Treat-to-target trials: uses, interpretation and review of concepts

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Treat-to-target trial designs compare investigational insulins with a standard insulin. Treat-to-target trials force-titrate insulin dosages to achieve a prespecified treatment goal. With comparable glycaemic control, comparisons of safety endpoints such as hypoglycaemia can be made to establish the risk-benefit profile of the new insulin. Glargine versus NPH showed comparable A1C reductions; however, A1C <7% without associated nocturnal hypoglycaemia was reached in more patients on glargine and overall hypoglycaemia was lower. Detemir versus glargine showed non-inferiority between the groups, however, with less weight gain and more injection site reactions with detemir. Detemir/aspart versus glargine/aspart showed non-inferiority between the treatments, however, with less weight gain in the detemir group but comparable risk of hypoglycaemia. Degludec in combination with aspart versus glargine/aspart showed comparable A1C reductions. However, degludec-treated patients had less overall hypoglycaemia and less nocturnal hypoglycaemia. Because insulin titrations are guided by goal attainment with each treatment, treat-to-target trials enable clinicians to determine differences in non-glycaemic treatment effects, such as rates of hypoglycaemia and weight gain, at the same level of glycaemic control.

Keywords: insulin aspart, insulin degludec, insulin detemir, insulin glargine, neutral protamine Hagedorn (NPH), treat-to-target trials, type 2 diabetes

Introduction

The goal of antihyperglycaemic therapy is to achieve good glycaemic control with a low rate of complications, particularly hypoglycaemia. Glycated haemoglobin (A1C) is a validated surrogate marker for estimating the success of long-term diabetes-related therapies. According to the Food and Drug Administration (FDA), the efficacy of glucose-lowering agents should be shown by a reduction in A1C, as the primary endpoint [1].

In early type 2 diabetes mellitus (T2DM), many patients may achieve A1C targets with lifestyle changes and non-insulin agents. However, because beta-cell function and glycaemic control deteriorate over time, most patients will eventually require insulin [2,3]. When insulin is aggressively titrated, treatment with almost any type of insulin enables patients to reach glycaemic control. However, different insulin regimens may produce differences in non-glycaemic outcomes such as hypoglycaemia, a major barrier to good glycaemic control and the second most common adverse drug reaction causing emergency room (ER) visits and hospitalizations [4]. To quantify this and other insulin effects, treat-to-target trials are recommended by the FDA as a means of evaluating the different insulins’ therapeutic potential [1].

According to the FDA guidance, new insulins should be compared with a standard insulin (and not placebo or a non-insulin agent) in clinical trials [1]. All treatment arms should aim to achieve similar glycaemic control, thus allowing for a comparison of safety endpoints, such as hypoglycaemia, to establish the risk-benefit profile of the new insulin. This is known as a ‘treat-to-target’ trial [1]. An understanding of the rationale for and the proper interpretation of treat-to-target trials can help clinicians enhance the management of their patients requiring insulin therapy [5]. This article is the first to address treat-to-target study design as a concept since the FDA advocated the use of treat-to-target studies and to provide examples that show the application of their findings to clinical practice.

Methods

PubMed was searched to find English-language publications on relevant articles published between 1995 and February 2012. Key search terms and phrases included ‘treat to target’, ‘type 2 diabetes’, ‘insulin’, ‘insulin therapy’. Clinical trials evaluating only patients with type 1 diabetes or studies including both type 1 and type 2 diabetes were excluded. The reference lists from identified articles were also searched.
Rationale FOR Treat-to-Target Trials

The first widely recognized treat-to-target trial was conducted by Riddle et al. [6]. Before this landmark trial was conducted, specific glucose targets were not prespecified and were generally left to the investigator’s discretion [5]. On average, mean A1C among patients in earlier trials was often less than ideal, typically higher than the prespecified targets, and usually around 8% or higher [7–10]. Achieving A1C levels >7.0% in a clinical trial setting was relatively rare, and patients participating in the studies were often subject to extended periods of suboptimal glycaemic control. It became unclear whether patients could achieve glycaemic goals with old or newinsulins, especially with hypoglycaemia limiting insulin titration.

As evidence regarding the long-term microvascular complications of suboptimal glycaemic control accumulated, achieving lower glycaemic targets became increasingly important. Consequently, the original imperative for using a treat-to-target study design was to determine if a given treatment can achieve glycaemic targets known to improve diabetes outcomes [11–13]. In treat-to-target trials of insulin therapy, insulin doses are titrated to enable patients to achieve a known and validated target level of glycaemic control. Recognizing that differences between treatments usually exist and are important to treatment decisions and given the potential for asymmetric titrations of different agents, treat-to-target trials were started to compare differences between treatments under study when those treatments are able to achieve the same glycaemic goals. Insulin doses should be titrated using structured and enforced titration schedules to optimize the achievement of glycaemic goals and to help ensure that all study groups achieve glycaemic parity. From these principles, overall A1C reductions in treat-to-target studies are expected to be the same among treatment groups, and no differences in efficacy are expected. Therefore, treat-to-target trials facilitate the evaluation of the utility of therapeutic agents by comparing secondary outcomes at similar A1C levels. Study outcomes often include safety endpoints and assessments of patient adherence, to provide clinically relevant information. Accordingly, treat-to-target trials can also be used to identify treatments that provide more broadly defined treatment success, such as composite endpoints of reaching target A1C levels with low rates of hypoglycaemia [6]. In short, the goal of treat-to-target trials is not to compare absolute therapeutic efficacy, but to compare secondary effects of treatment, including collateral benefit and adverse event (AE) comparisons between the treatments.

