



**HAL**  
open science

## How pharmacokinetic and pharmacodynamic (PK/PD) principles pave the way for optimal basal insulin therapy in type 2 diabetes

Sabine Arnolds, Bernd Kuglin, Christoph Kapitza, Tim Heise

► **To cite this version:**

Sabine Arnolds, Bernd Kuglin, Christoph Kapitza, Tim Heise. How pharmacokinetic and pharmacodynamic (PK/PD) principles pave the way for optimal basal insulin therapy in type 2 diabetes. International Journal of Clinical Practice, 2010, 64 (10), pp.1415. 10.1111/j.1742-1241.2010.02470.x . hal-00552669

**HAL Id: hal-00552669**

**<https://hal.science/hal-00552669>**

Submitted on 6 Jan 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**How pharmacokinetic and pharmacodynamic (PK/PD) principles pave the way for optimal basal insulin therapy in type 2 diabetes**

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-01-10-0056.FT10.R1
Wiley - Manuscript type:	Non-Systematic Review
Date Submitted by the Author:	26-Apr-2010
Complete List of Authors:	Arnolds, Sabine; PROFIL Institut für Stoffwechselforschung GmbH Kuglin, Bernd; PROFIL Institut für Stoffwechselforschung GmbH Kapitza, Christoph; PROFIL Institut für Stoffwechselforschung GmbH Heise, Tim; PROFIL Institut für Stoffwechselforschung GmbH
Specialty area:	

1  
2  
3 **How pharmacokinetic and pharmacodynamic (PK/PD) principles**  
4 **pave the way for optimal basal insulin therapy in type 2 diabetes**  
5  
6  
7

8 Sabine Arnolds, MD<sup>1</sup>, Bernd Kuglin, MD<sup>1</sup>, Christoph Kapitza, MD<sup>1</sup>, Tim  
9 Heise, MD<sup>1</sup>  
10  
11

12  
13  
14  
15 <sup>1</sup>PROFIL Institut für Stoffwechselforschung GmbH, Neuss, Germany  
16  
17  
18  
19  
20

21 **Correspondence to:**  
22

23 Dr. Sabine Arnolds  
24

25 PROFIL Institut für Stoffwechselforschung GmbH  
26

27 Hellersbergstrasse 9  
28

29 Neuss D-41460  
30

31 Germany  
32

33 Tel: +49 2131 4018 401  
34

35 Fax: +49 2131 4018 501  
36

37 Email: sabine.arnolds@profil-research.de  
38  
39

40 **Disclosures:**  
41

42 TH and CK are shareholders of a private research institute (PROFIL Insitut  
43 für Stoffwechselforschung GmbH) that received research grants from  
44 several pharmaceutical companies, including the insulin-producing  
45 companies Eli Lilly, Novo Nordisk and Sanofi-Aventis. In addition, TH  
46 received speaking honoraria from and is member of advisory boards of  
47 Novo Nordisk. SA and BK have no disclosures to make for this review.  
48  
49  
50  
51  
52  
53  
54  
55

Deleted: 107

Deleted: 4985

**Word Count:** Summary: [127](#) (250); main text: [4853](#) (excluding references, figures, and table). Figures: 1) PK/PD general figure; 2 and 3) Clamp figures; 4 and 5) PD figure (GIR curves) of different insulins. Table: 1.

### Review Criteria:

Information was gathered from literature published on PubMed (until 31 Oct 2009) on the topics of type 2 diabetes and insulin therapy, including basal insulin analogues, glucose clamps, pharmacokinetics, and pharmacodynamics.

### Message for the Clinic:

For insulin therapy, pharmacodynamic assessments have more clinical relevance than pharmacokinetic assessments. The glucose-clamp technique is the gold standard method to determine insulin PD and provides valuable information with respect to onset, peak, and duration of action. Glucose-clamp studies and clinical trials both demonstrate that once-daily administration of insulin glargine and insulin detemir provide effective blood glucose control and reduce risk of hypoglycaemic excursions relative to NPH insulin. [Apart from a theoretical understanding of insulin PD, appropriate education and training of both patient and health care worker are essential prerequisites to successful everyday insulin supplementation.](#)

**Abstract**

This pedagogical review illustrates the differences between pharmacokinetic (PK) and pharmacodynamic (PD) measures, using insulin therapy as the primary example. The main conclusion is that PD parameters are of greater clinical significance for insulin therapy than PK parameters. The glucose-clamp technique, the optimal method for determining insulin PD, is explained so that the reader can understand important studies in the literature. Key glucose-clamp studies that compare two basal insulin analogues—insulin glargine and insulin detemir—to NPH insulin and to each other are then presented. The review further explains how PD parameters have been translated into useful clinical concepts and simple titration algorithms for everyday clinical practice. Finally, the necessity of overcoming patient and/or physician barriers to insulin therapy and providing continuing education and training is emphasized.

Deleted: Finally, t

## Introduction

Endogenous insulin secretion, which is tightly regulated in healthy people to maintain euglycaemic plasma glucose levels between 4 and 6 mmol/L, consists of a rather constant, although still pulsatile, basal insulin secretion pattern complemented by markedly increased prandial insulin secretion. The latter depends on individual need and is highly variable in terms of quantity and duration (1). The main role of basal insulin is to limit lipolysis and hepatic glucose production in the fasting state, especially during the night, while ensuring sufficient glucose for cerebral function. The primary task of prandial insulin is to suppress hepatic glucose production and stimulate utilization of glucose by muscle, thus preventing hyperglycaemia after meals (2).

Numerous efforts have been undertaken by pharmaceutical companies to develop insulin formulations that closely mimic the kinetics of this complex endogenous insulin secretion pattern. Consequently, a variety of insulin analogues are now available for clinical use, including rapid-acting insulin analogues that can be administered before or during meals for prandial control (regular human insulin, insulin lispro, insulin aspart, and insulin glulisine), long-acting insulin analogs that can be administered once- or twice-daily for basal insulin supply (NPH insulin, insulin glargine, and insulin detemir), and insulin premixes that contain both basal and prandial insulins in a single injection (3). None of the analogue pre-mixes contain NPH.

This pedagogical review describes several key principles of pharmacokinetics (PK) and pharmacodynamics (PD) used in diabetes research. It further describes how these principles can be translated into clinical diabetology. The content has a particular focus on basal insulins for type 2 diabetes, but the concepts are generally applicable for many therapeutics. Our goal has been to address common questions on insulin pharmacology that arise frequently in discussions with general practitioners.

### Question 1: What is the pharmacology of endogenous insulin?

Insulin is secreted from pancreatic  $\beta$ -cells located in the islets of Langerhans and enters the circulation primarily in response to a rise in blood glucose. Apart from stimulating peripheral glucose utilisation in the main insulin-dependent tissues, i.e., skeletal muscles and adipose tissue, insulin antagonizes the effect of glucagon in the liver by inhibiting glucose and ketone body production. In addition, due to the anatomy of the blood circulation within the Langerhans islets, insulin directly inhibits glucagon secretion from neighbouring pancreatic  $\alpha$ -cells independently of blood glucose. In healthy non-obese adults, insulin is secreted at a basal rate of 0.5–1U/h (4), resulting in plasma concentrations of 5–15  $\mu$ U/mL in fasting conditions (5). Within 30 to 60 minutes of a meal, insulin levels rapidly increase to peak concentrations of 60–80  $\mu$ U/mL and return to baseline 2 to 4 hours later (5). In general, obese subjects show much higher basal and postprandial levels.

**Deleted:** ¶  
After secretion, the estimated biological half-life of insulin in the blood stream lies between 3 to 10 minutes. This value, however, is irrelevant for injections of commercial insulins because, as the circulating hormone is cleared from the blood, fresh insulin is continuously released from the subcutaneous depot produced by the injection. Consequently, at any time, the overall level of insulin in circulation depends on two different rates, the rate of insulin clearance from the blood stream, and the rate of insulin absorption from the subcutaneous depot. For commercial preparations, insulin levels in blood are driven primarily by the absorption rate from the depot, which lasts several hours for all insulin formulations available. As a result of these considerations, the elimination half-life (i.e., when serum insulin levels have decreased by 50% from their peak values) is a more clinically relevant parameter than the biological half-life, as the former factors in both the clearance and the absorption rates. ¶

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Once released from  $\beta$ -cells or a subcutaneous depot, insulin clearance appears to be a rather complex process. The liver and kidney are the main sites of insulin degradation, but insulin clearance is probably also mediated by insulin receptor dynamics and depends highly on insulin concentration (6).

**Key message for clinical practice:** In non-diabetic persons, insulin secretion and clearance are under complex regulatory pathways that respond exquisitely to metabolic conditions. Consequently, insulin replacement therapy in the setting of insulin resistance (type 2 diabetes) or insulin absence (type 1 diabetes) presents a daunting challenge for clinicians and patients.

