Basal insulin combined incretin mimetic therapy with glucagon-like protein 1 receptor agonists as an upcoming option in the treatment of type 2 diabetes: a practical guide to decision making

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Abstract: The combination of basal insulin and glucagon-like protein 1 receptor agonists (GLP-1 RAs) is a new intriguing therapeutic option for patients with type 2 diabetes. In our daily practice we abbreviate this therapeutic concept with the term BIT (basal insulin combined incretin mimetic therapy) in a certain analogy to BOT (basal insulin supported oral therapy). In most cases BIT is indeed an extension of BOT, if fasting, prandial or postprandial blood glucose values have not reached the target range. In our paper we discuss special features of combinations of short- or prandial-acting and long- or continuous-acting GLP-1 RAs like exenatide, lixisenatide and liraglutide with basal insulin in relation to different glycemic targets. Overall it seems appropriate to use a short-acting GLP-1 RA if, after the near normalization of fasting blood glucose with BOT, the prandial or postprandial values are elevated. A long-acting GLP-1 RA might well be given, if fasting blood glucose values are the problem. Based on pathophysiological findings, recent clinical studies and our experience with BIT and BOT as well as BOTplus we developed chart-supported algorithms for decision making, including features and conditions of patients. The development of these practical tools was guided by the need for a more individualized antidiabetic therapy and the availability of the new BIT principle.

Keywords: basal insulin, decision making, exenatide, glucagon-like protein 1 receptor agonist, individualized therapy, liraglutide, lixisenatide, type 2 diabetes mellitus

Introduction

The basal insulin combined therapy with incretin mimetic glucagon-like protein 1 receptor agonists (GLP-1 RAs), for which we use and would like to suggest the abbreviated term BIT, is a novel therapeutic strategy. It was introduced in clinical practice after its first regulatory approval in late 2011 and early 2012. BIT extends the concept of the basal insulin supported oral antidiabetic (OAD) therapy (BOT), which, during the last 10 years, has achieved acceptance as a basic therapeutic principle in the treatment of type 2 diabetes mellitus (T2DM). The combination of basal insulin with GLP-1 RAs adds some novel effects of pharmacological equivalents of GLP-1 to the approved positive actions of basal insulin. The

new therapeutic principle has recently received considerable attention [Nauck and Meier, 2011; Barnett, 2012; Balena *et al.* 2013; Cohen *et al.* 2013; Gallwitz, 2013; Holst and Vilsbøll, 2013; Brown *et al.* 2013; Reid, 2013; Vora, 2013; Ahrén, 2014; Tibaldi, 2014].

Therapy with GLP-1 RAs was introduced in clinical practice in 2005. At this time the limited effects and the failure of a monotherapy with OADs became more and more clear [Kahn *et al.* 2006]. The combination of different types of these medications and even the dipeptidyl peptidase 4 (DPP-4) inhibitors showed their limits in comparison with GLP-1 RAs. This was especially true for the recovery and preservation of endogenous

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insulin production and secretion, glucagon suppression and weight reduction [Brunton, 2014]. Therefore the idea, starting with studies of synthetic c-terminal amidated GLP-1 from Creutzfeld's group in Germany [Schmidt *et al.* 1985], that GLP-1 RAs could support the production of insulin was fascinating. With the detection of exendin 4 (exenatide) and its insulin secretion stimulating properties [Eng and Eng, 1992; Göke *et al.* 1993] the development of new GLP-1 RAs has continued, leading to other clinically approved or investigated substances like (in alphabetical order): albiglutide, dulaglutide, liraglutide, lixisenatide, semaglutide and taspoglutide. Because the GLP-1 RA response depends on a more or less functioning β cell as well as on hepatic and peripheral insulin resistance, preferred use of a combination with OAD medication was suggested, and for some, regulatory approval was achieved.

In clinical practice we observed that the effect of GLP-1 RAs in combination with OAD medication is unfortunately limited to a certain number of patients who reach near normoglycemia or show improvements in their weight or have a reduction in their blood pressure without adverse reactions. These limitations in the use of GLP-1 RAs in comparison to native GLP-1, which is able to normalize blood glucose without nausea and vomiting, were recently discussed [Nauck, 2013]. According to these authors, subcutaneous modifications of GLP-1 RAs or the application in subcutaneous tissue, irrigating subcutaneous nerves, which mediate gastrointestinal events, might be responsible for the differences in efficacy and side effects between GLP-1 and GLP-1 RAs.

Additionally GLP-1 RAs have different pharmacokinetic and pharmacodynamic properties and different effects regarding β -cell stimulation and inhibition of glucagon secretion, gastric emptying and satiety. The background of the resulting heterogeneity of the GLP-1 RA responses in clinical practice is unclear at present. Furthermore these responses probably consist of two components: the heterogeneity of different drug features and the heterogeneity of our patients. Regarding the latter, the pathophysiological heterogeneity in patients with T2DM, already present in the prediabetic state with impaired fasting glucose or impaired glucose tolerance (IGT) or both [Kanat *et al.* 2012], is in principal a matter of distinct defects in β -cell function and the degree of insulin resistance in the liver and skeletal muscle.

In contrast to the missing individualized concepts in the use of GLP-1 RAs in combination with an OAD or with insulin, there is a clear definition of the principles and the individual use of basal insulin in the basal insulin supported oral therapy called BOT. The early start of basal insulinization especially with longer-acting basal insulin seems more and more appropriate according to experimental data, for example, regeneration of the first phase and improvement of the second phase of insulin secretion [Pennartz *et al.* 2011], pooled analysis of prospective randomized clinical trials [Fonseca *et al.* 2011], observational trials, for example, EARLY [Hanefeld *et al.* 2012, 2014], a recently published open-label, randomized, prospective trial comparing the effects of insulin glargine *versus* metformin [Pistrosch *et al.* 2013], and the large and long-term randomized controlled trial (RCT) ORIGIN [Hanefeld *et al.* 2010; Gerstein *et al.* 2012]. The concept of early insulinization with basal insulin (after metformin therapy is initiated or if metformin is contraindicated) is also supported by Saxonian [Fachkommission Diabetes Sachsen, 2009; Rothe *et al.*, 2010] and German national guidelines [Nationale Versorgungsleitlinie Diabetes, 2014], international position statements [Inzucchi *et al.* 2012] and clinical practice. One of the main clinical targets of basal insulin therapy is the normalization of fasting blood glucose. On this background there should be a complete or at least a partial reconstitution of the first-phase insulin secretion as well as the optimization of the second phase. As mentioned above, recent studies have shown that treatment with insulin glargine can partially reverse both phases of insulin secretion, an effect even more pronounced when fasting normoglycemia is achieved by intravenous insulin infusion [Pennartz *et al.* 2011].

Additionally, in case of a further progression of β -cell failure (irreversible loss of first-phase and probably second-phase insulin secretion) with enhanced postprandial glucose values, basal insulin treatment is regarded a substitutive therapy. In patients with optimized fasting blood glucose values after BOT but with inadequate average glycemia [hemoglobin A1c (HbA1c) above target], it can be assumed that the postprandial glucose values are elevated. Even if fasting plasma glucose (FPG) was best controlled for years as demonstrated in the ORIGIN trial with insulin glargine [median FPG < 5.3 mmol/liter (< 95 mg/dl)], HbA1c has the tendency to increase slowly over time, obviously because complete control of

postprandial values was not achieved [Gerstein *et al.* 2012]. To reduce postprandial glucose, a variety of therapeutic options exist, which have to be adapted to the special conditions of the patient.

In general, individualization of antidiabetic therapy, a major aspect and demand of nearly all new international guidelines, position statements or recommendations on diabetes treatment, should theoretically be based on a strategic concept. This concept should include individually weighted targets (near normoglycemia *versus* near normal blood pressure *versus* lipid reduction *versus* weight reduction *versus* costs *versus* side effects). It should be based on the analysis of a family history of early atherosclerosis and genetically determined risk factors, individual psychosocial aspects, social environment and of course the individual pathophysiological background including all components of the metabolic syndrome [Hanefeld and Leonhardt, 1981], or as we recently suggested, the Metabolic Vascular Syndrome (MVS) [Fachkommission Diabetes Sachsen 2007, 2013; Scholz, 2010].

The definition of individual targets is possible despite being a complicated task in practice. With regard to near normoglycemia or less well controlled diabetes, the aims depend on some of the patients' life circumstances (age, self confidence, life expectancy, duration of diabetes, compliance, comorbidities, support etc.) according to new national guidelines [Nationale Versorgungsleitlinie Diabetes, 2014] and international position and consensus statements of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [Inzucchi *et al.* 2012], the American Association of Clinical Endocrinologists [Garber *et al.* 2013] and the periodically (at the beginning of the year) published practice recommendations of the ADA [American Diabetes Association, 2014].

According to our experience there is an unmet need for practical guidance on how to use the different GLP-1 RAs in combination with other antidiabetic medications. This seems especially true for the combination of basal insulin with GLP-1 RAs (BIT) as a possible extension of BOT, if prandial or postprandial blood glucose values are out of target range.

In this paper we suggest simplified guidance on the basis of reviewing studies and our own experience of how the different types of GLP-1 RAs and basal insulin may fit in a unifying concept of

determining treatment targets, integrating the knowledge of the heterogeneity of patients with T2DM and antidiabetic drugs. Additionally we provide a chart-supported guide for differential therapy using BOTplus or BIT if BOT has failed to achieve treatment targets, and we discuss their pros and cons.

Pathophysiological background

GLP-1 RAs are able to enhance or even to normalize the so-called 'incretin-effect' in relation to a meal-induced glucose transfer from the intestine to the blood in T2DM. Other metabolic effects of GLP-1 or GLP-1 RAs, not directly related to insulin secretion, are delayed gastric emptying and enhanced satiety, as well as the suppression of glucagon and its effects on liver gluconeogenesis during meals.

