Insulin Pumps

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Contents

Abstract

Insulin pump therapy (continuous subcutaneous insulin infusion, CSII) is a form of intensified insulin treatment involving subcutaneous infusion of short-acting insulin from a portable pump. There is a well-established evidence base for the effectiveness of CSII in type 1 diabetes, which includes reduction in HbA_{1c}, blood glucose variability, and all grades of hypoglycemia compared to MDI, but more research is needed on how new long-acting insulin preparations and more effective diabetes education will reduce the number who do not achieve target levels of control on MDI and who are thus candidates for CSII. Insulin pump therapy is an affordable, cost-effective therapeutic option for most healthcare

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settings. There is an increasing role for CSII in patients with poorly controlled type 2 diabetes who are not adequately managed on MDI, but smaller, cheaper, and simpler "patch" pumps are likely to be needed to make insulin pump therapy cost-effective in this type of diabetes.

Keywords
Insulin pump therapy · Continuous subcutaneous insulin infusion · CSII · Type 1 diabetes · Type 2 diabetes · Hypoglycemia · Glycemic control · Intensified insulin therapy

Introduction

The term "insulin pump therapy" is now synonymous with continuous subcutaneous insulin infusion (CSII), a type of intensified insulin treatment based on variable-rate infusion of short-acting insulin from a portable pump and delivered via a cannula implanted in the subcutaneous tissue. CSII was originally developed in the 1970s (Pickup et al. 1978) as an experimental procedure to test the effects of prolonged near-normoglycemia on diabetic microvascular complications (injection regimens of the time were not able to maintain strict glycemic control in type 1 diabetes), but it quickly entered routine clinical practice as a therapeutic option for selected people with type 1 diabetes. CSII use was particularly encouraged by the results of the DCCT (Diabetes Control and Complications Trial 1993) in the 1990s, which showed the importance of strict glycemic control in preventing diabetic microangiopathy and where the intensified arm in the trial consisted of either CSII or multiple daily insulin injections (MDI). The uptake of insulin pump therapy in the last 20 years or so has also been encouraged by the commercial availability of more reliable and flexible insulin pumps with adjustable infusion rates and alarm systems for malfunctions. The increasing evidence base for insulin pump effectiveness compared to MDI, and the appearance of several national and international guidelines that advise on the best use of CSII in clinical practice have also promoted the increasing use of insulin pump therapy.

The principle of CSII is to obtain better metabolic control in diabetes by mimicking non-diabetic insulin administration with a slow delivery of short-acting insulin throughout the day and night (basal insulin) and boosts at meal times (prandial insulin or boluses). The slow basal infusion of insulin with CSII (about 1 unit/h for an adult) has several pharmacological advantages that help in improving glycemic control. There is a much lower variability of subcutaneous insulin absorption with CSII (coefficient of variation [cv] about ±5%) compared to depot injections of long-acting insulin injections like isophane insulin (cv about ±50%) (Lauritzen et al. 1983), accounting for a reduction in within- and between-day blood glucose variability (see below). The constant and controllable basal infusion also produces flatter circulating insulin levels than many long-acting insulin formulations, especially at night, resulting in less risk of nocturnal hypoglycemia. The facility to automatically alter the basal rate at a preset time enables, for example, an

increase in rate during the hours before breakfast to counter the elevated blood glucose levels at this time in some patients (the "dawn phenomenon") (Koivisto et al. 1986), or the basal rate can be reduced to avoid hypoglycemia during and after exercise, not possible when depot insulin has been injected before exercise (Perkins and Ridell 2006).

The current practice of CSII is to use short-acting monomeric insulin in the pump (aspart, lispro or glulisine). It is recommended that CSII is initiated and supervised by a specialist team consisting of a physician with an interest and training in insulin pump therapy, a diabetes nurse educator and a dietician. Patients who are candidates for CSII should be motivated and willing to undertake CSII procedures, particularly frequent self-monitoring of blood glucose and carbohydrate counting. Further practical details of how to start and manage patients on CSII and some recent advances in pump therapy can be found elsewhere (Grunberger et al. 2014; Pickup 2012; Pozzilli et al. 2016).

