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RESEARCH

Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial

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ABSTRACT

Objectives To study the effect of insulin treatment in combination with metformin or an insulin secretagogue, repaglinide, on glycaemic regulation in non-obese patients with type 2 diabetes.

Design Randomised, double blind, double dummy, parallel trial.

Setting Secondary care in Denmark between 2003 and 2006.

Participants Non-obese patients (BMI ≤27) with preserved beta cell function.

Interventions After a four month run-in period with repaglinide plus metformin combination therapy, patients with a glycated haemoglobin (HbA_{1c}) concentration of 6.5% or more were randomised to repaglinide 6 mg or metformin 2000 mg. All patients also received biphasic insulin aspart 70/30 (30% soluble insulin aspart and 70% intermediate acting insulin aspart) 6 units once a day before dinner for 12 months. Insulin dose was adjusted aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l. The target of HbA_{1c} concentration was less than 6.5%. Treatment was intensified to two or three insulin injections a day if glycaemic targets were not reached.

Main outcome measure HbA_{1c} concentration.

Results Of the 459 patients who were eligible, 102 were randomised, and 97 completed the trial. Patients had had type 2 diabetes for approximately 10 years. At the end of treatment, HbA_{1c} concentration was reduced by a similar amount in the two treatment groups (insulin plus metformin: mean (standard deviation) HbA_{1c} 8.15% (1.32) *v* 6.72% (0.66); insulin plus repaglinide: 8.07% (1.49) *v* 6.90% (0.68); P=0.177). Total daily insulin dose and risk of hypoglycaemia were also similar in the two treatment groups. Weight gain was less with metformin plus biphasic insulin aspart 70/30 than with repaglinide plus biphasic insulin aspart 70/30 (difference in mean body weight between treatments −2.51 kg, 95% confidence interval −4.07 to −0.95).

Conclusions In non-obese patients with type 2 diabetes and poor glycaemic regulation on oral hypoglycaemic agents, overall glycaemic regulation with insulin in combination with metformin was equivalent to that with insulin plus repaglinide. Weight gain seemed less with insulin plus metformin than with insulin plus repaglinide.

Trial registration NCT00118963

INTRODUCTION

In patients with type 2 diabetes, metformin and insulin secretagogues (for example, sulphonylureas), alone or in combination with insulin, are among the most widely used oral hypoglycaemic agents.

Metformin is an oral hypoglycaemic agent that targets insulin resistance. In the UK Prospective Diabetes Study (UKPDS), metformin treatment reduced the risk of cardiovascular disease in obese patients with type 2 diabetes,[1 2] a finding recently reinforced by a study in a different setting.[3] Thus, metformin is the preferred glucose lowering drug to use as monotherapy or in combination with insulin in obese patients with type 2 diabetes.[1 2 4-7]

"Insulin providing" agents such as insulin secretagogues or insulin are considered the primary treatment for non-obese patients with type 2 diabetes,[1 4 5] because this group usually has more pronounced insulin secretion deficiencies and less insulin resistance than obese patients.[8] In the recent 10 year follow-up of the UKPDS, however, treatment with insulin secretagogues or insulin reduced cardiovascular events and mortality in a combined group of non-obese and obese patients with type 2 diabetes.[2]

Many patients with type 2 diabetes eventually experience glycaemic failure on oral hypoglycaemic agents, even in combination therapy, and need additional insulin treatment.[9-13] Observational[14 15] and randomised[16] studies in non-obese patients with type 2 diabetes have indicated that the glucose lowering effect of metformin is equal to that of insulin secretagogues as monotherapy. However, it is not known whether insulin plus metformin has a similar glucose lowering potency in non-obese patients with type 2 diabetes as an "insulin providing" combination regimen of insulin plus an insulin secretagogue. Despite this unsolved question, international consensus statements

currently recommend the use of metformin alone or in combination with insulin secretagogues or insulin in all patients with type 2 diabetes, regardless of BMI.[7]

Repaglinide is a meglitinide analogue: a short acting insulin secretagogue with a similar glucose lowering effect, lower risk of hypoglycaemia, and better effect on cardiovascular disease surrogate markers than other insulin secretagogues such as glibenclamide.[17-20] An observational study of cardiovascular events in patients with type 2 diabetes suggested that repaglinide has similar cardioprotective effects to metformin, whereas most sulphonylureas would be less effective than metformin.[21] Hence for long term use or as a metformin comparator in clinical trials, repaglinide could be considered the insulin secretagogue of choice, despite being more expensive than sulphonylureas.

