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Treatment patterns and glycated haemoglobin levels over 36 months in individuals with type 2 diabetes initiating second-line glucose-lowering therapy: The global DISCOVER study

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Abstract

Aims: To describe glucose-lowering treatment regimens and glycated haemoglobin (HbA1c) trajectories in individuals with type 2 diabetes (T2D) over 36 months of follow-up from the start of second-line therapy.

Materials and Methods: This data analysis from the 3-year, observational DISCOVER study programme included 14 687 participants from 37 countries with T2D initiating second-line glucose-lowering therapy. Treatment and HbA1c data were collected at baseline (start of second-line therapy) and at 6, 12, 24 and 36 months. Treatment regimen changes over follow-up were analysed using the McNemar test, with carry-forward imputation for intermediate missing values.

Results: A total of 11 592 participants had treatment data at baseline and 36 months, and 11 882 had HbA1c data at baseline. At baseline and 36 months, respectively, rates of oral monotherapy use were 12.1% and 12.4% ($P = 0.22$), rates of dual oral therapy use were 63.4% and 47.6% ($P < 0.0001$), rates of ≥ triple oral therapy use were 17.5% and 25.4% ($P < 0.0001$), and rates of injectable treatment use were 7.0% and 13.7% ($P < 0.0001$). Use of injectable drugs was most common among participants with an HbA1c level ≥64 mmol/mol (≥8.0%). Overall, 42.9% of participants changed treatment during follow-up. Mean HbA1c levels at baseline and 6 months were 67 mmol/mol (8.3%) and 55 mmol/mol (7.2%), respectively, remaining stable thereafter.

Conclusions: Dual oral therapy was the most common treatment regimen at the start of second-line treatment, and over half of the participants remained on the same treatment during follow-up.

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KEYWORDS
antidiabetic drug, glycaemic control, observational study, second-line treatment, type 2 diabetes

1 | INTRODUCTION

For individuals receiving glucose-lowering therapy for type 2 diabetes (T2D), changing from first- to second-line therapy may include the addition of a new glucose-lowering drug or switching treatment class, and is recommended when first-line therapy fails to control glycated haemoglobin (HbA1c) levels.[1-3] Although most guidelines recommend a target HbA1c level of 48 to 53 mmol/mol (6.5-7.0%) in otherwise healthy adults with T2D,[1-3] they also suggest tailoring glycaemic targets to individual patients.[1,2] Glucose-lowering treatment should be intensified if an individual does not achieve their target HbA1c level with first-line treatment.[3,4] Despite this recommendation, observational studies show that a substantial proportion of patients have poor glycaemic control for several years before treatment is intensified, a delay referred to as treatment inertia.[5]

Many glucose-lowering agents are available for second-line therapy, including sulphonylureas (SUs), dipeptidyl peptidase-4 (DPP-4) inhibitors, or sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and insulin. Global guidelines, including those from the European Association for the Study of Diabetes/American Diabetes Association, Diabetes Canada, the World Health Organization (WHO), and the International Diabetes Federation (IDF), suggest selecting second-line glucose-lowering treatments based on patient characteristics such as age, duration of diabetes, and presence of comorbidities, as well as risk of adverse events including hypoglycaemia and weight gain.[1,3,6-8] However, longitudinal data on glucose-lowering regimens and clinical outcomes after second-line treatment are lacking.

DISCOVER was a 3-year, prospective, observational study programme including individuals with T2D initiating second-line glucose-lowering therapy in six regions and 38 countries, including 778 clinical sites at rural and urban locations (NCT02322762 and NCT02226822).[9,10] At the start of second-line treatment, the median HbA1c level was 60 to 67 mmol/mol (7.6-8.3%) across regions, and the most commonly prescribed second-line therapies were metformin and DPP-4 inhibitor combinations (23.5%) and metformin and SU combinations (20.9%). The baseline analysis showed that at the start of second-line therapy, >50% and >30% of participants had HbA1c levels >64 mmol/mol (>8.0%) and >75 mmol/mol (>9.0%), respectively.[11] Poor glycaemic control (HbA1c >64 mmol/mol) at the start of second-line therapy was associated with low education levels, low country income, and longer time since T2D diagnosis.[11]

In the current analysis, we assessed glucose-lowering treatment patterns and HbA1c level trajectories from the start of second-line therapy to the end of the 3-year follow-up.

2 | MATERIALS AND METHODS

2.1 | Design

The methods for the DISCOVER study programme have been reported in detail elsewhere and are briefly summarized below. DISCOVER comprises two similar, 3-year, observational studies conducted simultaneously in 38 countries (DISCOVER [NTC02322762] in 37 countries and J-DISCOVER [NTC02226822] in Japan).[9,10] This analysis aims to describe the second-line treatment regimens and mean HbA1c level trajectories, overall and by second-line treatment regimen, over the 36-month follow-up.

