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Research: Educational and Psychological Issues

Twice- rather than once-daily basal insulin is associated with better glycaemic control in Type 1 diabetes mellitus 12 months after skills-based structured education in insulin self-management

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Abstract

Aim This study investigates the relationship between basal insulin regimen and glycaemic outcomes 12 months after skills-based structured education in the UK Dose Adjustment for Normal Eating (DAFNE) programme for Type 1 diabetes mellitus.

Method Retrospective analysis of data from 892 DAFNE participants from 11 UK centres.

Results Mean HbA₁c 12 months after DAFNE was lower in those using twice- rather than once-daily basal insulin after correcting for differences in baseline HbA₁c, age and duration of diabetes; difference –2 (95% CI –3 to –1) mmol/mol [–0.2 (–0.3 to –0.1)%], P = 0.009. The greatest fall in HbA₁c of –5 (–7 to –3) mmol/mol [–0.4 (–0.6 to –0.3)%], P < 0.001 occurred in those with less good baseline control, HbA₁c ≥ 58 mmol/mol, who switched from once- to twice-daily basal insulin. There was no difference in the 12-month HbA₁c between users of glargine, detemir and NPH insulin after correcting for other variables. Relative risk of severe hypoglycaemia fell by 76% and ketoacidosis by 63% 12 months after DAFNE. The rate of severe hypoglycaemia fell from 0.82 to 0.23 events/patient year in twice-daily basal insulin users. In the group with greatest fall in HbA₁c, the estimated relative risk for severe hypoglycaemia in twice-daily basal insulin users versus once daily at 12 months was 1.72 (0.88–3.36, P = 0.110).

Conclusion After structured education in adults with Type 1 diabetes mellitus, use of basal insulin twice rather than once daily was associated with lower HbA₁c, independent of insulin type, with significant reductions in severe hypoglycaemia and ketoacidosis in all groups.


Introduction

The Dose Adjustment for Normal Eating (DAFNE) programme provides structured education in flexible intensive insulin therapy for adults with Type 1 diabetes mellitus both within and beyond the UK [1]. Emphasis is placed on carbohydrate counting and meal-related short-acting insulin dose adjustment. Education and skills-based training on how to adjust basal insulin doses are also key components in the curriculum, but may be seen by users as having a secondary role [2]. DAFNE is based on the original German ITT course [3] and its efficacy has been demonstrated in a randomized controlled trial in which participants used exclusively twice-daily (bd) NPH as basal insulin [4]. However, long-acting insulin analogues are now frequently prescribed and are often injected once (od) rather than twice daily. There is little evidence on whether the type or frequency of injection of basal insulin influences glycaemic control after structured education. This study investigates the relationship between basal insulin regimen and glycaemic outcomes 12 months after DAFNE training.

Methods

We collected baseline and 12-month follow-up data for patients who had completed DAFNE training from the DAFNE research database from its inception in 2009 to
Exclusion criteria were pregnancy or continuous subcutaneous insulin infusion use at baseline or 12 months; missing HbA1c, basal insulin type or frequency at baseline or 12 months; and use of basal insulin other than once or twice daily. Analyses were performed for the whole cohort, and on a reduced cohort comprising patients with baseline HbA1c ≥ 58 mmol/mol (≥ 7.5%), an inclusion criterion in the DAFNE RCT [4]. HbA1c ≥ 58 mmol/mol (≥ 7.5%) identifies participants in whom improving glycaemic control is likely to be a prime objective of structured education additional to improving quality of life with diabetes. Data for severe hypoglycaemia were also analysed separately for those with HbA1c < 58 mmol/mol (< 7.5%) at baseline, as those with lower values already may have more incentive to use structured education to reduce their future risk of hypoglycaemia [6]. Glycaemic outcomes were assessed in relation to frequency of basal insulin injection and type using a linear multiple regression model for HbA1c. Negative binomial models and logistic regression modelling were used to analyse patterns in severe hypoglycaemia and ketoacidosis data. All models used population-averaged exchangeable correlation and robust standard errors to allow for clustering by centre. Analyses were performed using IBM SPSS Statistics for Windows, v. 21.0 (Armonk USA) and figures were drawn using R [7].