Although most of these effects are seen in the prandial or early postprandial situation, early night or fasting dysglycemia can be improved only by GLP-1 RAs but not through endogenous GLP-1 under normal conditions. The reasons for this are the special features of GLP-1 RAs in comparison with native GLP-1, longer half life and durable higher concentrations.

Differentiation of GLP-1 RAs

In principle, all GLP-1 RAs activate the GLP-1 receptor on β cells. But the resulting insulin secretion during a mixed meal is not only related to the action of GLP-1 RAs on β cells. Delayed gastric emptying, enhanced satiety related to gastric and cerebral signals as well as the suppression of glucagon and its effects on liver gluconeogenesis are also influenced by GLP-1 RAs at considerably different magnitudes. The clinical relevance of these differences is in discussion. Some of the possible relevant effects are summarized as follows.

Effects of GLP-1 RAs on first- and second-phase insulin secretion. One of the first most important events during the development of T2DM is the loss of the first phase of insulin secretion [Pratley and Weyer, 2001; Del Prato, 2003]. Different tests are available to prove the functional integrity of β -cells in this regard. For intravenous glucose a restoration of the first-phase insulin secretion was shown for exenatide [Fehse *et al.* 2005], liraglutide [Degn *et al.* 2004] and lixisenatide [Becker *et al.* 2014] (Figure 1) in patients pretreated with

Figure 1. Time course of insulin secretion rate (ISR) of the first-phase insulin release after subcutaneous injection of lixisenatide at 0 min and after an intravenous glucose load at 120 min in healthy subjects (HS) and patients with T2DM treated with placebo versus lixisenatide [Becker *et al.* 2014].

diet and exercise or metformin and sulfonylurea (SU) in patients with moderate obesity with a relatively short duration of diabetes (< 5 years) and good (HbA1c < 7%) to moderate (HbA1c about 8%) glycemic control.

Effect of GLP-1 RAs on gastric emptying. When estimating the stimulatory action of GLP-1 RAs on insulin secretion one has to take into account a second GLP-1 effect, retardation of gastric emptying which is different in the various GLP-1 RAs [Fineman *et al.* 2012]. The main results of a slower pass of the meal from the stomach to the intestine are a lowered flow of carbohydrates to the intestine and a decrease in postprandial glucose peaks and excursions. About 35% of the variance in glycemic response to oral glucose in patients with T2DM is due to gastric emptying [Jones *et al.* 1996]. Gastric emptying is influenced by a variety of individual factors, including long-term glycemic control, and is at least partially involved in the gastrointestinal symptom complexes of many patients with diabetes [Koch and Uwaifo, 2008].

Nevertheless the incretin effect to stimulate insulin secretion could be less pronounced if there is a stronger effect of GLP-1 RAs on gastric emptying. In comparison to continuous-acting GLP-1 RAs [exenatide long-acting release (LAR)] only the short-acting GLP-1 RAs (exenatide twice daily) have an insulin-sparing effect during a mixed meal [Degn *et al.* 2004]. The differences of short- and continuous-acting GLP-1 RAs in the

insulin-sparing effect cannot be explained by different plasma concentrations, for example, in case of exenatide twice daily and exenatide LAR because during the test meal period the concentrations of exenatide were higher in exenatide LAR compared with exenatide twice daily [Fineman *et al.* 2012]. Because both medications contain the same substance this suggests that the kind of preparation in the case of exenatide determines the insulin-sparing effect.

The continuous-acting liraglutide (1.2 and 1.8 mg/day) has a moderate effect on gastric emptying during the early phase after a breakfast meal in patients with T2DM. But most of its prandial glucose-lowering effect is related to enhanced insulin secretion [Flint *et al.* 2011].

Also lixisenatide, a short-acting GLP-1 RA, retards gastric emptying [Lorenz *et al.* 2013]. The retardation of gastric emptying is so effective that much less insulin is necessary to lower the prandial glucose to an even greater extent after a standard meal compared with liraglutide [Kapitza *et al.* 2013]. The calculated effect of GLP-1 RAs on insulin secretion therefore has to be adjusted not only to the absolute amount of loaded glucose but also to the retardation of glucose absorption. This means that the measured insulin secretion rate after the application of a GLP-1 RA might be lower than on another GLP-1 RA but sufficient to meet the respective patient needs [Ratner *et al.* 2009].

Effects of GLP-1 RAs on glucagon. For more than 40 years the ‘paradoxical’ response of glucagon after carbohydrate or protein ingestion is known for patients with diabetes type 1 (T1DM) and T2DM [Unger *et al.* 1970; Müller *et al.* 1970]. In healthy individuals a carbohydrate meal suppresses glucagon secretion, whereas a protein meal enhances glucagon secretion. Hyperglycemia artificially induced in healthy individuals leads to a suppression of the glucagon-stimulating effect of protein. In patients with T1DM and T2DM, the glucagon concentration in the fasted state is already too high compared with the elevated blood sugar, so there is a fasting hyperglucagonemia. Additionally the normal suppressive effect of a carbohydrate meal is diminished or even a ‘paradoxical’ rise of glucagon can be observed in some individuals with diabetes. The protein-stimulated glucagon secretion is ‘retained’ but inappropriately high in relation to the prandial and postprandial hyperglycemia compared

with healthy individuals under artificial hyperglycemic conditions. In summary, fasting hyperglucagonemia and prandial/postprandial ‘paradoxically’ elevated glucagon secretion both considerably contribute to the hyperglycemic state in T2DM [Shah *et al.* 2000]. Recently it was demonstrated that already in prediabetic states the normal pulsatile insulin-glucagon crosstalk (in simple terms, insulin high–glucagon low and *vice versa*) was lost [Rohrer *et al.* 2012]. According to new data there is a very early inhibitory effect of glucose on insulin but not on glucagon secretion, measurable *in vitro* 60–90 s after glucose increased. This early effect seems to be responsible for the physiological phase shift in the oscillatory secretion of insulin and glucagon and its disturbance might be the starting point for the crosstalk failure and the development of a diabetic state [Hellman and Grapengiesser, 2014].

GLP-1 RAs are effective means to reduce fasting and prandial/postprandial glucagon. Acute exenatide application diminished the mixed meal related increase in glucagon in T2DM [DeFronzo *et al.* 2008], explaining about one-third of the reduction in postprandial hyperglycemia [Cervera *et al.* 2008]. During longer-term exposure to exenatide (30 weeks) fasting glucagon was reduced significantly more with exenatide LAR compared with exenatide twice daily [Drucker *et al.* 2008]. However, exenatide twice daily had greater glucagon suppressive effect compared with the DDP-4 inhibitor sitagliptin when exenatide is given before breakfast and dinner [Berg *et al.* 2011].

At least in healthy individuals, exenatide does not suppress the glucagon release during exercise, preventing hypoglycemia during physical activity [Khoo *et al.* 2010]. Exenatide also suppresses glucagon in T1DM with and without residual insulin secretion [Ghazi *et al.* 2014].

For liraglutide a numerical but not significant difference in glucagon concentrations before and during a mixed meal was found in overweight Japanese patients with diabetes treated with liraglutide at a maximum dose of 0.9 mg/day [Matsumoto *et al.* 2013]. The incremental ratio of glucagon was significantly reduced during the early phase of meal ingestion (15–60 min after the start of the meal), leading to the conclusion that glucagon suppression at least in this early phase of meal ingestion contributes to the postprandial glucose-lowering effect of liraglutide.

Lixisenatide given in the morning before a standard meal in comparison to placebo reduced 2 h glucagon as well as 2 h glucose and 2 h insulin significantly in a meta-analysis of RCTs [Ahrén *et al.* 2014a] and in further studies [Rosenstock *et al.* 2014b]. Interestingly there was a trend for a stronger correlation between the (reduced) 2 h postprandial glucagon and the (reduced) 2 h postprandial plasma glucose (PPG) with lixisenatide than with placebo.

There are several possible explanations for the effect of GLP-1 RAs on glucagon. It may directly bind to GLP-1 receptors on pancreatic α -cells, although there are contradictory results about the presence and distribution of GLP-1 receptors in α -cell populations [Moens *et al.* 1996; Heller *et al.* 1997]. Recently it was shown in a new transgenic mouse model that only about 10% of pancreatic α -cells express GLP-1 receptors, whereas they are much more abundant in β - and in δ -cells [Richards *et al.* 2014]. These findings support the concept that the glucagon-suppressive effect of GLP-1 and GLP-1 RAs is mediated through somatostatin, released by δ -cells stimulated by GLP-1 RAs [de Heer *et al.* 2008].

Effects of GLP-1 RAs on fasting, prandial and postprandial glycemia. The different mode of actions of the various GLP-1 RAs and their formulations should have influence on their antihyperglycemic effects.

Indeed, differences between fasting and postprandial glycemia under the same GLP-1 RA substance exenatide but given twice a day or once weekly (LAR formulation) were shown [Drucker *et al.* 2008]. Although both exenatide formulations reduced fasting, prandial and postprandial glucose values, exenatide twice daily was superior in lowering glucose values after breakfast and dinner. On the contrary, exenatide LAR was superior in reducing fasting glycemia and HbA1c and more patients achieved HbA1c below 7%.

In another RCT comparing liraglutide with exenatide twice daily a predominant effect of liraglutide on fasting blood glucose and HbA1c was seen and in a higher number of patients a target HbA1c below 7% was achieved [Buse *et al.* 2009], whereas exenatide twice daily was more effective after breakfast and dinner again.

Also lixisenatide has an inherent pronounced effect on the reduction of postprandial blood glucose with once-daily administration, especially at

Table 1. Comparison of short-acting *versus* long-acting GLP-1 RAs [Meier *et al.* 2012] (reproduced with permission of the Nature Publishing Group).