Clinical Relevance of Treat-to-Target Trials

Treat-to-target trial results can provide important clinical insights. However, knowledge pertaining to the design, rationale and clinical interpretation of treat-to-target trials in primary care may be limited [14], possibly because training in longitudinal clinical opportunities, such as intensifying therapy in order to meet standard-of-care goals, may be suboptimal in many medical schools and residency programmes [15]. Nonetheless, the treat-to-target study design has been embraced by researchers in various disease states, such as diabetes and hypertension, to prevent the long-term consequences of these chronic diseases while choosing among a multiplicity of treatment choices of equivalent efficacy [16]. Treat-to-target studies of insulin regimens in patients with T2DM provide some assurance that the treatments under study can reach A1C goals [17], while also providing insight into the incidence of hypoglycaemia [18]; body weight changes [19]; dosing schedules; and final doses required to reach goals [5]. Although dose changes in clinical practice often occur slowly and in response to a deterioration of control from previous levels, the treat-to-target approach requires continued titration at frequent intervals until treatment targets are achieved [1,19,20]. Therefore, treat-to-target insulin trials provide physicians with a road map for clinical decision making. In fact, treat-to-target trials of insulin have been extremely valuable in establishing the principle of patient self-titration.

Design of Treat-to-Target Trials in Diabetes

Because treat-to-target trials essentially equalize glycaemic efficacy of the agents under study, the evaluation of differences in other measures of utility may differ from those used in traditional efficacy trials, such as placebo-controlled or active comparator studies of oral antidiabetic agents (OADs). In diabetes trials investigating non-insulin agents, a placebo may be used for comparison to active agents, which may result in unequal degrees of glycaemic control. This may cloud comparative interpretation of data such as rates of hypoglycaemia, as hypoglycaemia is sensitive to attained levels of A1C. Similarly, the same considerations apply when unequal glycaemic control is produced between multiple comparators. Typical outcome measures used as treatment goals in treat-to-target trials can include changes in A1C [21–23], fasting plasma glucose (FPG) [6,24,25] and postprandial glucose (PPG) levels [24]; the proportions of patients achieving A1C goals and specific composite goals [26]; and insulin doses. Other common study endpoints include rates of overall, nocturnal and severe hypoglycaemia [6,17,27–29]; the incidence of AEs; the rates of treatment discontinuations; changes in weight; markers of cardiovascular risk (e.g. changes in blood pressure, lipid levels, etc); patient-reported outcomes [22]; adherence [30,31]; cost-effectiveness [14] and quality of life [32].

