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REVIEW

Insulin plus incretin: A glucose-lowering strategy for type 2-diabetes

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Abstract

There are many advantages of combining incretin therapy [glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors] with insulin therapy as a glucose-lowering strategy in type 2 diabetes. One important advantage is the complementary mode of the mechanistic action of incretin and insulin therapy. Another advantage is the reduction in risk of hypoglycemia and weight gain when adding incretin therapy to insulin. Several clinical trials have studied the addition of GLP-1 receptor agonists [exenatide BID (twice daily), lixisenatide, albiglutide] or DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, alogliptin, linagliptin) to ongoing insulin therapy or adding insulin to ongoing therapy with a GLP-1 receptor agonist (liraglutide). These studies show improved glycemia in the presence of limited risk for hypoglycemia and weight gain with the combination of incretin therapy with insulin. This article reviews the background and clinical studies on this combination.

Key words: Type 2 diabetes; Glucose lowering; Insulin therapy; Glucagon-like peptide-1 receptor agonists; Dipeptidyl peptidase-4 inhibitors; Incretin therapy; Combination

Core tip: Incretin therapy (glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors) combined with insulin therapy is a glucose-lowering strategy in type 2 diabetes. The combination allows a complementary mode of mechanistic action and, as demonstrated in several clinical trials, is glucose-lowering in association with limited risk for hypoglycemia and weight gain. The combination is a promising strategy in patients in whom metformin with either incretin therapy or basal insulin is insufficient for adequate glycemic control. This article reviews the background and clinical studies on this combination.

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INSULIN IN COMBINATION WITH INCRETINS: A MORE COMMONLY USED GLUCOSE-LOWERING THERAPY

Life style changes accompanied by addition of metformin are often first line glucose reducing therapy in type 2 diabetes[1,2]. When metformin as the only pharmaceutical agent is insufficient for adequate glycemic control, several options are currently available. Of these, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and insulin were recently suggested by the joint position statement from the American Diabetes Association and the European Association of the Study of Diabetes to be potentials as an add-on to metformin[1]. They were suggested to be individualized to target the best combination for the individual patient. However, even after combination of metformin with any of these second-line thera-

pies, many patients still do not reach the glycemic target which is mainly due to the progression of the disease. At this stage, three-drug combinations are suggested to be used, involving metformin in combination with two of the other options. One such three-drug combination is the combination of insulin therapy with incretin therapy (+ metformin) as a glucose-reducing strategy of type 2 diabetes[2-6]. This article reviews the current evidence and experience for this combination.

BASIS FOR INCRETIN THERAPY

Incretin therapy is based on the anti-diabetic effects of GLP-1[7]. As an incretin hormone, GLP-1 is released from the gut after meal ingestion and augments insulin secretion in a glucose-dependent manner[7,8]. This effect on the beta cells is achieved through activating specific GLP-1 receptors, which are G protein coupled receptors[9]. GLP-1 also has an important effect to inhibit glucagon secretion[10]. These double effects on islet hormone secretion are of importance for the anti-diabetic action of incretin therapy and, furthermore, by targeting the double alpha and beta cell dysfunction, incretin therapy targets a main pathophysiological cause of the disease[11]. GLP-1 receptors are, however, also expressed in other cells and therefore GLP-1 also exhibits extra-islet effects, such as delay of gastric emptying[12] and satiety through a central effect in the hypothalamus[13]. GLP-1 also has the potential of preserving beta cell function through inhibition of apoptosis[14], although this has so far only been demonstrated in animal studies and not shown in humans.

The first study showing an anti-diabetic action of GLP-1 was published in 1992[15]. In the early development of GLP-1 as a therapy, GLP-1 had to be given as an intravenous infusion since the hormone is rapidly inactivated by DPP-4[16]. The two successful strategies for incretin therapy used this knowledge and today we have several GLP-1 receptor agonists which are not or only weakly inactivated by DPP-4 and DPP-4 inhibitors[17-20].

GLP-1 receptor agonists are injected subcutaneously once or twice daily [exenatide BID (twice daily), liraglutide, lixisenatide] or once weekly {exenatide once weekly [Quaque weekly (QW)]}. In addition, once weekly GLP-1 receptor agonists are in late clinical development (albiglutide, semaglutide, dulaglutide)[17,20]. The GLP-1 receptor agonists therefore differ in several respects, such as dosage regimen. However, GLP-1 receptor agonists also differ in other aspects, as was recently reviewed[17-20]. Thus, the different GLP-1 receptor agonists have different molecular structures and in this context, they may be derived from exendin-4, showing approximately 50% homology with native GLP-1 (exenatide, lixisenatide), or they may be true GLP-1 analogues with a structure showing a high (> 90%) homology to GLP-1 (liraglutide, albiglutide, semaglutide, dulaglutide). The GLP-1 receptor agonists also differ in molecular size since they may be similar in size to native GLP-1 (exenatide, lixisenatide, liraglutide, semaglutide) or be 15-20 times bigger because of fusion of GLP-1 with albumin (albiglutide) or immunoglobulin (dulaglutide).

DPP-4 inhibitors are oral agents given once or twice daily (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, tenelagliptin, anagliptin, gemagliptin)[18,19]. They are different from each other in terms of molecular structure, although they are all small molecules, and they also differ, besides in pharmacokinetics with relevance for dosing regimen, in elimination mechanisms, as was recently reviewed[21].

Incretin therapy is today established as an add-on treatment to metformin and is also used in other conditions; it results in reduction of both fasting and postprandial glucose and it is associated with a low risk of hypoglycemia and no weight gain (weight reduction or weight neutrality)[19,20,22].