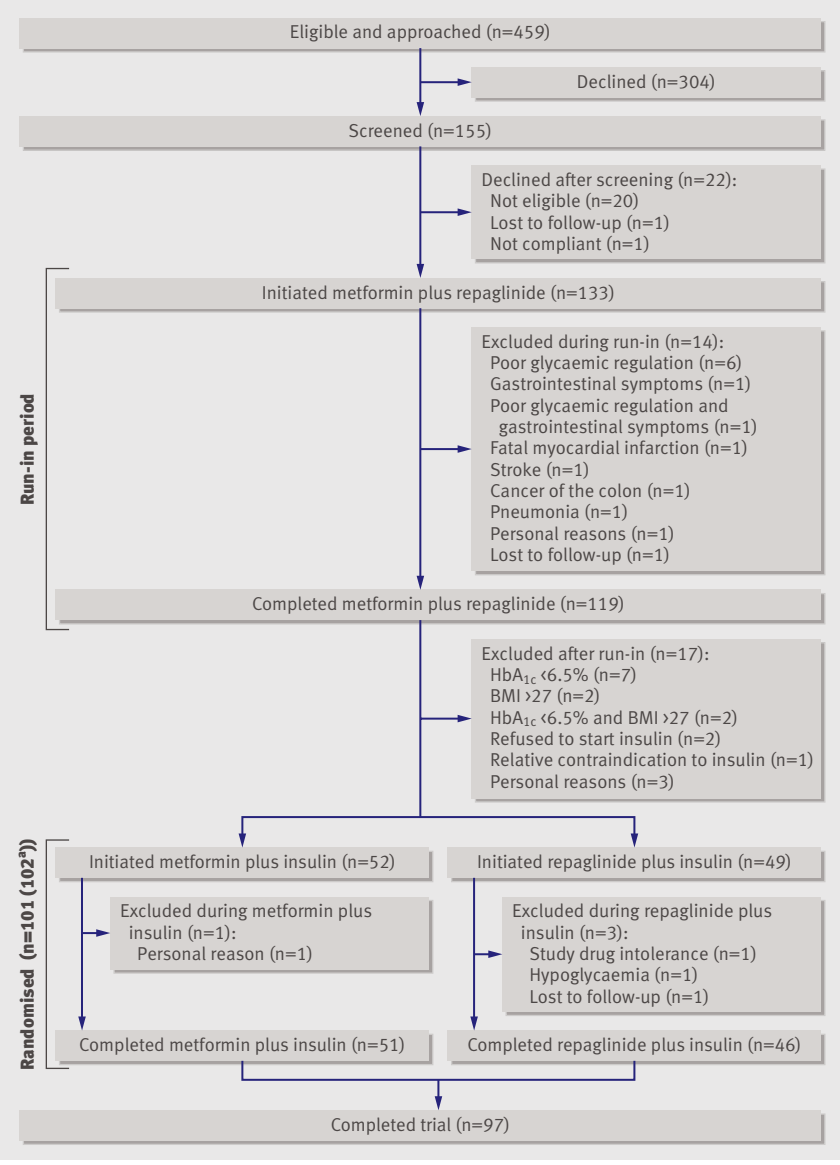

Fig 1 | Patient flow scheme. [a]One patient (randomised to insulin plus repaglinide) who did not start the study medication was excluded from all statistical analyses; therefore, 101 patients were included in the analysis

Several insulin treatment regimens are available for patients with type 2 diabetes. Biphasic insulin aspart 70/30 is a premixed insulin analogue that comprises 30% soluble insulin aspart and 70% intermediate acting insulin aspart. Premixed insulin analogues, including biphasic insulin aspart 70/30, have advantages compared with other insulin regimens such as the widely used basal insulin regimen (that is, a once daily intermediate acting insulin). Such advantages include lower glycated haemoglobin (HbA_{1c}), less pronounced fluctuations in blood glucose after meals and, in some studies, lower risk of hypoglycaemia.[22-29] Moreover, studies in various ethnic populations have indicated that biphasic insulin aspart 70/30 is safe and effective with up to three injections a day.[30-32] Such therapy could be more convenient than the basal bolus regimen (four daily injections) in patients who need multiple daily injections.[33]

In this trial we aimed to test the hypothesis that combination therapy for one year with metformin plus biphasic insulin aspart 70/30 has equal glucose lowering efficacy to the insulin secretagogue repaglinide plus biphasic insulin aspart 70/30 in non-obese patients with type 2 diabetes who have poor glycaemic control on combination therapy of oral hypoglycaemic agents.

METHODS

The study was an investigator initiated, single centre, prospective, randomised, double blind, double dummy, parallel trial of metformin plus biphasic insulin aspart 70/30 compared with repaglinide plus biphasic insulin aspart 70/30 (hereafter termed "insulin" in the Methods and Results sections).

Patients were enrolled between February 2003 and September 2004 at Steno Diabetes Center, Gentofte, Denmark. A targeted approach using electronic patient records as search objects for eligibility was used among approximately 5500 patients, about 40% of whom had type 2 diabetes. All potentially eligible non-obese patients with type 2 diabetes identified were invited to participate (fig 1). A total of 155 patients accepted and attended a screening visit. Of these, 53 patients declined to participate before randomisation. Information on patients' reasons for refusing to participate was not collected. Patients gave written informed consent at the screening visit.

A total of 459 patients were eligible for inclusion and were approached by trial clinicians to join the study, and 155 consented and entered the screening phase. A total of 133 patients with a BMI of 27 or less (corresponding to the criterion for non-obesity criteria used in the UKPDS) and an initial HbA_{1c} concentration of 6.5% or more were selected for inclusion (box 1).

After the screening period, patients entered a four month run-in period. All patients received combination therapy with metformin (1000 mg twice a day) plus repaglinide (2 mg three times a day) and stopped prior glucose lowering treatments. Doses were adjusted by forced titration to reach maximum tolerated doses (see web appendix 1).

Box 1: Inclusion, exclusion, and withdrawal criteria

Inclusion criteria

- Type 2 diabetes mellitus, defined as age at onset of diabetes ≥40 years; fasting serum C peptide ≥300 pmol/l or a non-fasting or glugacon stimulated serum C peptide ≥600 pmol/l (measured either during the screening or run-in period); and no history of persistent ketonuria or of ketoacidosis
- BMI ≤27*
- Insulin naive patients: HbA_{1c} ≥6.5% after a minimum of four months' treatment on oral hypoglycaemic agents as monotherapy or combination therapy
- Insulin treated patients: HbA_{1c} <9.5% at ongoing insulin therapy

Exclusion and withdrawal criteria

- Type 1 diabetes mellitus or secondary diabetes mellitus
- Weight loss of more than 5.0 kg during the 6 months before enrolment
- HbA_{1c} <6.5% at baseline
- BMI >27 at baseline
- Contraindications for the use of the study drugs (for example, clinical signs of heart, kidney, or liver failure†)
- Coexisting serious medical conditions†
- HbA_{1c} >10.5% at two separate visits with ≥1 month interval a minimum of four months after initiation of the randomised study drugs

*The UK Prospective Diabetes Study (UKPDS) defined "non-overweight" in patients with type 2 diabetes as weight within 120% of the ideal body weight according to weight for height tables.[13 34 35] Hence, the UKPDS investigators did not use BMI as the measure of obesity when allocating patients into treatment groups. The BMI corresponding to the 120% of ideal body weight in the weight for height tables used in the UKPDS would be about 27.

†See web appendix 1 for details.

At the end of the run-in period, 102 patients were randomly allocated to receive 12 months combination therapy with either repaglinide, insulin, and placebo metformin, or metformin, insulin, and placebo repaglinide. Active and placebo tablets were identical in appearance, taste, and smell. The maximum dose of repaglinide was 2 mg three times a day (total daily dose: 6 mg) and metformin 1000 mg twice a day (total daily dose: 2000 mg). The near maximum doses of metformin and repaglinide were chosen on the basis of previous dose-response studies, which showed only slight additional glucose lowering effect and more side effects with higher doses of both drugs.[36-38] Patients were advised to take tablets just before or during meals.

