulin therapy (kind of insulin, dosage and, if applicable, the number of daily injections) and the number of self-reported hypoglycaemic events grade 1 (<4.0 mmol/l), grade 2 (<3.5 mmol/l) and grade 3 (requiring third party help or losing consciousness) during the last two weeks. Blood pressure was measured using a blood pressure monitor (M6 comfort; OMRON Healthcare) using the highest mean of four measurements (two on each arm). Laboratory measurements included hemoglobin (Hb), creatinine, C-peptide, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, albumin, fibrinogen, aspartate aminotransferase (AST), alanine aminotransferase (ALT), y-glutamyl transpeptidase (gamma-GT), alkaline phosphatase and urine albumin/creatinine ratio and HbA1c. HbA1c was measured with a Primus Ultra2 system using high-performance liquid chromatography (reference value 4.0-6.0%). The six-day 24-hours interstitial glucose profiles were recorded using a blinded CGM device (iPro2, Medtronic, Northridge, CA, USA). The CGM device was inserted in the periumbilical area, and in pump users contralateral to the (implanted) insulin pump. Patients injecting insulin were asked not to inject insulin on the same side of the sensor insertion side. Patients were instructed to perform a minimum of 4 blood glucose self-measurements daily during the CGM period, using a validated blood glucose meter (Contour XT; Bayer) to calibrate the sensor. Time spent in hypoglycemia was defined as the percentage of CGM readings <4.0 mmol/l, time spent in euglycemia was defined as the percentage of CGM readings from 4.0 to 10.0 mmol/l, and time spent in hyperglycemia was defined as the percentage of CGM readings >10.0 mmol/l.

### OUTCOME MEASURES

The primary outcome measure was the difference in HbA1c over a period of 26 weeks between cases and controls adjusted for baseline differences. Secondary outcomes included differences in clinical aspects, CGM measures and laboratory measurements between groups.

### STATISTICAL ANALYSIS

The study was designed to test the hypothesis that CIPII would be non-inferior to SC insulin therapy in T1DM patients during a 26-week follow-up period with respect to the primary outcome measure. The criteria for non-inferiority required that the upper limits of the 95% confidence intervals (CI) were above the predefined margin for the difference in HbA1c. Based on the results of previous randomized clinical trials and discussion with experts, a non-inferiority margin (Δ) of -0.5% was chosen [6–8]. According to pre-specified protocol, both per protocol and intention-to-treat analysis were performed. A regression model based on covariate analysis (ANCOVA) was applied in order to take possible baseline imbalance in HbA1c into account. In the model the fixed factors CIPII and SC insulin therapy were used as determinants. The difference in scores was determined based on the b-coefficient of the particular (CIPII or SC, MDI or CSII) group. Significance of the b-coefficient was investigated with the Wald test based on a $p<0.05$. The quantity of the b-coefficient, with a 95% CI, gives the difference between both treatment modalities over the study period adjusted for baseline differences.

With the use of a standard deviation (SD) of 0.9%, estimated from the previous cross-over study, and a non-inferiority margin of -0.5%, we calculated that we would need to enrol 175 patients (35 CIPII, 140 SC insulin therapy) to show non-inferiority of CIPII therapy at a one-sided alpha level of 0.025 [6]. In order to compensate for loss-to-follow-up, intended group sample sizes were 40 and 150, respectively.

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and STATA version 12 (Stata Corp., College Station, TX: StataCorp LP). Results were expressed as mean (with SD) or median (with the interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. A significance level of 5% was used.

The study protocol was registered prior to the start of the study at the appropriate local (NL41037.075.12) and international registers (NCT01621308). The study protocol was approved by the local medical ethics committee and all patients gave informed consent.

# Results

### PATIENTS

From December 2012 through August 2013, a total of 335 patients were screened and received information about the study of which 190 agreed to participate. After baseline laboratory measurements, six patients were excluded because of reasons presented in Figure 1. Consequently, 184 patients were followed during the 26-week study period. After the first visit one patient withdrew informed consent due to lack of interest. Therefore, 183 patients were analysed.

Main baseline characteristics are presented in Table 1 and more detailed information is provided in Appendix 1. Age and gender were well matched between groups. No grade 3 hypoglycaemic events were reported. Compared to patients using SC insulin therapy, CIPII patients had a higher diastolic blood pressure, more microvascular complications, used more units of insulin per day and spent less time in hypoglycaemic range and more time in hyperglycaemic range during CGM recordings.

