Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Treatment of type 2 diabetes mellitus worldwide: Baseline patient characteristics in the global DISCOVER study

Marilia B. Gomes[a,*], *Wolfgang Rathmann*[b], *Bernard Charbonnel*[c], *Kamlesh Khunti*[d], *Mikhail Kosiborod*[e,f], *Antonio Nicolucci*[g], *Stuart J. Pocock*[h], *Marina V. Shestakova*[i], *Iichiro Shimomura*[j], *Fengming Tang*[e], *Hirotaka Watada*[k], *Hungta Chen*[l], *Javier Cid-Ruzafa*[m], *Peter Fenici*[n], *Niklas Hammar*[o], *Filip Surmont*[p], *Linong Ji*[q], *on behalf of the DISCOVER investigators*

[a] *Rio de Janeiro State University, Rio de Janeiro, Brazil*
[b] *German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany*
[c] *University of Nantes, Nantes, France*
[d] *University of Leicester, Leicester, UK*
[e] *Saint Luke's Mid America Heart Institute, Kansas City, MO, USA*
[f] *University of Missouri, Kansas City, MO, USA*
[g] *Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy*
[h] *London School of Hygiene and Tropical Medicine, London, UK*
[i] *Endocrinology Research Center, Diabetes Institute, Moscow, Russian Federation*
[j] *Graduate School of Medicine, Osaka University, Osaka, Japan*
[k] *Graduate School of Medicine, Juntendo University, Tokyo, Japan*
[l] *AstraZeneca, Gaithersburg, MD, USA*
[m] *Evidera, Barcelona, Spain*
[n] *AstraZeneca, Cambridge, UK*
[o] *Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*
[p] *AstraZeneca, Luton, UK*
[q] *Peking University People's Hospital, Beijing, PR China*

ARTICLE INFO

Article history:
Received 13 December 2018
Received in revised form
1 March 2019
Accepted 14 March 2019
Available online 20 March 2019

ABSTRACT

Aims: To describe the characteristics and treatment of patients with type 2 diabetes mellitus initiating a second-line glucose-lowering therapy in the global DISCOVER study programme. *Methods:* DISCOVER comprises two similar 3-year prospective observational studies (NCT02322762 and NCT02226822), involving 15,992 patients initiating a second-line glucose-lowering therapy in 38 countries across six regions (Africa, Americas, South-East Asia, Eastern Mediterranean, Europe and Western Pacific).

* Corresponding author at: Department of Medicine, Diabetes Unit, State University of Rio de Janeiro, Av 28 de Setembro 77, Rio de Janeiro CEP20555-030, Brazil.

E-mail addresses: mariliabgomes@gmail.com (M.B. Gomes), wolfgang.rathmann@ddz.de (W. Rathmann), Bernard.Charbonnel@univ-nantes.fr (B. Charbonnel), kk22@leicester.ac.uk (K. Khunti), mkosiborod@saint-lukes.org (M. Kosiborod), nicolucci@coresearch.it (A. Nicolucci), Stuart.Pocock@lshtm.ac.uk (S.J. Pocock), ftang@saint-lukes.org (F. Tang), Hungta.Chen@astrazeneca.com (H. Chen), Javier.Cid@evidera.com (J. Cid-Ruzafa), Peter.Fenici@astrazeneca.com (P. Fenici), Niklas.Hammar@ki.se (N. Hammar), Filip.Surmont@astrazeneca.com (F. Surmont), jiln@bjmu.edu.cn (L. Ji).

https://doi.org/10.1016/j.diabres.2019.03.024

Keywords:
Type 2 diabetes mellitus
Observational study
Clinical practice

Results: Overall, 54.2% of patients were male (across region range [ARR]: 37.7–58.6%). At baseline, mean age and time since diagnosis of type 2 diabetes mellitus were 57.2 (ARR: 53.1–61.9) and 5.6 (ARR: 4.6–6.9) years, respectively. Median glycated haemoglobin (HbA_{1c}) was 63.9 mmol/mol (8.0%; ARR: 7.6–8.3%). Microvascular and macrovascular complications were reported in 18.9% (ARR: 14.5–23.5%) and 12.7% (ARR: 5.0–26.6%) of patients, respectively. First-line treatments were mostly metformin monotherapy (55.6%; ARR: 42.5–83.6%) and combinations of metformin with a sulfonylurea (14.4%; ARR: 5.8–31.1%). The most commonly prescribed second-line therapies were combinations of metformin with a dipeptidyl peptidase-4 inhibitor (23.5%; ARR: 2.2–29.6%) or a sulfonylurea (20.9%; ARR: 13.6–57.1%).
Conclusions: DISCOVER demonstrates considerable global variation in the treatment of type 2 diabetes mellitus, and a need for more aggressive risk factor control.

1. Introduction

An estimated 425 million adults had diabetes worldwide in 2017, and this number is predicted to rise to 629 million by 2045 [1]. Type 2 diabetes mellitus accounts for approximately 90% of cases. This increase in the prevalence of type 2 diabetes mellitus will result in a large economic and social burden, and is likely to occur predominantly in low- to middle-income countries, where approximately three-quarters of people with type 2 diabetes mellitus live [1]. Cross-sectional studies have clearly demonstrated that glycaemic control and management of comorbidities are suboptimal in both high-income [2,3] and low- to medium-income countries [4,5]. In many regions, however, longitudinal data on glucose-lowering treatment patterns and associated outcomes are scarce or non-existent.

Sustained glycaemic control, along with the management of comorbidities such as hypertension and hyperlipidaemia, remains a key component of the effective treatment of patients with type 2 diabetes mellitus. Clinical guidelines recommend the use of metformin, in conjunction with lifestyle changes, as the first-line glucose-lowering therapy [6–11]. However, when metformin monotherapy fails to control glycated haemoglobin (HbA_{1c}) levels, there is no consensus on optimal subsequent treatments, and guidelines recommend an individualized and patient-centred approach to drug selection based on patient characteristics including age, duration of diabetes, presence of comorbidities and risk of adverse events including hypoglycaemia and weight gain [8]. Beyond glycaemic control, recent large cardiovascular outcome trials [12–15] and a large multinational observational study [16] have shown that some glucose-lowering therapies significantly reduce the risk of cardiovascular complications in patients with high cardiovascular risk, suggesting that treatment patterns may have a significant effect on the development of diabetes-related complications.

DISCOVER is a programme of observational research involving 15,992 patients with type 2 diabetes mellitus moving from a first-line to a second-line glucose-lowering therapy in 38 countries across six continents. First- and second-line treatments could be mono or combination therapies, and patients who were prescribed an injectable agent as first-line therapy were excluded. The aim of the study is to provide a global picture of type 2 diabetes mellitus treatment and clinical outcomes, including in many rarely studied low- and middle-income countries. The use of standardized data collection methodology allows comparison between regions and countries. Patients initiating second-line therapy were chosen as the focus of the study because of the diversity of treatment options recommended at this stage of disease progression. The aim of the present analysis was to describe the baseline characteristics and treatment of patients enrolled in the study, and to compare these characteristics between regions. The sampling methodology and diversity of clinical sites from which patients have been recruited is also described.

2. Subjects, materials and methods

The design and methodology of the DISCOVER study programme have been reported in detail elsewhere [17,18] and are briefly summarized below.

