

Vol.9 No.4 2010

## Glucose Variability in Type 1 Diabetes: Comparison Between Continuous Subcutaneous Insulin Infusion and Multiple Daily Injections of Insulin

Giuseppe Lepore and Roberto Trevisan  
*USC Diabetologia, Ospedali Riuniti di Bergamo, Bergamo, Italy*

### Role of glucose variability on diabetic long-term complications

An increasing number of studies suggest that variability of blood glucose concentration throughout the day and night not only affects quality of life, but also may represent an independent risk factor for diabetic complications (1, 2).

In the DCCT, the risk of diabetic retinopathy in type 1 diabetic patients at identical sustained levels of HbA1c was significantly reduced by intensive treatment. In the subgroups with sustained levels of HbA1c of 9% for the entire study duration, the risk of retinopathy was reduced by more than 50% in the intensive control group, even though these two subgroups of patients had the same HbA1c (3). A possible explanation for these unexpected findings is that glycaemic variability was lower in intensive control group.

Recently, Monnier et al. (4) showed a linear correlation between increased free radical production and the magnitude of glucose fluctuation in type 2 diabetic patients. No correlation was found between free radical production and HbA1c and 24-hour mean glucose concentration. These findings were not observed in type 1 diabetes: Wentholt et al. did not see a relation between high glucose variability and elevated levels of oxidative stress in patients with type 1 diabetes (5).

**INFUSYSTEMS INTERNATIONAL**  
 2492 Walnut Avenue, Suite 130  
 Tustin, Ca., 92780, USA  
 Email: [infusystems@yahoo.com](mailto:infusystems@yahoo.com)

#### EDITORIAL BOARD

**Editor in Chief:** J-L. Selam (USA)  
**Associate Editor:** D. Selam (USA)  
**Board Members**  
 U. Adamson (Danderyd, Sweden)  
 G. Bolli (Perrugia, Italy)  
 D. Bruttomesso (Padova, Italy)  
 M. Carvalheiro (Coimbra, Portugal)  
 H. Hanaire-Broutin (Toulouse, France)  
 R. Hanas (Uddevalla, Sweden)  
 D. Kerr (Bournemouth, United Kingdom)  
 T. Kunt (Annweiler, Germany)  
 H. Leblanc (Paris, France)  
 V. Lassmann-Vague (Marseille, France)  
 A. Liebl (Munche, Germany)  
 P-E. Lins (Danderyd, Sweden)  
 M. Massi-Benedetti (Perrugia, Italy)  
 C. Mathieu (Leuven, Belgium)  
 D. Owens (Penarth, United Kingdom)  
 T. Pieber (Graz, Austria)  
 M. Pinget (Strasbourg, France)  
 G. Rayman (Ipswich, United Kingdom)  
 R. Radermecker (Liège, Belgium)  
 E. Renard (Montpellier, France)  
 R. Renner (Munche, Germany)  
 Z. Rusavy (Czech Republic)  
 A. Scheen (Liège, Belgium)  
 A. Scott (Derby, United Kingdom)  
 A. Spijker (Den Haag, The Netherlands)  
 A. Tiengo (Padova, Italy)

#### PUBLISHER

**Publiscripts**  
 2492 Walnut Avenue, Suite 130  
 Tustin, Ca., 92780, USA  
 Tel: (949) 910 0991 - Fax: (949) 429 2160  
[www.publiscripts.com](http://www.publiscripts.com)

#### SPONSORED BY

**Novo Nordisk**  
**Dexcom**  
**Medtronic**



THE **CGM** Resource Center

*The place to go for Continuous Glucose Monitoring Insight, education, and tools*

DexCom™ is pleased to bring you this one-of-a-kind professional resource to enhance your practice's use of Continuous Glucose Monitoring (CGM). The mission of The CGM Resource Center is to provide diabetes health care professionals with a collection of valuable information, resources, and tools to assist you in your day-to-day patient and practice management.

**Welcome**

Log on today at [www.thecgmresourcecenter.com](http://www.thecgmresourcecenter.com)

WARNING: Continuous glucose monitoring devices, like the SEVEN® PLUS, are not designed to replace a blood glucose meter. Always confirm with a blood glucose meter before making any treatment decisions. Contact DexCom Toll Free at 877-369-2664 or [www.dexcom.com](http://www.dexcom.com) for detailed indications for use and safety information.



**dexcom**  
THE GLUCOSE SENSOR COMPANY™

Home

Education

Practice Management

CGM Library

CGM Community

LBL010887 Rev 01

It has also been suggested that glycaemic control may be more appropriately expressed in terms of glucose variability in conjunction with HbA1c, rather than by HbA1c alone (6).

The possible role of glucose variability in the development of retinopathy (7) and of peripheral and autonomic neuropathy in type 1 diabetes has been recently challenged (8).

In particular, Kilpatrick, analysing the DCCT database, showed that blood glucose variability does not appear to be an additional factor in the development of microvascular complications and that only elevation of mean blood glucose over time (as expressed by HbA1c) associates with proportionally greater risk of developing microangiopathy (7).

