OBSERVATIONAL STUDY REPORT SYNOPSIS

DISCOVER: DISCOVERing treatment reality of type 2 diabetes in real world setting

Multi-country, multicentre, observational, prospective, longitudinal cohort study of patients with type 2 diabetes initiating a second-line glucose-lowering therapy to assess treatment patterns, clinical outcomes and patient-reported outcomes in 37 countries across different geographical regions, over 3-years of follow-up.

Milestones:	Completion of protocol	15 August 2014
	First patient in	30 December 2014
	Last patient in	21 August 2019
	Database lock	October 2019 for most DISCOVER countries with the exception of Canada (25 October 2019) and France (20 December 2019)
	Completion of study report	17 February 2021
Phase of development:	Not applicable	
Sponsor:	AstraZeneca	
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The DISCOVER study protocol was approved by the appropriate clinical research ethics committees in each participating country and by the relevant institutional review board at each site. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice and local regulations for clinical research in participating countries.

Background/rationale: In many geographical regions, data on the management and outcomes of patients with type 2 diabetes (T2D) are scarce or non-existent. Where data sources are available, they do not contain enough detail to capture the entire patient journey. The DISCOVER study aimed to provide real world data on treatment patterns and associated outcomes in patients with T2D in different geographical regions.

Objectives:

- Primary objective
  - To describe the disease management patterns and clinical outcomes over 3 years in patients with T2D initiating a second-line glucose-lowering therapy (add-on or switching), after a first-line oral treatment with a monotherapy, dual therapy or triple therapy
- Secondary objectives
  - To describe treatment response (changes in glycated haemoglobin [HbA_{1c}], body weight, blood pressure and lipid profile from baseline and achievement of HbA_{1c} targets) overall and according to patient characteristics and second-line glucose-lowering treatment class
  - To describe further treatment changes during follow-up (e.g. initiation of third-line or later-line glucose-lowering therapy, initiation of insulin, switch between glucose-lowering medications or dose changes)
  - To assess the incidence of microvascular complications (e.g. nephropathy, neuropathy, retinopathy and non-traumatic amputation)
  - To assess the incidence of macrovascular complications (e.g. cardiovascular death, heart failure [HF], myocardial infarction and stroke)
  - To assess the incidence of hypoglycaemic events, including hospitalizations for hypoglycaemia
  - To assess patient-reported health-related quality of life (HRQoL)
  - To describe healthcare resource utilization
  - To assess risk factors (disease, patient and setting characteristics) associated with microvascular complications, macrovascular complications, hypoglycaemic events, HRQoL and healthcare resource utilization during follow-up
  - To assess factors associated with treatment choices at baseline.

Study design: DISCOVER is an observational, prospective, longitudinal, 3-year study conducted in 37 countries.

Settings: Physicians invited to participate in the DISCOVER study were selected across different specialties, care settings and geographical regions to ensure that findings were

representative of the management of patients with T2D in each country. Overall, 637 sites participated in the DISCOVER study.

Data sources: In most countries, data were collected by investigators using an electronic case report form via a web-based data capture system. Data were saved immediately to a central database. In Denmark, France, Norway and Sweden, some study variables were extracted from existing primary care electronic medical record (EMR) databases. In addition, in, Sweden, and Norway, data extracted from EMRs were merged with data from mandatory national health registries (e.g. information on hospitalizations, prescribed drugs, and cause of death) to create a de-identified study database. In Canada, all patients were identified retrospectively, using an existing EMR database and baseline data were extracted from this; during follow-up a short electronic case report form was also used to collect data not routinely captured in the EMR database.

Study population: A total of 14 123 patients with T2D initiating a second-line glucose-lowering therapy following first-line treatment with an oral monotherapy, dual therapy or triple therapy were included in the study.

Inclusion criteria

- Female or male patients aged ≥ 18 years
- T2D diagnosis
- Initiation of second-line glucose-lowering therapy (add-on or switching) after first-line oral treatment with a monotherapy, dual therapy or triple therapy.

Exclusion criteria

- Type 1 diabetes diagnosis
- Patient was pregnant at the time of enrolment
- Patient initiating a dual therapy after having previously received two different lines of monotherapy before (e.g. metformin → sulfonylurea → sulfonylurea + add-on)
- Patient was undergoing chemotherapy or receiving oral or intravenous steroids
- Patient was on dialysis or had had a renal transplant
- Patient was using insulin or an injectable agent as first-line treatment
- Patient was taking herbal remedies/natural medicines as first-line treatment
- Participation in an interventional trial.