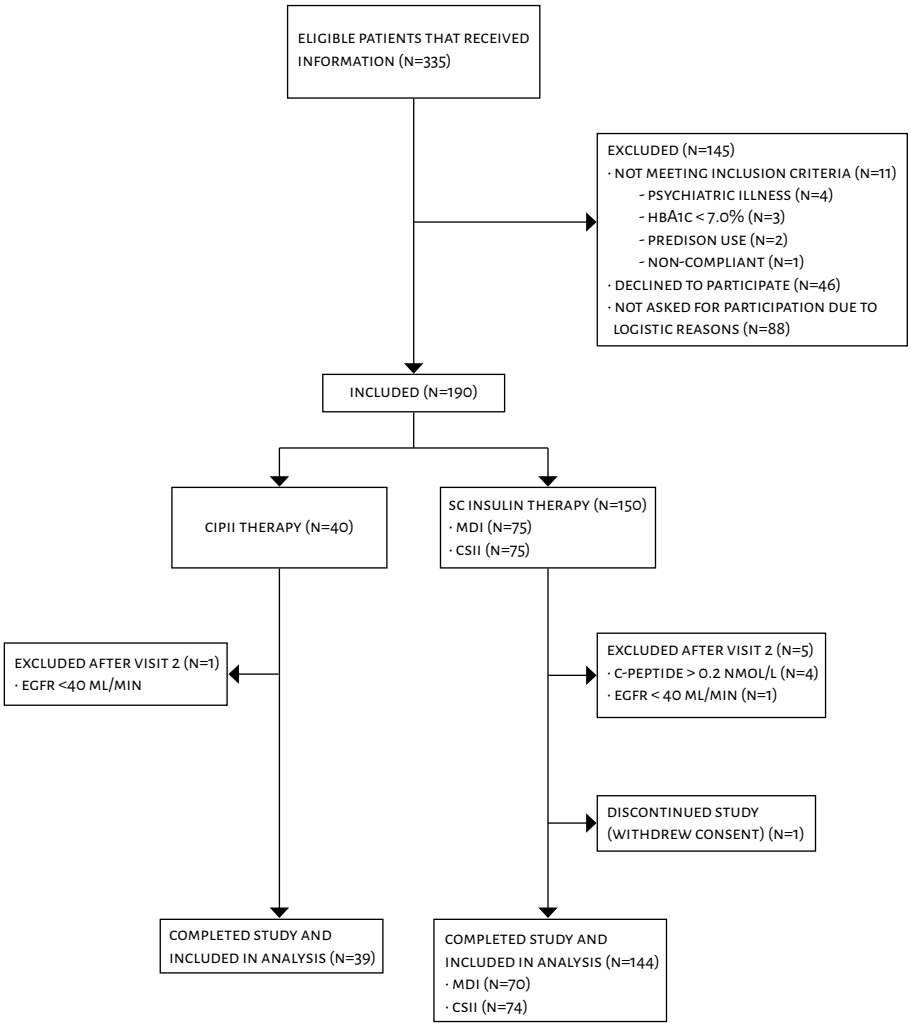
### PRIMARY OUTCOME - GLYCAEMIC CONTROL

Within the group of CIPII treated patients, HbA1c did not significantly changed while it decreased with -0.09% (95% CI -0.17, -0.01) among patients treated with SC insulin therapy (see Table 2). Taking baseline differences into account, the difference between treatment groups was -0.27% (95% CI -0.46, -0.09) and met the non-inferiority criterion of -0.5 % (see Figure 2). The results of the intention-to treat analyses did not differ from the per-protocol analysis (see Appendix 2). During study, the number of grade 1 hypoglycaemic episodes during the last 2 weeks decreased with -1.2 (95% CI -1.7, -0.7) among patients with SC insulin. Patients using SC insulin therapy spent less percentage of time in hyperglycemia (-9.3% (95% CI -15.8, -2.8)) and more in euglycemia (6.9% (95% CI 1.2, 12.5) as compared to patients using CIPII.

### SECONDARY OUTCOME - CLINICAL AND BIOCHEMICAL PARAMETERS

During follow-up, three patients experienced a macrovascular complication: one patient treated with CIPII had angina pectoris, one patient using MDI had a transient ischemic attack and one patients using CSII had a myocardial infarction. In two patients a new microvascular complication was diagnosed: one patient using MDI had nephropathy and patient using CSII had retinopathy..There was a decrease in systolic blood pressure (-5.6 mmHg, 95% CI -11.0, -0.1) and serum creatinin concentration (5.0 µmol/l, 95% CI 2.0, 7.5) over time among CIPII treated patients. Among SC treated patients systolic blood pressure (-3.4 mmHg, 95% CI -6.5, -0.2)

**FIGURE 1** **Patient flowchart.**




decreased and BMI (0.2 kg/m2, 95% CI 0.0, 0.4) increased over time. Concentrations of ALT (2.6 U/l, 95% CI 1. 2, 4.0) and serum creatinine (3.2 µmol/l, 95% CI 2.2, 4.2) increased in SC treated patients. Taking baseline differences into account, CIPII treated patients had significant lower concentrations of ALT as compared to patients treated with SC insulin therapy: 3.6 U/l (95% CI 1.2, 6.0). The results of measurements of all clinical and biochemical parameters performed at baseline and the end of the study and changes within and differences between groups are presented in the Appendix 3.

**TABLE 1** **Baseline characteristics.**

| Characteristic | All (n=184) | CIPII (n=39) | SC (n=145) |
|---|---|---|---|
| Male sex (%) | 67 (36) | 14 (36) | 53 (37) |
| Age (years) | 50 (12) | 50 (12) | 50 (12) |
| Current smokers (%) | 78 (43) | 20 (51) | 58 (40) |
| BMI (kg/m²) | 26.4 (4.5) | 25.9 (4.4) | 26.5 (4.6) |
| Systolic blood pressure (mmHg) | 137 (19) | 138 (17) | 136 (19) |
| Diastolic blood pressure (mmHg) | 80 (11) | 83 (10) | 79 (11)* |
| Diabetes duration (years) | 26 (13) | 29 (10) | 26 (13) |
| Microvascular complication present (%) | 87 (47) | 25 (64) | 62 (43)* |
| Macrovascular complication present (%) | 26 (14) | 7 (18) | 19 (13) |
| Creatinin (µmol/l) | 69 (13) | 70 (12) | 69 (13) |
| ALT (U/l) | 18 [14, 24] | 20 [15, 24] | 18 [14, 25] |
| Total cholesterol (mmol/l) | 4.8 (0.9) | 4.9 (1.0) | 4.8 (0.8) |
| Urine albuminuria:creatinin ratio (mg/mmol) | 0.9 [0.5, 1.8] | 1.2 [0.5, 1.8] | 0.9 [0.4, 1.7] |
| HbA1c (%) | 8.0 (1.0) | 8.3 (1.3) | 7.9 (0.8) |
| Fasting glucose (mmol/l) [a] | 8.6 (3.7) | 8.4 (3.8) | 8.6 (3.7) |
| Total insulin dose (IU/day) | 46 [36, 64] | 55 [42, 73] | 45 [35, 62]* |
| Hypoglycaemia grade 1 / 2† | 1 [0, 4] / 2 [0, 4] | 2 [0, 4] / 1 [0, 2] | 1 [0, 4] / 2 [1, 4] |
| Time spent in hypoglycaemia (%) | 5 [2, 10] | 2 [0, 7] | 6 [2, 11]* |
| Time spent in hyperglycaemia (%) | 40 [29, 52] | 46 [36, 67] | 39 [29, 50]* |
| Time spent in euglycaemia (%) | 53 [42, 62] | 49 [30, 59] | 54 [44, 62] |

