Comparative evaluation of incretin-based antidiabetic medications and alternative therapies to be added to metformin in the case of monotherapy failure†

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ABSTRACT

Aims/Introduction: To compare clinical consequences of using inretin-based medications versus conventional antidiabetic agents as add-on to metformin in case of monotherapy failure in patients with type 2 diabetes.

Materials and Methods: The medical literature including recent abstracts from international diabetes conferences was searched for reports from clinical trials with incretin mimetics (GLP-1 receptor agonists), inhibitors of dipeptidyl peptidase-4 (DPP-4, incretin enhancers) and conventional antidiabtic drugs coadministered with metformin after monotherapy failure. A scoring system is suggested to compare the clinical utility of using incretin-based versus conventional antidiabetic agents in this situation.

Results: Incretin mimetics and DPP-4 inhibitors on top of metformin treatment help achieve glycaemic control comparable to other efficient antidiabetic drugs, both if separate or head-to-head trials were considered. Incretin-based antidiabetic drugs did not cause hypoglycaemia (different from sulfonylureas, meglitinides and insulin) and weight gain (different from sulfonylureas, meglitinides, thiazolidinediones, and insulin). DPP-4 inhibitors were weight neutral, incretin mimetics lead to weight loss. The clinical profile of incretin-based medications received the highest scores, followed by α-glucosidase inhibitors, with far lower scores assigned to insulin, glitazones, and sulfonyureas (in this order).

Conclusions: Based on the results from clinical trials, incretin-based medications have been shown to be efficacious antidiabetic drugs with a favourable adverse event and tolerability profile. This leads to high scores using a novel system paying attention to multiple facets contributing to the selection of antidiabetic drugs for general recommendation and individual treatment choices.

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KEY WORDS: DPP-4 inhibitors, GLP-1 receptor agonists, Incretin-based antidiabetic drugs

INCRETIN-BASED ANTIDIABETIC MEDICATIONS

Two novel classes of antidiabetic medications make use of the antidiabetic properties of the incretin hormone glucagon-like peptide-1 (GLP-1)[1–4], the GLP-1 receptor agonists (or incretin mimetics) and inhibitors of the protease dipeptidyl peptidase-4 (DPP-4; 'incretin enhancers')[5]. The first representatives of these classes introduced into the USA and European markets were exenatide (USA, 2005)[6–8] and sitagliptin (2007)[9,10], followed by vildagliptin (Europe, 2008)[11,12]. More compounds have been approved[13] or are in development[14].

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In the case of incretin mimetics, novel programs aim towards using compounds minimally different from the parent hormone, GLP-1, (to avoid antibody formation) and longer intervals between injections (from once daily to up to once weekly). Clinical studies (phase 3, the LEAD program) have been presented at recent diabetes conferences in regard to liraglutide (Figure 1), and most of these liraglutide studies have been published[15–19]. The situation is similar for an extended-release preparation of exenatide (exenatide LAR)[20,21]. Earlier in development (phase 2 results reported) are lixisenatide (AVE 0010; Sanofi-Aventis, Paris, France) and taspoglutide (Ro 1583; Roche Pharma, Basel, Switzerland)[22].

Regarding DPP-4 inhibitors, phase 3 studies have been reported for alogliptin (Takeda Pharma, Osaka, Japan) [23,24], and phase 3 studies have also been presented in the case of saxagliptin (AstraZeneca, London, UK and Bristol-Myers Squibb, New York City, NY, USA)[13,25].

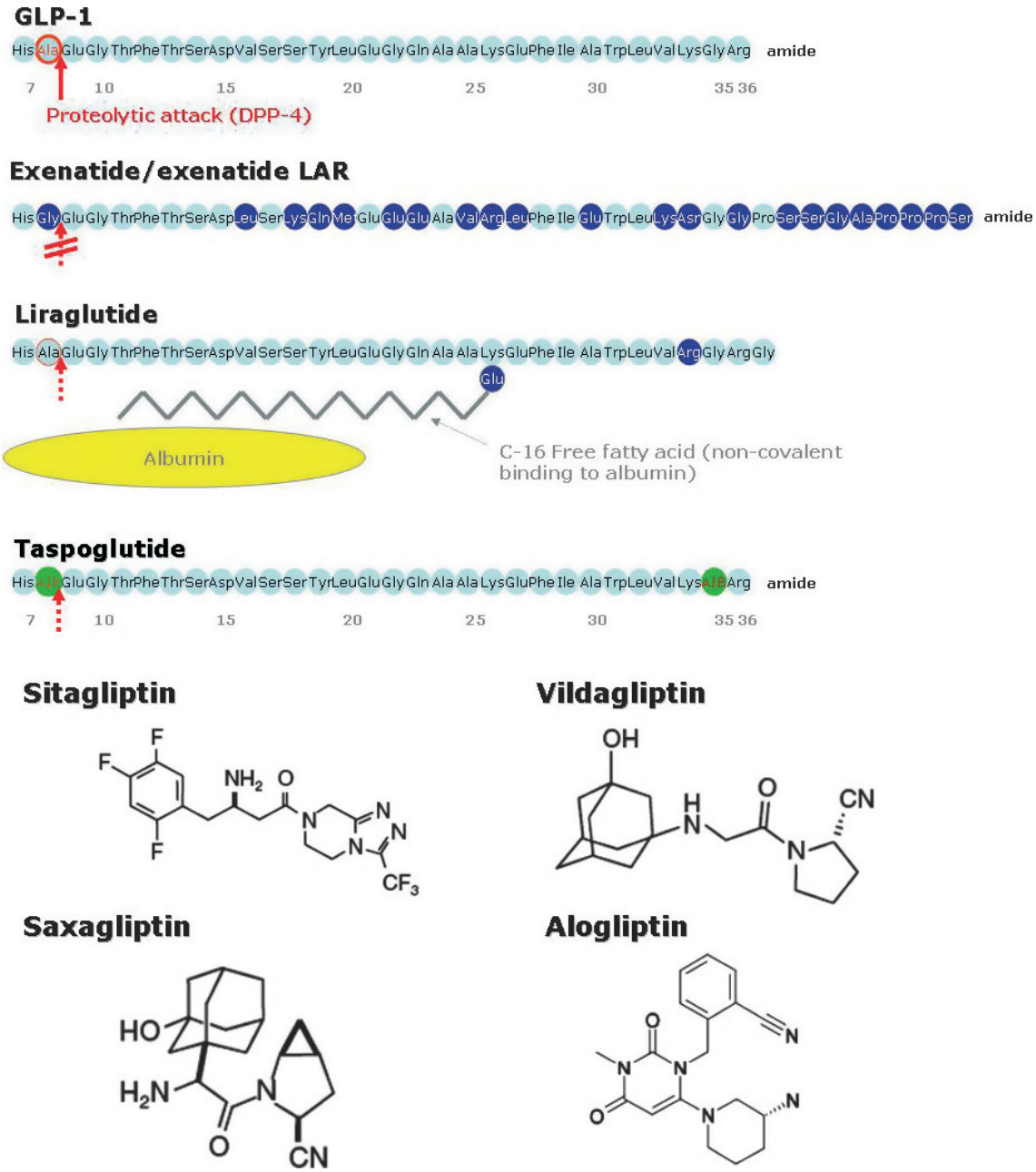

Figure 1 | Amino acid sequence of glucagon-like peptide-1 and peptide GLP-1 receptor agonists exenatide, liraglutide, and taspoglutide and chemical structures of the dipeptidyl peptidase-4 inhibitors sitagliptin, vildagliptin, saxagliptin, and alogliptin.