The starting dose of insulin was six units injected before dinner. Patients self adjusted insulin dose every third day according to a predefined algorithm, aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l (see web table A). The target HbA_{1c} concentration was less than 6.5%. If glycaemic targets were not reached, patients intensified to two or three insulin injections a day at three, six, or nine months using prespecified criteria (see web appendix 1). Doses were reduced if adverse events with possible relation to either of the study medications occurred. Once adverse events had resolved, drug dose was increased again; if adverse events recurred, the lower dose was continued.

According to local guidelines, patients who were not receiving concomitant treatment with aspirin or a statin initiated such treatments (see web appendix 1). Otherwise, non-vital changes in non-study medications were postponed until after the trial. Patients were asked not to make any lifestyle modifications during the trial.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen County, Denmark.

Outcome measures

The primary outcome was HbA_{1c} concentration (normal limits: 4.1-6.4%). Secondary outcomes were insulin doses, self monitored plasma glucose, measures of adiposity, and adverse events. Outcomes were assessed at enrolment (screening period: −4.5 and −4 months visits), at baseline (0 month visit), and on the last day of treatment (12 month visit). Clinical status was assessed at −2, 3, 6, and 9 months. Follow-up ended in February 2006.

HbA_{1c} concentration was measured by ion exchange high performance liquid chromatography (Tosoh Automated Glycohemoglobin Analyser HLC-723 G7, Tosoh Bioscience, Minato, Japan), aligned to the Diabetes Control and Complication Trial standard. HbA_{1c} concentration was measured in duplicate (each in a separately drawn sample) at all study visits. Blood sampling procedures as well as methods to assess the secondary outcomes and compliance are described elsewhere (see web appendix 1).

Statistics

Random allocation was centrally performed in blocks of three and four, stratified by baseline levels of HbA_{1c} and BMI (see web appendix 1). The 101 randomised patients were evaluated for screening, outcome, and safety variables, as well as for compliance and reporting of adverse events. For the primary outcome, the randomised population was analysed on an intention to treat basis, with last observation carried forward for missing values at the end of treatment. For HbA_{1c}, the last observation was carried forward only if both measurements were missing at the end of treatment. Only values obtained a minimum of three months after randomisation were used for last observation carried forward (one patient). Insulin dose was analysed in a similar way to the primary outcome, whereas other secondary outcomes were analysed without last observation carried forward (owing to non-fasting assessments at intermediate study visits; for example, measures of adiposity). The statistical tests of efficacy included measurements taken before randomisation, representing baseline (0 month); and after 12 months or last observation carried forward, representing the end of treatment. Hence, measurements obtained at intermediate study visits were included in the statistical analyses, except for measurements used for last observation carried forward. Differences in treatment efficacy between the randomised interventions were evaluated by comparison of end of treatment measurements with those taken at the baseline ("change from baseline"). The analysis of self monitored plasma glucose measurements included those measurements

made during the last two weeks before study visits (see web appendix 1).

The mean of the two measurements a visit of HbA_{1c} was used for descriptive statistics and as the baseline estimate; in contrast, both HbA_{1c} measurements from the end of treatment were evaluated in the primary outcome analysis. Thus, an analysis of covariance model was developed for the primary outcome, with patient as the random effect, treatment (metformin plus insulin or repaglinide plus insulin) as the fixed effect, and baseline levels as the covariate. The secondary outcomes, having only one measurement per visit, were analysed similarly but without a random effect. Hypoglycaemia was analysed by a Poisson regression model adjusted for overdispersion and exposure time. Categorical data were analysed either as odds ratios by logistic regression model, with treatment type as the fixed effect and baseline as the covariate, or as proportions by Wilcoxon rank sum test. Prespecified analyses on the basis of patient characteristics, as well as ancillary analyses of insulin doses and number of injections, were made by adding fixed effects and interaction terms to the analysis of covariance model.

Data are given as mean (standard deviation) or as median or geometric mean (range; or coefficient of variation) for non-normally distributed variables. Treatment effects are given as mean (standard error) or mean (95% confidence intervals). All data are reported as raw values except for differences between treatments and changes from baseline (treatment effects), which are reported as adjusted values. No corrections for multiple testing were performed.

The study was designed to have a statistical power of 80% to detect a 0.50% absolute difference in HbA_{1c} concentration, with an estimated standard deviation of 0.8% at a 5% two sided significance level. Accordingly, 100 enrolled subjects were required to allow for 16 drop outs. The difference in primary outcome considered to be clinically relevant—that is, the equivalence (non-inferiority) margin—was defined as an absolute HbA_{1c} difference between treatments of ±0.50%.[39 40] This value was chosen to increase the likelihood of detecting a potential difference of 0.6% in HbA_{1c}, as reported between the conventional and metformin treated groups in the UKPDS.[1] Statistical analyses were done with Statistical Analysis System, version 9.1.3 (SAS Institute, Cary, NC, USA) or Statistical Package for the Social Sciences, version 14.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 102 patients were randomly allocated to either study arm (fig 1). Among the 102 randomised patients, one individual (randomised to insulin plus repaglinide) who never started the study medication and who dropped out during the first week after randomisation was excluded from all statistical analyses. Therefore, 101 patients were included in the intention to treat analysis, 52 of whom initiated treatment with metformin plus insulin and 49 who started on repaglinide plus insulin. Among the 101 patients who were randomly allocated treatment, four patients (4.0%) dropped out (fig 1). Thus, 51 patients (98.1%) completed the 12 month treatment period with metformin plus insulin, and 46 patients (93.9%) completed repaglinide plus insulin. Screen failures or protocol deviations during the randomised interventions were observed in a further seven patients (see web appendix 1)—these patients were included in all analyses.