Individuals aged over 18 years who had T2D and who were initiating a second-line glucose-lowering therapy (add-on or switching) after first-line oral treatment were invited to enrol in DISCOVER from December 2014 to June 2016 and in J-DISCOVER from September 2014 to December 2015. Inclusion and exclusion criteria were kept to a minimum to reflect the diversity of patients treated in routine clinical practice (Table S1). Patients were excluded if they were receiving an injectable agent as first-line therapy. All study participants provided written informed consent.

Countries were grouped into regions according to WHO category: Africa (Algeria and South Africa); Americas (Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico and Panama); South-East Asia (India and Indonesia); Europe (Austria, Czech Republic, Denmark, France, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden and Turkey); the Eastern Mediterranean (Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia and United Arab Emirates); and the Western Pacific (Australia, China, Japan, Malaysia, South Korea and Taiwan). 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

complied with the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice, and the local regulations for clinical research. The overall distributions and characteristics of physicians and practices in each country were determined before starting the study in order to facilitate the recruitment of a representative sample of patients with T2D.

2.2 | Data collection

Data were collected at baseline (initiation of second-line therapy) and at 6, 12, 24 and 36 months using a standardized electronic case report form that was transferred to a central database via a web-based data capture system. Information on further treatment changes after second-line therapy was collected during follow-up. Some data were extracted from existing electronic health records in Canada, Denmark, France, Norway and Sweden.

Participant demographic data (such as sex, age, self-reported ethnicity, body mass index and duration of T2D) were collected at study baseline. Data collected at baseline and during follow-up included clinical variables (such as HbA1c and fasting plasma glucose [FPG] levels), and first- and second-line treatment. Data were measured and recorded according to routine clinical practice at each site. Participants were not obliged to attend study visits, and data collection was not compulsory for any of the clinical variables.

2.3 | Statistical analysis

2.3.1 | Baseline characteristics

Participants with data available on first- and second-line treatment were included in the analysis. Data from China (1292 patients) were excluded owing to changes in regulatory restrictions during study follow-up. Data for categorical variables are presented as numbers and percentages, and data for continuous variables are provided as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate.

2.3.2 | HbA1c levels and FPG during follow-up

Participants' HbA1c and FPG values are provided as mean (SD), with across-region ranges (ARRs), as appropriate. HbA1c control at each timepoint is described as the percentage of participants achieving HbA1c levels of <53 mmol/mol (<7.0%), 53 to <64 mmol/mol (7.0-<8.0%), 64 to <75 mmol/mol (8.0-<9.0%) or ≥75 mmol/mol (≥9.0%).

2.3.3 | Glucose-lowering treatment regimens

Treatment patterns were described at each timepoint and categorized as one, two, three or more, or four or more oral drugs, or any regimen that included injectable therapy. The rate of use of each treatment regimen was described as the number of participants at each timepoint receiving that regimen as a percentage of the total number of participants with information at that timepoint. The rate of use of each treatment regimen was also described according to HbA1c category at each timepoint. Differences between the rates of use of each treatment regimen at baseline and at 36 months were assessed using a McNemar test, at a significance level of 0.05.[12] The carry-forward approach was used to impute missing intermediate data, up to the last timepoint with available data. For example, if a participant had treatment information at baseline and 12 months, data were imputed at 6 months but not at 24 and 36 months. Statistical analyses were performed using the sas 9.4 statistical software system (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Baseline characteristics

Overall, 14 687 DISCOVER participants from 37 countries had first- and second-line treatment data available (3472 from Europe, 3360 from South-East Asia, 2684 from the Western Pacific, 2180 from the Eastern Mediterranean, 2001 from the Americas, and 810 from Africa). Of these, 11 592 (78.9%) had treatment information available at baseline and 36 months (Table 1); 46.7% were Asian, 26.1% were White, and 16.3% were Arabic, and 93.3% (10 817 / 11 592) had an available blood glucose measurement at baseline (HbA1c, FPG or both). The mean baseline HbA1c and FPG levels were 67 mmol/mol (8.3%) and 9.41 mmol/L, respectively.

3.2 | HbA1c level change over time

The mean HbA1c level trajectories overall and by region are shown in Figure 1. Mean HbA1c levels were 67 mmol/mol (8.3%), with an ARR of 63 to 72 mmol/mol (7.9-8.7%) at baseline and 55 mmol/mol (7.2%) 6 months after starting second-line treatment, with an ARR of 53 to 60 mmol/mol (7.0-7.6%). Levels remained stable during the remainder of the 36-month follow-up. A similar pattern over time was seen for mean FPG level.

At baseline and 6 months, 17.4% (2071 / 11 882) and 46.7% of participants (4093 / 8770), respectively, had an HbA1c level <53 mmol/mol (<7.0%), with rates of 46.0% to 46.9% during follow-up. At baseline and 6 months, 26.7% (3171 / 11 882) and 8.3% (730 / 8770) of participants respectively, had an HbA1c level >75 mmol/mol (>9.0%), with rates of 7.0% to 8.7% during follow-up (Figure 2).

