Associations between second-line glucose-lowering combination therapies with metformin and HbA1c, body weight, quality of life, hypoglycaemic events and glucose-lowering treatment intensification: The DISCOVER study

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Abstract

Aim: To explore the effects of second-line combination therapies with metformin on body weight, HbA1c and health-related quality of life, as well as the risks of hypoglycaemia and further treatment intensification in the DISCOVER study, a 3-year, prospective, global observational study of patients with type 2 diabetes initiating second-line glucose-lowering therapy.

Materials and Methods: Adjusted changes from baseline in weight, HbA1c and 36-item Short Form Health Survey version 2 (SF-36v2) summary scores at 6, 12, 24 and 36 months were assessed using linear mixed models. Risk of hypoglycaemia and further intensification were assessed using interval censored analyses.

Results: At baseline, 7613 patients received metformin in combination with a sulphonylurea (SU; 40.9%), a dipeptidyl peptidase-4 (DPP-4) inhibitor (48.3%), a sodium-glucose co-transporter-2 (SGLT-2) inhibitor (8.3%) or a glucagon-like peptide-1 (GLP-1) receptor agonist (2.4%). After 36 months, all combinations showed similar reductions in HbA1c (0.8%-1.0%), however, metformin plus a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist was associated with greater weight loss (1.9, 2.9 and 5.0 kg, respectively) than metformin plus an SU (1.3 kg, \( P < .0001 \)).

Proportions of further treatment intensification were similar across combinations (19.9%-26.2%). Patients prescribed metformin plus an SU more often reported one or more hypoglycaemic events (11.9%) than other combinations (3.9%-6.4%).

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Diabetes Obes Metab. 2021;23:1823–1833. wileyonlinelibrary.com/journal/dom

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1 | INTRODUCTION

When individuals with type 2 diabetes (T2D) are unable to achieve optimal glycaemic control (HbA1c levels ≤7.0% for most patients) with first-line metformin monotherapy, most clinical guidelines recommend the use of second-line dual therapy. However, the large number of glucose-lowering drugs available for second-line treatment can make decisions difficult for clinicians.

First introduced to clinical practice in the 1950s, sulphonylureas (SUs) were a cornerstone of the management of T2D. However, the shortcomings of certain SU therapies have been shown by observational studies and meta-analyses of randomized clinical trials, in which SU therapies, particularly first-generation SUs, were associated with greater risks of hypoglycaemia and major adverse cardiac events than therapy with newer orally administered agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors. In addition to minimizing the risk of hypoglycaemia, SGLT-2 inhibitors show substantial cardiovascular and renal benefits, making them an attractive choice for patients in whom these complications are of particular concern.

Incretin-based therapies with injectable glucagon-like peptide-1 (GLP-1) receptor agonists have shown favourable characteristics in comparison with SU therapy in terms of reduced rates of hypoglycaemia and cardiovascular events, while maintaining similar effects on glycaemic control. However, SUs remain a useful tool in clinical practice in many lower-income countries owing to their comparatively low cost and ease of accessibility, in addition to both metformin and SUs typically being free of charge for the patients.

DISCOVER is a global, prospective, 3-year observational study of patients with T2D initiating second-line glucose-lowering therapy. The current analysis of the DISCOVER study includes patients who received dual combination therapy with metformin and an SU, a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist as second-line therapy, and aims to compare the relative effectiveness of these different combination therapies on glycaemic control, weight loss, incidence of hypoglycaemia, risk of treatment intensification and health-related quality of life (HRQoL).

2 | MATERIALS AND METHODS

The methods for the DISCOVER study programme have been reported in detail elsewhere and are briefly summarized below.