RATIONALE FOR COMBINATION INSULIN THERAPY PLUS INCRETIN THERAPY

The combination of incretin therapy and insulin therapy was initially not clearly evident during the development of incretin therapy. Instead, incretin therapy was mainly developed for combination with oral antihyperglycemic agents, in particular metformin. This is still a very important combination. However, as discussed for GLP-1 receptor agonists[4] and DPP-4 inhibitors[2,3], incretin therapy offers mechanistic advantages when used in association with insulin, which makes this combination a promising strategy for treatment.

The mechanistic complementary actions of the two approaches relate to reduction in fasting glucose, reduction in postprandial glucose, the low risk for hypoglycemia and the prevention of weight gain. More mechanistic studies are required, however, for a full appreciation of the complementary actions of insulin and incretins in combination.

Fasting glucose

Reduction of fasting glucose is a major goal for glucose-lowering therapy since fasting glucose contributes largely to hemoglobin A1c (HbA1c)[23,24]. A main effect of basal insulin is the reduction of fasting glucose, which is achieved through increased peripheral (mainly muscle and fat tissue) glucose utilization and inhibited hepatic glucose output[25,26]. Also, GLP-1-receptor agonists and DPP-4 inhibitors reduce fasting glucose but this is achieved through other mechanisms than insulin; mainly a glucose-dependent inhibition of glucagon secretion from the islet alpha cells[10,27]. In addition, direct liver effects of GLP-1 may also contribute[28]. Hence, the combination of insulin with incretin therapy would be expected to complement each other to reduce fasting glucose.

Postprandial glucose

Postprandial glucose also contributes to HbA1c and is therefore a target for glucose-lowering therapy[23,24]. Postprandial glucose is mainly regulated by gastric emptying

and the meal-induced islet hormone responses[29-31]. These effects are not appreciably affected by basal insulin. In contrast, incretin therapy reduces postprandial glucose, although the mode of action to achieve this effect differs between GLP-1 receptor agonists and DPP-4 inhibitors. GLP-1 receptor agonists reduce postprandial glucose mainly by delaying gastric emptying[29-31]. This effect of GLP-1 shows, however, tachyphylaxis, meaning that during long-term and continuous stimulation, the effect is reduced[32,33]. Consequently, intermittently acting GLP-1 receptor agonists (exenatide BID, lixisenatide) have been shown to be more potent to reduce gastric emptying than continuously acting GLP-1 receptor agonists (liraglutide, exenatide QW)[34,35]. In contrast, DPP-4 inhibitors do not inhibit gastric emptying[36] but instead reduce postprandial glucose mainly through inhibiting postprandial glucagon levels and stimulating beta cell function[27,37]. Both incretin therapy strategies therefore reduce postprandial glucose and thus complement the lack of such an effect by insulin in the combination therapy.

Hypoglycemia

Hypoglycemia is an adverse event for glucose-lowering therapy and is occasionally the limitation factor for achieving good glycemic control. Hypoglycemia is associated with negative impact, such as unpleasant and sometimes dangerous symptoms, weight gain (due to defense eating), deterioration of glycemic control (due to reduced adherence to therapy and therapeutic goals because of fear of new hypoglycemic episodes), increased cardiovascular risk and increased risk for microvascular complications[38-41]. Insulin therapy is associated with a high risk of hypoglycemia[29-31]. In contrast, incretin therapy is associated with a low risk of hypoglycemia[30,31,39-47]. This is because the islet effect of GLP-1 is glucose dependent[7,9] and the glucagon counter-regulation to hypoglycemia is preserved or augmented[48-50]. Therefore, incretin therapy has the potential to prevent the hypoglycemia induced by insulin when the two treatments are used in combination.

Body weight

Since increased body weight is associated with long-term negative effects, prevention of weight gain or weight reduction is of importance for glucose-lowering therapies. Body weight is increased by insulin therapy[51]. This is due to the anabolic action of insulin but may also be due to the self-defense eating associated with hypoglycemic events. Incretin therapy, on the other hand, prevents weight gain since its lowering of glycemia is not associated with increased risk of hypoglycemia and therefore the therapy avoid the self-defense eating[52]. GLP-1 receptor agonists also induce satiety through effects on the satiety center in the hypothalamus, thereby inducing weight reduction[13]. Therefore, the combination of incretin therapy with insulin has a great advantage of preventing the weight gain induced by insulin.

Disease modifying effects

Type 2 diabetes is a progressive disease with is mainly due to a continuous decline in beta cell function[53]. It has been discussed whether insulin therapy and incretin therapy may have complementary disease modifying effects[5]. The rationale for this suggestion is that insulin has been suggested to improve beta cell function through its normalization of fasting glucose, thereby preventing glucotoxicity and may also result in "beta cell rest"[54]. On the other hand, GLP-1 based therapies may improve beta cell function so much that beta cell function will also be improved over a long-term perspective, particularly in association with inhibited beta cell apoptosis[7,9].

ADVANTAGES OF COMBINING INSULIN WITH INCRETIN THERAPY

The complementary actions of insulin and incretin therapy, as discussed above, may result in potential advantages that may be observed by using this combination as a glucose-lowering strategy when treating people with type 2 diabetes. The main advantages are: (1) the combined reduction of fasting and postprandial glycemia which will lower HbA1c; (2) the lower risk of hypoglycemia which is due to the protection against hypoglycemia with incretin therapy in association with the often observed reduction in insulin dose when using this combination; (3) the lower risk for weight gain, which again is due to the protection against weight gain by incretin therapy in association with reduced weight gain through reduction in the insulin dose; and (4) the potential long-term disease modifying prospect of the combination.

