

Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies

T. Heise¹ and T. R. Pieber²

¹Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

²Department of Internal Medicine, Karl Franzens University, Graz, Austria

While the advantages of the two basal insulin analogues, glargine and detemir, over neutral protamine Hagedorn are well established, the relative merit of the two compared with each other has been a matter of some controversy. The two analogues are popularly perceived to differ from each other in their pharmacodynamic (PD) profiles, in particular with regard to 'flatness' and duration of action. The aim of this review, therefore, is to give a complete overview on the available PD data of both analogues as derived with the glucose clamp technique. In order to improve parity across studies, a common definition for duration of action (time from injection to plasma glucose >8.3 mmol/l) was applied and study data were recalculated when necessary. Despite differences in methodological details, the results of most clamp studies were very consistent. Glargine and detemir both typically show a gentle rise and fall in glucose-lowering action over time. Duration of action with both analogues is dose dependent, but in the clinically relevant range of 0.35–0.8 U/kg it is close to 24 h in people with type 1 diabetes and in excess of this in people with type 2 diabetes. While both analogues seem to be very similar with regard to the mean shape of their PD profile and duration of action, detemir shows less within-subject variability in its metabolic effect. These findings in experimental glucose clamp studies are consistent with observations in clinical trials and support routine once daily use with either analogue, in particular in people with type 2 diabetes.

Keywords: basal analogues, insulin detemir, insulin glargine, isoglycaemic clamp study, pharmacodynamics

Received 18 April 2007; returned for revision 31 May 2007, 11 June 2007 and 12 June 2007; accepted 13 June 2007

Introduction

Insulin secretion in health is tightly regulated and maintains plasma glucose concentrations in the euglycaemic range (approximately 4–6 mmol/l). A more or less constant 'basal' level of secretion is supplemented periodically by intervals of greatly increased secretion according to metabolic need, with the ingestion of nutrients acting as a potent stimulus to increased insulin secretion [1].

Pharmaceutical companies have developed formulations of exogenously administered insulin that attempt to recreate the kinetics of endogenous insulin secretion. The absorption properties of rapid-acting insulin analogues (lispro, aspart and glulisine), for example, lead to pharmacodynamic (PD) profiles that replicate the normal prandial insulin response much better than previously available human insulin preparations for subcutaneous (s.c.) injection [2]. Basal insulin formulations

Correspondence:

Tim Heise, Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, D-41460 Neuss, Germany.

E-mail:

tim.heise@profil-research.de

attempt to recreate the low and constant plasma insulin levels seen between meals and overnight in normal physiology. The challenge here has been to produce formulations that are affordable to health provider services and convenient for the patient (requiring a low injection frequency, preferably once a day) and that produce the desired flat, reproducible PD profile of normal basal insulin secretion.

It is well established and widely accepted that basal human insulin preparations [Ultralente and neutral protamine Hagedorn (NPH) insulin] fall short of these desired properties [3,4]: they not only are suspensions that have to be thoroughly resuspended prior to injection, a requirement often ignored by many patients [5], but also show a pronounced peak effect, which can impose the risk of nocturnal hypoglycaemia. Furthermore, variability in the PD profile is high [6,7] – indeed, so high for Ultralente that it is hardly used any more [8]. The major disadvantage of NPH insulin, in addition to high variability, is its suboptimal duration of action: end of action is reported to occur after only 12–14 h [9–11]. For many patients, this means NPH insulin will not be able to substitute basal insulin unless given at least twice daily.

In light of these shortfalls, manufacturers have sought alternative approaches, and in recent years, two insulin analogues, insulin glargine and insulin detemir, have been licensed that attempt to meet the requirements demanded of an exogenous basal insulin therapy. The PD superiority over NPH insulin of these two analogues as basal insulins is widely accepted: both glargine and detemir have a longer duration of action and a reduced peak effect when compared with NPH insulin [3,4,12]. However, the relative merit of the two compared with each other has been a matter of some controversy. Insulin glargine has been widely cited to be a long-acting ‘peakless’ basal insulin with reduced variability that can be dosed once daily in all patients, whereas insulin detemir is often regarded as a ‘predictable’ insulin characterized by low intrasubject variability but with only intermediate action (requiring once or twice daily dosing) and a slight peak effect [12,13].

In order to investigate the evidence on which these perceptions are based, this review summarizes the available data from all glucose clamp studies available to date that have examined the time–action profiles of these analogues.

Clamp Study Data

This review focuses on results from isoglycaemic clamp studies as these are generally regarded as the gold-standard system for assessing the PD profiles of insulin

products [14,15]. In clamp studies, the PD effect of the study insulin is investigated by preventing the insulin-induced decrease in blood glucose concentration through a variable infusion of glucose. A plot of the amount of glucose over time [expressed as glucose infusion rate (GIR) in mg/kg/min] necessary to maintain blood glucose concentrations at the clamp level is closely representative of the PD effect of the study insulin. While this principle is used by all glucose clamp studies, differences in methodological and analytical detail often hamper comparisons between studies. Nevertheless, in order to obtain a complete overview, the data of different studies on the key issues for basal insulins, that is, duration of action, flatness and variability, have here been harmonized as far as possible. For this purpose, the authors reanalysed data from their own studies to obtain parameters comparable to other published data. It should be noted that the authors have not had access to the original data of others’ studies, so considerations of these are necessarily restricted to the published data.

Collectively, insulin glargine [6,7,9,16–19] and insulin detemir [6,11,18,20,21] have been examined in 10 published clamp studies. Studies not examining s.c. insulin administration [22,23], that used multiple insulin injections during one clamp [24] or that had a duration of below 24 h postdosing [25–27] were not included in this review. In addition, the study by Rave *et al.* [28] was excluded as the cohort was limited to Japanese ethnicity, whereas all other trials were carried out in Caucasians. Only two of these published studies have made direct PD comparisons between insulin detemir and insulin glargine [6,18]. Recently, a third direct comparison has been published in abstract form [29]. In order to gather a sound data set, this abstract and the related poster were included in this review, even though the study is not available as a full paper in a peer-reviewed journal at the time of writing this review. Summary data for the relevant published studies are presented in table 1.

