HbA_{1c} < 7.0% 6 months after initiation of second-line therapy in patients with uncontrolled type 2 diabetes is associated with good glycemic control at 3 years: the DISCOVER study

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DISCOVER

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Introduction

- In patients with type 2 diabetes (T2D), consistent glycemic control is crucial for the prevention of long-term vascular complications.[1]
- Guidelines recommend a target glycated hemoglobin (HbA_{1c}) level of < 7.0% for most patients.
- If HbA_{1c} levels exceed this target, glucose-lowering therapy should be intensified in a timely manner.[2]
  - However, many patients have HbA_{1c} levels ≥ 9.0% when initiating second-line therapy,[3] putting them at a heightened risk of complications.
- The DISCOVER study program comprises two similar 3-year, non-interventional, prospective studies carried out in 38 countries across all six World Health Organization (WHO) regions, which assessed treatment patterns and clinical outcomes in patients with T2D initiating a second-line glucose-lowering treatment (NCT02322762 and NCT02226822).[4]
- The aim of the present analysis is to assess HbA_{1c} levels after 3 years in a subset of DISCOVER patients who had HbA_{1c} levels ≥ 9.0% at initiation of second-line therapy, and to determine the factors associated with HbA_{1c} levels of < 7.0% after 3 years of follow-up.

Methods

Study design

- The DISCOVER study program has been conducted in the following countries and regions:
  - **Africa** – Algeria and South Africa
  - **Americas** – Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico and Panama
  - **South-East Asia** – India and Indonesia
  - **Europe** – Austria, Czech Republic, Denmark, France, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden and Turkey
  - **Eastern Mediterranean** – Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia and the United Arab Emirates
  - **Western Pacific** – Australia, China, Japan, Malaysia, South Korea and Taiwan.
- Between September 2014 and June 2016, patients with T2D initiating a second-line glucose-lowering therapy (add-on or switching) after first-line oral therapy were invited to participate in the study (N = 15 983; **Box 1**).
- Data were collected at baseline and 6, 12, 24 and 36 months according to routine clinical practice at each site, using a standardized electronic case report form.

Box 1. Key inclusion and exclusion criteria for the DISCOVER study.

Inclusion criteria	Exclusion criteria
• Diagnosis of T2D • Age ≥ 18 years[a] • Initiating a second-line therapy (add-on or switching)	• Diagnosis of T1D • Pregnancy • First-line therapy was insulin or another injectable agent • First-line therapy was with herbal remedies/natural medicines alone • Undergoing dialysis or has had a renal transplant

[a]Age ≥ 20 years in Japan.
T1D, type 1 diabetes; T2D, type 2 diabetes.

Statistical analysis

- Patients from China were excluded from the present analysis owing to governance issues preventing complete data from being available at the time of presentation.
- The current analysis included 2233 patients with HbA_{1c} levels ≥ 9.0% at baseline and who had HbA_{1c} measurements available at years 2 or 3.
- Factors associated with an increased likelihood of having HbA_{1c} levels of < 7.0% at 3 years were assessed using a hierarchical logistical regression model.
- Factors adjusted for in the model were sex, age, body mass index, systolic blood pressure, level of education, time since T2D diagnosis, smoking history, history of vascular complications and hypoglycemia, second-line therapy, country income at baseline, and HbA_{1c} at 6 months (< 7.0% or ≥ 7.0%).
  - Multiple imputation was used to account for missing covariates.

Results

Baseline characteristics and HbA_{1c} after 3 years

- Baseline characteristics of the overall population included in the analysis (N = 2233) and those of patients with HbA_{1c} levels < 7.0% or ≥ 7.0% at 3 years are shown in **Table 1**.

Table 1. Baseline characteristics of DISCOVER patients with HbA_{1c} levels ≥ 9.0% at baseline, overall and according to HbA_{1c} levels after 3 years of follow-up.

