Type 2 diabetes treatment and outcomes worldwide: A short review of the DISCOVER study programme

Kamlesh Khunti MD,^{1*} Linong Ji MD,² Jesús Medina PhD,³ Filip Surmont MD,⁴ Mikhail Kosiborod MD^{5,6,7}

¹University of Leicester, Leicester, UK; ²Peking University People's Hospital, Beijing, China;

³AstraZeneca, Madrid, Spain; ⁴AstraZeneca, Luton, UK; ⁵Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; ⁶University of Missouri, Kansas City, MO, USA; ⁷The George Institute for Global Health, Newtown, Australia

Correspondence: Kamlesh Khunti, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, UK. Tel: +44 (0)1162 548 005. Email: kk22@leicester.ac.uk

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/dom.13817](https://doi.org/10.1111/dom.13817)

ABSTRACT (176 words)

The global burden of type 2 diabetes (T2D) is increasing, indicating an urgent need for improved disease prevention and management strategies. Contemporary, global, real-world data, which are collected in a consistent way, on the characteristics, treatment and outcomes of people with T2D are lacking, particularly in low- and middle-income countries where disease burden is increasing most rapidly. The DISCOVER study programme (ClinicalTrials.gov identifiers: NCT02322762 and NCT02226822) is a global, prospective, 3-year programme of observational research, which has been designed to fill this knowledge gap. DISCOVER is being conducted in 38 countries across six continents, including several lower-middle- and upper-middle-income countries where patients have rarely or never been studied previously. A total of 15 992 people with T2D who had initiated a second-line glucose-lowering therapy have been recruited. Data being collected include information on demographics, clinical and treatment characteristics, socio-economic status, clinical outcomes, and patient-reported outcomes. Findings from DISCOVER will provide unique insights into current patterns of T2D care worldwide, which should contribute to informing clinical guidelines and health policy, and may help to improve patient care.

Keywords: epidemiology, observational, outcomes, treatment, type 2 diabetes

MAIN ARTICLE

1. Type 2 diabetes: a growing health challenge

The prevalence of diabetes, of which type 2 diabetes (T2D) constitutes the majority of cases, is increasing rapidly worldwide.¹⁻³ T2D imparts a substantial burden on healthcare systems, owing to the need for ongoing disease monitoring and the management of long-term complications. This burden is greatest in low- and middle-income countries where approximately 80% of people with T2D reside.² Despite treatment advances in the past two decades, the available evidence suggests that the attainment of adequate glycaemic control, and the management of additional risk factors for T2D-related complications, remains suboptimal in a substantial proportion of people with T2D worldwide.⁴⁻⁶ Moreover, global healthcare expenditure on T2D-related complications, such as cardiovascular and renal disease, is high and increasing.² These findings suggest that the current strategies for disease management are insufficient.

These data are alarming and indicate an urgent need for effective interventions to prevent new cases of T2D, reduce the development of complications, and to improve the care of people with established disease worldwide. However, data on the management and clinical outcomes of patients with T2D in real-world clinical practice, collected in a comprehensive and consistent way, are either lacking or scarce in many countries. This is particularly true in low- and middle-income countries where cultural factors and financial limitations may pose additional challenges to the management of people with T2D.

2. The global DISCOVER study

2.1. Design and rationale

The DISCOVER study programme (ClinicalTrials.gov identifiers: NCT02322762 and NCT02226822 [J-DISCOVER, in Japan])^{7,8} was set up to address the knowledge gaps in the management and clinical outcomes of people with T2D. The overarching aim of the programme is to describe patient characteristics, evolution of disease management patterns and clinical outcomes over 3 years in people with T2D who are initiating a second-line glucose-lowering therapy in a real-world setting. These patients were chosen as the focus of the study because of the diversity of treatment options recommended at this stage of the disease. Full inclusion and

exclusion criteria for the study are detailed in **Table 1**. DISCOVER is a non-interventional study and does not focus on any specific drugs or drug classes. In total, 15 992 participants in 38 countries across six continents have been enrolled (**Figure 1**) and follow-up will complete in August 2019.

2.2. Countries and representativeness

DISCOVER aims to provide a global picture of the management of patients with type 2 diabetes, and countries from several world regions were included, with a focus on countries from which limited or no data are currently available. For practical reasons, included countries had to be limited to a manageable number, and the feasibility of conducting observational research in individual countries was considered during the selection process. Patients from China, India and Japan account for over a third of the DISCOVER population, owing partly to the large population sizes of these countries. Approximately half of the patients enrolled in DISCOVER reside in a lower- or upper-middle income country (**Figure 1**), which will provide an opportunity to evaluate the impact of country income on treatment patterns and clinical outcomes in patients with T2D.

