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Determinants of Glycemic Response to Add-On Therapy with a Dipeptidyl Petidase-4 Inhibitor: A Retrospective Cohort Study Using a United Kingdom Primary Care Database

Jil Mamza, BPharm, MPH,[1] Rajnikant Mehta, BSc, MSc,[2] Richard Donnelly, MD, PhD,[1] and Iskandar Idris, DM[1]

[1]Division of Medical Sciences & Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital, Derby, United Kingdom.

[2]Trent Research Design Services, University of Nottingham, Nottingham, United Kingdom.

Abstract

Background: Apart from baseline glycated hemoglobin (HbA1c), little is known about clinical parameters that affect glycemic response to a dipeptidyl peptidase-4 (DPP4) inhibitor when used in routine clinical practice. We aimed to use a large primary care database to assess the variability in response to a DPP4 inhibitor when used as add-on therapy.

Materials and Methods: Data on 25,386 patients with type 2 diabetes, newly treated with a DPP4 inhibitor (2007–2013), were sourced from a United Kingdom general practice database via the Health Improvement Network database. Baseline clinical parameters of patients (n = 13,525) for whom a DPP4 inhibitor was added because of suboptimal glucose control (HbA1c >7%) were compared with 12-month follow-up data. An optimum response to the DPP4 inhibitor was defined as an HbA1c level of <7.0% at 12 months. Descriptive analyses and unadjusted comparisons using χ^2 and t tests were carried out to ascertain glycemic and body weight responses to treatment intensification with a DPP4 inhibitor. Predictor of response analyses were performed using multivariate logistic regression.

Results: Overall, 1,708 (13%) of our study population achieved an HbA1c level of <7%. Intensification with a DPP4 inhibitor was associated with significant reductions in HbA1c (–0.5%), body weight (–0.9 kg), and total cholesterol (–0.1 mmol/L) ($P < 0.001$). Independent predictors of achieving optimal HbA1c target of <7% included the use of metformin (adjusted odds ratio [OR] = 2.58; 95% confidence interval [CI], 2.18–3.04) and use of metformin plus sulfonylurea (1.42; 95% CI, 1.21–1.68) as opposed to no use. The independent predictors of suboptimal glucose control included a higher baseline HbA1c level (OR = 0.64; 95% CI, 0.61–0.68) (i.e., 1% increase in HbA1c was associated with a 36% reduced likelihood of response), longer diabetes duration (per every year increase) (OR = 0.85; 95% CI, 0.83–0.88), and intensification therapy below 9 months compared with 9–12 months.
Conclusions: There is a significant variability in glycemic response to a DPP4 inhibitor in routine practice. The best effect is achieved as add-on to metformin and metformin plus sulfonylurea, but responses are significantly lower with increased diabetes duration and among patients with high HbA1c levels at baseline.

Introduction

RANDOMIZED CLINICAL TRIALS (RCTS) have examined the efficacy and safety of different glucose-lowering therapy (GLT) either as mono- or combination therapy in patients with type 2 diabetes mellitus (T2D). Most patients require gradual escalation of therapy, and multiple treatment options are becoming more widely available, but there are few head-to-head clinical trials to compare outcomes in routine clinical practice using different dosing and drug sequencing options. In particular, the comparative effectiveness of a dipeptidyl peptidase-4 (DPP4) inhibitor as second-, third-, or fourth-line therapy beyond metformin is unclear.

Baseline glycated hemoglobin (HbA1c) is a well-recognized determinant of glycemic response to many different therapies, including DPP4 inhibitors, but beyond this little is known about which clinical or biochemical factors influence the glycemic response in everyday practice when DPP4 inhibitor is initiated as first-, second-, or third-line add-on therapy.

The aim of the present study was to use a large United Kingdom general practice database to evaluate the variability and determinants of glycemic response to DPP4 inhibitor therapy in routine clinical practice when added to metformin (MET) or sulfonylurea (SU)

monotherapy and when used as add-on to dual (MET + SU) or triple (MET + SU + glitazone) therapy.