Those patients who were invited but declined to participate were on average about three years older and had diabetes for two years longer than patients who agreed to participate (P=0.001 and P=0.002, respectively). By contrast, sex, body weight, BMI, and HbA_{1c} concentration did not differ significantly between these groups. Also, patients who were randomly assigned treatment did not have a significantly different duration of diabetes from those patients who were approached but not randomised (including those who declined invitation), whereas differences in age,

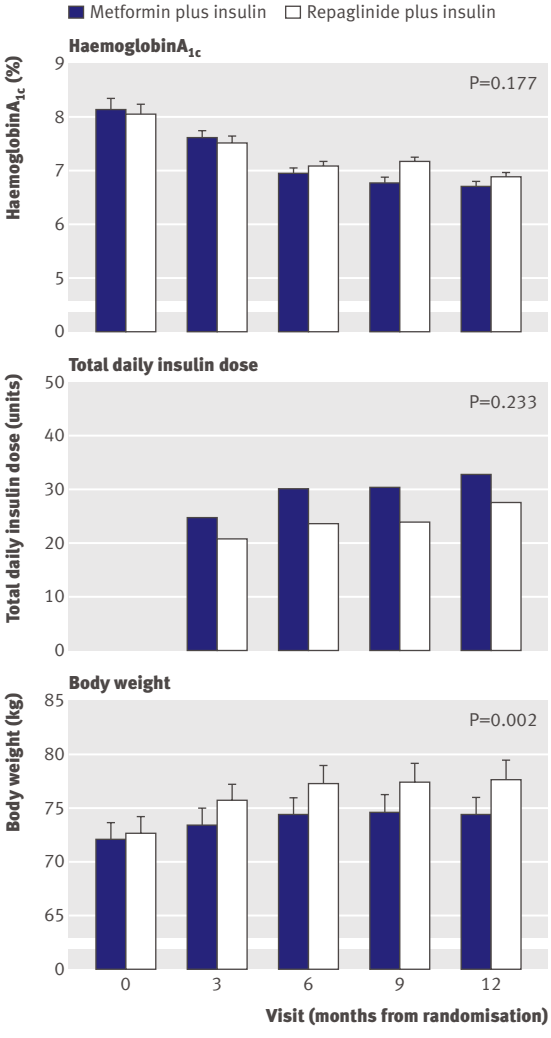

Fig 2 | Metabolic variables during 12 months of treatment with metformin plus insulin or repaglinide plus insulin. Data represent the number of patients with available data at each visit (that is, excluding drop outs), whereas P values represent tests with last observation carried forward

sex, body weight, BMI, and HbA_{1c} were similar to those between individuals who declined or agreed to participate.

All patients were white and aged approximately 60 years (table 1). About two thirds were male, and the median duration of diabetes was 8-12 years. The mean BMI was 24-25 and, before enrolment, about 80% of patients used oral hypoglycaemic agents and about 40% used insulin (about 20% of patients used both). Mean HbA_{1c} concentration at enrolment was 7.8%.

Regarding diabetes complications, about half of the participants had retinopathy, a quarter had microalbuminuria or macroalbuminuria, a third had cardiovascular disease (macroangiopathy), and most had neuropathy. A total of seven patients (7%) had positive glutamic acid decarboxylase 65 antibody titres, with a further four patients having weak positive titres (table 1). No patients had a family history of autosomally inherited diabetes.

Of the four patients who dropped out of the study after randomisation, all were glutamic acid decarboxylase 65 antibody negative and had a mean HbA_{1c} concentration at baseline of 7.46% and at screening of 8.18%.

Table 1 | Patient characteristics at enrolment (n=101)

	Metformin + insulin (n=52)	Repaglinide + insulin (n=49)
Gender (n (%))		
Men	31 (59.6)	31 (63.3)
Women	21 (40.4)	18 (36.7)
Age (years)*	63.0 (7.8)	63.7 (7.9)
Known duration of diabetes (years)†	8 (1-30)	12 (2-25)
Body weight (kg)*	72.82 (11.39)	73.84 (10.64)
Height (m)*	1.72 (0.10)	1.72 (0.08)
BMI*‡	24.53 (2.33)	24.88 (2.45)
Waist circumference (cm)*	92.21 (8.83)	92.39 (8.83)
Hip circumference (cm)*	96.31 (5.89)	96.96 (5.81)
Waist/hip ratio*	0.96 (0.07)	0.95 (0.07)
HaemoglobinA_{1c} concentration (%)*	7.80 (0.97)	7.82 (1.23)
Glutamic acid decarboxylase 65 antibodies§		
Positive	5 (9.6)	2 (4.1)
Weak positive	1 (1.9)	3 (6.1)
Negative	45 (86.5)	44 (89.8)
Late diabetes complications (n (%))		
Retinopathy		
None	28 (53.8)	24 (48.0)
Simplex	22 (42.3)	22 (45.8)
Proliferative	2 (3.8)	3 (6.3)
Macroangiopathy¶	19 (36.5)	16 (32.7)
Nephropathy**		
Normoalbuminuria	39 (75.0)	37 (75.5)
Microalbuminuria	11 (21.2)	7 (14.3)
Macroalbuminuria	2 (3.8)	5 (10.2)
Neuropathy††	42 (80.8)	43 (87.8)
Pre-study antihyperglycaemic treatment (n (%))		
Diet only	1 (1.9)	0 (0)
Oral agents (any use)‡‡	45 (86.5)	38 (77.6)
Metformin	33 (63.5)	25 (51.0)
Insulin secretagogues§§	38 (73.1)	33 (67.3)
Oral agents only‡‡	32 (61.5)	29 (59.2)
Metformin only	2 (3.8)	0 (0)
Insulin secretagogues only§§	6 (11.5)	10 (20.4)
Metformin plus an insulin secretagogue§§	24 (46.2)	19 (38.8)
Insulin (any use)	19 (36.5)	20 (40.8)
Insulin only	6 (11.5)	11 (22.4)
Insulin plus oral agents‡‡	13 (25.0)	9 (18.4)

*Mean (standard deviation).
†Median (range).
‡Mean (standard deviation) BMI at baseline was 24.28 (2.20) in the metformin plus insulin group and 24.49 (2.34) in the repaglinide plus insulin group.
§<5 U/ml=negative; 5-10 U/ml=weak positive; >10 U/ml=positive.
¶Previous cardiovascular disease considered of atherosclerotic origin.
**Normoalbuminuria, microalbuminuria, and macroalbuminuria: 24-hour urinary albumin excretion ≤29 mg, 30-299 mg, and ≥300 mg, respectively, in two out of three consecutive samples before enrolment.
††Symptomatic peripheral or autonomic neuropathy, or clinical signs of neuropathy.
‡‡Oral agents included metformin, repaglinide, or sulphonylureas.
§§Insulin secretagogues included repaglinide or sulphonylureas.