2.1. *Study design*

The DISCOVER study programme comprises two similar, 3-year, prospective, observational (non-interventional) studies conducted simultaneously in 38 countries: DISCOVER (NCT02322762) in 37 countries (Algeria, Argentina, Australia, Austria, Bahrain, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, France, India, Indonesia, Italy, Jordan, Kuwait, Lebanon, Malaysia, Mexico, the Netherlands, Norway, Oman, Panama, Poland, Russia, Saudi Arabia, South Africa, South Korea, Spain, Sweden, Taiwan, Tunisia, Turkey and the United Arab Emirates), and J-DISCOVER (NCT02226822) in Japan. The study protocol was approved by the appropriate clinical research ethics committees in each country, and the relevant institutional review boards at each site. The protocol complies with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice and the local regulations for clinical research.

2.2. *Site and investigator selection*

The characteristics of physicians and practices involved in the management of patients with type 2 diabetes mellitus

in each country were explored before starting the study, in order to recruit as representative as possible a selection of physicians and patients. Information was collated from peer-reviewed articles, reports published by international organizations such as the World Health Organization, and from local diabetes experts who acted as coordinating investigators in each country. Healthcare system characteristics considered included the proportions of different types of health care provider (primary care physicians, diabetologists, endocrinologists, cardiologists and other specialists) and practices (primary care centres, specialized diabetes centres and different types of hospitals) treating patients with type 2 diabetes mellitus in each country, as well as location (urban vs. rural and geographical distribution within a country) and funding source (public, private and mixed). A list of candidate sites that would match these characteristics as closely as possible was then established for each country, and all of these sites were invited to participate in the study. Among the invited sites, approximately one-third were subsequently able to take part and recruited patients into the study.

2.3. *Patient recruitment*

Inclusion and exclusion criteria were kept to a minimum to reflect routine clinical practice (Supplementary Table 1). Patients with type 2 diabetes mellitus initiating a second-line glucose-lowering treatment (add-on or switching) after first-line oral treatment with a monotherapy, dual therapy or triple therapy were invited by their physician to participate in the study. Patients using an injectable agent (ie, insulin or a glucagon-like peptide-1 [GLP-1] receptor agonist) as first-line therapy were excluded from the study, as they are likely to represent a group of patients with a more severe disease profile who should be studied separately. The study protocol stated that investigating physicians should invite consecutive eligible patients to take part in the study. All participating patients provided signed informed consent.

2.4. *Data collection*

Data at baseline (initiation of second-line therapy) were collected using a standardized electronic case report form, and were transferred to a central database via a web-based data capture system. Some data were extracted from existing electronic medical records and health registries in Canada, Denmark, France, Norway and Sweden; an abbreviated electronic case report form was used in these countries. Variables collected at baseline included: investigator characteristics; patient socio-demographics (including information on education level, working status and health insurance coverage); clinical data including laboratory test results; first-line glucose-lowering therapy (treatments received by patients before study baseline); second-line glucose-lowering therapy (treatments prescribed at study baseline); reason(s) for the change in glucose-lowering therapy; HbA_{1c} target set by the physician at the time of therapy change; comorbidities (including existing diabetes-related microvascular and macrovascular complications); and co-medications. In line with the observational nature of the study, clinical variables such as HbA_{1c} and fasting plasma glucose (FPG) were measured in accordance with routine clinical practice at each site. Diagnosis and classification of complications relied on the judgement of investigators and there was no external independent adjudication of events.

2.5. *Regional classification*

Descriptive baseline data are reported for the overall DISCOVER population and by regions, based on the World Health Organization regional classification (Supplementary Fig. 1): Africa (Algeria and South Africa); the Americas (Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico and Panama); South-East Asia (India and Indonesia); Europe (Austria, Czech Republic, Denmark, France, Italy, the 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).

2.6. *Statistical analysis*

Categorical data are presented as numbers and percentages. Mean (standard deviation [SD]) values, median (interquartile range [IQR]) values and across-region ranges (ARRs) are reported, when appropriate. Statistical analyses were carried out using the SAS statistical software system (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. *Site characteristics*

A total of 778 sites in 38 countries are participating in the study programme (Table 1). Approximately half of all sites are primary care centres (50.5%; ARR: 15.6–67.7%) and the majority are located in urban areas (72.5%; ARR: 51.6–100.0%). In Europe and the Western Pacific region, primary care centres are most common (67.7% and 51.3%, respectively); hospitals and specialized diabetes centres are most common in other regions (37.3–60.0%). Overall, the proportions of sites publicly and privately funded are 37.1% and 61.8%, respectively, with variability between regions; 1.0% of sites are both privately and publicly funded. Overall, investigators are mainly endocrinologists or diabetologists (45.7%), primary care physicians (33.7%) or internists (14.8%). However, the distribution of specialities also varies across regions. Primary care physicians are more common in Africa (50.0%) and Europe (71.8%) than in other regions, where investigators are predominantly specialists (endocrinologists, diabetologists or internists; 78.1–96.1%).

Where possible, we compared the characteristics of included sites and investigators to the information collated before the start of the study for each country. The results of this comparison are shown in Supplementary Fig. 2. Overall, some over-representation of sites from urban locations and specialist care centres was identified.

Table 1 – Characteristics of sites participating in the DISCOVER study.

	Total (N = 778)	Africa (n = 32)	Americas (n = 70)	South-East Asia (n = 41)	Europe (n = 308)	Eastern Mediterranean (n = 102)	Western Pacific (n = 225)
Type of centre							
Primary care centre	387 (50.5)	5 (15.6)	19 (27.5)	9 (22.5)	203 (67.7)	36 (35.3)	115 (51.3)
General/community hospital	91 (11.9)	1 (3.1)	2 (2.9)	8 (20.0)	22 (7.3)	13 (12.7)	45 (20.1)
University/teaching hospital	127 (16.6)	9 (28.1)	14 (20.3)	4 (10.0)	33 (11.0)	16 (15.7)	51 (22.8)
Specialized diabetes centre	64 (8.3)	5 (15.6)	19 (27.5)	12 (30.0)	15 (5.0)	9 (8.8)	4 (1.8)
Other type of centre	98 (12.8)	12 (37.5)	15 (21.7)	7 (17.5)	27 (9.0)	28 (27.5)	9 (4.0)
Missing	11	0	1	1	8	0	1
Location of centre							
Urban	555 (72.5)	29 (90.6)	68 (100.0)	33 (82.5)	210 (69.8)	100 (98.0)	115 (51.6)
Rural	211 (27.5)	3 (9.4)	0 (0.0)	7 (17.5)	91 (30.2)	2 (2.0)	108 (48.4)
Missing	12	0	2	1	7	0	2
Centre funding							
Public/governmental	283 (37.1)	12 (38.7)	11 (16.2)	8 (20.5)	161 (53.7)	27 (26.7)	64 (28.7)
Private	471 (61.8)	19 (61.3)	56 (82.4)	31 (79.5)	138 (46.0)	71 (70.3)	156 (70.0)
Mixed	8 (1.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.3)	3 (3.0)	3 (1.3)
Missing	16	1	2	2	8	1	2
Speciality of main investigator							
PCP/family doctor	259 (33.7)	16 (50.0)	2 (2.9)	4 (10.0)	216 (71.8)	3 (2.9)	18 (8.0)
Endocrinology/diabetology	351 (45.7)	6 (18.8)	50 (72.5)	30 (75.0)	62 (20.6)	49 (48.0)	154 (68.8)
Internal medicine	114 (14.8)	8 (25.0)	9 (13.0)	6 (15.0)	21 (7.0)	49 (48.0)	21 (9.4)
Cardiology	29 (3.8)	1 (3.1)	5 (7.2)	0 (0.0)	0 (0.0)	1 (1.0)	22 (9.8)
Nephrology	3 (0.4)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
Geriatrics	1 (0.1)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other speciality	11 (1.4)	1 (3.1)	1 (1.4)	0 (0.0)	2 (0.7)	0 (0.0)	7 (3.1)
Missing	10	0	1	1	7	0	1
Main type of patient referral							
Patient self-referral	460 (65.0)	23 (71.9)	32 (46.4)	21 (53.8)	176 (72.4)	35 (34.3)	173 (77.6)
Primary care referral	237 (33.5)	8 (25.0)	34 (49.3)	17 (43.6)	66 (27.2)	64 (62.7)	48 (21.5)
Secondary care referral	11 (1.6)	1 (3.1)	3 (4.3)	1 (2.6)	1 (0.4)	3 (2.9)	2 (0.9)
Missing	70	0	1	2	65	0	2
Estimated number of patients with type 2 diabetes mellitus per site and per month							
<10	70 (9.2)	1 (3.2)	4 (5.8)	0 (0.0)	65 (22.2)	0 (0.0)	0 (0.0)
10–20	90 (11.9)	3 (9.7)	9 (13.0)	3 (7.5)	67 (22.9)	0 (0.0)	8 (3.6)
21–50	149 (19.6)	13 (41.9)	16 (23.2)	10 (25.0)	66 (22.5)	22 (21.6)	22 (9.8)
>50	450 (59.3)	14 (45.2)	40 (58.0)	27 (67.5)	95 (32.4)	80 (78.4)	194 (86.6)
Missing	19	1	1	1	15	0	1