Materials and Methods

Study design and data source

We conducted a retrospective cohort analysis of data from The Health Improvement Network database, a validated electronic database that contains anonymous patient data from more than 400 general practices throughout England and Wales.[1] The study population comprised a cohort of patients identified as having T2D and registered with a general practice practice for >12 months before the index date. The index date (June 2007–May 2013) was defined as the date of initiation of DPP4 inhibitor therapy. The cohort included patients who were >18 years old with suboptimal glucose control (HbA1c >7.0%) 6 months or more after using other GLT. Patients were prescribed DPP4 inhibitor as add-on to other GLT. Standard computerized routines were used to identify and extract information on patient prescriptions for oral hypoglycemic agents using Read codes to derive the cohort of patients prescribed DPP4 inhibitor.

Treatment exposure

Exposure was to at least two prescriptions for DPP4 inhibitor, from the index date (the date of the first prescription) either until there was a switch to, or addition of, another antidiabeties drug or the 90th day following the index date when HbA1c was recorded, or 12 months after the index date. Patients were segregated into the following treatment groups based on the oral GLT they received at baseline: MET monotherapy, SU monotherapy, MET + SU as dual therapy, and triple therapy (MET + SU + glitazone).

Outcomes

The primary outcome was to determine the glycemic effect of intensification with DPP4 inhibitor in terms of achieving HbA1c target of <7% after exposure to DPP4 inhibitor, as well as the factors that may influence this response or nonresponse according to the use of DPP4 inhibitor as monotherapy or as add-on therapies.

Covariates

Covariates were selected a priori on the basis of clinical significance. These are baseline demographic and medical parameters, referred to as "predictors of interest," and they include age, gender, social deprivation score (measured using the Townsend index), body weight, body mass index, baseline HbA1c, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, smoking status, duration of DPP4 inhibitor therapy, estimated duration of diabetes, use of lipid-lowering drugs, antihypertensive drugs, aspirin, and comorbidities (e.g., coronary heart diseases, peripheral artery disease, cerebrovascular disease, hypoglycemia, and heart failure).

Statistical analysis

Baseline characteristics that might distinguish between "responders" and "nonresponders" to DPP4 inhibitor therapy were analyzed using the χ^2 test for binary variables and *t* test for continuous variables. Multivariate logistic regressions were carried out to identify covariates that were associated with a response within 12 months. Adjusted odds ratios (ORs) for predictors and confounding variables were calculated and expressed as point estimates with 95% confidence intervals (CIs) at the significance level of 0.05. Missing data were accounted for with multiple imputations using the chained equation model.[2]

Secondary analysis

Tests for interaction were carried out to compare the metabolic effects of a DPP4 inhibitor as add-on therapy to MET-only, SU-only, MET + SU, and MET + SU + glitazone regimens. Comparative analysis on changes in HbA1c levels at 12 months was carried out, and glycemic response end-point changes in HbA1c level were assessed based on baseline HbA1c categories of 7–7.5%, 7.5–8.0%, 8.0–9.0%, and ≥9%, respectively. In addition, the proportions of patients who achieved glycemic targets (<7.0%) were also described for the full cohort and for those with an HbA1c level of ≥7.5% at baseline. Sensitivity analysis was carried out to compare results of missing data with imputed data and to assess the reliability of the outcomes and the impact of missing data. All analyses were conducted using Stata software (version 13; StataCorp, College Station, TX).[3]

Bias

We ensured "new users" of DPP4 inhibitor were used to minimize biases associated with prevalent use of DPP4 inhibitors.[4] Post–index date exposure to any glucose-lowering therapy other than a DPP4 inhibitor was not permitted in our study to reduce confounding by indication. Patients were segregated into separate combination treatment groups to prevent confounding by comedication. The cohort was restricted to an estimated 12-month follow-up to reduce the risk of bias introduced by an overlapping treatment effect. [4]

Results

Patient characteristics

Of the 25,386 users of a DPP4 inhibitor, 13,525 patients fulfilled the criteria for cohort entry (Fig. 1). The cohort had a mean age of 62 years (60% male) and were predominantly obese (61% with a body mass index of $\geq$30 kg/m^2) (Table 1). Treatment groups included patients prescribed a DPP4 inhibitor as add-on therapy to MET alone (30%), SU alone (5%), MET + SU (50%), and MET + SU + glitazone (15%).

