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Global patterns of comprehensive cardiovascular risk factor control in patients with type 2 diabetes mellitus: Insights from the DISCOVER study

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Abstract

Aim: To investigate global patterns of cardiovascular risk factor control in patients with type 2 diabetes mellitus (T2D).

Methods: DISCOVER is an international, observational cohort study of patients with T2D beginning second-line glucose-lowering therapy. Risk factor management was examined among eligible patients (ie, those with the risk factor) at study baseline. Inter-country variability was estimated using median odds ratios (MORs).

Results: Among 14 343 patients with T2D from 34 countries, the mean age was 57.4 ± 12.0 years and the median (interquartile range) duration of T2D was 4.2 (2.0–8.0) years; 11.8% had documented atherosclerotic cardiovascular disease (ASCVD). Among eligible patients, blood pressure was controlled in 67.5% (9284/13756), statins were prescribed in 43.7% (5775/13208), angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers were prescribed in 55.6% (5292/9512), aspirin was prescribed in 53.3% of those with established ASCVD (876/1645), and 84.4% (12 102/14343) were non-smoking. Only 21.5% of patients (3088/14343) had optimal risk factor management (defined as control of all eligible measures), with wide inter-country variability (10%–44%), even after adjusting for patient and site differences (MOR 1.47, 95% confidence interval 1.24–1.66).

Conclusion: Globally, comprehensive control of ASCVD risk factors is not being achieved in most patients, with wide variability among countries unaccounted for by patient and site differences. Better country-specific strategies are needed to implement comprehensive cardiovascular risk factor control consistently in patients with T2D to improve long-term outcomes.

KEYWORDS
cardiac risk factors, global patterns, type 2 diabetes mellitus

1 | INTRODUCTION

Cardiovascular disease remains the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2D).[1] Control of individual risk factors such as blood pressure (BP), cholesterol, smoking, and glycaemic status has been shown to reduce the incidence of microvascular complications, cardiovascular complications, and mortality in multiple trials.[2–6] Moreover, interventions that address multiple cardiovascular risk factors in combination can potentially reduce the risk of cardiovascular events and death further.[7–9] Despite this potential benefit, many patients with T2D have suboptimal control of cardiovascular risk factors, which is at least partly attributable to the complex nature of chronic disease management.[10,11] Alarmingly, after the steady decline in atherosclerotic cardiovascular disease (ASCVD) events among patients with T2D in the last 15 years, there has been a recent resurgence in these morbid ischaemic complications, particularly among those diagnosed before the age of 65 years.[12] These disturbing statistics highlight the urgent public health imperative to refocus on aggressive cardiovascular risk reduction programmes in patients living with T2D.

There is little contemporary evidence for patterns of cardiovascular risk factor control in patients with T2D globally that could help inform care of these patients. As such, we used data from the DISCOVER study (ClinicalTrials.gov identifiers NCT02322762 and NCT02226822), a large observational study of patients with T2D in whom second-line therapy was initiated. We used data from patients from 38 countries across six continents to assess (a) global patterns of optimal comprehensive cardiovascular risk factor control, (b) variability among countries in achieving optimal risk factor control, and (c) the degree to which variability could be explained by differences in patient or site-level factors. The description of these practice patterns could inform strategies to achieve better comprehensive cardiovascular risk factor management and, in turn, improve long-term outcomes.

2 | METHODS

2.1 | Study population and protocol

DISCOVER (NCT02322762, NCT02226822) is a 3-year, non-interventional, prospective study assessing treatment and clinical outcomes in patients with T2D in 38 countries beginning a second-line therapy from September 2014 to June 13, 2016. Consecutive adult (≥18 years) patients with T2D were invited to participate at initiation of a second-line glucose-lowering treatment (add-on or switching) after first-line oral monotherapy, dual therapy, or triple therapy. Patients were excluded if they had type 1 diabetes, end-stage renal disease on dialysis or renal transplant, were pregnant, or had received insulin or another injectable agent or herbal/natural supplement alone as a first-line therapy. The 38 countries were grouped by six regions according to the World Health Organization (WHO) classification: (a) Africa: Algeria, South Africa; (b) Americas: Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico, Panama; (c) South-East Asia: India, Indonesia; (d) Europe: Austria, Czech Republic, Denmark, France, Italy, Netherlands, Norway, Poland, Russia, Spain, Sweden, Turkey; (e) Eastern Mediterranean: Bahrain, Egypt, Jordan, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia, United Arab Emirates; and (f) Western Pacific: Australia, China, Japan, Malaysia, South Korea, Taiwan. Data from patients enrolled from Denmark, Norway and Sweden were not included in the present analysis owing to high rates of incomplete baseline data for the Scandinavian countries. Data from China were not available at the time of publication for administrative reasons. Detailed review of literature and data from the national coordinating investigators from each country regarding national diabetes management practices (including type of physicians, practice location and type, and geographical distribution) informed the selection of sites within each country such that enrolled patients would represent as much as possible the care within that country. Study site characteristics according to WHO regions are described in Supplementary Table 1. The study protocol was approved by clinical research ethics committees in each participating country and the relevant institutional review boards at each site. The protocol complied with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and the local regulations for clinical research. All study participants provided written informed consent.