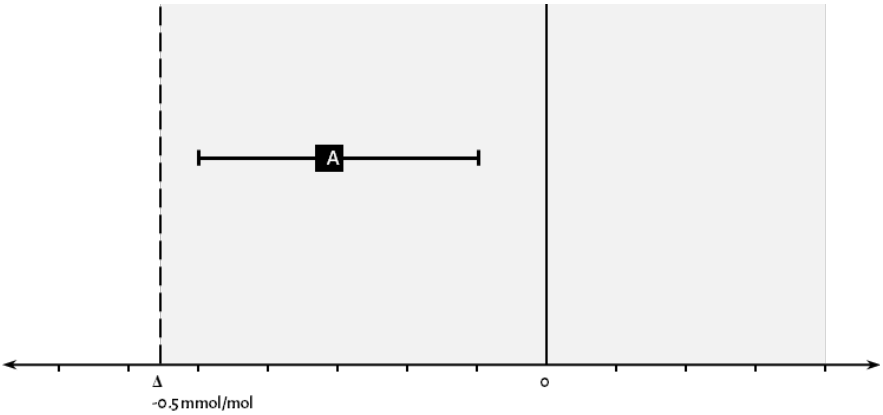
Data are presented as n (%), mean (SD) or median [IQR]. Variables may not add up because of rounding off. *p<0.05 as compared to CIPII, P-values are based on appropriate parametric and non-parametric tests. † Defined as the number of hypoglycaemic events < 4 (grade 1) and < 3.5 (grade 2) during the last 14 days. Abbreviations: ALT; alanine aminotransferase, BMI; Body Mass Index, CIPII; continuous intraperitoneal infusion, SC; subcutaneous. a based on n=32 (CIPII) and n=116 (SC).

**TABLE 2** **Change in glycaemic parameters within- and difference between groups.**

| Characteristic | CIPII Change | SC Change | Difference between SC vs. CIPII (baseline adjusted) |
|---|---|---|---|
| HbA1c (%) | 0.13 (-0.06, 0.33) | -0.09 (-0.17, -0.01) | -0.27 (-0.46, -0.09)* |
| Fasting glucose (mmol/l) [a] | 0.2 (-1.8, 2.3) | 1.0 (0.1, 1.9) | 1.0 (-0.6, 2.6) |
| Total insulin dose (IU/day) | -4.1 (-12.0, 3.8) | -1.3 (-3.2, 0.6) | -0.1 (-5.1, 5.0) |
| Hypoglycaemia grade 1† | -1.6 (-2.8, 0.4) | -1.2 (-1.7, -0.7)* | 0.2 (-0.5, 0.9) |
| Hypoglycaemia grade 2‡ | 0.8 (-0.2, 1.8) | 0.1 (-0.6, 0.7) | 0.2 (-1.0, 1.3) |
| Time spent in hypoglycaemia (%) | 0.3 (-1.8, 2.4) | 1.0 (-1.2, 3.3) | 3.2 (-1.0, 7.4) |
| Time spent in hyperglycaemia (%) | 1.4 (-5.6, 8.5) | -1.3 (-4.5, 1.9) | -9.3 (-15.8, -2.8)* |
| Time spent in euglycaemia (%) | -1.7 (-8.3, 4.8) | 0.2 (-2.7, 3.2) | 6.9 (1.2, 12.5)* |

Data are means (95% CI) differences within the groups and mean between the (SC vs CIPII insulin therapy) groups adjusted for baseline differences. *p<0.05. † Defined as the number of blood glucose value <4.0 mmol/l during the last 2 weeks ‡ Defined as the number of blood glucose value <3.5 mmol/l during the last 2 weeks. Abbreviations: CIPII; continuous intraperitoneal infusion, SC; subcutaneous. a based on n=36 (CIPII) and n=137 (SC).

**FIGURE 2** **Differences between treatment groups with 95%CI and the non-inferiority interval.**




Error bars indicate the 2-sided 95% CI. The blue dashed line at x=Δ indicates the pre-defined non-inferiority margin for the difference between CIPII and SC insulin treated patients of -0.5%. A: mean difference (95% CI) between CIPII and SC.

### MDI and CSII versus CIPII

In comparison with the CIPII group, MDI and CSII users had a lower HbA1c (-0.29% (95% CI -0.54, -0.04) for MDI users and -0.26% (95% CI -0.5, -0.01) for CSII users, respectively) and spent less time in hyperglycemia (-10.3%, (95% CI -17.6, -3.0) for MDI users and -8.6% (95% CI -15.5, -1.7) for CSII users, respectively) after adjustment for baseline differences. In addition, MDI users spent 8.2% (95% CI 2.0, 14.5) more time in the euglycaemic range than CIPII treated patients. Besides higher concentrations of ALT (4.0 U/l, 95% CI 0.8, 7.2 for MDI users and 3.2 U/l, 95% CI 0.1, 6.4 for CSII users, respectively) there were no other differences with respect to clinical and biochemical parameters (see Appendix 4).

# Discussion

CIPII is non-inferior to SC insulin therapy with respect to HbA1c among T1DM patients in poor glycaemic control. CIPII treated patients spent more time in the hyperglycemia and less in euglycemia as compared to patients using SC insulin therapy. Furthermore, besides lower ALT concentrations among CIPII treated patients, there were no other differences in clinical and biochemical parameters between T1DM patients treated with CIPII and SC insulin.