With regard to nephropathy, our group recently showed that continuous subcutaneous insulin infusion (CSII) reduced the progression of microalbuminuria with respect to multiple daily injections (MDI) therapy in a cohort of 220 type 1 diabetic patients followed up for a period of three years (9). We found a small, but significant, difference in albuminuria (AER) between CSII and MDI group both at the 2nd and 3rd year of follow-up. While the CSII group AER remained stable, a small

but significant increase was observed in the MDI group. To further explore the role of glycaemic control in the AER increase in relation to CSII or MDI treatment, we stratified the normoalbuminuric patients according to their mean HbA1c during the whole follow up period. In the CSII group, there was little difference in the change per year in albumin excretion rate between those with a mean HbA1c  $\leq 8\%$  and those with a mean HbA1c  $> 8\%$ . On the contrary, in the MDI group, the increase in AER during the follow-up was significantly greater in those with a mean HbA1c  $> 8\%$  in comparison with those with a mean HbA1c  $\leq 8\%$ . CSII may therefore be useful in decreasing the progressive increase in AER and that this result may be, at least in part, independent of the effect of CSII on long-term glycaemic control. A possibility is that a lower glucose variability in the CSII-treated patients may account for by the difference observed in AER.

A long-term multicentre (Padua, Bergamo, Brescia) clinical trial is ongoing to establish whether a lower blood glucose variability may slow the progressive increase in albumin excretion rate in type 1 diabetic patients with incipient nephropathy. To this aim, during the three year fol-

low-up period, simultaneous and repeated evaluations of continuous glucose monitoring and blood pressure profile are performed to test the impact on albumin excretion rate, renal hemodynamics and measures of blood glucose variability independently of mean HbA1c, and their possible association with oxidative stress in 60 microalbuminuric type 1 diabetic patients (30 patients treated with CSII and 30 treated with MDI). In a subgroup of Type 1 diabetic patients, real time glucose sensors will be regularly applied in order to get reduced blood glucose variability. The results of this prospective study could hopefully help to answer the open question on the role of glucose variability on diabetic microangiopathy.

#### Continuous Subcutaneous Insulin Infusion therapy and glucose variability

A decrease of glucose excursions with respect to multiple daily injections of insulin is a possible advantage of CSII therapy in type 1 diabetes. Some studies demonstrated that CSII reduces glucose variability compared with MDI using glargine as the basal insulin, in spite of similar HbA1c levels (10-11).

	CSII (n=10)	MDI (n=19)	
CV	0.36+/-0.07	0.42+/-0.09	p<0.05
CV/day	0.35+/-0.08	0.42+/-0.09	p<0.05
CV/night	0.37+/-0.07	0.42+/-0.09	n.s
CONGA4/day (mg/dl)	73.3+/-30.1	98.8+/-38.1	p<0.05
CONGA4/night (mg/dl)	64.5+/-50.3	81.1+/-29.8	p<0.05
MODD (mg/dl)	38.9+/-9.4	45.6+/-10.8	n.s

**Table 1:** Measures of glycaemic variability in the quartile of patients with HbA1c  $\leq 7.5\%$ .

On the contrary, in a recent randomized open parallel study, glucose variability, evaluated by the mean amplitude of glycaemic excursions (MAGE) in 43 type 1 diabetic patients, was similar in CSII treated group and in MDI group using glargine + lispro (12).

Only one study investigated this aspect of insulin treatment using continuous glucose monitoring systems (13). In this study, that had a small sample size (16 type 1 diabetic patients, with HbA1c <7%), patients treated with MDI had fewer hyperglycaemic and hypoglycaemic excursions than patients treated with CSII.

A possible explanation for these conflicting results is that different tools were used in these studies for the evaluation of glucose variability: there is not yet a gold standard technique to evaluate glycaemic variability (14).

Recently our group evaluated whether CSII reduces glucose variability with respect to MDI, in patients with comparable HbA1c levels. The analysis was conducted in 36 type 1 diabetic patients, treated with CSII (15 male and 21 female subjects, aged 35 ±12 years, duration of diabetes 16±11 years, HbA1c 8.3±1.5%) and 77 patients treated

with MDI (35 male and 42 female subject, aged 40±15 years, duration of diabetes 17±12 years, HbA1c 8.5 1±.4%). All patients used insulin analogs. To evaluate glucose variability, interstitial glucose concentration was measured continuously over 72h (by Continuous Glucose Monitoring System Gold, Medtronic).

Glucose variability was analysed by calculating mean amplitude of glycaemic excursions (MAGE), coefficient of variation (CV), continuous overall net glycaemic action (CONGA2 and CONGA4), and mean of daily differences (MODD) (15–17). CONGA2, CONGA4, and CV were also evaluated in the temporal division between day (0700–2300h) and night (2300–0700h).

To analyse the effect of average blood glucose control on these measures of variability, patients were divided in quartiles based on distribution of HbA1c (1st HbA1c ≤7.5%, 2nd HbA1c >7.5 and ≤8.3%, 3rd HbA1c >8.3 and ≤9.2%, 4th HbA1c >9.2%).

Data are expressed as means ±SD. The differences between groups were compared using ANOVA with Bonferroni correction post test. The baseline clinical data of the two

groups were not significantly different. The patients in the CSII quartile with the best metabolic control (HbA1c ≤7.5%) showed a significantly lower glucose variability than the MDI group (table 1). The indexes of glucose variability of the two groups were similar in the 2nd and 3rd quartile. In the quartile with the worst metabolic control (HbA1c >9.2%), the CSII group showed higher glucose variability than the MDI group (table 2).