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide LAR Liraglutide
Half life	2–5 h	12 h–several days
<i>Effects</i>		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)
GLP-1, glucagon-like peptide 1; LAR, long-acting release.		

breakfast and partially at lunch as known from exenatide twice daily. In an earlier study lixisenatide lowered blood glucose after breakfast to near 100 mg/dl (5.6 mmol/liter) [Distiller and Ruus, 2008]. It was also sufficient in relation to other meals compared with placebo. This pronounced reduction of the prandial glucose values after a meal was also visible in relation to the continuous-acting GLP-1 RA liraglutide [Kapitza *et al.* 2013]. Additionally this study shows that, compared with the first day of treatment (acute response), the effect of lixisenatide on prandial glucose excursions on a standard meal after a longer treatment period is even better.

The different pharmacodynamic properties of GLP-1 RAs were the basis of a differentiation of so-called ‘short-acting’ GLP-1 RAs such as exenatide twice daily or lixisenatide, and ‘continuous-acting’ or ‘long-acting’ GLP-1 RAs such as exenatide LAR or liraglutide [Fineman *et al.* 2012; Meier, 2012; Vidal, 2013]. With albiglutide given once a week [Matthews *et al.* 2008], recently approved in the US by the Food and Drug Administration [FDA, 2014] with a positive opinion for Europe by the European Medicines Agency (EMA) [EMA, 2014a] and with the investigational drug dulaglutide [Jimenez-Solem *et al.* 2010] also given once a week, the group of

continuous-acting GLP-1 RAs was recently extended. Albiglutide [Ahrén *et al.* 2014b; Woodward and Anderson, 2014] and dulaglutide [Umpierrez *et al.* 2014; Nauck *et al.* 2014] were found to preferentially suppress fasting glucose with improvement in overall glycemia. Compared with liraglutide the HbA1c reduction of albiglutide was lower with more injection site reactions but less gastrointestinal side effects [Pratley *et al.* 2014]. In contrast, in patients treated with maximum tolerated doses of metformin and pioglitazone, dulaglutide 0.75 mg/day and 1.5 mg/day compared with the short-acting exenatide twice a day was more effective in lowering HbA1c with more patients achieving HbA1c below 7% and 6.5% with a similar or even lower risk of hypoglycemia [Wysham *et al.* 2014].

Substance-dependent benefits of GLP-1 RA-based strategies

In a recent review features and properties of GLP-1 RAs and their effects on fasting and postprandial glucose levels, insulin and glucagon secretion, gastric-emptying rate, blood pressure, heart rate, body weight reduction and main side effects were summarized (Table 1). This schematic representation can be used basically as a guide for the differentiated treatment

with incretin-based therapeutics, including lixisenatide as a prandial and short-acting GLP-1 RA.

With respect to the application of GLP-1 RAs in the context of individualized T2DM therapy, the four main effects mentioned above are conceivable in many ways. As recently shown [Meier, 2013] the lowering of postprandial glucose with lixisenatide is possibly independent from β -cell function. In contrast, in the case of liraglutide, better HbA1c lowering was seen in patients with T2DM with retained β -cell function [Meier *et al.* 2011; Kozawa *et al.* 2012]. Using glucagon-stimulated c-peptide indices, a better response to liraglutide was seen in patients who had a better c-peptide response [Kondo *et al.* 2013]. During exenatide therapy the increase in postprandial glucose values was minimized even at a lower insulin secretion rate [Linnebjerg *et al.* 2008]. In agreement with these observations, the HbA1c glucose-lowering effect of exenatide twice daily was independent of diabetes duration up to more than 15 years after diabetes diagnosis [Rosenstock *et al.* 2012].

Additionally as a lower β -cell function often occurs in older patients with diabetes, the use of prandial active GLP-1 RAs such as lixisenatide or exenatide can be postulated to be advantageous for these stages of diabetes.

These and other clinical benefits of the different GLP-1 RAs are summarized in a recent critical analysis [Nauck *et al.* 2013].

In addition to the glucose-lowering effects of GLP-1 RAs discussed above, great benefits were seen, for example, avoidance of hypoglycemia because there is no insulin stimulation at low glucose levels, no risk of weight gain and a reduction of systolic blood pressure.

As already indicated, the different effects of GLP-1 RAs on reducing fasting and postprandial glucose even in the same patient are not only substance or structure related; they also depend obviously on other features, for example, on dose, time, sequence of substance application and drug formulation. The benefits of a GLP-1 RA therapy for individual patients in addition to their efficacy were summarized to be safety and easy manageability, without complex dosing or monitoring algorithms [Gallwitz, 2013].

Practical considerations

How can this knowledge be used for an individual therapeutic regime?

According to the new guidelines for patients with T2DM, specific features of patients, their abilities, preferences and living and surrounding conditions have to be included in decision making. However, there are formal criteria, included in the drug information sheet, limiting the use of different medications under certain circumstances.

Unfortunately the long-acting exenatide LAR can only be combined with OADs but not with insulin, although it could be a very interesting therapeutic option.

Practical approach in the use of GLP-1 RAs

In addition to the indications, comorbid conditions which might influence the use of GLP-1 RAs in general also have to be considered (Figure 2). Although they should play a role in the decision-making process, many of them were not studied thoroughly or were part of the exclusion criteria in clinical studies.

GLP-1 RAs can have a positive influence on existing comorbid conditions or even preventive effects on possible future complications, which should be considered.

Bearing in mind the situation for many antidiabetic medications, a German diabetes expert group has recently released a proposal for decision making to overcome this problem in the general use of antidiabetic medications for the first-line treatment of patients with T2DM [Tschöpe *et al.* 2013]. In addition to our own experience in the use of these medications in first- and second-line treatments and especially in BIT, we have taken into account the opinion of these experts in the selection and ranking of the conditions in Figures 2 and 4 and in the following.

First, obesity. Especially android obesity with visceral fat accumulation and nonalcoholic fatty liver disease (NAFLD) is a principal target in T2DM. This special kind of fat distribution is associated with insulin resistance, enhanced gluconeogenesis, hypertension, lipid dysregulation, inflammation, risk of thrombosis and many other risk factors for cardiovascular events [Lee *et al.* 2013]. Interestingly, the GLP-1 response to oral glucose is reduced in NAFLD and nonalcoholic

Comorbid conditions which may affect the use of GLP-1RA

Obesity (BMI ≥ 30 kg/m²) Preferred, if of android origin with visceral/liver fat accumulation Reduction in liver fat correlated with improvement in HbA1c	
Enhanced risk of hypoglycemia (older age, renal failure, medication) or need to avoid hypoglycemia (e.g. professional reasons)	
Age No use below 18 years, in older patients preferred use in 'young old' (65-79 years), no data in 'old old' (80-89 years) and older	
Previous macro- and microvascular diseases Until now, no additional risks observed, protective effects possible, Caution: preexisting maculopathy, higher grade retinopathy, longer diabetes duration	
Renal failure Use with care (lixisenatide: CrCl $< 50 \geq 30$ ml/min), dose reduction (exenatide: CrCl $< 60 \geq 30$ ml/min), not suggested (liraglutide: CrCl < 60 ml/min, exenatide and lixisenatide: CrCl < 30 ml/min).	
Liver disease Exenatide/lixisenatide: side effects not expected but no conclusive information, liraglutide: not suggested in mild, severe and very severe liver failure	
Gastrointestinal and pancreatic diseases Exenatide, liraglutide and lixisenatide are not recommended in patients with severe gastrointestinal diseases and contraindicated in patients with previous pancreatitis and pancreas carcinoma	

Figure 2. Comorbid conditions which may affect the use of GLP-1 RAs. BMI, body mass index; CrCl, creatinine clearance; GLP-1 RA, glucagon-like protein 1 receptor agonist; HbA1c, hemoglobin A1c.

Algorithm for optimizing BOT with short acting GLP-1 RA

Figure 3. Algorithm for optimizing basal insulin supported oral therapy (BOT) with short-acting glucagon-like protein 1 receptor agonists (GLP-1 RAs).

steatohepatitis in patients with insulin resistance, hyperinsulinemia and hyperglucagonemia but (still) without diabetes, one possible argument for the use of GLP-1 RAs under these conditions [Bernsmeier *et al.* 2014].

Indeed GLP-1 RA therapy reduced not only weight but more specifically also abdominal/visceral and liver fat and several biomarkers related to inflammation and insulin resistance [Tushuizen *et al.* 2006; Buse *et al.* 2007; Bunck *et al.* 2010;

Inoue *et al.* 2011; Cuthbertson *et al.* 2012; Shao *et al.* 2014] and, in initial studies, improved liver histology in patients with diabetes and NAFLD [Kenny *et al.* 2010]. Therefore, it makes sense to put this type of obesity in the first row of our table.

In a recent review about the effects of GLP-1 RAs on body weight in patients with diabetes [Vilsbøll *et al.* 2012], including randomized trials published between 2004 and 2011, groups of GLP-1 RA (exenatide given twice daily, exenatide given once weekly, as a long-acting release, and liraglutide given once daily) achieved a significantly greater weight loss than control groups (with different antidiabetic medication) of -2.8 kg [95% confidence interval (CI) -3.4 to -2.3]. The weight reduction was seen for trials in which the control group received insulin (-4.8 kg, 95% CI -5.1 to -4.5 ; six trials), OADs including metformin or SU compounds (-3.0 kg, 95% CI -4.9 to -1.2 ; three trials) and DPP-4 inhibitors (-2.0 kg, 95% CI -2.9 to -1.1 ; two trials).

