Supporting information

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

A systematic review

Ilze Dirnena-Fusini et al. 2020

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Literature search strategy

Table S1. Literature search strategy.

Embase		Pub	Med	Scop	ous	Central			
1	exp diabetes mellitus/	1	Diabetes mellitus[mh]	1	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]	9	#6 OR #7 OR #8	9	subcutaneous*:ti,ab,kw		
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]	18	TITLE-ABS-KEY (pump)	18	pump:ti,ab,kw		
19	infus*.ti,ab,kw.	19	absorption[tiab] OR absorption[ot]	19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	19	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18		
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					Γ			
29	27 6 and 11 and 14 and 17 and 28	┢		┢		E			

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 righthanded [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 CIPIIperiod 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].

8

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 metaanalysis.

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 CIPIIperiod [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 CSIIperiod (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 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 pg/mL/h vs. 5.1 pg/mL/h, p = 0.027; and 23.4 pg/mL/h vs. 10.3 pg/mL/h, p = 0.04, respectively) [89, 90]. A significantly larger incremental post-exercise AUC compared to post-exercise (23.4 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), the distance is a final dimensional difference is 2 (465PP 2) and 2 (465PP 2).

growth hormone binding protein (GHBP), 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 % and 42.5 % vs. 23.7 %, respectively, p < 0.01), but not after 24 months [79, 80], and at three months of the CIPII-period in another study (11.0 % vs. 3.6 %, p < 0.05) [86]. No difference was observed in one study [91], and another reported no changes in the AIA levels (p-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 % vs. 24.9 %, 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 it 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.

Sour	ce 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
Rando	mised follow-up studies				Cochrane risk of bias tool (CRB):
Liebl et 2009 [2 2000 [2 2000 [2 2000 [2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	, , , , , , , , , , , , , , , , , , ,	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 CSII and CIPII in type 1 diabetic patients.	HbA1c: Decreases in both groups (CIPII: - 0.5; CSII: - 0.6 %, p=0.374) SMBG: No change (CIPII: + 0.1; CSII: ± 0.0 mmol/L, p=NS) BG < 3 mmol/L: No change (All CIPII-period: 118.2; M1-3: 138.1; M4-12: 108.9; CSII: 115.8 events/patient-years, p=NS) Severe hypoglycaemia: Decreases (Before CIPII: 0.7; All CIPII- 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; CIPII vs CSII-period: p=0.013)	<u>CRB:</u> Unclear risk of bias: Random sequence generation, allocation concealment, blinding Low risk of bias: Incomplete outcome data, selective reporting, treatment procedure
Non-ra	andomised crossover studies		Strengthening	the Reporting of Observational Studies in Epidemiology (STROBE) ar	nd Thomas quality assessment toll (QAT):
Micoss al. 198 [84]		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 CSII and CIPII.	HbA1c: Decreases (CIPII: 6.2; CSII: 7.25 % (CIPII: 44; CSII: 56 mmol/mol), p<0.05) SMBG: No change (CIPII: 8.8; CSII: 9.7 mmol/l, p=NS) BG > 14 mmol/l: Decreases (CIPII: 8.9; CSII: 16.1 %, p<0.05) BG > 10mmol/l: No change (CIPII: 31.8; CSII: 44.7 %, p=NS) BG < 3.9 mmol/l: Decreases (CIPII: 4.5; CSII: 6.2 %, p<0.05) BG < 2.8 mmol/l: No change (CIPII: 1.2; CSII: 1.6 %, p=NS) MAGE: Decreases (CIPII: 6.9; CSII: 9.5 mmol/L, p<0.005)	STROBE: 15/22 QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Selection bias, study design Weak: Confounders
Beylot al. 198 [103]		CSII use: ND CSII f-u: 8 CIPII 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 ^{DT} : No change (CIPII: 6.2; CSII: 6.5 % (CIPII: 44; CSII:48 mmol/mol), p=ND)) SMBG ^{DT} : No change (CIPII: 8.20; CSII: 8.77 mmol/l, p=ND) Pre-prandial BG: No change (CIPII: 5.9; CSII: 5.4 mmol/L, p=ND) Endogenous glucose production in basal period: No change (CIPII: 2.92; CSII: 2.93mg/kg/min, p=ND) Glucose utilization in basal period: No change (CIPII: 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
Wredli Adams et al. 1 (techni report) [91]	son Age: 41.3 991 Diabetes duration: 23.2 ical Sex: 4/2	CSII use: 52+ CSII f-u: 8 (n=3) CIPII f-u: median 72	To determine the efficacy of a new percutaneous device.	HbA1c*: No change (CIPII: 7.6; CSII: 8.7 % (CIPII: 60; CSII: 72 mmol/mol), p=ND)	STROBE:15/22 QAT: Moderate: Selection bias, study design, data collection method Weak: Withdrawals and drop-outs Unclear: Confounders

Table S2.1. Intervention studies: Participant characteristics, description, outcomes: glycaemic control

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, 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; ^a dropouts in this study (at the end of the periods N= 36 (CIPII: 15 /CSII: 21); *, HbA1c calculated as mean of all determinations (every 4 weeks); ^{DT}: data calculated from table.

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-rando	nised crossover studies			ng the Reporting of Observational Studies in Epidemiology (STROBE) and T	nomas quality assessment toll (QA
Georgopo ulos 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.	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 drop-puts 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 CIPII 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 ^{FF} : 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))	STROBE: 18/22 QAT: Strong: Confounders, withdrawa 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 CIPII f-u: 52	To gain experience in assessing the feasibility of therapeutical 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) Ketoacidosis: 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 drop-ou
Georgopo ulos 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 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 -Vague et al. 1994 (short communi cation) [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 CIPII 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; Ketoacidosis, vomiting and/or nausea in the presence of hyperglycaemia (BG>13 mmol/L), more detains in the main article; ^{FF}, data extracted from figure.

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-randor	nised crossover studies			Reporting of Observational Studies in Epidemiology (STROBE)	
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	ND	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)	NP
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 insulin demands during 24 h in IPII and CSII patients. To compare HbA1c levels in CIPII and CSII patients.	HbA1c: Decreases (CIPII: M12: 8.5, p<0.05; M3: 8.6, p<0.05; CSII: 9.8 %)	STROBE: 17/22 QAT: Strong: Withdrawals and drop-outs Moderate: Selection bias, study design, confounders, data collection method
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.	HbA1c: No change (CIPII: 5.9; CSII: 6.1 %, p=NS) SMBG: No change (CIPII: 7.55; CSII: 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, da collection method, withdrawals and dr outs Moderate: Study design
Hanaire- Broutin 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) <u>16-hour blood glucose profile:</u> 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
Non-rando	mised crossover studies		Strengthening the Report	rting of Observational Studies in Epidemiology (STROBE) an	d Thomas quality assessment toll (QAT
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	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 collectior methods, selection bias Moderate: Confounders, withdrawa and drop-outs
Oskarsson et al. 1999 [90]	N = 7 Age: 42 Diabetes duration: 15 Sex: 5/2 HbA1c: 8.5 C-peptide: < 0.2 nM Reasons: Pmc	CSII use: 26+ CIPII 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 ₂ $_{max}$ 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)	<u>STROBE:16/22</u> <u>QAT:</u> Strong: Confounders, data collection methods, withdrawals and drop-out Moderate: Selection bias, study design
Oskarsson et al. 2000 [89]	N = 7 Age: 42 Diabetes duration: 17 Sex: 5/2 HbA1c: 8.6 C-peptide: Neg Reasons: Pmc	CSII use: 52+ CIPII 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-out Moderate: Selection bias, study design
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 CIPII 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 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

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.

	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 c	rossover studies		Strengthening the	Reporting of Observational Studies in Epidemiology (STROBE) ar	d Thomas quality assessment toll (QA
	Liebl et al. 2013(conf. Abstracts/ Poster) [94-96] Liebl et al. 2014 (c.poster) [97]	N = 12 (n = 10)* Age: 49 Diabetes duration: 30 Sex: 2/10 HbA1c: 9.0 (8.8)* C-peptide: ND Reasons: Pmc	CSII use: ND CIPII f-u: 104	To investigate the clinical long-term performance and safety of the new Accu-Chek DiaPort 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 %) BG (by CGM) > 10.0 mmol/I: Decreases (CIPII: M6: 38: CSII: 53 %, p=0.036) BG (by CGM) in range 3.9 - 10.0 mmol/I: Increases (CIPII: M6: 58; CSII: 45 %, p=0.027) Severe hypoglycaemia: No change (CIPII: 3 events/24 months; CSII: 12 events/12 months, p=ND)	NP
	Dassau et al. 2017 [78]	N = 10 Age: 49 Diabetes duration: 29 Sex: 7/3 HbA1c: 7.7 C-peptide: ND Reasons: Pmc	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.	BG (by CGM): Decreases (CIPII: 8.3; CSII: 10.5 mmol/L, p=0.004) BG > 14 mmol/L: Decreases (CIPII: 5.9; CSII: 23.0 %, p=0.0004) BG > 10mmol/L: Decreases (CIPII: 32.4; CSII: 53.5 %, p=0.0014) BG in range 3.9 to 10 mmol/L: Increases (CIPII: 65.7; CSII: 43.9 %, p=0.001) BG in range 4.4 to 7.8 mmol/L: Increases (CIPII: 39.8; CSII: 25.6 %, p=0.03) BG < 3.8mmol/L: No change (CIPII: 2.5; CSII: 4.1 %, p=0.42)	STROBE: 20/22 QAT: Strong: Data collection methods, withdrawals and drop-outs, study design Moderate: Selection bias, confounde
	Retrospective cross	sover studies				STROBE and QAT:
Glycaemic control	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 SCII.	HbA1c: No change (CIPII: 6.7; CSII: 6.64 %, p=ND) SD of BG: Decreases (CIPII: 3.3; CSII: 3.6 mmol/L/24h, p=0.038) Pre-prandial BG: No change (CIPII: 7.2; CSII: 7.8 mmol/L, p=0.051) Post-prandial BG: No change (CIPII: 8.7; CSII: 10.1 mmol/L, p=0.051) BG < 3.6 mmol/L: No change (CIPII: 3.6; CSII: 4.0	STROBE: 12/22 QAT: Weak: Study design Unclear: Selection bias, confounders data collection methods
	Catargi et al. 2002 [88]	N = 14 Age: 50.6 Diabetes duration: 28.0 Sex: 5/9 HbA1c: 7.8 C-peptide: Neg Reasons: ND	CSII use: ND CSII f-u: 6.4 Healing period: 6.4 CIPII f-u: 6.4 ^a	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) Pre-prandial BG: Decreases (CIPII: 7.8; CSII: 8.1 mmol/L, p<0.05) SMBG: Decreases (CIPII: 8.0; CSII: 8.5 mmol/L, p<0.01) SD of BG: Decreases (CIPII: 3.8; CSII: 4.4 mmol/L, p<0.01) Post-prandial BG: No change (CIPII: 8.2; CSII: 8.5 mmol/L, p=0.07)	STROBE: 15/22 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; ^a, three patients first were treated with CIPII, and then with CSII.

	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
-	Case-control studies					(STROBE) and Thomas quality assessment toll (QA
	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)	<u>STROBE: 18/22</u> <u>QAT:</u> 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) Pre-prandial BG ^{FF} : No change (CIPII: 7.3; CSII: 5.5 mmol/L, p=NS) Post-prandial BG: No change (p=NS)	STROBE: 14/22 QAT: Strong: Data collection methods Moderate: Study design, confounders Weak: Confounders Unclear: Selection bias, blinding
Glycaemic control	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
Case report				Critical appraisa	tool of Center for Evidence-based management:
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) (1): 12 CSII f-u (Lispro) (2): 3 CIPII use: 1.5+	To evaluate a new catheter design.	HbA1c: No change (CIPII: 5.9; CSII (1): 6.2; CSII (2): 6.1 %, p=ND) SMBG: No change (CIPII: 6.3; CSII (1): 7.8; CSII (2): 7.3 mmol/L, p=ND) Pre-prandial BG: No change (CIPII: 5.9; CSII (1): 6.4; CSII (2): 6.6 mmol/L, p=ND) Post-prandial BG: No change (CIPII: 6.6; CSII (1): 9.6; CSII (2): 8.8 mmol/L, p=ND) 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)	8/10 (2 cannot tell)

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.

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
Randomised	crossover studies with wash	-out period			Cochrane risk of bias tool (CRB)
Giacca 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)	<u>CRB:</u> Unclear risk of bias: Random sequence generation, allocation concealment, blinding Low risk of bias: Incomplete outcome data, selective reporting, treatment procedure
Randomised	l follow-up studies				Cochrane risk of bias tool (CRB):
Liebl et al. 2009 [5]	N = 60 ^a (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 CSII and CIPII in type 1 diabetic patients.	Mean daily insulin requirement: No change (CIPII: 44.2; CSII: 46.0 U/24h, p=ND)	<u>CRB:</u> Unclear risk of bias: Random sequence generation, allocation concealment, blinding Low risk of bias: Incomplete outcome data, selective reporting, treatment procedure
	nised crossover studies			Reporting of Observational Studies in Epidemiology (S	
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 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 CSII 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

Table S2.2. Intervention studies, Participant characteristics, description, outcomes: Insulin levels

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

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-rando	mised crossover studies		Strengthening the Repor	ting of Observational Studies in Epidemiology (S	TROBE) and Thomas quality assessment toll (QA
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 CIPII 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 (CIPII: 131.95; CSII: 152.79 pmol/L, p=ND) Plasma free insulin (night-time): Decreases (CIPII: 127.78; CSII: 163.2 pmol/L, p<0.05), Mean daily insulin requirement ^{DT} : No change (CIPII: 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 CIPII 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 (CIPII: 60; CSII: 133 minutes, p=0.006) Total insulin AUC (0-240 minutes): No change (CIPII (bolus 0.05 U/kg/BW): 56.1 mU; CSII (bolus 0.1 U/kg/BW): 94.6 mU, p=0.0023) Insulin AUC 0-60 min: No change (CIPII: 16.3; CSII: 20.6 mU, p=NS) Intra-patient CV (AUC 0-60 min): No change (CIPII: 19.8; CSII: 38.6 %, p=NS) Intra-patient CV (AUC 0-240 min): No change (CIPII: 11.5; CSII: 20.2 %, p=NS) Inter-patient peak time: No change (CIPII: 22.4; CSII: 28.3 %, p=NS) Inter-patient CV (AUC 0-60 min): No change (CIPII: 43.6; CSII: 27.9 %, p=NS) Inter-patient CV (AUC 0-240 min): No change (CIPII: 30.9; CSII: 29.7 %, p=NS) Inter-patient peak time: No change (CIPII: 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
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: 52+ CSII f-u: 8 (n=3) CIPII f-u: median 72	To determine the efficacy of a new percutaneous device.	Mean daily insulin requirement: No change (CIPII: 44.8 U/24h; CSII: ND)	<u>STROBE:15/22</u> <u>QAT:</u> Moderate: Selection bias, study design, data collection method Weak: Withdrawals and drop-outs Unclear: Confounders

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; CV, coefficient of variation; AUC, area under curve; ^{DT}, data calculated from table.

(rce Participant characteristics Lengtl (Number, age (mean years), CSII use diabetes duration (mean follow years), sex (Male/Female), IPII fol HbA1c (%), C-peptide, up (we reasons to participate		Reported study objectives	Outcomes (mean, p-value)	Methodological quality
_	Non-randomise	d crossover studies		Strengthening th	e Reporting of Observational Studies in Epidemiology (STRO	DBE) and Thomas quality assessment toll (QAT
	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.	Mean daily insulin requirement : No change (CIPII: 57.2; CSII: 52 (units of measurements are not provided, p=NS)	STROBE: 11/22 QAT: Strong: Data collection methods, withdrawal and drop-puts Moderate: Selection bias, study design, confounders
	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.	Mean daily insulin requirement : No change (CIPII: 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
lin leve	Lassmann- Vague et al. 1994 (short communicati on) [104]	N = 11 Age: 34.4 Diabetes duration: 22.4 Sex: 5/6 HbA1c: 6.9 C-peptide: Neg Reasons: ND	CSII use: 26+ CSII f-u: 4 CIPII f-u: 12	ND	Fasting insulin levels: No change (CIPII: M1: 111.12; M3: 114.59; CSII: 118.06 pmol/L, p=ND) Mean daily insulin requirement: No change (CIPII: 41.6; CSII: 40.5 U/24h, p=ND)	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 CIPII f-u: 40	ND	Fasting insulin levels: No change (CIPII: M3: 114.59; M10: 100; CSII: 118.06 pmol/L, p=NS) Mean daily insulin requirement: No change (CIPII: 62.4; CSII: 40.5 U/24h, p=NS)	NP
	Schnell et al. 1994 [105]	N = 5 Age: 25-62 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 insulin demands during 24 h in CIPII and CSII patients. To compare HbA1c levels in CIPII and CSII patients.	Mean daily insulin requirement: No change (CIPII: 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; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; NP, not possible to evaluate.

	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-random	ised crossover studies		Strengthe	ning the Reporting of Observational Studies in Epidemiology (STROBE) and Thomas quality assessment toll (QAT):
	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
Insulin levels	Hanaire- Broutin 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: 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.	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)	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.

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-randomi	ised crossover studies		Strengthening th	ne Reporting of Observational Studies in Epidemiology (ST	ROBE) and Thomas quality assessment toll (QA
Oskarsson et al. 1999 [90]	N = 7 Age: 42 Diabetes duration: 15 Sex: 5/2 HbA1c: 8.5 C-peptide: < 0.2nM Reasons: Pmc	CSII use: 26+ CIPII 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 CIPII in type 1 diabetic patients.	Fasting insulin levels: decreases (CIPII: 28.0; CSII: 48.1 pmol/L, p=0.043) Change in insulin levels during the time of exercises ^{FF} : No change (in the groups); increases (between groups, through the study, p<0.05) Mean daily insulin requirement: No change (CIPII: 38.4; CSII: 36.1 U/24h, p=0.06)	STROBE:16/22 QAT: Strong: Confounders, data collection methods withdrawals and drop-outs Moderate: Selection bias, study design
Oskarsson et al. 2000 [89]	N = 6 Age: 42 Diabetes duration: 17 Sex: 5/2 HbA1c: 8.6 C-peptide: Neg Reasons: Unsatisfactory on CSII	CSII use: 52+ CIPII 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 CIPII.	Fasting insulin levels: Decreases (CIPII: 35.8; CSII: 53.4pmol/L, p<0.01)	STROBE: 16/22 QAT: Strong: Confounders, data collection method: withdrawals and drop-outs Moderate: Selection bias, study design
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 CIPII 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 (CIPII: 43.6; CSII: 45.0 U/24h, p=0.69)	Strobe: 19/22 QAT: Moderate: Data collection methods, study design, withdrawals and drop-outs Poor: Selection bias, confounders
Liebl et al. 2013 (c.a) [94-96] Liebl et al 2014 (c.a) [97]	N = 12 (n = 10)* Age: 49 Diabetes duration: 30 Sex: 2/10 HbA1c: 9.0 (8.8)* C-peptide: ND Reasons: Pmc	CSII use: ND CIPII 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 (CIPII: M6: 45; CSII: 49 U, p=NS)	NP

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; ND, no data available; NS, Not significant; ^{FF}, 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	Length of: CSII use, CSII follow-up, IPII follow-up (weeks)	Reported study objectives	Outcomes (mean, p-value)	Methodological quality
	Non-randomis	ed crossover studies		Strengthening the	Reporting of Observational Studies in Epidemiology (S	TROBE) and Thomas quality assessment toll (QAT):
	Dassau et al.	N = 10	CSII use: 443	To compare closed-loop zone MPC	In in-clinical measurements: 24-hour total insulin	STROBE: 20/22
	2017 [78]	Age: 49 Diabetes duration: 29 Sex: 7/3	CSII f-u: 24h CIPII f-u: 4 to 20	using the DiaPort IP insulin delivery system with the traditional SC insulin delivery	delivery: Increases (CIPII: 43.66; CSII: 32.29 U, p<0.001) Mean daily insulin requirement: No change (CIPII:	<u>QAT:</u> Strong: Data collection methods, withdrawals and drop-outs, study design
		HbA1c: 7.7 C-peptide: ND Reasons: Pmc		method during a 24-hour in-clinic protocol.	ND; CSII: 43 U/24h)	Moderate: Selection bias, confounders
	Retrospective	crossover studies		Strengthening the R	eporting of Observational Studies in Epidemiology (STF	ROBE) and Thomas quality assessment toll (OAT):
Insulin levels	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 ed follow-up studies N = 101 (CIPII: 32 /CSII: 69) ^b Age: 50/48 Diabetes duration: 29/27 Sex: 14/25 / 30/44 HbA1c: 8.3/7.9 C-peptide: ND	CSII use: 1 CIPII use: 12 CSII/MDI use: 208+ CIPII use: 208+ CSII f-u: 27 CIPII f-u: 27	To assess the potential benefits of CIPII vs SCII. 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: Increase (CIPII: 39; CSII: 32 U/24h, p<0.05) Mean daily insulin requirement: No change (CIPII: 0.7; CSII: 0.6 U/24h/kg, p=NS)	STROBE: 12/22 QAT: Weak: Study design Unclear: Selection bias, confounders, data collection methods STROBE and QAT: STROBE: 16/22 QAT: Strong: Selection bias, study design, data collection method Moderate: Study design, withdrawals and dropouts
	Case-control st	Reasons: Pmc tudies				STROBE and QAT:
	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: ^b, for analysis participant nr. changed (dropouts).

	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
	Case-control stu				ting of Observational Studies in Epidemiology (STR	OBE) 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 ^{FF} : 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
levels	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-out Moderate: Study design
	Case report				Critical appraisal	tool of Centre for Evidence-based managemen
	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)

Legends: CSII, continuous subcutaneous insulin infusion; CIPII, continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; ND, no data available; NS, Not significant; ^{FF}, data extracted from figure.

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	C	Dutcomes (mean, p-val	ue)	Methodological quality
Non-randomis	ed crossover studies			e Reporting of Observa	tional Studies in Epide	miology (STROBE) and Th	omas quality assessment toll (QAT)
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: 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 CSII and CIPII.	HDL-cholesterol: Dect HDL ₂ cholesterol: Dect HDL ₃ cholesterol: No Fasting serum triglyco p<0.005)	change (CIPII: 5.1; CSII: reases (CIPII: 1.2; CSII: 1 creases (CIPII: 0.3; CSII: change (CIPII: 0.95; CSII erides: Increases (CIPII: No change (CIPII: 61.7; (.4 mmol/L, p<0.05) D.6 mmol/L, p<0.01) : 0.9 mmol/L, p=NS)	STROBE: 15/22 QAT: Strong: Data collection methods, withdrawals and drop-outs Moderate: Selection bias, study design Weak: Confounders
Georgopoulos et al. 1992 [83] Raccah et al. 1994 (letter)		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.	HDL cholesterol: No of Fasting plasma triglyon mmol/L, p=NS) Differences after fat i (no statistically signifi	change (CIPII: 4.6; CSII change (CIPII: 1.30; CSII ceride: No change (CIPII ingestion: Plasma TG ir cant changes in any tim ituents in fasting lipopr Sf 100-400: CIPII: 0.20; CSII: 0.29, p<0.008 CIPII: 0.594; CSII: 0.975, p<0.001 CIPII: 14.07; CSII: 13.93, p=NS	: 1.33 mmol/L, p=NS) : 1.23; CSII: 1.35 creased in both groups e point).	STROBE: 11/22 QAT: Strong: Data collection methods, withdrawals and drop-puts 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	ND	mmol/L, p=NS)	change (CIPII: M3: 4.74	; M10: 4.92; CSII: 5.03 II: M3: 0.88; M10: 0.83;	NP

Table S2.3. Intervention studies, Participant characteristics, description, outcomes: Intermediate metabolites

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.

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-randomise	d crossover studies		Stre	ngthening the Reporting of Observational Studies in Epidemiology (STROBE) and Th	omas quality assessment toll (QAT
Georgopoulos et al. 1994 [102] Guerci et al. 1996 [108]	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 ^{FF} : 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. > 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: (Sr > 100): Decreases (p=0.0002)	STROBE: 14/22 QAT: Strong: Data collection method, withdrawals and dropouts Moderate: Study design, confounders 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: 52+ CIPII f-u: 16	To determine the effects of IPII on qualitative lipoprotein abnormality.	Sr 60-100: No change (p=0.06) 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 triglyceride: No change (CIPII: 1.49; CSII: 1.57 mmol/L, p=NS) Total plasma lipids: No change (CIPII: 1.49; 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: 3.96; CSII: 2.46 mmol/L, p=NS) Lp B-PL: Increases (CIPII: 1.39; CSII: 1.17 mmol/L, p<0.01) Lp B-PL/apo B: Increases (CIPII: 3.95; CSII: 1.17 mmol/L, p<0.05) Lp no B-PL: 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 drop- outs 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; ^{FF}, data extracted from figure. Note: Retinyl esters – a marker of intestinal lipoproteins.

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
	ed crossover studies			• • •	Observational Studies in Epidemiology (ST		
Pacifico et al.	N = 8	CSII use: 12+	To evaluate the safety,		change (CIPII: 4.81; CSII: 4.72 mmol/L, p=		STROBE:19/22
1997 [98]	Age: 35.1	CIPII f-u: 52+	the efficacy and the		hange (CIPII: 1.14; CSII: 1.17 mmol/L, p=N	IS)	<u>QAT:</u>
	Diabetes duration: 19		results after 3 years of		e (CIPII: 3.05; CSII: 2.96 mmol/L, p=NS)		Strong: Study design, data
	Sex: 5/4		CIPII.		e (CIPII: 0.36; CSII: 0.35 mmol/L, p=NS)		collection methods, selection
	HbA1c: 6.5			• •	ge (CIPII: 0.29; CSII: 0.23 mmol/L, p=NS)		bias
	C-peptide: Neg				ge (CIPII: 0.43; CSII: 0.27 mmol/L, p=NS)		Moderate: Confounders,
	Reasons: Volunteers				ge (CIPII: 0.26; CSII: 0.27 mmol/L, p=NS)		withdrawals and drop-outs
					ge (CIPII: 0.07; CSII: 0.07 mmol/L, p=NS)		
					ge (CIPII: 0.89; CSII: 0.84 mmol/L, p=NS) ge (CIPII: 0.12; CSII: 0.09 mmol/L, p=NS)		
					ge (CIPII: 0.88; CSII: 0.81 mmol/L, p=NS)		
Duvillard et	N = 7	CSII use: ND	Compare if	• ·	o change (CIPII: 5.04; CSII: 5.33 mmol/L, p=	=0.45)	Strobe: 19/22
al. 2005	Age: 48	CIPII f-u: 12	replacement of SCII		change (CIPII: 1.47; CSII: 1.47 mmol/L, p=(QAT:
(Brief report)	Diabetes duration: 17		with IPII restores the		hange (CIPII: 3.1; CSII: 3.2 mmol/L, p=0.45		Moderate: Data collection
[106]	Sex: 6/1		normal physiological		ceride: No change (CIPII:1.28; CSII: 1.08 m	•	methods, study design,
Duvillard et	HbA1c: 7.34		gradient between the	•. •.	lipoprotein production and fractional ca		withdrawals and drop-outs
al. 2007	C-peptide: ND		portal vein and	No change (ND, p=NS)		Poor: Selection bias, confounde
[107]	Reasons: ND		peripheral circulation,	ApoA1: No change (C	IPII: 1.28; CSII: 1.34 g/L, p=0.45)		
			which is likely to	HDL composition:		_	
			modify lipoprotein	Esterified	No change (CIPII: 24.0; CSII: 20.1 %,		
			metabolism.	cholesterol:	p=0.45)		
				Free cholesterol:	No change (CIPII: 3.3; CSII: 3.4 %, p=0.99)		
				Triglycerides:	No change (CIPII: 2.1; CSII: 2.4 %, 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)		

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; Apo, apolipoprotein; trigl., triglycerides; chol., cholesterol.

	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
	Case-control st	tudies		Strengtheni	ng the Reporting of Observational Studies in Epidemiology (STROBE) and Th	nomas quality assessment toll (QA
•	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 IDDP.	 Plasma creatinine: No change (CIPII: 1.08; CSII: 1.11 mg/dl, p=NS) Plasma calcium: No change (CIPII: 9.3; CSII: 9.1 mg/dl, p=NS) Plasma magnesium: No change (CIPII: 1.81; CSII: 1.85 mg/dL, p=NS) Plasma phosphorus: No change (CIPII: 3.5; CSII: 3.3 mg/dL, p=NS) Plasma iPTH: No change (CIPII: 2.6; CSII: 2.7 mU/mL, p=NS) Osteocalcin: No change (CIPII: 5.7; CSII: 6.4 ng/mL, p=NS) Mean vitamin D intake: No change (CIPII: 89; CSII: 99 U/day, p=NS) Vitamin D metabolites: 25 OH D: Increases (CIPII: 22.1; CSII: 12.5 ng/mL, p<0.02) 24,25-(OH)₂D: Increases (CIPII: 2.3; CSII: 1.4 ng/mL, p<0.05) 1,25-(OH)₂D: No change (CIPII: 45; CSII: 35 pg/mL, p=NS) 	STROBE: 18/22 QAT: Strong: Data collection method, withdrawals and drop-outs 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.	Pre-meal insulin bolus (bolus + 4 h basal rate = 0.15 U/kg): Time point 0: FFA ^{FF} : Decreases (CIPII: 0.20; CSII: 0.47 mmol/L, p<0.05) Postprandial FFA ^{FF} : Decreases (at +30min: CIPII: 0.2; CSII: 0.45 mmol/L, p<0.05); decreases (+60 min; CIPII: 0.2; CSII: 0.47 nmol/L, p=0.05) Time point 0: lactate ^{FF} : No change (CIPII: 0.5; CSII: 0.45 mmol/L, p=NS) Postprandial lactate ^{FF} : Increases (at +30 minutes: CIPII: 0.7; CSII: 0.4 mmol/L, p=NS. At +60 min:: CIPII: 1.0; CSII: 0.5 mmol/L, p<0.05) Alanine ^{FF} : No change (p=NS) 3 OH butyrate ^{FF} : No change (p=NS)	STROBE: 14/22 QAT: Strong: Data collection methods Moderate: Study design, confounders Weak: Confounders Unclear: Selection bias
	Van Dijk et al. 2016 [93] Van Dijk et al. 2020 [117]	N = 181 (CIPII: 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 CIPII use: 208 CIPII 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.	 Calcium: no change (CIPII: 2.3; CSII: 2.3 mmol/L, p=ND) T₅₀ within groups: no change (CIPII baseline: 372; CIPII end: 362 minutes, difference within group: (median [with interquartile range (IQR)]) -10[-29,9] no change (CSII baseline: 360; CSII end: 359 minutes, difference within group: (median [with interquartile range (IQR)]) -0.2[-19,9] T₅₀ after follow-up: no change after (CIPII: 362; CSII: 359 minutes, difference CIPII vs. CSII: (median [with interquartile range (IQR)]) -8 [-22,7] 	STROBE: 21/22 QAT: Strong: Data collection method, study design Moderate: Confounders Unclear: Selection bias

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; ND, No data available; Neg, negative; NS, Not significant; FFA, Free fatty acids; iPTH, Immunoreactive parathyroid hormone; 25 OH D, Calcifediol; 24,25-(OH)₂D, (inactive) hydroxycalcidiol; 1,25-(OH)₂D, active form of vitamin D₃; 3 OH butyrate, beta-hydroxybutyrate (by-product of ketosis); ^{FF}, data extracted from figure; *, HbA1 c > 58 mmol/mol (7.5 %) or at least five incidents of hypoglycaemia (defined as glucose < 4.0 mmol/L).