In conclusion, in our population of type 1 diabetic patients, glucose variability was lower in the CSII group than in the MDI group only when glucose control was good (HbA1c ≤7.5%). This data confirms the result of a crossover study that compared CSII and MDI with glargine in 32 type 1 diabetic patients with good metabolic control (baseline HbA1c 7.6%) (11). The advantage of CSII with regard to glucose variability disappeared when HbA1c was >7.5%. Indeed, glucose variability was even worse in CSII-treated patients when HbA1c was >9.2%. This is likely the consequence of a more frequent use of correction boluses in patients of the CSII group than in those of the MDI group (3.2 ± 2.1 vs. 1.2 ± 1.3 correction boluses/day, P < 0.005). Our data suggest

	CSII (n=10)	MDI (n=19)	
CV +/-	0.58+/-0.12	0.60+/-0.13	n.s
CV/day	0.60+/-0.13	0.63+/-0.15	n.s
CV/night	0.56+/-0.12	0.58+/-0.12	n.s
CONGA4/day (mg/dl)	127.7.3+/-31.5	89.9+/-11.1	p<0.05
CONGA4/night (mg/dl)	115+/-31.6	83+/-41	p<0.05
MODD (mg/dl)	55.9+/-23.8	52.1+/-21.7	n.s

**Table 2:** Measures of glycaemic variability in the quartile >9.2%.

that CSII is particularly advantageous in decreasing glucose variability when strict metabolic control is difficult to maintain with MDI without disabling hypoglycaemia or disturbing glucose fluctuations.

### An unresolved issue

Although accumulating evidence suggests that glucose “variability” in terms of widely fluctuating glucose may have a deleterious effect in worsening the prognosis for diabetic complications, we are still awaiting for more detailed and ad hoc designed studies, particularly intervention studies to definitely prove that a more stable glucose profile is of added value above mean glucose levels. The increasing availability of continuous glucose monitoring system provides a unique opportunity to precisely evaluate glucose variability and we can be quite confident that in the near future the role of glucose fluctuations will be definitely clarified.

### References

1. **Ceriello A.** The emerging role of post-prandial hyperglycaemic spikes in the pathogenesis of diabetic complications. *Diabet Med* 15: 188-193, 1998
2. **Gallagher A, HomePD.** The effect of improved post-prandial blood glucose control on post-prandial metabolism and markers of vascular risk in people with type 2 diabetes. *Diabetes Res Clin Pract* 67: 196-203, 2005
3. **The DCCT Research Group.** The relationship of glycemic exposure to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44: 968-983, 1995
4. **Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C.** Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295:1681-7, 2006
5. **Wentholt IME, Kulik W, Michels RPJ, Hoekstra JBL, DeVries JH.** Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. *Diabetologia* 51: 183-190, 2008
6. **Hirsch IB, Brownlee M.** Should minimal blood glucose variability become the gold standard of glycemic control? *J Diabetes Complications* 19:178 –181, 2005
7. **Kilpatrick ES, Rigby AS, Atkin SL.** The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 1486-1490, 2006
8. **Siegelaar SE, Kilpatrick ES, Rigby AS, Atkin SL, Hoekstra JB, DeVries JH:** Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT. *Diabetologia* 52: 229-2232, 2009
9. **Lepore G, Bruttomesso D, Bonomo M, Dodesini AR, Costa S, Meneghini E, Corsi A, Nosari I, Trevisan R.** Continuous subcutaneous insulin infusion is more effective than multiple daily insulin injections in preventing albumin excretion rate increase in Type 1 diabetic patients. *Diabet Med* 26: 602-608, 2009
10. **Lepore G, Dodesini AR, Nosari I, Trevisan R.** Effect of continuous subcutaneous insulin infusion vs multiple daily insulin injection with glargine as basal insulin: an open parallel long-term study. *Diabetes Nutr Metab* 17:84-9, 2004
11. **Bruttomesso D, Crazzolaro D, Maran A, Costa S, Dal Pos M, Girelli A, Lepore G, Aragona M, Iori E, Valentini U, Del Prato S, Tiengo A, Buhr A, Trevisan R, Baritussio A.** In Type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine. *Diabet Med* 25:326-332, 2008
12. **Bolli G, Kerr D, Thomas R, Torlone E, Sola-Gazagnes A, Vitacolonna E, Selam JL, HomePD.** Comparison of a Multiple daily Insulin Injection regimen (Basal Once-Daily Glargine Plus Mealtime Lispro) and Continuous Subcutaneous Insulin Infusion (Lispro) in Type 1 Diabetes. *Diabetes Care* 32: 1170-1176, 2009
13. **Simon B, Treat V, Marco C, Rosenberg D, Joseph J, Hipszer B, Li Y, Chervoveva I, Padron-Massara L, Jabbour S.** A comparison of glycaemic variability in CSII vs. MDI treated type 1 diabetic patients using CGMS. *Int J Clin Pract* 62: 1858-1863, 2008
14. **Weber C, Schnell O.** The assessment of glycaemic variability and its impact on diabetes-related complications: an overview. *Diabetes Technol & Ther* 11: 623-633, 2009
15. **Lepore G, Dodesini AR, Corsi A, Nosari I, Trevisan R.** Continuous subcutaneous insulin infusion is better than multiple daily insulin injections in reducing glucose variability only in Type 1 Diabetes with good metabolic control. *Diabetes Care* 33: e81, 2010



**Diabetes Research Center**

University Clinical Investigators, Inc.

