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HbA1c trajectories over 3 years in people with type 2 diabetes starting second-line glucose-lowering therapy: The prospective global DISCOVER study

Brenda Bongaerts PhD[1] | Oliver Kuss PhD[2] | Fabrice Bonnet MD[3] | Hungta Chen PhD[4] | Andrew Cooper PhD[5] | Peter Fenici MD[6] | Marilia B. Gomes MD[7] | Niklas Hammar PhD[8,9] | Linong Ji MD[10] | Kamlesh Khunti MD[11] | Jesús Medina PhD[12] | Antonio Nicolucci MD[13] | Marina V. Shestakova MD[14] | Hirotaka Watada MD[15] | Wolfgang Rathmann MD[2]

[1]Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

[2]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Institute for Diabetes Research at Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

[3]University of Rennes, Rennes, France

[4]AstraZeneca, Gaithersburg, Maryland, USA

[5]AstraZeneca, Cambridge, UK

[6]Catholic University of the Sacred Heart, School of Medicine and Surgery, and Biomagnetism and Clinical Physiology International Center (BACPIC), Rome, and Medical Affairs, AstraZeneca S.p.A, Milan, Italy

[7]Department of Internal Medicine, Rio de Janeiro State University, Rio de Janeiro, Brazil

[8]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

[9]AstraZeneca, Mölndal, Gothenburg, Sweden

[10]Peking University People's Hospital, Beijing, China

[11]University of Leicester, Leicester, UK

[12]AstraZeneca, Madrid, Spain

[13]Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy

[14]Endocrinology Research Centre, Moscow, Russia

[15]Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan

Abstract

Aim: To identify distinct HbA1c trajectories in people with type 2 diabetes (T2D) starting second-line glucose-lowering therapy.

Materials and Methods: DISCOVER was a 3-year observational study of individuals with T2D beginning second-line glucose-lowering therapy. Data were collected at initiation of second-line treatment (baseline) and at 6, 12, 24 and 36 months. Latent class growth modelling was used to identify groups with distinct HbA1c trajectories.

Results: After exclusions, 9295 participants were assessed. Four distinct HbA1c trajectories were identified. Mean HbA1c levels decreased between baseline and 6 months in all groups; 72.4% of participants showed stable good levels of glycaemic control over the remainder of follow-up, 18.0% showed stable moderate levels of glycaemic control and 2.9% showed stable poor levels of glycaemic control. Only 6.7% of participants showed highly improved glycaemic control at month 6 and stable control over the rest of follow-up. For all groups, dual oral therapy use decreased over time, compensated for by the increasing use of other treatment regimens. Use of injectable agents increased over time in groups with moderate and poor glycaemic control. Logistic regression models suggested that participants from high-income countries were more probable to be in the stable good trajectory group.

Conclusions: Most people receiving second-line glucose-lowering treatment in this global cohort achieved stable good or highly improved long-term glycaemic control. One-fifth of participants showed moderate or poor glycaemic control during follow-up. Further large-scale studies are required to characterize possible factors associated with patterns of glycaemic control to inform personalized diabetes treatment.

Correspondence
Brenda Bongaerts, PhD, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany.
Email: brenda.bongaerts@med.uni-duesseldorf.de

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1 | INTRODUCTION

A variety of classes of glucose-lowering therapies are available for the treatment of type 2 diabetes (T2D), allowing physicians to follow individualized approaches to disease management in their patients.[1-4] Evidence-based, individualized treatment regimens require information about how people will probably respond to treatment, and can thus be supported by the identification of groups of patients who may experience favourable patterns of glycaemic changes over time with certain therapies.[5,6] Using latent class growth modelling, previous studies identified a large group of individuals with T2D who have stable levels of good glycaemic control after treatment. However, there are substantial differences in the HbA1c trajectories of groups exhibiting poor glycaemic control between studies.[7-10] For example, a longitudinal study of 1091 patients with T2D found that 52.8% had either moderate or poor glycaemic control after 2 years of follow-up,[7] whereas a separate longitudinal study of 20 816 patients newly diagnosed with T2D found that just 17.5% had either moderate or poor glycaemic control after 10 years of follow-up.[8] Such heterogeneity may potentially be attributable to differences in study populations and treatment regimens. Currently, no study has exclusively investigated HbA1c trajectories in people with T2D after initiation of second-line glucose-lowering therapy.

DISCOVER was a global observational study of more than 15 000 people with T2D starting second-line glucose-lowering therapy.[11] Participants were recruited from 2014 to 2016 from 38 countries across six regions (Africa, the Americas, South-East Asia, the Eastern Mediterranean, Europe and the Western Pacific) and were followed up for 3 years.[11] Using data from DISCOVER, we aim to identify HbA1c trajectory groups in individuals at an early stage of T2D progression. This is the first study on HbA1c trajectories in people with T2D starting second-line therapy, and the first study on HbA1c trajectories on a global level, including low- and middle-income countries rarely or never having been previously studied.[11,12] We also assess demographic, clinical and treatment characteristics associated with different trajectories.