CLINICAL STUDIES OF ADDING GLP-1 RECEPTOR AGONISTS TO INSULIN

Exenatide

The first proper clinical trial exploring the combination of incretin therapy with insulin was a study in 259 patients with type 2 diabetes who were treated with insulin glargine (± metformin and/or pioglitazone) with insufficient glycemic control (HbA1c 7.5%-10.5%; mean 8.4%). Patients were randomized to receive additional therapy with exenatide BID (n = 138) or placebo (n = 123) and the dose of insulin glargine was titrated to achieve a fasting glucose level less than 5.6 mmol/L[55]. After the study period of 30 wk, HbA1c was reduced by 1.7% in the group treated with exenatide BID as an add-on compared to 1.0% by placebo ($P < 0.001$). The daily insulin glargine dose had increased by 20 U (95%CI: 16-24) in the placebo group and by 13 U (95%CI: 9-17) in the exenatide BID-group ($P = 0.030$) (baseline insulin glargine dose was 48 U). Postprandial glucose was reduced in the exenatide BID-treated group (by 2.0 mmol/L, 95%CI: 1.5-2.5 mmol/L) but not changed in the placebo group ($P < 0.001$), whereas changes in fasting glucose did not differ between the two groups. Body weight was reduced (by 1.8 kg) in the exenatide BID group but increased (by 1.0 kg) in the placebo-treated group (baseline 94 kg). Furthermore, the number of hypoglycemic events did

Table 1 Published clinical trials with glucagon-like peptide-1 receptor agonists added to ongoing insulin therapy

		Exenatide BID		Lixisenatide	
Ref		56	58	59	60
Number of patients		259	495	446	311
Duration (wk)		30	24	24	24
HbA1c	Baseline	8.3 ± 0.9	8.4 ± 0.9	7.6 ± 0.5	8.5 ± 0.7
	Change	-1.7 (-1.9, -1.6)	-0.7 ± 0.1	-0.7 ± 0.1	-0.8 ± 0.2
	Baseline comparator	8.5 ± 1.0	8.4 ± 0.8	7.6 ± 0.5	8.5 ± 0.8
	Change comparator	-1.0 (-1.2, -0.9)	-0.4 ± 0.1	-0.4 ± 0.1	+0.1 ± 0.2
FPG (mmol/L)	Baseline	7.9 ± 2.1	8.1 ± 2.8	6.6 ± 1.7	7.8 ± 2.2
	Change	-1.6 (-1.9, -1.3)	-0.6 ± 0.2	-0.3 ± 0.2	-0.4 ± 0.3
	Baseline comparator	8.3 ± 2.3	8.0 ± 2.7	6.7 ± 2.0	7.7 ± 2.3
	Change comparator	-1.5 (-1.8, -1.2)	-0.6 ± 0.3	-0.5 ± 0.2	0.3 ± 0.3
Hypoglycemia	GLP-1RA	1.4[1]	206[2]	28[3]	42[3]; 33[4]
	Comparator	1.2[1]	522[2]	22[3]	24[3]; 28[4]
Body weight	Baseline	95 ± 20	89 ± 21	88 ± 22	66 ± 13
	Change	-1.8 (-2.4, -1.1)	-1.8 ± 0.2	0.3 ± 0.3	-0.4
	Baseline comparator	93 ± 21	88 ± 20	87 ± 21	66 ± 12
	Change comparator	1.0 (0.2, 1.7)	-0.5 ± 0.3	1.2 ± 0.3	+0.1

Insulin glargine was used in all studies. Occurrence of hypoglycemia was reported as number of episodes per patient year[1], number of events[2] or as percentage of patients with at least one hypoglycemic episode[3]. One study also reported percentage of patients not on sulfonylurea who experienced at least one hypoglycemic episode[4]. Variation in baseline is SD, variation in effect is SE. Variation within parenthesis is the 95%CI. FPG: Fasting glucose; GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c.

not differ significantly between the groups inspite of the difference in HbA1c (1.4 episodes per patient year in the exenatide BID-treated group *vs* 1.2 episodes per patient year in the placebo group) (Table 1).

In another study, a direct comparison was performed between adding exenatide BID *vs* short-acting prandial insulin lispro to ongoing insulin glargine (+ metformin) in patients who were inadequately controlled on insulin glargine + metformin. The study used an initial 12 wk titration phase with insulin glargine [fasting glucose (FPG) glucose target < 5.6 mmol/L]. Patients who failed to reduce HbA1c below 7% during this titration period (mean 8.3%) were randomized to receive additional exenatide BID (n = 316) or insulin lispro (n = 321). The results showed that after 30 wk, HbA1c had been reduced by 1.1% ± 0.1% in both groups (not significantly different). Fasting glucose was reduced by 0.5 ± 0.2 mmol/L in the exenatide group *vs* 0.2 ± 0.2 mmol/L in the insulin lispor group (P = 0.002) and whereas postprandial glucose was similarly reduced after breakfast and evening meals, it was more pronouncedly reduced by lispro at lunch (when exenatide was not given; P < 0.001). Body weight was reduced in the exenatide BID group (by 2.4 ± 0.2 kg) and increased in the insulin lispro group (by 2.1 ± 0.2 kg). The number of hypoglycemic events was lower in the exenatide group (n = 206) than in the insulin lispro group (n = 522)[56].

Lixisenatide

The GLP-1 receptor agonist lixisenatide has been examined as an add-on to basal insulin in three studies. In the first study, patients treated with basal insulin with inadequate glycemic control (HbA1c 7%-10%, mean 7.6%) were randomized to addition of lixisenatide (n = 328) or placebo (n = 167) without any insulin titration[57]. The used basal insulins in the study were insulin glargine (50%), insulin detemir (47%), neutral protamine Hagedorn (NPH) insulin (7%) or premix insulin (2%) and 80% of the patients were additionally treated with metformin. After the study period of 24 wk, HbA1c was reduced by 0.7% by lixisenatide and by 0.4% by placebo (P < 0.001). Fasting glucose was reduced in both groups but with no significant difference. In contrast, postprandial glucose was more pronouncedly reduced in the lixisenatide group (by 5.5 ± 0.5 mmol/L) than in the placebo group (by 1.7 ± 0.5 mmol/L, P < 0.001). Body weight (from baseline of 88 kg) was reduced by 1.8 kg by lixisenatide and 0.5 kg by placebo (P < 0.001). The daily insulin dose (mean 56 U at baseline) had been reduced by 5 U in the lixisenatide group and by 2 U in the placebo group. Twenty-eight percent of patients in the lixisenatide group reported hypoglycemia *vs* 22% in the placebo group.