Results

Of 1238 patients with 12-month data, 99 were excluded because of pregnancy or continuous subcutaneous insulin infusion use. There were 892 (78.3%) eligible patients with complete data. Mean (sd) age was 41.1 (13.6) years, duration of diabetes 18.9 (13.4) years; 47% were men. Baseline HbA1c was ≥ 58 mmol/mol (≥ 7.5%) in 739 (82.8%) patients.

At baseline, 3.8% of patients were using pre-mixed insulin, 31.6% basal insulin detemir (od 13.8%, bd 17.8%), 48% basal insulin glargine (od 42.4%, bd 5.6%) and 16.6% NPH (od 6.7%, bd 9.9%). At 12 months, basal insulin usage was detemir 40.2% (od 8.6%, bd 31.6%), glargine 42.0% (od 30.3%, bd 11.7%) and NPH 17.8% (od 1.6%, bd 16.2%). The pattern of basal insulin use for the reduced cohort both at baseline and at 12 months varied by < 1% from the above. Excluding those using mixed insulin, before DAFNE 65.4% (561/858) were using once-daily basal insulin. This decreased to 40.8% (350/858) after DAFNE (difference – 24.6%, 95% CI: –27.7% to –21.5%, P < 0.001).

HbA1c

There was a fall in HbA1c for the whole cohort of –2 (95% CI –3 to –1) mmol/mol [–0.2 (–0.3 to –0.1%)] P < 0.001. Those using twice-daily basal insulin at 12 months had a greater fall in HbA1c of –3 (–4 to –2) mmol/mol [–0.3 (–0.4 to –0.2)%], P < 0.001, whereas those using once-daily basal insulin showed no significant fall; difference –1 (–2 to –1)
mmol/mol [-0.1 (-0.2 to -0.1)%], P = 0.222. For the reduced cohort with less good control at baseline, there was a fall in HbA1c at 12 months of -4 (-4 to -3) mmol/mol [-0.3 (-0.4 to -0.2)%], P < 0.001; a fall of -5 (-7 to -3) mmol/mol [-0.4 (-0.5 to -0.3)%] in the subgroup using basal insulin twice daily, P < 0.001; and a fall of -2 (-3 to 0) mmol/mol [-0.2 (-0.3 to -0.1)%], P = 0.011 in the group using basal insulin once daily (Fig. 1).

Table 1 shows data from patients grouped according to their pattern of basal insulin injection at baseline and 12 months. Excluding baseline mixed insulin users, in the whole cohort, those that switched from once- to twice-daily basal insulin (od-bd) had a change in HbA1c of -3 (-5 to -2) mmol/mol [-0.3 (-0.4 to -0.2)%], P < 0.001, and in the group using twice-daily basal insulin both at baseline and 12 months (bd-bd) of -3 (-4 to -1) mmol/mol [-0.3 (-0.4 to -0.1)%], P < 0.001; there was no significant change in the HbA1c in the group who continued to use once-daily basal insulin (od-od), or in the small number of patients who changed from twice-daily to once-daily basal insulin (bd-od) (Table 1). The same pattern was found in the data for the reduced cohort with the greatest fall in HbA1c of -5 (-7 to -3) mmol/mol [-0.4 (-0.6 to -0.3)%], P < 0.001 in the od-bd group.

Change in HbA1c correcting for age, duration of diabetes and baseline HbA1c

The linear modelling analysis showed no difference in 12-month HbA1c between the three types of basal insulin, NPH, levemir and glargine, in the whole (P = 0.337) cohorts. However, the group using twice-daily basal insulin had a lower HbA1c at 12 months than those using once daily both in the whole cohort; 69 vs. 71 mmol/mol (8.4% vs. 8.6%), difference -2 mmol/mol, 95% CI: -3 to -1 [-0.2 (-0.3 to -0.1)%], P = 0.009 and in the reduced cohort; 71 vs. 74 mmol/mol (8.7% vs. 8.9%); difference -3 (-4 to -1) mmol/mol [-0.2 (-0.4 to -0.1)%], P = 0.006.

