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REVIEW ARTICLE

Continuous subcutaneous insulin infusion in diabetes: patient populations, safety, efficacy, and pharmacoeconomics

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Summary

The level of glycaemic control necessary to achieve optimal short-term and long-term outcomes in subjects with type 1 diabetes mellitus (T1DM) typically requires intensified insulin therapy using multiple daily injections or continuous subcutaneous insulin infusion. For continuous subcutaneous insulin infusion, the insulins of choice are the rapid-acting insulin analogues, insulin aspart, insulin lispro and insulin glulisine. The advantages of continuous subcutaneous insulin infusion over multiple daily injections in adult and paediatric populations with T1DM include superior glycaemic control, lower insulin requirements and better health-related quality of life/patient satisfaction. An association between continuous subcutaneous insulin infusion and reduced hypoglycaemic risk is more consistent in children/adolescents than in adults. The use of continuous subcutaneous insulin infusion is widely recommended in both adult and paediatric T1DM populations but is limited in pregnant patients and those with type 2 diabetes mellitus. All available rapid-acting insulin analogues are approved for use in adult, paediatric and pregnant populations. However, minimum patient age varies (insulin lispro: no minimum; insulin aspart: ≥2 years; insulin glulisine: ≥6 years) and experience in pregnancy ranges from extensive (insulin aspart, insulin lispro) to limited (insulin glulisine). Although more expensive than multiple daily injections, continuous subcutaneous insulin infusion is cost-effective in selected patient groups. This comprehensive review focuses on the European situation and summarises evidence for the efficacy and safety of continuous subcutaneous insulin infusion, particularly when used with rapid-acting insulin analogues, in adult, paediatric and pregnant populations. The review also discusses relevant European guidelines; reviews issues that surround use of this technology; summarises the effects of continuous subcutaneous insulin infusion on patients' health-related quality of life; reviews relevant pharmacoeconomic data; and discusses recent advances in pump technology, including the development of closed-loop 'artificial pancreas' systems. © 2015 The Authors. *Diabetes/Metabolism Research and Reviews* Published by John Wiley & Sons Ltd.

Keywords continuous subcutaneous insulin infusion; diabetes mellitus; paediatric; pregnancy; pharmacoeconomics; rapid-acting insulin analogue

Introduction

Numerous clinical trials have demonstrated that near-normal glucose control is associated with improved short-term and long-term outcomes in both type 1

diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [1–6]. For those patients who require insulin, the intensified regimens that are necessary to achieve this level of glycaemic control may be administered via multiple daily injections (MDI) [7] or by continuous subcutaneous insulin infusion (CSII) [8]. CSII requires the patient to wear a portable electromechanical pump that infuses insulin at pre-selected basal rates [9]. The rate can be boosted by the patient as required for food intake [9]. The pump itself comprises a battery-operated motor, a computerized control mechanism, an insulin reservoir and an infusion set (subcutaneous cannula and tubing). Recent advances in pump technology include the development of sensor-augmented pumps, in which the pump is integrated with a real-time continuous glucose monitor (CGM) [10]. Patch pumps (tubing-free pumps in which the reservoir and integrated infusion set adhere to the skin) represent another recent development [9].

Whilst recent advances in pump technology allow patients a considerable choice of pump features, the development of modified insulin molecules has also allowed a choice of insulin. Regular human insulin (RHI) may be used in CSII [7,11] but rapid-acting insulin analogues (RAIAs) are now considered to be the insulins of choice for use in pumps [8,12]. Differences among RAIAs in physicochemical stability and pump compatibility are discussed later in this review.

The use of CSII is increasing in many European countries, particularly among paediatric patients [13–15]. However, there is a wide variation in CSII usage among European countries (Figure 1), and Europe lags behind the United States in acceptance of this technology [9,14,16]. Potential reasons for low CSII usage in Europe include the following: insufficient numbers of physicians and diabetes educators trained in the benefits of, indications for and use of pumps; absence of clear referral pathways from first-opinion physicians to specialist pump centres; and inadequate or non-existent funding of these devices by national healthcare systems/insurance companies [14,16].

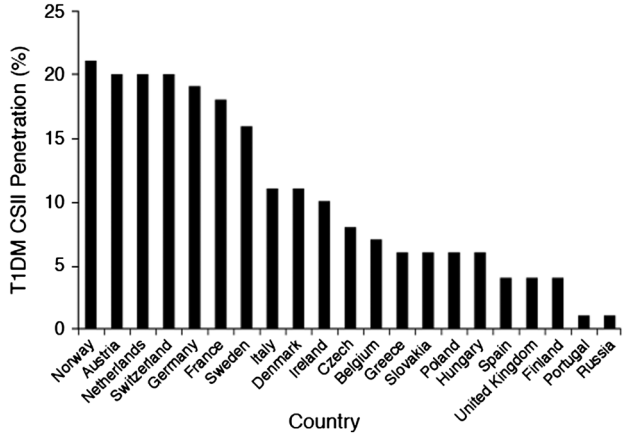

Figure 1. Continuous subcutaneous insulin infusion therapy penetration rates in patients with type 1 diabetes mellitus in European countries [14]

This comprehensive review summarises evidence for the efficacy and safety of CSII in adult, paediatric and pregnant subjects with diabetes; discusses relevant clinical guidelines; reviews issues that surround use of this technology; summarises the effects of CSII on patients' quality of life (QOL); reviews relevant pharmacoeconomic data; and discusses recent advances in pump technology. The review, which includes expert opinion from leading European diabetologists, focuses primarily on the use of RAIAs in CSII and on European data.

Comparison of continuous subcutaneous insulin infusion and multiple daily injections: clinical data

The insulin used in CSII is typically an RAIA [5]. For this reason, when evaluating the advantages and disadvantages of CSII, the ideal comparator is analogue-based MDI. To date, however, few such trials have been reported and those that do exist are generally small [5]. In the following summary, we have given preference to the strongest evidence available (i.e. the results of systematic reviews and meta-analyses) and to guideline recommendations. We acknowledge, however, that the meta-analyses cited were primarily published for the purposes of literature summary, rather than being 'decision-making meta-analyses', and may therefore give results that do not accurately reflect the relative merits of CSII and MDI in specific patient populations [17].

Use of continuous subcutaneous insulin infusion in adult patients

Systematic reviews, meta-analyses, and guideline recommendations

In systematic reviews and meta-analyses that considered studies in which a variety of insulins were used, no evidence was found for a difference between CSII and MDI in HbA_{1c} control or risk of severe hypoglycaemia in adults with T2DM [5,18–21]. This conclusion is reinforced by the results of a recent 12-month randomized clinical trial involving older patients with T2DM (≥60 years) in which glucose variability was not different between CSII (insulin lispro)-managed and MDI (insulin lispro and insulin glargine)-managed groups [22]. However, it is contradicted by an older study in which CSII (insulin lispro) provided better metabolic control than MDI (insulin lispro plus neutral protamine Hagedorn) in patients with T2DM who had failed to respond to conventional insulin therapy

[23]. A review published in 2010 concluded that although CSII has been shown to improve glucose control in patients with T2DM, the evidence to support its use in this population is inconsistent [24]. However, expression of a preference for CSII among study subjects has been more consistent, and this mode of insulin delivery has been shown to improve QOL and treatment satisfaction in patients with T2DM [24]. One gap in our understanding, identified by Bode [24], is whether CSII provides incremental clinical benefits for patients with T2DM after MDI has failed. This question was addressed by Reznik *et al.* [25] in a recent study in which 331 adult patients with T2DM who had poor glycaemic control despite MDI with insulin analogues were randomized to pump treatment (insulin lispro, aspart or glulisine) or to continue with MDI (insulin glargine or detemir, plus insulin lispro, aspart or glulisine). After 6 months, the pump therapy group had a significantly greater decrease in mean HbA_{1c} (1.1 *versus* 0.4%; $p < 0.0001$) and were receiving a significantly lower mean total daily insulin dose (97 *versus* 122 units; $p < 0.0001$). There was no significant difference between groups in bodyweight change (1.5 [pump] *versus* 1.1 [MDI] kg; $p = 0.322$), and the amount of time spent with a blood glucose level <3.9 mmol/L during a 6-day period of CGM was similar in the two groups (8.8 *versus* 5.1 min; $p = 0.767$). Reznik *et al.* concluded that, in patients whose T2DM is poorly controlled in spite of MDI, pump therapy is a safe and valuable treatment option [25].

