Continuous subcutaneous insulin infusion therapy and multiple daily insulin injections in type 1 diabetes mellitus: A comparative overview and future horizons

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Abstract

Introduction: Continuous subcutaneous insulin infusion therapy (CSII) is currently accepted as a treatment strategy for type 1 diabetes. Transition from multiple daily injection therapy (MDI; including basal-bolus regimens) to CSII is based on expectations of better metabolic control and less hypoglycaemic events. Evidence to date has not been always conclusive.

Areas covered: Evidence for CSII and MDI in terms of glycaemic control, hypoglycaemia and psychosocial outcomes are reviewed in adult and paediatric population with type 1 diabetes. Findings from studies on threshold-based insulin pump suspension and predictive low glucose management are outlined. Limitations of current CSII application and future technological developments are discussed.

Expert opinion: Glycaemic control and quality of life may be improved by CSII compared to MDI depending on baseline HbA1c and hypoglycaemia rates. Future studies are expected to provide evidence on clinical and cost effectiveness in those who will benefit the most. Training, structured education and support are important to benefit from CSII. Novel technological approaches linking continuous glucose monitoring and CSII may help to mitigate against frequent hypoglycaemia in those at risk. Development of glucose-responsive automated closed-loop insulin delivery systems may reduce the burden of disease management and improve outcomes in type 1 diabetes.

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Article highlights

- Continuous subcutaneous insulin infusion (CSII) therapy involves infusion of rapid-acting insulin analogue according to a pre-programmed basal profile to mimic basal insulin secretion, and meal boost insulin to manage post-prandial glucose excursions.
- Glycaemic control is improved by CSII in those suboptimally controlled by multiple daily injection (MDI) therapy with a greater treatment at high baseline HbA1c.
- Most trials were not powered to demonstrate significant differences in hypoglycaemia due to low reported baseline rates of hypoglycaemia; however those with the greatest hypoglycaemia burden at baseline benefitted significantly from CSII use.
- Findings from qualitative studies and validated quality of life questionnaires in adults and adolescents with type 1 diabetes as well as parents indicate that majority of CSII users experienced higher diabetes treatment satisfaction and diabetes-related quality of life measures compared to MDI, with very low discontinuation rates of CSII therapy.
- Further innovations in CSII technology are anticipated with the advent of threshold suspend features and closed-loop insulin delivery systems, which may further improve clinical outcomes.

1. Introduction

Type 1 diabetes is a chronic autoimmune condition characterised by inflammation and destruction of pancreatic B-cell, leading to absolute insulin deficiency and hyperglycaemia. The Diabetes Control and Complication Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study have had major influence on clinical practice^{1, 2}. Improvement of glycaemic control by intensive insulin therapy in the DCCT significantly reduced the risk of microvascular complications, while EDIC following the DCCT cohort demonstrated beneficial effects of intensive insulin therapy which persisted

17 years later, with reduced risk of cardiovascular events by 42 percent. The intensive treatment group in the DCCT received multiple daily insulin injection therapy (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. Participants in the DCCT treated with CSII achieved and maintained relatively lower glycated haemoglobin (HbA1c) levels compared to MDI users. However the rate of severe hypoglycaemia was notably higher in the group receiving intensive treatment by around two to three-fold.

An important difference to current practise is that modern recommended MDI therapy, known as basal-bolus regimen (once or twice daily injections of long-acting insulin analogues combined with rapid-acting insulin analogues at mealtimes) are not comparable to the older insulin therapy used in the DCCT. Modern insulin analogues have faster and less variable insulin action profiles compared to older human insulins³. The use of insulin analogues have been shown to reduce the relative rate of hypoglycaemia events by 29%, in those at highest risk⁴. Along with comprehensive diabetes self-care and structured education, clinical outcomes may therefore differ from earlier studies. As more expensive technology becomes integrated with day-to-day healthcare delivery, clinical and cost-effectiveness needs to be demonstrated. The present article outlines the current evidence of CSII and MDI in the adult and paediatric population with type 1 diabetes from the perspective of measured glycaemic outcomes and quality of life impact on people with type 1 diabetes and caregivers. The issues and limitations surrounding CSII application in clinical practice are discussed, together with updates on technological developments and recommendations for future research to address unanswered questions.