Main outcomes

The mean HbA_{1c} concentration decreased by approximately 1% during the initial six months of treatment in both treatment groups and stabilised thereafter. At the end of treatment, both treatment groups achieved a mean level of HbA_{1c} below 7.0%, with no significant difference between treatments (P=0.177; fig 2 and table 2).

The number of patients who achieved an HbA_{1c} concentration of less than 6.5% at the end of treatment was not significantly different between treatment groups (P=0.169; table 3). The glycaemic response to treatment did not seem to differ according to previous insulin treatment or known duration of diabetes. In those patients who had negative glutamic acid decarboxylase 65 antibody status, however, HbA_{1c} concentration was apparently lowered more with insulin plus metformin than with insulin plus repaglinide (difference in mean HbA_{1c} −0.27% (−0.55 to 0.00), P=0.052; P=0.037 for the interaction of treatment by glutamic acid decarboxylase 65 status).

The change in HbA_{1c} concentration from baseline seemed to vary according to the number of daily insulin injections at the end of treatment (fig 3). The mean self monitored plasma glucose concentration decreased to a similar extent in both treatment groups (P=0.103; table 2). At the end of treatment, the concentrations of self monitored plasma glucose appeared lower before and after breakfast in the metformin plus insulin group than in the repaglinide plus insulin group; however, these differences in self monitored plasma glucose did not reach statistical significance (before breakfast −0.54 mmol/l, 95% CI −1.10 to 0.01, P=0.055; 90 minutes after breakfast −0.98 mmol/l, 95% CI −1.96 to 0.00, P=0.051; fig 4).

There was no significant difference between treatments in the total daily insulin dose at the end of treatment (P=0.233; fig 2 and table 2). The proportion of patients who received insulin injections once a day, twice a day, or three times a day at the end of treatment was not significantly different between treatments (P=0.870). Likewise, there were no significant differences between treatment arms in the insulin dose at individual injections during the day (table 3).

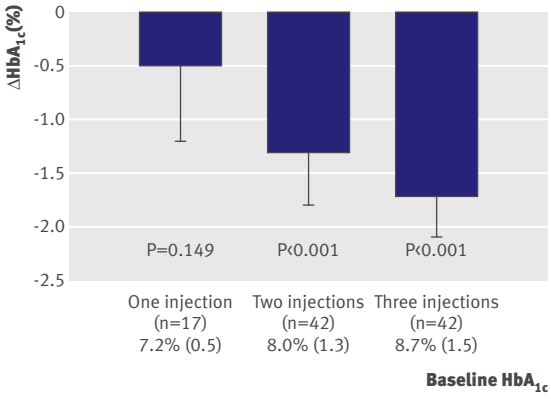

Fig 3 | Change in haemoglobinA_{1c} (HbA_{1c}) concentration from baseline at the end of treatment. Data represent subgroups of patients according to the number of daily insulin injections at the end of treatment. The mean (standard deviation) baseline HbA_{1c} concentration is indicated for each column. Changes from baseline are presented as mean (±2 standard errors of the mean). All estimates were produced by an analysis of variance model without adjustment for baseline HbA_{1c} concentration. In a similar model with adjustment for baseline HbA_{1c}, changes in HbA_{1c} from baseline were statistically significant in all subgroups (data not shown). Within each subgroup, the difference between metformin plus insulin and repaglinide plus insulin was not statistically significant in either of these models (data not shown). The number of patients shown in the figure represents the intention to treat population at baseline. Efficacy data are presented with last observation carried forward (one injection: n=14; two injections: n=42; three injections n=42)

In both treatment groups, body weight appeared to increase during the first 6 months but stabilised thereafter (fig 2). The change in body weight at the end of treatment appeared lower in the metformin plus insulin group than in the repaglinide plus insulin group (P=0.002; fig 2 and table 2).

Compliance and study drug exposure

The mean compliance of active study drugs was approximately 96% in both treatment groups. Approximately 30% of patients in either group received a reduced study drug dose, resulting in a mean study drug exposure of 1771 mg/day for metformin and 5.2 mg/day for repaglinide (table 3).

Adverse events

The number of either mild or nocturnal hypoglycaemic episodes, as well as the number of episodes of major hypoglycaemia, was not significantly different between treatments (table 4).

Besides the 15 major hypoglycaemic episodes, two serious adverse events potentially related to the study medication were recorded in the repaglinide plus insulin group (the drop-out patient with suspected allergic reaction to insulin and one patient with treatment emergent diarrhoea requiring hospital admission). During randomised treatment, a further 19 non-hypoglycaemia related serious adverse events considered unrelated to the study medication were recorded (metformin plus insulin: eight events; repaglinide plus insulin: 11 events; see web appendix 2). No cases of lactic acidosis occurred.

DISCUSSION

Principal findings

In this randomised, double blind study, 101 non-obese patients with type 2 diabetes who had glycaemic failure after four months on oral hypoglycaemic agents combination therapy received metformin plus biphasic insulin aspart 70/30 or repaglinide plus biphasic insulin aspart 70/30 for 12 months. Both treatment groups achieved similar and near optimal glycaemic regulation with similar doses of insulin, which suggests that metformin and repaglinide are equally effective diabetes treatments in such patients. Weight gain,

Table 2 | Metabolism related variables before and at the end of treatment

	Before treatment (mean (standard deviation or range))		End of treatment (mean (standard deviation or range))		Change from before treatment (mean (standard error, coefficient of variation, or 95% confidence interval))			
	Metformin + insulin (n=52)	Repaglinide + insulin (n=49)	Metformin + insulin (n=51)	Repaglinide + insulin (n=47)	ΔMetformin + insulin (n=51)	ΔRepaglinide + insulin (n=47)	ΔMetformin + insulin versus ΔRepaglinide + insulin	P value
Glycaemic control (primary outcome)								
HaemoglobinA_{1c} concentration (%)	8.15 (1.32)	8.07 (1.49)	6.72 (0.66)	6.90 (0.68)	−1.42 (0.09)	−1.23 (0.10)	−0.18 (−0.45 to 0.08)	0.177
Glycaemic control (secondary outcomes)								
Mean plasma glucose (mmol/l)*	10.66 (2.76)	10.55 (3.20)	7.63 (1.28)	8.02 (0.98)	−3.12 (0.17)	−2.72 (0.17)	−0.40 (−0.89 to 0.08)	0.103
Total daily insulin dose (units)†	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	32.96 (9 to 84)	28.25 (6 to 108)	32.96 (48.1)	28.25 (74.6)	1.17 (0.90 to 1.51)	0.233
Anthropometric variables								
Body weight (kg)	72.07 (10.98)	72.67 (10.16)	74.45 (12.27)	77.66 (12.11)	2.22 (0.54)	4.73 (0.57)	−2.51 (−4.07 to −0.95)	0.002

