Continuous Subcutaneous Insulin Infusion Therapy with Rapid-Acting Insulin Analogs in Insulin Pumps: Does it Work, How Does it Work, and what Therapies Work Better than Others?

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Abstract: Many patients are not optimally controlled on conventional insulin regimens. This review evaluates the practicalities and clinical success of continuous subcutaneous insulin infusion therapy with rapid-acting insulin analogs in insulin pumps in patients with type 1 and type 2 diabetes. In contrast to a multiple daily injection regimen, CSII provides patients with greater flexibility in the timing of meals and insulin dosing, resulting in improved quality of life and greater treatment adherence. CSII therapy with rapid-acting insulin analogs offers reliable glycemic control and proactive response to glucose variability, with a reduced risk of weight gain and hypoglycemia compared with regular human insulin in CSII.

While the clinical benefits of CSII versus multiple daily injection therapy in patients with type 1 diabetes are quite evident in studies in appropriately-selected patients, the benefits are more equal in patients with type 2 diabetes. Appropriate patient selection for CSII therapy may help ensure successful outcomes in diabetes treatment. Patients who are very poorly controlled on multiple daily injections may benefit from CSII therapy, with the greatest glycemic improvement associated with high baseline HbA1c levels. CSII therapy may be of particular benefit to patients with type 1 diabetes who are prone to hypoglycemia and patients with type 2 diabetes who are obese and uncontrolled on high doses of insulin; however, most important as a predictor of success is that patients desire CSII therapy.

Keywords: Continuous subcutaneous insulin infusion, diabetes, insulin pump, rapid-acting insulin analog.

INTRODUCTION

Glycemic targets have been set to guide the treatment of diabetes, and insulin consumption has increased in response to treatment needs; yet around the world many people with diabetes remain poorly controlled, with HbA1c levels typically ranging from 7.0–12.6 % [1]. Clearly, the therapeutic approach to diabetes management needs to be refined. One alternative is to provide insulin by continuous subcutaneous insulin infusion (CSII) using rapid-acting insulin analogs rather than conventional multiple daily injection therapy. This review will evaluate the practicalities and clinical outcomes of CSII therapy with rapid-acting insulin analogs in insulin pumps in adult patients with type 1 or type 2 diabetes. The suitability of CSII therapy and closed-loop glucose control in specialist patient groups such as children and pregnant women is beyond the scope of this manuscript, and the reader is referred to comprehensive reviews in these fields of study for further information [2-4]; neither will the impact of CSII therapy on the broad field of health economics or future technology developments and the need for ever-faster-acting insulins be addressed here.

RATIONALE FOR CSII THERAPY

The goal of insulin replacement therapy with CSII is to recreate the physiological insulin profile. In a person without diabetes, insulin secretion via pancreatic beta-cells occurs in a continuous manner over the course of the day (basal). Additional prandial (bolus) insulin secretion occurs in response to the postprandial spike in blood glucose following meals (known as PPG excursions). Physiological insulin replacement therapy ideally accommodates the fasting plasma glucose state between meals as well as PPG excursions following meals. Improper timing of either basal or bolus insulin doses may result in hypoglycemia or hyperglycemia.

The rapid-acting insulin analogs insulin aspart (IAsp), insulin glulisine, and insulin lispro (ILisp) were developed to more closely replicate the time–action profile of prandial insulin secretion than conventional insulin, and to address PPG excursions. Rapid-acting insulin analogs involve amino acid substitutions to the chemical structure of regular human insulin at locations involved in self-association, resulting in pharmacokinetic profiles that more closely mimic those of endogenous insulin compared with regular human insulin [5-8]. This allows for faster absorption of rapid-acting insulin analogs than of short-acting human insulin and eliminates the need for patients to wait 30 min after dosing for meals [5,9].

Although multiple daily injection therapy with rapid-acting insulin analogs improves upon the outcomes of multiple daily injections with regular human insulin [6,10-18], this approach is limited by the need for patients to adhere to a strict injection schedule and manually adjust injections based on frequent glucose monitoring. In contrast,
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rapid-acting insulin analogs are well suited to CSII therapy, in which insulin infusion can be pre-programmed to fluctuate in response to individually-determined, changing metabolic needs throughout the day. This need-based dosing provides patients with greater personal flexibility in the timing of meals [19].