Statistical Analyses in Treat-to-Target Trials

While the types of statistical methods used in treat-to-target trials can vary, two types are generally used: non-inferiority and superiority analyses. Non-inferiority analyses are designed to show that one treatment is non-inferior to another treatment in achieving the primary endpoint (e.g. A1C goals) by incorporating a justifiable non-inferiority margin (0.3 to 0.4%) [1]. This margin was chosen because the FDA considers an A1C reduction of >0.3% to be clinically meaningful; therefore, a difference in A1C of 0.3 to 0.4% between treatments could be considered clinically significant. Superiority analyses are designed to show that one treatment is superior to another based on changes in the primary endpoint. It usually involves a comparison between an investigational agent and either an active comparator or placebo, or between two different
| Author [study]                  | Trial length | Trial population                                                                 | Titration target, mmol/l (mg/dl)                                           | Tx arms                                                                 |
|--------------------------------|--------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Insulin detemir or insulin glargine versus neutral protamine Hagedorn (NPH) |              |                                                                                  |                                                                           |                                                                         |
| Riddle [6]                     | 24 weeks     | T2DM (N = 756) with inadequate control with 1 or 2 OADs                           | FPG ≤5.55 mmol/l (≤100 mg/dl)                                             | Continue 1 or 2 previous OADs, add: Bedtime glargine (n = 367) NPH (n = 389) Patients continued current OADs |
| Hermansen [23]                 | 26 weeks     | Insulin-naïve (N = 475) people with T2DM for ≥12 months                         | Prebreakfast and predinner PG targets of ≤5.99 mmol/l (≤108 mg/dl)          | NPH (n = 227) NPH 70/30 twice daily (n = 187)                           |
| Janka [37]                     | 24 weeks     | T2DM (N = 371) uncontrolled by OADs without insulin                              | FPG ≤5.55 mmol/l (≤100 mg/dl)                                             | NPH (n = 22.5)                                                         |
| Yki-Järvinen [46]              | 36 weeks     | T2DM (N = 110) uncontrolled on OADs (metformin and/or sulfonylurea)             | FPG 4.0–5.5 mmol/l (72–100 mg/dl)                                         | NPH plus metformin (n = 61)                                            |
| Insulin detemir or insulin degludec versus insulin glargine                 |              |                                                                                  |                                                                           |                                                                         |
| Hollander [18]                 | 52 weeks     | T2DM (N = 319) for ≥12 months who were receiving OADs or insulin with or without OADs | Prebreakfast (and predinner for detemir administered twice daily) plasma glucose target ≤5.99 mmol/l (≤108 mg/dl) Continue previous OADs other than secretagogues or α-glucosidase inhibitors, aspart, and add either: Detemir once or twice daily (n = 214) Glargine (n = 105) |
| Rosenstock [33]                | 52 weeks     | T2DM (N = 582) insulin-naïve adults ≥18 years old with diabetes ≥12 months, A1C 7.5–10.0%, BMI ≤40.0 kg/m² had to be taking 1 or 2 OADs ≥4 months on at least one-half the maximum recommended dose | FPG ≤6.05 mmol/l (≤109.1 mg/dl)                                           | Detemir (n = 254) Glargine (n = 131)                                    |
| Raskin [17]                    | 26 weeks     | T2DM (N = 385) patients ≥18 years old, with BMI ≤40 kg/m², A1C 7–11%, who had previously received any OADs, insulin, or insulin plus OADs | Prebreakfast plasma glucose target: ≤5.99 mmol/l (≤108 mg/dl)               | Detemir (n = 291) Glargine (n = 291)                                     |
| Swinnen [43]                   | 24 weeks     | Insulin-naïve T2DM (n = 973) subjects treated for >3 months with stable OADs (including metformin > 1 g/day) and with A1C 7.0–10.5% | Doses increased until fasting and predinner PG <5.64 mmol/l (<101.8 mg/dl) | Glargine (n = 478) Detemir (n = 486)                                    |
| Garber [34]                    | 1 year       | T2DM (N = 992) and A1C 7–10% after ≥3 months of any insulin regimen ±OADs       | FPG <4.99 mmol/l (<90 mg/dl)                                              | Degludec + aspart Glargine + aspart Use of metformin and/or pioglitazone was allowed |
| Insulin detemir or insulin glargine versus biphasic insulin                 |              |                                                                                  |                                                                           |                                                                         |
| Malone [36]                    | 32 weeks     | T2DM (N = 105) uncontrolled by OADs without insulin                              | FPG 4.99–6.99 mmol/l (90–126 mg/dl)                                       | Lispro Mix 75/25 plus metformin (n = 52) Glargine plus metformin (n = 53) |
| Malone [38]                    | 32 weeks     | T2DM (N = 97) uncontrolled by OADs with or without insulin                      | FPG and premeal blood glucose concentrations of 4.99–6.99 mmol/l (90–126 mg/dl); 2-h PPG of 7.99–9.99 mmol/l (144–180 mg/dl) | Lispro mixture plus metformin (n = 50) Glargine plus metformin (n = 47) |
| Author [study] | Trial length | Trial population | Titration target, mmol/l (mg/dl) | Tx arms |
|---------------|--------------|------------------|----------------------------------|---------|
| Raskin [39]   | 28 weeks     | T2DM (N = 233) insulin-naïve patients 18–75 years old with BMI ≤40 kg and A1C ≥ 8% previously treated with metformin ≥3 months before trial | FPG 4.44–6.10 mmol/l (80–110 mg/dl) | BIAsp 70/30 (n = 117) Glargine (n = 116) |
| Strojek [42]  | 26 weeks     | Insulin-naïve subjects (n = 480) with T2DM ≥18 years, A1C > 7.0–≤11.0%, with BMI ≤40 kg/m² | FPG level of 5.04–6.15 mmol/l (90.9–110.9 mg/dl) | In combination with metformin and glimepiride |
| Fogelfeld [25]| 24 weeks     | Insulin-naïve adult patients (n = 442) with T2DM for ≥1 year treated with ≥2 OADs without insulin and had A1C 7.5–10.0% and BMI 25.0 (Asia 23.0) to 45.0 kg/m² | FPG 5.04–7.26 mmol/l (90.9–130.9 mg/dl) | BIAsp 30 (n = 231) Glargine (n = 238) |
| Liebl [24]    | 26 weeks     | T2DM (N = 719) uncontrolled by OADs with or without basal insulin | Detemir titrated to achieve prebreakfast PG levels of 3.99–6.99 mmol/l (72–126 mg/dl) and aspart to achieve 90-min postprandial PG levels (≤3.99 mmol/l [≤180 mg/dl]) at each meal | Detemir once daily (n = 541) |
|               |              |                  | Breakfast and dinner doses of BIAsp were titrated to achieve PG levels of 3.99–6.99 mmol/l (72–126 mg/dl) before those meals | BIAsp twice daily (n = 178) |
| Other insulin trials |               |                  |                                 |         |
| Garber [40]   | 48 weeks     | T2DM (N = 100) for ≥12 months who were receiving OADs with or without insulin | Prebreakfast FPG of 4.44–5.55 mmol/l (80–100 mg/dl); predinner FPG 4.44–5.55 mmol/l (80–110 mg/dl) if week 15 A1C > 6.5%; and 2-h PPG of 5.55–7.77 mmol/l (100–140 mg/dl) if week 31 A1C > 6.5% | BIAsp 30 once daily (n = 100) BIAsp 30 2 times daily (n = 68) BIAsp 30 3 times daily (n = 25) |
| Yang [41]     | 24 weeks     | T2DM (N = 321) patients aged 18–75 years, BMI ≤32 kg/m², poorly controlled on OADs therapy (FPG ≥7.87 mmol/l [≥141.82 mg/dl]); A1C ≥ 7.5%, and had received ≥1 OADs for ≥6 months prior to study. Subjects had not used insulin therapy | Premeal blood glucose of 4.44–6.15 mmol/l (80–110.91 mg/dl) | All OADs were stopped prior to study BIAsp 30 BID (n = 160) BIAsp 30 TID (n = 161) |
| Holman [27]   | 52 weeks     | T2DM (N = 708) for ≥12 months with a suboptimal A1C level (7.0–10.0%) receiving maximally tolerated doses of metformin and sulfonylurea | Before meals 3.99–5.49 mmol/l (72–99 mg/dl), 2 h after meals 4.99–6.99 mmol/l (90–126 mg/dl) | Biphasic Prandial Basal |
Results from Representative Treat-to-Target Studies