Data on patient demographics, socio-economic factors, medical history, comorbidities, laboratory and vital status measurements, micro- and macrovascular complications, and medications were collected using a standardized electronic case report form.[13] Presence of cardiovascular risk factors,such as hypertension and hyperlipidaemia, were defined as per local investigator and per care guidelines used in that country. ASCVD was defined as presence of history of coronary artery disease, cerebrovascular disease or peripheral vascular disease, also as reported by local site investigators. Any microvascular complication was defined as presence of either diabetic retinopathy, nephropathy or neuropathy. As the study was observational in nature, all variables collected were measured during routine clinical care, and no additional measurement of laboratory or clinical variables was mandated.

2.2 | Definition of optimal cardiovascular risk factor management

Based on international diabetes guidelines,[14,15] optimal cardiovascular risk factor management was defined as control of all of the following risk factors among eligible patients: (a) systolic BP <140 mmHg (all patients); (b) statin prescription (patients aged ≥40 years or with ASCVD); (c) non-smoking status (all patients); (d) angiotensin-

converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) prescription (patients with hypertension or albuminuria); and (e) daily aspirin (patients with established ASCVD). As eligibility for the DISCOVER study included initiation of second-line glucose-lowering therapy, glycated haemoglobin (HbA1c) levels at presentation were likely to be suboptimally controlled in the majority of patients; thus glycaemic control was not included in the analysis of risk factor control. Optimal comprehensive cardiovascular risk factor control was defined as control of all eligible risk factors. Given the increasing focus of guidelines on statin treatment regardless of cholesterol level, LDL cholesterol concentration was not used to define optimal lipid control. Lifestyle counselling regarding physical activity and diet could not be reliably assessed owing to high rates of missing data.

We also conducted a secondary analysis and reported rates of individual risk factor control based on the following definitions: (a) systolic BP < 140 mmHg only among patients with history of reported hypertension; (b) LDL cholesterol <2.59 mmol/L among patients with a lipid panel checked within a year of baseline; (c) aspirin use for primary prevention (among patients aged 40 years or older at higher cardiovascular risk (defined as co-existing comorbidities of hypertension, hyperlipidaemia, chronic kidney disease or heart failure).

2.3 | Statistical analysis

Only baseline assessment data were used for these analyses. Continuous variables were described using mean and SD or median and interquartile range; categorical variables were described as frequency.

Rates of control of each cardiovascular risk factor and the composite of optimal cardiovascular risk factor control were calculated globally and for each WHO region. Using hierarchical logistic regression models, these global and WHO region-specific rates were adjusted for age, sex, history of ASCVD, and duration of T2D.

Intercountry variability in achieving optimal comprehensive cardiovascular risk factor control was explored using median odds ratios (MORs), which estimate the median value of the odds ratios obtained from comparing the odds of achieving optimal comprehensive cardiovascular risk factor control between two patients with identical risk factors from two randomly selected countries (ratio of the country with the highest odds and the country with the lowest odds, therefore, the MOR is always greater than or equal to 1). An MOR of 1 indicates no country-level variation in risk factor control, with higher MORs representing increased variability in risk factor control due to country, independent of patient- or site-level differences. The initial model included patient factors only (age, sex, body mass index, education, employment, ASCVD, duration of T2D, hypertension, hyperlipidaemia, smoking, heart failure, chronic kidney disease, microvascular disease), with a second model also including site-level characteristics (centre type [primary care, community, teaching centre, diabetes centre] and location [urban vs. rural], provider type, patient volume at enrolling centre, and availability of specialty care).