The conclusions of studies relating to the use of CSII in adult patients with T1DM are much more consistent than those relating to patients with T2DM: numerous systematic reviews and meta-analyses have concluded that this mode of insulin delivery – when used with a variety of insulins – is more effective than MDI at decreasing HbA_{1c} in the T1DM population [5,7,18–21,26,27]. The magnitudes of the differences between CSII and MDI in end-of-treatment HbA_{1c} in selected randomized controlled clinical trials are shown in Figure 2 [7]. Moreover, the improvements in glycaemic control that occur in this population after introduction of CSII – which are most marked in patients with poor control at baseline [5,28–30] – are frequently associated with a lower daily insulin dose than is required with MDI [5,26].

The clear evidence for superior efficacy of CSII over MDI in adult patients with T1DM is not matched by

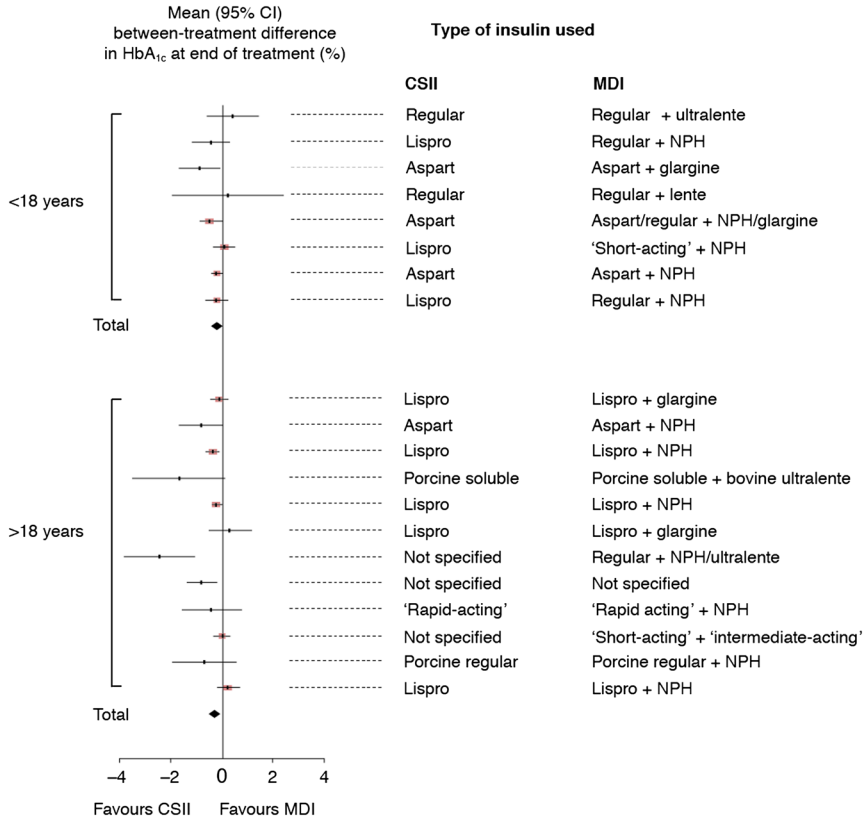

Figure 2. Meta-analysis: effects of CSII and MDI on HbA_{1c} in adult and paediatric patients with T1DM [7]. A meta-analysis of 12 randomised controlled trials involving a comparison of CSII and MDI in adult patients with T1DM demonstrated a statistically significant difference in HbA_{1c} in favour of CSII of 0.29% (95% CI, 0.06% to 0.52%). In paediatric patients, meta-analysis of eight trials also favoured CSII (0.22% [0.03% to 0.41%]). CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; NPH, neutral protamine Hagedorn; T1DM, type 1 diabetes mellitus

superior safety, the majority of reviews having reported no clear evidence for a beneficial effect of CSII, compared with MDI, on the risk of mild or severe hypoglycaemia in this population [19–21,31]. CSII has not, however, been accompanied by an increase in hypoglycaemic risk [31], and two recent reviews have concluded that the risk of severe hypoglycaemia is lower in patients using CSII than in those using MDI [7,28]. Current clinical guidelines generally support these clinical findings, although none recommends the first-line use of CSII in patients with T1DM (Table 1) [12,32–35].

Relative safety and efficacy of different insulins

The advent of modified insulin molecules has provided patients and physicians with substantial choice, although RAIAs are generally considered to be the preferred insulins for use in CSII [8]. This is supported by the results of several meta-analyses, the earliest of which concluded that, when used in CSII, RAIAs result in a modest but significant reduction in HbA_{1c} when compared with soluble insulin [36]. This meta-analysis, which included data on insulin aspart and insulin lispro only, also found that patients prefer RAIAs to soluble insulin [36]. A more recent meta-analysis, conducted by the Cochrane Collaboration, concluded that, in patients with T1DM who are using CSII, RAIAs are associated with a small but significant benefit in long-term glycaemic control when compared with RHI [37]. These two analyses have been superseded by a 2009 meta-analysis [31], which confirmed the findings of the earlier reports (improved glycaemic control with RAIAs [insulin aspart or insulin lispro] *versus* soluble insulin), as well as demonstrating lower hypoglycaemic risk when analogue insulins were used [31]. This meta-analysis was not, however, restricted to CSII.

Of the three RAIAs in current use, there are considerably more trial data relating to the use of insulin aspart and insulin lispro than to the use of insulin glulisine [37]. The more widespread use of insulins aspart and lispro is supported by CSII studies that have demonstrated higher rates of occlusion and symptomatic hypoglycaemia with insulin glulisine than with either of the other RAIAs [38–40].

Data comparing insulin aspart and insulin lispro are less clear-cut. For example, a small ($n = 17$) 3-day randomized, crossover trial that compared the effects of CSII with insulin aspart and insulin lispro on glycaemic stability found that post-prandial glucose levels were more stable with insulin aspart when the two preparations were infused as pre-meal boluses [41]. However, there were no differences in overall daily glucose stability when the two formulations were infused via CSII as basal insulins [41]. Using a different study design (randomized, open-label, parallel group), a larger patient group ($n = 146$), a considerably longer study duration (16 weeks), and different endpoints, Bode *et al.* [11] found no differences among buffered regular insulin, insulin aspart, and insulin lispro in mean change in HbA_{1c}, or incidences of hypoglycaemic events or clogs/blockages in pumps or infusion sets [11].

