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New insulins and new insulin regimens: a review of their role in improving glycaemic control in patients with diabetes

W Crasto,1 J Jarvis,1 K Khunti,2 M J Davies1,3

ABSTRACT
Effective glycaemic control can reduce and potentially prevent the microvascular and macrovascular complications of diabetes. Insulin is the mainstay of treatment for type 1 diabetes and is indicated in patients with type 2 diabetes who do not achieve optimal glycaemic control despite the use of oral hypoglycaemic agents. The advent of the so-called “designer” insulins, the insulin analogues, has offered new opportunities in the clinical management of diabetes. This review examines the efficacy of the different analogue insulins introduced thus far and goes on to explain their pharmacodynamics and pharmacokinetics. The review also examines the different types of insulin regimen currently used in clinical practice and discusses some of the factors that influence the choice of a particular insulin regimen. Further, irrespective of the insulin regimen used, the importance of prompt initiation and ongoing titration of insulin treatment to achieve optimal glycaemic targets is emphasised.

There are currently 2.3 million people with diabetes in the UK (80% with type 2 diabetes mellitus (T2DM)). With this figure rising annually, diabetes is one of the biggest challenges for the NHS in modern times. Type 1 diabetes mellitus (T1DM) is characterised by complete lack of insulin, and treatment with exogenous insulin is the mainstay of treatment. T2DM is characterised by insulin resistance and β cell failure, and high blood glucose concentrations can be controlled with oral antidiabetic agents (OADs) for a period after diagnosis. However, ~50% will require treatment with insulin because of progressive decline of β cell function, which was estimated to be ~4% each year in the UK Prospective Diabetes Study (UKPDS).1

Glycaemic control is assessed by measurement of glycosylated haemoglobin (HbA1c) concentrations, and tight glycaemic control can reduce and potentially prevent both the microvascular and macrovascular complications of diabetes. In spite of guidelines highlighting tight targets of HbA1c, this is seldom achieved. The National Diabetes Audit for 2004–2005 showed that only 58% of people with diabetes were achieving a target of 7.5% or less;2 and projected figures are expected to rise with the new NICE guidance,3 which suggests an optimal target of 6.5% for HbA1c in T2DM. In this review, we examine the potential of new insulin analogues to achieve good glycaemic control, and we look at their pharmacokinetics and pharmacodynamics. We also examine different insulin regimens for T1DM and T2DM and consider some of the factors that influence the choice of a particular insulin regimen. Finally, we go on to discuss the importance of early initiation and ongoing titration of insulin treatment in achieving optimal glycaemic targets.

BROAD APPROACHES TO INSULIN TREATMENT: SOME DEFINITIONS

Prandial insulin
The term “prandial” insulin (including regular or short-acting insulin) is used to describe insulin that is injected before a meal to cover the immediate rise in blood glucose resulting predominantly from the carbohydrate content of the meal.

Basal insulin
Basal insulins (including intermediate or long-acting insulin) provide a background concentration of insulin, aimed at controlling fasting hyperglycaemia and prandial blood glucose concentrations throughout the day.

TRADITIONAL INSULINS

Animal insulins
Animal insulins, made from the pancreatic extracts of animals (eg, cow and pig), were used up to the 1980s. Some of the problems encountered with these insulins are variable rates of absorption and insulin action, allergic skin reactions at injection sites, and problems with immunogenicity associated with reduced efficacy. They have been gradually phased out since the advent of human insulins, although a small number of patients continue to use animal insulin formulations.

Human insulin
Human insulin is “synthetic insulin” manufactured through DNA technology and not from human sources as the name suggests. It is almost identical with the insulin produced by the human pancreas. However, it is important to remember that the kinetics of human insulins has important limitations. “Short-acting” human insulin has a delayed onset of action of 20–30 min, which means that it needs to be injected at least half an hour before a meal for optimal effect. The prolonged duration of action of 6–8 h and variability in absorption produces a higher risk of hypoglycaemia. “Basal” human insulins (Neutral Protamine Hagedorn (NPH), Lente and Ultralente) have a variable onset of action. The peak of activity is after 4–10 h with a duration of action of <24 h. Owing to the profile of peaks with these insulins,
they are often considered undesirable for use as a basal insulin for some patients.5

NEW INSULINS IN THE MANAGEMENT OF DIABETES

The goal of developing insulins that more closely mimic normal pancreatic function has led to the launch of the so-called “designer insulins” or “insulin analogues”. They are grouped under “short-acting” and “long-acting” analogues (table 1).

Short-acting analogues

Short-acting analogues are formed by a subtle alteration in the spatial structure of the insulin molecule by recombinant DNA technology, which results in rapid dissociation and formation of stable monomers, which allows rapid absorption.