**Deleted:** There is a difference between the biological half-life (minutes) and the elimination half-life (hours) of commercial insulins. The latter parameter is the important one with respect to insulin treatment.

**Question 2:** What are the limitations of PK parameters relative to PD parameters for understanding therapeutic insulins?

**Deleted:** key measures in clinical pharmacology

In general, PK may be regarded as what the body does to a drug, and PD as what a drug does to the body. PK comprises the relationship between drug input—which includes adjustable factors like dose, dosage form, frequency, and route of administration—and the concentration achieved with time. PD, in contrast, comprises the relationship between drug concentration and both the intended and adverse effects produced with time (7). A simplified PK/PD scheme is shown in Figure 1.

The pharmacodynamics of a drug, i.e., the duration of its biological effects after administration, are the product of numerous target interactions and/or

1  
2  
3 downstream signalling events that occur in multiple cells and organs in  
4 response to the drug. The kinetics of these events occur over an extended  
5 time frame relative to that of drug availability. In the specific case of  
6 insulins, the temporal separation between the PK and PD profiles (Figure  
7 2) is the result of a series of insulin-specific phenomena, including the  
8 fraction and rate of absorption from subcutaneous tissue, the rate of  
9 binding to insulin receptors, and subsequent induction of metabolic  
10 processes, including elimination. Pharmacological profiles of different  
11 insulin preparations can only be understood when these PD effects are  
12 taken into account. This is especially true when considering the long-  
13 acting basal insulins (8).

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27 One PK term in particular, “half-life,” often presents significant  
28 misunderstandings when considered in relation to insulins. The elimination  
29 half-life ( $t_{1/2}$ ) is defined as the time necessary for the plasma  
30 concentration, as well as the amount of the drug in the body, to fall by one  
31 half after the distribution phase has ended and the elimination phase has  
32 begun (Figure 2). Thus, it always takes at least 4 elimination half-lives  
33 from the time of peak plasma concentration for a drug to be nearly  
34 completely eliminated from the body (50% + 25% + 12.5% + 6.25% =  
35 93.75%). It is important to know the elimination half-life of a drug when  
36 designing or prescribing a drug in order to evaluate its potential for  
37 accumulation.  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

**Deleted:** The systemic exposure-time profile of a drug is a function of the rate and extent of drug input, distribution, and elimination. The highest concentration is called the maximum concentration ( $C_{max}$ ), or maximum systemic exposure. The time of its occurrence is called time of maximum concentration ( $t_{max}$ ), or time of maximum exposure. Both depend on how fast the drug enters and is eliminated from the body. The area under the concentration-time curve over all time (AUC) is a measure of the total systemic exposure (7). ¶  
s described in the previous section, a

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

After secretion from the pancreas, the estimated biological half-life of insulin in the blood stream lies between 3 to 10 minutes. This value, however, is irrelevant for insulin injections in diabetic patients because, as the circulating hormone is cleared from the blood, fresh insulin is continuously released from the subcutaneous depot produced by the injection. For commercial preparations, insulin levels in blood are driven primarily by the more prolonged absorption rate from the depot, which lasts several hours for all insulin formulations available. As a result, the elimination half-life is a more clinically relevant parameter than the biological half-life.

These considerations also resolve what some clinicians may mistakenly view as a paradox regarding long-acting insulins, i.e., that they have elimination half-lives (often denoted in this context as “terminal half-lives”) of only 5 to 7 hours, and yet are recommended to be dosed once-daily. The key consideration here is that the elimination half-life only applies after the drug has been fully distributed. Because of the slow absorption of these agents, the distribution phase can last for many hours. In the case of insulin detemir, for instance, the distribution phase in adults lasts approximately 8 hours (9). The remaining 16 hours in the 24-hour period is covered by 2 to 3 elimination half-lives. Given the temporal delay for PD effects (Figure 2), insulin levels remain high enough across a 24-hour period to support once-daily administration.

**Deleted: ¶**

¶

**Key message for clinical practice:** There are important differences between PK and PD. PK parameters, including  $C_{max}$ ,  $t_{max}$ , AUC, and  $t_{1/2}$ , are primarily of theoretical interest. PD parameters, such as a drug's onset of pharmacologic action, maximum effect, and duration of action, significantly differ from the above-mentioned PK parameters.¶

¶

**Question 3: What are the limitations of measuring insulin PK?¶**

Focussing exclusively on the PK properties of insulin preparations would ignore the temporal shift that separates the rise and fall of the insulin concentration in blood and the rise and fall of its metabolic, i.e., blood glucose-lowering, action. The temporal separation between the PK and PD profiles is the result of a series of insulin-specific phenomena, including the fraction and rate of absorption from subcutaneous tissue, the rate of binding to insulin receptors, and subsequent induction of metabolic processes, including elimination. Pharmacological profiles of different insulin preparations can only be understood in light of these distinct parallel steps. This is especially true when considering the long-acting basal insulins. (8).¶

1  
2  
3 | Finally, another technical issue concerning insulin PK is the lack of  
4  
5  
6  
7  
8  
9 | assays are available for NPH insulin and insulin detemir (10), but for  
10  
11 | insulin glargine, neither commercial assays nor optimal alternative  
12  
13 | methods are available (11). Consequently, PK parameters published for  
14  
15 | insulin glargine are based on indirect measures and may, therefore, be  
16  
17 | less precise.

Deleted: 9

Deleted: 0

20  
21 | **Key message for clinical practice:** PK parameters are primarily of  
22  
23 | theoretical interest, while PD parameters are of more immediate practical  
24  
25 | interest. In particular, conclusions drawn from absolute values of serum  
26  
27 | insulin concentrations (PK parameter) are limited: they have little  
28  
29 | relevance for understanding the PD properties of the respective insulin  
30  
31 | and cannot be directly compared to each other. On the other hand,  
32  
33 | duration of action (PD parameter) is critical in determining dosing  
34  
35 | regimens for insulin, as it measures the period over which the drug exerts  
36  
37 | its biological effects.

Deleted: Again, PD is decisive in the case of insulin.

38  
39  
40  
41 | **Question 3: What is the best method to investigate insulin PD?**

Deleted: 4

42  
43 | The following challenges have to be borne in mind when assessing PD  
44  
45 | measurements of insulins, or other blood-glucose lowering agents, in  
46  
47 | human subjects. First, the initial/basal blood glucose level prior to  
48  
49 | administration of insulin is of importance, since the lower the blood  
50  
51 | glucose the higher the insulin sensitivity and *vice versa*. Second, there is a

Deleted: As described above, PD profiles are closely correlated to the course of the insulin concentration in blood, but occur with a certain delay.

1  
2  
3 high inter- and intra-individual variability with respect to both the effects of  
4 intake of a specific amount of carbohydrates and a given dose of insulin  
5  
6 (this necessarily imposes limitations on oral glucose tolerance and  
7  
8 standard meal tests, as well). Third, hypoglycaemia and consequent  
9  
10 counter-regulation following an insulin injection limits experiments in  
11  
12 healthy volunteers.  
13

14  
15  
16 The solution to the first challenge is to induce and maintain a fixed initial  
17  
18 blood glucose level in study subjects so that they have comparable  
19  
20 metabolic situations and insulin sensitivities at the beginning of the study.  
21  
22 The solution to the second is to ensure that subjects fast during the  
23  
24 investigational period to avoid problems related to food intake. Finally, the  
25  
26 solution to the third is to infuse glucose into patients who have just  
27  
28 received exogenous insulin in order to prevent hypoglycaemia and  
29  
30 counterregulation. This is the approach taken in glucose-clamp  
31  
32 experiments.  
33

Deleted: studies

34  
35  
36 The glucose-clamp technique is the gold standard method for investigating  
37  
38 PD profiles of insulin preparations (12). In clamp studies, insulin is injected  
39  
40 into subjects, and the subsequent PD effects are investigated by  
41  
42 preventing the expected decrease in blood glucose concentration with a  
43  
44 variable glucose infusion that “clamps” the blood glucose to a  
45  
46 predetermined level. A plot of the amount of glucose infused over time,  
47  
48 expressed as glucose infusion rate (GIR) in mg/kg/min necessary to  
49  
50 maintain blood glucose at the clamp level, accurately reflects the PD effect  
51  
52  
53  
54  
55

Deleted: 1

1  
2  
3 of the study insulin (13). Figure 2 shows the PK (serum insulin  
4 concentration) and PD (GIR) profiles of a soluble insulin during a  
5 euglycaemic glucose-clamp. Note the temporal shift between the PK and  
6 PD curves.  
7  
8  
9

Deleted: 2

10  
11  
12 A number of parameters of interest can be derived from PD profiles  
13 (Figure 3). These include the AUC, i.e., the overall glucose lowering  
14 effect/glucose disposal, and  $GIR_{max}$  and  $t_{max}$ , i.e., the magnitude and time  
15 of peak effect, respectively. Also relevant to patients are the time to 50%  
16 of maximum effect (early  $t_{50\%}$ ), i.e., the onset of action of the respective  
17 insulin, and the time when the maximum effect has fallen again by 50%  
18 (late  $t_{50\%}$ ), i.e., the vanishing effect/end of action. For basal insulins,  
19 important parameters include: duration of action, i.e., the time period  
20 between insulin injection and end of action; and the end of action, i.e., the  
21 time from injection of the study insulin to an increase in serum glucose  
22 concentration above a predetermined value (often 8.3 mmol/L) (13). The  
23 duration of action can only be measured reliably in people with type 1  
24 diabetes. In such patients, a declining metabolic effect of the study insulin  
25 causes an immediate rise in blood glucose. By contrast, in healthy people  
26 or patients with type 2 diabetes, duration of action can be overestimated  
27 due to endogenous insulin secretion. Duration of action is of relevance in  
28 patients who are deciding whether to inject basal insulin once- or twice-  
29 daily.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

Deleted: For short-acting insulins, the onset of insulin action determines whether or not to keep a time interval between the insulin injection and the meal.

