Can Long-Acting Insulin Analogues Replace Insulin Pump Therapy?

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Indications for CSII in type 1 diabetes?

- Frequent, unpredictable severe hypoglycaemia on MDI.

- Elevated HbA1c and unpredictable glycaemic fluctuations on MDI.

- A marked dawn phenomenon during MDI.
Severe hypoglycaemia
Severe hypoglycaemia CSII vs. insulin injection therapy (n=40, >6 mo treatment)
Bending, Pickup, Keen 1985

![Graph showing the comparison of severe hypoglycaemic events between CSII and injections for all patients, patients without proteinuria, and those with proteinuria. The graph indicates a statistically significant difference between the two methods for all patients (p<0.03) and a significant difference for patients without proteinuria (p = 0.005). There is no significant difference for patients with proteinuria (ns).]
Reduction in severe hypoglycaemia in the Oslo Study (1986): RCT of MDI (and CIT) vs. CSII

**Graph:**
- **MDI:**
  - Number of hypoglycaemia episodes: 14
- **CSII:**
  - Number of hypoglycaemia episodes: 2

Statistical significance:
- **p < 0.001**
Reduction in severe hypoglycaemia in 55 type 1 diabetic subjects: multiple insulin injections vs pumps Bode et al. 1996
Provisional Meta-Analysis of Severe Hypoglycaemia MDI vs CSII

- 21 trials

- Rate of severe hypoglycemia on MDI reduced by CSII by about 75% - from median 46 (23 - 81) to 12 (9 - 20) episodes / 100 patient-years

Pickup JC, et al. Unpublished Data
Severe hypoglycaemia is not improved by MDI with glargine or detemir vs. NPH regimens

**Glargine**
- Raskin et al Diabetes Care 2000; 23: 1666
- Warren et al Hlth Tech Assess 2004; 8: 1 (systematic review)

**Detemir**
- Russell-Jones et al Clin Ther 2004; 26: 724
- Hermansen et al Diabetologia 2004; 47: 622
- Home et al Diabetes Care 2004; 27: 1081
Detemir reduces any nocturnal hypoglycaemia but not severe hypoglycaemia (Home et al. 2004)

RCT 408 type 1 diabetic patients to NPH-based or one of 2 detemir regimens
Elevated HbA1c and glycaemic variability
Meta-analysis in general diabetic patients

HbA1c in RCTs of MDI vs. CSII, Pickup et al., 2002

[NB: small difference in HbA1c]
BUT

Reduction of HbA1c not well studied in (clinically-recommended) group of hypoglycaemia-prone type 1 diabetic patients
Reduction in HbA1c on switching to CSII is greater than expected in hypoglycaemia-prone type 1 diabetes.
Switching to CSII in hypoglycaemia-prone type 1 diabetes (n=27), Pickup et al Pract Diab Int 2005; 22: 10-14

Mean fall in HbA1c ~1.5%
Improvement in HbA1c on switching to CSII depends on HbA1c on MDI


\[ r = 0.79, \text{ } p < 0.0001 \]
HbA1c achievable on MDI is related to blood glucose variability on MDI


Subjects with high blood glucose variability on MDI resist improvement to avoid hypoglycaemia, thereby maintaining a high HbA1c

![Graph showing correlation between blood glucose variability and HbA1c on MDI. The linear correlation coefficient \(r = 0.6\) and significance level \(p = 0.017\).]
CSII reduces hypoglycaemia, and within- and between-day blood glucose variability (Pickup et al 2005)

Hypoglycaemia

- BG values < 3.5 mM (%)
  - MDI: 10.0%
  - CSII: 2.5%
  - p < 0.03

Within-day variability

- IQR daily BG (mM)
  - MDI: 7.5
  - CSII: 2.5
  - p < 0.01

Day-to-day variability

- IQR fasting BG (mM)
  - MDI: 8.0
  - CSII: 4.0
  - p < 0.01
Glargine or detemir improves glycaemic control in some patients (vs. NPH-based regimens)
Strategy for treating patients by CSII