‘Flatness’ of Basal Insulin Analogues

As there are no accepted standard measures of ‘flatness’, it is generally more informative to assess the shapes of the GIR–time curves. All available profiles determined in people with diabetes are presented in figure 1 for comparison (the mean profiles of Heise *et al.* [6] were calculated for this review and were not part of the original publication).

In the case of glargine, a very flat profile was reported in the early study in type 1 diabetes by Lepore *et al.* [9]. This

Table 1 Summary of methods and pharmacodynamic data in clamp studies involving basal insulin analogues

Citation and design	Subject type (n)	Clamp duration; level	Insulins	End of action (h)	Dose (U/kg)	Variability (mg/min/kg)
Heinemann [20]; Detemir doses given in escalating sequence	Healthy males; n = 11	24 h; 5.0 mmol/l	Detemir (600 nm)		0.15, 0.3, 0.6	
Brunner [21]; DB random sequence	Healthy males; n = 10	24 h; 80 mg/dl	Detemir (600 nm)		0.3, 0.6	
Heinemann [16]; DB random sequence	Healthy males; n = 15	30 h; 5.0 mmol/l	Glargine		0.4	
Scholtz [7]; DB parallel group; two repeated injections of assigned insulin	Healthy males; n = 36	24 h from injection. G infused to restore individual base level	Glargine		0.4	31% (17, 45)*; 27% (15, 38)†
Lepore [9]; two-part study	Type 1, n = 20	24 h or PG > 200 mg/dl; 130 mg/dl	Glargine	22.0 ± 4.0	0.3	
DB random sequence; (Glargine vs. NPH)						
6–9 months later: random sequence (Ultratard vs. CSII)						
Plank [11]; DB six-period crossover	Type 1, n = 12	24 h or PG > 11.1 mmol/l; 7.2 mmol/l	Detemir	7.6 ± 6.1	0.1	
Heise [6]; DB parallel group; four injections of assigned insulin	Type 1; n = 54	24 h or PG > 11.1 mmol/l; 5.5 mmol/l	Detemir	14.0 ± 5.3	0.2	
Luzio [17]; open, random sequence	Men with type 2 diabetes; n = 12	24 h G infused to restore individual base level	Glargine	21.5 ± 3.3	0.4	
				23.7 ± 0.9	0.8	
				23.9 ± 0.2	1.6	
				23.0‡ (15.4; 24.0)	0.4	27%§; 23%¶
				24.0‡ (18.7; 24.0)	0.4	48%§; 36%¶
				24**	0.5	
Klein [18]; DB, random sequence (Detemir vs. Glargine)	Men with type 2 diabetes; n = 27	(mean 7.7 mmol/l) 24 h; 5.0 mmol/l	Detemir	24	0.4	47%§
				24	0.8	
				24	1.4	40%¶
				24	0.4	215%§
				24	0.8	
				24	1.4	147%¶
Porcellati [29]; DB randomized crossover	Type 1; n = 20	24 h or PG > 200 mg/dl; 5.5 mmol/l	Glargine	24‡ (23; 24)	0.35	
Porcellati [19]; open, non-randomized sequence with experiments at the first and the seventh treatment day	Type 1; n = 20	24 h or PG > 200 mg/dl; 130 mg/dl	Detemir	17.5‡ (16; 24)	0.35	
			Glargine; Day 1	22‡ (19; 27)	0.3	
			Glargine; Day 7	25.6‡ (22; 28.5)	0.3	

CI, confidence interval; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; DB, double blind; G, glucose; GIR, glucose infusion rate; NPH, neutral protamine Hagedorn; PG, plasma glucose.

*GIR_{AUC₀₋₂₄}; intersubject CV 95% CI.

†GIR_{max}; intersubject CV.

‡Median [min; max].

§GIR_{AUC₀₋₂₄}; intrasubject CV.

¶GIR_{max}; intrasubject CV.