3.3 | Glucose-lowering treatment regimens

Overall treatment regimens at first line, second line (baseline) and follow-up visits are shown in Table 2. Drug regimens included

TABLE 1 Baseline characteristics of participants with treatment information at baseline and 36 months (N = 11 592), overall and according to treatment change

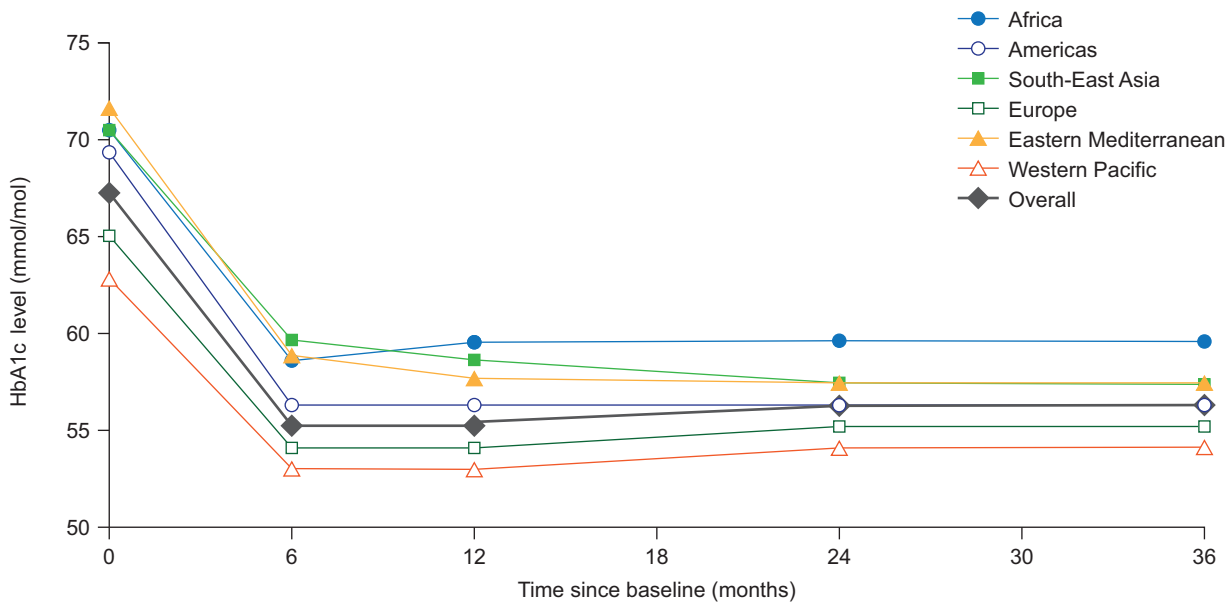
		Treatment change at any timepoint	
Characteristic	**Overall (N = 11 592)**	**Yes (n = 4972)**	**No (n = 6620)**
Female, n (%)	5367 (46.3)	2299 (46.2)	3068 (46.3)
Male, n (%)	6225 (53.7)	2673 (53.8)	3552 (53.7)
Age, years, mean (SD)	57.5 (11.9)	56.5 (12.0)	58.2 (11.8)
Ethnicity, n (%)			
White	2919 (26.1)	1297 (27.1)	1622 (25.4)
Black	199 (1.8)	43 (0.9)	156 (2.4)
Asian	5221 (46.7)	2333 (48.7)	2888 (45.2)
Hispanic	769 (6.9)	288 (6.0)	481 (7.5)
Arabic	1819 (16.3)	719 (15.0)	1100 (17.2)
Mixed race	123 (1.1)	50 (1.0)	73 (1.1)
Other	126 (1.1)	58 (1.2)	68 (1.1)
Missing, n	416	184	232
BMI, kg/m^2, mean (SD)	29.3 (5.9)	29.4 (6.0)	29.3 (5.8)
Missing, n	841	342	499
Blood glucose measurement, n (%)			
HbA1c and FPG	6833 (58.9)	2963 (59.6)	3870 (58.5)
HbA1c only	2489 (21.5)	1138 (22.9)	1351 (20.4)
FPG only	1495 (12.9)	621 (12.5)	874 (13.2)
No measurement	775 (6.7)	250 (5.0)	525 (7.9)
HbA1c, %, mean (SD)	8.3 (1.6)	8.4 (1.7)	8.1 (1.5)
Missing, n	2270	871	1399
HbA1c, n (%)			
<53 mmol/mol (<7.0%)	1637 (17.6)	634 (15.5)	1003 (19.2)
53 to <64 mmol/mol (7.0-<8.0%)	3073 (33.0)	1251 (30.5)	1822 (34.9)
64 to <75 mmol/mol (8.0-<9.0%)	2252 (24.2)	1018 (24.8)	1234 (23.6)
≥75 mmol/mol (≥9.0%)	2360 (25.3)	1198 (29.2)	1162 (22.3)
FPG, mmol/L, mean (SD)	9.41 (3.07)	172.8 (9.59 (3.19)	9.27 (2.96)
Missing, n	3264	1388	1876
Time since diagnosis, years, median (IQR)	4.2 (2.0-7.8)	4.1 (2.0-7.4)	4.3 (2.1-8.0)
Missing, n	271	123	148
Second-line treatment, n (%)			
One oral drug	1403 (12.1)	516 (10.4)	887 (13.4)
Two oral drugs	7346 (63.4)	3138 (63.1)	4208 (63.6)
Three or more oral drugs	2029 (17.5)	948 (19.1)	1081 (16.3)
Injectable drug[a]	814 (7.0)	370 (7.4)	444 (6.7)