THEORETICAL PROPERTIES OF MEDICATIONS BASED ON THE BIOLOGY OF GLP-1

Incretin-based antidiabetic medications have attractive properties that are tightly linked to the multiple mechanisms of antidiabetic actions of GLP-1. Because the biology of GLP-1 with regard to its role as a parent compound of antidiabetic medications has been highlighted elsewhere[1,5,26], only some important features will be presented here. Among insulinotropic agents, especially in comparison to sulfonylureas, GLP-1 is unique in that it stimulates insulin secretion in a highly glucose-dependent fashion. Below approximately 65 mg/dL glucose, no stimulation occurs at all. Until glucose levels of 110 mg/dL are reached, insulin secretion is stimulated to a very limited extent and only with higher glucose concentrations, the augmentation through GLP-1 can be called potent[27,28]. Sulfonylureas, in contrast, lead to stimulated insulin secretion even at rather low glucose concentrations, a mechanism potentially leading to hypoglycaemia[29]. Exenatide and liraglutide share this glucose-dependence (as assessed by hypoglycaemic clamp studies)[30,31].

At the level of the endocrine pancreas, GLP-1 stimulates (pro-)insulin biosynthesis[32] and, thereby, prevents the depletion of insulin stores[33]. In addition, GLP-1 suppresses glucagon secretion[34].

The ability of GLP-1, even when administered into the peripheral circulation, to have an influence on brain centres involved in the regulation of appetite and satiety[35], and to limit energy intake in human subjects with[36] and without[37] type 2-diabetes has led to the unique property of incretin mimetics as being the only insulinotropic antidiabetic agents not leading to weight gain, but rather, to weight loss[38].

The last point concerns the ability of GLP-1, incretin mimetics and DPP-4 inhibitors to promote growth of pancreatic endocrine β-cells, either in the form of replication/proliferation[39,40], or as differentiation from precursor cells[41]. In addition, GLP-1 has been shown to at least partially prevent apoptosis when β-cells or islets were incubated with compounds such as free fatty acids[33], cytokines[42] or hydrogen peroxide[43], agents that trigger apoptosis. In animal experiments, this has led to a rather rapid enhancement of β-cell mass, when GLP-1[44], exenatide[40], liraglutide[42], sitagliptin[45], or vildagliptin[46] have been used in rodents over periods from 48 h[44] up to several weeks. These observations have fostered hope that treatment with incretin mimetics and DPP-4 inhibitors will lead to similar changes in the human endocrine pancreas when used long enough. However, to date proof is lacking that there are persisting alterations in β-cell function or mass[47]. Basically, this can be regarded as an open question, because β-cell turnover is known to be much slower in human islets, and any detectable change will require periods of treatment longer than studies that have been reported so far. In the end, these properties might be the basis to expecting more 'durability', for example, a stable glycemic control with these new agents over a long period of time[48].

INCRETIN-BASED ANTIDIABETIC MEDICATIONS IN RECOMMENDED TREATMENT ALGORITHMS FOR TYPE 2 DIABETES

Based on these properties, incretin-based antidiabetic medications are regarded to be true innovations with a potential for broader use in the population of type 2 diabetic patients[2]. According to conventional reasoning, metformin should be used as the first-line antidiabetic drug in the typical overweight patient with type 2 diabetes, because it is cheap, does not lead to weight gain and hypoglycemia, and has proven a substantial reduction in cardiovascular events (e.g. myocardial infarction) to the extent that survival has been improved during the United Kingdom Prospective Diabetes Study[49], with a similar benefit persisting up to 10 years after the intervention[50]. Any other antidiabetic drug competing for the position of recommended initial treatment would need to show benefits of a similar quality. What to do when metformin monotherapy fails, is a far more difficult question. Basically, there are several options; sulfonylureas (glibenclamide [glyburide], glimepiride, glipizide, gliclazide and other less often prescribed drugs), meglitinides (repaglinide, nateglinide), α-glucosidase inhibitors (acarbose, miglitol), thiazolidinediones (rosiglitazone, pioglitazone), insulin (basal insulin added to oral antidiabetic agents, conventional insulin treatment (i.e. twice daily premixed insulin) intensified regimens with multiple daily injections of fast-acting insulin with and without basal insulin), and incretin-based antidiabetic medications. Current guidelines (e.g. as issued by the German Diabetes Association, Deutsche Diabetes-Gesellschaft[51]) list all available drugs (or classes), and leave it to the individual situation for the decision to be made as to which drug combination should be used for a given patient. Older guidelines (issued before 2006) often don't mention GLP-1 receptor agonists or DPP-4 inhibitors at all, because at the time of their writing, these agents had not been available at all or the experience with their use was limited. Of particular impact is the treatment algorithm authorized by both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) that was published in 2006[52]. It presents a rather restricted approach as only three treatment recommendations are seriously considered; insulin, if the most potent blood glucose-lowering effect is needed; sulfonylureas, when drug costs are of primary concern; and thiazolidindiones, when hypoglycemia needs to be strictly avoided. This leaves no space for incretin-based antidiabetic agents. The first author of the present position statement, David Nathan, has a critical opinion of the quality and quantity of data from clinical studies that have lead to the approval of incretin-based antidiabetic drugs[53], and thus has made it clear that he would not consider a broader recommendation at this point in time. Nevertheless, a recent update of the position statement of experts acting in the name of the ADA and EASD has now mentioned GLP-1 receptor agonists as 'tier 2 (less well-validated therapies)' recommendations[54].

