

Diabetes prescription patterns in Costa Rica and Panama among patients switching to a second-line medication. Evidence from the DISCOVER real-world diabetes registry.

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Abstract

Aims: to describe the prescriptions patterns of second line medications in patients with diabetes in Costa Rica and Panama.

Methods: DISCOVER is a registry of patients with type 2 diabetes that are switching from first- to second-line medications. We analyzed medication choice and reasons to switch by country.

Results: 219 patients were included, 127 in Costa Rica and 92 in Panama. The most frequently prescribed first-line medication was metformin, followed by sulphonylureas in Panama and a combination of metformin and dipeptidyl peptidase-4 inhibitors (iDPP4) in Costa Rica. DPP4 inhibitors plus metformin was the most commonly prescribed second line medication in both countries, followed by metformin combined with SGLT2 inhibitors in Costa Rica and iDPP4 in monotherapy in Panama. The main reason to switch was efficacy. When choosing the second-line medication, the main reasons were efficacy, weight loss, and hypoglycemia risk in both countries (tolerability was also common in Panama).

Conclusions: In these two Latin American countries the main reason to switch to second line medication was efficacy and the most prescribed agent was metformin plus iDPP4.

Introduction

The prevalence of type 2 diabetes has increased worldwide, from 8.3% in 2013 to 9.3% in 2019 (1, 2). This increase has been higher in low/middle income countries compared to high income ones. For 2025, in Central America (including Costa Rica and Panama) there will be more than 2 million patients with diabetes, a 162% increase from 1995(3, 4). The increase in these two countries is expected to be 8.1 and 10.5%, respectively (5). A recent meta-analysis showed that diabetes increased all cause and cardiovascular mortality at a greater extent in Latin American countries compared to high income ones (6).

Diabetes treatment includes behavioral and pharmacological approaches. There are several medications currently approved and choice depends on availability and healthcare system type. Costa Rica and Panama have both public and private healthcare systems. In Costa Rica, the only one public system is the Caja Costarricense del Seguro Social (Social Security System) that covers 95% of the population. In Panama, two public systems (not mutually exclusive) are available, the Ministerio de Salud (Health Ministry, 74.2% coverage) and Caja de Seguro Social (Social Security, 75% coverage). Private care is available in both countries and paid through insurance or out-of-pocket. Regarding diabetes treatment, different medications are available depending on each country and system type.

Globally, it is estimated that only 23% (30% in Latin America) of all patients with diabetes achieve targets(7). However, for treating physicians it is now a challenge to choose the treatment scheme suitable for each patient. Availability, affordability, patients' preference, side effects, and success rates, are just some of the determinants when choosing the appropriate medication(8). Current guidelines suggest

tailoring treatment choices depending on patient characteristics(9). However, in the real world, little is known about the reasons that drive physicians to stop and select an antidiabetic drug.

DISCOVER is a worldwide study designed to provide real-world data on how first- and second-line diabetes medications are prescribed. According to DISCOVER Latin America, there is a great heterogeneity between countries regarding when to start and how to select the second line medications (10). In that paper, Costa Rica and Panama were reported together as Central America and compared to other countries in Latin America (10). Given that Costa Rica and Panama are two countries with different healthcare systems we sought to describe prescription patterns using data from these local DISCOVER databases.

Materials And Methods

DISCOVER is an observational diabetes registry of patients switching from first- to second-line glucose-lowering medication (mono- or combination) in 38 countries across six continents (45). Patients were recruited from December 2014 to June 2016 for a 3-year follow-up after being prescribed a second-line medication. In this manuscript we report baseline data for Costa Rica and Panama. Enrolled patients underwent clinical assessments and received standard medical care as determined by their treating physician. Physicians invited to participate were selected across different specialties and healthcare settings to ensure that the findings would be representative of diabetes management in each country. The sponsor selected the sites and investigators in each country based on patient volume and investigator's experience in clinical trials. In Costa Rica, only private centers were selected given that the public ones at the time of enrollment were in the process of approval of new regulations regarding clinical studies. In Panama, 3 centers were invited to participate but one (private) did not recruit any patients. Therefore, the present study presents data from 6 private centers in Costa Rica and 2 (one public and one private) in Panama.