The incidence of infusion set clogging or other infusion site/set complications was also similar in insulin lispro- and insulin aspart-treated patients in two recent randomized, crossover, non-inferiority studies in which the pump reservoir remained unchanged for 6 days [42]. The overall rate of infusion site problems was low in both these studies and did not differ significantly between groups. Insulin lispro was non-inferior to insulin aspart in terms of daily mean self-monitored blood glucose during the entire treatment period (days 1 to 6) in both studies, and there was no significant difference between insulin lispro and insulin aspart in mean daily blood glucose levels on 5 of the 6 days in each study. However, on the final day of reservoir use (day 6), insulin lispro failed to demonstrate non-inferiority to insulin aspart for mean blood glucose levels. The rates of hypoglycaemia (total and documented) were significantly lower in the insulin lispro-treated patients. The difference between the two insulins in day 6 mean blood glucose levels is probably of limited clinical relevance because the majority of patients empty their reservoirs in less than 6 days in clinical practice.

Expert opinion

Although there is currently no clear evidence that the use of CSII is beneficial in adult patients with T2DM, long-term studies are required, particularly regarding the effect of CSII on the prevention of long-term complications. For patients with T1DM, CSII is more effective than MDI in reducing HbA_{1c}, but its differential effect on safety – and on severe hypoglycaemic risk in particular – is minimal. RAIAs are preferred over other insulins for use in CSII but the improvements in glycaemic control and reductions in hypoglycaemic risk seen with these agents are small. Unfortunately, guidelines for the use of CSII differ considerably among European countries and this does not help to promote the rational use of this technology, which could be associated with cost savings for healthcare systems. Efforts should be made to harmonize clinical guidelines among countries, a process that could be facilitated by the European Association for the Study of Diabetes and the International Society for Pediatric and Adolescent Diabetes.

Use of continuous subcutaneous insulin infusion in paediatric patients

To our knowledge, no studies have been published concerning the use of CSII in paediatric patients with T2DM, and this population is not covered. Randomized clinical trials and long-term studies regarding the use of

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Table 1. Guideline recommendations pertaining to the use of continuous subcutaneous insulin infusion in patients with diabetes

Patient population	Organization	Recommendations/statements
Adult		
T1DM	NICE [32]	Use of CSII restricted to patients who have experienced poor glycaemic control or 'disabling' hypoglycaemia when using MDI
	SFD [33]	CSII should be considered in patients who have: •persistently elevated HbA_{1c} despite intensified MDI •recurrent hypoglycaemia •marked glycaemic variability •variable insulin requirements •insulin allergy •experienced a negative impact of MDI on their social or professional life
T2DM	NICE [32]	CSII not recommended
	SFD [33]	Use of CSII supported in patients who have: •failed MDI •very high insulin requirements/insulin resistance •insulin allergy
Paediatric, T1DM		
<12 years (no lower limit)	NICE [32]	CSII is a treatment option if MDI is impractical or inappropriate
12–18 years	NICE [32]	Same criteria as adult patients for use of CSII All patients in this age group should undergo a trial of MDI therapy
All ages (no lower limit)	SFD [33]	All indications for use of CSII in adults apply to children and adolescents. In addition, CSII is considered to be first-line therapy in paediatric patients in whom MDI is not feasible for practical reasons and in those with: •neonatal/very early onset diabetes •glycaemic instability (very young children) •very low insulin requirements, especially at night (very young children) •nocturnal hypoglycaemia •pain and/or needle phobia
	IDF/ISPAD [34]	•CSII should be available and considered in paediatric/adolescent patients; when adequate education and support is provided, CSII is acceptable and successful even in young infants
All ages (no lower limit)	Consensus statement* [12]	Criteria for consideration of CSII include: •recurrent severe hypoglycaemia •suboptimal glycaemic control •wide fluctuations in blood glucose levels (regardless of HbA_{1c}) •microvascular complications •risk factors for macrovascular complications •lifestyle factors •eating disorders •pronounced dawn phenomenon •needle phobia •pregnancy/planned pregnancy •susceptibility to ketosis •competitive athletic endeavours
Pregnant		
T1DM and T2DM	NICE [35]	No evidence of statistically significant differences between CSII and MDI therapy in maternal or foetal outcomes
T1DM	NICE [32,35]	CSII is a treatment option for women with: •HbA_{1c} ≥8.5% (≥69.4 mmol/mol) despite a high level of care on MDI therapy •significant disabling hypoglycaemia
	SFD [33]	For patients who are planning a pregnancy/are currently pregnant, the mode of insulin administration should be subject to individualized risk/benefit analysis
T2DM	SFD [33]	Therapeutic value of CSII not yet established

CSII, continuous subcutaneous insulin infusion; IDF, International Diabetes Federation; ISPAD, International Society for Pediatric and Adolescent Diabetes; MDI, multiple daily injections; NICE, National Institute for Clinical Health and Excellence; QOL, quality of life; SFD, Société Francophone du Diabète; T1DM, type 2 diabetes mellitus; T2DM, type 2 diabetes mellitus

*Consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes

CSII in paediatric patients with T1DM are also few [12]. Exceptions include a case–control study designed to determine the long-term safety and efficacy of CSII in children [43]. The types of insulin used in CSII in this study were not specified. Compared with patients on MDI, those on CSII showed sustained improvements in glycaemic control

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over a 5-year period [43]. In a longer study that analysed data from a diabetes register, Dovc *et al.* [44] showed that metabolic control improved significantly over the period 2000 to 2011 in paediatric patients with T1DM in Slovenia and that, over this period, use of CSII was associated with significantly lower HbA_{1c} values than MDI. These children were diagnosed with T1DM when they were between 0 and 17 years of age. In addition, Sulmont *et al.* [45] reported the results of 8 years of follow-up in children in whom T1DM was diagnosed before 6 years of age. In this population, CSII was associated with better long-term metabolic control and a lower risk of severe hypoglycaemia than MDI, especially when CSII was initiated at the time of diagnosis. Recently, a population-based registry analysis also demonstrated a reduced risk of hypoglycaemia associated with the use of CSII in children [46]. These recent data support the results of the systematic reviews and meta-analyses summarized in the next section.

The challenges of treating diabetes in paediatric patients (neonates, young children and adolescents), the advantages of CSII over MDI in these age groups and issues surrounding the use of CSII during exercise are summarized in Table 2 [5,8,12,47–59].

Systematic reviews, meta-analyses, and guideline recommendations

In systematic reviews and meta-analyses that have considered studies in which a variety of insulins were used, the use of CSII in paediatric patients with T1DM has been associated with better glycaemic control (i.e. lower HbA_{1c}; Figure 2) than MDI [5,7,21,60,61]. As in adults, the magnitude of the improvement depends on the patient's HbA_{1c} prior to CSII initiation [5,62]. These analyses also showed that the use of CSII in paediatric patients is associated with lower insulin requirements [21,61] and lower hypoglycaemic risk [5] than MDI. However, these conclusions were not echoed by those of a recent systematic review of randomized controlled trials and selected observational studies carried out by the Agency for Healthcare Research and Quality in the United States, which found no difference between the effects of MDI and RAIA-based CSII (with various insulins) on HbA_{1c} or severe hypoglycaemia in children or adolescents with T1DM [19]. However, the criteria used for selection of studies in this review may have introduced bias. Current clinical guidelines generally support the use of CSII in paediatric patients with T1DM, with no lower age limit. Moreover, in contrast to the situation in adults, it is generally recommended that CSII may be used as first-line therapy in appropriately selected paediatric patients (Table 1) [12,32,33].