LITERATURE SEARCH STRATEGY AND METHODS OF ANALYSIS

The present overview is a relatively systematic compilation of results from clinical studies involving GLP-1 receptor agonists and DPP-4 inhibitors, and of potential competitors for the position as second-line add-on to metformin in the case of monotherapy failure. For that purpose, a literature search was carried out looking for publications, with the name of the drug in question in the title and 'metformin' in the abstract. In addition, abstracts from the 2007 and 2008 annual meetings of the ADA and EASD were screened with the help of the respective indices. Changes in HbA_{1c} and fasting glucose concentrations from baseline, the percentage of patients reaching an HbA_{1c} <7%, changes in bodyweight (*vs* baseline), the percentage of patients experiencing episodes of hypoglycemia, and the percentage reporting nausea and/or vomiting were collected and depicted as proportions (in %) or mean ± SEM. Important baseline characteristics (HbA_{1c}, body mass index),

the doses of the study drugs used and study duration were also recorded. A uniform color code was used in figures with sulfonylureas in (different shades of) red, thiazolidinedions in brown, premixed or NPH-insulin in dark grey, insulin glargine in violet, incretin mimetics in green, and DPP-4 inhibitors in blue. α-glucosidase inhibitors were also considered. Four comparisons were made, all from patients who received metformin as the background medication, as follows: (i) incretin mimetics versus placebo; (ii) DPP-4 inhibitors versus placebo; (iii) sulfonylureas and thiazolidinediones versus placebo; and (iv) direct comparisons of incretin mimetics or DPP-4 inhibitors with any of the comparator drugs. In the latter case, only the highest dose of the incretin-based medication was reported, if more than one dose had been part of the protocol. Statistical analysis was taken from the original reports. If no standard errors of the mean (SEM) were reported, but there were other measures of variation, SEM were recalculated.

INCRETIN MIMETICS *VS* PLACEBO (METFORMIN BACKGROUND)

The molecular nature of the incretin mimetics that are part of the present clinical analysis are shown in Figure 1, along with the primary structure of the parent compound, GLP-1. Exenatide is used with twice-daily injection of 5–10 μg[6–8,55,56]. Liraglutide is a minimally modified GLP-1 with a free fatty acid attached to promote binding to albumin as the mechanism for protracted action[57]. It should be used with once-daily dosing at 1.2 to 1.8 mg, with a 0.6 mg dose for initial treatment (slow uptitration to avoid side-effects)[15–17]. Lixisenatide C AVE 0010 is recommended for once-daily dosing based on the study shown in Figure 2[58,59]. Its complete molecular structure has not been disclosed. Exenatide LAR is exenatide with a retarded action profile as a result of microencapsulation, that is, the incagement of the active compound into a network of self-dissolving polymer fibres[21,60]. Taspoglutide is GLP-1 with two amino acids (in positions 2 and 35) replaced by α-amino butyric acid. Zinc chloride is added for retarded absorption[22]. Like exenatide LAR, it needs to be injected once weekly.

From Figure 2, a pattern of the clinical effects of adding a GLP-1 receptor agonist or placebo to metformin is obvious; HbA_{1c} is consistently lowered by approximately 1% in the case of relatively short-acting incretin mimetics, and by up to 2% for exenatide LAR, a long-acting preparation. Taspoglutide was studied for only 8 weeks, so the drop in HbA_{1c} underestimates the full effect seen after reaching a steady state[22]. Effects on fasting glycemia follow a similar pattern, suggesting that a more profound effect on fasting glucose concentrations with better pharmacokinetic 24 h coverage[61] adds to improved HbA_{1c} concentrations.

The proportions of patients reaching a HbA_{1c} <7% mirrors the ability of the compounds to lower average glycemia, with an impressive percentage (approximately 70–80%) for long-acting incretin mimetics[19–22].

All incretin mimetics led to weight loss. The extent of which depended on the duration of the studies, with larger weight loss after longer treatment periods.

Hypoglycemia was not reported at a rate higher than for placebo. The one apparent exception (exenatide LAR, Kim *et al.*[20]) was based on a small number of patients afflicted.

Nausea and/or vomiting were a common finding. For reasons of simplicity, proportions of patients reporting either nausea or vomiting were added for the purpose of preparing the figures. This method does not take into account that often nausea and/or vomiting occurred in the same subjects, and leads to higher figures than strictly analysing patients with either nausea or vomiting galore. The latter information, however, was not available from most of the study reports. It should be noted, that the high percentage of patients reporting nausea and vomiting contrasts with the much smaller number of patients withdrawing from the studies as a result of unbearable adverse gastrointestinal events. Uniformly, all studies reported side-effects to be mostly mild to moderate in severity, and to occur primarily when initiating treatment[19,62,63], with a much lower incidence with chronic treatment. There might be reduction in the incidence of gastrointestinal side-effects with longer-acting incretin mimetics[19].

DPP-4 INHIBITORS *VS* PLACEBO (METFORMIN BACKGROUND)

Figure 1 shows the chemical structure of the DPP-4 inhibitors included in the present analysis. The chemical nature of the compounds is quite different. Sitagliptin is recommended at a dose of 100 mg once daily[10] (or 50 mg twice daily, especially when used as part of a fixed combination pill[64]) in the absence of significant renal functional impairment. Vildagliptin is recommended at 50 mg twice daily[12]. Alogliptin has been used at doses of 12.5 and 25 mg once daily[24], and for saxagliptin, the reported doses have been between 2.5 and 20 mg[13,25] (Figure 3).

Treatment with DPP-4 inhibitors led to reductions in HbA_{1c} of between 0.5 and 1.0% (Figure 3), and to fasting glucose concentrations being lowered by approximately 15–30 mg/dL. HbA_{1c} <7% was reached by approximately 40–50% of the study participants. Mean changes in bodyweight remained within 1 kg from baseline. Hypoglycemia and gastrointestinal side-effects were absolutely no issue with any of the DPP-4 inhibitors (Figure 3).

COMPARATOR DRUGS (SULFONYLUREAS, THIZOLIDINEDIONES, OR INSULIN) *VS* PLACEBO (METFORMIN BACKGROUND)

Sulfonylurea compounds[65,66], such as thiazolidinediones[67–69], lowered HbA_{1c} by approximately 1% (Figure 4). Insulin reduced HbA_{1c} by approximately 2%, however, starting from higher baseline values. Sulfonylureas and thiazolidinediones reduced fasting glycemia by 20–50 mg/dL, and insulin was able to lower fasting glucose by up to 100 mg/dL. The

