



Inappropriate intensification of glucose-lowering treatment in older patients with type 2 diabetes: the global DISCOVER study

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ABSTRACT

Introduction Although individualized target glycated hemoglobin (HbA_{1c}) levels are recommended in older people with type 2 diabetes, studies report high levels of potential overtreatment. We aimed to investigate the proportion of older patients (aged ≥65 years) who potentially received an inappropriately intensive treatment (HbA_{1c} level <7.0% (53.0 mmol/mol)) in a global study. Factors associated with intensive glycemic management and using glucose-lowering medications associated with a high risk of hypoglycemia (high-risk medications (insulin, sulfonylureas, and meglitinides)) were also assessed. **Research design and methods** DISCOVER is a 3-year observational study program of 15 992 people with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries. Data were collected at baseline (initiation of second-line therapy) and at 6, 12, and 24 months. Factors associated with an inappropriately intensive treatment or using high-risk medications were assessed using a hierarchical regression model.

Results Of the 3344 older patients with baseline HbA_{1c} data in our analytic cohort, 23.5% received inappropriate treatment intensification. Among those who had follow-up HbA_{1c} data, 55.2%, 54.2%, and 53.5% were inappropriately tightly controlled at 6, 12, and 24 months, respectively, with higher proportions in high-income than in middle-income countries. The proportion of patients receiving high-risk medications was higher in middle-income countries than in high-income countries. Gross national income (per US\$5000 increment) was associated with increased odds of inappropriately intensive treatment but with decreased odds of receiving high-risk medications.

Conclusions A large proportion of older DISCOVER patients received an inappropriately intensive glucose-lowering treatment across the 2 years of follow-up, with substantial regional variation. The use of high-risk medications in these patients is particularly concerning.

INTRODUCTION

Guidelines generally recommend a glycated hemoglobin (HbA_{1c}) target level of ≤7.5%

Significance of this study

What is already known about this subject?

- Studies from high-income countries, such as the USA and the UK, show that a high proportion of older patients (aged ≥65 years) with type 2 diabetes are potentially overtreated (glycated hemoglobin (HbA_{1c}) level <7.0% (53.0 mmol/mol)) in routine clinical practice.

What are the new findings?

- We found that although gross national income (per US\$5000 increment) was associated with greater odds of an inappropriately intensive treatment, participants from lower-middle-income and upper-middle-income countries had greater odds of receiving high-risk glucose-lowering medication than those from high-income countries.
- Almost a quarter of older DISCOVER patients (aged ≥65 years) received inappropriate treatment intensification (HbA_{1c} level <7.0% (53.0 mmol/mol)) at baseline (initiation of second-line glucose-lowering treatment); for approximately half of the patients, treatment was inappropriately intensified during follow-up.

How might these results change the focus of research or clinical practice?

- Our findings demonstrate the need for a more personalized approach to treatment of type 2 diabetes, particularly among older patients from lower-middle-income and upper-middle-income countries.

(53.0 mmol/mol) in otherwise healthy older (aged ≥65 years) people with type 2 diabetes^{1–3} and an HbA_{1c} level of ≤8.5% in older individuals with complex comorbidities. An HbA_{1c} level target of >7.5% may therefore be more appropriate in some older patients^{1–7} because they are at an increased risk of hypoglycemic events⁸ and related complications, including falls,⁹ fractures,⁹ cognitive impairment,¹⁰ vascular complications,¹¹ and increased

mortality.¹² Stringent HbA_{1c} targets to control type 2 diabetes and diabetes-related complications in older individuals often result in complex treatment regimens, leading to an increased risk of polypharmacy (most commonly described as concomitant use of five or more medications), which has been linked to adverse drug events, drug–drug interactions, prescribing cascades, and in some cases poor treatment adherence.¹³ With this in mind, guidelines suggest an individualized treatment approach in older patients, with a focus on simple treatment regimens and glucose-lowering drugs that have a low risk of hypoglycemia, such as metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose cotransporter 2 (SGLT-2) inhibitors.^{17 18 14}

Studies from Europe and the USA suggest that these guidelines are not always followed in clinical practice, with high proportions of older patients potentially being overtreated (patients aged ≥ 65 years with an HbA_{1c} level of $< 7.0\%$ (53.0 mmol/mol)).^{14–18} This may partially explain the high number of hospitalizations for hypoglycemia among older patients from high-income countries.¹⁹ There is currently lack of available data on the inappropriate intensification of treatment of patients with type 2 diabetes from low-income and middle-income countries.

In order to fill this knowledge gap, we used data from the DISCOVER study program—a 3-year global prospective, observational study program investigating clinical outcomes, health-related quality of life, and treatment patterns in individuals with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries across 6 continents^{20 21}—to assess the prevalence of, and factors associated with, an inappropriately intensive treatment of older patients during the first 24 months of the study.

METHODS

Research design

The methods of the DISCOVER study program have been described in detail elsewhere.^{20 21} In brief, the DISCOVER study program comprises two similar 3-year non-interventional, prospective, observational studies of 15 992 patients with type 2 diabetes initiating second-line glucose-lowering therapy across 38 countries (DISCOVER (NCT02322762) in 37 countries and J-DISCOVER (NCT02226822) in Japan).^{20 21} Countries participating in the DISCOVER study are as follows: Algeria, Argentina, Australia, Austria, Bahrain, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, France, India, Indonesia, Italy, Japan, 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. In line with the non-interventional nature of the study, the protocol did not mandate the use of specific drugs. Treatment

decisions were made by physicians, as they would be in routine clinical practice.

Patient enrollment

Patients were enrolled in DISCOVER from December 2014 to June 2016 and in J-DISCOVER from September 2014 to December 2015. To ensure that data were as reflective of routine clinical practice as possible, inclusion and exclusion criteria were kept to a minimum. Briefly, patients aged ≥ 18 years who were initiating second-line glucose-lowering therapy (defined as adding a glucose-lowering drug or switching between therapies) were eligible for inclusion, provided that they were not pregnant, were not undergoing dialysis, and had no history of renal transplant, and if their first-line therapy was not an injectable agent, or a herbal remedy or natural medicine alone. Whereas J-DISCOVER enrolled only patients who were receiving oral monotherapy as first-line treatment, DISCOVER enrolled patients who were receiving any type of oral therapy (one or more oral agents, or a fixed-dose combination). Full inclusion and exclusion criteria are shown in online supplemental table 1. All eligible patients were invited to participate in the study by their physician and provided written informed consent. A list of participating investigators can be found in online supplemental appendix list 1.