**End of action not provided, but glycaemia did not increase during the 24-h clamps.

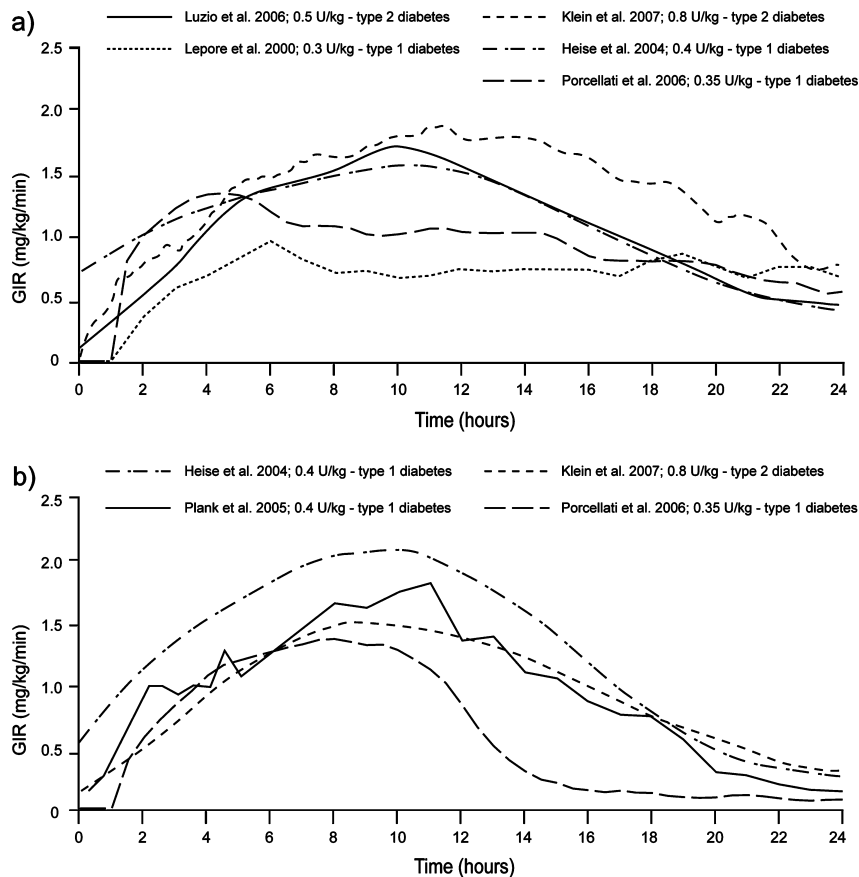


Fig. 1 Glucose infusion rate curves from key studies of basal insulin analogues in people with diabetes: (a) insulin glargine; (b) insulin detemir. Individual curves © of and reproduced with permission from: Springer Verlag [17]; American Diabetes Association [9]; Blackwell Publishing [18]; American Diabetes Association [6]; and American Diabetes Association [11]; curve for (Porcellati *et al.* [29] is from G. Bolli (pers. comm.).

profile is still popularly regarded as the defining one for the drug, although it has not been repeated in any of the subsequent clamp studies with insulin glargine. All other studies have been quite consistent in showing a gentle rise and fall in effect, regardless of whether they were conducted in healthy subjects [7,16], type 1 diabetes patients [6,29] or type 2 diabetes patients [17,18].

Studies of insulin detemir are also consistent in showing a gentle rise and fall. In fact, the mean shape of the time–action profile has been very consistent in the detemir studies, with the exception of the recent Porcellati study in type 1 diabetes [29] where there was an apparently rapid decline in action over the second 12-h period of the study. That this was found for the mean profile is curious as a sudden drop off in action was not seen in any of the individual patient GIR profiles reported in the large-scale repeat-clamp study by Heise *et al.* [6] or in any individual profile in the study of Plank *et al.* [11] in people with type 1 diabetes. The only avail-

able head-to-head comparison of glargine and detemir in people with type 2 diabetes [18] reported nearly superimposable PD profiles with 0.4 and 0.8 U/kg. In conclusion, the available studies, with only one exception [9], show a small peak with both insulin glargine and insulin detemir. Thus, while the two analogues certainly show a considerably flatter profile than NPH insulin, their mean profiles do not fully represent the physiological, peakless profile produced by endogenous basal insulin secretion in health.

Duration of Action of the Basal Analogues

It seems very simple to define duration of action in glucose clamp studies as the time from insulin injection to GIR returning to baseline again. In reality, however, GIR usually does not return to baseline in extended glucose clamp studies in healthy people. For instance, two clamp

studies in healthy volunteers [16,21] reported ongoing metabolic activity of NPH insulin at 24 h or even at 30 h, in clear contrast to clinical observations with NPH insulin. The determination of duration of action in healthy subjects may therefore be more confusing than helpful. The overestimation of duration of action in healthy people might be because of prolonged fasting and/or an increase in endogenous insulin secretion as both studies demonstrated ongoing and increasing metabolic activity also for placebo over 24 or 30 h [16,21].

Therefore, duration of action can only be measured reliably in people with diabetes in whom a vanishing metabolic effect of the study insulin will be manifest as a decrease in GIR and a subsequent rise in the subjects' glucose concentrations above the target clamp level. As the main aim of a basal insulin is to control blood glucose under fasting conditions, it has been proposed to define 'end of action' of an insulin preparation as the time from study drug injection to an increase in glucose concentrations above 8.3 mmol/l (150 mg/dl) [9]. As this definition is the clinically most relevant (defining the duration of fasting glucose control through a basal insulin) and as it can be applied to all available clamp data on basal insulin analogues in people with diabetes, it will be used for this review. Lepore *et al.* [9], Plank *et al.* [11] and Porcellati *et al.* [19,29] calculated duration of action as the time from onset to end of action. End of action was defined as outlined above, whereas onset of action was defined as the time after dosing, at which the rate of a basal intravenous (i.v.) insulin infusion (used to establish the glucose target-level pre-dosing) consistently decreased by 50% compared with the 20-min predosing time period. This definition cannot be applied to all studies in people with diabetes, however, as some studies [6,18] have simply ceased the i.v. insulin infusion immediately before injection of the study insulin. As the use of i.v. insulin is just an expedient for glucose clamp studies and not relevant for daily clinical practice, it seems justifiable to use insulin injection as starting point and an increase of blood glucose concentrations above 8.3 mmol/l as the end-point for the definition of duration of action.

In total, there are seven glucose clamp studies in people with type 1 [6,9,11,19,29] or type 2 diabetes [17,18]. The main difference between these studies, as far as end of action is concerned, is the difference in the blood glucose target level during the clamp. Glycaemia was clamped either at 5.0 mmol/l [6,18], 5.5 mmol/l [29] and 130 mg/dl (7.2 mmol/l) [9,19] or at an individualized level (mean 7.7 mmol/l) [17]. The chosen clamp glucose level will have an impact on the reported values for end of action as it obviously takes longer for glucose

to rise to the cut-off value of 8.3 mmol/l when starting at 5 mmol/l than when starting at 7.2 mmol/l. Nevertheless, describing the time in near-normoglycaemia (i.e. with glucose concentrations below 8.3 mmol/l) under a basal insulin while remaining fasting seems to be a clinically relevant measure for the duration of action. With these caveats, duration of action is hereafter defined as the interval between injection and the blood glucose level rising to 8.3 mmol/l, with reported data recalculated accordingly.