The Benefits of Insulin Pump Therapy in Type 1 Diabetes

Reduction in HbA_{1c}

There is still some controversy about the magnitude of the likely improvement in glycemic control when CSII is compared to modern MDI regimens. This is partly because in some trials both MDI and CSII might have been used suboptimally and because inappropriate types of patients have been entered in some trials (see below). The majority of randomized controlled trials (RCTs) of CSII vs. MDI have employed isophane-based MDI rather than long-acting insulin formulations with more predictable absorption like glargine, detemir, and degludec, which may offer improved control in their own right, at least in some patients. Also, the intensity of structured diabetes education applied during MDI in some trials has been variable, leading some to question whether the strict control of CSII could not be matched by best contemporary MDI regimens that include appropriate insulin regimens and educational approaches such as carbohydrate counting and insulin dosage adjustment. Equally, there are several measures to optimize CSII that are not always applied, including the use of bolus calculators, appropriate bolus profiles and timing of meal insulin, computer download of pump data to detect therapeutic errors and adjust infusion rates, and so on.

A number of meta-analyses of RCTs comparing glycemic control during CSII and MDI have shown that HbA_{1c} is on average about 0.3–0.6% lower on CSII than on MDI (Pickup et al. 2002; Weissberg-Benchell et al. 2003; Pickup and Sutton 2008; Misso et al. 2010). However, some of these analyses included RCTs from early insulin pump trials with now obsolete pumps or where non-monomeric insulin was used, or trials where there was a near-normal baseline (MDI) HbA_{1c}. This last point is important because there is clear evidence from pooled individual patient data from RCTs (Retnakaran et al. 2004), from meta-regression of the effect size in RCTs (Pickup and Sutton 2008), and from individual patient responses in clinic patients

(Pickup et al. 2006) that the greatest fall in HbA_{1c} is in those with worst control at baseline. Thus, a rather modest mean effect size of, say, 0.5% (5 mmol/mol) in a meta-analysis does not reflect the much larger expected difference of about 1.5% (16 mmol/mol) in those with an elevated baseline HbA_{1c} of, say, 9% (75 mmol/mol).

In the long-term (at least 5 years of pump therapy), some 90% of patients with type 1 diabetes maintain a lower HbA_{1c} on CSII than their starting HbA_{1c} on MDI but not all subjects achieve optimal control (Nixon et al. 2014) (Fig. 1). In about 30% of subjects switched from MDI to CSII because of elevated HbA_{1c}, HbA_{1c} improves over 1–2 years and good control is maintained over the entire period. In about 60% of patients, the HbA_{1c} improves on CSII reaching a nadir after 1–2 years, but then control starts to deteriorate somewhat. Some 10% of subjects do not improve at any time on insulin pump therapy.

It is unclear why a small proportion of patients with type 1 diabetes and poor glycemic control on MDI fail to benefit from CSII. These nonresponders do not appear to have an excessive fear of hypoglycemia that prevent them from tightening control, but they are more likely to have a higher BMI than responders (Nixon et al. 2014), suggesting a lack of dietary compliance and insulin resistance might be issues. Study of the psychological characteristics of CSII patients has also shown that nonresponders as a group have a high external locus of control, believing that their diabetes is dependent on external events and beyond their control (Aberle et al. 2009). It is not known whether psychological intervention can help to improve control in this group.

These varying long-term outcomes of CSII have emphasized the need for regular follow-up in the clinic, where worsening control can be detected at an early stage and measures instigated to re-establish near-normoglycemia. A check list of the main targets for review in poorly controlled pump patients is useful and covers bolus insulin timing, profiles and missed boluses, basal insulin, infusion set practice, diet review, and a consideration of sensor-augmented pump therapy.

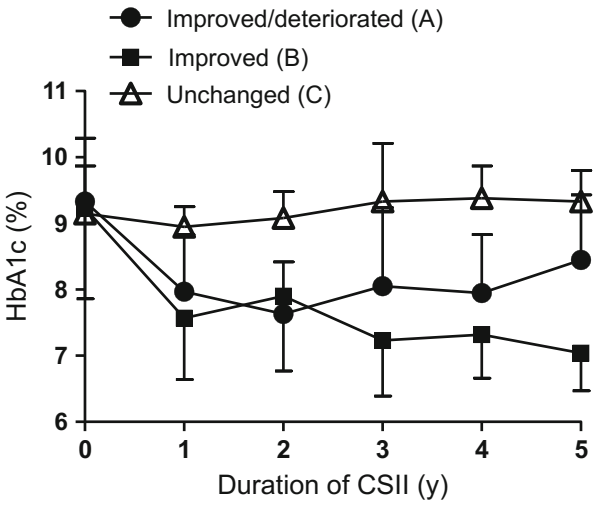

Fig. 1 Long-term changes in HbA_{1c} levels in people with poorly controlled type 1 diabetes switched from MDI to CSII. Patients can be divided into those where HbA_{1c} improves markedly and then worsens somewhat after about 2 years (A), those where HbA_{1c} improvement is maintained over at least 5 years (B), and those where HbA_{1c} does not significantly improve at any time (C). Data from Nixon et al. (2014)