In each country included in DISCOVER, efforts have been made to achieve as diverse and as representative a study population as possible while acknowledging the inherent difficulty of achieving a truly representative sample of sites and patients in observational studies, especially in countries where few data on disease prevalence and management currently exist. Prior to the selection of the study sites, data relating to the management of T2D (such as the types of practices visited by people with T2D, the specialties of the treating physicians, the geographical and rural or urban distribution of practices, and the source of funding of practices) were collated for each country from peer-reviewed articles, reports published by international healthcare organizations and insights from national experts. A list of sites that matched these characteristics as closely as possible was then produced for each country, and these sites were invited to participate in DISCOVER.⁹ Approximately one third of the invited sites, 778 sites in total (a breakdown of sites by region and country is available in **Figure 1**), were able to take part and

subsequently recruited patients into the study.¹⁰ The resulting DISCOVER population was heterogeneous and, in most countries, included patients from clinical settings with diverse characteristics.^{9, 10}

2.3 Data collection

The scope of DISCOVER is ambitious and holistic, with the goal of obtaining as detailed a picture as possible of the management of T2D across the globe, and to highlight specific areas for improvement in the included countries that might also be applicable to other countries. Data on physiological parameters (including height, weight and seated blood pressure), laboratory test results (including glycated haemoglobin [HbA_{1c}] and fasting plasma glucose measurements), glucose-lowering treatments (including reasons for treatment selection), socio-economic and demographic characteristics, and clinical and patient-reported outcomes (PROs) are collected by clinicians during routine visits.^{7, 8} A mixed methodology is used for data collection: investigators use an electronic (or paper) case report form to record patient clinical data at study visits and information from patient medical records is automatically extracted in countries where this is possible (Canada, Denmark, France, Norway and Sweden). A standardized case report form is used across all sites and countries to ensure the comparability of the data across different countries and regions. Questionnaires, including those that examine quality of life (36-item Short-Form Health Survey version 2 [SF-36v2]), fear of hypoglycaemia (Hypoglycaemia Fear Survey-II [HFS-II]), lifestyle and avoidance of treatment due to cost, are used to record PROs. In order to reflect routine clinical practice in each country, data collection was not mandatory for all variables, with the exception of variables used to assess eligibility at the enrolment visit and key information such as the dates of diabetes diagnosis and initiation of second-line therapy.

2.4. Key findings to date

Descriptive baseline data have been reported for the overall DISCOVER population (including participants in DISCOVER and in J-DISCOVER) and by region, based on the World Health Organization classification categories (**Figure 1**). Participants in DISCOVER were mostly Asian (49.7%) or Caucasian (25.6%) and more than 50% were male (54.2%; across-region range [ARR]: 37.7–58.6%). The mean age at initiation of second-line therapy was 57.2 years (standard

deviation: 12.0 years; ARR: 53.1–61.9 years); 21.3% of patients (ARR: 4.0–67.8%) did not have health insurance and more than 80% of patients (ARR: 68.1–88.9%) had received secondary or higher education.¹⁰ Globally, glycaemic levels were much higher than target among people with T2D at initiation of second-line therapy. The mean HbA_{1c} level was 8.3%, with an ARR of 8.1–8.7%. Notably, a large proportion of patients in lower-middle- and upper-middle-income countries had very high HbA_{1c} levels ($\geq 9.0\%$). In nine countries, eight of which had middle-income economies, HbA_{1c} levels were missing for more than 30% of participants. These findings suggest that HbA_{1c} levels are not measured routinely in all countries, although other reasons such as a lack of recording of HbA_{1c} data by physicians may also be responsible.¹¹ Patients in DISCOVER also had a high burden of vascular complications at baseline: the age- and sex-standardized prevalence of microvascular and macrovascular complications was 17.9% (ARR: 14.2–20.4%) and 9.2% (ARR: 4.1–18.8%), respectively, which is concerning given that these patients are relatively early in the disease (median time since diagnosis of T2D at baseline was 4.1 years).¹² Other important investigations, including measurements of estimated glomerular filtration rate, urine albumin-to-creatinine ratio and lipid parameters, were carried out even less frequently than HbA_{1c} level measurement, and the use of preventive treatments, such as statins, was lower than expected in this patient population.¹²

These early findings from the DISCOVER study indicate a need for more consistent monitoring and management of glycaemic levels, the use of effective preventive therapies, increased surveillance for complications and better control of risk factors among patients with T2D in clinical practice. Follow-up data from DISCOVER will build on these baseline findings and should offer insights into the progression of T2D following initiation of second-line therapy. Other notable findings include preliminary PRO data, which indicate important differences in access to appropriate diabetes healthcare between countries and regions. Evaluation of these data, together with data on clinical outcomes, will provide valuable insights into how access to treatment affects the care of patients with T2D across the globe.