In the second study on add-on with lixisenatide to basal insulin, lixisenatide was added to insulin glargine in patients who initially failed to control glycemia with oral agents (HbA1c 7%-10%, mean HbA1c 8.6%)[58]. After an initial titration phase of insulin glargine alone for 12 wk targeting a fasting glucose of 4.4-5.6 mmol/L (mean HbA1c was reduced to 7.6%), patients were randomized to lixisenatide (n = 223) or placebo (n = 223) together with ongoing insulin therapy (+ metformin) for 24 wk. It was found that mean HbA1c was further reduced to 7.0% in the lixisenatide group *vs* to 7.3% in the placebo group (P < 0.001). Fasting glucose was similarly reduced in both groups, whereas postprandial glucose was reduced more in the lixisenatide group (by 3.4 ± 0.5 mmol/L) than in the placebo group (0.1 ± 0.5 mmol/L; P < 0.001). Body weight was increased by 1.2 kg in the placebo group and by 0.3 kg in the lixisenatide group (baseline 86 kg) (P = 0.0012). Confirmed hypoglycemia was reported in 0.80 episodes per patient year in the lixisenatide group *vs* 0.44 in the placebo group.

Finally, the effect of adding lixisenatide to ongoing insulin therapy has also been examined in Asian patients with inadequate glycemic control on basal insulin [with (70%) or without sulfonylurea therapy][59]. Of the patients, 60% were treated with insulin glargine, 27% with insulin detemir and 13% with NPH insulin with a mean daily insulin dose of 25 U. The patients were randomized to addition of lixisenatide (n = 154) or placebo (n = 157) together with ongoing therapy with basal insulin ± sulfonylurea. After the 24 wk study period, HbA1c was reduced by 0.8% in the lixisenatide group *vs* increased by 0.1% in the placebo group (P < 0.001). There was a reduction in fasting glucose in the lixisenatide group compared to the placebo group (P = 0.0187) and postprandial

Table 2 Published clinical trials with dipeptidyl peptidase-4 inhibitors combined with basal ± prandial insulin

		Vildagliptin		Sitagliptin		Alogliptin	Saxagliptin	Linagliptin
Ref		62	63	64	65	67	69	70
Number of patients		296	449	641	124	390	455	1261
Study duration (wk)		24	24	24	24	26	52	24
Comparator		Stable insulin	Stable insulin	Stable insulin	Increasing insulin	Stable insulin	Stable insulin	Stable insulin
HbA1c (%)	Baseline	8.4 ± 1.0	8.8 ± 1.0	8.7 ± 0.9	9.2 ± 1.0	9.3 ± 1.1	8.7 ± 0.9	8.3 ± 0.1
	Change	-0.5 ± 0.1	-0.8 ± 0.1	-0.6 (-0.7, -0.5)	-0.6 (-0.9, -0.3)	-0.7	-0.8 ± 0.1	-0.6 ± 0.1
	Baseline placebo	8.4 ± 1.1	8.8 ± 1.0	8.6 ± 0.9	9.2 ± 1.1	9.3 ± 1.1	8.6 ± 0.9	8.3 ± 0.1
	Change placebo	-0.2 ± 0.1	-0.1 ± 0.1	0 (-0.1, 0.1)	-0.2 (-0.5, 0.3)	-0.1	-0.4 ± 0.1	-0.1 ± 0.1
FPG (mmol/L)	Baseline	9.3 ± 3.1	9.6 ± 2.6	9.8 ± 2.9	9.0 ± 3.3	10.3 ± 3.9	NR	8.2 ± 2.6
	Change	-0.8 ± 0.3	-0.8	-1.0 (-1.4, -0.7)	-1.0 (-2.7, -0.2)	-0.6 ± 0.3		-0.2 ± 0.2
	Baseline placebo	8.7 ± 3.1	9.1 ± 2.5	9.9 ± 3.3	8.4 ± 2.8	10.9 ± 4.3	NR	8.4 ± 2.6
	Change placebo	-0.2 ± 0.4	-0.2	-0.2 (-0.6, 0.2)	-1.3 (-1.8, -0.5)	0.3 ± 0.3		-0.3 ± 0.2
Hypoglycemia		113[1]	8.4[2]	16[2]	7[2]	20[2]	23[2]	23[2]
Hypoglycemia placebo		185[1]	7.2[2]	8[2]	14[2]	40[2]	27[2]	22[2]
Body weight (kg)	Baseline	95 ± 2	78 ± 16	87 ± 19	69 ± 12	87 ± 19	88 ± 18	BMI (31 ± 5)
	Change	1.3 ± 0.3	0.1	-0.1 (-0.2, 0.4)	-0.7 (-1.4, -0.1)	0.6 ± 0.2	0.8	-0.2 ± 0.1
	Baseline placebo	95 ± 2	79 ± 17	87 ± 18	66 ± 10	91 ± 21	86 ± 16	BMI (31 ± 5)
	Change placebo	0.6 ± 0.3	-0.4	-0.1 (-0.3, 0.4)	1.1 (0.2, 1.8)	0.6 ± 0.2	0.5	0.1 ± 0.1

In the studies long and medium acting insulin and premixed insulins were used. Occurrence of hypoglycemia was reported as number of events[1] or as percentage of patients with at least one hypoglycemic episode[2]. Variation in baseline is SD, variation in effect is SE. Variation within parenthesis is the 95%CI. FPG: Fasting glucose; BMI: Body mass index (kg/m^2); HbA1c: Hemoglobin A1c.

glucose was reduced by 8 mmol/L in the lixisenatide group but not changed in the placebo group ($P < 0.001$). Symptomatic hypoglycemia was more frequent with lixisenatide (42.9%) *vs* placebo (23.6%). In contrast, in patients not treated with sulfonylurea, hypoglycemia was similar between groups (32.6% *vs* 28.3%, respectively). Change in body weight was not significantly different between the groups whereas the daily insulin dose was reduced by 1.4 U in lixisenatide group *vs* by 0.1 U in the placebo group ($P = 0.0019$).