Response to DPP4 inhibitor therapy

Overall, the addition of a DPP4 inhibitor resulted in a 0.5% reduction in HbA1c level ($P < 0.001$). Approximately 13% of patients achieved an HbA1c level of <7% following co-administration of a DPP4 inhibitor, based on the criteria for response described previously. This response was not significantly different across gender or social deprivation index or among patients using antihypertensive or lipid-lowering medication. It was also not different with weight, body mass index, or smoking. Baseline HbA1c was significantly lower among responders compared with nonresponders (8.2% vs. 8.9%, respectively; $P < 0.001$) (Table 1). Co-administration of a DPP4 inhibitor was associated with a 0.9 kg reduction in body weight and a 0.1 mmol/L reduction in total cholesterol at 12 months ($P < 0.001$).

Factors influencing outcomes

After adjusting for confounders, the odds of responding to intensification with a DPP4 inhibitor is approximately 2.6 times more when the DPP4 inhibitor is co-administered with MET than when it is not (adjusted OR = 2.58; 95% CI, 2.18–3.04). The odds of response is also

increased by 42% when DPP4 inhibitor is added to MET + SU dual therapy as opposed to none (OR = 1.42; 95% CI, 1.21–1.68). On the other hand, the odds of not responding to DPP4 inhibitor independently decreased by 36% (OR = 0.64; 95% CI, 0.61–0.68) for each percentage unit increase in HbA1c level and also decreased by 15% (OR = 0.85; 95% CI, 0.83–0.88) for each unit increase in diabetes duration (years) (Table 2).

Effectiveness of DPP4 inhibitor as add-on therapy

We examined the glycemic effectiveness of DPP4 inhibitor when added to different oral glucose-lowering regimens. The baseline glucose-lowering medications that the patients received prior to intensification differed remarkably. Therefore, we did not compare effectiveness across treatment groups. The probability of response was predicted based on DPP4 treatment follow-up time in months (Fig. 2). We also assessed the probability of response according to different baseline HbA1c levels. In terms of absolute changes in HbA1c at 12 months, intensification with a DPP4 inhibitor was associated with HbA1c reduction between 0.2% and 0.6% across the treatment groups (Table 3). Table 3 summarizes the overall reductions in HbA1c, body weight, and total cholesterol across the respective treatment groups.

Furthermore, descriptive analysis of our cohort showed the proportion of patients who achieved the HbA1c target of <7.0% at 1 year. Our data show that adding DPP4 inhibitor to monotherapy involving MET versus MET + SU resulted in 47% versus 41%, respectively, of users meeting the target compared with 4% of SU only users (Fig. 3). In a subgroup of patients with a suboptimal HbA1c level above 7.5%, our data show similar proportion of patients met a target below 7% when DPP4 inhibitor was added to dual MET + SU regimen and the MET-only regimen (45% vs. 43%, respectively) (Fig. 4).

Discussion

Overall, this large cohort study in primary care showed a significant 0.5% reduction in HbA1c levels at 12 months after patients with suboptimal HbA1c levels from various oral glucose-lowering therapies were co-administered a DPP4 inhibitor as add-on treatment. The addition of DPP4 inhibitor to MET was found to be the most effective in terms of glycemic response. Co-administering DPP4 inhibitor with MET + SU therapy was also associated with

responders. Conversely, a higher HbA1c level at baseline and longer diabetes duration independently were associated with less likelihood of achieving an HbA1c target of <7%.