2.5. Future directions for the DISCOVER study

Data collected in the DISCOVER study have already substantially contributed to our understanding of the global management of people with T2D. To build on the success of the

study, the DISCOVER Global Registry (ClinicalTrials.gov identifier: NCT03549754),¹³ designed primarily as a quality improvement initiative, has been set up as a long-term, large-scale registry for collecting longitudinal, real-world data on disease management and associated outcomes in people with T2D from routine clinical settings worldwide. The scope of the registry is intended to be even broader than that of the DISCOVER study with the inclusion of more countries.¹³ Participation in the registry is voluntary and entails no cost to physicians. To date, almost 2000 patients from 11 countries have been enrolled in the registry, and a further 31 countries are actively engaged in the initiative.

2.6. Strengths and limitations of the DISCOVER study programme

Major strengths of DISCOVER are the large number of patients enrolled and the long follow-up period, which will provide valuable data on the association between second-line treatment selection and clinical outcomes.^{7, 10} DISCOVER is limited by issues inherent to observational research, including the potential for patient selection bias. The DISCOVER population contains a disproportionate number of patients with secondary or higher education, which might reflect a selection bias for patients of higher socioeconomic status who would be expected to receive a higher quality of care than more disadvantaged patients. Thus, findings from DISCOVER may over-estimate the quality of diabetes care and must be interpreted carefully. Completion of case report forms and electronic medical records rely on accurate and diligent recording of information by physicians. Moreover, the lack of mandatory variables in data collection introduces the possibility of missing data in analyses, although this may also provide important information on which variables are collected in routine clinical practice in participating countries.

3.0. Summary and conclusions

The global burden posed by T2D is substantial; addressing this major public health threat is an urgent priority. The generation of longitudinal real-world data is crucial to better understand patient characteristics, treatment patterns and outcomes, as well as temporal trends worldwide. Findings from the global DISCOVER study programme, and subsequently from the DISCOVER

Global Registry, will be instrumental in providing evidence that was not previously available regarding the management of people with T2D worldwide, with the ultimate goal of improving patient care and outcomes.

ACKNOWLEDGEMENTS

Medical writing support was provided by Lucy Ambrose, DPhil, of Oxford PharmaGenesis, Oxford, UK, and was funded by AstraZeneca.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this manuscript and to the review of intermediate drafts. They all approved the final version before submission.

CONFLICT OF INTEREST

KK, MK and LJ are members of the DISCOVER Scientific Committee and received support from AstraZeneca to attend DISCOVER planning and update meetings. JM and FS are employees of AstraZeneca. In addition, KK has received funds from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi, and research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi, and also acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands and the National Institute of Health Research Leicester Biomedical Research Centre. MK has received funds from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Glytec Systems, Intarcia, Janssen, Merck, Novo Nordisk, Novartis and Sanofi, and research support from AstraZeneca and Boehringer Ingelheim. LJ has received funds from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi and Takeda, and research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche and Sanofi.

FUNDING INFORMATION

The DISCOVER study programme is funded by AstraZeneca. DISCOVER is a non-interventional study, and no drugs were supplied or funded. Further information can be found at www.discoverdiabetes.com.