Chemistry of short-acting analogues

There are three types of short-acting insulin analogues: lispro, aspart and glulisine. Insulin lispro was the first short-acting analogue to be introduced in 1996. It is produced by reversal of amino acid positions at position 28 (proline) and position 29 (lysine) on the insulin B chain. It is available as Humalog and is included in some of the premixed formulations, Humalog Mix25 and Humalog Mix50. Insulin aspart is produced by replacing proline at position 28 on the B chain of insulin with aspartic acid. It is available as Novorapid and included in the premixed formulation, Novomix 30. Glulisine is synthesised by replacing the asparagine at position 29 with glutamic acid.

Pharmacokinetic and pharmacodynamic properties

The short-acting analogues share very similar pharmacokinetic and pharmacodynamic properties. They are absorbed within 10–15 min of a subcutaneous injection, peak within 30–90 min, and have a duration of action of 4–6 h. This more closely mimics normal physiological prandial insulin release. It also effectively eliminates the waiting period from the time of injection to the ingestion of a meal. Patients can therefore inject immediately before eating and this offers more flexibility and convenience. In very young children and older patients with variable food intake, the convenience of injecting even after the meal offers a distinct advantage.6 7

Clinical efficacy (table 2)

Studies in T1DM

The role of lispro in improving postprandial hyperglycaemia has been evaluated in a number of trials using regular human insulin as the comparator insulin.5 9 The results clearly show that postprandial glucose concentrations are lower with lispro, with continued benefits of up to a year in some studies.9

Studies in T2DM

Comparison of an analogue combination of lispro/glargine versus human insulin combination of regular insulin/NPH in T2DM showed that the analogue combination achieved lower postprandial glucose concentrations with significantly lower insulin doses to achieve prandial glucose targets and fewer episodes of nocturnal hypoglycaemia.10 Efficacy studies with aspart and glulisine have similarly shown improved postprandial glycemic control with fewer episodes of nocturnal hypoglycaemia than regular human insulin.11 12

Insulin lispro, aspart and glulisine have been shown to be effective at lowering postprandial glucose when added to OADs.6 13 14 In one study, significant reductions in glucose concentrations after a meal occurred with meal-time lispro (plus bedtime NPH) compared with meal-time regular human insulin plus NPH.15 When used in a continuous subcutaneous insulin infusion, insulin lispro was superior to regular insulin in reducing HbA1c, with a lower rate of hypoglycaemia.16

Effects on HbA1c

A meta-analysis by Plank et al17 compared short-acting analogues with regular insulin and showed only a small beneficial effect for glycaemic control (magnitude of difference in HbA1c was −0.12% (95% CI −0.17% to −0.07%) in patients with T1DM, whereas in patients with T2DM no such improvements were observed.

Hypoglycaemia

The greatest benefit is seen in the area of reduction of severe hypoglycaemia in T1DM. Studies with insulin lispro versus regular insulin in T1DM showed a 30% reduction in severe hypoglycaemia events (defined as coma or requiring glucagon or intravenous glucose), despite similar levels of glycaemic control.18 The analysis of overall hypoglycaemic episodes, however, showed only a small non-significant reduction with short-acting insulin analogues compared with treatment with regular insulin in both T1DM and T2DM.19

Summary of short-acting analogues

Short-acting analogues have similar profiles to each other and are equally effective for control of postprandial hyperglycaemia.19 In contrast with regular human insulin, they result in improved treatment satisfaction and treatment flexibility.20 Fewer trials have been published with insulin glulisine.14 21–24

Long-acting analogues

Long-acting analogues are produced by recombinant DNA technology by modifications to the insulin molecule, which promotes a longer duration of action (table 1).

Chemistry of long-acting analogues

Glargine and detemir are the currently available long-acting insulin analogues. Insulin glargine is produced by three different amino acid modifications to the B chain of the insulin molecule. It forms a microprecipitate after injection, which results in slow

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Table 1 Duration of action of insulin analogues

<table>
<thead>
<tr>
<th>Insulin analogues and available formulations in the UK</th>
<th>Onset of action</th>
<th>Peak action</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog)</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>4–6</td>
</tr>
<tr>
<td>Aspart (Novorapid)</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>4–6</td>
</tr>
<tr>
<td>Glulisine (Apidra)</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>4–6</td>
</tr>
<tr>
<td><strong>Premixed insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog Mix25 (25% lispro + 75% neutral protamine lispro)</td>
<td>Varies according to mixture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog Mix50 (50% lispro + 50% neutral protamine lispro)</td>
<td>Varies according to mixture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novomix 30 (30% aspart + 70% protamine/crystallised aspart)</td>
<td>Varies according to mixture</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-acting analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>2–4 h</td>
<td>None</td>
<td>20–24</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1–4 h</td>
<td>None</td>
<td>12–24</td>
</tr>
</tbody>
</table>
release from the injection site. Glargine is a clear insulin and cannot be mixed with other insulins. It is not approved for use in children below 6 years. Insulin detemir is produced by fatty acid acylation of the lysine residue on position B29, which results in prolonged duration of action due to self-association and reversible albumin binding after subcutaneous injection.

Pharmacokinetics and pharmacodynamics
Glargine has a smooth peakless profile of action lasting up to 24 h. Detemir has a mean duration of action of 20 h after administration of a 0.4 IU/kg dose. This was thought to necessitate twice-daily dosing, which has been used in many of the early clinical trials with detemir. At a higher dose, the duration of action increases beyond 20 h.