2 | METHODS

2.1 | Research design

DISCOVER was a 3-year prospective observational study programme of 15 983 people with T2D beginning second-line glucose-lowering therapy in 38 countries (DISCOVER [ClinicalTrials.gov identifier: NCT02322762] in 37 countries and J-DISCOVER [NCT02226822] in Japan).[11,12] Study methods have been described in detail previously.[11,12] Countries were grouped into regions according to World Health Organization categories[13] (Data S1, Table S1), and were categorized by gross national income using 2016 data from the World Bank.[14]

Participants were enrolled in DISCOVER from December 2014 to June 2016, and in J-DISCOVER from September 2014 to December 2015. To ensure that data were as reflective of routine clinical practice as possible, inclusion and exclusion criteria were kept to a minimum. Individuals with T2D were eligible for inclusion if they were starting second-line glucose-lowering therapy, provided that their first-line therapy was not an injectable agent or an herbal remedy/natural medicine alone. Second-line therapy was defined as the addition of one or more drugs, or a switch of drug to another class of hyperglycaemic drug, if first-line therapy was an oral form of monotherapy. Second-line therapy was defined as the discontinuation of a drug, a switch of at least one drug to another class of drug, or a third drug added, if first-line therapy was dual therapy. Similarly, so for first-line therapy being triple or quadruple drug therapy. Full inclusion and exclusion criteria are shown in Data S1, Table S2. Eligible individuals were invited to participate in the study by their physician and provided written informed consent. A list of participating investigators can be found in Data S2.

The study protocol was approved by the clinical research ethics committee in each participating country, along with the appropriate institutional review board at individual study sites. The protocol complied with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline and local regulations for clinical research.

2.2 | Data collection

Data were collected at baseline (the date of second-line therapy initiation) and during follow-up at 6, 12, 24 and 36 months using a standardized electronic case report form, and were transferred to a central database via a web-based data capture system. Data collected at baseline and during follow-up included participant demographics (such as sex, age, body mass index [BMI] and duration of diabetes), clinical variables (such as HbA1c levels) and first- and second-line glucose-lowering therapies. In line with the observational nature of the study, variables were measured by participating physicians in accordance with routine clinical practice and data collection for these variables was not mandatory.

2.3 | Statistical analysis

Participants in the DISCOVER study were included in the present HbA1c trajectory analysis if they had at least two HbA1c measurements during follow-up in addition to a baseline measurement. Data from China were excluded because of changes in regulatory requirements during the study (n = 1292). Data are presented as numbers (percentages), means (standard deviations [SDs]) and medians (interquartile ranges [IQRs]), as appropriate.

Latent class growth modelling was used to model HbA1c patterns and identify groups of participants with similar HbA1c trajectories over time (baseline to 36 months).[6] The maximum likelihood method was used to estimate model parameters, with polynomial functions fitted using quadratic and cubic orders. The Bayes Information Criterion (BIC) was used to help assess the optimal number of trajectory groups, with higher BIC values indicating a better model fit than lower values.[15,16] In addition, each HbA1c trajectory group had to contain at least 2.0% of our analytical cohort to avoid identification of groups containing only a small number of participants.[15,16] Very small groups increase statistical uncertainty and numerically destabilize models. The clinical interpretation of each trajectory model was also considered.

Logistic regression models were used to investigate the odds of participants being assigned to different HbA1c trajectory groups, with baseline covariates (sex, age, BMI, country income and second-line therapy [oral monotherapy, dual oral therapy, three or more oral therapies or an injectable agent]) as fixed effects. Our analyses were standard logistic models and hypothesis generating. Multiple imputation was used to impute any unreported data for the independent variables included in the logistic regression model. Iterative sequential regression was employed to sample missing values from the predictive distribution of each variable, conditional on all other variables included in the model. Variables included in the imputation model were the dependent variable (HbA1c trajectory groups) and independent variables (patient demographics [such as sex, age, BMI and country income] and first- and second-line glucose-lowering treatments). Ten randomly imputed datasets were generated in this way. Analyses were repeated on each imputed dataset and model estimates were pooled across imputations using Rubin's rule. Statistical analyses were performed using the SAS 9.4 statistical software system (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | HbA1c trajectory groups and baseline patient characteristics

Of the 14 691 eligible DISCOVER participants, 9295 (63%) had three or more HbA1c measurements, including a baseline measurement, and were included in the analysis (Figure 1).

Latent class growth modelling identified rising BIC values with increasing numbers of patient groups. Based on the criteria of plausible clinical interpretation and a minimum group size of 2.0% of participants, a four-group model (BIC: −60 535) was chosen.