PCP, primary care practitioner.

Data are reported as n (%), unless otherwise stated. Percentages calculated for all sites/investigators with data available; missing data are excluded.

3.2. Patient socio-demographics

A total of 15,992 patients were enrolled in the study programme (Supplementary Fig. 1; Table 2). Participants were mostly Asian (49.7%) or Caucasian (25.6%), and 54.2% (ARR: 37.7–58.6%) were male. At the time of initiation of second-line therapy, patients' mean age was 57.2 years (SD: 12.0 years) with the highest mean age in Europe (61.9 years) and the lowest in South-East Asia (53.1 years). A total of 52.3% (ARR: 42.4–63.1%) of patients were aged 41–60 years. Overall, 48.9% of patients were employed or self-employed (ARR: 39.4–55.5%), 28.0% were unemployed (ARR: 15.8–41.8%), and 22.2% were retired (ARR: 9.9–43.0%). The highest rates of unemployment were recorded in Africa (41.8%) and South-East Asia (41.4%), and the lowest in Europe (15.8%). Overall, 21.3% of patients did not have health insurance; this proportion varied greatly across regions from 4.0% in Europe to 67.8% in South-East Asia; overall, 62.5% of patients were covered by public health insurance (ARR: 11.7–91.3%). >80% of patients had received secondary or higher education (ARR: 68.1–88.9%). Most participants stated that they were lifetime non-smokers (69.4%; ARR: 56.1–91.7%) and lifetime alcohol abstainers (65.8%; ARR: 44.9–92.6%).

3.3. Patient baseline clinical variables

Clinical variables at baseline are reported in Table 3. The median time from diagnosis of type 2 diabetes mellitus to initiation of second-line therapy was 4.1 years (IQR: 1.9–7.9 years; mean [SD]: 5.6 [5.3]), and was lowest in South-East Asia and Western Pacific region (3.4 years) and highest in Africa (5.7 years). There was a high level of variability in median time from diagnosis of type 2 diabetes mellitus between countries (Supplementary Table 2). HbA_{1c} and/or FPG levels were the main measures of glycaemic control at the time of initiation of second-line therapy and were reported for 79.9% (ARR: 57.5–93.7%) and 69.9% (ARR: 36.2–84.5%) of patients, respectively; 11.1% (ARR: 1.7–30.7%) of patients had an FPG measurement but no HbA_{1c} measurement (data not shown). In addition, post-prandial glucose (PPG) and random glucose levels were reported in 31.4% and 17.8% of patients, respectively. A total of 7.1% of patients did not have any measure of blood glucose levels reported, ranging from 2.7% in the Eastern Mediterranean region to 34.7% in Africa (data not shown). The median HbA_{1c} level was 63.9 mmol/mol (8.0%) (IQR: 55.2–76.0 mmol/mol [7.2–9.1%]) and was similar across all regions (ARR: 59.6–67.2 mmol/mol [7.6–8.3%]) but varied between countries (Supplementary Table 2). The overall proportions of patients with HbA_{1c} levels $\leq$ 7.0%, 7.0 to $\leq$ 8.0%, 8.0 to $\leq$ 9.0%, > 9.0% or more were 17.6%, 31.6%, 23.3% and 27.5%, respectively. The median FPG level was 8.8 mmol/l (IQR: 7.3–10.9 mmol/l; ARR: 8.2–9.4 mmol/l).

The mean body mass index was 29.1 kg/m^2 (SD: 5.9 kg/m^2) with the lowest values found in the Western Pacific region (26.1 kg/m^2) and the highest in Europe (31.9 kg/m^2). Hypertension and hyperlipidaemia were recorded as comorbid conditions by the investigators for 51.5% and 45.6% of patients, respectively. Systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) levels were reported for 95.4% and 54.8% of patients, respectively. Among these patients, 67.7% had an SBP lower than 140 mmHg, and 43.4% had an LDL-C level lower than 100 mg/dl.

Microvascular complications (history of chronic kidney disease, retinopathy, retinal laser photocoagulation, autonomic neuropathy, peripheral neuropathy and erectile dysfunction), and macrovascular complications (history of coronary artery disease, heart failure, angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stroke, transient ischaemic attack, carotid artery stent, carotid endarterectomy, peripheral artery disease, diabetic foot, amputation and defibrillator use) were present in 18.9% (ARR: 14.5–23.5%) and 12.7% (ARR: 4.0–26.6%) of patients, respectively.

3.4. First- and second-line therapies

First- and second-line therapies are described in Table 4. The most prescribed first-line therapies were metformin monotherapy (55.6%; ARR: 42.5–83.6%) and combinations of metformin and a sulfonylurea (14.4%; ARR: 5.8–31.1%). The proportion of patients who received combinations of metformin and a sulfonylurea as first-line therapies was particularly high in South-East Asia and the Eastern Mediterranean region (31.1% and 23.9%, respectively).

Overall, the most prescribed second-line therapies were combinations of metformin and a dipeptidyl peptidase-4 (DPP–4) inhibitor (23.5%) and combinations of metformin and a sulfonylurea (20.9%). Combinations of metformin and a sulfonylurea were the most commonly prescribed second-line therapies in Africa (57.1%) and South-East Asia (24.8%), and combinations of metformin and a DPP-4 inhibitor were the most commonly prescribed second-line therapies in the Eastern Mediterranean region (29.6%), the Americas (29.2%), Europe (27.5%) and the Western Pacific region (24.8%). Monotherapies accounted for 12.8% of second-line treatments, but this proportion varied across regions (ARR: 4.9–15.8%). The overall prescription rate of insulin (on its own or as part of a combination) was 7.8% (ARR: 4.7–10.7%). Of the 1237 patients who received insulin, 957 (77.4%) had an HbA_{1c} measurement; mean HbA_{1c} was 9.9% (SD: 2.1%) (data not shown).

The main reason for initiating a second-line therapy reported by investigators was lack of efficacy of first-line therapy (88.9%) (Fig. 1a), and the main reasons for choosing second-line treatments were efficacy (61.4%), tolerability (22.3%), low risk of weight gain (17.8%) and low risk of hypoglycaemic events (17.0%) (Fig. 1b). Lack of efficacy was also the main reason reported for switching between monotherapies (data not shown).