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IQR, interquartile range; SD, standard deviation.
Note: Percentages are reported for all participants with data available; missing data are excluded. Study baseline refers to the initiation of second-line glucose-lowering therapy following first-line therapy.
[a]Glucagon-like peptide-1 receptor agonist or insulin, with or without oral therapy.

metformin, DPP-4 inhibitors, SUs, SGLT2 inhibitors, thiazolidinediones (TZDs), and alpha-glucosidase inhibitors. Injectable drugs included insulin or GLP-1RAs, alone or as part of a combination therapy. At each timepoint after baseline, a small number of participants were reported to be receiving no glucose-lowering treatment (0.2-0.9%).

3.3.1 | Treatment regimens from baseline to 36 months

The rate of use of oral monotherapy as first-line treatment was 76.4% (11 216 / 14 687), and 12.1% of participants (1784 / 14 687) received oral monotherapy at second line (Table 2). The rate of use of two oral



Number of participants with HbA1c level data, n (%)	Overall N = 14 687	Africa n = 810	Americas n = 2001	South-East Asia n = 3360	Europe n = 3472	Eastern Mediterranean n = 2180	Western Pacific n = 2864
Baseline	11 882	465 (57.4)	1530 (76.5)	2052 (61.1)	3000 (86.4)	2043 (93.7)	2792 (97.5)
6 months	8801	331 (40.9)	872 (43.6)	1465 (43.6)	2063 (59.4)	1679 (77.0)	2391 (83.5)
12 months	9878	355 (43.8)	851 (42.5)	2060 (61.3)	2610 (75.2)	1686 (77.3)	2316 (80.9)
24 months	9674	356 (44.0)	817 (40.8)	2103 (62.6)	2622 (75.5)	1612 (73.9)	2164 (75.6)
36 months	9366	354 (43.7)	784 (39.2)	2073 (61.7)	2465 (71.0)	1639 (75.2)	2051 (71.6)

FIGURE 1 Changes in mean glycated haemoglobin (HbA1c) during the 36 months of follow-up and availability of HbA1c level data at each timepoint, overall and by World Health Organization region. Study baseline refers to the initiation of second-line glucose-lowering therapy following first-line therapy

drugs as first-line treatment was 19.8% (2911 / 14 687), and 62.5% of participants (9179 / 14 687) received two oral drugs at second line. The rate of use of three or more oral drugs as first-line treatment was 17.5% (2029 / 14 687), and 17.0% of participants (2497 / 14 687) received three or more oral drugs at second line. At baseline and 36 months the rate of insulin use was 5.2% and 11.0%, respectively, and the rate of GLP-1RA use was 1.9% and 3.2%.

In the subgroup of participants with treatment information at baseline and 36 months (n = 11 592), the rate of use of oral monotherapy remained similar between baseline and 36 months at 12.1% and 12.4%, respectively ($P = 0.22$). The rate of use of two oral drugs decreased between baseline and 36 months from 63.4% to 47.6% ($P < 0.0001$). The rate of use of three or more oral drugs increased between baseline and 36 months from 17.5% to 25.4% ($P < 0.0001$). The use of injectable agents increased from 7.0% at second line, to 13.7% at 36 months ($P < 0.0001$).

3.3.2 | Treatment regimens by region

Treatment regimens by region are shown in Tables S2 to S7. The pattern of use of oral monotherapy in Africa, the Eastern Mediterranean and Europe was consistent with the overall population. In the Americas, the rate of oral monotherapy use was 8.6% (173 / 2001) at baseline and 13.3% (200 / 1504) at 36 months. In South-East Asia and the Western Pacific, respectively, the rate of use oral monotherapy was 15.9% (533 / 3360) and 14.1% (405 / 2864) at baseline and 15.6% (459 / 2938) and 11.7% (260 / 2226) at 36 months. In all regions, the rate of use of two oral drugs was higher at baseline than at 36 months. The rates of use of three or more oral drugs were lower at baseline than at 36 months in all regions.

Injectable drug use at baseline was most common in Europe (16.0%; 557 / 3472) and Africa (12.2%; 99 / 810), and least frequent in the Western Pacific (1.1%; 32 / 2864). In all regions, regimens that included an injectable drug were more frequently used at 36 months than at baseline.