Using this definition, the duration of action of insulin glargine was reported to be 22–24 h under single-dose conditions [6,9] and 24–25.6 h under steady-state conditions [18,19]. As pointed out by Lepore *et al.* [9], the mean duration of action of any basal insulin is likely to be underestimated in glucose clamps lasting only 24 h as a duration of action of more than 24 h will just be measured as being 24 h, whereas a shorter duration of action in individual clamps will decrease the mean value. However, no differences were observed for the duration of action of insulin glargine between clamp studies lasting 24 h [9] or 32 h [19], with both studies reporting a duration of action of 22 h for single-dose administration. A slight increase in duration of action was observed under steady-state conditions, indicating (in contrast to the conclusion of a previous pharmacokinetic study [30]) that there is a slight accumulation of insulin glargine in the first days of treatment. Nevertheless, all studies consistently report a mean duration of action of close to 24 h, supporting the once-daily administration implemented in the label of insulin glargine.

The same holds true for insulin detemir: at a dose of 0.4 U/kg, the mean duration of action of insulin detemir was 21.5 h, using the criteria outlined above [11]. A duration of action of close to 24 h was confirmed by a reanalysis of the data of Heise *et al.* [6]: median end of action in this study was found to occur at 23 h at a dose of 0.4 U/kg with insulin detemir, whereas a median of 24 h was obtained for glargine (table 1).

While these two studies of insulin glargine and insulin detemir showed a similar duration of action of the two analogues, a direct comparison in people with type 1 diabetes reported a considerably shorter end of action for detemir of only 17.5 h at a dose of 0.35 U/kg [29]. This is in clear contrast to previously reported values for the duration of action of 0.4 U/kg of insulin detemir in the same population (21.5–23 h [6,11]), although the clamp methodology was nearly identical in one of these studies [11]. It seems unlikely, that the small difference in dose (0.35 vs. 0.4 U/kg) led to the pronounced differences in duration of action of several hours as the

duration of action of 0.35 U/kg insulin glargine (24 h, range 23–24 h) was identical to previously reported values for 0.4 U/kg (24 h, range 18.7–24 h) [11] and even showed a considerably higher minimum. Thus, while the reasons for the discrepancy in duration of action are unclear, the abstrusely short duration of action of detemir in the recent direct comparison [29] are not in accordance with any of the previously reported values and can therefore be regarded as an outlier.

The only study comparing the end of action of insulin detemir with that of insulin glargine in people with type 2 diabetes (representing the vast majority of patients using insulin) did not show any differences between the two analogues [18], where end of action, defined as a rise in glucose to 8.3 mmol/l, occurred at 24 h for both insulins in the dose range of 0.4–1.4 U/kg. As the clamp experiments did not last longer than 24 h in this study, however, end of action was underestimated for the reasons mentioned above. This was most pronounced for the high doses as judged from the mean profiles provided in the publication. Obviously, glucose clamp data in people with type 2 diabetes might also be influenced by changes in endogenous insulin secretion during the experiment. This was the reason why only patients with low fasting C-peptide concentrations (0.48 ± 0.28 nmol/l for insulin detemir vs. 0.45 ± 0.29 nmol/l for insulin glargine) were enrolled in this study. Mean C-peptide levels remained stable at a low level in all experiments with either insulin (0.20, 0.24 and 0.27 nmol/l for insulin glargine at respective doses of 1.4, 0.8 and 0.4 U/kg and 0.22, 0.23 and 0.31 nmol/l for the corresponding doses of insulin detemir). These low values together with within-clamp coefficients of variation (CV) for C-peptide of not more than 31–56% for insulin glargine and 29–42% for insulin detemir rule out a major influence of endogenous insulin on the study results. Even though small contributions of endogenous insulin to the observed duration of action cannot be completely excluded, it is important to keep in mind that endogenous insulin will also be metabolically active under clinical conditions. Thus, if an insulin preparation controls fasting blood glucose over 24 h under highly experimental glucose clamp conditions in nearly completely immobilized patients, it will do the same (probably to an even greater extent) under daily real-life conditions.

The study by Klein *et al.* [18], together with that of Plank *et al.* [11], also demonstrated that the duration of action is dose dependent, that is, it increases with higher doses. This has also been demonstrated for prandial insulins [31,32], so that in general, the rate of absorption of s.c. injected insulin preparations seems to

be slower when higher doses are given [33]. Thus, when discussing duration of action, it is of high importance to use the values for clinically relevant doses. The clinically most relevant dose probably is around 0.4 U/kg as the mean daily doses for insulin detemir and NPH insulin were 0.37 and 0.39 U/kg in the phase 3 program of insulin detemir [6]. In an observational study of insulin detemir in more than 35 000 people with diabetes (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation; PREDICTIVETM), the mean effective total insulin doses in type 2 diabetes patients ranged from approximately 0.3 U/kg in patients initiating insulin [34] to approximately 0.8 U/kg in patients switching from premix to basal–bolus therapy [35]. Similarly, in the large-scale AT.LANTUS study [36] of glargine in type 2 diabetes, the mean total insulin dose at end of study was approximately 0.6 U/kg in a mixed cohort of basal + OAD (oral anti-diabetic drugs) – and basal–bolus-treated patients. In the original treat-to-target trial of glargine in insulin-naïve type 2 diabetes [37], the mean dose at end-point was 0.48 U/kg. In a recently reported study of once-daily detemir in insulin-naïve type 2 diabetes, the mean dose at end-point was similar at 0.4–0.5 U/kg, depending on administration time [38].

In conclusion, when a common definition is applied, the mean duration of action of both insulin glargine and insulin detemir in the clinically relevant dose range is close to 24 h in people with type 1 diabetes and at least 24 h in people with type 2 diabetes. With one exception, this finding has been reported consistently across all studies.