Timing of bolus insulin before meals. Many patients treated by CSII continue to administer the meal insulin bolus at the start of the meal (and a few give the insulin after the meal), encouraged perhaps by healthcare professionals who believe that the short-acting monomeric insulins are sufficiently quickly absorbed to control adequately meal-induced hyperglycemia when delivered at this time. But this practice can lead to excessive post-prandial blood glucose increases, and studies have shown that giving the bolus 15–20 min before the meal is an optimal timing that can reduce the blood glucose by 2–3 mmol/l compared to immediate pre-meal bolusing (Cobry et al. 2010).

Appropriate meal insulin profiles. High-fat meals cause late and excessive post-prandial hyperglycemia because fat delays gastric emptying and causes insulin resistance. The extended/square wave feature on modern pumps is an option for the bolus to be administered over some hours, instead of the usual immediate delivery. Square wave or dual wave (the combination of immediate and extended) meal insulin profiles have been shown to manage some high-fat meals better than traditional bolusing (Jones et al. 2005), and it is worth re-educating patients on the value and appropriate use of this technology.

Missed boluses. Missing meal boluses is common, especially in children and adolescents (Olinder et al. 2009), and a low number of boluses per day is highly correlated with elevated HbA_{1c} in pump patients. Reasons for missing boluses may include forgetting, not bothering, attempting to avoid hypoglycemia or avoiding weight gain. Missed boluses can be detected by computer downloads of pump data and advice to give the bolus 20 min before meals may help to remind the patient about giving meal boluses.

Basal insulin review. In addition to checking that the overnight and daytime basal rates are appropriate, it is worth noting that frequent basal rate changes throughout the day can be associated with poor and erratic control (Laimer et al. 2016), perhaps because several hours are needed for a new steady state circulating insulin to be reached after each step change in rate. In clinical practice, reducing the number of basal rate changes can often improve control, and most patients with type 1 diabetes can be managed by no more than two or three basal rates per day.

Infusion set practice. Infusion site lipohypertrophy is common: we found in a survey of non-metabolic complications of CSII that about 25% of patients reported obvious lipohypertrophy, most frequently in those with a long duration of CSII (Pickup et al. 2014), and it is probably much more frequent if careful examination for lipohypertrophy were made by healthcare professionals. Lipohypertrophy is a known cause of impaired insulin absorption and poor and erratic control and is caused by insulin administration, either by injection or infusion, over a period of time at the same site. We also found that use of the set for more than 3 days was associated more often with infusion set blockage, presumably due to insulin aggregation. It should be recommended, therefore, that patients rotate each new infusion set to a different anatomical site and limit use of each set to no more than 3 days.

Diet. Although overall the weight does not change in type 1 diabetic patients switched to CSII, about one third of type 1 diabetic patients gain weight on CSII and this makes optimal control more difficult. Some patients may believe the new dietary

freedom on the pump allows them to "eat anything," or calories formally lost as glycosuria in the hyperglycemic patient may be retained when CSII is started and better control is achieved. Review by the dietician is very helpful in limiting weight gain.

Reduction in Blood Glucose Variability and Hypoglycemia

Both within-day and between-day blood glucose variability are reduced by switching from MDI to CSII (Pickup et al. 2005). High glycemic variability is associated with a high frequency of hypoglycemia, and reducing variability is a major way in which CSII reduces hypoglycemia. All grades of hypoglycemia are reduced by switching from MDI to CSII. For example, meta-analysis of RCTs and observational studies of hypoglycemia-prone type 1 diabetic subjects shows that severe hypoglycemia is reduced by about 75% on CSII versus MDI (Pickup and Sutton 2008). Those subjects with the most frequent hypoglycemia during MDI have the largest improvement on CSII, and the reduction in severe hypoglycemia with CSII is maintained over several years (Quirós et al. 2016). Lesser degrees of hypoglycemia ("mild to moderate") are less well studied in RCTs but the percentage of self-monitored blood glucose levels <3.5 mmol/l is also reported to be about 75% less on CSII than MDI in some observational studies (Pickup et al. 2005).

