Physiologic effects of intraperitoneal versus subcutaneous insulin delivery in patients with diabetes mellitus type 1:
A systematic review

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## Literature search strategy

### Table 51: Literature search strategy.

| Embase                                                                 | PubMed                                                                  | Scopus                                                                 | Central                                                                 |
|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1 exp diabetes mellitus/                                               | 1 Diabetes mellitus[mh]                                                 | 1 TITLE-ABS-KEY (diabet*)                                              | 1 Diabet*:ti,ab,kw                                                     |
| 2 diabet* [ti,ab,kw.]                                                 | 2 diabet*[tiab] OR diabet*[ot]                                         | 2 TITLE-ABS-KEY (insulin resistan*)                                   | 2 insulin resistan*:ti,ab,kw                                          |
| 3 insulin resistan*[ti,ab,kw.]                                        | 3 insulin resistan*[tiab] OR insulin resistan*[ot]                     | 3 TITLE-ABS-KEY (impaired glucose tolerance)                           | 3 impaired glucose tolerance:ti,ab,kw                                 |
| 4 impaired glucose tolerance:ti,ab,kw.                                | 4 impaired glucose tolerance [tiab] OR impaired glucose tolerance [ot] | 4 TITLE-ABS-KEY (Wolfram syndrome)                                    | 4 Wolfram syndrome:ti,ab,kw                                           |
| 5 Wolfram syndrome:ti,ab,kw.                                          | 5 Wolfram syndrome [tiab] OR Wolfram syndrome [ot]                     | 5 #1 OR #2 OR #3 OR #4                                                 | 5 #1 OR #2 OR #3 OR #4                                                 |
| 6 1 or 2 or 3 or 4 or 5                                               | 6 #1 OR #2 OR #3 OR #4 OR #5                                           | 6 TITLE-ABS-KEY (peritoneum)                                          | 6 intraperitone*:ti,ab,kw                                             |
| 7 exp peritoneum/                                                     | 7 Peritoneum [mh]                                                      | 7 TITLE-ABS-KEY (intraperitoneal)                                     | 7 peritone*:ti,ab,kw                                                 |
| 8 exp intraperitoneal drug administration/                            | 8 peritoneum[tiab] OR peritoneum[ot]                                   | 8 TITLE-ABS-KEY (peritoneal cavity)                                   | 8 #6 OR #7                                                            |
| 9 exp peritoneal cavity/                                              | 9 intraperitoneal [tiab] OR intraperitoneal [ot]                       |                                                                        |                                                                        |
| 10 (peritone* or intraperitone*).ti,ab,kw.                            | 10 #7 OR #8 OR #9                                                      | 10 TITLE-ABS-KEY (subcutaneous*)                                     | 10 insulin:ti,ab,kw                                                  |
| 11 7 or 8 or 9 or 10                                                  | 11 Subcutaneous*[tw]                                                  | 11 TITLE-ABS-KEY (insulin)                                            | 11 inject*:ti,ab,kw                                                  |
| 12 exp subcutaneous drug administration/                             | 12 Insulin [mh]                                                       | 12 TITLE-ABS-KEY (inject*)                                            | 12 infus*:ti,ab,kw                                                   |
| 13 subcutaneous.ti,ab,kw.                                            | 13 Insulin [tiab] OR Insulin [ot]                                      | 13 TITLE-ABS-KEY (infus*)                                             | 13 admin*:ti,ab,kw                                                   |
| 14 12 or 13                                                           | 14 #12 OR #13                                                         | 14 TITLE-ABS-KEY (admin*)                                             | 14 absorption:ti,ab,kw                                              |
| 15 exp insulin derivative/                                            | 15 Drug administration routes[mh]                                     | 15 TITLE-ABS-KEY (absorption*)                                        | 15 therap*:ti,ab,kw                                                  |
| 16 insulin.ti,ab,kw.                                                 | 16 injection[tiab] OR injection[ot]                                    | 16 TITLE-ABS-KEY (therap*)                                            | 16 treatment:ti,ab,kw                                               |
| 17 15 or 16                                                           | 17 infusion[tiab] OR infusion[ot]                                      | 17 TITLE-ABS-KEY (insulin treatment)                                 | 17 insulin infusion system*:ti,ab,kw                                 |
| 18 exp injection/                                                    | 18 administration[tiab] OR administration[ot]                        |                                                                        |                                                                        |
| 19 infus*.ti,ab,kw.                                                  | 19 absorption[tiab] OR absorption[ot]                                 |                                                                        |                                                                        |
| 20 admin*.ti,ab,kw.                                                  | 20 therap*[tiab] OR therap*[ot]                                        | 20 #5 AND #9 AND #10 AND #11 AND #19                                  | 20 #5 AND #8 AND #9 AND #10 AND #19                                   |
| 21 absorption.ti,ab,kw.                                              | 21 treatment[tiab] OR treatment[ot]                                   |                                                                        |                                                                        |
| 22 inject*.ti,ab,kw.                                                 | 22 Infusion pump[mh]                                                  |                                                                        |                                                                        |
| 23 exp therapy/                                                      | 23 pump[tiab] OR pump [ot]                                            |                                                                        |                                                                        |
| 24 therap*.ti,ab,kw.                                                 | 24 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23        |                                                                        |                                                                        |
| 25 exp insulin treatment/                                            | 25 #6 AND #10 AND #11 AND #14 AND #24                                  |                                                                        |                                                                        |
| 26 exp pump/                                                          |                                                                        |                                                                        |                                                                        |
| 27 insulin pump.ti,ab,kw.                                            |                                                                        |                                                                        |                                                                        |
| 28 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27            |                                                                        |                                                                        |                                                                        |
| 29 6 and 11 and 14 and 17 and 28                                      |                                                                        |                                                                        |                                                                        |
Changes in the systematic review compared to the Protocol

During the data evaluation, we decided to restrict the results to a comparison of the effects of continuous subcutaneous insulin infusion (CSII) and continuous intraperitoneal insulin infusion (CIPII) only, as the pharmacokinetics (and possibly the pharmacodynamics) of multiple daily injections (MDI) differ between the two routes of administration. In general, we observed improved glycaemic control when continuous insulin delivery systems (either intravenous, subcutaneous, or intraperitoneal) were compared to MDI of insulin [1-4], and we concluded that reporting a comparison between CIPII and MDI or mixed MDI/CSII treatment would introduce unnecessary bias. The inability to compare MDI and CSII is also reflected by the differences in pharmacokinetics of the various insulin regimes used with MDI (short-, medium-, or long-lasting) versus the exclusive use of continuous short-lasting insulin infusions during CSII. Therefore, bias could be introduced based on differences in the daily profile of insulin delivery or the type of insulin used, and not just the route of administration per se. Furthermore, studies with missing or insufficient information pertaining to the methods of insulin delivery were also excluded.

In the Protocol, one of the outcomes was identified as ‘Different locations of IP and SC delivered insulin’. After the data extraction, however, we observed that in some included studies [5, 6], patients had been given the choice about where the intraperitoneal (IP) catheter was inserted; in addition, the location could also be changed during the study (e.g., after the replacement of an implanted pump). For instance, in one study, the pumps were placed on the left side of the abdomen in the IP space because all the participants were right-handed [6]. Therefore, the main outcome described as ‘Insulin absorption and parameters that can affect it: Different location of IP and subcutaneous (SC) delivered insulin; Different types of insulin used in the same location’ could not be evaluated.

Regarding the case-control studies, we revised the inclusion criteria, from “we need at least one before CIPII-period and one after CIPII-period measurement point”, to ‘the study is included if measurements from CSII and CIPII patients/periods are reported separately’.

During the data collection, we demoted some of the primary outcomes (Stated in the Protocol) to secondary outcomes. Consequently, we made a decision based on the clinical relevance of the results. The original primary and secondary outcomes were described as follows:

**Primary outcomes**

The main outcomes in the included studies were: (1) Glycaemic control (glycated haemoglobin A1c (HbA1c) levels, self-monitoring of blood glucose (SMBG), fasting blood glucose (BG) and mean BG levels, hypoglycaemic and hyperglycaemic events, time spent in normoglycaemia, and glucose variability), (2) Insulin
levels (fasting insulin level, time until maximum insulin level, maximum insulin level, and elevation of insulin level after administration of a pre-meal insulin bolus), (3) Mean daily insulin requirement.

Secondary outcomes
Secondary outcomes were physiological variables other than the primary outcomes, including the following: (1) Intermediate metabolites (levels of triglycerides, cholesterol, free fatty acids, lactate, ketone bodies, and apolipoproteins), (2) Counterregulatory hormones (levels of glucagon, catecholamines, growth hormone, insulin-like growth hormones, and binding proteins), (3) Other metabolic outcomes (levels of anti-insulin antibodies (AIA), sex hormone binding globulin (SHBG), and plasminogen activator inhibitor-1 (PAI-1)), (4) Any technical and/or physiological complications reported during the CIPII treatment.

Extended information not described in the results

Excluded articles and reasons for exclusion
The search strategy identified 1,517 records. After the removal of duplicates and irrelevant articles, 108 potentially eligible articles remained for consideration (Fig 1).

After full-text and manual reference screening of potential articles and the evaluation of the quality of evidence, 105 articles were included. After additional searches, four more articles were considered for inclusion. After the introduction of additional exclusion criteria (See section above titled: ‘Changes in the Systematic review compared to the Protocol’), 70 of the 109 articles were excluded for the following reasons:

- Forty-one articles did not report CSII and MDI patients/periods separately [7-47];
- two articles reported on only MDI and CIPII, but not CSII [48, 49];
- four technical reports lacked information on physiological effects [50-54];
- two reports were review articles [55, 56];
- three articles compared intravenous (IV) versus IP insulin administration [57-59];
- two articles exhibited biased reporting of the distribution of patients per group [60, 61];
- one article did not provide information about the distribution of patients per groups [62];
- five articles were missing information about pre-implantation SC insulin infusion/injection [63-67];
- one article was an epidemiological study [68];
- two articles assessed patients with a mixture of diabetes mellitus type 1 (DM1) and diabetes mellitus type 2 (DM2) [69, 70];
- two articles did not provide any relevant information [71, 72];
- one article assessed patients treated with IP insulin injections (IPII) delivered as separate boluses, not as a continuous infusion as was used for CIPII [73];
- two articles assessed a CIPII treatment period lasting less than one month [74, 75];
- one article investigated an SC peritoneal access device (SPAD). SPAD allows for absorption of insulin at the tissue close to the peritoneal lining, not from the inside of the peritoneal cavity [76];
- one article did not mention the length of the CSII and CIPII-periods [77].

In the second literature search (follow-up), which screened for studies published in 2016 to 2018, 209 additional records were identified. After the exclusion of irrelevant articles, only one additional article was included in the systematic review [78]. In the third literature search (follow-up) in which we screened studies from the year 2019, 84 additional records were identified. After the removal of all irrelevant articles, no additional articles were included in the systematic review. In the fourth literature search (follow-up) in which we screened for the studies published from 2017 to 2020, 241 records were identified. After the exclusion of irrelevant articles, four records were considered for inclusion; ultimately, only one was included in the systematic review.

In total, 32 studies from 39 articles were included in the systematic review.

Risk of biases
Some studies [79-81] included participants who received MDI therapy, however, the data were also separately available for the CSII and CIPII treatment groups.

One study that provided data for the CSII-period vs. the CIPII-period used a programmable implantable medication system (PIMS). Afterwards, the PIMS was changed to the MiniMed Implantable Pump (MIP). Because two different CIPII pumps were used, the data from the period in which patients were treated with a PIMS insulin pump were compared with the data from the CSII-period. Data pertaining to the complications experienced during the CIPII-period were extracted from both the PIMS and MIP periods [6]. One study included two different experiments with overlapping patient groups; however, data from the study’s second experiment fulfilled our inclusion criteria, and the data for the CIPII and CSII treated patients were extracted [82].

One study did not report essential unit information regarding the daily insulin expenditure [83]. However, we assumed that the insulin expenditure in Table 2 was reported as U/24 hours.

One study did not provide unit information for the mean amplitude of glycaemic excursion (MAGE) [84]. To try to obtain the missing information, we used the reference for the MAGE from the article provided by the authors [85], where, the reported unit was listed as ‘mg/100 mL’.
One study did not state whether the error of the reported data was listed as the SD or the standard error (SE) [86]. Another study did not describe the statistical analysis method [87]. A third study did not state the mean values of the patients’ HbA1c levels [5]. Consequently, these studies were excluded from the HbA1c meta-analyses.

In one study, the units for BG were defined differently in Table 2 (mg/mL) and in the main text (mg/dL); we assumed the correct units to be mg/dL, and those values were used in the analysis. The percentage of blood glucose levels that were high, low or in the normal range were not available due to missing information about the definition of the normal range in that study [88].

Two independent studies provided very similar base line data, with similar methodological description and with identical study periods. However, the authors did not state whether the data in these reports were derived from the same study, from two separate studies, or whether they contained partially overlapping patient populations [89, 90]. E-mails, sent to the authors by IDF to verify the uniqueness of these two studies were not answered.

Another two studies provided similar base line data, with the same year of publication [91, 92]. Those two studies had identical male: female sex ratios, and age ranges (Table 1); however, they differed in the lengths of the follow-up periods, and the baseline HbA1c levels. Therefore, we assumed that the follow-up periods in these two reports were from different time periods, although we cannot discount the possibility of an overlap in the follow-up for these two studies. One of these articles [91] reported HbA1c levels (Fig 2) in the addition to the insulin expenditure, the anti-insulin antibody levels, and complications that occurred during the CIPII-period (Table S2.6). From the other article [92] the data were derived from a figure showing changes in insulin levels, and it was not possible to determine the SD. Therefore, these data were not included in the meta-analysis.

In one study, the data reported in the text were given as the geometric mean values, whereas we used the estimated mean value (Table 2) [93].

One study was a multinational, open, randomised, controlled, crossover study [5]. Due to a high dropout rate (15 out of 30 patients in the CIPII group and 9 out of 30 in the CSII group), the results were analysed as a randomised follow-up study between two parallel treatment groups (i.e., before the crossover).

One study did not provide a definition of severe hypoglycaemia. During the extended periods of the study’s reporting (including conference posters presentations for data at 3, 6, 12, 24 months), the number of severe hypoglycaemic events reportedly increased during the CSII-period [94-97].
Results of the search
The primary search strategy identified 1,517 reports, and 21 more were added after screening of the reference lists. After abstract screening, 105 potentially eligible reports remained (Fig 1). After additional searches, four more articles were considered for inclusion in the analysis.

When applying the additional exclusion criteria (which are described above in the “Changes in the Systematic review compared to the Protocol), 70 of the 109 reports were excluded; these are described in the ‘Excluded reports and reasons for exclusion’ section above.

In total, 38 reports from 32 studies, including one report in Italian [98] and one in German [99], were included (Fig 1).

Data extraction and quality assessment
There was considerable heterogeneity among the studies (Tables S2.1 – S2.6), although most were crossover studies (23 of 32 studies), with at least three months of CSII treatment, followed by 1.5 to 14 months of CIPII treatment. More men (n = 167; 55 %) than women (n = 136; 45 %) were included in the CIPII-period. Thirty out of 32 studies reported the sex of participants, and the ages ranged from 19 to 82 years (Table 1). In the nine studies that reported age separately for each sex, the mean age range (min – max) was 37.1 years (19 – 67) in men and 32.6 years (18 – 50) in women.

Twenty-four studies originated from single European countries (Table 1), four originated from a French multicentre study (EVADIAC: EVALuation dans le Diabète des Implants ACTifs Group) [86, 88, 100, 101], three studies were from the USA [6, 83, 102], and one was a multinational study [5] (Table 1). All results of these studies are summarised in Tables S2.1 – S2.13.

Qualitative data analysis
Primary outcome: Glycaemic control
In addition to including patients who were already being treated with CSII, one randomised [5] and six nonrandomised studies [6, 84, 88, 91, 103, 104] provided participants with an additional CSII follow-up before transitioning them to the CIPII treatment. In three of these studies, the HbA1c levels decreased during this additional CSII follow-up period [5, 103, 104].

Randomised follow-up studies
One prospective, randomised, follow-up study (for details see the section titled, ‘Risk of biases’) observed equivalent reduction in HbA1c levels in the two treatment groups (CIPII: - 0.5 %; CSII: - 0.6 %, p = 0.374) and no difference in SMBG values during the twelve months of CIPII treatment and the six months of CSII treatment [5].
Non-randomised and retrospective crossover studies

Glycated haemoglobin A1c

Significantly lower (p < 0.05) mean HbA1c levels were reported during the CIPII treatment period in eight prospective studies and one retrospective study. HbA1c level decreased from 83.6 – 56.3 mmol/mol (9.8 – 7.3 %) to 60.7 – 44.3 mmol/mol (7.7 – 6.2 %) (Fig 2) [6, 83, 87-90, 94-97, 105].

No differences in mean HbA1c levels were reported in five studies [98, 101, 102, 106-108]. In one study the HbA1c levels decreased after three months of CIPII treatment (54.1 mmol/mol (7.1 %)), whereas no statistical difference was observed after 12 months of CIPII treatment compared to the previous CSII treatment (58.5 vs. 59.6 mmol/mol (7.5 % vs. 7.6 %)) [101]. Five studies did not report statistical analyses comparing the two treatments (Table S2.1) [86, 91, 103, 104, 109]. The lack of SD/SE data resulted in the exclusion of three of these studies from the meta-analysis (Fig 2) [5, 86, 87].

Self-monitored blood glucose

Three studies that reported on SMBG concentrations showed a decrease in BG levels from 7.8 – 10.5 mmol/L to 7.4 – 8.0 mmol/L (p < 0.05) [83, 88, 96, 102], whereas four studies reported no difference in SMBG levels (Fig S1, Table S2.1) [6, 84, 86, 108]. However, in one of these studies, SMBG levels decreased during the first 16 months of CIPII treatment, but was equal to those following CSII after 18 months [6]. Three studies did not conduct statistical testing to compare the two treatments [103, 104, 109].

Glucose variability

One study reported a lower MAGE value during the CIPII treatment period compared to the CSII treatment period (6.9 vs. 9.5 mmol/L, p < 0.005) [84]. Another five studies reported a decrease in SD of BG levels during CIPII-period compared to the CSII-period (3.0 – 3.8 mmol/L vs. 3.4 – 5.1 mmol/L, p < 0.04) (Table S2.1) [86, 88-90, 108].

Continuous glucose monitoring

One study reported decreased mean BG levels (measured by continuous glucose monitoring (CGM)) (8.3 vs. 10.5 mmol/L, p = 0.004), increased time spent in normoglycaemia (3.9 – 10.0 mmol/L, p = 0.001), and a narrower BG range (4.4 – 7.8 mmol/L, p = 0.03) in the CIPII-period than in the CSII-period [78]. Another study with CGM reported an increase in the time spent in normoglycaemia (3.9 – 10.0 mmol/L, p = 0.027) during the CIPII-period [94-97].

One study reported decreased pre-prandial BG levels (p < 0.05) [88], whereas another observed decreased post-prandial BG levels (p < 0.01) [87]. Two studies reported no difference in pre-prandial BG levels [86, 88]
and two studies reported no difference in post-prandial BG levels during the CIPII-period [86, 88]. One study did not conduct statistical comparison of the two treatments [103].

**Case-control studies**

Among the four included case-control studies that reported HbA1c levels, no difference was observed between the treatment groups (Fig 2) [82, 88, 99, 110-112]. One of these studies also reported no difference in pre-prandial and post-prandial BG levels [82].

**Case studies**

Only one case study was included, which reported no difference in glycaemic control between the CIPII and CSII treatments (Table S2.1) [113]. Due to large SD values, these results could not be included in the meta-analysis.

**Primary outcome: Hypo-/ hyperglycaemia**

**Randomised follow-up studies**

In one study, the frequency of severe hypoglycaemia (requiring hospitalization or IV glucose administration, or events accompanied by unconsciousness or seizure) was significantly reduced during the CIPII compared to the CSII follow-up periods (0.35 vs. 0.86 events/patient-years, p = 0.013). During the first three months after the initiation of CIPII treatment, the frequency of severe hypoglycaemic events was unchanged, whereas it was reduced in the subsequent nine months (0.72 vs. 0.15 events/patient-years). During CSII treatment the frequency of severe hypoglycaemia was 1.6 events per one patient-year at baseline which was reduced to 0.86 events per one patient-years during the CSII follow-up period [5]. No difference in the frequency of hypoglycaemic episodes (SMBG level < 3 mmol/L) was observed during the CIPII treatment period. Furthermore, no difference was observed between the first three months and the subsequent nine months of CIPII treatment (Tables S2.1 and S2.8) [5]. Statistical analyses were only reported for comparison between the CIPII and CSII treatment groups; no within-group analyses were performed.

**Non-randomised crossover studies**

**Severe hypoglycaemia and hypoglycaemic coma**

Four studies recorded severe hypoglycaemia, but none conducted any statistical analyses [6, 81, 94-98]. One study reported no difference in the frequency of hypoglycaemic coma events (CIPII: 0 vs. CSII: 0.54 events/patient-year) [81]. Another study reported that the frequency of severe hypoglycaemia (requiring assistance) was 0.43 events per one patient-year during the CIPII-period while no episodes of hypoglycaemic coma were observed [6].
One study reported 1.5 severe hypoglycaemic (requiring assistance) events per one patient-year during the CIPII compared to the 12 events per one patient-year during CSII-period [94-97]. Another study reported no severe hypoglycaemic (requiring assistance) events during the CIPII-period [81], and one study reported no difference in the occurrence of severe hypoglycaemia [98].

**Hypoglycaemia**

One study reported a reduction in the time spent in hypoglycaemia during CIPII-period (SMBG level < 3.9 mmol/L, \( p < 0.05 \)), whereas the duration of time spent with SMBG levels < 2.8 mmol/L was similar between the treatment periods [84]. On the contrary, one 24-hour BG profile study reported no difference in the time spent in hypoglycaemia (BG < 3.8 mmol/L, measured by CGM) [78]. Similarly, two other studies reported no difference in hypoglycaemic events (SMBG level < 3.0 mmol/L) [89, 90]. One study reported at least one hypoglycaemic event (SMBG level < 3.3 mmol/L) per patient during CIPII-period [6].

