A tale of two insulins: Understanding basal insulin therapy in type 2 diabetes

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Chapter

Continuation vs. discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes

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Abstract

Aims To compare combined use of basal insulin, metformin and insulin secretagogues with basal insulin and metformin in patients with type 2 diabetes starting basal insulin analogue therapy.

Methods This analysis was part of a 24-week trial, in which 964 insulin-naive patients with type 2 diabetes inadequately controlled on oral agents (including metformin), were randomised to insulins glargine or detemir. Secretagogues were stopped or maintained at the site-investigators’ discretion.

Results 57.6% of patients continued their secretagogue-treatment during the study. Compared with patients stopping secretagogues, those who continued experienced significantly more hypoglycaemia and weight gain. Insulin doses, however, were significantly lower: 0.6±0.4 vs. 0.8±0.4 units/kg/day (p<0.001). The difference between groups in mean HbA1c reduction was not statistically significant.

Conclusions In type 2 diabetic patients starting basal insulin analogue therapy, continuing both metformin and secretagogues results in more hypoglycaemia and weight gain and lower insulin doses than only maintaining metformin.
Introduction
In type 2 diabetes, when lifestyle interventions and oral therapy fail to achieve HbA1c <7%, the introduction of a basal insulin is advocated (1). While there is consensus that metformin should be continued during insulin initiation (1), it is still debated whether insulin secretagogues should be retained as well (2,3). Moreover, the discussion is hampered by a lack of well-controlled clinical trials examining this issue in the context of treatment with modern insulin preparations and systematic titration algorithms. Therefore, we compared combined use of basal insulin, metformin and insulin secretagogues with a combination of basal insulin and metformin in insulin-naive patients with type 2 diabetes starting basal insulin analogue therapy.

Methods
This analysis was part of a 24-week, multinational, parallel-group trial, in which 964 insulin-naive patients, aged 40-75 years, with type 2 diabetes inadequately controlled (HbA1c between 7.0 and 10.5%) on oral glucose-lowering drugs (including metformin ≥1 g/day), were randomised to insulin glargine once-daily or insulin detemir twice-daily. Glargine was administered at dinner or bedtime, but at the same time throughout the study, and detemir at breakfast and dinner. For both insulins the starting daily dose was 0.2 units/kg. Patients randomised to glargine were instructed to perform daily fasting home glucose measurements and to increase their insulin dose by 2 units every 2 days until their fasting plasma glucose (PG) was <5.6 mmol/l (100 mg/dl). Patients randomised to detemir were instructed to measure their glucose before breakfast and dinner and to titrate their daily doses every 2 days to first reach fasting PG <5.6 mmol/l and subsequently also pre-dinner PG <5.6 mmol/l (4).

All patients continued their treatment with metformin while thiazolidinediones were stopped at randomisation. Insulin secretagogues (sulfonylureas and glinides) were stopped at randomisation or maintained at stable dose throughout the study, at the discretion of the site-investigator, considering local guidelines (4).

Data were analysed using ANCOVA, ANOVA or logistic regression, adjusted for randomised treatment group, after confirmation of the absence of qualitative interaction.
Results
Of 865 patients using insulin secretagogues (together with the obligatory metformin) at study entry, 816 (94.3%) used sulfonylureas only, 38 used glinides only, and 11 used a combination of the two. In total, 498 patients (57.6%) continued their treatment with insulin secretagogues during the study (56.5 and 58.6% in the glargine and detemir group, respectively). In patients continuing vs. stopping secretagogues at randomisation, mean±SD HbA1c levels decreased from 8.8±0.9 and 8.5±0.9%, respectively, at baseline to 7.2±0.9% in both groups at study endpoint. The difference between groups in mean reduction in HbA1c was not statistically significant (-1.59±1.08% for patients continuing and -1.30±1.14% for patients stopping secretagogues, \( p=0.382 \)) (Table 1).

Compared with patients stopping secretagogue-treatment, patients who continued secretagogues in combination with a basal insulin analogue and metformin experienced significantly more hypoglycaemia (40.0 vs. 24.5% of patients had at least one symptomatic hypoglycaemic event [confirmed by PG \( \leq 3.1 \text{ mmol/l (56 mg/dl)} \] during the study, \( p<0.001 \)) and gained significantly more weight (+1.44±3.04 vs. +0.43±3.00 kg, \( p<0.001 \)). End-of-study daily insulin doses, however, were significantly lower in patients continuing secretagogues during combination therapy with a basal insulin analogue and metformin than in those stopping these agents: 52.5±39.8 vs. 67.0±44.8 units/day (\( p<0.001 \)) and 0.6±0.4 vs. 0.8±0.4 units/kg/day (\( p<0.001 \)) (Table 1).