Patient sociodemographic and clinical characteristics were compared between groups with suboptimal and optimal cardiovascular risk factor control using the *t*-test or Wilcoxon's rank sum test for continuous variables and the chi-squared or Fisher's exact test for categorical variables. A multivariable hierarchical logistic regression model was built to identify patient and site factors associated with optimal risk factor control within different countries.

We used complete-case analyses for all primary analyses. The rate of missing data for the primary analysis was less than 5%, with systolic BP information missing in 4.1%, smoking information missing in 2.5% and ASCVD information missing in 2.8% of the population. All analyses were conducted using SAS 9.4 software (SAS Institute, Cary, North Carolina). Two-sided *P* values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Study cohort

Among 15 992 patients with T2D beginning second-line therapy from 38 countries enrolled in DISCOVER, 1649 were excluded from Denmark, Norway, Sweden and China due to incomplete data at the time of publication. As such, our analysis included 14 343 participants from 34 countries: 53.8% were male, their mean (SD) age was 57.4 (12.0) years, mean (SD) body mass index was 29.3 (6.0) kg/m^2, and median (interquartile range) duration of T2D was 4.2 (2.0–8.0) years (Table 1). The mean duration of diabetes at baseline for our study cohort was 69.1 ± 64.4 months, and 12 121 patients (84.5%) had diabetes for at least 1 year. Prior to enrolment, 75.9% of patients were on oral monotherapy (8199 metformin, 1047 sulphonylureas, 1164 dipeptidyl peptidase-4 [DPP-4] inhibitors, 470 others), 20.3% of patients were on dual therapy (2138 metformin plus a sulphonylurea, 483 metformin plus a DPP-4 inhibitor, 169 metformin plus other, 114 other combinations) and 3.6% of patients were on triple therapy (215 on metformin +sulphonylureas+DPP-4 inhibitors, 184 on metformin+sulphonylureas +thiazolidinedianones, 116 other combinations). Lack of efficacy was cited as the most common reason for switching to second-line glucose-lowering treatment, cited in 89% of the study cohort. A total of 1645 patients (11.8%) had documented ASCVD (coronary artery disease, cerebrovascular disease, peripheral artery disease), 7568 (52.8%) had history of hypertension, and 559 (4.5%) had history of albuminuria. Their mean (SD) HbA1c was 67.2 (18.6) mmol/mol and mean (SD) LDL cholesterol level was 2.82 (1.0) mmol/L. ACE inhibitors/ARBs were prescribed in 38.5% (of overall cohort), beta-blockers in 14.3%, calcium channel blockers in 15.4% and diuretics were prescribed in 12.7% of the population.

3.2 | Cardiovascular risk factor control

A total of 942 patients (6.6%) were only eligible for two risk factor metrics, 4350 (30.3%) were eligible for three, 7694 (53.6%) were eligible for four, and 1357 (9.5%) were eligible for all five metrics. Among all eligible patients, BP was controlled in 67.5% (9284/13756), statin

TABLE 1 Baseline characteristics of patients with type 2 diabetes with and without optimal comprehensive cardiovascular risk factor control in the DISCOVER study