3.3.3 | Treatment regimens and HbA1c trajectories

Mean HbA1c trajectories by treatment regimen are shown in Figure 2. With all treatment regimens, mean HbA1c levels were higher at baseline than during follow-up. At all timepoints, the percentages of participants with HbA1c <53 mmol/mol (<7.0%) were higher in those using one or two oral agents than in those using other regimens, and the percentage of participants with HbA1c ≥75

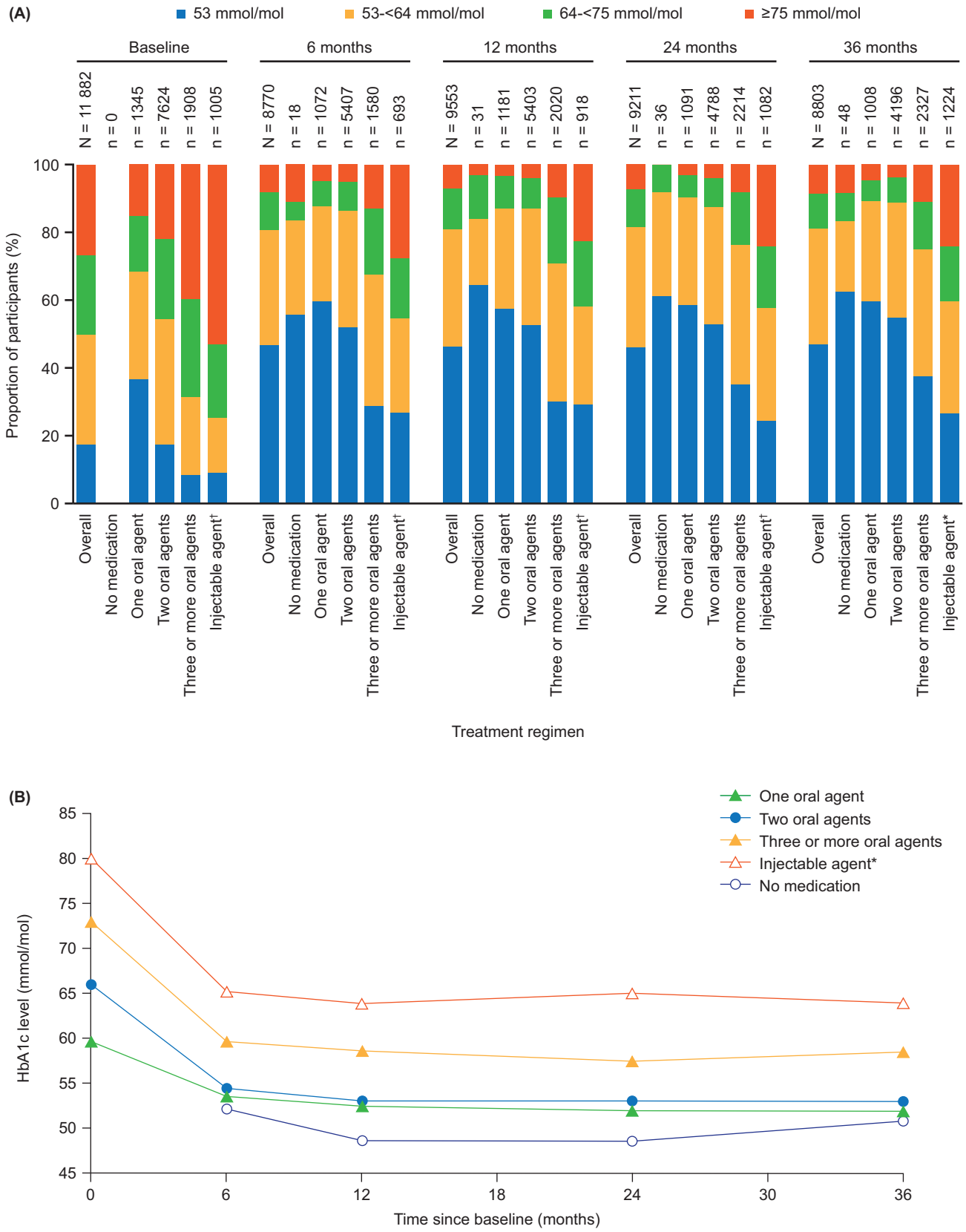


FIGURE 2 **A**, Proportion of participants in different glycated haemoglobin (HbA1c) categories and **B**, mean HbA1c level at baseline and 6, 12, 24 and 36 months according to treatment option at each timepoint. Imputation, using the carry-forward approach, was used to account for any intermediate missing treatment information, up to the last timepoint with available data. Study baseline refers to the initiation of second-line glucose-lowering therapy following first-line therapy. *Glucagon-like peptide-1 receptor agonist or insulin, with or without oral therapy

