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 HbA_{1c} 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.

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 HbA_{1c} 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 HbA$_{1c}$ 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 HbA$_{1c}$ 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**).
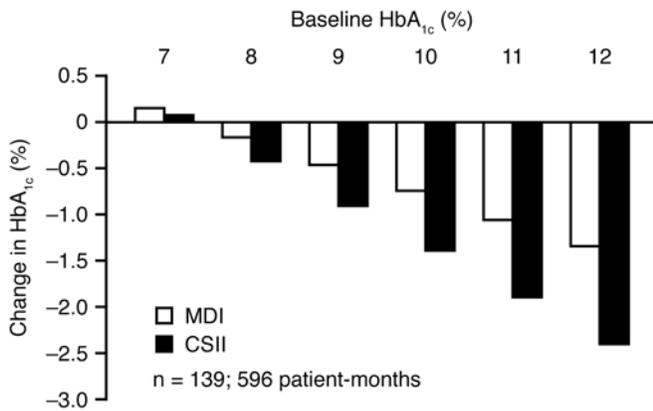
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Fig. (1). Predicted relative benefit of CSII over MDI in lowering HbA_{1c} increases as baseline HbA_{1c} rises [51]. Adapted with permission from The American Diabetes Association.

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 [42,44,48,50,52-69] (Tables **2** and **3**).

Glucose variability can persist in patients who appear to have good glycemic control (as assessed by HbA_{1c}) 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 levels following PPG excursions, and timely restoration of euglycemia reduces the risk of adverse cardiovascular outcomes associated with hyperglycemia [70].

CLINICAL PERFORMANCE OF CSII IN CONT-ROLLED 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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)

Reference	Patient Type (*n*)	Study Duration/ Type	Insulin Regimen (CSII/MDI)	HbA$_{1c}$ Baseline (%, CSII/MDI)	HbA$_{1c}$ Endpoint (%, CSII/MDI)	ΔHbA$_{1c}$* (%, CSII/MDI)	Minor Hypoglycemia	Major/ Severe Hypoglycemia	Nocturnal Hypoglycemia	Total Daily Insulin Dose (Baseline/Study End)
Ahern *et al.*, 2002 [52][†]	C (161)	12 mo/ prospective trial of MDI patients switched to CSII	ILisp	Preschool age (1–6 y): 7.1±0.9 School age (7–11 y): 7.9±1.0 Adolescents (12–18 y): 8.1±1.5	Preschool: 6.5±0.7 School age: 7.3±1.1 Adolescents: 7.4±1.2	Range: 0.6–0.7 (P≤0.02 *vs* baseline, for all three age groups)	NR	Pre-pump: 56 (0.35 number/ patient/y) CSII: 38 (0.24) (P<0.05 *vs* pre-pump)	NR	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±0.5/ 0.9±0.5 IU/kg/d
DeVries *et al.*, 2002 [44]	A (79)	16-wk/ open-label crossover randomized trial	IAsp/ NPH + IAsp	9.27±1.4/ 9.25±1.4	NR	0.91±1.28/ 0.07±0.70 (P=0.002), difference 0.84 (95% CI: -1.31 to -0.36)	+0.98±2.02/ -0.02±1.18 episodes/ patient-wk	3/6 (no. of patients)	NR	-15.8±15.06 *vs* 2.9±17.01 units/d, P<0.001 difference -18.76 units/d (95% CI: -26.45 to -11.07)
Doyle *et al.*, 2004 [53]	C (32)	16-wk/ randomized prospective trial	IAsp/IGlar + IAsp	8.1±1.2/ 8.2±1.1	7.2±1.0 (P<0.02 *vs* baseline; P<0.05 *vs* glargine group) /8.1±1.2	0.9/0.1*	NR	0/4 events	2/1 events	(1.4 units/kg at baseline *vs* 0.9 units/kg at 16 wk; P<0.01)
Gabbe *et al.*, 2000 [54]	P (60)	Duration of pregnancy and post-partum/ retrospective review of maternal and neonatal records	ILisp (*n*=23) or RHI (*n*=37)	NR	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: 9.1 Group 3: 7.1 (*P* = .02, all three groups)	Group 1: 1.5 Group 2: 1.8 Group 3: 0.8	Group 1: 13/24 (54.1%) Group 2: 15/24 (62.5%) Group 3: 7/12 (58.3%)	Group 1: 2 episodes in 1 patient Group 2: 8 episodes total in 6 patients Group 3: 0	NR	NR
Hirsch *et al.*, 2005 [55]	A (100)	10 wk/ open-label, randomized crossover trial	IAsp/IGlar + IAsp	CSII to MDI: 7.4±0.8 MDI to CSII: 7.5±0.8	CSII to MDI: 7.3±0.7 MDI to CSII: 7.1±0.7 (P>0.05)	CSII to MDI*: 0.1 MDI to CSII*: 0.4	5.6 *vs* 3.9 P<0.001	2/5 episodes	Minor: 2.2 *vs* 3.2 episodes/ subject/5-wk period (P=0.02)	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)

(Table 1) contd…..