Data collection

Data from China (n=1293) were not included because they were not available at the time of publication owing to governance reasons. Data were collected at baseline (initiation of second-line glucose-lowering therapy) and at 6, 12, and 24 months within a 4-month window (± 2 months) to reflect patient visits in routine clinical practice. Data were captured by the treating physician using a standardized electronic case report form (eCRF). Some data were extracted from existing electronic health records in Canada, Denmark, France, Norway, and Sweden. In these countries, data not routinely captured in electronic medical records, such as the reason(s) for treatment change, were obtained by the investigators using a questionnaire that was linked back to patients' medical records. Data collected at baseline and during follow-up included the following: patient demographics (such as sex, age, body mass index (BMI), and duration of type 2 diabetes); clinical variables (such as HbA_{1c} levels); and first-line and second-line glucose-lowering treatments. First-line and second-line therapy refers to a patient's first ever treatment regimen for type 2 diabetes (before study entry) and second treatment regimen (at study baseline), respectively. Treatment at each follow-up visit was recorded because participants may have changed treatment at other routine clinical visits not recorded as part of DISCOVER. Clinical variables were measured in accordance with routine clinical practice, and data collection for these variables was not mandatory.

Gross national income (GNI) per capita in the DISCOVER countries in 2015 was sourced from the

World Bank using the *Atlas* method (online supplemental figure 1).⁶ The *Atlas* conversion factor uses a country's exchange rate for the current and preceding 2 years, adjusted for the difference between the rate of inflation in that country and international inflation.

Statistical analyses

Our analytic cohort comprised older participants (aged ≥ 65 years) with an available baseline HbA_{1c} measurement (N=3344).²² Inappropriately intensive glucose-lowering treatment was defined (cross-sectionally) as participants having an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) at the time of data collection at baseline, and at 6, 12, and 24 months after baseline. Insulin, sulfonylureas, and meglitinides were considered medications associated with a high risk of hypoglycemia (high-risk glucose-lowering medications). It is important to note that, while there is no formal definition of inappropriate tight glycemic management in older individuals with type 2 diabetes, our definition is in line with other published studies and is in agreement with the current American Diabetes Association (ADA) guidelines.^{1 18 23}

Exploratory variables are presented as numbers (percentages), mean (SD), and median (IQR), as appropriate. P values were calculated, as a measure of statistical significance, using Student's t-test (continuous variables), χ^2 test (categorical variables), or Fisher's exact test (categorical variables). P values <0.05 were considered statistically significant.

Factors associated with having an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) at 12 months were assessed using a hierarchical regression model with country as a random effect, and with baseline covariates (sex, age, BMI, time since diabetes diagnosis, GNI, and medical history (microvascular complications, macrovascular complications, and chronic kidney disease)) as well as treatment with high-risk glucose-lowering medications at 12 months as fixed effects. A similar model was used to assess the factors associated with use of high-risk glucose-lowering medications at 12 months, with country as a random effect and with the aforementioned baseline covariates and HbA_{1c} level at 12 months as fixed effects. Multiple imputation was used to account for unreported data, which used iterative sequential regression to sample missing values from the predictive distribution of each variable, conditional to all other variables. Variables included in the imputation model were the dependent variables (HbA_{1c} level or use of high-risk medication); all the independent variables (patient demographics (such as sex, age, BMI, and duration of type 2 diabetes), clinical variables (such as HbA_{1c} levels), and first-line and second-line glucose-lowering treatments); and country. Ten randomly imputed data sets were generated in this way. Analyses were replicated on each imputed data set and the model estimates were pooled across imputations using Rubin's rules. All statistical analyses were performed using the SAS V.9.4 statistical software system.

RESULTS

Among the 14 699 DISCOVER participants, 11 891 (80.9%) had an HbA_{1c} measurement at baseline. Our analytic cohort comprised 3344 patients (28.1%) aged ≥ 65 years. At baseline, when initiating second-line glucose-lowering therapy, 785 (23.5%) patients aged ≥ 65 years had an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol; figure 1). Of these potentially inappropriately intensified patients, 252 (32.1%) received second-line treatment with high-risk glucose-lowering medications (figure 1A). Baseline characteristics were similar between patients with HbA_{1c} levels of $<7.0\%$ or $\geq 7.0\%$ (53.0 mmol/mol) at 12 months (table 1).

Follow-up data at 6, 12, and 24 months were available for 2431 (72.7%), 2578 (77.1%), and 2465 (73.7%) older patients, respectively. An HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) was noted in 1343 (55.2%), 1398 (54.2%), and 1320 (53.5%) patients at 6, 12, and 24 months, respectively (figure 1A). Among patients with HbA_{1c} levels of $<7.0\%$ (53.0 mmol/mol), high-risk glucose-lowering medications were prescribed in 474 (35.4%), 495 (36.0%), and 462 (36.1%) patients at 6, 12, and 24 months, respectively (figure 1A).

The proportion of patients with an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) varied between lower-middle-income, upper-middle-income, and high-income countries (figure 1B–D). Whereas the proportion of patients with an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) was highest in high-income countries, the proportion of patients receiving treatment with high-risk glucose-lowering medications was highest in middle-income countries at all time points.

In the hierarchical regression model, patients with a longer duration of diabetes and those who were prescribed treatment with high-risk glucose-lowering medications, at the time of their 12-month visit, had decreased odds of having an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) (figure 2). Country income (GNI per US\$5000 increment) was associated with increased odds of a patient having an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) at 12 months.

The proportion of patients receiving treatment with sulfonylureas at 12 months was significantly lower in patients with an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol; 29.5%) than in those with an HbA_{1c} level of $\geq 7.0\%$ (53.0 mmol/mol; 42.4%) (table 1). Similarly, the proportion of patients receiving treatment with insulin at 12 months was also significantly lower in patients with an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol; 2.3%) than in those with an HbA_{1c} level of $\geq 7.0\%$ (53.0 mmol/mol; 10.9%) (table 1).