TABLE 2 Overall treatment patterns at each timepoint

Treatment option	Glucose-lowering therapy					
	First-line therapy (N = 14 687)	Second-line therapy (baseline) (N = 14 687)	6 months (n = 13 460)	12 months (n = 12 806)	24 months (n = 12 106)	36 months (n = 11 592)
No glucose-lowering therapy	0 (0.0)	0 (0.0)	31 (0.2)	51 (0.4)	71 (0.6)	102 (0.9)
One oral drug	11 216 (76.4)	1784 (12.1)	1697 (12.6)	1626 (12.7)	1506 (12.4)	1438 (12.4)
Metformin	8509 (57.9)	265 (1.8)	369 (2.7)	403 (3.1)	402 (3.3)	404 (3.5)
SUs	1061 (7.2)	406 (2.8)	371 (2.8)	350 (2.7)	307 (2.5)	288 (2.5)
DDP-4 inhibitors	1171 (8.0)	634 (4.3)	539 (4.0)	476 (3.7)	423 (3.5)	394 (3.4)
Other	475 (3.2)	479 (3.3)	418 (3.1)	397 (3.1)	374 (3.1)	352 (3.0)
Two oral drugs	2911 (19.8)	9179 (62.5)	7943 (59.0)	7097 (55.4)	6172 (51.0)	5515 (47.6)
Metformin + SUs	2135 (14.5)	3115 (21.2)	2634 (19.6)	2364 (18.5)	2046 (16.9)	1813 (15.6)
Metformin + DPP-4 inhibitors	488 (3.3)	3678 (25.0)	3165 (23.5)	2770 (21.6)	2417 (20.0)	2168 (18.7)
Metformin + other	172 (1.2)	1118 (7.6)	972 (7.2)	870 (6.8)	755 (6.2)	677 (5.8)
Other combinations	116 (0.8)	1268 (8.6)	1172 (8.7)	1093 (8.5)	954 (7.9)	857 (7.4)
Three or more oral drugs	560 (3.8)	2497 (17.0)	2629 (19.5)	2741 (21.4)	2902 (24.0)	2945 (25.4)
Metformin + SU + DPP-4 inhibitors	219 (1.5)	1041 (7.1)	1082 (8.0)	1090 (8.5)	1061 (8.8)	997 (8.6)
Other combinations	299 (2.0)	1159 (7.9)	1199 (8.9)	1250 (9.8)	1365 (11.3)	1416 (12.2)
Four or more oral drugs	42 (0.3)	297 (2.0)	348 (2.6)	401 (3.1)	476 (3.9)	532 (4.6)
Injectable drug[a]	0 (0.0)	1227 (8.4)	1160 (8.6)	1291 (10.1)	1455 (12.0)	1592 (13.7)

Abbreviations: DPP-4, dipeptidyl peptidase-4; SU, sulphonylurea.
Note: Imputation, using the carry-forward approach, was used to account for any intermittent missing treatment information. Study baseline refers to the initiation of second-line glucose-lowering therapy following first-line therapy.
[a]Glucagon-like peptide-1 receptor agonist or insulin, with or without oral therapy.

mmol/mol (≥9%) was highest in those using injectable drugs. Across all timepoints after baseline, participants receiving no glucose-lowering therapy most commonly had an HbA1c level <53 mmol/mol (<7%).

3.3.4 | Changes in glucose-lowering treatment during follow-up

Of the 11 592 participants with treatment information available at baseline and 36 months, 42.9% (4972 / 11 592) changed treatment at least once during follow-up. Between consecutive timepoints, the proportions of participants who changed treatment were 16.2% (2179 / 13 460) from baseline to 6 months, 13.4% (1715 / 12 806) from 6 to 12 months, 16.9% (2042 / 12 106) from 12 to 24 months, and 15.9% (1839 / 11 592) from 24 to 36 months (Table S8).

Participants who did not change treatment during follow-up had commonly received a second-line regimen with one or two oral drugs. The use of three or more oral drugs or an injectable drug at baseline was more common in participants who changed treatment during follow-up than in those who did not. At each timepoint, among participants who changed treatment, 71.2% to 73.2% received either an additional oral drug or switched oral treatment class, 10.2% to 14.4% received an injectable drug, and 12.4% to 17.2% received fewer drugs or discontinued treatment altogether.

The mean (SD) age of participants was 56.5 (12.0) years in those who changed treatment at least once during follow-up, and 58.2 (11.8) years among those who did not change treatment. From baseline and during follow-up, mean HbA1c and FPG levels, respectively, were 68 mmol/mol (8.4%) and 9.59 mmol/L, among participants who changed treatment, and 65 mmol/mol (8.1%) and 9.27 mmol/L among those who did not change treatment.