2. Insulin therapy and delivery methods in clinical practise

2.1. Multiple daily injections

Evidence of intensive insulin therapy in reducing the risk of long-term diabetes related complications was first shown in the DCCT, and have subsequently been confirmed by other studies⁵. The MDI regimen of the DCCT control group consisted one or two fixed doses of insulin that did not vary with meals, whereas the MDI regimen of the intervention

group consisted of three or more daily insulin injections adjusted according to self-monitoring blood glucose results, dietary intake, and anticipated exercise. As mentioned earlier this has been superseded by modern insulin analogues administered in a manner replicating the endogenous insulin secretory profile by the healthy pancreas known as the basal-bolus MDI regimens. This consists of subcutaneous long-acting or basal insulin to maintain glucose homeostasis between meals and normalise glucose levels during fasting period, and quick or rapid-acting insulins to provide prandial insulin cover during meals. Basal-bolus regimens are now widely advocated by professional clinical bodies and is currently the primary strategy for intensive insulin therapy in type 1 diabetes. Subcutaneous insulin preparations currently available in clinical practice as part of the basal bolus strategy include soluble (regular) human insulin, Neutral Protamine Hagedorn (NPH) insulin and analogue insulins. These are subdivided according to duration of action into intermediate/long-acting insulins and quick/rapid-acting insulins.

NPH is a neutral suspension insulin created by the addition and crystallisation of protamine with regular insulin⁶. Its pharmacokinetic is more in keeping with an intermediate-acting rather than long-acting insulin. NPH insulin has an onset of action of approximately 2 to 4 hours. It reaches peak plasma concentration at 4 to 10 hours with duration of action up to 10 to 18 hours. It has several disadvantages; its peak action in plasma is often associated with nocturnal hypoglycaemia if given at night, and its pharmacokinetics is less predictable as subcutaneous absorption of NPH insulin can vary by up to 80%⁷.

The first long-acting insulin analogue introduced in clinical practice was glargine⁸. In glargine, the amino acid of regular insulin, glycine, is substituted for asparagine at position 2. It is less soluble at physiologic pH but more soluble at acidic pH, due to the addition of arginine residues to the B chain. As glargine precipitates at neutral pH, this leads to slower absorption following subcutaneous administration. Its pharmacokinetics is relatively peakless compared to NPH insulin, and has a duration of action of approximately 20 to 24 hours⁹. Another long-acting analogue currently being used in clinical practice is insulin detemir, in

which the amino acid threonine of regular insulin is removed at B30, and fatty acid acylation of lysine can be found at B29. This acylation allows the molecule to bind to albumin in plasma, thereby prolonging the duration of action of detemir in the systemic circulation¹⁰. Its half-life is slightly less than glargine (duration of action 18 to 22 hours), thereby necessitating twice daily administration by most MDI users. In contrast to glargine it does not form a precipitate after subcutaneous injection and has a neutral pH. A recent addition to the basal insulin analogue family is degludec, in which the DesB30 human insulin is acylated with hexadecandioic acid and forms stable di-hexamers compounds in the presence of phenol and zinc. The di-hexamer compounds initially self-associate into depot of multi-hexamer chains at the injection site, following subcutaneous injection and dispersion of phenol. The diffusion of zinc then causes the multi-hexameric depots to slowly and continuously release monomeric compounds of insulin degludec. As a result, insulin degludec has a prolonged half-life of 25 hours, and clinical studies have shown a four-fold reduction in day-to-day within subject pharmacodynamic variability, compared to insulin glargine¹¹.

Example of quick-acting insulin is regular (human) insulin. Regular insulin has an onset of action of 30 to 60 minutes, therefore it is advised to be administered subcutaneously 30 minutes prior to a meal. Its duration of action after injection is approximately 5 to 8 hours. In contrast, rapid-acting insulin which are insulin analogues, have faster onset than regular insulin (5 to 15 minutes), with faster peak concentration (0.5 to 2 hours) and shorter duration of action (3-5 hours)¹². Examples of these are insulin aspart, lispro and glulisine. Rapid-acting insulin analogues utilise various strategies to reduce insulin self-association, leading to earlier hypoglycaemic action compared to regular insulin. Among these strategies are introducing charge repulsion (in insulin aspart and glulisine) and stearic manipulation (lispro). As these analogues have significantly reduced lag-phase, they can be administered subcutaneously immediately with meals therefore allowing greater convenience and flexibility for users, although optimal postprandial glucose excursions is more likely to be achieved if given 15 minutes before meal¹³.

2.2. Continuous subcutaneous insulin infusion therapy

CSII was first used in type 1 diabetes in the 1970s^{14, 15}. Early generation CSII devices were bulky, unreliable, and delivered a single basal insulin infusion rate, with manually triggered boosts or boluses at meal times. Over the years, CSII devices have become smaller, more reliable and sophisticated, infusing rapid or quick acting insulin at preselected infusion rates with multiple programmable basal profiles to mimic basal insulin secretion. Modern CSII device have a number of bolus delivery profile options allowing different infusion rate patterns at mealtimes, and integrated on-board calculator which recommend insulin bolus dose based on manually entered glucose value, carbohydrate content and amount of insulin still active on board¹⁶.