Patient participation was on a voluntary basis and they could withdraw from the registry at any time without compromising their treatment. The protocol was approved by Comité Ético Científico Instituto Costarricense de Investigaciones Clínicas (CEC-ICIC) in Costa Rica and by the Comité de Bioética de la Investigación del Instituto Conmemorativo Gorgas de Estudios de la Salud in Panama. All participating patients provided signed informed consent.

To be included patients must be at least 18 years old and type 2 diabetes. In addition, they must require second-line (add-on or switching) after first-line oral medication, defined as any antidiabetic drug either monotherapy or fixed dose combination that was started after diagnosis. Patients with type 1 diabetes, pregnancy, on chemotherapy or steroids, undergoing dialysis or had received a renal transplant were excluded. Those taking alternative diabetes treatments (e.g., herbal remedies), insulin or an injectable agent as first-line treatment, initiating dual therapy after two different lines of monotherapy were also excluded. Other exclusion criteria included enrollment in any interventional trial and if the recruiting

physician considered that the patient had any other circumstance or condition that could significantly decrease the likelihood of follow-up (11).

Demographic and anthropometric data, laboratory results, past medical history, medications, and healthcare provider type were gathered. Waist circumference was measured by the investigator in a standardized manner. Weight and height were taken by the investigator or nurse (as standard of care in each center) and then used to calculate the body mass index (BMI). Normal weight, overweight, and obesity were classified according to BMI categories. Blood tests included glycosylated hemoglobin (HbA1c), total, high-(HDL), and low-(LDL) density cholesterol. Treatment targets were defined as HbA1c < 7% (53 mmol/mol), BP < 130/90 mm Hg, and LDL cholesterol < 70 mg/dl. Regarding treatment, choice of first- and second-line were recorded and the reasons to switch therapy. All data were collected from the patients' charts (electronically when available).

Descriptive statistics were used to summarize demographic variables, medications, changes in HbA1c, blood glucose, lipid profile, BMI, waist circumference, blood pressure and complications, hospitalizations and hypoglycemia events. Analyses were done comparing each country using chi-square (Fisher exact test when appropriate) and ANOVA (Mann-Whitney when not normally distributed) in STATA.

Results

A total of 219 patients in 8 different sites (6 in Costa Rica, 2 in Panama) were recruited, 127 in Costa Rica and 92 in Panama. Most (5 in Costa Rica, 1 in Panama) sites were specialized in diabetes care with endocrinologists/diabetologists.

Most of the patients were female (61%) and mean age was 58.7 (\pm 12.8) years (Table 1). Waist circumference and BMI were significantly different by country. The former was, on average, significantly higher in Costa Rica compared to Panama. Likewise, the prevalence of obesity was 72% in Costa Rica and 26% in Panama. About two thirds of patients in each country had hypertension and the prevalence of hyperlipidemia was significantly higher in Costa Rica compared to Panama. Intake of lipid lowering medications was also significantly higher in Costa Rica (Table 1).

Table 1
Baseline demographic characteristics of patients in the DISCOVER-CA*

	Total	Costa Rica	Panama	p
	n (%)	n (%)	n (%)	
Total	219 (100)	127 (57.9)	92 (42.0)	
Male	86 (39.30)	55 (43.3)	31 (33.7%)	
Age (mean, SD)**	58.7 ± 12.8	57.0 ± 13.6	61.1 ± 11.4	0.02
Year since diagnosis (median, IQR)**	4.91 (1.24–9.98)	5.54 (1.32–8.02)	7.83 (1.13–10.74)	
< 0.001				
Waist circumference (cm)**	99.5 ± 16.6	105.5 ± 16.6	90.8 ± 12.2	< 0.001
Body mass index				0.0004
≤25	25 (15.92)	10 (9.3)	15 (30.0)	
25 to <30	61 (38.85)	39 (36.4)	22 (44.0)	
30≥	71 (45.22)	58 (54.2)	13 (26.0)	
Hypertension \$	131 (59.8)	72 (56.7)	59 (64.1)	0.2
Hyperlipidemia \$	85 (38.80)	58 (45.7)	27 (29.3)	0.01
Concomitant medications				
Antihypertensives	134 (61.20)	81 (63.8)	53 (57.6)	0.3
Lipid lowering	103 (47)	70 (55.1)	33 (35.9)	0.004
Antiplatelet	33 (15.10)	21 (16.5)	12 (13.0)	0.4