2.1 | Study design

The global DISCOVER study programme comprised two similar, 3-year, non-interventional, prospective studies conducted simultaneously in 38 countries: DISCOVER (NCT02322762) in 37 countries and J-DISCOVER (NCT02226822) in Japan. The included countries were divided into regions according to the World Health Organization categories: Africa (Algeria and South Africa); Americas (Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico and Panama); Southeast Asia (India and Indonesia); Europe (Austria, the Czech Republic, Denmark, France, Italy, the Netherlands, Norway, Poland, Russia, Spain, Sweden and Turkey); Eastern Mediterranean (Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia and the United Arab Emirates); and Western Pacific (Australia, China, Japan, Malaysia, South Korea and Taiwan). The study protocols were approved by the appropriate clinical research ethics committees in each participating country and the relevant institutional review boards at each site. The protocols comply with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and the local regulations for clinical research.

2.2 | Patient recruitment

Adult patients with T2D who were initiating a second-line glucose-lowering therapy (add-on or switching) after first-line oral treatment were invited to participate in DISCOVER from September 2014 to June 2016. Inclusion and exclusion criteria were kept to a minimum to reflect the diversity of patients treated in routine clinical practice. Exclusion criteria included being pregnant, undergoing dialysis, having a history of renal transplant, and if the patient’s first-line therapy was an injectable agent or a herbal remedy/natural medicine alone. Full inclusion and exclusion criteria can be found in Table S1. All patients participating in the study provided written informed consent.

2.3 | Data collection

Data were collected at study baseline (initiation of second-line therapy), 6, 12, 24 and 36 months using a standardized case report form and transferred to a central database via a web-based data capture system. Variables collected included: physician and site characteristics; patient socioeconomic demographics; physiological indicators;
laboratory test results; change in glucose-lowering therapies and reason(s) for change; HbA1c level at the time of treatment change; co-morbidities including diabetes-related microvascular and macrovascular diseases; major hypoglycaemic events (defined as those that required an emergency room visit, hospital admission, a visit to a physician or other healthcare professional, or external help from a caregiver or family member) in the year before baseline; and minor hypoglycaemic events (defined as those which did not require external help) during the 4 weeks before baseline. Some data were extracted from existing electronic health records in Canada, Denmark, France, Norway and Sweden.

In line with the observational nature of the study, data were measured and recorded according to routine clinical practice at each site. Patients were not obliged to attend study visits, data collection was not compulsory for any of the clinical variables, methods used to measure clinical variables were not specified, and the occurrence of complication events was not adjudicated.

Changes in HRQoL were assessed using the 36-item Short Form Health Survey version 2 (SF-36v2) physical component summary (PCS) and mental component summary (MCS) scores. The SF-36v2 provides a generic measure of health status and consists of 36 questions across eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, role emotional, social functioning and mental health. Resulting PCS and MCS scores range from 0 to 100, and are normalized to the 2009 US population to enable comparison between studies. An increase in score indicates improved HRQoL. Local-language versions of the SF-36v2 questionnaire were used to assess HRQoL in the following 31 countries: Algeria, Argentina, Australia, Austria, Brazil, Colombia, Costa Rica, the Czech Republic, Denmark, Egypt, India, Indonesia, Italy, Jordan, Lebanon, Malaysia, Mexico, the Netherlands, Norway, Panama, Poland, Russia, Saudi Arabia, South Africa, South Korea, Spain, Sweden, Taiwan, Tunisia, Turkey and the United Arab Emirates.

2.4 Statistical analysis

In total, DISCOVER enrolled 15,983 patients. Patients from China (n = 1292) were excluded from the current analysis because of regulatory restrictions during study follow-up. Of the remaining 14,691 patients, 7613 were prescribed metformin in combination with an SU, a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist as second-line therapy and were included in this analysis.

The association of the different second-line metformin combination therapies with HbA1c level, weight, risk of hypoglycaemia, likelihood of further treatment intensification (initiation of three or more glucose-lowering drugs; switching to another dual combination therapy and discontinuation of glucose-lowering drugs were not counted as treatment intensification) and changes in SF-36v2 PCS and MCS scores were analysed using an intention-to-treat approach.