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-randon	nised crossover studies		Strengthe	ening the Reporting of Observational Studies in Epidemiology (STROBE) and	l Thomas quality assessment toll (QAT
Hanaire- Broutin 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.	Fasting growth hormone: No change (CIPII: M3: 3.46; M12: 1.47; CSII: 2.23 ng/mL) GHBP activity ^{DT} : Increases (CIPII: M3: 14.5; M12: 15.5; CSII: 10.2 %, p<0.0001)	STROBE: 16/22 QAT: Strong: Study design, data collectior methods, withdrawals and drop-out Moderate: Selection bias, confounders
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	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 _{2 max} during CSII and CIPII in type 1 diabetic patients.	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)	STROBE:16/22 QAT: Strong: Confounders, data collectior methods, withdrawals and drop-out Moderate: Selection bias, study design
Oskarsson et al. 2000 [89]	N = 7 Age: 42 Diabetes duration: 17 Sex: 5/2 HbA1c: 8.6 C-peptide: Neg Reasons: Unsatisfactory on CSII	CSII use: 52+ CIPII 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 CIPII.	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)	STROBE: 16/22 QAT: Strong: Confounders, data collection methods, withdrawals and drop-out Moderate: Selection bias, study design

Table S2.4. Intervention studies, Participant characteristics, description, outcomes: Counterregulatory hormones

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; ND, No data available; NS, Not significant; FFA GHBP, Growth hormone binding proteins; DT, data calculated from table.

ant Length of Reported study objective 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, IPII follow-up (weeks)	Reported study objectives	Outcomes (mean, p-value)	Methodological quality
	Non-random	ised follow-up studies		Strengthening the R	eporting of Observational Studies in Epidemiology (STRC	BE) and Thomas quality assessment toll (QAT):
/ outcomes: atory hormones	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.	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
ary ula	Case-control	studies				STROBE and QAT:
Secondary Counterregula	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 glucagon ^{FF} : No change (CIPII: 25; CSII: 25 pg/mL, p=NS) Postprandial glucagon ^{FF} (+30 minutes): No change (CIPII: 30; CSII: 20 pg/mL, p=NS)	<u>STROBE: 14/22</u> <u>QAT:</u> Strong: Data collection methods Moderate: Study design, confounders Weak: Confounders Unclear: Selection bias, blinding Not applicable: Withdrawals and drop-outs

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; Pmc, Poor metabolic control; c.a., Conference abstract; ND, No data available; NS, Not significant; NP, Not possible to evaluate; FF, data extracted from figure.

	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 c	· ·		Strengthening the Reporting	ng of Observational Studies in Epidemiology (STROBE) and	Thomas quality assessment toll (OAT):
	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: 52+ CSII f-u: 8 (n=3) CIPII f-u: median 18 (15 – 24 months)	To determine the efficacy of a new percutaneous device.	Anti-insulin antibodies: No change (CIPII: 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
S	Lassmann-Vague et al. 1994 (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+ CIPII f-u: 12	ND	SHBG levels in men: Decreases (CIPII: M1: 31; M3: 33; CSII: 39 nM/L, p<0.05) SHBG levels in women: Decreases (CIPII: M1: 67; M3: 63; CSII: 80 nM/L, p<0.01)	NP
Other outcomes	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	ND	Plasminogen activator inhibitor (PAI) 1 levels: No change (CIPII: M3: 4; M10: 6.6; CSII: 5.1 U/mL, p=NS)	NP
	Hanaire-Broutin 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.	Plasma IGF I ^{DT} : Increases (CIPII: M3: 114.0; M12: 146.9; CSII: 89.4 ng/mL, p<0.002) IGFBP-3 ^{DT} : Increases (CIPII: 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 [79] 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 CSII f-u: 4 CIPII 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) ^{DT} : Increases (CIPII: 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

Table S2.5. Intervention studies, Participant characteristics, description, outcomes: Other outcomes

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; SHBG, Sex hormone binding globulin; IGF 1, Insulin-like growth factor – 1; BP, Binding proteins; ¹⁶, 100 % is optical density between 1.5 and 2 U of AI IgG in solution; RIA, radioimmunoassay; ^{DT}, data calculated from table.

	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-randomise	d crossover studies		Strengthening the R	eporting of Observational Studies in Epidemiology (STROBE) an	d Thomas quality assessment toll (QAT)
	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 CIPII 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.	Fructosamine: No change (CIPII: 352; CSII: 348 μmol/L, p=0.69)	<u>Strobe: 19/22</u> <u>QAT:</u> Moderate: Data collection methods, study design, withdrawals and drop- outs Poor: Selection bias, confounders
mes	Dassau et al. 2017 [78]	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, study design Moderate: Selection bias, confounders
5 C	Non-randomise	d follow-up studies				STROBE and QAT:
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.	IGF-1: Increases (CIPII: 123; CSII: 107 μg/L, P=NS) IGFBP-1: Decreases (CIPII: 40.2; CSII: 85.4 μg/L, p=0.004) 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
Re	etrospective c	rossover studies				STROBE and QAT:
al. (Pi	eandidier et l. 1992 Preliminary esults) [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 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, dat collection methods
Ca	ase-control stu	ıdies				STROBE and QAT:
20 [1: Ar 20 [1: He	edman et al. 009 (c.a.) 111] rnqvist et al. 010 (c.a.) 110] edman et al. 014 [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.	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.

								Complica	tions (events,	/study) durin	g CIPII-perio	od				
Study ID	Study design	Nr. of partici- pants	Min. CIPII- period (months)	Min. CIPII- period (patient - years)™	Local infection/ inflam- mation	Severe abdo- minal pain	Severe insulin under- delivery (catheter obstruction / encapsulati on)	Eryt- hema	Pump change/ reimplan- tation	Catheter change	Necrosis in abdomi nal skin «pocket "	Exhaustion of batteries of pump	Peritoneal abscess	Loss of catheter	Removal of implanted system because of compli- cations	Insulin pumps technical problems
Liebl et al. 2009 [5]	RFUs [≇]	CIPII: 30	12	30	20	9	6	-	-	-	-	-	-	-	8	-
Wredling, Adamson et al. 1991 [91]	NRCs	6	15	9.4ª	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: 12ª -CSII: 9ª	-	-	-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

Table S2.6. Technical and physiological complications with intraperitoneal insulin pump and its attached system

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; ^a, dropouts in this study (at the end of the periods N = 36 (CIPII: 15 /CSII: 21); ^a, included patients with previous use of external CIPII (-EP) and with previous CSII (-CSII); ⁺, Renard et al. study is not included; TM, 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/Promed os E1 ^E	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	CS21 Hoechst U40 (regular)	-	Microjet Infuser or Promedos/ Promedos ^p	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/MiniMed ⁱ	Lower portion of the IP cavity	-	-	1/1
Walter et al. 1989 [99]	C-Cs	6	3	Semisynthe tic human insulin U100	Semisynthetic human insulin U40	-	Betatron II; AS8MP/Promed os E1	-	-	-	1/1
Wredling, Adamson et al. 1991 [91]	NRCs	12	15	-	Velosulin Human (2 mo, n=2), afterwards H-Tronin	Percuseal	-/- ^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	Percuseal	MiniMed 504-S /MiniMed 504- S ^E	-	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	ND	10	-	Hoechst 21 PH U100	Telemetry using a battery-operated programmer.	-/Infusaid 1000 ¹	-	-	-	1/1

Pitt et al. 1992 [6]	NRCs	3	34	-	Hoechst U400	PIMS	_E/_I	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 hours	3	HOE21gh U100 (human)	HOE21gh U100 (human)	-	Microjet MC- 20/Promedos ID 1 ¹	-	-	-	1/1
Renard et al. 1993 [81]	NRCs	2.4	12	Porcine (Velosulin) U100	Hoechst 21 PH U400 (for MiniMed pump) U100 (for Insufaid pump)	-	Portable pump/ MiniMed 2001 ¹ (n=6) or Insufaid 1000 ¹ (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
Lassmann- Vague et al. 1994 [104]	NRCs	6	3	-	Hoechst 21 PH U100 (for Infusaid) or U400 (for MIP)	-	ND/Infusaid 1000 ¹ or MiniMed MIP 2001 ¹	-	-	Mean of monthly blood glucose	2/2 (-1,0/1,3 mo)
Raccah et al. 1994 [109]	NRCs	3	10	-	-	-	ND/Infusaid 1000' (n=6) or MIP 2001' (MiniMed) (n=5)	-	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	-	-	1/2 (3,12 mo)
Lassmann- Vague et al.1995/1998 [79, 80]	NRCs	1	24	Actrapid U100 (n=3), Velosulin U100 (n=10), Ultratardu m U40 (n=2)	Hoechst 21 PH U100 (for Infusaid) or U400 (for MIP)	-	ND/ Infusaid 1000' (n=4) or MIP 2001' (n=11)	-	4	-	1/3 (3,12,24 mo)
Guerci et al. 1996 [108]	NRCs	14.2	4	-	Hoechst 21 PH U400	Battery-operated telemetry systems	ND ^E /MiniMed 2001 ¹	Lower left	-	Mean of monthly blood glucose	1/2 (2,4 mo)
Hanaire- Broutin et al. 1996 [101]	NRCs	3	12	-	-	-	ND ^E /MIP 2001 (MiniMed) ^I	-	>4	-	1/2 (3,12 mo)
Lassmann- 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 ⁱ	-	-	-	1/1

				Nordisk (n=5)							
Pacifico et al. 1997 [98]	NRCs	3	12	-	Hoechst 21 PH U400	-	ND/MIP 2001 ¹ (MiniMed)	Lower left	-	-	1/2 (6,12 mo)
Oskarsson et al. 1999 [90]	NRCs	6	11	-	-	-	MiniMed 506/ MiniMed 2001	-	-	-	1/1
Oskarsson et al. 2000 [89]	NRCs	12	11	-	-	-	MiniMed 506/ MiniMed 2001 ¹	-	5: morning, before lunch and dinner, 2 h after dinner, before bed	Mean of monthly blood glucose	1/1
Catargi et al. 2002 [88]	Retro. Cs	1.5	3*	Lispro U100	Hoechst 21 PH U400	Telemetry using a battery-operated programmer.	MiniMed 506 or 507/MIP 2001 ¹ or 2007 ¹ (MiniMed)	Lower left	>4	Mean of all BG values for the periods (45 days/ last 45 days)	1/1
Jeandidier et al. 2002 [115]	NRFUs	6	6	Regular or Lente or Humalog	Insuman Infusat U100	-	H-Tron/ MIP 2001 ¹ (MiniMed)	-	-	-	3/3 (0,3,6 mo)
Duvilard et al. 2005/2007 [106, 107]	NRCs	ND	3	-	-	-	MiniMed 506 or 507/Minimed 2007C ¹ or 2007A ¹	-	-	-	1/1
Liebl et al. 2009 [5]	RFUs	6	12	Lispro U100	Insuman Infusat U100 or H- Tronin 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 ^I (Medtronic/Mini med)	-	-	-	1/1
Liebl et al. 2013/2014 [94-97]	NRCs	-	24	-	-	DiaPort	ND/Accu-Chek ^E	-	-	-	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 ⁱ	-	-	-	2/2 (0,6 mo)
Dassau et al. 2017 [78]	NRCs	102	1	Fast acting	Insuman Infusat U100 (regular)	DiaPort	Accu-Check Spirit Combo ^{¢,E} / Accu-Check Spirit Combo ^{¢,E}	-	CGM (every 5 min)	-	1/1

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; ⁴, pump provided only for 24-hour glucose profile; PIMS, The programmable implantable medication system; MIP, MiniMed Implantable Pump; ^E, external insulin pump; ¹, implantable insulin pump; ^P, peristaltic pump; (–), no data available; mo: months. Note: Studies are sorted by year of publication.

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Study ID	Study design	Nr. of partici- pants	Minimal CIPII period (month)	Hypo- glycaemic coma	Severe hypo- glycaemic events/ patient-year (requiring assistance)	Hypo- glycaemic events/ patient year (BG < 3.0 mmol/L)	Time spent in hypo- glycaemia (BG < 2.8 mmol/L), % ± SD	Time spent in hypo- glycaemia (BG < 3.9 mmol/L), % ± SD	Time spent in normo- glycaemia (3.9 – 10.0 mmol/I) ^{AP} , %	Time spent in normo- glycaemia (4.4 – 7.8 mmol/L), %	Time spent in hyper- glycaemia (BG > 10 mmol/L), % ± SD	Time spent in hyper- glycaemia (BG > 14 mmol/L), % ± SD
Micossi et al. 1986 [84]	NRCs	6	1 ½	-	-	-	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 (MIP)	-	-	M2-16:15±5 M18:20±5 (MIP)	-
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	-	-	-	M3: 11.9±6.8 M6: 14.3±8.5 M9: 13.6±6.4 M12: 13.1±4.5	-
Pacifico et al. 1997 [98]	NRCs	8	12									
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

Table S2.8. Glycaemic control during the CIPII-period: Hypoglycaemia, normoglycaemia and hyperglycaemia events and/or time spent in

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; A^P, 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.

		Dat	ta in forest p	lot, HbA1c (%	6)						Original da	ita			
Study ID		CIPI	I		CSII			CIP	11			C	SII		Unit
	Mean	SD	Total	Mean	SD	Total	Mean	SD	SEM	Total	Mean	SD	SEM	Total	
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	1.2	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 ^ĸ	-	5	9.8	0.7 ^ĸ	-	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	%
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; CIPII, Continuous intraperitoneal insulin infusion; (–), no data; SD, standard deviation; SEM, standard error of means; SPSS, statistical software program; IDF, IIze Dirnena-Fusini; *, data given as mean (min-max) (CIPII 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.

		Data in f	forest plot,	, SMBG (m	mol/L)						Original d	lata			
Study ID		CIPII			CSII			(CIPII			C	SII		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; CIPII, Continuous intraperitoneal insulin infusion; (–), no data; SD, standard deviation; SEM, standard error of means; SPSS, statistical software program; IDF, IIze Dirnena-Fusini.

Table S2.11. Data modification for STATA: Insulin levels.

	Data in forest plot, insulin levels (pmol/L) Original data														
Study ID		CIPII			CSII				CIPII				CSII		Unit
	Mean	SD	Total	Mean	SD	Total	Mean	SD	SEM	Total	Mean	SD	SEM	Total	
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]	35.8	7.5	7	53.4	9.9	7	35.8	-	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 [103]	131.9	27.8	4	152.8	27.8	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.

	Dat	a in fores	t plot, chol	esterol levels (mmol/L)			Original data								
Study ID		CIPII			CSII			CIPII				C	Unit		
	Mean	SD	Total	Mean	SD	Total	Mean	SD	SE	Total	Mean	SD	SE	Total	-
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.

	Da	ta in fore	st plot, trig	lyceride le	vels (mmol/L) Original data										
Study ID		CIPII			CSII			CIPII				CSII			
	Mean	SD	Total	Mean	SD	Total	Mean	SD	SE	Total	Mean	SD	SE	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

Table S2.13. Data modification for STATA: triglyceride levels.

Legends: CSII, Continuous subcutaneous insulin infusion; CIPII, Continuous intraperitoneal insulin infusion; (–), no data; SD, standard deviation; SEM, standard error of means.

	Data in forest plot, insulin requirement (U/24 hours)							Original data								
Study ID		CIPII			CSII			CI	PII			CSII			Unit	
	Mean	SD	Total	Mean	SD	Total	Mean	SD	SE	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	48.6	-	4.22	6	SEM, U/24h	
Liebl et al. 2009 [5]	44.2	16.6	30	46	23.6	30	44.2	16.6	-	30	46	44.2	-	30	SD, U/24h	
Duvillard et al. 2005/2007 [106, 107]	43.6	9.8	7	45	17.8	7	43.6	9.8	-	7	45	17.8	-	7	SD, U/24h	
Hanaire-Broutin et al. 1996 [101]	39.1	10.6	18	39.6	8.9	18	39.1	-	2.5	18	39.6	-	2.1	18	SEM, U/24h	
Oskarsson et al. 2000 [89]	37.9	7.1	7	38.2	10.3	7	37.9	-	2.7	7	38.2	-	3.9	7	SEM, U/24h	
Georgopoulos et al. 1994 [102]	62.4	44.9	8	61.9	45.7	8	62.4	44.9	-	8	61.9	45.7	-	8	SD, U/24h	
Lassmann-Vague et al. 1994 [104]	41.6	12.9	11	40	13.3	11	41.6	-	3.9	11	40	-	4	11	SEM, U/24h	
Pacifico et al. 1997 [98]	42.8	6.6	8	40.8	8	8	42.8	6.6	-	8	40.8	8		8	SD, U/24h	
Oskarsson et al. 1999 [90]	38.4	7.7	7	36.1	7.4	7	38.4	-	2.9	7	36.1	-	2.8	7	SEM, U/24h	
Raccah et al. 1994 [109]	43.8	15.9	11	40.5	14.6	11	43.8	-	4.8	11	40.5	-	4.4	11	SEM, U/24h	
Jeandidier et al. 1992 [86]	39	11	8	32	13	8	39	11	-	8	32	13	-	8	SD, U/24h	
Dassau et al. 2017*	43.7	0.1	10	32.3	0.1	10	43.7	0.08	-	10	32.3	0.05	-	10	SD, U/24h	
Hedman et al. 2009/2014, Arnqvist et al. 2010 [110-112]	51.2	31.5	10	39.3	10.5	20	51.2	31.5	-	10	39.3	10.5	-	20	SD, U/24h	

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

Georgopoulos et al. 1992 7 7.7 1.2 7 9.8 1.4 -2.10 [-3.47, -0.73] 3. Liebl et al. 2013/2014 10 7.2 0.5 10 8.8 1.2 -1.60 [-2.41, -0.79] 5. Oskarsson et al. 1999 7 7.1 0.5 7 8.5 0.8 -1.40 [-2.10, -0.70] 6. Oskarsson et al. 2000 7 7.2 0.5 7 8.6 1.1 -1.40 [-2.30, -0.50] 5. Schnell et al. 1994 5 8.5 0.5 5 9.8 0.7 -1.30 [-2.05, -0.55] 5. Pitt et al. 1992 10 8.0 1.8 10 9.1 2.2 -1.10 [-1.68, -0.52] 6. Colette et al. 1989 13 8.0 1.4 11 8.9 2.0 -0.90 [-2.26, 0.46] 3. Georgopoulos et al. 1994 8 8.7 1.2 8 9.4 1.5 -0.60 [-1.44, 0.24] 5. Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 -0.50 [-1.13, 0.13] 6. Duvillard et al. 2005/2007	10 8.8 1.2 -1.60 [-2.41, -0.79] 5.67				n SD	Mean	Ν	Study
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Wredling, Adamson et al. 1991 6 7.6 0.4 6 8.7 0.6 -1.10 [-1.68, -0.52] 6. Colette et al. 1989 13 8.0 1.4 11 8.9 2.0 -0.90 [-2.26, 0.46] 3. Georgopoulos et al. 1994 8 8.7 1.2 8 9.4 1.5 -0.70 [-2.03, 0.63] 3. Raccah et al. 1994 11 6.3 1.0 11 6.9 1.0 -0.60 [-1.44, 0.24] 5. Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 -0.50 [-1.13, 0.13] 6. Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 -0.40 [-1.82, 1.02] 3. Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	5 9.8 0.7	0.8 0.7	9		0.5	8.5	5	Schnell et al. 1994
Colette et al. 1989 13 8.0 1.4 11 8.9 2.0 -0.90 [-2.26, 0.46] 3. Georgopoulos et al. 1994 8 8.7 1.2 8 9.4 1.5 -0.70 [-2.03, 0.63] 3. Raccah et al. 1994 11 6.3 1.0 11 6.9 1.0 -0.60 [-1.44, 0.24] 5. Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 -0.50 [-1.13, 0.13] 6. Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 -0.40 [-1.82, 1.02] 3. Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	10 9.1 2.2 -1.10 [-2.86, 0.66] 2.46	0.1 2.2	9	1	1.8	8.0	10	Pitt et al. 1992
Georgopoulos et al. 1994 8 8.7 1.2 8 9.4 1.5 -0.70 [-2.03, 0.63] 3. Raccah et al. 1994 11 6.3 1.0 11 6.9 1.0 -0.60 [-1.44, 0.24] 5. Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 -0.50 [-1.13, 0.13] 6. Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 -0.40 [-1.82, 1.02] 3. Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-0.54, 0.34] 7. Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.62, 0.42] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	6 8.7 0.6 -1.10 [-1.68, -0.52] 6.81	8.7 0.6	8		0.4	7.6	6	Wredling, Adamson et al. 1991
Raccah et al. 1994 11 6.3 1.0 11 6.9 1.0 Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8	11 8.9 2.0 -0.90 [-2.26, 0.46] 3.45	8.9 2.0	8	-	1.4	8.0	13	Colette et al. 1989
Catargi et al. 2002 14 7.3 0.8 14 7.8 0.9 Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 -0.50 [-1.13, 0.13] 6. Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-0.10, 0.90] 4. Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	8 9.4 1.5 -0.70 [-2.03, 0.63] 3.55	0.4 1.5	9		1.2	8.7	8	Georgopoulos et al. 1994
Selam et al. 1989 6 8.2 1.4 8 8.6 1.3 -0.40 [-1.82, 1.02] 3. Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-1.10, 0.90] 4. Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	11 6.9 1.0 -0.60 [-1.44, 0.24] 5.52	5.9 1.0	6		1.0	6.3	11	Raccah et al. 1994
Lassmann-Vague et al. 1994 11 6.8 0.7 11 6.9 1.0 -0.10 [-0.82, 0.62] 6. Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-1.10, 0.90] 4. Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	14 7.8 0.9	.8 0.9	7	1	0.8	7.3	14	Catargi et al. 2002
Duvillard et al. 2005/2007 7 7.2 1.0 7 7.3 0.9 -0.10 [-1.10, 0.90] 4. Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	8 8.6 1.3 -0.40 [-1.82, 1.02] 3.28	8.6 1.3	8		1.4	8.2	6	Selam et al. 1989
Guerci et al. 1996 14 5.9 0.6 14 6.0 0.6 -0.10 [-0.54, 0.34] 7. Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	11 6.9 1.0 -0.10 [-0.82, 0.62] 6.08	5.9 1.0	6		0.7	6.8	11	Lassmann-Vague et al. 1994
Hanaire-Broutin et al. 1996 18 7.5 0.8 18 7.6 0.8 -0.10 [-0.62, 0.42] 7.	7 7.3 0.9 -0.10 [-1.10, 0.90] 4.79	.3 0.9	7		1.0	7.2	7	Duvillard et al. 2005/2007
_ · · · · ·	14 6.0 0.6	6.0 0.6	6	1	0.6	5.9	14	Guerci et al. 1996
	18 7.6 0.8	.6 0.8	7	1	0.8	7.5	18	Hanaire-Broutin et al. 1996
	8 6.5 1.1 - 0.10 [-1.13, 1.33] 3.87	6.5 1.1	6		1.4	6.6	8	Pacifico et al. 1997
Walter et al. 1989 6 8.0 0.5 6 7.9 0.5 - 0.10 [-0.47, 0.67] 6.	6 7.9 0.5	.9 0.5	7		0.5	8.0	6	Walter et al. 1989
Hedman et al. 2009/2014 10 8.6 1.4 20 7.9 0.8 - 0.70 [-0.08, 1.48] 5.	20 7.9 0.8 - 0.70 [-0.08, 1.48] 5.78	.9 0.8	7	2	1.4	8.6	10	Hedman et al. 2009/2014
Overall • -0.61 [-0.94, -0.28]	-0.61 [-0.94, -0.28]							Overall
Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67.60\%$, $H^2 = 3.09$					3.09	6, H ² = 3	.60%	Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67$
Test of $\theta_i = \theta_j$: Q(18) = 53.48, p = 0.00						0	= 0.0	Test of $\theta_i = \theta_j$: Q(18) = 53.48, p =
Test of θ = 0: t(18) = -3.67, p = 0.00							0.00	Test of θ = 0: t(18) = -3.67, p = 0
-4 -2 0 2 Lower during CIPII Lower during CSII		-						

Figure S1a. Meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

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).

Length of the CIPII-period (months)		Treatme	ent		Contro Mean			Mean Diff with 95% C		Weight (%)
3										
Catargi et al. 2002	14	7.3	0.8	14	7.8	0.9		-0.50 [-1.13,	0.13]	6.54
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
Walter et al. 1989	6	8.0	0.5	6	7.9	0.5		0.10 [-0.47,	0.67]	6.87
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, H	H ² = 1	.00					•	-0.14 [-0.49,	0.20]	
Test of $\theta_1 = \theta_1$: Q(3) = 1.96, p = 0.58							1			
4										
Guerci et al. 1996	14	5.9	0.6	14	6.0	0.6		-0.10 [-0.54,	0.34]	7.45
Heterogeneity: τ ² = 0.00, 1 ² = .%, H ² =								-0.10 [-0.54,	0.34]	
Test of θ_i = θ_i : Q(0) = 0.00, p = .							1			
6										
Oskarsson et al. 2000	7	7.2	0.5	7	8.6	1.1		-1.40 [-2.30, -	0.50]	5.24
Georgopoulos et al. 1994	8	8.7	1.2	8	9.4	1.5		-0.70 [-2.03,	0.63]	3.55
Selam et al. 1989	6	8.2	1.4	8	8.6	1.3		-0.40 [-1.82,	1.02]	3.28
Hedman et al. 2009/2014	10	8.6	1.4	20	7.9	0.8		0.70 [-0.08,	1.48]	5.78
Heterogeneity: τ ² = 0.70, 1 ² = 70.84%,	H ² =	3.43						-0.42 [-1.41,	0.57]	
Test of $\theta_1 = \theta_1$: Q(3) = 12.43, p = 0.01										
10										
Raccah et al. 1994	11	6.3	1.0	11	6.9	1.0		-0.60 [-1.44,	0.24]	5.52
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 =$								-0.60 [-1.44,	0.24]	
Test of θ_i = θ_i : Q(0) = 0.00, p = .										
11										
Oskarsson et al. 1999	7	7.1	0.5	7	8.5	0.8		-1.40 [-2.10, -	0.70]	6.20
Heterogeneity: τ ² = 0.00, 1 ² = .%, H ² =							-	-1.40 [-2.10, -	0.70]	
Test of $\theta_1 = \theta_1$: Q(0) = 0.00, p = .							-			
12										
Georgopoulos et al. 1992	7	7.7	1.2	7	9.8	1.4		-2.10 [-3.47, -	0.73]	3.44
Schnell et al. 1994	5	8.5	0.5	5	9.8	0.7		-1.30 [-2.05, -	0.55]	5.92
Hanaire-Broutin et al. 1998	18	7.5	0.8	18	7.6	0.8		-0.10 [-0.62,	0.42]	7.08
Pacifico et al. 1997	8		1.4	8	6.5	1.1	-	0.10 [-1.13,	1.33]	3.87
Heterogeneity: $\tau^2 = 0.87$, $I^2 = 77.40\%$,	H ² =	4.43						-0.79 [-1.72,	0.15]	
Test of $\theta_1 = \theta_1$: Q(3) = 12.66, p = 0.01										
13										
Colette et al. 1989	13	8	1.4		8.9	2.0	_	-0.90 [-2.26,	0 491	3.45
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .%$, $H^2 =$		0	1.4		0.8	2.0			-	5.40
	• •							-0.90 [-2.26,	0.40]	
Test of $\theta_1 = \theta_1$: Q(0) = 0.00, p = .										
18										
Pitt et al. 1992	10	8	1.8	10	9.1	22		-1.10 [-2.88,	0.661	2.46
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 =$		-						-1.10 [-2.86,	-	
Test of $\theta_1 = \theta_1$: Q(0) = -0.00, p = .								1.101 2.00,	0.00]	
(c), c, c, c(c) = 0.00, p = .										
18.6										
Wredling, Adamson et al. 1991	6	7.6	0.4	6	8.7	0.6		-1.10 [-1.68, -	0.52]	6.81
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, $H^2 =$							-	-1.10 [-1.68, -	0.52]	
Test of $\theta_1 = \theta_1$: $Q(0) = -0.00$, $p = .$							•			
24										
Liebl et al. 2013/2014	10	7.2	0.5	10	8.8	1.2		-1.60 [-2.41, -	0.79]	5.67
Heterogeneity: τ ² = 0.00, 1 ² = .%, H ² =								-1.60 [-2.41, -	0.79]	
Test of $\theta_1 = \theta_1$: Q(0) = 0.00, p = .							-			
Overall							•	-0.61 [-0.94, -	0.28]	
Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67.60\%$,	H ² =	3.09								
Test of $\theta_1 = \theta_1$: Q(18) = 53.48, p = 0.00	0									
Test of group differences: Q ₁ (9) = 26.0	00. n =	= 0.00								
						5	-2 0	2		
						-4	-2 0 Lower during CIPII Lower du			

Legends: 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).