**Hyperglycaemia**

One study using CGM [78] reported less time spent in hyperglycaemia (BG > 10 mmol/L, \( p < 0.05 \)), whereas another study using SMBG reported no difference [84]. However, both reported a reduction in the time spent in severe hyperglycaemia (BG > 14 mmol/L, \( p < 0.05 \), measured by SMBG and CGM) during CIPII-period. (Tables S2.1 and S2.8) [78, 84].

**Primary outcome: Insulin levels**

**Randomised crossover and follow-up studies**

In one study, five patients being treated during the CIPII-period were crossed over to receive 96-hour CSII treatment temporarily. Insulin was infused for 12 hours at a fixed basal rate. Fasting serum free insulin levels were decreased during the CIPII-period compared to the CSII-period (30.8 vs. 45.0 pmol/L, \( p < 0.001 \)) [100]. Subsequently, insulin was infused a rate of 15 nmol/h for 150 minutes, then 42 nmol/h for the following 150 minutes. During these two short-term periods with increased infusion rates, the rate of appearance (Ra) of insulin in the systemic circulation was greater during CIPII treatment (\( p < 0.05 \) and \( p < 0.01 \), respectively) [100].

No difference in the mean daily insulin requirement was observed in a prospective study with 36 patients, although no statistical analyses were performed [5].

**Non-randomised crossover studies and follow-up studies**

Two studies reported lower fasting insulin levels (\( p < 0.05 \) and \( p < 0.01 \)) [89, 90], despite a higher basal insulin infusion rate during CIPII (\( p = 0.02 \)) [89]. Two studies reported no difference in fasting insulin levels between
the two periods [87, 109]. Another two studies did not perform statistical comparisons between treatments [103, 104]. Two studies (with 20-hour and 16-hour insulin profiles) reported decreased night-time insulin levels during CIPII (127.8 vs. 163.2 pmol/L, \( p < 0.05 \); and 70.1 vs. 128.5 pmol/L, \( p < 0.01 \), respectively) [87, 103].

Two studies reported earlier post-bolus maximum insulin levels, peripherally, during the CIPII-period (60 vs. 133.6 minutes, \( p < 0.006 \) [92]; and 60 vs. 180 minutes, \( p < 0.05 \) [87]). The latter study reported increased maximum insulin levels during the CIPII-period (179.18 vs. 125.01 pmol/L, \( p < 0.05 \) [87]). Furthermore, during the CIPII-period, insulin levels returned to baseline values three hours after administration of a pre-breakfast bolus, whereas during the CSII-period, the post-bolus insulin level remained elevated five-and-half hours later [87]. One study that performed insulin clamp testing reported no difference in the maximum insulin levels between the periods; however, the first measurement was recorded 30 minutes after the administration of insulin boluses [89]. One study reported increased insulin levels (\( p < 0.05 \)) during exercise in those receiving CSII, although, insulin levels did not change during exercise in the CIPII group [90].

One study reported a lower total area under curve (AUC) (16 hours) (72 vs. 100 mU/L/h, \( p < 0.01 \)) and a lower night-time AUC (12 vs 36 mU/L/h, \( p < 0.01 \)) during the CIPII period. The AUC following administration of an insulin bolus did not differ between the periods; however, the duration of the period for which the AUC was calculated was not specified [87].

In two studies, day-time mean insulin requirements were increased (\( p < 0.05 \)) during CIPII-period [86, 108]. However, in one of these studies, the insulin requirement was increased only during the first two months of CIPII treatment before decreasing to levels that were similar to those in the previous CSII-period [108].

Other studies reported no change in insulin requirements between the periods, 12 of which performed statistical analyses [83, 84, 89, 90, 94-98, 101, 102, 105-109] (Table S2.2.).

On the contrary, one 24-hour closed-loop artificial pancreas study reported increased insulin delivery during closed-loop CIPII than during closed-loop CSII (43.7 U vs. 32.3 U, \( p < 0.001 \)) [78].

**Case-control studies**

One study reported decreased mean night-time insulin levels in the CIPII-treated patients (65.56 vs. 86.53 pmol/L, \( p < 0.005 \)) [99], whereas two studies reported no difference in fasting insulin levels between the two groups [82, 114].

One study reported earlier peaking of post-bolus (0.15 U/kg) insulin levels in CIPII-treated patients (30 minutes vs. 60 minutes, p-value not reported), increased maximum insulin levels (263.91 vs. 145.84 pmol/L
(significance between groups starting 30 minutes after bolus administration, \( p < 0.05 \)), and a decreased duration of elevated insulin levels (180 minutes vs. 240 minutes, \( p \)-value not reported) [82]. No differences in the mean daily insulin requirement were reported in three studies that performed statistical analyses [99, 110-112, 114] (Table S2.2).

**Case reports**

One case report showed no difference in daily insulin requirements [113].

**Secondary outcomes: Intermediate metabolites**

All reports that analysed intermediate metabolites are summarised in Table S2.3.

**Non-randomised crossover studies**

One study reported decreased total cholesterol levels after six months of the CIPII-period compared to those in the CSII-period (4.56 mmol/L vs. 4.85 mmol/L, \( p = 0.044 \)) [102]. In the remaining six studies, no differences in total cholesterol levels were observed after six weeks to one year of CIPII treatment (Fig S2) [83, 84, 98, 106-109].

In one study, high-density lipoprotein (HDL)-cholesterol levels were lower during CIPII-periods compared to the CSII-periods (1.2 mmol/L vs. 1.4 mmol/L, \( p < 0.05 \)) [84]. In five studies, no difference in HDL-cholesterol levels was observed between the periods [83, 98, 102, 106-108]. No difference in low-density lipoprotein (LDL)-cholesterol levels was observed in four studies [98, 102, 106-108].

One study reported an increase in fasting serum triglyceride levels after the CIPII-period (1.5 mmol/L vs. 0.9 mmol/L, \( p < 0.005 \)) [84]. In six studies, no difference in triglyceride levels was observed between the two periods (Fig S3) [83, 98, 102, 106-109].

The chylomicron remnant levels, the ratio of retinyl ester: apoB lipoproteins, and the HDL compositions reported in the studies are provided in Table S2.3.

**Case-control studies**

One study reported decreased fasting free fatty acid (FFA) levels during the CIPII-period compared to the CSII-period (\( p = 0.05 \)), whereas during the 60 minutes after the administration of a pre-meal insulin bolus, no changes in FFA levels were observed within the groups. However, decreased FFA levels were observed in the CIPII-period after administration of a pre-meal insulin bolus (\( p = 0.05 \)) [82].

The measurements of lactate, vitamin D metabolites, creatinine, calcium, magnesium, phosphorus, parathyroid hormone, osteocalcin, and alanine reported in the studies are summarised in Table S2.3.
Secondary outcomes: counterregulatory hormones
All reported counterregulatory hormone analyses are summarised in Table S2.4.

Non-randomised crossover studies and follow-up studies
During a hypoglycaemic clamp, one study reported a significant incremental glucagon response during CIPII \( (p = 0.003) \), whereas the glucagon response was non-significant during CSII. Consequently, the maximal glucagon response was higher during CIPII \( (17.0 \text{ pg/mL vs. 7.5 pg/mL, } p = 0.048) \) [89]. One study reported increased glucagon levels post-exercise during CIPII-periods \( (p = 0.01) \); however, no difference in glucagon levels was observed between the CIPII and CSII-periods [90]. Significantly larger AUC was observed for the incremental glucagon response in the CIPII-period during hypoglycaemic insulin clamp testing and after intense exercise compared to pre-clamp testing and pre-exercise testing \( (44.4 \text{ pg/mL/h vs. 5.1 pg/mL/h, } p = 0.027; \text{ and } 23.4 \text{ pg/mL/h vs. 10.3 pg/mL/h, } p = 0.04, \text{ respectively}) \) [89, 90]. A significantly larger incremental post-exercise AUC compared to post-exercise \( (23.4 \text{ pg/mL/h vs. 10.3 pg/mL/h, } p = 0.04) \) was also observed [90].

Two studies reported no change in epinephrine and norepinephrine incremental responses between the two periods during respective hypoglycaemic insulin clamp testing [89] or intensive exercise [90].

The results of measured changes in growth hormone (GH), insulin like growth factor 1 (IGF-1) and 2 (IGF-2), growth hormone binding protein (GHB), insulin-like growth factor binding protein 2 (IGFBP-2) and 3 (IGFBP-3), and cortisol are summarised in Table S2.4.

Case-control studies
One study reported no difference in fasting and postprandial glucagon levels between the treatment groups [82].

Secondary outcome: Other metabolic outcomes
All other reported analyses are summarised in Table S2.5.

Non-randomised crossover and follow-up studies
Increased levels of anti-insulin antibodies (AIA) measured by enzyme-linked immunosorbent assay (ELISA), were observed after three and twelve months of the CIPII-period \( (39.3 \% \text{ and } 42.5 \% \text{ vs. } 23.7 \%, \text{ respectively, } p < 0.01) \), but not after 24 months [79, 80], and at three months of the CIPII-period in another study \( (11.0 \% \text{ vs. } 3.6 \%, \text{ p < 0.05}) \) [86]. No difference was observed in one study [91], and another reported no changes in the AIA levels \( (p\text{-value not reported}) \) [78].

One follow-up study observed increased AIA levels after six months of the CIPII-period vs. six months of the CSII-period \( (41.8 \% \text{ vs. } 24.9 \%, \text{ p = 0.009}) \), as measured by radioimmunoassay (RIA), although they observed no difference when AIA levels were measured by ELISA [115].
Studies reporting sex hormone binding globulin (SHBG) levels are summarised in Table S2.5.

Secondary outcome: Complications
All reported technical and physical complications are summarised in Table S2.6.

How to read the tables
The source column lists the main author and the year of publication. In cases where the authors and year of publication are the same for two studies, some additional information is provided in differentiation. Alternatively, when there is no information given in other columns, information is provided that could explain the missing data. For example, if there is no information provided under the ‘Reported study objectives’ and/or ‘methodological quality’ columns, it could be because information was extracted from a letter to the editor.

The ‘Participant characteristics’ column supplies information about the number of participants and some characteristics we believe are important for describing the actual patients. More detailed information can be found in the original publications.

In the ‘Length of’ column, we provide information about the duration of the CIPII and/or CSII-periods, and, if available, some information about patient follow-up. Most data are given as the means.

In the ‘Reported study objectives’ column we present the precise information as stated in the articles.

We extracted data from text, tables, and graphics, all of which is included in the ‘Outcomes’ column. In cases, where information was missing, possible biases are indicated in the systematic review’s Results section.

Some articles included figures showing measurements of continuous variables (for example, 16-hour measurements). From such figures, we extracted data from fasting periods and noted data that was significantly different between the two periods. If data for continuous variables measurements were not significantly different, it was mentioned in the Results without providing any additional data.

Units of the measurement are indicated after the CSII data (for example, HbA1C measurements, CIPII: 8.7; CSII: 8.8 %).

Definition of words used:

**Increases** means that in the CIPII-period, levels were statistically significantly higher ($p < 0.05$) than those in the CSII-period.

**Decreases** means that in the CIPII-period, levels are statistically significantly lower ($p < 0.05$) than those in the CSII-period.

**Decreases/increases in both** means that the values followed the same pattern when compared at different time-points.
**No change** means a statistically non-significant difference ($p > 0.05$) or the $p$-value not provided (ND). If possible, data are shown in parentheses.

**M3, M6, and M12**, for example, should be read as ‘three months’, ‘six months’, and ‘twelve months’.

The ‘Methodological quality’ column contains quality assessment tools that are appropriate for that particular study.
### Table S2.1. Intervention studies: Participant characteristics, description, outcomes: glycaemic control

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-------------------------------------------------------------------------------------------------------------------------------|------------|--------------------------|--------------------------|------------------------|
| Randomized follow-up studies | | | | | |
| Liebl et al. 2009 [5] | N = 60* (CPII: 30 /CSII: 30) Age: 50.5/45.3 | CSII use: ND CSII f-u: 26 CPII f-u: 52 | Comparison of frequency of hypoglycaemia, severe hypoglycaemia, metabolic control, diabetic QoL and safety between CSII and CPIII in type 1 diabetic patients. | HbA1c: Decreases in both groups (CPII: - 0.5; CSII: - 0.6 %, p=0.374) SMBG: No change (CPII: + 0.1; CSII: ± 0.0 mmol/L, p=NS) BG < 3 mmol/L: No change (All CPII-period: 118.2; M1-3: 138.1; M4-12: 108.9; CSII: 115.8 events/patient-years, p=NS) Severe hypoglycaemia: Decreases (Before CPII: 0.7; All CPII-period: 0.35, M1-3: 0.72; M4-12: 0.15, p=ND; Before CSII: 1.6; CSII-period: 0.86 events/patient-years, p=ND; CPII vs CSII-period: p=0.013) | CRB: Unclear risk of bias: Random sequence generation, allocation concealment, blinding Low risk of bias: Incomplete outcome data, selective reporting, treatment procedure |
| Non-randomized crossover studies | | | | | |
| Micossi et al. 1986 [84] | N = 6 Age: 38.8 Diabetes duration: 12.6 Sex: 3/3 HbA1c: 7.25 C-peptide: ≤ 0.02 pmol/mL Reasons: Pmc | CSII use: 12 CSII f-u: 6 CPII f-u: 6 | To investigate the hormonal and metabolic patterns produced by CPII in group of severely unstable DM1 who has previously responded poorly to CSII. To compare clinical and metabolic effects of CPII and CSII. | Glucose production in basal period: (CPII: 2.92; CSII: 5.9 mmol/L, p=NS) SMBG: No change (CPII: 8.8; CSII: 9.7 mmol/L, p=NS) BG < 14 mmol/L: Decreases (CPII: 8.9; CSII: 16.1 %, p<0.005) BG < 10mmol/L: No change (CPII: 31.8; CSII: 44.7 %, p=NS) BG < 3.9 mmol/L: Decreases (CPII: 4.5; CSII: 6.2 %, p<0.005) | STROBE: 15/22 QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Selection bias, study design Weak: Confounders |
| Beyl et al. 1987 [103] | N = 4 Age: 42 Diabetes duration: 21.5 Sex: 3/1 HbA1c: 7.6 (9.2 – 5) C-peptide: ND Reasons: Volunteers | CSII use: ND CSII f-u: 8 CPII f-u: 8 Washout: 1 day | To determine if IP insulin administration could, in addition to decreasing peripheral insulin levels, improve the insulin resistance of DM1. | HbA1c: Decreases (CPII: 6.2; CSII: 6.5 % (CPII: 44; CSII: 56 mmol/mol), p=ND) SMBG: No change (CPII: 8.20; CSII: 8.77 mmol/L, p=ND) Pre-prandial BG: No change (CPII: 5.9; CSII: 5.4 mmol/L, p=ND) Endogenous glucose production in basal period: No change (CPII: 2.92; CSII: 2.93mg/kg/min, p=ND) Glucose utilization in basal period: No change (CPII: 3.30; CSII: 3.62 mg/kg/min, p=ND) | STROBE: 15/22 QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Selection bias, study design, confounders |
| Wredling, Adamson et al. 1991 [91] | N = 6 Age: 41.3 Diabetes duration: 23.2 Sex: 4/2 HbA1c: 8.7 C-peptide: Neg Reasons: Pmc | CSII use: 52+ CSII f-u: 8 (n=3) CPII f-u: median 72 | To determine the efficacy of a new percutaneous device. | HbA1c*: No change (CPII: 7.6; CSII: 8.7 % (CPII: 60; CSII: 72 mmol/mol), p=ND) | Unclear: Confounders |

**Legends:** CSII, continuous subcutaneous insulin infusion; CPII, continuous intraperitoneal insulin infusion; ND, no data available; Pmc, Poor metabolic control; NS, Not significant; BG, blood glucose; MPG, mean plasma glucose; SMBG, self-monitored BG; MAGE, mean amplitude of glycaemic excursion; *: dropouts in this study (at the end of the periods N= 36 (CPII: 15/CSII: 21)); **: data calculated from table.
### Table S2.1. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------|-------------------------------------------------|--------------------------|------------------------|------------------------|
| Georgopoulos et al. 1992 [83] | N = 7 Age: 27 Diabetes duration: 12 Sex: 5/2 HbA1c: 9.8 C-peptide: ND Reasons: ND | CSII use: ND CSII f-u: 52-60 | To investigate whether long-term improved glycaemic control by intraperitoneal insulin infusion normalizes the compositional abnormalities of triglyceride (TG)-rich lipoproteins in DM1. | HbA1c: Decreases (CIPII: 7.7, CSII: 9.8 % (CIPII: 61; CSII: 84 mmol/mol), p<0.001) SMBG: Decreases (CIPII: 7.7; CSII: 10.5 mmol/L, p<0.02) | STROBE: 11/22 QAT: Strong: Data collection methods, withdrawals and dropputs Moderate: Selection bias, study design, confounders |
| Pitt et al. 1992 [6] | N = 10 Age: 33.2 Diabetes duration: 23.2 Sex: 8/2 HbA1c: 9.1 C-peptide: Neg Reasons: Volunteers | CSII use: 12+ CSII f-u: 8 CSII f-u: 240 | Document nearly 70 patient-years of experience with IP insulin delivery, with longest over 5 years, in 21 patients with type I diabetes. | HbA1c<sup>#</sup>: Decreases (CIPII: M18: 8.0, p<0.05; M16: 8.6, p=NS; M12: 8.0, p<0.05; M6: 7.5, p<0.05; CSII: 9.1 % (CIPII: M18: 64; M16: 70; M12: 64; M6: 58; CSII: 76 mmol/mol)) SMBG: No change (CIPII: M18: 7.8, p=NS; M16: 7.7, p<0.05; M12: 7.8, p<0.05; M6: 7.2, p<0.05; CSII: 8.9 mmol/L, p<0.05) BG < 3.3 mmol/L: No change (ND) | STROBE: 18/22 QAT: Strong: Confounders, withdrawals and dropouts Moderate: Selection bias, study design, data collection methods |
| Renard et al. 1993 [81] | N = 8 Age: 41.6 Diabetes duration: 14.0 Sex: 6/2 HbA1c: ND C-peptide: Neg Reasons: Volunteers | CSII use: 52 CSII f-u: 52 | To gain experience in assessing the feasibility of therapeutic mode in DM1 patients, who had previous long-term experience of ambulatory SC insulin delivery portable devices. | SMBG: Based on mixed results (MDI and CSII) data is not included in the review Severe hypoglycaemia: Decreases (CIPII: 0; CSII: 0.54 events/patient-year, p=ND) Hypoglycaemic coma: Decreases (CIPII: 0; CSII: 0.54 events/patient-years, p=ND) Ketoadosis: Decreases (CIPII: 0; CSII: 0.14 events/patient-years, p=ND) | STROBE: 19/22 QAT: Strong: Confounders, data collection methods Moderate: Selection bias, study design Weak: Withdrawals and dropouts |
| Georgopoulos et al. 1994 [102] | N = 8 Age: 37 Diabetes duration: 21.6 Sex: 5/3 HbA1c: 9.4 C-peptide: ND Reasons: ND | CSII use: ND CSII f-u: 26 | Test hypothesis that CIPII will decrease the level of circulating chylomicron remnants in patients with DM1. | HbA1c: No change (CIPII: 8.7; CSII: 9.4 %, p=NS) SMBG: Decreases (CIPII: 7.4; CSII: 7.82 mmol/L, p=0.027) | STROBE: 14/22 QAT: Strong: Data collection method, withdrawals and dropouts Moderate: Study design, confounders Unclear: Selection bias |
| Lassmann et al. 1994 (short communication) [104] | N = 11 Age: 34.4 Diabetes duration: 22.4 Sex: 5/6 HbA1c: 7.0 C-peptide: Neg Reasons: ND | CSII use: 26+ CSII f-u: 4 CSII f-u: 12 | ND | HbA1c: No change (CIPII: 6.8; CSII: 6.9 %, p=ND) SMBG: No change (CIPII: M1: 7.9; M3: 8.3; CSII: 8.3 mmol/L, p=ND) | NP |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; BG, blood glucose; SMBG, self-monitored BG; Severe hypoglycaemia, requiring assistance; Ketoadosis, vomiting and/or nausea in the presence of hyperglycaemia (BG>13 mmol/L), more details in the main article;<sup>#</sup>, data extracted from figure.
## Table S2.1 (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, CIPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------|--------------------------|-----------------------|
| Glycaemic control |                                                                                                                                  |                                                             |                          |                          |                       |
| Raccah et al. 1994 (letter) [109] | N = 11  
Age: 34.4  
Diabetes duration: 22.3  
Sex: 6/5  
HbA1c: 6.9  
C-peptide: ND  
Reasons: ND | CSII use: 12  
CIPII f-u: 40 | To compare insulin demands during 24 h in CIPII and CSII patients.  
To compare HbA1c levels in CIPII and CSII patients. | HbA1c: No change (CIPII: M10: 6.3; M3: 6.8; CSII: 6.9 %, p=ND)  
SMBG: No change (CIPII: M3: 8.3; M10: 8; CSII: 8.3 mmol/L, p=ND) | STROBE: 17/22  
QAT:  
Strong: Withdrawals and drop-outs  
Moderate: Selection bias, study design, confounders, data collection method |
| Schnell et al. 1994 [105] | N = 5  
Age: 35.8  
Diabetes duration: 20.2  
Sex: 1/4  
HbA1c: 9.8  
C-peptide: ND  
Reasons: ND | CSII use: 156-364  
CIPII f-u: 52 | To compare the effects of IP insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | HbA1c: No change (CIPII: M12: 8.5, p<0.05; M3: 8.6, p<0.05; CSII: 9.8 %) | STROBE: 16/22  
QAT:  
Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs  
Moderate: Study design |
| Guerci et al. 1996 [108] | N = 14  
Age: 40.0  
Diabetes duration: 16.4  
Sex: 9/5  
HbA1c: 6.1  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 52+  
CIPII f-u: 16 | To determine the effects of IP IPI on qualitative lipoprotein abnormality. | HbA1c: No change (CIPII: M12: 5.9; M3: 6.1 %, p=NS)  
SMBG: No change (CIPII: 7.55; CIPII: 7.78 mmol/L, p=NS)  
SD of BG: Decreases (CIPII: 3.0; CSII: 3.4 mmol/L, p<0.01) | STROBE: 16/22  
QAT:  
Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs  
Moderate: Study design |
| Hanaire-Brouin et al. 1996 [101] | N = 18  
Age: 43.0  
Diabetes duration: 20.0  
Sex: 11/7  
HbA1c: 7.6  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 128  
CIPII f-u: 52 | To evaluate the impact of IP insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | HbA1c: No change (M12: 7.5, p=NS; M3: 7.1, p<0.02; CSII: 7.6 %) | STROBE: 16/22  
QAT:  
Strong: Study design, data collection methods  
Moderate: Selection bias, confounders, withdrawals and drop-outs |
| Lassmann-Vague et al. 1996 [87] | N = 11  
Age: 36.3  
Diabetes duration: 17.8  
Sex: 6/5  
HbA1c: ND  
C-peptide: ND  
Reasons: ND | CSII use: ND  
CSII f-u: ND  
CIPII f-u: 8 | To compare plasma free insulin levels achieved in patients with DM1 chronically treated with CSII and CIPII. | HbA1c: Decreases (CIPII: 6.9; CSII: 7.7 %, p<0.001)  
16-hour blood glucose profile:  
BG during night (12:00 am): No change (CIPII: 9.1; CSII: 9.3 mmol/L, p=ND)  
4:00 am: No change (CIPII: 7.7; CSII: 7.9 mol/L, p=ND)  
Post-prandial BG (9:30 am): Decreases (CIPII: 7.8; CSII: 12.7 mmol/L, p<0.01)  
3:00 pm: Decreases (CIPII: 7.5; CSII: 12.8 mmol/L, p<0.01) | STROBE: 14/22  
QAT:  
Strong: Data collection method, withdrawals and drop-outs  
Moderate: Selection bias, study design  
Weak: Confounders |