4 | DISCUSSION

This multi-region, prospective observational study included 14 687 individuals with T2D and with first- and second-line glucose-lowering therapy data available. Mean HbA1c levels were 8.3% at the start of second-line therapy and 7.2% at 6 months, then remained stable to 36 months. Of the 11 592 participants with treatment information at baseline and 36 months, almost 43% changed treatment at least once

during follow-up, usually involving the addition of an oral glucose-lowering drug, the initiation of an injectable drug, or a switch between treatment classes.

Drugs used at first line were described in the previous baseline analysis (N = 15 992), and included, metformin monotherapy (55.6%), SU monotherapy (7.7%), and metformin in combination with an SU and/or DPP-4 inhibitor (1.4-14.4%).[11] The rate of use of SGLT2 inhibitors, TZDs and alpha-glucosidase inhibitors as first-line monotherapy or combination therapy was <10%.[11] In our analysis of treatment regimens, at the start of second-line treatment and at 36 months, the rate of use of oral monotherapy at these timepoints was similar at 12.1% and 12.4% ($P = 0.22$), the rate of use two oral drugs decreased from 63.4% to 47.6% ($P < 0.0001$) and the rate of use of three or more oral drugs increased from 17.5% to 25.4% ($P < 0.0001$). From the start of second-line treatment to the end of follow-up, the overall rate of use of injectable drugs increased from 7.0% to 13.7% ($P < 0.0001$), including both insulin (from 5.2% to 11.0%) and GLP-1RAs (from 1.9% to 3.2%).

In line with the treatment guidelines during the study period, oral regimens most commonly included metformin, DPP-4 inhibitors and SUs, and the use of "other combinations" including SGLT2 inhibitors was relatively low. In Europe, the United States and Japan, the first SGLT2 inhibitors were approved in 2012, 2013 and 2014, respectively, and thereafter treatment guidelines in high-income countries recommended SGLT2 inhibitors over SUs because of the risk of hypoglycaemic events with SUs.[1,4,7,8] In the previous baseline analysis, 17.0% of participants started second-line therapy because of hypoglycaemia with first-line therapy.[11] However, the DISCOVER programme included participants enrolled between 2014 and 2016, so may not reflect contemporary treatment patterns for SGLT2 inhibitors. In a DISCOVER analysis of 14 668 participants, SUs and DPP-4 inhibitors were widely used at first and second line, yet a SGLT2 inhibitor in combination with metformin was only used at second line (4.3%), and only 1.3% of participants received a GLP-1RA in combination with metformin.[13] These data suggested that for economic and other non-medical reasons, many patients are prescribed SUs rather than newer agents, such as SGLT2 inhibitors or GLP-1RAs when initiating second-line therapy.

In our analysis, the median (IQR) time from diagnosis to the initiation of second-line therapy was 4.2 (2.0-7.8) years, suggesting that participants received second-line treatment early in the disease process compared with other global observational studies.[5,14] For example, a UK Clinical Practice Research Datalink study including 81 573 patients showed that, in those initiating treatment with one, two or three oral glucose-lowering therapies, the median time to intensification with an addition oral drug was >7.2 years.[5] Moreover, studies from the United States have reported that among people with T2D, those who received treatment intensification within 6 months of metformin monotherapy failing, achieved HbA1c target levels more quickly than those with who received second-line treatment after 6 months.[15] Another study in the United Kingdom showed that, among patients initiated on metformin, the initiation of second-line treatment within 1 year of the first recorded HbA1c level of ≥53 mmol/mol (≥7%) was associated with achieving and maintaining a reduction in HbA1c more quickly than patients starting second-line treatment after 1 year of a recorded HbA1c level of ≥53 mmol/mol (≥7%).[16]

Within 3 years of starting second-line treatment in our study, treatment was changed at least once in 36.8%, 42.7% and 46.7% of participants receiving oral monotherapy, two oral drugs, or three or more oral drugs at second line, respectively. Among patients with HbA1c levels <64 mmol/mol (<8.0%) or ≥64 mmol/mol (≥8.0%) at baseline, 40.0% and 48.0%, respectively, had their treatment changed at least once during follow-up. The observation that fewer than half of participants with HbA1c levels >64 mmol/mol (>8.0%) had their treatment modified over follow-up may have been driven by specific regions. For example, in Africa, despite having mean HbA1c levels that were consistent with the overall cohort, only 12.6% to 13.4% of participants received treatment with three or more oral drugs during follow-up, compared with 19.5% to 25.4% of the overall cohort. This may reflect the limited availability and affordability of some treatments and the potential cost incurred with the use of an additional glucose-lowering drug.[17,18]