Excluding those using mixed insulin at baseline, linear modelling using the grouping according to pattern of basal insulin use showed an overall difference between groups at 12 months (P = 0.001). Post-hoc comparisons in the full cohort showed lower 12-month HbA1c in the od-bd group than the od-od group; difference -2 (95% CI -4 to -1) mmol/mol [-0.2 (-0.3 to -0.1)%], P < 0.001, and in the bd-bd group compared with the od-od group; difference -2 (-4 to -1) mmol/mol [-0.2 (-0.4 to -0.1)%], P = 0.005.

The same analyses performed in the reduced cohort showed difference: -3 (-6 to -1) mmol/mol [-0.3 (-0.5 to -0.1)%], P = 0.001 and difference: -3 (-5 to -1) mmol/mol [-0.3 (-0.5 to -0.1)%], P = 0.001, respectively.

Severe hypoglycaemia

Data on severe hypoglycaemia in the 12 months before and after DAFNE were available for 730 patients (81.8%) in the full cohort (Table 2) and 596 (80.1%) in the reduced cohort. Rate of severe hypoglycaemia fell from 0.85 to 0.20 episodes per patient per year in the full cohort, estimated relative risk

![FIGURE 1 Mean HbA1c at baseline and 12 months after structured education in DAFNE shown for the reduced cohort (baseline HbA1c ≥ 58 mmol/mol, ≥ 7.5%) and subgroups of participants analysed according to basal insulin regimen at 12 months, with 95% confidence intervals and P values derived from paired t-tests. The 12-month HbA1c is significantly lower than baseline in all subgroups.](image-url)
The effect of basal insulin injection frequency in Type 1 diabetes • H. E. Hopkinson et al.

### Table 1: Whole-cohort HbA1c data: participants grouped by frequency of basal insulin injection at baseline and 12 months. There was a significant fall in HbA1c for twice-daily basal insulin users who continue to use twice daily, and in once-daily basal insulin users who switch to twice daily after structured education in DAFNE.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline basal insulin regimen</th>
<th>12-month basal insulin regimen</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Difference between baseline and 12-month HbA1c mmol/mol (%)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Once daily</td>
<td>Once daily</td>
<td>341</td>
<td>72 (8.8)</td>
<td>71 (8.8)</td>
<td>−1 (−0.1)</td>
<td>−2 to 1 (−0.2 to 0.1)</td>
<td>0.281</td>
</tr>
<tr>
<td>2</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>220</td>
<td>71 (8.8)</td>
<td>68 (8.5)</td>
<td>−3 (−0.3)</td>
<td>−5 to −2 (−0.4 to −0.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>9</td>
<td>81 (9.7)</td>
<td>77 (9.3)</td>
<td>−4 (−0.4)</td>
<td>−17 to 8 (−1.3 to 0.7)</td>
<td>0.449</td>
</tr>
<tr>
<td>4</td>
<td>Twice daily</td>
<td>Twice daily</td>
<td>288</td>
<td>73 (8.8)</td>
<td>69 (8.5)</td>
<td>−3 (−0.3)</td>
<td>−4 to −1 (−0.4 to −0.1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 2: Event data for the full cohort for severe hypoglycaemia (n = 730) and diabetic ketoacidosis (n = 689) at baseline and 12 months after skills-based training in DAFNE.