Statistical methods: Descriptive data for sites, physicians and patients were reported as numbers and percentages (using the total number of participants with available data as the denominator), means (with standard deviations [SDs]) or medians (with interquartile ranges [IQRs]), and were reported for the overall DISCOVER population, World Health Organization regions and other relevant subgroups. Factors associated with patient characteristics, treatment

choices and outcomes were assessed using various multivariable analyses adjusted for relevant variables. The large sample size of the DISCOVER study programme ensured that most descriptive data collected were sufficiently precise and meaningful at a country level. Data with a relatively low frequency were analysed at a global and/or regional level. Proportions of missing data were reported for each variable in individual analyses and, where appropriate, imputation methods were used to account for missing data. No formal assessment of bias was conducted but, when appropriate, potential sources of bias were discussed in individual publications. Statistical analyses were performed using SAS® software, version 9.4 or higher (SAS Institute, Cary, NC, USA) and IVEware (University of Michigan, Ann Arbor, MI, USA).

Results: Results presented here are summaries of DISCOVER peer-reviewed articles that reported global results relevant to the study objectives outlined above that were published at the time this study report was completed. Results of relevant analyses close to publication at the time of report completion are also summarized. A full list of peer-reviewed DISCOVER articles published at the time of completion of this report is provided at the end of this synopsis. Not all study objectives had been addressed at this stage as analysis and publication of DISCOVER results were ongoing at the time of finalisation of the study report.

Baseline characteristics

The overall DISCOVER population comprised 15 992 patients. Participants were mostly Asian (49.7%) or Caucasian (25.6%), and 54.2% (across-region range [ARR]: 37.7–58.6%) were men. The mean age of patients was 57.2 years (SD: 12.0; ARR: 53.1–61.9 years). Overall, 48.9% of patients were employed or self-employed and 81.0% had received secondary or higher education. The proportion of patients with health insurance varied greatly across regions; 21.3% (ARR: 4.0–67.8%) did not have health insurance while 62.5% (ARR: 11.7–91.3%) were covered by public health insurance.

The median time from diagnosis of T2D to initiation of second-line therapy was 4.1 years (IQR: 1.9–7.9 years). The median HbA_{1c} level was 8.0% (IQR: 7.2–9.1%) and the median fasting plasma glucose level was 8.8 mmol/L (IQR: 7.3–10.9 mmol/L). Overall, the mean body mass index (BMI) was 29.1 kg/m^2 (SD: 5.9 kg/m^2), the mean systolic blood pressure was 132.3 mmHg (SD: 16.5 mmHg) and the mean low-density lipoprotein cholesterol level was 109.2 mg/dL (SD: 38.4 mg/dL). Hypertension and hyperlipidaemia were reported in 51.1% and 45.6% of patients, respectively.

Most commonly prescribed first-line treatments were metformin monotherapy (55.6%; ARR: 42.5–83.6%) and combinations of metformin and a sulphonylurea (14.4%; ARR: 5.8–31.1%). The second-line therapies most often prescribed were combinations of metformin with a dipeptidyl peptidase-4 (DPP-4) inhibitor (23.5%) or with a sulphonylurea (20.9%). The main reason for initiating second-line therapy reported by investigators was lack of efficacy of first-line therapy (88.9%).

Glycaemic control at baseline.

Glycaemic control at baseline was assessed in 11 891 patients with baseline HbA_{1c} measurements. The mean HbA_{1c} level at baseline was 8.3% (SD: 1.7%). Mean HbA_{1c} levels varied across regions and were highest in the Eastern Mediterranean region and lowest in the Western Pacific region (8.7% and 7.9%, respectively). Factors associated with poor glycaemic control at the time of treatment intensification included younger age, male sex, being a current smoker and having a history of microvascular complications.

The association between socioeconomic status and poor glycaemic control was investigated in a separate analysis of 11 359 patients with baseline HbA_{1c} measurements. The three most important factors associated with having an $HbA_{1c} \geq 9.0\%$ were living in lower-middle-income country (compared with a high-income country), being younger than 50 years and having only primary or no formal education.

Prevalence and incidence of microvascular complications

The prevalence of microvascular complications at baseline were assessed in 15 992 patients from 38 countries. The overall crude prevalence of microvascular complications was 18.8% (ARR: 14.5–23.5%), and those reported most often were peripheral neuropathy (7.7%) and chronic kidney disease (CKD; 5.0%).