**Legends:** CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; BG, blood glucose; SMBG, self-monitored BG; SD of BG, standard deviation of BG.
| Source | Participant characteristics (Number, age [mean years], diabetes duration [mean years], sex [Male/Female], HbA1c [%], C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--------------------------|-------------------------|
| Pacifico et al. 1997 [98] | N = 8  
Age: 35.1  
Diabetes duration: 19  
Sex: S/4  
HbA1c: 6.5  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 12+  
IPII f-u: 52+ | To evaluate the safety, the efficacy and the results after 3 years of CIPII | HbA1c: No change (M12: 6.6 CSII: 6.5 %, p=NS)  
Severe hypoglycaemia: No change (CIPII: 0.11 events/patients/year CSII: ND) | STROBE:19/22  
QAT:  
Strong: Study design, data collection methods, selection bias  
Moderate: Confounders, withdrawals and drop-outs |
| Oskarsson et al. 1999 [90] | N = 7  
Age: 42  
Diabetes duration: 15  
Sex: S/2  
HbA1c: 8.5  
C-peptide: < 0.2 nM  
Reasons: Pmc | CSII use: 26+  
IPII f-u: 47-82 | To assess the clinical relevance of the blood glucose, hypoglycaemia, glucagon secretion during exercise by comparing glycaemic and hormonal responses to a 40-min bicycle exercise test at 60% of VO \textsubscript{max} during CSII and CIPII in type 1 diabetic patients. | HbA1c: Decreases (CIPII: 7.1; CSII: 8.5 %, p<0.01)  
SD of BG (stability index): Decreases (CIPII: 3.5; CSII: 5.1 mmol/L, p=0.02)  
BG < 3.0 mmol/L: No change (CIPII: 0.7; CSII: 3.8 events/months, p=0.07) | STROBE:16/22  
QAT:  
Strong: Confounders, data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, study design |
| Oskarsson et al. 2000 [89] | N = 7  
Age: 42  
Diabetes duration: 17  
Sex: S/2  
HbA1c: 8.6  
C-peptide: Neg  
Reasons: Pmc | CSII use: 52+  
IPII f-u: 47-86 | To expose the patients to an identical hyperinsulinemic clamp with special emphasis on the glucagon response in the same patients during continuous treatment with CSII and CIPII. | HbA1c: Decreases (CIPII: 7.2 CSII: 8.6 %, p<0.01)  
SD of BG: Decreases (CIPII: 3.5; CSII: 5.1 to mmol/L, p=0.02)  
Pre-prandial BG: No change (CIPII: 6.3; CSII: 6.2 mmol/L p=NS)  
BG < 3.0 mmol/l: No change (CIPII: 0.7; CSII: 3.8 event/month, p=0.07) | STROBE:16/22  
QAT:  
Strong: Confounders, data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, study design |
| Duvillard et al. 2005 (Brief report) [106] | N = 7  
Age: 48  
Diabetes duration: 17  
Sex: 6/1  
HbA1c: 7.34  
C-peptide: ND  
Reasons: ND | CSII use: ND  
IPII f-u: 12 | Compare if replacement of SCI with IPII restores the normal physiological gradient between the portal vein and peripheral circulation, which is likely to modify lipoprotein metabolism. To compare HDL apolipoprotein (apo) A1 metabolism in patients treated with CSII and CIPII. | HbA1c: No change (CIPII: 7.24; CSII: 7.34 %, p=NS) | STROBE:19/22  
QAT:  
Moderate: Data collection methods, study design, withdrawals and drop-outs  
Poor: Selection bias, confounders |

Legend: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; BG, blood glucose; SMBG, self-monitored BG.
### Table S2.1. (Continued)

| Source                          | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------|--------------------------|-------------------------|
| Liebl et al. 2013 (conf. Abstracts/Poster) [94-96] | N = 12 [n = 10] *<br>Age: 49 <br>Diabetes duration: 30<br>Sex: 2/10<br>HbA1c: 9.0 (8.8)*<br>C-peptide: ND<br>Reasons: Pmc | CSII use: ND CSII f-u: 104 | To investigate the clinical long-term performance and safety of the new Accu-ChekDiaPort system. | HbA1c: Decreases (CIPII: M24*: 7.2, p=0.003; M12: 7.6, p=0.002; M6: 7.57, p<0.001; CSII: 9.0 %)<br>BG (by CGM) > 10.0 mmol/L: Decreases (CIPII: M6: 38: CSII: 53 %, p=0.036)<br>BG (by CGM) in range 3.9 - 10.0 mmol/L: Increases (CIPII: M6: 58; CSII: 45 %, p=0.027)<br>Severe hypoglycaemia: No change (CIPII: 3 events/24 months; CSII: 12 events/12 months, p=ND) | NP |
| Dassau et al. 2017 [78] | N = 10<br>Age: 49<br>Diabetes duration: 29<br>Sex: 7/3<br>HbA1c: 7.7<br>C-peptide: ND<br>Reasons: Pmc | CSII use: 443<br>CSII f-u: 24h<br>CIPII f-u: 4 to 20<br>Washout: 4 to 20 | To compare closed-loop zone MPC using the DiaPort IP insulin delivery system with the traditional SC insulin delivery method during a 24-hour in-clinic protocol. | BG (by CGM): Decreases (CIPII: 8.3; CSII: 10.5 mmol/L, p=0.004)<br>BG > 14 mmol/L: Decreases (CIPII: 5.9; CSII: 23.0 %, p=0.0004)<br>BG > 10 mmol/L: Decreases (CIPII: 32.4; CSII: 53.5 %, p=0.0014)<br>BG in range 3.9 to 10 mmol/L: Increases (CIPII: 65.7; CSII: 43.9 %, p=0.001)<br>BG in range 4.4 to 7.8 mmol/L: Increases (CIPII: 39.8; CSII: 25.6 %, p=0.03)<br>BG < 3.8 mmol/L: No change (CIPII: 2.5; CSII: 4.1 %, p=0.42) | STROBE: 20/22<br>QAT: Strong: Data collection methods, withdrawals and drop-outs, study design Moderate: Selection bias, confounders |
| Jeandidier et al. 1992 (Preliminary results) [86] | N = 8<br>Age: 33.5<br>Diabetes duration: 14.5<br>Sex: ND<br>HbA1c: 6.64<br>C-peptide: Neg<br>Reasons: ND | CSII use: 12 | To assess the potential benefits of CIPII vs SCII. | HbA1c: No change (CIPII: 6.7; CSII: 6.64 %, p=ND)<br>SD of BG: Decreases (CIPII: 3.3; CSII: 3.6 mmol/L/24h, p=0.038)<br>Pre-prandial BG: No change (CIPII: 7.2; CSII: 7.8 mmol/L, p=0.051)<br>Post-prandial BG: No change (CIPII: 8.7; CSII: 10.1 mmol/L, p=0.051)<br>BG < 3.6 mmol/L: No change (CIPII: 3.6; CSII: 4.0 events/week, p=ND) | STROBE and QAT: | STROBE: 12/22<br>QAT: Weak: Study design Unclear: Selection bias, confounders, data collection methods |
| Catargi et al. 2002 [88] | N = 14<br>Age: 50.6<br>Diabetes duration: 28.0<br>Sex: 5/9<br>HbA1c: 7.8<br>C-peptide: Neg<br>Reasons: ND | CSII use: ND<br>CSII f-u: 6.4<br>Healing period: 6.4<br>CIPII f-u: 6.4* | To compare the efficacy of IPII and CSII of therapy in terms of glycaemic control, glycaemic stability and hypoglycaemia frequency. | HbA1c: Decreases (CIPII: 7.3; CSII: 7.8 %, p<0.05)<br>Pre-prandial BG: Decreases (CIPII: 7.8; CSII: 8.1 mmol/L, p<0.05)<br>SMBG: Decreases (CIPII: 8.0; CSII: 8.5 mmol/L, p<0.01)<br>SD of BG: Decreases (CIPII: 3.8; CSII: 4.4 mmol/L, p<0.01)<br>Post-prandial BG: No change (CIPII: 8.2; CSII: 8.5 mmol/L, p=0.07) | STROBE: 15/22<br>QAT: Moderate: Study design, data collection method; withdrawals and drop-outs Unclear: Selection bias, confounders |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; BG, blood glucose; SMBG, self-monitored BG; CGM, continuous glucose monitoring; SD of BG, standard deviation of BG. Note, *, dropout in the study at 24months; +, three patients first were treated with CIPII, and then with CSII.
Table S2.1. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, CIPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|--------------------------|--------------------------|------------------------|
| Colette et al. 1989 [114] | N = 24 (CIPII: 13 /CSII: 11) Age: 30/32 Diabetes duration: 17/20 Sex: ND HbA1c: 8.0/8.9 C-peptide: ND Reasons: ND | CSII use: 40 CIPII use: 60 | Study the effects of prolonged tight diabetic control and insulin delivery through portal route on vitamin D metabolism in DM1. | HbA1c: No change (CIPII: 8.0; CSII: 8.9 %, p=NS) | STROBE: 18/22 QAT: Strong: Data collection method Moderate: Selection bias, study design, confounders |
| Selam et al. 1989 [82] | N = 14 (CIPII: 6 /CSII: 8) Age: 32/44.3 Diabetes duration: 16/23.1 Sex: 4/2 / 5/3 HbA1c: 8.3/8.7 C-peptide: ND Reasons: ND | CSII use: 52+ CIPII use: 26 | Compare the effects of intensive SC vs. implantable pump IP insulin delivery on intermediary metabolites in DM1 patients. | HbA1c: No change (CIPII: 8.2; CSII: 8.6 %, p=NS) | STROBE: 14/22 QAT: Strong: Data collection methods Moderate: Study design, confounders Weak: Confounders Unclear: Selection bias, blinding |
| Walter et al. 1989 [99] | N = 12 (CIPII: 6 /CSII: 6) Age: 28.3/26.6 Diabetes duration: 10.8/10.5 Sex: 6/0 / 6/0 HbA1c: 8.0/7.9 C-peptide: ND Reasons: ND | CSII use: 26+ CIPII use: 12+ | To compare metabolism control at night time in the patients with MDI and continuous insulin administration. | HbA1c: No change (CIPII: 8.0; CSII: 7.9 %, p=NS) | STROBE: 15/22 QAT: Strong: Data collection methods Moderate: Selection bias, study design, confounders Unclear: Blinding Not applicable: Withdrawals and drop-outs |
| Hedman et al. 2009 (c.a) [111] Arnqvist et al. 2010 (c.a.) [116] Hedman et al. 2014 [112] | N = 30 (CIPII: 10 /CSII: 20) Age: 53.1/52.8 Diabetes duration: 124.2/30.8 Sex: 5/5 / 10/10 HbA1c: 8.6/7.9 C-peptide: ND Reasons: Pmc | CSII use: 26+ CIPII use: 26+ | Investigate in cross-sectional study if the different modes of insulin administration, CIPII or CSII were associated with a change in the circulating IGF system. | HbA1c: No change (CIPII: 8.6; CSII: 7.9 %, p=NS) | STROBE: 21/22 QAT: Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs Moderate: Study design |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; BG, blood glucose; SMBG, self-monitored BG; SPAD, SC peritoneal access device; c.a., conference abstract; FF, data extracted from figure.
Table S2.1. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality | Critical appraisal tool of Center for Evidence-based management: |
|--------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------|--------------------------|------------------------|---------------------------------------------------------------|
| Case report |                                                                 |                                                                 | To evaluate a new catheter design.                             | HbA1c: No change (CIPII: 5.9; CSII (1): 6.2; CSII (2): 6.1 %, p=ND) | 8/10 (2 cannot tell) |                                                                 |
<sup>1</sup> Catargi et al. 2000 [113] | N = 1                                                                | Age: 32                                                          | CSII f-u (rapid-acting) (1): 12                                | SMBG: No change (CIPII: 6.3; CSII (1): 7.8; CSII (2): 7.3 mmol/L, p=ND) |                                                                 |                                                                 |
| | Diabetes duration: 6                                                            | Sex: 1/0                                                          | CSII f-u (Lispro) (2): 3                                       | Pre-prandial BG: No change (CIPII: 5.9; CSII (1): 6.4; CSII (2): 6.8 mmol/L, p=ND) |                                                                 |                                                                 |
| | HbA1c: ND                                                                         | C-peptide: Neg                                                     | CIPII use: 1.5+                                                  | Post-prandial BG: No change (CIPII: 6.6; CSII (1): 9.6; CSII (2): 8.8 mmol/L, p=ND) |                                                                 |                                                                 |
| | Reasons: Pmc                                                                      |                                                                 |                                                                 | LBGI*: No change (CIPII: 4.3; CSII (1): 5.5; CSII (2): 4.0, p=ND) |                                                                 |                                                                 |
| |                                                                                   |                                                                 |                                                                 | AUC (mean of 7 times/day SMBG): No change (CIPII: 43.9; CSII (1): 49.5; CSII (2): 44.3 h mmol/L, p=ND) |                                                                 |                                                                 |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; BG, blood glucose; LBGI, low blood glucose index. Note, LBGI* < 5, low or moderate risk of future severe hypoglycaemia; LBGI > 5, a high-risk; AUC, area under curve.
Table S2.2. Intervention studies, Participant characteristics, description, outcomes: Insulin levels

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, CIPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality | Cochrane risk of bias tool (CRB): |
|--------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--------------------------|------------------------|-----------------------------|
| Giacc et al. 1993 [100] | N = 5  
Age: 31 - 50  
Diabetes duration: 8 - 39  
Sex: 1/4  
HbA1c: 7.4  
C-peptide: Neg  
Reasons: Volunteers | CSII use: ND  
CSII f-u: 96+ hours  
CIPII f-u: 12+  
Washout: serum free insulin level measurements after IV insulin bolus | To compare the rate of appearance of insulin in the peripheral circulation during IP and SC insulin administration in T1D, in steady and non-steady state. | Fasting insulin levels: Decreases (CIPII: 30.8; CSII: 45.0 pmol/L, p<0.001)  
Plasma clearance rate of insulin: No change (CIPII: 14.7; CSII: 13.1 mL/kg*min, p=ND)  
Fasting recovery rate of insulin: Decreases (CIPII: 27; CSII: 40 %, p<0.001)  
Insulin infusion 15 nmol/L for 150 min + 42nmol/L for another 150 min: Increases recovery rate (with first increase (15nmol/h), p<0.05; with second increase (42nmol/h), p<0.01)  
Basal insulin requirement: No change (CIPII: 5.4; CSII: 5.6 nmol/h, p=ND) | CRB:  
Unclear risk of bias: Random sequence generation, allocation concealment, blinding  
Low risk of bias: Complete outcome data, selective reporting, treatment procedure | |
| Liebl et al. 2009 [5] | N = 60* (CIPII: 30 /CSII: 30)  
Age: 50.5/45.3  
Diabetes duration: 26.3/25.1  
Sex: (male) 73 %/43 %  
HbA1c: 8.2/8.3  
C-peptide: ND  
Reasons: Pmc | CSII use: ND  
CSII f-u: 26  
CIPII f-u: 52 | Comparison of frequency of hypoglycaemia, severe hypoglycaemia, metabolic control, diabetic QoL and safety between CSI and CIPII in type 1 diabetic patients. | Mean daily insulin requirement: No change (CIPII: 44.2; CSII: 46.0 U/24h, p=ND) | CRB:  
Unclear risk of bias: Random sequence generation, allocation concealment, blinding  
Low risk of bias: Complete outcome data, selective reporting, treatment procedure | |
| Micossi et al. 1986 [84] | N = 6  
Age: 38.8  
Diabetes duration: 12.6  
Sex: 3/3  
HbA1c: 7.25  
C-peptide: ≤ 0.02 pmol/ml | CSII use: 12  
CSII f-u: 6  
CIPII f-u: 6 | To investigate the hormonal and metabolic patterns produced by CIPII in group of severely unstable DM1 who has previously responded poorly to CSII. To compare clinical and metabolic effects of CSI and CIPII. | Mean daily insulin requirement: No change (CIPII: 46.02; CSII: 48.67 U/24h, p=NS) | STROBE: 15/22  
QAT:  
Strong: Data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, study design  
Weak: Confounders | |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; *, dropouts in this study (at the end of the periods N = 36 (CIPII: 15 /CSII: 21)).
### Table S2.2. (Continued)

| Source                  | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--------------------------|------------------------|
| Non-randomised crossover studies |                                                                                                                                 |                                               |                           |                          |                        |
| Beylot et al. 1987 [103] | N = 4  
Age: 42  
Diabetes duration: 21.5  
Sex: 3/1  
HbA1c: 7.6 (9.2 – 5)  
C-peptide: ND  
Reasons: Volunteers | CSII use: ND  
CSII f-u: 8  
CPII f-u: 8  
Washout: 1 day | To determine if IP insulin administration could, in addition to decreasing peripheral insulin levels, improve the insulin resistance of DM1. | Fasting insulin levels: No change (CPII: 131.95; CSII: 152.79 pmol/L, p=ND)  
Plasma free insulin (night-time): Decreases (CPII: 127.78; CSII: 163.2 pmol/L, p<0.05),  
Mean daily insulin requirement [%]: No change (CPII: 0.0.57; CSII: 0.0.59 U/kg/day, p=ND) | STROBE: 15/22  
QAT: Strong: Blinding, data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, study design, confounders |
| Wredling, Lui et al. 1991 [92] | N = 6  
Age: 42.8  
Diabetes duration: 24.0  
Sex: 4/2  
HbA1c: 7.7 – 10.2  
C-peptide: Neg  
Reasons: Pmc | CSII use: ND  
CSII f-u: 208  
CPII f-u: 38 | To compare the reproducibility of the plasma-insulin profile of IP and SC administered insulin in a group of C-peptide-negative, diabetic patients. | Pre-meal insulin bolus (time till max. conc.): Decreases (CPII: 60; CSII: 133 minutes, p=0.006)  
Total insulin AUC (0-240 minutes): No change (CPII (bolus 0.05 U/kg/BW): 56.1 μl; CSII (bolus 0.1 U/kg/BW): 94.6 μl, p=0.0023)  
Insulin AUC 0-60 min: No change (CPII: 16.3; CSII: 20.6 μl, p=NS)  
Intra-patient CV (AUC 0-60 min): No change (CPII: 19.8; CSII: 38.6 %, p=NS)  
Intra-patient CV (AUC 0-240 min): No change (CPII: 11.5; CSII: 20.2 %, p=NS)  
Inter-patient peak time: No change (CPII: 22.4; CSII: 28.3 %, p=NS)  
Inter-patient CV (AUC 0-60 min): No change (CPII: 43.6; CSII: 27.9 %, p=NS)  
Inter-patient CV (AUC 0-240 min): No change (CPII: 30.9; CSII: 29.7 %, p=NS)  
Inter-patient peak time: No change (CPII: 44.0; CSII: 28.0 %, p=NS) | STROBE: 15/22  
QAT: Strong: Data collection method  
Moderate: Study design  
Weak: Selection bias  
Unclear: Confounders  
Not applicable: Withdrawals and drop-outs |

### Insulin levels

| Source                  | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------|--------------------------|------------------------|
| Wredling, Adamson et al. 1991 [91] (Technical report) | N = 6  
Age: 41.3  
Diabetes duration: 23.2  
Sex: 4/2  
HbA1c: 8.7  
C-peptide: Neg  
Reasons: Pmc | CSII use: 52+  
CSII f-u: 8 (n=3)  
CPII f-u: median 72 | To determine the efficacy of a new percutaneous device. | Mean daily insulin requirement: No change (CPII: 44.8 U/24h; CSII: ND) | STROBE: 15/22  
QAT: Moderate: Selection bias, study design, data collection method  
Weak: Withdrawals and drop-outs  
Unclear: Confounders |

Legends: CSII, continuous subcutaneous insulin infusion; CPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; CV, coefficient of variation; AUC, area under curve; ND, data calculated from table.
Table S2.2. (Continued)

| Source | Participant characteristics | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-----------------------------|----------------------------------------------------------|---------------------|----------------------|------------------------|

Non-randomised crossover studies

| Source | Participant characteristics | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-----------------------------|----------------------------------------------------------|---------------------|----------------------|------------------------|