Changes from baseline at 6, 12, 24 and 36 months in weight and HbA1c level were assessed using repeated measures linear models. To limit the impact of potential confounding caused by differences in patient populations at baseline, these models were adjusted for a number of known confounders including age, sex, time since T2D diagnosis, region, history of hypoglycaemia, microvascular and macrovascular complications (neuropathy, retinopathy and neonauphathy) and macrovascular complications (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use), first-line therapy (with or without metformin), baseline weight and baseline HbA1c.

Changes from baseline at 6, 12, 24 and 36 months in SF-36v2 PCS and MCS scores were assessed using repeated measures linear models adjusted for age, sex, time since T2D diagnosis, region, history of hypoglycaemia, microvascular and macrovascular complications, first-line therapy, and baseline SF-36v2 PCS and MCS scores.

Time to the first patient-reported hypoglycaemic event (both major events in the period between study visits as well as minor events in the 4 weeks preceding a visit) and intensifying treatment to three or more glucose-lowering drugs were analysed using an interval censored survival model based on interviews at 6, 12, 24 and 36 months. Hazard ratios for incidence of hypoglycaemia and third-line treatment intensification were assessed using the same interval censored survival analysis and were adjusted for age, sex, time since T2D diagnosis, history of hypoglycaemia, microvascular and macrovascular complications, region, first-line therapy, body weight and baseline HbA1c.

All statistical analyses were performed using the SAS 9.4 statistical software system (SAS Institute Inc., Cary, NC, USA). A P value of less than .05 was considered statistically significant.

3 RESULTS

3.1 Patient baseline demographics and clinical characteristics

Of the 7613 DISCOVER participants included in this analysis, 3116 patients (40.9%) were prescribed metformin and an SU, 3678 patients (48.3%) were prescribed a combination of metformin and a DPP-4 inhibitor, 633 patients (8.3%) were prescribed metformin and an SGLT-2 inhibitor, and 186 (2.4%) were prescribed metformin and a GLP-1 receptor agonist as second-line therapy (Table 1). Overall, 53.2% of patients were male. The mean age was 57.0 years (standard deviation [SD]: 11.8 years) and was highest in patients prescribed metformin and a DPP-4 inhibitor (57.9 years [SD: 12.0 years]) and lowest in patients prescribed metformin and a GLP-1 receptor agonist (53.4 years [SD: 11.6 years]). The median time since T2D diagnosis was 4.0 years (interquartile range [IQR]: 1.8-7.1 years), and was highest in patients prescribed metformin and a GLP-1 receptor agonist (4.7 years [IQR: 2.0-8.0 years]) and lowest in patients prescribed metformin and an SGLT-2 inhibitor (3.5 years [IQR: 1.7-6.6 years]). Mean baseline HbA1c level at initiation of second-line therapy was 8.2% (SD: 1.5%) and was highest among patients prescribed metformin and an SU (8.5% [SD: 1.7%]) and lowest among patients prescribed metformin and a DPP-4 inhibitor (8.0% [SD: 1.4%]).
3.2 Changes in weight and HbA1c level during follow-up

At 6 and 12 months, metformin in combination with a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist was associated with a significantly greater reduction in HbA1c from baseline than metformin and an SU (Figure 1A). The greatest change in HbA1c from baseline was seen at 6 months in patients prescribed metformin and a GLP-1 receptor agonist. Beyond 12 months, metformin in combination with a DPP-4 inhibitor was the only combination therapy that

