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Инсулин деглудек – новый аналог инсулина сверхдлительного действия

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Достижение оптимального гликемического контроля является важным аспектом предупреждения и замедления прогрессирования ассоциированных с сахарным диабетом осложнений, а также снижения стоимости их лечения. Аналоги инсулина длительного действия гларгин и детемир, в отличие от инсулина НПХ, позволяют улучшить гликемический контроль при более низком риске гипогликемий. Однако страх развития гипогликемии и увеличения веса, а также сложность используемого режима все еще являются основными барьерами, препятствующими своевременной инициации и интенсификации инсулинотерапии. Инсулин деглудек (Тресиба®) – новый аналог инсулина сверхдлительного действия. После подкожного введения деглудек образует депо растворимых мультигексамеров, которые постепенно всасываются в кровоток, обеспечивая ровный, стабильный сахароснижающий эффект длительностью более 42 ч и низкую интра-индивидуальную вариабельность, в отличие от ныне используемых аналогов базального инсулина – инсулинов гларгин и детемир. В семи рандомизированных открытых контролируемых исследованиях 3-й фазы длительностью 26 или 52 недели, выполненных в дизайне с терапией до достижения цели (не выше), у пациентов с сахарным диабетом 1 и 2 типа инсулин деглудек обеспечил достижение такого же гликемического контроля, что и инсулин гларгин, при более низком риске ночных гипогликемий и хорошем профиле безопасности. Кроме того, исследования, изучавшие гибкий режим дозирования инсулина деглудек у пациентов с сахарным диабетом 1 типа, показали возможность изменения времени введения инсулина без ущерба для гликемического контроля и безопасности терапии.
Ключевые слова: *сахарный диабет; гликемический контроль; базальный инсулин; деглудек; гипогликемия*

Insulin degludec is a new ultra-long-acting insulin analogue

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Achieving optimal glycemic control is an important aspect of preventing and slowing the progression of diabetes-associated complications, and reducing the cost of their treatment. Long-acting insulin analogues, glargine and detemir, provide better metabolic control with reduced risk of hypoglycaemia as compared to NPH insulin. However, fear of hypoglycaemia and weight gain, as well as the complexity of regimen, are still the most important barriers to well-timed initiation and intensification of insulin therapy. Insulin degludec (Tresiba®) is a new ultra-long-acting insulin analogue. After subcutaneous injection degludec forms repository of soluble multi-hexamers, which are gradually absorbed to the bloodstream, providing a flat, stable antihyperglycemic effect lasting more than 42 h, and low intra-individual variability as opposed to currently used basal insulin analogues, insulin glargine and insulin detemir. In the seven randomized, open label, controlled phase 3 trials lasting 26 or 52 weeks, using treat-to-target (no more) non-inferiority design, insulin degludec provided glycemic control similar to that of insulin glargine with lower risk of nocturnal hypoglycaemia and good safety profile in patients with type 1 or 2 diabetes. Furthermore, trials examining a flexible dosing regimen of insulin degludec in patients with type 1 or 2 diabetes have shown that it is possible to vary the injection time without compromising glycemic control or safety of the therapy.
Key words: *diabetes mellitus, glycemic control; basal insulin; degludec; hypoglycaemia*

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Despite the large number of drugs approved for treatment of diabetes, insulin therapy still remains the most effective treatment for type 2 diabetes mellitus (T2DM) and the only pathogenetically justified and vital treatment for type 1 diabetes mellitus (T1DM) [1]. Moreover, the indications for insulin therapy in T2DM patients have recently significantly increased. According to the British prospective study UKPDS (United Kingdom Prospective Diabetes Study), 5–10% of patients with newly diagnosed T2DM require administration of insulin, and 10 years later, most patients require permanent insulin therapy to achieve and maintain the target parameters of glycaemic control [2]. The early and reasoned administration of insulin is a major contributor to long-term maintenance of the target parameters of glycaemic control and reduces the frequency of micro- and macro-vascular complications of diabetes [3–5]. However, the adherence of patients to a prescribed insulin therapy regimen is currently challenging and requires a patient to be strongly motivated. According to an international survey of DM patients receiving insulin therapy, more than half of the patients have confirmed that they deliberately skip prescribed insulin injections, and approximately 20% regularly do so [6]. In addition, it is well known that the omission of two injections of basal insulin per week leads to the increase in the HbA_{1c} level by 0.2–0.3% in T1DM patients [7]. Moreover, the low adherence of T1DM patients (especially the elderly ones) to the recommended daily treatment regimen may increase health care costs [8].

According to both patients and physicians, the main limitations of insulin therapy are hypoglycaemia and weight gain, and the most significant adverse effects of insulin therapy is complexity of the regimen used and the need for permanent adaptation of lifestyle to treatment [9].

Since the early 1980s, the main challenge in the development of new insulin preparations has been to make insulin therapy more physiological by drawing it as close as possible to the profile of action of endogenous insulin in a healthy person. The emergence of intermediate-acting insulin preparations and their administration both separately and in combination with short-acting insulin provided an opportunity to adapt the insulin therapy to the individual needs of a DM patient taking into account the features of the disease, patient's diet and lifestyle.

The development of basal insulin analogues (glargine, detemir) have made it possible to solve several important problems at once compared with the era when NPH and Lente insulin was used:

- the possibility of administering insulin 1–2 times a day because of the increased duration of action up to 24 hours. Approximately 40% of T2DM patients can achieve acceptable glycaemic control using only basal insulin therapy;
- the subtle peak of biological activity [11–12];
- a more stable and predictable effect because of the significant reduction in both intra- and inter-individual variations of pharmacokinetic and pharmacodynamic profiles of action of basal insulin analogues [12–14]; and
- the reduced risk of hypoglycaemia, especially severe and nocturnal episodes, while retaining the same effectiveness in reducing HbA_{1c} and blood glucose levels as human insulins [15–19].

Nevertheless, hypoglycaemia still remains a topical problem and a significant factor hindering well-timed adequate optimisation and intensification of insulin therapy.

According to the recent international surveys of physicians and T2DM patients who use traditional basal insulin analogues (GAPP2 GAPP study), 28% of patients report experiencing self-managed hypoglycaemia in the preceding month. A considerable portion of them confirmed that they intentionally omitted a dose (22%), changed the regimen and time of administration (24%) or decreased the basal insulin dose (14%) in the preceding 30 days, and more than 20% of patients reported that they tend to maintain higher blood glucose level than recommended to prevent nocturnal hypoglycaemia. Most patients (42%) have a fear of nocturnal hypoglycaemia, and only 23% have a fear of daytime hypoglycaemia [20].

The main problems of the currently available basal insulin analogues include their inability to provide permanent daily action within 24 hours in all T1DM and T2DM patients, lack of perfect peakless pharmacokinetic and pharmacodynamic profile, failure to maintain a constant level of target glycaemia during the day and especially at night, and, as a consequence, the inability to completely prevent the development of hypoglycaemia, especially at night. In addition, even mild recurring hypoglycaemia adversely affects the health and well-being of a patient and his/her mental, physical, and social functioning as well as increases the cost of diabetes treatment both for the patient and for the entire health care system [21]. Analysis of the actual clinical practice of treatment of T2DM indicates the late initiation of insulin therapy as well as the insufficient metabolic compensation of diabetes during insulin treatment, typically due to the administration of unreasonably low doses of insulin [22].

This review presents an analysis of the clinical benefits of treatment of T1DM and T2DM using a novel ultra-long-action basal insulin analogue, insulin degludec (Tresiba®).