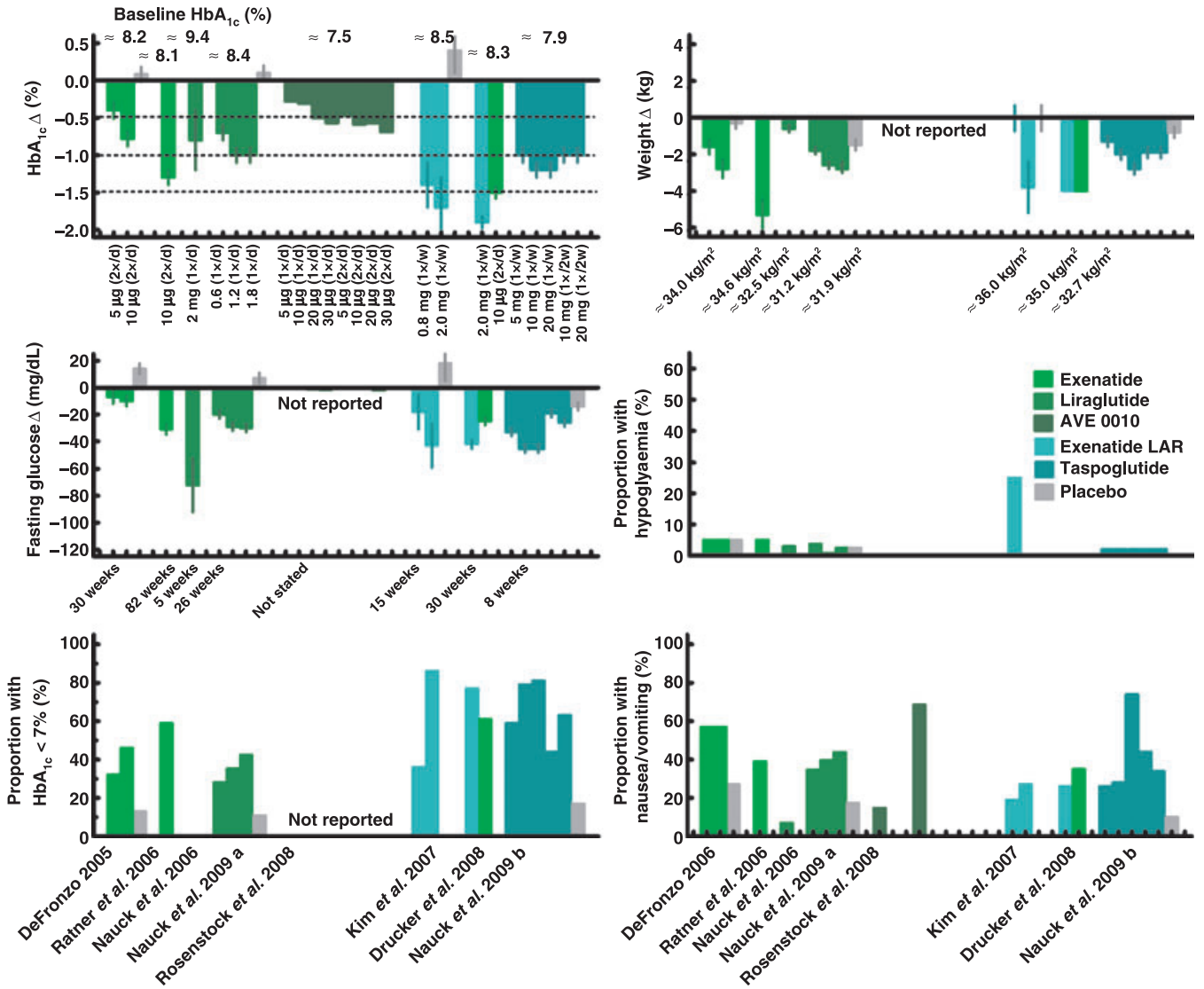

Figure 2 | Placebo-controlled clinical trials with GLP-1 receptor agonists exenatide, liraglutide, exenatide long-acting release (LAR), AVE 0010 (lixisenatide) and taspoglutide on a background of metformin treatment in patients no longer controlled with a single oral antidiabetic drug. Effects on HbA_{1c} and fasting plasma glucose, the proportion of patients reaching a HbA_{1c} <7.0%, changes in bodyweight, patients experiencing hypoglycemia or reporting nausea and/or vomiting are shown. Bars represent the change from baseline (error bars representing standard errors of the mean) or proportions. Data are taken from DeFronzo *et al.* 2005[7], Ratner *et al.* 2007[72], Nauck *et al.* 2006[62], Nauck *et al.* 2009a[17], Rosenstock *et al.* 2008[58], Kim *et al.* 2007[20], Drucker *et al.* 2008[21] and Nauck *et al.* 2009b[22].

proportion reaching a HbA_{1c} <7% was variable, in part depending on baseline conditions. In the case of insulin treatment, only approximately 50% reached this goal, despite the substantial drop versus baseline.

Uniformly, the patients gained weight with sulfonylurea, thiazolidinedione and insulin treatment, with up to 3 kg on average with insulin treatment.

As expected, hypoglycaemic episodes occurred with sulfonylurea and, more often, with insulin treatment, but not with thiazolidinedione treatment. Gastrointestinal side-effects were no issue with any of these medications.

DIRECT COMPARISONS OF INCRETIN-BASED ANTIDIABETIC MEDICATIONS (INCRETIN MIMETICS OR DPP-4 INHIBITORS) AND SULFONYLUREAS, THIZOLIDINEDIONES, OR INSULIN (METFORMIN BACKGROUND)

As a rule, in direct comparisons, DPP-4 inhibitors (sitagliptin and vildagliptin) were tested against other oral antidiabetic drugs, and incretin mimetics (exenatide and liraglutide) were tested against different insulin regimens (Figure 5). One exception to this rule is a study comparing liraglutide and glimepiride[17]. In none of the comparisons was the DPP-4 inhibitor of incretin