PRACTICAL ASPECTS OF INSULIN DELIVERY BY CSII

CSII with Insulin Pumps

Insulin pumps are portable, battery-operated, computerized units that are about the size of a pager. As medical devices, they are regulated by the US Food and Drug Administration and require precisely-documented processes for their design, construction and performance, development testing, product-ion testing, and field maintenance, and must contain comprehensive self-test and fault-indication capabilities. The insulin pump is attached to a disposable insulin reservoir and infusion set, comprised of a narrow plastic catheter with a soft plastic cannula, which is usually inserted subcutaneously in the abdomen (it may also be inserted in the leg, arm, or lower back). Depending on where the catheter is inserted, patients can keep the insulin pump unit in various places, such as a pocket or sock, or in a holster attached to a belt. There are several ins-lin pumps commercially available for patients with type 1 or type 2 diabetes [20]; for more information, please refer to the list published at http://forecast.diabetes.org/files/images/Jan13_pumps_2-27_spread.pdf

Insulin pumps are programmed to administer CSII in basal and bolus doses, including premeal, snack, and correction bolus between meals. Pumps may be also programmed to fit the needs of individual patients, including diurnal variability in insulin sensitivity/glucose tolerance resulting from a wide range of daily experiences (e.g., stress or physical activities), and are able to accommodate patients’ varying schedules [21]. Insulin pump adaptability includes the ability to calculate basal and bolus infusion rates according to the quantity of carbohydrate consumed, correction boluses to treat high blood glucose levels, insulin-to-carbohydrate ratios, and the amount of insulin left over from preceding bolus infusions. Some pumps can also influence the pharmacokinetic profile of insulin by changing the bolus shape and/or duration (i.e., dual wave or square wave) in response to meals, delivering a single insulin dose over a long time period (square wave) or one immediate dose followed by a second dose during the next few hours (dual wave). There are a number of published protocols for calculating initial pump settings when transferring a patient from a multiple daily insulin regimen to insulin pumps [22-25]. A comprehensive review of these is outside the scope of the current manuscript, but in summary either patient weight, previous daily insulin dose, or both are used to calculate initial hourly basal rates, carbohydrate to insulin ratio and insulin sensitivity factor (correction factor).

Disadvantages of Insulin Pumps

There are some disadvantages associated with the use of insulin pumps; for example, an improperly reconnected pump may leak insulin, a catheter may dislodge, or a pump may be physically damaged [26]. If a catheter disconnects and interrupts pump flow, it could lead to diabetic ketoacidosis if not quickly resolved. Longer than recommended use of infusion sets (e.g., >3 d) increases the risk of blockage or occlusion in the catheter if the stability of the insulin is compromised [27,28], and glycemic control in patients with type 1 diabetes on CSII therapy begins deteriorating 24 h after a change in the infusion line [29].

Several studies show less occlusion/blockage with rapid-acting insulin analogs, particularly IAsp vs regular human insulin and/or other rapid-acting analogs [27,30-33]. For example, in a 7-wk study of 19 patients with type 1 diabetes, CSII therapy with IAsp resulted in significantly less (P<0.05) crystal formation in the pump reservoir (0.3±0.3 vs 1.1±0.4 on a scale of 0 = none to 2 = moderate/many) and distal tubing (0.3±0.3 vs 0.7±0.4) compared with buffered human insulin [33].

It is generally recommended that rapid-acting insulin analogs be used in the pump reservoir for no more than 2 d, as longer periods of use increase the risk of blockage; however, a labeling change in 2009 extended the use of IAsp in CSII therapy to 6 d [34]. IAsp is the first rapid-acting insulin analog to be granted this extended in-use time.

Patient education is key in preventing potential errors arising from the improper use of insulin pumps. Common aspects of insulin pump misuse include failure to rotate the infusion site, failure to change infusion sites as recommended to optimize insulin absorption, irregular testing of blood glucose levels, inaccurate programming of bolus doses, inaccurate carbohydrate calculations, and ignoring bolus calculations [26].

Patient Selection

Appropriate selection of patients for CSII therapy with insulin pumps is crucial to achieving improved glycemic control. The success of treatment initiation will depend on patients’ (and in the case of children, their parents’) motivation to improve glycemic control, consistent adherence, and willingness to undergo strict medical supervision and education, which could involve an in-patient or out-patient hospital stay [35]. Patients switching from multiple daily injection to CSII should do so on a unit-by-unit basis and calculate meal-time insulin in a similar manner using carbohydrate counting and preprandial blood glucose (REF).

Good candidates for CSII therapy include patients who experience recurrent severe hypoglycemia or wide swings in blood glucose levels (regardless of their HbA1c levels), those who have poor glycemic control or microvascular complications and/or risk factors for macrovascular complications, or those whose metabolic control is adequate but whose quality of life is adversely affected by a multiple daily injection regimen [36-40]. Good candidates for CSII therapy with rapid-acting insulin analogs are patients with type 1 diabetes poorly controlled with multiple daily injections and prone to hypoglycemia [19,41-46] and patients with type 2 diabetes who are obese and uncontrolled on a high insulin dose [43,47-50]. Patients with type 1 and type 2 diabetes with high baseline HbA1c levels (>8.5 %) generally experience greater improvement in glycemic control and greater dose efficiency on CSII than with
multiple daily injections [42,44,48,50-69] (Fig. 1); (Tables 1-3).

![Graph showing Baseline HbA1c (%) and Change in HbA1c (%)](image)

Potential Clinical Advantages of CSII

Insulin pump therapy with CSII offers patients several potential advantages over multiple daily injections, including improved glycemic control and proactive response to glucose variability, reduced risk of hypoglycemia and weight gain, and lower total daily insulin requirements with a comparable incidence of diabetic ketoacidosis. Realization of many of these advantages is generally contingent upon the use of rapid-acting insulin analogs in CSII. Intensive insulin therapy in general may pose an increased risk of hypoglycemia; however, several studies of rapid-acting insulin analogs in CSII therapy show either no increase or a reduction of risk of hypoglycemia compared with conventional insulin treatment with MDI therapy [42,44,48,50-69] (Tables 2 and 3).