	Treatment		Contro			Mean Diff.	Weight	0.1		eatmer		Con			Mean Diff.	Weight
Study HbA1c ≤ 7%	N Mean SD	N	Mean	SD		with 95% CI	(%)	Study Case-Control study	N	Mean	SD I	N Me	an SD		with 95% CI	(%)
Raccah et al. 1994	11 6.3 1.0	11	6.9	1.0		-0.60 [-1.44, 0.2	6 5 5 2	Colette et al. 1989	13	8.0	1.4 1	1 80	20		-0.90 [-2.26, 0.	461 3.45
Lassmann-Vague et al. 1994	11 6.8 0.7	11	6.9	1.0		-0.10 [-0.82, 0.6		Selam et al. 1989				8 8.6				
												-			-0.40 [-1.82, 1.	
Guerci et al. 1996 Pacifico et al. 1997	14 5.9 0.6 8 6.6 1.4			0.6		-0.10[-0.54, 0.3		Walter et al. 1989 Hedman et al. 2009/2014			0.5	6 7.9 0 7.9			0.10[-0.47, 0.	
Heterogeneity: $\tau^2 = 0.00, I^2 = 0.0$		0	0.5	1.1		0.10 [-1.13, 1.3		Heterogeneity: $\tau^2 = 0.12$, $I^2 = 35$.				0 7.8	0.0		0.70 [-0.08, 1.	
Test of $\theta_i = \theta_j$: Q(3) = 1.33, p = 0					Ť	-0.16 [-0.50, 0.1	[7]	Test of $\theta_i = \theta_j$: Q(3) = 4.77, p = 0.		- 1.0	0				0.07 [-0.50, 0.	00]
HbA1c > 7%								Crossover study								
Georgopoulos et al. 1992	7 7.7 1.2	7	9.8	1.4 —		-2.10 [-3.47, -0.7	3] 3.44	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, -0.7	9] 5.67	Liebl et al. 2013/2014	10	7.2	0.5 1	0 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, -0.7	[0] 6.20	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, -0.5	5.24	Oskarsson et al. 2000	7	7.2	0.5	7 8.6	5 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, -0.5	5.92	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, 0.6	6] 2.46	Pitt et al. 1992	10	8.0	1.8 1	0 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, -0.5	6.81	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, 0.4	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
Georgopoulos et al. 1994	8 8.7 1.2	8	9.4	1.5		-0.70 [-2.03, 0.6	3.55	Raccah et al. 1994	11	6.3	1.0 1	1 6.9	1.0		-0.60 [-1.44, 0.	24] 5.52
Catargi et al. 2002				0.9		-0.50 [-1.13, 0.1		Catargi et al. 2002	14		0.8 1				-0.50 [-1.13, 0.	
Selam et al. 1989	6 8.2 1.4	8	8.6	1.3		-0.40 [-1.82, 1.0	3.28	Lassmann-Vague et al. 1994	11	6.8	0.7 1	1 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, 0.9	4.79	Duvillard et al. 2005/2007	7	7.2	1.0	7 7.3	8 0.9	_	-0.10[-1.10, 0.	
Hanaire-Broutin et al. 1996	18 7.5 0.8	18	7.6	0.8	-	-0.10 [-0.62, 0.4	12] 7.08	Guerci et al. 1996	14	5.9	0.6 1	4 6.0	0.6	-	-0.10[-0.54, 0.	34] 7.45
Walter et al. 1989	6 8.0 0.5	6		0.5		0.10[-0.47, 0.6		Hanaire-Broutin et al. 1996			0.8 1				-0.10[-0.62, 0.	
Hedman et al. 2009/2014		20	7.9	0.8		0.70 [-0.08, 1.4		Pacifico et al. 1997			1.4	8 6.5	5 1.1	_	0.10[-1.13, 1.	33] 3.87
Heterogeneity: $\tau^2 = 0.39$, $I^2 = 69$. Test of $\theta_i = \theta_i$: Q(14) = 46.29, p =					•	-0.74 [-1.14, -0.3	35]	Heterogeneity: $\tau^2 = 0.24$, $I^2 = 62$. Test of $\theta_i = \theta_j$: Q(14) = 37.43, p =		* = 2.6	5			•	-0.75 [-1.09, -0.	42]
Overall						-0.61 [-0.94, -0.2	281	Overall						•	-0.61 [-0.94, -0.	281
Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67$.	60% H ² = 3.09							Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67$.	60% H	² = 3.0	9					
Test of $\theta_i = \theta_i$: Q(18) = 53.48, p =						Λ		Test of $\theta_i = \theta_i$: Q(18) = 53.48, p =		0.0						
						A									B	
Test of group differences: Q _b (1)	= 4.80, p = 0.03			-4	-2 0	2		Test of group differences: Q _b (1) =	= 5.90, [b = 0.0	1		-4	-2 0		
Random-effects REML model								Random-effects REML model								
													trol			
Study	Treatment N Mean SD	N	Contro Mean			Mean Diff. with 95% CI	Weight (%)	Study		eatmei Mean		Con N Me	an SD		Mean Diff. with 95% CI	Weight (%)
CIPII ≤ 6 months	N Mean SD		Mean	SD		with 95% CI	(%)	No	N	Mean	SD I	N Me	an SD		with 95% CI	(%)
CIPII ≤ 6 months Oskarsson et al. 2000	N Mean SD 7 7.2 0.5	7	Mean 8.6	SD 1.1		with 95% Cl -1.40 [-2.30, -0.5	(%) 50] 5.24	No Georgopoulos et al. 1992	N	Mean 7.7	SD 1	N Me 7 9.8	an SD 8 1.4		with 95% CI -2.10 [-3.47, -0.	(%) 73] 3.44
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994	N Mean SD 7 7.2 0.5 8 8.7 1.2	7 8	Mean 8.6 9.4	SD 1.1 1.5		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6	(%) 50] 5.24 53] 3.55	No Georgopoulos et al. 1992 Liebl et al. 2013/2014	N 1 7 10	Mean 7.7 7.2	SD 1 1.2 0.5 1	N Me 7 9.8 0 8.8	an SD 3 1.4 3 1.2		with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0.	(%) 73] 3.44 79] 5.67
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8	7 8 14	Mean 8.6 9.4 7.8	SD 1.1 1.5 0.9	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1	(%) 50] 5.24 53] 3.55 13] 6.54	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999	N 1 7 10 7	Mean 7.7 7.2 7.1	SD 1 1.2 0.5 1 0.5	7 9.8 0 8.8 7 8.5	an SD 3 1.4 3 1.2 5 0.8	-	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0.	(%) 73] 3.44 79] 5.67 70] 6.20
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4	7 8 14 8	Mean 8.6 9.4 7.8 8.6	SD 1.1 1.5 0.9 1.3	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0	(%) 50] 5.24 53] 3.55 13] 6.54 52] 3.28	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000	N 1 7 10 7 7	Mean 7.7 7.2 7.1 7.2	SD 1 1.2 0.5 1 0.5 0.5	N Me 7 9.8 0 8.8 7 8.9 7 8.6	an SD 8 1.4 8 1.2 5 0.8 6 1.1		with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7	7 8 14 8 11	Mean 8.6 9.4 7.8 8.6 6.9	SD 1.1 1.5 0.9 1.3 1.0	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6	(%) 50] 5.24 53] 3.55 13] 6.54 52] 3.28 52] 6.08	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994	N 7 10 7 7 5	7.7 7.2 7.1 7.2 8.5	SD 1 1.2 0.5 1 0.5 0.5 0.5	N Mei 7 9.8 0 8.8 7 8.9 7 8.6 5 9.8	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7	*	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0	7 8 14 8 11 7	Mean 8.6 9.4 7.8 8.6 6.9 7.3	SD 1.1 1.5 0.9 1.3 1.0 0.9	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.9	(%) 50] 5.24 53] 3.55 13] 6.54 52] 3.28 52] 6.08 50] 4.79	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1989	N 1 7 10 7 7 5 13	Mean 7.7 7.2 7.1 7.2 8.5 8.0	SD 1 1.2 0.5 1 0.5 0.5 0.5 1.4 1	N Mei 7 9.8 0 8.8 7 8.9 7 8.6 5 9.8 1 8.9	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0		with 95% Cl -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6	7 8 14 8 11 7 14	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.9 -0.10 [-0.54, 0.3	(%) 50] 5.24 53] 3.55 13] 6.54 02] 3.28 52] 6.08 52] 6.08 50] 4.79 34] 7.45	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1989 Georgopoulos et al. 1994	N 1 7 10 7 5 13 8	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7	SD 1 1.2 0.5 1 0.5 0.5 1.4 1 1.2	N Mei 7 9.8 0 8.8 7 8.6 7 8.6 5 9.8 1 8.9 8 9.4	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5	- + + + + + + + + + +	with 95% Cl -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Walter et al. 1989	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5	7 8 14 8 11 7 14 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.9 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6	(%) 50] 5.24 53] 3.55 13] 6.54 52] 3.28 52] 6.08 52] 6.08 53] 7.45 57] 6.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 2000 Colette et al. 1994 Georgopoulos et al. 1994 Raccah et al. 1994	N 1 7 10 7 5 13 8 11	7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3	SD I 1.2	N Mer 7 9.8 0 8.8 7 8.6 7 8.6 5 9.8 1 8.9 8 9.4 1 6.9	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0	- + + + + + + + - + - + - +	with 95% Cl -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Walter et al. 1989 Hedman et al. 2009/2014	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4	7 8 14 8 11 7 14 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6	_	with 95% CI -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.74, 0.6 0.70 [-0.08, 1.4	(%) 50] 5.24 53] 3.55 13] 6.54 13] 6.54 12] 3.28 52] 6.08 30] 4.79 34] 7.45 57] 6.87 18] 5.78	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1989 Georgopoulos et al. 1994 Raccah et al. 1994 Selam et al. 1989	N 1 7 10 7 5 13 8 11 6	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2	SD I 1.2	N Me 7 9.8 0 8.8 7 8.6 7 8.6 5 9.8 1 8.9 8 9.4 1 6.9 8 8.6	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 5 1.3	- + + + + + + + + + +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.36, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0. -0.40 [-1.82, 1.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1989 Hedman et al. 2009/2014 Hederogeneity: r ² = 0.14, l ² = 49	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 1.4 1.0 14 5.9 0.6 4.4 0.8 0.7	7 8 14 8 11 7 14 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.9 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6	(%) 50] 5.24 53] 3.55 13] 6.54 13] 6.54 12] 3.28 52] 6.08 30] 4.79 34] 7.45 57] 6.87 18] 5.78	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1994 Georgopoulos et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007	N 1 7 10 7 5 13 8 11 6 7	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2	SD I 1.2	N Me 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 8 8.6 7 7.3	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 5 1.3 8 0.9	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.00, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.66 [-1.44, 0. -0.66 [-1.44, 0. -0.40 [-1.82, 1. -0.10 [-1.10, 0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selarn et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Walter et al. 1989 Hedman et al. 2009/2014	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 1.4 1.0 14 5.9 0.6 4.4 0.8 0.7	7 8 14 8 11 7 14 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5	_	with 95% CI -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.74, 0.6 0.70 [-0.08, 1.4	(%) 50] 5.24 53] 3.55 13] 6.54 13] 6.54 12] 3.28 52] 6.08 30] 4.79 34] 7.45 57] 6.87 18] 5.78	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996	N 1 7 10 7 5 13 8 11 6 7 14	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9	SD I 1.2 0.5 1 0.5 0.5 1 1.4 1 1 1.2 1.0 1 1.4 1 1 0.5 0.5 1.4 1 1.0 1 1 1 0.6 1 1 1	N Me 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 8 9.4 1 6.9 4 6.0	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 5 1.3 8 0.9 9 0.6	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.00, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.42, 1. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.54, 0.	(%) 73] 3.44 79] 5.67 70] 6.20 550 5.24 555 5.92 46] 3.45 63 3.55 24] 5.52 02] 3.28 90] 4.79 34] 7.45
$\label{eq:constraints} \begin{split} \textbf{CiPII} & \leq \textbf{6} \mbox{ months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1998 \\ Hedman et al. 2009/2014 \\ Heterogeneity: t^2 = 0.14, t^2 = 49 \\ Test of \theta_i = \theta_i; Q(\theta) = 14.78, p = 10 \end{split}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 1.4 1.0 14 5.9 0.6 4.4 0.8 0.7	7 8 14 8 11 7 14 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5	_	with 95% CI -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.74, 0.6 0.70 [-0.08, 1.4	(%) 50] 5.24 53] 3.55 13] 6.54 13] 6.54 12] 3.28 52] 6.08 30] 4.79 34] 7.45 57] 6.87 18] 5.78	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 1999 Oskarsson et al. 1994 Colette et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Haneire-Broutin et al. 1996	N 1 7 10 7 5 13 8 11 6 7 14 18	7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5	SD I 1.2 0.5 1 0.5 0.5 1.4 1 1.2 1 1.4 1 0.6 1 0.6 1 0.8 1	N Mea 7 9.8 0 8.8 7 8.6 5 9.8 1 6.9 8 9.4 1 6.9 8 8.6 7 7.3 4 6.0 8 7.6	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 5 1.3 8 0.9 9 0.6 5 0.8	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.62, 0.	(%) 73] 3.44 76] 5.67 70] 6.20 55] 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 34] 7.45 42] 7.08
$\label{eq:constraints} \hline \textbf{CiPII} \leq \textbf{6} \mbox{ months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1996 \\ Walter et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, r^2 = 49 \\ Test of \theta_i = \theta_i: Q(\theta_i) = 14.78, p = 10 \\ \hline \textbf{CiPII} > \textbf{6} \mbox{ months} \\ \hline \end{matrix}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.98 0.06	7 8 14 8 11 7 14 6 20	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8	_	with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.44, 0.3 0.10 [-0.44, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1	(%) 50] 5.24 33] 3.55 33] 6.54 32] 6.08 32] 6.08 300] 4.79 34] 7.45 57] 6.87 18] 5.78 5]	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1989 Georgopoulos et al. 1994 Raccah et al. 1994 Selam et al. 1996 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997	N 1 7 10 7 5 13 8 11 6 7 14 18 8	7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6	SD I 1.2 0.5 1 0.5 0.5 0.5 1 1.0 1 1.2 1.0 1 1.0 1 4 1.0 0.6 1 0.8 1 1.4 1.4 1.4 1.4	N Mee 7 9.6 0 8.6 7 8.6 5 9.6 5 9.8 1 6.5 8 9.4 1 6.5 4 6.6 8 7.6 8 6.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 2.0 4 1.5 9 1.0 3 1.3 8 0.9 0 0.6 5 0.8 5 1.1	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.30, -0. -1.30 [-2.05, -0. -0.90 [-2.26, -0. -0.70 [-2.03, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.0, -0. -0.10 [-0.54, -0. -0.10 [-0.54, -0. -0.10 [-1.31, -1. -0.10 [-1.31, -1.	(%) 73] 3.44 76] 5.67 70] 6.20 55] 5.24 55] 5.92 46] 3.45 63] 3.55 63] 3.55 74] 5.52 02] 3.28 90] 4.79 34] 7.45 42] 7.08 33] 3.87
$\label{eq:constraints} \hline \textbf{CiPil \leq 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49. \\ Test of \theta_i = \theta_i Q(\theta) = 14.78, p = l \\ \hline \textbf{CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ \hline \end{matrix}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.9E 0.05	7 8 14 8 11 7 14 6 20 7	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 —		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.74, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -2.10 [-3.47, -0.7	(%) 50] 5.24 33] 3.55 33] 6.54 32] 6.08 300] 4.79 344] 7.45 57] 6.87 189] 5.78 5] 7] 3.44	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1994 Georgopoulos et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Haneire-Broutin et al. 1996 Pacífico et al. 1997 Walter et al. 1989	N 1 7 7 5 13 8 11 6 7 14 18 8 6	7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.2 1.0 1 1.4 1 0.6 1.0 1.4 1 1.4 1.0 1.4 1.0 1.4 1.4 1.0 0.6 1 0.8 1 1.4 0.5 5 5	N Mee 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 1 6.9 7 7.3 8 9.4 6.5 7.4 6.5 7.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 3 1.3 9 0.6 5 0.8 5 1.1 9 0.5	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.20, 30, -0. -0.70 [-2.20, 30, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.54, 0. -0.10 [-0.62, 0. -0.10 [-0.47, -0. -0.10 [-0.47, -0	(%) 73] 3.44 79] 5.67 70] 6.20 5.05 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 34] 7.45 42] 7.08 33] 3.87 67] 6.87
$\label{eq:constraints} \hline {\mbox{CiPII} \le 6\mbox{months}} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49 \\ Test of \theta_i = \theta_i \ Q(\theta) = 14.78, p = 1 \\ \hline {\mbox{CiPII} > 6\mbox{months}} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ \hline \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 4.0%, H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5	7 8 14 8 11 7 14 6 20 7	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 9.8 8.8	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 1.2		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.9 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -2.10 [-3.47, -0.7 -1.60 [-2.41, -0.7	(%) 50] 5.24 33] 3.55 33] 6.54 12] 3.28 40] 4.79 44] 7.45 57] 6.87 48] 5.78 5] 73] 3.44 79] 5.67	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1899 Hedman et al. 2009/2014	N 1 7 7 7 5 13 8 11 6 7 14 18 8 6 10	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.0 8.6	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.2 1.0 1 1.0 1 1.4 1.0 1.4 1 0.6 1 1.4 0.8 1 1.4 0.5 1.4 2	N Mee 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 1 6.9 7 7.3 8 9.4 6.5 7.4 6.5 7.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 3 1.3 9 0.6 5 0.8 5 1.1 9 0.5	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -1.30 [-2.05, -0. -0.90 [-2.26, -0. -0.70 [-2.03, 0. -0.70 [-2.03, 0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.04, -0. -0.10 [-0.54, 0. -0.10 [-0.62, -0. -0.10 [-1.13, 1. -0.10 [-0.47, -0. -0.70 [-0.08, 1. -0.70 [-0.08, 1.	(%) 73] 3.44 79] 5.67 70] 6.20 50 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 00] 4.79 34] 7.45 42] 7.08 33] 3.87 67] 6.87 48] 5.78
CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Walter et al. 1989 Hedman et al. 2009/2014 Heterogeneity: r ² = 0.14, l ² = 49 Test of θ _i = θ _i : Q(8) = 14.78, p = 1 CIPII > 6 months Georgopoulous et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999	N Mean SD 7 7.2 0.5 8 0.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.9E 0.06 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.2 0.5	7 8 14 8 11 7 14 6 20 7 7 10 7	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.5	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 1.2 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.82, 0.6 -0.10 [-0.47, 0.5 -0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -2.10 [-3.47, -0.7 -1.60 [-2.41, -0.7 -1.40 [-2.10, -0.7	(%) 50] 5.24 33] 3.55 33] 6.54 12] 3.28 32] 6.08 4.79 44] 7.45 57] 6.87 48] 5.78 5] 73] 3.44 79] 5.67 70] 6.20	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedman et al. 2009/2014 Heterogeneity: r ² = 0.41, l ² = 71.	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.0 8.6	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.2 1.0 1 1.0 1 1.4 1.0 1.4 1 0.6 1 1.4 0.8 1 1.4 0.5 1.4 2	N Mee 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 1 6.9 7 7.3 8 9.4 6.5 7.4 6.5 7.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 3 1.3 9 0.6 5 0.8 5 1.1 9 0.5	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.20, 30, -0. -0.70 [-2.20, 30, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.54, 0. -0.10 [-0.62, 0. -0.10 [-0.47, -0. -0.10 [-0.47, -0	(%) 73] 3.44 79] 5.67 70] 6.20 50 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 00] 4.79 34] 7.45 42] 7.08 33] 3.87 67] 6.87 48] 5.78
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CIPII ≤ 6 months Oskarsson et al. 2000 Georgopoulos et al. 1994 Catargi et al. 2002 Selam et al. 1989 Lassmann-Vague et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Walter et al. 1998 Hedman et al. 2009/20014 Heterogeneity: $t^2 = 0.14$, $t^2 = 49$. Test of $\theta_i = \theta_i$ Q(θ) = 14.78, $p = 1$ CIPII > 6 months Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Schnell et al. 1994 Pitt et al. 1994	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 6 8.0 0.5 10 8.6 1.4 40% H ² = 1.98 0.06	7 8 14 8 11 7 14 6 20 7 10 7 5 10	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 7.9 8.8 8.8 8.8 8.5 9.8 9.1	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.60 [-2.41, -0.7 -1.40 [-2.05, -0.5 -1.10 [-2.86, 0.6	(%) 50) 5.24 313 3.55 313 6.54 322 6.08 300] 4.79 347 7.45 371 6.87 483 5.78 573 3.44 793 5.67 703 6.27 553 5.92 364 2.46	No Georgopoulos et al. 1992 Liebl et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1989 Georgopoulos et al. 1994 Raccah et al. 1994 Raccah et al. 1996 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedtman et al. 2009/2014 Heterogeneity: $r^2 = 0.41$, $l^2 = 71$. Test of $\theta_i = \theta_i$: Q(14) = 47.64, p_i =	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.0 8.6	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.2 1.0 1 1.0 1 1.4 1.0 1.4 1 0.6 1 1.4 0.8 1 1.4 0.5 1.4 2	N Mee 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.9 1 6.9 7 7.3 8 9.4 6.5 7.4 6.5 7.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 3 0.7 9 2.0 4 1.5 9 1.0 3 1.3 9 0.6 5 0.8 5 1.1 9 0.5	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -1.30 [-2.05, -0. -0.90 [-2.26, -0. -0.70 [-2.03, 0. -0.70 [-2.03, 0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.04, -0. -0.10 [-0.54, 0. -0.10 [-0.62, -0. -0.10 [-1.13, 1. -0.10 [-0.47, -0. -0.70 [-0.08, 1. -0.70 [-0.08, 1.	(%) 73] 3.44 79] 5.67 70] 6.20 50 5.24 55] 5.92 46] 3.45 63] 3.55 24] 5.52 00] 4.79 34] 7.45 42] 7.08 33] 3.87 67] 6.87 48] 5.78
$\label{eq:constraints} \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.98 0.05 7 7.7 1.2 10 7.2 0.5 7 7.1 0.5 5 8.5 0.5 10 8.5 0.5 10 8.6 1.4 6 7.7 1.2 10 7.2 0.5 7 7.1 0.5 5 8.5 0.5 10 8.0 1.8 6 7.6 0.4	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 7.9 9.8 8.8 8.5 9.8 9.1 8.7	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6		with 95% Cl -1.40 [-2.30, -0.5 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.3 -0.10 [-0.54, 0.3 -0.10 [-0.54, 0.3 -0.10 [-0.57, 0.1 -2.10 [-3.47, -0.7 -1.60 [-2.41, -0.7 -1.40 [-2.10, -0.7 -1.30 [-2.05, -0.5 -1.10 [-1.68, -0.5	(%) 50 5.24 31 3.55 31 6.54 32 6.08 30 4.79 34 7.45 37 6.87 48 5.78 49 5.67 49 5.67 49 5.67 49 5.67 5.92 5.92 5.92 5.92 5.92 5.93 5.94 5.93 5.93 5.93 5.93 5.93 5.93 5.93 5.93 5.93 5	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schnell et al. 1994 Colette et al. 1994 Colette et al. 1999 Georgopoulos et al. 1994 Raccah et al. 1994 Sclam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1989 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedman et al. 2009/2014 Heterogeneity. $r^2 = 0.41$, $l^2 = 71$. Test of 6, = 6; Q(14) = 47.64, p = Yes	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H 0.00	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.6 8.2 7.2 5.9 7.5 6.6	SD I 1.2 0.5 1 0.5 1 0.5 0.5 0.5 1 1.2 1.0 1 1.4 1.0 1 0.6 1 1.4 1.0 1.4 1 0.6 1 1.4 0.5 1.4 2 5 5 5	N Mex 7 9.6 0 8.8 7 8.6 5 9.8 6 8.8 9.4 6.0 8 7.3 4 6.6 7.6 7.5 9.0 7.5	an SD 3 1.4 3 1.2 5 0.8 5 1.1 5 0.8 6 1.0 6 1.0 6 0.8 6 0.8 6 0.8 6 0.8 7 0 9 0.8	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.62, 0. 0.10 [-0.62, 0. 0.10 [-0.47, 0. 0.10 [-0.47, 0. -0.70 [-0.08, 1. -0.61 [-1.01, -0.	(%) 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55 02] 3.28 90] 4.79 34] 7.45 42] 7.08 3] 3.87 67] 6.87 48] 5.78 21]
$\label{eq:constraints} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1999 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49 \\ \text{Test of } \theta_i = \theta_i \ Q(\textbf{8}) = 14.78, p = l \\ \hline \textbf{CIPII} > \textbf{6} \ \textbf{months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1999 \\ Schnell et al. 1994 \\ Pitt et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1989 \\ \hline \end{array}$	N Mean SD 7 7.2 0.5 8 7.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 4.0%, H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5 7 7.1 0.5 5 5.5 5.5 10 8.0 1.8 6 7.6 0.4 13 8.0 1.4	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 7.9 9.8 8.8 8.5 9.8 9.1 8.7 8.9	SD 1.1 1.5 0.9 1.3 1.0 0.9 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0		with 95% Cl -1.40 [-2.30, 0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-1.10, 0.5 -0.10 [-0.54, 0.7 -0.10 [-0.54, 0.7 -1.40 [-2.41, -0.7 -1.40 [-2.41, -0.7 -1.30 [-2.05, -0.5 -1.10 [-1.68, -0.5 -0.90 [-2.26, 0.4	(%) 524 533 553 544 545 547 548 549 549 544 544 544 544 544 544	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1989 Georgopoulos et al. 1994 Raccah et al. 1994 Raccah et al. 1994 Selam et al. 1899 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.41, l^2 = 71.$ Test of $\theta_i = \theta_i$ Q(14) = 47.64, p = Yes Pitt et al. 1992	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H 0.00	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 ² = 3.5	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.2 1.0 1 1.4 1.0 0.6 1.4 1.4 1.0 0.5 1.4 2 5 1.4 2 1.8 1.8 1	N Mee 7 9.8 7 8.8 7 8.6 5 9.8 1 8.9 1 6.6 8 9.4 6 7.5 4 6.0 6 7.5 0 7.5 0 9.4	an SD 3 1.4 3 1.2 5 0.8 6 1.1 7 2.0 4 1.5 5 1.0 6 0.8 5 1.1 7 0.0 6 0.8 5 1.1 7 0.0 8 0.9 9 0.6 6 0.8 7 0.8	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, -0. -0.70 [-2.03, 0. -0.70 [-2.03, 0. -0.60 [-1.44, -0. -0.40 [-1.82, 11. -0.10 [-1.04, -0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.62, 0. -0.70 [-0.08, 1. -0.61 [-1.01, -0. -1.10 [-2.86, 0.	(%) 73] 3.44 73] 3.44 79] 5.67 70] 6.20 50] 5.24 55] 5.92 46] 3.45 63] 3.55 202 3.28 90] 4.79 34] 7.45 42] 7.08 3] 3.87 67] 6.87 48] 5.78 21] 4.44
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$\label{eq:constraints} \hline \textbf{CiPil \le 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49 \\ Test of \theta_i = \theta_i \ Q(\theta) = 14.78, p = il \\ \textbf{CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1994 \\ Phit et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1994 \\ Hanaire-Broutin et al. 1996 \\ Hanaire-Broutin et al. 1996 \\ Heterogeneity: r^2 = 0.23, l^2 = 56 \\ \hline \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 4.0%, H ² = 1.9E 0.05 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.5 0.5 5 5.5 0.5 10 8.0 1.4 11 6.3 1.0 18 6.6 1.4 0.3%, H ² 0.8 1.4	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 10, -0.10 [-0.42, 0.6 -0.10 [-0.44, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, -0.7 -1.40 [-2.41, -0.7 -1.40 [-2.65, 0.5 -1.10 [-2.86, 0.4 -0.50 [-2.28, 0.4 -0.50 [-2.28, 0.4 -0.50 [-2.28, 0.4 -0.50 [-1.48, -0.5] -0.50 [-2.28, 0.4 -0.50 [-1.48, -0.5] -0.50 [-1.44, 0.25] -0.50 [-	(%) 50 5.24 51 3.55 51 6.54 52 6.08 52 6.08 54 7.4 54 7.45 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 51 5.5 51 5	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Selam et al. 1994 Selam et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1998 Hedman et al. 2009/2014 Heterogeneity: $7^2 = 0.41$, $1^2 = 71$. Test of $\theta_i = \theta_i$. Q(14) = 47.64, $p =$ Yes Pitt et al. 1992 Wredling, Adamson et al. 1991 Catargi et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $7^2 = 0.12$, $1^2 = 44$.	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H 6 0.00 6 14 11 62%, H	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.0 8.6 8.0 7.6 7.3 6.8	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 0.5 1 1.2 1.0 1 1.4 1 0 0.6 1 0.5 1.4 2 5 1.8 1 0.4 0.8 1 0.4 0.5 1.4 2 5 1.4 2 1.8 1 0.4 0.8 1 0.7	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.90 [-2.26, 0. -0.90 [-2.26, 0. -0.010 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.74, 0. -0.70 [-0.08, 1. -0.61 [-1.01, -0. -1.10 [-2.86, 0. -1.10 [-2.86, 0. -1.10 [-1.68, -0.	(%) 73 3.44 79 5.67 701 6.20 551 5.92 461 3.45 633 3.55 241 5.52 021 3.28 901 4.79 341 7.45 422 7.08 333 3.87 667 5.78 211 5.78 661 2.46 5.21 6.81 133 6.54 621 6.08
$\label{eq:constraints} \hline \textbf{CiPil \leq 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49. \\ Test of \theta_i = \theta_i Q(\theta) = 14.78, p = it \\ \textbf{CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1999 \\ Schnell et al. 1994 \\ Pitt et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1989 \\ Raccah et al. 1994 \\ Hanaire-Broutin et al. 1996 \\ Pacifico et al. 1997 \\ \hline \end{matrix}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 4.0%, H ² = 1.9E 0.05 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.5 0.5 5 5.5 0.5 10 8.0 1.4 11 6.3 1.0 18 6.6 1.4 0.3%, H ² 0.8 1.4	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, 0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, 0.7 -1.30 [-2.25, -0.5 -1.10 [-1.88, 0.6 -1.10 [-1.88, 0.6 -0.060 [-1.44, 0.2 -0.00 [-0.62, 0.4 0.10 [-1.14, 1.3]	(%) 50 5.24 51 3.55 51 6.54 52 6.08 52 6.08 54 7.4 54 7.45 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 57 6.87 51 5.5 51 5	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Georgopoulos et al. 1994 Raccah et al. 1994 Selam et al. 1996 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedman et al. 2000/2014 Heterogeneity. $r^2 = 0.41$, $r^2 = 71$. Test of 0, = 0; Q(14) = 47.64, p = Ytes Pitt et al. 1992 Wireding, Adamson et al. 1991 Catargi et al. 2002 Lassmann-Vague et al. 1994	N 1 7 10 7 5 13 8 11 6 7 14 18 8 6 10 83%, H 6 0.00 6 14 11 62%, H	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.0 8.6 8.0 7.6 7.3 6.8	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 0.5 1 1.2 1.0 1 1.4 1 0 0.6 1 0.5 1.4 2 5 1.8 1 0.4 0.8 1 0.4 0.5 1.4 2 5 1.4 2 1.8 1 0.4 0.8 1 0.7	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0. -0.40 [-1.82, 1. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.62, 0. -0.10 [-0.64, 1. -0.10 [-0.64, 1. -0.61 [-1.01, -0. -1.10 [-2.86, 0. -1.10 [-1.88, -0. -0.55 [-1.13, 0. -0.10 [-0.82, 0. -0.10 [-0.8	(%) 73 3.44 79 5.67 701 6.20 551 5.92 461 3.45 633 3.55 241 5.52 021 3.28 901 4.79 341 7.45 422 7.08 333 3.87 667 5.78 211 5.78 661 2.46 5.21 6.81 133 6.54 621 6.08
$\label{eq:constraints} \hline \textbf{CiPil \le 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1996 \\ Hedman et al. 2005/2007 \\ Guerci et al. 1998 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49. \\ Test of \theta_i = \theta_i \cdot Q(\theta) = 14.78, p = il \\ \textbf{CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1999 \\ Schnell et al. 1994 \\ Pitt et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1994 \\ Hanaire-Broutin et al. 1996 \\ Pacifico et al. 1997 \\ Heterogeneity: r^2 = 0.23, l^2 = 56 \\ Test of \theta_i = \theta_i \cdot Q(\theta) = 21.44, p = il \\ \textbf{Overall} \\ \hline \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 40% H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5 5 8.5 0.5 10 8.0 1.8 6 7.6 0.4 13 8.0 1.4 14 6.3 1.0 18 7.5 0.8 8 6.6 1.4 0.03% H ² = 2.27	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, 0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, 0.7 -1.30 [-2.25, -0.5 -1.10 [-1.88, 0.6 -1.10 [-1.88, 0.6 -0.060 [-1.44, 0.2 -0.00 [-0.62, 0.4 0.10 [-1.14, 1.3]	(%) 50 5.24 33 3.55 33 6.54 32 3.28 321 6.08 300 4.79 47 7.45 571 6.87 153 5.78 73 3.44 70 5.67 70 6.20 55 5.92 36 2.46 62 6.81 63 3.45 72 7.08 333 3.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1989 Hedman et al. 2002/2014 Heterogeneity. $r^2 = 0.41$, $r^2 = 71$. Test of $\theta_i = \theta_i$: Q(14) = 47.64, $p =$ Yes Pitte tal. 1992 Wireding, Adamson et al. 1991 Catargi et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.12$, $r^2 = 44$. Test of $\theta_i = \theta_i$: Q(3) = 5.04, $p = 0$	N 1 7 10 7 5 5 13 8 11 6 7 14 18 8 6 10 83%, H 10 6 83%, H 10 62%, H 11 7	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.7 6.3 8.7 6.3 8.7 7.2 5.9 7.5 6.6 8.0 8.6 8.6 8.6 8.6 8.6 8.7 6.3 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.7 5 9 7.5 6.5 8.0 8.7 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.2 7.1 7.2 7.1 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2	SD I 1.2 0.5 1 0.5 0.5 0.5 1 1.2 1.0 1 1 1.2 1.0 1 1.4 1.0 1 1.4 1 0.6 1 0.6 1 0.6 1 0.5 1.4 2 1.4 0.5 1.4 2 5 1.8 1 0.4 0.8 1 0.4 0.8 1 0.7 1 1.1 1 1 1 1 1	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - +	with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, 0. -0.40 [-1.82, 1. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.54, 0. -0.10 [-0.62, 0. -0.10 [-0.64, 1. -0.10 [-0.64, 1. -0.61 [-1.01, -0. -1.10 [-2.86, 0. -1.10 [-1.88, -0. -0.55 [-1.13, 0. -0.10 [-0.82, 0. -0.10 [-0.8	(%) 73] 3.44 79] 5.67 70] 6.20 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 33] 3.87 67] 6.87 48] 5.78 21] 5.4 66] 2.46 524 6.81 13] 6.54 62] 6.81 13] 6.54 62] 6.08 12] 5.74
$\label{eq:constraints} \hline {\bf CiPil \le 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: \tau^2 = 0.14, t^2 = 49 \\ Test of \theta_i = \theta_i \ Q(\theta) = 14.78, p = it \\ {\bf CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1994 \\ Post discussion et al. 1994 \\ Post discussion et al. 1999 \\ Schnell et al. 1994 \\ Phit et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1994 \\ Hanaire-Broutin et al. 1996 \\ Pacifico et al. 1997 \\ Heterogeneity: \tau^2 = 0.32, t^2 = 56 \\ Test of \theta_i = \theta_i \ Q(\theta) = 21.44, p = it \\ {\bf Overall} \\ Heterogeneity: \tau^2 = 0.32, t^2 = 67 \\ \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 5.9 0.6 6 8.0 0.5 10 8.6 1.4 4.0%, H ² = 1.98 0.06 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 8.0 1.8 6 7.6 0.4 13 8.0 1.4 11 6.3 1.0 18 7.5 0.8 8 6.6 1.4 0.3%, H ² = 2.27 0.01	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 10 -0.10 [-0.82, 0.6 -0.10 [-0.44, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, -0.7 -1.40 [-2.41, -0.7 -1.30 [-2.65, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-0.62, 0.4 0.90 [-1.31, 1.3 -0.98 [-1.39, -0.5]	(%) 50 5.24 33 3.55 33 6.54 32 3.28 321 6.08 300 4.79 47 7.45 571 6.87 153 5.78 73 3.44 70 5.67 70 6.20 55 5.92 36 2.46 62 6.81 63 3.45 72 7.08 333 3.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Watter et al. 1989 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.41$, $l^2 = 71$. Test of $\theta_i = \theta_i$: Q(14) = 47.64, p = Yes Pitt et al. 1992 Wirderig et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.12$, $l^2 = 44$. Test of $\theta_i = \theta_i$: Q(3) = 5.04, p = 0. Overall Heterogeneity: $r^2 = 0.32$, $l^2 = 67$.	N 1 7 7 7 5 13 8 11 6 7 14 18 8 6 10 83%, H 10 6 83%, H 10 6 2%, H 11 7 60%, H	Mean 7.7 7.2 7.1 7.2 8.5 8.0 8.7 6.3 8.7 6.3 8.7 6.3 8.7 7.2 5.9 7.5 6.6 8.0 8.6 8.6 8.6 8.6 8.6 8.7 6.3 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.6 8.7 5 9 7.5 6.5 8.0 8.7 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.1 7.2 7.2 7.1 7.2 7.1 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2 7.2	SD I 1.2 0.5 1 0.5 0.5 0.5 1 1.2 1.0 1 1 1.2 1.0 1 1.4 1.0 1 1.4 1 0.6 1 0.6 1 0.6 1 0.5 1.4 2 1.4 0.5 1.4 2 5 1.8 1 0.4 0.8 1 0.4 0.8 1 0.7 1 1.1 1 1 1 1 1	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - +	with 95% C1 -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -0.90 [-2.26, -0. -0.90 [-2.26, -0. -0.70 [-2.03, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.82, 1. -0.10 [-1.10, -0. -0.10 [-0.54, -0. -0.10 [-0.54, -0. -0.70 [-0.08, 1. -0.61 [-1.01, -0. -1.10 [-2.86, -0. -0.50 [-1.13, 0. -0.50 [-1.13, 0. -0.10 [-0.82, 0. -0.64 [-1.16, -0. -0.64	(%) 73] 3.44 79] 5.67 70] 6.20 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 33] 3.87 67] 6.87 48] 5.78 21] 5.4 66] 2.46 524 6.81 13] 6.54 62] 6.81 13] 6.54 62] 6.08 12] 5.74
$\label{eq:constraints} \hline {\bf CiPil \le 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1996 \\ Walter et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: \tau^2 = 0.14, t^2 = 49. \\ Test of \theta_i = \theta_i \ Q(\theta) = 14.78, p = it \\ {\bf CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1999 \\ Schnell et al. 1994 \\ Pitt et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Heterogeneity: \tau^2 = 0.23, t^2 = 56. \\ Test of \theta_i = \theta_i \ Q(\theta) = 21.44, p = it \\ {\bf Overall} \\ Heterogeneity: \tau^2 = 0.32, t^2 = 67. \\ Test of \theta_i = \theta_i \ Q(18) = 53.48, p = 57. \\ \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 7.3 0.8 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5 7 7.1 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 8.0 1.8 6 7.6 0.4 11 6.3 1.0 18 7.5 0.8 8 6.6 1.4 0.03 1.4 1.4 11 6.3 1.0 14 7.5 0.8 8	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 10 -0.10 [-0.82, 0.6 -0.10 [-0.44, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, -0.7 -1.40 [-2.41, -0.7 -1.30 [-2.65, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-0.62, 0.4 0.90 [-1.31, 1.3 -0.98 [-1.39, -0.5]	(%) 50 5.24 33 3.55 33 6.54 32 3.28 321 6.08 300 4.79 47 7.45 571 6.87 153 5.78 73 3.44 70 5.67 70 6.20 55 5.92 36 2.46 62 6.81 63 3.45 72 7.08 333 3.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1998 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.41$, $l^2 = 71$. Test of 6, = 6; Q(14) = 47.64, p = Yes Pitt et al. 1992 Wirderig et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.32$, $l^2 = 44$. Test of 6, = 6; Q(3) = 5.04, p = 0. Overall Heterogeneity: $r^2 = 0.32$, $l^2 = 67$. Test of 6, = 6; Q(18) = 53.48, p = 0.	N 1 7 10 7 5 13 8 11 6 7 14 18 8 8 6 10 83%, H 10 6 14 11 62%, H 17 7 60%, H 0.00	Mean 7.7 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.0 8.6 8.0 8.6 8.0 7.6 7.3 6.8 8.2 2 2 = 3.5	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.0 1 1.4 1.0 1.4 1 1.4 1.4 1.4 1.4 1.4 1.4 1.5 5 1.8 1.4 2.5 1 1.4 1.4 2.5 1.8 1 0.4 0.8 1 0.7 1 1 1	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - +	with 95% C1 -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -0.90 [-2.26, -0. -0.90 [-2.26, -0. -0.70 [-2.03, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.82, 1. -0.10 [-1.10, -0. -0.10 [-0.54, -0. -0.10 [-0.54, -0. -0.70 [-0.08, 1. -0.61 [-1.01, -0. -1.10 [-2.86, -0. -0.50 [-1.13, 0. -0.50 [-1.13, 0. -0.10 [-0.82, 0. -0.64 [-1.16, -0. -0.64	(%) 73] 3.44 79] 5.67 70] 6.20 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 33] 3.87 67] 6.87 48] 5.78 21] 5.4 66] 2.46 524 6.81 13] 6.54 62] 6.81 13] 6.54 62] 6.08 12] 5.74
$\label{eq:constraints} \hline {\bf CiPil \le 6 months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: r^2 = 0.14, l^2 = 49 \\ Test of \theta_i = \theta_i \ Q(\theta) = 14.78, p = i \\ {\bf CiPil > 6 months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1994 \\ Pitt et al. 1992 \\ Wredling, Adamson et al. 1991 \\ Colette et al. 1999 \\ Raccah et al. 1994 \\ Hetanaire-Broutin et al. 1996 \\ Pacifico et al. 1997 \\ Heterogeneity: r^2 = 0.23, l^2 = 56 \\ Test of \theta_i = \theta_i \ Q(\theta) = 21.44, p = i \\ {\bf Overall} \\ Heterogeneity: r^2 = 0.32, l^2 = 67. \\ \hline \end{array}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 7.3 0.8 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5 7 7.1 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 8.0 1.8 6 7.6 0.4 11 6.3 1.0 18 7.5 0.8 8 6.6 1.4 0.03 1.4 1.4 11 6.3 1.0 14 7.5 0.8 8	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 1.0 -0.10 [-0.82, 0.6 -0.10 [-0.54, 0.3 0.10 [-0.44, 0.3 0.10 [-0.44, 0.3 0.10 [-0.44, 0.7 -1.60 [-2.41, 0.7 -1.40 [-2.10, -0.7 -1.40 [-2.10, -0.7 -1.40 [-2.40, -0.7 -0.90 [-1.40, -0.2 -0.90 [-1.30, -0.5 -0.61 [-0.94, -0.2	(%) 50 5.24 33 3.55 33 6.54 32 3.28 321 6.08 300 4.79 47 7.45 571 6.87 153 5.78 73 3.44 70 5.67 70 6.20 55 5.92 36 2.46 62 6.81 63 3.45 72 7.08 333 3.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Watter et al. 1989 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.41$, $l^2 = 71$. Test of $\theta_i = \theta_i$: Q(14) = 47.64, p = Yes Pitt et al. 1992 Wirderig et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.12$, $l^2 = 44$. Test of $\theta_i = \theta_i$: Q(3) = 5.04, p = 0. Overall Heterogeneity: $r^2 = 0.32$, $l^2 = 67$.	N 1 7 10 7 5 13 8 11 6 7 14 18 8 8 6 10 83%, H 10 6 14 11 62%, H 17 7 60%, H 0.00	Mean 7.7 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.0 8.6 8.0 8.6 8.0 7.6 7.3 6.8 8.2 2 2 = 3.5	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.0 1 1.4 1.0 1.4 1 1.4 1.4 1.4 1.4 1.4 1.4 1.5 5 1.8 1.4 2.5 1 1.4 1.4 2.5 1.8 1 0.4 0.8 1 0.7 1 1 1	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9		with 95% CI -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.30 [-2.05, -0. -0.90 [-2.26, 0. -0.70 [-2.03, 0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.10, 0. -0.10 [-0.54, -0. -0.10 [-0.54, -0. -0.10 [-0.64, -0. -1.10 [-2.86, 0. -1.10 [-1.68, -0. -0.50 [-1.13, 1. -0.55 [-1.13, 0. -0.55 [-	(%) 73] 3.44 79] 5.67 70] 6.20 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 33] 3.87 67] 6.87 48] 5.78 21] 5.4 66] 2.46 524 6.81 13] 6.54 62] 6.81 13] 6.54 62] 6.08 12] 5.74
$\label{eq:constraints} \hline {\bf CiPII} \le {\bf 6} \mbox{ months} \\ Oskarsson et al. 2000 \\ Georgopoulos et al. 1994 \\ Catargi et al. 2002 \\ Selam et al. 1989 \\ Lassmann-Vague et al. 1994 \\ Duvillard et al. 2005/2007 \\ Guerci et al. 1989 \\ Hedman et al. 2009/2014 \\ Heterogeneity: \tau^2 = 0.14, t^2 = 49 \\ Test of \theta_i = 6; Q(\theta) = 14.78, p = it \\ {\bf CiPII} > {\bf 6} \mbox{ months} \\ Georgopoulos et al. 1992 \\ Liebl et al. 2013/2014 \\ Oskarsson et al. 1994 \\ Pitt et al. 1994 \\ Henarier-Brouth et al. 1996 \\ Pacifico et al. 1997 \\ Heterogeneity: \tau^2 = 0.32, t^2 = 56 \\ Test of \theta_i = \theta; Q(\theta) = 21.44, p = it \\ {\bf Overall} \\ Heterogeneity: \tau^2 = 0.32, t^2 = 67. \\ Test of \theta_i = \theta; Q(18) = 53.48, p = it \\ \end{tabular}$	N Mean SD 7 7.2 0.5 8 8.7 1.2 14 7.3 0.8 6 8.2 1.4 11 6.8 0.7 7 7.2 1.0 14 7.3 0.8 6 8.0 0.5 10 8.6 1.4 40%, H ² = 1.98 0.06 7 7.7 1.2 10 7.2 0.5 7 7.1 0.5 7 7.7 1.2 10 7.2 0.5 7 7.7 1.2 10 8.0 1.8 6 7.6 0.4 11 6.3 1.0 18 7.5 0.8 8 6.6 1.4 0.03 1.4 1.4 11 6.3 1.0 14 7.5 0.8 8	7 8 14 8 11 7 14 6 20 7 10 7 5 10 6 11 11 18	Mean 8.6 9.4 7.8 8.6 6.9 7.3 6.0 7.9 7.9 7.9 9.8 8.8 8.8 8.8 8.8 9.8 9.1 8.7 8.9 6.9 7.6	SD 1.1 1.5 0.9 1.3 1.0 0.6 0.6 0.5 0.8 1.4 1.2 0.8 0.7 2.2 0.6 2.0 1.0 0.8		with 95% Cl -1.40 [-2.30, -0.5 -0.70 [-2.03, 0.6 -0.50 [-1.13, 0.1 -0.40 [-1.82, 10 -0.10 [-0.82, 0.6 -0.10 [-0.44, 0.3 0.10 [-0.47, 0.6 0.70 [-0.08, 1.4 -0.21 [-0.57, 0.1 -1.40 [-2.41, -0.7 -1.40 [-2.41, -0.7 -1.30 [-2.65, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-2.86, 0.6 -1.10 [-1.68, -0.5 -1.10 [-0.62, 0.4 0.90 [-1.31, 1.3 -0.98 [-1.39, -0.5]	(%) 50 5.24 33 3.55 33 6.54 32 3.28 321 6.08 300 4.79 47 7.45 571 6.87 153 5.78 73 3.44 70 5.67 70 6.20 55 5.92 36 2.46 62 6.81 63 3.45 72 7.08 333 3.87	No Georgopoulos et al. 1992 Liebi et al. 2013/2014 Oskarsson et al. 1999 Oskarsson et al. 2000 Schneil et al. 1994 Colette et al. 1994 Colette et al. 1994 Colette et al. 1994 Raccah et al. 1994 Selam et al. 1994 Duvillard et al. 2005/2007 Guerci et al. 1996 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Walter et al. 1998 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.41$, $l^2 = 71$. Test of 6, = 6; Q(14) = 47.64, p = Yes Pitt et al. 1992 Wirderig et al. 2002 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.32$, $l^2 = 44$. Test of 6, = 6; Q(3) = 5.04, p = 0. Overall Heterogeneity: $r^2 = 0.32$, $l^2 = 67$. Test of 6, = 6; Q(18) = 53.48, p = 0.	N 1 7 10 7 5 13 8 11 6 7 14 18 8 8 6 10 83%, H 10 6 14 11 62%, H 17 7 60%, H 0.00	Mean 7.7 7.2 8.5 8.0 8.7 6.3 8.2 7.2 5.9 7.5 6.6 8.0 8.6 8.0 8.6 8.0 8.6 8.0 7.6 7.3 6.8 8.2 2 2 = 3.5	SD I 1.2 0.5 1 0.5 0.5 0.5 0.5 1.4 1 1.0 1 1.4 1.0 1.4 1 1.4 1.4 1.4 1.4 1.4 1.4 1.5 5 1.8 1.4 2.5 1 1.4 1.4 2.5 1.8 1 0.4 0.8 1 0.7 1 1 1	N Mei 7 9.8 0 8.8 7 8.6 5 9.8 1 8.9 1 6.8 8 9.4 6 7.5 4 6.0 7 7.5 0 7.5 0 9.7 0 9.7 0 9.7 6 8.1	an SD 3 1.4 4 1.2 5 0.8 3 1.4 4 1.5 9 2.0 4 1.5 9 2.0 4 1.5 6 1.3 6 0.8 5 1.1 9 0.6 6 0.8 6 0.8 7 0.6 7 0.6 9 0.9	- + + + + + + + - + - + - + - +	with 95% C1 -2.10 [-3.47, -0. -1.60 [-2.41, -0. -1.40 [-2.10, -0. -1.40 [-2.03, -0. -0.90 [-2.26, -0. -0.90 [-2.26, -0. -0.70 [-2.03, -0. -0.60 [-1.44, -0. -0.40 [-1.82, 1. -0.10 [-1.82, 1. -0.10 [-1.10, -0. -0.10 [-0.54, -0. -0.10 [-0.54, -0. -0.70 [-0.08, 1. -0.61 [-1.01, -0. -1.10 [-2.86, -0. -0.50 [-1.13, 0. -0.50 [-1.13, 0. -0.10 [-0.82, 0. -0.64 [-1.16, -0. -0.64	(%) 73] 3.44 79] 5.67 70] 6.20 55] 5.92 46] 3.45 63] 3.55 24] 5.52 02] 3.28 90] 4.79 33] 3.87 67] 6.87 48] 5.78 21] 5.4 66] 2.46 524 6.81 13] 6.54 62] 6.81 13] 6.54 62] 6.08 12] 5.74