<table>
<thead>
<tr>
<th>Injections</th>
<th>Events</th>
<th>Rate*</th>
<th>%†</th>
<th>Patients</th>
<th>Events</th>
<th>Range</th>
<th>Rate*</th>
<th>%†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td>455</td>
<td>0–40</td>
<td>0.82</td>
<td>20.9</td>
<td>284</td>
<td>0–12</td>
<td>0.15</td>
<td>6.7</td>
</tr>
<tr>
<td>Twice daily</td>
<td>275</td>
<td>0–50</td>
<td>0.89</td>
<td>23.3</td>
<td>446</td>
<td>0–12</td>
<td>0.23</td>
<td>9.2</td>
</tr>
<tr>
<td>NPH</td>
<td>138</td>
<td>0–8</td>
<td>0.52</td>
<td>21.0</td>
<td>142</td>
<td>0–6</td>
<td>0.15</td>
<td>5.6</td>
</tr>
<tr>
<td>Glargine</td>
<td>342</td>
<td>0–50</td>
<td>1.10</td>
<td>21.3</td>
<td>300</td>
<td>0–12</td>
<td>0.25</td>
<td>9.3</td>
</tr>
<tr>
<td>Detemir</td>
<td>227</td>
<td>0–20</td>
<td>0.68</td>
<td>22.5</td>
<td>288</td>
<td>0–12</td>
<td>0.16</td>
<td>8.3</td>
</tr>
<tr>
<td>Total</td>
<td>730</td>
<td>0–50</td>
<td>0.85</td>
<td>21.8</td>
<td>730</td>
<td>0–12</td>
<td>0.20</td>
<td>8.2</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td>434</td>
<td>0–3</td>
<td>0.07</td>
<td>4.8</td>
<td>272</td>
<td>0–1</td>
<td>0.03</td>
<td>2.9</td>
</tr>
<tr>
<td>Twice daily</td>
<td>255</td>
<td>0–3</td>
<td>0.05</td>
<td>4.3</td>
<td>417</td>
<td>0–2</td>
<td>0.02</td>
<td>1.7</td>
</tr>
<tr>
<td>NPH</td>
<td>116</td>
<td>0–2</td>
<td>0.08</td>
<td>6.9</td>
<td>121</td>
<td>0–1</td>
<td>0.02</td>
<td>1.7</td>
</tr>
<tr>
<td>Glargine</td>
<td>337</td>
<td>0–3</td>
<td>0.07</td>
<td>5.0</td>
<td>295</td>
<td>0–1</td>
<td>0.03</td>
<td>3.1</td>
</tr>
<tr>
<td>Detemir</td>
<td>214</td>
<td>0–3</td>
<td>0.04</td>
<td>2.3</td>
<td>273</td>
<td>0–2</td>
<td>0.02</td>
<td>1.5</td>
</tr>
<tr>
<td>Mixed</td>
<td>22</td>
<td>0–1</td>
<td>0.09</td>
<td>9.1</td>
<td>‒</td>
<td></td>
<td>‒</td>
<td>‒</td>
</tr>
<tr>
<td>Total</td>
<td>689</td>
<td>0–3</td>
<td>0.06</td>
<td>4.6</td>
<td>689</td>
<td>0–2</td>
<td>0.02</td>
<td>2.2</td>
</tr>
</tbody>
</table>

*Number of events per patient per year.
†Per cent of patients with at least one event.

0.24 (95% CI: 0.16–0.36, P < 0.001); from 0.83 to 0.20 episodes per patient per year in the reduced cohort, with relative risk 0.26 (95% CI: 0.16–0.40, P < 0.001). In the full cohort, the rate of severe hypoglycaemia in twice-daily basal insulin users fell from 0.89 to 0.23, and from 0.82 to 0.15 in once-daily users. The estimated odds ratio (OR) of severe hypoglycaemia after DAFNE compared to before DAFNE was 0.32 (95% CI: 0.27–0.38, P < 0.001) in the full cohort and 0.33 (95% CI: 0.26–0.42, P < 0.001) in the reduced cohort.

For patients who entered DAFNE with good glycaemic control [baseline HbA1c < 58 mmol/mol (7.5%), n = 134] there was no significant difference in severe hypoglycaemia at 12 months between once and twice-daily basal insulin users.

A negative binomial model was used to test for a difference in the rate of severe hypoglycaemia at 12 months between different types of basal insulin and frequency of basal insulin injection, adjusted for the number of severe hypoglycaemia events at baseline, HbA1c at 12 months, age and diabetes duration. This found no overall difference between 12-month severe hypoglycaemia rates for the three types of insulin (full cohort P = 0.389; reduced cohort P = 0.298). The estimated relative risk of severe hypoglycaemia for those using twice-daily compared with once-daily basal insulin was 1.85 (95% CI: 1.01–3.42, P = 0.049); in the reduced cohort with poorer baseline control 1.72 (95% CI: 0.88–3.36, P = 0.110); and in the small group with good baseline control 3.86 (95% CI: 0.55–24.88, P = 0.181).