This is the first study to compare the effects of long-term CIPII and SC insulin administration in a large population of poorly regulated T1DM patients receiving usual care. Since CIPII is a last-resort treatment option for T1DM, the group of CIPII treated patients is considered selected and more complex as compared to SC treated patients. This is emphasized by the higher frequency of microvascular complications and more hyperglycaemic profile among CIPII treated patients, as compared to SC treated patients, found at baseline in the current study. Although groups were matched on age and gender, patients were on therapy for >4 years, measurements were performed with a 26-week interval and outcomes were adjusted for baseline differences: the non-randomized design remains a limitation of the present study. In particular the complexity of the CIPII treated group, consisting of both patients with high HbA1c as well as frequent hypoglycaemic episodes due to various causes, and the modest number of available patients necessitated pragmatic measures in the study design. In order to reflect the heterogeneous nature of the CIPII group, a lower HbA1c inclusion criterion for SC treated patients was chosen. And although groups were well matched on age, gender, HbA1c and hypoglycaemic episodes at baseline, differences between groups that are known to influence glycaemic control, such as quality of life which is known to be lower among CIPII treated patients, could still be present [11,12]. Although hypothetical, the presence of such (unmeasured) differences between groups may have caused a (slight) underestimation of the effect of CIPII on glycaemic control. This would also be in line with the fact that superiority of CIPII, above SC insulin, therapy was only found in previous studies with a cross-over design, which minimize inter-patient variability and looks only at intra-patient changes, and not in studies with a parallel design [6–8]. While fully acknowledging these limitations, we feel that the current design is the best available for the present study objective given the real-life, clinical restrictions.

According to the study protocol, the HbA1c difference between both treatment groups was assessed using a non-inferiority method. Although the HbA1c difference of -0.27% (95% CI -0.46, -0.09) between CIPII and SC treated patients was negative, the 95% CI remained above

the predefined margin of -0.5%. Therefore it is concluded that CIPII is non-inferior to SC insulin therapy with respect to HbA1c in the treatment of T1DM.

The present study expands current knowledge regarding CIPII as a treatment modality for selected patients with T1DM. The effects of CIPII have been described previously in three randomized studies. After 6 months of cross-over treatment with CIPII and SC insulin, Haardt *et al*. reported a difference of 1.28% in favor of CIPII, with a reduction of glycaemic fluctuations and hypoglycaemic episodes [8]. In the 6-month parallel study by Selam *et al*. there were no differences between the SC and CIPII study group [7]. Among the 24 T1DM patients studied in a cross-over by Logtenberg *et al*. there was a HbA1c decrease of 0.76%, with 11% more time spent in euglycemia and without a change in hypoglycaemic events, in favor of CIPII [6]. Subsequent observational studies among CIPII treated patients found stabilisation of the HbA1c during long-term follow-up at an equal or lower level than before initiation of CIPII [9,10,13,14].

Although ALT concentrations were still within the normal range and the other liver enzymes were stable, this finding is remarkable. It might be hypothesized that, since IP insulin administration results in higher hepatic insulin concentrations than SC insulin administration this leads to altered hepatic metabolism secondary to higher insulinization [2,3,15].

At present, the costs of CIPII therapy seems to outweighs the advantages of CIPII with regard to glycaemic regulation for the majority of patients and health care systems [12]. Nevertheless, based on the short-term positive effects found in previous studies, including HbA1c improvements, less hypoglycaemic episodes and improved quality of life, and the findings of the present study among long-term CIPII-treated patients we advocate that CIPII using an implantable pump should be seen a valuable and feasible last-resort treatment option for selected patients with T1DM who are unable to reach glycaemic control with SC insulin therapy [6,8,12,14].

# Conclusions

For the long-term treatment of poorly regulated patients with T1DM, CIPII is non-inferior to SC insulin therapy with respect to HbA1c. Except for lower ALT concentrations among CIPII treated patients within the normal range, there are no differences in clinical and biochemical parameters. This study supports the effectiveness of long-term CIPII therapy as last-resort treatment in T1DM.

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**APPENDIX 1** **Baseline characteristics.**

| Characteristic | All (n=184) | CIPII (n=39) | SC (n=145) | MDI (n=71) | CSII (n=74) |
|---|---|---|---|---|---|
| Male sex (%) | 67 (36) | 14 (36) | 53 (37) | 23 (33) | 30 (41) |
| Age (years) | 49.9 (0.9) | 49.6 (2.0) | 50.0 (1.1) | 52.2 (13.1) | 47.8 (12.4)† |
| Current smokers (%) | 78 (43) | 20 (51) | 58 (40) | 28 (39) | 30 (41) |
| Current alcohol use (%) | 58 (32) | 10 (26) | 48 (33) | 24 (34) | 24 (32) |
| Weight (kg) | 79.9 (16.2) | 80.2 (14.7) | 79.8 (16.7) | 78.8 (17.4) | 80.8 (16.0) |
| BMI (kg/m²) | 26.4 (4.5) | 25.9 (4.4) | 26.5 (4.6) | 26.4 (4.9) | 26.6 (4.3) |
| Systolic blood pressure (mmHg) | 136.7 (18.7) | 138.3 (16.8) | 136.3 (19.2) | 137.0 (19.7) | 135.6 (18.8) |
| Diastolic blood pressure (mmHg) | 79.7 (10.6) | 83.1 (10.3) | 78.7 (10.5)* | 76.9 (10.3)* | 80.5 (10.4)† |
| Diabetes duration (years) | 26.2 (12.5) | 28.8 (9.6) | 25.5 (13.1) | 23.8 (13.8)* | 27.1 (12.3) |
| Retinopathy (%) | 64 (35) | 17 (44) | 47 (32) | 19 (27) | 28 (38) |
| Neuropathy (%) | 53 (29) | 20 (51) | 33 (23)* | 19 (27) | 14 (19) |
| Nephropathy (%) | 5 (3) | 2 (5) | 3 (2) | 1 (1) | 2 (3) |
| Macrovascular complication present (%) | 26 (14) | 7 (18) | 19 (13) | 10 (14) | 9 (12) |
| Angina pectoris | 3 (2) | 1 (3) | 2 (1) | 1 (1) | 1 (1) |
| Myocardial infarction | 2 (1) | 0 (0) | 2 (1) | 1 (1) | 1 (1) |
| Coronary artery bypass grafting | 7 (4) | 2 (5) | 5 (3) | 2 (3) | 3 (4) |
| Percutaneous transluminal coronary angioplasty | 3 (2) | 0 (0) | 3 (2) | 2 (3) | 1 (1) |
| Stroke | 1 (1) | 0 (0) | 1 (1) | 1 (1) | 0 (0) |
| Transient ischaemic attack | 4 (2) | 1 (3) | 3 (2) | 2 (3) | 1 (1) |
| Peripheral artery disease | 6 (3) | 3 (8) | 3 (2) | 1 (1) | 2 (3) |
| Hb (mmol/l) | 8.6 (0.8) | 8.6 (0.9) | 8.6 (0.8) | 8.4 (0.8) | 8.7 (0.8) |
| Creatinin (µmol/l) | 69.3 (13.0) | 69.7 (12.3) | 69.4 (13.1) | 68.9 (14.0) | 69.4 (12.4) |
| Fibrinogen (g/l) | 3.0 (0.6) | 3.1 (0.5) | 2.9 (0.6)* | 3.0 (0.6) | 2.8 (0.7)*† |
| Alkaline phosphatase (U/l) | 73.1 (20.4) | 78.1 (18.6) | 71.6 (20.3) | 72.2 (19.6) | 71.5 (21.9) |
| Gamma-GT (U/l) | 19.0 [14.0, 27.0] | 22.0 [14.0, 36.0] | 18.5 [14.0, 26.8] | 16.5 [12.8, 23.8] | 21.0 [14.0, 27] |
| AST (U/l) | 23.0 [19.0, 27.0] | 24.0 [20.0, 25.0] | 23.0 [19.0, 27.0] | 23.0 [20.0, 27.0] | 23.0 [18.0, 28.3] |
| ALT (U/l) | 18.0 [14.0, 24.0] | 20.0 [15.0, 24.0] | 18.0 [14.0, 25.0] | 18.0 [14.8, 23.5] | 18.0 [13.0, 25.0] |
| Total cholesterol (mmol/l) | 4.8 (0.9) | 4.9 (1.0) | 4.8 (0.8) | 4.8 (0.8) | 4.7 (0.8) |
| HDL (mmol/l) | 1.8 (0.5) | 1.7 (0.5) | 1.8 (0.5) | 1.8 (0.6) | 1.7 (0.4) |
| LDL (mmol/l) | 2.6 (0.8) | 2.7 (0.9) | 2.6 (0.7) | 2.5 (0.8) | 2.6 (0.7) |