Baseline and follow-up data from the full 36 months of the study were used to assess changes in severity of CKD following initiation of second-line glucose-lowering therapy in 5835 patients with a baseline and at least one follow-up serum creatinine measurement. During follow-up, CKD progressed in 15.7% of patients.

Prevalence and incidence of macrovascular complications

The prevalence of macrovascular complications at baseline were assessed in 15 992 patients from 38 countries. The overall crude prevalence of macrovascular complications was 12.7% (ARR: 4.0–26.7%), and those reported most commonly were coronary artery disease (crude prevalence: 8.2%) and HF (crude prevalence: 3.3%).

Baseline and follow-up data from the full 36 months of the study were used to assess the incidence of and factors associated with the occurrence of HF in 14 057 patients from 36 countries. Overall, 2.1% of patients had a diagnosis of HF at enrolment. Among 9300 patients from 32 countries with follow-up data available, the incidence of HF was 2.6 cases per 1000 patient-years. Factors associated with an increased risk of incident HF included older age and a history of coronary artery disease or hypertension.

Prevalence and incidence of hypoglycaemic events

Baseline and follow-up data from the first 24 months of the study were used to assess the occurrence of major (reported in the year before the baseline visit or between study visits) and minor (reported in the 4 weeks preceding a visit) hypoglycaemic events in 13 695 patients from 36 countries. Overall, the proportion of patients reporting a hypoglycaemic event was 3.9% before baseline, 3.5% between baseline and 6 months, and 2.8% between both 6 and 12 months and 12 and 24 months.

Patient-reported outcomes

Baseline patient-reported HRQoL was assessed using 36-item Short-Form Health Survey version 2 (SF-36v2) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. PCS and MCS scores were available for 8284 and 8309 patients, respectively. Overall, the mean PCS score was 48.0 (SD: 7.8; ARR: 47.5–50.0) and the mean MCS score was 45.5 (SD: 10.4; ARR: 44.4–49.6). Factors associated with higher individual or combined PCS and MCS scores included male sex, younger age, lower BMI, having no history of macrovascular complications or CKD and having health insurance.

Factors associated with patient-reported fear of hypoglycaemia at baseline were assessed using results from the Hypoglycaemia Fear Survey-II (HFS-II). HFS-II behaviour and worry scores were available for 6014 and 6217 patients, respectively. Factors associated with lower individual or combined HFS-II behaviour and worry scores included male sex, younger age, lower BMI and having health insurance.

Factors associated with vascular complications

Factors associated with a history of microvascular or macrovascular complications at baseline were assessed in 15 992 patients from 38 countries. Factors positively associated with both microvascular and macrovascular complications included male sex and having a low level of education, longer duration of T2D or a history of minor or major hypoglycaemic events. Increased mean baseline HbA_{1c} levels were positively associated with microvascular complications and being either a former or current smoker was positively associated with macrovascular complications.

Factors associated with hypoglycaemic events

Factors associated with major and minor hypoglycaemic events were assessed in 13 695 patients from 36 countries using baseline and follow-up data from the first 24 months of the study. Factors positively associated with a report of a hypoglycaemic event before baseline and during follow-up included female sex, treatment at a university/teaching hospital (compared with a specialised diabetes care centre), the use of glucose monitoring equipment and having a history of macrovascular complications. Second-line treatment choice and region of residence also affected the odds of experiencing a hypoglycaemic event during follow-up.

Factors associated with baseline treatment choice

Patterns of first- and second-line treatment choices and factors associated with the second-line treatment choice were assessed in 14 668 patients from 37 countries. Overall, 57.9% of patients received metformin monotherapy as first-line treatment and 22.8% received metformin in combination with another treatment. At second line, the most common treatments were metformin with a DPP-4 inhibitor (25.1%) and metformin with a sulphonylurea (21.3%).

Factors associated with the choice of second-line therapy were assessed in study participants who received metformin monotherapy at first line. Factors associated with receiving a DPP-4 inhibitor with metformin rather than a sulphonylurea with metformin included having an HbA_{1c} level < 7.0% and not experiencing a minor hypoglycaemic event in the previous 4 weeks. Conversely, factors associated with receiving insulin with metformin rather than a sulphonylurea with metformin included having an HbA_{1c} level ≥ 9.0% and experiencing a major hypoglycaemic event in the previous year.