Georgopoulos et al. 1992 [83]
N = 7
Age: 27
Diabetes duration: 12 weeks
Sex: 5/2
HbA1c: 9.8
C-peptide: ND
Reasons: ND
CSII use: ND
CPII f-u: 52-60
To investigate whether long-term improved glycemic control by intraperitoneal insulin infusion normalizes the compositional abnormalities of triglyceride (TG)-rich lipoproteins in DM1.
Mean daily insulin requirement: No change (CPII: 57.2; CSII: 52 (units of measurements are not provided, p=NS)
STROBE: 11/22
QAT:
Strong: Data collection methods, withdrawals and dropouts
Moderate: Selection bias, study design, confounders

Georgopoulos et al. 1994 [102]
N = 8
Age: 37
Diabetes duration: 21.6 weeks
Sex: 5/3
HbA1c: 9.4
C-peptide: ND
Reasons: ND
CSII use: ND
CPII f-u: 26
Test hypothesis that IPII will decrease the level of circulating chylomicron remnants in patients with DM1.
Mean daily insulin requirement: No change (CPII: 62.4; CSII: 61.9 U/24h, p=NS)
STROBE: 14/22
QAT:
Strong: Data collection method, withdrawals and dropouts
Moderate: Study design, confounders
Unclear: Selection bias

Lassmann-Vague et al. 1994 (short communication) [104]
N = 11
Age: 34.4
Diabetes duration: 22.4 weeks
Sex: 5/6
HbA1c: 6.9
C-peptide: Neg
Reasons: ND
CSII use: 26+
CPII f-u: 4
CPII f-u: 12
ND
Fasting insulin levels: No change (CPII: M1: 111.12; M3: 114.59; CSII: 118.06 pmol/L, p=ND)
Mean daily insulin requirement: No change (CPII: 41.6; CSII: 40.5 U/24h, p=ND)

Raccah et al. 1994 (letter) [109]
N = 11
Age: 34.4
Diabetes duration: 22.3 weeks
Sex: 6/5
HbA1c: 6.9
C-peptide: ND
Reasons: ND
CSII use: 12
CPII f-u: 40
ND
Fasting insulin levels: No change (CPII: M3: 114.59; M10: 100; CSII: 118.06 pmol/L, p=NS)
Mean daily insulin requirement: No change (CPII: 62.4; CSII: 40.5 U/24h, p=NS)

Schnell et al. 1994 [105]
N = 5
Age: 25-62
Diabetes duration: 20.2 weeks
Sex: 1/4
HbA1c: 9.8
C-peptide: ND
Reasons: ND
CSII use: 156-364
CPII f-u: 52
To compare insulin demands during 24 h in CPII and CSII patients.
To compare HbA1c levels in CPII and CSII patients.
Mean daily insulin requirement: No change (CPII: 46; CSII: 48 U/24h, p=NS)
STROBE: 17/22
QAT:
Strong: Withdrawals and drop-outs
Moderate: Selection bias, study design, confounders, data collection method

Legends: CSII, continuous subcutaneous insulin infusion; CPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; NP, not possible to evaluate.
Table S2.2. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------------------|--------------------------|-----------------------|
| Guerci et al. 1996 [108] | N = 14 Age: 40.0 Diabetes duration: 16.4 Sex: 9/5 HbA1c: 6.1 C-peptide: Neg Reasons: Volunteers | CSII use: 52+ CIPII F-u: 16 | To determine the effects of IPII on qualitative lipoprotein abnormality. | Mean daily insulin requirement: No change (CIPII: M2: 0.69, p<0.01; M4: 0.64; CSII: 0.60 U/kg/24h, p=NS) | STROBE: 16/22 QAT: Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs Moderate: Study design |
| Hanaire-Brouin et al. 1996 [101] | N = 18 Age: 43.0 Diabetes duration: 20.0 Sex: 11/7 HbA1c: 7.6 C-peptide: Neg Reasons: Volunteers | CSII use: 128 CIPII F-u: 52 | To evaluate the impact of intraperitoneal insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | Mean daily insulin requirement: No change (CIPII: 39.4; CSII: 39.1 U/24h, p=NS) | STROBE: 16/22 QAT: Strong: Study design, data collection methods, withdrawals and drop-outs Moderate: Selection bias, confounders |
| Lassmann-Vague et al. 1996 [101] | N = 11 Age: 36.3 Diabetes duration: 17.8 Sex: 5/5 HbA1c: ND C-peptide: ND Reasons: Volunteers | CSII use: ND CSII F-u: ND CIPII F-u: 8 | To compare plasma free insulin levels achieved in patients with DM1 chronically treated with CSII and CIPII. | Fasting insulin levels (7:00 am): No change (CIPII: 60.42; CSII: 66.67 pmol/L, p=NS) Plasma free insulin (night-time (12:00 am)): Decreases (CIPII: 70.15; CSII: 128.48 pmol/L, p<0.01) Pre-meal insulin bolus (time till max conc.): Decreases (CIPII: 1 h; CSII: 3 h, p<0.05) (max. insulin conc.): Increases (CIPII: 179.18; CSII: 125.01 pmol/L, p<0.05) elevation (return to basal concentration): Decreases (CIPII: 3 h; CSII: did not return till next bolus) Total insulin AUC: Decreases (CIPII: 72; CSII: 100 μU/mL, p<0.01) Night-time AUC: Decreases (CIPII: 12; CSII: 36 μU/mL, p<0.01) AUC after insulin bolus: No change (CIPII: 32; CSII: 30 μU/mL, p=NS) Mean daily insulin requirement: No change (1.3 U/h) | STROBE: 14/22 QAT: Strong: Data collection method, withdrawals and drop-outs Moderate: Selection bias, study design Weak: Confounders |
| Pacifico et al. 1997 [98] | N = 8 Age: 35.1 Diabetes duration: 19 Sex: 5/4 HbA1c: 6.5 C-peptide: Neg Reasons: Volunteers | CSII use: 12+ CIPII F-u: 52+ | To evaluate the safety, the efficacy and the results after 3 years of CIPII. | Mean daily insulin requirement: No change (CIPII: 42.8; CSII: 40.8 U/24h, p=NS) | STROBE: 19/22 QAT: Strong: Study design, data collection methods, Selection bias Moderate: Confounders, withdrawals and drop-outs |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; NP, not possible to evaluate; AUC, area under curve.
### Table S2.2. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex [Male/Female], HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------|--------------------------|------------------------|
| **Non-randomised crossover studies**                                                                                                                                                                                                 |
| Oskarsson et al. 1999 [90] | **N = 7**<br>Age: 42<br>Diabetes duration: 15<br>HbA1c: 8.5<br>C-peptide: < 0.2nM<br>Reasons: Pmc | CSII use: 26+<br>CPII f-u: 47-82 | To assess the clinical relevance of the BG, hypoglycaemia, glucagon secretion during exercise by comparing glycaemic and hormonal responses to a 40-min bicycle exercise test at 60 % of VO\(_2\)max during CSII and CPII in type 1 diabetic patients. | Fasting insulin levels: decreases (CPII: 28.0; CSII: 48.1 pmol/L, p=0.043)<br>Change in insulin levels during the time of exercises\(^2\): No change (in the groups); increases (between groups, through the study, p<0.05)<br>Mean daily insulin requirement: No change (CPII: 38.4; CSII: 36.1 U/24h, p=0.06) | STROBE: 16/22<br>QAT: Strong: Confounders, data collection methods, withdrawals and drop-outs<br>Moderate: Selection bias, study design |
| Oskarsson et al. 2000 [89] | **N = 6**<br>Age: 42<br>Diabetes duration: 17<br>HbA1c: 8.6<br>C-peptide: Neg<br>Reasons: Unsatisfactory on CSII | CSII use: 52+<br>CPII f-u: 69 | To expose the patients to an identical hyperinsulinemic challenge with special emphasis on the glucagon response in the same patients during continuous treatment with CSII and CPII. | Fasting insulin levels: Decreases (CPII: 35.8; CSII: 53.4 pmol/L, p<0.01)<br>Change in plasma hormone levels from basal level to peak level in time of insulin clamp; and change between CPII and CSII: Insulin (+30 min): Increases in both (CPII: 66.9, p=0.01; CSII: 42.4 pmol/L, p=0.03); No change (p=0.32)<br>Basal rate: Increases (CPII: 1.34; CSII: 1.14 U/h, p=0.02)<br>Bolus doses: Decreases (CPII: 7.1; CSII: 11.6 U/24h, p=0.04)<br>Mean daily insulin requirement: No change (CPII: 37.9; CSII: 38.2 U/24h, p=0.95) | STROBE: 16/22<br>QAT: Strong: Confounders, data collection methods, withdrawals and drop-outs<br>Moderate: Selection bias, study design |
| Duvillard et al. 2005 (Brief report) [106] | **N = 7**<br>Age: 48<br>Diabetes duration: 17<br>HbA1c: 7.34<br>C-peptide: ND<br>Reasons: ND | CSII use: ND<br>CPII f-u: 12 | Compare if replacement of SCII with IPII restores the normal physiological gradient between the portal vein and peripheral circulation, which is likely to modify lipoprotein metabolism. To compare HDL apolipoprotein (apo) AI metabolism in patients treated with CSII and IPII. | Mean daily insulin requirement: No change (CPII: 43.6; CSII: 45.0 U/24h, p=0.69) | STROBE: 19/22<br>QAT: Moderate: Data collection methods, study design, withdrawals and drop-outs<br>Poor: Selection bias, confounders |
| Duvillard et al. 2007 [107] | **N = 7**<br>Age: 48<br>Diabetes duration: 17<br>HbA1c: 9.0 (8.8)*<br>C-peptide: ND<br>Reasons: ND | CSII use: ND<br>CPII f-u: 104 | To investigate the clinical long-term performance and safety of the new Accu-Chek DiaPort system. | Mean daily insulin requirement: No change (CPII: M6: 45; CSII: 49 U, p=NS) | NP |
| Liebl et al. 2013 (c.a) [94-96] | **N = 12 (n = 10)**<br>Age: 49<br>Diabetes duration: 30<br>HbA1c: 9.0 (8.8)*<br>C-peptide: ND<br>Reasons: Pmc | CSII use: ND<br>CPII f-u: 104 | To investigate the clinical long-term performance and safety of the new Accu-Chek DiaPort system. | Mean daily insulin requirement: No change (CPII: M6: 45; CSII: 49 U, p=NS) | NP |
| Liebl et al. 2014 (c.a) [97] | **N = 12**<br>Age: 49<br>Diabetes duration: 30<br>HbA1c: 9.0 (8.8)*<br>C-peptide: ND<br>Reasons: Pmc | CSII use: ND<br>CPII f-u: 104 | To investigate the clinical long-term performance and safety of the new Accu-Chek DiaPort system. | Mean daily insulin requirement: No change (CPII: M6: 45; CSII: 49 U, p=NS) | NP |

Legend: CSII, continuous subcutaneous insulin infusion; CPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; \(^2\), data extracted from figure; *, dropouts in the study; Pmc, Poor metabolic control.
| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|------------------------|
| **Non-randomised crossover studies** | | | | |
| Dussau et al. 2017 [78] | N = 10  
Age: 49  
Diabetes duration: 29  
Sex: M/F 7/3  
HbA1c: 7.7  
C-peptide: ND  
Reasons: Pmc | CSII use: 443  
CSII f-u: 24h  
CIPII f-u: 20 to 20 | To compare closed-loop zone MPC using the DiaPort IP insulin delivery system with the traditional SC insulin delivery method during a 24-hour in-clinic protocol. | In in-clinical measurements: 24-hour total insulin delivery: Increases (CIPII: 43.66; CSII: 32.29 U, p<0.001)  
Mean daily insulin requirement: No change (CIPII: ND; CSII: 43 U/24h) | STROBE: 20/22  
QAT: Strong: Data collection methods, withdrawals and drop-outs, study design  
Moderate: Selection bias, confounders |
| **Retrospective crossover studies** | | | | |
| Jeandidier et al. 1992 (Preliminary results) [86] | N = 8  
Age: 33.5  
Diabetes duration: 14.5  
Sex: ND  
HbA1c: 6.64  
C-peptide: Neg  
Reasons: ND | CSII use: 1  
CIPII use: 12 | To assess the potential benefits of CIPII vs CSII. | Mean daily insulin requirement: Increase (CIPII: 39; CSII: 32 U/24h, p<0.05) | STROBE: 12/22  
QAT: Weak: Study design  
Unclear: Selection bias, confounders, data collection methods |
| **Non-randomised follow-up studies** | | | | |
| Van Dijk et al. 2016 [93] | N = 101 (CIPII: 32 /CSII: 69)  
Age: 50/48  
Diabetes duration: 29/27  
Sex: 14/25 / 30/44  
HbA1c: 8.3/7.9  
C-peptide: ND  
Reasons: Pmc | CSII/MDI use: 208+  
CIPII use: 208+  
CIPII f-u: 27  
CIPII f-u: 27 | To compare the effects of CIPII to SC insulin therapy, on the GH-IGF-1 axis in a large prospective, observational matched case-control study in T1DM patients. | Mean daily insulin requirement: No change (CIPII: 0.7; CSII: 0.6 U/24h/kg, p=NS) | STROBE: 16/22  
QAT: Strong: Selection bias, study design, data collection method  
Moderate: Study design, withdrawals and drop-outs |
| **Case-control studies** | | | | |
| Colette et al. 1989 [114] | N = 24 (CIPII: 13 /CSII: 11)  
Age: 30/32  
Diabetes duration: 17/20  
Sex: ND  
HbA1c: 8.0/8.9  
C-peptide: ND  
Reasons: ND | CSII use: 40  
CIPII use: 60 | Study the effects of prolonged tight diabetic control and insulin delivery through portal route on vitamin D metabolism in insulin dependent diabetic patients. | Fasting insulin levels: No change (CIPII: 115.28; CSII: 140.98 pmol/L, p=NS) | STROBE: 18/22  
QAT: Strong: Data collection method, withdrawals and drop-outs  
Moderate: Selection bias, study design, confounders |

**Legends:** CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; Pmc, Poor metabolic control; c.a, conference abstract. Note: *, for analysis participant nr. changed (dropouts).
### Table S2.2. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CIPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-------------------------------------------------------------------------------------------------|------------------------------------------------|--------------------------|--------------------------|------------------------|
| **Case-control studies** | | | | | **Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Thomas quality assessment toll (QAT):** |
| Selam et al. 1989 [82] | N = 14 (CIPII: 6 / CSII: 8) Age: 32/44.3 Diabetes duration: 16/23.1 Sex: 4/2 / 5/3 HbA1c: 8.3/8.7 C-peptide: ND Reasons: ND | CSII use: 52+ CIPII use: 26 | Compare the effects of intensive SC vs. implantable pump IP insulin delivery on intermediary metabolites in DM1 patients. | Fasting insulin levels: No change (NS) Pre-meal insulin bolus (bolus + 4 h basal rate = 0.15 U/kg) (time till max conc.): No change (CIPII: 30 min; CSII: 60 min, p=ND) (max. insulin conc.): Increases (CIPII: 263.91; CSII: 145.84 pmol/L) (at +30 min, p<0.05); elevation (return to basal concentration): Decreases (CIPII: 180; CSII: 240 minutes, p=ND). | STROBE: 14/22 QAT: Strong: Data collection methods Moderate: Study design, confounders Weak: Confounders Unclear: Selection bias, blinding Not applicable: Withdrawals and drop-outs |
| Walter et al. 1989 [99] | N = 12 (CIPII: 6 / CSII: 6) Age: 28.3/26.6 Diabetes duration: 10.8/10.5 Sex: 6/0 / 6/0 HbA1c: 8.0/7.9 C-peptide: ND Reasons: ND | CSII use: 26+ CIPII use: 12+ | To compare metabolism control at night time in the patients with ICT and continuous insulin administration. | Mean night insulin values (At night (23:00–7:00)): Decreases (CIPII: 65.56; CSII: 86.53 pmol/L, p<0.005). Mean daily insulin requirement: No change (CIPII: 0.56; CSII: 0.55 U/kg/24h, p=NS) | STROBE: 15/22 QAT: Strong: Data collection methods Moderate: Selection bias, study design, confounders Unclear: Blinding Not applicable: Withdrawals and drop-outs |
| Hedman et al. 2009 (poster) [111] Arnqvist et al. 2010 (poster) [116] Hedman et al. 2014 [112] | N = 30 (CIPII: 10 / CSII: 20) Age: 53.1/52.8 Diabetes duration: 124.2/30.8 Sex: 5/5 / 10/10 HbA1c: 8.6/7.9 C-peptide: ND Reasons: Pmc | CSII use: 26+ CIPII use: 26+ | Investigate in cross-sectional study if the different modes of insulin administration, CIPII or CSII were associated with a change in the circulating IGF system. | Mean daily insulin requirement: No change (CIPII: 51.2; CSII: 39.3 U/24h, p=0.260) | STROBE: 21/22 QAT: Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs Moderate: Study design |
| **Insulin levels** | | | | | | |
| Catargi et al. 2000 [113] | N = 1 Age: 32 Diabetes duration: 6 Sex: 1/0 HbA1c: ND C-peptide: Neg Reasons: Pmc | CSII f-u: (rapid-acting insulin) (1): 12 CSII f-u (Lispro): 12 CIPII: 1.5+ | To evaluate a new catheter design | Mean daily insulin requirement: No change (CIPII: 52; CSII (1): 51.2; CSII (2): 50.9, p=ND) | 8/10 (2 cannot tell) |

**Legend:** CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; NS, data extracted from figure.
| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Non-randomised crossover studies | Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Thomas quality assessment tool (QAT): Methodological quality |
|--------|-------------------------------------------------------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Micossi et al. 1986 [84] | N = 6  
Age: 38.8  
Diabetes duration: 12.6  
Sex: 3/3  
HbA1c: 7.25  
C-peptide: ≤ 0.02 pmol/mL  
Reasons: Poor glucose control  
CSII use, CSII follow-up, CIPII follow-up (weeks) | CSII use: 12  
CSII F-u: 6  
CIPII f-u: 6 | Total cholesterol: No change (CIPII: 5.1; CSII: 4.4 mmol/L, p=NS)  
HDL cholesterol: Decreases (CIPII: 0.3; CSII: 0.6 mmol/L, p=0.001)  
Fasting serum triglycerides: Increases (CIPII: 1.5; CSII: 0.9 mmol/L, p<0.005)  
Mean daily glycerol: No change (CIPII: 61.7; CSII: 35.4 µmol/L, p=NS)  
STROBE: 15/22  
QAT: Moderate: Selection bias, study design, confounders |
| Georgopoulos et al. 1992 [83] | N = 7  
Age: 27  
Diabetes duration: 12  
Sex: 5/2  
HbA1c: 9.8  
C-peptide: ND  
Reasons: ND  
CSII use: ND  
CIPII f-u: 52-60 | To investigate whether long-term improved glycaemic control by intraperitoneal insulin infusion normalizes the compositional abnormalities of triglyceride (TG)-rich lipoproteins in DM1.  
Total cholesterol: No change (CIPII: 4.6; CSII: 4.9 mmol/L, p=NS)  
HDL cholesterol: No change (CIPII: 1.3; CSII: 1.33 mmol/L, p=NS)  
Fasting plasma triglycerides: No change (CIPII: 1.23; CSII: 1.35 mmol/L, p=NS)  
Differences after fat ingestion: Plasma TG increased in both groups (no statistically significant changes in any time point), Mean ratios of constituents in fasting lipoprotein mass:  
Total cholesterol-triglyceride:  
CIPII: 0.20; CSII: 0.29, p=0.008  
CIPII: 0.375; CSII: 0.483, p<0.01  
Total cholesterol-phospholipid:  
CIPII: 0.594; CSII: 0.975, p<0.001  
CIPII: 0.73; CSII: 1.295, p<0.004  
Lipid-protein:  
CIPII: 14.07; CSII: 13.93, p=NS  
CIPII: 10.16; CSII: 10.92, p=NS  
STROBE: 15/22  
QAT: Moderate: Selection bias, study design, confounders |
| Raccah et al. 1994 [letter] [109] | N = 11  
Age: 34.4  
Diabetes duration: 22.3  
Sex: 6/5  
HbA1c: 6.9  
C-peptide: ND  
Reasons: ND  
CSII use: 12  
CIPII f-u: 40 | To investigate the hormonal and metabolic patterns produced by CIPII in group of severely unstable DM1 who has previously responded poorly to CSII. To compare clinical and metabolic effects of CSII and CIPII.  
Total cholesterol: No change (CIPII: 4.7; CSII: 4.9 mmol/L, p=NS)  
HDL cholesterol: Decreases (CIPII: 0.3; CSII: 0.6 mmol/L, p=0.05)  
Fasting plasma triglycerides: No change (CIPII: 0.9; CSII: 0.9 mmol/L, p=NS)  
Mean daily glycerol: No change (CIPII: 61.7; CSII: 35.4 µmol/L, p=NS)  
STROBE: 15/22  
QAT: Moderate: Selection bias, study design, confounders |