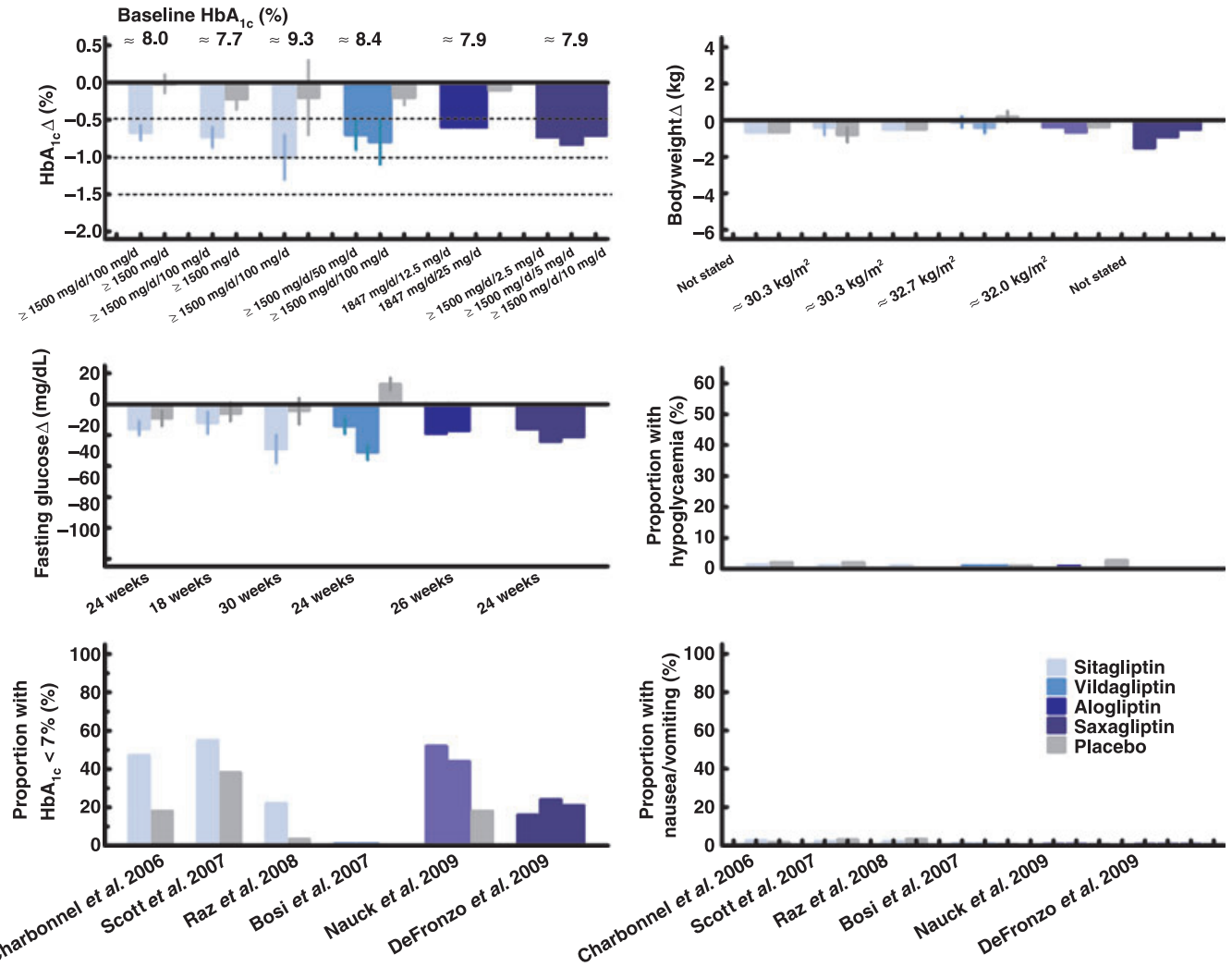

Figure 3 | Placebo-controlled clinical trials with DPP-4 inhibitors sitagliptin, vildagliptin, alogliptin and saxagliptin on a background of metformin treatment in patients no longer controlled with a single oral antidiabetic drug. Effects on HbA_{1c} and fasting plasma glucose, the proportion of patients reaching a HbA_{1c} <7.0%, changes in bodyweight, patients experiencing hypoglycemia or reporting nausea and/or vomiting are shown. Bars represent the change from baseline (error bars representing standard errors of the mean) or proportions. Data are taken from Charbonnel *et al.*[9], Scott *et al.*[73], Raz *et al.*[74], Bosi *et al.*[75], Nauck *et al.*[24] and DeFronzo *et al.*[13].

mimetic weaker in terms of lowering HbA_{1c}. Insulin glargine was more potent in reducing fasting glycemia than exenatide[55], but not compared with liraglutide[18]. Given the similar effect on HbA_{1c} and the lower ability to reduce fasting glucose, this is compatible with the short duration of action of unretarded exenatide (and, consecutively, a comparatively weak effect on fasting glycemia) and its decelerating effect on gastric emptying[70], virtually abolishing postprandial rises in glycemia after the meals that exenatide had been administered before[19]. The relatively weak effect on fasting glucose, thus, is compensated for by exenatide's postprandial glucose-lowering activity. There were no significant differences between any of the incretin-based antidiabetic medications and the comparators in the ability to reach a HbA_{1c} <7%.

In contrast to the similar effects on glycemic control, there were clear differences in bodyweight, which increased with sulfonylureas, thioazolidinediones and insulin, but remained unchanged or was slightly reduced with DPP-4 inhibitors, and was consistently and substantially reduced with incretin mimetics (both exenatide and liraglutide).

Neither sitagliptin nor liraglutide caused significant hypoglycemia in any of the studies with a strict metformin background medication, whereas glipizide[10] and glimepiride (sulfonylureas)[17] treatment was accompanied by hypoglycemia in a significantly higher proportion of patients. In studies that allowed sulfonylureas (and metformin) as background medication (indicated by a light grey background area)[18,55,56], this unique advantage of incretin mimetics was lost, although a weak trend towards less