Clinical efficacy (table 3)
Studies in T1DM
A number of clinical efficacy studies have compared glargine with basal human insulin (NPH) in T1DM. When used in a basal bolus regimen in T1DM, similar glycaemic control was achieved irrespective of the timing of the administration or if the dose was split. Splitting the dose of glargine resulted in significant weight gain. Twice-daily administration of detemir has shown similar or slightly better glycaemic control, with reduced risk of nocturnal hypoglycaemia and less weight gain compared with NPH. However, detemir shows less within-subject variability in blood glucose concentrations compared with NPH or glargine, which suggests that detemir has a more predictable glucose-lowering effect. In a recent 26-week randomised controlled trial in subjects with T1DM, who received detemir twice a day or glargine once a day in a basal bolus regimen, equivalent glycaemic control and weight gain was seen between the two groups with no differences in overall hypoglycaemic events.

Studies in T2DM
Glargine used as a once-daily basal injection in T2DM has been shown to achieve good glycaemic control, with marginal weight gain in most patients. When compared with rosiglitazone (added as a third agent to dual OADs), its clinical efficacy was found to be superior if baseline HbA1c was >9.5%. In comparison with NPH, glargine provides at least comparable glycaemic control, with a reduced incidence of hypoglycaemia.

In terms of its effects on fasting blood glucose, detemir was found to exhibit more predictable values than NPH. In the
Levemir Treat-to-Target Study, twice-daily detemir added to OADs in T2DM with suboptimal control achieved target HbA1c concentrations (<7%) with fewer hypoglycaemic events in significantly more patients than those receiving NPH. 69

**Effects on HbA1c**

Studies in T1DM have shown equal efficacy for effects of both glargine and detemir on HbA1c, 40 and similar results for comparisons between either analogue as add-on therapy to OADs in T2DM.

**Hypoglycaemia**

Two meta-analyses 41 42 have shown significantly reduced rates of hypoglycaemia (especially nocturnal) with glargine. Rosenstock et al 43 highlighted that, although the proportion of patients achieving a HbA1c of <7.0% was similar for glargine and NPH, hypoglycaemia was significantly reduced with glargine. They concluded that the reduced risk of hypoglycaemia could allow more aggressive targeting of HbA1c targets.

Studies with detemir have shown that the reduction in intrapatient variability of fasting glucose concentrations is a major contributor to the reduced risk of hypoglycaemia with detemir relative to NPH. 60 61 However, a Cochrane review of long-term trials in T2DM comparing long-acting analogues with NPH insulin showed only a “theoretical advantage” of improved metabolic control, stating that clinical benefits were related to reduced nocturnal hypoglycaemia. 45

**Summary**

Glargine and detemir have shown similar efficacy for glycaemic control; however, a higher proportion of patients need twice-daily dosing with detemir. The cost–benefit ratio of these analogues has yet to be established, and this caution is reflected in the UK NICE guidelines, which recommend the use of glargine as an option for people with T1DM, but not routinely for those with T2DM except in certain groups—for example, those who require assistance to administer insulin injections and in patients whose lifestyle is restricted by recurrent symptomatic hypoglycaemia.

**INSULIN REGIMENS**

**Insulin regimens in T1DM (table 4)**

Insulin regimens in T1DM are no longer a “one size fits all” approach, and individualisation of therapy is required to obtain glycaemic targets set out by organisations such as the ADA and ISAPD. 46 47 Intensive insulin therapy has proven long-term benefits, but needs close supervision (including frequent blood glucose monitoring) and is not without the risk of severe hypoglycaemia, which has a major impact on quality of life.
Table 4 Insulin regimens in type 1 diabetes (T1DM)

<table>
<thead>
<tr>
<th>Insulin regimen</th>
<th>Study</th>
<th>No of subjects</th>
<th>Study length (months)</th>
<th>Treatment</th>
<th>HbA1c change</th>
<th>Hypos</th>
<th>Weight gain (kg)</th>
<th>Quality of life benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice daily/ biphasic</td>
<td>Saliman et al(^a)</td>
<td>50</td>
<td>6</td>
<td>Group AI = “old” T1DM on MII</td>
<td>−1.9%*</td>
<td>No clear information but 2 pts in AI and 2 in All had 1 or more hypos</td>
<td>ns</td>
<td>−</td>
<td>MII = regimen using premixed regular and NPH in 30/70, 40/60 or 50/50 proportions plus RHI to cover midday meal + SMBG and pt education</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group AI = “new” T1DM on MII</td>
<td>−3.3%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group B = Mixtard or mixture of NPH + RHI MDI</td>
<td>−0.8%</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Basal bolus</td>
<td>Pérez Méndez et al(^a)</td>
<td>59</td>
<td>84</td>
<td>CSII</td>
<td>−0.7% (from year 1 to year 7)</td>
<td>0.32 (events/pt/year severe hypo)</td>
<td>ns</td>
<td>−</td>
<td>Prospective study over 7 years showed long-term improvement with MDI</td>
</tr>
<tr>
<td>CSII</td>
<td>Liton et al(^a)</td>
<td>9</td>
<td>13.7</td>
<td>CSII</td>
<td>−1.6%*</td>
<td>0.09* (events/pt/month)</td>
<td>ns</td>
<td>−</td>
<td>Study cohort included toddlers 10–40 months with T1DM; HbA1c &gt; 9.5% at baseline</td>
</tr>
<tr>
<td>Fox et al(^a)</td>
<td>26</td>
<td>6</td>
<td>6</td>
<td>NPH + short-acting analogue CSII</td>
<td>ns</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