Relative safety and efficacy of different insulins

Although RAIAs are considered to be the insulins of choice for paediatric patients using CSII [8,12], there are few studies on this topic. A 2004 study involving young children showed that when compared with RHI, insulin lispro was associated with improved post-prandial glucose excursions and better parental satisfaction [63]. The overall safety and efficacy of the two insulin preparations were, however, similar. A more recent comparison of insulin aspart and insulin lispro found that these two RAIAs were of similar safety and efficacy when used in CSII in children and adolescents with T1DM [64]. It should be noted that in Europe, insulin glulisine is approved only for use in children ≥6 years of age [65]. Insulin aspart may be used in children aged ≥2 years [66], and insulin lispro can be used in patients of any age [67]. Insulin lispro was the first RAIA to be approved for clinical use and, as a result, has been used in CSII in numerous studies in paediatric patients [68].

Expert opinion

CSII with RAIA is becoming the treatment of choice in paediatric patients with T1DM, with a penetration of at least 50% in the United States [69] and in several European centres [44]. There are obvious practical advantages associated with the flexibility of CSII, in that it allows individual age-appropriate basal insulin infusion rates to be set [70] and erratic behaviour to be followed by multiple small prandial and/or correction boluses. When using CSII, age-appropriate structured continuous education of the entire family – and possibly also of kindergarten/school personnel [71] – is of paramount importance. To be optimal, such education should be provided by a multidisciplinary team with a strong emphasis on psychosocial support and nutritional education, including the counting of carbohydrates. For patients who are using CSII, the time spent in hypoglycaemia, the frequency of hypoglycaemia [72] and the frequency of severe hypoglycaemia [73] can be reduced by using a sensor-augmented insulin pump with an automated insulin-suspend function, which suspends insulin delivery at a pre-defined low glucose concentration. Sensor-augmented pumps may eventually be superseded by artificial pancreas systems, in which CSII with RAIA are incorporated into closed-loop insulin delivery systems. The success of such systems has already been demonstrated [74] and is discussed in a later section of this article.

Use of continuous subcutaneous insulin infusion in pregnancy

Pregnancy in patients with diabetes is associated with risks to both mother and foetus [35]. The comparative safety and efficacy of CSII and MDI in pregnant women who have pre-existing diabetes have been the subject of a number of studies [75]. In contrast, the use of CSII in women with gestational diabetes has not been well explored [76] and is not covered in this review.

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Table 2. Paediatric patients: challenges of treating diabetes and use of CSII

Age group	Problem	Comments	Overview
Neonates			
	Unpredictable/variable feeding pattern	Compared with MDI, CSII better facilitates adaptation of insulin regimen to current feeding regimen (continuous enteral or parenteral feeding *versus* intermittent bottle feeding) [47,48]	In neonates, CSII is safe, the subcutaneous infusion lines are well tolerated and CSII is more physiological, more accurate and easier to manage than MDI [47]
	Low insulin requirement	Accurate dosing of small amounts of insulin is easier with CSII than with MDI [47] Little guidance is available regarding insulin dilution, but case reports describing successful dilution of insulin lispro with a compatible diluent or normal saline have been published [12,49]; insulin dilution is not necessary with the latest generation of insulin pumps (minimum infusion rate 0.025 U/h)	
Young children			
	Glycaemic variability, risk of hypoglycaemia and DKA caused by erratic eating and exercise patterns Reluctance of school to oversee and administer MDI; school not knowledgeable regarding use of MDI	Compared with MDI, CSII improves control of blood glucose fluctuations and HbA_{1c}; reduces risk of hypoglycaemia and dawn phenomenon [5] CSII preferable to poorly managed MDI [5]	In addition to its clinical advantages in young children, CSII provides improved lifestyle flexibility for both child and family [5]
Adolescents			
	Poor adherence to CSII-related tasks due to social and psychological factors [8,50–52]	Problem is CSII-specific; however, the same problem of poor adherence pertains to MDI in this population [8]	In adolescents, CSII is associated with high levels of satisfaction and, when compared with MDI, with a greater sense of control, increased independence and increased flexibility in diet and daily schedule [12,58]
	Factitious manipulation of pump [53]	Problem is CSII-specific	
	Missed meal-time boluses [54]	Problem is CSII-specific	
	Development of insulin resistance	May be managed more effectively with CSII than with MDI [8]	
	Changes in sleep and activity patterns	May be managed more effectively with CSII than with MDI [8]	
All ages	Whether to leave CSII pump on, turn it off or reduce the infusion rate during exercise	Some studies conclude that it is preferable to discontinue basal insulin infusion during exercise (to reduce the risk of hypoglycaemia during or after exercise), [55,56] and some that it is preferable to keep the pump on [57] In patients with T1DM who take regular moderate-to-heavy aerobic exercise, RAIA-based CSII reduces post-exercise hyperglycaemia and the risk of post-exercise late-onset hypoglycaemia, when compared with MDI [59]	Advising patients is difficult because relevant data are sparse and, where they do exist, confusing [55–57,59]: studies performed in older children and adolescents have yielded conflicting results; use of CSII by young children during sporting activities has not been explored

CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; MDI, multiple daily injections; RAIA, rapid-acting insulin analogue; T1DM, type 1 diabetes mellitus

Systematic reviews, meta-analyses and guideline recommendations

The strength of evidence comparing CSII and MDI in pregnant women with diabetes is currently insufficient [5,19,75–78], the majority of the studies available to date being retrospective and all being observational [75]. Only randomized controlled trials would allow a valid comparison of the effects of these two insulin regimens on relevant outcomes in this population [5,19,35,75–77]. This lack of data is reflected by current guideline recommendations (Table 1).

Relative safety and efficacy of different insulins

Of the three RAIAs currently available, all are approved for use in pregnancy [65–67]. However, no clinical trials involving the use of insulin glulisine in pregnant patients have been published, and experience with this RAIA in pregnant women is limited [65]. For this reason, caution is advised in the use of insulin glulisine in this population [65]. In contrast, insulin lispro has been widely used in pregnant women, and insulin aspart has been compared with RHI in two randomized trials [66,67]. These studies have led regulatory authorities to conclude that there is no evidence of an adverse effect of insulin lispro or insulin aspart on pregnancy or on the health of the foetus/newborn [66,67], a conclusion that is shared by the authors of several recent reviews [79–81]. These findings are largely echoed by current guideline recommendations on the use of RAIAs in pregnant patients (Table 3) [35].

The majority of studies that have investigated the use of insulin aspart and insulin lispro in pregnancy have not incorporated CSII, and the relative efficacy and safety of different insulin preparations when used in CSII to treat pregnant women have therefore not been well addressed in the scientific literature. One study that did compare the effects of insulin lispro and RHI when administered via both MDI and CSII found that insulin lispro was associated with fewer hypoglycaemic comas and a lower risk of pre-term birth but a higher risk of the infant being small-for-gestational-age [82]. This latter finding contrasts with those of other studies in which no adverse effect of insulin lispro on perinatal outcomes has been found [80,81]. As pointed out by the authors of this study, the apparent associations between insulin lispro and foetal outcomes should be investigated further, not least because these findings are not supported by other reviews and studies, the majority of which have reported similar perinatal outcomes in RHI-treated and insulin lispro-treated women [67,80,81,83].