Characteristic	Total n = 14 343	Cardiovascular risk factors with optimal control		P*
		Yes n = 3088	No n = 11 255	
Demographics				
Age, years, mean ± SD	57.4 ± 12.0	54.2 ± 13.5	58.2 ± 11.5	<0.001
Male sex, n (%)	7714 (53.8)	1585 (51.3)	6129 (54.5)	0.002
Self-reported ethnicity, n (%)				<0.001
White	3608 (26.4)	582 (19.6)	3026 (28.3)	
Black	304 (2.2)	68 (2.3)	236 (2.2)	
Mixed	211 (1.5)	43 (1.4)	168 (1.6)	
Asian	6310 (46.2)	1548 (52.0)	4762 (44.5)	
Hispanic	936 (6.8)	249 (8.4)	687 (6.4)	
Arabic	2142 (15.7)	470 (15.8)	1672 (15.6)	
Other	160 (1.2)	16 (0.5)	144 (1.3)	
Education level, n (%)				<0.001
No formal education	397 (3.1)	74 (2.5)	323 (3.2)	
Primary (1–6 years)	2028 (15.6)	346 (11.9)	1682 (16.6)	
Secondary (7–13 years)	6414 (49.3)	1308 (45.0)	5106 (50.5)	
University or higher (≥13 years)	4175 (32.1)	1181 (40.6)	2994 (29.6)	
Main working status, n (%)				<0.001
Employed	4914 (36.5)	1125 (37.9)	3789 (36.1)	
Self-employed	1668 (12.4)	392 (13.2)	1276 (12.1)	
Disabled	69 (0.5)	9 (0.3)	60 (0.6)	
Not working	3990 (29.6)	913 (30.8)	3077 (29.3)	
Retired	2765 (20.5)	515 (17.4)	2250 (21.4)	
Health insurance coverage, n (%)				<0.001
Private	2029 (15.4)	568 (20.1)	1461 (14.1)	
Public/governmental	7647 (57.9)	1480 (52.3)	6167 (59.5)	
Mixed	354 (2.7)	66 (2.3)	288 (2.8)	
No insurance	3168 (24.0)	717 (25.3)	2451 (23.6)	
Tobacco smoking, n (%)				<0.001
Non-smoker	9831 (70.3)	2570 (83.2)	7261 (66.6)	
Former smoker	2271 (16.2)	518 (16.8)	1753 (16.1)	
Current smoker	1889 (13.5)	0 (0.0)	1889 (17.3)	
Vitals and laboratory values				
Body mass index, kg/m^2, mean ± SD	29.3 ± 6.0	28.9 ± 5.8	29.5 ± 6.1	<0.001
Systolic BP, mmHg, mean ± SD	132.4 ± 16.6	123.5 ± 9.5	134.8 ± 17.2	<0.001
Diastolic BP, mmHg, mean ± SD	79.7 ± 10.0	76.2 ± 7.9	80.7 ± 10.2	<0.001
HbA_{1c}, mmol/mol, mean ± SD	67.2 (18.6)	67.2 (17.4)	67.2 (19.0)	0.090
LDL cholesterol, mmol/L, mean ± SD	2.82 (1.0)	2.76 ± 1.02	2.85 ± 0.99	<0.001
Serum creatinine, umol/L, mean ± SD	88.42 ± 88.42	88.42 ± 88.42	88.42 ± 88.42	0.298
Medical history at baseline				
Time since T2D diagnosis, months, median (IQR)	50.4 (24.3, 95.9)	49.1 (23.8, 85.6)	51.0 (24.5, 97.5)	<0.001
Atherosclerotic cardiovascular disease, n (%)	1645 (11.8)	292 (9.5)	1353 (12.5)	<0.001
Heart failure, n (%)	516 (3.6)	57 (1.8)	459 (4.1)	<0.001
Chronic kidney disease, n (%)	759 (5.3)	139 (4.5)	620 (5.5)	0.026
Albuminuria, n (%)	559 (4.5)	76 (2.7)	483 (5.0)	<0.001
Hypertension, n (%)	7568 (52.8)	1288 (41.7)	6280 (55.8)	<0.001

TABLE 1 (Continued)