Molecular structure, mechanism of action and clinical pharmacology

Insulin degludec (Tresiba®) is an acylated recombinant DesB30 human insulin incorporating a hexadecane dicarboxylic acid residue connected at the LysB29 position via γ-L-glutamic acid (linker) (Fig. 1).

Pharmacodynamic studies have demonstrated that insulin degludec specifically binds to the human insulin receptor, activates tyrosine phosphorylation and has the same biological and pharmacological effects as human

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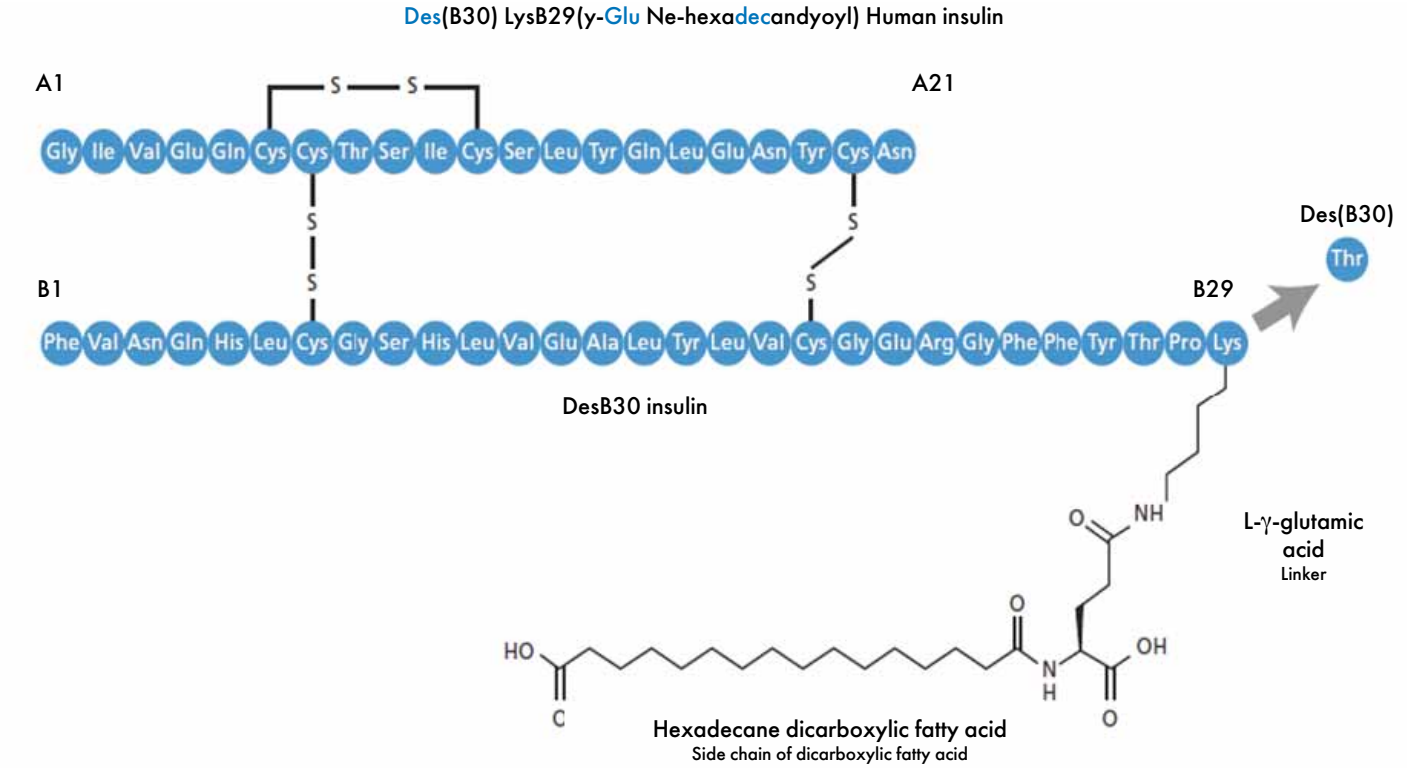

Figure 1. Primary structure of insulin degludec.

insulin [23].

In injection solutions, insulin degludec predominantly forms dihexamers. Each unit of insulin degludec solution contains 6 nmol of insulin, similar to preparations of human insulin and insulin glargine.

After subcutaneous injection, insulin degludec forms a depot of soluble but stable multi-hexamers due to self-association. These multi-hexamers gradually, slowly, and with constant velocity dissociate to monomers, which are absorbed into the bloodstream and provide metabolic effects [24]. As a result, the half-life (t½) of degludec elimination from subcutaneous fat depots reaches 25 hours, which is twofold longer than that of the currently used basal insulin analogues and does not depend on the dose of insulin used [25]. A high t½ of insulin degludec after subcutaneous administration primarily reflects the delayed absorption of insulin degludec from the site of injection, as the elimination rate in this case is determined by the rate of absorption into microcirculation. In addition, the steady-state t½ of insulin degludec is approximately 5 hrs after intravenous injection.

It is of great importance that the onset of the effect of insulin degludec does not differ significantly from that of traditionally used basal insulins (NPH, glargine, and detemir), whereas the duration of action of insulin degludec after a single injection reaches 42 hrs or even longer [26, 27].

Injection of insulin degludec once a day results in equilibrium (steady state) within 2–3 days, regardless of the administered dose of insulin and the type of diabetes mellitus (Fig. 2) [25, 27, 28].

Upon reaching a steady state, insulin degludec demonstrates a perfectly flat, stable pharmacokinetic and pharmacodynamic profile of action (Fig. 3) [27], which can only be achieved when using insulin with a duration of action exceeding the dosing interval (24 hrs).

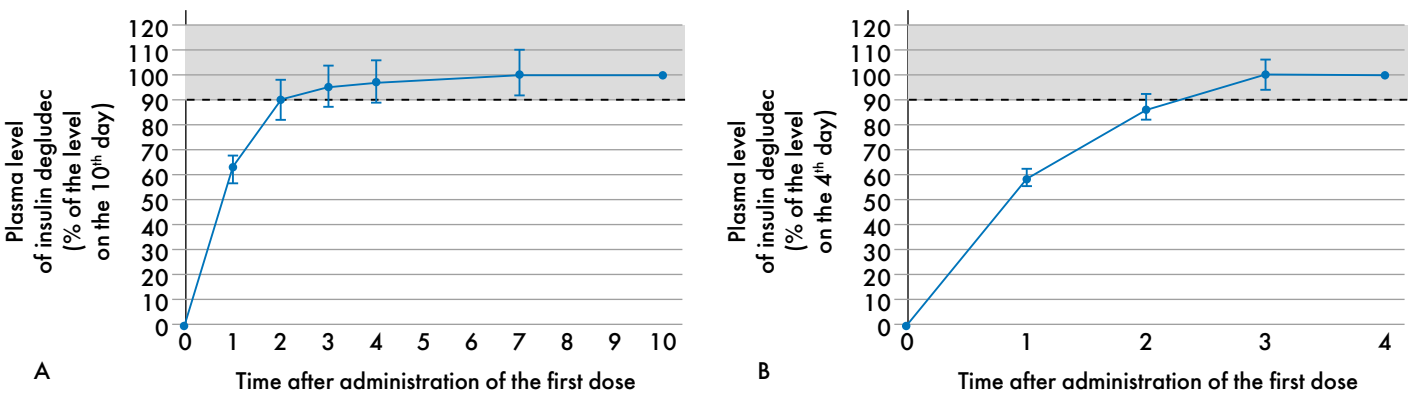

Figure 2. Relative plasma level of insulin degludec after a single administration (0.4 IU/kg) to T1DM (A) and T2DM (B) patients.