Table 3. Guideline recommendations pertaining to the use of rapid-acting insulin analogues in pregnant patients with diabetes [35]

Recommendations
●There is no evidence that either insulin aspart or insulin lispro has adverse effects on pregnancy or on the foetus
●Insulin lispro and insulin aspart have advantages over RHI during pregnancy
●lower risk of hypoglycaemia
●lower post-prandial glucose excursions
●improved overall glycaemic control
●better patient satisfaction
●Insulin lispro and insulin aspart may offer benefits over NPH
●greater flexibility
●improved glycaemic control
●The use of insulin glulisine is not recommended because of a lack of relevant safety data

NPH, neutral protamine Hagedorn; RHI, regular human insulin

Expert opinion

To date, there is no evidence for a benefit of CSII in women with pre-gestational diabetes. However, the key objective in the management of diabetes in women with a planned or existing pregnancy is to reach the lowest possible level of HbA_{1c} (thereby minimizing the risk of malformations and foetal complications related to hyperglycaemia [e.g. large-for-gestational-age]) whilst minimizing the risk of hypoglycaemia (thereby improving maternal QOL and reducing the risk of the baby being small-for-gestational-age). Among pregnant women and their caregivers, CSII is often preferred to MDI because of its greater flexibility for fine-tuning insulin delivery and because it does not require MDI, which can become particularly onerous if the number of insulin injections increases because of a need to administer correction doses. CSII also allows caregivers to bypass existing uncertainty about the risk of long-acting insulin analogues during pregnancy. It is acknowledged, however, that several case series involving the use of long-acting insulin analogues during pregnancy have shown no evidence of increased maternal or neonatal risk. Similarly, observational reports that have compared the use of insulin lispro or insulin aspart with that of RHI during pregnancy have revealed no evidence of deleterious outcomes when RAIAs are used in either MDI or CSII regimens. In addition, because of their pharmacodynamic profiles, RAIAs are easier to manage than RHI in terms of reducing post-meal glucose spikes without increasing late post-meal hypoglycaemia. Overall, therefore, although no specific studies have assessed either the benefits of CSII or the choice of RAIAs during pregnancy in women with diabetes, accumulated experience supports the easier and more comfortable management of glucose control with CSII using RAIAs in this situation. Moreover, because there is evidence to show that CSII using RAIAs is more effective than MDI and/or RHI in achieving optimal glucose control outside pregnancy, there is no rationale for prohibiting the use of CSII and/or RAIAs before or during pregnancy. Conversely, there is no rationale for prescribing CSII and/or RAIAs to a woman with diabetes during pregnancy when she is reluctant to receive these regimens.

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Issues related to the use of continuous subcutaneous insulin infusion in clinical practice

A number of issues surround the effective use of insulin pumps (summarized in Table 4) [11,12,38–40,84–100]. These include frequency of infusion set and injection site change, under-delivery or over-delivery of insulin and dermatological complications. Of these, under-delivery of insulin and its consequences (hyperglycaemia and diabetic ketoacidosis [89]) are potentially the most serious. The speed with which hyperglycaemia can develop in CSII-treated patients is related to the small size of the subcutaneous insulin depot and the short duration of action of RAIAs [101]. Occlusion within the pump or infusion set is one of the possible causes for insulin delivery failure in CSII-treated patients. Controlled studies that examine the factors that may contribute to occlusion are therefore directly relevant to clinical practice.

Occlusions

The incidence of occlusion is affected by catheter wear time [87] and by the specific RAIA used. For example, in a laboratory-based study that involved pumps administering insulin aspart, insulin lispro or insulin glulisine for 5 days, occlusions were rare and independent of choice of RAIA in the first 72 h of the infusion [87]. However, after this time, the incidence of occlusion increased substantially, particularly with insulin glulisine [87]. These data emphasize the importance of changing catheters at least every 72 h, irrespective of the insulin used [40,87]. Differences among RAIAs in propensity for occlusion may be related to the physicochemical stability of the individual molecule [38]. Occlusions may be caused by the formation of insulin complexes (fibrils) within the infusion set or by isoelectric precipitation of insulin [38]. *In vitro* studies have shown that RAIAs differ in their propensity for fibril formation and in the pH at which they precipitate [38,102]. However, when attempting to compare the risk of occlusion of different RAIAs, the most relevant data are those generated *in vivo*. In a 13-week, prospective, randomized, open-label, crossover controlled clinical trial involving patients on CSII therapy, van Bon *et al.* [39] found that the monthly rate of unexplained hyperglycaemic episodes and/or perceived catheter set occlusions was significantly higher in insulin glulisine-treated patients than in those who were receiving either insulin lispro or insulin aspart [39]. A recent systematic review that aimed to determine the stability and performance of RAIAs used for CSII also concluded that the risk of occlusion is higher with insulin glulisine than with insulins aspart or lispro *in vitro*, and *in vivo* when the infusion duration extends beyond approximately 3 days [40]. The conclusions made by van Bon *et al.* [39] relating to the primary endpoint of their study (no significant difference among insulin glulisine, insulin lispro and insulin aspart in CSII use with respect to the incidence of at least one unexplained hyperglycaemic event and/or perceived catheter set occlusion) have attracted some criticism [103]. Other factors that had a significant effect on the risk of unexplained hyperglycaemia/infusion set occlusion in the study by van Bon *et al.* [39] included the time interval between infusion set changes (9% decrease in risk for each 6 h increase in interval; $p < 0.0001$) and body mass index (6% decrease for each 1 kg/m^2 increase; $p = 0.046$). The authors concluded that these relationships occurred because patients who experienced few problems changed their catheters less frequently and because more obese patients had higher insulin infusion rates [39].

Expert opinion

For patients receiving CSII, it is desirable to change the infusion set every 48 to 72 h and to rotate the injection site. Indeed, it is of the utmost importance to regularly change the infusion set within the period recommended for the product(s) being used to achieve stable and optimal glycaemic control and to minimize the risk of adverse events. Regardless of the RAIA used, however, it is important that further improvements are made in the quality of catheters and infusion sets.

Quality of life and pharmacoeconomics

The potential impact on a patient's QOL and the financial implications of the mode of insulin administration form an important part of any decision about whether to embark on CSII [5]. From a health service standpoint, these two factors are inextricably intertwined because a relatively expensive intervention may be deemed cost-effective if it is associated with improved QOL.