Glucose variability can persist in patients who appear to have good glycemic control (as assessed by HbA1c) but experience prolonged hyperglycemia following meals (as assessed by an oral glucose tolerance test). Protracted PPG excursions occur when insulin does not enter the bloodstream in time to respond to meals, resulting in hyperglycemia. Subsequently, if poorly-timed insulin injections are absorbed when PPG is lessening, hypoglycemia may ensue. Correctly-timed bolus insulin delivery in CSII therapy works to normalize blood glucose by euglycemia reduces the risk of adverse cardiovascular outcomes associated with hyperglycemia [70].

CLINICAL PERFORMANCE OF CSII IN CONTROLLED STUDIES: TYPE 1 DIABETES

The efficacy of CSII therapy with rapid-acting insulin analogs is particularly striking in studies of type 1 diabetes, where it has been proven a safe and effective alternative to multiple daily injections in various patient populations, including children and adolescents [48,49,55-57,59], adults [42,44,55,56,59-61,68,69], the elderly [58,61,62,71], and pregnant women [54,57] (Tables 2 and 3). IAsp and ILisp are labeled for use in each of these patient populations [34,72], supported by studies using multiple daily injections or CSII therapy [73-76].

Adults with Type 1 Diabetes

Several studies in adult patients with type 1 diabetes confirm an improved balance between control and tolerability, often with better control and reduced hypoglycemia, greater versatility, and lower insulin consumption for CSII therapy with rapid-acting insulin analogs vs multiple daily injections with insulin analogs or regular human insulin (Tables 2 and 3).

In a recent meta-analysis, significant HbA1c improvement was associated with CSII therapy with the rapid-acting insulin analogs IAsp and ILisp vs multiple daily injections with regular human insulin and insulin analogs [59]. This meta-analysis, which examined 11 randomized controlled trials of at least 12-wk duration involving patients with type 1 diabetes, reported a significant decrease in HbA1c with CSII vs multiple daily injection therapy, regardless of the rapid-acting insulin analog used (ILisp [-0.2 (-0.4; -0.1)%; P=0.001] or IAsp [-0.6 (-1.0; -0.2)%; P=0.002]). The overall standardized difference in mean was -0.3 (-0.4; -0.1)% (P<0.001) in favor of CSII therapy among patients aged >10 y. At least one severe hypoglycemic event occurred in 16 and 21 patients receiving CSII vs multiple daily injection therapy, respectively; however, the between-treatment difference was not significant [59].

In the 5-Nations trial, 246 adults with type 1 diabetes demonstrated improved glycemic control and lower incidence of hypoglycemia with CSII vs multiple daily injection therapy [56]. Subjects were randomized to either CSII with ILisp or MDI with NPH + ILisp for 6 mo, and then switched to the other treatment. By the end of the crossover trial, CSII produced significantly lower HbA1c levels (7.45 vs 7.67 %; P<0.001) and mean blood glucose values (154.97 vs 169.39 mg/dL; P<0.001) compared with MDI, with fewer blood glucose level fluctuations (±70.28 vs ±77.49 mg/dL, respectively; P<0.001). Hypoglycemic episodes were considerably less frequent and mean total daily insulin requirement was significantly reduced by 26% (P<0.0001) with CSII vs multiple daily injection therapy. Difference in body weight between the two therapies was not significant [56].

