Long-Acting Insulin Analogs Versus Insulin Pump Therapy for the Treatment of Type 1 and Type 2 Diabetes

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Insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) is now an established form of intensive insulin treatment. It is pertinent to ask, however, if multiple daily injection (MDI) regimens based on new long-acting insulin analogs such as glargine and detemir have now replaced the need for CSII. In type 1 diabetes, CSII reduces the frequency of severe hypoglycemia compared with isophane-based MDIs, but the rate of severe hypoglycemia is usually similar on glargine- or detemir-based MDIs compared with isophane-based MDIs. CSII reduces A1C and glycemic variability compared with isophane-based MDIs; but glargine and detemir do not improve A1C or variability in many patients, particularly those who are prone to hypoglycemia. Head-to-head comparisons of CSII with MDI based on glargine indicate lower A1C, fructosamine, or glucose levels on CSII. It can be concluded that long-acting insulin analogs have not yet replaced the need for insulin pump therapy in type 1 diabetes, and CSII is the best current therapeutic option for some type 1 diabetic subjects. In type 2 diabetes, CSII and MDI produce similar glycemic control, although there is little study of MDI based on long-acting analogs compared with pumps. It is possible that CSII will be beneficial in selected patient groups with type 2 diabetes, but this requires further study.

Diabetes Care 31 (Suppl. 2):S140–S145, 2008

For many decades, it has been accepted that poor glycemic control in insulin injection–treated diabetes is mainly due to the inadequacies of insulin pharmacology (1,2). Regular (short-acting) insulin is absorbed too slowly from the subcutaneous site to control postprandial hyperglycemia, and the delayed absorption then results in late hypoglycemia. Both of these problems have now been much improved by the introduction of more quickly absorbed monomeric insulins (3). The problems of long-acting insulin formulations such as isophane and lente have taken longer to improve: they produce "hill-like" blood concentration and action profiles, resulting in a peak of over-insulinization in the middle of the night with a consequent risk of hypoglycemia, and a waning in insulinization before breakfast, resulting in fasting hyperglycemia (1,2,4). Moreover, these delayed-action insulin suspensions also have huge variability of subcutaneous absorption (1), contributing to much of the unpredictability in within- and between-day blood glucose control.

The development of insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) nearly 30 years ago (5) did much to overcome the problems of long-acting insulin injections. The constancy of the basal delivery allows for a near-flat blood insulin profile, adjustable at preset times to suit the changing needs of the patient throughout the day. The controlled delivery of small insulin amounts substantially reduces glycemic variability (6,7). For many years, these advantages have allowed a superiority of insulin pump therapy over insulin injection regimens, at least as far as the frequency of hypoglycemia is concerned. In recent years, new long-acting insulin analogs such as glargine and detemir have entered clinical practice; these are soluble in the insulin vial rather than being suspensions, have more predictable absorption, achieve more constant blood levels, and have at least the potential for significantly improved control (8,9).

It is therefore important now to ask if glargine and detemir have replaced the need for CSII in type 1 diabetes. These insulin analogs are cheaper and easier to use than insulin pumps, are not subject to the potential malfunction that any electromechanical device must risk, and need less staff time to administer and supervise. Is it then time to call a halt to the expansion of insulin pump therapy?

We therefore need to discuss the reasons for using insulin pump therapy in modern clinical practice and to consider whether glargine and detemir can substitute with equal or better performance. CSII has been much less used in insulin-requiring type 2 diabetes, but it is also pertinent to ask if CSII can match the performance of multiple daily injection (MDI) in this type of diabetes (including MDI regimens based on glargine or detemir).