The advantage of CSII compared to MDI is the planned and immediate adjustments that can be made to insulin delivery, in concordance to the varying degree of glycaemia levels which may occur throughout the day. Examples include gradual increase in insulin infusion rate overnight to address the dawn phenomenon and temporary suspension or decrease in insulin infusion rate following increased physical activity or fasting. Conventional CSII devices consist of a subcutaneous infusion set (catheter and tubing system), insulin reservoir (both replaced every 2 to 3 days) and a portable electromechanical pump. A recent innovation in CSII design has been the advent of the patch or "tubing-less" ("tubing-minimal") pump which integrate the infusion set, reservoir unit, pump and automated inserter into a single unit which adheres directly to the user's skin, allowing more discretion and freedom of movement.

The uptake of CSII in clinical practice varies globally, with an estimated 20-25% of type 1 diabetes in the US and Norway using CSII, to around 6% in the United Kingdom^{17, 18}. This may partly be explained by differences in the provision of service and support cost in different countries¹⁹. The National Health Service in the United Kingdom provides funding for CSII based on recommendations from the National Institute for Health and Clinical Excellence (NICE) technology appraisal committee. NICE supports CSII use in adults and

children ≥ 12 years of age with type 1 diabetes whose HbA1c remains above 69mmol/mol (8.5%) or suffers from recurrent disabling hypoglycaemia during attempts to achieve target hbA1c level, despite optimized basal-bolus insulin therapy and best efforts from the patient and diabetes team. CSII is recommended in children younger than 12 years and whom MDI is considered impractical or inappropriate, with the expectation of reverting to trial of MDI between ages 12 to 18 years. NICE also includes provider-specific recommendations such as availability of trained specialist team of diabetes specialist nurse, dietitian and diabetologist, and user engagement with structured education programmes tailored for CSII application.

These recommendations are not exclusive to the UK however, and are broadly in line with recommendations in other developed countries²⁰. In spite of its potential benefits, CSII implementation requires significant commitment and governance due to the underlying risks and inherent costs associated with CSII therapy. Examining the evidence for efficacy, safety as well as cost-effectiveness of CSII is therefore important to better understand its role and benefits in the management of type 1 diabetes.

3. Evidences from paediatric studies

3.1. Glycaemic control

Two large paediatric diabetes registries, the T1D Registry in the US and the Prospective Diabetes Follow-up Registry in Germany and Austria, recently evaluated the clinical outcomes of participants under the age of six on CSII and MDI²¹. The T1D Registry showed that those on CSII had significantly lower average HbA1c levels and were more likely to achieve levels less than 7.5%. The Prospective Diabetes Follow-up Registry however showed no difference between CSII and MDI. The CSII and MDI groups in the T1D Registry had comparable age, BMI z score and total daily insulin dose, whilst CSII users in the Prospective Diabetes Follow-up Registry were significantly younger (4.9years vs. 5.3years, $p < 0.001$). Between the two registries, HbA1c levels discrepancy was greatest among MDI than among CSII users. Long-term glycaemic control in 345 children on CSII

was compared with matched controls on MDI in a single centre observational study²². In spite of similar glycaemic control at baseline (HbA1c 8% in both groups), CSII users had significantly lower HbA1c throughout the follow-up period compared to the MDI group (mean HbA1c difference 0.7% over 5 years).

Limited numbers of randomised controlled studies comparing CSII with MDI have been performed in the paediatric population. Early randomised controlled studies included participants using regular insulin rather than analogues in the CSII group, or early generation CSII with limited capacity to alter basal rates and bolus profiles^{23, 24}. This limits the generalisability to modern CSII application and practice. A recent meta-analysis evaluated randomised controlled studies compared glycaemic control in children and adolescents on CSII using rapid-acting analogues, and MDI therapy receiving at least three injections per-day (with long- and rapid-acting analogues or NPH and regular insulin). The pooled mean between-group difference in HbA1c change from baseline was not significantly different [mean between group HbA1c difference -0.14% (95% CI -0.48 to 0.20)] and were comparable among adolescents > 12 years and children < 12 years²⁵. A criticism of most comparative studies and meta-analyses is the inclusion of MDI participants not on recommended analogue-based basal-bolus MDI regimen as comparator for CSII (see Table 1). This may introduce a bias in favour of CSII given the perceived benefits of analogues against regular and NPH insulin, and argumentation that analogue-based basal-bolus MDI may have comparable glycaemic effects to CSII²⁶.

3.2. Hypoglycaemia

Due to the heterogeneity in reporting and definition of hypoglycaemia, only studies with data on severe hypoglycaemia deemed clinically significant (associated with seizure or loss of consciousness²⁷) will be stated. In an observational study (n=255), significant reduction in the incidence rate of severe hypoglycaemia was shown in CSII users compared to MDI users on NPH insulin (31.8/100-patient-years vs. 46.1/100-patient-years, p=0.04)²⁸. This was confirmed by another long-term observational study of over 1,160 person-years of

follow-up, which showed significantly lower rate of severe hypoglycaemia by 30 % in CSII user compared MDI (7.2 vs 10.2 per 100 patient-years, $p=0.013$)²².