**Legends:** CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; NP, not possible to evaluate; TG, triglycerides; FFA, free fatty acids; HDL, high density lipoprotein; LDL, low density lipoprotein.
Table S2.3. (Continued)

| Source | Participant characteristics | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-----------------------------|-------------------------------------------------------------|---------------------------|--------------------------|-----------------------|
| Georgopoulos et al. 1994 [102] | N = 8 Age: 37 Diabetes duration: 21.6 Sex: 5/3 HbA1c: 9.4 C-peptide: ND Reasons: ND | CSII use: ND CIPII f-u: 26 | Test hypothesis that IPII will decrease the level of circulating chylomicron remnants in patients with DM1. | Fasting: Total cholesterol: Decreases (CIPII: 4.56; CSII: 4.85 mmol/L, p=0.044) HDL cholesterol: No change (CIPII: 1.26; CSII: 1.30 mmol/L, p=NS) LDL cholesterol: No change (CIPII: 2.87; CSII: 3.10 mmol/L, p=NS) Plasma triglycerides: No change (CIPII: 0.93; CSII: 0.93 mmol/L, p=NS) Differences after fat ingestion \[\text{FSF} = 100\] Max. conc. TG SF > 100: No change (follows similar pattern) (CIPII: 0.6; CSII: 0.7 mmol/L, p=NS) Time till TG SF > 100 max conc.: No change (follows similar pattern) (CIPII: 4; CSII: 4 hours, p=NS) Plasma TG SF. 20-100: No change (follows similar pattern) (p=NS) ApoB SF. 20-100: No change (p=NS) Retinyl esters SF > 100: Decreases (+4 hours: CIPII: 2500; CSII: 6000 µg/L, p=0.05) Retinyl esters SF 20-100: No change (follows similar pattern) decreases (+ 8 hours; CIPII: 450; CSII: 700 µg/L, p=0.075) Retinyl ester: apoB ratio: ($S>100$): Decreases (p=0.0002) S: 60-100: No change (p=0.06) | STROBE: 14/22 QAT: Strong: Data collection method, withdrawals and dropouts Moderate: Study design Unclear: Selection bias |
| Guerci et al. 1996 [108] | N = 14 Age: 40.0 Diabetes duration: 16.4 Sex: 9/5 HbA1c: 6.1 C-peptide: Neg Reasons: Volunteers | CSII use: S2+ CIPII f-u: 16 | To determine the effects of IPII on qualitative lipoprotein abnormality. | Fasting: Total cholesterol: No change (CIPII: 5.01; CSII: 4.97 mmol/L, p=NS) HDL cholesterol: No change (CIPII: 1.49; CSII: 1.57 mmol/L, p=NS) LDL cholesterol: No change (CIPII: 1.49; CSII: 1.57 mmol/L, p=NS) Plasma triglycerides: No change (CIPII: 1.13; CSII: 1.11 mmol/L, p=NS) Total plasma lipids: No change (CIPII: 3.02; CSII: 2.95 mmol/L, p=NS) Apo A-I: No change (CIPII: 3.96; CSII: 4.06 mmol/L, p=NS) Apo B: No change (CIPII: 2.56; CSII: 2.46 mmol/L, p=NS) Lp B-PL: Increases (CIPII: 1.36; CSII: 1.09 mmol/L, p<0.01) Lp B-PL/apo B: Increases (CIPII: 1.39; CSII: 1.17 mmol/L, p<0.05) Lp B-TC: No change (CIPII: 3.51; CSII: 3.35 mmol/L, p=NS) Lp no B-PL: No change (CIPII: 1.75; CSII: 1.88 mmol/L, p=NS) Lp no B-TC: No change (CIPII: 1.50; CSII: 1.62 mmol/L, p=NS) | STROBE: 16/22 QAT: Strong: Selection bias, confounders, data collection method, withdrawals and dropouts Moderate: Study design |

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, not significant; HDL, high density lipoprotein; LDL, low density lipoprotein; LpB, Apo B-containing lipoprotein particles; LP no B, no-apo-B containing particles; SF, lipoprotein size; TC, total cholesterol; PL, plasma lipids; VLDL, very-low-density lipoproteins; \[\text{FSF} = 100\], data extracted from figure. Note: Retinyl esters – a marker of intestinal lipoproteins.
### Table S2.3. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|--------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------|--------------------------|------------------------|
| Pacifico et al. 1997 [98] | N = 8  
Age: 35.1  
Diabetes duration: 19  
Sex: 5/4  
HbA1c: 6.5  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 12+  
CPII f-u: 52+ | To evaluate the safety, the efficacy and the results after 3 years of CPIII. | Total cholesterol: No change (CIPII: 4.81; CSII: 4.72 mmol/L, p=NS)  
HDL cholesterol: No change (CIPII: 1.14; CSII: 1.17 mmol/L, p=NS)  
LDL (chol.): No change (CIPII: 3.05; CSII: 2.96 mmol/L, p=NS)  
LDL (trigl.): No change (CIPII: 0.36; CSII: 0.35 mmol/L, p=NS)  
VLDL (chol.): No change (CIPII: 0.29; CSII: 0.23 mmol/L, p=NS)  
VLDL (trigl.): No change (CIPII: 0.43; CSII: 0.27 mmol/L, p=NS)  
HDL2 (chol.): No change (CIPII: 0.26; CSII: 0.27 mmol/L, p=NS)  
HDL2 (trigl.): No change (CIPII: 0.07; CSII: 0.07 mmol/L, p=NS)  
HDL3 (chol.): No change (CIPII: 0.89; CSII: 0.84 mmol/L, p=NS)  
HDL3 (trigl.): No change (CIPII: 0.12; CSII: 0.09 mmol/L, p=NS)  
Triglyceride: No change (CIPII: 0.88; CSII: 0.81 mmol/L, p=NS) | STROBE:19/22  
QAT: Strong: Study design, data collection methods, selection bias  
Moderate: Confounders, withdrawals and drop-outs |
| Duvillard et al. 2005 (Brief report) [106]  
Duvillard et al. 2007 [107] | N = 7  
Age: 48  
Diabetes duration: 17  
Sex: 6/1  
HbA1c: 7.34  
C-peptide: ND  
Reasons: ND | CSII use: ND  
CPII f-u: 12 | Compare if replacement of SCII with CPII restores the normal physiological gradient between the portal vein and peripheral circulation, which is likely to modify lipoprotein metabolism. | Total cholesterol: No change (CIPII: 5.04; CSII: 5.33 mmol/L, p=0.45)  
HDL cholesterol: No change (CIPII: 1.47; CSII: 1.47 mmol/L, p=0.99)  
LDL cholesterol: No change (CIPII: 3.1; CSII: 3.2 mmol/L, p=0.45)  
Fasting plasma triglyceride: No change (CIPII:1.28; CSII: 1.08 mmol/L, p=0.22)  
Apo B100-containing lipoprotein production and fractional catabolic rates: No change (ND, p=NS)  
ApoA1: No change (CIPII: 1.28; CSII: 1.34 g/L, p=0.45)  
HDL composition:  
- Esterified cholesterol: No change (CIPII: 24.0; CSII: 20.1 %, p=0.45)  
- Free cholesterol: No change (CIPII: 3.3; CSII: 3.4 %, p=0.99)  
- Triglycerides: No change (CIPII: 2.1; CSII: 22.7 %, p=0.99)  
- Phospholipids: No change (CIPII: 25.2; CSII: 22.7 %, p=0.99)  
- Proteins: No change (CIPII: 45.5; CSII: 51.2 %, p=0.13) | STROBE:19/22  
QAT: Moderate: Data collection methods, study design, withdrawals and drop-outs  
Poor: Selection bias, confounders |

**Legends:** CSII, continuous subcutaneous insulin infusion; CPIII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; trigl., triglycerides; chol., cholesterol.
### Table S2.3. (Continued)

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate | Case-control studies | Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Thomas quality assessment tool (QAT): |
|--------|---------------------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------------------------------------------|
| Colette et al. 1989 [114] | N = 24 (CIP II: 13 / CSII: 11) Age: 30/32 Diabetes duration: 17/20 Sex: ND HbA1c: 8.0/8.9 C-peptide: ND Reasons: ND | CSII use: 40 CIP II use: 60 | Study the effects of prolonged tight diabetic control and insulin delivery through portal route on vitamin D metabolism in IDDP. |
| Selam et al. 1989 [82] | N = 14 (CIP II: 6 / CSII: 8) Age: 32/44.3 Diabetes duration: 16/23.1 Sex: 4/2 / 5/3 HbA1c: 8.3/8.7 C-peptide: ND Reasons: ND | CSII use: 52+ CIP II use: 26 | Compare the effects of intensive SC vs. implantable pump IP insulin delivery on intermediary metabolites in DM1 patients. |
| Van Dijk et al. 2016 [93] | N = 181 (CIP II: 39 / CSII: 74) Age: 49.6/47.9 Diabetes duration: 28.5/24.7 Sex: 14/25/30/44 HbA1c: 66.9/63.4 C-peptide: neg Reasons: Poor glucose control* | CSII use: 208 CSII follow-up: 26 | To test the hypothesis that among persons with T1DM treated with IP insulin therapy there is a decreased calcification propensity (expressed as a higher T50) as compared with treatment with SC insulin therapy. |

#### Outcomes (mean, p-value)
- **Plasma creatinine**: No change (CIP II: 1.08; CSII: 1.11 mg/dl, p=NS)
- **Plasma calcium**: No change (CIP II: 9.3; CSII: 9.1 mg/dl, p=NS)
- **Plasma magnesium**: No change (CIP II: 1.81; CSII: 1.85 mg/dl, p=NS)
- **Plasma phosphorus**: No change (CIP II: 3.5; CSII: 3.3 mg/dl, p=NS)
- **Plasma iPTH**: No change (CIP II: 2.6; CSII: 2.7 mU/mL, p=NS)
- **Osteocalcin**: No change (CIP II: 5.7; CSII: 6.4 ng/mL, p=NS)
- **Mean vitamin D intake**: No change (CIP II: 89; CSII: 99 U/day, p=NS)
- **Vitamin D metabolites**: 25 OH D: Increases (CIP II: 22.1; CSII: 12.5 mg/mL, p<0.02)
- **24,25-(OH)2D**: Increases (CIP II: 2.3; CSII: 1.4 mg/mL, p<0.05)
- **1,25-(OH)2D**: No change (CIP II: 45; CSII: 35 pg/mL, p=NS)

### Secondary outcomes: Intermediate metabolites

- **Pre-meal insulin bolus (bolus + 4h basal rate = 0.15 U/kg): Time point 0: FFA**: Decreases (CIP II: 0.20; CSII: 0.47 mmol/L, p<0.05)
- **Postprandial FFA**: Decreases (at +30min: CIP II: 0.2; CSII: 0.45 mmol/L, p<0.05); decreases (+60 min: CIP II: 0.2; CSII: 0.47 mmol/L, p=0.05)
- **Time point 0: lactate**: No change (CIP II: 0.5; CSII: 0.45 mmol/L, p=NS)
- **Postprandial lactate**: Increases (at +30 minutes: CIP II: 0.7; CSII: 0.4 mmol/L, p=NS)
- **Alanine**: No change (p=NS)
- **3 OH butyrate**: No change (p=NS)
- **Calcium**: No change (CIP II: 2.3; CSII: 2.3 mmol/L, p=NS)
- **T50 within groups**: no change (CIP II baseline: 372; CIP II end: 362 minutes, difference within group: median [with interquartile range (IQR)]) -29.9
- **no change (CIP II baseline: 360; CIP II end: 359 minutes, difference within group: median [with interquartile range (IQR)]) -21.9)
- **no change (CIP II baseline: 362; CIP II end: 359 minutes, difference within group: median [with interquartile range (IQR)]) -8.7

#### Methodological quality
- **STROBE**: 18/22
- **QAT**: Strong: Data collection method, withdrawals and drop-outs

#### Legends
- CSII, Continuous subcutaneous insulin infusion; CIP II, Continuous intraperitoneal insulin infusion; ND, No data available; Neg, negative; NS, Not significant; FFA, Free fatty acids; iPTH, Immunoreactive parathyroid hormone; 25 OH D, Calcifiediol; 24,25-(OH)2D, (inactive) hydroxycalcidiol; 1,25-(OH)2D, active form of vitamin D; 3 OH butyrate, beta-hydroxybutyrate (by-product of ketosis); *data extracted from figure; **HbA1c ≥ 58 mmol/mol (7.5 %) or at least five incidents of hypoglycaemia (defined as glucose < 4.0 mmol/L).
Table S2.4. Intervention studies, Participant characteristics, description, outcomes: Counterregulatory hormones

| Source                  | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------|--------------------------|------------------------|
| Non-randomised crossover studies | To evaluate the impact of intraperitoneal insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | Fasting growth hormone: No change (CIPII: M3: 3.46; M12: 1.47; CSII: 2.23 ng/mL) | | Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Thomas quality assessment tool (QAT): | STROBE: 16/22 | QAT: Strong: Study design, data collection methods, withdrawals and drop-outs Moderate: Selection bias, confounders |
| Hanaire-Broutin et al. 1996 [101] | N = 18 Age: 43.0 Diabetes duration: 20.0 Sex: 11/7 HbA1c: 7.6 C-peptide: < 0.2nM Reasons: Unsatisfactory on CSII | CSII use: 128 CIPII f-u: 52 | | Change in hormone levels from pre- to post-exercises; and change between CIPII and CSII: Glucagon: Increases (CIPII: 15.1, p=0.01; CSII: 7.4 pg/mL, p=0.08); no change (CIPII vs CSII: p=0.07) Epinephrine: Increases in both groups (CIPII: 0.81, p=0.03; CSII: 0.43 nmol/L, p=0.009); no change (CIPII vs CSII: p=0.49) Norepinephrine: Increases in both groups (CIPII: 3.75, p=0.006; CSII: 4.02 nmol/L, p=0.006); no change (CIPII vs CSII: p=0.09) Growth hormone: Increases in both groups (CIPII: 9.4, p=0.03; CSII: 11.9 mg/mL, p=0.01); no change (CIPII vs CSII: p=0.34) Cortisol: Increases in both groups (CIPII: 135.1, p=0.02; CSII: 92.9 nmol/L, p=0.03); no change (CIPII vs CSII: p=0.47) C-peptide: No change (CIPII: -0.02, p=0.19; CSII: -0.01 nmol/L, p=0.59); no change (CIPII vs CSII: p=0.91) | | |
| Oskarsson et al. 1999 [90] | N = 7 Age: 42 Diabetes duration: 15 Sex: 5/2 HbA1c: 8.5 C-peptide: < 0.2nM Reasons: Unsatisfactory on CSII | CSII use: 26+ CIPII f-u: 61 | | Change in plasma hormone levels from basal level to peak level in time of hyperinsulinemia; and change between CIPII and CSII: Glucagon: Increases (CIPII: 17.0, p=0.003; CSII: 7.5 pg/mL, p=0.06); increases (CIPII vs CSII: p=0.048) Epinephrine: Increases in both groups (CIPII: 2.05, p=0.004; CSII: 2.92 nmol/L, p=0.04); no change (CIPII vs CSII: p=0.50) Norepinephrine: Increases (CIPII: 0.91, p=0.003; CSII: 0.74 nmol/L, p=0.11); no change (CIPII vs CSII: p=0.68) Growth hormone: Increases in both groups (CIPII: 13.4, p=0.02; CSII: 19.3 mg/mL, p=0.03); no change (CIPII vs CSII: p=0.34) Cortisol: Increases in both groups (CIPII: 286, p=0.0003; CSII: 277 nmol/L, p=0.0003); no change (CIPII vs CSII: p=0.77) C-peptide: No change (CIPII: 0.02, p=0.30; CSII: 0.05 nmol/L, p=0.74); no change (CIPII vs CSII: p=0.44) | | |
| Oskarsson et al. 2000 [89] | N = 7 Age: 42 Diabetes duration: 17 Sex: 5/2 HbA1c: 8.6 C-peptide: < 0.2nM Reasons: Unsatisfactory on CSII | CSII use: 52+ CIPII f-u: 69 | | | | 

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; ND, No data available; NS, Not significant; FFA GHB, Growth hormone binding proteins; PT, data calculated from table.
Table S2.4. (Continued)

| Source                  | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex [Male/Female], HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPPI follow-up (weeks) | Reported study objectives                                                                 | Outcomes (mean, p-value) | Methodological quality |
|-------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------|-----------------------|
| Van Dijk et al. 2016    | N = 113 (CPIII: 39/CSII: 74)                                                                                     | CSII/MDI use: 208+ CIPII use: 208+ CSII f-u: 27 CIPII f-u: 27 | To compare the effects of CIPII to SC insulin therapy, on the GH-IGF-1 axis in a large prospective, observational matched case-control study in T1DM patients. | Growth hormone: Decreases (CIPII: 0.63; CSII: 1.39 µg/L, p=0.039) | STROBE: 16/22 QAT: Strong: Selection bias, study design, data collection method; Moderate: Study design, withdrawals and drop-outs |
| Selam et al. 1989 [82]  | N = 14 (CPII: 6 /CSII: 8)                                                                                        | CSII use: 52+ CIPII use: 26                                  | Compare the effects of intensive SC vs. implantable pump IP insulin delivery on intermediary metabolites in DM1 patients. | Fasting glucagon #: No change (CIPII: 25; CSII: 25 pg/mL, p=NS) | STROBE: 14/22 QAT: Strong: Data collection methods; Moderate: Study design, confounders; Weak: Confounders; Unclear: Selection bias, blinding; Not applicable: Withdrawals and drop-outs |

Non-randomised follow-up studies

Secondary outcomes: Counterregulatory hormones

Case-control studies

STROBE and QAT:

Legends: CSII, Continuous subcutaneous insulin infusion; CPIII, Continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; c.a., Conference abstract; ND, No data available; NS, Not significant; NP, Not possible to evaluate; #, data extracted from figure.
### Table S2.5. Intervention studies, Participant characteristics, description, outcomes: Other outcomes

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), Hba1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------|--------------------------|------------------------|
| **Non-randomised crossover studies** | | | | | |
| Wredling, Adamson et al. 1991 (Technical report) [91] | N = 6  
Age: 41.3  
Diabetes duration: 23.2  
Sex: 4/2  
Hba1c: 8.7  
C-peptide: Neg  
Reasons: Pmc | CSII use: S2+ CSII f-u: 8 (n=3)  
CPII f-u: median 18 (15 – 24 months) | To determine the efficacy of a new percutaneous device. | Anti-insulin antibodies: No change (CPIII: 34.8; CSII: 21.7 %, p=NS) | STROBE: 15/22  
QAT: Moderate; Selection bias, study design, data collection method  
Weak: Withdrawals and drop-outs  
Unclear: Confounders |
| Lassmann et al. 1995 (short communication) [104] | N = 11  
Age: 34.4  
Diabetes duration: 22.4  
Sex: 5/6  
Hba1c: 6.9  
C-peptide: Neg  
Reasons: ND | CSII use: 26+ CPII f-u: 12 | ND | SHBG levels in men: Decreases (CPIII: M1: 31; M3: 33; CSII: 39 nM/L, p<0.05)  
SHBG levels in women: Decreases (CPIII: M1: 67; M3: 63; CSII: 80 nM/L, p<0.01) | NP |
| Raccah et al. 1994 (letter) [109] | N = 11  
Age: 34.4  
Diabetes duration: 22.3  
Sex: 6/5  
Hba1c: 6.9  
C-peptide: ND  
Reasons: ND | CSII use: 12 CPII f-u: 40 | ND | Plasminogen activator inhibitor (PAI) 1 levels: No change (CPIII: M3: 4; M10: 6.6; CSII: 5.1 U/mL, p=NS) | NP |
| Hanaire-Brouitin et al. 1996 [101] | N = 18  
Age: 41.0  
Diabetes duration: 20.0  
Sex: 11/7  
Hba1c: 7.6  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 128 CPII f-u: 52 | To evaluate the impact of intraperitoneal insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | Plasma IGF I \( \text{ng/mL} \): Increases (CPIII: M3: 114.0; M12: 146.9; CSII: 89.4 ng/mL, p<0.002)  
IGFBP-3 \( \text{ng/mL} \): Increases (CPIII: M3: 2275; M12: 3534; CSII: 1974 ng/mL, p<0.0001) | STROBE: 16/22  
QAT: Strong; Study design, data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, confounders |
| Lassmann-Vague et al. 1995 [76]  
Lassmann-Vague et al. 1998 (letter) [80] | N = 15  
Age: 36  
Diabetes duration: 20.9  
Sex: 8/9  
Hba1c: 7.1  
C-peptide: Neg  
Reasons: ND | CSII use: ND  
CPIII f-u: 4 CPIII f-u: 104 | To assess immunogenicity of intraperitoneal insulin infusion via implanted pumps by two methods. To evaluate the possible influence of an increased antibody level on metabolic and clinical parameters. | Anti-insulin antibodies* (measured by using RIA) \( \text{mU/mL} \): Increases (CPIII: M3: 39.9, p<0.01; M12: 42.5, p<0.01; M24: 48, p=0.964; CSII: 23.7 %) | STROBE: 12/22  
QAT: Moderate; Selection bias, study design, data collection method  
Weak: Withdrawals and dropouts  
Unclear: Confounders |

### Other outcomes

| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), Hba1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------|--------------------------|------------------------|
| Lassmann et al. 1996 [79] | N = 10  
Age: 35.5  
Diabetes duration: 20.0  
Sex: 8/2  
Hba1c: 6.7  
C-peptide: Neg  
Reasons: Volunteers | CSII use: 128 CPII f-u: 10 | To determine the impact of intraperitoneal insulin therapy, which results in preferential insulin absorption by the portal system, on the hepatic growth hormone-resistant state of DM1. | Plasma IGF I \( \text{ng/mL} \): Increases (CPIII: M3: 114.0; M12: 146.9; CSII: 89.4 ng/mL, p<0.002)  
IGFBP-3 \( \text{ng/mL} \): Increases (CPIII: M3: 2275; M12: 3534; CSII: 1974 ng/mL, p<0.0001) | STROBE: 16/22  
QAT: Strong; Study design, data collection methods, withdrawals and drop-outs  
Moderate: Selection bias, confounders |