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 (\leq 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 (\leq 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.

Subgroups	Studies		Mean Diff. with 95% Cl	P-value
HbA1c levels before starting CIPII treatn				
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: $Q_b(1) = 4.80$, p				
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: $Q_b(1) = 5.96$, p	o = 0.01			
Duration of CIPII-period				
$CIPII \le 6 months$	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: $Q_b(1) = 7.49$, p	0 = 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	4		-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: $Q_b(9) = 26.00$,	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: $Q_b(1) = 0.01$, p	0 = 0.93			
Overall		•	-0.61 [-0.94, -0.28]	0.0002
Heterogeneity: $\tau^2 = 0.32$, $I^2 = 67.60\%$, H^2	² = 3.09			
Test of $\theta_i = \theta_j$: Q(18) = 53.48, p < 0.01				
	-3	-2 -1 0 Lower during CIPII Lower	1 during CSII	

Figure S1d. Overall subgroup meta-analysis of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

Legends: CIPII, continuous intraperitoneal insulin infusion; CSII, continuous subcutaneous insulin infusion.

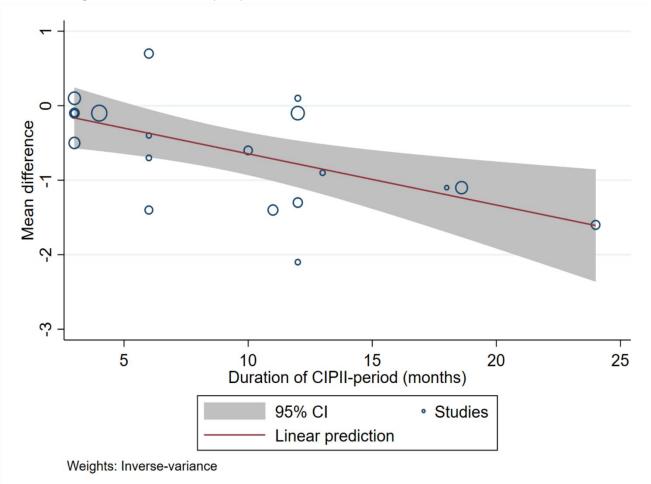


Figure S1e. Meta-regression analysis bubble-plot of HbA1c (%) in patients during CIPII treatment compared to that during control treatment (CSII).

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.

		Mean Difference		
Study		with 95% CI	P-value	Duration of CIPII-period (months)
Catargi et al. 2002		-0.50 [-1.13, 0.13]	0.120	3
Lassmann-Vague et al. 1994		-0.33 [-0.80, 0.15]	0.178	3
Duvillard et al. 2005/2007		-0.28 [-0.71, 0.14]	0.193	3
Walter et al. 1989		-0.14 [-0.49, 0.20]	0.407	3
Guerci et al. 1996		-0.13 [-0.40, 0.14]	0.355	4
Oskarsson et al. 2000		-0.28 [-0.64, 0.08]	0.123	6
Georgopoulos et al. 1994		-0.30 [-0.64, 0.04]	0.081	6
Selam et al. 1989		-0.30 [-0.62, 0.02]	0.064	6
Hedman et al. 2009/2014		-0.21 [-0.57, 0.15]	0.253	6
Raccah et al. 1994		-0.24 [-0.58, 0.09]	0.149	10
Oskarsson et al. 1999		-0.38 [-0.76, 0.01]	0.054	11
Georgopoulos et al. 1992		-0.48 [-0.89, -0.07]	0.023	12
Schnell et al. 1994		-0.55 [-0.95, -0.15]	0.008	12
Hanaire-Broutin et al. 1996		-0.50 [-0.87, -0.13]	0.008	12
Pacifico et al. 1997		-0.47 [-0.83, -0.12]	0.009	12
Colette et al. 1989		-0.49 [-0.83, -0.15]	0.005	13
Pitt et al. 1992		-0.50 [-0.84, -0.17]	0.003	18
Wredling, Adamson et al. 1991		-0.55 [-0.87, -0.23]	0.001	18.6
Liebl et al. 2013/2014		-0.61 [-0.94, -0.28]	0.000	24
	-1 -0.5 0 Lower during CIPII Lowe	0.5 er during CSII		

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).

		0			· · ·				
a : 1	Treatment	Contro			Mean Diff.	Weight	Treatment Control	Mean Diff.	Weight
Study	N Mean SD	N Mear	SD		with 95% CI	(%)	Study N Mean SD N Mean SD	with 95% CI	(%)
HbA1c ≤ 7 %				_		1 10 70	Case-Control study		0.07
Jeandidier et al. 1992 Heterogeneity: τ ² = 0.00		8 7.7	1.2 —		-0.50 [-2.00, 1.00	-	Selam et al. 1989 6 7.3 2.0 8 5.5 1.4	- 1.80 [0.03, 3.57]	
• •					-0.50 [-2.00, 1.00]	Heterogeneity: $\tau^2 = 0.00$, $l^2 = .%$, $H^2 = .$	1.80 [0.03, 3.57]	
Test of $\theta_i = \theta_j$: Q(0) = 0.0	00, p = .						Test of $\theta_i = \theta_i$: Q(0) = -0.00, p = .		
HbA1c > 7 %							Crossover study		
Catargi et al. 2002	14 7.8 1.1	14 8.2	1.2 -		-0.40 [-1.25, 0.45] 24.50	Jeandidier et al. 1992 8 7.2 1.8 8 7.7 1.2 —	-0.50 [-2.00, 1.00]	10.76
Oskarsson et al. 2000	7 6.3 0.8	7 6.2	1.1		0.10 [-0.91, 1.11] 19.73	Catargi et al. 2002 14 7.8 1.1 14 8.2 1.2 —	-0.40 [-1.25, 0.45]	24.50
Beylot et al. 1987	4 5.9 0.5	4 5.4	0.3		0.50 [-0.07, 1.07] 36.94	Oskarsson et al. 2000 7 6.3 0.8 7 6.2 1.1 -	0.10 [-0.91, 1.11]	19.73
Selam et al. 1989	6 7.3 2.0	8 5.5	1.4		1.80 [0.03, 3.57] 8.07	Beylot et al. 1987 4 5.9 0.5 4 5.4 0.3	0.50 [-0.07, 1.07]	36.94
Heterogeneity: $\tau^2 = 0.15$	5, I ² = 41.61%, H ²	= 1.71		-	0.29 [-0.32, 0.89]	Heterogeneity: τ ² = 0.09, I ² = 30.48%, H ² = 1.44	0.07 [-0.46, 0.60]	
Test of $\theta_i = \theta_j$: Q(3) = 5.9	95, p = 0.11						Test of $\theta_i = \theta_j$: Q(3) = 3.77, p = 0.29		
Overall				•	0.20 [-0.34, 0.74	1	Overall	0.20 [-0.34, 0.74]	
Heterogeneity: T ² = 0.12	2. I ² = 32.48%. H ²	= 1.48			_		Heterogeneity: τ ² = 0.12, l ² = 32.48%, H ² = 1.48		
Test of $\theta_i = \theta_i$: Q(4) = 6.9	94, p = 0.14				Λ		Test of $\theta_i = \theta_i$: Q(4) = 6.94, p = 0.14	D	
Test of group difference		- 0.24			A		Test of group differences: $Q_b(1) = 3.35$, p = 0.07	D	
lest of group difference	s: Q _b (1) = 0.91, p	- 0.34							
Random-effects REML m	odol		-2	0 2	4		-2 0 2 Random-effects REML model	4	
Trandom-enects Treme in									
Chudu	Treatment	Contr			Mean Diff.	Weight	Treatment Control Study N Mean SD N Mean SD	Mean Diff. with 95% CI	Weight (%)
Study	N Mean SD	in Mear	5D		with 95% CI	(%)	No		(70)
CIPII ≤ 6 months							Jeandidier et al. 1992 8 7.2 1.8 8 7.7 1.2	-0.50 [-2.00, 1.00]	10.76
Jeandidier et al. 1992	8 7.2 1.8		1.2 —		-0.50 [-2.00, 1.00		Oskarsson et al. 2000 7 6.3 0.8 7 6.2 1.1	0.10 [-0.91, 1.11]	
Catargi et al. 2002	14 7.8 1.1	14 8.2	1.2 -	╼	-0.40 [-1.25, 0.45] 24.50	Selam et al. 1989 6 7.3 2.0 8 5.5 1.4	- 1.80 [0.03, 3.57]	
Oskarsson et al. 2000	7 6.3 0.8	7 6.2	1.1	#	0.10 [-0.91, 1.11] 19.73	Heterogeneity: $r^2 = 0.49$, $l^2 = 49.01\%$, $H^2 = 1.96$	0.35 [-0.78, 1.47]	
Beylot et al. 1987	4 5.9 0.5	4 5.4	0.3		0.50 [-0.07, 1.07	36.94	Test of $\theta_i = \theta_i$: Q(2) = 3.98, p = 0.14		
Selam et al. 1989	6 7.3 2.0	8 5.5	1.4		- 1.80 [0.03, 3.57] 8.07	·····		
Heterogeneity: $\tau^2 = 0.12$	2, I ² = 32.48%, H ²	= 1.48		-	0.20 [-0.34, 0.74	1	Yes		
Test of $\theta_i = \theta_i$: Q(4) = 6.	94. p = 0.14						Catargi et al. 2002 14 7.8 1.1 14 8.2 1.2 —	-0.40 [-1.25, 0.45]	24.50
							Beylot et al. 1987 4 5.9 0.5 4 5.4 0.3	0.50 [-0.07, 1.07]	36.94
Overall					0.20 [-0.34, 0.74	1	Heterogeneity: τ ² = 0.27, I ² = 66.14%, H ² = 2.95	0.11 [-0.77, 0.98]	
Heterogeneity: $\tau^2 = 0.12$	$1^2 = 22.400/10^2$	- 1 40			0.20 [-0.34, 0.74	1	Test of $\theta_i = \theta_i$: Q(1) = 2.95, p = 0.09		
		= 1.48			\frown				
Test of $\theta_i = \theta_j$: Q(4) = 6.	94, p = 0.14						Overall 🔶	0.20 [-0.34, 0.74]	
Test of group difference	es: Q _b (0) = 0.00, p) = .					Heterogeneity: $\tau^2 = 0.12$, $I^2 = 32.48\%$, $H^2 = 1.48$	_	
			-2	0 2	4		Test of $\theta_i = \theta_j$: Q(4) = 6.94, p = 0.14		
Random-effects REML m	lahon		-2	0 2	4		Test of group differences: Q _b (1) = 0.11, p = 0.74	$\boldsymbol{\nu}$	
							-2 0 2		
							-2 0 2 Random-effects REML model	4	
							Nandom-Greeke NEWE HIUDER		

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 (\leq 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 (\leq 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 S2b. Summarised subgroup meta-analysis of fasting blood glucose (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

			Mean Diff.	
Subgroups	Studies		with 95% CI	P-value
HbA1c levels before starting CIPII treatment	nt			
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: $Q_b(1) = 0.91$, p =	0.34			
Ohudu hara				
Study type			4 00 1 0 00 0 571	0.047
Case-Control study	1		- 1.80 [0.03, 3.57]	
Crossover study	4		0.07 [-0.46, 0.60]	0.796
Test of group differences: $Q_b(1) = 3.35$, p =	0.07			
Duration of CIPII-period				
CIPII ≤ 6 months	5		0.20 [-0.34, 0.74]	0.472
Test of group differences: $Q_b(0) = 0.00$, 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: $Q_b(2) = 4.28$, 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]	
Test of group differences: $Q_b(1) = 0.11$, p =				0.000
Overall		-	0.20 [-0.34, 0.74]	0.472
Heterogeneity: $\tau^2 = 0.12$, $I^2 = 32.48\%$, $H^2 =$	1.48			
Test of $\theta_i = \theta_j$: Q(4) = 6.94, p = 0.14				
	-2	0 2	4	
	_	ing CIPII Lower during CSII		

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).