A meta-analysis of randomised controlled studies in participants on MDI and on CSII with insulin analogues reported similar rate of severe hypoglycaemia between the treatment group, but had notably wide confidence interval [pooled incidence rate ratio based upon events per person-year of 0.99 (95% CI 0.57-1.71)]²⁵. Hypoglycaemia rates are known to increase with diabetes duration, and as children generally have shorter duration of diabetes than adults the baseline rates of severe hypoglycaemia in this population are considerably lower^{29, 30}. Studies included in the meta-analysis were of short duration (less than 6 months) with low reported baseline rates of severe hypoglycaemia, and thus were not statistically powered to show any significant difference between treatment groups.

3.3. Quality of life and carers perspective

In a prospective pre and post-CSII study involving children and adolescents between ages 4 to 16 year, significant increase in diabetes-specific quality of life (QOL) was shown across the whole age range following transition to CSII³¹. Formal comparisons using validated measures in six randomised controlled studies found comparable effects on general QOL, but CSII users had higher treatment satisfaction measures compared to MDI²⁵. The strength of evidences is limited by the different measures used to assess QOL outcomes. A comprehensive battery of cognitive tests were applied to children aged 6 to 16 years in a pilot uncontrolled study at baseline and 6 to 8 weeks after starting CSII³². The study reported significant improvements in scores related to perceptual reasoning, selective attention, divided attention, cognitive flexibility and working memory. Several small randomised controlled studies ($n=16-38$ participants) which included parental diabetes-specific QOL scores showed no significant difference between the CSII and MD groups^{33, 34}. However in one study an increase in QOL scores in the fathers of the CSII group was reported at the 6-month follow-up period³⁵.

4. Evidences from adult studies

4.1. Glycaemic control

A Cochrane review of adults with type 1 diabetes showed significant difference in HbA1c favouring CSII compared to MDI [weighted mean difference -0.3% (95% CI -0.1 to -0.4)]²⁴. In a subgroup analysis of medium-term duration studies (one to six months), an estimated mean difference of HbA1c of -0.3% (95% CI -0.5 to -0.1) in favour of CSII was reported, while in studies longer than 6 months the mean difference was relatively smaller (-0.2% [95% CI -0.4 to 0.1]). A recent meta-analysis of randomised controlled studies compared CSII using insulin analogues, with MDI³⁶. A significant decrease of HbA1c in favour of the CSII group was found (combined mean between group difference -0.30% [95% CI -0.58% to -0.02%]). The degree of HbA1c reduction was greater in studies with higher HbA1c before CSII initiation. Retrospective analysis of data over 5 years from 272 CSII users confirmed that higher HbA1c at start of CSII intervention led to significantly greater HbA1c reduction compared to MDI control group (HbA1c reduction of 0.25% [95% CI 0.11 to 0.39] in participants with baseline HbA1c of 9.0% and BMI of 25 kg/m²)³⁷.

4.2. Hypoglycaemia

Estimated effects on hypoglycaemia may be misleading as most studies were limited by participant numbers, duration and frequency of hypoglycaemic episodes, thus statistically under-powered. As studies used different scales and definitions for non-severe hypoglycaemia, only studies reporting severe hypoglycaemia events will be summarised.

A Cochrane review reported lower incidence of severe hypoglycaemia events for CSII than MDI, but no meta-analysis of the data was provided²⁴. In a meta-analysis which included randomised controlled and before/after studies of participants with significant risk of severe hypoglycaemia (initial rate >10 episodes/100 patients years of treatment), those on CSII had significantly reduced rate of severe hypoglycaemia compared to MDI (rate ratio of 2.89 [95% CI 1.45 to 5.76] for RCTs and 4.34 [2.87 to 6.56] for before/after studies)²⁹. Sub-

analysis showed that older participants and those with high frequency of hypoglycaemia at baseline had the greatest reduction in severe hypoglycaemia. A meta-analysis of three randomised controlled trials comparing CSII using insulin analogues and MDI showed similar pooled incidence of severe hypoglycaemia in both groups³⁶. The confidence interval of the pooled odds ratio was notably wide [0.74 (95% CI 0.30 to 1.83)], likely due to the small number of participants involved in each study (less than 50 in each intervention group) and the relatively low rates of severe hypoglycaemia episodes.

