Prescription of DPP4 inhibitors: Indication and effect on glycosylated hemoglobin in a primary care institution of Colombia

Prescripción de inhibidores de la DPP-4: indicación y efecto sobre la hemoglobina glicosilada en un primer nivel de Colombia

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Resumen

Introducción y Objetivo: en Colombia se recomiendan los inhibidores de la Dipeptidil Peptidasa-IV (iDPP4) como segunda opción para el manejo de la diabetes mellitus tipo 2. No se ha evaluado el cumplimiento e impacto de esta recomendación. Como objetivo se buscó determinar la prescripción de los iDPP4 según las recomendaciones de la Guía de Práctica Clínica colombiana, y su efecto sobre la hemoglobina glicosilada (HbA1c). **Materiales y métodos:** estudio descriptivo que incluyó pacientes con diabetes mellitus tipo 2 que consultaron a un primer nivel entre 2016 y 2018, y tenían formulado un iDPP4, con al menos dos consultas de seguimiento. Se incluyeron variables sociodemográficas, clínicas, tratamiento y comorbilidades. La prescripción no ajustada se definió como la falta de cumplimento de la recomendación de la guía colombiana. Se empleó estadística descriptiva y pruebas X^2 para la comparación de variables categóricas. Se aplicó un modelo de regresión logística binaria. **Resultados:** hubo 207 pacientes de los cuales 112 cumplieron criterios de inclusión, 77 eran mujeres (68,8%). El 68,8% de los pacientes presentaron una prescripción no ajustada del iDPP4. Hubo una reducción total de 0,21%, con una media de 198,2±124 días entre la primera y segunda medición de HbA1c de control (reducción de 0,55% cuando la prescripción se ajustaba a la guía colombiana y 0,05% cuando no). **Conclusión:** hay un limitado impacto de los iDPP4 frente a la reducción de HbA1c y poco seguimiento de la guía colombiana en pacientes de primer nivel de atención.

Palabras clave: Diabetes mellitus; Inhibidores de la Dipeptidil-peptidasa IV; Hipoglucemiantes; Hemoglobina A glucada; Prescripciones de medicamentos; Guía de práctica clínica.

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Abstract

Introduction and objective: In Colombia, Dipeptidyl-Peptidase IV (DPP4) inhibitors are recommended as second-best choice for type 2 diabetes mellitus treatment. However, no evaluation of the accomplishment or impact of this recommendation was performed. The objective was to determine the prescription of the DPP4 inhibitor according to the Colombian Clinicial Practice Guide regarding type 2 diabetes mellitus treatment, and its effects on glycosylated hemoglobin (HbA1c). **Materials and methods**: A descriptive study that included patients with type 2 diabetes mellitus who attended a first level between 2016 and 2018, had a prescription for DPP4 inhibitor and at least two control appointments. Variables included were sociodemographic, clinics, treatment and comorbidities. The unadjusted prescription was defined as the lack of accomplishment of Colombian guidelines. Descriptive statistics and X^2 test were used for the comparison of categorical variables. A binary logistic regression model was applied. **Results**: 112 out of 207 patients accomplished inclusion criteria, of which 77 were women (68.8%). Also, 68.8% of the patients had an unadjusted prescription of the iDPP4. There was a 0.21% total reduction in HbA1c levels, with a mean of 198.2 ± 124 days between the first and second control measurement (reduction of 0.55% when the prescription was adjusted to the guidelines and 0.05% if it was unadjusted). **Conclusion**: There is a limited impact of DPP4 inhibitors regarding the reduction of HbA1c and metabolic control, and there is a slight follow-up to the Colombian guidelines in patients who attend a first level.

Keywords: Diabetes mellitus; Dipeptidyl-peptidase IV Inhibitors; Hypoglycemic agents; Glycated hemoglobin A; Prescriptions; Guideline adherence.

Introduction

Type 2 diabetes mellitus (DM2) is a chronic metabolic disease characterized by a deficit in the production or the effect of insulin in the tissues, generating a state of hyperglycemia that, if not treated properly, induces micro and macrovascular complications in the long term[1].

According to the World Health Organization (WHO), the worldwide prevalence of diabetes mellitus (DM) in adults is 8.7%, which means that more than 420 million people suffer from this condition[2]. In Colombia, the estimated prevalence is 7.2%[3], with Valle del Cauca, Norte de Santander, Risaralda, Santander and Antioquia being the five departments with the highest number of patients with this pathology[4].

By consensus, metformin, a biguanide, is the first-line treatment for DM2[5]. Although considered as an effective drug, a significant proportion of patients fail to achieve good metabolic control despite receiving adequate doses and adhering to non-pharmacological measures. It is often necessary to increase oral therapy in patients who do not achieve metabolic control goals by two or three fold, based on the HbA1c levels[5].