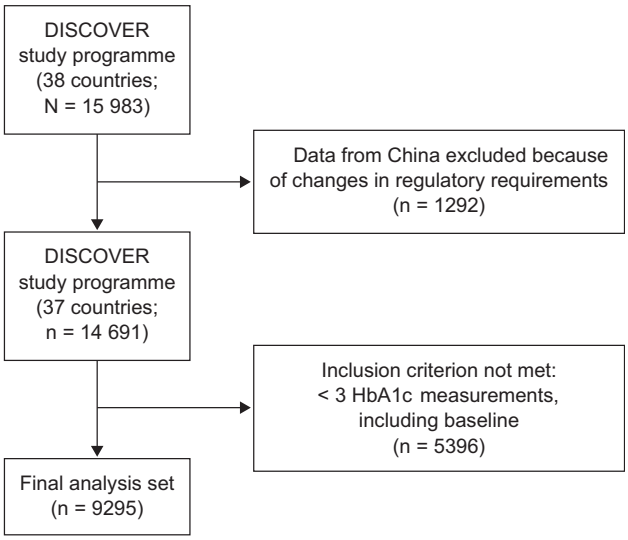

FIGURE 1 Number of participants eligible for analysis

HbA1c trajectories of the resulting four groups are shown in Figure 2. A total of 72.4% of the study population were defined as having 'stable good' levels of glycaemic control, characterized by baseline mean HbA1c levels of 7.6% (59.6 mmol/mol) followed by a decrease in HbA1c level to 6.8% (50.8 mmol/mol) at 6 months and HbA1c levels remaining stable at less than 7.0% (< 53.0 mmol/mol) over the rest of the follow-up period. A total of 18.0% of participants were defined as having 'stable moderate' levels of glycaemic control. In these patients, after an initial fall in HbA1c levels from 8.9% (73.8 mmol/mol) at baseline to 8.3% (67.2 mmol/mol) at 6 months, concentrations remained well above international recommendations for target HbA1c levels of less than 7.0% (< 53.0 mmol/mol).[17] A third trajectory group, comprising 6.7% of the population, was defined as having 'highly improved' levels of glycaemic control. These participants had a high baseline HbA1c level of 11.7% (104.4 mmol/mol), which decreased to 7.8% (61.7 mmol/mol) by 6 months and further decreased to 7.3% (56.3 mmol/mol) by 12 months, remaining stable thereafter. The fourth trajectory group, comprising 2.9% of the study population, was defined as having 'stable poor' levels of glycaemic control. These participants had a high baseline HbA1c level of 11.6% (103.3 mmol/mol), which decreased to 10.9% (95.6 mmol/mol) after 6 months, followed by a small gradual decrease to 10.4% (90.2 mmol/mol) by 36 months.

Baseline characteristics of the analytical cohort overall and by HbA1c trajectory group are shown in Table 1. At baseline, the mean age of participants ranged from 52.3 (SD: 11.2) years in the stable poor group to 59.3 (SD: 12.0) years in the stable good group. The proportion of female participants ranged from 41.3% in the highly improved group to 51.9% in the stable poor group. The mean baseline BMI was similar across the four trajectory groups, while the median duration of T2D ranged from 3.2 (IQR: 1.1-7.3) years in the highly improved group to 4.8 (IQR: 2.3-8.8) years in the stable moderate

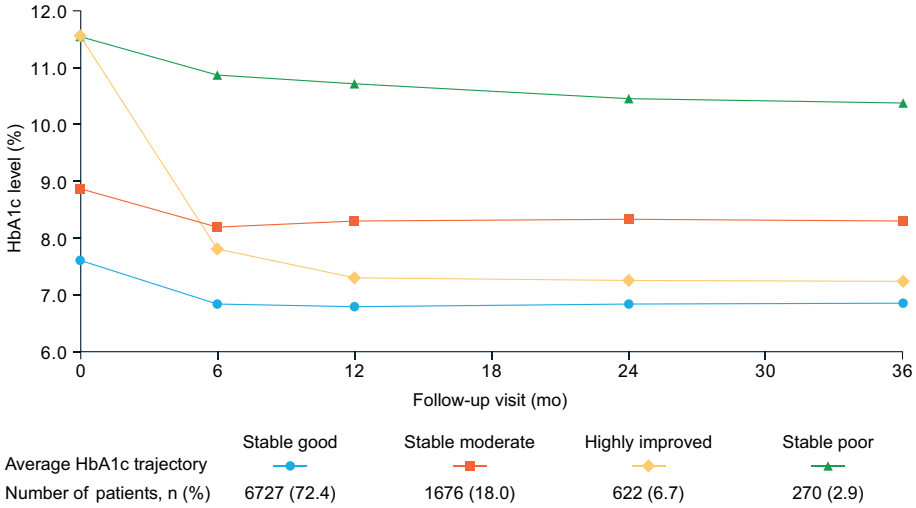

FIGURE 2 Mean HbA1c trajectories of participants assigned to each trajectory group. [a]Stable good group (72.4% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable average HbA1c levels < 7.0% (< 53.0 mmol/mol) for the remainder of follow-up. Stable moderate group (18.0% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable levels for the remainder of follow-up; however, the mean HbA1c level at 36 months remained on average > 7.0% (> 53.0 mmol/mol). Highly improved group (6.7% of the cohort): a steep decrease in HbA1c level between baseline and 6 months before remaining stable for the remainder of follow-up. Stable poor group (2.9% of the cohort): a high baseline HbA1c with a small decrease in HbA1c level over time; however, the mean HbA1c level at 36 months remained high

group. The rate of microvascular co-morbidities at baseline was 21.4% in the stable good group, 22.3% in the stable moderate group, 25.4% in the highly improved group and 25.6% in the stable poor group.

Among the different forms of second-line glucose-lowering therapies at baseline, use of injectable agents was observed most frequently in the stable poor group, whereas oral monotherapy and dual oral therapies were most frequently used in the stable good group. The proportion of participants in each HbA1c trajectory group varied substantially across regions.

3.2 | Logistic regression of factors associated with glycaemic control

Logistic regression models assessing factors associated with different HbA1c trajectories showed that older participants (aged 65-74 and ≥ 75 years) and those treated in a high-income country were more probable to be in the stable good group than in the other trajectory groups (Figure 3). Participants who received three or more oral therapies or an injectable agent were more probable to be in the stable moderate, highly improved or stable poor groups than in the stable good group (relative to those receiving oral monotherapy).

3.3 | Treatment regimens during follow-up

The proportion of participants in each HbA1c trajectory group who received oral monotherapy, dual oral therapy, three or more oral therapies or an injectable agent (glucagon-like peptide-1 receptor agonist or insulin, with or without one or more oral therapies) at each time point is detailed in Figure 4.