*Costa Rica and Panama; ** mean ± standard deviation; \$ as reported by treating physician

At the first visit, about one-third of patients in Costa Rica and nearly one quarter in Panama were lacking an HbA1c. For those who did, the number of patients with high blood pressure at physical exam was significantly higher in Panama (51%) compared to Costa Rica (25.8%). Most patients in both countries did not have any cholesterol results. Regarding total cholesterol, HDL, and LDL, most patients had high levels and there was no difference by country (Table 2).

Table 2
Patients with chronic disease risk factors screening tests and abnormal results. Costa Rica and Panama, DISCOVER -CA

	Costa Rica		Panama		p	
	(n = 127)		(n = 92)			
	Missing	n (%)	Missing	n (%)		
		n (%)		n (%)		
HbA1c > 7% (53 mmol/mol)*	25 (32.5)	67 (65.6)	31 (23.5)	42(68.8)	0.6	
Blood pressure > 130/90 mmHg	15 (16.8)	29 (25.8)	14 (12.2)	40 (51.3)	0.0003	
Cholesterol >180 mg/dL	64 (69.6)	26(41.3)	56 (50.4)	24 (66.7)	0.01	
HDL < 40M/50W mg/dL	66 (72.5)	34 (55.7)	59 (52.5)	20 (60.6)	0.2	
LDL > 70 mg/dL	68 (72.5)	50 (84.7)	57 (52.5)	28 (80.0)	0.3	

Reasons to switch to second-line medication did not differ by country. About two thirds switched due to lack of efficacy (Table 3) and about 20% due to side effects. Switching medication due to a hypoglycemic event was rare. To choose the second-line medication, there were significant differences between countries. In Costa Rica, the medication effect on weight loss was the most common followed by efficacy and tolerability. In Panama, it was efficacy followed by tolerability and weight. In both countries, cost was a not a common reason to choose the second-line medication.

Table 3
Reasons for switching from first- to second-line and choosing second-line therapy in the DISCOVER-CA*

n (%)	All 219 (100)	Cost Rica 127 (58)	Panama 92 (42)	p
Reasons to switch from fist- to second-line				
Lack of efficacy	146 (66.7)	88 (69.3)	58 (63)	0.33
Hypoglycemic event	5 (2.30)	2 (1.6)	3 (3.3)	0.4
Weight gain	13 (5.90)	5 (3.9)	8 (8.7%)	0.1
Side effect	39 (17.80)	24(18.9)	15 (16.3)	0.6
Affordability	3 (1.40)	3 (2.4)	0 (0)	
Reasons for choosing second line				
Efficacy	96 (43.80)	46 (36.2)	50 (54.3)	0.01
Tolerability	58 (26.50)	39 (30.7)	19 (20.7)	0.1
Weight	73 (33.3)	62 (48.8)	11 (12.0)	< 0.00001
Hypoglycemia	38 (17.40)	27 (21.3)	11 (12.)	0.07
Patient request	1 (0.50)	0 (0)	1 (1.1)	
Convenience	23 (10.50)	19 (15)	4 (4.3)	0.01
Access	23 (10.50)	12 (9.4)	11 (12)	0.5
Cost	9 (4.10)	7 (5.5)	2 (2.2)	0.2

The most frequently prescribed first-line medication was metformin (MET) (Table 4). While sulphonylureas (SU) were the second most commonly prescribed in Panama, they only accounted for 3% in Costa Rica. The second most common scheme used in Costa Rica was a combination of MET and dipeptidyl peptidase-4 inhibitors (iDPP4) (only 2% in Panama). The most common combination used as first-line in Panama was MET plus SU. Regarding second-line, while 11 different medications were prescribed in Costa Rica, only 7 in Panama. The MET plus iDPP4 combination was the most commonly used in both countries. Although this accounted for most in Panama (58.7%), it was only prescribed in 24% of patients in Costa Rica. MET plus (iSGLT2) accounted for another 20% of the prescriptions in Costa Rica. Only one patient started insulin (as monotherapy) on second-line and none in Panama.