Comparing patients continuing secretagogue-treatment with those discontinuing these tablets in the two separate treatment groups (insulin glargine or insulin detemir) yielded similar results (data not shown).
Table 1 Comparison of continuation vs. discontinuation of insulin secretagogues when initiating basal insulin analogue therapy in combination with metformin in insulin-naive patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Glycaemic control</th>
<th>Continuation (n=498)</th>
<th>Discontinuation (n=367)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in HbA1c level (%)</td>
<td>-1.59±1.08</td>
<td>-1.30±1.14</td>
<td>0.382</td>
</tr>
<tr>
<td>Patients attaining HbA1c &lt;7% at study endpoint</td>
<td>208 (41.8)</td>
<td>156 (42.5)</td>
<td>0.705</td>
</tr>
<tr>
<td>Hypoglycaemiaa</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patients with at least one hypoglycaemic event</td>
<td>199 (40.0)</td>
<td>90 (24.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycaemia event rate per patient-year</td>
<td>3.2±7.6</td>
<td>1.6±5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daily insulin dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Units</td>
<td>52.5±39.8</td>
<td>67.0±44.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Units per kg</td>
<td>0.6±0.4</td>
<td>0.8±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>1.44±3.04</td>
<td>0.43±3.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean±SD or n (%).

Hypoglycaemia was defined as symptomatic hypoglycaemia confirmed by a home plasma glucose measurement ≤3.1 mmol/l (56 mg/dl).

Discussion

Our main finding was that in insulin-naive patients with type 2 diabetes starting basal insulin analogue therapy, continuing both metformin and insulin secretagogues resulted in a greater frequency of hypoglycaemia and more weight gain compared with maintaining only metformin in combination with basal insulin analogue. Daily insulin doses, however, were significantly lower in patients continuing insulin secretagogues. In addition, our analyses suggest that these differences between patients continuing vs. stopping secretagogues at insulin initiation do not depend on the basal insulin preparation used. Although we also found a 0.3%-difference in HbA1c reduction (in favour of the continuation of insulin secretagogues), this was not statistically significant, which was probably related to our method of analysis. As is recommended for the analysis of baseline and follow-up measurements in controlled trials (5), we performed an analysis of covariance (ANCOVA) for change in HbA1c. This method controls for any imbalance between groups at baseline. There was indeed a difference in baseline glycaemic control in our study: patients who continued insulin secretagogues at randomisation had higher mean baseline HbA1c than those who discontinued. This is probably explained...
by prescription bias. Site-investigators may have been more inclined to retain secretagogue-treatment when a patient’s baseline HbA1c was high and to discontinue it when baseline HbA1c was relatively low. Therefore, a controlled trial, randomising type 2 diabetic patients starting basal insulin therapy in addition to treatment with metformin and insulin secretagogues to either continuation or discontinuation of secretagogues, is highly desirable. In conclusion, we found that in patients with type 2 diabetes starting basal insulin analogue therapy, continuing both metformin and insulin secretagogues results in more hypoglycaemia and weight gain and lower daily insulin doses than maintaining only metformin in combination with basal insulin. Controlled trials are urgently needed, however, to advance the discussion on this important clinical question, which so far has been dominated by voiced opinions (1,6), but lacks formal evidence.

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Duality of interest
Sanne G.H.A. Swinnen is employed by the Department of Internal Medicine of the Academic Medical Centre, Amsterdam, the Netherlands, partly through funding from Novo Nordisk and sanofi-aventis for the conduct of clinical trials. Marie-Paule Dain is employed as Diabetes Medical Director at sanofi-aventis. Didac Mauricio has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck and sanofi-aventis. J. Hans DeVries has received honoraria for consultancy work as well as research funding from Novo Nordisk and sanofi-aventis. Joost B.L. Hoekstra has received honoraria for consultancy work from Novartis and sanofi-aventis. Frits Holleman is the principal investigator of this study, he has served on advisory boards for sanofi-aventis and received a study grant from Novo Nordisk.
References