In the multivariable model, high BMI at baseline (per 5 kg/m² increment), 12-month HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol, vs $\geq 7.0\%$), and shorter duration of type 2 diabetes were associated with decreased odds of being treated with high-risk glucose-lowering medication (figure 3). Country income (GNI per US\$5000 increment) was also associated with decreased odds of being

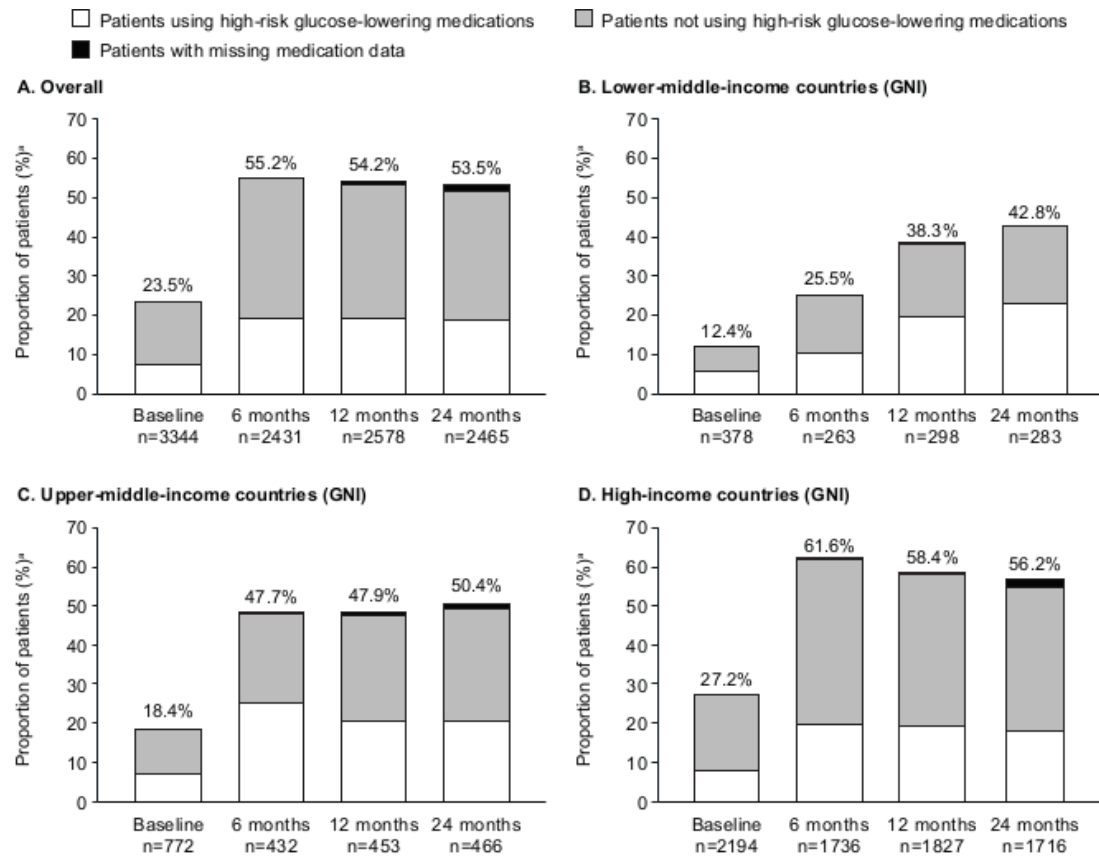


Figure 1 Proportion of older patients (aged ≥ 65 years) with HbA_{1c} level of $<7.0\%$ treated with or without high-risk glucose-lowering medications (insulin, sulfonylureas, and/or meglitinides): (A) overall, (B) lower-middle-income countries (GNI: US\$1005–US\$3955), (C) upper-middle-income countries (GNI: US\$3956–US\$12 235), and (D) high-income countries (GNI: \geq US\$12 236). This analysis included older patients with treatment information available at baseline and at 6, 12, and 24 months. ^aPatients aged ≥ 65 years and had an HbA_{1c} level of $<7.0\%$. GNI, gross national income; HbA_{1c}, glycated hemoglobin.

treated with high-risk glucose-lowering medications at 12 months.

CONCLUSIONS

In an observational analysis of a large global cohort of patients with type 2 diabetes, we found that a quarter of older participants had an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) at baseline and approximately half of participants had an HbA_{1c} level of $<7.0\%$ (53.0 mmol/mol) during follow-up. The overall increase in the proportion of patients receiving inappropriately intensive treatment could be explained, in part, by the fact that all DISCOVER participants were initiating second-line glucose-lowering therapy (defined as add-on or switching), which may result in a decrease in the overall mean HbA_{1c} level between baseline and 6 months. Thereafter, the proportion of participants for whom therapy was inappropriately tight remained high, possibly because some physicians failed to recognize inappropriate intensification and adapt treatment accordingly.

The proportion of patients who were overly intensively treated varied across countries in all income brackets. A novel finding was that patients in high-income countries were more likely to have intensive glycemic control, potentially reflecting stricter treatment regimens, with

a greater emphasis placed on glucose monitoring and achieving glycemic targets, and better access to health-care. The increased prevalence of baseline vascular complications in patients from high-income countries, compared with patients from lower-middle-income countries seen in a previous analysis of DISCOVER data,¹¹ may also play a part in driving the high rate of inappropriately intensively treated diabetes, with a focus on ensuring that these patients achieve good glycemic control to minimize their risk of diabetes-related vascular complications. Intensive glycemic control and the presence of comorbidities that require medical treatment may place some patients at an increased risk of polypharmacy, with low HbA_{1c} levels only achieved, in some cases, through the use of multiple glucose-lowering medications. In the USA, 57% of women and 59% of men reported using more than five different medications on a weekly basis, with older adults with type 2 diabetes at high risk of polypharmacy.¹³ Similarly, in Italy, 51.7% of older individuals (aged ≥ 65 years) with type 2 diabetes were reported to have polypharmacy, with comorbidities and diabetes-related complications shown to be associated with increased risk of polypharmacy.²⁴

At each time point, approximately one-third of overly intensively controlled patients received a

Table 1 Characteristics of DISCOVER study patients aged ≥ 65 years, according to HbA_{1c} level after 12 months of follow-up