	Total N = 2233	HbA_{1c} < 7.0% at 3 years n = 626	HbA_{1c} ≥ 7.0% at 3 years n = 1607
Age, years	54.4 (11.2)	54.5 (11.7)	54.3 (11.0)
Male, %	58.0	60.1	57.2
BMI, kg/m²	29.8 (6.0)	29.8 (6.2)	29.8 (5.9)
SBP, mmHg	133.3 (16.6)	132.8 (17.1)	133.6 (16.4)
DPB, mmHg	80.3 (9.6)	79.6 (10.2)	80.6 (9.4)
HbA_{1c}, %	10.4 (1.4)	10.3 (1.3)	10.5 (1.4)
Time since T2D diagnosis, years	5.5 (5.2)	4.6 (4.7)	5.9 (5.3)
Patients with HbA_{1c} < 7.0% at 6 months, n (%)	379 (24.2)	203 (41.3)	176 (16.4)
Missing	668	134	534
Education level, n (%)			
No formal education	79 (3.9)	22 (3.8)	57 (3.9)
Primary (1–6 years of education)	353 (17.3)	82 (14.2)	271 (18.5)
Secondary (7–13 years of education)	964 (47.2)	286 (49.7)	678 (46.2)
University/higher education (> 13 years)	648 (31.7)	186 (32.3)	462 (31.5)
Missing	189	50	139
Smoking status, n (%)			
Non-smoker	1492 (68.3)	405 (65.9)	1087 (69.2)
Ex-smoker	328 (15.0)	104 (16.9)	224 (14.3)
Current smoker	366 (16.7)	106 (17.2)	260 (16.5)
Missing	47	11	36
Medical history, n (%)			
Microvascular complications[a]	512 (22.9)	142 (22.7)	370 (23.0)
Missing	2	1	1
Macrovascular complications[b]	248 (11.1)	59 (9.5)	189 (11.8)
Missing	5	3	2
Major hypoglycemia[c]	19 (0.9)	7 (1.2)	12 (0.8)
Missing	126	45	79
Minor hypoglycemia[d]	55 (2.6)	15 (2.6)	40 (2.6)
Missing	120	45	75
Second-line therapy, n (%)			
Monotherapy[e]	153 (6.9)	36 (5.8)	117 (7.3)
≥ 2 glucose-lowering drugs[e]	1757 (78.7)	524 (83.7)	1233 (76.7)
Insulin[f]	323 (14.5)	66 (10.5)	257 (16.0)
Country income,[g] n (%)			
Lower-middle income	785 (35.2)	206 (32.9)	579 (36.0)
Upper-middle income	647 (29.0)	189 (30.2)	458 (28.5)
High income	801 (35.9)	231 (36.9)	570 (35.5)

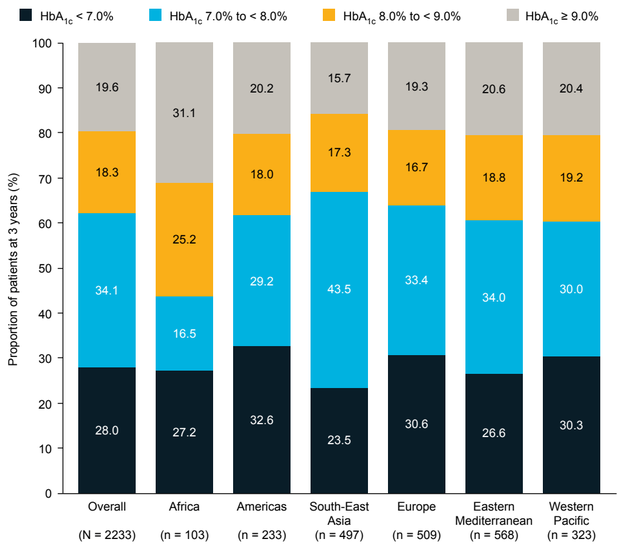
Percentages are reported for all patients with data available; missing data are excluded. Data are presented as mean (standard deviation) unless otherwise stated. [a]Includes nephropathy, retinopathy and neuropathy. [b]Includes coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use. [c]Requiring third-party assistance, in the year before baseline. [d]Not requiring third-party assistance, in the 4 weeks before baseline. [e]Excludes insulin. [f]As monotherapy or as a part of combination therapy. [g]Country income estimated using gross national income per capita as reported by World Bank bandings for fiscal year 18 (lower-middle income: US$1005–3995; upper-middle income: US$3956–12 235; high income: ≥ US$12 236).[5]
BMI, body mass index; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure; T2D, type 2 diabetes.