CSII AND MDI IN TYPE 1 DIABETES

If we consider that the clinical indications for a trial of CSII are those conditions where there is a substantial evidence base for improved effectiveness of pumps over standard therapy, then four main problems are apparent (10): frequent unpredictable severe hypoglycemia, an elevated A1C, glycemic fluctuations, and a marked dawn phenomenon, all in spite of continued best attempts with optimized insulin injection therapy given as MDI. We must note too that the concept of MDI includes not only insulin given in a physiological (basal/bolus) manner, but also structured diabetes education, blood glucose self-monitoring with appropriate adjustment of insulin dosage, dietary advice, and frequent contact with health care professionals.

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J.C.P. has received honoraria for speaking engagements and/or consulting fees from Medtronic, LifeScan, and Novo Nordisk. E.R. reports no duality of interest.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection.

DOI: 10.2337/dc08-s235

Hypoglycemia

The evidence base for CSII reducing the frequency of severe hypoglycemia (where third-party assistance is needed) compared with non-analog MDI is very strong and has led to this clinical problem being the main indication for pump therapy in many countries (11). The hypoglycemia-reducing effect was discovered some 20 years ago, first in a comparison of severe hypoglycemia rates in groups of matched type 1 diabetic subjects treated by either CSII or insulin injections (12) and then in a randomized controlled trial of MDI, conventional injection therapy, and CSII (the Oslo Study) (13). Lower rates of severe hypoglycemia during CSII versus MDI have been confirmed in many subsequent studies in adults and children (14–20). Table 1 gives some examples of studies using modern (i.e., monomeric) insulins and pumps. In general, one can expect the frequency of severe hypoglycemia to be reduced by ~75% on CSII.

In contrast, in most studies, severe hypoglycemia has not been reduced by switching to either glargine- or detemir-based MDI regimens (21–25) (Fig. 1), a conclusion that is also supported by a systematic review of glargine (25). It is important to note that, in many cases, long-acting insulin analogs, with their improved predictability and flatter absorption profile, can lower the frequency of (nonsevere) nocturnal hypoglycemia (24). This improvement with long-acting analog–based MDI in certain poorly controlled patients is part of the rationale for using a sequential treatment strategy for poorly controlled type 1 diabetes, where the efficacy of MDI is always explored before CSII (see below)—it is certainly the case that *some* patients are helped by best modern MDI regimens, although not usually, and unfortunately, as far as severe hypoglycemia is concerned.

Some caution is needed in the interpretation of these studies on hypoglycemia. First, the definition of severe hypoglycemia varies between studies. Although usually taken to mean episodes where third-party assistance is needed (26) and recorded as recalled episodes by patients or relatives, or recorded hospital visits for hypoglycemia, certain patient groups may not be comparable with others in respect to hypoglycemia. For example, recording of severe hypoglycemic episodes in preschool children may include uncontrolled shaking and inconsolable crying in some studies (27), and children will clearly need more frequent third-party assistance than adults. Second, there are no head-to-head comparisons of the rate of severe hypoglycemia during MDI regimens based on glargine or detemir with CSII, largely because the duration of study was too short for hypoglycemia to have been accurately estimated. Such studies are therefore still needed.

Table 1—*Some recent studies comparing severe hypoglycemia in type 1 diabetes during CSII and MDI*

	Patient group	Hypoglycemia reduction (%)
Randomized controlled trials		
Cohen et al. (15)	Adolescents	79
Weintrob et al. (16)	Pediatric	66
Hoogma et al. (17)	Adults	60
Before/after studies		
Hunger-Dathe et al. (18)	Adults	72
Linkeschova et al. (19)	Adults	93
Bruttomesso et al. (20)	Adults	71

Elevated A1C and glycemic variability

There has been some uncertainty about the relative effect of CSII and MDI at improving glycemic control as measured by A1C, but it is now clear from several studies that the change in A1C when switching from MDI to CSII depends on the initial A1C values on injections: the most poorly controlled patients on MDI improve the most on CSII (28–30) (Fig. 2). Interestingly, one factor that is a major determinant of A1C on MDI is the glycemic variability, the swings both within and between days (28). This is important because the target group of hypoglycemia-prone type 1 diabetic subjects often maintain a high A1C because they may have learned that their large fluctuations in blood glucose will precipitate hypoglycemia when attempts are made to tighten control with MDI (28). Such patients do well on insulin pumps, with the lower glycemic variability on CSII (7) being one of the factors allowing a reduced frequency of hypoglycemia and lower A1C.