	Overall n=2578	HbA _{1c} level after 12 months of follow-up		P value*
		HbA _{1c} <7.0% n=1398	HbA _{1c} $\geq 7.0\%$ n=1180	
Sex, male, n (%)	1422 (55.2)	788 (56.4)	634 (53.8)	0.188
Missing, n	3	1	2	
Age, years, mean (SD)	72.2 (5.5)	72.4 (5.5)	71.9 (5.5)	0.042
HbA _{1c} level at baseline, %, mean (SD)	7.8 (1.3)	7.4 (1.2)	8.3 (1.3)	<0.001
BMI, kg/m ² , mean (SD)	24.6 (4.3)	24.4 (4.3)	25.1 (4.2)	0.018
Missing, n	1777	884	893	
Country GNI, n				
Lower-middle	298	114	184	<0.001
Upper-middle	453	217	236	<0.001
High	1827	1067	760	<0.001
Time since diagnosis, years, mean (SD)	7.8 (6.4)	7.4 (6.2)	8.3 (6.4)	<0.001
Missing, n	109	66	43	
Medical history, n (%)				
Macrovascular complications	676 (26.3)	370 (26.6)	306 (26.0)	0.712
Missing, n	10	8	2	
Microvascular complications	759 (29.5)	406 (29.1)	353 (29.9)	0.661
Missing, n	4	4		
Chronic kidney disease	323 (12.5)	192 (13.8)	131 (11.1)	0.041
Missing, n	4	4	0	
First-line treatment†, n (%)				
Metformin	1699 (65.9)	872 (62.4)	827 (70.1)	<0.001
DPP-4 inhibitors	559 (21.7)	309 (22.1)	250 (21.2)	0.573
Sulfonylureas	488 (18.9)	204 (14.6)	284 (24.1)	<0.001
α -glucosidase inhibitors	85 (3.3)	58 (4.1)	27 (2.3)	0.008
Meglitinides	62 (2.4)	31 (2.2)	31 (2.6)	0.498
SGLT-2 inhibitors	26 (1.0)	13 (0.9)	13 (1.1)	0.663
Thiazolidinediones	60 (2.3)	35 (2.5)	25 (2.1)	0.518
Treatment at 12 months‡, n (%)				
Metformin	1680 (66.7)	866 (63.0)	814 (71.3)	<0.001
DPP-4 inhibitors	1514 (60.2)	861 (62.6)	653 (57.2)	0.005
Sulfonylureas	889 (35.3)	405 (29.5)	484 (42.4)	<0.001
α -glucosidase inhibitors	145 (5.8)	89 (6.5)	56 (4.9)	0.092
GLP-1 receptor agonists	68 (2.7)	41 (3.0)	27 (2.4)	0.341
Meglitinides	143 (5.7)	73 (5.3)	70 (6.1)	0.375
SGLT-2 inhibitors	259 (10.3)	134 (9.7)	125 (10.9)	0.323
Thiazolidinediones	242 (9.6)	134 (9.7)	108 (9.5)	0.806
Insulin	157 (6.2)	32 (2.3)	125 (10.9)	<0.001
Missing	61	23	38	

Percentages were calculated for all patients with data available; patients with missing data were excluded.

*P value was calculated using Student's t-test.

†Treatment categories are not mutually exclusive, and each category includes monotherapies and combination therapies.

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GNI, gross national income; HbA_{1c}, glycated hemoglobin; SGLT-2, sodium glucose cotransporter 2.

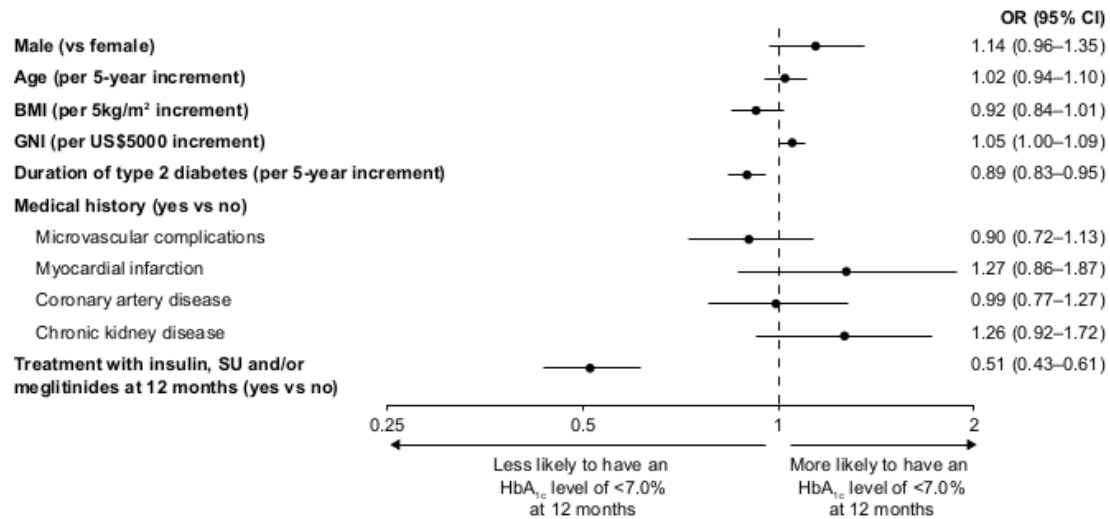


Figure 2 Baseline factors associated with odds of having HbA_{1c} level of <7.0% at 12 months of follow-up. OR was calculated using hierarchical logistic model, adjusted for baseline covariates and treatment at 12 months of follow-up, with country as a random effect. BMI, body mass index; GNI, gross national income; HbA_{1c}, glycated hemoglobin; SU, sulfonylurea.

glucose-lowering treatment associated with a high risk of hypoglycemia. However, patients in lower-middle-income and upper-middle-income countries were more likely to use medications with a high risk of hypoglycemia. This may be indicative of the limited availability and affordability of alternative glucose-lowering therapies, such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, in middle-income countries.^{25–27} As such, there seems to be a substantial global opportunity for quality improvement by adopting a personalized treatment approach to decrease the risk of hypoglycemia in older patients with type 2 diabetes.

Our findings are in line with a previous study in the USA in which half of the participants with type 2 diabetes who were aged ≥75 years were prescribed therapies associated

with a high risk of hypoglycemia, despite having an HbA_{1c} level of <7.0% (53.0 mmol/mol).^{15,18} A similar study in the UK found that 35.7% of people with type 2 diabetes aged ≥70 years were prescribed either insulin or a sulfonylurea; of these individuals, one-third had an HbA_{1c} level of <7.0% (53.0 mmol/mol).¹⁶ Finally, the Guideline Adherence to Enhance Care (GUIDANCE) study of people aged >65 years with type 2 diabetes in eight European countries found that 44.7% of patients were prescribed either insulin or a sulfonylurea despite having an HbA_{1c} level of <7.0% (53.0 mmol/mol).¹⁷ In addition, these studies were all conducted in either Europe or the USA and are therefore not representative of a global population. Our study extends these previous findings to a global cohort of patients from countries with varied income levels.