Riddle et al. published the results of the first diabetes treat-to-target trial comparing glargine to neutral protamine Hagedorn (NPH) in 2003 [6]. Numerous treat-to-target studies followed [17,24,33–35]. The designs of large treat-to-target trials in T2DM are summarized in Table 1, including the treatment target for each trial. [6,17,18,21,23–25,27,33,34,36–46]. Treatment targets, titration schedules and titration intervals vary from insulin to insulin and from study to study and are determined, at least in part, by the pharmacokinetic half-life of the preparation. Because patients in any given treat-to-target trial should ultimately achieve a similar level of glycaemic control, the specifics of the titration algorithm used in the
Table 2. Insulin efficacy and impact on weight in treat-to-target trials involving >100 patients with type 2 diabetes per treatment arm.

| Author [study] | Tx arms | Start of trial A1C | Percentages that reached treatment targets | End of trial A1C | Wt change |
|----------------|---------|---------------------|------------------------------------------|----------------|-----------|
| **Insulin detemir or insulin glargine versus NPH** | | | | | |
| Riddle [6]    | Continue 1 or 2 previous OADs, add: Bedtime glargine (n = 367) | 8.61% | 33.2% | 6.96% | +3.0 ± 0.2 kg |
|                | Once daily NPH (n = 389) | 8.56% | 26.7%* | 6.97% | +2.8 ± 0.2 kg |
| Hermansen [23] | Patients continued current OADs Detemir BID (n = 227) NPH (n = 225) | 8.6% | 26% | 6.8% | 83.6 kg |
|                | | | | | |
| **Janka [37]** | Glargine plus OAD (n = 177) | 8.85% | FPG ≤5.55 mmol/l (≤100 mg/dl): 31.6% A1C ≤7%: 49% | 7.15% | | |
|                | NPH 70/30 twice daily (n = 187) | 8.83% | FPG ≤5.55 mmol/l (≤100 mg/dl): 15%* | 7.49% | +2.1 ± 4.2 kg |
| **Yki-Järvinen [46]** | Glargine plus metformin (n = 61) | 9.5% | NR | 7.14% | +2.6 ± 0.6 kg |
|                | NPH plus metformin (n = 49) | 9.6% | NR | 7.16% | +3.5 ± 0.7 kg |
| **Insulin detemir or insulin degludec versus insulin glargine** | | | | | |
| Hollander [18] | Continue previous OADs other than secretagogues or α-glucosidase inhibitors, aspart, and add either: Detemir once or twice daily (n = 214) Glargine (n = 105) | 8.6% | 36.2% | 7.19% | +2.8 kg |
|                | Detemir (n = 291) | 8.64% | A1C ≤7.0%: 33% Fasting and pre-dinner PG ≤6.05 mmol/l (≤109.09 mg/dl): 25% | 7.2% | +3.0 kg |
|                | Glargine (n = 291) | 8.62% | A1C ≤7.0%: 35% Fasting and pre-dinner PG ≤6.05 mmol/l (≤109.09 mg/dl): 20% | 7.1% | +3.9 kg* |
| **Raskin [17]** | Detemir (n = 254) | 8.42% | A1C <7.0%: 43% A1C <7.0% without hypoglycaemia: 41% | 7.13% | +1.2 ± 3.9 kg |
|                | Glargine (n = 131) | 8.42% | A1C <7.0%: 57% A1C <7.0% without hypoglycaemia: 56% | 6.92%* | +2.7 ± 3.94 kg* |
| **Swinnen [43]** | Glargine (n = 478) | 8.7 ±0.9 | 27.5% | −1.46 ± 1.09% | +1.4 ± 3.2 kg |
|                | Detemir (n = 486) | 8.7 ±0.9 | 25.6% | −1.54 ± 1.11% | +0.6 ± 2.9 kg* |
| **Garber [34]** | Degludec + aspart Glargine + aspart Use of metformin and/or pioglitazone was allowed | 8.3% | A1C <7.0%: 50% | −1.2% change | 3.6 ± 4.9 kg |
|                | | | | −1.3% change | 4.0 ± 4.6 kg |