4.3. Quality of life

In a randomised controlled study, 50 participants on NPH-based insulin therapy were randomised to either lispro-based CSII or lispro and glargine-based MDI for 24 weeks³⁸. Diabetes treatment-satisfaction scores were significantly higher in those on CSII. The 5-Nations trial randomised two hundred and seventy-two participants to CSII or NPH-based MDI, in which the CSII group showed significantly higher overall scores for diabetes-specific quality of life domains and improvement in mental health perception³⁹. Observational studies have similarly reported significant improvements in QOL and treatment satisfaction scores in CSII users compared to MDI^{40, 41}. A large case-control study involving 481 CSII and 860 MDI users (of which 90% were on glargine-based MDI) from 62 centres confirmed the findings from smaller aforementioned studies, with higher diabetes-treatment satisfaction scores as well as less fear of hypoglycaemia in CSII users⁴⁰.

Findings from formal validated measures of QOL are in concordance with anecdotal evidence observed in usual clinical practice, where most CSII users self-report improvements in well-being and mood when transitioned from MDI to CSII. Discontinuation rate for CSII, either by choice or otherwise, is reportedly low at most clinical centres⁴². This highlights the potential psychosocial benefits of CSII on the life of those with type 1 diabetes, beyond glycaemic control per se.

5. Combining insulin delivery with continuous glucose monitoring: What benefit does it add?

5.1. Continuous glucose monitoring with multiple daily insulin injections

Real-time continuous glucose monitoring (CGM) allows users to make immediate adjustments to their insulin doses, food intake and physical activity by inspecting glucose values and trends, and by responding to low and high glucose alarms. The present generation of real-time CGM devices utilises a minimally invasive subcutaneously implanted needle-type amperometric enzyme electrode to measure interstitial glucose concentration by detecting changes in the electric current caused by the enzymatic catalysation of glucose by glucose oxidase into hydrogen peroxide, and display new glucose readings every 1 to 5 minutes⁴³.

Comparative analyses of CGM in CSII vs. MDI users are challenging as most studies included participants who were on mixed modes of insulin delivery, or were using either real-time or retrospective CGM (sensor values were masked to participants). The HypoCompass study was a 24-week 2 x 2 factorial randomised controlled trial which studied the effects of different methods of insulin delivery and glucose monitoring on restoring hypoglycaemia awareness and preventing severe hypoglycaemia in participants with hypoglycaemia unawareness (Gold score ≥ 4)⁴⁴. A sub-analysis comparing CGM-MDI with CGM-CSII therapy showed no significant differences at follow-up in biochemical hypoglycaemia measures, severe hypoglycaemia episodes, Gold scores and HbA1c. However the analysis is weakened by the fact that it did not differentiate between real-time and retrospective CGM users in the CSII and MDI groups. No published studies to date have evaluated CGM effectiveness with MDI compared to CSII alone.

5.2. Sensor-augmented pump

Sensor-augmented pump therapy (SAP) combines real-time CGM with CSII, an example of which is the Paradigm Veo (Medtronic Diabetes, Northridge, CA, USA). SAP provides users with real-time CGM glucose profile whilst using CSII, making it a useful adjunctive tool to aid with retrospective and immediate insulin dose adjustments. Capillary glucose measurements are still needed however, to inform any premeal or correction insulin boluses. The first large multicentre randomised control trial, the STAR3 study, compared the efficacy of SAP with MDI in children and adults⁴⁵. Subjects on SAP achieved lower HbA1c levels (7.5% vs. 8.1%, $p < 0.001$), without increased incidence of hypoglycaemia. Improvement in HbA1c was still observed at 18-months follow-up⁴⁶. In a 26-week study comparing SAP with MDI, 87 adults with type 1 diabetes were randomised to either SAP or MDI therapy with rapid-acting insulin analogue before meals and long-acting analogues or human insulin⁴⁷. The study showed a significant improvement in the primary outcome (mean difference in change in HbA_{1c} after 26 weeks) in favour of SAP (-1.21% (95% confidence interval -1.52 to -0.90 , $P < 0.001$). This was achieved without increasing time spent hypoglycaemic (CGM values below 4.0 mmol/l), with between-group difference 0.0% (95% CI -1.6 to 1.7 , $P = 0.96$).

The benefit of adding CGM to CSII was confirmed by a meta-analysis of 4 randomised controlled studies ranging between 15 weeks to 1 year duration, which reported greater reduction in HbA1c for SAP than MDI (combined mean between-group difference from baseline -0.68% [95% CI -0.81 to -0.54])³⁶. The authors were unable to perform a pooled-analysis on the incidence of severe hypoglycaemia due to the different measures used by the included studies, and as a result were unable to draw a definitive conclusion. A large ($n=263$) single arm observational study showed that benefits of SAP persisted after 36 months in terms of HbA1c improvements (decreased from 8.7% to 7.3%, $p < 0.001$), as well as treatment satisfaction (improvement in Diabetes Treatment Satisfaction Questionnaire score by 9 points, $p < 0.001$)⁴⁸.