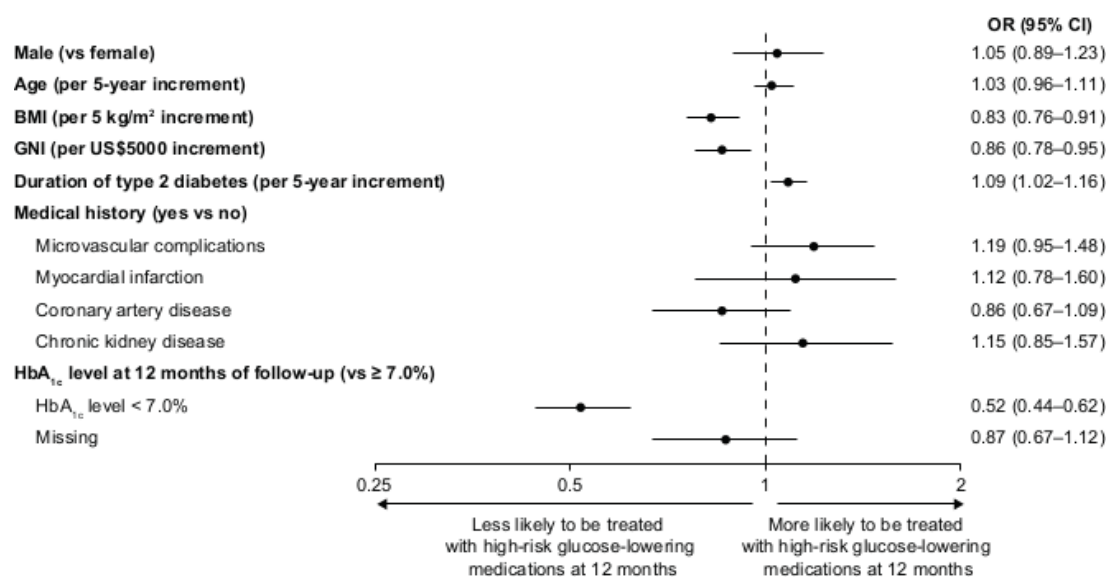


Figure 3 Baseline factors associated with odds of being treated with insulin, sulfonylureas, and/or meglitinides at 12 months. Data on treatment regimen at 12 months were available for 2980 patients. OR was calculated using hierarchical logistic model, adjusted for baseline covariates and HbA_{1c} level at 12 months of follow-up, with country as a random effect. BMI, body mass index; GNI, gross national income; HbA_{1c}, glycated hemoglobin.

Our results, in combination with those of previous studies, indicate that many older patients are still potentially being inappropriately tightly controlled.^{15–17} These individuals may thus be at an increased risk of polypharmacy, with adherence to stringent glycemic targets requiring treatment with multiple glucose-lowering medications.¹³ The addition of multiple glucose-lowering medications to the treatment regimen of older individuals is associated with an increased risk of drug–drug interactions and other adverse events.²⁸ The use of glucose-lowering medications that are associated with hypoglycemia in a substantial proportion of these patients is of particular concern. Data from previous studies have shown severe hypoglycemia to be a common cause of hospitalization among older individuals with type 2 diabetes, with the proportion of individuals hospitalized for hypoglycemia exceeding that of hyperglycemia.^{29,30} Given the association between inappropriately intensive treatment and risk of hypoglycemia, there may be a need for some physicians to consider treatment regimen simplification (discontinuation of at least one glucose-lowering agent or a reduction in dosage) in some older patients, as per the current ADA guidelines.¹ The benefits and risks of different combinations of glucose-lowering therapies, in combination with medications for associated comorbidities, must be weighed and discussed with the individual and/or caregiver.¹³ Primary health-care practitioners may also benefit from education on how to recognize and manage potentially inappropriate treatment intensifications in older patients. Too tightly controlled glycemia may also result from, at least in part, variables we were unable to measure, such as physician preference and experience, medication costs and availability, and number of physician visits. However, without studying the long-term effects of inappropriate treatment intensification on patient outcomes, our data do not support treatment de-intensification in these patients.

The primary strengths of the DISCOVER study program are both the large number of patients enrolled and the range of treatment sites and countries included, some of which have rarely been studied before. Data collection with a standardized eCRF allowed for the comparison of results between countries and regions. The observational nature of DISCOVER provided an ideal setting to investigate global treatment patterns, with minimal external influence and all treatment decisions made by the physician, as in routine clinical practice. However, our results must be interpreted with several limitations in mind. Although DISCOVER sites were selected to optimize diversity in each country, it is unclear if our findings truly reflect the quality of care within each country or can be generalized outside of the countries and regions included in the study. Participation in DISCOVER may have caused some healthcare practitioners to make different treatment decisions than they would if the data were not being recorded. Given that participants enrolled in DISCOVER were all initiating second-line glucose-lowering therapy, our findings may also not be representative of the entire

type 2 diabetes population and may overestimate the proportion of older individuals who are inappropriately strictly managed. Given their involvement in DISCOVER, participating physicians and sites may also be more focused on quality of care than others. This may have resulted in an over-representation of more advanced treatment centers. In line with the observational nature of the study, there was no requirement to record all study variables and a complete data set was not available for all patients. Although these analyses highlight a subset of patients whose treatments are inappropriately intensive, associations between intensive glycemic control and potential adverse effects related to severe hypoglycemia could not be assessed due to the limited follow-up time. Of note, only a small number of participants experienced major hypoglycemic events during the first 12 months after baseline (no participants among those receiving inappropriate treatment intensification at baseline but no high-risk medication and three participants among those receiving inappropriate treatment intensification at baseline and high-risk medications; data not shown). Finally, our definition of an inappropriately intensive glucose-lowering treatment in this older population was based on an HbA_{1c} level of <7.0%, in line with ADA guidelines, which recommend an HbA_{1c} level of <7.5% in older patients. However, lower HbA_{1c} targets may be appropriate for some of these patients. For example, patients early in the disease process, who are otherwise healthy without comorbidities, may benefit from initial tight glycemic control to reduce the risk of microvascular complications and may have been misclassified as being inappropriately tightly controlled.¹

To conclude, in a global cohort of patients with type 2 diabetes initiating second-line glucose-lowering therapy, we found that 23.5% of older patients treated in routine clinical practice are potentially receiving an inappropriately intensive treatment, leaving them at an increased risk of polypharmacy and possible downstream complications, such as severe hypoglycemia. This proportion of patients increased to more than 50% during follow-up, with substantial variation between regions. Overall, up to one-third of these patients, or more in lower-middle-income and upper-middle-income countries, received treatment with high-risk glucose-lowering medication, potentially leaving them at an even greater risk of hypoglycemia. This highlights the inequality of type 2 diabetes care across the globe and also the need for a more personalized approach to treatment of type 2 diabetes in older patients, with a greater consideration of the benefit to risk ratio of intensive glycemic control. Future analyses could provide information on outcomes associated with inappropriate treatment intensifications and the possible benefits and harms of complex treatment regimens and treatment with high-risk medications and could complement results from interventional studies.