| | | | | | |
|---|---|---|---|---|---|
| Triglycerids (mmol/l) | 0.8 [0.6, 1.1] | 1.0 [0.7, 1.6] | 0.8 [0.6, 1.0] | 0.8 [0.6, 1.2] | 0.8 [0.6, 1.0]* |
| Urine albuminuria:creatinin ratio (mg/mmol) | 0.9 [0.5, 1.8] | 1.2 [0.5, 1.8] | 0.9 [0.4, 1.7] | 1.0 [0.5, 2.3] | 0.8 [0.4, 1.4] |
| HbA1c (%) | 8.0 (0.97) | 8.3 (1.32) | 7.9 (0.81) | 7.8 (0.86) | 8.0 (0.34) |
| Fasting glucose (mmol/l)[a] | 8.6 (3.7) | 8.4 (3.8) | 8.6 (3.7) | 8.6 (3.8) | 8.8 (3.7) |
| Total insulin dose (IU/day) | 46.3 [35.7, 64.0] | 54.7 [41.6, 73.0] | 44.6 [35.2, 62.1]* | 48.0 [38.0, 64.0] | 42.0 [33.1, 59.6]*† |
| Hypoglycaemia grade 1† | 1.0 [0.0, 4.0] | 2.0 [0.0, 4.0] | 1.0 [0.0, 4.0] | 0.0 [0.0, 3.0] | 1.5 [0.0, 5.0] |
| Hypoglycaemia grade 2‡ | 2.0 [0.0, 4.0] | 1.0 [0.0, 2.0] | 2.0 [1.0, 4.0] | 1.0 [0.0, 3.0] | 3.0 [1.0, 5.0]*† |
| Hypoglycaemia grade 3 ¥ | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] |
| Time spent in hypoglycaemia (%) | 5 [2. 10] | 2 [0, 7] | 6 [2, 11] * | 10 [ 3, 15] | 4 [1, 7] |
| Time spent in hyperglycaemia (%) | 40 [29,52] | 46 [36, 67] | 39 [29, 50] * | 35 [23, 44] | 41 [32, 51] |
| Time spent in euglycaemia (%) | 53 [42, 62] | 49 [30, 59] | 54 [44, 62] | 56 [43, 62] | 52 [45, 62] |

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 as compared to CIPII, † p<0.05 for MDI versus CSII. P-values are based on appropriate parametric and non-parametric tests. Retinopathy, neuropathy and nephropathy categories do not add up to microvascular category as presented in Table 1. Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CSII; continuous intraperitoneal insulin infusion, CIPII; continuous intraperitoneal infusion, Gamma-GT; Gamma-glutamyl transpeptidase, HDL; high density lipoprotein, LDL; low density lipoprotein, MDI; multiple daily injections, SC; subcutaneous. [a] based on n=32 (CIPII), n=56 (MDI) and n=69 (CSII).

**APPENDIX 2** Results of the per protocol and intention to treat analysis for the primary outcome.

**Intention to treat analysis (n=184)**

| | CIPII | SC | Difference between means (95% CI) |
|---|---|---|---|
| Baseline | 8.3 (1.32) | 7.9 (0.81) | -0.39 (-0.83, -0.05) |
| Follow-up | 8.4 (1.29) | 7.8 (0.86) | -0.59 (1.04, -0.16) |
| Difference between CIPII and SC adjusted for baseline differences | | | -0.27 (-0.46, 0.09) |

Data are means (SD) and difference between means (95% CI).