- Evaluating investigational medications from pharmaceutical companies on diabetic subjects under FDA-approved study protocols.
- For Phase 1-4 Clinical Trials
- Tel: +1 714 734 7944
- Website: [www.uciinc.net](http://www.uciinc.net)

# Sensor-augmented pump therapy - the step between CSII and artificial pancreas?

Andreas Thomas and Martin Schönauer

*Medtronic GmbH, Germany*

## State of the art of insulin pump therapy (CSII)

The development of an artificial pancreas was first proposed by A.H. Kadish (1) more than four decades ago. This so-called closed-loop system appeared and still appears to be best possible solution for insulin treatment, especially for patients with type 1 diabetes. This kind of system was realised as early as the 1970s with the Biostator. This was a device as large as a table, to which the patient was connected. Blood sugar was measured in blood obtained from a vein and insulin was infused directly via a venous access, just like glucose in the case of falling blood sugar levels. At the time, it was optimistically thought that the equipment only needed to be sufficiently reduced in size for patients to be offered a portable system suitable for everyday use. It was expected that the substantial obstacles, namely the fact that sensors for continuous glucose measuring were not yet available and the problem of the unfavourable risk-benefit ratio associated with infusion of insulin and glucose via a venous port, would soon be overcome (2).

Pursuit of the goal of physiological insulin administration led to the development of small insulin pumps and hence to insulin pump therapy (CSII - continuous subcutaneous insulin infusion). After a hesitant start in the eighties, an established form of insulin therapy was developed (3). At present between 10% and 20% of patients with type 1 diabetes are treated with CSII in a number of western countries, such as Germany, Netherlands, France, Switzerland and Austria (3). In 2009 this rate was actually more than 35% in the USA (4, 5). One of the essential preconditions for the widespread use of CSII was the wide availability of self-monitoring of blood glucose levels. This made it possible to adjust the insulin to the patient's current need and to control functioning of the infusion system (pump, reservoir and infusion set). However, this was an open system (open-loop), which means insulin delivery is not controlled by a glucose sensor and relevant algorithms. In a sense, it is therefore a compromise on the vision of an artificial pancreas. The most important advantage of CSII is that, using solely short-acting insulin, it adjusts the basal insulin dosage to the diabetic's individual physiological insulin requirement, which can only be depicted with variable basal rate

programming in patients with type 1 diabetes (6). This results in a number of advantages over multiple dose injection therapy (MDI):

- In most pump patients, insulin delivery based on demand leads to close-to-normal glycaemia with HbA1c around 7%, without increasing the risk of hypoglycaemia (7-9). The lower HbA1c compared with MDI lessens the progression of diabetic complications and may even cause their regression to some extent (10, 11). Markedly smaller blood sugar fluctuations can also be seen, which in turn is likely to be associated with a reduction of vascular risk (12-14).

- Even diabetics who achieve their target blood sugar levels with difficulty or not at all on MDI usually achieve comparably better control with the aid of an insulin pump.

- Various options for bolus delivery allow optimal insulin adjustment to meals with a variable glycaemic index (15-17). High post-prandial blood sugar peaks, which are a risk factor for the development of macrovascular diseases (proven at least for type 2 diabetes (18, 19), are more likely to be avoided.

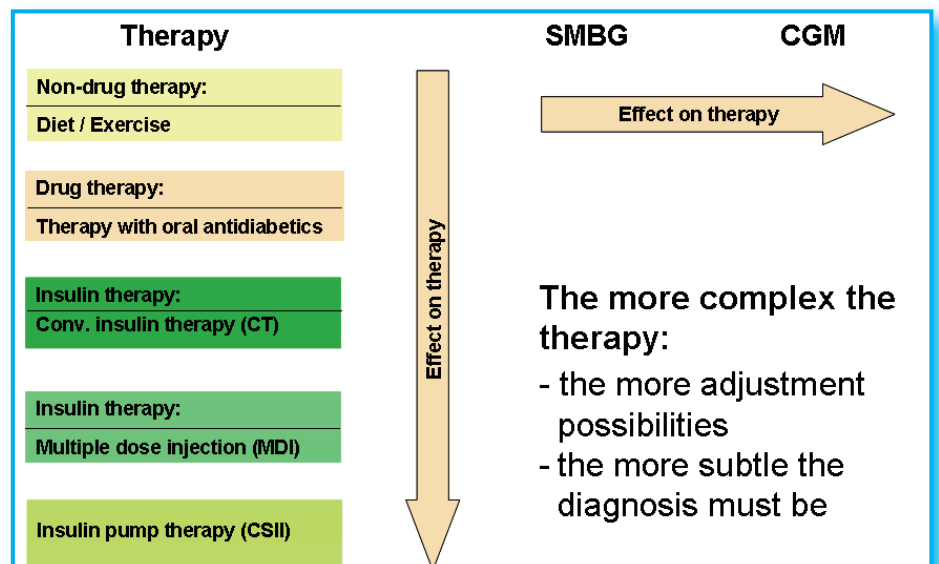
- The pump allows patients to achieve a more flexible daily profile that is influenced far less by the insulin therapy. This leads to an increase in the diabetic's exercise tolerance and functional capacity. Consequently everyday work activities (e.g. business travellers, doctors, etc.) can be managed better.