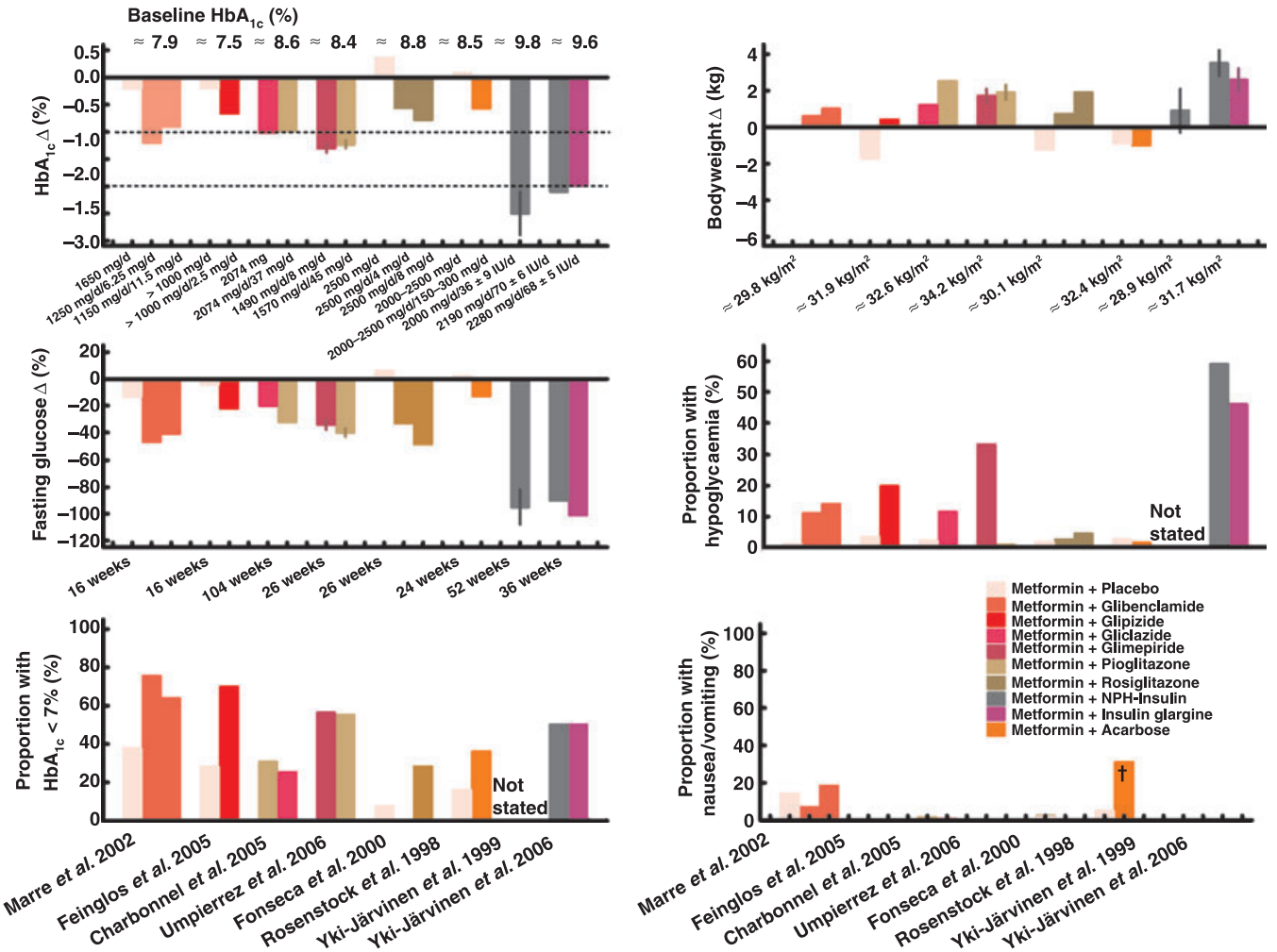

Figure 4 | Placebo-controlled clinical trials of other medications (oral antidiabetic drugs or insulin) recommended as an alternative to incretin-based medications in patients no longer well controlled with metformin. Effects on HbA_{1c} and fasting plasma glucose, the proportion of patients reaching a HbA_{1c} <7.0%, changes in bodyweight, patients experiencing hypoglycemia or reporting nausea and/or vomiting are shown. Bars represent the change from baseline (error bars representing standard errors of the mean) or proportions. *Flatulence. Data are taken from Marre *et al.*[65], Feinglos *et al.*[66], Holman *et al.*[76], Charbonnel *et al.*[67], Umpierrez[68], and Fonseca *et al.*[69], Rosenstock *et al.*[77], Yki-Järvinen *et al.*[78] and Yki-Järvinen *et al.*[79].

hypoglycemia remained. This is compatible with the known biological interaction of GLP-1 and sulfonylureas at the level of the endocrine pancreatic β-cell; once the ATP-dependent potassium channel is closed (by a sulfonylurea), the stimulation of insulin secretion is no longer glucose-dependent and can lead to hypoglycemia[29,71].

Gastrointestinal adverse events occurred with incretin mimetics, but not with any other drug class.

Based on the data from clinical studies presented so far, it was obvious that the comparisons were not at all unfavourable for incretin-based medications, but that a more generalizable score might be necessary to judge the clinical value of incretin mimetics and DPP-4 inhibitors in comparison to other antidiabetic drugs.

A COMPREHENSIVE SCORING SYSTEM TO JUDGE THE CLINICAL VALUE OF USING DIFFERENT ANTIDIABETIC DRUGS

A meaningful score should allow judging multiple facets of the consequences of using a particular drug (combination). It should focus on aspects that might be important contributors to the decision of which drug to choose or to recommend as part of treatment algorithms/guidelines or in the choice of drugs for an individual patient. It should be sensitive to differences in environmental conditions, which differ between countries. In the end, the score should make clear whether the overall assessment is positive, neutral or negative.

The suggested score presented here is composed of the following 12 items: (i) the potency to lower glycemia as judged by

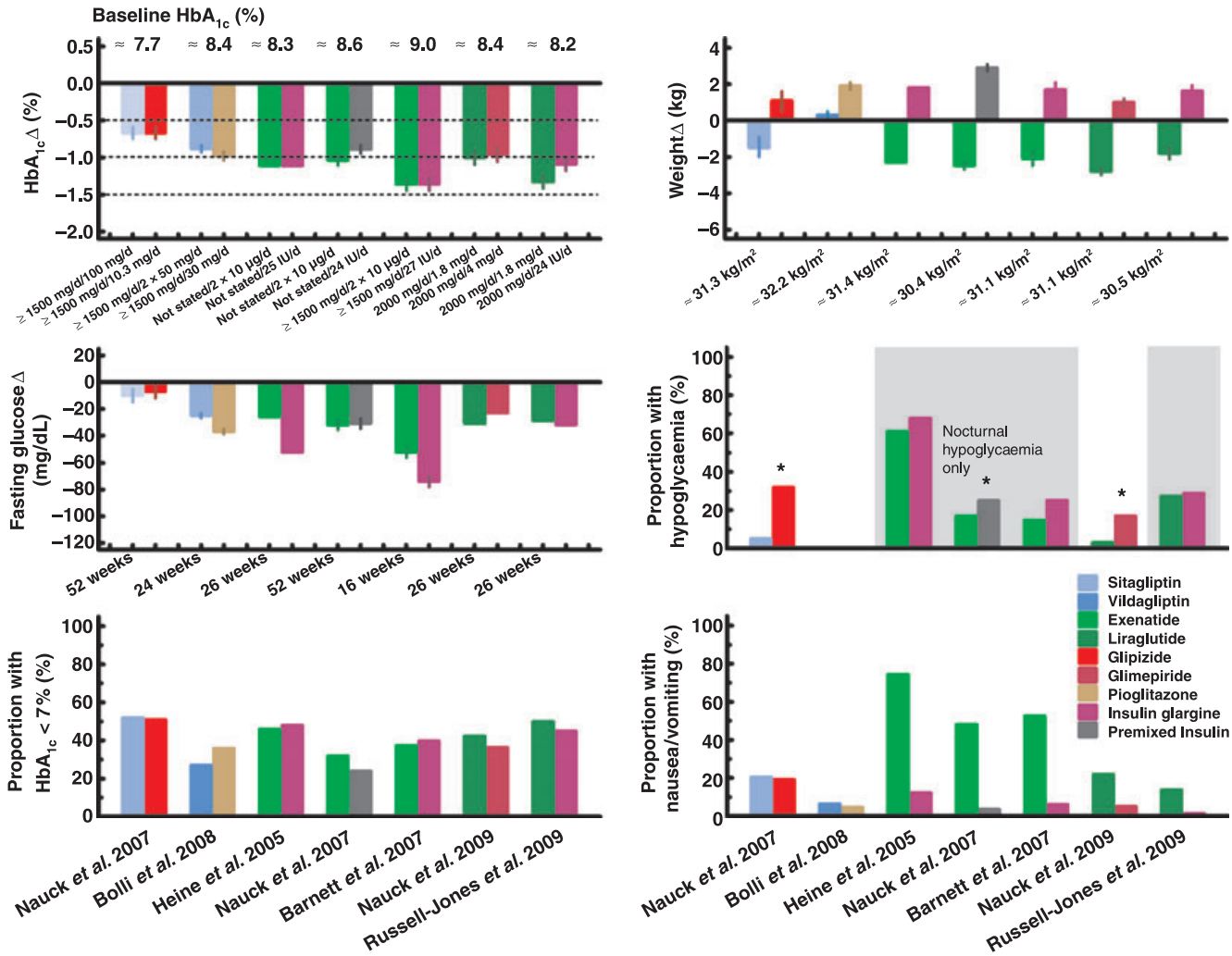

Figure 5 | Direct comparison of incretin-based antidiabetic medications (GLP-1 receptor agonists or DPP-4 inhibitors) and other antidiabetic drugs (oral agents or insulin) in patients no longer well controlled on metformin treatment alone. Effects on HbA_{1c} and fasting plasma glucose, the proportion of patients reaching a HbA_{1c} <7.0%, changes in bodyweight, patients experiencing hypoglycemia or reporting nausea and/or vomiting are shown. Bars represent the change from baseline (error bars representing standard errors of the mean) or proportions. Data are taken from Nauck *et al.*[10], Bolli *et al.*[80], Heine *et al.*[55], Nauck *et al.*[56], Barnett *et al.*[81], Nauck *et al.*[17] and Russell-Jones[18].