Study		reatment	N	Contr	ol SD			Mean Diff. with 95% CI	Weight	Study	Treatment	Contr Mean			Mean Diff. with 95% Cl	Weigh
Study	N	Mean SD	/ N	mean	50			with 95% CI	(%)	Study	N Mean SD N	w mean	SD		WITN 95% CI	(%)
HbA1c ≤ 7 %										Case-Control study						
Raccah et al. 1994		100.0 71.4			89.9			-18.10 [-85.94, 49.7		Colette et al. 1989	13 115.3 67.6 1	1 141.0	103.6 —		25.70 [-94.64, 43.24]	-
Lassmann-Vague et al. 1994			3 11	118.1	89.8		•	3.50 [-63.76, 56.7		Heterogeneity: $\tau^2 = 0.00$, $I^2 = .9$					-25.70 [-94.64, 43.24]]
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$		$H^{2} = 1.00$						-9.94 [-54.99, 35.1	1]	Test of $\theta_i = \theta_j$: Q(0) = -0.00, p =						
Test of $\theta_i = \theta_j$: Q(1) = 0.10, p =	0.75															
HbA1c > 7 %										Crossover study	4 404 0 07 0		07.0	_		
	40	445.0 07.0			100.0			05 70 6 04 64 40 0		Beylot et al. 1987	4 131.9 27.8				-20.90 [-59.43, 17.63]	
Colette et al. 1989		115.3 67.6						-25.70 [-94.64, 43.2		Oskarsson et al. 1999		7 48.1	20.9		-20.10 [-36.17, -4.03]	-
Beylot et al. 1987		131.9 27.8			27.8			-20.90 [-59.43, 17.6	•	Raccah et al. 1994	11 100.0 71.4 1		89.9 -		18.10 [-85.94, 49.74]	
Oskarsson et al. 1999	7	28.0 5.8			20.9	-	-	-20.10 [-36.17, -4.0		Oskarsson et al. 2000	7 35.8 7.5		9.9	-	-17.60 [-26.80, -8.40]	-
Oskarsson et al. 2000	7		57		9.9	1		-17.60 [-26.80, -8.4	•	Giacca et al. 1993	5 30.8 13.6		23.3		-14.20 [-37.85, 9.45]	
Giacca et al. 1993	5	30.8 13.6			23.3		•	-14.20 [-37.85, 9.4		Lassmann-Vague et al. 1996	11 60.4 23.1 1		30.0		-6.30 [-28.68, 16.08]	-
Lassmann-Vague et al. 1996		60.4 23.1	1 11	66.7	30.0	_	-	-6.30 [-28.68, 16.0		Lassmann-Vague et al. 1994	11 114.6 48.3 1	1 118.1	89.8		-3.50 [-63.76, 56.76]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$		$H^2 = 1.00$				•		-16.86 [-23.87, -9.8	5]	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$				•	-16.61 [-23.57, -9.64]]
Test of $\theta_i = \theta_j$: Q(5) = 1.19, p =	0.95									Test of $\theta_i = \theta_j$: Q(6) = 1.31, p =	0.97					
Overall								-16.70 [-23.62, -9.7	7]	Overall				•	-16.70 [-23.62, -9.77]	1
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%.	$H^2 = 1.00$								Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%. H ² = 1.00			-		
Test of $\theta_1 = \theta_1$: Q(7) = 1.38, p =								Λ		Test of $\theta_1 = \theta_1$: Q(7) = 1.38, p =						
Test of group differences: Q _b (1		9. p = 0.77						A		Test of group differences: Q _b (1					D	
	,	-,,,			-100	-50	0 5				,, ,		-100	-50 0	50	
Random-effects REML model					-100	-50	0 5	0		Random-effects REML model			-100	-50 0	50	
										Random Choola REME model						
Study		reatment Mean SD	N	Contr				Mean Diff. with 95% Cl	Weight (%)	Study	Treatment N Mean SD N	Contr	SD		Mean Diff. with 95% CI	Weigh (%)
CIPII ≤ 6 months	IN	Wearr 5D		Wear	30			With 55 % CI	(70)	No	N Mean 3D I	Weall	30		with 55 % CI	(70)
Beylot et al. 1987	4	131.9 27.8		152.8	27.8			-20.90 [-59.43, 17.6	3] 3.23	Colette et al. 1989	13 115.3 67.6 1	1 1110	102.6		25 70 1 04 64 43 24	1.01
Oskarsson et al. 1999	4	28.0 5.8			20.9	_				Oskarsson et al. 1999		7 48.1	20.9		 - 25.70 [-94.64, 43.24] -20.10 [-36.17, -4.03] 	
Giacca et al. 1993	5		55		20.9		_	-20.10 [-36.17, -4.0		Raccah et al. 1999	11 100.0 71.4 1		20.9 89.9 -			
	-						.	-14.20 [-37.85, 9.4							18.10 [-85.94, 49.74]	
Lassmann-Vague et al. 1996	11	60.4 23.1			30.0		•	-6.30 [-28.68, 16.0		Oskarsson et al. 2000	7 35.8 7.5		9.9	•	-17.60 [-26.80, -8.40]	
Lassmann-Vague et al. 1994		114.6 48.3	5 11	118.1	89.8			3.50 [-63.76, 56.7		Lassmann-Vague et al. 1996	11 60.4 23.1 1	1 66.7	30.0		-6.30 [-28.68, 16.08]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$		H = 1.00				•		-15.20 [-25.98, -4.4	3]	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$				•	-16.99 [-24.42, -9.56]	J
Test of $\theta_i = \theta_j$: Q(4) = 1.20, p =	0.88									Test of $\theta_i = \theta_j$: Q(4) = 1.10, p =	0.89					
CIPII > 6 months										Yes						
Colette et al. 1989	13	115.3 67.6	5 11	141.0	103.6 -			-25.70 [-94.64, 43.2	4] 1.01	Beylot et al. 1987	4 131.9 27.8	4 152.8	27.8		-20.90 [-59.43, 17.63]	3.23
Raccah et al. 1994	11	100.0 71.4	11	118.1	89.9			-18.10 [-85.94, 49.7	4] 1.04	Giacca et al. 1993	5 30.8 13.6	5 45.0	23.3		-14.20 [-37.85, 9.45]	8.58
Oskarsson et al. 2000	7	35.8 7.5	57	53.4	9.9		ŀ	-17.60 [-26.80, -8.4	0] 56.66	Lassmann-Vague et al. 1994	11 114.6 48.3 1	1 118.1	89.8		-3.50 [-63.76, 56.76]	1.32
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%.	$H^2 = 1.00$				•		-17.75 [-26.79, -8.7	1]	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%, H ² = 1.00				-14.77 [-33.89, 4.34]	1
Test of $\theta_i = \theta_j$: Q(2) = 0.05, p =										Test of $\theta_i = \theta_j$: Q(2) = 0.23, p =						
								-16.70 [-23.62, -9.7	71	Overall					-16.70 [-23.62, -9.77]	1
Overall								-10.70[-23.02, -9.7	(1	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$	100% $H^2 = 1.00$			•	-10.10[-23.02, -9.11]	1
Overall Ustoregonithu $r^2 = 0.000$ $r^2 = 0$	0.000	$u^2 = 1.00$					1			$\pi e e f o d e n e i t V$; $T = 0.00, I = 0$.00%, H = 1.00					
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$		H ² = 1.00								• • •						
		H ² = 1.00						C		Test of $\theta_i = \theta_j$: Q(7) = 1.38, p =						
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$	0.99				_			C		• • •	0.99				D	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$ Test of $\theta_i = \theta_j$: Q(7) = 1.38, p =	0.99				-100	-50	0 5			Test of $\theta_i = \theta_j$: Q(7) = 1.38, p =	0.99		-100	-50 0		

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% Cl	P-value
HbA1c levels before starting CIPII treatment	Judioo			- raide
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: $Q_b(1) = 0.09$, $p = 0.7$	7			
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: $Q_b(1) = 0.07$, $p = 0.8$	0			
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: $Q_b(1) = 0.13$, p = 0.7	2			
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: $Q_b(5) = 0.86$, p = 0.9	7			
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: $Q_b(1) = 0.04$, $p = 0.8$	3			
Overall Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: Q(7) = 1.38, p = 0.99		•	-16.70 [-23.62, -9.77]	0.000
	-100) -50 0 Lower during CIPII Lower dur	50 ring CSII	

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).

Study	Treatment N Mean SD N	Control Mean SD		Mean Diff. Weight with 95% CI (%)	Study	Treatment Control N Mean SD N Mean		Mean Diff. Weight with 95% CI (%)
HbA1c ≤ 7 %					Case-Control study			
Lassmann-Vague et al. 1994	11 41.6 12.9 11	40.0 13.3		1.60 [-9.35, 12.55] 7.02	Liebl et al. 2009	30 44.2 16.6 30 46.0	23.6 —	-1.80 [-12.12, 8.52] 7.89
Pacifico et al. 1997	8 42.8 6.6 8	40.8 8.0	-	2.00 [-5.19, 9.19] 16.28	Hedman et al. 2009/2014	10 51.2 31.5 20 39.3	10.5	11.90 [-3.16, 26.96] 3.71
Raccah et al. 1994	11 43.8 15.9 11	40.5 14.6		3.30 [-9.46, 16.06] 5.17	Heterogeneity: $\tau^2 = 50.44$, $I^2 =$	53.75%, H ² = 2.16	-	3.91 [-9.33, 17.14]
Jeandidier et al. 1992	8 39.0 11.0 8	32.0 13.0		7.00 [-4.80, 18.80] 6.04	Test of $\theta_i = \theta_j$: Q(1) = 2.16, p =	= 0.14		
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.	.00%, H ² = 1.00		•	2.99 [-1.95, 7.93]				
Test of $\theta_i = \theta_j$: Q(3) = 0.58, p =	0.90				Crossover study			
					Micossi et al. 1986	6 46.0 10.7 6 48.6	10.3 —	-2.60 [-14.48, 9.28] 5.96
HbA1c > 7 %					Duvillard et al. 2005/2007	7 43.6 9.8 7 45.0	17.8 —	-1.40 [-16.45, 13.65] 3.71
Micossi et al. 1986	6 46.0 10.7 6	48.6 10.3		-2.60 [-14.48, 9.28] 5.96	Hanaire-Broutin et al. 1996	18 39.1 10.6 18 39.6	8.9 📥	-0.50 [-6.89, 5.89] 20.57
Liebl et al. 2009	30 44.2 16.6 30	46.0 23.6		-1.80 [-12.12, 8.52] 7.89	Oskarsson et al. 2000	7 37.9 7.1 7 38.2	10.3 -	-0.30 [-9.57, 8.97] 9.79
Duvillard et al. 2005/2007	7 43.6 9.8 7	45.0 17.8		-1.40 [-16.45, 13.65] 3.71	Georgopoulos et al. 1994	8 62.4 44.9 8 61.9	45.7	
Hanaire-Broutin et al. 1996	18 39.1 10.6 18	39.6 8.9		-0.50 [-6.89, 5.89] 20.57	Lassmann-Vague et al. 1994	11 41.6 12.9 11 40.0	13.3 —	1.60 [-9.35, 12.55] 7.02
Oskarsson et al. 2000	7 37.9 7.1 7	38.2 10.3		-0.30 [-9.57, 8.97] 9.79	Pacifico et al. 1997	8 42.8 6.6 8 40.8	8.0 -	2.00 [-5.19, 9.19] 16.28
Georgopoulos et al. 1994	8 62.4 44.9 8	61.9 45.7 -		- 0.50 [-43.89, 44.89] 0.43	Oskarsson et al. 1999	7 38.4 7.7 7 36.1	7.4	2.30 [-5.61, 10.21] 13.44
Oskarsson et al. 1999	7 38.4 7.7 7	36.1 7.4	-	2.30 [-5.61, 10.21] 13.44	Raccah et al. 1994	11 43.8 15.9 11 40.5	14.6 —	3.30 [-9.46, 16.06] 5.17
Hedman et al. 2009/2014	10 51.2 31.5 20		—	11.90 [-3.16, 26.96] 3.71	Jeandidier et al. 1992	8 39.0 11.0 8 32.0		7.00 [-4.80, 18.80] 6.04
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.				0.41 [-3.17, 4.00]	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$			1.14 [-1.95, 4.22]
Test of $\theta_i = \theta_j$: Q(7) = 3.03, p =					Test of $\theta_i = \theta_j$: Q(9) = 2.04, p =			
Overall			•	1.30 [-1.60, 4.20]	Overall		•	1.30 [-1.60, 4.20]
Heterogeneity: $r^2 = 0.00$, $I^2 = 0$.	.00%, H ² = 1.00			Λ	Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$	0.00%, H ² = 1.00		
Test of $\theta_i = \theta_j$: Q(11) = 4.30, p =	= 0.96			Δ	Test of $\theta_i = \theta_j$: Q(11) = 4.30, p	= 0.96		R
Test of group differences: $Q_{b}(1)$) = 0.68, p = 0.41	_			Test of group differences: $Q_b(1)$	1) = 0.16, p = 0.69		
		-50	0	50			-50 0	50
Random-effects REML model					Random-effects REML model			
Study	Treatment N Mean SD N	Control Mean SD		Mean Diff. Weight with 95% CI (%)	Study	Treatment Control N Mean SD N Mean		Mean Diff. Weight with 95% CI (%)
CIPII ≤ 6 months					No			
Micossi et al. 1986	6 46.0 10.7 6	48.6 10.3		-2.60 [-14.48, 9.28] 5.96	Micossi et al. 1986	6 46.0 10.7 6 48.6	10.3 —	-2.60 [-14.48, 9.28] 5.96
Duvillard et al. 2005/2007	7 43.6 9.8 7	45.0 17.8		-1.40 [-16.45, 13.65] 3.71	Liebl et al. 2009	30 44.2 16.6 30 46.0	23.6 —	-1.80 [-12.12, 8.52] 7.89
Oskarsson et al. 2000	7 37.9 7.1 7	38.2 10.3	-	-0.30 [-9.57, 8.97] 9.79	Duvillard et al. 2005/2007	7 43.6 9.8 7 45.0	17.8	-1.40 [-16.45, 13.65] 3.71
Georgopoulos et al. 1994		61.9 45.7 -		- 0.50 [-43.89, 44.89] 0.43	Hanaire-Broutin et al. 1996	18 39.1 10.6 18 39.6	8.9 -	-0.50 [-6.89, 5.89] 20.57
	8 62.4 44.9 8							
	8 62.4 44.9 8 11 41.6 12.9 11			1.60 [-9.35, 12.55] 7.02	Oskarsson et al. 2000		10.3 -	-0.30 [-9.57, 8.97] 9.79
		40.0 13.3	-		Oskarsson et al. 2000 Georgopoulos et al. 1994	7 37.9 7.1 7 38.2	10.3	
Lassmann-Vague et al. 1994 Jeandidier et al. 1992	11 41.6 12.9 11	40.0 13.3 32.0 13.0	- - - -	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04		7 37.9 7.1 7 38.2	T	-0.30 [-9.57, 8.97] 9.79
Lassmann-Vague et al. 1994 Jeandidier et al. 1992	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20	40.0 13.3 32.0 13.0	- - - - -	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04	Georgopoulos et al. 1994	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 8 42.8 6.6 8 40.8	45.7	-0.30 [-9.57, 8.97] 9.79
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$.	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00	40.0 13.3 32.0 13.0		1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71	Georgopoulos et al. 1994 Pacifico et al. 1997	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 8 42.8 6.6 8 40.8 7 38.4 7.7 7 36.1	45.7 8.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00	40.0 13.3 32.0 13.0		1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 9 8 42.8 6.6 8 40.8 7 38.4 7.7 7 36.1 11 43.8 15.9 11 40.5	45.7 8.0 7.4 14.6	-0.30 [-9.57, 8.97] 9.79
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$.	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00	40.0 13.3 32.0 13.0	*	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 8 42.8 6.6 8 40.8 7 38.4 7.7 7 36.1 11 43.8 15.9 11 40.5 8 39.0 11.0 8 32.0	45.7 8.0 7.4 14.6 13.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: 7 ² = 0.00, 1 ² = 0. Test of θ ₁ = θ ₁ : Q(6) = 3.37, p = CIPII > 6 months	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00	40.0 13.332.0 13.039.3 10.5	+++++++++++++++++++++++++++++++++++++++	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 8 42.8 6.6 8 40.8 7 38.4 7.7 7 36.1 11 43.8 15.9 11 40.5 8 39.0 11.0 8 32.0 10 51.2 31.5 20 39.3	45.7 8.0 7.4 14.6 13.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$; $Q(6) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00 0.76	 40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 		1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 2.02 [-2.77, 6.82]	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$; $Q(6) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00 0.76 30 44.2 16.6 30 18 39.1 10.6 18	 40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 	+++++++++++++++++++++++++++++++++++++++	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 2.02 [-2.77, 6.82] -1.80 [-12.12, 8.52] 7.89 -0.50 [-6.89, 5.89] 20.57	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$: $Q(\theta) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 00%, H ² = 1.00 0.76 30 44.2 16.6 30 18 39.1 10.6 18 8 42.8 6.6 8	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0	***	1.60 [-9.35, 12.55] 7.02 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 2.02 [-2.77, 6.82] -1.80 [-12.12, 8.52] 7.89 -0.50 [-6.89, 5.89] 20.57 2.00 [-5.19, 9.19] 16.28	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_l = \theta_l$: $Q(\theta) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999	11 41.6 12.9 11 8 39.0 11.0 8 10 51.2 31.5 20 000%, H ² 1.00 9 10 0.76	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4	***	1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 13.44	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$ Test of $\theta_i = \theta_i$; Q(10) = 4.29, p	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29]
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_l = \theta_l$: Q($\theta_l = 3.37$, p = CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4	***	1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 13.44 3.30 -9.46, 16.06 5.17	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$ Test of $\theta_i = \theta_i$: Q(10) = 4.29, p Yes Lassmann-Vague et al. 1994	7 37.9 7.1 7 38.2 8 62.4 44.9 8 61.9 8 42.8 6.6 8 40.8 7 38.4 7.7 7 36.1 11 43.8 15.9 11 40.5 8 39.0 11.0 8 32.0 10 51.2 31.5 20 39.3 0.00%, H ² = 1.00 = 0.93	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_l = \theta_l$: $Q(\theta) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 13.44	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$ Test of $\theta_i = \theta_i$; Q(10) = 4.29, p	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29]
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $\tau^2 = 0.00$, $t^2 = 0$. Test of $\theta_i = \theta_i$; $Q(6) = 3.37$, $p =$ CIPI > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Heterogeneity: $\tau^2 = 0.00$, $t^2 = 0$.	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 13.44 3.30 -9.46, 16.06 5.17	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$ Test of $\theta_i = \theta_i$; Q(10) = 4.29, p Yes Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00$, $l^2 = 1$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$; $Q(6) = 3.37$, $p =$ CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1999 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$; $Q(4) = 0.79$, $p =$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 3.44 3.30 -9.46, 16.06 5.17 0.88 -2.76, 4.53	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1999 Hadman et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00, l^2 = c$ Test of $\theta_i = \theta_i$: Q(10) = 4.29, p Yes Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00, l^2 = c$ Test of $\theta_i = \theta_i$: Q(0) = -0.00, p	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02 1.60 [-9.35, 12.55]
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$: Q(6) = 3.37, p = CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$: Q(4) = 0.79, p = Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0$.	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 3.44 3.30 -9.46, 16.06 5.17 0.88 -2.76, 4.53	$ \begin{array}{l} \label{eq:constraints} & {\rm Georgopoulos} \mbox{ et al. 1994} \\ {\rm Pacifico \mbox{ et al. 1997} } \\ {\rm Oskarsson \mbox{ et al. 1999} } \\ {\rm Raccah \mbox{ et al. 1994} } \\ {\rm Jeandidier \mbox{ et al. 1994} } \\ {\rm Jeandidier \mbox{ et al. 1994} } \\ {\rm Hedman \mbox{ et al. 1994} } \\ {\rm Hedman \mbox{ et al. 1994} } \\ {\rm Hedman \mbox{ et al. 1994} } \\ {\rm Heterogeneity: \mbox{ r}^2 = 0.00, \mbox{ l}^2 = 0 \\ {\rm Test \mbox{ of } \theta_i = \theta_i; \mbox{ Q}(0) = 0.00, \mbox{ p} \\ \end{array} \\ \hline \\ {\rm Heterogeneity: \mbox{ r}^2 = 0.00, \mbox{ l}^2 = 0 \\ \hline \\ {\rm Overall} \\ \\ {\rm Heterogeneity: \mbox{ r}^2 = 0.00, \mbox{ l}^2 = 0 \\ \hline \end{array} $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02 1.60 [-9.35, 12.55]
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$: Q(6) = 3.37, p = CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_i = \theta_i$: Q(4) = 0.79, p = Overall	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 3.44 3.30 -9.46, 16.06 5.17 0.88 -2.76, 4.53	Georgopoulos et al. 1994 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Jeandidier et al. 1994 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = C$ Test of $\theta_i = \theta_i$: Q(10) = 4.29, p Yes Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00$, $l^2 = 1$ Test of $\theta_i = \theta_i$: Q(0) = -0.00, p.	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02 1.60 [-9.35, 12.55]
Lassmann-Vague et al. 1994 Jeandidier et al. 1992 Hedman et al. 2009/2014 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_1 = \theta_1$: Q(6) = 3.37, p = CIPII > 6 months Liebl et al. 2009 Hanaire-Broutin et al. 1996 Pacifico et al. 1997 Oskarsson et al. 1999 Raccah et al. 1994 Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_1 = \theta_1$: Q(4) = 0.79, p = Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0$. Test of $\theta_1 = \theta_2$: Q(11) = 4.30, p =	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	40.0 13.3 32.0 13.0 39.3 10.5 46.0 23.6 39.6 8.9 40.8 8.0 36.1 7.4		1.60 -9.35, 12.55 7.02 7.00 -4.80, 18.80 6.04 11.90 -3.16, 26.96 3.71 2.02 -2.77, 6.82 - -1.80 -12.12, 8.52 7.89 -0.50 -6.89, 5.89 20.57 2.00 -5.19, 9.19 16.28 2.30 -5.61, 10.21 3.44 3.30 -9.46, 16.06 5.17 0.88 -2.76, 4.53	$ \begin{array}{l} \label{eq:constraints} & {\rm Georgopoulos} \mbox{ et al. 1994} \\ {\rm Pacifico \mbox{ et al. 1997} } \\ {\rm Oskarsson \mbox{ et al. 1999} } \\ {\rm Raccah \mbox{ et al. 1994} } \\ {\rm Jeandidier \mbox{ et al. 1994} } \\ {\rm Jeandidier \mbox{ et al. 1994} } \\ {\rm Hedmon \mbox{ et al. 1994} } \\ {\rm Hedmon \mbox{ et al. 1994} } \\ {\rm Hedmon \mbox{ et al. 1992} } \\ {\rm Hedmon \mbox{ et al. 1992} } \\ {\rm Hedmon \mbox{ et al. 2009/2014} } \\ {\rm Heterogeneity: \mbox{ r}^2 = 0.00, \mbox{ l}^2 = 0 \\ {\rm Test \mbox{ of } \theta_i = \theta_i; \mbox{ Q}(0) = -0.00, \mbox{ p} \\ \end{array} \\ \hline \\ {\rm Heterogeneity: \mbox{ r}^2 = 0.00, \mbox{ l}^2 = 0 \\ {\rm Test \mbox{ of } \theta_i = \theta_i; \mbox{ Q}(1) = 4.30, \mbox{ p} \\ \end{array} $	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	45.7 8.0 7.4 14.6 13.0 10.5 •	-0.30 [-9.57, 8.97] 9.79 -0.50 [-43.89, 44.89] 0.43 2.00 [-5.19, 9.19] 16.28 2.30 [-5.61, 10.21] 13.44 3.30 [-9.46, 16.06] 5.17 7.00 [-4.80, 18.80] 6.04 11.90 [-3.16, 26.96] 3.71 1.28 [-1.73, 4.29] 1.60 [-9.35, 12.55] 7.02 1.60 [-9.35, 12.55]

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 (\leq 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 (\leq 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.

			Mean [)iff.	
Subgroups	Studies		with 959	6 CI	P-value
HbA1c levels before starting CIPII treatment					
HbA1c ≤ 7 %	4		2.99 [-1.9	5, 7.93]	0.235
HbA1c > 7 %	8	-	0.41 [-3.1]	7, 4.00]	0.821
Test of group differences: $Q_b(1) = 0.68$, $p = 0.41$					
Study type					
Case-Control study	2	•	3.91 [-9.33	3, 17.14]	0.563
Crossover study	10		1.14 [-1.9	5, 4.22]	0.471
Test of group differences: $Q_b(1) = 0.16$, $p = 0.69$					
Duration of CIPII-period					
CIPII ≤ 6 months	7		2.02 [-2.7]	7, 6.82]	0.407
CIPII > 6 months	5	-	0.88 [-2.70	6, 4.53]	0.634
Test of group differences: $Q_b(1) = 0.14$, $p = 0.71$					
Duration of CIPII-period (months)					
1.5	1	•	-2.60 [-14.4	3, 9.28]	0.668
3	3	•	2.88 [-4.20), 9.96]	0.425
6	3	•	3.83 [-6.3	3, 14.04]	0.462
10	1	•	3.30 [-9.46	6, 16.06]	0.612
11	1		2.30 [-5.6	1, 10.21]	0.569
12	3		0.18 [-4.1	5, 4.52]	0.935
Test of group differences: $Q_b(5) = 1.25$, $p = 0.94$					
Controlled CSII follow-up-period					
No	11		1.28 [-1.73	3, 4.29]	0.404
Yes	1	•	1.60 [-9.3	5, 12.55]	0.775
Test of group differences: $Q_b(1) = 0.00$, $p = 0.96$					
Overall		•	1.30 [-1.60	0, 4.20]	0.379
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$					
Test of $\theta_i = \theta_j$: Q(11) = 4.30, p = 0.96			_		
	-20 Lov	0 -10 0 10 ver during CIPII Lower during CS	20 SII		

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).

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).

	٦	Freatme	nt		Contro	bl		Mean Diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
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 [-1.46, 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							•	-0.62 [-1.01, -0.23]	
Heterogeneity: $\tau^2 = 0.13$, $I^2 = 4$	1.73	%, H ² =	1.72	2					
Test of $\theta_i = \theta_j$: Q(8) = 15.74, p	= 0.0	5							
Test of θ = 0: t(8) = -3.09, p =	0.002	2							
							-4 -3 -2 -1 0 1	2	
								during CSII	

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).