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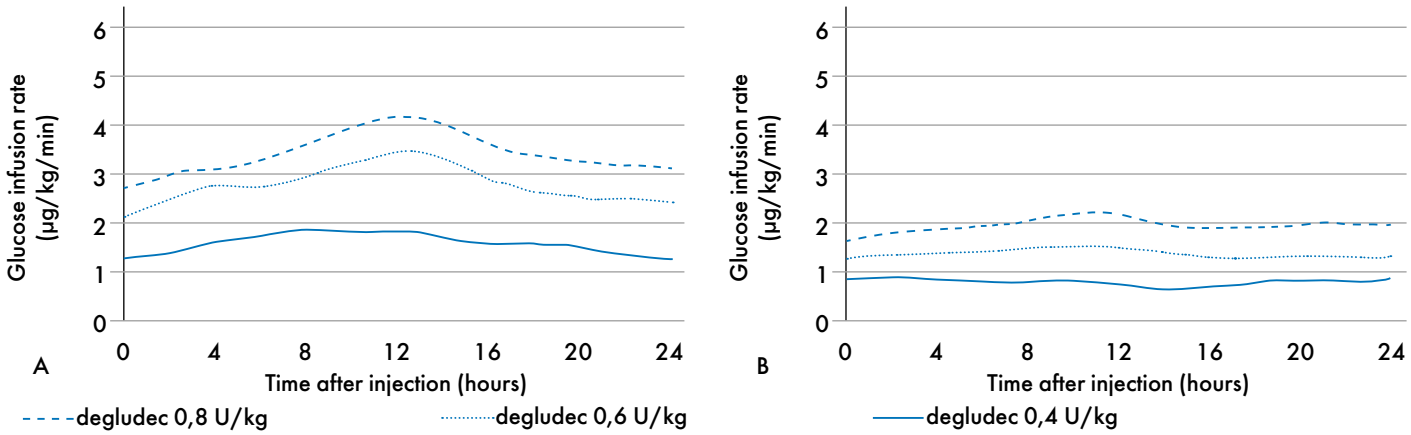

Figure 3. Pharmacodynamic profile of insulin degludec (100 units) in T1DM (A) and T2DM (B).

Such a profile reduces the variation more than fourfold compared with insulin glargine (Fig. 4) [29] and therefore provides more predictable hypoglycaemic effects.

Thus, the pharmacokinetic and pharmacodynamic profiles of insulin degludec indicate its slow and continuous absorption, which provides a gradual and sustained reduction in blood glucose level when administered once a day and achievement of equilibrium state during the first 2–3 days. This is an important feature of basal insulin degludec, which ensures the attainment of target glycaemic control between meals and at night with a low risk of hypoglycaemia, which are quite difficult clinical problems when using the currently available basal insulin analogues.

Clinical benefits of insulin degludec therapy in T1DM and T2DM patients: the results of a phase 3 clinical trial.

The efficacy and safety of insulin degludec has been extensively studied in the BEGIN™ clinical trial (9 international, multicentre, randomised, controlled phase 3a trials lasting 26–52 weeks and involving approximately 9000 T1DM and T2DM patients, who previously either received or did not receive insulin therapy) (Fig. 5).

The possibility of flexible dosing of the novel basal insulin degludec (in 8 and 40 hrs) was studied in the two patient types, taking into account its flat and stable profile for 42 hrs or longer.

Before proceeding to discuss the efficacy and safety of insulin degludec, it should be noted that all of these studies have "treat-to-target" non-inferiority (with the achievement of efficacy equivalent (not lower) to that of the reference drug) design (FPG reduction to 4.0–4.9 mmol/l) using the same titration algorithm [30]. The point is that when designing new insulins, it is necessary to take into consideration the fact that insulin is the most powerful antihyperglycaemic drug, which effect does not depend on the residual β-cell function and is only limited by the risk of hypoglycaemia. Given this fact and according to FDA (Food and Drug Administration) requirements, a new insulin should effectively reduce glucose level at least as well as existing insulin preparations to ensure safety with respect to the development of hypoglycaemia and maintain optimal glycaemic control (HbA_{1c}) for a long time.

This review is not aimed at presenting the results of all of the currently completed and published studies on the efficacy and safety of insulin degludec but rather at discussing the major clinical benefits of the new insulin compared with the existing basal analogues confirmed by the results of seven phase 3 clinical trials.

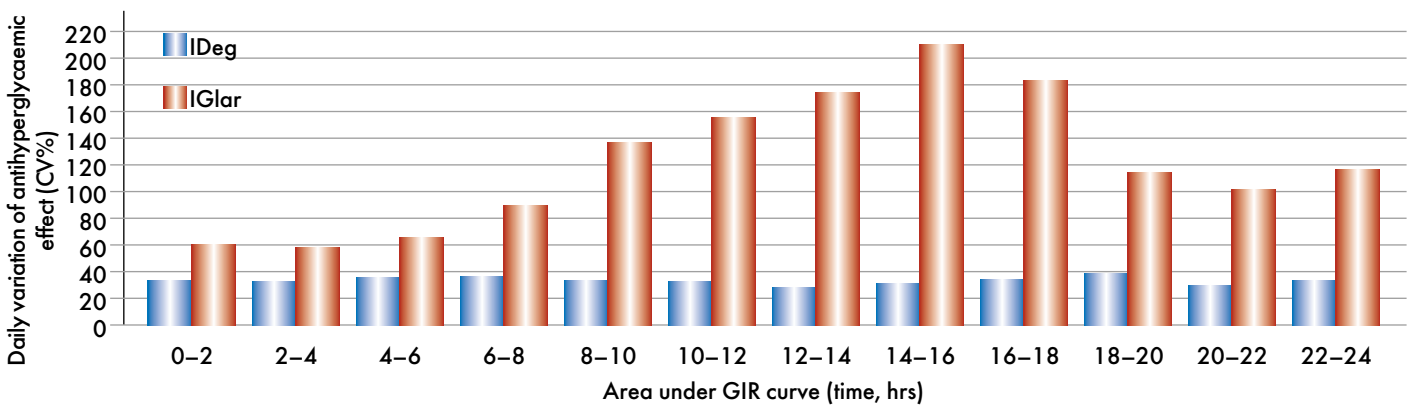

Figure 4. Intra-individual variation of insulin degludec compared with insulin glargine (0.4 U/kg, n = 53).