4. Discussion

DISCOVER is a unique, global research programme that assesses the characteristics, treatment and outcomes of patients with type 2 diabetes mellitus after initiating second-line glucose-lowering therapy. DISCOVER includes 778 clinical sites representing primary and secondary care, rural and urban locations, and different funding sources.

Table 2 – Socio-demographic characteristics of patients participating in the DISCOVER study.

	Total (N = 15,992)	Africa (n = 812)	Americas (n = 2002)	South-East Asia (n = 3360)	Europe (n = 3479)	Eastern Mediterranean (n = 2182)	Western Pacific (n = 4157)
Sex							
Male	8664 (54.2)	306 (37.7)	963 (48.1)	1852 (55.1)	1856 (53.4)	1278 (58.6)	2409 (58.0)
Missing	4	0	0	0	4	0	0
Self-reported ethnicity							
Caucasian	3917 (25.6)	105 (12.9)	480 (29.4)	1 (0.0)	3020 (94.8)	165 (7.6)	146 (3.5)
Black	310 (2.0)	235 (29.0)	61 (3.7)	0 (0.0)	13 (0.4)	0 (0.0)	1 (0.0)
Mixed	213 (1.4)	91 (11.2)	115 (7.0)	0 (0.0)	4 (0.1)	0 (0.0)	3 (0.1)
Asian	7610 (49.7)	177 (21.8)	9 (0.6)	3339 (99.5)	20 (0.6)	72 (3.3)	3993 (96.1)
Hispanic	942 (6.2)	1 (0.1)	928 (56.8)	0 (0.0)	11 (0.3)	0 (0.0)	2 (0.0)
Arabic	2151 (14.0)	200 (24.7)	4 (0.2)	2 (0.1)	12 (0.4)	1933 (88.9)	0 (0.0)
Other	174 (1.1)	2 (0.2)	36 (2.2)	15 (0.4)	104 (3.3)	5 (0.2)	12 (0.3)
Missing	675	1	369	3	295	7	0
Age, years							
Mean (SD)	57.2 (12.0)	54.9 (11.2)	58.3 (11.8)	53.1 (11.3)	61.9 (10.9)	53.8 (10.8)	58.5 (12.6)
Median (IQR)	58.0 (48.3–65.7)	54.9 (48.0–63.0)	58.3 (50.5–66.3)	53.0 (43.0–63.0)	62.2 (54.3–69.4)	53.9 (46.7–61.0)	58.1 (49.8–67.4)
18–30	228 (1.4)	16 (2.0)	23 (1.1)	75 (2.2)	13 (0.4)	34 (1.6)	67 (1.6)
31–40	1192 (7.5)	69 (8.5)	117 (5.8)	391 (11.6)	99 (2.8)	224 (10.3)	292 (7.0)
41–50	3340 (20.9)	198 (24.4)	386 (19.3)	934 (27.8)	442 (12.7)	588 (26.9)	792 (19.1)
51–60	5028 (31.4)	290 (35.7)	653 (32.6)	1059 (31.5)	1034 (29.7)	789 (36.2)	1203 (28.9)
61–70	4126 (25.8)	175 (21.6)	526 (26.3)	715 (21.3)	1192 (34.3)	418 (19.2)	1100 (26.5)
71–80	1730 (10.8)	61 (7.5)	239 (11.9)	162 (4.8)	577 (16.6)	122 (5.6)	569 (13.7)
>80	348 (2.2)	3 (0.4)	58 (2.9)	24 (0.7)	122 (3.5)	7 (0.3)	134 (3.2)
Missing	0	0	0	0	0	0	0
Education level							
No formal education	471 (3.2)	57 (7.3)	50 (3.2)	26 (0.8)	78 (2.5)	158 (7.7)	102 (2.7)
Primary (1–6 years)	2295 (15.8)	183 (23.3)	442 (28.7)	343 (10.4)	588 (19.1)	360 (17.6)	379 (10.0)
Secondary (7–13 years)	7190 (49.4)	420 (53.5)	587 (38.1)	1431 (43.2)	1781 (58.0)	767 (37.5)	2204 (58.0)
Higher education (>13 years)	4599 (31.6)	125 (15.9)	463 (30.0)	1514 (45.7)	626 (20.4)	759 (37.1)	1112 (29.3)
Missing	1437	27	460	46	406	138	360
Main working status							
Employed	5465 (36.3)	262 (32.6)	473 (29.9)	877 (26.2)	1096 (34.1)	954 (45.5)	1803 (44.9)
Self-employed	1893 (12.6)	59 (7.3)	343 (21.7)	755 (22.5)	171 (5.3)	209 (10.0)	356 (8.9)
Disabled	82 (0.5)	6 (0.7)	6 (0.4)	0 (0.0)	59 (1.8)	2 (0.1)	9 (0.2)
Not working	4216 (28.0)	336 (41.8)	428 (27.1)	1388 (41.4)	507 (15.8)	684 (32.6)	873 (21.7)
Retired	3337 (22.2)	140 (17.4)	330 (20.9)	332 (9.9)	1381 (43.0)	247 (11.8)	907 (22.6)
Other	67 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	67 (1.7)
Missing	932	9	422	8	265	86	142

Health insurance coverage							
Private	2042 (13.6)	165 (20.6)	517 (32.3)	597 (18.9)	130 (3.9)	467 (22.3)	166 (4.1)
Public/governmental	9412 (62.5)	466 (58.3)	783 (48.8)	371 (11.7)	3047 (91.3)	1228 (58.7)	3517 (86.7)
Mixed	386 (2.6)	16 (2.0)	137 (8.5)	51 (1.6)	26 (0.8)	69 (3.3)	87 (2.1)
No insurance	3211 (21.3)	153 (19.1)	166 (10.4)	2144 (67.8)	134 (4.0)	327 (15.6)	287 (7.1)
Missing	941	12	399	197	142	91	100
Tobacco smoking							
Non-smoker	10,831 (69.4)	633 (78.9)	1299 (66.1)	3066 (91.7)	2001 (59.9)	1579 (74.0)	2253 (56.1)
Ex-smoker	2537 (16.3)	93 (11.6)	460 (23.4)	128 (3.8)	791 (23.7)	189 (8.9)	876 (21.8)
Current smoker	2232 (14.3)	76 (9.5)	205 (10.4)	151 (4.5)	546 (16.4)	366 (17.2)	888 (22.1)
Missing	392	10	38	15	141	48	140
Alcohol drinking							
Lifetime abstainer	9901 (65.8)	557 (69.5)	980 (61.9)	2992 (89.9)	1643 (50.4)	1953 (92.6)	1776 (44.9)
Former drinker	1618 (10.8)	177 (22.1)	221 (14.0)	127 (3.8)	320 (9.8)	44 (2.1)	729 (18.4)
Drinker	3518 (23.4)	67 (8.4)	382 (24.1)	210 (6.3)	1299 (39.8)	111 (5.3)	1449 (36.6)
Missing	955	11	419	31	217	74	203

IQR, interquartile range; SD, standard deviation.
Data are reported as n (%), unless otherwise stated. Percentages calculated for all patients with data available; missing data are excluded.

Together with a broad spectrum of investigators (including primary care practitioners, diabetologists, endocrinologists and other specialists), the diversity of sites provides a comprehensive picture of the management of patients with type 2 diabetes mellitus in different clinical settings around the world. In addition, the observational design, minimal inclusion/exclusion criteria and global reach of DISCOVER ensure that adults of all ages with different backgrounds, ethnicities and socio-economic status are included.