Poor diabetic control

GP or hospital consultant

Pump Clinic in Hospital, assessed by Consultant

Pump nurse and dietitian, optimize control on injections, including glargine/detemir, assess suitability for pump

Control improved

Control not improved

Not suitable for pump treatment

Not suitable for pump treatment

Trial of pump treatment

~75% of referred
Mean HbA1c is not always improved by glargine or detemir vs. NPH

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>NPH</th>
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<td>Raskin et al 2000</td>
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<td>Russell-Jones 2004</td>
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HbA1c is similar on MDI with NPH vs. MDI with glargine in hypoglycaemia-prone type 1 diabetes (Pickup et al 2005)
HbA1c during glargine MDI is further improved by CSII (Pickup et al 2005)

\[ p < 0.001 \]

8.7 ± 1.2%  
7.2 ± 1.0%

Treatment

Glargine MDI  
CSII
CSII vs MDI with glargine
Doyle et al. 2004

- RCT over 16 weeks
- 32 type 1 diabetic subjects allocated to glargine/aspart or CSII with aspart
- HbA1c significantly lower during CSII
CSII vs. aspart and glargine MDI
Hirsch et al 2005

- 100 type 1 diabetic patients, RCT with cross over, 5 weeks each treatment
- CSII vs. aspart + glargine MDI
- AUC of glucose measured using CGMS – lower during CSII

![Graph showing AUC glucose comparison between CSII, MDI, CSII, and MDI with P values of <0.001 for both comparisons and thresholds of ≥ 4.4 mM and ≥ 7.8 mM.](image)
The dawn phenomenon

Rise in blood glucose in hours preceding breakfast
Basal infusion rate can be increased at preset time to counter dawn phenomenon.

Meal boosts and slow basal insulin throughout 24 hours for diabetic subjects: meal time boosts and slow basal insulin throughout 24 hours.

Insulin injections with CSII.

Basal infusion rate can be increased at preset time to counter dawn phenomenon.
Dawn phenomenon can often be managed by glargine or detemir.
Now less of a problem on MDI regimens.

(Home et al 2004)
Dawn phenomenon is becoming a less frequent reason for using CSII
CSII vs MDI with analogues in type 2 diabetes

Comparable glycaemic control
CSII vs MDI with glargine in type 2 diabetes
(Herman et al Diabetes Care 2005; 28: 1568)

- RCT 107 type 2 DM allocated to CSII or MDI (glargine + aspart) for 1 year
- No difference in HbA1c between groups
- No difference in BMI, hypoglycaemia or treatment satisfaction between groups
Finally

Not everything is perfect with CSII!
Variability of Fasting Blood Glucose on CSII: 4 Patients

Female aged 30 years
MDI HbA1c 8.4%
CSII HbA1c 5.2%

Female aged 51 years
MDI HbA1c 9%
CSII HbA1c 5.7%

Female aged 36 years
MDI HbA1c 8.0%
CSII HbA1c 6.1%

Male aged 34 years
MDI HbA1c 7.8%
CSII HbA1c 6.8%
We still need improved insulin delivery

Better glucose monitoring?
Closing-the-loop?
Summary (1)

- In type 1 diabetes, CSII reduces the frequency of severe hypoglycaemia on MDI - glargine and detemir do not usually do so.

- CSII improves HbA1c and glycaemic variability compared to NPH-based MDI – glargine and detemir do in some but not in many patients, particularly hypoglycaemia-prone subjects.
Summary (2)

• In type 2 diabetes, glycaemic control seems to be similar during CSII and MDI with analogues (but more research is needed)

• Long-acting insulin analogues have not yet replaced the need for insulin pump therapy in type 1 diabetes

• CSII is the best current therapeutic option for many type 1 diabetic patients
But will still need better insulin delivery in diabetes