The Ministry of Health and Social Protection of Colombia (MinSalud), in its Clinical Practice Guide (GPC) for the diagnosis, treatment and follow-up of DM2 in the population older than 18 years[5], promotes the use of DPP4 inhibitors as the best second option in combination with biguanides in patients with poor control of their disease. This recommendation, published in 2016, represented a significant change in the management of the disease, as it replaces sulfonylureas as second-line treatment in patients who have not achieved control with metformin. The recommended doses for this group of hypoglycemic agents is 100 mg / day for Sitagliptin, 5 mg / day for linagliptin and saxagliptin, and 25 mg / day for alogliptin[5,6]. This differs from the recommendations of the American Diabetes Association (ADA) guidelines, which suggest indicating a second oral anti-diabetic drug according to each patient's associated comorbidities[6].

In Colombia, studies assessing both compliance with the GPC recommendations for DM2 and the impact of such measures on disease control have not yet been published. Therefore, the objective of this study was to determine the effect on HbA1c of the DPP4 inhibitor prescription based on the recommendations of the Colombian GPC for the management of DM2.

Materials and methods

This is a descriptive study in patients over 18 years of age diagnosed with DM2 who consulted the Hospital San Pedro y San Pablo in La Virginia, Risaralda, primary care institution, between June 1, 2016 and June 30, 2018. Patients were prescribed with DPP4 inhibitors for the first time by their treating physician,

and attended at least two follow-up appointments during the study period. Evidence of the use and delivery of the formulated DPP4 inhibitor in the clinical history of all patients was a requirement. Patients under 18 years of age and those of older age, who were not receiving DPP4 inhibitor, were excluded. Individuals who attended a follow-up appointment, but had no record of at least two HbA1c measurements in the study period were also excluded.

The clinical records were used as a unit of analysis and the information was obtained through a data collection instrument developed with Epi Info 7.0 software, which includes the following variables:

Sociodemographic variables: Sex, age, type of affiliation to the General System of Social Security in Health (SGSSS), origin and marital status.

Risk factors, complications, and comorbidities (yes/no): Sedentary lifestyle, overweight, first-degree relatives with DM2, tobacco consumption, alcohol consumption, retinopathy, neuropathy, diabetic nephropathy and over 50 years of coronary heart disease, history of diabetic ketoacidosis and hyperosmolar hyperglycemic state, high blood pressure, cardiovascular disease, dyslipidemia, obesity, hypothyroidism, heart failure and stroke.

Clinical and laboratory variables: Care by general practitioner or specialist during first consultation (yes/no), total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), triglycerides (mg/dL), urinalysis (yes/no), complete blood count (mg/dL), creatinine (mg/dL), body mass index (kg/m^2), abdominal girth (cm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and cardiovascular risk estimated by Framingham modified for Colombia >10%.

Pharmacological treatment and co-medication: Name of anti-diabetic drug, presentation, concentration, dosage; co-medication (yes/no): hypolipemic agents, antihypertensives, platelet antiaggregants, non-steroidal anti-inflammatory drugs (NSAIDs) and antiulcer drugs.

Prescription of DPP4 inhibitors and effect on HbA1c: prescription of DPP4 inhibitor (adjusted/not adjusted), HbA1c value (%), reduction in HbA1c (yes/no), metabolic control (yes/no), follow-up appointment (number).

People with HbA1c less than 7.0% were accepted as patients with metabolic control regardless of the Framingham cardiovascular risk score. DPP4 inhibitor prescriptions were accepted as adjusted to the GPC recommendation in patients who were formulated and complied with the indication of the drug according to the GPC, which is[5]:

- In patients with DM2 who have not reached the therapy goal with metformin monotherapy (HbA1c > 7.0%), adding a DPP4 inhibitor is recommended as the first option (GPC recommendation number 16).

The SPSS software version 23 for Windows (IBM, USA) was used to analyze the data. Descriptive statistics such as median, standard deviation, minimum and maximum values, confidence intervals for continuous variables, and percentages for categorical variables were used. Chi square tests were performed to compare categorical variables; p-values, ORs and confidence intervals were included.

A binary logistic regression model was applied based on the variance of the HbA1c values (reached metabolic control: yes/no) and the prescription —adjusted or not— of DPP4 inhibitors according to the recommendations of the GPC as dependent variables. Variables associated in a statistically significant manner in the bivariate analyses were the independent variables. A $p<0.05$ was established as the level of statistical significance. Regarding information and confounding bias, a p-value less than 0.05 was established, being stricter than the Hosmer-Lemeshow criterion in order to reduce the overestimation of results. An appropriate analysis was used for categorical variables.

This research was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira in the minimal risk category, respecting the principles established by the Declaration of Helsinki. In no case were personal details of the patients taken into account.

Results

Sociodemographic description

Two-hundred and seven patients with a diagnosis of DM2 and DPP4 inhibitor prescription were identified, and 112 of them met the inclusion criteria as described in **Figure 1**; 77 were women (68.8%). The main socio-demographic characteristics are described in **Table 1**.