### Table 1

| Characteristic                  | Total (N = 7613) | Second-line therapy | P value
|---------------------------------|------------------|---------------------|--------
|                                 |                  | MET + SU (n = 3116) | MET + DPP-4i (n = 3678) | MET + SGLT-2i (n = 633) | MET + GLP-1 RA (n = 186) |
| Male                           | 4050 (53.2)      | 1497 (48.0)         | 2107 (57.3)          | 357 (56.4)          | 89 (47.8)               | <.001   |
| Age, years, mean (SD)           | 57.0 (11.8)      | 56.4 (11.5)         | 57.9 (12.0)          | 55.8 (11.5)         | 53.4 (11.6)             | <.001   |
| Age <65 years                   | 5666 (74.4)      | 2421 (77.7)         | 2607 (70.9)          | 482 (76.1)          | 156 (83.9)              | <.001   |
| Age 65 to <75 years             | 1501 (19.7)      | 533 (17.1)          | 814 (22.1)           | 130 (20.5)          | 24 (12.9)               |         |
| Age ≥75 years                   | 446 (5.9)        | 162 (5.2)           | 257 (7.0)            | 21 (3.3)            | 6 (3.2)                 |         |
| Region                          |                  |                     |                     |                    |                        |        |
| Africa                          | 493 (6.5)        | 464 (14.9)          | 20 (0.5)             | 0 (0.0)             | 9 (4.8)                 | <.001   |
| Americas                        | 1370 (18.0)      | 579 (18.6)          | 584 (15.9)           | 176 (27.8)          | 31 (16.7)               |         |
| Southeast Asia                  | 1412 (18.5)      | 832 (26.7)          | 522 (14.2)           | 54 (8.5)            | 4 (2.2)                 |         |
| Europe                          | 1906 (25.0)      | 566 (18.2)          | 955 (26.0)           | 259 (40.9)          | 126 (67.7)              |         |
| Eastern Mediterranean           | 1009 (13.3)      | 335 (10.8)          | 648 (17.6)           | 12 (1.9)            | 14 (7.5)                |         |
| Western Pacific                 | 1423 (18.7)      | 340 (10.9)          | 949 (25.8)           | 132 (20.9)          | 2 (1.1)                 |         |
| Weight, kg, mean (SD)           | 81.3 (18.9)      | 78.8 (17.4)         | 80.5 (18.4)          | 91.7 (19.9)         | 105.4 (21.0)            | <.001   |
| Missing, n                      | 412              | 154                 | 224                 | 17                 | 17                      |         |
| Time since T2D diagnosis, years, median (IQR) | 4.0 (1.8-7.1) | 4.0 (1.9-7.2) | 3.9 (1.6-7.0) | 3.5 (1.7-6.6) | 4.7 (2.0-8.0) | .003 |
| Missing, n                      | 220              | 36                  | 142                 | 27                 | 15                      |         |
| HbA1c                           | 8.2 (1.5)        | 8.5 (1.7)           | 8.0 (1.4)            | 8.1 (1.5)           | 8.2 (1.7)               | <.001   |
| Missing, n                      | 1390             | 890                 | 427                 | 54                 | 19                      |         |
| HbA1c group, n (%)              |                  |                     |                     |                    |                        |        |
| <7.0%                           | 1030 (16.6)      | 280 (12.6)          | 607 (18.7)           | 105 (18.1)          | 38 (22.8)               | <.001   |
| 7.0% to <8.0%                   | 2256 (36.3)      | 683 (30.7)          | 1294 (39.8)          | 231 (39.9)          | 48 (28.7)               |         |
| 8.0% to <9.0%                   | 1498 (24.1)      | 585 (26.3)          | 760 (23.4)           | 113 (19.5)          | 40 (24.0)               |         |
| ≥9.0%                           | 1439 (23.1)      | 678 (30.5)          | 590 (18.1)           | 130 (22.5)          | 41 (24.6)               |         |
| Missing, n                      | 1390             | 890                 | 427                 | 54                 | 19                      |         |
| History of complications        |                  |                     |                     |                    |                        |        |
| Macrovascularb                  | 1121 (14.8)      | 424 (13.6)          | 581 (15.9)           | 90 (14.3)           | 26 (14.1)               | .073    |
| Missing, n                      | 25               | 2                   | 16                  | 5                  | 2                       |        |
| Microvascularc                  | 1339 (17.6)      | 582 (18.7)          | 627 (17.1)           | 103 (16.3)          | 27 (14.5)               | .162    |
| Missing, n                      | 10               | 1                   | 7                   | 2                  | 0                       |        |
| Hypoglycaemiae                  | 232 (3.0)        | 109 (3.5)           | 108 (2.9)            | 7 (1.1)             | 8 (4.3)                 | .009    |

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; MET, metformin; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes.