Despite the improvement in mean HbA1c following the addition of a DPP4 inhibitor to ongoing treatment, only 13% of patients "responded" to treatment intensification. This relatively low percentage of responders reflects the difficulties in achieving HbA1c target in a challenging cohort of patients who have failed to achieve optimal glucose levels with other oral glucose-lowering drugs. The co-administration of a DPP4 inhibitor with MET independently predicted response to therapy and resulted in a significant ($P < 0.001$) reduction of HbA1c (–0.6%), body weight (–1.0 kg), and total cholesterol (0.2 mmol/L) at 12 months. Similar results were obtained in previous systematic reviews and meta-analysis of RCTs where treatment with sitagliptin + MET alone was found to be more effective at improving HbA1c levels than MET alone.[5] A review by Chatterjee[6] compared DPP4 inhibitors with MET monotherapy, as well as DPP4 inhibitors + MET with other glucose-lowering drugs (e.g., SU, basal insulin, pioglitazone, and glucagon-like peptide-1 agonist). That study reported that DPP4 inhibitor monotherapy was less effective in reducing HbA1c levels and weight than Metformin alone. This, as well as data derived from our study, shows that DPP4 inhibitor are most efficacious when prescribed early in the course of diabetes, particularly in combination with MET. Evidence has shown that MET increases glucagon-like peptide-1 secretion,[7] which may account for the observed synergistic effects of a DPP4 inhibitor with MET.

Interestingly, despite the neutral effects of DPP4 inhibitors on body weight[8] and evidence showing approximately 90% inhibition of plasma DPP-4 activity and an approximately threefold increased in active glucagon-like peptide-1 level with sitagliptin in obese patients with diabetes,[9] body mass index did not play any role in determining whether adding DPP4 inhibitor in routine clinical practice would result in achieving HbA1c target.

In contrast to RCT evidence showing the efficacy of DPP4 inhibitors when used as an add-on therapy to SU,[10,11] real-world data observed in this study suggest that concurrent use of a SU is a predictor of nonresponse to a DPP4 inhibitor. We have shown that with an increased baseline HbA1c level (>7%), DPP4 inhibitor + SU resulted in the least response and smallest reduction in HbA1c level compared with other regimens. We speculate that these discordant results may be explained by the fact that, for a given second-line glucose-lowering therapy, the patient population analyzed in routine clinical practice has a longer disease duration due to

significant delays in the addition of glycemic therapy compared with patients recruited into RCTs. In a previous study using the Health Improvement Network database, in patients with T2D, after failure of glycemic control with oral GLT, insulin initiation was delayed for at least 1.8 years in 25% of cases and for almost 5 years in 50% of cases.[12]

Studies examining the use of DPP4 inhibitor as a third- or fourth-line therapy (e.g., regimens involving the combination of MET, SU, and thiazolidinediones) are lacking. A recent study[13] showed initial combination therapy with sitagliptin and pioglitazone yielded significantly greater reductions in HbA1c level (between 0.4 and 0.7%) than monotherapy of either drug. Combination therapy was found to be generally well tolerated; however, hypoglycemia and weight gain were reported in all treatment groups compared with the sitagliptin monotherapy group over the 54 weeks of the study. Our study showed that addition of a DPP4 inhibitor to the MET + SU + TZD regimen resulted in the least reduction of HbA1c level among patients with baseline HbA1c levels above 8%. Crude ORs suggest adding a DPP4 inhibitor to this triple therapy regimen was not associated with any significant response. This may reflect increased disease duration, where the use of insulin may be the most appropriate treatment choice in many patients.

Our analysis was subject to some limitations inherent to observational studies; for example, our exposure data relate to prescriptions so we cannot be certain that glucose-lowering drugs were actually used. However, should there be any overestimation of exposure to the medications in our analysis, such a misclassification would be non-differential and only bias results towards unity. Potential residual confounders such as ethnicity, compliance, indications for different drug treatments, compliance, and differences in dosages administered to patient groups were not accounted for. In addition, as MET is the standard first-line medication, its use is much more likely to be enhanced by these residual confounders and may account for the small differences between first-line MET and SU users. Despite these limitations, our study highlights the effectiveness of DPP4 inhibitor therapy as an add-on to MET in real-world practice. We have shown how simple clinical and demographic parameters may influence outcomes following DPP4 inhibitor therapy among patients with suboptimal glucose control.