Reference	Patient Type (*n*)	Study Duration/ Type	Insulin Regimen (CSII/MDI)	HbA$_{1c}$ Baseline (%, CSII/MDI)	HbA$_{1c}$ Endpoint (%, CSII/MDI)	Δ HbA$_{1c}$* (%, CSII/MDI)	Minor Hypoglycemia	Major/ Severe Hypoglycemia	Nocturnal Hypoglycemia	Total Daily Insulin Dose (Baseline/Study End)
Hoogma *et al.*, 2006 [56]	A (246)	6 mo/ randomized, controlled crossover	ILisp/NPH + ILisp	CSII to MDI: 8.2±1.4 MDI to CSII: 8.3±1.1	CSII: 7.45 MDI: 7.67	23% difference in mean EOT HbA$_{1c}$ in favor of CSII (P<0.001)	Incidence ratio: 1.12 (95% CI: 1.08–1.17)	Incidence ratio: 2.61 (95% CI: 1.59–4.29)	NR	0.53±0.14/0.71± 0.23 IU/kg body weight/d
Lapolla *et al.*, 2003 [57]	P (93)	Duration of pregnancy/ observational	RHI or ILisp/bolus RHI + basal RHI	7.7±1.6/ 7.2±1.4	6.4±1.2/ 6.3±1.0	1.3/0.9*	16.7%/14.3%	1 hypogly-cemic coma/1 hypogly-cemic coma	NR	CSII: 40±11/62±23 U MDI: 37±14 U/52±21 U
Lepore *et al.*, 2005 [58]	E (82)	31.9±14.5 mo (range 4–55 mo)/ observational	ILisp or IAsp/RHI or RAIAs + NPH or IGlar	NR	NR	First 3 mo: CSII *vs* MDI: 8.35±1.06 *vs* 9.39±1.35 (P<0.001) Overall mean change CSII: 1.15±0.84 (P<0.001)	NR	0.10±0.02/ 0.35±0.07 episodes/ patient-y (P<0.001)	NR	38.8±12.3/ 52.1±17.5 units/d (P<0.001)
Monami *et al.*, 2010 [59]	A/C	≥12 wk/ meta-analysis of 11 RCTs	RAIAs/ RAIAs	Total: 8.5	Total: 7.6±0.9/ 7.9±0.8	Standardized difference in mean: -0.3 [-0.4; -0.1], in favor of CSII (P<0.001)	NR	Between-group difference in rate of severe hypogly-cemia: MH-OR 0.80 (0.39;1.63) (P=0.53)	NR	Total: 39.4±13.0/ 56.9±23.1 IU/kg/d
Pickup *et al.*, 2002 [60]	A/C‡	2 mo to 2 y/ meta-analysis of 12 RCTs	ILisp, actrapid, velosulin, or RHI/ isophane, lente, or ultralente +RHI or RAIAs	NR	NR	Standardized mean difference in favor of CSII: 0.44 (0.20–0.63)	NR	NR	NR	Standardized mean difference in dose: 0.58 (0.34–0.83), or 7.58 units/d
Pickup *et al.*, 2008 [61]	A/C/E	≥6 mo/meta-analysis of 22 studies (RCTs, before/after studies)	IGlar or IDet + RHI or RAIAs for both groups	NR	NR	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<0.001); All studies: 0.62 (0.47–0.78)	NR	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)	NR	NR

(Table 1) contd…..