Data are presented as n (%) unless otherwise stated. Percentages are reported for all patients with data available; missing data are excluded.

Continuous variables compared using one-way analysis of variance; categorical variables compared using chi-squared or Fisher’s exact test.

Includes coronary artery disease, cerebrovascular disease, peripheral artery disease (including diabetic foot disease and amputation), heart failure and implantable cardioverter defibrillator use.

Includes nephropathy, retinopathy and neuropathy (peripheral and autonomic neuropathy and erectile dysfunction).

Hypoglycaemic events that required an emergency room visit, a hospital admission, a visit to a physician or other healthcare professional, or third-party assistance, in the year before baseline, or self-reported events which did not require third-party assistance in the 4 weeks before baseline.
maintained a significantly greater reduction in HbA1c level in comparison with metformin and an SU.

Combinations of metformin with a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist were associated with significantly greater weight loss than metformin and an SU (Figure 1B). Overall, treatment with metformin and a GLP-1 receptor agonist was associated with the greatest adjusted weight loss at all time points, with an adjusted decrease in weight from baseline of 5.0 kg after 36 months. Treatment with metformin and an SU was associated with the smallest adjusted weight loss at all time points, with an adjusted decrease in weight from baseline of 1.3 kg after 36 months.

### 3.3 Occurrence of hypoglycaemia during follow-up

Figure 2 shows the cumulative proportion of patients reporting at least one hypoglycaemic event for each metformin combination therapy. Hypoglycaemia was most often reported by patients prescribed

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**FIGURE 1** Adjusted changes from baseline in (A) HbA1c levels and (B) weight at 6, 12, 24 and 36 months according to second-line glucose-lowering therapy. *Denotes statistically significant differences (P < .05). †Changes in HbA1c and weight estimated using repeated measures linear models adjusted for age, sex, time since type 2 diabetes diagnosis, history of hypoglycaemia, microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use), region, first-line therapy (with metformin vs. without metformin), baseline HbA1c and weight. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea
metformin and an SU at all time points during the 3-year follow-up period. Compared with patients prescribed metformin and an SU, the risk of hypoglycaemia over 3 years was significantly lower in patients prescribed metformin and a DPP-4 inhibitor (hazard ratio [HR]: 0.47; 95% confidence interval [CI]: 0.38-0.59), an SGLT-2 inhibitor (HR: 0.28; 95% CI: 0.16-0.48) or a GLP-1 receptor agonist (HR: 0.31; 95% CI: 0.11-0.84).

3.4 | Treatment intensification during follow-up

Figure 3 shows the proportion of patients intensifying to three or more glucose-lowering drugs during follow-up for each metformin combination therapy. After 36 months, further treatment intensification had occurred in 21.9% of patients prescribed metformin and an SU, 24.9% of patients prescribed metformin and a DPP-4 inhibitor, 19.9% of patients prescribed metformin and an SGLT-2 inhibitor, and 26.2% of patients prescribed metformin and a GLP-1 receptor agonist. After adjusting for the covariates outlined above, the proportion of patients requiring treatment intensification was not significantly different between those prescribed metformin and an SU in comparison with those prescribed metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist.