A prospective study [Cuthbertson *et al.* 2012] demonstrated that GLP-1 RA therapy (with exenatide or liraglutide) for 6 months in patients with obese T2DM treated with metformin and SU/DPP-4 inhibitors dramatically improved hepatic steatosis. Intrahepatic lipid content (IHL) measured by proton magnetic resonance spectroscopy has been reduced by 42%. Patients with the highest pretreatment IHL had the greatest absolute reduction in IHL. Interestingly, the individual changes in IHL did not correlate with changes in total body weight, total abdominal fat, visceral adipose tissue or subcutaneous tissue, but it did correlate with reduction in HbA1c.

The German diabetes expert group [Tschöpe *et al.* 2013] suggested using the following antidiabetic medication as second-line treatment in patients with metformin who fail to achieve treatment targets [fasting plasma glucose of 3.9 – 7.2 mmol/liter (70 – 130 mg/dl) or postprandial plasma glucose below 10.0 mmol/liter (180 mg/dl)] in order of weight benefit: GLP-1 RAs, DPP-4 inhibitors, acarbose, bile acid sequestrants and amylin analogs. In case of indicated insulin treatment the group suggested considering a basal insulin supplementation.

In summary, there are many good reasons to use GLP-1 RAs in obese patients with diabetes, especially when a high liver fat content (steatosis hepatis) is present, even as first-line drugs but

normally after metformin or if metformin is contraindicated.

Second, risk of hypoglycemia. Many patients have conditions leading to increased risk of hypoglycemia when treated with SU and short-acting or mixed insulins. Other patients have occupations that exclude the ingestion of substances with hypoglycemic potential. In a recent meta-analysis, hypoglycemia with glucose up to 3.1 mmol/liter (≤ 56 mg/dl) or up to 2.8 mmol/liter (≤ 50 mg/dl) was experienced by 10.1% (95% CI 7.3–13.8%) and 5.9% (95% CI 2.5–13.4%) and severe hypoglycemia by 0.8% (95% CI 0.5–1.3%) of patients with any SU treatment, with the lowest risk for gliclazide [Schopman *et al.* 2014]. Although the risk of severe hypoglycemia seems to be low, the authors acknowledge that the real-world risk of hypoglycemia might be considerably higher compared with RCTs.

Hypoglycemia, including silent hypoglycemic episodes, have tremendous effects on cardiovascular morbidity and mortality [Hanefeld *et al.* 2013; Mellbin *et al.* 2013; Stahn *et al.* 2014] as well as on cerebral function [Feinkohl *et al.* 2014].

In a recent survey the main predictors of self-reported severe hypoglycemia (about 11%) in multiethnic patients with T2DM age 30–80 years and treated with different antidiabetic medications were as follows: near normal (HbA1c $< 6\%$) and very poor glycemic control (HbA1c $> 9\%$) unrelated to the age of patients, duration of diabetes and use of insulin [Lipska *et al.* 2013]. These observations support the results of the ACCORD trial. Patients with Diabetes who failed to achieve a lower HbA1c level despite intensive or standard diabetes treatment experienced high rates of severe hypoglycemia [Miller *et al.* 2010]. One of the most prevalent causes of hypoglycemia in this study was variation in food intake (about 50% of all events) [Bonds *et al.* 2012]. In another recent report, risk of having hypoglycemia was increased for renal failure, autonomic neuropathy, adrenocortical insufficiency and in patients with mental disorders, including dementia, depression, anxiety and affective disorders [Kostev *et al.* 2014]. According to their mode of action, GLP-1 RAs in monotherapy or added to metformin or glitazones do not enhance the risk of hypoglycemia [Fonseca, 2014].

Third, age

Many older patients have problems with complex kinds of antidiabetic therapies because of decline

in cognitive function, loss of social support, erratic meals and coexisting chronic illnesses. In a consensus report of the ADA [Kirkman *et al.* 2012] a relaxation of HbA1c targets was suggested depending on comorbid conditions. For healthy patients (few coexisting chronic illnesses, intact cognitive and functional status with longer remaining life expectancy), HbA1c less than 7.5%, fasting plasma glucose of 5.0–7.2 mmol/liter (90–130 mg/dl) and bedtime plasma glucose of 5.0–8.3 mmol/liter (90–150 mg/dl) is suggested. If the health status is more complex (multiple chronic illnesses or there are two or more impaired activities of daily living), the suggestion is HbA1c less than 8%, fasting plasma glucose of 5.0–8.3 mmol/liter (90–150 mg/dl) and bedtime plasma glucose of 5.6–10.0 mmol/liter (100–180 mg/dl). In very complex or poor health status (long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more impaired activities of daily living), HbA1c less than 8.5%, fasting plasma glucose of 5.6–10.0 mmol/liter (100–180 mg/dl) and bedtime plasma glucose of 6.1–11.1 mmol/liter (110–200 mg/dl) is sufficient. With these suggestions and the detrimental effects of hypoglycemia on older people in mind, there seems to be an indication for the use of GLP-1 RAs at least in the above-mentioned healthy patients and even in the more complex health stages, although randomized controlled BIT studies evaluating any potential benefit in older people are missing [Vora, 2013]. In retrospective observational studies there seems to be a certain preference for GLP-1 RA use in the ‘young old’ (65–79 years) compared with the ‘old old’ (80–89 years) with the notion that the ‘old-old’ had the same mean HbA1c values (about 7%) with less antidiabetic medication [Thompson *et al.* 2013].

Because of missing, study-based evidence the above-mentioned German diabetes expert group generally suggested the preferred use of metformin, GLP-1 RAs and DPP-4 inhibitors and long-acting insulins over other treatment options (SU, glinides and glitazones) in older patients [Tschöpe *et al.* 2013].

Fourth, micro- and macrovascular diseases. Improvement of body weight, blood lipids, blood pressure and inflammatory markers, clearly documented effects of GLP-1 RAs, should all lead to a reduced risk of micro- and macrovascular events. Because the first randomized, long-term clinical trials with GLP-1 RAs and micro- and

macrovascular events as end points are expected to finish in 2016, only experimental data, retrospective data and results of short-term studies and meta-analyses are available. Positive metabolic and blood pressure effects in patients with diabetes were worked out in recently published original articles [Best *et al.* 2011; Lønborg *et al.* 2012; Nathanson *et al.* 2012], reviews [Mannucci and Dicembrini, 2012; Burgmaier *et al.* 2013] and *in vitro* and *in vivo* studies in animals supporting an indirect (mediated via improvement of glycemia) and a direct nonglucose-dependent protective effect of GLP-1 RAs on the cardiovascular system.

One randomized study in patients without diabetes with prior myocardial infarction and primary transcutaneous revascularization has shown that, in comparison with placebo, the GLP-1 RA exenatide is able to produce a small reduction in infarct size after reperfusion [Lønborg *et al.* 2012]. This effect was seen at a plasma concentration three times higher than the concentration achieved by the usually suggested subcutaneous dose. In patients with T2DM with heart failure an exenatide infusion improved cardiac index and decreased the pulmonary capillary wedge pressure without serious adverse events, despite an increase in heart rate and a higher blood pressure in few patients [Nathanson *et al.* 2012]. However, in a 6-month short-term trial with GLP-1 RAs in obese patients with T2DM no changes in brachial artery endothelial-dependent flow-mediated dilation and endothelial-independent glyceryl trinitrate function and carotid intima-medial thickness were found [Hopkins *et al.* 2013].

In a retrospective analysis of a large database of patients with diabetes treated with exenatide twice daily (about 40,000 patients) and other antidiabetic medications (about 400,000 patients), exenatide-treated patients were significantly less likely to have a cardiovascular disease (CVD) event as well as CVD-related and all cause-related hospitalizations than patients not treated with exenatide, although the exenatide-treated patients had more prior ischemic heart disease, obesity, hyperlipidemia, hypertension or other comorbidities at baseline [Best *et al.* 2011].

In meta-analyses of patients with T2DM with different antidiabetic medications, GLP-1 RAs in comparison with OADs and insulin reduced systolic and diastolic blood pressure and total cholesterol concentrations as well as other components

of the metabolic vascular syndrome, with a small but significant enhancement of heart rate [Robinson *et al.* 2013; Monami *et al.* 2014a; Katout *et al.* 2014]. All GLP-1 RA meta-analyses regarding CVD actually have considerable limits because most finished and analyzed RCTs were not specifically designed to answer CVD questions. According to a recent sequential analysis based on RCTs until January 2013, the accumulated sample size for GLP-1 RAs *versus* placebo was only 11% (7445 of 65,212) and for GLP-1 RAs *versus* an active comparator it was only 13% (10,157 of 79,198) of the required information size [Wu *et al.* 2014]. In order to gain clarity about cardiovascular benefits and risks of GLP-1 RAs, more long-term trials and population-based studies are required.

Diabetic retinopathy (DR), one of the most severe microvascular long-term complications of hyperglycemia, can temporarily or progressively be worse after initiation of a glucose-lowering therapy. A few years ago a dramatic case report about the development of a DR after initiation of exenatide was reported [Brooks and Lissett, 2009]. In a recent study with exenatide [Varadhan *et al.* 2011], 30% ($n = 49$) of patients had a progression of DR, although 96% ($n = 47$) had improvement in HbA1c.

A new developed maculopathy was documented in 15 patients without indication for laser therapy. With greater reduction of HbA1c the proportion of patients with progression of DR was higher. Also the degree of worsening of DR was proportionate to HbA1c reduction.

In a follow-up study of 39 of these patients [Varadhan *et al.* 2014], 31 had an improvement or no documented change, although HbA1c showed a rebound in 23 patients. Eight patients had progression of DR. Only two of these patients had a sustained reduction in HbA1c. From the 15 patients with maculopathy, in 12 patients there was a regression without laser treatment and a stable status was seen in the other 3 patients. Of the 14 patients who had developed DR for the first time since the beginning of the GLP-1 RA therapy, 10 patients showed an improvement in DR on follow up and a further 3 remained stable.