Albiglutide

A study compared the effects of the once weekly GLP-1 receptor agonist albiglutide ($n = 285$) *vs* insulin lispro ($n = 281$) to ongoing insulin glargine therapy (+ oral agents, no sulfonylurea) in patients with type 2 diabetes with inadequate glycemic control (mean HbA1c 8.5%)[60]. There was a titration algorithm for insulin glargine to achieve fasting glucose of 4.4-7.2 mmol/L. After the 26 wk study period, HbA1c was similarly reduced by albiglutide (0.8% ± 0.1%) and by insulin lispro (0.7% ± 0.2%). Fasting glucose was reduced in both groups with no significant difference. Body weight (baseline 92 kg) was reduced 0.7 ± 0.2 kg by albiglutide and increased by 0.8 ± 0.2 kg by insulin lispro ($P < 0.001$). Mean insulin glargine dose did not change during the study. Thirty-two percent of patients on albiglutide experienced hypoglycemia *vs* 50% with insulin lispro.

CLINICAL STUDIES OF ADDING DPP-4 INHIBITORS TO INSULIN

Vildagliptin

The first study examining a DPP-4 inhibitor in combination with insulin added vildagliptin (*vs* placebo) to insulin treated patients with insufficient glycemic control (HbA1c 7.5%-11%, mean HbA1c 8.4%; $n = 296$)[61]. Patients were treated with basal and prandial insulin (mean 2.8 injections per day, mean daily insulin dose 82 U). After the 24 wk study period, HbA1c was reduced by 0.5% in the vildagliptin group *vs* 0.2% in the placebo group (baseline 8.4%) ($P = 0.01$). During the course of the study, there were 113 hypoglycemic events in the vildagliptin group compared to 185 in the placebo group and whereas there were 6 episodes of severe hypoglycemia in the placebo group, no severe hypoglycemic episode was seen in the vildagliptin group. The mean daily insulin dose was reduced by 1.9 U in the vildaglitpin *vs* increased by 2.4 U in the placebo group. Change in body weight did not differ between the groups (Table 2).

Another study examined the addition of vildagliptin to ongoing insulin (+ metformin) therapy in 449 patients over 24 wk[62]. The patients were treated with long-acting insulin (22%), intermediate acting insulin (17%) and premixed insulin (60%), with a mean daily insulin dose of 40 U. They had insufficient glycemic control (HbA1c 7.5%-11%; mean HbA1c 8.8%). It was found that HbA1c was reduced by vildagliptin by 0.8% and by placebo by 0.1% ($P < 0.001$). Fasting glucose was reduced in the vildagliptin group but not in the placebo group ($P = 0.050$). Hypoglycemia was reported in 8.4% of patients in the vildagliptin group and by 7.2% in the placebo group. The daily insulin dose was 41 U at baseline and slightly reduced in both groups with no difference. There was no change in body weight in any of the groups.

Sitagliptin

The first study examining the combination of sitagliptin with insulin therapy added the DPP-4 inhibitor *vs* placebo to ongoing insulin (+ metformin) treatment over 24 wk in 641 patients with poorly controlled type 2 diabetes

(HbA1c 7.5%-11%, mean HbA1c 8.6%)[63]. Seventy-four percent of the patients were treated with long-acting or intermediate-acting insulin and 26% were treated with premixed insulin. After the 24 wk study period, HbA1c was reduced by 0.6% by sitagliptin *vs* no change by placebo ($P < 0.001$). Fasting glucose was reduced in the sitagliptin group but not in the placebo group ($P < 0.001$). Similarly, postprandial glucose was reduced in the sitagliptin group (by -1.7 mmol/L, 95%CI: -2.2, -1.2) but not changed in the placebo group (0.3 mmol/L, 95%CI: -0.2-0.7) ($P < 0.001$). Hypoglycemia was observed in 16% of the patients on sitagliptin *vs* 8% of patients on placebo. Insulin dose was reduced by 0.1 U in the sitagliptin and by 1.6 U in the placebo group (baseline 44 U for long acting insulin and 67-74 U with premixed insulin). Body weight was reduced by 0.1 kg in both groups.

Another study compared adding sitagliptin to insulin therapy *vs* increasing the insulin dose in 140 patients on insulin therapy (+ oral agents) who had inadequate glycemic control (baseline HbA1c 7.5%-11%, mean HbA1c 9.2%). Patients were treated with insulin glargine alone (48%), insulin glargine together with rapid acting insulin (23%) or NPH insulin in combination with regular insulin (29%); mean daily insulin dose was 37 U. It was found that over the 24 wk study period, sitagliptin (mean insulin dose reduced by 2 U) reduced HbA1c by 0.6%, whereas increasing the insulin dose (by 10 U) reduced HbA1c by 0.2% ($P < 0.005$)[64]. Fasting glucose was reduced by approximately 1 mmol/L in both groups with no significant difference. Hypoglycemia occurred in 7 events per patient year in the sitagliptin group *vs* 14.3 events per patient year in the insulin group. Body weight was reduced by 0.7 kg in the sitagliptin group *vs* increased by 1.1 kg in the insulin group ($P < 0.05$).