- An increased insulin requirement (e.g. during infection) or reduced requirement (e.g. during sport) can be simply responded to by temporary adjustment of the basal insulin dose.

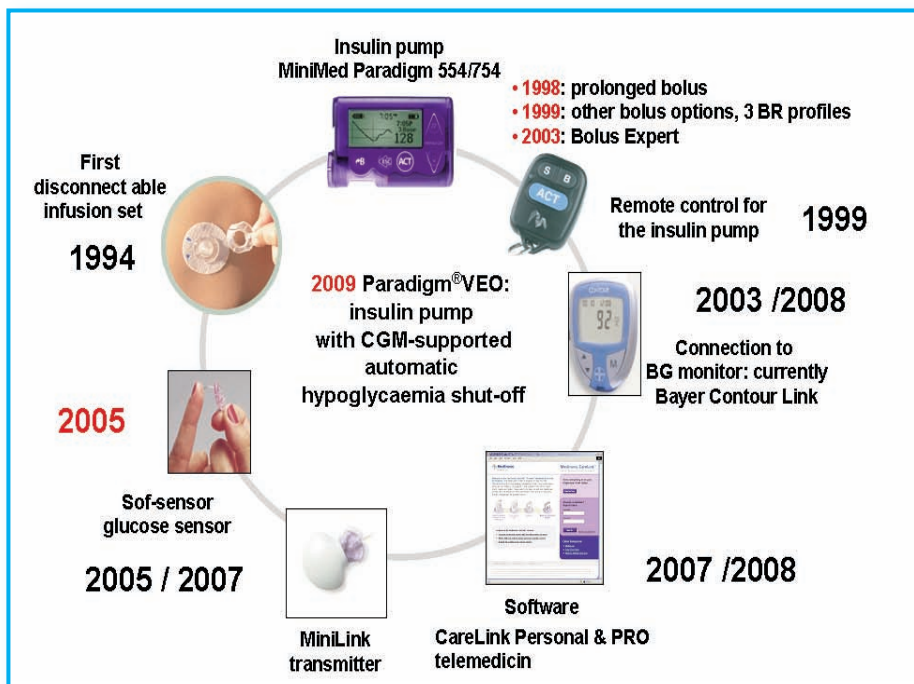
The conceptual and clinical advantages (improvement in HbA1c and/or decrease in hypoglycaemic events) are all the more impressive, the worse the initial situation was on the previous MDI (20). The advantages of CSII have been demonstrated by a large number of experimental and clinical trials but particularly by meta-analyses of randomised, controlled clinical trials (RCTs) (21, 22). In the meta-analysis by Pickup et al. (21) on 22 studies with a high evidence level, it was shown that in patients with frequent hypoglycaemic episodes their rate decreased by a factor of 4.19, hence to 23.9%. At the same time, HbA1c improved by an average of 0.61%. This improvement was also confirmed by the meta-analysis of Jeitler et. al. (22) (improvement of mean HbA1c: 0.55%). Hence, CSII versus MDI is not only demonstrably more physiological but also more successful, even if not every patient can realise these advantages.

## Use of continuous glucose monitoring (CGM) in CSII for sensor-augmented pump therapy (SaP)

Patients usually measure their blood sugar after getting up/before breakfast, again before meals and finally before going to bed. They



**Figure 1:** Treatment options for patients with diabetes mellitus and the helpful/necessary diagnostic options (SMBG = self-monitoring of blood glucose; CGM = continuous glucose monitoring).



**Figure 2:** Innovations and components of the Paradigm® VEO insulin pump system with the option of sensor-augmented pump (SaP) therapy resulting from connection to the glucose sensor.

will take additional measurements sporadically, if their blood sugar is not within the desired range or they feel they are having or about to have a hypoglycaemic episode. A total of 5 - 6 blood sugar measurements a day form the diagnostic basis for CSII. However, CSII has various possible ways of controlling insulin delivery (different bolus options, temporary change to the basal rate). If these are utilised, a more extensive database of glucose levels than that provided by self-measurement of glucose at specific time points is valuable. The use of a glucose sensor with continuous, automatic glucose measurement at intervals of a few minutes (CGM) proves very advantageous for this purpose, more than with all other treatment options (Figure 1). The use of a sensor means not only that the open-loop is gaining the essential component for further development into a closed-loop system, but it also turns CSII into a new form of therapy, namely sensor-augmented pump (SaP) therapy.

A glucose sensor used for CGM is minimally invasive, which means a small needle electrode is pushed under the skin and measures glucose in the interstitial space with the aid of chemical principles familiar from self-monitoring of blood glucose (conversion of glucose into gluconic acid and hydrogen peroxide with the aid of the enzyme glucose oxidase, dissociation of the hydroxide peroxide at an electrode and measurement of the resulting flow of current dependent on the glucose concentration) (23). A measurement is taken every 10 seconds. These individual measurements are combined to form a mean measurement over 5 min and indicated on a display. A sensor is used for 6 days. This gives the patient an opportunity to influence his glucose profile directly, which mainly includes active avoidance of hypoglycaemic events. Adjustable alert thresholds for hypoglycaemic and hyperglycaemic levels help patients do this. The advantages of CGM with current glucose lev-