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Contributors BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR agreed on the general content of the manuscript. BB, WR, HC, and FT developed the statistical analysis plan, which was conducted by HC and FT. The first draft of the manuscript was developed by BB, and WR, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, and HW contributed to its development. BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR approved the final version of the manuscript before its submission. An AstraZeneca team reviewed the manuscript during its development and was given the opportunity to make suggestions. However, the final content was determined by BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR. BB and WR are the guarantors of this work.

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Competing interests BHC, MG, LJ, KK, MK, AN, MS, IS, HW, and WR are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. BB and SVA have no competing interests to disclose. HC, AC, PF, and JM are employees of AstraZeneca. In addition, BHC has received payment from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Takeda. MG has received honoraria from Merck Serono. LJ has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda, Sanofi, and Roche; and research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, and Sanofi. KK has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Pfizer; research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Pfizer; 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 NIHR Applied Research Collaboration and the Leicester Biomedical Research Centre. MK has received honoraria from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, GlaxoSmithKline, Glytec Systems, Intarcia, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, and Sanofi; and research support from AstraZeneca and Boehringer Ingelheim. AN has received honoraria from AstraZeneca, Eli Lilly, Medtronic, and Novo Nordisk; and research support from Artsana, Dexcom, Novo Nordisk, and Sanofi. MS has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Servier; and research support from Novo Nordisk and Sanofi. IS has received honoraria from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Kowa Pharmaceuticals America, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, and Takeda; and research support from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Japan Foundation for

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Ethics approval The study protocols were approved by the relevant clinical research ethics committees in each country and institutional review boards at each site (online supplemental appendix table 1), and complied with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and the local regulations for clinical research.

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Data availability statement Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

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Potential overtreatment of older patients with type 2 diabetes: the global DISCOVER study

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Table 1 ethical committee approvals

Country	Authority/Committee Name
Algeria	Central ethics committee of CHU Beni Messous
Argentina	Comite de Bioetica del Instituto de Investigaciones Clinicas Rosario Comite de Bioetica en Investigacion de Ciencias de la Salud Comite de Docencia e Investigacion, Hospital San Martin de Parana Comite de Ética Dr Carlos Barclay Comité de Ética y Revisión Institucional Centro Médico FamyI Comité Independiente de Ética de Investigación en Salud Prof. Dr. Marcelino Ruscullada Comite Provincial de Bioetica - Ministerio de Salud Provincia de Santa Fe IEC - Comité Independiente de Ética para Ensayos en Farmacología Clínica (FEFyM) SIPROSA Sistema Provincial de Salud
Australia	Bellberry Human Research Ethics Committees
Austria	BASG - Bundesamt für Sicherheit im Gesundheitswesen (Austria) Ethikkommission der Medizinischen Universität Innsbruck
Bahrain	Research and Research Ethics Committee Royal Medical Services, Bahrain Defence Force
Brazil	CEP da Faculdade de Jaguariúna (CEP-FAJ) CEP da Faculdade de Medicina da Universidade de São Paulo - FMUSP/SP CEP da Faculdade de Medicina de São José do Rio Preto – FAMERP CEP da Faculdade de Medicina do ABC/SP CEP da Irmandade da Santa Casa de Misericórdia de Porto Alegre / RS CEP da Irmandade da Santa Casa de Misericórdia de São Paulo/ISCMSP CEP da Pontificia Universidade Catolica de Campinas / PUC Campinas CEP da Pontificia Universidade Católica do Paraná - PUC/PR CEP da Real Benemérita Associação Portuguesa de Beneficência - Hospital São Joaquim CEP da Universidade Caxias do Sul / RS CEP da Universidade Positivo CEP do Centro Universitário de Brasília – UNICEUB CEP do Centro Universitario Franciscano CEP do Hospital das Clínicas da Universidade Federal de Goiás CEP do Hospital de Clínicas da Universidade Federal do Parana - HCUFPR / PR CEP do Hospital e Maternidade Angelina Caron/PR CEP do Hospital Lifecenter CEP do Hospital Moinhos de Vento/ RS CEP do Hospital Pró-Cardíaco/RJ CEP do Hospital Universitario - CAS/UFJF/MG CEP do Hospital Universitario Pedro Ernesto CEP do Hospital Universitario Walter Cantidio - HUWC / CE CEP do Instituto de Ciência e Tecnologia - UNESP Campus de São José dos Campos CEP Investiga - Instituto de Pesquisas CONEP - Comissão Nacional de Ética em Pesquisa
Canada	Advarra's CIRBI

Colombia	<p>Comité de Bioética en Investigación Clínica Farallones</p> <p>Comité de Estudios Medicos S.A.S CREIMED</p> <p>Comité de Ética e Investigación Biomédica de la Fundación Valle del Lili</p> <p>Comité de Ética en Investigación Clínica de la Costa</p> <p>Comite de Etica en Investigacion del Centro Medico Imbanaco</p> <p>Comité de Ética en Investigación. Medplus Medicina Prepagada S.A.</p> <p>Comite de Etica en la Investigacion CAIMED</p> <p>Comite de Investigaciones y Etica en Investigaciones Hospital Pablo Tobon Uribe</p> <p>Comite Institucional de Etica e Investigacion Clinica</p> <p>Comité Institucional de Ética en Investigación C.I.E.I CAFAM</p>
Costa Rica	<p>Comité Ético Científico del Instituto Costarricense de Investigaciones Clínicas</p> <p>Comité Ético Cientifico Universidad Ciencias Médicas</p>
Denmark	No ethics committee approval was needed for the DISCOVER study
Egypt	Ministry of Health & Population Central Directorate for Research and Health Development
France	CPP Sud Ouest et Outre Mer II
India	<p>Clinical Trial Ethics Committee</p> <p>CLINICOM</p> <p>Ethics Committee - Apollo Hospitals</p> <p>Ethics Committee of Diabetes Thyroid Hormone Research Institute</p> <p>Ethics Committee, Diacon Hospital (Diabetes Care and Research Center)</p> <p>Ethics Committee, Inamdar Multispecialty Hospital</p> <p>Independent Ethics Committee, BYL Nair Hospital & TN Medical College</p> <p>Institutional Ethics Committee, BGS Global Hospital</p> <p>Institutional Ethics Committee Clinical Studies</p> <p>Institutional Ethics Committee Fortis Hospital</p> <p>Institutional Ethics Committee of Jothydev's Diabetics and Research centre</p> <p>Institutional Ethics Committee of Kovai Diabetes Speciality Centre and Hospital</p> <p>Institutional Ethics Committee of Rama Krishna Mission Seva Prathisthan</p> <p>Institutional Ethics Committee, Apollo Gleneagles Hospitals</p> <p>Institutional Ethics Committee, Oyster and Pearl Hospital</p> <p>Institutional Ethics Committee, Poona Medical Research Foundation pune</p> <p>Institutional Ethics Committee-The Calcutta Medical Research Institute</p> <p>Integrity Ethics Committee</p> <p>League Health Ethics Committee</p> <p>Manipal University Ethics Committee</p> <p>Medanta Institutional Ethics Committee</p> <p>Medisys clinisearch ethical review board</p> <p>St John's Medical College & Hospital Institutional Ethics Committee</p> <p>The Ethics Committee, Dr. V. Seshiah Diabetes Research Institute, Dr. Balaji Diabetes Care Centre</p> <p>Virtuous Institutional Medical Research Ethics Committee</p>
Indonesia	<p>Ethical Committee of Research Faculty of Medicine Brawijaya</p> <p>Komisi Etik Penelitian Fakultas Kedokteran Universitas Udayana/RSUP Sanglah Denpasar</p> <p>The Committee of Medical Research Ethics of The Faculty of Medicine University of Indonesia</p>