Do long-acting insulin analog–based MDI regimens (using glargine or detemir) achieve a lower A1C than MDI regimens using isophane as the long-acting insulin formulation? There is no doubt that a proportion of type 1 diabetic patients who are poorly controlled on isophane-based MDI regimens are helped by switching to glargine or detemir; nocturnal mild or moderate hypoglycemia and fasting hyperglycemia may be reduced (see DAWN PHENOMENON below). Therefore, we strongly support the use of these analogs in all patients before a trial of CSII is commenced. However, several randomized controlled trials (21–24,31) have shown that mean A1C is not different during isophane-based MDI compared with long-acting analog-based MDI regimens (Table 2). In a recent study of hypoglycemia-prone type 1 diabetic subjects, who therefore tended to have an elevated A1C, we were unable to lower the elevated A1C by changing from isophane to glargine (means ± SD, A1C 9.0 ± 1.4 vs. 9.1 ± 1.5%, isophane vs. glargine) (7). However, changing most

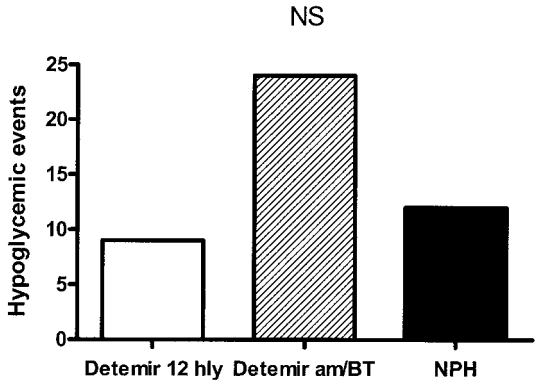

Figure 1—*Number of severe hypoglycemic episodes in type 1 diabetic subjects allocated to MDI based on detemir given every 12 hours, or before breakfast (am) and at bedtime (BT), versus NPH-based MDI. Data from Home et al. (24).*

of the glargine-treated type 1 diabetic patients to CSII resulted in a marked improvement in mean A1C (Fig. 3).

Two head-to-head randomized comparisons of long-acting analog MDI regimens with CSII confirm the view that pump therapy can achieve improved glycemic control compared with analog-based MDI. Doyle et al. (32) allocated 32 type 1 diabetic subjects to aspart and glargine MDI or CSII using aspart over 16 weeks and showed significantly lower A1C on the pump. Hirsch et al. (33) randomized 100 type 1 diabetic subjects to glargine/aspart MDI or CSII with aspart for 5 weeks and showed both a significantly lower fructosamine and area under the curve of glucose, as measured by a continuous glucose monitoring system during CSII compared with glargine MDI (Fig. 4). In a study comparing CSII and MDI with varying use of glargine in young children aged 1.7–6.1 years, no difference was found in glycemic control between the groups (34), but the glycemic targets for both pump and injections were understandably set high at an A1C of 7.7–8.5% in this young group. Thus, suboptimal control was achieved in both groups.

Dawn phenomenon

The prebreakfast increase in blood glucose concentration that occurs in many patients treated by isophane insulin-based MDI can of course be effectively managed by CSII through increasing the basal rate at an appropriate time during the night (35). However, it is also the case that long-acting analog regimens are associated with a lower fasting blood glucose level than isophane MDI, and the dawn phenomenon can be successfully managed by glargine or detemir in many patients (24,25). The dawn phenomenon is now one of the less common reasons for starting patients on CSII in our pump clinic.