- After 3 years, HbA_{1c} levels were:
  - < 7.0% in 626 patients (28.0%)
  - 7.0% to < 8.0% in 761 patients (34.1%)
  - 8.0% to < 9.0% in 408 patients (18.3%)
  - ≥ 9.0% in 438 patients (19.6%) (**Figure 1**).
- The proportion of patients with HbA_{1c} levels ≥ 9.0% after 3 years was greatest in Africa (31.1%) and lowest in South-East Asia (15.7%).

Factors associated with good glycemic control at 3 years

- Factors associated with achieving HbA_{1c} levels of < 7.0% at 3 years are shown in **Figure 2**.
- Having an HbA_{1c} level < 7.0% at 6 months (24.2% of patients; vs HbA_{1c} level ≥ 7.0% at 6 months) was most strongly associated with an increased likelihood of having an HbA_{1c} level < 7.0% after 3 years.
- Initiating second-line therapy with two or more glucose-lowering drugs (31.0% of patients; vs insulin [on its own or as part of a combination therapy]) was also associated with an increased likelihood of having an HbA_{1c} level < 7.0% after 3 years, and having a time since T2D diagnosis ≥ 10 years (17.9% of patients; vs < 5 years) was associated with a decreased likelihood of having an HbA_{1c} level < 7.0% at 3 years.

Figure 1. Proportion of DISCOVER patients with different HbA_{1c} levels after 3 years of follow-up among those who had HbA_{1c} levels ≥ 9.0 at baseline, overall and by WHO region.

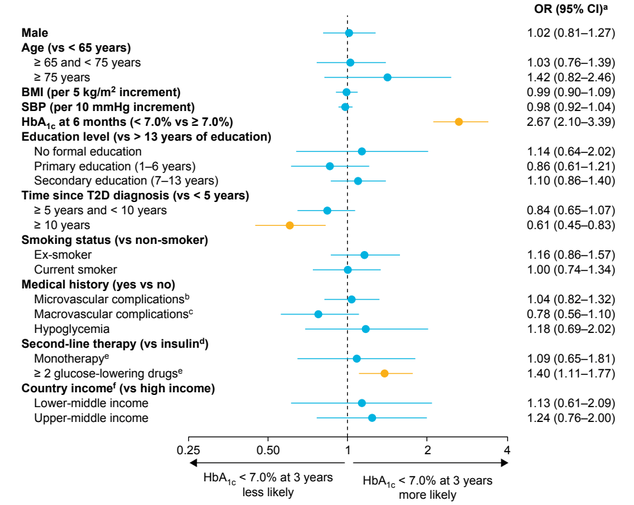


HbA_{1c}, glycated hemoglobin; WHO, World Health Organization.

Strengths and limitations

- The DISCOVER study includes data from a large, heterogeneous population of patients with T2D, including data from many countries that have rarely or never been studied before.
- In line with routine clinical practice, some variables of interest were not collected at all time points.
- It was not possible to assess patient adherence to glucose-lowering medication.

Figure 2. Factors associated with having an HbA_{1c} level < 7.0% after 3 years of follow-up.



Statistically significant factors ($p < 0.05$) are shown in yellow.
[a]ORs estimated using a hierarchical regression model adjusted for all variables in the figure. [b]Includes nephropathy, retinopathy and neuropathy. [c]Includes coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use. [d]On its own or as part of a combination therapy. [e]Excludes insulin. [f]Country income estimated using gross national income per capita as reported by World Bank bandings for fiscal year 18 (lower-middle income: US$1005–3995; upper-middle income: US$3956–12 235; high income: ≥ US$12 236).[5]
BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated hemoglobin; OR, odds ratio; SBP, systolic blood pressure; T2D, type 2 diabetes.

Conclusions

- Fewer than a third of patients with HbA_{1c} levels ≥ 9.0% when initiating second-line glucose-lowering therapy had an HbA_{1c} level < 7.0% after 3 years of follow-up.
- Having an HbA_{1c} level < 7.0% at 6 months was the single greatest predictor of having an HbA_{1c} level < 7.0% at 3 years.
- Receiving multiple oral glucose-lowering medications at second-line (as opposed to insulin) also increased the likelihood of having an HbA_{1c} level < 7.0% after 3 years.
- A longer time between T2D diagnosis and initiation of second-line therapy was associated with a decreased likelihood of having an HbA_{1c} level < 7.0% after 3 years.
- Together, these findings suggest that early, intense intervention is key to achieving long-term glycemic control in patients with HbA_{1c} levels > 9.0% at initiation of second-line therapy.

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