Children with Type 1 Diabetes

Improved glycemic control and reduced incidence of hypoglycemia have been confirmed in several studies in pediatric and adolescent patients with type 1 diabetes comparing CSII to multiple daily injection therapy [35,77], and CSII with rapid-acting insulin analogs in particular to MDI therapy [52,53,59,63] (Table 2). In a 16-wk study of 32 subjects aged 8–21 y randomized to CSII therapy with IAsp or multiple daily injections with insulin glargine (IGlar) + IAsp, results revealed significant reductions in HbA1c with CSII vs multiple daily injections [53]. Although prebreakfast fasting self-measured blood glucose levels were similar between groups (148 ± 94 vs 149 ± 95 mg/dL, respectively), lunch, dinner, and bedtime mean blood glucose levels were
Table 1. Studies in Patients with Type 1 Diabetes Comparing Therapy with Rapid-Acting Insulin Analogs in CSII vs Multiple Daily Injection Therapy (Mean Values)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Type (n)</th>
<th>Study Duration/Type</th>
<th>Insulin Regimen (CSII/MDI)</th>
<th>HbA1c Baseline (% CSII/MDI)</th>
<th>HbA1c Endpoint (% CSII/MDI)</th>
<th>Δ HbA1c (%) CSII/MDI</th>
<th>Minor Hypoglycemia</th>
<th>Major/Severe Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Total Daily Insulin Dose (Baseline/Study End)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahern et al., 2002 [52]</td>
<td>C (161)</td>
<td>12 mo/ prospective</td>
<td>ILisp</td>
<td>Preschool age (1–6 y): 7.1±0.9</td>
<td>Preschool: 6.5±0.7</td>
<td>Range: 0.6–0.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Preschool: 0.7±0.2/0.8±0.2 IU/kg/d School age: 1.0±0.6/0.9±0.3 IU/kg/d Adolescent: 1.3±0.8/0.9±0.5 IU/kg/d</td>
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<tr>
<td></td>
<td></td>
<td>trial of MDI patients switched to CSII</td>
<td></td>
<td>School age (7–11 y): 7.9±1.0 Adolescents (12–18 y): 7.4±1.2</td>
<td>School age: 7.3±1.1 Adolescents: 7.4±1.2</td>
<td>(P&lt;0.02 vs baseline, for all three age groups)</td>
<td>0.91±1.28/0.07±0.70 (P=0.002, difference 0.84 (95% CI: -1.31 to -0.36)</td>
<td>+0.98±2.02/-0.02±1.18 episodes/patient-wk</td>
<td>3/6 (no. of patients)</td>
<td>-15.8±15.06 vs 2.9±17.01 units/d, P&lt;0.001 difference -18.76 units/d (95% CI: 26.45 to -11.07)</td>
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<tr>
<td>DeVries et al., 2002 [44]</td>
<td>A (79)</td>
<td>16-wk/ open-label</td>
<td>IAsp/ NPH + IAsp</td>
<td>9.27±1.4/9.25±1.4</td>
<td>NR</td>
<td>0.90±0.1</td>
<td>NR</td>
<td>0/4 events</td>
<td>2/1 events</td>
<td>1.4 units/kg at baseline vs 0.9 units/kg at 16 wk; P&lt;0.01</td>
</tr>
<tr>
<td>Doyle et al., 2004 [53]</td>
<td>C (32)</td>
<td>16-wk/ randomized</td>
<td>IAsp/Iglar + IAsp</td>
<td>8.1±1.2/8.2±1.1</td>
<td>7.2±1.0 (P&lt;0.02 vs baseline; P&lt;0.05 vs glargine group) /8.1±1.2</td>
<td>0/04 events</td>
<td>NR</td>
<td>0/4 events</td>
<td>2/1 events</td>
<td>1.4 units/kg at baseline vs 0.9 units/kg at 16 wk; P&lt;0.01</td>
</tr>
<tr>
<td>Gabbe et al., 2000 [54]</td>
<td>P (60)</td>
<td>Duration of pregnancy and post-partum/ retrospective review of maternal and neonatal records</td>
<td>ILisp (n=23) or RHI (n=37)</td>
<td>NR</td>
<td>Third trimester: Group 1 (CSII just initiated): 6.1 Group 2 (MDI): 6.6 Group 3 (CSII using pumps before pregnancy): 6.3 Postpartum: Group 1: 7.2 Group 2: 7.1 Group 3: 7.1 (P = .02, all three groups)</td>
<td>Group 1: 1.5 Group 2: 1.8 Group 3: 3.0</td>
<td>5.6 vs 3.9 P&lt;0.001</td>
<td>2/5 episodes</td>
<td>CSII to MDI: 42.3±17.9 U (baseline)/42.1±19.2 (CSII)/46.0±18.2 (MDI) MDI to CSII: 41.6±16.1 (baseline)/39.6±17.5 (CSII)/46.2±20.5 (MDI)</td>
<td>CSII to MDI: 42.3±17.9 U (baseline)/42.1±19.2 (CSII)/46.0±18.2 (MDI) MDI to CSII: 41.6±16.1 (baseline)/39.6±17.5 (CSII)/46.2±20.5 (MDI)</td>