The authors concluded that the deterioration in retinal function is transient and reversible during continuation of GLP-1 RA treatment. As possible

risk factors for a persistent deterioration, they identified pre-existent maculopathy, higher grade of retinopathy and longer duration of diabetes.

In accordance with the German diabetes expert group [Tschöpe *et al.* 2013], although there are very limited data about the micro- and macrovascular effects of GLP-1 RAs from clinical trials, it seems appropriate to also include GLP-1 RAs in the therapeutic portfolio of patients with cardiovascular as well as cerebrovascular diseases.

Fifth, renal failure. GLP-1 RAs can be used in early stages of renal failure at different degrees according to their regulatory approval. In a recent review the difference in the elimination kinetics of GLP-1 RAs and their relationship with clinical outcomes at various stages of renal failure were analyzed [Filippatos and Elisaf, 2013]. Although exenatide is cleared by glomerular filtration, no dosage adjustment of exenatide is required for patients with mild to moderate renal impairment. However, the recommended starting dosage of 5 µg exenatide may not be suitable for patients with end-stage renal disease or severe renal impairment [creatinine clearance (CrCl) < 30 ml/min]. The exenatide dose should be based on renal function rather than age in older patients with T2DM.

In patients with T2DM with albuminuria, exenatide reduced urinary type IV collagen and 24 h urine albumin as well as transforming growth factor β1 [Zhang *et al.* 2012]. Other renoprotective effects against increased renal oxidative stress under chronic hyperglycemia were recently shown in an experimental animal model [Fujita *et al.* 2014].

According to the regulatory approval, treatment in renal failure has to be done with care (lixisenatide: CrCl < 50 and ≥ 30 ml/min), dose reduction (exenatide: CrCl < 60 and ≥ 30 ml/min) or is not suggested (liraglutide: CrCl < 60 ml/min; exenatide and lixisenatide: CrCl < 30 ml/min).

In one case report a reversible pancreatitis/pancreatic tail swelling was seen in an older patient with end-stage renal disease on liraglutide [Nakata *et al.* 2012]. However, two cases of severe renal failure were reported in patients with diabetes receiving GLP-1 RAs [Dubois-Laforgue *et al.* 2013].

In a recent review about safety of GLP-1 RA use in renal failure [Giorda *et al.* 2014], the authors

concluded that liraglutide has a slightly wider database than either exenatide or lixisenatide in favor of its use in patients with renal impairment. But the scant evidence does not allow more special conclusions or recommendations. The German diabetes expert group [Tschöpe *et al.* 2013] rated microalbuminuria (no firm recommendations) and renal failure as neutral (with low evidence) and generally suggested glitazones, glinides, insulin, and more recently DPP-4 inhibitors.

Sixth, hepatic failure. Data on GLP-1 RA therapy in patients with hepatic impairment in clinical studies are scarce. In the documents for the regulatory approval of exenatide it was stated that an increase in blood concentrations of exenatide is not expected because exenatide has been mainly renally excreted. For liraglutide, the use was not suggested in mild, moderate and severe liver failure and for lixisenatide the pharmacokinetics was not expected to be affected by liver disease. In a recent review about the safety of GLP-1 RAs in patients with hepatic impairment [Giorda *et al.* 2014], no clear conclusion could be drawn because of scarcity of information. Additional clinical trials are strongly suggested. The German diabetes expert group [Tschöpe *et al.* 2013] graded liver failure as being neutral (not recommended and not contraindicated, no conclusive recommendations) in relation to GLP-1 RA therapy. The group suggested, because of the possible hepatic side effects of all other antidiabetic medications, the use of insulin is the remaining option for glycemic control.

Seventh, pancreatic and gastrointestinal dysfunction. Based on some experimental, animal (mainly rodents) and human data, concerns were expressed that GLP-1 RA therapy might have detrimental effects on human pancreas and thyroid [Elashoff *et al.* 2011; Butler *et al.* 2013]. Some of the arguments have already at least partially been refuted [Drucker, 2013; Nauck, 2013]. Even if there is an increased risk for pancreatitis with incretin therapies, the risk should be limited to 1.5 times the diabetic population [Nauck and Meier, 2014].

Recent meta-analyses of patients treated with GLP-1 RAs have not shown an enhanced risk in the development of pancreatitis [Monami *et al.* 2014c; Li *et al.* 2014]. This view has been supported by a recently published joint statement of the EMA with the FDA [Egan *et al.* 2014].

Nevertheless, the use of GLP-1 RAs should be avoided in patients with previously or actually known pancreatitis or in patients with severe gastrointestinal symptoms or diseases and previous thyroid cancer or multiple endocrine neoplasia.

We should also avoid the use of any GLP-1 RAs in patients with a history of pancreas carcinoma, although the recently released statements of the EMA and the FDA actually found no evidence for an increased carcinoma risk. Nevertheless further long-term observation of side effects of GLP-1 RAs is reasonable and necessary regarding the usual time lag between drug exposure and clinical symptoms, especially in chronic or malignant diseases.

Practical approach of BIT with liraglutide and insulin detemir or insulin degludec or any other basal insulin

The use of longer-acting liraglutide is actually no longer limited to a combination with insulin detemir after a certain treatment period with liraglutide and OADs. Recently a positive opinion of the EMA [EMA, 2014b] adopted a new indication to include the combination of liraglutide with any basal insulin. The EMA additionally adopted a new indication to include the combination of the longer-acting insulin degludec with any GLP-1 receptor agonist [EMA, 2014c]. These decisions will provide the basis for a more intense use of liraglutide and insulin degludec in the BIT concept at least in Europe but probably in the future also worldwide and in the USA, where glargine is the leading basal insulin [Turner *et al.* 2014]. The results of recent clinical studies in obese patients with T2DM using the combination of liraglutide and insulin degludec plus continued metformin but discontinuation of SU as a special kind of BIT were encouraging: favorable results for glycemia (-0.5% HbA1c), induction of a further slight weight loss after randomization, and no severe hypoglycemic events as well as very low rates of minor hypoglycemia and other side effects [DeVries *et al.* 2012]. In a recently published study comparing BIT (liraglutide added to insulin degludec and metformin) *versus* BOTplus (adding a single daily dose of insulin aspart to insulin degludec and metformin) in patients with T2DM with baseline HbA1c of 7.7%, the BIT improved HbA1c (-0.74%), with 49% of patients achieving an HbA1c less than 7% without weight gain and confirmed hypoglycemia [Mathieu *et al.* 2014]. If the new combination of insulin degludec and liraglutide (IDeg/Lira) is additionally approved

in a fixed form by the EMA and the FDA, the concept of BIT will gain even more acceptance in clinical practice.

At the moment, if we have a patient who is obese, receiving liraglutide and metformin or SU but fasting and postprandial values cannot be kept in the target range, we gradually add insulin detemir in the evening (at high fasting glucose values) or morning (if prandial or postprandial glucose values are out of range) or twice daily if glucose targets with a once daily approach are not reached. At the beginning of combination therapy with liraglutide we stop the use of a SU to avoid the risk of hypoglycemia. According to the above-mentioned new indications for insulin degludec and liraglutide [EMA, 2014b], it is advised that, when adding insulin degludec to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

When adding GLP-1 receptor agonists to insulin degludec, it is recommended that the dose of insulin degludec is reduced by 20% to minimize the risk of hypoglycemia. Subsequently, dosage should be adjusted individually.

In our daily practice with liraglutide and insulin detemir in combination therapy this kind of BIT is well tolerated and long lasting, and this should be true for the combination of liraglutide with insulin degludec as well. Nevertheless in the former combination we have observed some patients with low or, over time, reduced effects on body weight and glycemia. A few patients were switched to a BIT scheme with shorter-acting GLP-1 RAs with success, possibly because of their long lasting retardation effect on gastric emptying.

Practical approach of BIT with exenatide or lixisenatide and basal insulin

Because of the widespread use of the BOT regime with insulin glargine, it seems reasonable to simply extend this treatment option to BIT by adding prandial acting exenatide or lixisenatide, if postprandial glucose values exceed the treatment target. This kind of BIT will also gradually reduce fasting blood glucose values. In Figure 3 a treatment algorithm is suggested.

In accordance with this strategy, exenatide twice daily [Riddle *et al.* 2010; Buse *et al.* 2011; Tobin *et al.* 2012] as well as lixisenatide [Seino *et al.* 2012; Riddle *et al.* 2013a, 2013b] effectively lowered

prandial/postprandial glucose values in patients on basal insulin, supporting the BIT concept.

Both prandial-acting GLP-1 RAs have nearly comparable effects on glucose profiles, average glycemia and number of patients achieving target HbA1c values according to a recently published study [Rosenstock *et al.* 2013], fulfilling noninferiority criteria for lixisenatide *versus* exenatide. In comparison to exenatide given twice daily, the patients with once daily applied lixisenatide had slightly lower weight loss but experienced a lower incidence of hypoglycemia and fewer gastrointestinal side effects.

So, if we have a patient with high prandial/postprandial blood glucose values, high body weight, but a tendency to some hypoglycemic events during BOT, a tendency for overall gastrointestinal discomfort and the wish for once daily injection (for the GLP-1 RA), we would surely prefer lixisenatide over exenatide.

If we have a more robust patient with obesity, and the main aims are to lower prandial/postprandial blood glucose and body weight (and liver fat), with possibly two or three 'main' meals, without hypoglycemic tendency who has never experienced gastrointestinal discomfort and has no problems with two injections (of GLP-1 RAs), we would probably try exenatide twice daily.