Characteristic	Total n = 14 343	Cardiovascular risk factors with optimal control		P*
		Yes n = 3088	No n = 11 255	
Hyperlipidaemia, n (%)	6852 (47.8)	2129 (69.0)	4723 (42.0)	<0.001
Any microvascular complication, n (%)	10 468 (73.0)	2373 (76.9)	8095 (72.0)	<0.001
cardiovascular medications				
ACE inhibitors/ARBs	5524 (38.5)	1413 (45.8)	4111 (36.5)	<0.001
Beta-blockers	2046 (14.3)	330 (10.7)	1716 (15.2)	<0.001
Calcium channel blockers	2213 (15.4)	353 (11.4)	1860 (16.5)	<0.001
Diuretics	1825 (12.7)	361 (11.7)	1464 (13.0)	0.051
Any lipid-lowering drugs	6824 (47.6)	2658 (86.1)	4166 (37.0)	<0.001
High-intensity statins	1662 (13.3)	586 (21.0)	1076 (11.1)	<0.001
Low-intensity statins	4706 (32.8)	2066 (66.9)	2640 (23.5)	<0.001
Fibrates	623 (4.3)	137 (4.4)	486 (4.3)	0.774
Any anti-platelet drugs	2601 (18.1)	772 (25.0)	1829 (16.3)	<0.001
Site characteristics				
Type of centre, n (%)				<0.001
Primary care centre	4524 (32.5)	1009 (33.4)	3515 (32.2)	
General/community hospital	1896 (13.6)	353 (11.7)	1543 (14.2)	
University/teaching hospital	2052 (14.7)	400 (13.2)	1652 (15.2)	
Specialized diabetes centre	2914 (20.9)	726 (24.0)	2188 (20.1)	
Other	2534 (18.2)	531 (17.6)	2003 (18.4)	
Location, n (%)				<0.001
Urban	11 600 (83.5)	2618 (87.1)	8982 (82.5)	
Rural	2295 (16.5)	388 (12.9)	1907 (17.5)	
Centre funding, n (%)				<0.001
Public/governmental	4049 (29.3)	810 (27.0)	3239 (29.9)	
Private	9638 (69.7)	2167 (72.3)	7471 (69.0)	
Mixed	133 (1.0)	19 (0.6)	114 (1.1)	
Main type of patient referral, n (%)				<0.001
Patient self-referral	6400 (46.2)	1279 (42.7)	5121 (47.2)	
Primary care referral	7285 (52.6)	1678 (56.0)	5607 (51.7)	
Secondary care referral	158 (1.1)	39 (1.3)	119 (1.1)	
Estimated number of patients with T2D per month, n (%)				<0.001
<10	686 (4.9)	79 (2.6)	607 (5.6)	
10–20	584 (4.2)	124 (4.1)	460 (4.2)	
21–50	2457 (17.7)	575 (19.0)	1882 (17.3)	
>50	10 185 (73.2)	2241 (74.2)	7944 (72.9)	
Availability of specialty care at the site, n (%)	5196 (37.3)	920 (30.5)	4276 (39.2)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; HbA1c, glycated haemoglobin; IQR, interquartile range; T2D, type 2 diabetes mellitus.

*Comparisons made between two groups using Pearson's chi-squared test or Fisher's exact test for categorical variables or t-test or Wilcoxon rank sum test for continuous variables.

treatment was prescribed in 43.7% (5775/13208), ACE inhibitor/ARB treatment was prescribed in 55.6% (5292/9512 of patients with hypertension or albuminuria), aspirin was prescribed in 53.3% (876/1645), and 84.4% (12 102/14343) were non-smoking (Table 2). Overall, 21.5% (3088/14343) of patients had optimal risk factor control, meaning they had no uncontrolled risk factors. Table 1 shows the differences in patient and site characteristics between those with and without optimal combined cardiovascular risk factor control.

Among patients with known history of hypertension, BP was controlled in 57.1% (4185/7332). Among patients who had a lipid panel checked within a year of baseline, LDL cholesterol 2.59 mmol/L was present in 43.8% (3436/7842). Aspirin use for primary prevention

TABLE 2 Overall and World Health Organization region-specific rates of cardiovascular risk factor control

	Region[a]						
Risk factor control	**Overall (n = 14 343)**	**Africa (n = 812)**	**Americas (n = 2002)**	**South-East Asia (n = 3360)**	**Europe (n = 3123)**	**Eastern Mediterranean (n = 2182)**	**Western Pacific (n = 2864)**
Systolic BP < 140 mmHg	9284/13 756 (67.5)	548/809 (67.7)	1323/1916 (69.1)	2529/3322 (76.1)	1630/2913 (56.0)	1302/2031 (64.1)	1952/2765 (70.6)
Statin treatment	5775/13 208 (43.7)	344/739 (46.5)	778/1881 (41.4)	1318/2898 (45.5)	1289/3047 (42.3)	901/1956 (46.1)	1145/2687 (42.6)
Nonsmoking status	12 102/14 343 (84.4)	726/812 (89.4)	1759/2002 (87.9)	3194/3360 (95.1)	2489/3123 (79.7)	1768/2182 (81.0)	2166/2864 (75.6)
ACE inhibitor/ARB for hypertension/ albuminuria	5292/9512 (55.6)	297/565 (52.6)	799/1333 (59.9)	939/2047 (45.9)	1606/2487 (64.6)	675/1240 (54.4)	976/1840 (53.0)
Secondary prevention with aspirin for ASCVD	876/1645 (53.3)	55/72 (76.4)	95/202 (47.0)	53/124 (42.7)	393/752 (52.3)	139/209 (66.5)	141/286 (49.3)
Optimal comprehensive risk factor control[b]	3088/14 343 (21.5)	192/812 (23.6)	443/2002 (22.1)	963/3360 (28.7)	448/3123 (14.3)	488/2182 (22.4)	554/2864 (19.3)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure.