In the stable good group (baseline HbA1c level of 7.6% [59.6 mmol/mol]), dual oral therapy was the most common second-line regimen initiated at baseline (69.7% of participants in this group). The slight decrease in use of dual oral therapy during follow-up was matched by an increase in the use of three or more oral therapies, although dual oral therapy accounted for 56.1% of treatment at 36 months. Proportions of oral monotherapy and injectable therapy users were low and remained stable throughout follow-up (Figure 4A). At baseline and 36 months, respectively, in the stable good group, the most commonly used drugs were metformin (75.7% and 76.1%), dipeptidyl peptidase-4 inhibitors (57.3% and 58.5%) and sulphonylureas (34.1% and 35.6%) (Data S1, Figure S1).

In the stable moderate group (baseline HbA1c level of 8.9% [73.8 mmol/mol]), dual oral therapy was the most common second-line regimen at baseline (53.9%), but its use decreased rapidly over time, reaching 28.9% at 36 months of follow-up. The use of three or more oral therapies and injectable agents increased, with three or more oral therapies becoming the most common regimen by the end of follow-up (36.6%) (Figure 4B). Metformin was the most commonly used drug from baseline to 36 months, with the proportions of users being 81.2% and 80.4%, respectively (Data S1, Figure S1).

In the highly improved group (baseline HbA1c level of 11.7% [104.4 mmol/mol]), there was a steady decrease in the use of dual oral therapy from baseline (55.5%) to 36 months of follow-up (37.9%). This was met by an increase in the use of three or more oral therapies from

TABLE 1 Baseline characteristics of participants in the entire cohort and by HbA1c trajectory group

	Overall	Trajectory group[a]			
		Stable good	Stable moderate	Highly improved	Stable poor
Participants, n (%)[b]	9295 (100.0)	6727 (72.4)	1676 (18.0)	622 (6.7)	270 (2.9)
Female, n (%)[b]	4003 (43.1)	2879 (42.8)	727 (43.4)	257 (41.3)	140 (51.9)
Age, y, mean (SD)[b]	58.1 (12.0)	59.3 (12.0)	55.8 (11.9)	54.1 (10.7)	52.3 (11.2)
BMI, kg/m^2, mean (SD)[b]	29.3 (5.8)	29.2 (5.8)	29.9 (5.6)	29.1 (5.8)	30.5 (7.0)
HbA1c level, %, mean (SD)[b]	8.2 (1.6)	7.6 (0.9)	8.9 (1.0)	11.7 (1.3)	11.6 (1.8)
Duration of type 2 diabetes, y, median (IQR)[b]	4.2 (2.1-8.0)	4.2 (2.0-7.9)	4.8 (2.3-8.8)	3.2 (1.1-7.3)	4.1 (2.2-7.9)
First-line therapy, n (%)[b]					
Metformin monotherapy	5417 (58.3)	4034 (60.0)	892 (53.2)	345 (55.5)	146 (54.1)
Other monotherapies	2002 (21.5)	1626 (24.2)	252 (15.0)	92 (14.8)	32 (11.9)
Metformin + SU	1129 (12.1)	600 (8.9)	332 (19.8)	132 (21.2)	65 (24.1%)
Metformin + DPP-4i	311 (3.3)	206 (3.1)	69 (4.1)	28 (4.5)	8 (3.0)
Other combinations[c]	436 (4.7)	261 (3.9)	131 (7.8)	25 (4.0)	19 (7.0)
Second-line therapy, n (%)[b]					
Oral monotherapy	1048 (11.3)	859 (12.8)	142 (8.5)	29 (4.7)	18 (6.7)
Dual oral therapy	6065 (65.3)	4691 (69.7)	903 (53.9)	345 (55.5)	126 (46.7)
Three or more oral therapies	1445 (15.5)	820 (12.2)	427 (25.5)	131 (21.1)	67 (24.8)
Injectable agent[d]	737 (7.9)	357 (5.3)	204 (12.2)	117 (18.8)	59 (21.9)
Region, n (%)[b]					
Africa	344 (3.7)	215 (3.2)	81 (4.8)	30 (4.8)	18 (6.7)
Americas	852 (9.2)	580 (8.6)	168 (10.0)	76 (12.2)	28 (10.4)
South-East Asia	1534 (16.5)	997 (14.8)	356 (21.2)	116 (18.6)	65 (24.1)
Europe	2472 (26.6)	1860 (27.6)	427 (25.5)	141 (22.7)	44 (16.3)
Eastern Mediterranean	1735 (18.7)	1128 (16.8)	385 (23.0)	156 (25.1)	66 (24.4)
Western Pacific	2358 (25.4)	1947 (28.9)	259 (15.5)	103 (16.6)	49 (18.1)
Country income, n (%)[b,e]					
Lower middle	2430 (26.1)	1630 (24.2)	515 (30.7)	202 (32.5)	83 (30.7)
Upper middle	2099 (22.6)	1375 (20.4)	446 (26.6)	188 (30.2)	90 (33.3)
High	4766 (51.3)	3722 (55.3)	715 (42.7)	232 (37.3)	97 (35.9)
Medical history, n (%)[f]					
Macrovascular complications[g]	1158 (12.5)	898 (13.4)	180 (10.7)	56 (9.0)	24 (8.9)
Missing	31	28	0	3	0
Microvascular complications[h]	2038 (21.9)	1438 (21.4)	373 (22.3)	158 (25.4)	69 (25.6)
Missing	10	9	0	1	0
Major hypoglycaemic event[i]	72 (0.8)	48 (0.8)	18 (1.1)	4 (0.7)	2 (0.8)
Missing	548	398	90	46	14
Minor hypoglycaemic event[j]	271 (3.1)	196 (3.1)	55 (3.5)	13 (2.2)	7 (2.7)
Missing	516	373	88	41	14
Chronic kidney disease	567 (6.1)	431 (6.4)	88 (5.3)	36 (5.8)	12 (4.4)
Missing	10	9	0	1	0

Note: Data are reported as n (%) unless otherwise stated.