In patients where hypoglycemia persists with CSII, the addition of continuous glucose monitoring (CGM), often called "sensor-augmented pump therapy," should be offered. The most advanced form of this is the use of low-glucose insulin-suspend (LGS) pumps, where the basal infusion rate is automatically suspended for up to 2 h when CGM-measured glucose concentrations fall below a preset threshold or when hypoglycemia is predicted to occur over some horizon, usually 30 min. Several, observational studies and RCTs indicate that the duration of nocturnal hypoglycemia and the frequency of severe hypoglycemia are further reduced with LGS pumps compared to traditional CSII (Bergenstal et al. 2013; Choudhary et al. 2011, 2013; Ly et al. 2013).

Reduced Mortality

Comparatively little is known about long-term clinical outcomes such as vascular disease in patients treated by CSII vs. MDI, but recent information on mortality from the Swedish National Diabetes Registry is of note (Steineck et al. 2015). Here, data on 2441 type 1 diabetic patients on CSII were compared with 15,727 on MDI, and cardiovascular events or deaths were studied over a mean 6.8-year follow-up. All-cause mortality was reduced by 27% on CSII, coronary heart disease (CHD) mortality by 45%, and stroke and CHD mortality by 42%. There are many reasons why mortality may be less on CSII; HbA_{1c} levels were similar in the two groups (a mean of 7.9 vs. 8.0% [63 vs. 64 mmol/mol], CSII vs. MDI), but the number of patients experiencing ≥ 3 episodes of hypoglycemia was significantly less on CSII,

possibly pointing to less risk of hypoglycemia-induced cardiac arrhythmias. A high frequency of severe hypoglycemia is strongly related to increased mortality in both type 1 and type 2 diabetes (McCoy et al. 2012). Other risk factors that may influence cardiovascular disease such as glycemic variability and lifestyle factors such as diet and exercise were not measured in this study.

Improved Quality of Life and Treatment Satisfaction

The discontinuation rate for CSII is low, less than 5% at most centers (Pickup 2012), indicating a good overall level of satisfaction with the treatment, though it is somewhat higher in adolescents and females (de Vries et al. 2011). Some RCTs comparing glycemic control and quality of life during CSII and MDI (for example, as assessed by measures such as the SF-36 score) show a clear benefit with insulin pumps (deVries et al. 2002), but other studies have shown little or no improvement in quality of life with CSII. One may speculate that this may be because patients in some trials were relatively well controlled with little hypoglycemia and therefore had a good quality of life at baseline, and thus were expected to show little improvement in quality of life on switching to CSII. Probably the largest improvement in quality of life with CSII then is with patients suffering from frequent severe hypoglycemia and prolonged elevated HbA_{1c} on MDI.

CSII in Children

Insulin pump therapy has been used safely and effectively in children and adolescents since CSII first entered clinical practice in the 1970s (Tamborlane et al. 1979) and it continues to be a popular therapy in this age group (Kordonouri et al. 2011). However, uptake of pumps in young people with type 1 diabetes varies markedly between countries (as it does in adults): a recent survey of data from more than 54,000 type 1 diabetic patients in three large registries in Germany/Austria, the US Type 1 Diabetes Exchange and in England and Wales showed that uptake was 41% in Germany/Austria, 47% in USA but only 14% in England and Wales (Sherr et al. 2016). Interestingly, HbA_{1c} was highest in the low-use countries: 8.9% versus 8.0% and 8.3% (74 vs. 64 vs. 67 mmol/mol), England and Wales versus Germany/Austria versus USA, though there may be several reasons (such as socioeconomic status) why patients in some countries have a poorer diabetes control than others.

Special considerations for the use of CSII in young people include the fact that children are often unwilling or unable to perform MDI, particularly with the need for supervised midday injections at school, so many practitioners and guidelines consider it is appropriate to start CSII in children without them having first “failed” on MDI (National Institute for Health and Care Excellence 2008). Also, adolescents are more likely to discontinue the pump (de Vries et al. 2011) and may achieve somewhat worse control than adults, perhaps related to the known insulin resistance of adolescence, and to erratic sleep and exercise patterns, and adherence issues.