CV – coefficient of variation; GIR – glucose infusion rate

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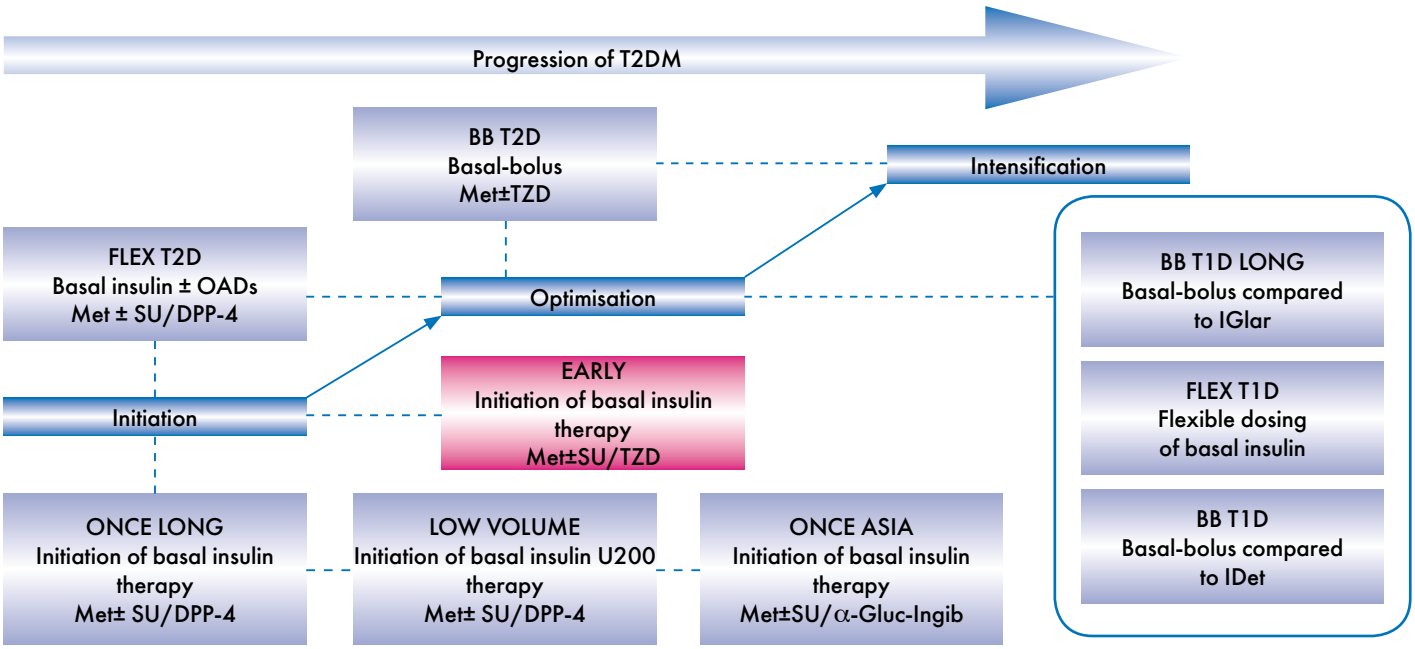

Figure 5. Protocol of the BEGIN™ clinical trial.

EFFICACY OF THE NEW BASAL INSULIN

In all seven studies presented in this review, insulin degludec was compared with insulin glargine, which is the basal insulin analogue traditionally used in clinical practice. All of the studies demonstrated that insulin degludec is not inferior to the reference drugs with respect to efficacy of reducing HbA_{1c} (primary endpoint) (Table 1) when administered in a single equivalent or even lower dose [31–37].

Thus, treatment with basal insulin alone led to an equally effective reduction in HbA_{1c} (by 1.18% and 1.07% when using degludec and glargine, respectively) in T2DM patients after 52 weeks [31].

During the basal-bolus therapy using degludec and glargine insulins, the decrease in HbA_{1c} in T2DM patients was also approximately the same (1.29% and 1.18%, respectively) [32].

Similarly, 52-week basal-bolus insulin therapy with insulin degludec and insulin glargine resulted in clinically significant reduction in HbA_{1c} by 0.40% (baseline HbA_{1c} = 7.7%) in T1DM patients [33]. The average difference between the compared treatment groups was insignificant and did not exceed 0.1%.

In general, a decrease in fasting plasma glucose (FPG) at the end of the test period was more pronounced in the case of administration of insulin degludec compared with insulin glargine in all of the studies. The average difference between the experimental groups ranged from 0.35 to 0.46 mmol/l. This advantage of insulin degludec therapy in

Table 1

Clinical efficacy of insulin degludec (reduced HbA_{1c} and FPG) in phase 3 clinical trials compared to insulin glargine

Studied population	Compared therapies	HbA_{1c}, %	HbA_{1c} dynamics [95% CI]	FPG, mmol/l	FPG dynamics [95% CI]
T2DMBasal (±OADs), 12 months	Degludec	-1,06	0,09 [-0,04; 0,19]	-3,76	-0,43 [-0,74; -0,13]
	Glargine	-1,19		-3,30	
T2DMBasal (±OADs), 6 months	Degludec, 200 Units	-1,30	0,04 [-0,11; 0,19]	-3,7	-0,42 [-0,78; -0,06]
	Glargine	-1,32		-3,38	
T2DMBasal (±OADs), 6 months (Asia)	Degludec	-1,24	0,11 [-0,03; 0,24]	-2,88	0,09 [-0,41; 0,23]
	Glargine	-1,35		-2,97	
T2DMBasal (±OADs), 6 months	Degludec, flexible dosing	-1,28	0,04 [-0,12; 0,20]	-3,15	-0,42 [-0,82; -0,02]
	Glargine	-1,26		-2,78	
T2DM BB, 12 months	Degludec	-1,17	0,08 [-0,05; 0,21]	-2,44	-0,29 [-0,65; 0,06]
	Glargine	-1,29		-2,14	
T1DM BB, 12 months	Degludec	-0,40	-0,01 [-0,14; 0,11]	-1,27	0,12
	Glargine	-0,39		-1,39	
T1DM BB, 6 months	Degludec, flexible dosing	-0,40	0,17 [0,04; 0,30]	-1,30	-0,03
	Glargine	-0,58		-1,33	

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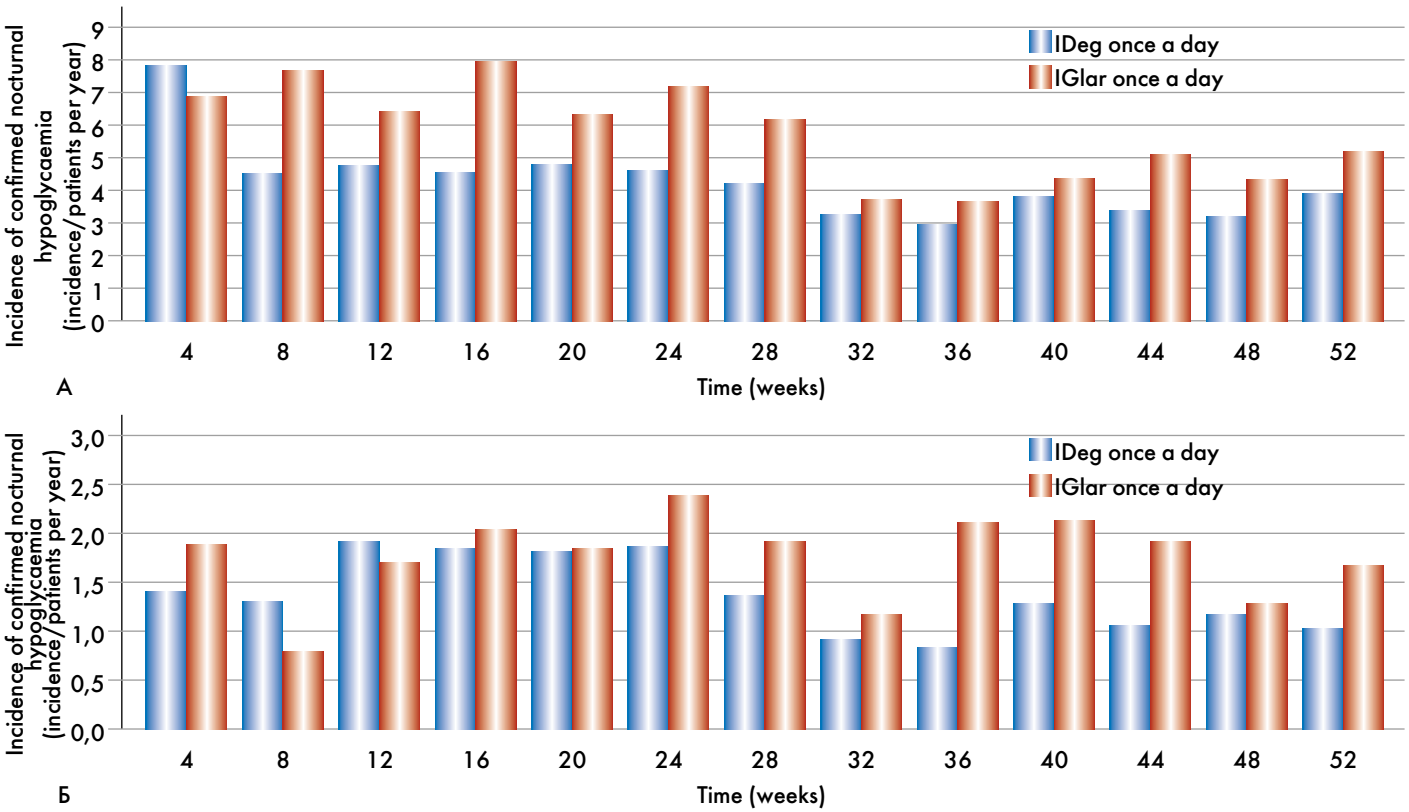