Quality of life

Health-related quality of life (HRQOL) in CSII-treated patients with diabetes has been assessed using both generic and diabetes-specific instruments [104]. Although some HRQOL studies/instruments have shown that the QOL of patients using CSII is equivalent [105,106] or inferior [106,107] to that of those using MDI, the majority has found that CSII (when used with a variety of insulins) is associated with significant improvements in HRQOL/patient satisfaction [5,19,20,104,108–111]. This improved HRQOL/patient satisfaction has been demonstrated in

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Table 4. Issues related to the use of CSII in clinical practice

Issue/potential cause	Potential consequences	Incidence/prevalence	Preventive measures
Insufficiently frequent infusion set change			
Non-adherence to product registration information	Poor glycaemic control; increased day-to-day variability in plasma glucose levels; increased risk of infusion site problems (e.g. itching, bruising, swelling, pain) [84–86]	Incidence *in vivo* not documented	Change infusion set more frequently (every 48–72 h) [85,86,100]
Failure of insulin delivery			
Occlusion within infusion set	Hyperglycaemia ± DKA	Incidence varies among studies; ≤1 clog/blockage per 4 weeks is typical [11]	Change catheter at least every 72 h [40,87]; use an RAIA with a relatively low risk of occlusion (insulin aspart or insulin lispro preferred to insulin glulisine) [39,40,87]
Excessive catheter wear time [40,87]	—	Incidence *in vivo* not documented	—
Formation of insulin complexes (fibrils)/ isoelectric precipitation of insulin (related to physicochemical stability of RAIA used) [38]	—	Incidence *in vivo* not documented	—
Pump failure/malfunction	Hyperglycaemia ± DKA	Malfunction rate: 25 per 100 pump-years with complete failure in 44% of cases of malfunction (prospective study involving 640 consecutive new pumps manufactured by four different companies between 2001 and 2007 [92]	Use pump with evidence of superior reliability
Planned pump disconnection	Glycaemic control unaffected by disconnection to change infusion set but for longer disconnection (30 min), blood glucose increases by approximately 1 mg/dL (0.056 mmol/L) for each minute of infusion interruption [88]	Incidence *in vivo* not documented	Minimize time for which pump disconnected
Unplanned pump disconnection	Hyperglycaemia ± DKA [89]	Incidence *in vivo* not documented	Use new-generation, tubing-free patch pumps
Hydrostatic effects	25% decrease in insulin delivery when insulin pumped 80–100 cm upwards (bench-based study with programmed infusion rate of 1 U/h; effect most evident at low basal infusion rates; effect demonstrated using insulin aspart) [90]	Incidence *in vivo* not documented	Wear pump horizontally and use short tubing or use new-generation, tubing-free patch pumps [99]
Over-delivery of insulin			
Reduced atmospheric pressure (as during air travel) leads to formation of bubbles/ expansion of existing bubbles and displacement of insulin from cartridge (effect demonstrated using insulin aspart) [91]	Hypoglycaemia [91]	Incidence *in vivo* not documented	Use new-generation, tubing-free patch pumps
Hydrostatic effects	23% increase in insulin delivery when insulin pumped 80–100 cm downwards (bench-based study with programmed infusion rate of 1 U/h; effect most evident at low basal infusion rates; effect demonstrated using insulin aspart) [90]	Incidence *in vivo* not documented	Wear pump horizontally and use short tubing or use new-generation, tubing-free patch pumps [93,99]

(Continues)

Table 4. (Continued)

Issue/potential cause	Potential consequences	Incidence/prevalence	Preventive measures
Dermatological complications			
Allergy to bandage adhesive [93,94] Irritation, inflammation, and infection at infusion site [93,94]	Reduced patient comfort Reduced patient comfort; increased likelihood of CSII discontinuation [95]	Incidence *in vivo* not documented Adults • Irritation and/or infection: 0.06 to 12 per patient per year [12] Children/adolescents (n = 50, insulin aspart or lispro only, cross-sectional study) • Scar $<$ 3 mm diameter: 94% • Erythema not associated with nodules: 66% • Subcutaneous nodules: 62% [95]	Change adhesive type Change infusion set at least every 48–72 h [85]; consider changing catheter type (adverse event rate is influenced by catheter model) [96]
Lipodystrophy (lipoatrophy and lipohypertrophy) [97]	Unpredictable insulin absorption; poor glycaemic control [97,98]	Adults and children (n = 430, cross-sectional study) • Lipohypertrophy: 64% [98] Children/adolescents (n = 50, insulin aspart or lispro only, cross-sectional study) • Lipohypertrophy: 42% [95]	Rotate injection sites [97,98]

CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; RAIA, rapid-acting insulin analogue

adults with T1DM [5,19,20,110] and T2DM [109], adolescents with T1DM [5,19,108,111], children with T1DM [5,19,111] and parents of children with diabetes [5]. In one study involving 577 adolescents, the favourable impact of CSII, when compared with MDI, on treatment satisfaction, perceived clinical efficacy, and reduction in treatment interference with daily activities was most evident in those patients with lower overall HRQOL [108], suggesting that the benefits of CSII may be most apparent in this group. CSII is also commonly associated with a lower fear of hypoglycaemia than MDI, a benefit that extends to both adult patients and caregivers of children with diabetes [5,104].

Some of the most interesting – and most relevant – work relates to patients who have used CSII from the onset of diabetes. To date, such studies involve only paediatric patients. Skogsberg *et al.* [112] followed 72 children and adolescents with T1DM who were randomized to treatment with MDI (neutral protamine Hagedorn and insulin aspart) or CSII (insulin aspart) at the time of disease onset. Treatment satisfaction was significantly higher in the CSII group at all screening visits (1, 6, 12 and 24 months) (Figure 3) [112]. Kordonouri *et al.* [113] also found a significant beneficial effect of CSII (with or without a CGM) on QOL in paediatric patients and the wellbeing of their primary caregivers when this therapy was instituted at diagnosis.

Expert opinion

Ultimately, the improved QOL experienced by patients and their families in association with the use of CSII

Figure 3. Treatment satisfaction in children treated with CSII (insulin aspart) or MDI (neutral protamine Hagedorn and insulin aspart) over a 2-year period [112]. Treatment satisfaction was measured using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) in children with T1DM treated with CSII (n = 34; dotted lines, diamonds) or MDI (n = 38; straight lines, squares). The results are presented as mean ± 95% CI. CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; T1DM, type 1 diabetes mellitus * $p < 0.05$

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may turn out to be the strongest argument in favour of this method of insulin administration. In addition, the flexibility that is inherent in CSII and the ability to administer multiple bolus doses of rapid-acting insulin painlessly allow insulin therapy to be tailored to diverse challenges such as those posed by neonates with diabetes, patients attending kindergarten, fussy eaters and adults with shift-work. Most diabetologists agree that psychosocial issues are extremely important in determining the long-term prognosis of patients with diabetes. Thus, improved QOL may eventually be a critical factor in improving psychosocial outcomes and may outweigh the short-term cost increases associated with CSII.

Pharmacoeconomics

The major costs associated with CSII are pump purchase/depreciation and consumables [5]. Other costs include those associated with pump servicing and training in the use of CSII [5]. These costs would be reduced by improvements in insulin stability within the pump and pump lifespan [5,114,115].

All current health-economic comparisons of CSII and MDI have concluded that CSII (when used with a variety of insulins) is more expensive than MDI [5,116–118]. Recent data from a European country (United Kingdom), published in 2010, estimate the annual cost of consumables (e.g. tubing, cannulae) and pump (assuming a 4-year lifespan) at about £1800–£2000 and £430–£720, respectively [5]. This is approximately £1700 more than the annual cost of analogue-based MDI [5]. However, assuming that CSII is associated with a reduction in HbA_{1c} of 1.2% compared with MDI, this mode of insulin delivery is deemed cost-effective [5]. Other groups have reached similar conclusions [117], citing incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year gained with CSII compared with MDI of £25 648 (~€37 036) (2003 costs) [116] and £37 712 (~€46 235; 2008 publication) [32]. These ICERs are sensitive to the patient's baseline HbA_{1c} and to assumptions made regarding improvements in glycaemic control and adverse event rates. Such calculations underlie the recommendation of the National Institute for Health and Care Excellence (NICE) that, in adult patients with T1DM, CSII is a treatment option only in those whose HbA_{1c} has remained ≥8.5% (69.4 mmol/mol) on MDI therapy despite a high level of care [32].