Abbreviations: BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitors; IQR, interquartile range; SD, standard deviation; SU, sulphonylureas.

[a]Stable good group (72.4% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable average HbA1c levels < 7.0% (< 53.0 mmol/mol) for the remainder of follow-up. Stable moderate group (18.0% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable levels for the remainder of follow-up; however, the mean HbA1c level at 36 months remained on average > 7.0% (> 53.0 mmol/mol). Highly improved group (6.7% of the cohort): a steep decrease in HbA1c level between baseline and 6 months before remaining stable for the remainder of follow-up. Stable poor group (2.9% of the cohort): a high baseline HbA1c with a small decrease in HbA1c level over time; however, the mean HbA1c level at 36 months remained high.

[b]100% of data available.

[c]Two or more agents.

[d]Glucagon-like peptide-1 receptor agonist or insulin.

[e]Categorized using the 2016 World Bank classification.

[f]Percentages were calculated for all participants with data available; participants with missing data were excluded.

[g]Macrovascular complications include coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use.

[h]Microvascular complications include nephropathy, retinopathy and neuropathy.

[i]Major hypoglycaemic events are those 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.

[j]Minor hypoglycaemic events did not require third-party assistance and occurred in the 4 weeks before baseline.[14]

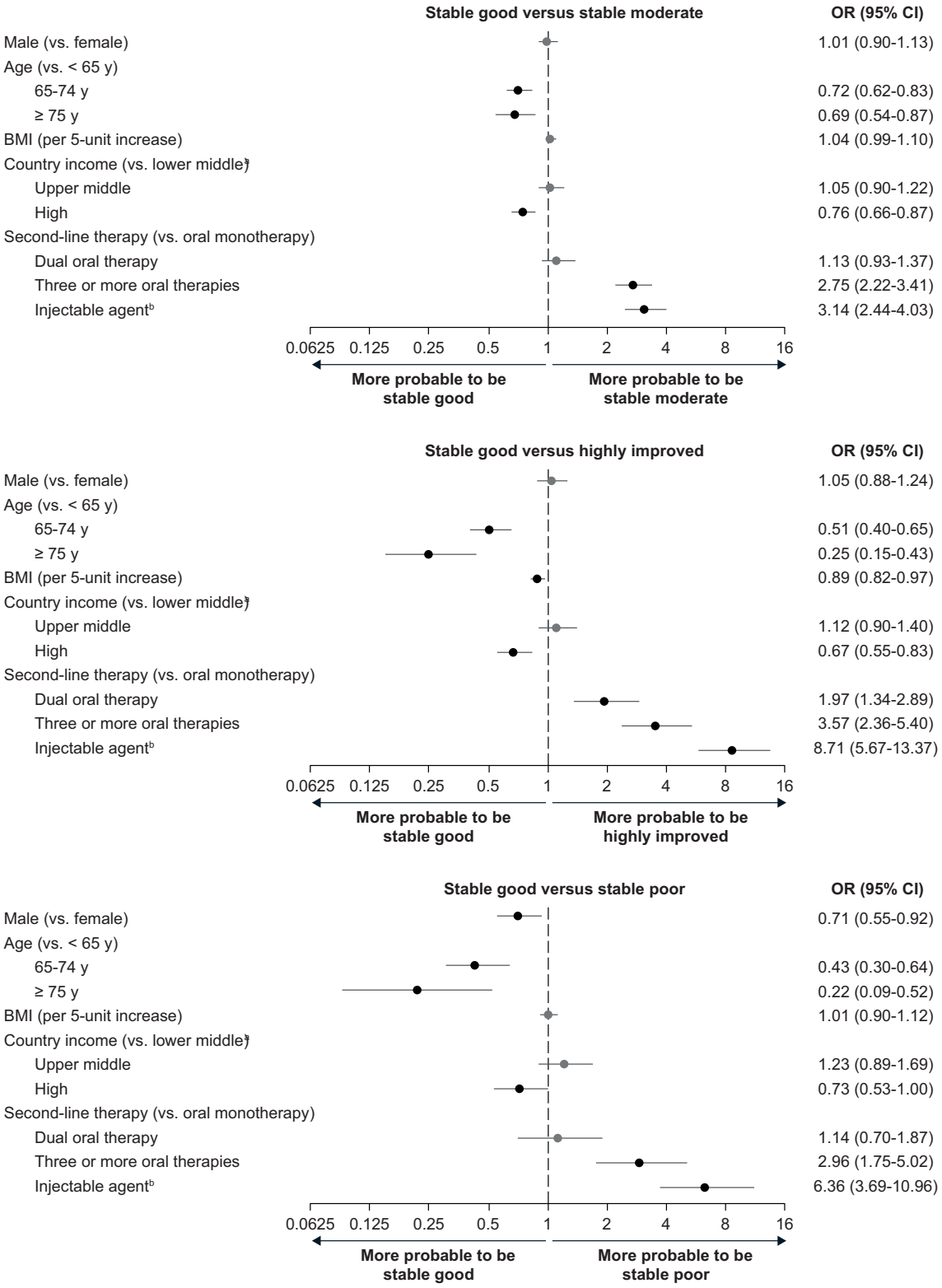

FIGURE 3 Multivariate logistic regression analysis of factors associated with the odds of a participant belonging to an HbA1c trajectory group. ORs were calculated using a logistic regression model adjusted for all variables in the figure. Statistically significant factors are coloured in black. BMI, body mass index; CI, confidence interval; OR, odds ratio. [a]Country income categorized using the 2016 World Bank classification.[14] [b]Injectable agents include glucagon-like peptide-1 receptor agonists and insulin