Regarding glycaemic control, at the start of second-line treatment and at 6 months, 17.4% and 46.7% of participants, respectively, had an HbA1c level <53 mmol/mol (<7.0%). Participants in Africa, South-East Asia, and the Eastern Mediterranean had a higher mean HbA1c level than those in Europe and the Western Pacific at all timepoints. Overall, our analysis showed that 46.0% to 46.9% of participants had an HbA1c level <53 mmol/mol (<7.0%) during follow-up, which is relatively high compared with previous observational studies. In the first year of the International Diabetes Management Practices Study, the rate of attainment of HbA1c levels <53 mmol/mol (<7.0%) was 37.3% in Asia, 36% in Eastern Europe, and 36% in Latin America.[19] In an observational study of individuals treated with basal insulin in the United States, approximately 38% achieved an HbA1c level <53 mmol/mol (<7.0%) in the first year of follow-up, with a further 8% in the second year of follow-up.[20] In an observational study in the United States and five European countries, the general HbA1c target of <53 mmol/mol (<7.0%) was achieved by 20.9% and 27.8% of participants at 3 and 24 months, respectively, after basal insulin initiation, with or without oral glucose-lowering drugs.[21]

The relatively high rate of participants achieving an HbA1c level <53 mmol/mol (<7.0%) at 6 months after starting second-line treatment observed in our study may be associated with the mean age of the study population, which was 57.5 years, compared with 63.3 years in the US/European study and 62.0 years in the US study of basal insulin.[20,21] In addition, the relatively rapid improvement in glycaemic levels observed at 6 months after starting second-line treatment could be explained by the fact that 88.9% of participants were initiating second-line therapy as a result of suboptimal glycaemic control.[11] In our study, mean HbA1c levels were 67 mmol/mol (8.3%) at the start of second-line therapy and 55 mmol/mol (7.2%) at 6 months, and although the data are descriptive, this suggests that treatment intensification had an effect on glycaemic control.

Target HbA1c levels should be personalized to each patient and a target HbA1c level of 48 to 53 mmol/mol (6.5-7.0%) may not be appropriate for all individuals. For example, individuals with complex

comorbidities may have less stringent glycaemic goals with an individualized target HbA1c level of >53 mmol/mol (>7.0%).[1] In fact, a previous DISCOVER study report showed that 70.2% of patients had been set an individualized glycaemic control target; targets were 53 mmol/mol (7.0%) for 2513 patients (49.6%), <53 mmol/mol (<7.0%) for 2073 patients (40.9%), ≥53 mmol/mol (≥7.0%) for 484 patients (9.6%).[22] As such, a proportion of participants with an HbA1c level of 53 to <64 mmol/mol (7.0-<8.0%) may be considered as having reached their individualized HbA1c target and therefore did not receive treatment intensification during follow-up.

The results of this analysis should be interpreted with the following strengths and limitations in mind. The large number of participants and the range of treatment sites and countries included in the study, some of which have rarely been studied before, constitute one of the primary strengths of the DISCOVER study programme. Use of the standardized electronic case report form allowed the comparison of results between countries and regions. Like some other observational studies, true representativeness was challenging to achieve in DISCOVER, as the inclusion of random samples of sites, physician specialties and patients is often not feasible. Although study sites were selected to optimize diversity in each country, participating physicians and sites may be more likely to focus on quality of care than others, potentially resulting in an over-representation of more advanced treatment centres. Countries were grouped by WHO region to assess differences in treatment patterns and glycaemic control in different parts of the world. However, these results by WHO region should be interpreted with caution because availability of medications and healthcare systems may vary across countries within a given region. Because participants enrolled in DISCOVER were all initiating second-line glucose-lowering therapy, our findings do not represent the entire T2D population. Given the observational nature of the study, participants were not required to attend every study visit and there was no requirement to record data for all study variables, meaning that a complete dataset was not available for all participants. Overall, 2270 of the 11 592 participants (19.6%) who had treatment data available at baseline and 36 months did not have a recorded baseline HbA1c level. However, 1495 of these participants did have a recorded baseline FPG level that, given the similar trend in HbA1c and FPG levels during follow-up, can be considered as a substitute measurement of the pattern of glycaemic control in these participants. Finally, our analysis did not distinguish between participants with different HbA1c level targets, meaning that some participants with seemingly suboptimal glycaemic control may have reached their individualized HbA1c target and therefore may not necessarily require treatment intensification.

In conclusion, although we report a substantial and stable decrease in HbA1c level among individuals with T2D after initiation of second-line glucose-lowering treatment, an HbA1c level <53 mmol/mol (<7.0%) was reported in fewer than half of participants during the 36 months of follow-up. Almost 43% of participants changed treatment at least once during follow-up, which, for most participants, represented either treatment intensification (addition of an oral glucose-lowering drug or initiation of an injectable drug) or a switch between treatment classes. Although most participants achieved stable glycaemic control and an HbA1c level <64 mmol/mol (<8.0%) on their reported treatment regimen, our findings suggest that guidelines on the timely intensification of treatment might not always be followed in clinical practice. There remains a need for use of effective and easy-to-administer glucose-lowering drugs in patients early on in their disease trajectories, to minimize unnecessary treatment intensification and improve glycaemic control.

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. Bernard H. Charbonnel is the guarantor of this work.

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CONFLICTS OF INTEREST

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PEER REVIEW

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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." cd_value_code="text

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SUPPORTING INFORMATION

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

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