In summary, the results of this study support the use of a DPP4 inhibitor as a second-line therapeutic option, especially among non-obese patients whose glucose control remains suboptimal despite MET treatment. In view of the potential long-term beneficial effects of DPP4

inhibitor on β-cell function and on mass,[14] as well as a previous study in a different ethnic group,[15] this study supports the earlier use of a DPP4 inhibitor in patients with T2D. Robust RCTs are, however, required to fully investigate the effectiveness of DPP4 inhibitors as an add-on to various combination therapies in patients unresponsive to various oral glucose-lowering drugs.

Author Disclosure Statement

No competing financial interests exist.

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TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS PRESCRIBED DIPEPTIDYL PEPTIDASE-4 INHIBITOR AS ADD-ON THERAPY

Variable	*Total (*n = *13,525)*	*Responders (*n = *1,708)*	*Nonresponders (*n = *11,817)*	P *value*
Age (years)	62.3 (12.2)	62.9 (12.0)	62.2 (12.2)	0.04
HbA1c (%)	8.8 (1.5)	8.2 (1.3)	8.9 (1.5)	< 0.001
SBP (mm Hg)	134.7 (15.3)	134.3 (15.0)	134.8 (15.3)	0.3
DBP (mm Hg)	77.5 (9.6)	76.9 (9.6)	77.6 (9.6)	0.004
TC (mmol/L)	4.3 (1.1)	4.2 (1.0)	4.3 (1.1)	< 0.001
HDL (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.2
LDL (mmol/l)	2.2 (0.9)	2.2 (0.9)	2.3 (0.9)	0.01
TGC (mmol/L)	2.2 (2.3)	2.1 (3.8)	2.2 (2.0)	0.2
Weight (kg)	93.2 (21.0)	93.5 (21.3)	93.1 (21.0)	0.6
Diabetes duration (years)[a]	0.8 (1.8)	0.3 (1.7)	0.9 (1.8)	< 0.001
BMI (kg/m^2)	32.5 (6.5)	32.5 (6.8)	32.5 (6.5)	0.9

Gender				
Male	8,113 (60)	1,036 (61)	7,077 (60)	—
Female	5,412 (40)	672 (39)	4,740 (40)	0.5
HbA1c category (%)				
7–7.5	2,306 (17)	541 (32)	1,765 (15)	—
7.5-8	2,621 (19)	454 (27)	2,167 (18)	< 0.001
8-9	4,051 (30)	445 (26)	3,606 (31)	< 0.001
≥9	4,547 (34)	268 (16)	4,279 (36)	< 0.001
BMI category (kg/m^2)				
Normal (<25)	1,248 (9)	169 (10)	1,079 (9)	—
Overweight (25–29.9)	4,060 (30)	504 (30)	3,556 (30)	0.3
Obese (≥ 0)	8,217 (61)	1,035 (61)	7,182 (61)	0.4
Smoking status				
Nonsmoker	5,238 (39)	665 (39)	4,573 (39)	—
Current	2,053 (15)	246 (14)	1,807 (15)	0.4
Ex-smoker	6,234 (46)	797 (47)	5,437 (46)	0.9
Townsend Deprivation Index				
Least deprived	2,992 (22)	402 (24)	2,590 (22)	—
Less	2,875 (21)	373 (22)	2,502 (21)	0.6
Average	2,811 (21)	355 (21)	2,456 (21)	0.3
More	2,732 (20)	323 (19)	2,409 (20)	0.1
Most deprived	2,115 (16)	255 (15)	1,860 (16)	0.1
Comorbidity				
CHD	7,822 (58)	986 (58)	6,836 (58)	0.9
PAD	2,277 (17)	255 (15)	2,022 (17)	0.02
Cerebrovascular	3,071 (23)	402 (24)	2,669 (23)	0.4
Heart failure	1,595 (12)	198 (12)	1,397 (12)	0.8
Hypoglycemia	2,478 (18)	277 (16)	2,201 (19)	0.02
Other medication				
Aspirin	5,270 (39)	705 (41)	4,565 (39)	0.04
Antihypertensive	9,869 (73)	1,265 (74)	8,604 (73)	0.2
LLT	10,537 (78)	1,339 (78)	9,198 (78)	0.6
Oral antidiabetes drugs				
MET monotherapy	4,054 (30)	794 (46)	3,260 (28)	< 0.001
SU monotherapy	705 (5)	62 (4)	643 (5)	0.002
MET + SU	6,790 (50)	703 (41)	6,087 (52)	< 0.001
MET + SU + TZD	1,76 (15)	149 (9)	1,827 (15)	< 0.001
Follow-up (months)				
9–12	8,740 (65)	1,388 (81)	7,352 (62)	—
6 to <9	1,484 (11)	96 (6)	1,388 (12)	< 0.001
3 to <6	1,627 (12)	110 (6)	1,517 (13)	< 0.001
0 to <3	1,674 (12)	114 (7)	1,560 (13)	< 0.001

