review article

Diabetes, Obesity and Metabolism 16: 193–205, 2014.

REVIEW ARTICLE

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

Date submitted 4 January 2013; date of first decision 15 February 2013; date of final acceptance 6 May 2013

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.

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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 new insulins, 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 insulins 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

Table 1. Design of treat-to-target studies of insulin therapies involving ≥50 patients with type 2 diabetes per treatment arm.

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) Once daily NPH (n = 389)
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)	Patients continued current OADs Detemir BID (n = 227) NPH (n = 225)
Janka [37]	24 weeks	T2DM (N = 371) uncontrolled by OADs without insulin	FPG ≤5.55 mmol/l (≤100 mg/dl)	Glargine plus OAD (n = 177) NPH 70/30 twice daily (n = 187)
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)	Glargine plus metformin (n = 61) NPH plus metformin (n = 49)
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-naive adults ≥18 years old with diabetes ≥ 12 months, A1C 7.5–10.0%, BMI ≤40.0 kg/m^2) 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 = 291) Glargine (n = 291)
Raskin [17]	26 weeks	T2DM (N = 385) patients ≥ 18 years old, with BMI ≤40 kg/m^2, 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 = 254) Glargine (n = 131)
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)

doi:10.1111/dom.12129

Table 1. Continued

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/m^2	FPG level of 5.04–6.15 mmol/l (90.9–110.9 mg/dl)	In combination with metformin and glimepiride BIAsp 30 (n = 231) Glargine (n = 238)
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/m^2	FPG 5.04–7.26 mmol/l (90.9–130.9 mg/dl)	Insulin lispro protamine suspension (n = 223) Detemir (n = 219) once daily at bedtime
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 (≤9.99 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/m^2, 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 dl)	Biphasic Prandial Basal

Table 1. Continued

Author [study]	Trial length	Trial population	Titration target, mmol/l (mg/dl)	Tx arms
Blonde [21]	20 weeks	Insulin-naïve subjects with T2DM (N = 244) suboptimally treated with OADs	FPG 3.93–5.04 mmol/l (70.9–90.9 mg/dl) FPG 4.44–6.11 mmol/l (80–110 mg/dl)	Detemir once daily (n = 122) Detemir once daily (n = 122)
Dailey [45]	26 weeks	Subjects with T2DM (N = 876) treated with insulin therapy for ≥6 months with A1C levels 6.0–11.0%	2-h PPG 6.66–8.88 mmol/l (120–160 mg/dl) and FPG 4.99–6.66 mmol/l (90–120 mg/dl)	Glulisine plus NPH (n = 453) Regular human insulin (RHI) plus NPH (n = 441)
Rosenstock [44]	24 weeks	Subjects with T2DM (N = 374) with inadequate glycaemic control (A1C ≥7.5–≤12%) previously treated with insulin glargine (≥30 U/day) plus oral agents	FPG <6.11 mmol/l (<110 mg/dl)	Lispro mix 50/50 3 times daily (n = 187) Glargine at bedtime plus lispro administered at meals (n = 187)

BMI, body mass index; BIAsp, biphasic insulin aspart; FPG, fasting plasma glucose; NPH, neutral protamine Hagedorn; OADs, oral antidiabetic agents; T2DM, type 2 diabetes mellitus.

treatment regimens. Superiority can be difficult to show in treat-to-target insulin trials because insulin can always be titrated up to a desired goal. Non-inferiority is often tested first, but both non-inferiority and superiority can be evaluated in the same trial typically in a stepwise, or hierarchical, manner. When only non-inferiority is tested and demonstrated, additional studies or analysis can be conducted to determine superiority. Likewise, studies can be designed to only test superiority. This is rarely performed as titration protocols to the same glucose targets likely eliminate major outcome differences in glycaemic control.