Figure 6. Incidence of confirmed nocturnal hypoglycaemia in T1DM (A) and T2DM (B) patients during the month-long basal-bolus therapy [adapted from Gerberetal. Lancet 2012; 379:1498-1507].

reducing FPG was significant in 5 of 7 studies, which among others included patients who were previously insulin-naive and started treatment using only basal insulin.

Importantly, the dose of basal insulin at the end of the study was lower by 10–12% when using insulin degludec.

It should also be noted that all of the benefits of insulin degludec that were demonstrated in clinical studies of T2DM are characteristic of both the Caucasian and Mongoloid races [36]. The latter fact is characterised by the features of diet and lifestyle and also by the pathophysiology of DM.

The results of clinical studies of insulin degludec in T1DM and T2DM patients have demonstrated that the novel basal ultralong-acting insulin can significantly improve glycaemic control with a lower risk of hypoglycaemia, especially nocturnal risk compared with the traditional insulin analogues [32].

Both degludec and glargine were very rarely responsible for severe hypoglycaemic conditions (no more than 2% of patients) in T2DM patients who received only basal insulin in combination with oral antidiabetic drugs (OADs) [31, 34, 37]. Moreover, after completion of titration of insulin doses (the period of maintenance therapy), the incidence of severe hypoglycaemia was significantly lower for therapy with insulin degludec than that with insulin glargine [31].

Intensification of insulin therapy by adding prandial insulin to the basal insulin, of course, leads to significant improvement in glycaemic control. At the same time, it inevitably increases the risk of hypoglycaemia, including severe cases compared with basal insulin therapy alone. However, even with intensive basal-bolus therapy using degludec, severe hypoglycaemia events were reported only in ~ 4.5% of patients [32].

Similarly, during the basal-bolus insulin therapy severe hypoglycaemia was registered in 10–12% of T1DM patients [33].

Severe nocturnal hypoglycaemia was also rare (registered in less than 3–4% of patients) in the program of clinical trials of degludec [31–35].

The incidence of confirmed hypoglycaemic episodes during therapy of T2DM using insulin degludec (both in combination with OADs and in the basal-bolus therapy) was lower than that in the control group [31, 32, 34.3 7] and did not differ significantly in T1DM patients [33 35].

The incidence of confirmed nocturnal hypoglycaemia (hypoglycaemic episodes developed between midnight and 6 am) was lower in all phase 3 studies of insulin degludec; in 5 of the 8 studies with insulin glargine, it was significantly lower during the treatment with new insulin compared with the reference preparation, regardless of the regimen of insulin therapy, injection time (fixed or flexible dosing), DM type, and previous experience of insulin therapy (Fig. 7). The development of nocturnal hypoglycaemia was 25% less likely during the administration of insulin degludec than insulin glargine, both in T1DM and T2DM patients, even when used in a basal-bolus regimen. This advantage of insulin degludec was most pronounced after completion of titration of basal insulin dose (Fig. 6).

Such a low risk of nocturnal and severe nocturnal hypoglycaemia is indicative of a very good safety profile of insulin degludec, as nocturnal hypoglycaemia adversely

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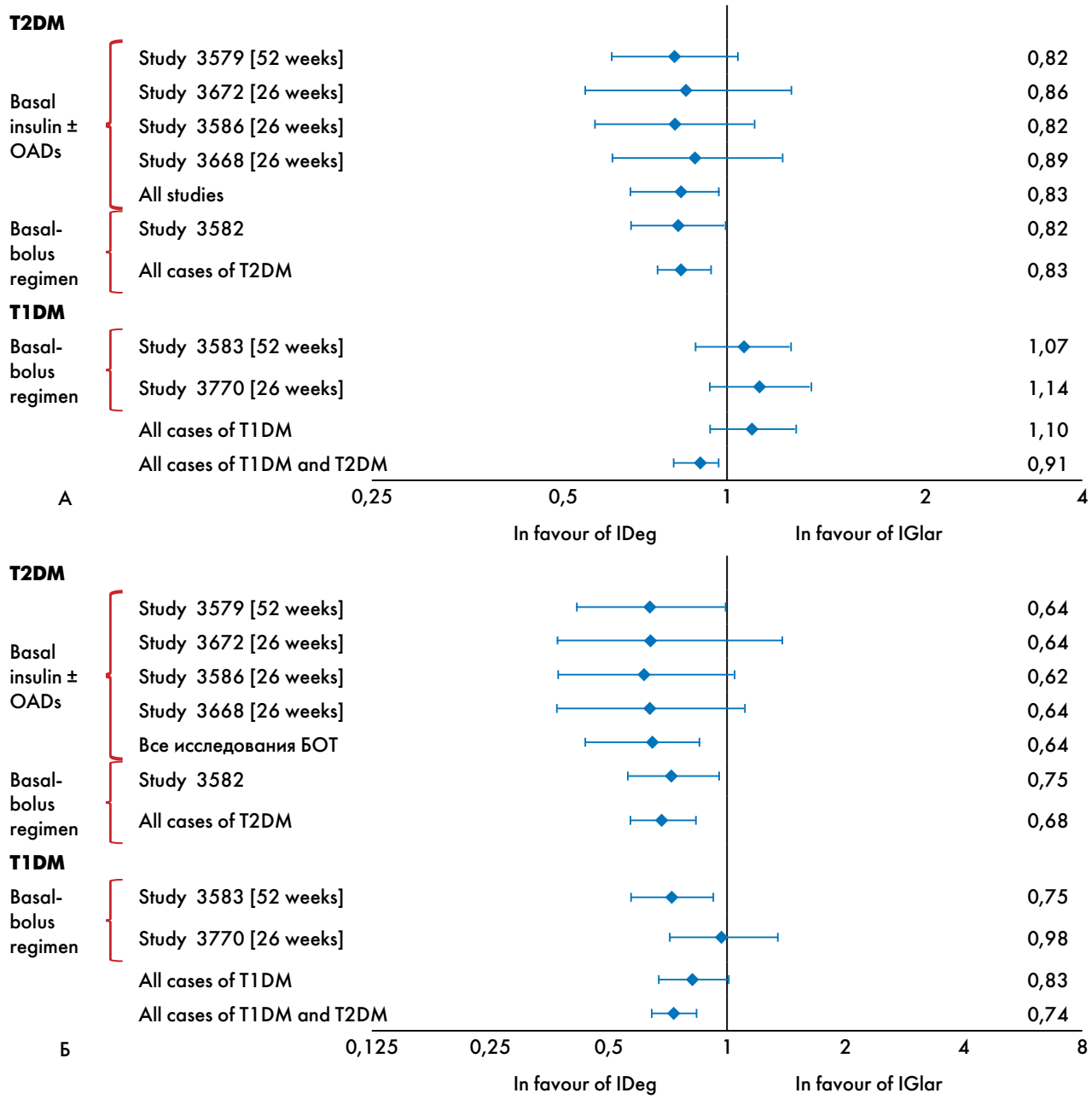