Of 11 837 patients who received metformin at first line on its own or as part of a combination therapy, 15.1% discontinued metformin when second-line therapy was initiated. Factors associated with metformin discontinuation included having CKD, older age and experience of a major hypoglycaemic event. The incidence of metformin discontinuation also varied across regions.

Conclusion: The DISCOVER study provides unprecedented global insights into the management of patients with T2D and associated outcomes after initiation of second-line glucose-lowering therapy. The results from DISCOVER indicate that management of T2D and its complications remains suboptimal in many patients worldwide, with differences in treatment and outcomes across regions. Strategies are needed to ensure that glucose levels are adequately monitored by routinely measuring HbA_{1c} levels and that glucose-lowering therapies are intensified in a timely fashion, as recommended by guidelines. More efforts are also needed to ensure that diabetes-related complications such as cardiovascular diseases are diagnosed early and managed efficiently, for example by prescribing glucose-lowering drugs with cardiovascular benefits to appropriate patients. However, such improvements to current clinical practice may be challenging in lower-income countries with limited healthcare resources.

Peer-reviewed DISCOVER study articles published at the time the report was completed

- 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;31:1188–96. doi: 10.1016/j.jdiacomp.2017.03.011.
- Kosiborod M, Gomes MB, Nicolucci A *et al*. Vascular complications in patients with type 2 diabetes: prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovasc Diabetol* 2018;17:150. doi: 10.1186/s12933-018-0787-8.
- Pintat S, Fenici P, Hammar N *et al*. Eligibility of patients with type 2 diabetes for sodium-glucose cotransporter 2 inhibitor cardiovascular outcomes trials: a global perspective from the DISCOVER study. *BMJ Open Diabetes Res Care* 2019;7:e000627. doi: 10.1136/bmjdrc-2018-000627.
- Gomes MB, Rathmann W, Charbonnel B *et al*. Treatment of type 2 diabetes mellitus worldwide: baseline patient characteristics in the global DISCOVER study. *Diabetes Res Clin Pract* 2019;151:20–32. doi: 10.1016/j.diabres.2019.03.024.
- Nicolucci A, Charbonnel B, Gomes MB *et al*. Treatment patterns and associated factors in 14 668 people with type 2 diabetes initiating a second-line therapy: results from the global DISCOVER study programme. *Diabetes Obes Metab* 2019;21:2474–85. doi: 10.1111/dom.13830.
- Khunti K, Chen H, Cid-Ruzafa J *et al*. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: results from the global DISCOVER study programme. *Diabetes Obes Metab* 2020;22:66–78. doi: 10.1111/dom.13866.
- Ling S, Sun P, Zaccardi F *et al*. Durability of glycaemic control in patients with type 2 diabetes after metformin failure: prognostic model derivation and validation using the DISCOVER study. *Diabetes Obes Metab* 2020;22:828–37. doi: 10.1111/dom.13966.
- Khunti K, Ji L, Medina J, Surmont F, Kosiborod M. Type 2 diabetes treatment and outcomes worldwide: a short review of the DISCOVER study programme. *Diabetes Obes Metab* 2019;21:2349–53. doi: 10.1111/dom.13817.
- Wang JS, Chen H, Tang F, Sheu WH. Associations of fear of hypoglycemia with second-line use of insulin secretagogues or insulin and subsequent glycemic control in patients with type 2 diabetes: an analysis using data from the DISCOVER study. *Int J Clin Pract* 2020:e13485. doi: 10.1111/ijcp.13485.
- Khunti K, Gomes MB, Kosiborod M *et al*. Metformin discontinuation in patients beginning second-line glucose-lowering therapy: results from the global observational DISCOVER study programme. *BMJ Open* 2020;10:e034613. doi: 10.1136/bmjopen-2019-034613.
- Rathmann W, Charbonnel B, Gomes MB *et al*. Socioeconomic factors associated with hypoglycaemia in patients starting second-line glucose-lowering therapy: the DISCOVER study. *Diabetes Res Clin Pract* 2020;165:108250. doi: 10.1016/j.diabres.2020.108250.

- Patel KK, Gomes MB, Charbonnel B *et al*. Global patterns of comprehensive cardiovascular risk factor control in patients with type 2 diabetes mellitus: insights from the DISCOVER study. *Diabetes Obes Metab* 2021;23:39–48. doi: 10.1111/dom.14180.