	Treatment	Control	Mean Diff. Weight	Treatment Control	Mean Diff. Weight
Study	N Mean SD N	Mean SD	with 95% CI (%)	Study N Mean SD N Mean SD	with 95% CI (%)
HbA1c ≤ 7 %				Crossover study	
Guerci et al. 1996	14 7.6 0.5 14	4 7.8 0.7	-0.20 [-0.65, 0.25] 22.17	Pitt et al. 1992 10 7.8 0.4 10 8.9 0.6 -	-1.10 [-1.55, -0.65] 22.27
Raccah et al. 1994	11 8.0 1.8 1	1 8.3 0.8	-0.30 [-1.46, 0.86] 8.32	Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	-2.80 [-4.53, -1.07] 4.42
Lassmann-Vague et al. 1994	4 11 8.3 1.8 1	1 8.3 1.2	0.00 [-1.28, 1.28] 7.23	Micossi et al. 1986 6 8.8 1.3 6 9.7 1.4 -	-0.90 [-2.43, 0.63] 5.43
Heterogeneity: T ² = 0.00, I ² =	= 0.00%, H ² = 1.00		-0.19 [-0.59, 0.21]	Beylot et al. 1987 4 8.2 0.9 4 8.8 1.3	-0.60 [-2.15, 0.95] 5.31
Test of $\theta_i = \theta_j$: Q(2) = 0.12, p	p = 0.94			Catargiet 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
HbA1c > 7 %				Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 -	-0.20 [-0.65, 0.25] 22.17
Pitt et al. 1992	10 7.8 0.4 1	0 8.9 0.6	-1.10 [-1.55, -0.65] 22.27	Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 —	-0.30 [-1.46, 0.86] 8.32
Georgopoulos et al. 1992	7 7.7 1.2	7 10.5 2.0	-2.80 [-4.53, -1.07] 4.42	Lassmann-Vague et al. 1994 11 8.3 1.8 11 8.3 1.2 —	0.00 [-1.28, 1.28] 7.23
Micossi et al. 1986	6 8.8 1.3	6 9.7 1.4 ·	-0.90 [-2.43, 0.63] 5.43	Heterogeneity: $\tau^2 = 0.13$, $I^2 = 41.73\%$, $H^2 = 1.72$	-0.62 [-1.01, -0.23]
Beylot et al. 1987	4 8.2 0.9	\$ 8.8 1.3	-0.60 [-2.15, 0.95] 5.31	Test of $\theta_i = \theta_i$: Q(8) = 15.74, p = 0.05	
Catargi et al. 2002	14 8.1 1.0 14	4 8.5 0.9	-0.40 [-1.10, 0.30] 15.57		
Georgopoulos et al. 1994	8 7.4 1.1	3 7.8 1.1	-0.40 [-1.48, 0.68] 9.29	Overall 🔶	-0.62 [-1.01, -0.23]
Heterogeneity: T ² = 0.09, I ² =	= 29.04%, H ² = 1.41		-0.88 [-1.34, -0.42]	Heterogeneity: $\tau^2 = 0.13$, $I^2 = 41.73\%$, $H^2 = 1.72$	
Test of $\theta_i = \theta_j$: Q(5) = 8.32, p	p = 0.14			Test of $\theta_i = \theta_j$: Q(8) = 15.74, p = 0.05	
				Test of group differences: $Q_{c}(0) = 0.00$, $p = .$	
Overall			-0.62 [-1.01, -0.23]		
Heterogeneity: T ² = 0.13, I ² =	= 41.73%, H ² = 1.72		•	-4 -2 0 Random-effects REML model	
Test of $\theta_i = \theta_j$: Q(8) = 15.74,	p = 0.05		Δ	Random-effects REML model	D
Test of group differences: Q	h(1) = 4.85 n = 0.03				
	(i) = 4.00, p = 0.00	-4	-2 0 2		
Random-effects REML model	al.	-4	-2 0 2		
Study	Treatment N Mean SD N	Control Mean SD	Mean Diff. Weight with 95% CI (%)	Treatment Control Study N Mean SD N Mean SD	Mean Diff. Weight with 95% CI (%)
Study CIPII ≤ 6 months					
		Mean SD		Study N Mean SD N Mean SD	
CIPII ≤ 6 months	N Mean SD N	Mean SD 5 9.7 1.4	with 95% CI (%)	Study N Mean SD N Mean SD N Mean SD	with 95% CI (%)
CIPII ≤ 6 months Micossi et al. 1986	N Mean SD N 6 8.8 1.3 (Mean SD 5 9.7 1.4 4 8.8 1.3	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42
CIPII ≤ 6 months Micossi et al. 1986 Beylot et al. 1987	N Mean SD N 6 8.8 1.3 0 4 8.2 0.9 4	Mean SD 5 9.7 1.4 4 8.8 1.3 4 8.5 0.9	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% Cl (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29
CIPII ≤ 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002	N Mean SD N 6 8.8 1.3 0 4 8.2 0.9 4 14 8.1 1.0 14	Mean SD 5 9.7 1.4 4 8.8 1.3 4 8.5 0.9 3 7.8 1.1	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% Cl (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17
CIPII ≤ 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994	N Mean SD N 6 8.8 1.3 4 4 8.2 0.9 4 14 8.1 1.0 1 8 7.4 1.1 4 14 7.6 0.5 1	Mean SD 9.7 1.4 8.8 1.3 8.5 0.9 3 7.8 1.1 4 7.8 0.7	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32
CIPII ≤ 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996	N Mean SD N 6 8.8 1.3 0 4 8.2 0.9 - 14 8.1 1.0 1- 8 7.4 1.1 4 14 7.6 0.5 1- 4 11 8.3 1.8 1	Mean SD 9.7 1.4 8.8 1.3 8.5 0.9 3 7.8 1.1 4 7.8 0.7	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32
CIPII ≤ 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996 Lassmann-Vague et al. 1994	N Mean SD N 6 8.8 1.3 (4 8.2 0.9 (4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.8 1 1.4 1.8 1 1.4	Mean SD 9.7 1.4 8.8 1.3 8.5 0.9 3 7.8 1.1 4 7.8 0.7	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32
CIPII \leq 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00, l^2 =$	N Mean SD N 6 8.8 1.3 (4 8.2 0.9 (4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.8 1 1.4 1.8 1 1.4	Mean SD 9.7 1.4 8.8 1.3 8.5 0.9 3 7.8 1.1 4 7.8 0.7	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: r ² = 0.58, l ² = 69.87%, H ² = 3.32 Test of 6, = 6; Q(3) = 8.16, p = 0.04 Image: Content of the image: Conten of the image: Conten of the image: Conten of the	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32
CIPII \leq 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00, l^2 =$	N Mean SD N 6 8.8 1.3 (4 8.2 0.9 (4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.4 1.8 1 1.4 1.8 1 1.4	Mean SD 9.7 1.4 8.8 1.3 8.5 0.9 3 7.8 1.1 4 7.8 0.7	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: r ² = 0.58, l ² = 69.87%, H ² = 3.32 Test of θ ₂ = θ ₁ : Q(3) = 8.16, p = 0.04 Yes	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22]
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CIPII \leq 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00, t^2 =$ Test of $\theta_i = \theta_i; Q(5) = 1.25, p$ CIPII > 6 months	N Mean SD N 6 8.8 1.3 0 4 8.2 0.9 0 14 8.1 1.0 1 8 7.4 1.1 1 14 7.6 0.5 1 4 11 8.3 1.8 1 0 0.0%, H ² 1.00 0 0 0 0.94 10 7.8 0.4 10	Mean SD 5 9.7 1.4 4 8.8 1.3 4 8.5 0.9 3 7.8 1.1 4 7.8 0.7 1 8.3 1.2	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03]	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: τ ² = 0.58, l ² = 69.87%, H ² = 3.32 Test of θ ₁ = θ ₁ : Q(3) = 8.16, p = 0.04 • Yes Pitt et al. 1992 10 7.8 0.4 10 8.9 0.6 Micossi et al. 1986 6 8.8 1.3 6 9.7 1.4	with 95% CI (%) -2.80 [.4.53, .1.07] 4.42 -0.40 [.1.48, 0.68] 9.29 -0.20 [.0.65, 0.25] 22.17 -0.30 [.1.46, 0.86] 8.32 -0.70 [.1.62, 0.22] 20.70 -1.10 [.1.55, -0.65] 22.27 -0.90 [.2.43, 0.63] 5.43
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$\label{eq:constraints} \begin{split} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneity: } \textbf{\tau}^2 = 0.00, \textbf{I}^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(5) = 1.25, \textbf{p} \\ \hline \textbf{CIPII > 6 months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1992} \end{split}$	N Mean SD N 6 8.8 1.3 4 4 8.2 0.9 4 14 8.1 1.0 1 14 8.1 1.0 1 14 7.6 0.5 1 4 11 8.3 1.8 1 = 0.00%, H ² 1.00 0 p 0.94 1 7.7 1.2 11 8.0 1.8 1	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.68] 8.32 -0.70 [-1.62, 0.22] - -1.10 [-1.55, -0.65] 22.27 -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.96] 5.31 -0.40 [-1.10, 0.30] 15.57
$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneily: } r^2 = 0.00, l^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \end{tabular}; \end{tabular} \mathbf{CiPII} > 6 \mbox{ months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Raccah et al. 1994} \end{array}$	N Mean SD N 6 8.8 1.3 4 4 8.2 0.9 4 14 8.1 1.0 1 14 8.1 1.0 1 14 7.6 0.5 1 4 11 8.3 1.8 1 = 0.00%, H ² 1.00 0 0 p 0.94 1 7.7 1.2 1 10 7.8 0.4 1 7.7 1.2 1 11 8.0 1.8 1 7 1 1.8 1 = 7.243%, H ² 3.63 3 3 3 3	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.20 [-0.65, 0.25] 22.17 -0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.86] 8.32	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 8.0 1.8 11 8.3 0.8 Heterogeneity: 7 ² 0.58, 1 ² 69.87%, H ² 3.32 Test of θ ₂ 9(3) = 8.16, p = 0.04 Yes Pitt et al. 1992 10 7.8 0.4 10 8.9 0.6 Micossi et al. 1986 6 8.8 1.3 6 9.7 1.4 Beylot et al. 1987 4 8.2 0.9 4 8.8 1.3 Catargi et al. 2002 14 8.1 1.0 14 8.5 0.9	with 95% CI (%) -2.80 [4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.25] 22.27 -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23
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$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII} \le \textbf{6} \mbox{ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.00, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(5) = 1.25, \ \textbf{p} \\ \hline \textbf{CIPII > 6 months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.74, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(2) = 5.53, \ \textbf{p} \\ \hline \textbf{Overall} \\ \hline \textbf{Heterogeneity: } r^2 = 0.13, r^2 = \\ \hline \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.86] 8.32 -1.24 [-2.40, -0.07] -	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: $\tau^2 = 0.58$, $t^2 = 69.87\%$, $H^2 = 3.32$ Test of $\theta_i = \theta_i$: Q(3) = 8.16, p = 0.04 Heterogeneity: T ² = 0.09, l ² = 0.04 Heterogeneity: T ² = 0.09, l ² = 29.00%, H ³ = 1.3 6 9.7 1.4 Beylot et al. 1987 4 8.2 0.9 4 8.8 1.3 Catargi et al. 2002 14 8.1 1.0 14 8.5 0.9 Lassmann-Vague et al. 1994 11 8.3 1.8 11 8.3 1.2 Image at theterogeneity: $\tau^2 = 0.09$, $t^2 = 29.50\%$, $H^2 = 1.42$	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 5.31 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23 -0.72 [-1.20, -0.23] 7.23
CIPII S 6 months Micossi et al. 1986 Beylot et al. 1987 Catargi et al. 2002 Georgopoulos et al. 1994 Guerci et al. 1996 Lassmann-Vague et al. 1994 Heterogeneity: $r^2 = 0.00, r^2 =$ Test of $\theta_i = \theta_i; Q(5) = 1.25, p$ CIPII > 6 months Pitt et al. 1992 Georgopoulos et al. 1994 Heterogeneity: $r^2 = 0.74, r^2 =$ Test of $\theta_i = \theta_i; Q(2) = 5.53, p$ Overall	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.86] 8.32 -1.24 [-2.40, -0.07] -	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.18 11 8.3 0.8 Heterogeneity: $\tau^2 = 0.58$, $t^2 = 69.87\%$, $H^2 = 3.32$ Test of $\theta_1 = \theta_1$; Q(3) = 8.16, p = 0.04 Image: the state of the stat	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.23] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23 -0.72 [-1.20, -0.23] 9.72
$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII} \le \textbf{6} \mbox{ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.00, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(5) = 1.25, \ \textbf{p} \\ \hline \textbf{CIPII > 6 months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.74, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(2) = 5.53, \ \textbf{p} \\ \hline \textbf{Overall} \\ \hline \textbf{Heterogeneity: } r^2 = 0.13, r^2 = \\ \hline \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.86] 8.32 -1.24 [-2.40, -0.07] -	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: $\tau^2 = 0.58$, $t^2 = 69.87\%$, $H^2 = 3.32$ Test of $\theta_i = \theta_i$: Q(3) = 8.16, p = 0.04 Heterogeneity: T ² = 0.09, l ² = 69.7%, H ² = 3.32 Test of $\theta_i = 0$; Q(3) = 8.16, p = 0.04 Yes Pitt et al. 1987 4 8.2 0.9 4 8.8 1.3 Catargi et al. 1987 4 8.2 0.9 4 8.8 1.3 Lassmann-Vague et al. 1994 11 8.3 1.8 11 8.3 1.2 Image: test of $\theta_i = \theta_i$: Q(4) = 4.54, p = 0.34 Image: test of $\theta_i = \theta_i$: Q(4) = 4.54, p	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 5.31 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23 -0.72 [-1.20, -0.23] 7.23
$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII \le 6 \ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.00, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(5) = 1.25, p \\ \hline \textbf{CIPII > 6 \ months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.74, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(2) = 5.53, p \\ \hline \textbf{Overall} \\ \hline \textbf{Heterogeneity: } r^2 = 0.13, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(8) = 15.74, \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7.8 1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] - -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.86] 8.32 -1.24 [-2.40, -0.07] -	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.18 11 8.3 0.8 Heterogeneity: $\tau^2 = 0.58$, $t^2 = 69.87\%$, $H^2 = 3.32$ Test of $\theta_i = \theta_i$: Q(3) = 8.16, p = 0.04 Image: the state of the stat	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.23] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23 -0.72 [-1.20, -0.23] 9.72
$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII \le 6 \ months} \\ \hline \textbf{Micossi et al. 1986} \\ \hline \textbf{Beylot et al. 1987} \\ \hline \textbf{Catargi et al. 2002} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Guerci et al. 1996} \\ \hline \textbf{Lassmann-Vague et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.00, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(5) = 1.25, p \\ \hline \textbf{CIPII > 6 \ months} \\ \hline \textbf{Pitt et al. 1992} \\ \hline \textbf{Georgopoulos et al. 1994} \\ \hline \textbf{Heterogeneity: } r^2 = 0.74, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(2) = 5.53, p \\ \hline \textbf{Overall} \\ \hline \textbf{Heterogeneity: } r^2 = 0.13, r^2 = \\ \hline \textbf{Test of } \theta_i = \theta_i; \ \textbf{Q}(8) = 15.74, \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Image Mean SD 5 9.7 1.4 .4 4 8.8 1.3 .4 4 8.5 0.9 .3 7 8.1.1 .1 4 7.8 0.7 1 8.3 1.2 0 8.9 0.6 7 10.5 2.0 1 8.3 0.8	with 95% Cl (%) -0.90 [-2.43, 0.63] 5.43 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.00, 0.30] 15.57 -0.40 [-1.48, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 0.00 [-1.28, 1.28] 7.23 -0.30 [-0.63, 0.03] -1.10 [-1.55, -0.65] 22.27 -2.80 [-4.53, -1.07] 4.42 -0.30 [-1.46, 0.88] 8.32 -1.24 [-2.40, -0.07] -0.62 [-1.01, -0.23]	Study N Mean SD N Mean SD No Georgopoulos et al. 1992 7 7.7 1.2 7 10.5 2.0 Georgopoulos et al. 1994 8 7.4 1.1 8 7.8 1.1 Guerci et al. 1996 14 7.6 0.5 14 7.8 0.7 Raccah et al. 1996 14 7.6 0.1 14 7.8 0.7 Raccah et al. 1994 11 8.0 1.8 11 8.3 0.8 Heterogeneity: $\tau^2 = 0.58$, $t^2 = 69.87\%$, $H^2 = 3.32$ Test of $\theta_1 = \theta_1$; Q(3) = 8.16, p = 0.04 Image: the state of	with 95% CI (%) -2.80 [-4.53, -1.07] 4.42 -0.40 [-1.46, 0.68] 9.29 -0.20 [-0.65, 0.25] 22.17 -0.30 [-1.46, 0.86] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 8.32 -0.70 [-1.62, 0.22] 5.31 -0.60 [-2.15, 0.95] 5.31 -0.40 [-1.10, 0.30] 15.57 0.00 [-1.28, 1.28] 7.23 -0.62 [-1.01, -0.23] D

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 (\leq 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 (\leq 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.

Subgroups	Studies		Mean Diff. with 95% Cl	P-value
HbA1c levels before starting CIPII treatme				
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: $Q_b(1) = 4.85$, p	= 0.03			
Study type				
Crossover study	9		-0.62 [-1.01, -0.23]	0.002
Test of group differences: $Q_b(0) = 0.00$, 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: $Q_b(1) = 2.31$, 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: $Q_b(7) = 15.45$, p	0 = 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: $Q_b(1) = 0.00$, p	= 0.97			
Overall		•	-0.62 [-1.01, -0.23]	0.002
Heterogeneity: $\tau^2 = 0.13$, $I^2 = 41.73\%$, $H^2 = 41.73\%$	= 1.72			
Test of $\theta_i = \theta_j$: Q(8) = 15.74, p = 0.05			_	
		-4 -3 -2 -1 0 1	2	
		Lower during CIPII Lower du	ring CSII	

Figure S5c. Summarised subgroup meta-analysis of SMBG (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

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).

	٦	reatme	nt		Contro	bl		Mean Diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Duvillard et al. 2005/2007	7	5.0	0.6	7	5.4	0.7		-0.40 [-1.08, 0.28]	17.58
Georgopoulos et al. 1994	8	4.6	0.8	8	4.8	0.8		-0.20 [-0.98, 0.58]	13.34
Georgopoulos 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
Guerci 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							+	-0.06 [-0.35, 0.22]	
Heterogeneity: $\tau^2 = 0.00$, I^2	= 0.0	$00\%, H^2$	= 1.0	00					
Test of $\theta_i = \theta_j$: Q(6) = 2.99,	p = 0	.81							
Test of θ = 0: t(6) = -0.43, p	o = 0.	67							
						-2	-1 0 1 2	ו 2	
							r during CIPII Lower during		

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 Contr N Mean SD N Mear		Mean Diff. with 95% CI	Weight (%)	Study	Treatment N Mean SE		ontrol Mean SD)	Mean Diff. with 95% Cl	Weight (%)
HbA1c ≤ 7 %					Crossover study						
Raccah et al. 1994	11 4.9 2.3 11 5.0	1.3	-0.10 [-1.66, 1.46]	3.36	Duvillard et al. 2005/2007	7 5.0 0.6	67	5.4 0.7		-0.40 [-1.08, 0.28]	17.58
Guerci et al. 1996	14 5.0 0.6 14 5.0	0.6 -	0.00 [-0.44, 0.44]	41.52	Georgopoulos et al. 1994	8 4.6 0.8	8 8	4.8 0.8		-0.20 [-0.98, 0.58]	13.34
Pacifico et al. 1997	8 4.8 0.8 8 4.7	0.8	0.10 [-0.68, 0.88]	13.34	Georgopoulos et al. 1992	7 4.6 1.1	17	4.9 1.3		-0.30 [-1.56, 0.96]	5.15
Heterogeneity: T ² = 0.00,	l ² = 0.00%, H ² = 1.00	+	0.02 [-0.36, 0.39]		Raccah et al. 1994	11 4.9 2.3	3 11	5.0 1.3		-0.10 [-1.66, 1.46]	3.36
Test of $\theta_i = \theta_j$: Q(2) = 0.0	17, p = 0.97				Guerci et al. 1996	14 5.0 0.6	6 14	5.0 0.6	-#-	0.00 [-0.44, 0.44]	41.52
					Pacifico et al. 1997	8 4.8 0.8	8 8	4.7 0.8	_	0.10 [-0.68, 0.88]	13.34
HbA1c > 7 %					Micossi et al. 1986	6 5.1 1.2	2 6	4.4 0.9		0.70 [-0.50, 1.90]	5.69
Duvillard et al. 2005/2007		0.7	-0.40 [-1.08, 0.28]	17.58	Heterogeneity: T ² = 0.00, I ²	= 0.00%, H ² = 1	1.00		+	-0.06 [-0.35, 0.22]	
Georgopoulos et al. 1994		0.8	-0.20 [-0.98, 0.58]		Test of $\theta_i = \theta_j$: Q(6) = 2.99,	p = 0.81					
Georgopoulos et al. 1992		1.3	-0.30 [-1.56, 0.96]								
Micossi et al. 1986	6 5.1 1.2 6 4.4	0.9	— 0.70 [-0.50, 1.90]	5.69	Overall				+	-0.06 [-0.35, 0.22]	
Heterogeneity: T ² = 0.00,		-	-0.17 [-0.62, 0.27]		Heterogeneity: T ² = 0.00, I ²	= 0.00%, H ² = 1	1.00				
Test of $\theta_i = \theta_j$: Q(3) = 2.50	i0, p = 0.48				Test of $\theta_i = \theta_j$: Q(6) = 2.99,	p = 0.81					
					Test of group differences: C	$D_{\rm b}(0) = 0.00$, p =					
Overall		+	-0.06 [-0.35, 0.22]		reet er group unterenteer e	45(0) 0.000, p			-2 -1 0 1	2	
Heterogeneity: $\tau^2 = 0.00$,	, I ² = 0.00%, H ² = 1.00		~		Random-effects REML mode	al			-2 -1 0 1	2	
Test of $\theta_i = \theta_j$: Q(6) = 2.99	9, p = 0.81		Δ		Random-enects REME mode	ei				R	
Test of group differences:	:: Q _b (1) = 0.42, p = 0.52										
		-2 -1 0 1	2								
Random-effects REML mo	odel										
	Treatment Contr		Moon Diff	Moight		Treatment	0				
Study	Treatment Contr N Mean SD N Mean		Mean Diff. with 95% Cl	Weight (%)	Study	Treatment N Mean SE		ontrol Mean SD)	Mean Diff. with 95% CI	Weight (%)
Study CIPII ≤ 6 months	Treatment Contr N Mean SD N Mear		Mean Diff. with 95% Cl	Weight (%)	Study No	Treatment N Mean SD)	Mean Diff. with 95% CI	Weight (%)
	N Mean SD N Mean		with 95% CI	(%)	No		D N M			with 95% CI	(%)
CIPII ≤ 6 months Duvillard et al. 2005/2007	N Mean SD N Mean 7 7 5.0 0.6 7 5.4	n SD	with 95% CI -0.40 [-1.08, 0.28]	(%)	No Duvillard et al. 2005/2007	N Mean SE	0 N M	Mean SD		with 95% Cl -0.40 [-1.08, 0.28]	(%)
CIPII ≤ 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8	0.7	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58]	(%) 17.58 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994	N Mean SE 7 5.0 0.6 8 4.6 0.8	DNN 37 38	Mean SD 5.4 0.7 4.8 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58]	(%) 17.58 13.34
CIPII ≤ 6 months Duvillard et al. 2005/2007	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0	0.7	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44]	(%) 17.58 13.34 41.52	No Duvillard et al. 2005/2007	N Mean SE 7 5.0 0.6 8 4.6 0.8	0 N N 6 7 8 8 1 7	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96]	(%) 17.58 13.34 5.15
CIPII ≤ 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1986	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4	0.7 0.8 0.6	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 41.52 5.69	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3	0 N N 6 7 8 8 1 7 8 11	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] 0.10 [-1.66, 1.46]	(%) 17.58 13.34 5.15 3.36
CIPII 5 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1986 Heterogeneity: τ^2 = 0.00,	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 6 5.1 1.2 6 4.4 1 ² 0.00%, H ² 1.0 1.2	0.7 0.8 0.6	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44]	(%) 17.58 13.34 41.52 5.69	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6	N N 5 7 3 8 1 7 3 11 5 14	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6		with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44]	(%) 17.58 13.34 5.15 3.36 41.52
CIPII ≤ 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1986	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 6 5.1 1.2 6 4.4 1 ² 0.00%, H ² 1.0 1.2	0.7 0.8 0.6	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 41.52 5.69	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8	N N 5 7 3 8 1 7 3 11 5 14 3 8	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 5.15 3.36 41.52 13.34
CIPII 5 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1986 Heterogeneity: τ^2 = 0.00,	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 6 5.1 1.2 6 4.4 1 ² 0.00%, H ² 1.0 1.2	0.7 0.8 0.6	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 41.52 5.69	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $r^2 = 0.00, r^2$:	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8 = 0.00%, H ² = 1.2 1.4	N N 5 7 3 8 1 7 3 11 5 14 3 8	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6		with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44]	(%) 17.58 13.34 5.15 3.36 41.52 13.34
$\label{eq:ciPI} \begin{array}{c} \textbf{CIPI} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Guerci et al. 1996} \\ \mbox{Micossi et al. 1986} \\ \mbox{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \mbox{Test of } \theta_i = \theta_i \text{: } \textbf{Q}(3) = 2.60 \\ \mbox{CIPI} > \textbf{6} \mbox{ months} \end{array}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%, H^2 = 1.00$ 8, p = 0.44 8 9 9 1.4 1.00 1.0	0.7 0.8 0.6 0.9	with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] -0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25]	(%) 17.58 13.34 41.52 5.69	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8 = 0.00%, H ² = 1.2 1.4	N N 5 7 3 8 1 7 3 11 5 14 3 8	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 5.15 3.36 41.52 13.34
$\label{eq:ciPI} \begin{array}{c} \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Guerci et al. 1996} \\ \mbox{Micossi et al. 1986} \\ \mbox{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \mbox{Test of } \textbf{\theta}_i = \textbf{\theta}_i \text{: } \textbf{Q}(3) = 2.60 \\ \\ \mbox{CIPII} > \textbf{6} \mbox{ months} \\ \\ \mbox{Georgopoulos et al. 1992} \end{array}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%, H^2 = 1.00$ 8 9 9 2 7 4.6 1.1 7 4.9	n SD 0.7 0.8 0.6 0.9 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] — 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96]	(%) 17.58 13.34 41.52 5.69 5.15	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $r^2 = 0.00$, l^2 : Test of $\theta_i = \theta_i$: Q(5) = 1.34, p	N Mean SE 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8 = 0.00%, H ² = 1.2 1.4	N N 5 7 3 8 1 7 3 11 5 14 3 8	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 5.15 3.36 41.52 13.34
$\label{eq:constraints} \hline \textbf{CIPI} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Guerci et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \mbox{Test of } \textbf{\theta}_i = \textbf{\theta}_i \cdot \textbf{Q}(3) = 2.60 \\ \mbox{CIPI} > \textbf{6} \mbox{months} \\ \mbox{Georgopoulos et al. 1994} \\ \mbox{Raccah et al. 1994} \\ \hline \end{matrix}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%, H^2 = 1.00$ 8 8 8 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46]	(%) 17.58 13.34 41.52 5.69 5.15 3.36	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1994 Raccah et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $\tau^2 = 0.00$, t^2 = Test of $\theta_i = \theta_i$: Q(5) = 1.34, g	N Mean SL 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8 = 0.00%, H ² = 1. p = 0.93 =	D N S 7 S 8 I 7 S 11 S 14 S 8 .000	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19]	(%) 17.58 13.34 5.15 3.36 41.52 13.34
CIPI ≤ 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1996 Heterogeneity: $r^2 = 0.00$, Test of $\theta_i = \theta_i$: Q(3) = 2.60 CIPII > 6 months Georgopoulos et al. 1994 Pacifico et al. 1997	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%, H^2 = 1.00$ 8 9 9 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0 8 4.8 0.8 8 4.7	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $r^2 = 0.00, l^2$: Test of $\theta_i = \theta_i$: Q(5) = 1.34, g Yes Micossi et al. 1986	N Mean SL 7 5.0 0.6 8 4.6 0.8 7 4.6 1.1 11 4.9 2.3 14 5.0 0.6 8 4.8 0.8 = 0.00%, H ² = 1. p = 0.93 6 5.1 1.2	D N S 7 S 8 I 7 S 11 S 14 S 8 .00	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Test of } \theta_i = \theta_i; \mbox{Q}(3) = 2.6i \\ \mbox{CIPII} > \textbf{6} \mbox{ months} \\ \mbox{Georgopoulos et al. 1992} \\ \mbox{Raccah et al. 1994} \\ \mbox{Pacifico et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ Micossi et al. 1$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1994 Guerci et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $\tau^2 = 0.00, t^2$: Test of $\theta_i = \theta_i$: Q(5) = 1.34, p Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.00, t^2$:	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N S 7 S 8 I 7 S 11 S 14 S 8 .00	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19]	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
CIPI ≤ 6 months Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Guerci et al. 1996 Micossi et al. 1996 Heterogeneity: $r^2 = 0.00$, Test of $\theta_i = \theta_i$: $Q(3) = 2.6i$ CIPII > 6 months Georgopoulos et al. 1994 Pacifico et al. 1997	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $r^2 = 0.00, l^2$: Test of $\theta_i = \theta_i$: Q(5) = 1.34, g Yes Micossi et al. 1986	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N S 7 S 8 I 7 S 11 S 14 S 8 .00	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Test of } \theta_i = \theta_i; \mbox{Q}(3) = 2.6i \\ \mbox{CIPII} > \textbf{6} \mbox{ months} \\ \mbox{Georgopoulos et al. 1992} \\ \mbox{Raccah et al. 1994} \\ \mbox{Pacifico et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ \mbox{Heterogeneity: } r^2 = 0.00, \\ \mbox{Micossi et al. 1997} \\ Micossi et al. 1$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] -0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88] -0.03 [-0.64, 0.59]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1994 Guerci et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: $\tau^2 = 0.00, t^2$: Test of $\theta_i = \theta_i$: Q(5) = 1.34, p Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.00, t^2$:	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N S 7 S 8 I 7 S 11 S 14 S 8 .00	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		 with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] 0.70 [-0.50, 1.90] 0.70 [-0.50, 1.90] 	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \hline \textbf{CIPI} \leq \textbf{6} \mbox{ months} \\ \mbox{Duvillard et al. 2005/2007} \\ \mbox{Georgopoulos et al. 1996} \\ \mbox{Guerci et al. 1996} \\ \mbox{Micossi et al. 1996} \\ \mbox{Heterogeneity: } 1^2 = 0.00, \\ \mbox{Test of } \boldsymbol{\theta}_i = \boldsymbol{\theta}_i; \mbox{Q}(3) = 2.6l \\ \mbox{CIPII > 6 months} \\ \mbox{Georgopoulos et al. 1992} \\ \mbox{Raccah et al. 1997} \\ \mbox{Heterogeneity: } 1^2 = 0.00, \\ \mbox{Test of } \boldsymbol{\theta}_i = \boldsymbol{\theta}_i; \mbox{Q}(2) = 0.2t \\ \mbox{Overall} \\ \hline \mbox{Overall} \\ \hline \end{matrix}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 1^2 0.0%, H^2 1.00 6 88, p = 0.44 11 4.9 2.3 11 5.0 8 4.8 0.8 8 4.7 1 ² 0.00%, H^2 = 1.00 9, p = 0.87 19 10.00 10.00 10.00 10.00 10.00	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1997 Heterogeneity: $r^2 = 0.00, r^2$ Test of $\theta_i = \theta_i$: Q(5) = 1.34, g Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, r^2$ Test of $\theta_i = \theta_i$: Q(0) = 0.00, g Overall	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2 N N 3 7 3 8 1 7 3 11 3 11 3 14 3 8 000	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] - 0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] - 0.70 [-0.50, 1.90]	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \begin{array}{ c c } \hline CIPI \leq 6 \mbox{ months} \\ \hline Duvillard et al. 2005/2007 \\ \hline Georgopoulos et al. 1996 \\ \hline Guerci et al. 1996 \\ \hline Micossi et al. 1986 \\ \hline Heterogeneity: \tau^2 = 0.00, \\ \hline Test of \theta_i = \theta_i; \end{cases} \ Q(3) = 2.6l \\ \hline CIPII > 6 \mbox{ months} \\ \hline Georgopoulos et al. 1992 \\ \hline Raccah et al. 1997 \\ \hline Heterogeneity: \ \tau^2 = 0.00, \\ \hline Test of \theta_i = \theta_i; \end{cases} \ Q(2) = 0.2t \\ \hline Overall \\ \hline Heterogeneity: \ \tau^2 = 0.00, \end{array}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 1^2 0.00%, H^2 1.00 88, p = 0.44 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0 8 4.7 1^2 0.00%, H^2 1.00 9 p = 0.87 1 1.00	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] -0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88] -0.03 [-0.64, 0.59]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1997 Heterogeneily: τ ² = 0.00, τ ² = Test of θ _i = θ _i : Q(5) = 1.34, g Micossi et al. 1986 Heterogeneily: τ ² = 0.00, τ ² = Test of θ _i = θ _i : Q(0) = 0.00, g Overall Heterogeneity: τ ² = 0.00, τ ² =	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2 N N 3 7 3 8 1 7 3 11 3 11 3 14 3 8 000	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		 with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] 0.70 [-0.50, 1.90] 0.70 [-0.50, 1.90] 	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \begin{split} \hline \textbf{CIPII} &\leq \textbf{6} \mbox{ months} \\ & \text{Duvillard et al. 2005/2007} \\ & \text{Georgopoulos et al. 1996} \\ & \text{Guerci et al. 1996} \\ & \text{Micossi et al. 1996} \\ & \text{Micossi et al. 1996} \\ & \text{Heterogeneity: } \tau^2 = 0.00, \\ & \text{Test of } \theta_i = \theta_i \colon Q(3) = 2.6i \\ \\ & \textbf{CIPII} > \textbf{6} \mbox{ months} \\ & \text{Georgopoulos et al. 1992} \\ & \text{Raccah et al. 1997} \\ & \text{Heterogeneity: } \tau^2 = 0.00, \\ & \text{Test of } \theta_i = \theta_i \colon Q(2) = 0.2i \\ \\ & \textbf{Overall} \\ & \text{Heterogeneity: } \tau^2 = 0.00, \\ & \text{Test of } \theta_i = \theta_i \colon Q(6) = 2.9i \\ \end{split}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%$, $H^2 = 1.00$ 8 8 4.7 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0 8 4.7 $1^2 = 0.00\%$, $H^2 = 1.00$ 9 p = 0.87 9 9 1 9 1 1 9 1	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] -0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88] -0.03 [-0.64, 0.59]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(5) = 1.34, g Yes Micossi et al. 1986 Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(0) = 0.00, g Overall Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(6) = 2.99, g	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N N 5 7 3 8 1 7 3 11 5 14 3 8 0.00 2 6	Mean SD 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8		 with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] 0.70 [-0.50, 1.90] 0.70 [-0.50, 1.90] 	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \begin{array}{ c c } \hline CIPI \leq 6 \mbox{ months} \\ \hline Duvillard et al. 2005/2007 \\ \hline Georgopoulos et al. 1994 \\ \hline Guerci et al. 1996 \\ \hline Micossi et al. 1996 \\ \hline Heterogeneity: $t^2 = 0.00, \\ \hline Test of $\theta_i = \theta_i$: $Q(3) = 2.61 \\ \hline CIPII > 6 \mbox{ months} \\ \hline Georgopoulos et al. 1992 \\ \hline Raccah et al. 1994 \\ \hline Pacifico et al. 1994 \\ \hline Heterogeneity: $t^2 = 0.00, \\ \hline Test of $\theta_i = \theta_i$: $Q(2) = 0.21 \\ \hline Overall \\ \hline Heterogeneity: $t^2 = 0.00, \\ \hline \end{array}$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%$, $H^2 = 1.00$ 8 8 4.7 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0 8 4.7 $1^2 = 0.00\%$, $H^2 = 1.00$ 9 p = 0.87 9 9 1 9 1 1 9 1	n SD 0.7 0.8 0.6 0.9 1.3 1.3 0.8	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] - 0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88] -0.03 [-0.64, 0.59] -0.06 [-0.35, 0.22]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1997 Heterogeneily: τ ² = 0.00, τ ² = Test of θ _i = θ _i : Q(5) = 1.34, g Micossi et al. 1986 Heterogeneily: τ ² = 0.00, τ ² = Test of θ _i = θ _i : Q(0) = 0.00, g Overall Heterogeneity: τ ² = 0.00, τ ² =	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N N 5 7 3 8 1 7 3 11 5 14 3 8 0.00 2 6	Mean SDC 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8 4.4 0.9		with 95% Cl -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] 0.70 [-0.50, 1.90] 0.70 [-0.50, 1.90] -0.06 [-0.35, 0.22]	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69
$\label{eq:constraints} \begin{array}{l} \hline \textbf{CIPII} \leq \textbf{6} \mbox{ months} \\ \hline \textbf{Duvillard et al. 2005/2007} \\ \hline \textbf{Georgopoulos et al. 1996} \\ \hline \textbf{Micossi et al. 1996} \\ \hline \textbf{Micossi et al. 1996} \\ \hline \textbf{Micossi et al. 1996} \\ \hline \textbf{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \text{: } \textbf{Q}(3) = 2.61 \\ \hline \textbf{CIPII} > \textbf{6} \mbox{ months} \\ \hline \textbf{Georgopoulos et al. 1992} \\ \hline \textbf{Raccah et al. 1997} \\ \hline \textbf{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \text{: } \textbf{Q}(2) = 0.21 \\ \hline \textbf{Overall} \\ \hline \textbf{Heterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \text{: } \textbf{Q}(6) = 2.91 \\ \hline \textbf{Oterstof } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 2.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 0.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Q}(6) = 0.91 \\ \hline \textbf{Meterogeneity: } \textbf{T}^2 = 0.00, \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 = 0.00 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 = 0.00 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 = 0.00 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{T}^2 \\ \hline \textbf{Test of } \theta_i = \theta_i \textbf{Test of } \theta_i Test o$	N Mean SD N Mean 7 7 5.0 0.6 7 5.4 4 8 4.6 0.8 8 4.8 14 5.0 0.6 14 5.0 6 5.1 1.2 6 4.4 $1^2 = 0.00\%$, $H^2 = 1.00$ 8 8 4.7 2 7 4.6 1.1 7 4.9 11 4.9 2.3 11 5.0 8 4.7 $1^2 = 0.00\%$, $H^2 = 1.00$ 8 4.8 0.8 8 4.7 $1^2 = 0.00\%$, $H^2 = 1.00$ 9 $p = 0.81$ 5.0 5.0 5.0 $1^2 = 0.00\%$, $H^2 = 1.00$ 9.9 $P = 0.81$ 5.0 5.0 5.0	n SD 0.7 0.8 0.6 0.9 1.3 1.3	with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] 0.00 [-0.44, 0.44] -0.70 [-0.50, 1.90] -0.07 [-0.40, 0.25] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.10 [-0.68, 0.88] -0.03 [-0.64, 0.59]	(%) 17.58 13.34 41.52 5.69 5.15 3.36 13.34	No Duvillard et al. 2005/2007 Georgopoulos et al. 1994 Georgopoulos et al. 1992 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(5) = 1.34, g Yes Micossi et al. 1986 Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(0) = 0.00, g Overall Heterogeneity: r ² = 0.00, 1 ² Test of θ ₁ = θ ₁ : Q(6) = 2.99, g	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	D N N 5 7 3 8 1 7 3 11 5 14 3 8 0.00 2 6	Mean SDC 5.4 0.7 4.8 0.8 4.9 1.3 5.0 1.3 5.0 0.6 4.7 0.8 4.4 0.9		 with 95% CI -0.40 [-1.08, 0.28] -0.20 [-0.98, 0.58] -0.30 [-1.56, 0.96] -0.10 [-1.66, 1.46] 0.00 [-0.44, 0.44] 0.10 [-0.68, 0.88] -0.11 [-0.40, 0.19] 0.70 [-0.50, 1.90] 0.70 [-0.50, 1.90] 	(%) 17.58 13.34 5.15 3.36 41.52 13.34 5.69