\(^a\)p<0.05 for between-treatment differences.

CSII, continuous subcutaneous insulin infusion; D, dinner; hypo, episode of hypoglycaemia; MDI, multiple daily injections; MII, modified intensified insulin therapy; NPH, Neutral Protamine Hagedorn; ns, non-significant; OAD, oral antidiabetic agent; pt, patient; QOL, quality of life; RCT, randomised controlled trial; RHI, regular human insulin; SMBG, self-monitoring blood glucose.

Diabetes education and self-management skills are key to achieving good control.\(^a\) The aim is to teach people how to accurately adjust their insulin to match carbohydrate intake by carbohydrate counting, use of exchanges or rough estimation. With experience, freedom from dietary restrictions can be achieved, thus providing a better quality of life and improved satisfaction with treatment. Successful teaching programmes, such as the DAFNE (Dose Adjustment For Normal Eating) programme, have now been widely rolled out in many centres in the UK.

Insulin regimens used in T1DM include:

- Twice-daily regimen (premixed or free mixing of short-acting and intermediate-acting insulin)
- Basal bolus regimen
- Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy

**Twice-daily regimen**

Twice-daily injections of short-acting and intermediate-acting insulin may involve free mixing of the two. These insulins also come in a premixed formulation. Insulin dose and timing are adjusted according to blood glucose concentrations, meal times or other factors. The timings of meals and exercise are relatively rigid, with minimal room for flexibility, and nocturnal hypoglycaemia can be a problem. This regimen may involve snacking between meals to prevent hypoglycaemia, potentially causing weight gain, and some patients may require three injections a day. Some centres have reported good results with an intensive twice-daily injection approach with a rigid meal schedule.\(^a\)\(^b\)\(^c\)

**Basal bolus regimen**

The basic principle behind the basal bolus regimen is to offer a more physiological replacement of insulin. It also offers flexibility with injections in patients with variable lifestyles. Short-acting insulin (regular insulin or short-acting insulin analogues) is used for each meal, and basal insulin (NPH, glargine or detemir) is used as a background insulin to cover fasting and preprandial carbohydrate concentrations. Insulin doses can be adjusted in response to blood glucose patterns, carbohydrate intake, anticipated activity and stress. This regimen requires frequent blood glucose monitoring and insulin titration. The glycaemic durability using a basal bolus regimen was tested in a 7-year observational study in T1DM and showed an improvement from a mean HbA1c of 7.5% in the first year to 6.8% in year 7 of follow-up without significantly increased incidence of hypoglycaemia.\(^a\)\(^b\)\(^c\) The use of insulin analogues in basal bolus regimens is ideal for many patients and has shown improved patient treatment satisfaction.\(^a\)\(^b\)\(^c\)

**CSII (insulin pump therapy)**

Insulin pumps are battery-operated devices that are worn by the patient, delivering a continuous infusion of a short-acting insulin through a catheter inserted in the skin, which is changed by the patient every 2–3 days.\(^a\)\(^b\)\(^c\) The continuous infusion provides for basal (background) insulin requirements, and pre-programming the infusion rate can cover periods of activity, physical exercise, inactivity and sleep. Basal rates as low as 0.05 IU/h can be delivered by insulin pumps, and bolus doses of insulin are triggered to cover carbohydrate content in the food at meal times.

CSII is used mainly when glucose targets are difficult to achieve, and intensive insulin therapy results in an unacceptable and unpredictable incidence of hypoglycaemia.\(^a\)\(^b\)\(^c\) Although some studies have shown beneficial results with reduction in the frequency of nocturnal hypoglycaemia,\(^a\)\(^b\)\(^c\) most randomised controlled studies did not demonstrate improvements in glycaemic control.\(^a\)\(^b\)\(^c\) Meta-analyses of studies on CSII therapy have revealed a cumulative reduction of −0.5% to −0.9% in HbA1c when compared with multiple daily injection (MDI) therapy.\(^a\)\(^b\)\(^c\)\(^d\) Recent reviews indicate that quality of life benefits improve with CSII,\(^a\)\(^b\) although further research is needed to accurately assess the level of quality of life benefits.\(^a\)\(^b\)\(^c\)