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<tr>
<td>Hirsch et al., 2005 [55]</td>
<td>A (100)</td>
<td>10 wk/ open-label, randomized crossover trial</td>
<td>IAsp/Iglar + IAsp</td>
<td>CSII to MDI: 7.4±0.8 MDI to CSII: 7.5±0.8</td>
<td>CSII to MDI: 7.3±0.7 MDI to CSII: 7.1±0.7 (P&lt;0.05)</td>
<td>CSII to MDI: 0.1 MDI to CSII: 0.4</td>
<td>5.6 vs 3.9 P&lt;0.001</td>
<td>2/5 episodes</td>
<td>Minors: 2.2 vs 3.2 episodes/subject/5-wk period (P=0.02)</td>
<td>CSII to MDI: 42.3±17.9 U (baseline)/42.1±19.2 (CSII)/46.0±18.2 (MDI) MDI to CSII: 41.6±16.1 (baseline)/39.6±17.5 (CSII)/46.2±20.5 (MDI)</td>
</tr>
<tr>
<td>Reference</td>
<td>Patient Type (n)</td>
<td>Study Duration/Type</td>
<td>Insulin Regimen (CSII/MDI)</td>
<td>HbA1c Baseline (%, CSII/MDI</td>
<td>HbA1c Endpoint (% CSII/MDI)</td>
<td>Δ HbA1c (%) CSII/MDI</td>
<td>Minor Hypoglycemia</td>
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<td>Total Daily Insulin Dose (Baseline/Study End)</td>
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<tr>
<td>Hoogma et al., 2006 [56]</td>
<td>A (246)</td>
<td>6 mo/ randomized, controlled crossover</td>
<td>ILisp/NPH + ILisp</td>
<td>CSII to MDI: 8.2±1.4</td>
<td>MDI to CSII: 8.3±1.1</td>
<td>CSII: 7.45 MDI: 7.67</td>
<td>21% difference in mean EOT HbA1c in favor of CSII (P&lt;0.001)</td>
<td>Incidence ratio: 1.12 (95% CI: 1.08–1.17)</td>
<td>Incidence ratio: 2.61 (95% CI: 1.59–4.29)</td>
<td>NR</td>
</tr>
<tr>
<td>Lapolla et al., 2005 [57]</td>
<td>P (93)</td>
<td>Duration of pregnancy/observational</td>
<td>RHI or ILisp/bolus RHI + basal RHI</td>
<td>7.7±1.6/7.2±1.4</td>
<td>6.4±1.2/6.3±1.0</td>
<td>1.30±0.9†</td>
<td>16.7%/14.3%</td>
<td>NR</td>
<td>NR</td>
<td>CSII: 37±14 U/52±21 U</td>
</tr>
<tr>
<td>Lepore et al., 2005 [58]</td>
<td>E (82)</td>
<td>31.9±14.5 mo (range 4–55 mo)/observational</td>
<td>ILisp or ILasp/RHI or RAIAs + NPH or IGlar</td>
<td>NR</td>
<td>NR</td>
<td>First 3 mo: CSII vs MDI: 8.3±1.06/9.39±1.35 (P&lt;0.001) Overall mean change CSII: 1.15±0.84 (P&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Total: 38.4±12.3/52.1±17.5 units/d (P&lt;0.001)</td>
</tr>
<tr>
<td>Monani et al., 2010 [59]</td>
<td>A/C</td>
<td>≥12 wk/ meta-analysis of 11 RCTs</td>
<td>RAIAs/RAIAs</td>
<td>Total: 8.5</td>
<td>Total: 7.6±0.9/7.9±0.8</td>
<td>Standardized difference in mean: -0.3 [-0.4; -0.1], in favor of CSII (P&lt;0.001)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pickup et al., 2002 [60]</td>
<td>A/C†</td>
<td>2 mo to 2 yr meta-analysis of 12 RCTs</td>
<td>ILisp, actrapid, velosulin, or RHI/ isophane, lente, or ultralente +RHI or RAIAs</td>
<td>NR</td>
<td>NR</td>
<td>Standardized mean difference in favor of CSII: 0.44 (0.20–0.63)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Standardized mean difference in dose: 0.58 (0.34–0.83), or 7.58 units/d</td>
</tr>
<tr>
<td>Pickup et al., 2008 [61]</td>
<td>A/C/E</td>
<td>≥26 mo/meta-analysis of 22 studies (RCTs, before/after studies)</td>
<td>IGLar or IDet + RHI or RAIAs for both groups</td>
<td>NR</td>
<td>NR</td>
<td>Mean difference in treatment in favor of CSII - RCTs: 0.21 (0.13–0.30) Before/after studies: 0.72 (0.55–0.90) (P&lt;0.001); All studies: 0.62 (0.47–0.78)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Rate ratio: RCTs: 2.89 (95% CI: 1.45–5.76); Before/after studies: 4.34 (2.87–6.56); All studies: 4.19 (2.86–6.13)</td>
</tr>
</tbody>
</table>
significantly lower for subjects receiving CSII vs multiple daily injection therapy (P<0.01). Total daily insulin dose also declined significantly with CSII (P<0.01), while it remained the same with multiple daily injections. No significant change in body mass index occurred in either group [53].