CSII in Pregnancy

Insulin pumps may be used effectively in pregnancy and in the preconception period, under the same guidelines for nonpregnant subjects – when an elevated HbA_{1c} or hypoglycemia persists with MDI (see below) – though since glycemic targets are lower in pregnancy, an appropriate indication might be when an $HbA_{1c} < 6.1\%$ (43 mmol/mol) (or according to national pregnancy guidelines) cannot be achieved on MDI without disabling hypoglycemia. There is no evidence that glycemic control or pregnancy outcomes such as pre-eclampsia, congenital abnormalities, birth weight, neonatal hypoglycemia, and stillbirths are different on MDI vs. CSII, though there are comparatively few RCTs available on this topic (Mukhopadhyay et al. 2007). More research is needed, particularly in pregnant diabetic women who have failed to achieve glycemic targets on MDI before being randomized to CSII.

Cost-Effectiveness of CSII

A systematic review of 11 formal cost-effectiveness studies of CSII vs. MDI in type 1 diabetes in eight countries has shown that it may be considered value for money for healthcare systems in all or most settings (Roze et al. 2015). CSII was on average 1.4 times more costly than MDI in this review but the higher lifetime costs are partially offset by cost-savings from reduced diabetes-related complications. With a base case HbA_{1c} of 8.7% (72 mmol/mol), the mean incremental cost-effectiveness ratio (ICER) was Euros 30,862 (US $40,143) per quality-adjusted life year (QALY) gained. The results were highly sensitive to the degree of reduction in HbA_{1c} and frequency of hypoglycemia, with the best affordability in those with worst control at baseline. What is considered value for money will differ between countries and healthcare systems, but since the unofficial willingness-to-pay threshold used by the widely influential UK National Institute for Health and Care Excellence (NICE) is <£30,000 (Euros 36,158) per QALY, CSII will be considered cost-effective in most countries.

Insulin Pump Therapy in Type 2 Diabetes

Until recently, CSII was usually reserved for selected patients with type 1 diabetes, and many guidelines (e.g., NICE 2008) do not recommend insulin pump therapy in type 2 diabetes because of the poor and conflicting evidence of effectiveness in the limited number of RCTs that have been published (Raskin et al. 2003; Wainstein et al. 2005). However, a number of observational studies in the last decade or so have indicated that many patients with type 2 diabetes who are poorly controlled on MDI may achieve a significant improvement in HbA_{1c} on switching to CSII (Edelman et al. 2010; Leinung et al. 2013), and the reduction appears to be maintained over many years (Morera et al. 2016).

A recent large, multicenter RCT has added further weight to the evidence base for use of CSII in type 2 diabetes. In the OpT2mise trial (Reznik et al. 2014), patients underwent a pre-randomization period of optimization designed to improve control on MDI, and only those with a persistently elevated HbA_{1c} (8–12%, 64–108 mmol/mol) and insulin dose of 0.7–1.8 units/kg were randomized to continued MDI or CSII. After 6 months, the mean HbA_{1c} difference between CSII and MDI was 0.7% (8 mmol/mol), favoring pump therapy, with a 20% insulin dose reduction and no increased hypoglycemia. Those with the highest baseline HbA_{1c} enjoyed the greatest reduction on CSII, a difference of 1.1% (12 mmol/mol) for those with an HbA_{1c} of 9.3–11.5% (78–102 mmol/mol) on MDI.

There are several reasons why control in type 2 diabetes may be better on CSII. For example, there is evidence that large depot doses of long-acting insulin formulations like glargine that are given in the insulin-resistant type 2 diabetic patient are more poorly absorbed than the same dose of insulin administered as the slow infusion of CSII (Parkner et al. 2008). Treatment satisfaction also tends to be better with CSII than MDI in type 2 diabetes (Raskin et al. 2003), so adherence to treatment may be improved with pump therapy.

Trials to date of insulin pumps in type 2 diabetes have used the traditional pumps used for type 1 diabetes, but there is increasing evidence that sophisticated pumps with flexible basal rate and bolus dose adjustment, and bolus calculators are not required for type 2 diabetes. Most patients with type 2 diabetes can be managed with a single basal rate throughout the 24 h (Edelman et al. 2010) with a simple meal-time insulin delivery. A number of manufacturers are now developing simpler, cheaper "patch" pumps which use one of a limited number of preset basal rates and simple (say 2-unit amount) meal-insulin delivery. These are likely to be more suitable and cost-effective for the large number of potential candidates for CSII in the type 2 diabetes community.