*Estimated treatment difference: 0.08; 95% CI: −0.05 to 0.21.
| Author [study]          | Tx arms                                      | Start of trial A1C | Percentages that reached treatment targets                                                                 | End of trial A1C | Wt change |
|------------------------|----------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------|------------------|-----------|
| Insulin detemir or insulin glargine versus biphasic insulin |                                                                      |                    |                                                                                                             |                  |           |
| Malone [36]            | Lispro Mix 75/25 plus metformin (n = 52)     | 8.7%               | A1C ≤ 7.0%: 42%<br>FPG 4.99–6.99 mmol/l (90–126 mg/dl): 45%                                                  | 7.4%            | +2.5 kg   |
|                        | Glargine plus metformin (n = 53)             | 8.7%               | A1C ≤ 7.0%: 18%<br>FPG 4.99–6.99 mmol/l (90–126 mg/dl): 65%                                                  | 7.8%*           | +2.6 kg   |
| Malone [38]            | Lispro mixture plus metformin (n = 50)       | 8.50%              | A1C ≤ 7.0%: 30%<br>FPG ≤ 6.99 mmol/l (≤126 mg/dl): 34%                                                      | 7.54%           | +0.49 kg  |
|                        | Glargine plus metformin (n = 47)             | 8.48%              | A1C ≤ 7.0%: 12%<br>FPG ≤ 6.99 mmol/l (≤126 mg/dl): 51%                                                      | 8.14%           | –0.16 kg* |
| Raskin [39]            | BIAsp 70/30 (n = 117)                        | 9.7%               | A1C ≤ 7.0%: 66%<br>A1C ≤ 6.5%: 42%                                                                       | 6.91%           | +5.4 ± 4.8 kg |
|                        | Glargine (n = 116)                           | 9.8%               | A1C ≤ 7.0%: 40%<br>A1C ≤ 6.5%: 28%                                                                       | 7.41%*          | +3.5 ± 4.5 kg* |
| Strojek [42]           | In combination with metformin and glimepiride| 8.5%               | 44.9%                                                                                                      | 7.1%            | +1.74 kg  |
|                        | BIAsp 30 (n = 231)                           |                    |                                                                                                             |                  |           |
|                        | Glargine (n = 238)                           | 8.5%               | 45.7%                                                                                                      | 7.3%            | +1.67 kg  |
|                        | Fogelfeld [25]                              |                    |                                                                                                             |                  |           |
|                        | Lispro protamine suspension (n = 223)        | 8.8%               | 34.9%                                                                                                      | 7.3%            | +1.88 ± 3.16 kg |
|                        | Detemir (n = 219)                            | 8.8%               | 31.2%                                                                                                      | 7.5%*           | +0.36 ± 2.85 kg* |
| Liebl [24]             | Detemir once daily (n = 541)                 | 8.52% ± 1.13%      | 60%                                                                                                         | 6.96%           | +2.4 kg   |
|                        | BIAsp twice daily (n = 178)                  | 8.40% ± 1.03%      | 50%                                                                                                         | 7.17%           | +2.1 kg   |
| Other insulin trials   |                                              |                    |                                                                                                             |                  |           |
| Garber [40]            | BIAsp 30 once daily (n = 100)                | 8.6%               | 21%                                                                                                         | 7.2%            | 5 kg increase in mean body weight |
|                        | BIAsp 30 2 times daily (n = 68)              | 8.7%               | 52%                                                                                                         | 6.8%            |           |
|                        | BIAsp 30 3 times daily (n = 25)              | 8.7%               | 60%                                                                                                         | 6.9%            |           |
| Yang [41]              | All OADs were stopped prior to study BIAsp 30 BID (n = 160) | 9.52 ± 1.4         | A1C ≤ 7.0%: 51.3%<br>A1C ≤ 6.5%: 34.4%                                                                   | 7.01%           | +3.87 ± 0.28 kg |
|                        | BIAsp 30 TID (n = 161)                       | 9.55 ± 1.5         | A1C ≤ 7.0%: 65.8%<br>A1C ≤ 6.5%: 46.6%                                                                  | 6.68%           | +4.09 ± 0.27 kg |
|                        |                                              |                    |                                                                                                             |                  |           |
Table 2. Continued

| Author [study] | Tx arms          | Start of trial A1C | Percentages that reached treatment targets | End of trial A1C | Wt change |
|----------------|------------------|--------------------|------------------------------------------|-----------------|-----------|
| Holman [27]    | Biphasic         | 7.3 ± 0.89         | 17.0%†                                   | 7.3 ± 0.9†      | +4.7 kg   |
|                | Prandial         | 7.2 ± 0.91         | 23.9%†                                   | 7.2 ± 0.9†      | +5.7 kg   |
|                | Basal            | 7.4 ± 1.0          | 8.1%†                                    | 7.6 ± 1.0       | +1.9 kg   |
|                |                  |                    |                                          |                 |           |
| Blonde [21]    | Detemir once daily (n = 122) | 7.99%             | 64.3%‡                                   | 7.77%           | +0.89 ± 0.36 kg‡ |
|                |                  |                    |                                          |                 |           |
| Dailey [45]    | Glulisine plus NPH (n = 435) | 7.58%             | 54.5%‡                                   | 7.11%*‡         | +5.7 kg   |
|                | RHI plus NPH (n = 441) | 7.52%             | 54.5%‡                                   | 7.22%*†         | +1.8 kg   |
| Rosenstock [44]| Lispro mix 50/50 | 7.52%             | 54.5%‡                                   | 7.22%           | +2.0 kg   |
|                | administered at meals (n = 187) | 7.52%             | 54.5%‡                                   | 7.22%           | +2.0 kg   |

NR, not reported; NPH, neutral protamine Hagedorn; OADs, oral antidiabetic agents.