3.5 | Changes in SF-36v2 PCS and MCS scores during follow-up

At all time points, patients prescribed metformin and an SU experienced a small reduction in adjusted SF-36v2 PCS score from baseline, and after 24 months, patients prescribed metformin and a DPP-4 inhibitor also experienced a small reduction in SF-36v2 PCS score from baseline (Figure 4A). Metformin with an SGLT-2 inhibitor was associated with a statistically significant increase in SF-36v2 PCS score compared with metformin and an SU at all time points. At 36 months, adjusted SF-36v2 PCS scores were significantly higher in patients prescribed metformin and a DPP-4 inhibitor or an SGLT-2 inhibitor in comparison with patients prescribed metformin and an SU (adjusted SF-36v2 score difference: 0.49 [95% CI: 0.08-0.90] and 1.46 [95% CI: 0.77-2.15], respectively).

Similarly, metformin in combination with an SU was associated with comparatively lower adjusted SF-36v2 MCS scores than metformin and a DPP-4 inhibitor or an SGLT-2 inhibitor. Adjusted SF-36v2 MCS scores improved from baseline to 6 months in all combination groups. At 12 months, adjusted SF-36v2 MCS scores improved from baseline in all combination groups except patients taking metformin and a GLP-1 receptor agonist. At 24 and 36 months, adjusted SF-36v2 MCS scores were lower than baseline in patients taking metformin and an SU, but were higher than baseline in all three other

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**FIGURE 2** Kaplan–Meier estimate of proportion of patients reporting at least one hypoglycaemic event during follow-up. †Hazard ratios of reporting at least one hypoglycaemic event during follow-up in comparison with metformin (MET) + sulphonylurea (SU), adjusted for age, sex, time since type 2 diabetes diagnosis, history of hypoglycaemia, microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use), region, first-line therapy (with MET vs. without MET), baseline HbA1c and weight. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

| Second-line combination therapy (vs. MET + SU) | Hazard ratio† | 95% CI |
|-----------------------------------------------|--------------|-------|
| MET + DPP-4i                                  | 0.47         | 0.38-0.59 |
| MET + SGLT-2i                                  | 0.28         | 0.16-0.48 |
| MET + GLP-1 RA                                 | 0.31         | 0.11-0.84 |
combination groups (Figure 4B). At 36 months, adjusted SF-36v2 MCS scores were significantly higher in patients prescribed metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist in comparison with patients prescribed metformin and an SU (adjusted SF-36v2 score difference: 1.12 [95% CI: 0.56-1.68], 2.71 [95% CI: 1.76-3.65] and 1.95 [95% CI: 0.04-3.86], respectively).

**DISCUSSION**

The current analysis provides novel insights into the varying effects of different therapies combined with metformin on HbA1c levels, weight loss, occurrence of hypoglycaemia, microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use), region, first-line therapy (with MET vs. without MET), baseline HbA1c and weight. DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

Hypoglycaemia can have substantial consequences for patients with T2D, including long-term adverse effects on the central nervous and cardiovascular systems and mortality. In the current analysis, combination therapy with metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist all showed a substantially lower risk of hypoglycaemic events than metformin and an SU. This finding is in line with previous observational studies, including a nationwide study of patients with T2D in Sweden that showed a substantially higher risk of hypoglycaemia with metformin and an SU in comparison with metformin and a DPP-4 inhibitor. Previous meta-analyses of second-line metformin-based combination therapies have also shown an increased incidence of hypoglycaemia in patients taking metformin and an SU in comparison with metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist. The results of the current analysis confirm these findings in a global cohort assessed prospectively over 36 months of follow-up, adding further evidence to suggest that combination therapy with metformin and an SU carries a higher risk of hypoglycaemia than suitable alternatives.
Although SF-36v2 MCS and PCS scores were generally lowest among patients prescribed metformin in combination with an SU, the changes in scores from baseline were modest. For PCS scores, a 1-point difference has been shown to have a measurable effect on patients’ inability to work, hospitalization and mortality. Using this benchmark, combination therapy with metformin and a GLP-1 receptor agonist was associated with noticeably higher PCS scores for the first 24 months, whereas combination therapy with metformin and an SGLT-2 inhibitor was associated with noticeably higher MCS scores after 12 months. SF-36v2 PCS and MCS scores tended to decrease in each cohort over time, with the notable exception of the MCS scores of patients prescribed metformin and an SGLT-2 inhibitor, which continued to increase slightly between follow-up visits.