els have been demonstrated in several RCTs. Among these, the JDRF (Juvenile Diabetes Research Foundation) studies are hitherto the largest and methodologically best RCTs involving CGM (24, 25). As a result of the application and dependent on the level of use of CGM, the HbA1c levels in JDRF 1 study (baseline HbA1c > 7-10%, 322 patients with type 1 diabetes) improved over 6 months (as a result of adequate use of CGM in adults aged over 25 years, the effect was only significant in this age group with a 0.5% HbA1c improvement) [24]. In well-controlled patients with type 1 diabetes (JDRF < 7 study, 129 patients with type 1 diabetes), this value did remain constant at 6.4%, although the time spent in the range of hypoglycaemic glucose levels ( $\leq 70$  mg/dl) was reduced by 41% (from a daily average of 91 min to 54 min). In this trial, all three age groups showed good compliance in terms of adequate use of the CGM system, which is why the positive effect was relevant irrespective of the age group (25).

These improvements become visible particularly on CSII because of the potential fine control of therapy. The Paradigm® VEO system comprises the insulin pump, with the option of transferring the current glucose levels recorded by a glucose sensor via a wireless interface to the system display (Figure 2). These data can also be incorporated into the bolus delivery calculation (BolusWizard™) and, after suitable confirmation by a conventional blood sugar measurement, entered into the insulin bolus calculation. As with the previous model (Paradigm®REAL-Time) under normal conditions the glucose sensor does not yet intervene automatically in glycaemic regulation but offers the patient a complete overview of his glucose profile. The system hence works as an “open system”, either in CSII mode (i.e. without the CGM component) or in SaP mode (if a glucose sensor is being used).

The superiority of SaP over classic CSII has been demonstrated in RCTs, for example in the multicentre REAL Trend study (Figure 3)

Closing the loop  
with the  
Paradigm® VEO™ System

The MiniMed Paradigm® VEO™ System

A new era in diabetes management

www.medtronic-diabetes.co.uk

UC20110426EE

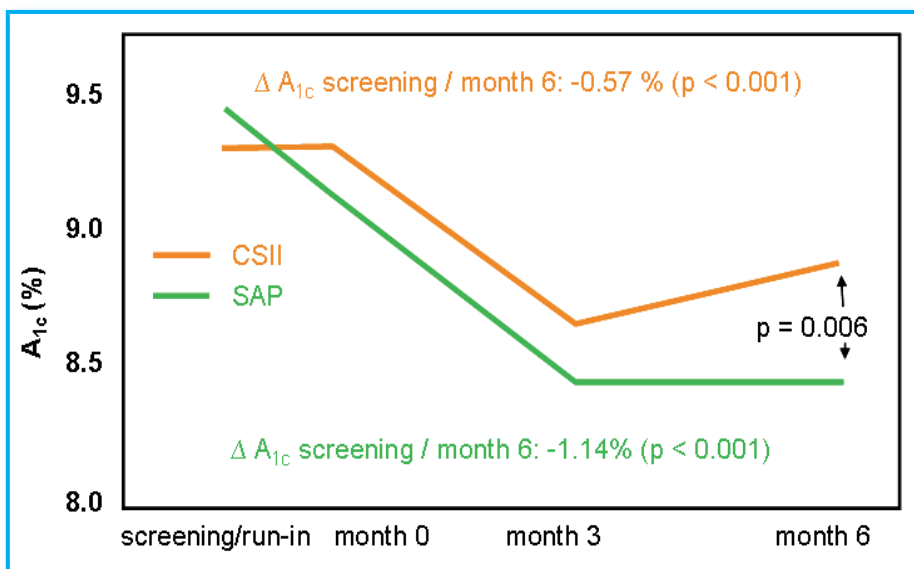
(26). In this study, the patients had previously been treated with ICT, on which they displayed inadequate glycaemic control. On SaP, their HbA<sub>1c</sub> improved by 1.23% over the course of the 6 months of the study (group of 91 patients who wore the sensor > 70% of the time) or by 1.14% (all patients, n = 115). By comparison, the percentage improvement on CSII was only 0.55%.

Besides to the REAL trend study, further randomized, controlled studies showed similar positive results. One example is the Eurythmics study in which was examined the SaP compared to the MDI (27). The SaP showed positive outcomes in case of new onset of type 1 diabetes in pediatric patients, too. In comparison to using conventional pump treatment (CSII) combined to self-monitoring blood glucose measurements the sensor-augmented insulin pump therapy from the onset of type 1 diabetes had a lower C-peptide loss during the first 12 months (ONSET trial (28)). The decreasing of glycaemic variability may have protective effects on beta cell function.

#### Sensor-augmented pump therapy (SaP) with automated hypoglycaemia management – the first step to artificial pancreas

The Paradigm® VEO system is the first to offer the possibility of treatment control by means of a glucose sensor. The system initially sounds an alert if there is a risk of or an actual hypoglycaemic event (depending on the threshold setting). If the patient does not respond to these alerts because he is deeply asleep, for example, the insulin pump automatically suspends insulin delivery for 120 min (this function is known as LGS - low glucose suspend). After this period of time, it automatically switches back on if the patient has not already done so manually. By this mechanism, hypoglycaemia can largely be avoided (29). Hyperglycaemia or even diabetic ketoacidosis are unlikely to arise because of the relatively short suspension of 120 min maximum. It is therefore the first time that a glucose sensor intervenes directly in therapy, making it a major advance towards an automated insulin pump system and hence towards an artificial pancreas.