Although clinical guidelines recommend monitoring HbA_{1c} to support treatment decisions, approximately one in five patients did not have an HbA_{1c} measurement recorded when initiating second-line treatment, suggesting that HbA_{1c} is not routinely measured in some clinical settings and geographic regions. This suboptimal HbA_{1c} reporting may be partly explained by the fact that HbA_{1c} measurement is not affordable for some patients in many low- to middle-income countries [19]. Our results suggest that, in such situations, other measures of glycaemia such as PPG, FPG and self-monitoring of blood glucose may have been used by some physicians as alternatives to monitor glucose levels and to support treatment decisions in routine clinical practice. However, 7.1% of patients had no recorded measure of blood glucose levels, a higher proportion than would be expected since all patients were changing treatment at the time of their inclusion in the study.

As expected in a population of patients who were escalating from first- to second-line therapy, mean HbA_{1c} levels were above the target of 7.0% recommended by guidelines [8,10]. Mean HbA_{1c} levels were largely similar across all regions and were consistently high. Overall, >50% of patients for whom HbA_{1c} levels were reported had a measurement higher than 8.0%, and approximately 30% had a measurement higher than 9.0%. This suggests suboptimal glycaemic control and delayed treatment intensification in a large proportion of patients, increasing their risk of microvascular and macrovascular complications [20,21]. The prevalence of vascular complications and associated risk factors (hypertension and hyperlipidaemia) also highlighted an opportunity to improve the early management of patients with type 2 diabetes mellitus.

The most common first-line therapy was metformin monotherapy in all regions. However, overall only 55.6% of all patients received metformin monotherapy at first-line, a lower proportion than has been reported in some recent retrospective observational studies conducted in Western countries [22–25]. In these studies, 65–91% of patients newly diagnosed with type 2 diabetes mellitus received metformin monotherapy as first-line treatment. This difference may be explained, at least in part, by lower metformin monotherapy usage in South-East Asia, the Eastern Mediterranean and the Western Pacific, where less than 50% of patients were prescribed metformin monotherapy at first line. The proportions of patients receiving metformin monotherapy as first-line treatment in Africa, the Americas and Europe were 83.6%, 77.1% and 67.1%, respectively; similar to the previous reports [22–25].

Overall and in Africa, South-East Asia, Europe and the Eastern Mediterranean region, the second most commonly prescribed first-line treatment consisted of a combination of

Table 3 – Baseline clinical characteristics of patients participating in the DISCOVER study.

	Total (N = 15,992)	Africa (n = 812)	Americas (n = 2002)	South-East Asia (n = 3360)	Europe (n = 3479)	Eastern Mediterranean (n = 2182)	Western Pacific (n = 4157)
Time from diagnosis to initiation of second-line therapy, years							
Mean (SD)	5.6 (5.3)	6.9 (5.7)	6.2 (6.3)	4.6 (4.1)	6.6 (5.4)	5.8 (5.3)	5.1 (5.4)
Median (IQR)	4.1 (1.9–7.9)	5.7 (2.9–9.3)	4.4 (1.9–8.7)	3.4 (2.0–6.1)	5.4 (2.7–9.1)	4.2 (2.1–8.0)	3.4 (1.0–7.6)
Missing	397	0	62	1	154	2	176
HbA_{1c}, mmol/mol							
Mean (SD)	67.7 (18.6)	70.3 (20.2)	69.3 (20.6)	70.8 (18.5)	65.4 (17.1)	71.1 (17.2)	64.9 (18.6)
Median (IQR)	63.9 (55.2–76.0)	63.9 (57.2–79.2)	63.9 (55.2–79.2)	67.2 (58.5–81.4)	62.0 (55.0–72.0)	67.2 (59.6–79.2)	59.6 (53.0–71.6)
Missing	3208	345	471	1309	476	137	470
HbA_{1c}, %							
Mean (SD)	8.3 (1.7)	8.6 (1.9)	8.5 (1.9)	8.6 (1.7)	8.1 (1.6)	8.7 (1.6)	8.1 (1.7)
Median (IQR)	8.0 (7.2–9.1)	8.0 (7.4–9.4)	8.0 (7.2–9.4)	8.3 (7.5–9.6)	7.8 (7.2–8.7)	8.3 (7.6–9.4)	7.6 (7.0–8.7)
<7.0	2249 (17.6)	57 (12.2)	262 (17.1)	274 (13.4)	561 (18.7)	196 (9.6)	899 (24.4)
7.0 to <8.0	4039 (31.6)	162 (34.7)	460 (30.0)	530 (25.8)	1056 (35.2)	507 (24.8)	1324 (35.9)
8.0 to <9.0	2983 (23.3)	94 (20.1)	336 (21.9)	515 (25.1)	732 (24.4)	648 (31.7)	658 (17.8)
≥9.0	3513 (27.5)	154 (33.0)	473 (30.9)	732 (35.7)	654 (21.8)	694 (33.9)	806 (21.9)
Missing	3208	345	471	1309	476	137	470
FPG, mmol/l							
Mean (SD)	9.5 (3.1)	9.7 (3.5)	9.8 (3.4)	9.3 (3.0)	9.3 (3.0)	10.1 (3.3)	9.0 (2.9)
Median (IQR)	8.8 (7.3–10.9)	8.7 (7.3–11.3)	8.8 (7.4–11.3)	8.8 (7.1–10.9)	8.6 (7.4–10.5)	9.4 (7.8–11.7)	8.2 (7.0–10.3)
Missing	4811	518	611	625	890	338	1829
PPG, mmol/l							
Mean (SD)	12.6 (4.3)	12.4 (4.6)	11.2 (4.2)	13.1 (4.2)	11.5 (3.8)	14.0 (3.9)	11.8 (4.4)
Median (IQR)	12.0 (9.6–14.9)	11.3 (9.5–13.4)	10.7 (8.2–13.6)	12.5 (10.3–15.5)	10.8 (9.0–13.1)	13.3 (11.4–16.1)	11.0 (8.6–14.3)
Missing	10,973	723	1794	1219	2721	1471	3045
Random glucose, mmol/l							
Mean (SD)	11.2 (4.4)	13.6 (5.7)	11.2 (5.6)	12.1 (4.7)	10.3 (3.6)	12.8 (4.0)	10.3 (4.0)
Median (IQR)	10.3 (8.0–13.3)	11.9 (9.6–16.7)	9.7 (7.5–12.8)	12.0 (8.4–15.0)	9.5 (7.9–11.8)	12.3 (10.0–15.2)	9.4 (7.4–12.3)
Missing	13,153	644	1795	2997	2940	1785	2992
BMI, kg/m^2							
Mean (SD)	29.1 (5.9)	30.6 (6.2)	30.6 (6.1)	27.3 (4.5)	31.9 (6.1)	31.1 (5.7)	26.1 (5.0)
Median (IQR)	28.1 (25.0–32.3)	29.7 (26.3–34.0)	29.6 (26.4–34.0)	26.8 (24.2–29.8)	31.1 (27.6–35.1)	30.4 (27.3–34.1)	25.4 (22.9–28.3)
Missing	1235	13	202	208	261	326	225
SBP, mmHg							
Mean (SD)	132.3 (16.5)	134.2 (18.6)	131.2 (17.7)	128.8 (15.2)	136.4 (16.6)	133.3 (15.7)	131.6 (16.0)
Median (IQR)	130.0 (120.0–140.0)	130.0 (120.0–142.0)	130.0 (120.0–140.0)	130.0 (120.0–138.0)	135.0 (125.0–145.0)	130.0 (120.0–140.0)	130.0 (120.0–140.0)
<140	10,332 (67.7)	548 (67.7)	1323 (69.1)	2529 (76.1)	1805 (56.5)	1302 (64.1)	2825 (71.0)
Missing	740	3	86	38	282	151	180