Table 2—*Some randomized controlled trials showing a comparable mean A1C percentage during isophane (NPH)-based MDI and long-acting analog–based MDI in type 1 diabetes*

	Mean A1C (%)	
	NPH	Analog
Raskin et al. (21)	7.6	7.5 (glargine) (NS)
Ratner et al. (31)	7.5	7.5 (glargine) (NS)
Hermansen et al. (23)	8.1	7.9 (detemir) (NS)
Home et al. (24)	7.9	7.8 (detemir) (NS)
Russell-Jones et al. (22)	8.4	8.3 (detemir) (NS)

NS, no significant difference between groups.

Other considerations when choosing CSII or MDI in type 1 diabetes

The relative disadvantages of CSII compared with injection treatment include the extra cost of pump and supplies and trained personnel needed to supervise the therapy, although recent cost-benefit analyses have concluded that CSII is fully cost-effective when the improved quality of control and its likely effect on reducing the risk of tissue complications are taken into account (36,37). Although the frequency of diabetic ketoacidosis is no higher during CSII than injection therapy (12), patients treated by insulin pumps are at potential risk of more rapid development of ketoacidosis than with injection therapy where there is a subcutaneous reservoir of insulin from the long-acting formulation. It should be noted that many patients may not meet the requirements for compliance and ability to manage the procedures of CSII or may just prefer to use MDI as their form of optimized therapy.

It must be underlined again that CSII is not needed (at least on clinical grounds) in those type 1 diabetic patients who are well controlled and do not have problems of hypoglycemia on MDI, whether using long-acting analogs or not. There may be several other reasons for preferring MDI over CSII, including local resources, expertise, and patient preference (10).

CSII AND MDI IN TYPE 2 DIABETES

The problem of poor control in type 2 diabetes

Gradual loss of β-cell insulin secretion and persistent insulin resistance result, sooner or later, in the requirement for insulin therapy in most type 2 diabetic patients. To prevent complications in type 2 diabetes, strictly reinforced targets of blood glucose control provide further support for the need of optimized therapy. Initial bedtime basal insulin injection, sometimes combined with oral antidiabetic drugs, is among the most widely used regimens, but maintaining blood glucose control will then often need adaptations of insulin regimens toward MDI (38).

The availability of short- and long-acting insulin analogs in recent years does not alter this strategy, although a reduced incidence of hypoglycemia and a trend toward less weight increase have been reported in the use of long-acting analogs instead of NPH insulin for basal insulin coverage (39,40). Because of insulin resistance, a common feature of type 2 diabetes, large insulin doses are often needed to achieve tight blood glucose control, especially in very obese subjects and/or patients with liver steatosis (41). Further weight increase after initiation of insulin therapy is a frequent phenomenon that promotes failure to reach treatment targets, i.e., an A1C level <7%. In agreement with this observation, impaired insulin bio-

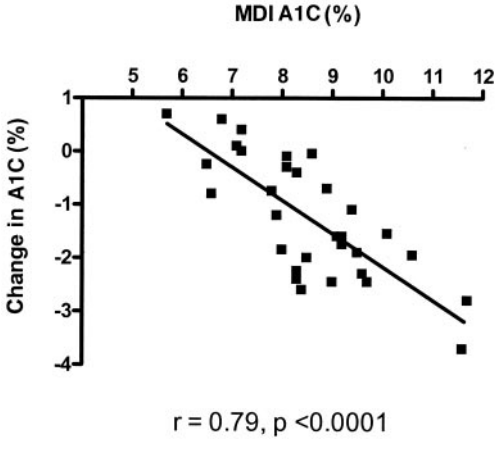

Figure 2—*Correlation in type 1 diabetes between the A1C on MDI and the subsequent change in A1C when patients were switched to CSII. From Pickup et al. (28), with permission.*