Deleted: other

Deleted: 2

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Glucose clamps can be performed “manually” or, more accurately, by an automated procedure using a Biostator (MTB Medizintechnik, Ulm, Germany), which measures the arterialed blood glucose concentration every minute and adjusts the GIR according to a negative feedback algorithm based on the deviations of the glucose measurements from the clamp glucose target level (8).

**Deleted:** . In manual clamps, arterialed plasma glucose is measured at intervals of several minutes, and the investigator continually adjusts the GIR to maintain the clamp glucose target level. The Biostator, in contrast

**Key message for clinical practice:** The glucose-clamp technique is the gold standard method for describing insulin PD. Parameters derived from the glucose infusion rate curve provide valuable information for addressing whether to keep an interval between insulin injection and a meal, or whether to inject a basal insulin once- or twice-daily. An understanding of PD thus helps to optimize insulin therapy.

**Question 4:** What should the “ideal” basal insulin look like and how do current products compare?

**Deleted:** 5

From a pharmacological point of view, key characteristics of an “ideal” basal insulin should include:

**Deleted:** As this review focuses on basal insulins, it is of interest to describe key characteristics of an “ideal” basal insulin f

- The PD profile should be flat (peakless) and should be associated with a low risk of hypoglycaemia (which might be caused by nocturnal peak activity several hours after injection).
- The duration of action should be around 24 hours in order to control fasting plasma glucose (FPG) with just one injection per day.

- Variability within individual patients should be low, meaning that identical doses of insulin administered to the same patient on different occasions should lead to identical and predictable effects, thus lowering the risk of hypoglycaemia or hyperglycaemia.

The next sections describe current basal insulin preparations in terms of these ideal characteristics.

### NPH insulin

NPH (Neutral Protamine Hagedorn), introduced by Hagedorn in 1946, contains protamine and insulin in “isophane” amount, i.e., there is neither an excess of protamine nor of insulin. The addition of zinc at low concentrations allows the protamine to form crystals with insulin at neutral pH. NPH insulin is a suspension and must be properly re-suspended before injection, which may contribute to increased variability when not done carefully (14). A representative glucose-clamp study (15) described the PK and PD of NPH insulin, and highlighted its limitations; a short duration of action ( $14 \pm 3$  hours), a significant peak at  $4.5 \pm 0.5$  hours, and a high inter-individual variability.

Deleted: 3

Deleted: 4

Deleted: comparing

Deleted: insulin glargine with

Deleted: , ultralente, and continuous subcutaneous infusion of insulin lispro in 20 subjects with type 1 diabetes

Deleted: the

Deleted: of NPH insulin

Deleted: too

Deleted: greater

Deleted: compared with insulin glargine

### Insulin glargine

In 2000, insulin glargine became the first basal insulin analogue available.

Insulin glargine differs from human insulin at position A21 of the A chain (substitution of asparagine with glycine) and position B31 and B32 of the B

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

chain (addition of two arginines). These changes shift the isoelectric point from pH 5.4 to 6.7 (16). Insulin glargine is injected as a clear acidic solution (pH 4), which forms microprecipitates that must dissolve before absorption can take place. Precipitation and slow re-dissolution are inherently associated with substantial variability. Nonetheless, the time-action profile of insulin glargine is flatter and of longer duration compared to NPH insulin (15).

Deleted: 5

Deleted: 4

Deleted: , as will be shown from clinical study results described below

### Insulin detemir

Insulin detemir differs from human insulin in that threonine at position B30 has been removed and that lysine at B29 has been acylated with a 14-carbon fatty acid (myristic acid). The prolonged duration of action for insulin detemir is attributable to a combination of increased self-association (hexamer stabilization and hexamer-hexamer interaction) and albumin binding due to the acylation. Insulin detemir is highly albumin-bound (98.8%) in the interstitial fluid and in plasma (17). The analogue is supplied as a clear neutral solution and remains in solution in the subcutaneous depot, in the circulation, and in the target tissues until interaction with the insulin receptor. Absorption of insulin detemir is therefore dependent on neither appropriate re-suspension before injection and dissolution of crystals, as is the case with NPH insulin, nor on formation and re-dissolution of microprecipitates, as is the case for insulin glargine. Insulin detemir has a much flatter and longer time-action profile compared with NPH insulin (13), as well as reduced variability compared to insulin glargine (13).

Deleted: 6

Deleted: Clinical study data presented below show that i

Deleted: 2

Deleted: 2

**Key message for clinical practice:** Insulin glargine and insulin detemir differ from NPH insulin both in structure and in their mechanisms of protracted activity. Both analogues have time-action profiles that are flatter and of longer duration of action than NPH insulin.

**Question 5: What are the results from PD glucose-clamp studies with basal insulin analogues?**

The information of most clinical relevance for basal insulins involves the critical issues of flatness, duration of action, and variability. For flatness and duration of action, one needs to look at the GIR curves from a number of published glucose-clamp studies (15,18-22), which have been summarized in a recent review (13). For insulin glargine, all available studies, with one exception (15), showed a very gentle rise and fall over time, indicating a relatively flat activity profile with some evidence of a very broad, albeit small, peak. Mean duration of action was close to 24 hours in patients with type 1 diabetes and at least 24 hours in people with type 2 diabetes around the clinically relevant dose range of 0.4 U/kg. The same conclusions—a much flatter profile than NPH insulin and duration of action of around 24 hours—were consistently proven for insulin detemir by all studies, apart from one outlier (22).

A recent glucose-clamp study (23) compared duration of action of insulin glargine and insulin detemir after single and repetitive doses (administration over 7 days) in subjects with type 1 diabetes. Both basal

Deleted: 6

Deleted: 4

Deleted: 7

Deleted: 1

Deleted: 2

Deleted: 4

Deleted: 1

Deleted: published in abstract form

Deleted: 2

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

insulins had durations of action approximating 24 hours, although the duration of action after a single dose was shorter for insulin glargine than insulin detemir ( $19.8 \pm 14.4$  hours versus  $25.9 \pm 4.6$  hours, respectively), whereas the durations of action after repetitive doses were  $23.3 \pm 4.9$  hours for insulin detemir and  $27.1 \pm 7.7$  hours for insulin glargine. In addition, two other clamp studies in type 1 (21) and type 2 diabetes (20) showed that duration of action of basal insulin analogues was dose-dependent, i.e., that higher doses resulted in longer durations of action, as is observed for all insulins and, indeed, for all pharmaceuticals.

Deleted: 0

Deleted: 19

Deleted: Thus, the highest doses used in the trials (1.6 U/kg [20] and 1.4 U/kg [19]) caused the longest duration of action.

Deleted:

Deleted: This dose-dependency was also demonstrated for short-acting insulin analogues (23) and seems to reflect a slower rate of absorption of subcutaneous insulin preparations at higher doses (24).

“Within-subject variability” is defined as the degree of difference in the glucose-lowering effect from one injection to another within the same patient. For basal insulin analogues, this relates to the consistency of the 24-hour PD profile from one injection to the next, which can only be assessed in repeat clamp studies. Such a study (19) was performed in subjects with type 1 diabetes who underwent 24-hour glucose-clamp analyses with insulin detemir (n=18), insulin glargine (n=16), or NPH insulin (n=17). Each subject received four single subcutaneous doses of each basal insulin on four different clamp days; all insulins were administered at the same dose (0.4 U/kg). Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine. The coefficients of variation for the PD endpoint  $GIR-AUC_{(0-24\ h)}$  were 27% for insulin detemir, 48% for insulin glargine, and 68% for NPH insulin. Lower within-subject variability for insulin detemir was also confirmed in patients with type 2 diabetes in another clamp study

Deleted: 8

Deleted: 19

(20), although the latter study had the limitation that no replicate experiments with identical doses were conducted, so the results had to be dose-corrected to investigate variability.