In practice we have also successfully switched between both kinds of BIT, for example, a patient on exenatide unexpectedly experienced a higher degree of gastrointestinal discomfort and was more fortunate with lixisenatide; and a patient on lixisenatide, who did not achieve sufficient control of late evening postprandial blood glucose, had better control with twice daily exenatide.

Should we reduce the dose of basal insulin during initiation of short-acting GLP-1 RAs?

Because it might be that adding a short-acting GLP-1 RA to continued BOT improves endogenous insulin secretion and reduces prandial and postprandial blood glucose, theoretically there is a certain risk of additional hypoglycemia at least at the beginning of BIT.

In our experience with more patients with hyperglycemia under hospital conditions, we found no real risk if we continued with the initial basal insulin dose in the case of insulin detemir and insulin glargine. This might be different in

outpatient clinical settings, where the patient's daily activities are not under medical control and the patient already has hypoglycemia. So it seems advisable under these conditions to reduce the dose of the basal insulin, especially if high or very high doses were used, to avoid any kind of hypoglycemia. For insulin glargine an advisable titration could follow the standard regime approved in clinical studies, for example, in the case of fasting plasma glucose less than 4.0 mmol/liter (< 72 mg/dl) a reduction of 2 units per day is advised [Yki-Järvinen *et al.* 2007]. Regarding the new combination of insulin degludec with liraglutide according to the published positive summary of opinion of the EMA, if a GLP-1 RA is added to insulin degludec, the dose of insulin degludec should be reduced by 20% [EMA, 2014a].

BOTplus versus BIT: postprandial hyperglycemia as treatment target

Many studies have shown an importance of fasting, prandial and postprandial plasma glucose for the development of microvascular and macrovascular diseases.

Starting with the hypothesis that the loss of the first phase of insulin secretion in response to a meal challenge test leads to increasing postprandial hyperglycemia, even in recently diagnosed individuals [Coates *et al.* 1994; Pratley and Weyer, 2001; Del Prato, 2003], it seems reasonable that postprandial hyperglycemia is a key factor in T2DM. Many studies found, in addition, that increasing postprandial hyperglycemia is not only a major point in conversion from pathological glucose tolerance to early diabetes stages with near normal fasting blood glucose, but also in patients with near normal glycemic control and enhanced glucose excursions. Postprandial glycemia excursions make an even greater contribution to HbA1c values when the glycemic control improves in patients treated with antidiabetic medications [Monnier *et al.* 2003, 2007; Bonora *et al.* 2006].

Postprandial hyperglycemia is one of the most important problems from the beginning of the disease until later stages when normal glucose control is targeted. Some studies also confirmed that postprandial hyperglycemia is an independent cardiovascular risk factor whether or not these studies are based on 2 h glucose levels after oral glucose tolerance test or after meal challenge tests [Hanefeld *et al.* 2000; Balkau *et al.* 2004; Ceriello *et al.* 2004; Cavalot *et al.* 2006, 2011; Meier *et al.*

2009]. The obvious idea to prevent CVDs by lowering postprandial hyperglycemia was examined in the STOP-NIDDM trial and the reduction of incidence of new cardiovascular events in people with IGT has been shown [Chiasson *et al.* 2003]. According to the results of several outcome studies like ACCORD [Gerstein *et al.* 2008], VADT [Duckworth *et al.* 2009], ADVANCE [Patel *et al.* 2008] and HEART2D [Raz *et al.* 2009] in combination with the data of UKPDS [Turner *et al.* 1998; Stratton *et al.* 2000] and DCCT/EDIC [Nathan *et al.* 2005] and their long-term follow ups, the UKPDS 10-year post-trial monitoring [Holman *et al.* 2008] and the Epidemiology of Diabetes Interventions and Complications observational follow up [Nathan and DCCT/EDIC Research Group, 2014], it seems plausible that bearing the 'metabolic memory' [Nathan *et al.* 2005] and the 'glycemic thresholds' [Zoungas *et al.* 2012] for the association of HbA1c levels with vascular complications and death in mind, hyperglycemic control should start as early as possible to show a beneficial effect.

Lowering postprandial glycemia as part of the 'glycose triad' [Monnier *et al.* 2006; Ceriello, 2010] seems to be valuable and necessary, and according to the recently published International Diabetes Federation *Guideline for Management of PostMeal Glucose in Diabetes* is supported by a high level of evidence [International Diabetes Federation, 2011].

BOTplus versus BIT: pros and cons

In the following section of our paper we present available data from RCTs using BOTplus or BIT in patients with T2DM and in summary a graded chart (Figure 4) as support for an individualized decision-making process.

BOTplus. The addition of one bolus of short-acting insulin to BOT (BOTplus) has received some attention in recent years after interesting and stimulating results were published [Lankisch *et al.* 2008; Davidson *et al.* 2011; Owens *et al.* 2011; Del Prato *et al.* 2012; Mathieu *et al.* 2014]. The results were implemented in a therapeutic strategy, dependent on the previous treatment and actual glycemic situation [Ampudia-Blasco *et al.* 2011].

BIT. Randomized, prospective controlled BIT studies have been performed in recent years for some of the now clinically used or forthcoming GLP-1 RAs: exenatide *versus* placebo added to

Figure 4. BOTplus versus BIT: a clinical decision guide [example: green and purple points denote two patients with different characteristics]. BIT, basal insulin combined incretin mimetic therapy; BOTplus, basal insulin supported oral therapy with the addition of one bolus of short-acting insulin; GFR, glomerular filtration rate; NAFLD, nonalcoholic fatty liver disease. Graphic design adapted from [Inzucchi *et al.* 2012; Ismail-Beigi *et al.* 2011].

insulin glargine and metformin or pioglitazone [Buse *et al.* 2011] or added to insulin glargine and metformin [Riddle *et al.* 2010]; lixisenatide *versus* placebo added to basal insulin and SU [Seino *et al.* 2012] or added to basal insulin and metformin [Riddle *et al.* 2013a] or added to insulin glargine and metformin or glitazone [Riddle *et al.* 2013b]; liraglutide, when insulin detemir was given in a previous treatment with liraglutide and metformin in comparison to a group, which continued with unchanged treatment (observational arm) [DeVries *et al.* 2012]; liraglutide, when added to insulin degludec and metformin *versus* one single injection of prandial insulin aspart added to insulin degludec and metformin [Mathieu *et al.* 2014]; and albiglutide *versus* prandial insulin lispro three times a day added to insulin glargine and OAD medication in some patients [Rosenstock *et al.* 2014a].

Treatment efficacy

BOTplus. In the first study of this kind [Lankisch *et al.* 2008] in two groups of patients

with T2DM on BOT with HbA1c slightly above the target range (basal HbA1c 7.3% in both groups) a single injection of insulin glulisine was given before breakfast or before the main meal. There was a significant and comparable improvement of HbA1c in the breakfast group (−0.31%) and in the main meal-time group (−0.36%).

In an additional proof of concept study [Owens *et al.* 2011] patients with T2DM underwent a 3-month run-in period on insulin glargine, titrated to optimize fasting blood glucose. In patients with HbA1c at least 7%, the HbA1c and fasting plasma glucose levels decreased significantly in the 3 months after randomization in both a basal-plus-bolus and a basal-insulin-only group. A significantly greater reduction of HbA1c was observed in the basal-plus-bolus group *versus* the basal-insulin-only group (−0.37% *versus* −0.11%) and significantly more participants in the basal-plus-bolus group reached HbA1c less than 7.0% than in the basal-insulin-only group (22.4% *versus* 8.8%).

In an open-label, parallel-group, 1:1:1 randomized study of adults with T2DM on OADs (HbA1c $\geq 8\%$), patients with HbA1c above 7% after a 14-week titration with insulin glargine were assigned to one, two or three times daily insulin glulisine for 24 weeks [Davidson *et al.* 2011]. HbA1c decreased from randomization to week 24 by -0.44% , -0.36% and -0.43% in the three groups, respectively. The HbA1c-lowering effect of the once a day insulin glulisine group (BOTplus) was not inferior to the effect in the other two groups, although the percentage of patients achieving an acceptable overall glycemia (HbA1c $< 7.0\%$) at week 24 was 30%, 33% and 46%. However, severe hypoglycemia occurred in twice as many patients in the insulin glulisine three times a day group compared with the other two treatment groups (18 *versus* 8 *versus* 9 events) and this group had a significantly higher event rate than the once daily group.

In another randomized trial [Del Prato *et al.* 2012] insulin glargine was used for about 8–16 weeks to achieve a target fasting plasma glucose of up to 5.6 mmol/liter (≤ 100 mg/dl). In patients with fasting plasma glucose of up to 7 mmol/liter (≤ 126 mg/dl) one dose of insulin glulisine was added at the meal with the highest postprandial plasma glucose excursion and then titrated to target 2 h postprandial plasma glucose of less than 7.8 mmol/liter (< 140 mg/dl) monitored by telecare or self-measured blood glucose (SMBG). HbA1c levels were significantly reduced by insulin glargine titration from about 8.8% to 7.9% resp. to 7.8%. Addition of insulin glulisine significantly reduced HbA1c in both groups (-0.7%). The target HbA1c ($\leq 7\%$) was achieved in 45.2% *versus* 54.8% without a significant difference between groups.

In a study with a once-daily injection of short-acting insulin to basal insulin, insulin aspart was added to insulin degludec and continuing metformin [Mathieu *et al.* 2014]. Addition of the short-acting insulin resulted in a significant reduction of HbA1c from 7.7% to 7.3%, whereas fasting blood glucose did not change [steady at 6.1 mmol/liter (110 mg/dl)]. Postprandial plasma glucose was numerically reduced at each meal. The largest reduction in prandial increments was seen at the main evening meal [prandial increment week 0: 2.4 mmol/liter (43 mg/dl); week 26: 1.4 mmol/liter (25 mg/dl)] with insulin aspart injected pre breakfast by 5.4%, pre lunch by 47.3% and pre evening meal by 47.3% of subjects. The nine-point SMBG

profile improved from a mean of 8.0 mmol/liter (144 mg/dl) to 7.0 mmol/liter (126 mg/dl).