There is currently intensive research work on further steps towards a closed-loop system. In the creation of an “artificial pancreas”, the key challenge is to develop algorithms for controlled insulin delivery based on measured glucose levels, while subcutaneous measurement and subcutaneous insulin delivery are favoured in view of the cost-benefit-risk relationship and the available hardware. The measurement of glucose in the interstitial fluid and the resulting physiological time lag to the blood glucose concentration as well as the non-physiological infusion of insulin into subcutaneous tissue pose a special challenge to this algorithm. It should further be noted that insulin must be delivered in such a way that



**Figure 3:** HbA<sub>1c</sub> trend in patients with good compliance (n = 91: 59 on CSII, 32 on SaP) in the REAL Trend study (26) (definition of compliance: wearing the sensor > 70% of the time).

the glucose concentration can be predicted as lying in the normoglycaemic range. Previous studies show that normoglycaemic glucose regulation is achieved solely in the basal phase (without food intake and without physical activity) but unphysiologically high glucose levels occur after meals. The problem is essentially due to subcutaneous exogenous insulin, which unlike endocrine insulin is peripherally active first and only then hepatically active (so that gluconeogenesis is not immediately halted) and its pharmacodynamics are independent of the glucose stimulus. For this purpose, the short-acting insulin analogues currently available on the market are still too slow. In any event, however, the activities and the number of studies and publications on this subject have markedly increased.

#### Summary

Sensor-augmented pump therapy is a major advance towards a closed-loop system. In the process, the glucose sensor, which is an essential component of the artificial pancreas, is being introduced directly into insulin pump therapy (Figure 4). Assuming continuous use of the CGM component, the positive effects of CSII are markedly enhanced. Automated intervention when hypoglycaemia is ignored or not noticed, means that the lowest level of a closed-loop has already been realised in a marketable product. After decades of waiting, the diabetology vision of an artificial pancreas now seems within reach.

#### Address for correspondence

**Dr. Andreas Thomas**  
Medtronic GmbH  
Earl Bakken Platz 1  
01796 Meerbusch  
Germany  
andreas.thomas@medtronic.com

**Dr. Med. Martin Schönauer**  
Akademische Lehrpraxis der Universität Leipzig  
Diabetes-Zentrum DDG  
August-Bebel-Str. 71  
D-04275 Leipzig  
www.schoenauer-leipzig.de

#### Conflict of Interest

Dr. Andreas Thomas is Scientific Manager of Medtronic, Diabetes Division.

Dr. Martin Schönauer is a diabetologist, with no commercial interests in respect of the technology and therapy presented.

#### References

- Kadish AH.** Automation control of blood sugar a servomechanism for glucose monitoring and control. *Trans Am Soc Artif Intern Organs* 1963; 9: 363-367
- Feedback-Controlled and Preprogrammed Insulin Infusion in Diabetes Mellitus. Georg-Thieme Verlag Stuttgart, New York 1978
- Henrichs HR.** Diabetestherapie mit Insulinpumpen. UNI-MED Verlag AG 2003
- Bode B. Pump therapy. *Diabetic Medicine* 2006 (Suppl. 4); 23: 426-427
- Bode B:** Insulin pumps for Type 2 Patients. 69th ADA Scientific Session 2009 New Orleans
- Koivisto VA, Yki-Jarvinen H, Helve E et al.** Pathogenesis and prevention of the dawn phenomenon in diabetic patients treated with CSII. *Diabetes* 1986; 35: 78 – 82
- Pickup J, Mattock M, Kerry S:** Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* Volume 324 (2002), 1-6
- Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R:** Insulin Pump Therapy: A meta-analysis. *Diabetes Care*, Volume 26 (4) (2003), 1079-1087
- Bode BW, Steed RD, Davidson PC:** Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care* 19; 1996: 324 – 327
- Aragona M, Giannarelli R, Coppelli A et al.** Improvement of retinopathy in Type 1 diabetic patients treated with continuous subcutaneous insulin infusion (CSII). *Diabetes Metabol.* 2003; 29: 4S235
- Lüddeke HJ, Hofmann W, Guder WG et al.** Urinary albumin concentration in 52 CSII treated type 1 diabetic patients during a follow-up of 4 years. *Diabetes und Stoffwechsel* 2002; 11 (Suppl. 1): 115
- Hanefeld M, Fischer S, Julius U, Schulze J,**

Schwanebeck U, Schmechel H, Ziegelasch HJ and Lindner J. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow up. *Diabetologica* 1996; 39: 1577-1583

13. Piconi L, Quagliaro L, DaRos R, Assaloni R, Giugliano D, Esposito K, Szabo C and Ceriello A. Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly (ADP-ribose) polymerase. *J Thromb Haemost* 2004; 2: 1453-1459.

14. Risso A, Mercuri F, Quagliaro L, Damante G and Ceriello A. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab* 2001; 281: E924-E930

(15. Chase HP, Saib SZ, MacKenzie T, Hansen MM, Garg SK: Post-prandial glucose excursions following four methods of bolus insulin administration in subjects with Type 1 diabetes. *Diabetic Medicine* 19, 2002: 317 – 321

16. Lee MS, Cao M, Sajid A, Haynes M, Choi L, DeLeon R, Rother C: The Dual-Wave Bolus Feature in CSII Controls Prolonged Post-Prandial Hyperglycemia Better Than Standard Bolus in Type 1.