It is important to note, though, that a mean duration of action does not necessarily represent the duration of action in each individual patient. It is striking that standard deviations (s.d.) in the duration of action can be considerable, suggesting that the blood glucose-lowering action and the ability to dose once or twice daily will differ substantially between individual patients. This is also illustrated in the individual profiles in the publication of Heise *et al.* [6], which clearly show that the duration of action of insulin preparations varies between patients and also within any one individual. Thus, even with a mean duration of action of 25.6 h, which is the longest reported for insulin glargine [19], blood glucose will not be controlled over 24 h with one injection in all patients. It would also be very interesting to see how often duration of action of a basal insulin will be below 24 h in any one individual. An investigation of the within-subject variability of the duration of action, however, would require clamp procedures enduring more than 24 h. Otherwise, if metabolic action surpasses the

total length of the clamp procedure, both mean value and variability will inevitably be underestimated. It is no surprise, therefore, that the within-subject variability in duration of action in the study of Heise *et al.* [6] showed comparably low values for both insulin glargine and insulin detemir; the mean CV (calculated as the ratio of s.d. and mean values) were 7.1 and 6.6%, respectively.

Variability

The within-subject variability of the metabolic effect has been investigated in only three of the clamp studies, whereas the variability of effect between subjects is reported in all. However, it is within-subject variability that is of much greater potential clinical concern. Within-subject variability will affect the extent to which blood glucose levels fluctuate in individual patients from one day to another. When this variability is superimposed on a peak effect in blood glucose-lowering activity, it follows that it can become a major contributing factor in the precipitation of nocturnal hypoglycaemic events and hence a limiting factor in the glycaemic control that can be achieved. In contrast, between-subject variability merely implies that doses will need to be individually titrated. Within-subject variability, defined as the degree of difference in the glucose-lowering effect from one injection to another in the same patient, can only be assessed in repeat-clamp studies, that is, one insulin preparation is given several times to one individual. It is also important to recognize that diurnal fluctuations in the insulin or GIR within an individual subject (e.g. as reported by Gerich *et al.* [39]) should be regarded as a parameter for flatness, not for variability; in this account, variability concerns the consistency of the 24-h PD profile from injection to injection rather than the constancy of effect over 24 h.

Two studies of insulin glargine have suggested that *between*-subject variability is reduced in comparison to NPH, one in healthy volunteers [16] and one in patients with type 1 diabetes [9], but no study has reported significantly lower *within*-subject variability for insulin glargine. A study in healthy volunteers by Scholtz *et al.* showed similar levels of within-subject variability comparing glargine with NPH insulin [7]. Numerically lower values for within-subject variability comparing glargine with NPH insulin were reported by Heise *et al.* [6], but significance was not tested. It should be noted, however, that in these experimental studies, NPH insulin was very thoroughly resuspended before injection, as recommended, whereas in a clinical setting it is known that patients often fail to perform an adequate resuspension before injection, this being a major source

of within-subject variability with the use of NPH insulin [5,40]. Thus, it seems plausible that the variability of insulin glargine, which is injected as a solute, will be lower than that of NPH insulin in a clinical setting. However, this has not yet been confirmed by clinical study data.

In the case of insulin detemir, significantly lower within-subject variability has been demonstrated in patients with type 1 diabetes in comparison with both NPH insulin and glargine for the parameters of $GIR_{(AUC)}$ and $GIR_{(max)}$ [6]. In type 2 diabetes, detemir again showed significantly lower within-subject variability in these parameters in comparison to glargine [18]. This was also true of an additional experimental acylated insulin that was also assessed in this study, implying that reduced within-subject variability might be an inherent property of albumin-binding insulin analogues.

In conclusion, the available data from repeat-clamp studies suggest that insulin detemir has advantages over insulin glargine with regard to within-subject variability.

Clinical Data

It is beyond the scope of this article to give a comprehensive account of the clinical profiles of glargine and detemir as elucidated in clinical trials, and several review articles have in any case already done this (e.g. Peterson [41], Thisted *et al.* [42], Home and Kurtzhals [43]). It is worth commenting, however, on some clinical findings that appear to illustrate the underlying PD profiles of the basal analogues and hence relate directly to the predictions that can be made by the clamp study data.

As per label, the original clinical trials of insulin glargine involved nearly exclusively once-daily dosing schedules (as part of basal-bolus therapy), with many showing efficacy and/or tolerability advantages in comparison to NPH insulin, even when the latter was able to be dosed twice daily [44–48]. These outcomes are consistent with the clamp studies' finding that glargine has a more prolonged and flatter action than NPH insulin. More recently, however, data have come to light to suggest that many patients with type 1 diabetes, in which glycaemia is more wholly under the control of exogenous insulin than it is in type 2 diabetes, will benefit from splitting the basal glargine dose. For example, Albright *et al.* [49] reported a cohort with basal-bolus-treated type 1 diabetes, whose basal insulin was switched from NPH insulin to glargine. This was titrated to a fasting plasma glucose target, with additional titration of mealtime rapid-acting analogues. For 24% of patients, titration of the lunchtime bolus

resulted in mid-afternoon hypoglycaemia, but reduction of the dose then led to persistent predinner hyperglycaemia. This was only corrected by splitting the basal dose, whereupon HbA_{1c}, which initially deteriorated (from 7.9 to 8.1%), subsequently improved to 7.4%.

This observation is consistent with a waning of effect, at least in some patients, but it is not inconsistent with the mean duration of action of (close to or slightly above) 24 h observed in the clamp trials as duration of action will be lower in some individuals. Indeed, subsequent studies that have reported multi-point, self-monitored blood glucose profiles or the diurnal distribution of hypoglycaemia also suggest that the mean effect of glargine can wane considerably across 24 h [50–52]. In accordance with these findings, late-afternoon hyperglycaemia was reported in 32% of people with type 1 diabetes when glargine was used once daily at dinner time in combination with rapid-acting insulin analogues [53]. Thus, while insulin glargine can be used once daily in the majority of patients, twice-daily treatment is indicated in 15–30% of people with type 1 diabetes [52].

Most clinical trials of insulin detemir in type 1 diabetes have been carried out using twice-daily dosing. One exception reported significant reductions in fasting glucose levels, body weight and glucose fluctuations and near-significant improvements in HbA_{1c} levels with once-daily insulin detemir compared with NPH insulin (as part of basal–bolus therapy), albeit that this study cohort had previously been receiving a once-daily basal insulin schedule [54]. Interim results of the ADAPT study, however, in which patients with type 1 diabetes were randomized to receive once- or twice-daily insulin detemir (with mealtime insulin aspart) suggest that once-daily insulin detemir is non-inferior to twice-daily dosing with regard to HbA_{1c}, even though doses were significantly lower in the once-daily treatment arm [55].