### Notes
- CSII, Continuous subcutaneous insulin infusion; CPII, Continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, No data available; NS, Not significant; NP, Not possible to evaluate; SHBG, Sex hormone binding globulin; IGF 1, Insulin-like growth factor – 1; BP, Binding proteins; %, 100 % is optical density between 1.5 and 2 U of Al IgG in solution; RIA, radioimmunoassay; \( \text{mU/mL} \), data calculated from table.
### Table S2.5. (Continued)

| Source | Participant characteristics (Number, age [mean years], diabetes duration [mean years], sex [Male/Female], HbA1c [%], C-peptide, reasons to participate) | Length of: CSII use, CIPII follow-up, (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|-------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------|--------------------------|------------------------|
| **Non-randomised crossover studies** | | | | | |
| Duvillard et al. 2005 (Brief report) [106] | N = 7 Age: 48 Diabetes duration: 17 Sex: 6/1 HbA1c: 7.34 C-peptide: ND Reasons: ND | CSII use: ND CIPII f-u: 12 | Compare if replacement of SCII with IPPI restores the normal physiological gradient between the portal vein and peripheral circulation, which is likely to modify lipoprotein metabolism. | Fructosamine: No change (CIPII: 352; CSII: 348 µmol/L, p=0.69) | STROBE: 19/22 | QAT: Moderate: Data collection methods, study design, withdrawals and drop-outs Poor: Selection bias, confounders |
| Duvillard et al. 2007 [107] | N = 10 Age: 49 Diabetes duration: 29 Sex: 7/3 HbA1c: 7.7 C-peptide: ND Reasons: Poor metabolic control | CSII use: 443 CSII f-u: 24h CIPII f-u: 4 to 20 Washout: 4 to 20 | To compare closed-loop zone MPC using the DiaPort IP insulin delivery system with the traditional SC insulin delivery method during a 24-hour in-clinic protocol. | Anti-insulin antibodies: No change (ND) | STROBE: 20/22 | QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Study design, selection bias, confounders |
| **Other outcomes** | | | | | |
| | | | | | |
| Jeandidier et al. 2002 [115] | N = 24 (CIPII: 13/CSII: 11) Age: 36.8/43.1 Diabetes duration: 19.2/24.4 Sex: 6/7/6/5 HbA1c: ND C-peptide: Neg Reasons: ND | CSII/MDI use: ND CSII f-u: 26 CIPII f-u: 26 | To assess the antigenicity of the insulin Hoechst 21PH using CSII and to compare the antigenicity of this insulin when administered IP or SC. | Anti-insulin antibodies: (measured by using RIA): Increases (CIPII: M6: 41.8; CSII: M6: 24.9 %, p=0.009) ELISA: No change (CIPII: M6: 10.1; CSII: 4.4 %, p=0.07) | STROBE: 16/22 | QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Selection bias, study design, confounders |
| Van Dijk et al. 2016 [93] | N = 113 (CIPII: 39/CSII: 74) Age: 50/48 Diabetes duration: 29/27 Sex: 14/25 / 30/44 HbA1c: 8.3/7.9 C-peptide: ND Reasons: Pmc | CSII/MDI use: 208+ CIPII use: 208+ CSII f-u: 27 CIPII f-u: 27 | To compare the effects of CIPII to SC insulin therapy, on the GH-IGF-1 axis in a large prospective, observational matched case-control study in T1DM patients. | IGFBP-1: Increases (CIPII: M6: 107 µg/L, P=NS) IGFBP-3: Increases (CIPII: 3.75; CSII: 3.22 mg/L, p=0.015) | STROBE: 16/22 | QAT: Strong: Selection bias, study design, data collection method Moderate: Study design, withdrawals and drop-outs |

**Legends:** CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; ND, No data available; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay.
| Source | Participant characteristics (Number, age (mean years), diabetes duration (mean years), sex (Male/Female), HbA1c (%), C-peptide, reasons to participate) | Length of: CSII use, CSII follow-up, IPII follow-up (weeks) | Reported study objectives | Outcomes (mean, p-value) | Methodological quality |
|--------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------|--------------------------|------------------------|
| **Retrospective crossover studies** | | | | | |
| Jeandier et al. 1992 (Preliminary results) [86] | N = 8 Age: 33.5 Diabetes duration: 14.5 Sex: ND HbA1c: 6.64 C-peptide: Neg Reasons: ND | CSII use: 1 CII use: 12 | To assess the potential benefits of CIPII vs SCII. | Anti-insulin antibodies: Increases (CIPII: 11.0; CSII: 3.6 %, p<0.05) | STROBE: 12/22 QAT: Weak: Study design Unclear: Selection bias, confounders, data collection methods |
| **Case-control studies** | | | | | |
| Hedman et al. 2009 (c.a.) [111] | N = 30 (CIPII: 10 /CSII: 20) Age: 53.1/52.8 Diabetes duration: 124.2/30.8 Sex: 5/5 / 10/10 Hedman et al. 2014 [112] | CSII use: 26+ CII use: 26+ | Investigate in cross-sectional study if the different modes of insulin administration, CIPII or CSII were associated with a change in the circulating IGF system. | Fasting levels of bioactive IGF-I: Increases (CIPII: 1.83; CSII: 1.16 µg/L, p=0.024). Total IGF-I: Increases (CIPII: 120; CSII: 81 µg/L, p=0.007) IGF-II: Increases (CIPII: 1050; CSII: 879 µg/L, p=0.015) IGFBP-1: Decreases (p=0.013) IGFBP-2: No change (p=NS) | STROBE: 21/22 QAT: Strong: Selection bias, confounders, data collection method, withdrawals and drop-outs Moderate: Study design |

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, No data available; NS, Not significant; NP, Not possible to evaluate; IGF 1, Insulin-like growth factor – 1; BP, Binding proteins.
Table S2.6. Technical and physiological complications with intraperitoneal insulin pump and its attached system

| Study ID | Study design | Nr. of participants | Min. CIPII-period (months) | Min. CIPII-period (patient-years) | Local infection/inflammation | Severe abdominal pain | Severe insulin under-delivery (catheter obstruction / encapsulation) | Erythema | Pump change/reimplantation | Catheter change | Necrosis in abdominal skin «pocket» | Exhaustion of batteries of pump | Peritoneal abscess | Loss of catheter | Removal of implanted system because of complications | Insulin pumps technical problems |
|----------|--------------|---------------------|---------------------------|----------------------------------|-------------------------------|------------------------|------------------------|---------------------|------------------------|-----------------|------------------------|-----------------------------|-----------------|-----------------|---------------------------------|-----------------------------|
| Liebl et al. 2009 [5] | RFUs a | CIPII: 30 | 12 | 30 | 20 | 9 | 6 | - | - | - | - | - | - | - | 8 | - |
| Wredling, Adamson et al. 1991 [91] | NRCs | 6 | 15 | 9.4 | 1 | 3 | 4 | 6 | - | - | - | - | - | - | 5 | - |
| Pitt et al. 1992 [6] | NRCs | 10 | 34 | 28.3 | - | - | 6 | ? | 12 | 1 | - | - | - | - | 1 | 2 |
| Renard et al. 1993 [81] | NRCs | 8 | 12 | -EP: 12 | -CSII: 9 | - | - | -EP: 13 | -CSII: 0 | - | 0 | - | - | - | 0 | 26 |
| Schnell et al. 1994 [105] | NRCs | 5 | 12 | 5 | - | - | 1 | 1 | - | - | - | - | - | - | 1 | 1 | - |
| Hanaire-Broutin et al. 1996 [101] | NRCs | 18 | 12 | 18 | - | - | - | - | - | - | - | - | - | - | - | 0 |
| Pacifico et al. 1997 [98] | NRCs | 8 | 12 | 8 | - | - | 6 | - | - | - | 1 | 2 | - | - | 9 | 1 |
| Liebl et al. 2013/2014 [94-97] | NRCs | 12 | 24 | 24 | 5 | - | - | - | 1 | 8 | - | - | - | - | - | - |
| Dassau et al. 2017 [78] | NRCs | 10 | 1 | 0.8 | - | - | 0 | - | - | - | - | - | - | - | - | 0 |
| Jeandidier et al. 1992 [86] | Retro.Cs | 8 | 10 | 6.7 | - | - | 8 | - | - | - | - | - | - | - | 8 | - |
| **TOTAL** | | **115** | **144** | **130.2** | **26** | **12** | **44** | **6** | **14** | **9** | **1** | **2** | **1** | **1** | **31** | **29** |

Legends: CIPII, Continuous intraperitoneal insulin infusion; RCs, Randomised crossover study; RFUs, Randomised follow-up study; NRCs, Non-randomised crossover study; Retro.Cs, Retrospective crossover study; C-Cs, Case-control study; NRFUs, Non-randomised follow-up study; (–), no data available; a, authors provided data; b, dropouts in this study (at the end of the periods N = 36 (CIPII: 15 /CSII: 21); c, included patients with previous use of external CIPII (-EP) and with previous CSII (-CSII); d, Renard et al. study is not included; e, multiplication of the number of patients and min. CIPII-period
### Table S2.7. Methodological aspects of the included studies.

| Study ID          | Study design | Min. CSII period (month) | Min. CIPII period (month) | CSII-period insulin | CIPII-period insulin | CIPII implantation system | Insulin pump (CSII/CIPII) | CIPII catheter position (quadrant) | SMBG tests (times/day) | SMBG parameter | Nr. of laboratory visits during the study (CSII/CIPII) |
|-------------------|--------------|--------------------------|---------------------------|---------------------|----------------------|--------------------------|--------------------------|--------------------------------|------------------------|----------------|----------------------------------------|
| Micossi et al. 1986 [84] | NRCs         | 12                       | 1 ½                       | -                   | -                    | Siemens                  | Microjet syringe/Promedos E1¹ | 4 cm below umbilicus           | 6: Fasting, before and 2-h after lunch and dinner, at bedtime | -              | 1/1                                     |
| Beylot et al. 1987 [103] | NRCs         | 2                        | 2                         | Porcine             | -                    | Siemens AG              | Betatron IICPJ 9200/Promedos | Umbilical area               | 3-6                    | Mean of all BG data from second months of treatment | 1/1                                     |
| Colette et al. 1989 [114] | C-Cs         | 7                        | 10                        | Actrapid (regular) or CS21 Hoechst U40 (regular) | -                   | Microjet Infuser or Promedos/ Promedos² | Through umbilicus             | -                          | -                      | 1/1                                     |
| Selam et al. 1989 [82] | C-Cs         | 12                       | 6                         | Hoechst U400 (surfactant stabilized) | PIMS (telemetry using a battery-operated programmer) | ND/MiniMed¹              | Lower portion of the IP cavity | -                          | -                      | 1/1                                     |
| Walter et al. 1989 [99] | C-Cs         | 6                        | 3                         | Semisynthetic human insulin U100 | -                   | Betatron II; AS8MP/Promedos E1 | -                          | -                          | -                      | 1/1                                     |
| Wredling, Adamson et al. 1991 [91] | NRCs         | 12                       | 15                        | Velosulin Human (2 mo, n=2), afterwards H-Tronin | Percusel         | -/-,E                   | Upper right (n=1), upper left (n=2), lower left (n=3) | -                          | -                      | 1/ every 4 weeks                            |
| Wredling, Liu et al. 1991 [92] | NRCs         | 24                       | 6.9                       | Velosulin Human U100 | H-Tronin U100       | Percusel                  | MiniMed S04-S /MiniMed S04-5² | -                          | 4: before each meal + before evening snack | -                          | 2/2                                     |
| Georgopoulos et al. 1992 [83] | NRCs         | ND                       | 12                        | -                   | -                    | PIMS                     | -/-                       | -                          | 4-6                    | Mean blood glucose over 4 weeks before end of the period | 1/1                                     |
| Jeandidier et al. 1992 [86] | Retro. Cs | 10                        | -                         | Hoechst 21 PH U100   | Telemetry using a battery-operated programmer. | -/Infusaid 1000¹        | -                          | -                          | -                      | 1/1                                     |
| Study                          | Type | Hours | NRCs | Action 1 | Action 2               | Action 3               | Action 4               | Action 5               | Action 6               | Action 7               | Action 8               |
|-------------------------------|------|-------|------|----------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Pitt et al. 1992 [6]          | NRCs | 3     | 34   | -        | Hoechst U400            | -                      | -                      | Left from umbilicus above or below the waistline | 2-4                    | Mean of all BG values for the 2 mo before and each 2 mo after implantation | 2/9                    |
| Giacca et al. 1993 [100]      | RCs  | 96    | 3    | HOE21gh U100 (human) | HOE21gh U100 (human) | -                      | Microjet MC-20/Promedos ID 1 | -                      | -                      | -                      | 1/1                    |
| Renard et al. 1993 [81]       | NRCs | 2.4   | 12   | Porcine (Velosulin) U100 | Hoechst 21 PH U400 (for MiniMed pump) U100 (for Insuafaid pump) | -                      | Portable pump/MiniMed 2001 (n=6) or Insuafaid 1000 (n=2) | -                      | -                      | -                      | 1/4 (3,6,9,12 mo)      |
| Georgopoulos et al. 1994 [102]| NRCs | ND    | 6    | -        | -                      | -                      | -                      | -                      | 4-6                    | Mean blood glucose over 4 weeks before end of the period | 1/1                    |
| Lassman- Vague et al. 1994 [104] | NRCs | 6     | 3    | -        | Hoechst 21 PH U100 (for Insuafaid) or U400 (for MIP) | -                      | ND/Infuaid 1000 (n=6) or MiniMed MIP 2001 (n=5) | -                      | -                      | Mean of monthly blood glucose | 2/2 (-1,0/1,3 mo)     |
| Raccab et al. 1994 [109]      | NRCs | 3     | 10   | -        | -                      | -                      | -                      | ND/Infuaid 1000 (n=6) or MIP 2001 (n=11) | 4-5                    | Mean of monthly blood glucose | 1/3 (1,3,10 mo)       |
| Schnell et al. 1994 [105]     | NRCs | 36    | 12   | -        | Percuseal               | -                      | Left of right above navel | -                      | -                      | Mean of monthly blood glucose | 1/2 (3,12 mo)         |
| Lassman- Vague et al. 1995/1998 [79, 80] | NRCs | 1     | 24   | Actrapid U100 (n=3), Velosulin U100 (n=10), Ultrastradum U40 (n=2) | Hoechst 21 PH U100 (for Insuafaid) or U400 (for MIP) | -                      | ND/ Infuaid 1000 (n=4) or MIP 2001 (n=11) | -                      | 4                      | Mean of monthly blood glucose | 1/3 (3,12,24 mo)     |
| Guerci et al. 1996 [108]      | NRCs | 14.2  | 4    | -        | Hoechst 21 PH U400      | Battery-operated telemetry systems | ND'/MiniMed 2001 (n=11) | Lower left               | -                      | Mean of monthly blood glucose | 1/2 (2,4 mo)          |
| Hanaire- Brouitin et al. 1996 [101] | NRCs | 3     | 12   | -        | -                      | -                      | ND'/MIP 2001 (MiniMed) | -                      | >4                     | -                      | 1/2 (3,12 mo)          |
| Lassman- Vague et al. 1996 [87] | NRCs | ND    | 2    | Actrapid Novo (n=6) or Velosulin | Hoechst 21 PH U100 (n=4) U400 (n=7) | -                      | ND/ND'                 | -                      | -                      | -                      | 1/1                    |
| Study                              | Treatment | NRCs | Insulin | Insulin | Telemetry | Telemetry Details | NRCs Details | Insulin Details |
|-----------------------------------|-----------|------|---------|---------|-----------|------------------|--------------|-----------------|
| Pacifico et al. 1997 [98]        | NRCs      | 3    | 12      | -       | ND/MIP 2001' (MiniMed) | Lower left | -              | 1/2 (6.12 mo)   |
| Oskarsson et al. 1999 [90]       | NRCs      | 6    | 11      | -       | MiniMed 506/ MiniMed 2001' | -          | 5: morning, before lunch and dinner, 2 h after dinner, before bed | 1/1 |
| Oskarsson et al. 2000 [89]       | NRCs      | 12   | 11      | -       | MiniMed 506/ MiniMed 2001' | -          | Mean of monthly blood glucose | 1/1 |
| Catargi et al. 2002 [88]         | Retro. Cs | 1.5  | 3*      | Lispro U100 | Telemetry using a battery-operated programmer | MiniMed 506 or 507/MIP 2001' or 2007' (MiniMed) | Lower left | >4              | 3/3 (0,3,6 mo)  |
| Jeandidier et al. 2002 [115]     | NRFUs     | 6    | 6       | Regular or Lente or Humalog | Insuman U100 | H-Tron/ MIP 2001' (MiniMed) | -          | -              | 1/1 |
| Duvilard et al. 2005/2007 [106, 107] | NRCs | ND   | 3       | -       | -         | MiniMed 506 or 507/Minimed 2007C or 2007A' | -          | -              | 1/1 |
| Liebl et al. 2009 [5]            | RFUs      | 6    | 12      | Lispro U100 | Insuman U100 or H-Tron U100 | Diaport | H-TRONplus/H-TRONplus | Lower left or right | 4: prior each meal+ before bedtime | -              | 1/1 |
| Hedman et al. 2009/2014 [111, 112] Arnqvist et al. 2010 [110] | C-Cs | 6    | 6       | Aspart U100 (Novo rapid) or lispro U100 (Humalog) | Semisynthetic human insulin of porcine origin (Sanofi) U400 | - | ND/MIP 2007C' (Medtronic/Mini med) | -              | -              | 1/1 |
| Liebl et al. 2013/2014 [94-97]   | NRCs      | -    | 24      | -       | DiaPort | ND/Accu-Chek® | -          | -              | 1/4 (3,6,12,24 mo) |
| van Dijk et al. 2016 [93] van Dijk et al 2020 [117] | NRFUs | 48   | 48      | Fast acting | Human U400 (of E. coli origin) | - | ND/MIP 2007D' | -          | -              | 2/2 (0,6 mo) |
| Dassau et al. 2017 [78]          | NRCs      | 102  | 1       | Fast acting | Insuman U100 (regular) | DiaPort | Accu-Check Spirit Combo®/ Accu-Check Spirit Combo® | - | CGM (every 5 min) | - | 1/1 |

* indicates that the study was conducted in children only.
Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; RCs, Randomised crossover study; RFUs, Randomised follow-up study; NRCs, Non-randomised crossover study; Retro.Cs, Retrospective crossover study; C-Cs: Case-control study; NRFUs, Non-randomised follow-up study; ND, No data available; Asterix (*), three patients first were treated with CIPII, and then with CSII; *, pump provided only for 24-hour glucose profile; PIMS, The programmable implantable medication system; MIP, MiniMed Implantable Pump; ⁵, external insulin pump; ¹, implantable insulin pump; ², peristaltic pump; –, no data available; mo: months. Note: Studies are sorted by year of publication.
### Table S2.8. Glycaemic control during the CIPII-period: Hypoglycaemia, normoglycaemia and hyperglycaemia events and/or time spent in

| Study ID          | Study design | Nr. of participants | Minimal CIPII period (month) | Hypoglycaemic coma | Severe hypoglycaemia events/ patient-year (requiring assistance) | Hypoglycaemic events/ patient year (BG < 3.0 mmol/L) | Time spent in hypoglycaemia (BG < 2.8 mmol/L), % ± SD | Time spent in hypoglycaemia (BG < 3.9 mmol/L), % ± SD | Time spent in normoglycaemia (3.9 – 10.0 mmol/L), % | Time spent in normoglycaemia (4.4 – 7.8 mmol/L), % | Time spent in hyperglycaemia (BG > 10 mmol/L), % ± SD | Time spent in hyperglycaemia (BG > 14 mmol/L), % ± SD |
|-------------------|-------------|---------------------|-------------------------------|--------------------|---------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Micossi et al. 1986 [84] | NRCs        | 6                   | 1½                            | -                  | -                                                             | -                                                | 1.65±0.51                                                     | 4.51±2.42                                                    | -                                                        | -                                                        | 31.84±19.66                                                  | 8.9±8.69                                                   |
| Pitt et al. 1992 [6]      | NRCs        | 10                  | 84                            | 0                  | 0.43                                                          | >1/patient                                      | -                                                            | 8.8-6.0                                                        | -                                                        | -                                                        | M2:16.15±5                                                  | M18.20±5                                                   |
| Renard et al. 1993 [81]   | NRCs        | 8                   | 12                            | 0                  | 0                                                             | -                                                | M3: 10.0±7.2                                                 | M6: 7.6±7.7                                                   | M9: 6.1±5.5                                                 | M12: 6.1±6.1                                               | -                                                        | -                                                        |
| Pacifico et al. 1997 [98] | NRCs        | 8                   | 12                            | -                  | -                                                             | 8.4                                             | -                                                            | -                                                            | -                                                        | -                                                        | -                                                        | -                                                        |
| Oskarsson et al. 1999 [90] | NRCs        | 7                   | 11                            | -                  | -                                                             | 8.4                                             | -                                                            | -                                                            | -                                                        | -                                                        | -                                                        | -                                                        |
| Oskarsson et al. 2000 [89] | NRCs        | 7                   | 11                            | -                  | -                                                             | 8.4                                             | -                                                            | -                                                            | -                                                        | -                                                        | -                                                        | -                                                        |
| Liebl et al. 2009 [5]     | RFUs        | (CIPII: 30 /CSII: 30) | 12                            | -                  | Total: 0.35: M1-3: 0.72; M4-12: 0.15                           | Total:118.2: M1-3: 138.1; M4-12: 108.9         | -                                                            | -                                                            | -                                                        | -                                                        | -                                                        | -                                                        |
| Liebl et al. 2013/2014 [94-97] | NRCs       | 12                   | (n=10)*                        | 24                 | 1.5                                                           | -                                                | -                                                            | -                                                            | M6: 58                                                   | -                                                        | M6: 38                                                   | -                                                        |
| Dassau et al. 2017 [78]   | NRCs        | 10                  | 1                             | -                  | -                                                             | -                                                | 2.5±2.9                                                     | 65.7±9.2                                                      | 39.8±7.6                                                  | 32.4±8.9                                                  | 5.9±5.6                                                   | -                                                        |

**Legends:** RCs, Randomised crossover study; RFUs, Randomised follow-up study; NRCs, Non-randomised crossover study; Retro.Cs, Retrospective crossover study; C-Cs, Case-control study; NRFUs, Non-randomised follow-up study; ND, No data available; **m**, suggested BG range for artificial pancreas systems; (-), no data available; Asterix (*), dropouts in the study; M, month.
Table S2.9. Data modification for STATA: HbA1c.