**Elderly Patients with Type 1 Diabetes**

The efficacy and safety of CSII and rapid-acting insulin analogs are also evident in studies of elderly patients with type 1 diabetes [58,62,71], including a 1-y study of 34 patients (aged >50 y) previously on multiple daily injection therapy with once-daily IGLar (n=10) or twice-daily NPH (n=24) [62]. After switching to CSII therapy and supplementing their regimens with premeal insulin analogs, patients experienced significant (P<0.01) drops in HbA1c at 6 mo and 1 y and a decrease in rates of severe hypoglycemia with CSII therapy compared with multiple daily injections [62].

**CLINICAL PERFORMANCE OF CSII IN CONTROLLED STUDIES: TYPE 2 DIABETES**

The results of studies comparing CSII with rapid-acting insulin analogs and multiple daily injection therapy in patients with type 2 diabetes are conflicting: some indicate superior glycemic control and greater reduction in hypoglycemia with CSII vs multiple daily injections [47,48,50,64,66,68], while others demonstrate an equivalent rather than a superior effect [65,67,69] (Table 3).

**Poorly-Controlled Patients**

Berthe et al. [64] assessed metabolic control with CSII vs multiple daily injections in a crossover study of 17 patients with very poorly controlled type 2 diabetes (baseline HbA1c...
9.0 ± 1.6 %), finding improved glycemic control with CSII therapy. Patients on conventional insulin therapy were randomized to three daily injections of either ILisp + NPH or CSII + ILisp, for 12 wk before switching to the other

<table>
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<tr>
<th>Reference</th>
<th>Patient Type (n)</th>
<th>Study Duration/Type</th>
<th>Insulin Regimen (CSII/MDI)</th>
<th>HbA1c Baseline (%, CSII/MDI)</th>
<th>HbA1c Endpoint (%, CSII/MDI)</th>
<th>ΔHbA1c (%, CSII/MDI)</th>
<th>Minor Hypoglycemia</th>
<th>Major/Severe Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Total Daily Insulin Dose (Baseline/Study End)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berthe et al., 2007 [64]</td>
<td>A (17)</td>
<td>24 wk/ randomized, crossover</td>
<td>ILisp/NPH + ILisp</td>
<td>9.0±1.6</td>
<td>7.7±0.8 (-1.3)/ 8.6±1.6 (-0.4)</td>
<td>P&lt;0.03</td>
<td>1.3±0.4</td>
<td>CSII: 7 episodes MDI: 8 episodes</td>
<td>NR</td>
<td>CSII: 1.0±0.3/1.0±0.2 units/kg/d MDI: 1.0±0.3/2.0±0.3 units/kg/d</td>
</tr>
<tr>
<td>Herman et al., 2005 [65]</td>
<td>E (107)</td>
<td>12 mo/RCT</td>
<td>ILisp/IGlar + ILisp</td>
<td>8.4±1.1/8.1±1.2</td>
<td>6.6±0.8/6.4±0.8</td>
<td>-1.7±1.0/-1.6±1.2</td>
<td>1.0±1.2</td>
<td>48 (81%)/49 (90%)</td>
<td>NR</td>
<td>CSII: NR (baseline)/108±63 units MDI: NR/108±62 units</td>
</tr>
<tr>
<td>Kesavadev et al., 2009 [66]</td>
<td>A (46)</td>
<td>MDI patients switched to CSII for 6 mo</td>
<td>IAsp</td>
<td>8.1±1.4</td>
<td>7.6±1.2</td>
<td>-0.5</td>
<td>(P&lt;0.001; 95% CI: 0.161–0.921)</td>
<td>NR</td>
<td>NR</td>
<td>43.3±23.4/44.0±23.7 U</td>
</tr>
<tr>
<td>Lynch et al., 2010 [48]</td>
<td>A (131)</td>
<td>17 mo (range 3–39 mo)/retrospective claims analysis</td>
<td>Long-acting insulin only or long-acting + rapid-acting insulins or any combo of ≥2 insulins</td>
<td>8.9</td>
<td>8.0</td>
<td>-0.9</td>
<td>(P&lt;0.001)</td>
<td>NR</td>
<td>0.02±0.095 events/subject/mo</td>
<td>NR</td>
</tr>
<tr>
<td>Raskin et al., 2003 [67]</td>
<td>A (132)</td>
<td>24 wk/open-label, randomized, parallel-group</td>
<td>IAsp/NPH + IAsp</td>
<td>8.2±1.37/8.0±1.08</td>
<td>7.6±1.22 (-0.62±1.11)/ 7.5±1.17 (-0.46±0.89)</td>
<td>(P&lt;0.05)</td>
<td>-0.62±1.11/-0.46±0.89</td>
<td>54% (34/63)/59% (36/61)</td>
<td>NR</td>
<td>16% (10/62)/22% (13/59)</td>
</tr>
<tr>
<td>Wainstein et al., 2005 [50]</td>
<td>A/E (40, ITT)</td>
<td>48 wk/ randomized, crossover</td>
<td>ILisp/NPH + RHI or humulin R</td>
<td>CSII to MDI: 10.2±1.4/ MDI to CSII: 10.3±1.2 Period 1: CSII to MDI: 7.9±1.0/ MDI to CSII: 8.4±1.3 Period 2: CSII to MDI: 8.8±1.4/ MDI to CSII: 8.8±1.5</td>
<td>-0.8±1.5 during CSII/ +0.4±1.3 during MDI (P=0.007)</td>
<td>NR</td>
<td>3 events on pump therapy/2 events on MDI</td>
<td>NR</td>
<td>CSII to MDI: 99.3±24.5/87.2±25.4 units/d MDI to CSII: 113.4±28.04/118.7±31.3 units/d (P=0.003)</td>
<td></td>
</tr>
</tbody>
</table>

A. Adult (aged ≥18 to <65 y); C, child (aged <18 y); E, elderly (aged ≥65 y).

*All values for change in HbA1c are those reported in the original studies except that indicated with *, for which the endpoint value has simply been subtracted from baseline.
mean HbA1c]; P<0.001). The rate of severe hypoglycemic events significantly from baseline to follow-up (8.4–22.9% [using number of patients reaching target HbA 1c <7 % increased experienced a mean HbA 1c decrease of 0.8% (P<0.001). The statistically significant improvement in HbA 1c levels after controlled adults with type 2 diabetes (baseline HbA 1c >8.5 %) that included the elderly, patients demonstrated significant decrease in HbA1c, with higher baseline HbA 1c ([48]. All treatment groups experienced a statistically- significant. Both treatments produced a significant improvement in treatment satisfaction (P<0.0001), although between-group difference was not statistically- significant. Weight gain was similar with both treatments (P=0.70) [65].