Figure 7. The relative risk of the overall confirmed (A) and nocturnal confirmed (B) hypoglycaemia in phase 3 clinical trials of insulin degludec (data from specially designed meta-analysis).

affects the health, well-being, and performance of DM patients and may even increase the risk of sudden death. In addition, they are dangerous because they may remain unidentified in most patients.

A metaanalysis of hypoglycaemia was planned in accordance with FDA requirements. It is characterised by estimating the proportion of patients who had at least one episode of hypoglycaemia during the entire treatment period. The analysis demonstrated that therapy with insulin degludec is associated with significantly rarer development of hypoglycaemic states [40]. The overall incidence of confirmed and nocturnal confirmed hypoglycaemia registered during phase 3 trials of insulin degludec (2 studies with T1DM and 5 studies with T2DM patients, n = 4330) was lower by 9% and 26% during therapy with insulin degludec compared with insulin glargine. An even more pronounced difference was observed between the compared basal insulins in T2DM patients (lower by 17% and 32%, respectively), especially in patients who were previously insulin-naive (lower by 17% and 36%, respectively) (Fig. 7). The post-hoc analysis revealed that the risk of severe hypoglycaemia (in the basal regimen) is lower by 86% in T2DM patients treated with insulin degludec compared with those treated with insulin glargine [40].

It is quite natural that the difference in the incidence of hypoglycaemia was less significant in patients with T1DM and a long experience of intensive insulin therapy, but even in this population, the incidence of confirmed nocturnal hypoglycaemia was lower by 17% than during treatment with insulin glargine [40].

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From the clinical viewpoint, the results of the presented meta-analysis indicate that in T2DM patients who were previously insulin-naïve, the initiation of insulin therapy with the novel basal insulin degludec was associated with a significantly lower risk of hypoglycaemia regardless of the treatment regimen (basal insulin ± OADs or basal-bolus therapy). Thus, when using insulin degludec in combination with OADs, we can avoid development of 33 episodes of confirmed hypoglycaemia and 13 episodes of confirmed nocturnal hypoglycaemia per 100 patients per year compared with the insulin glargine commonly used in clinical practice. The administration of degludec in a basal-bolus regimen results in an annual decrease in the incidence of confirmed and nocturnal confirmed hypoglycaemia by 232 and 59 episodes per 100 patients, respectively [40].

The currently published results of long-term therapy with insulin degludec (during 2 years) confirm the efficacy and long-term stability of achieved glycaemic control as well as long-term safety of the novel заменить на ultralong-acting basal insulin analogue degludec [41, 42].

Possibility of flexible dosing

The possibility of more flexible dosing during the day without compromising the efficacy and safety of achieving optimal glycaemic control is an additional benefit of the therapy with insulin degludec, which is due to the increased duration of action of the drug. According to the results of randomised controlled trials in T2DM patients, insulin degludec does not increase the risk of hypoglycaemia when being administered at intervals of 8 and 40 hrs (overall incidence of confirmed hypoglycaemia was 3.6 vs. 3.5 episodes/patient-year, incidence of nocturnal hypoglycaemia – 0.6 vs. 0.8 episodes/patient-year) and makes it possible to achieve the same decrease in HbA_{1c} and fasting plasma glucose ($p = 0.04$) with an everyday administration of insulin glargine once a day at the same time (according to administration instructions) [34, 35]. In this case, daily doses of insulin (0.5–0.6 IU/kg/day) and weight gain by the end of the study (1.5 kg in the group of insulin degludec and 1.3 kg in the group of insulin glargine) were almost identical in both groups.

Oncological safety in preclinical studies

Numerous in vitro studies on animal models have demonstrated that insulin degludec has a lower affinity for the insulin receptor than native human insulin (5–15%), both in animals (rats, dogs, pigs) and humans [23]. In addition, the normal affinity ratio to the insulin receptor (IR) and the affinity of insulin degludec to the IGF-1 receptor are significantly lower (2%) than those of human insulin [23]. In turn, this is indicative of a low mitogenic activity of the new insulin (5–9% of cell mitogenic capacity of human insulin). Moreover, the activation of signal after stimulation of IR with insulin degludec decreases at the same rate as after stimulation with human insulin [23]. This is indicative of more rapid dissociation of degludec with the insulin receptor, which is another important factor of mitogenicity. In general, the ratio of mitogenic and metabolic effects of insulin degludec corresponds to that of human insulin.

Clinical safety

Therapy with insulin degludec is well-tolerated. The profile of adverse events (including laboratory parameters) registered during the phase 3 clinical trials of insulin degludec (approximately 11 thousand DM patients), in general, does not differ from that of insulin glargine with respect to the structure and frequency of adverse reactions. Most adverse events (AEs) were mild and required no changes in therapy.

The incidence of AEs that required the withdrawal of treatment and, consequently, the premature withdrawal of the patient from the study, as well as the incidence of severe AEs, were also comparable to those in the control group (incidence of severe AEs was 16.1 and 15.0 cases per 100 patient-years of exposure, respectively).

The incidence of allergic reactions and reactions at the injection site when using insulin glargine and degludec did not differ (1.3 and 0.9 cases per 100 patient-years of exposure, and 7.0 and 9.0 cases per 100 patient-years of exposure, respectively).

The incidence of malignant neoplasms was also similar in the treatment groups of insulin glargine and degludec (0.9 and 0.8 cases per 100 patient-years of exposure, respectively). The most common neoplasm locations included the skin, gastrointestinal tract, breast, thyroid gland, and bladder. Neoplasms of the skin and colon were somewhat more frequently detected in the insulin degludec group, whereas there was cancer of the breast, thyroid gland and bladder in the insulin glargine group. Most cases of neoplasms in the insulin degludec group were registered during the first 3 months and therefore are unlikely to be related to the newly prescribed therapy.

No significant differences with respect to the influence on weight of T1DM and T2DM patients were observed between the groups being compared [31, 33].

No evidence of the formation of neutralising antibodies in T1DM and T2DM patients was obtained in clinical studies. In addition, the level of anti-degludec antibodies did not correlate with the level and dynamics of HbA_{1c}, as well as with the total daily dose of insulin at the end of the study [31, 33–35, 43].