**Key message for clinical practice:** Glucose-clamp studies have compared the PK and PD of insulin glargine, insulin detemir, and NPH insulin. The results, apart from one outlier, are consistent: both basal insulin analogues exhibit flatter time-action profiles and longer durations of action (around 24 hours) than NPH insulin. Insulin detemir, in addition, shows less variability compared to both NPH insulin and insulin glargine.

Deleted: 7

**Question 6: How do phase 1 and 2 glucose-clamp studies predict clinical outcome data?**

Ideally, results from glucose-clamp studies on basal insulin analogues should be applicable in the clinic when one wants to determine the optimal balance between metabolic control and hypoglycaemia. A basal insulin analogue, when compared to NPH insulin, should result in: comparable metabolic control with less hypoglycaemic episodes; improved metabolic control with comparable hypoglycaemic events; or, in the best case scenario, improvement in both. Does this actually hold true in phase 3 trials?

Deleted: Specifically, if dosed correctly, a

Deleted: that exhibits a flat time-action profile, a duration of action of about 24 hours, and low within-subject variability should enable once-daily dosing and,

Deleted: A number of large-scale clinical studies with both insulin glargine and detemir have been published in the last years that examine their efficacy and safety.

### Insulin glargine versus NPH insulin

In a number of clinical trials, patients with type 2 diabetes exhibited comparable HbA<sub>1c</sub> reductions (24-27) and rates of achieving target HbA<sub>1c</sub>

Deleted: 3

Deleted: 6

Deleted: 25-28

goals ( $\leq 7.0\%$ ) (24,27) when administered insulin glargine or NPH insulin. Moreover, there was a consistent and significant reduction of hypoglycaemia risk with insulin glargine compared to NPH insulin for both overall symptomatic (11%,  $p=0.0006$ ) and nocturnal (26%,  $p<0.0001$ ) hypoglycaemic events (24,28). In one meta-analysis (24), risks of overall severe and severe nocturnal hypoglycaemia were reduced by 46% ( $p=0.0442$ ) and 59% ( $p=0.0231$ ), respectively, although another (25) did not find significant differences in confirmed or severe episodes. One study (27) showed a lower rate of hypoglycaemic excursions and less variability of FPG in subjects taking insulin glargine compared to NPH insulin.

- Deleted: 3
- Deleted: 6
- Deleted: 25,28
- Deleted: 3
- Deleted: 7
- Deleted: 25,29
- Deleted: 3
- Deleted: 25
- Deleted: 4
- Deleted: 26
- Deleted: 6
- Deleted: 28

### Insulin detemir versus NPH insulin

Large randomised clinical trials comparing insulin detemir and NPH insulin have demonstrated that glycaemic control with insulin detemir was similar to, or better than, NPH insulin (29,30). Use of insulin detemir was associated with a significant reduction in the risk of nocturnal hypoglycaemia in the majority of studies (31-37) (up to 87 or 90% risk reduction compared to NPH insulin [35,38]).

Insulin detemir therapy also provided more predictable glycaemic control and less intra-patient variability than NPH insulin in both type 1 and type 2 diabetes (29,32,36,38-42). In most trials (32,36,38-42), intra-patient variation in self-measured FPG was significantly lower with insulin detemir than NPH insulin. In addition, nocturnal plasma glucose profiles were more stable, with lower glucose fluctuations (32,36). Increased intra-patient

- Deleted: 8
- Deleted: 29
- Deleted: 30,31
- Deleted: 0
- Deleted: 6
- Deleted: 32-38
- Deleted: 4
- Deleted: 7
- Deleted: 36,39
- Deleted: 8
- Deleted: 1
- Deleted: 5
- Deleted: 7
- Deleted: 1
- Deleted: 30,33,37,39-43
- Deleted: 1
- Deleted: 5
- Deleted: 7
- Deleted: 1
- Deleted: 33,37,39-43
- Deleted: 1
- Deleted: 5
- Deleted: 33,37

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

variability with insulin therapy may increase the risk of hypoglycaemia, as was shown from a meta-analysis (43) and two further publications (44,45).

Deleted: 2

Deleted: 44

Deleted: 3

Deleted: 4

Deleted: 45,46

These studies showed a positive correlation between incidence of hypoglycaemia and the coefficients of variation in FPG: a reduction of 2.7% in the within-patient variation in FPG resulted in 2.77% fewer hypoglycaemic events per subject per year, independent of the type of treatment (43). Thus, a decrease in intra-patient variability, as seen with insulin detemir, is worth noting—not only from glucose-clamp study results, but also from the clinical data described above.

Deleted: 2

Deleted: 44

### Insulin glargine versus insulin detemir

Four head-to-head clinical trials comparing insulin glargine and insulin detemir have been published, including one study in type 1 diabetes (46) and three in type 2 diabetes (47,49). One 52-week treat-to-target trial evaluated both analogues in a basal-bolus regimen with mealtime insulin aspart in 319 type 2 subjects treated with oral antidiabetic drugs (OADs) or insulin, with or without OADs (47). A second 52-week study compared insulin detemir with insulin glargine administered as add-on therapy to OADs in 582 insulin-naïve subjects with type 2 diabetes (48). In both trials insulin detemir and insulin glargine were equally effective in optimizing HbA<sub>1c</sub>. The two analogues were associated with comparable hypoglycaemia risks and variabilities, but insulin detemir therapy was associated with less weight gain. Another head-to-head study (49) was a double-blind, randomized, crossover study in subjects with type 2 diabetes that included continuous glucose monitoring after careful insulin titration

Deleted: 5

Deleted: 47

Deleted: 6

Deleted: 8

Deleted: 48-50

Deleted: 6

Deleted: 48

Deleted: 7

Deleted: 49

Deleted: 8

Deleted: 50

over several days. In this study, once-daily dosing of insulin detemir provided glycaemic control similar to that of insulin glargine over a 24-hour period.

**Key message for clinical practice:** Insulin glargine and insulin detemir can be dosed once per day and provide equal (or better) metabolic control than NPH insulin. Use of the analogues is associated with a significant reduction in (primarily) nocturnal hypoglycaemic events. Insulin detemir may have an advantage over insulin glargine with respect to intra-subject variability in type 1 diabetes (46) and weight gain in type 2 diabetes (47), although the latter has to be mentioned in connection with higher insulin detemir doses being used.

Deleted: 5

Deleted: 47

Deleted: 6

Deleted: 48

**Question 7: Treatment strategies with basal insulin analogues in type 2 diabetes: what is the evidence from clinical trials?**

Deleted: 8

According to a consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (50), initiation of insulin therapy in patients with type 2 diabetes should start with either bedtime intermediate-acting or bedtime or morning long-acting insulin (10 units or 0.2 U/kg). A recent review on insulin therapy in type 2 diabetes (51) also concluded that once-daily basal insulin added to oral medication is an ideal starting point. However, all next steps, from one to two or even more daily injections, is controversial and should be considered carefully with the respective patient. An important issue is the early intensification of insulin therapy to achieve and keep target HbA<sub>1c</sub>

Deleted: 49

Deleted: 51

Deleted: 0

Deleted: 52

values. In the 3-year 4-T study (52,54) investigating complex insulin regimens in type 2 diabetes, 68 to 82% of patients received an additional type of insulin to achieve a median HbA<sub>1c</sub> level of 6.9% and, thus, needed “complex” regimens.

Deleted: 1  
 Deleted: 3  
 Deleted: 53-55  
 Deleted: , whose key data are presented below,

A recent meta-analysis on optimal insulin regimens in type 2 diabetes (55) found greater HbA<sub>1c</sub> reductions in insulin-naïve patients treated with biphasic or prandial insulin, compared to basal insulin (0.45% [p=0.0006] and 0.45% [p=0.02], respectively), but with lesser reductions of fasting glucose (0.93 mmol/L [16.8 mg/dL; p=0.01] and 2.20 mmol/L [39.7 mg/dL; p<0.00001], respectively). Moreover, minor hypoglycaemic events were inconsistently reported as either higher than or equivalent to basal insulin, and there was greater weight gain with prandial compared to basal insulin (1.86 kg, p=0.0006).

Deleted: 4  
 Deleted: 56

In the 3-year 4-T study (52,53), 708 subjects with type 2 diabetes and inadequate glycemic control on metformin and sulfonylurea were randomly assigned to receive prandial insulin aspart, basal insulin detemir, or biphasic insulin aspart. Starting in the second year, sulfonylureas were replaced by an additional insulin (basal insulin added to prandial insulin, prandial insulin three times daily added to basal insulin, and prandial insulin at lunch added to biphasic insulin) if HbA<sub>1c</sub> levels were above 6.5%. An important feature of this study was its long duration and the standardization of insulin regimens.