| Study ID                                      | Data in forest plot, HbA1c (%) | Original data |
|-----------------------------------------------|--------------------------------|---------------|
|                                               | CII                           | CSII          | CII            | CSII            | Unit           |
|                                               | Mean  | SD  | Total | Mean  | SD  | Total | Mean  | SD  | SEM | Total | Mean  | SD  | SEM | Total | %, SD |
| Georgopoulos et al. 1992 [83]                 | 7.7   | 1.2 | 7     | 9.8   | 1.4 | 7     | 7.7   | 1.2 | -   | 7     | 9.8   | 1.4 | -   | 7     | %, SD |
| Liebl et al. 2013/2014 [94-97]                | 7.2   | 0.5 | 10    | 8.8   | 1.3 | 10    | 7.2   | 0.54 | -   | 10    | 8.8   | 1.15 | -   | 10   | %, SD |
| Oskarsson et al. 1999 [90]                    | 7.1   | 0.5 | 7     | 8.5   | 0.8 | 7     | 7.1   | -   | 0.2 | 7     | 8.5   | -   | 0.3 | 7     | %, SEM |
| Oskarsson et al. 2000 [89]                    | 7.2   | 0.5 | 7     | 8.6   | 1.1 | 7     | 7.2   | -   | 0.2 | 7     | 8.6   | -   | 0.4 | 7     | %, SEM |
| Schnell et al. 1994 [105]                     | 8.5   | 0.5 | 5     | 9.8   | 0.7 | 5     | 8.5   | 0.5* | -   | 5     | 9.8   | 0.7* | -   | 5     | %, SD |
| Wredling, Adamson et al. 1991 [91]            | 7.6   | 0.4 | 6     | 8.7   | 0.6 | 6     | 7.6*  | -   | -   | 6     | 8.7*  | -   | -   | 6     | %, (min-max) |
| Pitt et al. 1992 (data extracted from figure by IDF) [6] | 8   | 1.8 | 10    | 9.1   | 2.2 | 10    | -     | -   | -   | 10    | -     | -   | -   | 10    | %, SEM |
| Colette et al. 1989 [114]                     | 8     | 1.4 | 13    | 8.9   | 2   | 11    | 8     | -   | 0.4 | 13    | 8.9   | -   | 0.6 | 11    | %, SEM |
| Georgopoulos et al. 1994 [102]                | 8.7   | 1.2 | 8     | 9.4   | 1.5 | 8     | 8.7   | 1.2 | -   | 8     | 9.4   | 1.5 | -   | 8     | %, SD |
| Raccah et al. 1994 [109]                      | 6.3   | 1   | 11    | 6.9   | 1   | 11    | 6.3   | -   | 0.3 | 11    | 6.9   | -   | 0.3 | 11    | %, SEM |
| Catargi et al. 2002 [88]                      | 7.3   | 0.8 | 14    | 7.8   | 0.9 | 14    | 7.3   | 0.8 | -   | 14    | 7.8   | 0.9 | -   | 14    | %, SD |
| Selam et al. 1989 (SD calculated in SPSS by IDF) [82] | 8.2   | 1.4 | 6     | 8.6   | 1.3 | 8     | -     | -   | -   | 6     | -     | -   | -   | 8     | %, SD |
| Lassmann-Vague et al. 1994 [104]              | 6.8   | 0.7 | 11    | 6.9   | 1   | 11    | 6.8   | -   | 0.2 | 11    | 6.9   | -   | 0.3 | 11    | %, SEM |
| Guerci et al. 1996 [108]                      | 5.9   | 0.6 | 14    | 6     | 0.6 | 14    | 5.9   | 0.63 | -   | 14    | 6     | 0.6 | -   | 14    | %, SD |
| Hanaire-Boutin et al. 1996 [101]              | 7.5   | 0.8 | 18    | 7.6   | 0.8 | 18    | 7.5   | -   | 0.2 | 18    | 7.6   | -   | 0.2 | 18    | %, SEM |
| Duvillard et al. 2005/2007 [106, 107]         | 7.2   | 1   | 7     | 7.3   | 0.9 | 7     | 7.24  | 1   | -   | 7     | 7.34  | 0.94 | -   | 7     | %, SD |
| Pacifico et al. 1997 [98]                    | 6.6   | 1.4 | 8     | 6.5   | 1.1 | 8     | 6.6   | 1.4 | -   | 8     | 6.5   | 1.1 | -   | 8     | %, SD |
| Walter et al. 1989 [99]                      | 8     | 0.5 | 6     | 7.9   | 0.5 | 6     | 8     | 0.5 | -   | 6     | 7.9   | 0.5 | -   | 6     | %, SD |
| Hedman et al. 2009/2014, Arnqvist et al. 2010 [110-112] | 8.6   | 1.4 | 10    | 7.9   | 0.8 | 20    | 8.6   | 1.4 | -   | 10    | 7.9   | 0.8 | -   | 20    | %, SD |

Legends: CSII, Continuous subcutaneous insulin infusion; CII, Continuous intraperitoneal insulin infusion; [-], no data; SD, standard deviation; SEM, standard error of means; SPSS, statistical software program; IDF, Ilze Dirnena-Fusini; *, data given as mean (min-max) (CII 7.6 (7.0 – 8.6); CSII 8.7 (7.0 – 9.5)); †, Authors of the study did not provide statistical term for difference (SD or SEM), decision to use SD or SEM was made by reproducing statistical test by using raw data from article.
Table S2.10. Data modification for STATA: SMBG.

| Study ID | Data in forest plot, SMBG (mmol/L) | Original data |
|----------|-----------------------------------|---------------|
|          | CII | CSII | CII | CSII | Unit |
|          | Mean | SD | Total | Mean | SD | Total | Mean | SD | SEM | Total | Mean | SD | SEM | Total |
| Pitt et al. 1992 (data extracted from figure) [6] | 7.8 | 0.4 | 10 | 8.9 | 0.6 | 10 | - | - | - | 10 | - | - | - | 10 | mg/dL, SEM |
| Georgopoulos et al. 1992 [83] | 7.7 | 1.2 | 7 | 10.5 | 2 | 7 | 7.7 | 1.2 | - | 7 | 10.5 | 2 | - | 7 | mM, SD |
| Micossi et al. 1986 [84] | 8.8 | 1.3 | 6 | 9.7 | 1.4 | 6 | 8.8 | - | 0.55 | 6 | 9.68 | - | 0.58 | 6 | mmol/L, SEM |
| Beylot et al. 1987 (SD calculated in SPSS by IDF) [103] | 8.2 | 0.9 | 4 | 8.8 | 1.3 | 4 | - | - | - | 4 | - | - | - | 4 | mmol/L |
| Catargi et al. 2002 [88] | 8.1 | 1 | 14 | 8.5 | 0.9 | 14 | 145.4 | 18.3 | - | 14 | 153.3 | 17.3 | - | 14 | mg/dL, SD |
| Georgopoulos et al. 1994 [102] | 7.4 | 1.1 | 8 | 7.8 | 1.1 | 8 | 7.4 | 1.1 | - | 8 | 7.8 | 1.1 | - | 8 | mmol/L, SD |
| Guerci et al. 1996 [108] | 7.6 | 0.5 | 14 | 7.8 | 0.7 | 14 | 7.55 | 0.47 | - | 14 | 7.78 | 0.7 | - | 14 | mmol/L, SD |
| Raccah et al. 1994 [109] | 8 | 1.8 | 11 | 8.3 | 0.8 | 11 | 151 | - | 9.3 | 11 | 146 | - | 5.5 | 11 | mg/dL, SEM |
| Lassmann-Vague et al. 1994 [104] | 8.3 | 1.8 | 11 | 8.3 | 1.2 | 11 | 151 | - | 8 | 11 | 151 | - | 9 | 11 | mg/dL, SEM |

Legends: SMBG, self-monitoring of blood glucose; CSII, Continuous subcutaneous insulin infusion; CII, Continuous intraperitoneal insulin infusion; (–), no data; SD, standard deviation; SEM, standard error of means; SPSS, statistical software program; IDF, Ilze Dirnena-Fusini.
# Table S2.11. Data modification for STATA: Insulin levels.

| Study ID | Data in forest plot, insulin levels (pmol/L) | Original data |
|----------|---------------------------------------------|---------------|
|          | CIPII | CSII | CIPII | CSII | CIPII | CSII | Unit |
|          | Mean  | SD   | Total | Mean  | SD   | Total | Mean  | SD   | SEM | Total | Mean  | SD   | SEM | Total | Unit |
| Oskarsson et al. 1999 [90] | 28   | 5.8  | 7     | 48.1 | 20.9 | 7     | 28    | -    | 2.2 | 7     | 48.1 | -    | 7.9 | 7     | pmol/L, SEM |
| Oskarsson et al. 2000 [89] | 3.58 | 7.5  | 7     | 53.4 | 9.9  | 7     | 3.58  | -    | 2.9 | 7     | 53.4 | -    | 3.8 | 7     | pmol/L, SEM |
| Giacca et al. 1993 [100] | 30.8 | 13.6 | 5     | 45   | 23.3 | 5     | 30.8  | -    | 6.1 | 5     | 45   | -    | 10.4 | 5     | pmol/L, SEM |
| Beylot et al. 1987 | 131.9 | 27.8 | 4     | 152.8 | 23.3 | 4     | 19    | -    | 2   | 4     | 22   | -    | 2    | 4     | mU/L, SEM |
| Colette et al. 1989 [114] | 115.3 | 67.6 | 13    | 141  | 103.6| 11    | 16.6  | -    | 2.7 | 13    | 20.3 | -    | 4.5  | 11    | µU/mL, SEM |
| Lassmann-Vague et al. 1996 [87] | 60.4 | 23.1 | 11    | 66.7 | 30   | 11    | 8.7   | -    | 1   | 11    | 9.6   | -    | 1.3  | 11    | mU/L, SEM |
| Raccah et al. 1994 [109] | 100  | 71.4 | 11    | 118.1| 89.9 | 11    | 14.4  | -    | 3.1 | 11    | 17   | -    | 3.9  | 11    | mU/L, SEM |
| Lassmann-Vague et al. 1994 [104] | 114.6 | 48.3 | 11    | 118.1| 89.8 | 11    | 16.5  | -    | 2.1 | 11    | 17   | -    | 3.9  | 11    | µU/mL, SEM |

**Legends:** CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; [--], no data; SD, standard deviation; SEM, standard error of means.

# Table S2.12. Data modification for STATA: cholesterol levels.

| Study ID | Data in forest plot, cholesterol levels (mmol/L) | Original data |
|----------|-----------------------------------------------|---------------|
|          | CIPII | CSII | CIPII | CSII | CIPII | CSII | Unit |
|          | Mean  | SD   | Total | Mean  | SD   | Total | Mean  | SD   | SE  | Total | Mean  | SD   | SE  | Total | Unit |
| Duvillard et al. 2005/2007 [106, 107] | 5    | 0.6  | 7     | 5.4  | 0.7  | 7     | 5.04  | 0.58 | -   | 7     | 5.36  | 0.72 | -   | 7     | mmol/L, SD |
| Georgopoulos et al. 1994 [102] | 4.6  | 0.8  | 8     | 4.8  | 0.8  | 8     | 4.56  | 0.83 | -   | 8     | 4.85  | 0.8  | -   | 8     | mmol/L, SD |
| Georgopoulos et al. 1992 [83] | 4.6  | 1.1  | 7     | 4.9  | 1.3  | 7     | 4.6   | 1.1  | -   | 7     | 4.9   | 1.3  | -   | 7     | mM, SD |
| Raccah et al. 1994 [109] | 4.9  | 2.3  | 11    | 5    | 1.3  | 11    | 4.92  | -    | 0.69| 11    | 5.03  | -    | 0.38| 11    | mM, SEM |
| Guerci et al. 1996 [108] | 5    | 0.6  | 14    | 5    | 0.6  | 14    | 5.01  | 0.59 | -   | 14    | 4.97  | 0.65 | -   | 14    | mmol/L, SD |
| Pacifico et al. 1997 [98] | 4.8  | 0.8  | 8     | 4.7  | 0.8  | 8     | 185.8 | 31   | -   | 8     | 182.5 | 33   | -   | 8     | mg/dL, SD |
| Micossi et al. 1986 [84] | 5.1  | 1.2  | 6     | 4.4  | 0.9  | 6     | 5.1   | -    | 0.5 | 6     | 4.4   | -    | 0.38| 6     | mmol/L, SEM |

**Legends:** CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; [--], no data; SD, standard deviation; SEM, standard error of means.
Table S2.13. Data modification for STATA: triglyceride levels.

| Study ID                        | Data in forest plot, triglyceride levels (mmol/L) | Original data |
|---------------------------------|--------------------------------------------------|---------------|
|                                 | CII | CSII | CII | Total | CII | CSII | CII | SE | Total | CII | CSII | CII | SE | Total | Unit |
|                                 | Mean | SD  | Total | Mean | SD  | Total | Mean | SD  | SE  | Total | Mean | SD  | Total | Mean | SD  | Total |      |
| Georgopoulos et al. 1992 [83]   | 1.2  | 0.3  | 7     | 1.3  | 0.4  | 7     | 1.23 | 0.27 | -   | 7     | 1.35 | 0.27 | -   | 7    | mM, SD |
| Georgopoulos et al. 1994 [102]  | 0.9  | 0.2  | 8     | 0.9  | 0.3  | 8     | 0.93 | 0.2  | -   | 8     | 0.93 | 0.3  | -   | 8    | mmol/L, SD |
| Raccah et al. 1994 [109]        | 0.8  | 0.3  | 11    | 0.8  | 0.3  | 11    | 0.83 | -    | 0.1 | 11    | 0.83 | -    | 0.1 | 11    | mM, SEM |
| Guerci et al. 1996 [108]        | 1.1  | 0.6  | 14    | 1.1  | 0.4  | 14    | 1.13 | 0.56 | -   | 14    | 1.1  | 0.4  | -   | 14    | mmol/L, SD |
| Pacifico et al. 1997 [98]       | 0.9  | 0.3  | 8     | 0.8  | 0.3  | 8     | 77.6 | 25.6 | -   | 8     | 71.6 | 27.6 | -   | 8    | mg/dL, SD |
| Duvillard et al. 2005/2007 [106, 107] | 1.3  | 0.3  | 7     | 1.1  | 0.2  | 7     | 1.29 | 0.29 | -   | 7     | 1.1  | 0.24 | -   | 7    | mmol/L, SD |
| Micossi et al. 1986 [84]        | 1.5  | 0.4  | 6     | 0.9  | 0.3  | 6     | 1.5  | -    | 0.17 | 6     | 0.9  | -    | 0.12 | 6    | mmol/L, SEM |

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; [-], no data; SD, standard deviation; SEM, standard error of means.
Table S2.14. Data modification for STATA: insulin requirement

| Study ID | Data in forest plot, insulin requirement (U/24 hours) | Original data |
|----------|------------------------------------------------------|---------------|
|          | CIPII | CSII | CIPII | CSII | CIPII | CSII | CIPII | CSII | Unit |
|          | Mean | SD  | Total | Mean | SD  | Total | Mean | SD  | SE  | Total |
| Micossi et al. 1986 [84] | 46.0 | 10.7 | 6 | 48.6 | 10.3 | 6 | 46.0 | - | 4.37 | 6 |
| Liebl et al. 2009 [5] | 44.2 | 16.6 | 30 | 46 | 23.6 | 30 | 44.2 | 16.6 | - | 30 |
| Duvillard et al. 2005/2007 [106, 107] | 43.6 | 9.8 | 7 | 45 | 17.8 | 7 | 43.6 | 9.8 | - | 7 |
| Hanaire-Broutin et al. 1996 [101] | 39.1 | 10.6 | 18 | 39.6 | 8.9 | 18 | 39.1 | - | 2.5 | 18 |
| Oskarsson et al. 2000 [89] | 37.9 | 7.1 | 7 | 38.2 | 10.3 | 7 | 37.9 | - | 2.7 | 7 |
| Georgopoulos et al. 1994 [102] | 62.4 | 44.9 | 8 | 61.9 | 45.7 | 8 | 62.4 | 44.9 | - | 8 |
| Lassmann-Vague et al. 1994 [104] | 41.6 | 12.9 | 11 | 40 | 13.3 | 11 | 41.6 | - | 3.9 | 11 |
| Pacifico et al. 1997 [98] | 42.8 | 6.6 | 8 | 40.8 | 8 | 8 | 42.8 | 6.6 | - | 8 |
| Oskarsson et al. 1999 [90] | 38.4 | 7.7 | 7 | 36.1 | 7.4 | 7 | 38.4 | - | 2.9 | 7 |
| Raccah et al. 1994 [109] | 43.8 | 15.9 | 11 | 40.5 | 14.6 | 11 | 43.8 | - | 4.8 | 11 |
| Jeandidier et al. 1992 [86] | 39 | 11 | 8 | 32 | 13 | 8 | 39 | 11 | - | 8 |
| Dassau et al. 2017* | 43.7 | 0.1 | 10 | 32.3 | 0.1 | 10 | 43.7 | 0.08 | - | 10 |
| Hedman et al. 2009/2014, Arnlqvist et al. 2010 [110-112] | 51.2 | 31.5 | 10 | 39.3 | 10.5 | 20 | 51.2 | 31.5 | - | 10 |

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; (–), no data; SD, standard deviation; SEM, standard error of means, Asterix (*), 24-hour measurements
Figure S1a. Meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

| Study                          | Treatment | Control | Mean Diff. with 95% CI | Weight (%) |
|-------------------------------|-----------|---------|------------------------|------------|
| N                | Mean | SD | N     | Mean | SD |                |            |
| Georgopoulos et al. 1992     | 7     | 7.7 | 1.2 | 7    | 9.8 | 1.4           | -2.10 [-3.47, -0.73] | 3.44 |
| Liebl et al. 2013/2014       | 10    | 7.2 | 0.5 | 10   | 8.8 | 1.2           | -1.60 [-2.41, -0.79] | 5.67 |
| Oskarsson et al. 1999        | 7     | 7.1 | 0.5 | 7    | 8.5 | 0.8           | -1.40 [-2.10, -0.70] | 6.20 |
| Oskarsson et al. 2000        | 7     | 7.2 | 0.5 | 7    | 8.6 | 1.1           | -1.40 [-2.30, -0.50] | 5.24 |
| Schnell et al. 1994          | 5     | 8.5 | 0.5 | 5    | 9.8 | 0.7           | -1.30 [-2.05, -0.55] | 5.92 |
| Pitt et al. 1992             | 10    | 8.0 | 1.8 | 10   | 9.1 | 2.2           | -1.10 [-2.86, 0.66]  | 2.46 |
| Wredling, Adamson et al. 1991| 6     | 7.6 | 0.4 | 6    | 8.7 | 0.6           | -1.10 [-1.68, -0.52] | 6.81 |
| Colette et al. 1989          | 13    | 8.0 | 1.4 | 11   | 8.9 | 2.0           | -0.90 [-2.26, 0.46]  | 3.45 |
| Georgopoulos et al. 1994     | 8     | 8.7 | 1.2 | 8    | 9.4 | 1.5           | -0.70 [-2.03, 0.63]  | 3.55 |
| Raccah et al. 1994           | 11    | 6.3 | 1.0 | 11   | 6.9 | 1.0           | -0.60 [-1.44, 0.24]  | 5.52 |
| Catargi et al. 2002          | 14    | 7.3 | 0.8 | 14   | 7.8 | 0.9           | -0.50 [-1.13, 0.13]  | 6.54 |
| Selam et al. 1989            | 6     | 8.2 | 1.4 | 8    | 8.6 | 1.3           | -0.40 [-1.82, 1.02]  | 3.28 |
| Lassmann-Vague et al. 1994   | 11    | 6.8 | 0.7 | 11   | 6.9 | 1.0           | -0.10 [-0.82, 0.62]  | 6.08 |
| Duvillard et al. 2005/2007    | 7     | 7.2 | 1.0 | 7    | 7.3 | 0.9           | -0.10 [-1.10, 0.90]  | 4.79 |
| Guerci et al. 1996           | 14    | 5.9 | 0.6 | 14   | 6.0 | 0.6           | -0.10 [-0.54, 0.34]  | 7.45 |
| Hanaire-Brouin et al. 1996   | 18    | 7.5 | 0.8 | 18   | 7.6 | 0.8           | -0.10 [-0.62, 0.42]  | 7.08 |
| Pacifico et al. 1997         | 8     | 6.6 | 1.4 | 8    | 6.5 | 1.1           | 0.10 [-1.13, 1.33]   | 3.87 |
| Walter et al. 1989           | 6     | 8.0 | 0.5 | 6    | 7.9 | 0.5           | 0.10 [-0.47, 0.67]   | 6.87 |
| Hedman et al. 2009/2014      | 10    | 8.6 | 1.4 | 20   | 7.9 | 0.8           | 0.70 [-0.08, 1.48]   | 5.78 |

Overall

Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67.60\%$, $H^2 = 3.09$

Test of $\theta = 0$: $Q(18) = 53.48$, $p = 0.00$

Test of $\theta = 0$: $t(18) = -3.67$, $p = 0.00$

Legends: Treatment, continuous intraperitoneal insulin infusion; Control, continuous subcutaneous insulin infusion.
Figure S1b. Subgroup meta-analysis of HbA1c (%) according to duration in patients during CIPII treatment compared to that during control treatment (CSII).

Legend: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).
Figure S1c. Subgroup meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).

Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %);

Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies);

Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months);

Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.
Figure S1d. Overall subgroup meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                             | Studies | Mean Diff. with 95% CI | P-value |
|---------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment |         |                        |         |
| HbA1c ≤ 7%                            | 4       | -0.16 [-0.50, 0.17]    | 0.332   |
| HbA1c > 7%                            | 15      | -0.74 [-1.14, -0.35]   | 0.000   |
| Test of group differences: Q_5(1) = 4.80, p = 0.03 |

| Study type                       |         |                        |         |
|----------------------------------|---------|------------------------|---------|
| Case-Control study               | 4       | 0.07 [-0.50, 0.65]     | 0.800   |
| Crossover study                  | 15      | -0.75 [-1.09, -0.42]   | 0.000   |
| Test of group differences: Q_5(1) = 5.96, p = 0.01 |

| Duration of CIPII-period          |         |                        |         |
|-----------------------------------|---------|------------------------|---------|
| CIPII ≤ 6 months                  | 9       | -0.21 [-0.57, 0.15]    | 0.253   |
| CIPII > 6 months                  | 10      | -0.98 [-1.39, -0.56]   | 0.000   |
| Test of group differences: Q_5(1) = 7.49, p = 0.01 |

| Duration of CIPII-period (months) |         |                        |         |
|-----------------------------------|---------|------------------------|---------|
| 3                                 | 4       | -0.14 [-0.49, 0.20]    | 0.407   |
| 4                                 | 1       | -0.10 [-0.54, 0.34]    | 0.659   |
| 6                                 | 4       | -0.42 [-1.41, 0.57]    | 0.404   |
| 10                                | 1       | -0.60 [-1.44, 0.24]    | 0.159   |
| 11                                | 1       | -1.40 [-2.10, -0.70]   | 0.000   |
| 12                                | 1       | -0.79 [-1.72, 0.15]    | 0.099   |
| 13                                | 1       | -0.90 [-2.26, 0.46]    | 0.196   |
| 18                                | 1       | -1.10 [-2.86, 0.66]    | 0.221   |
| 18.6                              | 1       | -1.10 [-1.68, -0.52]   | 0.000   |
| 24                                | 1       | -1.60 [-2.41, -0.79]   | 0.000   |
| Test of group differences: Q_5(9) = 26.00, p = 0.00 |

| Controlled CSII follow-up-period  |         |                        |         |
|-----------------------------------|---------|------------------------|---------|
| No                                | 15      | -0.61 [-1.01, -0.21]   | 0.003   |
| Yes                               | 4       | -0.64 [-1.16, -0.12]   | 0.015   |
| Test of group differences: Q_5(1) = 0.01, p = 0.93 |

**Overall**

Heterogeneity: $I^2 = 0.32$, $I^2 = 67.60\%$, $H^2 = 3.09$

Test of $\theta = 0$, $Q(18) = 53.48$, $p < 0.01$

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S1e. Meta-regression analysis bubble-plot of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).
Figure S1f. Cumulative meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII) according to duration of CIPII treatment.