Expert opinion

A growing number of national and international registries that involve the collation of real-world patient data are becoming available. In the future, these registries may allow more accurate pharmacoeconomic analyses. Currently, such analyses are driven by potential reductions in HbA_{1c} or rates of severe hypoglycaemia requiring hospitalization. Management of diabetes is moving rapidly into the area of sensor-augmented therapy and will eventually encompass closed-loop approaches to insulin therapy (discussed in the next section). In conjunction with these advances, healthcare funders should be encouraged to support the delivery of well-run registries. Such data will be of the utmost importance in the allocation of funds for modern insulins, pumps and technology, advances that may only become financially advantageous several years after implementation.

Recent advances in continuous subcutaneous insulin infusion technology

Conventional CSII delivers insulin at pre-selected basal rates, with additional user-initiated bolus infusions. In contrast, a closed-loop insulin delivery system or 'artificial pancreas' delivers insulin at a rate that varies depending on the patient's interstitial glucose level [119]. This is achieved by integrating the insulin pump with a CGM and a control algorithm that modulates the pump's insulin delivery rate in real time in response to the prevailing level of glycaemia (Figure 4) [119]. Closed-loop systems have demonstrated a number of advantages over sensor-augmented CSII [119], and clinical trials involving their use are slowly moving from controlled laboratory conditions to transitional and home settings [72,120,121] as the technology and sophistication of the devices become more advanced. The complexity (and resultant cost) of

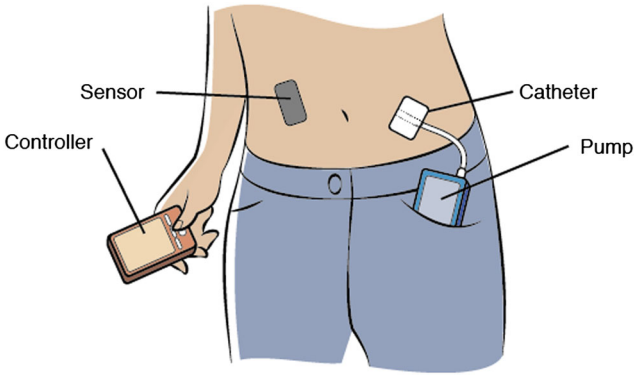

Figure 4. Components of a closed-loop insulin delivery system [119]. Interstitial glucose levels, measured by the sensor, are transmitted to the controller, which contains a control algorithm. This modulates the pump's insulin infusion rate in real time. All communication is wireless

such pumps may not be necessary for patients with T2DM, for whom simple disposable patch pumps may be more appropriate [24].

Technological advances in continuous glucose monitors

The vast majority of glucose assays are electrochemical, utilizing glucose oxidase [122]. Currently, CGMs predominantly use subcutaneously implanted amperometric sensors that provide continuous monitoring of glycaemia [122]. The sensor is connected to a small on-skin potentiostat, which may transmit information wirelessly to the computer within the pump or to a dedicated handheld device [122]. Research is currently underway to develop a subcutaneously implanted glucose monitoring and transmitting device that includes an integrated miniature power source [122]. Several initiatives in the development of fully implantable long-term glucose sensors have also been reported [123].

The clinical effectiveness of real-time continuous glucose monitoring was recently determined in a meta-analysis, which showed that this technology is associated with significantly lower HbA_{1c} and exposure to hypoglycaemia than self-monitoring of blood glucose in patients with T1DM [124]. The improvement in glycaemic control was greatest in patients who used the sensors most frequently and those who had the highest HbA_{1c} at baseline [124].

Technological advances in pump technology

In addition to the development of bolus calculators and options for modulation of bolus shape [125], recent pump advances have allowed the incorporation of algorithms that suspend insulin delivery when glucose levels reach a certain threshold [72,126] or when hypoglycaemia is predicted [127]. Both strategies are effective in preventing overall and nocturnal hypoglycaemia [72,73,127]. For example, a recent randomized study involving 247 patients showed that incorporation of the threshold-suspend feature into sensor-augmented pump therapy was associated with a significant 32% reduction in the incidence of nocturnal hypoglycaemic events [72].

Technological advances in closed-loop systems

Closed-loop systems that increase insulin delivery in a glucose-responsive fashion are yet to be made commercially available. These artificial pancreas systems combine an external pump and sensor with a variable insulin infusion rate algorithm [128]. The majority of current systems use a model predictive control (MPC) algorithm that links insulin delivery and meal ingestion to glucose excursions [119]. Although capable of achieving near-normal glucose concentrations overnight, artificial pancreas systems are challenged by meals and exercise. These problems can be ameliorated by announcing meals and exercise to the control algorithms using a bolus wizard, as is standard with conventional CSII, or by the addition of small manual pre-meal 'priming' boluses [128]. Initially studied under controlled laboratory conditions, closed-loop systems are now undergoing trials in transitional and home settings [129].

Closed-loop studies performed under controlled laboratory conditions

When used in adults with T1DM in an overnight study that compared closed-loop delivery of insulin aspart (MPC-based algorithm) with conventional CSII with insulin aspart, the closed-loop approach was associated with significant improvements in glycaemic control and hypoglycaemic risk [130]. In a more recent study involving both adults and adolescents receiving insulin lispro, Breton *et al.* [131] compared the performance of open-loop CSII with that of two artificial pancreas systems, one designed to prevent extreme glucose excursions (standard control to range), the other to achieve near normoglycaemia (enhanced control to range [eCTR]). These options in tuning insulin delivery were enabled by the multi-modular concept of MPC [132]. Both artificial pancreas systems were superior to open-loop CSII during a 22-h hospitalization period that included meals and exercise. However, eCTR provided the most physiological control, with patients in near normoglycaemia 97% of the time and in tight glycaemic control 77% of the time [131]. Closed-loop systems have been similarly successful in paediatric patients. When compared with standard CSII in a population of children and adolescents, manual closed-loop insulin delivery (infusion rate calculated by algorithm, delivery rate adjusted by nurse) was associated with reduced risk of nocturnal hypoglycaemia [133], and in children <7 years, a closed-loop approach reduced the severity of overnight hyperglycaemia (*versus* standard CSII) without increasing hypoglycaemic risk [134]. Insulin aspart was used in both these studies. Closed-loop systems have also been used in pregnant women. Murphy *et al.* [135] investigated the performance of closed-loop insulin delivery of insulin aspart using an MPC algorithm over a 24-h period during both early (12–16 weeks) and late (28–32 weeks) gestation in ten women. The algorithm performed well at both time-points, suggesting that overnight closed-loop insulin delivery has the potential to be used safely during pregnancy.

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Closed-loop studies performed under transitional or home conditions

The success of laboratory studies has led researchers to investigate the performance of artificial pancreas systems in transitional and home situations. In an overnight study conducted in the setting of a diabetes camp, adolescent patients had less nocturnal hypoglycaemia and better overnight glycaemic control when treated with an artificial pancreas system than with a sensor-augmented pump (Figure 5) [74]. In a longer study (42 h), Kovatchev *et al.* [120] evaluated the performance of a wearable artificial pancreas system that used a smart phone as a closed-loop control platform in patients who were maintained as outpatients or in a hybrid hospital–hotel setting. Patients operated the system via the user interface for the first 14 h of the study and then in closed-loop mode for the remaining 28 h. System communication functioned correctly for 98% of the study duration, demonstrating that integration of smart phones into closed-loop systems is worthy of further investigation [120].