Data for before treatment (baseline; 0 months) and end of treatment (12 months with last observation carried forward) are presented as raw absolute (unadjusted) values and are summarised as mean (standard deviation), whereas data for the changes from baseline are baseline adjusted changes (including last observation carried forward) and are summarised as mean (standard error or 95% confidence interval, except for insulin dose†). The last observation was carried forward for HbA_{1c} and insulin dose, but not for mean plasma glucose or body weight. The number of patients in each column represents the maximum number of patients with available measurements either at baseline or in the intention to treat analysis at the end of treatment.

*Mean of seven point self monitored plasma glucose.

†Baseline and end of treatment data are presented as geometric mean (range), whereas changes from baseline are presented as either geometric mean (coefficient of variation) or the ratio between treatment effects (95% confidence interval).

however, seemed less with metformin plus biphasic insulin aspart 70/30 than with repaglinide plus biphasic insulin aspart 70/30.

The incidence of mild symptomatic and major hypoglycaemia was not significantly different between treatments. The rate of major hypoglycaemia was 0.1-0.2 per year, which corresponds to one such episode every five to ten years per patient. The number of non-hypoglycaemia related serious adverse events was low.

We used near maximal daily doses of metformin (2000 mg) and repaglinide (6 mg) and observed a tendency towards lower pre-breakfast and post-breakfast levels of self monitored plasma glucose with insulin plus metformin (p=0.055 and p=0.051, respectively; fig 4). Hence, we cannot exclude the possibility that in our population of non-obese patients with type 2 diabetes, higher doses of metformin and repaglinide would have resulted in notable glycaemic differences between treatment groups.

In contrast to present consensus statements recommending that insulin secretagogues are stopped after initiation of insulin therapy,[7] our data suggest a clinically relevant effect of insulin and insulin secretagogues in combination, even in patients with long standing diabetes in whom beta cell failure otherwise could be anticipated (that is, in the present study patients had preserved beta cell function despite approximately 10 years of diabetes). Patients in our study achieved good glycaemic control using a single oral hypoglycaemic agent in combination with insulin therapy. Such therapy could thus be more convenient than two or more oral hypoglycaemic agents in combination with insulin therapy. This suggestion is supported to some degree by the observed low drop out rate and satisfactory compliance.

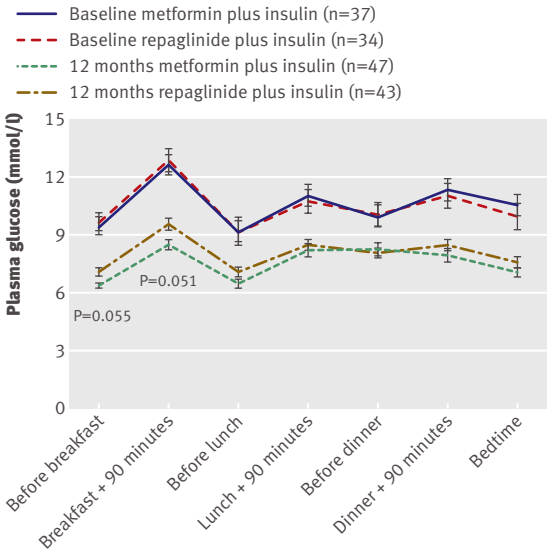

Fig 4 | Seven point self monitored plasma glucose measurements at baseline and at the end of treatment (12 months). Data are presented as mean (standard error of the mean)

Table 3 | Other assessments at the end of treatment

	Metformin + insulin (n=52)	Repaglinide + insulin (n=49)	P value
Number of subjects with haemoglobinA_{1c} concentration <6.5% (n (%))	22 (42.3)	14 (28.6)	0.169
Frequency of insulin injections (n (%))			0.870
Once a day	7 (13)	7 (14)	
Twice a day	23 (44)	19 (39)	
Three times a day	21 (40)	21 (43)	
Insulin dose (units; geometric mean (coefficient of variation))			0.253
Breakfast*	13.1 (52.8)	10.5 (77.4)	0.132
Lunch*	6.3 (64.1)	6.4 (74.6)	0.971
Dinner*	18.6 (51.8)	16.7 (75.3)	0.422
Compliance			
Number of patients with reduced active dose during follow-up† (n (%))	18 (34.6)	15 (30.6)	—‡
Percentage compliance (mean (SD))§			
Active tablets	96.8 (6.1)	96.1 (10.6)	—‡
Placebo metformin tablets	—	96.8 (4.9)	—
Placebo repaglinide tablets	94.2 (8.7)	—	—
Study drug exposure (mg/day; mean (SD))§	1771 (441)	5.2 (1.1)	—‡

*The insulin doses at each injection are presented as geometric means.
†Reduced study drug doses were considered to be any study drug dose less than the maximum intended doses (that is, less than metformin/placebo 2000 mg daily and repaglinide/placebo 6 mg daily, respectively) of any duration and at any time after initiation of randomised treatments.
‡Not compared statistically.
§Data refer to those patients with available data (metformin plus insulin: n=52; repaglinide plus insulin: n=48).

Strengths and limitations of study

The initial sample frame of 459 eligible patients is somewhat small; however, we used targeted electronic searches to reach the desired number of participants, so approaching all patients at the study site (about 5500 patients) was not needed. As expected, approached patients who declined were slightly older than those who accepted, but HbA_{1c} concentration and BMI (that is, the main phenotypic characteristics of the population of interest) were not significantly different between these groups. Hence, we do not believe the number of eligible patients or the recruitment process to have confounded the conclusions.