A third study examined the add-on of sitagliptin ($n = 236$) *vs* placebo ($n = 232$) to patients who were treated with insulin (long-acting, intermediate-acting or premixed insulin) in combination with metformin over 6 mo. It was found that with the addition of sitagliptin, HbA1c was reduced by 0.8% (baseline 8.5%) *vs* no change in HbA1c after addition of placebo ($P < 0.001$). Relative to the placebo group, fasting glucose was reduced by 1.0 mmol/L and postprandial glucose by 2.0 mmol/L. Hypoglycemia was observed in 18% of patients in the sitagliptin group *vs* 8% in the placebo group[65].

Alogliptin

Alogliptin (two doses) or placebo was added to ongoing insulin therapy alone (40%) or with metformin in 390 patients with inadequate glycemic control (HbA1c $\geqslant$ 8.0%; baseline HbA1c 9.3%)[66]. The insulin treatment that was used was premixed insulin or insulin combinations (64%), as well as long-acting basal insulin alone (34%) or short-acting insulin alone (2%); mean daily insulin dose was 57 U. During the course of the 26 wk study, daily insulin dose was kept constant. Alogliptin reduced HbA1c by 0.6% (12.5 mg daily; $n = 131$) and 0.7% (25 mg daily; $n = 129$) *vs* a reduction by 0.1% in the placebo group ($n = 130$) ($P < 0.001$). Fasting glucose was reduced by aloglitin in the 25 mg group (by -0.6 ± 0.3 mmol/L *vs* the placebo group (0.3 ± 0.3 mmol/L; $P = 0.030$) but not changed in the 12.5 mg group. The number of patients reporting hypoglycemia was lower in the two alogliptin groups (21% and 20%, respectively) than in the placebo group (40%; $P < 0.001$). There was no difference in hypoglycemia events (24%-27% of patients reported hypoglycemic episodes in the three groups). Body weight increased by 0.6 kg (baseline 88 kg) in all groups.

Saxagliptin

Saxagliptin or placebo was added to ongoing insulin therapy (basal insulin or premixed insulin ± metformin) in 455 patients with inadequate glycemic control (HbA1c 7.5-11). During the course of the 24 wk study, daily insulin dose was kept constant[67]. Placebo-adjusted reduction in HbA1c by saxagliptin was 0.4% ($P < 0.001$). There was no difference in hypoglycemia events (18% with saxagliptin, 20% with placebo). Body weight was increased by 0.4 kg in the saxagliptin group and by 0.2 kg in the placebo group. An extension phase of this study showed sustained effects over 52 wk[68].

Linagliptin

Linagliptin or placebo was added to ongoing basal insulin therapy (± metformin and/or pioglitazone) in 1261 patients with inadequate glycemic control (HbA1c 7-10). During the study, daily insulin dose was kept constant during the first 24 wk but could thereafter be titrated according to fasting glucose[69]. After 24 wk, HbA1c was reduced by 0.6% (baseline 8.3%) by linagliptin and by 0.1% by placebo ($P < 0.001$). Placebo-adjusted reduction in fasting glucose with linagliptin was 0.6 mmol/L (95%CI: -0.9-0.4). During the following 28 wk, insulin dose was increased by 2.6 U in the linagliptin group and by 4.2 U in the placebo group but with no further change in HbA1c. There was no difference in hypoglycemia events (23% with linagliptin, 22% with placebo after 24 wk). Body weight was reduced by 0.3 kg in the linagliptin group and by 0.04 kg in the placebo group.

COMPARING CONTROLLED TRIALS COMBINING ADDING INCRETIN THERAPY TO INSULIN

As outlined above, the reduction in HbA1c, fasting and postprandial glucose, the lower risk of hypoglycemia, the prevention of weight gain and the potential disease modification are the main advantages of combining incretin therapy with insulin. Except for any direct evidence of a disease modifying effect of the combination, the controlled trials summarized above include information on these aspects and therefore it is of interest to compare their results in this regard (Tables 1 and 2).

HbA1c

The mean reduction in HbA1c in the controlled clinical studies adding incretin therapy to stable dose for 6 mo

was -0.8% ± 0.1% compared to -0.3% ± 0.1% when placebo was added ($P < 0.001$; Tables 1 and 2). There does not seem to be a difference between the two different strategies of incretin therapy since the placebo-adjusted reduction in HbA1c was -0.6% ± 0.2% for GLP-1 receptor agonists ($n = 4$ studies) *vs* -0.5% ± 0.1% for DPP-4 inhibitors ($n = 6$ studies).

Fasting glucose

Fasting glucose is also reduced by adding incretin therapy to stable dose of insulin. It was found to be reduced by -0.7 ± 0.1 mmol/L by the incretin therapy *vs* by -0.3 ± 0.1 mmol/L in the placebo groups ($P = 0.027$; Tables 1 and 2). There does not seem to be a difference between the two different strategies of incretin therapy since fasting glucose was reduced by 0.2 ± 0.2 mmol/L by GLP-1 receptor agonists ($n = 4$ studies) *vs* by -0.6 ± 0.2 mmol/L by DPP-4 inhibitors ($n = 5$ studies).

Postprandial glucose

A few studies also examined postprandial glucose after adding incretin therapy to a stable dose of insulin. They showed that postprandial glucose was markedly reduced when adding GLP-1 receptor agonists exenatide BID[55] and lixisenatide[58], whereas after adding the DPP-4 inhibitor sitagliptin, postprandial glucose was more modestly reduced[63].