Long-term complications of diabetes can have a marked impact on patients’ HRQoL. Achieving optimal glycaemic control is a cornerstone of delaying the onset of these complications, and although all four metformin combinations showed similar reductions in Hba1c levels after 12 months, early attainment and maintenance of optimal glycaemic control is key for delaying long-term microvascular and macrovascular complications of T2D. Additionally, weight reduction has been associated with improved HRQoL in patients with T2D, and both weight loss and SF-36v2 scores were typically higher among patients prescribed a DPP-4 inhibitor and an SGLT-2 inhibitor in the current analysis. GLP-1 receptor agonists have been shown to be effective agents for inducing weight loss in patients with and without T2D, and although treatment with metformin and a GLP-1 receptor agonist was the most effective at reducing weight throughout the whole of follow-up in the current analysis, difficulty with administration of an injectable agent, fear of pain at the injection site, or potential adverse effects of GLP-1 receptor agonist treatment, may have resulted in the comparatively modest changes in SF-36v2 scores in these patients after 36 months. Despite these observed differences,
in weight loss, hypoglycaemia and reported HRQoL, the proportions of patients requiring treatment intensification over 3 years were similar in those receiving combinations of metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor, a GLP-1 receptor agonist or an SU.

Interestingly, although sole use of SUs is associated with weight gain, and DPP-4 inhibitors are typically weight-neutral in T2D, we found that patients in the current study receiving metformin and either an SU or a DPP-4 inhibitor experienced, on average, modest weight loss from baseline. While use of SUs on their own is typically associated with weight gain, combinations of metformin and an SU have been shown to be associated with modest weight loss. Indeed, the weight loss seen in patients prescribed an SU or a DPP-4 inhibitor was less than in patients prescribed metformin plus either an SGLT-2 inhibitor or a GLP-1 receptor agonist, as may be expected given the weight loss typically associated with these drug classes.

The primary strength of the DISCOVER study programme is the large number of participants and wide range of participating practices from across the globe, including many countries which have rarely been studied before. In addition, the range of data collected by the DISCOVER study enabled the assessment of multiple outcomes. The prospective nature of the DISCOVER study enabled assessment of changes in weight and HbA1c level over a long period following initiation of second-line glucose-lowering therapy. However, DISCOVER patients were initiating second-line therapy and therefore were probable to be in the early stages of T2D, so we were not able to assess directly whether there were any differences in the incidence of vascular and renal complications of T2D, which tend to develop over a long period of time. In line with the observational nature of the study, follow-up visits and data collection were not mandatory; however, this is reflective of real-world clinical practice. While major hypoglycaemic events were recorded if they took place within 12 months of the visit, minor hypoglycaemic events were only recorded if they took place in the 4 weeks preceding a visit and relied on participant recollection, potentially introducing recall bias and an under-reporting. Differences in adverse cardiovascular and hypoglycaemic events between different SUs have been observed in previous studies; however, the current analysis did not distinguish between different therapies or doses within a treatment class, and adherence to glucose-lowering medication was not assessed. The numbers of patients prescribed metformin with an SGLT-2 inhibitor or a GLP-1 receptor agonist were comparatively small and, as such, these results should be interpreted with caution. The DISCOVER study was also largely conducted prior to the introduction of the more recent guidelines for the treatment of T2D, which are now in favour of SGLT-2 inhibitor or GLP-1 receptor agonist treatments for the majority of patients where cost is not an issue.