[a]Values for all regions are n/N (%). The denominators in the table represent the number of patient eligible to have that risk factor controlled.

[b]Optimal comprehensive risk factor control is defined as patients with optimal control of all eligible risk factors for that population.

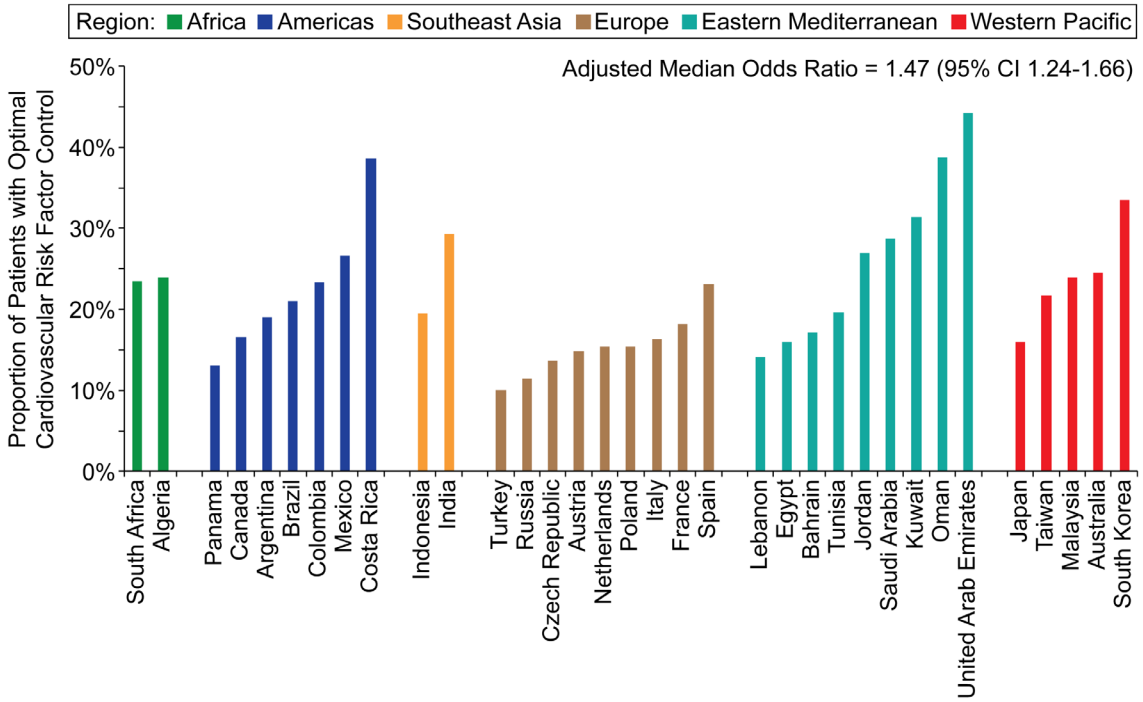

FIGURE 1 Variability among countries in optimal comprehensive cardiovascular risk factor control in patients with type 2 diabetes enrolled in the DISCOVER study. Median odds ratios (MORs) estimate the median value of the odds ratios from two patients with identical risk factors from two randomly selected countries. An MOR of 1 indicates no country-level variation in cardiovascular risk factor control, with higher MORs representing increased variability in risk factor control due to country specific effect, independent of patient and site-level differences

TABLE 3 World Health Organization region-specific rates of cardiovascular risk factor control (%) adjusted for age, sex, atherosclerotic cardiovascular disease and duration of type 2 diabetes mellitus

	Region[a]					
Risk factor control	Africa (n = 812)	Americas (n = 2002)	South-East Asia (n = 3360)	Europe (n = 3123)	Eastern Mediterranean (n = 2182)	Western Pacific (n = 2864)
Systolic BP < 140 mmHg	70.0	70.3	75.1	57.9	62.9	72.0
Statin treatment	47.9	43.9	48.5	41.9	47.9	43.5
Nonsmoking status	90.0	89.2	96.6	79.6	85.5	78.0
ACE inhibitors/ARBs for hypertension/albuminuria	53.6	60.8	48.6	60.7	56.1	51.9
Secondary prevention with aspirin for ASCVD	76.4	45.3	41.3	51.7	65.6	48.7

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure.
[a]Values for all regions are %.

among high-risk patients with T2D was low at 21.5% (2048/9510; **Supplement Table 2**).