The once-daily utility of insulin detemir is also illustrated by the results of an ongoing, observational study, PREDICTIVE™ [56]. In this study, once-daily use of detemir has been reported in 49–62% of patients with type 1 diabetes [56,57] and in 77–88% of people with type 2 diabetes [36,56]. Collectively, these clinical data are consistent with the reported mean duration of action of (close to) 24 h in most of the glucose clamp studies. In addition, they show that the study of Porcellati *et al.* [29], which reported a far shorter duration of action of detemir than the other clamp trials, is not in accordance with clinical experience. The percentage of patients with type 1 diabetes using once-daily injections of insulin detemir appears somewhat lower in PREDICTIVE™ than in reports involving insulin glargine. While this is

perhaps in accordance with the numerically slightly longer durations of action for insulin glargine in clamp studies (table 1), this discrepancy might also reflect pre-conceptions and expectations of the physicians participating in PREDICTIVE™ rather than purely clinical needs.

The insulin detemir trials are consistent with the clamp trials reported by Heise *et al.* [6] and Klein *et al.* [18] in that they indicate reduced within-subject variability in glycaemia. Compared with NPH insulin, lower s.d. in fasting glycaemia have been consistently reported in clinical studies in both type 1 [54,58–62] and type 2 diabetes [63,64]. One study incorporating 72-h continuous glucose monitoring also demonstrated that insulin detemir is associated with more limited glycaemic fluctuations than NPH insulin [62].

The reduced incidence of hypoglycaemia observed with both glargine [37,45,46,48,65–77] and detemir [38,54,58–61,64,78,79] in comparison with NPH insulin is consistent with the flatter profile of both analogues observed in glucose clamp studies. It should be noted, though, at least for insulin detemir, that the reduced incidence of hypoglycaemia might be not only because of a reduced peak effect of the insulin analogues but also because of less variability in the metabolic effect.

Only two clinical studies have been reported that make direct comparisons between glargine and detemir. In the only available clinical head-to-head comparison in type 1 diabetes [44], insulin detemir was associated with reduced variability of predinner glucose levels and with significantly less nocturnal and severe hypoglycaemia than insulin glargine. A study in people with type 2 diabetes [80] found no difference between the two analogues with regard to HbA_{1c}, blood glucose variability or incidence of hypoglycaemia, although significantly less weight gain was seen with insulin detemir. It seems rather unlikely that the unequal titration algorithms in these studies (demanding twice-daily detemir [44] or once- or twice-daily [80] detemir) favoured detemir for outcome parameters such as weight gain and (nocturnal and severe) hypoglycaemia, but further studies with equal dosing regimens will be required to determine the extent of parity between glargine and detemir. Interestingly, the patients on twice-daily insulin detemir did not obtain better results than those treated with one injection per day in the Rosenstock study [80]. This indicates that people with type 2 diabetes whose condition is not well controlled with once-daily detemir might need prandial insulin supplementation rather than an additional shot of a basal insulin.

In conclusion, the clinical data support the results of most glucose clamp studies. While the weight advantage of insulin detemir over the other available basal insulins has been observed consistently in numerous trials, the lower incidence of nocturnal and severe hypoglycaemia compared with insulin glargine [44] needs to be confirmed in future studies with equal titration and dosing algorithms.

Conclusion

Despite some differences in methodological detail, the results of most glucose clamp studies of the two basal insulin analogues have been very consistent. While the duration of action of both analogues increases with dose, in a clinically relevant dose range of 0.35–0.8 U/kg, the duration of action is close to 24 h in people with type 1 diabetes and in excess of 24 h in people with type 2 diabetes. These observations are consistent with the outcomes reported in clinical trials of these analogues.

The profiles of both analogues are characterized by a gentle rise and fall in the glucose-lowering action over 24 h. While, subjectively, this may not be describable as a 'peaked' profile, it cannot be considered the desired completely 'peakless' profile of the ideal basal insulin. Clear advantages for insulin glargine with regard to the flatness of the profile [9,19] or the duration of action [29] can be regarded as outlier findings, not supported by the majority of clamp studies, and they are not in accordance with clinical data. These suggest that both insulin glargine and insulin detemir are suited to routine use in once-daily schedules in type 2 diabetes, while in type 1 diabetes once-daily dosing will often, although not always, be possible. Nevertheless, both analogues clearly have a longer duration and a flatter profile of action than NPH insulin and hence represent a clinically important refinement of insulin therapy.

References

- Polonsky KS, Given BD, Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 1988; **81**: 442–448.
- Lindholm A. New insulins in the treatment of diabetes mellitus. *Best Pract Res Clin Gastroenterol* 2002; **16**: 475–492.
- Roskamp RH, Park G. Long-acting insulin analogs. *Diabetes Care* 1999; **22** (Suppl. 2): B109–B113.
- Bolli GB, Owens DR. Insulin glargine. *Lancet* 2000; **356**: 443–445.
- Jehle PM, Micheler C, Jehle DR, Breitig D, Boehm BO. Inadequate suspension of neutral protamine Hagedorn (NPH) insulin in pens. *Lancet* 1999; **354**: 1604–1607.
- Heise T, Nosek L, Ronn BB *et al.* Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 2004; **53**: 1614–1620.
- Scholtz HE, Pretorius SG, Wessels DH, Becker RH. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. *Diabetologia* 2005; **48**: 1988–1995.
- Lindstrom T, Olsson PO, Arnqvist HJ. The use of human ultralente is limited by great intraindividual variability in overnight plasma insulin profiles. *Scand J Clin Lab Invest* 2000; **60**: 341–347.
- Lepore M, Pampanelli S, Fanelli C *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; **49**: 2142–2148.
- Hirsch IB. Insulin analogues. *N Engl J Med* 2005; **352**: 174–183.
- Plank J, Bodenlenz M, Sinner F *et al.* A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care* 2005; **28**: 1107–1112.
- Peterson GE. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. *Curr Med Res Opin* 2006; **22**: 2613–2619.
- Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 2006; **145**: 125–134.
- Heinemann L, Anderson JH Jr. Measurement of insulin absorption and insulin action. *Diabetes Technol Ther* 2004; **6**: 698–718.
- EMEA/CPMP. Note for Guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (London, 30 May 2002, CPMP/EWP/1080/00). Available from URL: <http://www.emea.eu.int/pdfs/human/ewp/108000en.pdf>. Accessed 10 April 2007.
- Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; **23**: 644–649.
- Luzio S, Dunseath G, Peter R, Pauvaday V, Owens DR. Comparison of the pharmacokinetics and pharmacodynamics of biphasic insulin aspart and insulin glargine in people with type 2 diabetes. *Diabetologia* 2006; **49**: 1163–1168.
- Klein O, Lyng J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time–action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes Obes Metab* 2007; **9**: 290–299.