Limitations with insulin pumps do exist. Weight gain may occur with improved control, undetected interruptions in insulin delivery may result in diabetic ketoacidosis, irritation or infection at the infusion site may occur, and hypoglycaemia has been known to occur in a malfunctioning pump.
<table>
<thead>
<tr>
<th>Insulin regimen</th>
<th>Study</th>
<th>No of subjects</th>
<th>Study length (months)</th>
<th>Treatment</th>
<th>HbA1c change</th>
<th>Hypos</th>
<th>Weight gain (kg)</th>
<th>Quality of life benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal with OADs</td>
<td>Rosenstock et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>217</td>
<td>6</td>
<td>Gla (od) + Met/SU</td>
<td>-1.66%</td>
<td>7.7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>+1.7</td>
<td>–</td>
<td>Superior efficacy with Gla if baseline HbA1c &gt; 9.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rosi (4 mg) + Met/SU</td>
<td>-1.51%</td>
<td>3.4</td>
<td>+3.0&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BIAsp (bd) + Met/SU</td>
<td>-1.3%</td>
<td>5.7</td>
<td>+4.7</td>
<td></td>
<td>QOL benefits similar between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IAAsp (tds) + Met/SU</td>
<td>-1.4%</td>
<td>12.0</td>
<td>+5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Det (bd or bd) + Met/SU</td>
<td>-0.8%</td>
<td>2.3 (events/pt/year)</td>
<td>+1.9</td>
<td></td>
<td>With HbA1c &lt; 8.5%, equal efficacy between regimens; reduced weight gain and hypo with Det</td>
</tr>
<tr>
<td></td>
<td>Hermansen et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>476</td>
<td>6</td>
<td>Det (bd) + OADs</td>
<td>-1.8%</td>
<td>Overall and nocturnal hypo</td>
<td>1.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td>Insulin-naïve patients with T2DM. More pts reached target HbA1c without hypox with Det</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPH (bd) + OADs</td>
<td>-1.9%</td>
<td></td>
<td>2.8</td>
<td></td>
<td>Higher insulin doses with Det. Weight gain with Det similar to Gla on bd regimen. Withdrawal rates higher with Det</td>
</tr>
<tr>
<td></td>
<td>Rosenstock et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>582</td>
<td>12</td>
<td>Det (bd or bd) + OADs</td>
<td>-1.5%</td>
<td>5.8</td>
<td>+3.0&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
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<td></td>
<td></td>
<td>Gla (od) + OADs</td>
<td>-1.5%</td>
<td>6.2 (events/pt/year)</td>
<td>+3.9</td>
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<tr>
<td>Twice daily premixed (biphasic)</td>
<td>Raskin et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>233</td>
<td>7</td>
<td>BIAsp70/30 (bd) + OADs</td>
<td>-2.79&lt;sup&gt;*&lt;/sup&gt;</td>
<td>3.4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>+5.4&lt;sup&gt;*&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>Gla (od) + OADs</td>
<td>-2.36%</td>
<td>0.7 (events/pt/year)</td>
<td>+3.5</td>
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<tr>
<td>Prandial insulin</td>
<td>Bretzel et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>418</td>
<td>11</td>
<td>Gla (od) + OADs</td>
<td>-1.7%</td>
<td>5.2&lt;sup&gt;*&lt;/sup&gt;</td>
<td>+3.01</td>
<td>More QOL benefits with Gla compared with IL</td>
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<td>IL (tds) + OADs</td>
<td>-1.9%</td>
<td>24.0</td>
<td>+3.54</td>
<td></td>
<td>Gla was not inferior to tds IL</td>
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<tr>
<td>Basal bolus</td>
<td>Rosenstock et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>374</td>
<td>6</td>
<td>IL mix 50/50 (tds) + OADs</td>
<td>-1.85%</td>
<td>51.2</td>
<td>+4.0</td>
<td></td>
<td>Aggressive titration possible in Gla+IL group, with 69% achieving HbA1c targets vs 54% in premix group</td>
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<td></td>
<td>Gla (od) + IL (tds) + OADs</td>
<td>-2.12&lt;sup&gt;*&lt;/sup&gt;</td>
<td>48.7 (events/pt/year)</td>
<td>+4.5</td>
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<tr>
<td>CSII</td>
<td>Raskin et al&lt;sup&gt;a&lt;/sup&gt;</td>
<td>132</td>
<td>6</td>
<td>CSII (IAAsp)</td>
<td>-0.62%</td>
<td>0.8</td>
<td>+1.7</td>
<td></td>
<td>More patient satisfaction with CSII vs MDI&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>MDI (IAAsp tds + NPH)</td>
<td>-0.46%</td>
<td>1.2 (events/pt/month)</td>
<td>+0.7</td>
<td></td>
<td>OADs discontinued. Shows analogues are compatible in CSII and could be preferred option for IIT</td>
</tr>
</tbody>
</table>

<sup>*</sup>p<0.05 for between-treatment differences.