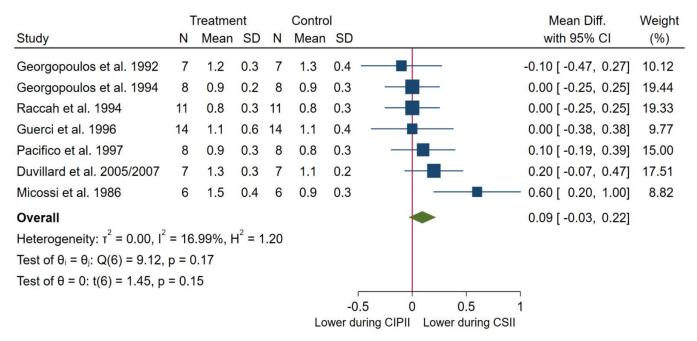
Legends: Treatment, continuous intraperitoneal insulin infusion (CIPII); Control, continuous subcutaneous insulin infusion (CSII). Figure A: Subgroup analysis according to HbA1c levels before starting CIPII treatment (\leq 7 % and > 7 %); Figure B: Subgroup analysis according to study type (Case-Control studies and Crossover studies); Figure C: Subgroup analysis according to length of the CIPII-period (\leq 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 Stu	dies	Mean Diff. with 95% Cl	P-value
HbA1c levels before starting CIPII treatment			
HbA1c ≤ 7 %	·	0.02 [-0.36, 0.39]	0.929
HbA1c > 7 %		-0.17 [-0.62, 0.27]	0.442
Test of group differences: $Q_b(1) = 0.42$, p = 0.52			
Study type			
Crossover study 7	·	-0.06 [-0.35, 0.22]	0.668
Test of group differences: $Q_b(0) = 0.00$, $p = .$			
Duration of CIPII-period			
CIPII ≤ 6 months 4		-0.07 [-0.40, 0.25]	0.658
CIPII > 6 months		-0.03 [-0.64, 0.59]	0.936
Test of group differences: $Q_b(1) = 0.02$, 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		-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: $Q_b(5) = 2.71$, p = 0.74			
Controlled CSII follow-up-period			
No 6	• <u> </u>	-0.11 [-0.40, 0.19]	0.470
Yes		- 0.70 [-0.50, 1.90]	0.253
Test of group differences: $Q_b(1) = 1.64$, p = 0.20			
Overall Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	•	-0.06 [-0.35, 0.22]	0.668
Test of $\theta_i = \theta_i$: Q(6) = 2.99, p = 0.81			
$1001 \text{ or } 0^{-1} = 0^{-1}$. $Q(0) = 2.33, p = 0.01$		7	
	-2 -1 0 1 Lower during CIPII Lower during CS	2	
	contracting on in cover during of	20	

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).



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).

Study		eatment Mean	t SD N	Contro Mean				Mean Diff. with 95% CI	Weight (%)	Study		reatn Mea	nent n SD		Contro Mean				Mean Diff. with 95% Cl	Weigh (%)
HbA1c ≤ 7 %									()	Crossover study		mod			moun	00				(70)
Raccah et al. 1994	11	0.8 0	0.3 11	0.8	0.3			0.00 [-0.25, 0.25	19.33	Georgopoulos et al. 1992	7	12	0.3	7	1.3	0.4 -			-0.10 [-0.47, 0.27]	10.13
Guerci et al. 1996	14	1.1 (0.6 14	1.1	0.4	T		0.00 [-0.38, 0.38		Georgopoulos et al. 1994	8	0.9			0.9	0.3			0.00 [-0.25, 0.25]	
Pacifico et al. 1997	8	0.9 (0.3 8	0.8	0.3		_	0.10 [-0.19, 0.39		Raccah et al. 1994	11	0.9			0.9	0.3			0.00 [-0.25, 0.25]	
Heterogeneity: $\tau^2 = 0.00$, I^2						-		0.03 [-0.14, 0.20		Guerci et al. 1994	14					0.3				
Test of $\theta_i = \theta_i$: Q(2) = 0.30,						-							0.6		1.1			-	0.00 [-0.38, 0.38]	
										Pacifico et al. 1997	8	0.9		8	0.8	0.3			0.10 [-0.19, 0.39]	
HbA1c > 7 %										Duvillard et al. 2005/2007	7		0.3						0.20 [-0.07, 0.47]	
Georgopoulos et al. 1992	7	1.2 (0.3 7	1.3	0.4 -			-0.10 [-0.47, 0.27	10.12	Micossi et al. 1986	6		0.4		0.9	0.3	_		0.60 [0.20, 1.00]	
Georgopoulos et al. 1994	8	0.9 0	0.2 8	0.9	0.3			0.00 [-0.25, 0.25	19.44	Heterogeneity: r ² = 0.00, I ²			, H [*] = 1	.20			-		0.09 [-0.03, 0.22]	
Duvillard et al. 2005/2007	7	1.3 (0.3 7	1.1	0.2		<u> </u>	0.20 [-0.07, 0.47	17.51	Test of $\theta_i = \theta_j$: Q(6) = 9.12,	p = 0).17								
Micossi et al. 1986	6	1.5 (0.4 6	0.9	0.3	-	_	0.60 [0.20, 1.00	8.82											
Heterogeneity: $\tau^2 = 0.05$, I^2	= 65.9	1%, H ²	= 2.93					0.16 [-0.11, 0.43		Overall			2				-		0.09 [-0.03, 0.22]	
Test of $\theta_i = \theta_i$: Q(3) = 8.08,	p = 0.0)4								Heterogeneity: T ² = 0.00, I ²			, H ² = 1	.20						
, , , , ,										Test of $\theta_i = \theta_j$: Q(6) = 9.12,	p = 0).17								
Overall						•		0.09 [-0.03, 0.22]		Test of group differences: C	J₀(0)	= -0.0	0, p =							
Heterogeneity: $\tau^2 = 0.00$, I^2	= 16.9	9%, H ²	= 1.20							0	. ,					-0.5	5 0	0.5 1	_	
Test of $\theta_i = \theta_i$: Q(6) = 9.12,	p = 0.1	7						Λ							Lo		ing CIPII Lowe			
Test of group differences: C	D.(1) =	0.59 n	= 0.44					A									ing on in Lono	a annig e en	D	
reat of group uncrenoca. G	Sep(1) =	0.00, p	- 0.44		~	. 0	0.5 1	<i>1</i> \												
					-0.5															
				Lo			ver during CSII													
	_				wer dur															
Dis John		eatment		Contro	wer duri			Mean Diff.	Weight	Chudu		reatn			Contro				Mean Diff.	Weigh
Study			t SD N	Contro	wer duri			Mean Diff. with 95% CI	Weight (%)	Study			nent n SD						Mean Diff. with 95% CI	Weigh (%)
CIPII ≤ 6 months	N	Mean	SD N	Contro Mean	wer duri I SD			with 95% CI	(%)	No	Ν	Mea	n SD	N	Mean	SD	_		with 95% CI	(%)
CIPII ≤ 6 months Georgopoulos et al. 1994	N	Mean (SD N 0.2 8	Contro Mean 0.9	wer duri I SD 0.3			with 95% Cl 0.00 [-0.25, 0.25	(%)	No Georgopoulos et al. 1992	N 7	Mea	n SD 0.3	N 7	Mean	SD 0.4 -			with 95% CI -0.10 [-0.47, 0.27]	(%)
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996	N 8 14	Mean (0.9 (1.1 (SD N 0.2 8 0.6 14	Contro Mean 0.9 1.1	wer duri SD 0.3 0.4			with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38	(%) 19.44 9.77	No Georgopoulos et al. 1992 Georgopoulos et al. 1994	N 7 8	Mea 1.2 0.9	n SD 0.3 0.2	N 7 8	Mean 1.3 0.9	SD 0.4 - 0.3	-		with 95% CI -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25]	(%) 10.12 19.44
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007	N 8 14 7	Mean 3 0.9 (1.1 (1.3 (SD N 0.2 8 0.6 14 0.3 7	Contro Mean 0.9 1.1 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.20 [-0.07, 0.47]	(%) 19.44 9.77 17.51	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994	N 7	Mea 1.2 0.9 0.8	n SD 0.3 0.2 0.3	N 7 8 11	Mean 1.3 0.9 0.8	SD 0.4 - 0.3 0.3	-		with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25]	(%) 10.12 19.44 19.33
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986	N 8 14 7 6	Mean 3 0.9 (1.1 (1.3 (1.5 (SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25, 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994	N 7 8	Mea 1.2 0.9 0.8 1.1	n SD 0.3 0.2 0.3 0.6	N 7 8 11 14	Mean 1.3 0.9 0.8 1.1	SD 0.4 - 0.3			with 95% CI -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25]	(%) 10.12 19.44 19.33
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007	N 8 14 7 6	Mean 3 0.9 (1.1 (1.3 (1.5 (SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.20 [-0.07, 0.47]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994	N 7 8 11	Mea 1.2 0.9 0.8	n SD 0.3 0.2 0.3 0.6	N 7 8 11 14	Mean 1.3 0.9 0.8 1.1	SD 0.4 - 0.3 0.3		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25]	(%) 10.12 19.44 19.33 9.77
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986	N 8 14 7 6 = 58.3	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²)	SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25, 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996	N 7 8 11 14 8	Mea 1.2 0.9 0.8 1.1 0.9	n SD 0.3 0.2 0.3 0.6	N 7 8 11 14 8	Mean 1.3 0.9 0.8 1.1 0.8	SD 0.4 - 0.3 0.3 0.4 0.3		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38]	(%) 10.12 19.44 19.33 9.77 15.00
CIPI \leq 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.04$, I ²	N 8 14 7 6 = 58.3	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²)	SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25, 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997	N 7 8 11 14 8 7	Mea 1.2 0.9 0.8 1.1 0.9 1.3	n SD 0.3 0.2 0.3 0.6 0.3 0.3	N 7 8 11 14 8 7	Mean 1.3 0.9 0.8 1.1 0.8	SD 0.4 - 0.3 0.3 0.4 0.3		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
CIPI \leq 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.04$, I ²	N 8 14 7 6 = 58.3	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²)	SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1 1.1	wer duri SD 0.3 0.4 0.2			with 95% Cl 0.00 [-0.25, 0.25, 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007	N 7 8 11 14 8 7 = 0.0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H	n SD 0.3 0.2 0.3 0.6 0.3 0.3	N 7 8 11 14 8 7	Mean 1.3 0.9 0.8 1.1 0.8	SD 0.4 - 0.3 0.3 0.4 0.3		- -	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
CIPII S 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.04$, l^2 Test of $\theta_i = \theta_j$: Q(3) = 6.98,	N 8 14 7 6 = 58.3 p = 0.0	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²)	SD N 0.2 8 0.6 14 0.3 7 0.4 6	Contro Mean 0.9 1.1 1.1 0.9	wer duri SD 0.3 0.4 0.2		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25, 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00]	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, l^2$	N 7 8 11 14 8 7 = 0.0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H	n SD 0.3 0.2 0.3 0.6 0.3 0.3	N 7 8 11 14 8 7	Mean 1.3 0.9 0.8 1.1 0.8	SD 0.4 - 0.3 0.3 0.4 0.3		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
CIPII ≤ 6 months Georgopoulos et al. 1994 Guerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986 Heterogeneity: $\tau^2 = 0.04$, l^2 Test of $\theta_i = \theta_i$: Q(3) = 6.98, CIPII > 6 months	N 8 14 7 6 = 58.3 p = 0.0	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²))7	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40	Contro Mean 0.9 1.1 1.1 0.9	wer duri SD 0.3 0.4 0.2 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47 0.60 [0.20, 1.00 0.18 [-0.07, 0.42	(%) 19.44 9.77 17.51 8.82	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, l^2$	N 7 8 11 14 8 7 = 0.0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H	n SD 0.3 0.2 0.3 0.6 0.3 0.3	N 7 8 11 14 8 7	Mean 1.3 0.9 0.8 1.1 0.8	SD 0.4 - 0.3 0.3 0.4 0.3		- -	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
$\label{eq:constraints} \begin{aligned} \text{CIPII} &\leq 6 \text{ months} \\ \text{Seorgopoulos et al. 1994} \\ \text{Suerci et al. 1996} \\ \text{Duvillard et al. 2005/2007} \\ \text{Micossi et al. 1986} \\ \text{Heterogeneity: } \tau^2 = 0.04, \ l^2 \\ \text{Test of } \theta_i = \theta_i; \ Q(3) = 6.98, \\ \text{CIPII} > 6 \text{ months} \\ \text{Georgopoulos et al. 1992} \end{aligned}$	N 1 8 14 7 6 = 58.3 p = 0.0 7 11	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²) 07 1.2 (0.8 (SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47 0.60 [0.20, 1.00 0.18 [-0.07, 0.42 -0.10 [-0.47, 0.27	(%) 19.44 9.77 17.51 8.82 10.12 19.33	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, l^2$ Test of θ, = θ _i ; Q(5) = 2.32,	N 7 8 11 14 8 7 = 0.0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0.9 1.3 0.9 1.3 0.0%, H	n SD 0.3 0.2 0.3 0.6 0.3 0.3	N 7 8 11 14 8 7 10	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2			with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
$\begin{aligned} \textbf{CIPII} &\leq \textbf{6} \text{ months} \\ \text{Seorgopoulos et al. 1994} \\ \text{Suerci et al. 1996} \\ \text{Duvillard et al. 2005/2007} \\ \text{Micossi et al. 1986} \\ \text{Heterogeneity: } \tau^2 &= 0.04, 1^2 \\ \text{Test of } \theta_i &= \theta_i; \ Q(3) &= 6.98, \\ \textbf{CIPII > 6 months} \\ \text{Seorgopoulos et al. 1992} \\ \text{Raccah et al. 1994} \end{aligned}$	N 1 8 14 7 6 58.3 p = 0.0 7 11 8	Mean 9 0.9 (1.1 (1.3 (1.5 (0%, H ²) 07 1.2 (0.8 (0.9 (SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 7 0.3 11 0.3 8	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47 0.60 [0.20, 1.00 0.18 [-0.07, 0.42 -0.10 [-0.47, 0.27, 0.00 [-0.25, 0.25	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, r^2$ Test of $\theta_i = \theta_i; Q(5) = 2.32, r^2$	N 7 8 11 14 8 7 = 0.0 p = 0 6	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80	$\begin{array}{c c}n & SD\\ \hline 0.3\\ 0.2\\ 0.3\\ 0.6\\ 0.3\\ 0.3\\ 1^2 = 1.0\\ 0.4\end{array}$	N 7 8 11 14 8 7 10	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16]	(%) 10.12 19.44 19.33 9.77 15.00 17.51 8.82
CIPII S 6 months Georgopoulos et al. 1994 Suerci et al. 1996 Duvillard et al. 2005/2007 Micossi et al. 1986 Heterogeneity: $r^2 = 0.04$, l^2 Test of $\theta_i = \theta_i$: Q(3) = 6.98, CIPII > 6 months Georgopoulos et al. 1992 Raccah et al. 1994 Pacifico et al. 1997	N 1 8 14 7 6 = 58.3 p = 0.0 7 11 8 = 0.00	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²))7 1.2 (0.8 (0.9 (%, H ² =	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 7 0.3 11 0.3 8	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47 0.60 [0.20, 1.00 0.18 [-0.07, 0.42 -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, l^2$ Test of $\theta_i = \theta_i$; Q(5) = 2.32, Yes Micossi et al. 1986	N 7 8 11 14 8 7 = 0.0 p = 0 6 = .%,	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80	$\begin{array}{c c}n & SD\\ \hline 0.3\\ 0.2\\ 0.3\\ 0.6\\ 0.3\\ 0.3\\ 1^2 = 1.0\\ 0.4\end{array}$	N 7 8 11 14 8 7 10	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16]	(%) 10.12 19.44 19.33 9.77 15.00 17.51 8.82
$\label{eq:constraints} \begin{split} & \text{CIPII $ \le $ 6$ months} \\ & \text{Georgopoulos et al. 1994} \\ & \text{Guerci et al. 1996} \\ & \text{Duvillard et al. 2005/2007} \\ & \text{Micossi et al. 1986} \\ & \text{Heterogeneity; $ $ r^2 $ = 0.04, $ 1^2$ } \\ & Test of $ \theta_i = \theta_i$ $ Q(3) = 6.98, $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $ $$	N 1 8 14 7 6 = 58.3 p = 0.0 7 11 8 = 0.00	Mean 3 0.9 (1.1 (1.3 (1.5 (0%, H ²))7 1.2 (0.8 (0.9 (%, H ² =	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 7 0.3 11 0.3 8	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38, 0.20 [-0.07, 0.47 0.60 [0.20, 1.00 0.18 [-0.07, 0.42 -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, l^2$ Test of $\theta_i = \theta_i$: Q(5) = 2.32, Yes Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, l^2$	N 7 8 11 14 8 7 = 0.0 p = 0 6 = .%,	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80	$\begin{array}{c c}n & SD\\ \hline 0.3\\ 0.2\\ 0.3\\ 0.6\\ 0.3\\ 0.3\\ 1^2 = 1.0\\ 0.4\end{array}$	N 7 8 11 14 8 7 10	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.38, 0.38] 0.10 [-0.19, 0.39] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16]	(%) 10.12 19.44 19.33 9.77 15.00 17.51 8.82
$\begin{aligned} \textbf{CIPII} \leq \textbf{6} \text{ months} \\ \text{Georgopoulos et al. 1994} \\ \text{Guerci et al. 1996} \\ \text{Duvillard et al. 2005/2007} \\ \text{Micossi et al. 1986} \\ \text{Heterogeneity: } \tau^2 = 0.04, \ l^2 \\ \text{Test of } \theta_i = \theta_i; \ Q(3) = 6.98, \\ \text{CIPII > 6 months} \\ \text{Georgopoulos et al. 1992} \\ \text{Raccah et al. 1994} \\ \text{Pacifico et al. 1997} \\ \text{Heterogeneity: } \tau^2 = 0.00, \ l^2 \\ \text{Test of } \theta_i = \theta_i; \ Q(2) = 0.70, \\ \text{Overall} \end{aligned}$	N 14 7 6 = 58.3 p = 0.0 7 11 8 = 0.00 p = 0.7	Mean : 0.9 (0 1.1 (0 1.3 (0 1.5 (0) 0%, H ² 1.2 (0 0.8 (0 0.9 (0 %, H ² =	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 7 0.3 11 0.3 8 ± 1.00	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00 0.18 [-0.07, 0.42] -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39 0.01 [-0.16, 0.18]	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, r^2$ Test of θ _i = θ _i ; Q(5) = 2.32, Yes Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, r^2$ Test of θ _i = θ _i ; Q(0) = 0.00, r	N 7 8 11 14 8 7 = 0.0 p = 0 0 6 = .%, p = .	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80 1.5 H ² =	$\begin{array}{c} n & SD \\ 0.3 \\ 0.2 \\ 0.3 \\ 0.6 \\ 0.3 \\ 0.3 \\ 0.3 \\ 1^2 = 1.0 \\ 0.4 \\ \end{array}$	N 7 8 11 14 8 7 10 6	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.10 [-0.19, 0.38] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16] 0.60 [0.20, 1.00] 0.60 [0.20, 1.00]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
$\begin{aligned} \textbf{CIPII } & \textbf{6 months} \\ \textbf{Georgopoulos et al. 1994} \\ \textbf{Guerci et al. 1996} \\ \textbf{Duvillard et al. 2005/2007} \\ \textbf{Micossi et al. 1986} \\ \textbf{Heterogeneity: } \textbf{τ^2} = 0.04, \textbf{1^2} \\ \textbf{Test of } \textbf{θ}_i = \textbf{θ}_i \textbf{Q}(3) = 6.98, \\ \textbf{CIPII > 6 months} \\ \textbf{Georgopoulos et al. 1992} \\ \textbf{Raccah et al. 1994} \\ \textbf{Pacifico et al. 1997} \\ \textbf{Heterogeneity: } \textbf{τ^2} = 0.00, \textbf{1^2} \\ \textbf{Test of } \textbf{θ}_i = \textbf{θ}_i \textbf{Q}(2) = 0.70, \\ \textbf{Test of } \textbf{θ}_i = \textbf{θ}_i \textbf{Q}(2) = 0.70, \\ \end{aligned}$		Mean : 0.9 (0 1.1 (0 1.3 (0 1.5 (0) 0%, H ² 1.2 (0 0.8 (0 0.9 (0 %, H ² 9%, H ²	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 7 0.3 11 0.3 8 ± 1.00	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00 0.18 [-0.07, 0.42] -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39 0.01 [-0.16, 0.18]	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, r^2$ Yes Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, r^2$ Test of $\theta_i = \theta_i$; $Q(0) = 0.00, r^2$ Overall Heterogeneity: $r^2 = 0.00, r^2$	N 7 8 11 14 8 7 = 0.0 p = 0 6 = .%, p = . = 16.	Mea 1.2 0.9 0.8 1.1 0.9 1.3 00%, H .80 1.5 , H ² =	$\begin{array}{c} n & SD \\ 0.3 \\ 0.2 \\ 0.3 \\ 0.6 \\ 0.3 \\ 0.3 \\ 0.3 \\ 1^2 = 1.0 \\ 0.4 \\ \end{array}$	N 7 8 11 14 8 7 10 6	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.10 [-0.19, 0.38] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16] 0.60 [0.20, 1.00] 0.60 [0.20, 1.00]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
$\begin{aligned} \textbf{CIPII} &\leq \textbf{6} \text{ months} \\ & \text{Georgopoulos et al. 1994} \\ & \text{Guerci et al. 1996} \\ & \text{Duvillard et al. 2005/2007} \\ & \text{Micossi et al. 1986} \\ & \text{Heterogeneity: } \tau^2 = 0.04, l^2 \\ & \text{Test of } \theta_i = \theta_i; Q(3) = 6.98, \\ & \text{CIPII} > \textbf{6} \text{ months} \\ & \text{Georgopoulos et al. 1992} \\ & \text{Raccah et al. 1994} \\ & \text{Pacifico et al. 1997} \\ & \text{Heterogeneity: } \tau^2 = 0.00, l^2 \\ & \text{Test of } \theta_i = \theta_i; Q(2) = 0.70, \\ & \text{Otrall} \\ & \text{Heterogeneity: } \tau^2 = 0.00, l^2 \\ & \text{Test of } \theta_i = \theta_i; Q(6) = 9.12, \\ & \text{Test of } \theta_i = \theta_i; Q(6) = 9.12, \end{aligned}$	N I 8 14 7 6 = 58.3 p = 0.0 7 11 8 = 0.00 p = 0.7 = 16.9 p = 0.1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 11 0.3 8 : 1.00 = 1.20	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3		ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00 0.18 [-0.07, 0.42] -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39 0.01 [-0.16, 0.18]	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, r^2$ Test of θ _i = θ _i ; Q(5) = 2.32, Yes Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, r^2$ Test of θ _i = θ _i ; Q(0) = 0.00, r ² Test of θ _i = θ _i ; Q(0) = 0.00, r ² Test of θ _i = θ _i ; Q(6) = 9.12,	N 7 8 11 14 8 7 = 0.0 p = 0 6 = .%, p = . = 16. p = 0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80 1.5 , H ² = 999%, .17	$\begin{array}{c} n & SD \\ \hline 0.3 \\ 0.2 \\ 0.3 \\ 0.6 \\ 0.3 \\ 0.3 \\ 0.3 \\ 0.3 \\ 1^2 = 1.0 \\ 0.4 \\ \end{array}$	N 7 8 11 14 8 7 00 6	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2		-	with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.10 [-0.19, 0.38] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16] 0.60 [0.20, 1.00] 0.60 [0.20, 1.00]	(%) 10.12 19.44 19.33 9.77 15.00 17.51
$\begin{aligned} \textbf{CIPII} &\leq \textbf{6} \text{ months} \\ \text{Seorgopoulos et al. 1994} \\ \text{Suerci et al. 1996} \\ \text{Duvillard et al. 2005/2007} \\ \text{Micossi et al. 1986} \\ \text{Heterogeneity: } \tau^2 &= 0.04, \ l^2 \\ \text{Test of } \theta_i &= \theta_i; \ Q(3) &= 6.98, \\ \text{CIPII } &> \textbf{6} \text{ months} \\ \text{Seorgopoulos et al. 1994} \\ \text{Pacifico et al. 1994} \\ \text{Pactico et al. 1997} \\ \text{Heterogeneity: } \tau^2 &= 0.00, \ l^2 \\ \text{Test of } \theta_i &= \theta_i; \ Q(2) &= 0.70, \\ \text{Overall} \\ \text{Heterogeneity: } \tau^2 &= 0.00, \ l^2 \end{aligned}$	N I 8 14 7 6 = 58.3 p = 0.0 7 11 8 = 0.00 p = 0.7 = 16.9 p = 0.1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	SD N 0.2 8 0.6 14 0.3 7 0.4 6 = 2.40 0.3 11 0.3 8 : 1.00 = 1.20	Contro Mean 0.9 1.1 1.1 0.9 1.3 0.8	0.3 0.4 0.2 0.3 0.4 - 0.3	ng CIPII Lov	ver during CSII	with 95% Cl 0.00 [-0.25, 0.25 0.00 [-0.38, 0.38 0.20 [-0.07, 0.47, 0.60 [0.20, 1.00 0.18 [-0.07, 0.42] -0.10 [-0.47, 0.27 0.00 [-0.25, 0.25 0.10 [-0.19, 0.39 0.01 [-0.16, 0.18]	(%) 19.44 9.77 17.51 8.82 10.12 19.33 15.00	No Georgopoulos et al. 1992 Georgopoulos et al. 1994 Raccah et al. 1994 Guerci et al. 1994 Guerci et al. 1996 Pacifico et al. 1997 Duvillard et al. 2005/2007 Heterogeneity: $r^2 = 0.00, r^2$ Yes Micossi et al. 1986 Heterogeneity: $r^2 = 0.00, r^2$ Test of $\theta_i = \theta_i$; $Q(0) = 0.00, r^2$ Overall Heterogeneity: $r^2 = 0.00, r^2$	N 7 8 11 14 8 7 = 0.0 p = 0 6 = .%, p = . = 16. p = 0	Mea 1.2 0.9 0.8 1.1 0.9 1.3 0%, H .80 1.5 , H ² = 999%, .17	$\begin{array}{c} n & SD \\ \hline 0.3 \\ 0.2 \\ 0.3 \\ 0.6 \\ 0.3 \\ 0.3 \\ 0.3 \\ 0.3 \\ 1^2 = 1.0 \\ 0.4 \\ \end{array}$	N 7 8 11 14 8 7 00 6	Mean 1.3 0.9 0.8 1.1 0.8 1.1	SD 0.4 - 0.3 0.3 0.4 0.3 0.2			with 95% Cl -0.10 [-0.47, 0.27] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.00 [-0.25, 0.25] 0.10 [-0.19, 0.38] 0.20 [-0.07, 0.47] 0.04 [-0.07, 0.16] 0.60 [0.20, 1.00] 0.60 [0.20, 1.00]	(%) 10.12 19.44 19.33 9.77 15.00 17.51 8.82

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 (\leq 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 (\leq 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.