- 19 Porcellati F, Rosetti P, Ricci NB *et al.* Pharmacokinetics and pharmacodynamics of the long-acting insulin analog glargine after one week of use as compared to its first administration in subjects with type 1 diabetes mellitus. *Diabetes Care* 2007; **30**: 1261–1263.
- 20 Heinemann L, Sinha K, Weyer C, Loftager M, Hirschberger S, Heise T. Time–action profile of the soluble, fatty acid acylated, long-acting insulin analogue NN304. *Diabet Med* 1999; **16**: 332–338.
- 21 Brunner GA, Sendhofer G, Wutte A *et al.* Pharmacokinetic and pharmacodynamic properties of long-acting insulin analogue NN304 in comparison to NPH insulin in humans. *Exp Clin Endocrinol Diabetes* 2000; **108**: 100–105.
- 22 Scholtz HE, Pretorius SG, Wessels DH, Venter C, Potgieter MA, Becker RH. Equipotency of insulin glargine and regular human insulin on glucose disposal in healthy subjects following intravenous infusion. *Acta Diabetol* 2003; **40**: 156–162.
- 23 Dagogo-Jack S, Askari H, Morrill B, Lehner LL, Kim B, Sha X. Physiological responses during hypoglycaemia induced by regular human insulin or a novel human analogue, insulin glargine. *Diabetes Obes Metab* 2000; **2**: 373–383.
- 24 Bott S, Tusek C, Jacobsen LV *et al.* Insulin detemir under steady-state conditions: no accumulation and constant metabolic effect over time with twice daily administration in subjects with type 1 diabetes. *Diabet Med* 2006; **23**: 522–528.
- 25 Kuerzel GU, Shukla U, Scholtz HE *et al.* Bio-transformation of insulin glargine after subcutaneous injection in healthy subjects. *Curr Med Res Opin* 2003; **19**: 34–40.
- 26 Hordern SV, Wright JE, Umpleby AM, Shojaee-Moradie F, Amiss J, Russell-Jones DL. Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp. *Diabetologia* 2005; **48**: 420–426.
- 27 Hompesch M, Troupin B, Heise T *et al.* Time-action profile of insulin detemir and NPH insulin in patients with type 2 diabetes from different ethnic groups. *Diabetes Obes Metab* 2006; **8**: 568–573.
- 28 Rave K, Nosek L, Heinemann L, Frick A, Becker R. Time–action profile of the long-acting insulin analogue insulin glargine in comparison to NPH insulin in Japanese volunteers. *Diabetes Metab* 2003; **29**: 430–431.
- 29 Porcellati F, Rossetti P, Ricci NB *et al.* Pharmacokinetics and -dynamics of therapeutic doses of the ‘long-acting’ insulin analogues glargine and detemir at steady-state in type 1 diabetes. *Diabet Med* 2006; **23** (Suppl. 4): 341 (Abstract).
- 30 Heise T, Bott S, Rave K, Dressler A, Roskamp R, Heinemann L. No evidence for accumulation of insulin glargine (LANTUS): a multiple injection study in patients with type 1 diabetes. *Diabet Med* 2002; **19**: 490–495.
- 31 Heinemann L, Woodworth J. Pharmacokinetics and metabolism of insulin lispro. *Insulin Lispro: A New Rapid-acting Insulin Analog*, Chapter III. *Drugs Today (Barc)* 1998; **34** (Suppl. C): 23–36.
- 32 Nosek L, Heinemann L, Kaiser M, Arnolds S, Heise T. No increase in the duration of action with rising doses of insulin aspart. *Diabetes* 2003; **52** (Suppl. 1): 551–P.
- 33 Lauritzen T. Pharmacokinetic and clinical aspects of intensified subcutaneous insulin therapy. *Dan Med Bull* 1985; **32**: 104–118.
- 34 Dornhorst A, Hernandez FO, Koenen C, Lüddecke H-J. Initiating insulin detemir improves glycaemic control without weight gain in OAD-treated, insulin naive patients with type 2 diabetes: results from the PREDICTIVE™ study. *Diabet Med* 2006; **23** (Suppl. 4): 136 (P370).
- 35 Tsur A, Hansen JB, Yenigun M. Switching from premix insulin to BB therapy with insulin detemir and insulin aspart improves glycaemic control and reduces hypoglycaemia, without weight gain, in type 2 patients: 3-month results from the PREDICTIVE™ study. *Diabet Med* 2006; **23** (Suppl. 4): 347 (P966).
- 36 Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R. Improvement of glycaemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005; **28**: 1282–1288.
- 37 Riddle MC, Rosenstock J, Gerich J. Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26**: 3080–3086.
- 38 Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006; **28**: 1569–1581.
- 39 Gerich J, Becker RH, Zhu R, Bolli GB. Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes Technol Ther* 2006; **8**: 237–243.
- 40 Heinemann L. Variability of insulin absorption and insulin action. *Diabetes Technol Ther* 2002; **4**: 673–682.
- 41 Peterson GE. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. *Curr Med Res Opin* 2006; **22**: 2613–2619.
- 42 Thisted H, Johnsen SP, Rungby J. An update on the long-acting insulin analogue glargine. *Basic Clin Pharmacol Toxicol* 2006; **99**: 1–11.
- 43 Home P, Kurtzhals P. Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother* 2006; **7**: 325–343.
- 44 Pieber TR, Treichel HC, Robertson LI, Mordhorst L, Gall MA. Insulin therapy in type 1 diabetes – insulin detemir plus insulin aspart is associated with less risk of major as well as nocturnal hypoglycaemia than