5.3. Threshold based insulin pump suspension and predictive low glucose management

SAP with automated insulin suspension represents the first step towards automated glucose-responsive insulin delivery systems. The low-glucose suspend (LGS) function (Paradigm Veo, Medtronic Diabetes, Northridge, CA, US) allows insulin to be automatically suspended for up to 2 hours when sensor glucose falls below a present threshold which is determined by the user or healthcare provider, and the hypoglycaemic alarm is not acknowledged. There are no published data comparing LGS with MDI, with SAP being the active comparator in randomised controlled studies. Post-marketing studies in children and adults have reported reduced duration of hypoglycaemia especially in those at greatest risk of nocturnal low glucose events^{49, 50}. LGS led to significantly lower rate of second and subsequent hypoglycaemia episodes, as well as lower rate of hypoglycaemia events overall. In spite of temporary insulin suspension, no evidence of increased ketosis or deterioration in HbA1c was observed. The ASPIRE In-Home was a large randomised controlled study which evaluated the effects of LGS compared with SAP on HbA1c and nocturnal hypoglycaemia in patients at risk with at least two nocturnal hypoglycaemic events during run-in phase⁵¹. The mean area under the curve for nocturnal hypoglycaemic events was lower by 37.5% compared to SAP with comparable HbA1c, thus confirming that LGS can reduce nocturnal hypoglycaemia episodes without deterioration of glycaemic control.

The predictive low glucose management (PLGM) function of the Medtronic 640G CSII device was recently introduced into clinical practise in Europe. In comparison to LGS, the hypoglycaemia-prediction algorithm and automatic pump suspension of the PLGM system enables insulin delivery to be suspended when hypoglycaemia is predicted and insulin delivery automatically restarted when hypoglycaemia risk recedes. Preliminary efficacy and safety data in an outpatient setting over 21 nights showed that PLGM reduced the proportion of nights with sensor glucose < 3.9 mmol/l by 40%⁵². Mean overnight glucose and morning fasting glucose was reported to be higher than control nights (without PLGM).

The investigators had to modify the hypoglycaemia-prediction horizon of the algorithm twice during the experiment, as pump suspensions occurred frequently leading to elevated overnight and morning glycaemia levels. A randomised controlled study evaluated PLGM use at home compared to conventional SAP for 42 nights⁵³. The primary endpoint of the study, percentage of nights with at least one sensor glucose values < 3.3 mmol/l, was approximately halved by PLGM (odds ratio 0.52 [95% CI 0.43-0.64]; $P < 0.001$). There was no difference in overnight sensor glucose levels > 10 mmol/l (57 vs. 59% of nights, $p=0.17$). Current results suggest that use of LGS or PLGM systems do not mitigate against overnight or early morning hyperglycaemia.

6. Limitations and potential solutions

6.1. Technical and mechanical issues

In spite of technological applications in modern CSII devices such as alerts and alarms for catheter occlusion or pump failures, CSII users may still be exposed to significant and potentially life-threatening conditions if there is lack of vigilance. As there is no subcutaneous depot of long-acting insulin during CSII use, interruption of insulin delivery due to catheter displacement, catheter/tubing occlusion, battery failure or depletion of insulin supply puts the user at risk of diabetic ketoacidosis especially if the interruption is prolonged. In a cross-sectional survey of 92 CSII users, nearly half reported some form of pump mechanism malfunction⁵⁴. This includes unintended stoppage of CSII delivery and keypad/button problems on the CSII device. Approximately ten percent of those surveyed also reported frequent kinking or blockage of infusion set, with an increasing trend associated with use of infusion set for longer than 3 days. This highlights the importance of user and healthcare provider adherence to proper CSII care and practice guidelines to mitigate against potential and relatively common hazards. It also underpins the need for regulation of CSII devices to ensure safety standards are met and improve reliability of CSII components by manufacturers⁵⁵.

6.2. Insulin absorption and pharmacokinetics

Subcutaneous absorption and action of insulin via CSII may be altered by local site reactions such as inflammation or lipohypertrophy. The quantitative effects of lipohypertrophy on changes in insulin pharmacokinetics and pharmacodynamics are still poorly understood due to the lack of well-conducted studies in this area⁵⁶. As a potential source of glycaemic variability, this may be of significant clinical concern given that a recent survey of CSII users revealed that approximately one in four may have lipohypertrophy⁵⁴. Therefore identifying and avoiding user-driven factors such as repeated injections/infusion with needles/catheters at the same body site should be common practise for all CSII users and healthcare professionals providing clinical care. Future development of alternative infusion delivery mechanism such as intra-dermal microneedle or use of hyaluronidase enzyme may accelerate the action and improve the pharmacokinetic consistency of insulin analogues used in CSII devices^{57, 58}.