In conclusion, the results from this analysis of a global cohort of patients with T2D, one of few studies assessing multiple outcomes in patients prescribed different combination therapies with metformin, showed that despite long-term reductions in HbA1c being similar across all four examined second-line therapies, combinations of metformin and a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist outperformed combinations of metformin and an SU in reducing weight, while also minimizing the risk of hypoglycaemia. Combination therapy with metformin and an SU was almost always associated with the greatest negative change in PCS and MCS scores, while combinations of metformin and an SGLT-2 inhibitor were associated with consistently improved HRQoL throughout follow-up. These real-world data suggest that metformin in combination with a DPP-4 inhibitor, an SGLT-2 inhibitor or a GLP-1 receptor agonist holds significant benefits at second line in comparison with metformin and an SU, adding additional evidence to support guidance which recommends SU combination therapies only if cost or availability is an issue.

ACKNOWLEDGEMENTS

The authors would like to thank all the investigators and patients participating in the DISCOVER study programme. Medical writing support was provided by Bobby Thompson, MSc(Res), of Oxford PharmaGenesis, Oxford, UK, and was funded by AstraZeneca. The DISCOVER study programme is funded by AstraZeneca. DISCOVER is a non-interventional study and no drugs were supplied or funded.

CONFLICT OF INTEREST

K.K., M.B.G., L.J., A.N., W.R., M.V.S. and H.W. are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. A.C., P.L., A.S. and H.C. are employees of AstraZeneca. F.T. is an employee of St Luke’s Mid-America Heart Institute and has received funding from AstraZeneca. In addition, K.K. has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda, Servier and Pfizer, research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Pfizer, and also acknowledges support from the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC-EM) and the NIHR Leicester Biomedical Research Centre. B.C. has received honoraria from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Takeda. M.B.G. has received honoraria from Merck-Serono. L.J. has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda, Sanofi and Roche, research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche and Sanofi, honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda, Sanofi and Roche, and research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche and Sanofi. A.N. has received honoraria from AstraZeneca, Eli Lilly, Medtronic and Novo Nordisk, and research support from Artsana, Dexcom, AlfaSigma, Novo Nordisk, Pidkare, Sanofi, Shionogi, Sobi and Theras. W.R. has received research support from Novo Nordisk. M.V.S. has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Servier, research support from Novo Nordisk and Sanofi, honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharpe & Dohme, Novo Nordisk, Sanofi and...
Servier, and research support from Novo Nordisk and Sanofi. H.W. has received honoraria from Astellas Pharma, AstraZeneca, Boehrlinger Ingelheim, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eli Lilly, Kissié Pharmaceutical, Kowa Pharmaceuticals America Inc., Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho and Takeda, and research support from Abbott, Astellas Pharma, AstraZeneca, Bayer, Benefit One Health Care, Boehrlinger Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eli Lilly, Johnson & Johnson, Kissié Pharmaceutical, Kowa Pharmaceuticals America Inc., Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nitta Boseki, Novartis, Novo Nordisk, Ono Pharmaceutical, Pfizer, Sanofi, Sanwa Kagaku Kenkyusho, Taisho Toyama Pharmaceutical, Takeda and Terumo Corp.

AUTHOR CONTRIBUTIONS
The general content of the manuscript was agreed upon by all authors, and all authors contributed to manuscript development. All authors approved the final version of the manuscript before its submission. An AstraZeneca team reviewed the manuscript during its development and was allowed to make suggestions. However, the final content was determined by the authors. K.K. is the guarantor of this work.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14400.

DATA AVAILABILITY STATEMENT
Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Khunti K, Charbonnel B, Cooper A, et al. Associations between second-line glucose-lowering combination therapies with metformin and HbA1c, body weight, quality of life, hypoglycaemic events and glucose-lowering treatment intensification: The DISCOVER study. Diabetes Obes Metab. 2021;23:1823-1833. https://doi.org/10.1111/dom.14400