*Significant versus active comparator.
†Significant versus basal insulin.

The study by Riddle et al. was a randomized, open-label, parallel, 24-week multicenter, non-inferiority trial comparing glargine to NPH [6]. This study included 756 patients with inadequately controlled T2DM (A1C ≥ 7.5%) on one or two oral agents. Patients received bedtime glargine or NPH once daily, and titrated to a goal FPG < 5.55 mmol/l (<100 mg/dl).

At the end of the study, A1C levels were comparable between the glargine and NPH groups (6.96% vs. 6.97%). A majority of patients in both groups (approximately 60%) achieved A1C ≤ 7%. However, a significantly greater percent of patients attained A1C ≤ 7% without documented nocturnal hypoglycaemia ([≤3.99 mmol/l (<72 mg/dl)]) in the insulin glargine group than in the NPH group (33.2 vs. 26.7%, p < 0.05). In addition, the overall rate of symptomatic hypoglycaemia was 21% lower in the glargine than NPH group; the rate of nocturnal hypoglycaemia was 42% lower with glargine. These data show that while both agents provided comparable glycaemic control, glargine did so with less hypoglycaemia compared with NPH. In fact, those treated with glargine were more likely to achieve the A1C goal set by the ADA without experiencing nocturnal hypoglycaemia.

In 2008, Rosenstock et al. conducted a 52-week multinational, randomized, open-label, parallel-group, non-inferiority trial comparing clinical outcomes following supplementation of OADs with detemir or glargine among patients with T2DM [33]. Approximately 582 insulin-naive adults with no history of previous insulin use, a baseline A1C of 7.5 to 10.0% and a body mass index of less than 40 kg/m² were included.

Insulin was actively titrated to target FPG ≤ 5.9 mmol/l (≤108 mg/dl). An additional morning dose of detemir was permitted in certain subjects who achieved an FPG < 6.9 mmol/l (<126 mg/dl) but had predinner plasma glucose values > 6.9 mmol/l (>126 mg/dl).

After 52 weeks, A1C decreased from 8.6% at baseline to 7.2 and 7.1% in the detemir and glargine groups, respectively. No between-group difference was noted, thereby meeting the criteria for non-inferiority between the agents. Less weight gain was observed in patients assigned to detemir compared with glargine in completers (3.0 vs. 3.9 kg, p = 0.01), as well as in the intention-to-treat population (2.7 vs. 3.5 kg, p = 0.03), even though mean daily dosages were greater among the detemir group [0.78 U/kg (0.52 with once-daily dosing, 1.00 U/kg with twice-daily dosing)] than in the glargine group (0.44 IU/kg).

Injection site reactions also occurred more frequently among the detemir-treated patients compared with those on insulin glargine (4.5 vs. 1.4%). These data indicate that both glargine and detemir provide effective glycaemic control with a low rate of hypoglycaemia, but detemir was associated with less weight gain and more injection-site reactions.

In 2009, Raskin et al. published the results of a 26-week, treat-to-target non-inferiority trial that compared efficacy and safety of basal-bolus therapy with detemir and aspart versus glargine and aspart (N = 385) [17]. The study design specified
Table 3. Rates of hypoglycaemia with insulin in treat-to-target trials involving >100 patients with type 2 diabetes per treatment arm.