21.1% to 29.8% (Figure 4C). Again, the most commonly used glucose-lowering drug was metformin (84.6% at baseline and 83.2% at 36 months) (Data S1, Figure S1). In the stable poor group (baseline HbA1c level of 11.6% [103.3 mmol/mol]), where mean HbA1c levels remained high, there was a large decrease in the use of dual oral therapy from 46.7% at baseline to 12.8% at 36 months. This was largely

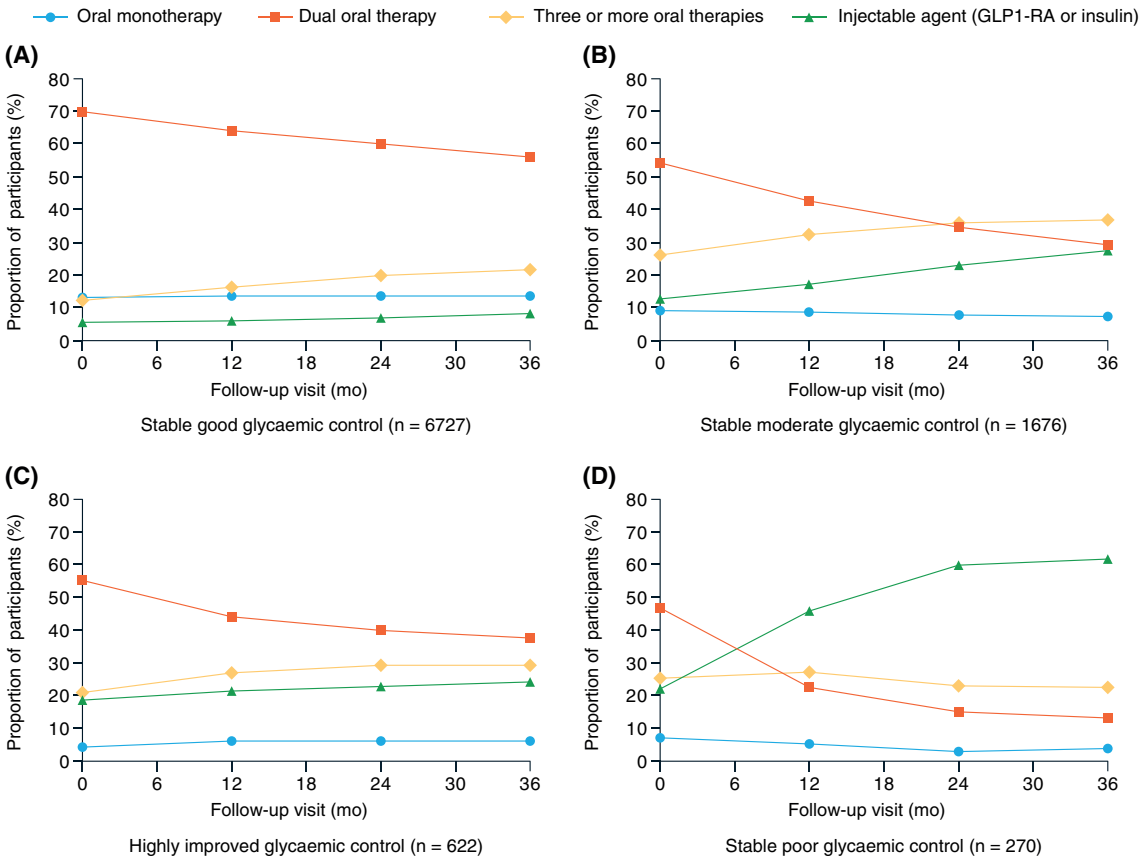

FIGURE 4 Second-line glucose-lowering therapy regimens from baseline to 36 months in the A, Stable good, B, Stable moderate, C, Highly improved, and D, Stable poor glycaemic control groups. GLP1-RA, glucagon-like peptide-1 receptor agonist

compensated for by an increase in the use of injectable agents, from 21.9% at baseline to 61.5% at 36 months (Figure 4D). The large increase in the use of injectable agents largely corresponded to an increase in the use of insulin, from 18.5% at baseline to 58.7% at 36 months (Data S1, Figure S1).

4 | DISCUSSION

This analysis from the DISCOVER global observational study of people with T2D starting second-line glucose-lowering therapy identified four distinct HbA1c trajectories, all of which showed a clear decrease in mean HbA1c level between baseline and 6 months. In all groups after 6 months, either the decrease in HbA1c levels slowed down or the HbA1c levels stabilized. Although there was a continued modest decrease in HbA1c levels in the stable poor group by 12 months, the levels remained very high during the 3-year follow-up, reflected in a shift from mainly dual oral therapy to injectable agents. By contrast, the highly improved group, which had a similar mean HbA1c level to the stable poor group at baseline, showed highly improved glycaemic control during the remainder of follow-up, with treatment with injectable agents remaining comparatively stable and few participants switching from dual oral therapy to three or more oral therapies.