**Per protocol analysis (n=183)**

| | CIPII | SC | Difference between means (95% CI) |
|---|---|---|---|
| Baseline | 8.3 (1.32) | 7.9 (0.83) | -0.39 (-0.84, -0.05) |
| Follow-up | 8.4 (1.29) | 7.8 (0.86) | -0.59 (1.04, -0.16) |
| Difference between CIPII and SC adjusted for baseline differences | | | -0.27 (-0.46, -0.09) |

Data are means (SD) and difference between means (95% CI).

**APPENDIX 3** Outcomes during baseline and final visit, changes within- and differences between groups.

| Characteristic | CIPII | | | SC | | | Difference between |
|---|---|---|---|---|---|---|---|
| | Baseline | End | Change within CIPII group | Baseline | End | Change within SC group | SC vs. CIPII (baseline adjusted) |
| **Clinical and biochemical** | | | | | | | |
| BMI (kg/m²) | 25.9 (4.4) | 26.2 (4.4) | 0.3 (-0.0, 0.7) | 26.5 (4.6) | 26.7 (4.5) | 0.2 (0.0, 0.4)* | -0.1 (-0.5, 0.2) |
| Systolic blood pressure (mmHg) | 138.3 (16.8) | 132.7 (15.4) | -5.6 (-11.0,-0.1)* | 136.7 (19.0) | 133.3 (19.2) | -3.4 (-6.5,-0.2)* | 1.4 (-4.3, 7.1) |
| Diastolic blood pressure (mmHg) | 83.1 (10.3) | 81.8 (9.8) | -1.3 (-5.0, 2.4) | 78.9 (10.5) | 78.4 (10.4) | -0.5 (-2.2, 1.3) | 1.4 (-4.7, 1.9) |
| Hb (mmol/l) | 8.6 (0.9) | 8.5 (0.9) | -0.1 (-0.3, 0.1) | 8.6 (0.8) | 8.6 (0.7) | 0.1 (-0.0, 0.1) | 0.2 (-0.001, 0.3) |
| Creatinin (µmol/l) | 69.7 (12.3) | 74.4 (14.8) | 5.0 (2.0, 7.5)* | 69.4 (13.1) | 72.6 (13.6) | 3.2 (2.2, 4.2)* | -1.6 (-3.9, 0.8) |
| Fibrinogen | 3.1 (0.5) | 3.2 (0.7) | 0.1 (-0.2, 0.3) | 2.9 (0.6) | 2.9 (0.6) | 0.0 (-0.1, 0.1) | -0.1 (-0.3, 0.03) |
| Alkaline phosphatase (U/l) | 78.1 (18.6) | 78.3 (17.9) | 0.3 (-3.4, 3.9) | 71.6 (20.3) | 71.6 (22.9) | -0.0 (-2.4, 2.4) | -1.1 (-5.7, 3.7) |
| Gamma-GT (U/l) | 22.0 [14.0, 36.0] | 21.0 [13.0, 40.0] | -0.3 (-4.8, 4.3) | 19.0 [14.0, 27.0] | 19.0 [13.0, 25.0] | -0.4 (-2.4, 1.6) | -0.8 (-5.1, 3.5) |
| ALT (U/l) | 20.0 [15.0, 24.0] | 10.0 [16.0, 23.0] | -2.2 (-6.0, 1.6) | 18.0 [14.0, 25.0] | 22.0 [18.5, 26.0] | 2.6 (1.2, 4.0)* | 3.6 (1.2, 6.0)* |
| AST (U/l) | 24.0 [20.0, 25.0] | 18.0 [15.0, 25.0] | -3.6 (-6.5,-0.7)* | 23.0 [19.0, 27.0] | 20.0 [16.0, 25.0] | -2.7 (-4.1,-1.3)* | 0.9 (-1.8, 3.7) |
| Albumin | 44.2 (2.3) | 44.3 (2.5) | 0.2 (-0.7, 1.0) | 43.3 (2.6) | 43.5 (2.4) | 0.2 (0.1, 0.5) | -0.3 (-0.9, 0.4) |
| Total cholesterol | 4.9 (1.0) | 4.7 (0.9) | -0.2 (-0.4, 0.0) | 4.8 (0.8) | 4.7 (0.9) | 0.0 (-0.1, 0.1) | 0.1 (-0.1, 0.3) |
| HDL-cholesterol | 1.7 (0.5) | 1.6 (0.4) | -0.0 (-0.1, 0.1) | 1.8 (0.5) | 1.8 (0.5) | 0.0 (-0.0,0.1) | 0.8 (-0.02, 0.2) |
| LDL-cholesterol | 2.8 (0.9) | 2.7 (0.9) | -0.2 (-0.4, 0.1) | 2.6 (0.7) | 2.5 (0.8) | -0.1 (0.1,-0.2) | 0.0 (-0.2, 0.2) |
| Triglycerids | 1.0 [0.7, 1.6] | 1.0 [0.8, 1.7] | 0.1 (-0.1, 0.2) | 0.8 [0.6, 1.0] | 0.8 [0.6, 1.2] | 0.1 (-0.0, 0.1) | -0.1 (-0.2, 0.1) |
| Urine albuminuria:creatinin ratio (mg/mmol)[b] | 1.2 [0.5, 1.8] | 0.6 [0.5, 1.6] | -4.3 (-10.2, 1.6) | 0.9 [0.4, 1.7] | 0.6 [0.4, 1.2] | -14.1 (-39.5, 11.4) | -0.4 (-3.4, 2.7) |
| **Glycaemic** | | | | | | | |
| HbA1c (%) | 8.3 (1.32) | 8.4 (1.29) | 0.13 (-0.06, 0.33) | 7.9 (0.81) | 7.8 (0.86) | -0.09 (-0.17, -0.01)* | -0.27 (-0.46, -0.09)* |
| Fasting glucose (mmol/l) [a] | 8.4 (3.8) | 8.6 (4.1) | 0.2 (-1.8, 2.3) | 8.6 (3.7) | 9.6 (4.2) | 1.0 (0.1, 1.9)* | 1.0 (-0.6, 2.6) |
| Total insulin dose (IU/day) | 57.1 [43.4, 74.2] | 57.7 [42.6, 71.0] | -4.1 (-12.0, 3.8) | 45 [36, 62] | 44 [34.2, 58.6] | -1.3 (-3.2, 0.6) | -6.2 (-14.0, 1.6) |
| Hypoglycaemia grade 1† | 2.0 [0.0, 4.0] | 0.0 [0.0, 2.0] | -1.6 (-2.8, 0.4) | 1.0 [0.0, 4.0] | 0.0 [0.0, 2.0] | -1.2 (-1.7, -0.7)* | 0.2 (-0.5, 0.9) |
| Hypoglycaemia grade 2‡ | 1.0 [0.0, 2.0] | 2.0 [1.0, 4.0] | 0.8 (-0.2, 1.8) | 2.0 [1.0, 4.0] | 2.0 [0.5, 4.0] | 0.1 (-0.6, 0.7) | 0.2 (-1.0, 1.3) |
| Hypoglycaemia grade 3 ¥ | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | -0.1 (-0.3, 0.1) | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 (-0.0, 0.0) | 0.0 (-0.0, 0.1) |
| Time spent in hypoglycaemia (%) | 2 [0, 7] | 2 [0, 6] | 0.3 (-1.8, 2.4) | 6.0 [2.0, 12.0] | 6 [2, 11] | 1.0 (-1.2, 3.3) | 3.1 (-1.0, 7.4) |
| Time spent in hyperglycaemia (%) | 46 [36, 67] | 50 [33, 65] | 1.4 (-5.6, 8.5) | 6 [2, 11] | 37 [23, 50] | -1.3 (-4.5, 1.9) | -9.3 (-15.8, -2.8)* |
| Time spent in euglycaemia (%) | 49 [30, 59] | 46 [32, 61] | -1.7 (-8.3, 4.8) | 39 [29, 50] | 55 [44, 65] | 0.2 (-2.7, 3.2) | 6.9 (1.2, 12.5)* |