Continuous use of artificial pancreas systems in the patient's home is the ultimate goal. The feasibility of this approach has been demonstrated by Nimri *et al.* [121], who compared the safety and efficacy of closed-loop and sensor-augmented pump therapy in 15 patients over a total of 8 nights (crossover design). The closed-loop system was associated with significant improvements in various measures of hypoglycaemia, and the study demonstrated the feasibility, safety and efficacy of the closed-loop system under home conditions.

Bi-hormonal systems

The insulin-only systems described earlier may ultimately be superseded by bi-hormonal devices that infuse both insulin and glucagon. Such systems have been tested under both closed-loop [136] and semi-automated hybrid control conditions [137,138]. The latter, which involves the addition of a partial meal-priming insulin bolus, has achieved excellent glycaemic control when using insulin lispro, with minimal hypoglycaemia in trials of 51 h duration that involved the consumption of high-carbohydrate meals and exercise [137]. A closed-loop system with full meal bolus using insulin aspart has demonstrated similar performance, albeit over a shorter time period [138].

Pump security

Recognition that closed-loop systems are vulnerable to unauthorized access ('hacking') has led professional groups to publish design standards and governmental agencies to enact device regulations [139]. As a result, hardware and software manufacturers have developed new products [139] that should improve the security of insulin pumps in general and of artificial pancreas systems in particular.

Expert opinion

Improved glycaemic control and reduced risk of hypoglycaemia appear achievable with closed-loop systems that combine commercial sensors, pumps and RAIAs. Results from early transitional and short home studies are promising, demonstrating progression towards real-life clinical use in T1DM. Closed-loop systems continue to be limited by factors such as glucose sensor reliability, delays in insulin absorption and instrumentation/human factors, but these are gradually being addressed, underpinned by the development of new-generation systems including, for

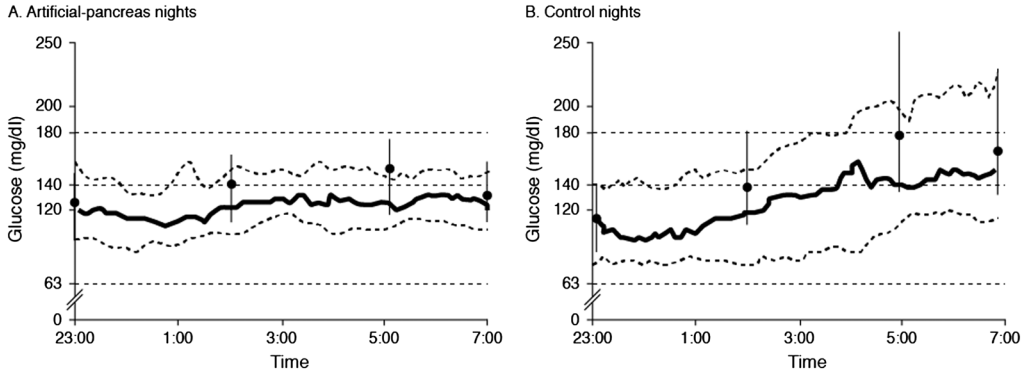

Figure 5. Nocturnal glycaemic control in adolescent patients with type 1 diabetes mellitus using an 'artificial pancreas' or a sensor-augmented pump [74]. Sensor glucose profiles obtained with an artificial pancreas (A) and a sensor-augmented insulin pump (B). The type(s) of insulin used in this study was not specified. Solid black line and adjacent dashed lines: median glucose level and interquartile range. Circles and vertical lines: median capillary glucose measurements and interquartile range. The horizontal dashed lines indicate blood glucose levels of 180 mg/dL (10.0 mmol/L) and 63 mg/dL (3.5 mmol/L [the threshold for hypoglycaemia])

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example, glucagon co-delivery. Performance over longer periods is being assessed in home studies that focus mainly, but not entirely, on overnight use.

Conclusions

This review has focused on the use of CSII in patients with diabetes and on the use of RAIAs as the insulins of choice in this delivery system. CSII has a number of advantages over MDI for patients with T1DM and, as a result, is now widely recommended for use in both adult and paediatric populations. These recommendations are based on widespread evidence of superior glycaemic control, lower daily insulin requirements, reduced risk of hypoglycaemia and better HRQOL/patient satisfaction. The reduction in hypoglycaemic risk has been demonstrated most consistently in paediatric patients. Among the three RAIAs currently available, substantial evidence has been provided regarding the use of insulin aspart and insulin lispro. Pharmacoeconomic data consistently show that CSII is more expensive than MDI. However, the efficacy, safety and HRQOL advantages associated with this technology have led many groups and organizations to conclude that CSII is cost-effective in selected patient groups. Certainly, individual human factors are of utmost importance in the pathway leading to CSII use, and the search for a more flexible lifestyle has been a driving force toward CSII use in recent years [140].

The success of conventional 'open-loop' CSII has led to the development of closed-loop insulin delivery systems, which have now reached the stage of small-scale, short-duration clinical trials in patients' homes. If these systems fulfil their early promise and prove able to provide safe and effective glycaemic control in complex situations, they will transform the lives of people with insulin-dependent diabetes.

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Author contributions

All authors made substantial contributions to the conception and design of this article, and to the critical appraisal of content, and have read and approved the final version.

Conflicts of interest

Paolo Pozzilli reports having received speaker's honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Sanofi, and Takeda, and having received research grants to University Campus Bio-Medico, Rome, from Boehringer Ingelheim, Eli Lilly, Medtronic, Novartis, Roche Diagnostics, and Sanofi.

Tadej Battelino reports having received research grants to the University of Ljubljana from GluSense, Medtronic, Novo Nordisk, and Sanofi, having served on advisory boards for Bayer, Eli Lilly, Medtronic, Novo Nordisk, and Sanofi, and having served on speaker panels for Bayer, Eli Lilly, Novo Nordisk, Medtronic, and Sanofi. He was supported in part by the Slovene National Research Agency ARRS grants P3-0343 and J3-4116.

Thomas Danne reports having received speaker's honoraria from A. Menarini Diagnostics and Dexcom, and having served as a consultant to Boehringer Ingelheim, Eli Lilly, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, and Sanofi.

Roman Hovorka reports having received speaker's honoraria from B. Braun, Eli Lilly, Medtronic, Minimed Lifescan, and Novo Nordisk, having served on advisory panels for Animas, Eli Lilly, Medtronic, and Minimed, having received license fees from B. Braun and Beckton Dickinson, and having been involved in patent applications and having served as a consultant to B. Braun, Beckton Dickinson, Profil, and Sanofi.

Przemyslawa Jarosz-Chobot reports having received speaker's honoraria from Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Roche, and Sanofi and having received consultant's honoraria from Eli Lilly, Medtronic, Roche, and Sanofi.

Eric Renard reports having served as a consultant/advisor to A. Menarini Diagnostics, Abbott, Cellnovo, Dexcom, Eli Lilly, Johnson & Johnson (Animas, LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics, and Sanofi-Aventis, and having received research grant or material support from Abbott, Dexcom, Insulet, and Roche Diagnostics.

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