Hypoglycemia

In the studies where incretin therapy has been added to insulin compared to ongoing insulin, the occurrence of hypoglycemia was not different between the incretin treatment and placebo in most studies (Tables 1 and 2). Since in most of these studies HbA1c is lower after addition of incretin therapy compared to placebo, an increased risk of hypoglycemia would be expected after incretin therapy. Since the opposite was the case, a conclusion is that incretin therapy will reduce the risk of hypoglycemia. This conclusion is also evident in the studies in which incretin therapy as an add-on to basal insulin was compared with the active comparator of either adding short-acting insulin[56,60] or increasing the insulin dose[64]. A reason for the low risk of hypoglycemia when adding incretin therapy to insulin therapy could be the reduced dose of insulin which often accompanies the combination. It may, however, also be caused be a sustainment of the glucagon counterregulation to hypoglycemia, as was recently demonstrated for the DPP-4 inhibitor vildagliptin when added to insulin; the sustained glucagon counterregulation assures a sufficient hepatic glucose response to prevent hypoglycemia[50].

Weight gain

Body weight was significantly reduced by -0.9 ± 0.5 kg by adding GLP-1 receptor agonists to ongoing insulin therapy compared to 0.4 ± 0.4 kg in the placebo groups, corresponding to a placebo-adjusted reduction by -1.4 ± 0.5 kg (Table 1). In contrast, DPP-4 inhibitors are weight neutral when added to insulin with a placebo-adjusted change in body weight of -0.2 ± 0.1 kg (Table 2).

OTHER STUDIES COMBINING INCRETIN THERAPY WITH INSULIN

Adding insulin to a GLP-1 receptor agonist

One study has examined the addition of basal insulin to patients who are treated with a GLP-1 receptor agonist with insufficient glycemic control. The study initially examined addition of liraglutide to patients failing glycemic control on metformin (± sulfonylurea; sulfonylurea was removed at start of study) ($n = 988$)[70]. After 12 wk, patients who were still uncontrolled (HbA1c > 7%) were randomized to continue metformin plus liraglutide or addition of insulin detemir to titrate fasting glucose to 4-6 mmol/L. After another 26 wk, HbA1c had been reduced by 0.5% by the combination of insulin detemir plus liraglutide, whereas those on liraglutide alone (all with metformin) had no further change in HbA1c ($P < 0.001$). FPG decreased more in the liraglutide + insulin group than in the liraglutide control group ($P < 0.001$). Hypoglycemia rates were 9.2% in the group given insulin detemir and liraglutide *vs* 1.3% with liraglutide alone. Body weight (baseline 96 kg) decreased by 3.5 kg by liraglutide during the initial period and then by 0.16 kg with insulin detemir and liraglutide *vs* by 0.95 kg with liraglutide without insulin detemir ($P = 0.03$).

Initial combination of incretin therapy with insulin

Liraglutide has been examined in a fixed ratio combination with insulin degludec in a randomized study in subjects with type 2 diabetes[71]. It was a large trial in which patients treated with metformin ± pioglitazone and inadequate glycemic control (baseline HbA1c 8.3%) were randomized to the addition of insulin degludec ($n = 414$), liraglutide ($n = 415$) or the combination of insulin degludec and liraglutide ($n = 834$). After 26 wk of treatment, HbA1c had been reduced by 1.4% with insulin degludec alone, 1.3% with liraglutide alone and 1.9% with insulin degludec in combination with liraglutide. Body weight had increased by 2.2 kg with insulin degludec alone, was reduced by 2.4 kg by liraglutide and was neutral with the combination. Cumulative episodes of hypoglycemia were 1.3 per patient in the insulin degludec group and reduced to 0.9 per patient in the combination group (0.1 in the liraglutide alone group).

Another study randomized 217 patients who had insufficient glycemic control on metformin ± sulfonylurea to receiving sitagliptin plus sulfonylurea or sitagliptin plus insulin detemir (all on metformin). After the 26 wk study period, sitagliptin had reduced HbA1c by 0.9% (mean baseline HbA1c 8.5%), whereas sitagliptin plus insulin detemir had decreased HbA1c by 1.4%. Hypoglycemia was reported in 1.3% of patients in the insulin detemir plus sitagliptin group and 1.7% in the sitagliptin alone group. Body weight decreased in both arms with a mean decrease of -1.7 kg in the sitagliptin control group *vs* -0.8

kg with sitagliptin plus insulin detemir group[72].

Uncontrolled studies combining incretin therapy with insulin

There are also a few uncontrolled studies of combining insulin therapy and incretin therapy in patients with type 2 diabetes which arrive at similar conclusions as the previously summarized controlled trials. One retrospective report showed that addition of exenatide BID to 188 insulin-treated patients resulted in a reduction in HbA1c by 0.66% (baseline 8.1%) after 6 mo with a persistent effect throughout two years; mean insulin dose could be reduced by 15% and only 4% of patients experienced hypoglycemia[73]. Furthermore, a study in obese patients with type 2 diabetes added exenatide BID (n = 21) or liraglutide (n = 40) to ongoing insulin therapy and showed a reduction in HbA1c in these patients by 1.0% (baseline 8.9%) after 7 mo. At the same time, the daily insulin dose was reduced from 91 U to 52 U and only a few hypoglycemia episodes were reported[74]. Moreover, a study in severely insulin resistant obese subjects treated with insulin U-500 (mean daily dose 192 U) received liraglutide for twelve weeks which reduced HbA1c by 1.4% (mean baseline HbA1c 8.5%) and at the same time the insulin dose was reduced by 28%. There were no reports of hypoglycemia and body weight was reduced by 5 kg (baseline body weight 136 kg)[75].