HbA_{1c} determinations; (ii) the proven ability to prevent microvascular; (iii) the proven ability to prevent macrovascular complications; (iv) the overall attractiveness of the mode(s) or action for the drug in question; (v) the potential to elicit life-threatening adverse events; (vi) the potential to cause unpleasant, but harmless, side-effects; (vii) cardiovascular safety (as assessed by appropriately sized long-term clinical trials assessing cardiovascular outcome); (viii) effects on bodyweight; (ix) the potential to provoke episodes of hypoglycemia; (x) the necessity to use (and spend additional) money for blood glucose self monitoring; (xi) the potential for supporting a long-term 'durability' of glycemic control; and (xii) last but not least, costs. For each item, a maximum of two scoring points can be given for the best possible influence this drug has on the parameter in question; 0 points indicating a neutral (average) influence, negative scores indicating an estimate below average, and positive scores supporting better than average influence. The reference should be the totality of alternative treatment options available, but only with respect to this particular parameter. In principle, this scoring system is flexible and other parameters could be added, and some parameters could be removed if necessary. A further refinement is the assignment of different weights to any given parameter so that, for example, in an environment where costs have a heavy influence on the choice of drugs, this can be adopted by assigning a heavy weight to costs and to de-emphasise other parameters that are thought to not contribute as much to the overall treatment choice. We have asked some renowned experts in the field (for their names and places of origin, see acknowledgements) to contribute their personal opinion on calculating a summary score that allows to compare the preference for different antidiabetic

Table 1 | Scoring system to describe the value of different antidiabetic drug classes when combined with metformin

Drug class parameter	Sulfonylureas	Thiazolidinediones	α-Glucosidase inhibitors	Insulin	DPP-4 inhibitors	Incretin mimetics	*P*-value
(a) Without assigning a weight to the parameters							
Efficacy regarding glycemic control	$1.1 \pm 0.1^{c,d}$	$1.1 \pm 0.2^{c,d}$	$0.0 \pm 0.2^{a,b,d,e,f}$	$1.9 \pm 0.1^{a,b,c,e,f}$	$0.7 \pm 0.2^{c,d,f}$	$1.4 \pm 0.2^{c,d}$	<0.001
Prevention of microvascular complications	$1.2 \pm 0.2^{b,c,d,e,f}$	$0.5 \pm 0.2^{a,d}$	$0.2 \pm 0.1^{a,b,d}$	$1.9 \pm 0.1^{a,c,e,f}$	$0.2 \pm 0.1^{a,d}$	$0.4 \pm 0.2^{a,d}$	<0.001
Prev. of macrovascular complications	$-0.4 \pm 0.1^{b,c,d,f}$	0.4 ± 0.2^{a}	$0.6 \pm 0.2^{a,e,f}$	$0.6 \pm 0.2^{a,e,f}$	$0.0 \pm 0.1^{c,d}$	$0.1 \pm 0.1^{a,c,d}$	<0.001
Attractive mode(s) of action	$-0.4 \pm 0.3^{b,c,d,e,f}$	0.9 ± 0.2^{a}	$0.3 \pm 0.1^{a,e,f}$	0.8 ± 0.2^{a}	$1.2 \pm 0.1^{a,c}$	$1.4 \pm 0.2^{a,c}$	<0.001
Potential for seriously harmful AE	$0.3 \pm 0.3^{b,c}$	$-0.7 \pm 0.3^{a,c,e}$	$1.2 \pm 0.2^{a,b,d,f}$	$0.0 \pm 0.4^{c,e}$	$0.9 \pm 0.2^{b,d,f}$	$0.0 \pm 0.2^{c,e}$	<0.001
Potential to cause unpleasant SE	0.0 ± 0.2^{e}	-0.9 ± 0.3^{e}	-0.8 ± 0.4^{e}	-0.2 ± 0.3^{e}	$1.3 \pm 0.3^{a,b,c,d,f}$	-0.6 ± 0.2^{e}	<0.001
Proven cardiovascular safety	$-0.3 \pm 0.2^{c,d}$	$-0.4 \pm 0.2^{c,d}$	$0.9 \pm 0.2^{a,b,e,f}$	$0.6 \pm 0.2^{a,b,e,f}$	-0.2 ± 0.2^{cd}	$-0.1 \pm 0.1^{c,d}$	<0.001
Effects on bodyweight	$-1.3 \pm 0.1^{b,c,e,f}$	$-1.9 \pm 0.1^{a,c,d,e,f}$	$0.4 \pm 0.1^{a,b,d,f}$	$-1.5 \pm 0.2^{b,c,e,f}$	$0.2 \pm 0.1^{a,b,d,f}$	$1.8 \pm 0.1^{a,b,c,d,e}$	<0.001
Potential to cause hypoglycemia	$-1.5 \pm 0.1^{b,c,e,f}$	$1.3 \pm 0.2^{a,d}$	$1.4 \pm 0.2^{a,d}$	$-1.9 \pm 0.1^{b,c,e,f}$	$1.4 \pm 0.2^{a,d}$	$1.4 \pm 0.2^{a,d}$	<0.001
Need for glucose self-monitoring	$-1.0 \pm 0.1^{b,c,d,e,f}$	$1.3 \pm 0.2^{a,c,e}$	$1.3 \pm 0.2^{a,b,d,e,f}$	$-1.9 \pm 0.1^{a,c}$	$1.4 \pm 0.2^{a,b,c}$	$1.4 \pm 0.2^{a,c}$	<0.001
Potential for durability of glycemic control	$-1.3 \pm 0.2^{b,c,d,e,f}$	$1.2 \pm 0.2^{a,c,e}$	$0.0 \pm 0.2^{a,b,d,e,f}$	$0.6 \pm 0.2^{a,c}$	$0.6 \pm 0.1^{a,b,c}$	$0.9 \pm 0.2^{a,c}$	<0.001
Drug costs per day	$1.9 \pm 0.1^{b,c,d,e,f}$	$-0.9 \pm 0.2^{a,c,d,f}$	$0.3 \pm 0.2^{a,b,d,e,f}$	$-0.4 \pm 0.2^{a,b,c,e,f}$	$-1.3 \pm 0.1^{a,c,d,f}$	$-1.8 \pm 0.1^{a,b,c,d}$	<0.001
Σ	-1.8 ± 0.8	1.9 ± 1.1	5.7 ± 1.0	0.5 ± 0.9	6.4 ± 0.6	6.4 ± 0.5	<0.001
Rank	6	4	3	5	1	1	
(b) Assigning a weight to the parameters							
Efficacy regarding glycemic control	$5.1 \pm 0.7^{c,d}$	$5.3 \pm 0.9^{c,d}$	$-0.1 \pm 1.0^{a,b,d,e,f}$	$9.3 \pm 0.4^{a,b,c,e,f}$	$3.3 \pm 0.7^{c,d,f}$	$6.9 \pm 0.8^{c,d,e}$	<0.001
Prev. of microvasc. complications	$5.8 \pm 0.8^{b,c,d,e,f}$	$2.4 \pm 0.8^{a,d}$	$0.9 \pm 0.5^{a,d}$	$9.4 \pm 0.4^{a,b,c,e,f}$	$0.8 \pm 0.6^{a,d}$	$1.7 \pm 0.8^{a,d}$	<0.001
Prev. of macrovascular complications	$-1.9 \pm 0.6^{b,c,d,e,f}$	1.8 ± 0.8^{a}	$2.9 \pm 0.8^{a,e,f}$	$2.9 \pm 0.9^{a,e,f}$	$0.1 \pm 0.4^{a,c,d}$	$0.6 \pm 0.4^{a,c,d}$	<0.001
Attractive mode(s) of action	$-0.5 \pm 0.7^{b,d,e,f}$	2.5 ± 0.8^{a}	$0.8 \pm 0.5^{e,f}$	2.1 ± 0.8^{a}	$3.0 \pm 0.5^{a,c}$	$3.4 \pm 0.7^{a,c}$	<0.001
Potential for seriously harmful AE	0.9 ± 1.4^{c}	$-2.5 \pm 1.2^{c,e}$	$4.8 \pm 1.2^{a,b,d}$	$-0.3 \pm 1.6^{c,e,f}$	$4.1 \pm 0.8^{b,d,f}$	$0.3 \pm 1.1^{c,e}$	<0.001
Potential to cause unpleasant SE	-0.2 ± 0.7^{e}	-2.8 ± 0.9^{e}	-2.0 ± 1.2^{e}	-0.7 ± 1.1^{e}	$3.6 \pm 0.9^{a,b,c,d,f}$	-1.8 ± 0.5^{e}	<0.001
Proven cardiovascular safety	$-1.1 \pm 0.6^{c,d}$	$-1.0 \pm 0.7^{c,d}$	$2.8 \pm 0.8^{a,b,d,e,f}$	$1.6 \pm 0.5^{a,b,e,f}$	$-0.8 \pm 0.7^{c,d}$	$-0.6 \pm 0.6^{c,d}$	<0.001
Effects on bodyweight	$-4.5 \pm 0.4^{b,c,e,f}$	$-6.6 \pm 0.6^{a,c,e,f}$	$1.6 \pm 0.5^{a,b,d,f}$	$-5.5 \pm 0.7^{c,e,f}$	$0.8 \pm 0.3^{a,b,d,f}$	$6.2 \pm 0.6^{a,b,c,d,e}$	<0.001
Potential to cause hypoglycemia	$-5.4 \pm 0.7^{b,c,e,f}$	$4.3 \pm 0.6^{a,d}$	$4.6 \pm 0.7^{a,d}$	$-6.8 \pm 0.5^{b,c,e,f}$	$5.1 \pm 0.8^{a,d}$	$5.1 \pm 0.8^{a,d}$	<0.001
Need for glucose self-monitoring	$-2.9 \pm 0.4^{b,c,d,e,f}$	$3.6 \pm 0.5^{a,d}$	$3.5 \pm 0.6^{a,d}$	$-5.6 \pm 0.4^{a,b,e,f}$	$3.9 \pm 0.6^{a,d}$	$3.9 \pm 0.6^{a,d}$	<0.001
Potential for durability of glycemic control	$-4.0 \pm 0.7^{b,c,d,e,f}$	$4.2 \pm 0.8^{a,c,e}$	$0.0 \pm 0.7^{a,b,d,f}$	$2.7 \pm 1.0^{a,c}$	$1.6 \pm 0.4^{a,b}$	$2.8 \pm 0.6^{a,c}$	<0.001
Drug costs per day	$7.8 \pm 0.6^{b,c,d,e,f}$	$-3.9 \pm 0.9^{a,c,d,f}$	$0.8 \pm 0.9^{a,b,d,e,f}$	$-1.7 \pm 0.9^{a,b,d,e,f}$	$-4.9 \pm 0.6^{a,c,d}$	$-7.0 \pm 0.6^{a,b,c,d}$	<0.001
Σ	$-0.9 \pm 3.6^{c,e,f}$	$7.3 \pm 4.4^{c,e,f}$	$20.6 \pm 4.2^{a,b,d}$	$7.4 \pm 3.6^{c,e,f}$	$20.5 \pm 2.8^{a,b,d}$	$21.6 \pm 2.5^{a,b,d}$	<0.001
Rank	6	5	2	4	3	1	