A logistic regression model was used to test if there was a difference in the number of people having at least one severe hypoglycaemia event at 12 months between the different types of insulin and the number of injections. This model was adjusted for HbA1c at 12 months, age, duration and if the
individual had severe hypoglycaemia at baseline or not. The estimated OR for severe hypoglycaemia of those using twice-daily basal insulin compared with those using once-daily basal insulin in the full cohort was 2.68 (95% CI: 1.29–3.52, \( P = 0.003 \)) and in the reduced cohort 1.80 (1.02–3.16, \( P = 0.041 \)).

In the full cohort, the estimated OR for severe hypoglycaemia between basal insulin pairs were glargine : NPH 2.68 (95% CI: 1.38–5.21, \( P = 0.004 \)), detemir : NPH 1.57 (95% CI: 0.64–3.81, \( P = 0.323 \)) and glargine : detemir 1.71 (95% CI: 0.97–3.01, \( P = 0.062 \)); respective ratios in the reduced cohort were 2.81 (95% CI: 1.14–6.95, \( P = 0.025 \)), 1.28 (95% CI: 0.46–3.53, \( P = 0.637 \)) and 2.20 (95% CI: 1.18–4.12, \( P = 0.014 \)).

Modelling analyses using the grouping according to pattern of basal insulin use (Table 1) showed no difference in estimated relative risk or in OR for severe hypoglycaemia between groups 1 to 4.

Diabetic ketoacidosis

Ketoacidosis data were available for 689 patients (77.2%) in the full cohort (Table 2) and 577 (78.1%) in the reduced cohort. Absolute numbers of episodes were small; 44 at baseline and 16 at 12 months. In the full cohort, rates of ketoacidosis fell from 0.06 to 0.02 episodes per patient per year, estimated relative risk 0.37 (95% CI: 0.20–0.68, \( P = 0.001 \)), and in the reduced cohort from 0.07 to 0.02 episodes per patient per year, relative risk 0.37 (95% CI: 0.18–0.72, \( P = 0.004 \)). The estimated OR of ketoacidosis after DAFNE compared with before DAFNE in the full cohort was 0.46 (95% CI: 0.27–0.76, \( P = 0.002 \)) and in the reduced cohort was 0.44 (95% CI: 0.25–0.76, \( P = 0.003 \)).

In the negative binomial model comparing the rates of ketoacidosis at 12 months, adjusting for the number of ketoacidosis episodes at baseline, HbA1c at 12 months, age and duration of diabetes, there was no difference in the estimated relative risk of ketoacidosis for those using twice- compared with once-daily basal insulin: full cohort 1.26 (95% CI: 0.44–3.59, \( P = 0.665 \)); reduced cohort 1.22 (95% CI: 0.39–3.78, \( P = 0.734 \)). In the logistic regression model testing for a difference in the number of people having at least one ketoacidosis episode at 12 months between the different types of basal insulin and the number of injections, adjustment was made for HbA1c at 12 months, age, duration and if the individual had a ketoacidosis episode at baseline or not. There was no difference in the estimated OR ratio for diabetic ketoacidosis in twice-daily basal insulin users compared to once daily: full cohort 1.20 (95% CI: 0.41 to 3.56, \( P = 0.739 \)); reduced cohort \( P = 0.808 \). There is an overall difference in number of people having at least one ketoacidosis episode at 12 months between the different types of basal insulin: full cohort \( P = 0.004 \); reduced cohort \( P = 0.025 \). We have not investigated for differences in ketoacidosis rates between individual basal insulins due to the low total number of episodes.

Modelling analyses using the grouping according to pattern of basal insulin use (Table 1) showed no difference in estimated relative risk or in OR for ketoacidosis between groups 1 to 4.