Data are mean (SD) for continuous variables and frequency (percentage) for categorical variables.

[a]Estimated as time from first glucose-lowering therapy.

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; MET, metformin; PAD, peripheral arterial disease; SBP, systolic blood pressure; SU, sulfonylurea; TC, total cholesterol; TGC, triglyceride; TZD, thiazolidinedione.

TABLE 2. LOGISTIC REGRESSION MODEL FOR ATTAINING <7.0% GLYCATED HEMOGLOBIN TARGET UPON ADDITION OF DIPEPTIDYL PEPTIDASE-4 INHIBITOR

	Unadjusted		*Adjusted*	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
Age (years)	1.003 (1.00, 1.01)	0.3		
HbA1c (%)	0.651 (0.62, 0.69)	< 0.001	0.643 (0.61, 0.68)	< 0.001
DBP (mm Hg)	0.992 (0.99, 1.00)	0.01		
TC (mmol/L)	0.971 (0.90, 1.05)	0.5		
LDL (mmol/L)	1.006 (0.92, 1.10)	0.9		
Diabetes duration (Years)[a]	0.850 (0.82, 0.88)	< 0.001	0.852 (0.83, 0.88)	< 0.001
Comorbidity				
PAD				
No				
Yes	0.849 (0.73, 0.98)	0.8	0.876 (0.76, 1.01)	0.08
Hypoglycemia				
No				
Yes	0.921 (0.80, 1.06)	0.3		
Other medications				
Aspirin				
No				
Yes	1.004 (0.90, 1.12)	0.9		
Oral antidiabetes drugs				
MET monotherapy				
No				
Yes	2.892 (2.39, 3.50)	< 0.001	2.577 (2.19, 3.04)	< 0.001
SU monotherapy				
No				
Yes	1.347 (0.98, 1.85)	0.07		
MET + SU				
No				
Yes	1.553 (1.29, 1.87)	< 0.001	1.424 (1.21, 1.68)	< 0.001
Treatment duration (months)				
9–12	1 (1.00, 1.00)	—	1.00	—
6 to <9	0.419 (0.34, 0.52)	< 0.001	0.417 (0.34, 0.52)	< 0.001
3 to <6	0.470 (0.38, 0.58)	< 0.001	0.466 (0.38, 0.57)	< 0.001
0 to <3	0.470 (0.38, 0.58)	< 0.001	0.471 (0.38, 0.58)	< 0.001

[a]Estimated as time from first glucose-lowering therapy.

CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; MET, metformin; OR, odds ratio of predictors of response or nonresponse; PAD, peripheral arterial disease; SU, sulfonylurea; TC, total cholesterol; TZD, Thiazolidinedione.