bd, twice a day; BIAsp, biphasic insulin aspart; CSII, continuous subcutaneous insulin infusion; Det, detemir; Gla, glargine; hypo, episode of hypoglycaemia; IL, insulin lispro; IAAsp, insulin aspart; IIT, intensive insulin therapy; MDI, multiple daily injections; Met, metformin; NPH, Neutral Protamine Hagedorn; ns, non-significant; OAD, oral antidiabetic agent; od, once a day; pt, patient; QOL, quality of life; RCT, randomised controlled trial; RHI, regular human insulin; Rosi, rosiglitazone; SU, sulfonylureas; tds, three times a day.
Factors Influencing choice of regimen in T1DM

Age considerations
Treatment of diabetes in infants and toddlers is associated with lower awareness of hypoglycaemia, variable food intake, and unpredictable physical activity. In the UK, toddler age groups are usually started on once-daily or twice-daily injections. A simplistic approach of a twice-daily premixed insulin regimen has been used by many clinicians with good results. For toddlers, it may be safe to administer short-acting insulin after meals to match variable food intake. CSII therapy in toddlers is safe and well tolerated, but debate about its actual benefit in this age group continues.

Quality of life benefits
CSII offers significant benefit over MDI for some patients in terms of diabetes management and quality of life benefits, although the sheer number of tasks required for safe and effective treatment is significantly greater. From a pooled analysis of three randomised controlled trials, Retnakaran and colleagues showed that the relative benefit of CSII over MDI increased as baseline HbA1c increased, which suggests that CSII can benefit patients with initial poor metabolic control.

Cost-effectiveness
In reality, the cost of CSII does limit its use, although in a computerised CORE Diabetes model to determine cost-effectiveness of intensive insulin interventions (CSII versus MDI) in a UK healthcare setting, the results favoured CSII treatment, with a borderline incremental cost-effectiveness ratio of £25 648 per quality-adjusted life year gained.

Special situations
Insulin requirements in patients with T1DM increase with advancing pregnancy, and it can be suggested that basal bolus regimens are more effective than twice-daily insulin regimens. There are a few reports on the safety of glargine or detemir in pregnancy, whereas the short-acting analogues, lispro and aspart, are considered safe for use. However, more robust safety data are required. Use of CSII is safe in pregnancy and should be considered in women who do not achieve optimal control on basal bolus regimens or in whom hypoglycaemia is considered a problem.

Insulin regimens in T2DM (table 5)
The International Diabetes Federation global guidelines recommend that optimal targets in T2DM should be <6.5%. In the UKPDS, achieving a target HbA1c of <7% was associated with a significant reduction in long-term microvascular complications. In clinical practice, insulin treatment in T2DM is usually initiated in response to the failure of OADs. Although initiation of insulin may seem simplistic, healthcare professionals must ensure that insulin has been initiated in a timely manner, the regimen to be used has been considered, and titration is effective in order to achieve optimal glucose targets. Hypoglycaemia and weight gain are the main barriers to optimising insulin therapy.

Types of insulin regimens used in T2DM (with or without OADs) are:
- Basal-only regimen
- Twice-daily premixed insulin regimen
- Prandial insulin regimen
- Basal bolus regimen
- CSII

Add-on to oral treatment
Insulin with OADs (particularly focusing on basal insulin)
The combination of insulin and OADs is a useful step when glycaemic control is not achieved with OADs alone. When dual or even triple OADs fail to control hyperglycaemia, the decision to persist with a third oral agent or to initiate insulin may be indicated by clinician or patient preference. Although oral agents such as thiazolidinediones are useful in some patients, insulin can be easily added to existing treatment. In a study exploring the option of adding either insulin glargine or another oral agent (rosiglitazone) to existing sulfonylurea and metformin treatment, glargine was more cost-effective, caused less weight gain, and showed greater reductions in HbA1c when baseline was >9.5%.

The 4T Study (Treating to Target in Type 2 Diabetes) is a 3-year ongoing study examining 708 patients with poorly controlled diabetes receiving treatment with metformin and sulfonylurea randomised to receive either basal insulin detemir once a day (or twice a day), biphasic insulin aspart twice a day or prandial insulin aspart three times a day. Interim first year results showed that the decrease in HbA1c was significantly greater in the biphasic and prandial groups (7.3% and 7.2%) than in the basal group (7.6%, p<0.001), although hypoglycaemia and weight gain were lower with basal insulin. Prandial insulin was associated with a twofold increase in hypoglycaemic events and a 21% increase in weight. The authors of this study concluded that “while most patients are likely to need more than one type of insulin to achieve target glucose concentrations, the findings suggest that basal insulin is a useful first line add-on to OADs”.

Choice of basal insulin
Both intermediate-acting insulins (eg, NPH) and long-acting analogues (eg, glargine or detemir) are commonly used, although a number of studies support the use of analogues.

In the Treat to Target Trial, a single bedtime injection (NPH or glargine) was added to existing oral agents, and insulin doses were titrated against a fasting glucose of 5.6 mmol/l. The mean HbA1c decreased from 8.6% at baseline to <7% in both groups in 6 months; however, less hypoglycaemia (especially nocturnal) was seen in the glargine group.