CSII therapy produced only a slight advantage over multiple daily injections in a 24-wk, parallel-group study in which 132 moderately-controlled CSII-naïve patients with type 2 diabetes were randomized to either CSII therapy (with IAsp) or multiple daily injections (with NPH + IAsp) [67]. HbA1c values decreased in both groups from baseline to study end (P<0.05). Patients on CSII therapy also reported lower 8-point blood glucose values at most time points, although significance was only seen at 90 min after breakfast. Mean rates of hypoglycemic episodes were similar in both groups [67].

Obese Patients with Type 2 Diabetes

In a crossover study of 40 obese adults with uncontrolled type 2 diabetes, CSII treatment significantly improved glycemic control without significant change in weight or insulin dose [50]. Patients were randomized to CSII therapy (with ILisp) or multiple daily injections (with NPH + RHI) for 18 wk, then switched to the other therapy following a 12-wk washout period of MDI therapy plus metformin in between. Treatment with CSII produced a mean reduction in

### Table 3. Studies in Patients with Type 1 or Type 2 Diabetes Comparing Therapy with Rapid-Acting Insulin Analogs in CSII vs Multiple Daily Injection Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Type (a)</th>
<th>Study Duration/Type</th>
<th>Insulin Regimen (CSII/MDI)</th>
<th>HbA1c Baseline (%, CSII/MDI)</th>
<th>HbA1c Endpoint (%, CSII/MDI)</th>
<th>ΔHbA1c (%) (P&lt;0.001 vs baseline; P&lt;0.05 vs MDI)/ 8.2±1.0 (P&lt;0.05 vs baseline)</th>
<th>ΔHbA1c (%) (P&lt;0.001 vs baseline; P&lt;0.05 vs MDI)/ 8.2±1.0 (P&lt;0.05 vs baseline)</th>
<th>Minor Hypoglycemia</th>
<th>Major/Severe Hypoglycemia</th>
<th>Nocturnal Hypoglycemia</th>
<th>Total Daily Insulin-Dose (Baseline/Study End)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derosa et al., 2009 [68]</td>
<td>A (64)</td>
<td>12 mo/ randomized, case-control</td>
<td>ILisp/I Glar + ILisp</td>
<td>9.2±2.0/ 9.3±2.1</td>
<td>7.6±0.8/ 7.4±0.8</td>
<td>1.6/1.1</td>
<td>0.7/1.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>47 IU/NR</td>
</tr>
<tr>
<td>Jeitler et al., 2008 [69]†</td>
<td>A/C/E (33)</td>
<td>5 wk to 2 y/ meta-analysis of 22 RCTs</td>
<td>RHI or RAIA/P, NPH I Glar, ultralente, lente, or monodor + RAIA or RHI</td>
<td>NR</td>
<td>NR</td>
<td>Adults T1D : weekly events per patient: 0.9-3.3/ 1.1-3.3; Adults T2D: 1.1/2 events/patient/wk 0.8/1.2 events/patient/30 d</td>
<td>Adults T1D : weekly events per patient: 0.9-3.3/ 1.1-3.3; Adults T2D: 1.1/2 events/patient/wk 0.8/1.2 events/patient/30 d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

A, Adult (aged ≥18 to <65 y); C, child (aged <18 y); E, elderly (aged ≥65 y).

All values for change in HbA1c are those reported in the original studies except that indicated with *, for which endpoint value has simply been subtracted from baseline.

†Only mean data provided for adults with T1D. §Adolescents. ¶Higgins I² statistic to assess heterogeneity between trials, provides the percentage of variability in effect estimates resulting from heterogeneity. This range is from only 6 of 17 studies reviewed; others reported 0 or inconsistent methods of tracking events; Based on 2 studies.
HbA1c (-0.8 ± 1.5%) vs a mean increase in HbA1c (+0.4 ± 1.3%) with multiple daily injections (P=0.007). Hypoglycemic events were minimal in both groups [50].

INTERPRETING THE RESULTS OF CSII THERAPY VS MULTIPLE DAILY INJECTIONS IN TYPES 1 AND 2 DIABETES

The advantage of CSII with rapid-acting insulin analogs is less well supported in type 2 diabetes than in type 1 diabetes; the underlying differences between the different disease states may explain these results. Since insulin is replaced in type 1 diabetes rather than supplemented, glycemic improvement may be easier to detect. Risk of hypoglycemia is also greater with insulin in type 1 diabetes than in type 2 diabetes, so risk reduction may be more apparent in patients with type 1 diabetes.