6.3. Cost-effectiveness

The higher cost of CSII compared to MDI presents another limitation to its wider use. In the UK, the annualised cost of CSII with a 4-6 year warranty is approximately £1,700 greater than MDI⁵⁹. This includes the unit cost of CSII device and consumables related to infusion sets and reservoirs; however it does not factor in expenditures on staff and education time. Utilising the Centre for Outcomes Research (CORE) model and based on assumptions of HbA1c as well as QOL improvements, NICE in the UK deem CSII to be cost-effective based on a willingness to pay threshold of £20,000 to £30,000 per quality-adjusted life year gained⁴². The estimated cost per quality-adjusted life year improves in favour of CSII, if the expected reduction in HbA1c is greater due to expected reduced complications risk and health-care costs. The CORE model outcome assumes an average age of 40 years at baseline and is greatly influenced by HbA1c reduction rather than indices or impact of hypoglycaemia. The existing economic model does not adequately address the paediatric population or the individual and societal burden in those at greatest risk of hypoglycaemia, such as loss of productivity at work or school and mental health issues related to fear of

hypoglycaemia. There is therefore a need to re-appraise the analysis of CSII cost-effectiveness with various stakeholders so that those who may benefit the most from CSII are also included.

7. Expert opinion

The ongoing debate of CSII and MDI use in clinical practise has stemmed from the growing need by clinicians as well as health care service-providers to ascertain the relative benefit of one intervention against the other. Clinicians and people with type 1 diabetes face significant challenges when intensifying insulin therapy to reduce the risk of complications. The overall evidence currently point towards modest improvements in HbA1c level, severe hypoglycaemia rates and QOL measures in favour of CSII compared to MDI, but also that CSII may benefit some more than others. An important limitation is that many studies do not provide adequate information related to the extent of patient education, and whether self-management skills provided to both groups were comparable. Some analyses included participants not on analogue-based basal-bolus MDI regimens, and information on adherence to skills such as carbohydrate counting are lacking. These insufficiencies may confound reported outcomes, highlighting the need for well-designed powered studies with the comparator following “best clinical practice” and ensuring equal provisions for self-management skills and education among CSII and MDI users.

In reviewing data to address clinical decision-making, few studies and meta-analysis currently focus on those with significant and proven clinical need. Analysis should be focused on groups with the highest baseline HbA1c and hypoglycaemia burden rather than those who are already managing well on MDI, as it is the former rather than latter who may benefit the most when transitioned to CSII. Due to the relatively shorter duration of diabetes and hypoglycaemia exposure in the paediatric population, there is still a need for well-conducted statistically powered studies. This is especially true given the benefit of CSII to date in terms of lifestyle flexibility and psychosocial impact for parents and children with type 1 diabetes. Early evidence are also starting to emerge about the potential benefit of CSII in

lowering cardiovascular mortality compared to MDI⁶⁰. The exact mechanism however is unknown, and the finding remains to be verified and replicated in other cohorts.

The importance of self-empowerment and education has to be addressed in any form of insulin therapy in type 1 diabetes. Observational studies have shown that those who are motivated to invest the time and effort, and are well-educated in their diabetes self-care are more likely to achieve better glycaemic control. Family-centred, structured education programme in specialist centres and routine clinical care among the paediatric population have shown more personal engagement by family members around diabetes-related tasks, however the improvements in HbA1c was relatively modest^{61, 62}. In addition, ensuring optimal training and education to families and those needing it the most can be challenging, as reported by a qualitative study evaluating the feasibility of an education programme carried out across paediatric clinics in the UK⁶³. Among the reported barriers were organisational difficulties and time-commitment by staff members, reflecting real-world feasibility issues. Adult diabetes education courses such as Dose Adjusted for Normal Eating (DAFNE) in the UK which are delivered by trained diabetes educators, have shown benefits in glycaemic control and quality of life^{64, 65}. Optimisation of MDI therapy using programmes such as DAFNE should therefore be offered to all adults with type 1 diabetes.

The support and engagement to optimise their MDI therapy should be continuous during the course of their care with both parties fully involved, rather than to be used as a short-term bridge before CSII initiation. Transitioning to CSII, users and healthcare providers should acknowledge that realising the full potential of CSII involves similar if not more commitment to self-care, as well as a good knowledge base of insulin therapy. Trained pump educators should be available to provide support after transitioning to CSII, for example in downloading and reviewing glucose/insulin data from CSII devices, and helping make appropriate adjustments to insulin delivery settings. Future studies determining the benefits of CSII over MDI following exposure to structured educational programmes should ensure that such programmes cater for comprehensive CSII training and re-training.