Italy	AIFA - Agenzia Italiana del Farmaco CE MI Area 3 Comitato Etico Unico (CEUR) per la Basilicata Comitato Etico Area Vasta Nord Ovest Comitato Etico ASST Sette Laghi Comitato Etico dell'Area Vasta Emilia Nord (AVEN) Comitato Etico della Azienda Ospedaliera Ospedale Treviglio-Caravaggio di Treviglio Comitato Etico della Romagna Comitato Etico dell'Azienda Ospedaliero-Universitaria Ospedali Riuniti di Foggia Comitato Etico dell'IRCCS Multimedica di Sesto San Giovanni Comitato Etico Lazio 2 Comitato Etico Milano Area 3 Comitato Etico Referente per l'area di Pavia
Jordan	Institutional Review Board Jordan University of Science and Technology King Abdulla University Hospital International Pharmaceutical Research Center Istishari Hospital institutional review board Jordan University Hospital institutional review board Royal medical services institutional review board
Kuwait	Research Affairs/Ethical Review Committee, Dasman Diabetes Institute
Lebanon	American University of Beirut institutional review board Ethics committee of Mount Lebanon Hospital Hammoud hospital institutional review board Institutional review board Rafik Hariri University hospital
Malaysia	Human Research Ethics Committee USM (HREC) Medical Research & Ethics Committee National Medical Ethics Committee
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Netherlands	METC St Elisabeth
Norway	Regional Committees for Medical and Health Research Ethics
Oman	Ethics & Scientific Research Committee and Royal Hospital
Panama	Comite de Bioetica de la Investigacion del Instituto Conmemorativo Gorgas de Estudios de la Salud

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Saudi Arabia	<p>KFMC IRB (King Fahad Medical City)</p> <p>Khamis Mushayt Armed Forces Hospital Research Ethics Committee</p> <p>KSUMC-IRB (King Saud University Medical city)</p> <p>IMC-IRB (International Medical Center)</p> <p>SGH-IRB (Saudi German Hospital)</p>
Spain	<p>Agencia Española del Medicamento y Productos Sanitarios (Spain)</p> <p>CEIC Autonómico de Andalucía</p> <p>CEIC del Área de Segovia</p> <p>CEIC del Hospital Universitario de Fuenlabrada</p> <p>CEIC Fundació Gol i Gurina</p> <p>CEIC Hospital Clínico de Salamanca</p> <p>CEIC Hospital Universitario Virgen del Rocío</p> <p>CEIC Hospital Universitario Central de Asturias</p> <p>CEIC Hospital Universitario de Elche</p> <p>CEIC Hospital Universitario Puerta del Mar</p> <p>CEIC Hospital Universitario Ramon y Cajal</p> <p>CEIC Hospital Universitario Virgen Macarena</p> <p>CEIC Hospital Virgen de la Arrixaca</p> <p>Fundacion Jimenez Diaz</p> <p>Hospital Universitari i Politecnic La Fe</p> <p>Hospital Universitario de La Princesa</p> <p>RA Asturias</p> <p>RA Castilla y Leon</p> <p>RA Cataluna</p> <p>RA Comunidad Valenciana</p> <p>RA Madrid</p> <p>RA Murcia</p>
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Turkey	Erciyes University Medical Faculty Ethics committee
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Wu Dai,	Michiel Dogger,	Ihab Fardon,
Paola D'Angelo,	Nicholas Doong,	Nabil Fawzy,
Ferdinandus de Looze,	Rahul Dosi,	Anika Fenando,
Maristela de Oliveira Beck,	Ana Clarissa Duin Fortes,	Felipe Ferre Larrosa,
R.J. De Vos,	Irina Dvoryashina,	Pablo Fletcher,
Eva Decroli,	Grzegorz Dzida,	Evelyn Fliesser-Görzer,
Gary Chaudhury,	Christoph Ebenbichler,	Martin Forseth,
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Roger Chen,	Tomas Edelsberger,	Gustavo Daniel Frechtel,
Hui Chen,	Stig Ekkert,	Mario Fritsch Neves,
Jung-Fu Chen,	Salah El Ghazaly,	Graciela Viviana Fuente,
Chih Hao Chen Ku,	Abdelaziz El Kady,	M Fulat,
Elena Chernaya,	Nabil El Kafrawy,	Geirmund Furnes,
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Chung Gu Cho,	Kamil El Zein,	Pedro Alberto Garcia Hernandez,
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Fernando Gomez Peralta,	Eric Hernandez Triana,	Linong Ji,
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Guillermo Gonzalez Galvez,	John Hickey,	Carola Johansson,
Amelia Gonzalez Gamarra,	Kristin Hjörleifsdottir,	Catharina Jonason,
Juan Jose Gorgojo Martinez,	Joost Hoekstra,	Siti Juhariah,
Bozena Gornikiewicz- Brzezicka,	Hans Högström,	Sandeep Julka,
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Kirsten Grete Walaas,	Stian Holmvik,	Shailaja Kale,
M Greyling,	Bertram Hölzl, F Hoosen,	Sanjay Kalra,
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Sanjay Gupta,	Chien-Ning Huang,	Sülbiye Karaburgu,
Sonsoles Gutiérrez Medina,	Yi-Jen Hung,	Igor Karen,
Suzae Hachim,	Chii-Min Hwu,	Alexandra Kautzky- Willer,
Jihad Haddad,	Jaime Orlando Ibarra Gomez,	Ghassan Kawar,
Khadija Hafidh,	Attia Ibrahim,	Mark Kennedy,
	Ahmed Ismail abdelghany,	Jose Francisco Kerr Saraiva,
	Rina Istarowati,	Jothydev Kesavadas,