Deleted: Three-year results of the 4-T study investigating complex insulin regimens in type 2 diabetes were recently published (53,54), and the key data should be considered in this review as they are relevant to patient treatment.  
 Deleted: 1  
 Deleted: 2  
 Deleted: is trial,

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Less than 45% of all patients reached the HbA<sub>1c</sub> target of  $\leq 6.5\%$  (and even less than one third in the biphasic group). In addition, there were striking differences in outcomes between the first and third years. Although the basal regimen was least successful in the first year, it was effective after three years, probably due to a progressive increase of the insulin dose. The basal insulin regimen, which was equivalent to the other regimens after the first year in patients with HbA<sub>1c</sub> values of 8.5% or less, was superior to both prandial and biphasic insulin after three years in terms of weight gain and the rate of hypoglycaemia. Thus, the 4-T study supports the initiation of treatment with basal insulin.

This conclusion is in line with the concept that fasting hyperglycaemia contributes more than postprandial hyperglycemias to HbA<sub>1c</sub> levels. As shown by Monnier, the relative contribution of fasting hyperglycaemia to HbA<sub>1c</sub> levels increased gradually as diabetes worsened, whereas that of postprandial glucose excursions was predominant in relatively well controlled patients (56). Thus, it makes sense to focus on FPG during insulin initiation. Several studies investigated treatment algorithms for insulin glargine (27,57,59) and insulin detemir (60,61) (Table 1). A number of these algorithms depend on patient-managed self-titration, which has proven to be safe and efficacious.

**Key message for clinical practice:** Insulin glargine and insulin detemir are ideally suited for insulin initiation and can be effectively and safely self-titrated by patients using simple titration algorithms. When titrated appropriately, a majority of patients can achieve an HbA<sub>1c</sub> of  $<7.0\%$ . In

Deleted: 5

Deleted: 57

Deleted: —not only from a pharmacological point of view, but also from considerations of the course of the disease—

Deleted: Basal insulin preparations preferably address this issue.

Deleted: 6

Deleted: 6

Deleted: 8

Deleted: 28,58-60

Deleted: 59

Deleted: 0

Deleted: 61,62

those patients in whom hypoglycaemia is considered to be a problem, insulin dose adjustments should be followed more closely.

**Question 8: Which factors – keeping insulin PD on one’s mind – have an impact on appropriate (basal) insulin substitution in “real life”?**

Patient and/or physician barriers to insulin initiation or intensification often need to be overcome before insulin therapy can be implemented successfully (62,63). One of the key patient barriers is fear of hypoglycaemia, which can be managed by appropriate training, introduction of blood glucose self-monitoring (50,62), use of basal insulin analogues (62), and translation of PD concepts into practical clinical dosing regimens. Decisions on insulin dose adjustments should be knowledge-based. Thus, the patient should be enabled to differentiate whether a high fasting glucose value resulted from deficiency in insulin, diet violation the prior evening, or from nocturnal hypoglycaemia and counter-regulation. Training should be provided to deal with the specific situations of illness, fever and demobilisation, and unplanned exercise or extra meals. General practitioners who face time constraints or lack familiarity with tailored insulin treatment should obtain continuing education and should have a hot line to specialists for rapid consultation (63).

Deleted: 9

Deleted: First, there might be p

Deleted: (61,62)

Deleted: that

Deleted: P

Deleted: include e.g.,

Deleted: . The latter

Deleted: handled

Deleted: 49

Deleted: 1

Deleted: 1

Deleted: as outlined above

Deleted: life messages

Deleted: :

Deleted: ,

Deleted: , e.g.

Deleted: has

Deleted: lack of

Deleted: in

Deleted: S

Deleted: and measures should be trained like what to do in case

Deleted: or if there have been

Deleted: c

Deleted: ,

Deleted: get

Deleted: , e.g.

Deleted: 2

Formatted: Font: Not Bold

Deleted: Apart from

**Key message for clinical practice:** In addition to a thorough understanding of insulin PD, appropriate education, empowerment, and

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

training of both the patient and the health care worker are essential prerequisites to successful management of everyday insulin therapy.

Deleted: an

Deleted: ly

Deleted: ing

## Conclusions

Measurements of serum insulin concentrations in patients with diabetes do not add value to clinical practice. Moreover, the biological half-life of insulin is unimportant to either its efficacy or duration of action. Instead, the PD profile is far more informative than the PK profile in terms of determining dosing frequency and expectations of efficacy over a given period of time.

The optimal method for assessing PD parameters is the glucose-clamp technique. Results of studies using this technique have demonstrated that insulin glargine and insulin detemir have flatter, but not completely peakless, time-action profiles compared to NPH insulin. The basal insulin analogues also have comparable durations of action of around 24 hours, with less intra-subject variability for insulin detemir. These conclusions have been confirmed in clinical trials, which have shown that once-daily dosing of insulin glargine and insulin detemir is possible and that these two basal analogues provide equal metabolic control relative to NPH insulin in terms of HbA<sub>1c</sub>. Compared to NPH insulin, use of insulin glargine and insulin detemir is associated with less hypoglycaemic events (particularly nocturnal ones), lower FPG, and—with a slight advantage for insulin detemir—less intra-subject variability of fasting glucose. Patients

Deleted: Finally, p

1  
2 can self-titrate the two basal insulin analogues effectively and safely by  
3  
4 means of simple titration algorithms.  
5  
6

7  
8 Finally, in addition to a sufficient knowledge about insulin PD, appropriate  
9 education, empowerment and training of both the patient and the health  
10 care worker are essential to overcome potential barriers to insulin therapy,  
11 deal with specific situations, and successfully implement everyday insulin  
12 supplementation. These steps, if followed through appropriately, should  
13  
14  
15  
16  
17  
18 facilitate patient care and improve quality of life for patients with type 2  
19  
20  
21 diabetes.  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

Formatted: Justified

Deleted: i

Deleted: being considered

Deleted: ¶

**Acknowledgments**

The authors thank David Norris, PhD for editorial assistance provided during the preparation of this manuscript. This assistance was paid for through funding supplied by Novo Nordisk to Ecosse Medical Communications, LLC (Princeton, NJ).

For Peer Review Only

## References

1. 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.
2. Owens DR, Bolli GB. Beyond the era of NPH insulin – long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. *Diabetes Technol Ther* 2008; **10**: 333-349.
3. Berger M. Towards more physiological insulin therapy in the 1990s. *Diabetes Res Clin Pract* 1989; **6**: S25-31.
4. White J, Campbell R. Diabetes mellitus. In: Herfindal ET, Gourley DR, editors. *Textbook of Therapeutics: drug and disease management*. Baltimore: Williams & Wilkins; 1996: 357-386.
5. Galloway JA, Chance RE. Improving insulin therapy: achievements and challenges. *Horm Metab Res* 1994; **26**: 591-598.
6. Koschorreck M, Gilles ED. Mathematical modelling and analysis of insulin clearance in vivo. **BMC Systems Biology** 2008; **2**: 43.
7. Tozer TN, Rowland M. Opening comments. In: Klingler A. *Introduction to pharmacokinetics and pharmacodynamics*. The

1  
2  
3 quantitative basis of drug therapy. Baltimore: Lippincott Williams &  
4  
5 Wilkins; 2006: 1-12.

- 6  
7  
8  
9 8. Heinemann L. Time-action profiles of insulin preparations. Mainz:  
10  
11 Kirchheim & Co GmbH; 2004.

12  
13  
14  
15 9. [Danne T, Lüpke K, Walte K, von Scheutz W, Gall M-A. Insulin](#)  
16  
17 [detemir is characterized by a consistent pharmacokinetic profile](#)  
18  
19 [across age-groups in children, adolescents, and adults with type 1](#)  
20  
21 [diabetes. \*Diabetes Care\* 2003; \*\*26\*\*: 3087-3092\).](#)

Formatted: Bullets and Numbering

22  
23  
24  
25 10. Bott S, Tusek C, Jacobsen LV, Endahl L, Draeger E, Kapitza C, et  
26  
27 al. Insulin detemir under steady-state conditions: no accumulation  
28  
29 and constant metabolic effect over time with twice daily  
30  
31 administration in subjects with type 1 diabetes. *Diabet Med* 2006;  
32  
33 **23**: 522-528.

Formatted: Bullets and Numbering

34  
35  
36  
37 11. Owen WE, Roberts WL. Cross-reactivity of three recombinant  
38  
39 insulin analogs with five commercial insulin immunoassays. *Clin*  
40  
41 *Chem* 2004; **50**: 257-259.

Formatted: Bullets and Numbering

42  
43  
44  
45 12. Committee for Proprietary Medicinal Products (CPMP). The  
46  
47 European Agency for the Evaluation of Medicinal Products (EMA).  
48  
49 London, 30 May 2002 [cited 2009 Oct 21]. Available from:  
50  
51 <http://www.emea.europa.eu/pdfs/human/ewp/108000en.pdf>.

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

13. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal insulin analogues based on isoglycaemic clamp studies. *Diabetes Obes Metab* 2007; **9**: 648-659.

Formatted: Bullets and Numbering

14. 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.

Formatted: Bullets and Numbering

15. Lepore M, Pampanelli S, Fanelli C, Porcellatic F, Bartocci L, Di Vincenzo A, 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.