- insulin glargine plus insulin aspart at comparable levels of glycaemic control in type 1 diabetes. *Diabetologia* 2005; **48** (Suppl. 1): O242.
- 45 Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care* 2000; **23**: 639–643.
 - 46 Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* 2001; **24**: 631–636.
 - 47 Schober E, Schoenle E, Van Dyk J, Wernicke-Panten K. The Pediatric Study Group of Insulin Glargine. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2002; **15**: 369–376.
 - 48 Hershon KS, Blevins TC, Blevins TC, Blevins TC. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. *Endocr Pract* 2004; **10**: 10–17.
 - 49 Albright ES, Desmond R, Bell DS. Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* 2004; **27**: 632–633.
 - 50 Hamann A, Matthaer S, Rosak C, Silvestre L. HOE901/4007 Study Group. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2003; **26**: 1738–1744.
 - 51 Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with type 1 diabetes using meal-time insulin aspart. *Diabet Med* 2006; **23**: 879–886.
 - 52 Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with type 1 diabetes using insulin lispro at meal-times. *Diabet Med* 2006; **23**: 46–52.
 - 53 Porcellati F, Rossetti P, Fanelli C, Bolli G. Optimized use of insulin glargine in intensive treatment of type 1 diabetes mellitus: benefits and a new question. *Diabetes* 2005; **54** (Suppl. 1): 524–P.
 - 54 Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther* 2004; **26**: 724–736.
 - 55 Le Floch J, Eschwège E, Levy M *et al.* Interim results of a French multi-centre trial comparing insulin detemir once daily vs. twice daily in people with type 1 diabetes: the ADAPT study. *Diabet Med* 2006; **23** (Suppl. 4): P927.
 - 56 Dornhorst A, Luddeke HJ, Sreenan S *et al.* Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. *Int J Clin Pract* 2007; **61**: 523–528.
 - 57 Gallwitz B, Ackermann RW, Dornhorst A. Switching from a human to an insulin analogue BB regimen with insulin detemir/insulin aspart improves glycaemic control and reduces hypoglycaemic episodes in type 1 patients: results from the PREDICTIVE™ study. *Diabet Med* 2006; **23** (Suppl. 4): 326.
 - 58 Kolendorf K, Ross GP, Pavlic-Renar I *et al.* Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in type 1 diabetes. *Diabet Med* 2006; **23**: 729–735.
 - 59 Vague P, Selam JL, Skeie S *et al.* Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003; **26**: 590–596.
 - 60 Home P, Bartley P, Russell-Jones D *et al.* Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care* 2004; **27**: 1081–1087.
 - 61 Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med* 2007; **24**: 27–34.
 - 62 Hermansen K, Fontaine P, Kukolja KK *et al.* Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia* 2004; **47**: 622–629.
 - 63 Haak T, Tiengo A, Draeger E, Suntum M, Waldhäusl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab* 2005; **7**: 56–64.
 - 64 Raslova K, Bogoev M, Raz I *et al.* Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract* 2004; **66**: 193–201. Erratum in *Diabetes Res Clin Pract* 2006; **72**: 112.
 - 65 Ashwell SG, Amiel SA, Bilous RW *et al.* Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med* 2006; **23**: 285–292.
 - 66 Eliaschewitz FG, Calvo C, Valbuena H *et al.* Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Arch Med Res* 2006; **37**: 495–501.
 - 67 Fonseca V, Bell DS, Berger S, Thomson S, Mecca TE. A comparison of bedtime insulin glargine with bedtime neutral protamine Hagedorn insulin in patients with type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study. *Am J Med Sci* 2004; **328**: 274–280.

- 68 Fritsche A, Schweitzer MA, Haring H-U; the 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med* 2003; **138**: 952–959.
- 69 Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern Med J* 2005; **35**: 536–542.
- 70 HOE 901/2004 Study Investigators Group. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in type 2 diabetic patients. *Diabet Med* 2003; **20**: 545–551.
- 71 Massi Benedetti M, Humburg E, Dressler A, Ziemer M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Horm Metab Res* 2003; **35**: 189–196.
- 72 Murphy NP, Keane SM, Ong KK *et al.* Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care* 2003; **26**: 799–804.
- 73 Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. *Diabetes Care* 2000; **23**: 157–162.
- 74 Porcellati F, Rossetti P, Pampanelli S *et al.* Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 2004; **21**: 1213–1220.
- 75 Rossetti P, Pampanelli S, Fanelli C *et al.* Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care* 2003; **26**: 1490–1496.
- 76 Yki-Jarvinen H, Dressler A, Ziemer M; HOE 901/300s Study Group. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care* 2000; **23**: 1130–1136.
- 77 Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M *et al.* Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006; **49**: 442–451.
- 78 Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home PD on behalf of the Levemir Treat-to-Target Study Group. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006; **29**: 1269–1274.
- 79 De Leeuw I, Vague P, Selam JL *et al.* Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab* 2005; **7**: 73–82.
- 80 Rosenstock J, Davies M, Home PD, Larsen J, Tamer SC, Scherthaner G. Insulin detemir added to oral anti-diabetic drugs in type 2 diabetes provides glycemic control comparable to insulin glargine with less weight gain. *Diabetes* 2006; **55** (Suppl. 1): 555–P.