DBP, mmHg							
Mean (SD)	79.9 (10.0)	80.1 (10.5)	80.6 (10.6)	79.9 (8.4)	81.1 (9.6)	79.8 (9.7)	78.6 (10.9)
Median (IQR)	80.0 (72.0–86.0)	80.0 (71.0–87.0)	80.0 (73.0–87.0)	80.0 (74.0–85.0)	80.0 (75.0–87.0)	80.0 (73.0–85.0)	80.0 (71.0–85.0)
Missing	753	3	86	41	282	154	187
Hypertension	8226 (51.5)	463 (57.0)	1147 (57.3)	1470 (43.8)	2351 (68.0)	871 (39.9)	1924 (46.3)
Missing	21	0	0	0	21	0	0
LDL-C, mg/dl							
Mean (SD)	109.2 (38.4)	105.2 (36.4)	102.4 (40.3)	102.5 (36.2)	112.0 (42.3)	114.3 (39.1)	110.9 (34.8)
Median (IQR)	105.0 (83.0–132.0)	104.2 (79.0–127.0)	97.6 (73.4–127.0)	99.0 (78.4–123.0)	106.0 (82.5–137.0)	111.0 (87.0–139.0)	109.0 (88.0–132.0)
<100	3808 (43.4)	138 (44.1)	517 (53.0)	684 (50.2)	914 (43.2)	437 (38.6)	1118 (39.0)
Missing	7227	499	1027	1997	1361	1049	1294
Hyperlipidaemia	7284 (45.6)	324 (39.9)	979 (48.9)	1176 (35.0)	1918 (55.5)	910 (41.7)	1977 (47.6)
Missing	21	0	0	0	21	0	0
Microvascular complications[a]	3011 (18.9)	118 (14.5)	302 (15.1)	556 (16.5)	812 (23.5)	399 (18.3)	824 (19.8)
Missing	21	0	0	0	21	0	0
Macrovascular complications[b]	2028 (12.7)	74 (9.1)	232 (11.6)	135 (4.0)	915 (26.6)	218 (10.0)	454 (10.9)
Missing	45	0	0	0	45	0	0

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; PPG, post-prandial glucose; SBP, systolic blood pressure; SD, standard deviation.

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

[a] Microvascular complications included a history of chronic kidney disease, retinopathy, retinal laser photocoagulation, autonomic neuropathy, peripheral neuropathy and erectile dysfunction.

[b] Macrovascular complications included a history of coronary artery disease, heart failure, angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stroke, transient ischaemic attack, carotid artery stent, carotid endarterectomy, peripheral artery disease, diabetic foot, amputation and implantable cardioverter defibrillator use.

metformin and a sulfonylurea. Prescription of combination therapies as first-line treatment may reflect initiation of pharmacological therapy in patients with high HbA_{1c} levels; physicians may have adopted a similar approach to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) treatment algorithm, which recommends the use of metformin with a second agent for newly diagnosed patients with an HbA_{1c} level of 7.5% or more [8]. It should be noted, however, that combinations of metformin and sulfonylureas come last in the hierarchy of first-line therapies suggested by the AACE/ACE for patients with an HbA_{1c} level of 7.5% or more. Alternatively, physicians may prescribe lower doses of more than one medication in order to address more than one physio-pathologic aspect of the disease, and reduce the risk of adverse events. The high prevalence of the use of combinations of metformin and sulfonylureas is likely to be driven by the low cost of these drugs rather than clinical evidence, particularly in low- to middle-income countries. In addition, many countries participating in DISCOVER have limited formularies, with sodium–glucose-linked transporter type 2 inhibitors and DPP-4 inhibitors being rarely available [26,27]. Slightly more than 20% of patients received a first-line therapy that did not include metformin.

Second-line therapies varied greatly across regions. The most prescribed second-line therapies were combinations of metformin and a sulfonylurea (Africa, South-East Asia and the Western Pacific region), and combinations of metformin and a DPP-4 inhibitor (Americas, Europe and the Eastern Mediterranean region). Of note, approximately 13% of patients received a single glucose-lowering agent as second-line therapy, suggesting that many patients switched between monotherapies. Although switching between monotherapies may be appropriate for patients who did not tolerate their first-line treatment, such switches are not in line with guideline recommendations for the majority of patients for whom lack of efficacy was reported as a reason for treatment change [6–11]. Insulin (on its own or as part of a combination) was prescribed in 7.8% of patients, for whom the mean HbA_{1c} level was 9.9%. This high mean HbA_{1c} level was similar to levels reported in other observational studies of patients initiating insulin [28,29] and is consistent with the recommendations of clinical guidelines [6,8,10].

4.1. *Strengths and limitations*

The DISCOVER study programme includes nearly 16,000 patients, with global coverage including many countries that have rarely or never been studied before regarding the management and outcomes of patients with type 2 diabetes mellitus. Previous international studies have usually focussed on patients with more advanced disease; for example, A_1chieve and IMPROVE both studied patients receiving insulin therapy, and the International Diabetes Management Practice Study included patients with a mean diabetes duration of 8.4 years [5]. DISCOVER therefore provides unique insights into treatment practices at an earlier point in disease progression, at a stage where guideline recommendations diversify. Long-term follow-up will provide an opportunity to assess the associations between treatment choices and clinical outcomes.

Table 4 – First- and second-line therapies of patients participating in the DISCOVER study.

	Total (N = 15,992)	Africa (n = 812)	Americas (n = 2002)	South-East Asia (n = 3360)	Europe (n = 3479)	Eastern Mediterranean (n = 2182)	Western Pacific (n = 4157)
First-line therapy							
Metformin monotherapy	8882 (55.6)	679 (83.6)	1543 (77.1)	1505 (44.8)	2331 (67.1)	1057 (48.5)	1767 (42.5)
SU monotherapy	1229 (7.7)	27 (3.3)	137 (6.8)	186 (5.5)	268 (7.7)	288 (13.2)	323 (7.8)
DPP-4i monotherapy	1194 (7.5)	1 (0.1)	40 (2.0)	43 (1.3)	53 (1.5)	19 (0.9)	1038 (25.0)
Other monotherapy[a]	630 (3.9)	2 (0.2)	18 (0.9)	33 (1.0)	61 (1.8)	13 (0.6)	503 (12.1)
Metformin + SU	2304 (14.4)	73 (9.0)	135 (6.7)	1045 (31.1)	287 (8.3)	522 (23.9)	242 (5.8)
Metformin + DPP-4i	501 (3.1)	1 (0.1)	94 (4.7)	123 (3.7)	95 (2.7)	131 (6.0)	57 (1.4)
Metformin + SU + DPP-4i	217 (1.4)	1 (0.1)	14 (0.7)	97 (2.9)	26 (0.7)	70 (3.2)	9 (0.2)
Metformin + other(s)	848 (5.3)	25 (3.1)	13 (0.6)	291 (8.7)	323 (9.3)	42 (1.9)	154 (3.7)
Other combinations	183 (1.1)	3 (0.4)	8 (0.4)	37 (1.1)	32 (0.9)	39 (1.8)	64 (1.5)
Missing	4	0	0	0	3	1	0
Second-line therapy							
Metformin monotherapy	315 (2.0)	8 (1.0)	40 (2.0)	56 (1.7)	76 (2.2)	27 (1.2)	108 (2.6)
SU monotherapy	441 (2.8)	26 (3.2)	28 (1.4)	87 (2.6)	172 (4.9)	32 (1.5)	96 (2.3)
DPP-4i monotherapy	669 (4.2)	3 (0.4)	69 (3.4)	133 (4.0)	161 (4.6)	72 (3.3)	231 (5.6)
Other monotherapy[b]	625 (3.9)	3 (0.4)	43 (2.1)	256 (7.6)	107 (3.1)	37 (1.7)	179 (4.3)
Metformin + SU	3336 (20.9)	464 (57.1)	578 (28.9)	832 (24.8)	566 (16.3)	331 (15.2)	565 (13.6)
Metformin + DPP-4i	3756 (23.5)	18 (2.2)	584 (29.2)	522 (15.5)	956 (27.5)	645 (29.6)	1031 (24.8)
Metformin + SU + DPP-4i	1054 (6.6)	1 (0.1)	71 (3.5)	360 (10.7)	141 (4.1)	440 (20.2)	41 (1.0)
Metformin + other(s)[c]	3103 (19.4)	188 (23.2)	381 (19.0)	803 (23.9)	766 (22.0)	317 (14.5)	648 (15.6)
Other combinations[c]	1449 (9.1)	14 (1.7)	62 (3.1)	153 (4.6)	179 (5.1)	129 (5.9)	912 (21.9)
Insulin[d]	1240 (7.8)	87 (10.7)	146 (7.3)	158 (4.7)	352 (10.1)	151 (6.9)	346 (8.3)
Missing	4	0	0	0	3	1	0