Table 4
First and second line medications in Costa Rica and Panama, DISCOVER-CA

	Costa Rica		Panama	
Medication type	First	Second	First	Second
Metformin	75 (59.1)	2 (1.6)	67 (72.8)	3 (3.3)
Sulphonylureas	4 (3.1)		13 (14.1)	1 (1.1)
iDPP4 ¹	15 (11.8)	11 (8.7)		13 (14.1)
SGLT2 inhibitor ²		14 (11.0)		
Other mono	1 (0.8)			
Metformin + Sulphonylureas	7 (5.5)	9 (7.1)	10 (10.1)	3 (3.3)
Metformin + iDPP4	23 (18.1)	31 (24.4)	2 (2.2)	54 (58.7)
Metformin + SGLT2 inhibitor		26 (20.5)		
Other dual	2 (1.6)	7 (5.5)		7 (7.6)
Metformin + Sulphonylureas + iDPP4		3 (2.4)		9 (9.8)
Other three		22 (17.3)		
Other four		1 (0.8)		
Insulin		1 (0.8)		

1. iDPP4: Dipeptidyl peptidase 4 inhibitor 2. SGLT2 inhibitor: sodium glucose cotransporter-2 inhibitor

Discussion

According to our findings, the most common second-line medication prescribed in Costa Rica and Panama was a combination of MET plus iDPP4, followed by MET plus iSGLT2s in Costa Rica and iDPP4s monotherapy in Panama. To the best of our knowledge, this is the first study to analyze diabetes medications switching patterns in a real-world setting in Central America.

DISCOVER also includes data on CVD risk factors including blood pressure and cholesterol levels(11). In our sample, most patients had a history of hypertension and up to 50% had high blood pressure at clinical examination. Even though the prevalence of hypertension was lower in Costa Rica, use of antihypertensive drugs was higher compared to Panama. This may be due, in part, that hypertension report as a diagnosis could be lower in the former compared to the latter. Regarding cholesterol, nearly half our sample was taking a lipid-lowering drug, and these were more frequent in Costa Rica. Prevalence

of hypertension has been reported between 60% (Thailand and Mexico) and 80% (Scotland) and hypercholesterolemia between 35% (Mexico) and over 55% (Scotland, Iran, England, Colombia, Thailand, and United States) (12). Therefore, CVD risk factors among patients with diabetes in Costa Rica and Panama appear to be in the lower range compared to other countries (12).

The number of patients with missing data in both countries should be a matter of concern. Even for HbA1c, not all patients had baseline measurements. Why patients lack this information deserves further research. It might be due that some tests were performed outside of the 3-month window that was allowed in DISCOVER(11). For blood pressure, nearly 20% of the patients did not have the data registered in their chart. Missing data has also been reported elsewhere. Blood pressure was not recorded in 7.7% of patients with diabetes in Colombia, 16% in England, 0.5% in Iran, 3% in México, 15.1% in Scotland, 0.34% in Thailand and 10.5% in the United States. Cholesterol results were not available in 1.15%, 33.3%, 1.4%, 10%, 32.8%, 0.54% and 22.9% respectively (12). Strikingly, lower income countries have a higher rate of reporting of blood pressure and blood cholesterol compared to higher income ones. Even if this represents failure to document in the medical record, it should be a matter of concern as blood pressure and cholesterol control are interventions that decrease mortality in patients with diabetes.

Glycemic control (through HbA1c) was far from optimal despite the use of oral antidiabetic agents. Approximately one-third of patients in Costa Rica and Panama had HbA1c levels below 7% compared to 15.6% reported in Latin America.(10) When using HbA1c as a marker of glucose control our results in Costa Rica and Panama are similar to those reported on a systematic review in Latin America ⁽³⁷⁾ and are consistent with previous reports ^[2,26]. In the United States, 26% of patients met glucose targets, and in 27% of Colombian males and 24% of Colombian women(12). Our registry includes patients switching to second-line medication and therefore it is expected that most of them would have high HbA1c. However, the results show that there is a delay initiation of second line therapies and clinical inertia is a worldwide recognized issue.