The basal analogues offer equal efficacy in terms of glycaemic control as shown in a direct comparison in patients with T2DM. In a 52-week multinational randomised controlled trial, insulin-naive T2DM patients were randomised to either detemir or glargine once a day, and active dose titration was performed to achieve fasting glucose targets. An additional dosing for detemir was permitted. HbA1c decreased by 1.5% with both insulins, and 52% of participants achieved a HbA1c of <7%. Weight gain was lower with once-daily detemir, but was comparable to glargine once a day and detemir twice a day. Rates of hypoglycaemia were similar; however, higher insulin doses and more injections were needed with detemir to achieve targets (55% of participants in the detemir arm required twice-daily dosing).

Twice-daily premixed insulin regimen (with OADs compared with basal insulin regimens)
Twice-daily premixed insulin or biphasic insulin regimens can potentially target both fasting and postprandial hyperglycaemia. Using this approach, Raskin et al compared the efficacy of a premix 70/30 insulin aspart twice a day or glargine once a day added to metformin ± thiazolidinediones in T2DM. At

Main messages

- The pharmacodynamic and pharmacokinetic profile of insulin analogues offers a distinct advantage over "traditional" human insulins.
- The short-acting analogues offer the convenience of injecting immediately before or with a meal; hence patients can enjoy a more flexible lifestyle.
- The long-acting analogue insulins are easy to initiate and titrate and can be used in different insulin regimens; however, effective glycaemic control can only be achieved with optimal dosing and dose titration.
- Patient education and self-management should form a central part of our strategy in the management of all patients with diabetes.
- Individualisation of treatment, quality of life, hypoglycaemia and weight gain are other important considerations in patients with diabetes on insulin therapy.

Prandial insulin regimen

Prandial insulins with or without the continuation of oral agents can be used to address postprandial hyperglycaemia, with distinct improvements in HbA1c concentrations. In the APOLLO study, the addition of once-daily glargine or prandial insulin in patients poorly controlled with oral agents was equally effective. However, basal insulin treatment is usually considered as a safe and simpler option and is often more acceptable to patients because of a higher incidence of hypoglycaemia, more injections and weight gain with prandial insulin therapy.

Basal bolus regimen

The benefits of an intensive insulin regimen in reducing diabetes-related complications was seen in the UKPDS. Moreover, early initiation of an intensive regimen has been shown to reduce the impact of glucotoxicity and preserve β cell function. A basal bolus regimen mimics more closely the normal physiological insulin action and has demonstrated good glycaemic control in clinical studies. The efficacy of a basal bolus regimen versus premixed insulin was compared in patients with a baseline HbA1c of 9% in both groups, previously treated with insulin glargine plus OADs. At 24 weeks, HbA1c was lower with a basal bolus regimen (6.78 vs 6.95%, p = 0.021), although there was a significant reduction in HbA1c in both groups.

CSII

CSII remains an option in patients who have poor glycaemic control on MDI. Studies using CSII in T2DM have found comparable glycaemic control versus MDI with improved patient satisfaction.

INITIATION AND TITRATION OF INSULIN THERAPY

It is increasingly recognised that early initiation and subsequent titration of insulin therapy with patient education plays a key role in achieving glycaemic targets and long-term maintenance of glycaemic control. Initiating insulin therapy can be difficult because of a number of barriers, as outlined above. With diabetes care becoming more community based, it is essential to explore simpler options to help primary care doctors deal with patients requiring insulin therapy.

Insulin doses can be initiated and titrated using a simple protocol which is easy to follow. For example, basal insulin dosing with glargine is usually started at 10 IU or 0.1–0.2 IU/kg body weight. This is titrated by 2 IU at 3-day intervals until fasting glucose targets (70–130 mg/dl or 3.89–7.22 mmol/l) are achieved with no manifest hypoglycaemia. A larger dose increment of 4 IU is advised if the fasting glucose readings remain ≥180 mg/dl (or ≥10 mmol/l). Most patients may ultimately require insulin doses as much as 0.5–1.0 IU/kg. The 4T Study used a predefined algorithm for insulin titration and a patient-specific insulin starting dose. This study found that a higher starting insulin dose (2–76 IU/day) did not result in severe hypoglycaemia.

In the AT.LANTUS study, Davies and colleagues compared two treatment algorithms in patients with suboptimally controlled T2DM. One of the titration algorithms (algorithm 1) was physician led and involved weekly interventions, whereas algorithm 2 was patient led with adjustments made after every 3 days. After 24 weeks, there was a significantly greater HbA1c reduction with algorithm 2 without significant difference in the incidence of severe hypoglycaemia between the two groups. Their findings showed that such a regimen can be effectively started in the community and in secondary (hospital-based) care. Insulin initiation in groups involves less time and is a cost-effective option and should be considered in both primary and secondary care.