| Author [study] | Tx arms | Overall hypo rates | Nocturnal hypo rates | Severe hypo rates |
|----------------|---------|--------------------|----------------------|------------------|
| **Insulin detemir or insulin glargine versus NPH** | | | | |
| Riddle [6] | Continue 1 or 2 previous OADs, add Bedtime glargine (n = 367) | 9.2 events/pt-year | Total number of events/pt-year: 4.0 | 3.0 events/pt-year |
| | Once-daily NPH (n = 389) | 12.9 events/pt-year* | Total number of events/pt-year: 6.9* | 5.1 events/pt-year* |
| Hermansen [23] | Patients continued current OADs Detemir BID (n = 227) | Detemir associated with a 47% lower risk for any hypoglycaemic event* | Detemir associated with a 55% lower risk for nocturnal events* | N/A |
| Janka [37] | Glargine plus OAD (n = 177) NPH 70/30 twice daily (n = 187) | 4.07 events/pt-year | 0.51 events/pt-year | 0 events/pt-year |
| | Glargine plus metformin (n = 61) | 5.4 events/pt-year | NR | 0 events/pt-year |
| | NPH plus metformin (n = 49) | 8.0 events/pt-year | NR | 0 events/pt-year |
| **Insulin detemir or insulin degludec versus insulin glargine** | | | | |
| Hollander [18] | Continue previous OADs other than secretagogues or α-glucosidase inhibitors, aspart, and add either: Detemir once or twice daily (n = 214) | 73.8% of patients | 44.9% of patients | 4.7% of patients |
| | Glargine (n = 105) | 80.0% of patients | 50.5% of patients | 5.7% of patients |
| Rosenstock [33] | Detemir (n = 291) | 5.8 episodes/pt-year | 1.3 episodes/pt-year | Rare |
| | Glargine (n = 291) | 6.2 episodes/pt-year | 1.3 episodes/pt-year | 0 episodes/pt-year |
| Raskin [17] | Detemir (n = 254) | Daytime events: 14.15 events/pt-year | 4.23 events/pt-year | 0.09 events/pt-year |
| | Glargine (n = 131) | 13.80 events/pt-year | 3.38 events/pt-year | 0.12 events/pt-year |
| Swinnen [43] | Glargine (n = 478) | Symptomatic: With PG ≤3.11 mmol/l (≤56 mg/dl): 2.10 ± 5.16/pt-year | With PG ≤3.11 mmol/l (≤56 mg/dl): 1.02 ± 3.51/pt-year | All severe: 0.16 ± 1.42/pt-year |
| | | With PG ≤3.88 mmol/l (≤70 mg/dl): 5.79 ± 12.30/pt-year | With PG ≤3.88 mmol/l (≤70 mg/dl): 2.33 ± 6.93/pt-year | Daytime severe: 0.06 ± 0.69/pt-year |
| | | Asymptomatic: 0.88 ± 4.43/pt-year | Nighttime severe: 0.10 ± 1.03/pt-year | Nocturnal severe: 0.08 ± 0.63/pt-year |
| | | Symptomatic: With PG ≤3.11 mmol/l (≤56 mg/dl): 2.55 ± 7.38/pt-year | With PG ≤3.11 mmol/l (≤56 mg/dl): 0.90 ± 3.55/pt-year | All severe: 0.08 ± 0.63/pt-year |
| | | With PG ≤3.88 mmol/l (≤70 mg/dl): 6.67 ± 13.12/pt-year | With PG ≤3.88 mmol/l (≤70 mg/dl): 1.70 ± 4.93/pt-year | Daytime severe: 0.04 ± 0.32/pt-year |
| | | Asymptomatic: 1.47 ± 6.47/pt-year | | |
| Garber [34] | Degludec + aspart | 11.1 episodes/pt-year | 1.4 episodes/pt-year | Nocturnal severe: 0.04 ± 0.45/pt-year |
| | Glargine + aspart | 13.6 episodes/pt-year* | 1.8 episodes/pt-year* | NR |
| | Use of metformin and/or pioglitazone was allowed | | | NR |
### Table 3. Continued

| Author [study] | Tx arms | Overall hypo rates | Nocturnal hypo rates | Severe hypo rates |
|----------------|---------|--------------------|----------------------|------------------|
| **Insulin detemir or insulin glargine versus biphasic insulin** | | | | |
| Malone [36] | Lispro Mix 75/25 plus metformin (n = 52) | 0.68 episodes/pt/30 days | 11% | NA |
| | Glargine plus metformin (n = 53) | 0.39 episodes/pt/30 days | 12% | NA |
| Malone [38] | Lispro mixture plus metformin (n = 50) | 0.61 episodes/pt/30 days | 0.14 episodes/pt/30 days | NA |
| | Glargine plus metformin (n = 47) | 0.44 episodes/pt/30 days | 0.34 episodes/pt/30 days | NA |
| Raskin [39] | BIAsp 70/30 (n = 117) | 3.4 ± 6.6 episodes/pt-year | NA | 0 episodes |
| | Glargine (n = 116) | 0.7 ± 2.0 episodes/pt-year* | NA | 1 episode |
| Strojek [42] | In combination with metformin and glimepiride | All events: 6.5/pt-year | Nocturnal: 1.1/pt-year | 3 events |
| | BIAsp 30 (n = 231) | Glargine (n = 238) | All events: 4.8/pt-year | Nocturnal: 0.5/pt-year | 3 events |
| | Lispro protamine suspension (n = 223) | 68.9% of patients | 45.8% of patients | 5 patients |
| | Detemir (n = 219) once daily at bedtime | 65.2% of patients | 32.5%* | 2 episodes |
| Liebl [24] | Detemir once daily (n = 541) | Non-severe events: 31% of patients | 7.4% of patients | 5 patients (0.9%) had 11 episodes |
| | Biphasic insulin aspart twice daily (n = 178) | Non-severe events: 28% of patients | Nocturnal non-severe: 4.8% of patients (QD) | 6.3% of patients (BID) |
| **Other insulin trials** | | | | |
| Garber [40] | BIAsp 30 once daily (n = 100) | 15.4 events/pt-year | No severe events | 3 patients |
| | BIAsp 30 2 times daily (n = 68) | 22.4 events/pt-year | No severe events | 3 patients |
| | BIAsp 30 3 times daily (n = 25) | 12 events/pt-year | No severe events | 1 patient |
| Yang [41] | All OADs were stopped prior to study | 23% (91 events) | No significant differences between groups | 1 patient had 1 event |
| | BIAsp 30 BID (n = 160) | 19% (65 events) | | 3 patients had 5 events, 1 of which was nocturnal |
| | BIAsp 30 TID (n = 161) | | | |
| Holman [27] | Biphasic | 5.7 events/pt-year | N/A | 0.0 events/pt-year |
| | Prandial | 12.0 events/pt-year | N/A | 0.0 events/pt-year |
| | Basal | 2.3 events/pt-year | N/A | 0.0 events/pt-year |
| Blonde [21] | Detemir once daily (n = 122) | 52% | 30.6% | 1 patient |
| | Detemir once daily (n = 122) | 41% | 20.5% | 0 patients |
| Dailey [45] | Glulisine plus NPH (n = 435) | 51.7% | 21.4% | 0.0041 events/pt-month |
| | RHI plus NPH (n = 441) | 53.6% | 24.5% | 0.0037 events/pt-month |
| Rosenstock [44] | Lispro mix 50/50 3 times daily (n = 187) | 51.2 episodes/pt-year | 4.78 episodes/pt-year | 6 events: |
| | Glargine at bedtime plus lispro administered at meals (n = 187) | 48.7 episodes/pt-year | 6.27 episodes/pt-year | 0.10 events/pt-year |