The identification of a large cohort of participants with good glycaemic control (72.4%) is consistent with findings from previous studies in individuals with newly diagnosed diabetes.[8,9] A systematic review of nine studies investigating HbA1c trajectories in individuals with T2D between 2 and 13.6 years of follow-up revealed that up to 89% of participants formed a large group with stable mean HbA1c levels just above 7.0% (53.0 mmol/mol).[5] The review found a wide range in the proportion of participants belonging to a group with a stable HbA1c level (15%-89%); this may be partly explained by differences in study populations such as duration of T2D, prevalence of obesity, use of different glucose-lowering medications and local differences in quality of care. Furthermore, different definitions of glycaemic control make it challenging to compare studies directly.

Treatment regimen at baseline and during follow-up varied between the four HbA1c trajectory groups. Dual oral therapy use was highest in the stable good group at all time points, probably because this group had good glycaemic control at baseline and throughout follow-up, with no need to intensify treatment. The proportion of participants who received an injectable agent almost tripled during follow-up in the stable poor group, probably because of high HbA1c levels at baseline and throughout follow-up. This observation is in line with the results of a large longitudinal study in the United States and five European countries, which indicated that initiation of basal insulin

treatment, with or without oral glucose-lowering drugs, was related to a failure to achieve an HbA1c target of 7.0% or less after 3 and 24 months of treatment.[18]

In all four trajectory groups metformin remained the most commonly used drug at all time points, showing that its use was a stable factor in treatment, regardless of the regimen. Apart from metformin, the most frequently used therapies were sulphonylureas and dipeptidyl peptidase-4 inhibitors in all groups. In line with the published literature, there was a modest yet steady increase in the use of sodium-glucose co-transporter-2 inhibitors in all groups over the entire follow-up period.[19]

The likelihood of being in the stable moderate, highly improved and stable poor groups (compared with the stable good group) was significantly higher in participants receiving second-line therapy regimens including three or more oral therapies or an injectable agent than in those receiving second-line monotherapy. Indeed, more intensive treatments, such as multiple therapies and injectable agents, are more probable to be prescribed to patients with less well-controlled T2D. In the stable poor group, with both high baseline HbA1c levels and the comparatively frequent use of injectables, participants were comparatively young (52.3 vs. 58.1 years in the population overall), with a comparatively high rate of microvascular co-morbidity at baseline (25.6% vs. 21.9% in the overall population). Baseline characteristics and suboptimal glycaemic control during follow-up in the stable poor group may be indicative of a more severe metabolic phenotype, or may have been associated with factors such as poor adherence to injectable therapy. Regarding the effect of age on outcomes among people with T2D, previous studies have shown a more severe metabolic phenotype in younger individuals than in their older counterparts,[20] as well as lower levels of treatment adherence.[21] Furthermore, data from Project Dulce in the United States revealed that people with T2D aged younger than 50 years had higher, less stable HbA1c levels than those aged 50 years or older.[22] Of note, in our study, participants aged 65 years or older, particularly those aged 75 years or older, were more probable to be in the stable good group than those aged younger than 65 years.

Participants from high-income countries were more probable to be in the stable good group than in the other three trajectory groups. This may, at least in part, reflect a higher quality of diabetes care or greater availability of novel glucose-lowering therapies in these countries than in lower-income countries. Countries with a lower socioeconomic status have also been shown to be associated with unstable and poor glycaemic control, with a sharp increase in HbA1c levels seen in the first 5 years following T2D diagnosis in this group of patients.[23]

The large number of participants and the range of treatment sites and countries, some of which have rarely been studied before, are some of the primary strengths of the DISCOVER study. Use of a standardized electronic case report form allowed comparison of results between countries and regions. Although DISCOVER sites were selected to optimize diversity in each country, it is unclear whether our findings truly reflect the quality of care within each country or can be generalized outside the countries and regions included in the study. The proportion of patients in each HbA1c trajectory group varied across regions, suggesting that different diabetes phenotypes may be more prevalent in some regions than in others, although BMI and duration of T2D were similar across HbA1c trajectories.

As participants enrolled in DISCOVER were all beginning second-line glucose-lowering therapy, our findings are not representative of the entire T2D population. Given the observational nature of the study, there was no requirement to record all study variables, and a complete dataset was not available for all participants. Indeed, the entire DISCOVER cohort could not be included in this analysis as only those with three or more HbA1c level measurements, including a baseline measurement, were eligible. This criterion meant that a large proportion of participants was excluded from the analysis (n = 5396). This has the potential to introduce selection bias, as those participants with a greater number of HbA1c measurements may have been better monitored, better managed or may have had characteristics related to more favourable diabetes management. However, in order to adequately assess a trajectory, at least three HbA1c measurements are required. Additionally, the observational nature of this study prevents the control of regression to the mean; however, the trajectories of groups with similar baselines differed remarkably.

In conclusion, our findings support current diabetes care guidelines in advocating a personalized treatment strategy. As the aim of this study was to identify distinct HbA1c trajectories, future studies will be key in further investigations of underlying behavioural, genetic, phenotypical and regional and socioeconomic factors associated with different patterns of glycaemic control, further helping to guide healthcare practitioners treating patients on an individual basis.