DPP-4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea.

Data are reported as n (%). Percentages calculated for all patients with data available; missing data are excluded.

[a] Including α-glucosidase inhibitors, thiazolidinediones, meglitinides and sodium–glucose cotransporter-2 inhibitors.

[b] Including α-glucosidase inhibitors, thiazolidinediones, meglitinides, sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists.

[c] Excluding insulin.

[d] On its own or as part of combinations.

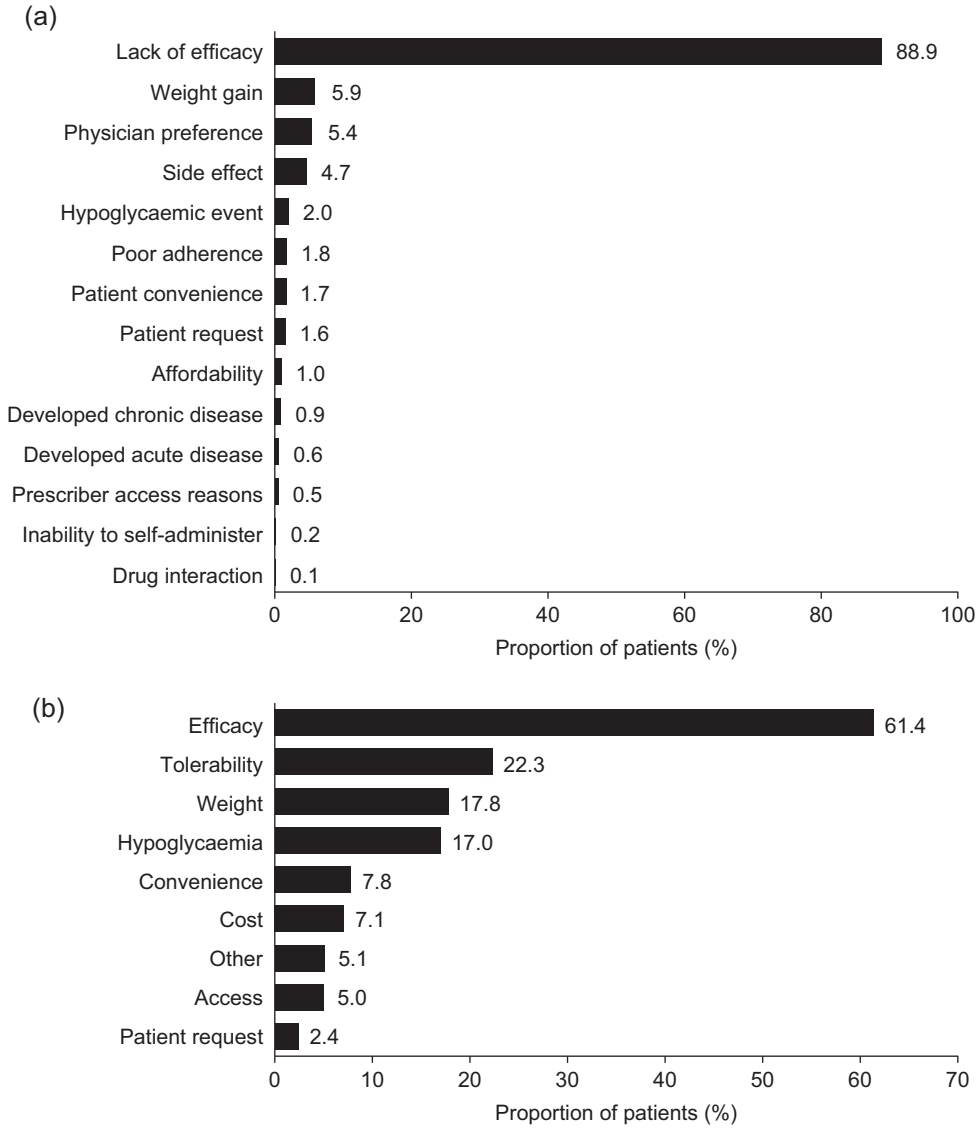

Fig. 1 – Reasons cited by investigators for (a) changing first-line therapy and (b) choosing a second-line therapy for patients participating in the DISCOVER study. Multiple reasons could be selected.

The large population size of DISCOVER will provide the opportunity to analyse events with low incidences, and the use of a standardized electronic case report form for data collection allows the comparison of results within and across countries and regions.

Although sites were carefully selected to be as representative as possible of the management of type 2 diabetes mellitus in each participating country, as in any observational study of this nature it was not possible to obtain a fully representative sample (Supplementary Fig. 1). There are several reasons for this including low numbers of sites in some countries, infrastructure challenges that prevented the inclusion of some sites in rural locations, and the fact that some centres, often those involved in primary care, did not have the capability of running observational research or failed to meet other quality requirements. In some countries, little information was available to be collated before the start of the study.

Patient selection bias should also be considered; for example, more than three-quarters of participants were reported to have secondary or higher education, a greater proportion than would be anticipated and potentially reflecting an increased willingness among educated patients to take part in the study. In addition, less than a third of patients reported alcohol or tobacco use, which may indicate selective disclosure or suppression of information. Together, these observations may also reflect a selection bias for patients of higher socio-economic status, which should be considered when interpreting the results from the DISCOVER study. Indeed, these patients are likely to receive better care and therefore to have better outcomes than the general population of patients initiating a second-line glucose-lowering therapy.

Nevertheless, the patient population included in DISCOVER is large and heterogeneous, resulting in a unique opportunity to assess associations between clinical

outcomes, treatment options and other factors in a global context. Over-representation of urban locations, secondary care and highly educated patients is likely to lead to an over-estimate, rather than an underestimate, of the quality of care in at least some countries. Another possibility is that over-representation of secondary care may result in the inclusion of patients with more severe disease, who are more likely to be referred to hospitals and for specialist management.

The observational design of DISCOVER also means that data are collected in accordance with routine clinical practice at each participating site. Data collection was not mandatory for any variable, and the study protocol did not specify standardized methods to measure clinical variables such as HbA_{1c}. Methodology may therefore vary across sites and countries. The results, however, are reflective of clinical practice. Finally, events such as occurrence of complications were not adjudicated, and diagnosis relied on the judgement of treating physicians.