REFERENCES

1. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *The Lancet*. 2016;387:1513–1530.
2. International Diabetes Federation. IDF Diabetes Atlas, Eighth edition. Available at <https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html>. Accessed January 4, 2019.
3. World Health Organization. Global report on diabetes. Available at <https://www.who.int/diabetes/global-report/en/>. Accessed January 4, 2019.
4. Edelman SV, Polonsky WH. Type 2 diabetes in the real world: the elusive nature of glycemic control. *Diabetes Care*. 2017;40:1425–1432.
5. Khunti K, Ceriello A, Cos X, De Block C. Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: A meta-analysis. *Diabetes Res Clin Pract*. 2018;137:137–148.
6. Blonde L, Aschner P, Bailey C, Ji L, Leiter LA, Matthaai S, Global Partnership for Effective Diabetes M. Gaps and barriers in the control of blood glucose in people with type 2 diabetes. *Diab Vasc Dis Res*. 2017;14:172–183.
7. Ji L, Bonnet F, Charbonnel B, Gomes MB, Kosiborod M, Khunti K, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Shimomura I, Watada H, Fenici P, Hammar N, Hashigami K, Macaraeg G, Surmont F, Medina J. 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;31:1188–1196.
8. Katakami N, Mita T, Takahara M, Hashigami K, Kawashima M, Shimomura I, Watada H, group JDs. 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;9:165–175.
9. Rathmann W, Medina J, Kosiborod M, Nicolucci A, Cid-Ruzafa J, Fenici P, Hammar N, Surmont F, Khunti K. The DISCOVER study: diversity of sites, physicians, and patients. *Pharmacoepidemiol Drug Saf*. 2018;27:228.
10. Gomes MB, Rathmann W, Charbonnel B, Khunti K, Kosiborod M, Nicolucci A, Pocock SJ, Shestakova MV, Shimomura I, Tang F, Watada H, Chen H, Cid-Ruzafa J, Fenici P, Hammar N, Surmont F, Ji L, investigators D. Treatment of type 2 diabetes mellitus worldwide: Baseline

patient characteristics in the global DISCOVER study. *Diabetes Res Clin Pract.* 2019;151:20-32.

11. Khunti K, Arya N, Cid-Ruzafa J, Fenici P, Gomes MB, Hammar N, Ji L, Kamal S, Kosiborod M, Pocock S, Shestakova MV, Shimomura I, Tang F, Watada H, Nicolucci A. Glycaemic control in 14,005 patients with type 2 diabetes initiating second-line therapy in 36 countries: the DISCOVER study [poster]. Presented at the 77th Scientific Sessions of the American Diabetes Association (ADA), June 9–13, 2017, San Diego, CA, USA.

12. Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Watada H, Shimomura I, Chen H, Cid-Ruzafa J, Fenici P, Hammar N, Surmont F, Tang F, Khunti K, investigators D. Vascular complications in patients with type 2 diabetes: prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovasc Diabetol.* 2018;17:150.

13. Clinicaltrials.gov. DISCOVER Global Registry. Available at <https://clinicalTrials.gov/ct2/show/NCT03549754>. Accessed January 15, 2019.

TABLES

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
<ul style="list-style-type: none"> • Diagnosis of T2D • Age ≥ 18 years[†] • Initiating a second-line therapy (add-on or switching) after a first-line oral treatment with monotherapy, dual therapy, or triple therapy[‡] • Provision of written informed consent
Exclusion criteria
<ul style="list-style-type: none"> • Type 1 diabetes • Pregnancy • Initiation of dual therapy after having previously received two different lines of monotherapy (e.g. initiation of a combination of a sulphonylurea and a DPP-4 inhibitor after successive metformin monotherapy and sulphonylurea monotherapy) • Current treatment with chemotherapy or oral or intravenous steroids • Undergoing dialysis or has had a renal transplant • First-line treatment was insulin or an injectable agent[‡] • First-line treatment was herbal remedies/natural medicines alone • Participation in an interventional trial • Condition/circumstance which, in the opinion of the investigator, could significantly compromise the 3-year follow-up (e.g. life-threatening comorbidities, tourist, non-native speaker or does not understand the local language where interpreter services are not reliably available, psychiatric disturbances, dementia, alcohol or drug abuse) • Not willing to sign the informed consent form

[†] ≥ 20 years in Japan. [‡]In Japan, only patients using an oral monotherapy as first-line treatment were included. [‡]Patients who received short-term initial treatment with insulin followed by oral therapy were eligible if the treatment with insulin lasted no more than 2 weeks and occurred at least 6 months before initiation of second-line therapy. In such cases, insulin was considered not as a first-line treatment, but as an acute treatment to lower glycaemic levels quickly before starting regular treatment.

DPP-4, dipeptidyl peptidase-4; T2D, type 2 diabetes.

FIGURES

Figure 1. Countries (coloured according to income) participating in the DISCOVER study programme, the number of patients enrolled in each country and the number of participating study sites per country.