Formatted: Bullets and Numbering

16. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. *Diabetes Obes Metab* 2009; **11**: 5-19.

Formatted: Bullets and Numbering

17. Home P, Kurtzhals P. Insulin detemir: from concept to clinical experience. *Expert Opin Pharmacother* 2006; **7**: 325-343.

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

18. 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.

Formatted: Bullets and Numbering

19. Heise T, Nosek L, Biilmann Rønn B, Endahl L, Heinemann L,  
Kapitza C, 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.

Formatted: Bullets and Numbering

20. Klein O, Lyngé 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.

Formatted: Bullets and Numbering

21. Plank J, Bodenlenz M, Sinner F, Magnes C, Görzer E, Regittig W,  
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.

Formatted: Bullets and Numbering

22. Porcellati F, Rossetti P, Busciantella NR, Marzotti S, Lucidi P, Luzio  
S, et al. Comparison of pharmacokinetics and dynamics of the long-  
acting insulin analogs glargine and detemir at steady state in type 1

Formatted: Bullets and Numbering

1  
2 diabetes. A double-blind, randomized, crossover study. *Diabetes*  
3  
4 *Care* 2007; **30**: 2447-2452.  
5  
6

7  
8 23. Bock G, Wutte A, Köhler G, Korsatko S, Semlitsch B, Pieber TR.  
9

10 Pharmacodynamics and pharmacokinetics of long-acting insulin  
11 analogues detemir and glargine after 7 days of use and after its first  
12 administration in subjects with type 1 diabetes. *Diabetologia* 2008;  
13  
14 **51** (Suppl 1): S390.  
15  
16  
17

Formatted: Bullets and Numbering

18  
19  
20  
21 24. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z,  
22

23 Salzman A. Reduced hypoglycaemia risk with insulin glargine.  
24  
25 *Diabetes Care* 2005; **28**: 950-955.  
26  
27

Deleted: <#>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.¶  
¶  
<#>Lauritzen T. Pharmacokinetic and clinical aspects of intensified subcutaneous insulin therapy. *Dan Med Bull* 1985; **32**: 104-118.¶  
¶

Formatted: Bullets and Numbering

28  
29 25. Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V.  
30

31 Safety and efficacy of glargine compared with NPH insulin for the  
32 treatment of type 2 diabetes: a meta-analysis of randomized  
33 controlled trials. *Diabet Med* 2008; **25**: 924-932.  
34  
35  
36  
37

Formatted: Bullets and Numbering

38  
39 26. Goykhman S, Drincic A, Desmangles JC, Rendell M. Insulin  
40

41 glargine: a review 8 years after its introduction. *Expert Opin*  
42  
43 *Pharmacother* 2009; **10**: 705-718.  
44  
45

Formatted: Bullets and Numbering

46  
47  
48 27. Riddle MC, Rosenstock R, Gerich J on behalf of the Insulin  
49

50 Glargine 4002 Study Investigators. The treat-to-target trial:  
51  
52  
53  
54  
55

Formatted: Bullets and Numbering

1  
2 randomized addition of glargine or NPH insulin to oral therapy of  
3  
4 type 2 diabetic patients. *Diabetes Care* 2003; **26**: 3080-3086.  
5  
6

7  
8  
9 **28.** Yki-Järvinen H, Dressler A, Ziemer M, The HOE 901/3002 Study  
10 Group. Less nocturnal hypoglycaemia and better post-dinner  
11 glucose control with bedtime insulin glargine compared with  
12 bedtime NPH insulin during insulin combination therapy in type 2  
13 diabetes. *Diabetes Care* 2000; **23**: 1130-1136.  
14  
15  
16  
17  
18

Formatted: Bullets and Numbering

19  
20  
21 **29.** Morales J. Defining the role of insulin detemir in basal insulin  
22 therapy. *Drugs* 2007; **67**: 2557-2584.  
23  
24  
25

Formatted: Bullets and Numbering

26  
27 **30.** Philis-Tsimikas A. An update on the use of insulin detemir, with a  
28 focus on type 2 diabetes (drug evaluation update). *Expert Opin*  
29 *Pharmacother* 2008; **9**: 2181-2195.  
30  
31  
32

Formatted: Bullets and Numbering

33  
34  
35 **31.** Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy  
36 and safety of insulin detemir compared to Neutral Protamine  
37 Hagedorn insulin in patients with type 1 diabetes using a treat-to-  
38 target basal-bolus regimen with insulin aspart at meals: a 2-year,  
39 randomized, controlled trial. *Diabet Med* 2008; **25**: 442-449.  
40  
41  
42  
43  
44

Formatted: Bullets and Numbering

45  
46  
47 **32.** Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J.  
48 Effects of QD insulin detemir or Neutral Protamine Hagedorn on  
49  
50  
51  
52  
53  
54  
55

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

blood glucose control in patients with type 1 diabetes mellitus using a basal-bolus regimen. *Clin Ther* 2004; **26**: 724-736.

**33.** Kølendorf K, Ross GP, Pavlic-Renar I, Perriello G, Philotheou A, Jendle J, 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.

Formatted: Bullets and Numbering

**34.** Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P, on behalf of the Detemir 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.

Formatted: Bullets and Numbering

**35.** Philis-Tsimikas A, Charpentier G, Clauson P, Martinez Ravn G, 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.

Formatted: Bullets and Numbering

**36.** Vague P, Selam J-L, Skeie S, De Leeuw I, Elte JWF, Haahr H, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in

Formatted: Bullets and Numbering

1  
2 patients with type 1 diabetes on a basal-bolus regimen with  
3 premeal insulin aspart. *Diabetes Care* 2003; **26**: 590-596.  
4  
5  
6  
7

8  
9 **37.** Standl E, Lang H, Roberts A. The 12-month efficacy and safety of  
10 insulin detemir and NPH insulin in basal-bolus therapy for the  
11 treatment of type 1 diabetes. *Diabetes Technol Ther* 2004; **6**: 579-  
12 588.  
13  
14  
15  
16

Formatted: Bullets and Numbering

17  
18  
19 **38.** Haak T, Tiengo A, Draeger E, Suntu M, Waldhäusl W. Lower  
20 within-subject variability of fasting blood glucose and reduced  
21 weight gain with insulin detemir compared to NPH insulin in patients  
22 with type 2 diabetes. *Diabetes Obes Metab* 2005; **7**: 56-64.  
23  
24  
25  
26  
27

Formatted: Bullets and Numbering

28  
29 **39.** Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lüddecke  
30 H-J. Insulin detemir improves glycaemic control with less  
31 hypoglycaemia and no weight gain in patients with type 2 diabetes  
32 who were insulin naïve or treated with NPH or insulin glargine:  
33 clinical practice experience from a German subgroup of the  
34 PREDICTIVE study. *Diabetes Obes Metab* 2007; **9**: 418-427.  
35  
36  
37  
38  
39  
40  
41

Formatted: Bullets and Numbering

42  
43 **40.** Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three  
44 multiple injection regimens for type 1 diabetes: morning plus dinner  
45 or bedtime administration of insulin detemir vs. morning plus  
46 bedtime NPH insulin. *Diabet Med* 2005; **22**: 850-857.  
47  
48  
49  
50  
51  
52  
53  
54  
55

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

[41.](#) Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg J-E, Abrams P, et al., on behalf of the Study To Evaluate The Administration Of Detemir Insulin Efficacy, Safety and Suitability (Steadiness) Study Group. 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.

Formatted: Bullets and Numbering

[42.](#) Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall M-A. 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.

Formatted: Bullets and Numbering

[43.](#) Heller S, Kim H, Draeger E. Within-person variation in fasting blood glucose is correlated to incidence of hypoglycaemia in people with type 1 diabetes treated with insulin detemir and NPH insulin [abstract]. *Diabetologia* 2004; **47** Suppl 1: A303.

Formatted: Bullets and Numbering

[44.](#) Gin H, Hanaire-Broutin H. Reproducibility and variability in the action of injected insulin. *Diabetes Metab* 2005; **31**: 7-13.

Formatted: Bullets and Numbering

[45.](#) Guerci B, Sauvanet JP. Subcutaneous insulin: pharmacokinetic variability and glycemic variability. *Diabetes Metab* 2005, **31**: 4S7-4S24.

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

46. Pieber TR, Treichel H-C, Hompesch B, Philotheou A, Mordhorst L, Gall M-A, et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. *Diabet Med* 2007; **24**: 635-642.

Formatted: Bullets and Numbering

47. Hollander P, Cooper J, Bregnhøj J, Bang Pedersen C. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther* 2008; **30**: 1976-1987.

Formatted: Bullets and Numbering

48. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008; **51**: 408-416.

Formatted: Bullets and Numbering

49. King AB. Once-daily insulin detemir is comparable to once-daily insulin glargine in providing glycaemic control over 24 h in patients with type 2 diabetes: a double-blind, randomized, crossover study. *Diabetes Obes Metab* 2009; **11**: 69-71.