Inappropriate patient selection for CSII therapy may also explain the absence of striking differences in study outcomes in type 2 diabetes. For example, patients included in the studies by Raskin et al. [67] and Herman et al. [65] had mean baseline HbA1c levels (≤8.4%) that were not high enough to render their patients appropriate for CSII therapy. In contrast, patients in the study by Berthe et al. [64] did have high mean baseline HbA1c levels (9.0 ± 1.6%) and experienced significant HbA1c decreases by study end; however, the types of insulin used in the study were not clarified. The advantages of CSII therapy are best assessed on an individual basis, with careful selection of appropriate candidates for this therapy.

FUTURE CONSIDERATIONS

Closed-loop insulin-control systems (also known as the ‘artificial pancreas’) depend upon a combination of CSII and continuous glucose measurement technologies via a controller. Pioneered in the 1960s by Weller et al. [78], the first portable pump was designed by Arnold Kadish in 1964 [79]. Since that time, a number of companies have developed commercially-available glucose monitors and insulin pumps, but only in recent years have these devices been manufactured to function in unison.

To date, the benefit of closed-loop pumps has been shown primarily in children and adolescents with type 1 diabetes by reducing the risk of nocturnal hypoglycemia in this population [80]; despite this, the approach to the development and adoption of closed-loop systems in the clinical setting is likely to be gradual [81]. Significant, challenging development milestones must be achieved in all three components of the artificial pancreas in order to make this technology practical for and available to a wider range of patient groups. Insulin pumps must become smaller and more user-friendly, continuous glucose monitors must become more accurate and more responsive, and controllers will require individualized algorithms that adapt to the needs of the individual in real time. Until these milestones are reached, the lessons learned from early investigation of closed-loop systems can be applied to users of CSII therapy – for instance, the administration of small amounts of insulin 15 min prior to meals to suppress the preabsorptive phase of hepatic glucose output, which contributes significantly to PPG [82].

Ultimately, the artificial pancreas can offer patients with type 1 or type 2 diabetes normoglycemia, with a reduced risk of diurnal and nocturnal hypoglycemia and mitigation of prolonged post-prandial hyperglycemia [80,83]. Results from recent studies such as the Sensor-Augmented Pump Therapy for A1c Reduction (STAR) show promise that sensor-augmented pump therapy can provide patients with the tools they need to reach target HbA1c levels [84]. Findings in this and other sensor-augmented pump studies include the clear and unmistakable message that efficacy is linked to usage duration: the more time a patient spends on a sensor-augmented pump, the greater the improvement in HbA1c levels that patient will experience.

In the long-term, successful and widespread adoption of new technologies such as sensor-augmented insulin pumps or the artificial pancreas depends upon the creation of a reliable infrastructure to educate and support both patients and practitioners in the technical and clinical use of pump technology [81].

CONCLUSIONS

CSII therapy with rapid-acting insulin analogs using insulin pumps is a valid alternative to multiple daily injections in patients with type 1 and type 2 diabetes. The clinical benefits of CSII therapy have been clearly demonstrated in type 1 diabetes, with patients experiencing improved glycemic control, a proactive response to glucose variability, reduced risk of hypoglycemia and weight gain, and lower total daily insulin consumption compared with multiple daily injection therapy. The benefits of CSII therapy vs multiple daily injections are more equal in patients with type 2 diabetes; this may be explained by various distinctions between the type 1 and type 2 diabetes disease state.

The appropriate selection of patients for CSII therapy with insulin pumps will help to ensure successful diabetes treatment outcomes. Patients who are very poorly controlled on multiple daily injections may benefit from CSII, with the greatest glycemic improvement associated with high baseline HbA1c. In particular, CSII therapy may benefit patients with type 1 diabetes who are prone to hypoglycemia and patients with type 2 diabetes who are obese and uncontrolled on high doses of insulin. More long-term, randomized controlled trials comparing CSII therapy with rapid-acting insulin analogs vs multiple daily injections are necessary and warranted to further explore the potential of CSII therapy with insulin pumps, particularly in patients with type 2 diabetes and in the pediatric population.

ABBREVIATIONS

BID = Twice daily
CI = Confidence interval
CSII = Continuous subcutaneous insulin infusion
EOT = End of treatment
ER = Emergency room
IASp = Insulin aspart
IDet = Insulin detemir
IGlar = Insulin glargine
ILisp = Insulin lispro
ITT = Intention-to-treat
MDI = Multiple daily injection
MH-OR = Mantel-Haenszel odds ratio for 95% confidence interval
NPH = Not reported
PPG = Postprandial glucose
RAIA = Rapid-acting insulin analog
RCT = Randomized controlled trial
RHI = Regular human insulin
SD = Standard deviation
T1D = Type 1 diabetes
T2D = Type 2 diabetes
TDD = Total daily dose

CONFLICTS OF INTEREST
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REFERENCES


Continuous Subcutaneous Insulin Infusion Therapy