Reference	Patient Type (*n*)	Study Duration/ Type	Insulin Regimen (CSII/MDI)	HbA$_{1c}$ Baseline (%, CSII/MDI)	HbA$_{1c}$ Endpoint (%, CSII/MDI)	Δ HbA$_{1c}$* (%, CSII/MDI)	Minor Hypoglycemia	Major/ Severe Hypoglycemia	Nocturnal Hypoglycemia	Total Daily Insulin Dose (Baseline/Study End)
Retnakaran *et al*., 2004 [42]	A (139)	>2 wk/ pooled analysis of 3 RCTs	RAIAs/ RAIAs	NR	NR	Pooled estimate of treatment effect, CSII *vs* MDI: 0.35 (95% CI: -0.10; 0.80; P=0.08)	Overall hypoglycemia: 2.2/2.0 events/wk Pooled estimate of percentage difference in hypoglycemic risk (CSII – MDI): 9.7% (95% CI: -11.3;35.8, P=0.39)	NR	NR	Estimate for reduction in TDD CSII *vs* MDI: Fixed effects model: 11.3 units/d (7.8–14.8)
Siegel-Czarkowsi *et al*., 2004 [62]	E (34)	1 y/ prospective study in which MDI patients were switched to CSII	IGlar + premeal insulin analog or BID NPH + premeal insulin analog	7.64±0.19	6 mo: 7.23±0.20 1 y: 7.01±0.10 (P<0.01 *vs* baseline)	0.63*	NR	Patients treated in ER for hypogly-cemia: 1/7 (when on MDI prior y) Patients experien-cing hypogly-cemic seizures: 1/9	NR	NR
Skogsberg *et al*., 2008 [63]	C (72)	24 mo/open, randomized, parallel	IAsp/ NPH + IAsp	8.2±0.4/ 8.4±0.5	6.5±0.4 (SD 0.13±0.31)/ 6.7±0.5 (0.30±0.21)	1.7/1.7*	Perceived frequencies: 1.7±0.4/ 1.7±0.4	NR	NR	CSII: 0.74±0.10/ 0.74±0.09 U/kg MDI: 0.85±0.15/ 1.07±0.06 (CSII *vs* MDI at 24 mo; P=0.001)

A, Adult (aged ≥18 to <65 years); C, child (aged <18 years); E, elderly (aged ≥65 years); P, pregnant women.
*All values for change in HbA$_{1c}$ are those reported in the original studies except those indicated with *, for which endpoint values have simply been subtracted from baseline. †All patients switched from multiple daily injections to CSII therapy. Almost all patients received ILisp CSII. ‡Adolescents.

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 HbA$_{1c}$ 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 HbA$_{1c}$

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

Reference	Patient Type (*n*)	Study Duration/Type	Insulin Regimen (CSII/MDI)	HbA$_{1c}$ Baseline (%, CSII/MDI)	HbA$_{1c}$ Endpoint (%, CSII/MDI)	ΔHbA$_{1c}$* (%, CSII/MDI)	Minor Hypoglycemia	Major/Severe Hypoglycemia	Nocturnal Hypoglycemia	Total Daily Insulin Dose (Baseline/Study End)
Berthe *et al*., 2007 [64]	A (17)	24 wk/ randomized, crossover	ILisp/NPH + ILisp	9.0±1.6	7.7±0.8 (-1.3)/ 8.6±1.6 (-0.4) P<0.03	1.3/0.4[a]	CSII: 7 episodes MDI: 8 episodes	NR	NR	CSII: 1.0±0.3/1.0±0.2 units/kg/d MDI: 1.0±0.3/1.2±0.3 units/kg/d
Herman *et al*., 2005 [65]	E (107)	12 mo/RCT	ILisp/IGlar + ILisp	8.4±1.1/ 8.1±1.2	6.6±0.8/ 6.4±0.8	-1.7±1.0/ -1.6±1.2	1.08/1.22 events/wk No. patients with ≥1 episode: 48 (81%)/ 49 (90%)	No. patients with ≥1 episode: 3/6 CSII: 4 episodes in 49.87 person-y follow-up; 0.08 events/ person-y MDI: 12 events in 51.43 person-y follow-up; 0.28 events/ person-y	NR	CSII: NR (baseline)/ 108±63 units MDI: NR/108±62 units
Kesavadev *et al*., 2009 [66]	A (46)	MDI patients switched to CSII for 6 mo	IAsp	8.1±1.4	7.6±1.2	-0.5 (P<0.001; 95% CI: 0.161– 0.921)	NR	NR	NR	43.3±23.4/ 44.0±23.7 U
Lynch *et al*., 2010 [48]	A (131)	17 mo (range 3–39 mo)/ retrospective claims analysis	Long-acting insulin only or long-acting + rapid-acting insulins or any combo of ≥2 insulins	8.9	8.0	-0.9 (P<0.001)	NR	0.024±0.095 events/subject/ mo	NR	NR
Raskin *et al*., 2003 [67]	A (132)	24 wk/open-label, randomized, parallel-group	IAsp/NPH + IAsp	8.2±1.37/ 8.0±1.08	7.6±1.22 (-0.62±1.11)/ 7.5±1.17 (-0.46±0.89) (P<0.05)	-0.62±1.11/ -0.46±0.89	54% (34/63)/ 59% (36/61)	NR	16% (10/62)/ 22% (13/59)	CSII: 0.75±0.46/ 0.7 units/kg MDI: 0.69±0.39/ 0.8 units/kg
Wainstein *et al*., 2005 [50]	A/E (40, ITT)	48 wk/ randomized, crossover	ILisp/NPH + RHI or humulin R	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	-0.8±1.5 during CSII/ +0.4±1.3 during MDI (P=0.007)	NR	3 events on pump therapy/ 2 events on MDI	NR	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)

A, Adult (aged ≥18 to <65 y; C, child (aged <18 y); E, elderly (aged ≥65 y).
*All values for change in HbA$_{1c}$ are those reported in the original studies except that indicated with *, for which the endpoint value has simply been subtracted from baseline.