Cardiovascular safety

Cardiovascular conditions are the main cause of mortality in T2DM [44]. In addition, the large scale population studies ACCORD, ADVANCE and VADT demonstrated that improvement in glycaemic control (HbA_{1c}) alone is not always followed by reduction of the risk of macrovascular complications [45–47]. Growing attention to the primary prevention and reduction of cardiovascular risk factors, such as dyslipidaemia, diabetes mellitus and obesity, have raised the problem of the safety of some drugs (e.g., sibutramine and rosiglitazone) to a new level. Therefore, when designing new drugs for treating DM, close attention should be paid to their cardiovascular safety. Moreover, comparing the data on safety of a new drug with those existing and available for

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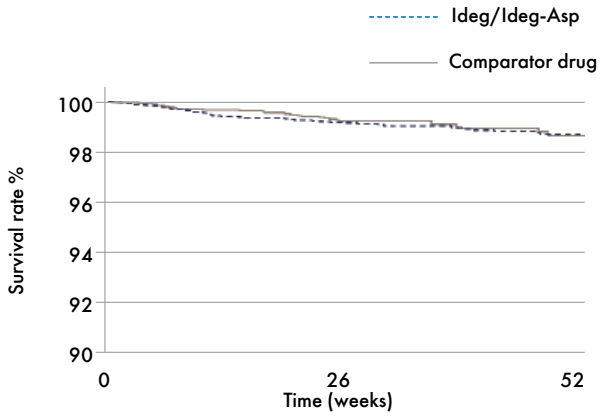

Number of exposed patients

Ideg Ideg-Asp	5647	4919	1840
Comparator drug	3312	2901	654

Figure 8. Incidence rate according to a preliminary MACE analysis in studies of insulin degludec and insulin degludec-aspart.

clinical use is a prerequisite for registration of the former [48, 49]. If the relative risk of adverse cardiovascular events when using a new drug is 1.8 and above, the submission of results of specially designed studies on cardiovascular safety is required to obtain approval from the regulatory authorities.

Preliminary analysis of the major adverse cardiovascular events (MACE analysis), such as death from cardiovascular causes, acute coronary syndrome (acute myocardial infarction or hospitalisation for unstable angina) and stroke, have demonstrated that the relative risk of these events when administering insulin degludec and degludec aspart was similar to that when using the comparator drugs (Fig. 8) [50].

It was a study of the general population of patients, but had insufficient data from patients with high cardiovascular risk as well as an insufficiently long observation period (follow-up was over 2 years only in 20% of patients), which were among the limitations of this analysis that complicated the interpretation of results.

Considering this and the new FDA requirements for the registration of new medications for diabetes, including insulins, Novo Nordisk Company initiated a special investigation into the long-term cardiovascular safety of insulin degludec (DEVOTE) aimed at a comprehensive study of cardiovascular risks of therapy with insulin degludec, particularly but not exclusively in patients with high cardiovascular risk.

Health-related quality of life

DM has a negative impact on the health-related quality of life (QOL) of patients. It was found that the negative effect can be caused by the disease itself, its complications, complexity of the treatment regimen being used, fear of injections (both for administration of drugs and the need for constant monitoring of blood glucose level), as well as fear of hypoglycaemia and weight gain [51–53]. This can adversely affect patients' adherence to regimens of treatment prescribed by a physician, which in turn leads to deterioration of glycaemic control.

In addition, poor QOL, as well as long ineffective control and hypoglycaemia, has negative economic consequences as a result of absenteeism, reduced working efficiency and productivity.

Therefore, modern guidelines for the treatment of diabetes recommend choosing therapeutic approaches that provide a stable, peakless glycaemic profile and the ability to achieve target glycaemic parameters without the risk of hypoglycaemia.

Reducing risk of hypoglycaemia may be an important argument for both physician and patient when discussing the need for administration of insulin as well as more active insulin dose titration and well-timed intensification of therapy in the future, which will certainly contribute to achieving more adequate glycaemic control.

Metaanalysis of phase 3 clinical trials have demonstrated that both basal and basal-bolus regimens of the administration of insulin degludec improved the health-related QOL in T1DM and T2DM patients, which was evaluated according to SF-36® general questionnaire, a conventionally used and most often cited questionnaire in clinical and population studies [54–55].

In particular, the most significant improvement in the insulin-naive T2DM patients who received basal insulin degludec during clinical trials was identified in such QOL parameters (domains) as physical pain and viability (Fig. 9) [31 54, 56].

Similarly, basal-bolus therapy in T2DM patients contributed to the improvement of estimates of both the total and individual QOL parameters, which were better at the end of the study period compared with those for insulin glargine (Fig. 10) [32, 55].

The benefits of insulin degludec regarding the impact on health-related QOL in T1DM patients were less significant than those in T2DM patients; however, this trend was observed for most domains (Fig. 11) [33, 55, 57].

What is the cause of such an effect?

As noted above, hypoglycaemia and the fear of hypoglycaemia are among the main reasons for the deterioration of health-related QOL, which adversely affects both the physical and mental health of DM patients as well as their adherence to treatment. Therefore, the reduced incidence of hypoglycaemia is one of the possible causes of positive impact of the administration of insulin degludec on QOL.

POSSIBLE USE OF INSULIN DEGLUDEC IN CLINICAL PRACTICE

The peakless, protracted profile of action of the new ultralong-acting insul degludec and its clinical benefits demonstrated in the large scale international clinical trial program allow us to recommend it for T1DM and T2DM patients who require basal insulin treatment and

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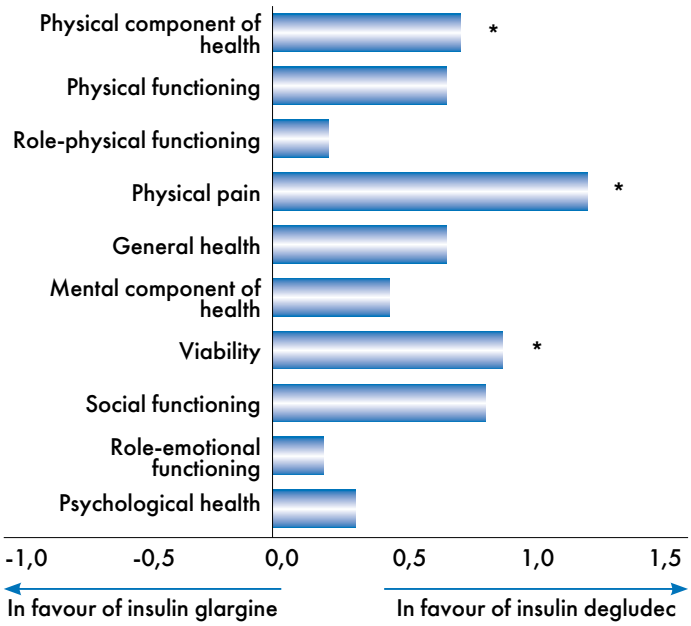

Figure 9. Differences in the dynamics of the estimated quality of life score during treatment with insulin degludec and insulin glargine in insulin-naive T2DM patients (results of meta-analysis of phase 3 BEGIN™ clinical trials).