3.3 | Risk factor control by WHO region

Smoking was the most well-controlled risk factor across all WHO regions, with non-smoking rates varying from 75.6% to 95.1%. Statin treatment was the least well-controlled risk factor, with more than half of the eligible study cohort in all WHO regions not being on a statin; rates of statin use varied from 41.4% to 46.5%. There was substantial variability in individual and combined cardiovascular risk factor control across countries and WHO regions (Figure 1 and Tables 2 and 3). Optimal risk factor control ranged across regions from 19.3% in the Western Pacific to 28.7% in South-East Asia.

3.4 | Variability in optimal comprehensive risk factor control among countries

In the hierarchical model that accounted for patient demographic and clinical factors, the MOR for optimal risk factor control was 1.42 (95% confidence interval [CI] 1.23, 1.57), indicating that two hypothetically identical patients would have 1.42 times different odds in optimal risk factor control in one country versus another. This variability did not meaningfully change after adjustment for site characteristics (adjusted MOR 1.47, 95% CI 1.24, 1.66; Figure 1), suggesting that patient and site characteristics were not the primary drivers of this observed variability.

3.5 | Factors associated with optimal comprehensive risk factor control within countries

In adjusted analyses, the patient factors older age, higher body mass index, history of hypertension, smoking, and microvascular complications were associated with decreased odds of optimal risk factor control, whereas higher education (post-secondary level), history of hyperlipidaemia and chronic kidney disease were associated with greater odds of optimal risk factor control (**Supplement Table 3**).

4 | DISCUSSION

Despite the importance of risk factor management in the prevention of ASCVD, we found suboptimal rates of cardiovascular risk factor control in a global study of patients with T2D. Rates of individual risk factor control ranged from 44% with statin prescription to 84% with non-smoking status, and only approximately one in five patients had optimal cardiovascular risk factor control, as defined by no uncontrolled risk factors. In addition, there was significant variation among countries in achievement of optimal comprehensive cardiovascular risk factor control, which was not explained by differences in patient and site characteristics. Further investigation is needed to explore the structural factors across these different healthcare delivery systems that could be the key drivers of these variations in care.

Prior studies have consistently found that comprehensive cardiovascular risk factor control significantly reduces the risk of major cardiovascular events and death in patients with T2D, both in primary[8,16,17] and secondary[7,18] prevention populations. Among 271 174 Swedish patients with T2D, those with multiple cardiovascular risk factors under control had a similar to no excess risk of major cardiac events compared with the general population without diabetes.[17] The benefits of risk factor control are even more pronounced in patients with T2D and known ASCVD, at least in absolute terms. In a *post hoc* analysis of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with diabetes and ASCVD, there was a stepwise decrease in the risk of the composite of myocardial infarction, stroke, or cardiovascular death over a median of 3 years of follow-up with each cardiovascular risk factor controlled.[18] As a result, optimal control of cardiovascular risk factors is strongly supported in multiple guideline statements for patients with T2D.[14,15]

Despite this strong evidence base and guideline recommendation, a large treatment gap is evident in the optimal control of cardiovascular risk factors in patients with T2D.[10,17,19] Among 292 170 patients with diabetes in a large British outpatient primary care database, only 14.7% had optimal control of glycaemia and all cardiovascular risk factors including BP, lipids, statins and smoking a year after their initial diagnosis,[19] despite higher rates of prescription of ACE inhibitors/ARBs, statin and anti-hypertensive medications ranging from 47% to 71% compared to our study cohort. Among all adults with T2D enrolled in a nationally representative survey in the United States, only 16% had optimal control of glycaemia and all cardiovascular risk factors. Only 30% of patients in TECOS had optimal cardiovascular risk factor control, even in a secondary prevention population in a clinical trial setting where rates of aspirin, statin and ACE inhibitor/ARB prescription were 80% and higher.[18] This treatment gap may be even more pronounced in low-/middle-income countries, with the International Diabetes Management Practice Study showing that only 3.6% of patients had optimal control of the combination of glucose level, BP and lipids.[20] Our study extends the results of the previous studies by providing important insights into contemporary patterns of cardiovascular risk factor control in a real-world setting globally (including in several countries and regions that have little or no previously collected data), finding that these treatment gaps continue to persist with only one in five patients having optimal comprehensive cardiovascular risk factor control. Overall rates of prescription of anti-hypertensive medications and ACE inhibitors/ARBs in our study cohort was also lower than some of the studies above, being 50% and 39%, respectively. Our study further shows the high variability in care across different regions around the world, even after accounting for differences in patient and site characteristics. As such, it is possible that there are other unmeasured socio-economic or structural factors in processes of care for these patients that may be contributing to this high variability in care that was not captured by the variables collected in the study.