In summary, BOTplus is an acceptable alternative to a more intensive insulin treatment and can be used safely and effectively to reduce postprandial hypoglycemia and HbA1c, especially if given at the largest meal.

BIT. GLP-1 RAs added to basal insulin with different OAD medications significantly reduced elevated HbA1c values in comparison to placebo added to the same medication by -0.69% for exenatide *versus* placebo added to insulin glargine and metformin or pioglitazone [Buse *et al.* 2011], -0.88% for lixisenatide *versus* placebo added to basal insulin and SU [Seino *et al.* 2012], -0.36% for lixisenatide *versus* placebo added to basal insulin and metformin [Riddle *et al.* 2013a], -0.32% for lixisenatide *versus* placebo added to insulin glargine and metformin or glitazone [Riddle *et al.* 2013b], -0.5% for liraglutide when insulin detemir was added to a previous treatment with liraglutide and metformin compared with a group that continued with unchanged treatment (observational arm) [DeVries *et al.* 2012] and -0.16% for albiglutide *versus* prandial insulin lispro added to insulin glargine and OAD [Rosenstock *et al.* 2014a].

In another study, a once-daily injection of liraglutide was added to insulin degludec and continuing metformin [Mathieu *et al.* 2014]. The addition of liraglutide resulted in a significant reduction of HbA1c from 7.7% to 7.0%, whereas fasting blood glucose did not change significantly [6.4 mmol/liter (115 mg/dl) *versus* 6.3 mmol/liter (113 mg/dl)]. The largest numerical reduction in prandial increments was seen at breakfast [week 0: 3.9 mmol/liter (70 mg/dl); week 26: 3.1 mmol/liter (56 mg/dl)]. In addition, there was an improvement in the nine-point SMBG profile from a mean of 8.0 mmol/liter (144 mg/dl) to 7.0 mmol/liter (126 mg/dl).

Most of the randomized studies have shown that GLP-1 RAs in combination with basal insulin (BIT) are more effective compared with BOT alone in reducing HbA1c and body weight and, if the patients are already treated with insulin, sometimes the insulin dose can be reduced considerably [Gallwitz, 2013].

BOTplus versus BIT. Actually there are only two fully published studies comparing BOTplus with BIT. One study is an indirect study comparing BIT (insulin glargine and lixisenatide)

with BOTplus (insulin glargine and short-acting insulin once a day) on the basis of a propensity score match of data extracted from randomized trials [Raccach *et al.* 2014]. In this study BIT compared with BOTplus reached a significantly higher score in the number of patients reaching the treatment target of HbA1c less than 7% plus having no weight gain and no hypoglycemic events. Additionally the overall likelihood of reaching HbA1c less than 7% for the BIT *versus* BOTplus group was 1.97 times higher. The composite endpoint of HbA1c less than 7%, no weight gain and no documented symptomatic hypoglycemia was achieved by 29.2% of patients with BIT *versus* 15.3% with BOTplus. For patients in the BIT group compared with the BOTplus group, the likelihood of reaching HbA1c less than 7%, no weight gain and no symptomatic hypoglycemia was 2.58 times higher in the BIT group compared with the BOTplus group on a highly significant level.

The other trial is a RCT comparing the effects of adding once daily liraglutide (IDeg + Lira) or once daily insulin aspart (IDeg + Asp) with the largest meal in patients with T2DM that is inadequately controlled (HbA1c $\geq$ 7%) on BOT (insulin degludec plus metformin) [Mathieu *et al.* 2014]. IDeg + Lira reduced HbA1c significantly more than IDeg + Asp (−0.32% points, 95% CI −0.53 to −0.12) with significantly more patients achieving HbA1c less than 7% without confirmed hypoglycemia and without weight gain in the IDeg + Lira group (49.4%, 40/81) compared with the IDeg + Asp group (7.2%, 6/83).

Regarding efficacy criteria, these two studies support a preferred use of BIT *versus* BOTplus in patients with T2DM with HbA1c targets of less than 7% without weight gain and hypoglycemia.

Practical approach for selection of BIT *versus* BOTplus in patients with high postprandial glucose values and comorbidities

In this paper we have already suggested how different treatment options and patient-specific conditions can be integrated in the selection process for different kinds of BIT. This principle can now be extended to the decision-making process regarding advantages and disadvantages of BIT *versus* BOTplus.

In Figure 4 we selected some patient characteristics, which, according to conclusions from the above-mentioned studies and our own practical experience,

may be helpful for an individualized therapeutic strategy using BOTplus or BIT. The graphical analogy to a figure in the recently published ADA/EASD consensus statement guidelines on individualized treatment of patients with T2DM [Ismail-Beigi *et al.* 2011; Inzucchi *et al.* 2012], although we selected different patient features, should help to remind us that we do not have to only individualize treatment targets. We should and can also use personal features of our patients to individualize drug treatment strategies like BIT and BOTplus.

To use Figures 2 and 4 in your practice, simply make points in the table and on the scale. In summary, the pictures of the points will give you a more or less convincing idea of which kind of therapy may fit most of the needs and preferences of your patients. As an example, we have chosen in Figure 4 two different patients (green points and purple points), where it is relatively easy, according to the resulting picture, to make a decision between BOTplus and BIT.

Although we selected the same comorbid disease conditions in Figures 2 and 4, the consequences of the use of GLP-1 RAs and basal insulin as part of BIT may differ in comparison to their application as first-line medication (if metformin is contraindicated) or as second-line medication (add on to metformin or another OAD).

Therefore we have analyzed the available clinical evidence for the use of BOTplus and BIT in relation to each of these comorbid disease conditions. Additionally we have now included the pros and cons of BOTplus in comparison with BIT according to available clinical data.

Obesity

BOTplus. In all the above-mentioned BOTplus studies there was virtually no or only a slight change in body weight and body mass index from baseline to endpoint [Lankisch *et al.* 2008; Owens *et al.* 2011; Del Prato *et al.* 2012]. In the once daily (BOTplus), twice daily, three times daily insulin glulisine added to titrated glargine study [Davidson *et al.* 2011] body weight increased by 3.8 kg, 3.9 kg and 4.1 kg, respectively. In the study where insulin aspart was added to insulin degludec and metformin (BOTplus), body weight increased by 0.9 kg [Mathieu *et al.* 2014].

BIT. In all placebo and active comparator controlled BIT studies there were changes in weight from

baseline in both groups and differences between groups for exenatide (−1.78 kg) *versus* placebo (+0.96 kg) on insulin glargine and metformin or pioglitazone, difference 2.74 kg [Buse *et al.* 2011]; for lixisenatide (−0.38 kg) *versus* placebo (+0.06 kg) on basal insulin $\pm$ SU, difference −0.43 kg [Seino *et al.* 2012]; for lixisenatide (+0.28 kg) *versus* placebo (+1.16 kg) on basal insulin plus SU, difference 0.89 kg [Riddle *et al.* 2013b]; for lixisenatide (−1.80 kg) *versus* placebo (−0.52 kg), difference 1.28 kg [Riddle *et al.* 2013a]; for liraglutide with insulin detemir (−0.16 kg) *versus* liraglutide without insulin detemir (−0.95 kg), difference 0.8 kg [DeVries *et al.* 2012]; for liraglutide (−2.8 kg) *versus* once daily insulin aspart (+0.9 kg) on insulin degludec, difference −3.8 kg [Mathieu *et al.* 2014]; and for albiglutide (−0.73 kg) *versus* three times daily prandial lispro (+0.81 kg) on insulin glargine with some patients on OAD, difference −1.5 kg [Rosenstock *et al.* 2014a].

BOTplus *versus* BIT. Regarding changes in fat distribution, for example, visceral *versus* subcutaneous *versus* liver fat there are no studies in patients on BOTplus or BIT. But according to results of the above-mentioned magnetic resonance spectroscopy studies of fat distribution [Cuthbertson *et al.* 2012] using GLP-1 RAs in patients treated with metformin, SU or DPP-4 inhibitors, it can be assumed that also in the case of BIT, there will probably be a reduction in visceral fat and especially in liver fat.

This assumption is supported by the observation that in patients with poorly controlled T2DM, treated for 7 months with basal insulin as an add on to metformin, a reduction in liver fat was documented, although body weight increased [Juorinen *et al.* 2007]. These results together with the reduction in liver fat by GLP-1 RAs suggest that the combination of GLP-1 RAs with basal insulin (BIT) might have favorable effects on body weight and liver fat.

Hypoglycemia

Overall there is an increasing risk of hypoglycemia with more intensive antidiabetic treatment, especially when SU or insulin is used [Monami *et al.* 2014b; Geller *et al.* 2014]. However, as in the ORIGIN trial, although the treatment with insulin glargine *versus* standard care was associated with an increased risk of severe and nonsevere hypoglycemia, the relative risk of cardiovascular outcomes with hypoglycemia was lower with insulin glargine based glucose-lowering therapy [Mellbin *et al.* 2013].

So far, BOT as one basis of BOTplus or BIT seems to be an advantageous pretreatment before adding an additional injection of a short-acting insulin (BOTplus) or a GLP-1 RA (BIT) in preventing cardiovascular events.

BOTplus. In all the above-mentioned BOTplus studies the risk of mild or moderate hypoglycemia was very low without severe hypoglycemic events.

BIT. There were no group differences in hypoglycemic events in all the above-mentioned BIT studies.