Further innovation in diabetes technology is anticipated. The advent of SAP shows that integration of CSII with real-time CGM may provide additional benefit to glycaemic control in both adults and youth with type 1 diabetes, provided CGM use is high and consistent. Automated insulin delivery suspension at low or predicted low CGM levels may confer additional protection against hypoglycaemia, especially in those at greatest risk. Rapid progress is also being made in the development of closed-loop insulin delivery systems also known as the “artificial pancreas”, which uses a control algorithm that automatically smoothly modulates (increases and decreases) CSII insulin delivery based on real-time CGM values⁶⁶. Results from closed-loop clinical studies conducted in controlled research facility and unsupervised home settings have been promising⁶⁷⁻⁶⁹. Recently a three month application of closed-loop insulin delivery in real-world free-living conditions showed significant improvements in glycaemic control and reduction of hypoglycaemia events compared to optimised SAP⁷⁰. Larger and longer multicentre studies are being planned, and closed-loop insulin delivery systems may act as a ‘bridge’ until a biological cure for type 1 diabetes is found.

Advances in diabetes treatment and technology have the potential to reduce the considerable demands type 1 diabetes management has on people with type 1 diabetes and their caregivers. In those unable to achieve their glycaemic goal in spite of sufficient support, CSII may benefit them whilst potentially improving their quality of life. Well-conducted studies in those who would likely benefit from CSII most are still needed to provide further guidance and information to healthcare providers, and evidence for its use in clinical practice.

Table 1. Summary of studies comparing CSII with analogue- or NPH-based basal-bolus MDI regimens with HbA1c and hypoglycaemia endpoints.

Reference	Population	Study design	CSII intervention	MDI regimen	Number of participants	Study duration	Main findings
DeVries	Adults	Randomised parallel design	CSII therapy with rapid-acting insulin analogue	NPH-based basal insulin plus mealtime aspart	62	16 weeks	Mean HbA1c was 0.84% (95% CI -1.31 to -0.36) lower in the CSII group compared with the MDI group ($P = 0.002$). Number of patients with severe hypoglycaemia episodes was similar in either group.
Hoogma	Adults	Randomised parallel design	CSII therapy with rapid-acting insulin analogue	NPH-based basal insulin plus mealtime lispro	272	6 months	Hba1c values were similar at baseline (8.3 ± 1.1 vs. $8.2 \pm 1.4\%$), and reduced significantly in the CSII compared to MDI group (7.45 vs. 7.67% , $P < 0.001$). CSII users had significantly fewer severe hypoglycaemia events (0.5 vs. 0.2 events per patient year, $P < 0.001$)
Skogsberg	Paediatrics	Randomised parallel design	CSII therapy with rapid-acting insulin analogue	NPH-based basal insulin plus mealtime aspart	72	24 months	HbA1c was similar at baseline ($8.2 \pm 0.4\%$ in the CSII group and $8.4 \pm 0.5\%$ in the MDI group, $p = 0.57$). There was no significant difference in HbA1c after 24 months (6.5 ± 0.4 vs. $6.7 \pm 0.5\%$, $p = 0.66$). There were no significant differences in severe hypoglycaemia between the two groups.
Bolli	Adults	Randomised parallel design	CSII therapy with rapid-acting insulin analogue	Analogue-based basal bolus therapy	50	24 weeks	Mean A1C reduction was similar in the two groups (CSII - $0.7 \pm 0.7\%$; MDI - $0.6 \pm 0.8\%$) with a baseline-adjusted difference of -0.1% (95% CI -0.5 to 0.3). The incidence of overall hypoglycaemia events was similar in either group.
Doyle	Paediatrics	Randomised parallel design	CSII therapy with rapid-acting insulin analogue	Analogue-based basal bolus therapy	32	16 weeks	HbA _{1c} levels in the CSII group significantly decreased from $8.1 \pm 1.2\%$ to $7.2 \pm 1.0\%$ at 16 weeks ($P < 0.02$ vs. baseline and $P < 0.05$ vs. MDI group). No significant difference in HbA1c was observed in the MDI group. Five episodes of severe hypoglycaemia occurred in the MDI group, and none in the CSII group.
Bergenstal	Adults and paediatrics	Randomised parallel design	Sensor-augmented pump therapy with rapid-acting insulin analogue	Analogue-based basal bolus therapy	495	12 months	Baseline mean HbA1c level (8.3% in both groups) decreased to 7.5% in the sensor-augmented pump therapy group (-0.8 ± 0.8 percentage points), compared with 8.1% in the injection-therapy group (-0.2 ± 0.9 percentage points). Between-group difference was -0.6 percentage points (95% confidence interval CI -0.7 to -0.4 ; $P < 0.001$). Rate of severe hypoglycaemia did not differ between the tow two groups.

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