- Lower-middle income (GNI per capita = \$1006–3955)
- Upper-middle income (GNI per capita = \$3956–12 235)
- High income (GNI per capita > \$12 235)

Africa Algeria (n = 293) (14 sites) South Africa (n = 519) (18 sites)	Europe Austria (n = 209) (12 sites) Czech Republic (n = 454) (17 sites) Denmark (n = 41) (9 sites) France (n = 264) (110 sites) Italy (n = 361) (11 sites) Netherlands (n = 162) (37 sites) Norway (n = 79) (18 sites) Poland (n = 324) (13 sites) Russia (n = 588) (17 sites) Spain (n = 225) (13 sites) Sweden (n = 236) (33 sites) Turkey (n = 536) (18 sites)	Eastern Mediterranean Bahrain (n = 70) (1 site) Egypt (n = 583) (38 sites) Jordan (n = 271) (13 sites) Kuwait (n = 51) (2 sites) Lebanon (n = 348) (15 sites) Oman (n = 31) (1 site) Saudi Arabia (n = 519) (9 sites) Tunisia (n = 214) (15 sites) United Arab Emirates (n = 95) (8 sites)	Western Pacific Australia (n = 167) (14 sites) China (n = 1293) (31 sites) Japan (n = 1869) (140 sites) Malaysia (n = 334) (14 sites) South Korea (n = 236) (13 sites) Taiwan (n = 258) (13 sites)
Americas Argentina (n = 299) (14 sites) Brazil (n = 437) (22 sites) Canada (n = 386) (1 site) Colombia (n = 206) (10 sites) Costa Rica (n = 127) (6 sites) Mexico (n = 455) (15 sites) Panama (n = 92) (2 sites)			
South-East Asia India (n = 3139) (28 sites) Indonesia (n = 221) (13 sites)			

Countries participating in DISCOVER are divided into regions according to World Health Organization (WHO) categories. Income data are from the World Bank. Available at:

<http://databank.worldbank.org/data/download/site-content/OGHIST.xls>. Accessed 24 April 2019.

GNI, gross national income.

- Lower-middle income (GNI per capita = \$1006–3955)
- Upper-middle income (GNI per capita = \$3956–12 235)
- High income (GNI per capita > \$12 235)

Africa

Algeria (n = 293)
(14 sites)
South Africa (n = 519)
(18 sites)

Americas

Argentina (n = 299)
(14 sites)
Brazil (n = 437)
(22 sites)
Canada (n = 386)
(1 site)
Colombia (n = 206)
(10 sites)
Costa Rica (n = 127)
(6 sites)
Mexico (n = 455)
(15 sites)
Panama (n = 92)
(2 sites)

South-East Asia

India (n = 3139)
(28 sites)
Indonesia (n = 221)
(13 sites)

Europe

Austria (n = 209)
(12 sites)
Czech Republic (n = 454)
(17 sites)
Denmark (n = 41)
(9 sites)
France (n = 264)
(110 sites)
Italy (n = 361)
(11 sites)
Netherlands (n = 162)
(37 sites)
Norway (n = 79)
(18 sites)
Poland (n = 324)
(13 sites)
Russia (n = 588)
(17 sites)
Spain (n = 225)
(13 sites)
Sweden (n = 236)
(33 sites)
Turkey (n = 536)
(18 sites)

Eastern Mediterranean

Bahrain (n = 70)
(1 site)
Egypt (n = 583)
(38 sites)
Jordan (n = 271)
(13 sites)
Kuwait (n = 51)
(2 sites)
Lebanon (n = 348)
(15 sites)
Oman (n = 31)
(1 site)
Saudi Arabia (n = 519)
(9 sites)
Tunisia (n = 214)
(15 sites)
United Arab Emirates (n = 95)
(8 sites)

Western Pacific

Australia (n = 167)
(14 sites)
China (n = 1293)
(31 sites)
Japan (n = 1869)
(140 sites)
Malaysia (n = 334)
(14 sites)
South Korea (n = 236)
(13 sites)
Taiwan (n = 258)
(13 sites)

dom_13817_dom-19-0283-ra-file002.eps

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Khunti, K;Ji, L;Medina, J;Surmont, F;Kosiborod, M

Title:

Type 2 diabetes treatment and outcomes worldwide: A short review of the DISCOVER study programme

Date:

2019-07-14

Citation:

Khunti, K., Ji, L., Medina, J., Surmont, F. & Kosiborod, M. (2019). Type 2 diabetes treatment and outcomes worldwide: A short review of the DISCOVER study programme. DIABETES OBESITY & METABOLISM, 21 (11), pp.2349-2353. <https://doi.org/10.1111/dom.13817>.

Persistent Link:

<http://hdl.handle.net/11343/286082>