Hypo, hypoglycaemia; NR, not reported; OADs, oral antidiabetic agents; PG, plasma glucose.  
*Significant versus active comparator.  
†Significant versus basal insulin.
that detemir would be considered non-inferior if the upper limit of the 95% confidence interval for the difference in A1C was <0.4. As expected, both groups had significant reductions in A1C from baseline (−1.1% with detemir; −1.3% with glargine; both p < 0.001); detemir was non-inferior to glargine in reducing A1C (LS mean of glargine minus detemir: 0.207; 95% CI: 0.0149–0.3995). In addition, patients treated with detemir gained significantly less weight than patients treated with glargine (1.2 ± 3.96 kg vs. 2.7 ± 3.94 kg, p = 0.001). Hypoglycaemia risk was comparable between groups.

Degludec, an ultra-long acting, once-daily basal insulin therapy under investigation in the USA and approved in the EU, Japan and Mexico, has been associated with reduced rates of hypoglycaemia compared with insulin glargine [47]. Two large studies comparing degludec and glargine in patients with type 1 or type 2 diabetes, known as the BEGIN™: Basal-Bolus (BB) trials, have been published. The BEGIN BB T2 study was a 1-year, open-label, treat-to-target trial in patients with T2DM. Garber et al. compared the efficacy and safety of degludec and glargine administered once daily in a basal-bolus regimen in combination with rapid-acting aspart as the mealtime insulin. The 992 patients included in the study were previously treated with insulin and oral antidiabetic agents (metformin and pioglitazone) and could continue using metformin and/or pioglitazone in the trial [34]. At the end of the study, patients in the two groups had comparable reductions of A1C (−1.2% for degludec; −1.3% for glargine). However, patients in the degludec group experienced an 18% reduction in overall hypoglycaemia (estimated rate ratio: 0.82; 95% CI: 0.69–0.99; p = 0.0359) and 25% reduction of nocturnal hypoglycaemia compared with the glargine group (estimated rate ratio: 0.75; 95% CI: 0.58–0.99; p = 0.0399). Weight gain was comparable between groups (3.6 kg with degludec and 4.0 kg with insulin glargine).

**Conclusion**

In clinical trials and clinical practice, glycaemic control with insulin therapy has been suboptimal. The introduction of the treat-to-target study design has enabled and even required the rigorous use of insulin titration regimens to enable more patients to achieve glycaemic control, and to allow clinicians to better evaluate the AEs across various insulin regimens at equal levels of glycaemic control.

In recent years, treat-to-target studies of patients with T2DM have shown that insulin detemir and insulin glargine show efficacy equivalent to NPH, with a reduced incidence of hypoglycaemia (particularly nocturnal hypoglycaemia) [6,23]. Moreover, insulin detemir is associated with less weight gain than glargine or NPH [17,18,33]. Most recently, treat-to-target studies comparing the ultra-long-acting basal insulin, degludec and glargine have shown that degludec provides glycaemic control similar to that seen with glargine but with lower rates of hypoglycaemia [34,35].

Because treat-to-target trials are designed to produce equal degrees of glycaemic control, they are able to reveal differences in safety, tolerability and clinical utility when insulin dosing and efficacy is maximized. Such studies have only limited utility for evaluations of treatment efficacy since the same glucose target is used for all treatment arms of the trial. Treat-to-target trials have been useful in comparing new and emerging insulin therapies to those of established regimens. In addition, treat-to-target studies provide tested algorithms for dosing and titrating insulin therapies that may assist clinicians in their management of patients with suboptimal glycaemic control on insulin therapy. Ultimately, results from treat-to-target trials provide clinicians important information that can be used in daily clinical practice to select insulin regimens that provide optimal efficacy and tolerability in their patients.

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**Conflict of Interest**

A. J. G. generated the outline, rewrote drafts and approved the final version. A. J. G. is a board member of The American Association of Clinical Endocrinologists; served as a consultant to Novo Nordisk, Daiichi Sankyo, Merck, Takeda, Santarus, LipoScience, Boehringer Ingelheim, Sekris and Lexicon; provided expert testimony on behalf of Novo Nordisk; received payment for lectures from Merck, Novo Nordisk, Santarus and Daiichi Sankyo; and received grants from Novo Nordisk.

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