4.2. *Conclusions*

Baseline data from the DISCOVER study highlight substantial variations in healthcare systems, characteristics and treatment of patients with type 2 diabetes mellitus between geographic regions. The great diversity of prescribed treatments confirms that uncertainty remains regarding the optimal choice of second-line therapy in clinical practice. Among this population of patients initiating second-line therapy, HbA_{1c} levels and the prevalence of vascular complications and associated risk factors were high, highlighting a global need for more aggressive risk-factor management. The 3-year follow-up of DISCOVER patients will allow the comparison of outcomes associated with different therapies, thus providing insights on the optimal use of available glucose-lowering drugs.

Acknowledgements

The authors would like to thank all investigators and patients participating in the DISCOVER study. Medical writing support was provided by Stéphane Pintat PhD of Oxford PharmaGenesis, Oxford, UK, and was funded by AstraZeneca.

Author contributions

The general content of the manuscript was agreed upon by all authors. All authors contributed to its 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. MBG is the guarantor of this work.

Conflicts of interest

Marilia B. Gomes, Bernard Charbonnel, Kamlesh Khunti, Mikhail Kosiborod, Antonio Nicolucci, Stuart J. Pocock, Wolfgang Rathmann, Marina V. Shestakova, Iichiro Shimomura, Hirotaka Watada, and Linong Ji are members of the DISCOVER Scientific Committee and received support from AstraZeneca to attend DISCOVER planning and update meetings. Filip Surmont, Hungta Chen and Peter Fenici are employees of AstraZeneca. Niklas Hammar is a former employee of AstraZeneca. Javier Cid-Ruzafa is an employee of Evidera. Marilia B. Gomes has received honoraria from Merck-Serono. Bernard Charbonnel has received honoraria from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharpe & Dohme, Novartis, Novo Nordisk, Sanofi, and Takeda. Kamlesh Khunti has received honoraria 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 (NIHR CLAHRC – EM) and the National Institute of Health Research (NIHR) Leicester Biomedical Research Centre. Mikhail Kosiborod has received honoraria from AstraZeneca, Amgen, Sanofi, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Takeda, Novo Nordisk, ZS Pharma, Glytec Systems, and Merck, and research support from AstraZeneca, Gilead, Sanofi, and Genentech. Antonio Nicolucci has received honoraria from Novo Nordisk, Medtronic, AstraZeneca, and Eli Lilly, and research support from Novo Nordisk, Sanofi-Aventis, Artsana, and Dexcom. Stuart J. Pocock has received honoraria from AstraZeneca. Wolfgang Rathmann has received honoraria from AstraZeneca and research support from Novo Nordisk. Marina V. Shestakova has received honoraria from Eli Lilly, Merck Sharpe & Dohme, Sanofi, Novo Nordisk, Boehringer Ingelheim, and AstraZeneca, and research support from Sanofi. Iichiro Shimomura has received honoraria from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Kowa, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, and Takeda Pharmaceutical, and research support from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Japan Foundation for Applied Enzymology, Japan Science and Technology Agency, Kowa, Kyowa Hakko Kirin, Midori Health Management Center, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Suzuken Memorial Foundation, and Takeda Pharmaceutical. Fengming Tang has received research support from AstraZeneca. Hirotaka Watada has received honoraria from Boehringer Ingelheim, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eli Lilly, Kowa, Merck Sharp & Dohme, Novo Nordisk, Novartis, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, Takeda, Astellas Pharma, Mitsubishi Tanabe Pharma, AstraZeneca, Kyowa Hakko Kirin, and Kissei Pharma, and research support from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eli Lilly, Kissei Pharma, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Novartis, Novo Nordisk, Pfizer, Sanofi, Sanwakagaku Kenkyusho, Takeda, Terumo Corp, Astellas Pharma, Abbott, Ono Pharmaceutical, Kyowa Hakko Kirin, Kowa, Johnson & Johnson, Taisho Toyama Pharmaceutical, Nitto Boseki, Bayer, Bristol-Myers Squibb, and Benefit one Health care. Linong Ji has received honoraria from Eli Lilly, Bristol-Myers Squibb, Novartis, Novo Nordisk, Bayer, Merck Sharp & Dohme, Takeda, Sanofi, Roche, Boehringer

Ingelheim, and AstraZeneca, and research support from Roche, Sanofi, Merck Sharp & Dohme, AstraZeneca, Novartis, Eli Lilly, and Bristol-Myers Squibb.

Role of funding source

The DISCOVER study is funded by AstraZeneca. DISCOVER is a non-interventional study, and no drugs were supplied or funded.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.024.

REFERENCES

[1] International Diabetes Federation. IDF diabetes atlas. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017.
[2] Stone MA, Charpentier G, Doggen K, Kuss O, Lindblad U, Kellner C, et al. Quality of care of people with type 2 diabetes in eight European countries: findings from the Guideline Adherence to Enhance Care (GUIDANCE) study. Diabetes Care 2013;36:2628–38.
[3] Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care 2013;36:2271–9.
[4] Gomes MB, Gianella D, Faria M, Tambascia M, Fonseca RM, Rea R, et al. Prevalence of type 2 diabetic patients within the targets of care guidelines in daily clinical practice: a multi-center study in Brazil. Rev Diabet Stud 2006;3:82–7.
[5] Chan JC, Gagliardino JJ, Baik SH, Chantelot JM, Ferreira SR, Hancu N, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). Diabetes Care 2009;32:227–33.
[6] American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2017;40:S1–S129.
[7] Chinese Diabetes Society. Chinese guidelines for type 2 diabetes prevention (2013). Chin J Diabetes. 2014;22:2–42.
[8] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract 2015;21:438–47.
[9] International Diabetes Federation. Global guideline for type 2 diabetes: 2012.
[10] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58 (3):429–42. https://doi.org/10.1007/s00125-014-3460-0.
[11] Qaseem A, Barry MJ, Humphrey LL, Forciea MA. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166:279–90.
[12] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
[13] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[14] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[15] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
[16] Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study. Circulation 2017;136:249–59.
[17] Ji L, Bonnet F, Charbonnel B, Gomes MB, Kosiborod M, Khunti K, 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.
[18] Katakami N, Mita T, Takahara M, Hashigami K, Kawashima M, Shimomura I, 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;9:165–75.
[19] World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: 2011.
[20] Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100.
[21] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[22] Desai NR, Shrank WH, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, et al. Patterns of medication initiation in newly diagnosed diabetes mellitus: quality and cost implications. Am J Med 2012;125(302):e1–7.
[23] Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open 2016;6:e010210.
[24] Datta-Nemdharry P, Thomson A, Beynon J, Donegan K. Patterns of anti-diabetic medication use in patients with type 2 diabetes mellitus in England and Wales. Pharmacoepidemiol Drug Saf 2017;26:127–35.
[25] Brouwer ES, West SL, Kluckman M, Wallace D, Masica AL, Ewen E, et al. Initial and subsequent therapy for newly diagnosed type 2 diabetes patients treated in primary care using data from a vendor-based electronic health record. Pharmacoepidemiol Drug Saf 2012;21:920–8.
[26] Bazargani YT, de Boer A, Leufkens HG, Mantel-Teeuwisse AK. Selection of essential medicines for diabetes in low and middle income countries: a survey of 32 national essential medicines lists. PLoS ONE 2014;9:e106072.
[27] World Health Organization National medicines formularies: 2017
[28] Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. Diabetol Metab Syndr 2013;5:57.
[29] Khunti K, Damci T, Meneghini L, Pan CY, Yale JF. Study of Once Daily Levemir (SOLVE): insights into the timing of insulin initiation in people with poorly controlled type 2 diabetes in routine clinical practice. Diabetes Obes Metab 2012;14:654–61.