Treatment responses did not seem to be heterogeneous according to baseline patient characteristics such as diabetes duration or previous insulin use, but may have been affected by the presence of autoimmune disease as determined by the presence of glutamic acid decarboxylase 65 antibodies. Only 7% of participants had signs of autoimmune disease. It is possible that those patients without signs of autoimmunity might have had a better glucose lowering response to insulin and metformin than to insulin plus an insulin secretagogue. More precisely, the effect of metformin was significantly different to that of repaglinide according to glutamic acid decarboxylase 65 status (interaction: P=0.037) and, in those patients without signs of autoimmunity, the lower 95% confidence interval limit of −0.55% in difference in HbA_{1c} concentration between treatments exceeded the predefined ±0.50% equivalence margin. Importantly, although analyses

Table 4 | Hypoglycaemic episodes during follow-up after randomisation in the intention to treat population

	Metformin + insulin (n=52)			Repaglinide + insulin (n=49)			Metformin + insulin versus repaglinide + insulin	
	Number of patients (%)	Number of episodes	Rate per patient years of exposure	Number of patients (%)	Number of hypoglycaemic episodes	Rate per patient years of exposure	Relative risk (95% confidence interval)	P value
All symptomatic episodes*	51 (98.08)	1238	23.2	47 (95.92)	1418	29.9	0.77 (0.53 to 1.14)	0.198
Nocturnal episodes†‡	32 (61.54)	211	3.9	30 (61.22)	212	4.5	0.88 (0.46 to 1.69)	0.708
All major episodes¶	4 (7.69)	5	0.1	8 (16.33)	10	0.2	0.44 (0.13 to 1.47)	0.185
All minor episodes§	50 (96.15)	1233	23.1	47 (95.92)	1408	29.7	0.78 (0.53 to 1.15)	0.206
Plasma glucose ≤3.5 mmol/l	41 (78.85)	475	8.9	38 (77.55)	417	8.8	1.01 (0.62 to 1.64)	0.965
Plasma glucose >3.5 mmol/l or plasma glucose not available‡	46 (88.46)	758	14.2	47 (95.92)	991	20.9	0.68 (0.41 to 1.13)	0.135

*"All symptomatic episodes" is the sum of all major and all minor episodes.
†Nocturnal hypoglycaemic episodes are symptomatic episodes occurring during night time as defined by the patient or between 2300 and 0700.
‡In some patients, a number of events occurred that were recorded as "not quantifiable"—that is, events were reported to have occurred, but the number of these was either not reported or unknown. These events were categorised among "Nocturnal episodes" and, if events were not nocturnal, as "plasma glucose not available". Such events was recorded (Nocturnal episodes/plasma glucose not available) 6/7 times in 5/7 patients in the metformin plus insulin group and 6/5 times in 4/5 patients in the repaglinide plus insulin group. These events were included in the number of patients reporting events, but not in the number of events.
§Minor hypoglycaemic episodes are symptomatic episodes not recorded as major (nocturnal episodes are included).
¶Major hypoglycaemic episodes are episodes where the patient was not able to treat himself or herself, or unconsciousness induced by hypoglycaemia (nocturnal episodes are included).

according to patient characteristics were prespecified, these data are only hypothesis generating and should be addressed more appropriately in future trials. Mean BMI among participants was slightly below 25 at enrolment, concordant with the notion that at least 20% of white patients with type 2 diabetes have a BMI of less than 25 and 35% have a BMI of less than 27.[41-43] Thus, our study population represented white patients with type 2 diabetes having a non-obese phenotype.

Some drug intolerance with respect to gastrointestinal side effects could be anticipated in metformin naive patients (who we expected to be more frequent among non-obese patients with type 2 diabetes). Hence, we used a run-in period to establish study drug tolerance (to potentially minimise the drop-out rate), as well as failure on oral hypoglycaemic agents combination therapy. Moreover, by ensuring similar glucose lowering treatments for all patients at baseline, the run-in period served to minimise any confounding effect of chance differences between groups in previous glucose lowering therapies.

We used a treat to target regimen, including patient self titration of insulin dose and increasing the number of injections. Hence, an apparently greater reduction in HbA_{1c} concentration was expected as the number of injections increased. In the present study, self monitored plasma glucose results agreed with HbA_{1c} measurements, and we did not observe differences in insulin doses between treatment groups. The latter supports the notion that observed differences between treatment groups, such as weight gain, resulted from differences between metformin and repaglinide actions (rather than from possible differences in insulin doses)—the key question that we aimed to address.

We did not adjust for multiple testing. Hence, we emphasise that conclusions can only be drawn from the results for the primary outcome (HbA_{1c} concentration)—other outcomes are hypothesis generating. We believe multiple testing should be addressed by replicate studies rather than by, for example, post hoc modifications of P values.[44]

Body weight was a secondary outcome; thus, our data on this variable must be interpreted cautiously. Nonetheless, BMI, as an adiposity measure, was an inclusion criterion and a stratifying variable. Hence, chance findings were probably less likely to occur for body weight than for other secondary outcomes.

Comparison with other studies

Most studies investigating combination therapy of insulin plus oral hypoglycaemic agents have been of short duration—six months or less,[45-47] and only rarely up to one year.[6 23] Also, most studies failed to reach optimal or near optimal glycaemic regulation.[6 23 45-47] In the UKPDS, patients stopped taking oral hypoglycaemic agents when insulin therapy was initiated.[35] Hence, besides the present study, we are unaware of other such comparative studies in non-obese patients with type 2 diabetes.

In obese patients with type 2 diabetes, however, combination therapy of insulin plus metformin seems to be superior to insulin plus an insulin secretagogue in reducing HbA_{1c} concentration, body weight, or hypoglycaemia.[6 45 48] Also, metformin plus intermediate acting insulin produced lower levels of HbA_{1c} than repaglinide plus intermediate acting insulin in obese patients with type 2 diabetes, as well as lower fasting and postprandial plasma glucose levels despite similar insulin doses.[45] The apparently lesser weight gain of about 2.5 kg with metformin plus biphasic insulin aspart 70/30 compared with repaglinide plus biphasic insulin aspart 70/30 in our study agrees with findings in obese patients with type 2 diabetes.[6 45] We used biphasic insulin aspart 70/30 instead of the otherwise widely used basal insulin regimen. Recently, results from clinical practice, clinical trials and a meta-analysis demonstrated favourable glycaemic potentials, such as lower HbA_{1c} concentration, with

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of metformin in non-obese patients with type 2 diabetes is controversial