First-line medication choice was in agreement with most evidence-based guidelines that include MET alone or in combination with DDP4 inhibitors(4)(13, 14). In addition, SU alone or in combination was prescribed in 15.5% of patients (13, 14) In a cohort of patients in the United States starting second-line medication, only 8% of patients had received MET for at least 60 days before switching and up to 35% had for less than 60 days, despite being recommended as first line therapies in all guidelines at that moment(15). Therefore, according to our findings, choice of first line medication in these two countries are made based on the available guidelines.

When choosing second-line medications, better efficacy, weight loss, tolerability, and lower risk of hypoglycemia were the most common reported reasons in Costa Rica and Panama. Weight gain was an important factor in one third of the cases and this seems logical given the high prevalence of overweight or obesity our registry (overweight or obesity in our sample ranged from 70 to 90%). In Costa Rica, the most commonly prescribed were MET combined with iDPP4 followed by MET combined with iSGLT2. In Panama, MET combined with iDPP4 and iDPP4 monotherapy were the most common. In Costa Rica,

iSGLT2 and iDPP4s are available only in the private system at lower cost than in high-income countries and similarly priced. According to our findings, cost is not one of the reasons for choosing the second-line medication (even in Costa Rica where patients usually pay for medication out-of-pocket). In Panama, iDPP4s are available in the public health system and iSGLT2 only in the private one. This can explain, in part, the higher prescription of iDPP4s. Under similar circumstances (access and healthcare system) as in Panama, iDPP4s are preferred over SU. Despite guideline recommendations in 2016, GLP1 receptor agonists were not prescribed(16). This might be due that at the time when patients were enrolled in DISCOVER GLP1 receptor agonists and thiazolidinediones were not readily available. Therefore, our findings suggest that the main drivers for second line prescription are efficacy, side effects, and weight loss. Drug availability and access limit the number of options that are available.

According to our findings, second-line prescription patters differ to those in high-income countries. In the United States, SU are still the most widely prescribed followed by iDPP4 and iSGLT2s(17). The difference in the use of SU might be explained by the healthcare system and pricing, since the price of SU are much lower than iDPP4 or iSGLT2 in the United States. In Denmark, Norway and Sweden, SU were the most common second-line and iDPP4 in Finland(18). During 2014–2016, in Korea iDPP4 were the most frequently prescribed, followed by SU and iSGLT2. In this paper, choice of second-line medication might also be determined by physician specialty, where internal medicine physicians tended to choose newer agents (19). Also, iSGLT2 and iDPP4 were most often prescribed in tertiary hospitals compared to clinics as well as in urban setting compared to rural ones(19). Recently, this change in prescription patterns has also been described in the United Kingdom, where iDPP4 use almost doubled as second-line from 2010 to 2017, becoming the most commonly prescribed second-line medication after 2016, followed by SU and iSGLT2. This change was accompanied by a decrease in weight, blood pressure and hypoglycemia rates(20).

Our study has strengths and limitations. To the best of our knowledge, this is the first real-world description of diabetes prescription outside of clinical trials in two Central America countries. In addition, this prospective registry allowed to document the reasons to change from first- to second-line medications. A small sample size and the fact that patients voluntarily enrolled in the registry might introduce “healthy volunteer” selection bias limiting the generalizability of our findings. Furthermore, we only document prescription and not adherence to medications. Finally, lifestyle modifications (e.g., physical activity, diet) that influence response to treatment are not considered.

In conclusion, our findings provide evidence that when switching to second-line medications efficacy, side-effects and weight loss appear to be the main drivers as opposed to costs and is in line to what current guidelines recommend.

Declarations

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Declarations

Ethics approval and consent to participate: the study was approved by the Comité Ético Científico Instituto Costarricense de Investigaciones Clínicas (CEC-ICIC) in Costa Rica and by the Comité de Bioética de la Investigación del Instituto Conmemorativo Gorgas de Estudios de la Salud in Panama. Participation was on a voluntary basis and all participants signed a written informed consent.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interest: Authors have no relevant conflict of interest to disclose.

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Author's contributions: C.C., P.G., M.V., L.R., F.A., C.S., A.C., G.R. participated in the study and were in charge of attending patients, wrote the main manuscript and prepared tables 1-4. All authors reviewed the manuscript. Medical writing support was provided by J Barnoya and funded by AstraZeneca.

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