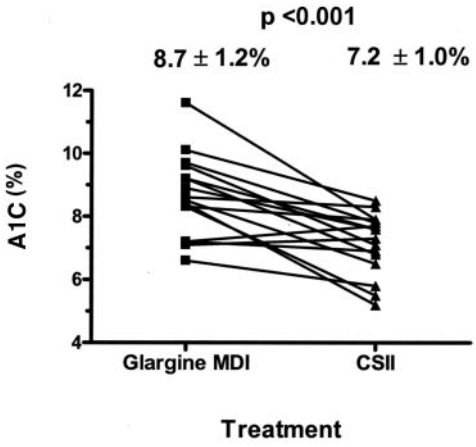

Figure 3—*A1C in hypoglycemia-prone type 1 diabetic subjects when treated by MDI based on glargine and after switching to CSII.*

availability and action have been correlated with an excess of fat mass, in both the visceral abdominal and subcutaneous compartments in type 2 diabetic patients (41). Persistent hyperglycemia in spite of increasing insulin doses can seem a hopeless situation in a significant number of insulin-treated type 2 diabetic patients. Moreover, the burden of MDI, while adequate blood glucose control is hardly achieved and body weight is increasing, is poorly accepted by these patients.

CSII as a management strategy in type 2 diabetes

In such cases, transitory intravenous insulin infusion has been shown to allow blood glucose control, probably because of obtaining higher plasma insulin levels that can overcome the severe insulin resistance related to chronic hyperglycemia and overweight. Afterward, blood glucose control can be achieved by using CSII (42), although this combined intravenous/subcutaneous approach has not been widely adopted. CSII has also been considered in recent years as a potential routine means of improving blood glucose control in type 2 diabetic patients who remain difficult to control while using insulin injections, because it provides a more physiological plasma insulin profile and because of the notable successes in controlling type 1 diabetes (described above) (43).

At least three randomized controlled studies have compared the potential benefits of CSII versus MDI in insulin-requiring type 2 diabetic patients, although the benefits of pumps compared with MDI based on long-acting analogs has practically not been addressed. The first trial by Raskin et al. (44) comparing CSII with aspart insulin versus MDI with basal NPH and mealtime aspart insulin reported a similar effectiveness of the two therapies on A1C reduction, although eight-point daily blood glucose profiles showed a lower glycemic trend with CSII, with significantly better postbreakfast control. Interestingly, 93% of CSII-treated patients preferred this therapy in terms of convenience, flexibility, and ease of use.

A more recent trial by Herman et al. (45) compared CSII with lispro insulin versus MDI with glargine and lispro insulin in insulin-treated type 2 diabetic patients >60 years of age. No significant difference between the two therapies was noted for A1C decrease, incidence of severe or nonsevere hypoglycemia, weight gain, or quality of life. A series of obese type 2 diabetic subjects, uncontrolled in spite of high insulin doses, were enrolled in a crossover trial reported by Wainstein et al. (46) where CSII with lispro insulin was compared with MDI using three injections of regular insulin and one injection of NPH, while metformin was continued with both insulin treatment regimens. Intention-to-treat analysis showed a significant reduction of A1C and significantly lower postmeal excursions based on continuous glucose monitoring system recordings with CSII. No difference in weight and hypoglycemia occurrence was apparent between the two insulin regimens.

Since these studies assessed different patient profiles using various MDI regimens versus CSII, a conclusion from the accumulated data cannot be drawn. However, interesting information has been provided on the feasibility of CSII in type 2 diabetic patients and pointers given about which patients could be good candidates for pump therapy. Socially active subjects looking for flexibility would likely be ranked first among them. Reduction of postmeal excursions with CSII as shown in two trials supports considering this therapy in patients for whom blood glucose spikes are likely to be particularly deleterious, e.g., those with retinal macular edema or cardiovascular lesions. A further step that may be considered for some patients remaining difficult to control with even CSII is implantable insulin pump therapy, since a randomized trial comparing implantable pump therapy versus MDI in insulin-requiring type 2 diabetic patients showed significant benefits in terms of reduced blood glucose fluctuations, mild clinical hypoglycemia, body weight improvement, and quality of life, although it was similarly effective on A1C levels (47). Hence, pump therapy might share similar indications in type 1 and type 2 diabetic patients—failure to achieve satisfactory glycemic control on MDI, usually because of elevated A1C rather than severe hypoglycemia in the case of type 2 diabetes.