AUTHOR CONTRIBUTIONS

All authors contributed to the development of the manuscript and approved the final version before submission. B.B., W.R. and O.K. developed the statistical analysis plan, which was conducted by H.C. An AstraZeneca team reviewed the manuscript during its development and was given the opportunity to make suggestions. However, the final content was determined by the authors. B.B. and W.R. are the guarantors of this work.

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CONFLICT OF INTEREST

B.B. and O.K. have no competing interests to disclose. W.R., F.B., M. B.G., L.J., K.K., A.N., 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. H.C., A.C., P.F. and J.M. are employees of AstraZeneca. N.H. is a former employee of AstraZeneca. In addition, W.R. has received research support from Novo Nordisk; F.B. has received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, Novo Nordisk, Sanofi and Takeda; M.B.G. has received honoraria from Merck Serono; L.J. has received honoraria from AstraZeneca, Bayer, Boehringer

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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.

ORCID

Brenda Bongaerts https://orcid.org/0000-0003-4695-7185
Oliver Kuss https://orcid.org/0000-0003-3301-5869
Fabrice Bonnet https://orcid.org/0000-0001-9255-8228
Marilia B. Gomes https://orcid.org/0000-0003-4458-4741
Linong Ji https://orcid.org/0000-0003-1305-1598
Kamlesh Khunti https://orcid.org/0000-0003-2343-7099
Antonio Nicolucci https://orcid.org/0000-0002-5939-6850
Hirotaka Watada https://orcid.org/0000-0001-5961-1816
Wolfgang Rathmann https://orcid.org/0000-0001-7804-1740

REFERENCES

1. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2020;43(2):487-493.
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701.
3. Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010-2017. *Diabetes Obes Metab*. 2019;21(7):1576-1584.
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379.
5. Luo M, Tan KHX, Tan CS, Lim WY, Tai ES, Venkataraman K. Longitudinal trends in HbA1c patterns and association with outcomes: a systematic review. *Diabetes Metab Res Rev*. 2018;34(6):e3015.
6. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109-138.
7. Chang HY, Wahlqvist ML, Liu WL, et al. Management trajectories in the type 2 diabetes integrated delivery system project in Taiwan: accounting for behavioral therapy, nutrition education and therapeutics. *Asia Pac J Clin Nutr*. 2014;23(4):592-606.
8. Laiteerapong N, Karter AJ, Moffet HH, et al. Ten-year hemoglobin A1c trajectories and outcomes in type 2 diabetes mellitus: the Diabetes & Aging Study. *J Diabetes Complications*. 2017;31(1):94-100.
9. Rathmann W, Schwandt A, Hermann JM, et al. Distinct trajectories of HbA1c in newly diagnosed type 2 diabetes from the DPV registry using a longitudinal group-based modelling approach. *Diabet Med*. 2019;36(11):1468-1477.
10. Walraven I, Mast MR, Hoekstra T, et al. Distinct HbA1c trajectories in a type 2 diabetes cohort. *Acta Diabetol*. 2015;52(2):267-275.
11. Ji L, Bonnet F, Charbonnel B, et al. Towards an improved global understanding of treatment and outcomes in people with type 2 diabetes: rationale and methods of the DISCOVER observational study program. *J Diabetes Complications*. 2017;31(7):1188-1196.
12. Katakami N, Mita T, Takahara M, et al. Rationale and design for the J-DISCOVER study: DISCOVERing the treatment reality of type 2 diabetes in a real-world setting in Japan – a protocol. *Diabetes Ther*. 2018;9(1):165-175.
13. World Health Organization. *World Health Statistics*. Geneva: World Health Organisation; 2022. https://www.who.int/gho/publications/world_health_statistics/en/. Accessed September 20, 2022.
14. World Bank. *Classification of Country Income*. 2022.http://databank.worldbank.org/data/download/site-content/OGHIST.xls. Accessed September 20, 2022.
15. Kim SY. Determining the number of latent classes in single- and multiphase growth mixture models. *Struct Equ Modeling*. 2014;21(2):263-279.
16. Schwarz G. Estimating the dimension of a model. *Ann Stat*. 1978;6(2):461-464.
17. International Diabetes Federation. *Global Guideline for Type 2 Diabetes*. Brussels: International Diabetes Federation. 2012. https://www.

idf.org/e-library/guidelines/79-global-guideline-for-type-2-diabetes. Accessed September 20, 2022.
18. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. *Diabetes Obes Metab*. 2017;19(8):1155-1164.
19. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159(4):262-274.
20. Koye DN, Ling J, Dibato J, Khunti K, Montvida O, Paul SK. Temporal trend in young-onset type 2 diabetes – macrovascular and mortality risk: study of U.K. primary care electronic medical records. *Diabetes Care*. 2020;43(9):2208-2216.
21. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
22. Benoit SR, Fleming R, Philis-Tsimikas A, Ji M. Predictors of glycemic control among patients with type 2 diabetes: a longitudinal study. *BMC Public Health*. 2005;5:36.
23. Hemo B, Geva D, Shahar DR, Golan R, Heymann AD. Distinct trajectories in HbA1c are associated with different all-cause mortality and morbidity in newly diagnosed patients with type 2 diabetes. *Prim Care Diabetes*. 2020;14(5):413-419.

SUPPORTING INFORMATION

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

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