BOTplus *versus* BIT. In the matched population of the BIT *versus* BOTplus study based on a propensity score match of data extracted from randomized trials [Raccah *et al.* 2014], the likelihood of achieving an HbA1c less than 7% and no symptomatic hypoglycemia was 1.9 times and for HbA1c less than 7% and no severe hypoglycemia was 1.97 times higher for the BIT *versus* BOTplus group. In the IDeg + Lira *versus* IDeg + IAsp study the rate of confirmed overall hypoglycemia was 1.0 and 8.15 episodes per patient year of exposure (PYE), respectively. The hypoglycemia risk was considerably and significantly lower by 87% in the IDeg + Lira group with an estimated risk ratio (IDeg + Lira/IDeg + IAsp) of 0.13 (95% CI 0.08–0.21). The same was true for nocturnal confirmed hypoglycemia (0.17 *versus* 1.11 per PYE), which was lower by 86% with an estimated risk ratio of 0.14 (95% CI 0.05–0.40) [Mathieu *et al.* 2014].

Taking efficacy criteria (e.g. HbA1c reduction) and comorbidities into account, we would conclude that patients who are obese with a certain higher risk of hypoglycemia or patients who have to avoid hypoglycemic episodes because of other reasons (e.g. preexisting CVD or professional circumstances) should be better candidates for BIT compared with BOTplus, as suggested in our algorithm.

Age

BOTplus. Although there are no special prospective data about an age-dependent effect of BOTplus strategies on glycemic or cardiovascular outcome parameters, the age-related risk of more hypoglycemic events with insulin therapy has to be considered. Especially in patients older than 80 years, the hypoglycemia-associated risk of visiting an emergency department is more than two-fold and the risk of being hospitalized is nearly fivefold compared with patients aged 45–64 years [Geller *et al.* 2014]. Using a subgroup

identification algorithm in a retrospective, hypothesis-generating study comparing insulin-naïve patients treated with mixed insulin (with a short-acting component) targeting postprandial hyperglycemia with a group of patients on basal insulin, younger patients (≤ 56 years) with higher levels of fasting insulin (> 11.4 $\mu\text{IU/ml}$) seem to have the greatest benefit in HbA1c reduction with mixed insulin [Hardin *et al.* 2013].

BIT. As already mentioned above, BIT studies evaluating the benefit in older people are missing [Vora, 2013], although there seems to be a certain preference for BIT in the ‘young old’ (65–79 years) [Thompson *et al.* 2013].

BOTplus versus BIT. Because of the higher hypoglycemic risk associated with the use of short-acting insulin added to a basal one in BOTplus, at least patients in the older age groups up to age 80 years should have the benefit of more secure therapy with BIT. However, the higher rate of gastrointestinal side effects, renal failure and age- or comorbidity-related unintended weight loss might limit the use of BIT in older age.

Micro- and macrovascular diseases

Vascular diseases are often recognized before the manifestation or the diagnosis of T2DM and are some of the main comorbidities predicting the further outcome of the patient. Their presence has influence on the decision-making process for treatment strategies because of safety reasons and the need for further protection.

BOTplus. According to a recent Cochrane update based on RCTs comparing intensive *versus* conventional treatment of patients with T2DM [Hemmingsen *et al.* 2013], the intensive treatment, including insulin treatment, seemed to reduce the risk of microvascular complications, whereas there was no effect on macrovascular diseases.

BIT. The favorable effects of GLP-1 RAs on many risk factors for CVDs and also the more specific protective effects on the cardiovascular system as mentioned above should be retained also in combination with basal insulin. Long-term studies are awaited.

BOTplus versus BIT. At least theoretically BIT might be favorable in the long-term regarding cardiovascular safety and protection in comparison to BOTplus because of reduced risk of

hypoglycemia, weight loss and improvement in metabolic and hemodynamic risk factors. This view is supported by the above mentioned retrospective [Raccah *et al.* 2014] and prospective [Mathieu *et al.* 2014] comparisons of the two treatment strategies.

Renal and hepatic failure

BOTplus. As with all insulin treatment strategies renal failure has to be taken into account in BOT because of the reduced degradation of insulin and the associated risk of hypoglycemia, which are dependent on renal function. On the other hand insulin and also BOTplus is rather indicated in renal failure, when other antidiabetic medication fails or is contraindicated [Williams and Garg, 2014]. In hepatic failure one has to consider the reduced capacity of gluconeogenesis and the reduced amount of liver glycogen, as well as problems with glycogenolysis to prevent hypoglycemia. But as in renal failure, insulin therapy might be the only option for safe and effective diabetes treatment.

BIT. The use of GLP-1 RAs in renal failure and consequently also the use of BIT is very limited. All GLP-1 RA treatments are not suggested for patients with hepatic failure because of scarcity of information (see above).

BOTplus versus BIT. In the case of renal or hepatic failure, BOTplus is the preferred option, compared with BIT, for antidiabetic treatment.

Pancreatic and gastrointestinal dysfunction

BOTplus. There is no restriction in the use of insulin and BOTplus in patients with pancreatic or gastrointestinal dysfunction. Nevertheless, in the former, a reduced glucagon response and changes in digestion have to be considered, and in the latter, an unpredictable resorption of nutrients.

BIT. Although safety concerns, as already mentioned, are now widely diminished, GLP-1 RAs alone or in BIT are not suggested for use in patients with previous or current dysfunctions of the pancreas, stomach and gut.

BOTplus versus BIT. Because of the possibility of enhanced side effects in patients with pancreatic or gastrointestinal dysfunction, BOTplus should be the preferred treatment option in these patients with diabetes compared with BIT.

Patient's preference

All the above-mentioned guidelines, consensus reports, position statements and recommendations suggest a discussion of benefits, disadvantages and risks of a suggested therapy with the patient as part of individualized therapeutic concepts. Regarding the choice between basal insulin combined incretin mimetic therapy with GLP-1 RAs (BIT) and BOTplus, the authors of a recently published paper suggested a very useful sample checklist for determining patient preference [Hirsch *et al.* 2014], which in the last line of Figure 4 is the crucial parameter. We suggest using the checklist for the evaluation of patient preference.

Limitations, open questions and perspectives

Although GLP-1 RAs have been available in clinical practice for some years, the knowledge about their value for the treatment of different stages and phenotypes of T2DM and metabolic vascular syndrome is limited. Our suggestions for a table and chart supported decision guide are an attempt to bridge the gap between practical needs and scientific knowledge. They are based on extrapolation from pathophysiology, clinical studies and personal experience and will have to be improved by information from new scientific and clinical data but also from the growing experience of our readers. Regarding interesting perspectives of GLP-1 RAs and BIT, new data support the use of GLP-1 RAs in BIT as an alternative not only for BOTplus but also for intensive conventional insulin treatment in patients with T2DM [Rosenstock *et al.* 2014a]. Also for patients with T1DM, the BIT concept might provide a very interesting therapeutic alternative in reducing the total daily dose of insulin and the risk of hypoglycemia [Unger, 2013]. Moreover GLP-1-based therapies may be therapeutic options for nonalcoholic fatty liver disease [Armstrong *et al.* 2013] and obesity with and without diabetes [Madsbad, 2014]. In respect of a more specific therapy for different types of diabetes, a recently published difference in glucagon response of patients with maturity onset diabetes of the young (MODY), with MODY 2 caused by mutations in the glucokinase gene and MODY 3 caused by mutations in the hepatocyte nuclear factor α gene (HNF1A diabetes) demonstrated the 'typical' paradoxical increase of glucagon in patients with MODY 3 but not in those with MODY 2 [Østoft *et al.* 2014a]. These observations seem to be the pathophysiological basis of the successful use of liraglutide in a patient with MODY 3 [Docena *et al.* 2014] and in a small randomized series of such

patients in comparison with glimepiride with less hypoglycemia [Østoft *et al.* 2014b] reported recently. The new data may open up new avenues in the differential therapy of monogenetic types of diabetes.

Last but not least, there is much hope that GLP-1-based therapies may reduce the cardiovascular burden in our patients with diabetes, based on many plausible arguments, *in vitro* observations and initial data for vascular protection *in vivo*, with some contradictory study results [Forst *et al.* 2012; Oyama *et al.* 2014]. Large-scaled randomized, prospective, clinical studies and their subanalyses are under way to answer the many open questions in the near future [Tibaldi, 2014].

Summary

GLP-1 RAs added to basal insulin, or *vice versa*, for which we use for the first time the abbreviation BIT, is a new therapeutic strategy. It might be the first step to a more individualized therapy of incretin-supported insulin therapy or insulin-supported incretin therapy (ISI, according to Mehnert) [Mehnert, 2012], when (in the future) the use of insulin is not restricted to basal insulin but also includes normal or short-acting insulins. Moreover, the BIT concept might even be extended to T1DM, as suggested from initial clinical studies.

We see BIT as a useful extension of BOT, especially in patients with T2DM and metabolic vascular syndrome [Scholz, 2010]. In contrast to the combination of a basal insulin with a short-acting insulin taken during the main meal (BOTplus), BIT has the advantage of a lower risk of hypoglycemia, contributes to weight stability or even facilitates weight loss, and opens up a chance for reduction of liver fat and hepatic insulin resistance. BIT is limited to patients without more severe renal or hepatic failure or enhanced gastrointestinal and pancreatic disease susceptibility. The overall decision to administer a GLP-1 RA or a short-acting insulin to basal insulin depends not only on treatment targets but also on the patient's personal and surrounding conditions and the patient's preferences. Careful consideration of each of these factors is necessary and can even be very helpful in the right adjustment of therapeutic targets and the selection of the most effective and convenient therapeutic regime. In our article we describe some of these features and present chart-supported algorithms and examples of how to use GLP-1 RAs and BIT in comparison to BOTplus for a more individualized treatment in our daily clinical practice.

Conflict of interest statement

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