Hesham Khalfan,	Johan Larsson,	Laura Maffei,
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German Henry	Xuefeng Li,	Cruz,
Kleisinger,	Yiming Li,	Paolo Marengo,
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Ferit Kerim Küçükler,	Bassem Louzir,	Noel Mikha,
Weimar Kunz Sebba	Song Lu,	E Mitha,
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Estêvão Lanna	Noureddine Maalem,	Rihab Mohamed El Nour,
Figueiredo,	Zeina Maani,	Fatiha Mohammedi,
Daan Lansdorp,	Josef Machacek,	Norhaliza Mohd Ali,
		Rudy Mokodompit,

Dora Inés Molina de Salazar,	Mohamed Ouertani,	Luis Carlos Ramirez,
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Horng-Yih Ou,	Sheetal Raj M,	Made Ratna Saraswati,
Haroun Ouertani,	Yuli Rakhmawati,	
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Ramazan Sari, Laksmi Sasiarini,	Jaganmani Sreekanth, Andrzej Stankiewicz,	Paranthaman Vengadasalam,
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Essam Shabaan,	Lars Henrik T Sutterud,	Balaji Vijayam,
Dilip Shah,	Ireneusz Szymczyk,	Juan Villagordoa Mesa,
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Claudio Slon,	Zinet Turki Marrakchi,	Bin Wu,
Djoko Wahono Soeatmadji,	Alparslan Kemal Tuzcu,	Guangda Xiang,
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Neale Somes,	Irina Ulyanova,	Sunjie Yan,
Weihong Song,	Galina Varvarina,	Tao Yang,
Bhavana Sosale,	Esdras Martin Vasquez,	Wei-Shiung Yang,
Radhakrishna Sothiratnam,	ZFA Vawda,	Yin Yee Kian,
Harald Sourij,	Kjersti Veholmen,	Feng-Chieh Yen,

Müge Özsan Yılmaz,

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Rozita Zakaria,

Ivana Zavaroni,

Jitka Zemanova,

Lihui Zhang,

Ying Zhang,

Jun Zhu,

Mei Zhu,

Hendra Zufry.

Supplementary Table 1 Inclusion and exclusion criteria of the DISCOVER study program.

Inclusion criteria
<ul style="list-style-type: none"> • Diagnosis of type 2 diabetes • 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 sulfonyleurea and a dipeptidyl peptidase-4 inhibitor after successive metformin monotherapy and sulfonyleurea monotherapy) • Current treatment with chemotherapy or oral or intravenous steroids • Undergoing dialysis or has had a renal transplant • First-line treatment was insulin or other 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

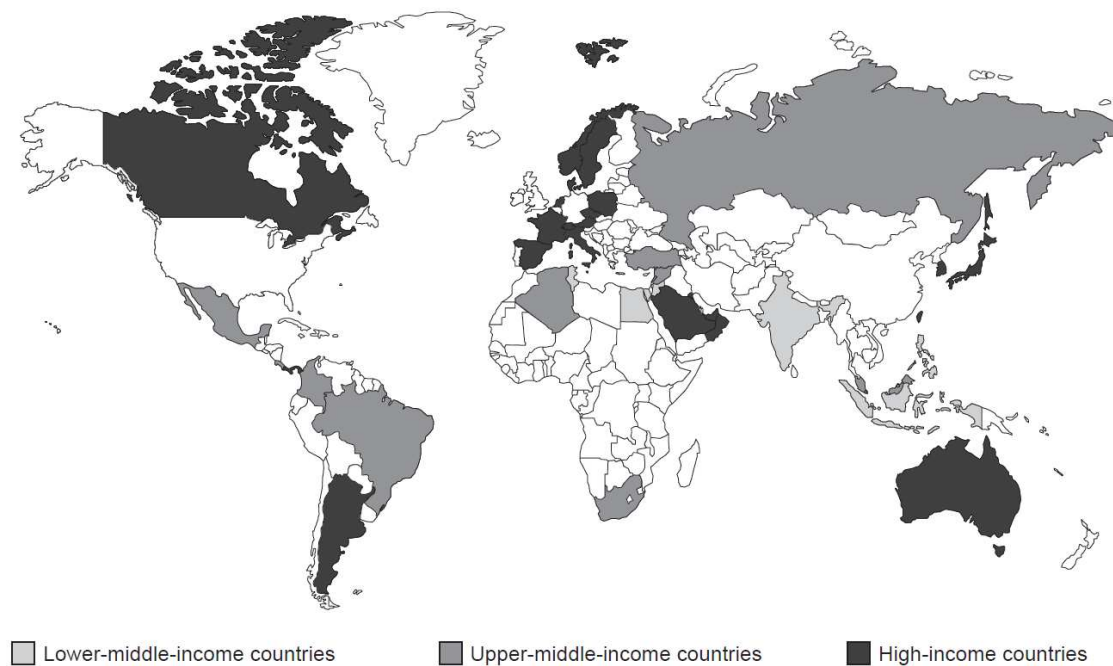
* ≥ 20 years in Japan. [†]In Japan, only patients using an oral monotherapy as first-line treatment

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.



Supplementary Figure 1 DISCOVER countries categorized by 2015 gross national income (GNI) per capita into lower-middle-income (US\$1046–4125), upper-middle-income (US\$4126–12 735), and high-income (\geq US\$12 736) countries.

Countries were as follows: lower-middle income (Egypt, India, Indonesia, Jordan, and Tunisia); upper-middle income (Algeria, Argentina, Brazil, Colombia, Costa Rica, Lebanon, Malaysia, Mexico, Russia, South Africa, and Turkey); and high income (Australia, Austria, Bahrain, Canada, Czech Republic, Denmark, France, Italy, Japan, Kuwait, the Netherlands, Norway, Oman, Panama, Poland, Saudi Arabia, South Korea, Spain, Sweden, Taiwan, and the United Arab Emirates).