Our study highlights a critical opportunity to improve care and outcomes in patients with T2D globally. Most patients with T2D have one or more cardiovascular risk factors, and consistently prioritizing control of factors such as hypertension, smoking, proteinuria, and dyslipidaemia could have a substantial global impact on the cardiovascular morbidity and mortality associated with T2D. Certain patient factors such as older age, obesity, known history of hypertension and history of microvascular complications of diabetes were associated with poor optimal cardiovascular risk factor control in our study cohort. Education and increased awareness of these higher-risk patient factors among physicians and care providers can help improve cardiovascular risk factor control among these patients. Never has the imperative to focus and increase the efforts on risk factor control been more important than now, with recent US data suggesting increases in cardiac events among young and middle-aged patients with T2D along with a plateau in improvements in older patients.[12] While identifying new drugs and therapies that decrease

cardiovascular risk is important, the results of the present study suggest that we also need to focus on optimizing well-established interventions for reducing cardiovascular risk – interventions with an extensive evidence base that are relatively affordable. Gaps in provision of care (due to poor identification or lack of resources) and patient adherence to and engagement with treatment may be responsible for poor risk factor control. These gaps may also differ among countries. Nearly 80% of people with diabetes live in low-/middle-income countries,[21] and many do not have access to basic healthcare and medications.[22,23] Due to the low cost of interventions targeting cardiovascular risk factor control, they are likely to not only be cost-effective, but cost-saving, especially in higher-risk diabetes patients, emphasizing the importance of implementing these even in relatively resource-poor healthcare environments. Future research should focus on identifying effective strategies to increase cardiovascular risk factor control in patients with T2D across countries with different economies, societal structures, and healthcare systems.

Our findings should be interpreted in the context of the following potential limitations. First, DISCOVER includes a wide range of countries across six continents and attempted to enrol a representative population within each included country; however, it is unclear if our findings truly reflect care within each country or all generalizable outside of the included countries. Given their participation in DISCOVER, it is possible that participating sites may be more focused on quality care, which would indicate that our estimates are best-case scenarios. Second, given the relatively low prevalence of ASCVD in our cohort, the results may not be reflective of rates of cardiovascular risk factor control for secondary prevention. Our study reflects control of risk factors among patients who are at a relatively early stage of diabetes, with the mean duration of diabetes being ~4 years, even though >80% of the study population had diabetes for at least 1 year or longer. All patients in the study, by virtue of the inclusion criteria, required escalation of diabetes therapy. Our study cohort also had lower rates of comorbidities such as chronic kidney disease and albuminuria, making the cohort lower-risk, potentially affecting the generalizability of the findings. Third, lifestyle counselling on physical activity and diet is also an important aspect of cardiovascular risk factor control, along with adherence to medications, but these measures could not be accounted for in the present study owing to high rates of missing data. Fourth, we applied the same definition of risk factor control across all countries, realizing that there may be some country-specific differences in guidelines for quality care.

In conclusion, in a global study of 14 343 patients with relatively early-stage T2D across 34 countries, the majority did not have optimal control of cardiovascular risk factors, with a large variation in risk factor control among countries. This variability was not explained by differences in patient, provider, or site characteristics, suggesting that it might be related to structural differences in healthcare systems. To improve long-term cardiovascular outcomes in patients with T2D, better strategies are needed to implement current guidelines to provide comprehensive cardiovascular risk factor control in all patients with T2D.

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The initial draft of the manuscript was by K.K.P. 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. K.K.P. is the guarantor of this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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