There is insufficient evidence to support the use of metformin or an insulin secretagogue in addition to insulin therapy in non-obese patients with type 2 diabetes

WHAT THIS STUDY ADDS

In non-obese patients with type 2 diabetes, biphasic insulin aspart 70/30 plus metformin and biphasic insulin aspart 70/30 plus the insulin secretagogue repaglinide are both safe and effective means of glycaemic regulation

Biphasic insulin aspart 70/30 plus metformin and biphasic insulin aspart 70/30 plus repaglinide provide equal glycaemic control and have an equal risk of hypoglycaemia

Weight gain appeared less with insulin plus metformin than with insulin plus repaglinide

biphasic insulin aspart 70/30 compared with the basal insulin regimen. [22 23 28 49] Thus, given these considerations and those as outlined with respect to the non-obese phenotype, our present findings can probably be generalised to a wider population.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes trial in mainly obese patients with type 2 diabetes and cardiovascular disease did not find significant differences between insulin sensitising and insulin providing treatment regimens on cardiovascular outcomes or mortality.[50] Major hypoglycaemia, however, was more frequent with insulin provision than insulin sensitisation. Accordingly, in the present study major hypoglycaemia appeared nominally more frequent with repaglinide plus biphasic insulin aspart 70/30 than with metformin plus biphasic insulin aspart 70/30 (16% *v* 8% of patients, respectively; table 4). Our study was not statistically powered to show differences in major hypoglycaemia or "hypoglycaemic safety." Nevertheless, a clinically relevant difference in major hypoglycaemia could exist, despite being statistically insignificant in this study.

The observed risk of major hypoglycaemia with insulin plus repaglinide was very similar to that in the intensive glucose control group in the Action to Control Cardiovascular Risk in Diabetes trial.[51] Increased mortality with intensive compared with conventional glucose control was also observed in that trial; however, the cause of the increased mortality remains to be identified. Thus, in our opinion, changing the glucose lowering treatment should be considered in patients experiencing frequent or major hypoglycaemic events on treatment with insulin and insulin secretagogues.

We aimed to lower HbA_{1c} concentration to below 6.5%. The choice of target is supported by clinical event studies in which an HbA_{1c} target of less than 6.0% was associated with increased mortality,[51] whereas an HbA_{1c} target of 6.5% or less was associated with a reduced risk of microvascular complications without an adverse increase in the risk of cardiovascular disease or mortality.[52]

We did not include an insulin only group (that is, an insulin plus placebo oral hypoglycaemic agents group) primarily owing to the well established superiority of insulin plus oral hypoglycaemic agents compared with an insulin only regimen; for example, for glycaemic regulation in obese patients with type 2 diabetes.[3 6 46 53-55] Likewise, we did not investigate insulin on top of combination therapy with metformin plus repaglinide. The 96% increase in mortality among patients on combination treatment with metformin or insulin secretagogues observed in the UKPDS is worrisome [1]—especially when combination therapy is used for long term treatment (for example, with insulin treatment). Notably, combination therapy with two or more oral hypoglycaemic agents in patients with type 2 diabetes has recently been subject to further safety concerns.[51]

The 1-2 percentage points lowering of HbA_{1c} concentration in our study is promising. In the UKPDS, a 0.9 percentage points difference in HbA_{1c} concentration was associated with improved clinical outcomes.[2 35] We cannot draw any conclusions about long term clinical outcomes from the present study in about 100 non-obese patients with type 2 diabetes treated for 12 months. However, provided that lowering of HbA_{1c} concentration has in itself beneficial microvascular and macrovascular effects without adverse effects on mortality (as suggested by, for example, the UKPDS as well as by recent meta-analyses),[2 35 56 57] our results of near optimal glycaemic regulation with insulin plus metformin or plus repaglinide suggest these therapies might be used favourably in non-obese patients with type 2 diabetes.

Conclusions

At present, there is an almost complete lack of evidence to guide treatment choices, including the use of metformin, for non-obese patients with type 2 diabetes. The present study adds to the evidence base for treatment of hyperglycaemia in patients with type 2 diabetes. In non-obese patients with long standing type 2 diabetes and glycaemic failure after four months of oral hypoglycaemic agents combination therapy, treatment with metformin plus biphasic insulin aspart 70/30 or repaglinide plus biphasic insulin aspart 70/30 resulted in near optimal and equivalent glycaemic regulation after one year. The difference in the incidence of major hypoglycaemia between the two treatment groups was not significant, although it seemed more frequent with repaglinide plus biphasic insulin aspart 70/30 treatment. Metformin plus biphasic insulin aspart 70/30 seemed to be associated with less weight gain, despite the fact that the insulin dose used was the same in the two treatment arms.

This study suggests that in non-obese patients with type 2 diabetes, the use of metformin or, in those patients who remain free of significant hypoglycaemia, an insulin secretagogue as an adjunct therapy to insulin might have beneficial effects on glycaemic control. Future studies should further address clinical events during interventions.

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Contributors: LT, OP, H-HP, AAV, and SSL conceived and designed the study. LT, MF, BBN, BVH, AAV, and SSL acquired the data. Analysis and interpretation of data was undertaken by LT, OP, H-HP, AAV, and SSL. AAV and SSL drafted the manuscript. AAV and SSL undertook the statistical analyses. AAV, H-HP, and SSL obtained funding. Administrative, technical, or material support was provided by MF, BBN, BVH, AAV, and SSL. Critical revision of the manuscript for important intellectual content was provided by SSL, LT, MF, BBN, BVH, OP, H-HP, and AAV. All authors had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. AAV is guarantor.

Competing interests: SSL, LT, MF, BBN, BVH, OP, H-HP, and AAV have reported equity in Novo Nordisk A/S. LT, H-HP, and AAV have received funds from Novo Nordisk A/S for research. SSL and AAV have received fees from Novo Nordisk A/S for speaking and AAV has received fees from Novo Nordisk A/S for organising education. SSL, LT, MF, BBN, BVH, OP, H-HP, and AAV are present or former employees at Steno Diabetes Center, Gentofte, Denmark. Steno Diabetes Center is an independent academic institution owned by Novo Nordisk A/S and the Novo Nordisk Foundation.

Data sharing: Full study protocol, statistical analysis plan, and statistical code available from the corresponding author.

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