TABLE 3. DESCRIPTIVE ANALYSIS OF GLYCATED HEMOGLOBIN, WEIGHT, AND CHOLESTEROL RESPONSES AFTER INTENSIFICATION WITH DIPEPTIDYL PEPTIDASE-4 INHIBITOR

Parameter	*MET alone*	*SU alone*	*MET + SU*	*MET + SU + TZD*
Number of patients [*n* (%)]	4,054 (30)	705 (5)	6,790 (50)	1,976 (15)
Age (years)	60 (0.2)	70 (0.5)	63 (0.1)	63 (0.3)
HbA1c (%)	8.5 (0.02)	9.0 (0.06)	9.0 (0.02)	8.8 (0.03)
Duration of diabetes (years)[a]	0.9 (0.03)	1.0 (0.07)	0.8 (0.02)	0.6 (0.04)
Pr response	0.18 (0.01)	0.10 (0.01)	0.11 (0.01)	0.07 (0.01)
Overall change in HbA1c (%)[b]	–0.58 (0.02)	–0.42 (0.05)	–0.48 (0.02)	–0.21 (0.03)
Subgroup HbA1c change in HbA1c (%)				
7 to <7.5%	–0.19 (0.04)	0.25 (0.1)	0.06 (0.04)[c]	0.35 (0.1)
7.5 to <8.0%	–0.32 (0.04)	–0.25 (0.10)	–0.16 (0.03)	0.15 (0.05)
8.0–9.0%	-0.61 (0.04)	-0.23 (0.08)	-0.33 (0.03)	–0.14 (0.05)
≥9.0%	–1.18 (0.04)	–0.88 (0.08)	–0.93 (0.02)	–0.77 (0.05)
Change in weight (kg)[b]	–1.0 (0.07)	–0.20 (0.2)[c]	–0.74 (0.05)	–1.46 (0.1)
Change in TC (mmol/L)[b]	–0.17 (0.01)	–0.06 (0.03)[c]	–0.1 (0.01)	–0.12 (0.02)

Data are mean (SE) values unless indicated otherwise.

[a]Estimated as time from first glucose-lowering therapy.

[b]Absolute change.

[c] $P > 0.05$ for significant difference.

HbA1c, glycated hemoglobin; MET, metformin; Pr response, predicted probability of response; SU, sulfonylurea; TC, total cholesterol; TZD, thiazolidinedione.

FIG. 1. Study population selection flow chart. DPP4, dipeptidyl peptidase-4; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist; GLT, glucose-lowering therapy; HbA1c, glycated hemoglobin; MET, metformin; OAD, oral antidiabetes drug; SGLT2i, sodium–glucose cotransporter type 2 inhibitor; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

FIG. 2. Predicted probability of response to intensification with a dipeptidyl peptidase-4 inhibitor over time. The probability of responding to intensification with a dipeptidyl peptidase-4 inhibitor was consistently higher when added to metformin (MET) versus sulfonylurea (SU) monotherapies or to MET + SU dual therapy, with the highest probability of responders after 9 months of treatment. Response to dipeptidyl peptidase-4 inhibitor co-administration with triple regimen was poor. HbA1c, glycated hemoglobin; TZD, thiazolidinedione.

FIG. 3. Proportion of patients achieving the glycated hemoglobin target level of <7.0% at 1 year. Among patients who achieved the glycated hemoglobin target level of <7%, the addition of dipeptidyl peptidase-4 inhibitor to ongoing metformin (MET) monotherapy accounted for 47% versus 41% for patients with ongoing MET + sulfonylurea (SU) dual therapy. TZD, thiazolidinedione.

FIG. 4. Subgroup with a glycated hemoglobin level of ≥7.5% at baseline and proportion achieving the glycated hemoglobin target level of <7.0%. Co-administration of dipeptidyl peptidase-4 inhibitor with metformin (MET) + sulfonylurea (SU) dual therapy among patients with a glycated hemoglobin level of ≥7.5% at baseline resulted in similar proportions of patients meeting optimal glucose lowering as with MET monotherapy (45% vs. 43%, respectively). TZD, thiazolidinedione.