Subgroups	Studies		Mean Diff. with 95% Cl	P-value
HbA1c levels before starting CIPII treatmen	t			
HbA1c ≤ 7 %	3	e	0.03 [-0.14, 0.20]	0.699
HbA1c > 7 %	4		0.16 [-0.11, 0.43]	0.248
Test of group differences: $Q_b(1) = 0.59$, p =	0.44			
Study type				
Crossover study	7		0.09 [-0.03, 0.22]	0.147
Test of group differences: $Q_b(0) = -0.00$, 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: $Q_b(1) = 1.19$, 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: $Q_b(5) = 8.43$, 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: $Q_b(1) = 6.80$, p =	0.01			
Overall Heterogeneity: $\tau^2 = 0.00$, $I^2 = 16.99\%$, $H^2 =$ Test of $\theta_i = \theta_j$: Q(6) = 9.12, p = 0.17	1.20	•	0.09 [-0.03, 0.22]	0.147
	-0.5	5 0 0.5	1	
	Lower du	Iring CIPII Lower during CSII		

Figure S7c. Summarised subgroup meta-analysis of triglycerides (mmol/L) in patients during CIPII treatment compared to that during control treatment (CSII).

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: beta $1 = 0$; no small-study effects
beta1 = -1.10
SE of beta $1 = 1.017$
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

References

- 1. Hofmann, H.M.H., P.A.M. Weiss, and J.G. Haas, *Continuous insulin delivery systems for the pregnant diabetic patient*. Acta Diabetologica Latina, 1986. **23**(3): p. 201-214.
- 2. Rautiainen, P., H. Tirkkonen, and T. Laatikainen, *Glycemic Control in Adult Type 1 Diabetes Patients with Insulin Glargine, Insulin Detemir, or Continuous Subcutaneous Insulin Infusion in Daily Practice.* Diabetes Technol Ther, 2018. **20**(5): p. 363-369.
- 3. Ruiz-de-Adana, M.S., et al., *Comparison between a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) using continuous glucose monitoring in metabolically optimized type 1 diabetes patients: A randomized open-labelled parallel study.* Med Clin (Barc), 2016. **146**(6): p. 239-46.
- 4. Rys, P.M., et al., Continuous subcutaneous insulin infusion vs multiple daily injections in pregnant women with type 1 diabetes mellitus: a systematic review and meta-analysis of randomised controlled trials and observational studies. Eur J Endocrinol, 2018. **178**(5): p. 545-563.
- 5. Liebl, A., et al., A reduction in severe hypoglycaemia in type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. Diabetes, Obesity and Metabolism, 2009. **11**(11): p. 1001-1008.
- 6. Pitt, H.A., C.D. Saudek, and H.A. Zacur, *Long-term intraperitoneal insulin delivery*. Ann Surg, 1992. **216**(4): p. 483-91; discussion 491-2.
- 7. Schade, D.S., et al., *The peritoneal absorption of insulin in diabetic man: a potential site for a mechanical insulin delivery system.* Metabolism, 1979. **28**(3): p. 195-7.
- 8. Advances in peritoneal dialysis : proceedings of the Second International Symposium on Peritoneal Dialysis : Berlin (-West), June 16-19, 1981 / editors, G.M. Gahl, M. Kessel, K.D. Nolph. International congress series ; no. 567, ed. G.G. Gahl, 1938-, M.M. Kessel, 1926-, and K.D. Nolph. 1981, Amsterdam ; Princeton, NJ : Excerpta Medica ; New York, N.Y. : Sole distributors for the USA and Canada, Elsevier North-Holland, 1981.
- 9. Schade, D.S., et al., *Prolonged peritoneal insulin infusion in a diabetic man.* Diabetes Care, 1980. **3**(2): p. 314-317.
- 10. Schade, D.S., et al., *Normalization of plasma insulin profiles with intraperitoneal insulin infusion in diabetic man.* Diabetologia, 1980. **19**(1): p. 35-9.
- 11. Schade, D.S., et al., *Intraperitoneal delivery of insulin by a portable microinfusion pump*. Metabolism, 1980. **29**(8): p. 699-702.
- 12. Schade, D.S., R.P. Eaton, and N.M. Friedman, *Five-day programmed intraperitoneal insulin delivery in insulindependent diabetic man.* Journal of Clinical Endocrinology and Metabolism, 1981. **52**(6): p. 1165-1170.
- 13. Irsigler, K., et al., *Long-term continuous intraperitoneal insulin infusion with an implanted remote-controlled insulin infusion device*. Diabetes, 1981. **30**(12): p. 1072-5.
- 14. Selam, J.L., et al., *Total implantation of a remotely controlled insulin minipump in a human insulin-dependent diabetic*. Artif Organs, 1982. **6**(3): p. 315-9.
- 15. Selam, J.L., A. Slingeneyer, and B. Hedon, *Long-term ambulatory peritoneal insulin infusion of brittle diabetes with portable pumps: Comparison with intravenous and subcutaneous routes.* Diabetes Care, 1983. **6**(2): p. 105-111.
- 16. Fonseca, V.A., R.K. Menon, and P.M.S. O'Brien, *Diabetic pregnancy managed with intraperitoneal insulin.* Diabetic Medicine, 1987. **4**(1): p. 74-76.
- 17. Saudek, C.D., et al., A preliminary trial of the programmable implantable medication system for insulin delivery. N Engl J Med, 1989. **321**(9): p. 574-9.
- 18. Walter, H., et al., *Implantation of programmable infusion pumps for insulin delivery in type I diabetic patients.* Klinische Wochenschrift, 1989. **67**(11): p. 583-587.
- 19. Mirouze, J., et al., *Experience with external insulin pumps using the intraperitoneal route in 31 type I diabetic patients continuously followed for at least four years.* Diabetes, Nutrition and Metabolism Clinical and Experimental, 1990. **3**(3): p. 185-189.
- 20. Selam, J.L., et al., *Clinical trial of programmable implantable insulin pump for type I diabetes*. Diabetes Care, 1992. **15**(7): p. 877-885.
- 21. Hopkins, K.D., et al., Intraperitoneal insulin affects insulin-like growth factor binding protein-1 in a wellcontrolled type I diabetic patient. Diabetes Care, 1993. **16**(10): p. 1404-5.
- 22. Bauersachs, R., et al., *Hormone and substrate levels after long-term continuous intraperitoneal insulin infusion in insulin-dependent diabetes mellitus.* Diab.Nurt.Metab, 1993. **6**: p. 25-32.

- 23. Olsen, C.L., et al., *Long-term safety and efficacy of programmable implantable insulin delivery systems.* International Journal of Artificial Organs, 1993. **16**(12): p. 847-854.
- 24. Haardt, M.J., et al., *A cost-benefit comparison of intensive diabetes management with implantable pumps versus multiple subcutaneous injections in patients with type I diabetes.* Diabetes Care, 1994. **17**(8): p. 847-857.
- 25. Ruotolo, G., et al., *Normalization of lipoprotein composition by intraperitoneal insulin in IDDM: Role of increased hepatic lipase activity.* Diabetes Care, 1994. **17**(1): p. 6-12.
- 26. Selam, J.L., et al., *Alterations in reverse cholesterol transport associated with programmable implantable intraperitoneal insulin delivery.* Metabolism: Clinical and Experimental, 1994. **43**(6): p. 665-669.
- Bagdade, J.D., et al., Intraperitoneal insulin therapy corrects abnormalities in cholesteryl ester transfer and lipoprotein lipase activities in insulin-dependent diabetes mellitus. Arteriosclerosis and Thrombosis, 1994.
 14(12): p. 1933-1939.
- 28. Pinget, M., et al., *Multicentre trial of a programmable implantable insulin pump in type I diabetes.* International Journal of Artificial Organs, 1995. **18**(6): p. 322-325.
- 29. Hanaire-Broutin, H., et al., *Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM. A multicenter study. The EVADIAC Study Group. Evaluation dans le Diabete du Traitement par Implants Actifs.* Diabetes Care, 1995. **18**(3): p. 388-92.
- 30. Jeandidier, N., et al., *Intraperitoneal insulin pump therapy during pregnancy: Two cases.* Practical Diabetes International, 1995. **12**(6): p. 280-280.
- 31. Jeandidier, N., et al., *Five cases of hyperthyroidism in type I diabetic patients treated with intraperitoneal insulin infusion.* Diabetes Care, 1995. **18**(6): p. 888-9.
- 32. Jeandidier, N., et al., *Immunogenicity of intraperitoneal insulin infusion using programmable implantable devices*. Diabetologia, 1995. **38**(5): p. 577-84.
- Bagdade, J.D. and F.L. Dunn, Improved lipoprotein surface and core lipid composition following intraperitoneal insulin delivery in insulin-dependent diabetes mellitus. Diabetes and Metabolism, 1996. 22(6): p. 420-426.
- 34. Logtenberg, S.J., et al., *Improved glycemic control with intraperitoneal versus subcutaneous insulin in type 1 diabetes: A randomized controlled trial.* Diabetes Care, 2009. **32**(8): p. 1372-1377.
- 35. Logtenberg, S.J., et al., *Health-related quality of life, treatment satisfaction, and costs associated with intraperitoneal versus subcutaneous insulin administration in type 1 diabetes: A randomized controlled trial.* Diabetes Care, 2010. **33**(6): p. 1169-1172.
- 36. Logtenberg, S.J.J., et al., *30 month post trial follow up of HbA1c with continuous intraperitoneal insulin infusion in type 1 diabetes.* Diabetologia, 2010. **53**: p. S8.
- 37. Schaepelynck, P., et al., A recent survey confirms the efficacy and the safety of implanted insulin pumps during long-term use in poorly controlled type 1 diabetes patients. Diabetes Technol Ther, 2011. 13(6): p. 657-60.
- 38. Van Dijk, P.R., et al., *Effect of intraperitoneal insulin administration on IGF-1 concentrations in type 1 diabetes.* Diabetologia, 2012. **55**: p. S382.
- 39. van Dijk, P.R., et al., *Effect of i.p. insulin administration on IGF1 and IGFBP1 in type 1 diabetes.* Endocrine Connections, 2014. **3**(1): p. 17-23.
- 40. Van Dijk, P., et al., *Continuous intraperitoneal insulin infusion in type 1 diabetes: A 6 year post trial follow-up.* Diabetes Technology and Therapeutics, 2014. **16**: p. A20-A21.
- 41. Bilo, H.J.G., et al., *Continuous intraperitoneal insulin infusion versus subcutaneous insulin for type 1 diabetes: A prospective, case-control trial proving noninferiority.* Diabetologia, 2014. **1**): p. S89.
- 42. van Dijk, P.R., et al., *Report of a 7 year case-control study of continuous intraperitoneal insulin infusion and subcutaneous insulin therapy among patients with poorly controlled type 1 diabetes mellitus: favourable effects on hypoglycaemic episodes.* Diabetes Res Clin Pract, 2014. **106**(2): p. 256-63.
- 43. van Dijk, P.R., et al., *After 6 years of intraperitoneal insulin administration IGF-I concentrations in T1DM patients are at low-normal level.* Growth Hormone and IGF Research, 2015. **25**(6): p. 316-319.
- 44. van Dijk, P.R., et al., *Intraperitoneal versus subcutaneous insulin therapy in the treatment of type I diabetes mellitus*. Netherlands Journal of Medicine, 2015. **73**(9): p. 399-409.
- 45. Van Dijk, P.R., et al., *Continuous intraperitoneal insulin infusion versus subcutaneous insulin therapy in the treatment of type 1 diabetes: Effects on glycemic variability.* Diabetes Technology and Therapeutics, 2015. **17**(6): p. 379-384.

- 46. van Dijk, P.R., et al., *Different routes of insulin administration do not influence serum free thiols in type 1 diabetes mellitus*. Endocrinol Diabetes Metab, 2019. **2**(4): p. e00088.
- 47. Boering, M., et al., *Effects of intraperitoneal insulin versus subcutaneous insulin administration on sex hormonebinding globulin concentrations in patients with type 1 diabetes mellitus*. Endocrine Connections, 2016. **5**(3): p. 136-142.
- 48. Mirouze, J., et al., *One year continuous run with a totally implantable insulin infusion pump in a human diabetic.* Transactions American Society for Artificial Internal Organs, 1983. **29**: p. 709-713.
- 49. Rouaud, R., et al., *Long term ambulatory peritoneal insulin infusion operating life of the chronic catheters and the portable pumps* Pacing and Clinical Electrophysiology, 1988. **11**(6): p. 790-976.
- 50. van Dijk, P.R., et al., *Complications of continuous intraperitoneal insulin infusion with an implantable pump.* World journal of diabetes, 2012. **3**(8): p. 142-148.
- 51. Gin, H., et al., *Clinical evaluation of a newly designed compliant side port catheter for an insulin implantable pump: the EVADIAC experience. Evaluation dans le Diabete du Traitement par Implants Actifs.* Diabetes Care, 2001. **24**(1): p. 175.
- 52. Belicar, P. and V. Lassmann-Vague, *Local adverse events associated with long-term treatment by implantable insulin pumps. The French EVADIAC Study Group experience. Evaluation dans le Diabete du Traitement par Implants Actifs.* Diabetes Care, 1998. **21**(2): p. 325-6.
- 53. Renard, E., et al., *Insulin underdelivery from implanted pumps using peritoneal route. Determinant role of insulin pump compatibility.* Diabetes Care, 1996. **19**(8): p. 812-7.
- 54. Renard, E., et al., Catheter Complications Associated With Implantable Systems for Peritoneal Insulin Delivery: An analysis of frequency, predisposing factors, and obstructing materials. Diabetes Care, 1995.
 18(3): p. 300.
- 55. Mirouze, J., et al., *Clinical experience in human diabetics with portable and implantable insulin minipumps.* Life Support Syst, 1983. **1**(1): p. 39-49.
- 56. Irsigler, K. and H. Kritz, On the clinical application of the insulin infusion in the open-loop-system. [German]. Zeitschrift fur die Gesamte Innere Medizin und Ihre Grenzgebiete, 1981. **36**(1): p. 8-19.
- 57. Liebl, A., et al., *Successful treatment of type 1 diabetes with intraperitoneal insulin infusion when subcutaneous insulin application is not possible: Two case reports.* Diabetes, 2012. **61**: p. A230-A231.
- 58. Schade, D.S., R.P. Eaton, and R.M. Warhol, *Subcutaneous peritoneal access device for type I diabetic patients nonresponsive to subcutaneous insulin.* Diabetes, 1982. **31**(5 I): p. 470-473.
- 59. Irsigler, K., et al., *Preprogrammed insulin infusion with a portable pump system*. Horm Metab Res Suppl, 1979(8): p. 193-7.
- 60. Selam, J.L., et al., *Randomized comparison of metabolic control achieved by intraperitoneal insulin infusion with implantable pumps versus intensive subcutaneous insulin therapy in type I diabetic patients.* Diabetes Care, 1992. **15**(1): p. 53-8.
- 61. Jeandidier, N., et al., *Decreased severe hypoglycemia frequency during intraperitoneal insulin infusion using programmable implantable pumps* [1]. Diabetes Care, 1996. **19**(7): p. 780.
- 62. Renard, E., B. Guerci, and N. Jeandidier, *Long-term safety and efficacy of intraperitoneal insulin infusion from implanted pumps in a large series of patients with type 1 diabetes and initial high glucose variability.* Diabetologia, 2018. **61 (Supplement 1)**: p. S31.
- 63. Stephen, R.L., J.G. Maxwell, and J.J. Harrow, *Intervention in nephropathy due to insulin-dependent diabetes mellitus (IDDM)*. Kidney International, 1985. **28**(SUPPL. 17): p. S-60-S-65.
- 64. Broussolle, C., N. Jeandidier, and H. Hanaire-Broutin, *French multicentre experience of implantable insulin pumps*. Lancet, 1994. **343**(8896): p. 514-515.
- 65. Olsen, C.L., et al., *Insulin antibody responses after long-term intraperitoneal insulin administration via implantable programmable insulin delivery systems.* Diabetes Care, 1994. **17**(3): p. 169-176.
- 66. Udelsman, R., et al., *Implanted programmable insulin pumps: one hundred fifty-three patient years of surgical experience*. Surgery, 1997. **122**(6): p. 1005-11.
- 67. Udelsman, R., et al., *Intraperitoneal delivery of insulin via mechanical pump: surgical implications*. Langenbecks Arch Surg, 2000. **385**(6): p. 367-72.
- 68. Dufaitre-Patouraux, L., et al., *Continuous intraperitoneal insulin infusion does not increase the risk of organspecific autoimmune disease in type 1 diabetic patients: results of a multicentric, comparative study.* Diabetes Metab, 2006. **32**(5 Pt 1): p. 427-32.

- 69. DeVries, J.H., et al., *Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay.* Diabet Med, 2002. **19**(6): p. 496-501.
- 70. Stephen, R., et al., *Long-term intraperitoneal insulin treatment: Preliminary Studies in 12 diabetic patients."*. Diabetic Renal-Retinal Syndrome, 1982. **2**: p. 447.
- 71. Campbell, I.W., et al., *Treatment of type I diabetic with subcutaneous insulin resistance by a totally implantable insulin infusion device ("Infusaid").* Diabetes Res, 1984. **1**(2): p. 83-8.
- 72. Othonos, N., et al., *Continuous intra-peritoneal insulin infusion: An alternative option for insulin administration.* Diabetic Medicine, 2017. **34**(Supplement 1): p. 16.
- 73. Schade, D.S., et al., *The intravenous, intraperitoneal, and subcutaneous routes of insulin delivery in diabetic man.* Diabetes, 1979. **28**(12): p. 1069-72.
- 74. Gooch, B.R., N.N. Abumrad, and R.P. Robinson, *Exercise in insulin-dependent diabetes mellitus: The effect of continuous insulin infusion using the subcutaneous, intravenous, and intraperitoneal sites.* Diabetes Care, 1983. **6**(2): p. 122-128.
- 75. Gooch, B.R., et al., *Near normalization of metabolism of IDDM: Comparison of continuous subcutaneous* (*CSII*) versus intraperitoneal (*CIPII*) insulin delivery. Hormone and Metabolic Research, 1984. **16**(SUPPL. 1): p. 190-194.
- 76. Dandona, P., V. Fonseca, and O. Fernando, *Control of diabetes through a subcutaneous peritoneal access device (SPAD) in patients with resistance to subcutaneous injected insulin.* Diabetes Research, 1987. 5(1): p. 47-50.
- 77. Hermans, M.P., et al., *Fasting and postprandial plasma glucose and peripheral insulin levels in insulindependent diabetes mellitus and non-insulin-dependent diabetes mellitus subjects during continuous intraperitoneal versus subcutaneous insulin delivery.* Transplantation Proceedings, 1995. **27**(6): p. 3329-3330.
- 78. Dassau, E., et al., Intraperitoneal insulin delivery provides superior glycaemic regulation to subcutaneous insulin delivery in model predictive control-based fully-automated artificial pancreas in patients with type 1 diabetes: a pilot study. Diabetes Obes Metab, 2017. **19**(12): p. 1698-1705.
- 79. Lassmann-Vague, V., et al., *Immunogenicity of long-term intraperitoneal insulin administration with implantable programmable pumps: Metabolic consequences.* Diabetes Care, 1995. **18**(4): p. 498-503.
- 80. Lassmann-Vague, V., et al., *Autoimmunity and intraperitoneal insulin treatment by programmable pumps* [14] (multiple letters). Diabetes Care, 1998. **21**(11): p. 2041-2044.
- 81. Renard, E., et al., *Experience with intraperitoneal insulin infusion from implantable programmable systems in Type 1 (insulin-dependent) diabetes mellitus previously treated by external pumps*. Diabete et Metabolisme, 1993. **19**(4): p. 364-371.
- Selam, J.L., et al., Comparison of intraperitoneal and subcutaneous insulin administration on lipids, apolipoproteins, fuel metabolites, and hormones in type I diabetes mellitus. Metabolism, 1989. 38(9): p. 908-12.
- 83. Georgopoulos, A. and C.D. Saudek, *Normalization of composition of triglyceride-rich lipoprotein subfractions in diabetic subjects during insulin infusion with programmable implantable medication system.* Diabetes Care, 1992. **15**(1): p. 19-26.
- 84. Micossi, P., E. Bosi, and M. Cristallo, *Chronic continuous intraperitoneal insulin infusion (CIPII) in type I diabetic patients non-satisfactorily responsive to continuous subcutaneous insulin infusion (CSII)*. Acta Diabetologica Latina, 1986. **23**(2): p. 155-164.
- 85. Service, F.J., et al., *Mean Amplitude of Glycemic Excursions, a Measure of Diabetic Instability.* Diabetes, 1970. **19**(9): p. 644-655.
- 86. Jeandidier, N., et al., *Comparison of intraperitoneal insulin infusion (using implantable pump) and subcutaneous insulin administration: Preliminary results of a crossover study*. Transplantation Proceedings, 1992. **24**(3): p. 948-949.
- 87. Lassmann-Vague, V., et al., *Insulin kinetics in type I diabetic patients treated by continuous intraperitoneal insulin infusion: Influence of anti-insulin antibodies.* Diabetic Medicine, 1996. **13**(12): p. 1051-1055.
- 88. Catargi, B., et al., *Comparison of blood glucose stability and HbA1c between implantable insulin pumps using U400 hoe 21pH insulin and external pumps using lispro in type 1 diabetic patients: A pilot study.* Diabetes and Metabolism, 2002. **28**(2): p. 133-137.
- 89. Oskarsson, P.R., et al., *Continuous intraperitoneal insulin infusion partly restores the glucagon response to hypoglycaemia in type 1 diabetic patients.* Diabetes Metab, 2000. **26**(2): p. 118-24.

- 90. Oskarsson, P.R., et al., *Metabolic and hormonal responses to exercise in type 1 diabetic patients during continuous subcutaneous, as compared to continuous intraperitoneal, insulin infusion.* Diabetes and Metabolism, 1999. **25**(6): p. 491-497.
- 91. Wredling, R., et al., *Experience of long-term intraperitoneal insulin treatment using a new percutaneous access device*. Diabetic Medicine, 1991. **8**(6): p. 597-600.
- 92. Wredling, R., et al., Variation of insulin absorption during subcutaneous and peritoneal infusion in insulindependent diabetic patients with unsatisfactory long-term glycaemic response to continuous subcutaneous insulin infusion. Diabete Metab, 1991. **17**(5): p. 456-9.
- 93. Van Dijk, P.R., et al., *Different effects of intraperitoneal and subcutaneous insulin administration on the GH-IGF-1 axis in type 1 diabetes.* Journal of Clinical Endocrinology and Metabolism, 2016. **101**(6): p. 2493-2501.
- 94. Liebl, A., et al., Evaluation of the new Accu-Chek diaport, a port system for continuous intraperitoneal insulin infusion, in patients with type 1 diabetes: First 3-month results. Diabetes Technology and Therapeutics, 2013.
 15: p. A13.
- 95. Liebl, A., et al., *Evaluation of the New ACCU-CHEK (R) DIAPORT, a Port System for Continuous Intraperitoneal Insulin Infusion, in Patients With Type 1 Diabetes: First 6-Month Results.* Diabetes 2013. **62**: p. pp.A247-A248.
- 96. Liebl , A., et al., *Evalution of the new ACCU-CHEK DIAPORT system, a port system for continous intraperitoneal insulin infusion, in patients with type 1 diabetes: final 12-month results, in International diabetes federation (IDF) World diabetes congress 2013, 2-6 December.* 2013: Melbourne, Australia.
- 97. Liebl, A., et al., *Long-term clinical evaluation of the new Accu-Chek diaport, a port system for continuous intraperitoneal insulin infusion: 24-month results.* Diabetes, 2014. **63**: p. A241.
- 98. Pacifico, A., et al., *Our experience with programmable implantable pump for intraperitoneal insulin infusion. [Italian].* Giornale Italiano di Diabetologia, 1997. **17**(1): p. 21-27.
- 99. Walter, H., et al., *Peripheral hyperinsulinemia in type I diabetics: Reduction via continuous infusion. [German].* Aktuelle Endokrinologie und Stoffwechsel, 1989. **10**(4): p. 224-228.
- 100. Giacca, A., et al., *Peritoneal and subcutaneous absorption of insulin in type I diabetic subjects*. J Clin Endocrinol Metab, 1993. **77**(3): p. 738-42.
- 101. Hanaire-Broutin, H., et al., *Effect of intraperitoneal insulin delivery on growth hormone binding protein, insulin-like growth factor (IGF)-I, and IGF-binding protein-3 in IDDM.* Diabetologia, 1996. **39**(12): p. 1498-1504.
- 102. Georgopoulos, A. and C.D. Saudek, *Intraperitoneal insulin delivery decreases the levels of chylomicron remnants in patients with IDDM*. Diabetes Care, 1994. **17**(11): p. 1295-1299.
- 103. Beylot, M., et al., *Insulin-mediated glucose disposal in type 1 (insulin-dependent) diabetic subjects treated by continous subcutaneous or intraperitoneal insulin fusion.* Diabete et Metabolisme, 1987. **13**(4): p. 450-456.
- 104. Lassmann-Vague, V., et al., *SHBG (sex hormone binding globulin) levels in insulin dependent diabetic patients according to the route of insulin administration.* Hormone and Metabolic Research, 1994. **26**(9): p. 436-437.
- 105. Schnell, O., et al., *Continuous intraperitoneal insulin therapy via port-system in type 1 diabetes with delayed absorption of subcutaneously applied insulin [Kontinuierliche intraperitoneale insulintherapie mit portsystem bei typ 1 diabetikern mit subkutaner insulinaufnahmestorung]*. Diabetes und Stoffwechsel, 1994. **3**: p. 51-55.
- 106. Duvillard, L., et al., Comparison of apolipoprotein B100 metabolism between continuous subcutaneous and intraperitoneal insulin therapy in type 1 diabetes. Journal of Clinical Endocrinology and Metabolism, 2005.
 90(10): p. 5761-5764.
- 107. Duvillard, L., et al., *No change in apolipoprotein AI metabolism when subcutaneous insulin infusion is replaced by intraperitoneal insulin infusion in type 1 diabetic patients.* Atherosclerosis, 2007. **194**(2): p. 342-347.
- 108. Guerci, B., et al., Intraperitoneal insulin infusion improves the depletion in choline- containing phospholipids of lipoprotein B particles in type I diabetic patients. Metabolism: Clinical and Experimental, 1996. **45**(4): p. 430-434.
- 109. Raccah, D., et al., Intraperitoneal insulin administration does not modify plasminogen activator inhibitor 1 levels in IDDM patients. Diabetes Care, 1994. **17**(8): p. 941-2.
- 110. Arnqvist, H., et al., *Higher circulating IGF-I bioactivity and total IGF-I with intraperitoneal insulin delivery than with CSII in type 1 diabetes.* Growth Hormone and IGF Research, 2010. **20**: p. S24-S25.
- 111. Hedman, C.A., et al., *Intraperitoneal insulin delivery gives higher circulating IGF-I activity than CSII in type 1 diabetes.* Diabetologia, 2009. **52 (S1)**: p. S376-S377.

- 112. Hedman, C.A., et al., *Intraperitoneal insulin delivery to patients with type 1 diabetes results in higher serum IGF-I bioactivity than continuous subcutaneous insulin infusion.* Clin Endocrinol (Oxf), 2014. **81**(1): p. 58-62.
- 113. Catargi, B., et al., *Glucose profiles in a type 1 diabetic patient successively treated with CSII using regular insulin, lispro and an implantable insulin pump.* Diabetes Metab, 2000. **26**(3): p. 210-4.
- 114. Colette, C., et al., *Effect of different insulin administration modalities on vitamin D metabolism of insulindependent diabetic patients.* Hormone and Metabolic Research, 1989. **21**(1): p. 37-41.
- 115. Jeandidier, N., et al., *Comparison of antigenicity of Hoechst 21PH insulin using either implantable intraperitoneal pump or subcutaneous external pump infusion in type 1 diabetic patients.* Diabetes Care, 2002. **25**(1): p. 84-8.
- 116. Arnqvist, H., et al., *OR9,53 Higher circulating IGF-I bioactivity and total IGF-I with intraperitoneal insulin delivery than with CSII in type 1 diabetes.* Growth Hormone & IGF Research, 2010. **20**: p. S24-S25.
- 117. van Dijk, P.R., et al., *Favourable serum calcification propensity with intraperitoneal as compared with subcutaneous insulin administration in type 1 diabetes.* Ther Adv Endocrinol Metab, 2020. **11**: p. 2042018820908456.