CONCLUSIONS— MDI using glargine or detemir has achieved significant improvement in diabetes control in many type 1 diabetic subjects, particularly with regard to improved glycemic variability and reduced nocturnal hypo-

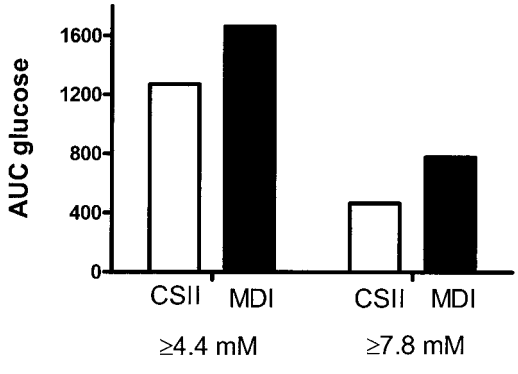

Figure 4—*Area under the curve (AUC) for glucose (either ≥4.4 or ≥7.8 mmol/l) measured by a continuous glucose monitoring system in type 1 diabetic subjects treated by CSII or MDI based on glargine. Data from Hirsch et al. (33).*

glycemia and fasting blood glucose concentrations. However, many type 1 diabetic patients continue to have poor control after best attempts with analog-based MDI because of frequent severe hypoglycemia and/or elevated A1C. These people are usually markedly improved by switching to CSII, and thus based on present evidence, we conclude that long-acting insulin analogs have not replaced the need for insulin pump therapy.

Further clinical studies are needed to provide stronger evidence on the indications for pump treatment in type 2 diabetes. The performance of CSII should be assessed in the subsets of patients who are the most eligible candidates. Perhaps more rigorous assessment of glycemic control by using continuous glucose monitoring would also be fruitful. The need for a more evidence-based approach to indications is supported by the higher cost of CSII and the higher number of type 2 diabetic patients. Health care systems and insurance organizations are unlikely to accept patient preference on its own as the main indication for CSII.

Questions from the audience

Have you found that A1C deteriorates in pump-treated patients? Although many patients can maintain an excellent and constant level of A1C during CSII, the A1C in some patients does worsen after a year or two. In response to this, we have now instituted a "refresher course" for established CSII patients in the Insulin Pump Clinic, where the pump nurse, dietitian, and doctor reeducate the patient in pump procedures. First indications are that this is helping to keep glycemic control at optimal levels.

Why can't we normalize the A1C on CSII? It is possible to identify potentially correctable or understandable factors and largely uncorrectable or inexplicable factors that influence poor control on pump therapy. The first category includes cannula problems, pump malfunctions, poor timing or miscalculated or forgotten bolus doses at meals, intercurrent drugs such as alcohol and steroids, illness, and exercise. In the second category are problems in the pharmacology of insulin, such as delayed and unpredictable absorption from the subcutaneous site, variability of insulin sensitivity, and diabetic gastroparesis, with its delayed and erratic absorption of food.

A trial of an insulin pump is clearly suitable for poorly controlled patients on MDI: Are pumps also useful in patients with a normal or near-normal A1C on MDI? As we have demonstrated (Fig. 2), CSII will achieve little or no improvement in A1C in patients with a normal A1C on MDI. Therefore, in patients who have a near-normal A1C and *no other clinical problems* on MDI, there is, in my opinion, no clinical indication for insulin pump therapy (personal preference is another issue). However, a normal or only moderately elevated A1C can of course disguise and be compatible with a serious problem of hypoglycemia in a patient, and here a trial of CSII is definitely indicated.

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