Key references

Current research questions

► Have we really found ways to optimally use and titrate “traditional” human insulins?
► What is the clinical efficacy and safety of insulin analogues during pregnancy?
► In type 2 diabetes mellitus, does basal bolus therapy have more advantages over other conventional insulin regimens?
► Are the “advantages of analogues” in type 2 diabetes mellitus overemphasised? Are improvements in HbA1c accompanied by long-term benefits in clinical outcomes?
► How do insulin analogues affect quality of life?
► What are the health economic implications for using insulin analogues?
► What is the role of “insulin analogues and glucagon-like peptide 1” combination therapy in the management of patients with type 2 diabetes mellitus?

CONCLUSIONS
Insulin analogues and new approaches to initiation and intensification have provided the impetus to make insulin therapy simple to use, allowing patients with diabetes to have a more flexible lifestyle. Quality of life, hypoglycaemia and weight gain are important considerations when moving patients from conventional to intensive regimens. This needs open and frank discussions with patients and carers. Regimens using analogue insulins can be easy to initiate and titrate with a low risk of hypoglycaemia. However, much remains to be learned about how to maximise the efficacy of any insulin, old or new. Patient education should form a central part of our management strategy, empowering patients with diabetes with the requisite skills and knowledge to self-manage their condition more effectively.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/ FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Short-acting analogues in the management of diabetes
A. Short-acting analogues are formed by alteration in the structure of the insulin molecule by recombinant DNA technology
B. The short-acting analogues, lispro, aspart and glulisine, differ from each other in their pharmacokinetic and pharmacodynamic properties
C. Short-acting analogues must be injected 30 min before each meal
D. Short-acting analogues are not as effective as regular human insulin for the control of postprandial hyperglycaemia
E. Improved glycaemic control (improvements in HbA1c) have been noted with short-acting analogues compared with regular insulin in patients with type 1 and type 2 diabetes

2. Long-acting analogues in the management of diabetes
A. Glargine is a clear insulin and cannot be mixed with any other insulin
B. When compared with a glitazone, added as a third agent to dual OADs, the clinical efficacy of glargine is superior in patients with baseline HbA1c >9.5%
C. The proportion of patients with type 2 diabetes achieving an HbA1c of ≤7.0% with glargine or NPH added to oral agents is similar; however, hypoglycaemia is significantly reduced with glargine
D. Reduced intrapatient variability of fasting glucose concentrations with detemir is a major contributor to the reduced risk of hypoglycaemia relative to NPH
E. UK NICE guidelines recommend the use of glargine in all patients with type 1 and type 2 diabetes

3. Insulin regimens in type 1 diabetes
A. Premixed insulin regimen may involve snacking between meals to prevent hypoglycaemia, potentially causing weight gain
B. Diabetes education and self-management skills are key to achieving good glycaemic control
C. CSII/insulin pump therapy is mainly used when glucose targets are difficult to achieve with intensive insulin therapy and associated with unacceptable and unpredictable hypoglycaemia
D. Limitations with insulin pumps include hypoglycaemia, weight gain, interruptions in insulin delivery, irritation or infection at the infusion site
E. The cumulative reduction in HbA1c is ~1.9% with CSII therapy compared with MDI therapy

4. Insulin regimens in type 2 diabetes
A. The option of adding basal insulin analogue instead of a third oral agent to a combination of sulfonylurea and metformin therapy is associated with weight gain and increased hypoglycaemia and is less cost-effective
B. The basal analogues, glargine and detemir, offer equal efficacy in terms of glycaemic control in patients with type 2 diabetes
C. The AT.LANTUS study showed that a basal insulin regimen can be effectively started in the community and in secondary (hospital-based) care
D. The early initiation of an intensive regimen has been shown to reduce the impact of glucotoxicity and preserve β cell function
E. Lower insulin doses and fewer injections may be needed with detemir compared with glargine to achieve optimal glycaemic targets in type 2 diabetes

5. Initiation and titration of insulin therapy
A. The 4T study found that a higher starting insulin dose (2–76 IU per day) did not result in severe hypoglycaemia
B. Early initiation and subsequent titration of insulin therapy with patient education plays a key role in achieving glycaemic targets in T2DM
C. After starting basal insulin therapy, patients should titrate insulin doses on a monthly basis and after supervision from their own healthcare provider
D. Insulin initiation in groups is not a cost-effective option
E. Quality of life, hypoglycaemia and weight gain are important considerations when moving patients from conventional to intensive regimens

Competing interests: MJD has received funds for research and honoraria for speaking at meetings and has served on Advisory Boards for Lilly, Sanofi Aventis, MSD and Novo Nordisk. KK has received funds for research and honoraria for speaking at meetings and/or served on Advisory Boards for Astra Zeneca, GSK, Lilly, Novartis, Pfizer, Servier, Sanofi Aventis, MSD and Novo Nordisk.

REFERENCES


**Answers**

1. (A) T; (B) F; (C) F; (D) F; (E) F
2. (A) T; (B) T; (C) T; (D) T; (E) F
3. (A) T; (B) T; (C) T; (D) T; (E) F
4. (A) F; (B) T; (C) T; (D) T; (E) F
5. (A) T; (B) T; (C) F; (D) F; (E) T