Guidelines and Indications for Best Use of CSII (Table 1)

In the UK, NICE considers that CSII is a treatment option in adults with type 1 diabetes either: when HbA_{1c} remains elevated ($\geq$8.5%, 69 mmol/mol) after best attempts with MDI or when there is continued disabling hypoglycemia on MDI (National Institute for Health and Care Excellence 2008). In children, in addition to the above indications, CSII may be used when in the opinion of the physician MDI is considered impractical. The cut-off HbA_{1c} of 8.5% (69 mmol/mol) in these guidelines is the level at which CSII is thought to be cost-effective and affordable for the National Health Service in the UK, rather than the level below which microvascular complications are not thought to occur and lowering of HbA_{1c} not thought to be worthwhile. Other healthcare systems may set this level at a lower HbA_{1c} value, say 7.5% (58 mmol/mol), though this recommendation is not always based on formal cost-effectiveness calculations. The American Association of Clinical Endocrinologists and the American College of Endocrinology have recommended CSII in type 1

Table 1 Suggested indications for a trial of insulin pump therapy in diabetes

In type 1 diabetes
When there is continued elevated HbA_{1c} after best attempts with MDI, including basal-bolus insulin injection therapy with long-acting insulin analogues such as glargine, detemir, and degludec), frequent SMBG, structured diabetes education, and frequent contact with a multidisciplinary team of healthcare professionals. Note: CSII has been shown to be cost-effective for most healthcare systems when the baseline $HbA_{1c} \geq 8.5\%$ (69 mmol/mol), but this cut-off may vary between national guidelines, re-imbursement and healthcare systems, according to the "willingness-to-pay" threshold.
When there is continued disabling hypoglycemia after best attempts with MDI. Note: Usually, this is in the judgment of the physician, as the definition of "disabling" is not agreed, but for most healthcare systems it refers to frequent episodes of severe hypoglycemia, requiring third party assistance.
In children and adolescents, when there is elevated HbA_{1c} and disabling hypoglycemia on MDI, as above, but also when in the judgment of the physician MDI is considered inappropriate of impractical CSII may be started without having first "failed" on MDI.
In the first trimester of pregnancy or pre-conceptually when target HbA_{1c} levels (<6.1%, 43 mmol/mol, or according to national guidelines) cannot be achieved without disabling hypoglycemia.
When funding is available and a specialist team of trained healthcare professionals is available to initiate and supervise follow-up, CSII may be trialed for those who may not necessarily have grossly elevated HbA_{1c} levels or frequent severe hypoglycemia but may have a personal preference for this therapy because of potential benefits in lifestyle flexibility, well-being, and ability to perform confidently and effectively.
In type 2 diabetes
When there is continued elevated HbA_{1c} in spite of best attempts to reach target glycemic levels with MDI and structured diabetes education and other adjunctive therapy such as GLP-1 inhibitors. Note: Many national guidelines do not yet recommend the routine use of CSII in type 2 diabetes or have not established a cut-off HbA_{1c} level above which CSII is cost-effective, but guidance is under active review

CSII continuous subcutaneous insulin infusion, *GLP* glucagon-like peptide, *MDI* multiple daily insulin injections, *SMBG* self-monitoring of blood glucose

diabetes when patients "do not reach glycemic goals despite adherence to maximum MDI."

There is continued debate on whether the use of CSII should be expanded to include patients with lesser degrees of poor diabetes control who just prefer insulin pump therapy as their form of intensive insulin therapy or who wish to enjoy the improved quality of life and flexibility of lifestyle associated with CSII. When funding and the specialist team of healthcare professionals are available for supervision, there seems no reason to exclude such patients (Table 1).

Summary

There is a well-established evidence base for the effectiveness of CSII in type 1 diabetes, which includes reduction in HbA_{1c} and all grades of hypoglycemia compared to MDI, but more research is needed on how new long-acting insulin

preparations and more effective diabetes education will reduce the number who do not achieve target levels of control on MDI. There is an increasing role for CSII in patients with poorly controlled type 2 diabetes who are not managed on MDI, but smaller, cheaper, and simpler patch pumps are likely to be needed to make insulin pump therapy cost-effective in this type of diabetes.

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