SAFETY OF THE COMBINATION OF INSULIN AND INCRETIN THERAPY

Incretin therapy has been shown to be safe with high tolerability and the only consistent adverse event is nausea and vomiting during the initial treatment period with GLP-1 receptor agonists[17-20,76]. Local injection site reactions (nodules and/or erythema) sometimes occur in association with treatment with GLP-1 receptor agonists, although such reactions are rare and commonly transient. Antibodies may be formed against GLP-1 receptor agonists; more commonly with exendin-4-based agonists (exenatide, lixisenatide) than after GLP-1-based agonists. In contrast, adverse events are rare during treatment with DPP-4 inhibitors, as evident from pooled analysis of clinical trials[77,78]. Recently, there has been a discussion about whether there is an increased risk of acute pancreatitis in incretin therapy. However, pooled or meta-analysis analyses have not demonstrated any increased risk when compared to placebo or other comparators[76-79]. Nevertheless, it is important to follow patients on GLP-1 receptor agonists in this regard and in patients with a history of acute pancreatitis, incretin therapy should not be given. Rodent data also suggest that GLP-1 receptor agonists may be associated with medullary thyroid carcinoma[80]. This has not, however, been observed in other animal species or humans, possibly because C-cells in humans have a lower expression of GLP-1 receptors than rodent C-cells[81].

Incretin therapy has also been discussed in relationship to cardiovascular safety and meta-analyses have shown that there is no detrimental effect of GLP-1 receptor agonists[82] or DPP-4 inhibitors[83]. Furthermore, several cardiovascular safety trials with incretin therapy are at present ongoing and two such recently published studies showed no increased risk for cardiovascular disease with saxagliptin[84] or alogliptin[85].

Also, insulin therapy is safe with the only concern being the increased risk of hypoglycemia and weight gain, expected adverse events through the glucose-lowering actions of the therapy. By combining incretin therapy and insulin, there is no additional concern for safety or tolerability, as evident from the studies reported in this review[55-69]. Hence, the number of adverse events is not higher in the incretin therapy + insulin treatment groups than in placebo groups in placebo-controlled clinical trials on GLP-1 receptor agonists or DPP-4 inhibitors as an add-on to insulin therapy, except the nausea and vomiting for the GLP-1 receptor agonists. This also includes recently discussed potential adverse events such as acute pancreatitis.

Some practical aspects need to be taken into account for incretin therapy. This includes the dose reduction of sitagliptin, vildagliptin, saxagliptin and alogliptin in patients with renal impairment due to their renal excretion. Furthermore, exenatide and liraglutide should be cautiously used in patients with renal impairment due to insufficient experience in this patient group. Furthermore, in patients with hepatic impairment, vildagliptin is not recommended. As for all new treatment combinations, however, the combination of incretin therapy with insulin also needs careful follow-up for examining potential adverse events which have not yet been observed.

SUMMARY AND CLINICAL POSITIONING OF INCRETIN PLUS INSULIN COMBINATION

The combination of insulin therapy with incretin therapy is attractive due to experience that this combination improves glycemia with a low risk of increasing risk for hypoglycemia and low risk of weight gain. The combination is therefore of particular value in patients on insulin therapy in whom HbA1c is not sufficiently reduced. In some patients, insufficient improvement of glycemia may be caused by clinical inertia with reluctance to increase the insulin dose due to fear of hypoglycemia or weight gain. Addition of incretin therapy with its lower risk of hypoglycemia and low risk of weight gain may therefore prevent the clinical inertia in these patients.

Incretin addition is also of value in patients who have insufficient reduction in HbA1c by intensified basal insulin therapy due to persistent high postprandial glycemia or frequent hypoglycemia. Incretin therapy offers advantages over addition of prandial insulin in these patients. Of particular importance is the prevention of hypoglycemia, since hypoglycemia is associated with both short-

term and long-term negative impact, not least on cardiovascular outcomes. The combination of incretin therapy with insulin may therefore provide advantages both in the short-term and by reducing long-term complications to the disease.

A main indication for the combination of incretin therapy and insulin is thus in patients who are treated with basal insulin (± metformin) in whom there is insufficient glycemic control and/or an unacceptable high rate of hypoglycemia and/or unacceptable weight gain. In patients with HbA1c levels which are not very high (< 7.5%), it is advisable to reduce the basal insulin dose when starting incretin therapy. The combination of incretin therapy with insulin is also an important treatment strategy in patients who are treated with metformin and incretin therapy in combination and in whom the glycemic control is insufficient, *i.e.*, to add basal insulin therapy to incretin therapy (+ metformin). The combination with incretin therapy and insulin may thus be introduced in either way, starting with incretin therapy or starting with insulin. It is also a possibility to start immediately with initial combination with incretin therapy and insulin in patients who are treated with metformin and who are in insufficient metabolic control. Such an early introduction of the combination may be a solution to the unmet need to start aggressive therapy early on during the disease development to achieve long-term control. Further studies are required to examine the long-term effects of this initial combination. One important set of trials would be studies comparing this treatment strategy with other three-drug combinations. This would be of interest to further analyze the potential for the combination of incretin plus insulin therapy (+ metformin). What would also be of value would be to compare different incretin therapies (different GLP-1 receptor agonists and different DPP-4 inhibitors) to elucidate potential differences in effects of the different compounds when combined with insulin. More mechanistic studies would also be of value, for example to examine the relationship between insulin therapy and incretin hormones for the regulation of hepatic glucose output, glucose utilization and islet function and, furthermore, to study impact of the combination therapy on gastric emptying and satiety. Moreover, it would also be of great value to analyze the cardiovascular outcome of this three-drug combination. This would be possible in sub-group analysis on the cardiovascular outcome trials of incretin treatment in which patients on insulin therapy have also been enrolled. Finally, studies directly aiming at examining the potential disease modifying effect of the combination of incretin therapy and insulin are important; these studies need to have a long duration and include mechanistic studies on islet function.

The combination of incretin therapy with insulin (± metformin) is thus a promising glucose-lowering strategy in type 2 diabetes, allowing a more intensified treatment at an earlier stage of the disease with a lower risk for hypoglycemia and weight gain when compared to other intensifying therapies.

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