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 treatment. HbA$_{1c}$ levels decreased from 9.0 % to 7.7 % with CSII therapy, and to 8.6 % with multiple daily injections (P<0.03). Hypoglycemia rates did not increase for either treatment [64].

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**

Reference	Patient Type (*n*)	Study Duration/Type	Insulin Regimen (CSII/MDI)	HbA$_{1c}$ Baseline (%, CSII/MDI)	HbA$_{1c}$ Endpoint (%, CSII/MDI)	Δ HbA$_{1c}$* (%, CSII/MDI)	Minor Hypoglycemia	Major/Severe Hypoglycemia	Nocturnal Hypoglycemia	Total Daily Insulin Dose (Baseline/Study End)
Derosa *et al.*, 2009 [68]	A (64)	12 mo/ randomized, case-control	ILisp/IGlar + ILisp	9.2±2.0/ 9.3±2.1	7.6±0.8 (P<0.0001 *vs* baseline; P<0.05 *vs* MDI)/ 8.2±1.0 (P<0.05 *vs* baseline)	1.6/1.1*	NR	NR	NR	CSII: 47 IU/NR (study end value: P<0.01 *vs* MDI) MDI: 55 IU/NR
Jeitler *et al.*, 2008 [69]†	A/C‡/E (33)	5 wk to 2 y/ meta-analysis of 22 RCTs	RHI or RAIAs/ NPH IGlar, ultralente, lente, or monotard + RAIA or RHI	NR	NR	Adults T1D: -0.4 (95% CI: -0.65; -0.20; I^2=72%)§; between-treatment difference in favor of CSII	Adults T1D : weekly events per patient: 0.9-3.1/ 1.1-3.3 Adults T2D¶: 1.1/1.2 events/patient wk 0.8/1.2 events/ patient/30 d	Adults T1D : Proportion of patients with episodes: 0.0-0.13/ 0.0-0.4 Adults T2D⁻: 0.1/0.2 event rate/patient-y Children T1D: 3/6 events	NR	NR

A, Adult (aged ≥18 to <65 y); C, child (aged <18 y); E, elderly (aged ≥65 y).
*All values for change in HbA$_{1c}$ 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 I^2 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 1 of 2 studies; the other reported 0 severe events; ⁻Based on two studies.

In a 12-mo retrospective claims analysis of 131 poorly-controlled adults with type 2 diabetes (baseline HbA$_{1c}$ >8.5 %) that included the elderly, patients demonstrated statistically significant improvement in HbA$_{1c}$ levels after switching to CSII therapy with rapid-acting insulin analogs [48]. All treatment groups experienced a statistically-significant decrease in HbA$_{1c}$, with higher baseline HbA$_{1c}$ correlating with greater decrease in HbA$_{1c}$ (correlation -0.7%). Patients receiving rapid-acting insulin analogs experienced a mean HbA$_{1c}$ decrease of 0.8% (P<0.001). The number of patients reaching target HbA$_{1c}$ <7 % increased significantly from baseline to follow-up (8.4–22.9% [using mean HbA$_{1c}$]; P<0.001). The rate of severe hypoglycemic events remained similar to baseline [48].

In contrast, a 12-mo, prospective, randomized controlled trial of 107 older adults (mean age 60 y) with type 2 diabetes yielded similar results for both CSII therapy with ILisp and multiple daily injections with IGlar + ILisp in terms of improved glycemic control, safety, and patient satisfaction [65]. HbA$_{1c}$ levels were similar between groups at baseline, and mean HbA$_{1c}$ levels fell by similar percentages, although between-group difference and hypoglycemia rates were not statistically significant. Both treatments produced a signifi-cant 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]. HbA$_{1c}$ 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

HbA_{1c} (-0.8 ± 1.5%) *vs* a mean increase in HbA_{1c} (+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 HbA_{1c} 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 HbA_{1c} levels (9.0 ± 1.6 %) and experienced significant HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}. 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 = Neutral protamine Hagedorn

NR = 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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