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 [a] based on n=116 and n=32 [b] based on n=137 and n=36. † Defined as the number of blood glucose value <4.0 mmol/l during the last 2 weeks ‡ Defined as the number of blood glucose value <3.5 mmol/l during the last 2 weeks. ¥ Defined as the number of hypoglycaemic episodes requiring third party help or losing consciousness during the last 2 weeks. Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CIPII; continuous intraperitoneal infusion, Gamma-GT; Gamma-glutamyl transpeptidase, HDL; high density lipoprotein, LDL; low density lipoprotein, SC; subcutaneous. † Defined as a number of blood glucose value <4.0 mmol/l during the last 2 weeks.

**APPENDIX 4** Outcomes during baseline and final visit, changes within the MDI and CSII groups and differences with the CIPII group.

| Characteristic | MDI | | | | CSII | | | |
|---|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Change within MDI group | Difference between MDI and CIPII (baseline adjusted) | Visit 1 | Visit 2 | Change within CSII group | Difference between CSII and CIPII (baseline adjusted) |
| **Clinical and biochemical** | | | | | | | | |
| BMI (kg/m²) | 26.4 (4.9) | 26.6 (4.9) | 0.2 (-0.2, 0.4) | -0.1 (-0.6, 0.4) | 26.7 (4.2) | 26.9 (4.2) | 0.2 (-0.1, 0.4) | -0.1 (-0.6, 0.4) |
| Systolic blood pressure (mmHg) | 137.2 (19.8) | 137.8 (20.6) | 0.6 (-4.1, 5.2) | 5.6 (-2.0, 13.1) | 136.1 (18.4) | 129.0 (16.7) | -7.1 (-11.3, -2.3)* | -2.7 (-10.2, 4.8) |
| Diastolic blood pressure (mmHg) | 77.1 (10.4) | 79.0 (10.9) | 1.9 (-0.5, 4.3) | 0.1 (-4.4, 4.5) | 80.7 (10.4) | 78.0 (10.0) | -2.7 (-5.2, -0.2)* | -2.7 (-7.0, 1.7) |
| Hb (mmol/l) | 8.4 (0.8) | 8.6 (0.7) | 0.1 (0.0, 0.3)* | 0.2 (-0.0, 0.4) | 8.7 (0.8) | 8.7 (0.7) | -0.0 (-0.1, 0.1) | 0.1 (-0.1, 0.3) |
| Creatinin (µmol/l) | 69.5 (13.9) | 72.7 (14.5) | 3.3 (1.9, 4.6)* | -1.5 (-4.7, 1.7) | 69.4 (12.4) | 72.5 (12.7) | 3.1 (1.6, 4.7)* | -1.6 (-4.8, 1.6) |
| Fibrinogen | 3.0 (0.6) | 3.0 (0.5) | 0.0 (-0.1, 0.1) | -0.1 (-0.4, 0.1) | 2.8 (0.7) | 2.8 (0.6) | 0.0 (-0.1, 0.1) | -0.2 (-0.4, 0.1) |
| Alkaline phosphatase (U/l) | 71.8 (18.6) | 71.3 (16.8) | -0.6 (-3.0, 1.9) | -1.6 (-8.1, 4.9) | 71.5 (21.9) | 71.9 (27.4) | 0.5 (-3.5, 4.4) | -0.6 (-7.0, 5.8) |
| Gamma-GT (U/l) | 17 [12.5, 24.5] | 18.0 [13.0, 23.0] | 0.1 (-1.9, 2.0) | -0.5 (-6.4, 5.5) | 21.0 [14.0, 27.8] | 18.0 [13.0, 28.3] | -0.9 (-4.3, 2.5) | -1.1 (-6.9, 4.7) |
| ALT (U/l) | 18.0 [15.0, 24.0] | 22.0 [19.0, 27.0] | 2.8 (0.8, 4.8)* | 4.0 (0.8, 7.2)* | 18.0 [13.0, 25.0] | 21.0 [18.0, 25.0] | 2.4 (0.4, 4.4)* | 3.2 (0.1, 6.4)* |
| AST (U/l) | 23.0 [20.0, 26.5] | 21.0 [16.0, 25.0] | -1.7 (-3.5, 0.1) | 1.8 (-1.9, 5.5) | 23.0 [18.0, 28.3] | 19.5 [15.8, 25.0] | -3.6 (-5.7, -1.5)* | 0.1 (-3.5, 3.8) |
| Albumin | 43.2 (2.8) | 43.3 (2.4) | 0.1 (-0.3, 0.5) | -0.4 (-1.3, 0.5) | 43.5 (2.4) | 43.7 (2.3) | 0.3 (-0.2, 0.7) | -0.2 (-1.0, 0.7) |
| Total cholesterol | 4.8 (0.8) | 4.8 (0.9) | 0.1 (-0.1, 0.2) | 0.2 (-0.1, 0.5) | 4.7 (0.8) | 4.6 (0.8) | -0.1 (-0.3, 0.0) | 0.0 (-0.2, 0.2) |