Formatted: Bullets and Numbering

50. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and

Formatted: Bullets and Numbering

1  
2 adjustment of therapy. A consensus statement of the American  
3  
4 Diabetes Association and the European Association for the Study of  
5  
6 Diabetes. *Diabetes Care* 2009; **32**: 193-203.  
7  
8

9  
10  
11 51. Van Avendonk MJP, Rutten GEHM. Insulin therapy in type 2  
12  
13 diabetes: what is the evidence? *Diabetes Obes Metab* 2009; **11**:  
14  
15 415-432.  
16

Formatted: Bullets and Numbering

17  
18  
19 52. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL,  
20  
21 Keenan JF, et al for the 4-T Study Group. Three-year efficacy of  
22  
23 complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;  
24  
25 361: 1736-1747.  
26

Formatted: Bullets and Numbering

27  
28  
29 53. Roden M. Optimal insulin treatment in type 2 diabetes. *N Engl J*  
30  
31 *Med* 2009; 361: 1801-1803.  
32

Formatted: Bullets and Numbering

33  
34  
35 54. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S,  
36  
37 et al, for the 4-T Study Group. Addition of biphasic, prandial, or  
38  
39 basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;  
40  
41 **357**: 1716-1730.  
42

Formatted: Bullets and Numbering

43  
44  
45 55. Lasserson DS, Glasziou P, Perera R, Holman RR, Farmer AJ.  
46  
47 Optimal insulin regimens in type 2 diabetes mellitus: systematic  
48  
49 review and meta-analyses. *Diabetologia* 2009; **52**: 1990-2000.  
50  
51

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

56. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. *Diabetes Care* 2003; **26**: 881-885.

Formatted: Bullets and Numbering

57. Barnett A. Dosing of insulin glargine in the treatment of type 2 diabetes. *Clin Ther* 2007; **29**: 987-999.

Formatted: Bullets and Numbering

58. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R, ATLANTUS Study Group. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005; **28**: 1282-1288.

Formatted: Bullets and Numbering

59. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, Vähätalo M, Virtamo H, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006; **49**: 442-451.

Formatted: Bullets and Numbering

60. Meneghini L, Koenen C, Weng W, Selam J-L. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes – results of the randomized, controlled, PREDICTIVE™ 303 study. *Diabetes Obes Metab* 2007; **9**: 902-913.

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

61. Blonde DL, Merilainen M, Karwe V, Raskin P, for the TITRATE™ Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets – the TITRATE™ study. *Diabetes Obes Metab* 2009; **11**: 623-631.

Formatted: Bullets and Numbering

62. Tibaldi J, Rakel RE. Why, when and how to initiate insulin therapy in patients with type 2 diabetes. *Int J Clin Pract* 2007; **61**: 633-644.

Formatted: Bullets and Numbering

Formatted: Font: Italic

Formatted: Font: Bold

63. Kunt T, Snoek FJ. Barriers to insulin initiation and intensification and how to overcome them. *Int J Clin Pract* 2009; **63** (Suppl. 164): 6-10.

Formatted: Bullets and Numbering

Formatted: Font: Italic

Formatted: Font: Bold

64. Rave KM, Nosek L, de la Peña A, Seger M, Ernst CS, Heinemann L, Batycky RP, Muchmore DB. Dose response of inhaled dry-powder insulin and dose equivalence to subcutaneous insulin lispro. *Diabetes Care* 2005; **28**: 2400-2405.

Formatted: Bullets and Numbering

Formatted: Font: Bold

## Figure Legends

**Figure 1.** Relationship between pharmacokinetics (PK) and pharmacodynamics (PD).

**Figure 2.** Comparison of PK (serum insulin concentrations) and PD (glucose infusion rate) over time after a single subcutaneous injection of insulin. The difference between the two curves illustrates the temporal separation between PK and PD effects.

**Figure 3.** Key PD parameters from a glucose-clamp experiment.

**Figure 4.** Glucose infusion rates in glucose-clamp experiments on rapid-acting insulins (64).

Deleted: 3

**Figure 5.** Glucose infusion rates in glucose-clamp experiments on long-acting insulins.

**Table 1.** Treatment Algorithms for Insulin Glargine and Insulin Detemir in Type 2 Diabetes

<b>Insulin glargine (GLAR)</b>			
<b>Author</b>	<b>Study/ Number of patients</b>	<b>Intervention</b>	<b>Algorithm</b>
Riddle (Diabetes Care 2003)	24-wk Treat- to-Target- Trial  n=756	GLAR or NPH once daily at bedtime	Starting dose: 10 U/day If mean FPG (mmol/L) over previous 3 days: ≥5.6-< 6.7 → 0-2 U ≥6.7-< 7.8 → 2 U ≥7.8-<10.0 → 4 U ≥10.0 → 6-8 U AND no PG < 4.0 mmol/L
Davies (Diabetes Care 2005)	AT.LANTUS  n=4961	GLAR; clinic-vs- patient- managed dose titration	Clinic-managed titration: as in Riddle study  Patient-managed titration: 2 IU↑ every 3 days, no PG < 4 mmol/L
Yki-Järvinen (Diabetologia 2006)	36-wk LANMET Trial  n=110	Bedtime GLAR vs NPH	Patient-managed titration: 2 IU↑ every 3 days, if FPG above 4.0-5.6 mmol/L, stop titration if ≥ 1 hypoglycemic event
<b>Insulin detemir (DET)</b>			
<b>Author</b>	<b>Study details</b>	<b>Intervention</b>	<b>Algorithm details</b>
Meneghini (Diabetes Obes Metab 2007)	PREDICTIVE 303 TRIAL  n=5604	DET as add- on to OAD or as replacement of pre-study insulin	Patient-managed titration: every 3 days: mean adjusted FPG (mmol/L) < 4.4 → 3U↓ 4.4-6.1 → no change > 6.1 → 3U↑  vs. Physician-managed titration: according to standard of care
Blonde (Diabetes Obes Metab 2009)	20-wk TITRATE Trial  n=244	DET once daily, insulin- naïve patients on OAD	Two FPG (mmol/L) titration targets: 1) 3.9-5.0, 2) 4.4-6.1. Titration as in PREDICTIVE