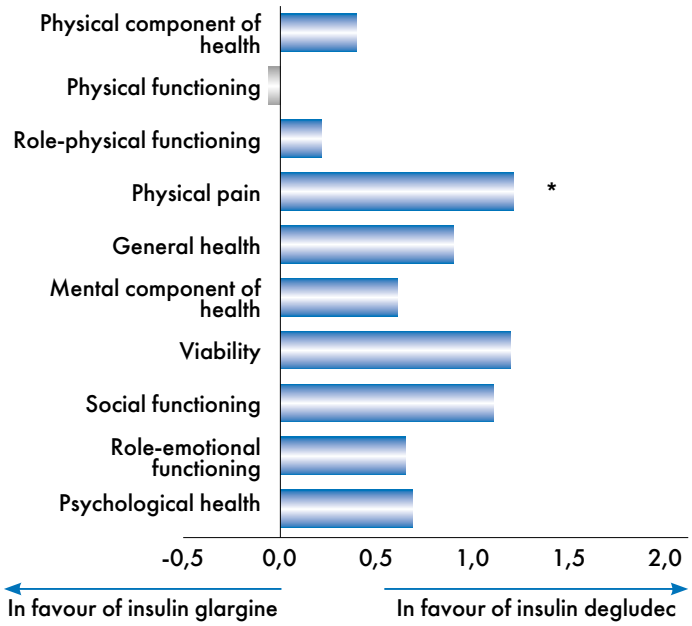

Figure 10. Differences in the dynamics of the estimated quality of life score during basal-bolus treatment with insulin degludec and insulin glargine in T2DM patients (results of phase 3 BEGIN Basal-Bolus Type 2 trials).

especially for patients who had frequent episodes of hypoglycaemia (especially nocturnal) during the prior therapy, including patients with high cardiovascular risk. The reduction of the risk of hypoglycaemia in these patients during treatment with insulin degludec makes it possible to achieve better glycaemic control as safe as possible and simultaneously improves patients' adherence to the prescribed treatment.

In addition, the possibility of using a fixed dose along with a flexible variation of administration time (ranging from 8 to 40 h) is an undeniable advantage in the treatment of diabetes in patients who have an active, unpredictable lifestyle associated with non-fixed work schedule, business trips or frequent travels (especially when crossing time zones), allowing for the safe maintenance of effective glycaemic control, regardless of the situation.

During the clinical trial of the new ultralong-acting basal insulin degludec, its efficacy and safety in the treatment of diabetes as well as the possibility of its administration using both the traditional single fixed dosing regimen and flexible regimen was demonstrated. Both physicians and patients could individually select the optimal time of administration in 2 studies with the flexible dosing of insulin degludec.

In all of the studies, the dose of basal insulin was chosen in accordance with the approved titration algorithm based on the average (over the preceding 3 days) plasma glucose level before breakfast. When using a basal-bolus therapy, the dose of prandial insulin was titrated based on the average plasma glucose level before meals. Considering the emergence of the therapeutic effect of the therapy with both basal insulin analogues as early as the first day, as well as the long action of insulin degludec, it was recommended to pay close attention to prandial insulin dose titration 8 weeks after treatment initiation.

Moreover, when comparing different algorithms of titration of the dose of ultra-long-acting insulin degludec in T2DM patients, it has been demonstrated that both the "simple" algorithm, involving dose adjustments based on a single measurement of FPG (before breakfast), and "phased" algorithm, involving dose adjustment based

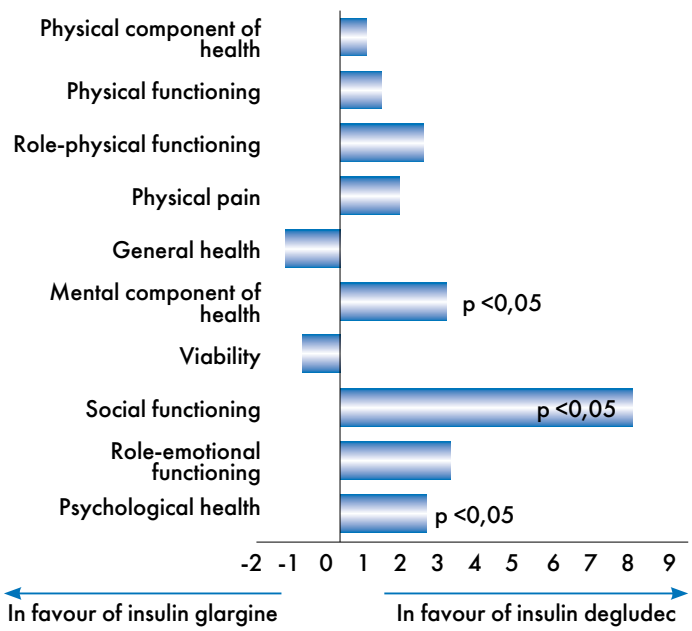

Figure 11. Differences in the dynamics of the estimated quality of life score during basal-bolus treatment with insulin degludec and insulin glargine in T1DM patients.

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on three consecutive measurements of FPG, are equally effective in improving glycaemic control, safety and tolerability [58]. The choice of algorithm depends on an individual patient and desired goals. The use of the simplified titration algorithm provides more freedom in achieving good glycaemic control for the patient, which makes therapy more comfortable, while reducing costs for glycaemic control.

Taking into account the experience gained during the clinical studies and official recommendations for its use, insulin degludec (Tresiba®) is recommended for treating T1DM and T2DM in adults. It can be used both as a monotherapy (in combination with OADs or alone) and in combination with prandial insulin (in the basal-bolus regimen). The Tresiba® formulation has ultralong-acting and should be administered subcutaneously once a day (the minimum interval between injections should be at least 8 hrs but not more than 40 hrs). As with other insulin formulations, the dose should be individually adjusted in each case based on the patient's needs.

The recommended initial dose in combination with OADs in T2DM insulin-naive patients is the same as the recommended starting doses of other basal insulin analogues (glargine, detemir), which is 10 IU once a day. T1DM patients and T2DM patients who previously received insulin are also recommended to use degludec once a day, regardless of the previous dosage frequency of intermediate/longacting insulin. In this case, the dose of insulin Tresiba® should match the previously used daily dose of basal insulin. It is recommended to titrate the dose of insulin degludec once a week to achieve and/or maintain the average fasting plasma glucose (based on FPG measurements during the previous two days) within the target values (4.0–4.9 mmol/l). It should be borne in mind that some patients may require an adjustment of the dosage of both basal insulin and other antidiabetic drugs when switching from other basal insulin preparations. Therefore, careful monitoring of blood glucose is required during the dose adjustment. The dose of insulin Tresiba® can be reduced by 20% after reaching stable optimal glycaemic control (HbA_{1c} <8%) in T1DM patients, which allows for further reduction of the risk of hypoglycaemia during intensive therapy.

CONCLUSION

The design and implementation of the first basal insulin analogues (glargine, detemir) into clinical practice heralded a new era of treatment of DM, when the reduction of the risk of hypoglycaemia became a strong requirement when designing new drugs and choosing a treatment strategy along with the effective achievement of adequate glycaemic control.

Insulin degludec (Tresiba®) is a new ultra-long-acting basal insulin analogue. It has been approved in Japan, Europe, Mexico, India, Argentina and Russia. Insulin Tresiba® is included in Russian clinical guidelines (algorithms of specialised medical care to patients with diabetes mellitus) [59].

The implementation of insulin degludec (Tresiba®) in clinical practice expands the possibilities of achieving stable glycaemic control (especially with regard to fasting glucose) in T1DM and T2DM patients and significantly reduces the risk of hypoglycaemic episodes, especially nocturnal episodes, and provides patients with more convenient and flexible dosing of basal insulin and contributes to improving their well-being, quality of life, and satisfaction with treatment compared to traditional basal insulin analogues. Insulin degludec also reduces the costs (including the indirect costs) of DM therapy.

CONFLICT OF INTERESTS

The authors declare the absence of funding for the preparation and review of the manuscript. M.V. Shestakova participated in the phase 3 clinical trial of insulin degludec. Novo Nordisk Company was allowed to comment on the manuscript during the review process. All of the changes were made by the authors on the basis of the submitted scientific data, taking into account the comments provided.

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