In statistical analyses of treat-to-target trials, any evaluation of change in A1C from baseline includes adjustments for differences between groups in A1C at baseline. Such studies are analysed with an intention-to-treat method. In this method, all patients randomized to a treatment are counted as outcomes even if they receive no medications whatsoever. They may drop out for a variety of reasons, but it is assumed that the agent to which they were randomized played a role in their dropping out. To account for this discontinuation of patients during trials, statistical analyses often use the last observation carried forward (LOCF) approach to account for missing data. The LOCF approach is easy to apply, provides transparency when patients do not complete the trials, and has been the method preferred by the FDA. The LOCF method is particularly important in studies evaluating a poorly tolerated or difficult to use drug. In these studies, the less-tolerated agent will be associated with more dropouts, resulting in final A1C levels based solely on those who tolerated the agent. This leads to a biased result which can be corrected only by imputing end-of-study values from the patient's last completed visit. There are two methods for such imputation. In one, the patients' last visit value for a given parameter can be extrapolated linearly to the end of the study period. Alternatively, the rate of change for the imputed parameter can be modelled for each patient and used to extrapolate the value at the end of study period. This approach is often referred to as a repeated measures model. On occasion, the end-of-study data are analysed without the imputation of data from patients who withdrew during the course of the study. These are known as per protocol or completer analyses. They are usually regarded as secondary analyses.

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)	8.6%	26%	6.8%	83.6 kg
	NPH (n = 225)	8.5%	16%*	6.6%	85.1 kg Difference: +1.58 kg [95% CI −2.18 to 0.98]*
Janka [37]	Glargine plus OAD (n = 177)	8.85%	FPG ≤5.55 mmol/l (≤100 mg/dl): 31.6% A1C ≤ 7%: 49%	7.15%	+1.4 ± 3.4 kg
	NPH 70/30 twice daily (n = 187)	8.83%	FPG ≤5.55 mmol/l (≤100 mg/dl): 15%* A1C ≤ 7%: 39%	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)	8.6%	36.2%	7.19%	+2.8 kg
	Glargine (n = 105)	8.8%	36.7%	7.03%	+3.8 kg
Rosenstock [33]	Detemir (n = 291)	8.64%	A1C ≤ 7.0%: 33% Fasting and predinner 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 predinner 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 ± 3.96 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	8.3%	A1C < 7.0%: 50%	−1.2% change	3.6 ± 4.9 kg
	Glargine + aspart Use of metformin and/or pioglitazone was allowed	8.3%	A1C < 7.0%: 50%	−1.3% change Estimated treatment difference: 0.08; 95% CI: −0.05 to 0.21	4.0 ± 4.6 kg

Table 2. Continued

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% 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%* 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% 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% 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% A1C ≤ 6.5%: 42%	6.91%	+5.4 ± 4.8 kg
	Glargine (n = 116)	9.8%	A1C < 7.0: 40%* A1C ≤ 6.5%: 28%*	7.41%*	+3.5 ± 4.5 kg*
Strojek [42]	In combination with metformin and glimepiride BIAsp 30 (n = 231)	8.5%	44.9%	7.1%	+1.74 kg
	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) once daily at bedtime	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% A1C ≤ 6.5%: 34.4%	7.01% Change from baseline: −2.48 ± 0.07%*	+3.87 ± 0.28 kg
	BIAsp 30 TID (n = 161)	9.55 ± 1.5	A1C ≤ 7.0%: 65.8%* A1C ≤ 6.5%: 46.6%*	6.68% Change from baseline: −2.81 ± 0.07%* Between group difference: −0.33%*	+4.09 ± 0.27 kg