Figure 1



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

Figure 2

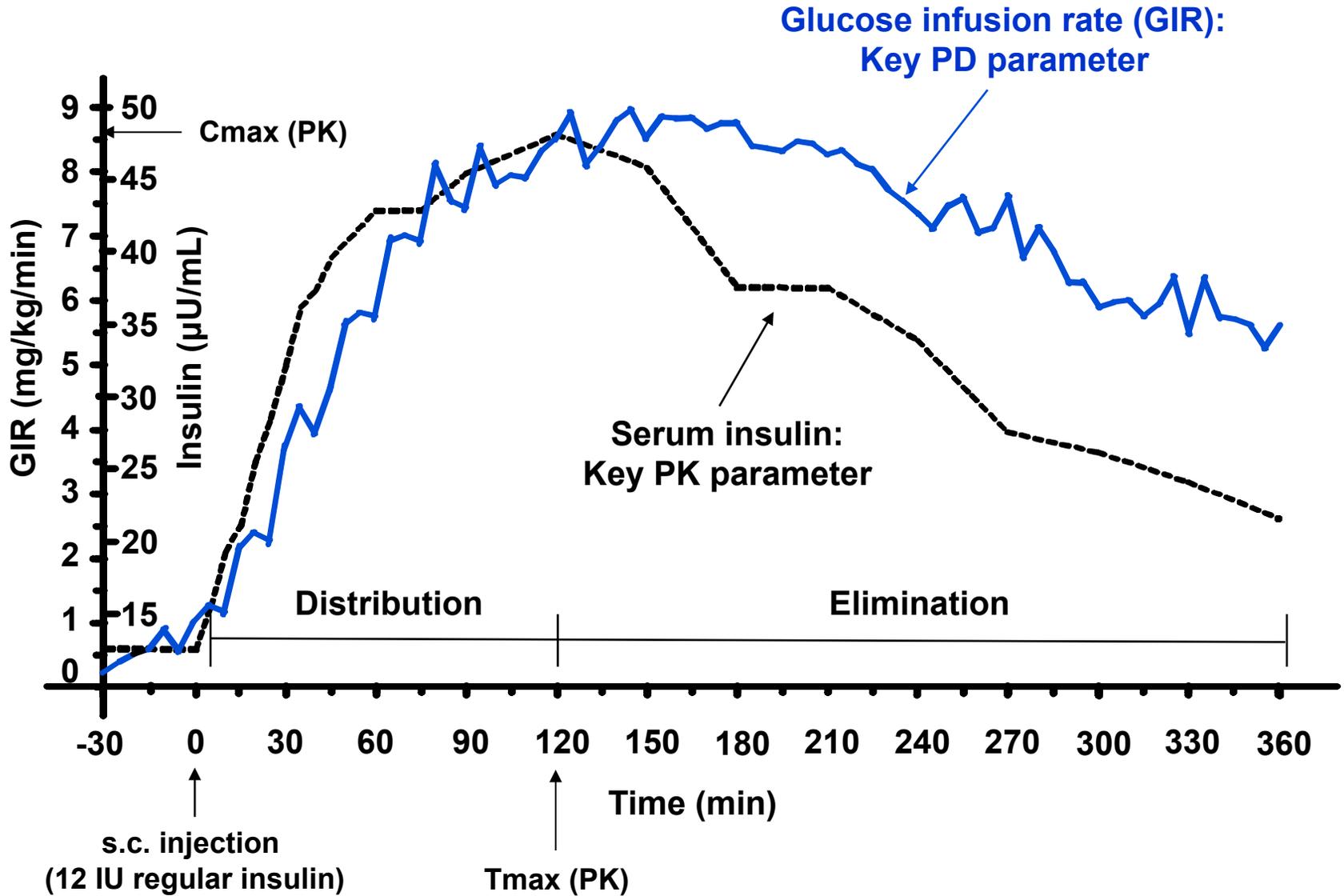


Figure 3

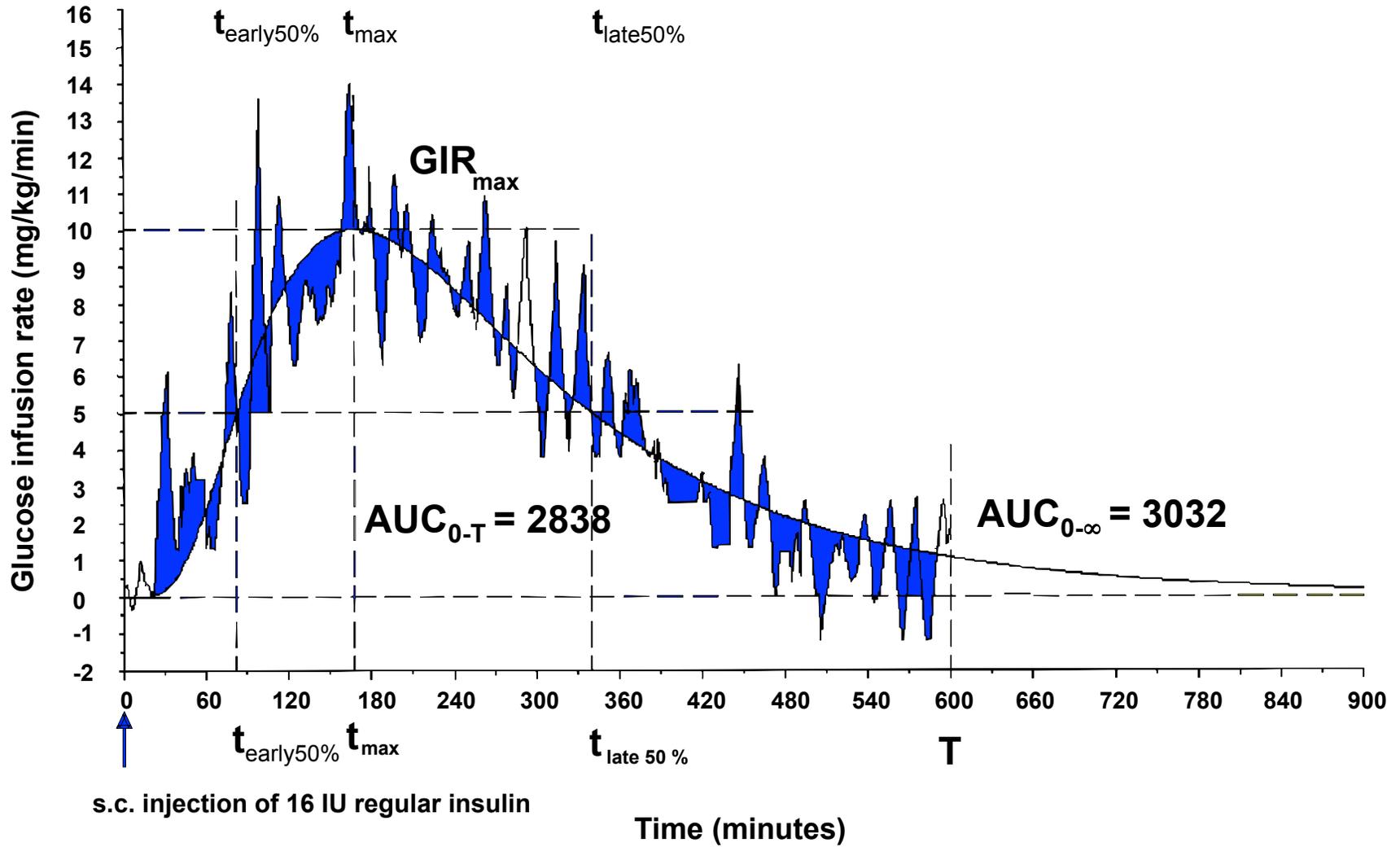


Figure 4

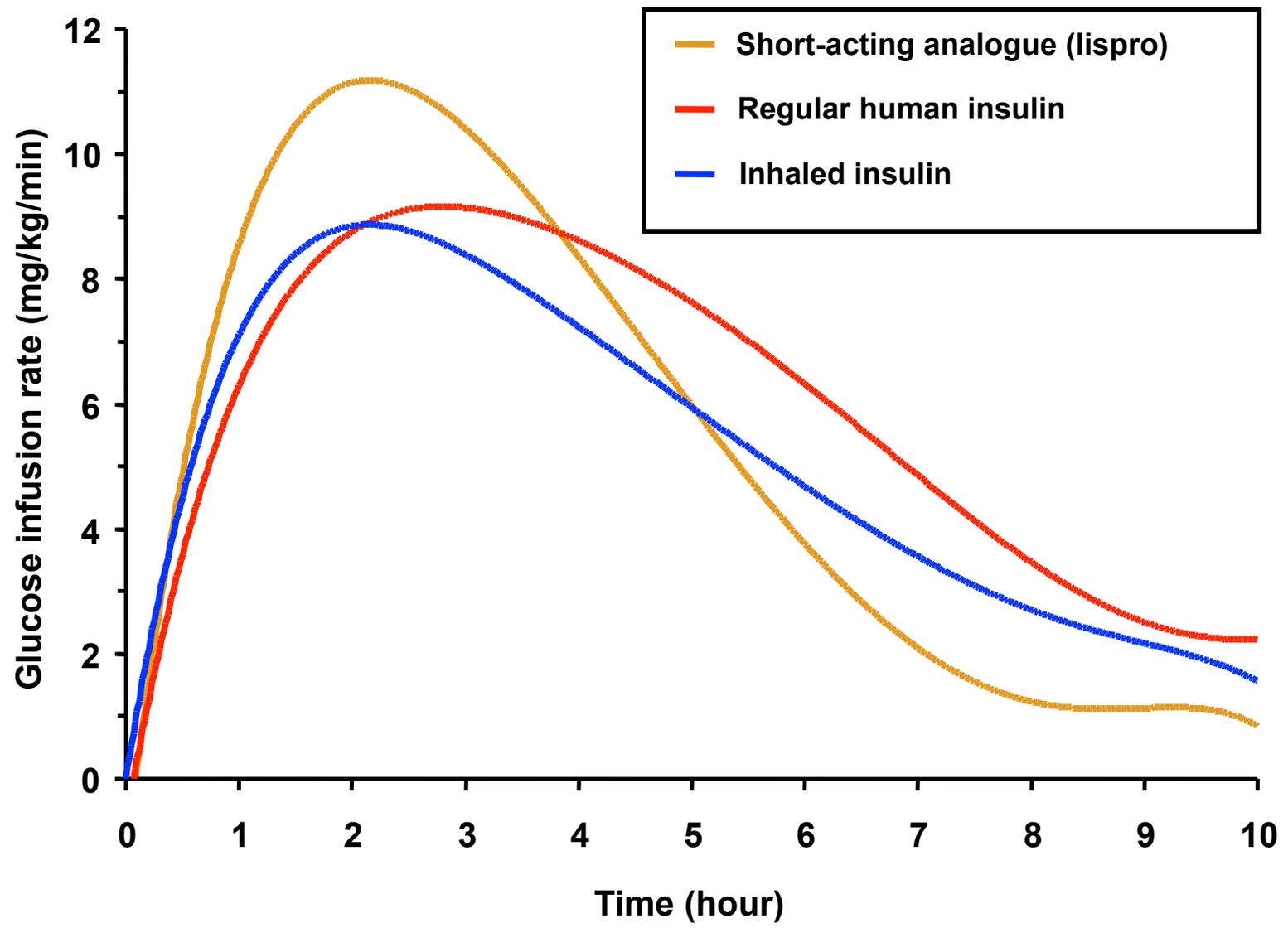


Figure 5