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).
Figure S2a. Subgroup meta-analysis of fasting blood glucose (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

**Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %).**

**Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies).**

**Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months).**

**Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.**

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**Legends:** Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).
Figure S2b. Summarised subgroup meta-analysis of fasting blood glucose (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                              | Studies | Mean Diff. with 95% CI | P-value |
|----------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment |         |                        |         |
| HbA1c < 7 %                            | 1       | -0.50 [-2.00, 1.00]    | 0.513   |
| HbA1c > 7 %                            | 4       | 0.29 [-0.32, 0.89]     | 0.353   |
| Test of group differences: $Q_n(1) = 0.91, p = 0.34$ |         |                        |         |
| Study type                             |         |                        |         |
| Case-Control study                     | 1       | 1.80 [0.03, 3.57]      | 0.047   |
| Crossover study                        | 4       | 0.07 [-0.46, 0.60]     | 0.796   |
| Test of group differences: $Q_n(1) = 3.35, p = 0.07$ |         |                        |         |
| Duration of CIPII-period               |         |                        |         |
| CIPII ≤ 6 months                       | 5       | 0.20 [-0.34, 0.74]     | 0.472   |
| Test of group differences: $Q_n(0) = 0.00, p =$. |         |                        |         |
| Duration of CIPII-period (months)      |         |                        |         |
| 2                                      | 1       | 0.50 [-0.07, 1.07]     | 0.086   |
| 3                                      | 2       | -0.42 [-1.17, 0.32]    | 0.262   |
| 6                                      | 2       | 0.79 [-0.85, 2.42]     | 0.346   |
| Test of group differences: $Q_n(2) = 4.28, p = 0.12$ |         |                        |         |
| Controlled CSII follow-up-period       |         |                        |         |
| No                                     | 3       | 0.35 [-0.78, 1.47]     | 0.549   |
| Yes                                    | 2       | 0.11 [-0.77, 0.98]     | 0.809   |
| Test of group differences: $Q_n(1) = 0.11, p = 0.74$ |         |                        |         |
| Overall                                |         |                        |         |
| Heterogeneity: $\tau^2 = 0.12, I^2 = 32.48\%, H^2 = 1.48$ |         |                        |         |
| Test of $\theta_1 = \theta_2$: $Q(4) = 6.94, p = 0.14$ |         |                        |         |

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S3a. Subgroup meta-analysis of fasting insulin (pmol/L in patients during CIPII treatment compared to that during control treatment (CSII)).

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months); Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.
Figure S3b. Summarised subgroup meta-analysis of fasting insulin (pmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                                      | Studies | Mean Diff. with 95% CI | P-value |
|------------------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment   |         |                        |         |
| HbA1c ≤ 7 %                                    | 2       | -9.94 [-54.99, 35.11]  | 0.665   |
| HbA1c > 7 %                                    | 6       | -16.86 [-23.87, -9.85] | 0.000   |
| Test of group differences: Q(1) = 0.09, p = 0.77|         |                        |         |
| Study type                                     |         |                        |         |
| Case-Control study                             | 1       | -25.70 [-94.64, 43.24] | 0.465   |
| Crossover study                                | 7       | -16.61 [-23.57, -9.64] | 0.000   |
| Test of group differences: Q(1) = 0.07, p = 0.80|         |                        |         |
| Duration of CIPII-period                       |         |                        |         |
| CIPII ≤ 6 months                               | 5       | -15.20 [-25.98, -4.43] | 0.006   |
| CIPII > 6 months                               | 3       | -17.75 [-26.79, -8.71] | 0.000   |
| Test of group differences: Q(1) = 0.13, p = 0.72|         |                        |         |
| Duration of CIPII-period (months)              |         |                        |         |
| 2                                              | 2       | -9.98 [-29.33, 9.37]   | 0.312   |
| 3                                              | 2       | -12.77 [-34.78, 9.24]  | 0.255   |
| 6                                              | 1       | -20.10 [-36.17, -4.03] | 0.014   |
| 10                                             | 1       | -18.10 [-85.94, 49.74] | 0.601   |
| 11                                             | 1       | -17.60 [-26.80, -8.40] | 0.000   |
| 13                                             | 1       | -25.70 [-94.64, 43.24] | 0.465   |
| Test of group differences: Q(5) = 0.86, p = 0.97|         |                        |         |
| Controlled CSII follow-up-period               |         |                        |         |
| No                                             | 5       | -16.99 [-24.42, -9.56] | 0.000   |
| Yes                                            | 3       | -14.77 [-33.89, 4.34]  | 0.130   |
| Test of group differences: Q(1) = 0.04, p = 0.83|         |                        |         |

Overall: Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
Test of $\theta = 0$; $Q(7) = 1.38$, p = 0.99

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S4a. Subgroup meta-analysis of daily insulin dose (U/24 hours) in patients during CIPII treatment compared to that during control treatment (CSII).

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months); Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.
Figure S4b. Summarised subgroup meta-analysis of daily insulin dose (U/24 hours) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                                | Studies | Mean Diff. with 95% CI | P-value |
|------------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment |         |                        |         |
| HbA1c ≤ 7 %                              | 4       | 2.99 [-1.95, 7.93]     | 0.235   |
| HbA1c > 7 %                              | 8       | 0.41 [-3.17, 4.00]     | 0.821   |
| Test of group differences: $Q_a(1) = 0.68$, $p = 0.41$ |         |                        |         |
| Study type                               |         |                        |         |
| Case-Control study                       | 2       | 3.91 [-9.33, 17.14]    | 0.563   |
| Crossover study                          | 10      | 1.14 [-1.95, 4.22]     | 0.471   |
| Test of group differences: $Q_a(1) = 0.16$, $p = 0.69$ |         |                        |         |
| Duration of CIPII-period                 |         |                        |         |
| CIPII ≤ 6 months                         | 7       | 2.02 [-2.77, 6.82]     | 0.407   |
| CIPII > 6 months                         | 5       | 0.88 [-2.76, 4.53]     | 0.634   |
| Test of group differences: $Q_a(1) = 0.14$, $p = 0.71$ |         |                        |         |
| Duration of CIPII-period (months)        |         |                        |         |
| 1.5                                      | 1       | -2.60 [-14.48, 9.28]   | 0.668   |
| 3                                        | 3       | 2.88 [-4.20, 9.96]     | 0.425   |
| 6                                        | 3       | 3.83 [-6.38, 14.04]    | 0.462   |
| 10                                       | 1       | 3.30 [-9.46, 16.06]    | 0.612   |
| 11                                       | 1       | 2.30 [-5.61, 10.21]    | 0.569   |
| 12                                       | 3       | 0.18 [-4.15, 4.52]     | 0.935   |
| Test of group differences: $Q_a(5) = 1.25$, $p = 0.94$ |         |                        |         |
| Controlled CSII follow-up-period         |         |                        |         |
| No                                       | 11      | 1.28 [-1.73, 4.29]     | 0.404   |
| Yes                                      | 1       | 1.60 [-9.35, 12.55]    | 0.775   |
| Test of group differences: $Q_a(1) = 0.00$, $p = 0.96$ |         |                        |         |

**Overall**

| Heterogeneity: $I^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ | Test of $\theta = \theta_0$: $Q(11) = 4.30$, $p = 0.96$ | $1.30 [-1.60, 4.20]$ | 0.379 |

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S5a. Meta-analysis of SMBG (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Study                   | Treatment | N  | Mean | SD  | Control | N  | Mean | SD  | Mean Diff. with 95% CI | Weight (%) |
|-------------------------|-----------|----|------|-----|---------|----|------|-----|----------------------|------------|
| Pitt et al. 1992        | 10        | 7.8| 0.4  | 10  | 8.9     | 0.6|      |     | -1.10 [-1.55, -0.65]  | 22.27      |
| Georgopoulos et al. 1992| 7         | 7.7| 1.2  | 7   | 10.5    | 2.0|      |     | -2.80 [-4.53, -1.07]  | 4.42       |
| Micossi et al. 1986     | 6         | 8.8| 1.3  | 6   | 9.7     | 1.4|      |     | -0.90 [-2.43, 0.63]   | 5.43       |
| Beylot et al. 1987      | 4         | 8.2| 0.9  | 4   | 8.8     | 1.3|      |     | -0.60 [-2.15, 0.95]   | 5.31       |
| Catargi et al. 2002     | 14        | 8.1| 1.0  | 14  | 8.5     | 0.9|      |     | -0.40 [-1.10, 0.30]   | 15.57      |
| Georgopoulos et al. 1994| 8         | 7.4| 1.1  | 8   | 7.8     | 1.1|      |     | -0.40 [-1.48, 0.68]   | 9.29       |
| Guerci et al. 1996      | 14        | 7.6| 0.5  | 14  | 7.8     | 0.7|      |     | -0.20 [-0.65, 0.25]   | 22.17      |
| Raccah et al. 1994      | 11        | 8.0| 1.8  | 11  | 8.3     | 0.8|      |     | -0.30 [-1.45, 0.86]   | 8.32       |
| Lassmann-Vague et al. 1994| 11   | 8.3| 1.8  | 11  | 8.3     | 1.2|      |     | 0.00 [-1.28, 1.28]    | 7.23       |

**Overall**

Heterogeneity: $I^2 = 0.13$, $I^2 = 41.73\%$, $H^2 = 1.72$

Test of $\theta = 0$: $Q(8) = 15.74$, $p = 0.05$

Test of $\theta = 0$: $I(8) = -3.09$, $p = 0.002$

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII); SMBG, self-monitoring of blood glucose.
Figure S5b. Subgroup meta-analysis of SMBG (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months); Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.
Figure S5c. Summarised subgroup meta-analysis of SMBG (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                              | Studies | Mean Diff. with 95% CI | P-value |
|----------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment |         |                        |         |
| HbA1c ≤ 7 %                            | 3       | -0.19 [-0.59, 0.21]    | 0.345   |
| HbA1c > 7 %                            | 6       | -0.88 [-1.34, -0.42]   | 0.000   |
| Test of group differences: Q(4) = 4.85, p = 0.03 |         |                        |         |
| Study type                             |         |                        |         |
| Crossover study                        | 9       | -0.62 [-1.01, -0.23]    | 0.002   |
| Test of group differences: Q(0) = 0.00, p = . |         |                        |         |
| Duration of CIPII-period               |         |                        |         |
| CIPII ≤ 6 months                       | 6       | -0.30 [-0.63, 0.03]    | 0.074   |
| CIPII > 6 months                       | 3       | -1.24 [-2.40, -0.07]   | 0.037   |
| Test of group differences: Q(4) = 2.31, p = 0.13 |         |                        |         |
| Duration of CIPII-period (months)      |         |                        |         |
| 1.5                                    | 1       | -0.90 [-2.43, 0.63]    | 0.249   |
| 2                                      | 1       | -0.60 [-2.15, 0.95]    | 0.448   |
| 3                                      | 2       | -0.31 [-0.92, 0.31]    | 0.330   |
| 4                                      | 1       | -0.20 [-0.65, 0.25]    | 0.384   |
| 6                                      | 1       | -0.40 [-1.48, 0.68]    | 0.467   |
| 10                                     | 1       | -0.30 [-1.46, 0.86]    | 0.613   |
| 12                                     | 1       | -2.80 [-4.53, -1.07]   | 0.001   |
| 18                                     | 1       | -1.10 [-1.55, -0.65]   | 0.000   |
| Test of group differences: Q(7) = 15.45, p = 0.03 |         |                        |         |
| Controlled CSII follow-up-period       |         |                        |         |
| No                                     | 4       | -0.70 [-1.62, 0.22]    | 0.138   |
| Yes                                    | 5       | -0.72 [-1.20, -0.23]   | 0.004   |
| Test of group differences: Q(1) = 0.00, p = 0.97 |         |                        |         |
| Overall                                |         | -0.62 [-1.01, -0.23]   | 0.002   |

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S6a. Meta-analysis of cholesterol (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Study                     | Treatment | Control |
|---------------------------|-----------|---------|
|                           | N | Mean | SD | N | Mean | SD | Mean Diff. with 95% CI | Weight (%) |
| Duvillard et al. 2005/2007| 7 | 5.0  | 0.6| 7 | 5.4  | 0.7| -0.40 [-1.08, 0.28]     | 17.58      |
| Georgopoulou et al. 1994  | 8 | 4.6  | 0.8| 8 | 4.8  | 0.8| -0.20 [-0.98, 0.58]     | 13.34      |
| Georgopoulou et al. 1992  | 7 | 4.6  | 1.1| 7 | 4.9  | 1.3| -0.30 [-1.56, 0.96]     | 5.15       |
| Raccah et al. 1994        | 11| 4.9  | 2.3| 11| 5.0  | 1.3| -0.10 [-1.66, 1.46]     | 3.36       |
| Guerri et al. 1996        | 14| 5.0  | 0.6| 14| 5.0  | 0.6| 0.00 [-0.44, 0.44]      | 41.52      |
| Pacifico et al. 1997      | 8 | 4.8  | 0.8| 8 | 4.7  | 0.8| 0.10 [-0.68, 0.88]      | 13.34      |
| Micossi et al. 1986       | 6 | 5.1  | 1.2| 6 | 4.4  | 0.9| 0.70 [-0.50, 1.90]      | 5.69       |

Overall

Heterogeneity: $I^2 = 0.00$, $H^2 = 1.00$

Test of $\theta = \theta$: Q(6) = 2.99, $p = 0.81$

Test of $\theta = 0$: t(6) = -0.43, $p = 0.67$

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).
Figure S6b. Subgroup meta-analysis of cholesterol (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Study          | Treatment | Control | Mean Diff | Weight (%) |
|----------------|-----------|---------|-----------|------------|
| HbA1c ≥ 7.0%   | 7.5       | 7.1     | 0.4       | 0.03       |
|               | 0.5       | 0.4     | 0.1       | 0.02       |
| HbA1c ≤ 7.0%   | 7.0       | 7.0     | 0.0       | 0.00       |
|               | 0.5       | 0.5     | 0.0       | 0.00       |

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7 % and > 7 %); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII-period (≤ 6 months and > 6 months); Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII-period.
Figure S6c. Summarised subgroup meta-analysis of cholesterol (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                                      | Studies | Mean Diff. with 95% CI | P-value |
|------------------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment  |         |                        |         |
| HbA1c ≤ 7 %                                   | 3       | 0.02 [-0.36, 0.39]     | 0.929   |
| HbA1c > 7 %                                   | 4       | -0.17 [-0.62, 0.27]    | 0.442   |
| Test of group differences: Q_τ(1) = 0.42, p = 0.52 |         |                        |         |

| Study type                                      |         |                        |         |
| Crossover study                                | 7       | -0.06 [-0.35, 0.22]    | 0.668   |
| Test of group differences: Q_τ(0) = 0.00, p = . |         |                        |         |

| Duration of CIPII-period                       |         |                        |         |
| CIPII ≤ 6 months                               | 4       | -0.07 [-0.40, 0.25]    | 0.658   |
| CIPII > 6 months                               | 3       | -0.03 [-0.64, 0.59]    | 0.936   |
| Test of group differences: Q_τ(1) = 0.02, p = 0.89 |         |                        |         |

| Duration of CIPII-period (months)              |         |                        |         |
| 1.5                                            | 1       | 0.70 [-0.50, 1.90]     | 0.253   |
| 3                                              | 1       | -0.40 [-1.08, 0.28]    | 0.251   |
| 4                                              | 1       | 0.00 [-0.44, 0.44]     | 1.000   |
| 6                                              | 1       | -0.20 [-0.98, 0.58]    | 0.617   |
| 10                                             | 1       | -0.10 [-1.66, 1.46]    | 0.900   |
| 12                                             | 2       | -0.01 [-0.68, 0.65]    | 0.973   |
| Test of group differences: Q_τ(5) = 2.71, p = 0.74 |         |                        |         |

| Controlled CSII follow-up-period               |         |                        |         |
| No                                             | 6       | -0.11 [-0.40, 0.19]    | 0.470   |
| Yes                                            | 1       | 0.70 [-0.50, 1.90]     | 0.253   |
| Test of group differences: Q_τ(1) = 1.64, p = 0.20 |         |                        |         |

**Overall**
- Heterogeneity: $t^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$
- Test of $\theta = \theta$: $Q(6) = 2.99$, $p = 0.81$

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Figure S7a. Meta-analysis of triglycerides (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Study                     | Treatment | Control | Mean Diff. with 95% CI | Weight (%) |
|---------------------------|-----------|---------|------------------------|------------|
| Geogopoulos et al. 1992  | 7         | 7       | -0.10 [-0.47, 0.27]    | 10.12      |
| Geogopoulos et al. 1994  | 8         | 8       | 0.00 [-0.25, 0.25]     | 19.44      |
| Raccah et al. 1994       | 11        | 11      | 0.00 [-0.25, 0.25]     | 19.33      |
| Guerci et al. 1996       | 14        | 14      | 0.00 [-0.38, 0.38]     | 9.77       |
| Pacifico et al. 1997     | 8         | 8       | 0.10 [-0.19, 0.39]     | 15.00      |
| Duvillard et al. 2005/07 | 7         | 7       | 0.20 [-0.07, 0.47]     | 17.51      |
| Micossi et al. 1986      | 6         | 6       | 0.60 [0.20, 1.00]      | 8.82       |

Overall

Heterogeneity: $\hat{t}^2 = 0.00$, $I^2 = 16.99\%$, $H^2 = 1.20$
Test of $\theta = 0$: $Q(6) = 9.12$, $p = 0.17$
Test of $\theta = 0$: $t(6) = 1.45$, $p = 0.15$

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII).
Figure S7b. Subgroup meta-analysis of triglycerides (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (≤ 7% and > 7%); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII period (≤ 6 months and > 6 months); Figure D: Subgroup analysis according to whether or not there was an additional controlled CSII follow-up-period with subsequent CIPII period.
Figure S7c. Summarised subgroup meta-analysis of triglycerides (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

| Subgroups                                      | Studies | Mean Diff. with 95% CI | P-value |
|-----------------------------------------------|---------|------------------------|---------|
| HbA1c levels before starting CIPII treatment  |         |                        |         |
| HbA1c ≤ 7 %                                   | 3       | 0.03 [-0.14, 0.20]     | 0.699   |
| HbA1c > 7 %                                   | 4       | 0.16 [-0.11, 0.43]     | 0.248   |
| Test of group differences: Qx(1) = 0.59, p = 0.44 |         |                        |         |
| Study type                                    |         |                        |         |
| Crossover study                               | 7       | 0.09 [-0.03, 0.22]     | 0.147   |
| Test of group differences: Qx(0) = -0.00, p = . |         |                        |         |
| Duration of CIPII-period                      |         |                        |         |
| CIPII ≤ 6 months                              | 4       | 0.18 [-0.07, 0.42]     | 0.153   |
| CIPII > 6 months                              | 3       | 0.01 [-0.16, 0.18]     | 0.887   |
| Test of group differences: Qx(1) = 1.19, p = 0.27 |         |                        |         |
| Duration of CIPII-period (months)             |         |                        |         |
| 1.5                                           | 1       | 0.60 [0.20, 1.00]      | 0.003   |
| 3                                             | 1       | 0.20 [-0.07, 0.47]     | 0.142   |
| 4                                             | 1       | 0.00 [-0.38, 0.38]     | 1.000   |
| 6                                             | 1       | 0.00 [-0.25, 0.25]     | 1.000   |
| 10                                            | 1       | 0.00 [-0.25, 0.25]     | 1.000   |
| 12                                            | 2       | 0.02 [-0.21, 0.25]     | 0.847   |
| Test of group differences: Qx(5) = 8.43, p = 0.13 |         |                        |         |
| Controlled CSII follow-up-period              |         |                        |         |
| No                                            | 6       | 0.04 [-0.07, 0.16]     | 0.455   |
| Yes                                           | 1       | 0.60 [0.20, 1.00]      | 0.003   |
| Test of group differences: Qx(1) = 6.80, p = 0.01 |         |                        |         |
| Overall                                       |         | 0.09 [-0.03, 0.22]     | 0.147   |

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.
Data for Egger’s test from STATA

**HbA1c**

| meta bias, egger random(reml) tdistribution |
|--------------------------------------------|
| Effect-size label: Mean Diff.              |
| Effect size: _meta_es                      |
| Std. Err.: _meta_se                        |
| Regression-based Egger test for small-study effects |
| Random-effects model                       |
| Method: REML                               |
| H0: beta1 = 0; no small-study effects      |
| beta1 = -1.10                              |
| SE of beta1 = 1.017                        |
| t = -1.08                                  |
| Prob > t = 0.2932                          |

**Daily insulin dose**

| Model and method |
|------------------|
| Model: Random-effects |
| Method: REML      |
| . meta bias, egger random(reml) tdistribution |
| Effect-size label: Mean Diff. |
| Effect size: _meta_es |
| Std. Err.: _meta_se |
| Regression-based Egger test for small-study effects |
| Random-effects model |
| Method: REML |
| H0: beta1 = 0; no small-study effects |
| beta1 = 0.43 |
| SE of beta1 = 0.834 |
| t = 0.51 |
| Prob > t = 0.6212 |
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