*Diabetes Diabetes* 52 Suppl.1 (2003), A438

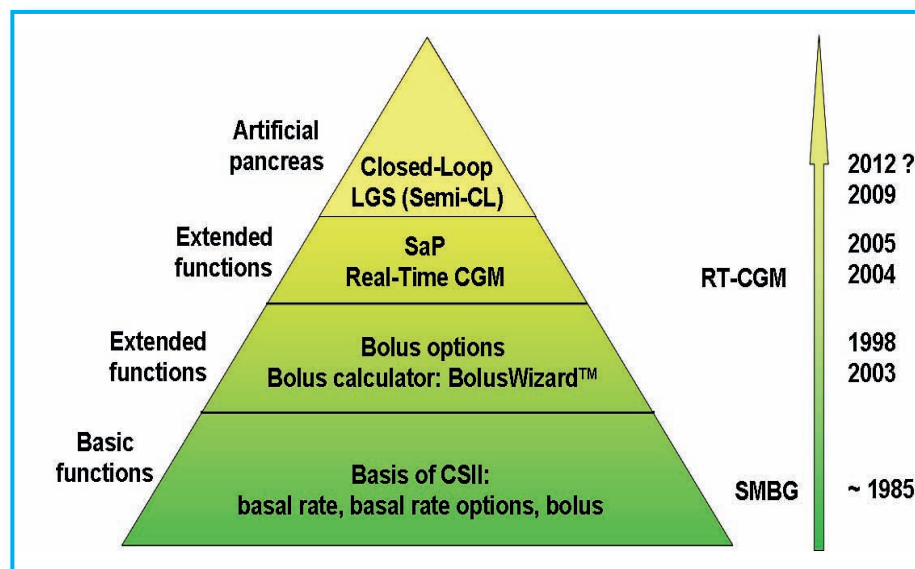
17. Jones SM, Quarry JL, Caldwell-McMillan M et al. Optimal Insulin Pump Dosing and Postprandial Glycemia Following a Pizza Meal Using the Continuous Glucose Monitoring System. *Diabetes Technology & Therapeutics* 2005; 7: 233 - 240

18. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, and Temelkova-Kurktschiev T: Insulin Secretion and Insulin Sensitivity Pattern Is Different in Isolated Impaired Glucose Tolerance and Impaired Fasting Glucose: The Risk Factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes Study.

*Diabetes Care* 26 (2003): 868-874

19. Monnier L, Emilie Mas E, Ginot C, Michel F, Villon L, Cristol J-P, Colette C: Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes. *JAMA* 2006; 295 (14), 1681 – 1687

20. Pickup JC, Kidd J, Burmiston D et al. Effectiveness of continuous subcutaneous insulin



**Figure 4:** Development of CSII from its initial basic functions via extended functions and the use of CGM through to the closed-loop system (CL). The years and decisive influences in terms of measuring technology are shown on the right (LGS - low glucose suspend).

infusion in hypoglycaemia-prone type 1 diabetes. *Practical Diabetes International* 2005; 22: 10 – 14

21. Pickup J, Sutton AJ Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion.

*Diabetic Medicine* 2008; 25: 765 – 774

22. Jeitler K, Horvath K, Berghold A et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008; 51: 941-951

23. Mastrototaro, JJ: The MiniMed Continuous Glucose Monitoring System. *Diabetes Technology and Therapeutics* 2000; 2 (Suppl. 1): 13-18

24. JDRF Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *NEJM* 2008; 359:1464-1476

25. Beck RW for JDRF CGM Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009; 32:1378-1383 1476

26. Raccach D, Sulmont V, Reznik Y, Guerci B, Hanaire H, Jeandidier N, Nicolino M: Incremental Value of Continuous Glucose Monitoring When Starting Pump Therapy in Patients With Poorly Controlled Type 1 Diabetes. *Diabetes Care* 2009; 32:2245-2250 (REAL Trend Study)

27. Hermanides J, Nørgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, Diem P, Fermon C, Wentholt IME, Hoekstra JBL, DeVries JH. Sensor augmented pump therapy substantially lowers HbA1c; a randomized controlled trial. *Diabetologia* 2009; 52 (Suppl. 1), S43

28. Danne T, Pankowska E, Rami B, Kapellen T, Coutant R, Hartmann R, Aschmeier B, Blaesig S, Marquardt E, Walte K, Lange K, Kordonouri O. The ONSET trial of sensor-enhanced CSII in children with new onset type 1 diabetes. 20th World Diabetes Congress, Montreal 2009, 0528, Abstract book 175

29. Buckingham BA, Cobry E, Clinton P et al. Preventing Hypoglycemia Using Predictive Alarm Algorithms and Insulin Pump Suspension. *Diabetes Technology & Therapeutics* 2009; 11:93-97



**NovoRapid®** –  
the insulin of choice for  
CSII treatment



[www.novorapid.com](http://www.novorapid.com)

Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark  
Tel: +45 4444 8888 Fax: +45 4449 0555 [www.novonordisk.com](http://www.novonordisk.com)

**NovoRapid®**  
(insulin aspart)  
**Rapid, flexible control™**