Discussion

This analysis of clinical audit data from UK DAFNE services has shown an increased HbA1c benefit from twice- rather than once-daily usage of basal insulin 12 months after DAFNE training in insulin self-management skills for Type 1 diabetes mellitus. The most clinically meaningful fall in HbA1c of 5 mmol/mol (0.4%) was associated with patients who embarked on DAFNE with higher baseline HbA1c ≥ 58 mmol/mol (7.5%) and were using the recommended twice-daily basal insulin regimen after DAFNE. By contrast, the North American Type 1 Diabetes Exchange Clinic Registry have published data in abstract form without finding any difference in outcomes between once-daily and twice-daily basal insulin users [8]. A recent systematic review and network meta-analysis [9] examined both randomized and non-randomized studies comparing basal insulin regimens in people with Type 1 diabetes mellitus. The analysis was primarily designed to consider differences between insulin types, but studies using one insulin type at different injection frequencies were also included. This analysis also found no systematic differences in HbA1c between once- and twice-daily basal insulin use for any of NPH, detemir or glargine. The data used in these analyses are from a variety of centres with no unifying educational curriculum and so differ markedly from our study population of people who have received uniform guidance for dose adjustment. We may, therefore, be able to detect differences relating to the insulin regimen because of consistency both in the meal-related insulin replacement and in basal insulin dose-adjustment behaviours; and outcomes may relate to the difference between randomized trials and participant preference for once- or twice-daily basal insulin use. In clinical practice, patients embark on DAFNE training with a variety of issues including HbA1c above target, problematic hypoglycaemia and a desire for dietary freedom. Our study does not allow us to explain the rationale behind choices of basal insulin regimen.

One possible reason for clinicians recommending analogue basal insulin over NPH may be concern over hypoglycaemia. These data confirm earlier reports of a major reduction in severe hypoglycaemia 12 months after the ITTP and DAFNE [6,10,11], which is largely independent of HbA1c (above or below 58 mmol/mol, 7.5%), insulin type or injection frequency. We propose the 76% reduced risk of severe hypoglycaemia arises from the total DAFNE education package, not just the basal insulin regimen. The statistical modelling corrects for baseline hypoglycaemia events as well as HbA1c, both of which can be linked to future severe hypoglycaemia risk. For participants with baseline HbA1c ≥ 58 mmol/mol (7.5%) using twice-daily basal
insulin at 12 months the fall in mean HbA1c of 5 mmol/mol (0.4%) could provide a ~15% reduction in estimated risk of microvascular complications. Although the estimated relative risk of severe hypoglycaemia in this group compared with the once-daily users was 1.72 (OR 1.8), given the large fall in absolute risk of hypoglycaemia after DAFNE, this equates to a difference in absolute risk of one severe hypoglycaemic episode every 14 months reducing to one every 3 years in twice daily users vs. one every 13 months reducing to one every 5 years in once-daily basal insulin users. There is evidence that severe hypoglycaemic events are recalled accurately by users at 12 months [12] and more than 90% of participants in this study were event-free at 12 months.

The reduced rate of ketoacidosis seen in all groups is also likely to be related to DAFNE self-management education in toto rather than basal insulin regimen. There were differences between the modelling results comparing severe hypoglycaemia between basal insulin types with a tendency towards more events in glargine users compared with NPH and detemir. Our data do not allow us to examine behaviours such as exercise and adherence to self-monitoring, or participants’ or professionals’ preferences for different basal regimens. One possible explanation is reverse causation, with clinicians prescribing glargine and promoting twice-daily basal insulin regimens in people most prone to hypoglycaemia.

Analogue basal insulin has been reported to be associated with more reproducible action profiles than NPH [13], although this has not been tested for clinical impact in patients with advanced insulin self-management skills. In the current study, there was no significant difference between the HbA1c at 12 months for users of different basal insulin types, suggesting that any biological variability between insulin types may not be clinically relevant in this setting. High-quality skills-based structured education is a more powerful intervention for the outcomes considered here than the influence of basal insulin type.

The mechanisms by which a twice-daily basal insulin regimen is associated with improved HbA1c at 12 months compared with once daily cannot be established in a study of this type. Our data are retrospective and on-going research into optimum basal insulin regimens is required.

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**Competing interests**

The DAFNE organisation has received sponsorship from Eli Lilly, Novo Nordisk and Sanofi-aventis in support of non-promotional educational activities.

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Dr Ian Lawrence had the original idea for this analysis in 2005.

**References**