Grading system: −2, the worst possible; −1, moderately negative; 0, neutral; 1, moderately positive; 2, the best possible influence on the parameter in question. Assigning weight, the importance of the given parameter is expressed as a number between 1 (least important) and 5 (very important). Mean ± SEM ($n = 16$); *P*-values were calculated by ANOVA, superscript letters indicate a significant difference ($P < 0.05$ by Duncan's *post hoc*-test) to (a) sulfonylureas, (b) thiazolidinediones, (c) α-glucosidase inhibitors, (d) insulin, (e) DPP-4 inhibitors, (f) incretin mimetics. AE, adverse events; α-GI, α-glucosidase inhibitors; DPP-I, DPP-4 inhibitors; SE, side-effects; SU, sulfonylureas; TZD, thiazolidinediones.

drugs that can be added to metformin in the case of monotherapy failure. Surprisingly, we received opinions pointing to a rather uniform judgement, allowing the detection of significant differences between different candidate drugs, both with respect to individual parameters analysed separately and with respect to an overall summary score, that might help in identifying preferences for certain drug choices (Table 1). The weights assigned to the different items varied between 2.4 ± 0.3 (lowest weight for 'attractive mode(s) of action') and 4.8 ± 0.1 (highest weight for both 'efficacy regarding glycemic control' and 'prevention of microvascular complications'). These differences were highly significant ($P < 0.0001$ by ANOVA). In the lower part of Table 1, each score from the upper part of the Table (unweighted) was multiplied by the individual weight assigned by the same diabetes specialist. Thus, individual and summary scores paying attention to both the raw score and the weight are displayed. With both methods, incretin-based medications and α-glucosidase inhibitors rank highest in the opinion of our experts, whereas insulin, thiazolidinediones and especially sulfonyureas receive the lowest scores.

In conclusion, when comparing potential medications to be added to metformin when treatment needs to be intensified,

incretin-based medications have proven that their efficacy has been at least comparable with competing antidiabetic drugs. This, together with other properties (no promotion of hypoglycemia and weight gain), makes them a serious contender as a good choice when treatment needs to be intensified at the stage of metformin failure. Certainly, this conclusion will be supported if long-term studies add evidence that these medications have the potential to prevent diabetic complications and maintain adequate glycemic control over a long period of time (durability).

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