doi:10.1111/dom.12129

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	8.6 ± 0.8	17.0%†	7.3 ± 0.9†	+4.7 kg
	Prandial	8.6 ± 0.8	23.9%†	7.2 ± 0.9†	+5.7 kg
	Basal	8.4 ± 0.8	8.1%	7.6 ± 1.0	+1.9 kg
Blonde [21]	Detemir once daily (n = 122)	7.99%	64.3%	6.77%	+0.89 ± 0.36 kg
	Detemir once daily (n = 122)	7.94%	54.5%	7.00%	+0.12 ± 0.36 kg
Dailey [45]	Glulisine plus NPH (n = 435)	7.58%	A1C ≤ 7.0%: 53.5%	7.11%*	+1.8 kg
	RHI plus NPH (n = 441)	7.52%	A1C ≤ 7.0%: 50.6%	7.22%	+2.0 kg
Rosenstock [44]	Lispro mix 50/50 3 times daily (n = 187)	8.83%	A1C ≤ 7.0%: 54%	6.95%	+4.0 kg
	Glargine at bedtime plus lispro administered at meals (n = 187)	8.89%	A1C ≤ 7.0%: 69%*	6.78%*	+4.5 kg

NR, not reported; NPH, neutral protamine Hagedorn; OADs; oral antidiabetic agents.
*Significant versus active comparator.
†Significant versus basal insulin.

study are somewhat arbitrary. Key efficacy and safety results are reviewed in Table 2 [6,17,18,21,23–25,27,33,34,36–46] and Table 3 [6,17,18,21,23–25,27,33,34,36–46]. Key results and clinical implications of representative insulin treat-to-target studies are described.

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-naïve 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/m^2 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:	9.2 events/pt-year	Total number of events/pt-year: 4.0	3.0 events/pt-year
	Bedtime glargine (n = 367)		Events ≤3.11 mmol/l (≤56 mg/dl): 1.3	
	Once-daily NPH (n = 389)	12.9 events/pt-year*	Total number of events/pt-year: 6.9*	5.1 events/pt-year*
			Events ≤3.11 mmol/l (≤56 mg/dl): 2.5*	
Hermansen [23]	Patients continued current OADs	Detemir associated with a 47% lower risk for any hypoglycaemic event*	Detemir associated with a 55% lower risk for nocturnal events*	N/A
	Detemir BID (n = 227)			
	NPH (n = 225)			
Janka [37]	Glargine plus OAD (n = 177)	4.07 events/pt-year	0.51 events/pt-year	0 events/pt-year
	NPH 70/30 twice daily (n = 187)	9.87 events/pt-year*	1.04 events/pt-year*	0.05 events/pt-year
Yki-Järvinen [46]	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:	73.8% of patients	44.9% of patients	4.7% of patients
	Detemir once or twice daily (n = 214)			
	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		Nocturnal severe: 0.10 ± 1.03/pt-year
	Detemir (n = 486)	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 ± 15.12/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		Nocturnal severe: 0.04 ± 0.45/pt-year
Garber [34]	Degludec + aspart	11.1 episodes/pt-year	1.4 episodes/pt-year	NR
	Glargine + aspart	13.6 episodes/pt-year*	1.8 episodes/pt-year*	NR
	Use of metformin and/or pioglitazone was allowed			

doi:10.1111/dom.12129

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
Fogelfeld [25]	Lispro protamine suspension (n = 223)	68.9% of patients	45.8% of patients	5 episodes
	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 Nocturnal non-severe: 4.8% of patients (QD) 6.3% of patients (BID)	5 patients (0.9%) had 11 episodes
	Biphasic insulin aspart twice daily (n = 178)	Non-severe events: 28% of patients	7.3% of patients Nocturnal non-severe: 6.3% of patients	0 episodes
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)			
	BIAsp 30 TID (n = 161)	19% (65 events)		3 patients had 5 events, 1 of which was nocturnal
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: 0.10 events/pt-year
	Glargine at bedtime plus lispro administered at meals (n = 187)	48.7 episodes/pt-year	6.27 episodes/pt-year	4 events: 0.04 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.

Acknowledgements

Nicole Cooper of MedVal Scientific Information Services, LLC, provided medical writing and editorial assistance, funding for which was provided by Novo Nordisk Inc.

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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