| HDL-cholesterol | 1.8 (0.6) | 1.9 (0.6) | 0.0 (-0.1, 0.1 | 0.1 (-0.0, 0.3) | 1.7 (0.4) | 1.8 (0.5) | 0.0 (-0.1, 0.1) | 0.1 (-0.1, 0.2) |
| LDL-cholesterol[a] | 2.5 (0.8) | 2.5 (0.7) | -0.0 (-0.2, 0.2) | 0.1 (-0.1, 0.3) | 2.5 (0.7) | 2.6 (0.7) | -0.5 (-0.3, -0.0)* | -0.0 (-0.3, 0.3) |
| Triglycerides | 0.8 [0.7, 1.2] | 0.8 [0.7, 1.3] | 0.1 (-0.0, 0.2) | -0.1 (-0.3, 0.2) | 0.8 [0.6, 1.1] | 0.8 [0.6, 1.1] | 0.0 (-0.1, 0.1) | -0.1 (-0.3, 0.1) |
| Urine micro-albuminuria:creatinin ratio (mg/mmol)[b] | 1.0 [0.5, 2.2] | 0.7 [0.4, 2.6] | -26.5 (-79.6, 26.6) | 1.0 (-3.2, 5.2) | 0.8 [0.4, 1.4] | 0.5 [0.4, 1.0] | -2.5 (-6.9, 1.9) | -1.6 (-5.8, 2.5) |
| **Glycaemic** | | | | | | | | |
| HbA1c (%) | 7.8 (0.83) | 7.7 (0.75) | -0.10 (-0.21, 0.02) | -0.29 (-0.54, -0.04)* | 8.0 (0.81) | 7.9 (0.94) | -0.08 (-0.19, 0.05) | -0.26 (-0.5, -0.01)* |
| Fasting glucose (mmol/l) [a] | 8.6 (3.8) | 10.1 (3.8) | 1.4 (-0.2, 3.0) | 1.4 (-0.8, 3.7) | 8.6 (3.7) | 9.3 (3.7) | 0.7 (-0.4, 1.7) | 0.7 (-1.4, 2.8) |
| Total insulin dose (IU/day) | 48.0 [38.0, 65.0] | 46.5 [36.3, 60.0] | -1.7 (-4.1, 0.7) | 0.6 (-6.2, 7.4) | 42.0 [33.1, 59.7] | 40.8 [31.7, 58.1] | -0.1 (-3.9, 2.1) | -0.8 (-7.7, 6.1) |
| Hypoglycaemia grade 1† | 0.0 [0.0, 3.0] | 0.0 [0.0, 1.0] | -1.0 (-1.6, -0.3)* | -0.1 (-0.9, 1.0) | 1.5 [0.0, 5.0] | 0.0 [0.0, 2.0] | -1.4 (-2.1, -0.7)* | 0.4 (-0.6, 1.3) |
| Hypoglycaemia grade 2‡ | 1.0 [0.0, 3.0] | 2.0 [0.0, 3.0] | 0.1 (-0.7, 0.9) | -0.2 (-1.8, 1.3) | 3.0 [1.0, 5.0] | 2.0 [1.0, 5.0] | 0.1 (-0.9, 1.1) | 0.6 (-1.0, 2.2) |
| Hypoglycaemia grade 3 ¥ | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | 0.0 (-0.0, 0.1) | 0.1 (-0.0, 0.1) | 0.0 [0.0, 0.0] | 0.0 [0.0, 0.0] | -0.0 (-0.1, 0.0) | 0.0 (-0.1, 0.1) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Time spent in hypoglycaemia (%) | 10 [3, 15] | 8 [5, 14] | -1.3 (4.0, 1.3) | 2.9 (-2.0, 7.8) | 4 [1, 7] | 4 [2, 9] | 0.3 (-1.8, 2.4) | 3.4 (-1.1, 7.9) |
| Time spent in hyperglycaemia (%) | 35 [23, 44] | 32 [20,48] | 0.0 (-4.2, 4.2) | -10.3 (-17.6, -3.0)* | 41 [32, 51] | 39 [27, 51] | 1.4 (-5.6, 8.5) | -8.6 (-15.5, -1.7)* |
| Time spent in euglycaemia (%) | 56 [43, 62] | 57 [44, 68] | 1.3 (-2.3, 5.0) | 8.2 (2.0, 14.5)* | 52 [45, 62] | 52 [44,63] | -1.7 (-8.3, 4.9) | 5.7 (-0.5,11.8) |

Data are presented as n (%), mean (SD) or median [IQR]. *p<0.05 [a] based on n=116 and n=32 [b] based on n=137 and n=36. † Defined as the number of blood glucose value <4.0 mmol/l during the last 2 weeks ‡ Defined as the number of blood glucose value <3.5 mmol/l during the last 2 weeks. ¥ Defined as the number of hypoglycaemic episodes requiring third party help or losing consciousness during the last 2 weeks. Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CSII; continuous intraperitoneal insulin infusion, CIPII; continuous intraperitoneal infusion, Gamma-GT; Gamma-glutamyl transpeptidase, HDL; high density lipoprotein, LDL; low density lipoprotein, MDI; multiple daily injections.