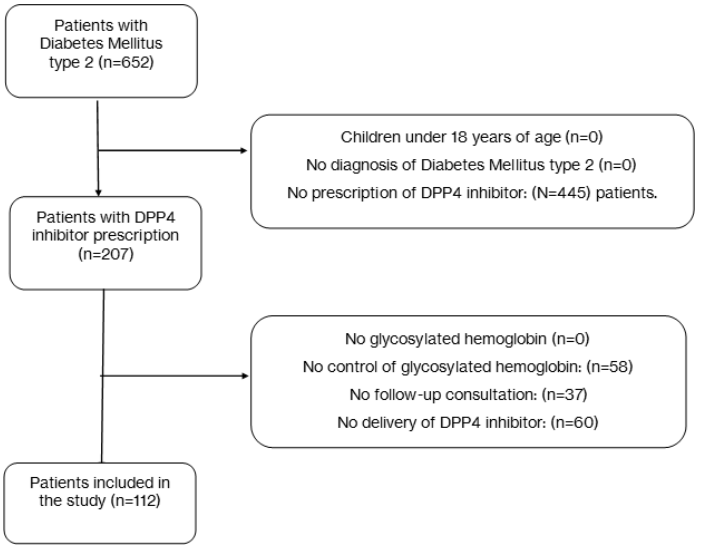

Figure 1. Flowchart of the patient selection process for inclusion in the study.

Table 1. Sociodemographic characteristics of 112 patients with a prescription of DPP4 inhibitor at Hospital San Pedro y San Pablo in La Virginia, Risaralda, 2016-2018.

Variable	N	%
Age (median/SD[a])	59.4/11.7	
Women	77	68.8
Marital status		
Single/Other	69/31	61.6/38.4
Type of affiliation to the SGSSS[b]		
Subsidized	103	92.0
Contributive	9	8.0
Origin		
La Virginia	102	91.1
Other municipalities of Risaralda	10	8.9

[a] Standard deviation, [b] General System of Social Security in Health

Risk factors, complications and comorbidities

Five types of complications associated with DM2 were observed in the study population, with diabetic retinopathy being the most frequent, as described in Table 2.

Clinical variables

In this study, patient care was provided by internal medicine specialists and general practitioners. 58.9% (n=66) of the patients presented a Framingham risk, modified for Colombia, greater than 10%. The main clinical variables are described in Table 3.

Anti-diabetic drugs and co-medication

The DPP4 inhibitors formulated were sitagliptin, vildagliptin and linagliptin. Concomitant use of other anti-diabetic drugs such as metformin, glibenclamide, and insulin was reported. Table 4 describes the drug therapy used in the patients under study.

Prescription of DPP4 inhibitors and reduction of glycosylated hemoglobin

Regarding the formulation of DPP4 inhibitors and the reduction of HbA1c, it was found that the prescription of 68.8% (n=77) of the patients were not adjusted to the GPC recommendation. There was a total reduction of 0.21% in HbA1c, with a median of 198.2 ± 124.0 days between the first and second control measurement. Moreover, during the study period, 5% (n=5) of the patients who were off-target achieved metabolic control. The reduction of HbA1c in patients with a DPP4 inhibitor adjusted prescription, compared to those who did not follow the GPC recommendations, was 0.55% and 0.05%, respectively.

Table 2. Risk factors, complications and comorbidities of 112 patients prescribed with DPP4 inhibitors at Hospital San Pedro y San Pablo in La Virginia, Risaralda, 2016-2018.

Variable	N	%
Risk factors		
Sedentary lifestyle	63	56.3
Overweight	60	53.6
First-degree relative with diabetes mellitus	27	24.1
Smoker	9	8.0
Alcoholism	9	8.0
Complications		
Diabetic retinopathy	82	73.2
Diabetic nephropathy	39	34.8
Cardiovascular disease	30	26.8
Diabetic neuropathy	28	25.0
DKA/HHS[a]	2	1.8
Comorbidities		
High blood pressure	82	73.2
Dyslipidemia	69	61.6
Obesity	52	46.4
Hypothyroidism	15	13.4
Heart failure	3	2.7
Stroke	1	0.9

[a] Diabetic ketoacidosis/hyperglycemic hyperosmolar state.

Table 3. Clinical variables of 112 patients with DPP4 inhibitor prescription at Hospital San Pedro y San Pablo in La Virginia, Risaralda, 2016-2018.

Variable	N	%
General practitioner/specialist care	77/35	68.8/31.2
Complete blood count	89	79.5
Urinalysis	86	76.8
Altered urinalysis	59	52.7
Creatinine	100	89.3
Median/SD[a], mg/dL	1.05/0.2	
Total cholesterol	93	83.0
Median/SD, mg/dL	189.7/55.2	
Triglycerides	91	81.3
Median/SD, mg/dL	248.5/203.3	
HDL[b]	91	81.3
Median/SD, mg/dL	45.7/13.6	
LDL[c]	92	82.1
Median/SD, mg/dL	97.8/42.9	
Body Mass Index (median/SD) kg/m2	29.5/5.7	
Abdominal girth	81	72.3
Median/SD, mg/dL	98.2/11.9	
Blood pressure >140/90 mmHg on consultation	30	26.8
Systolic blood pressure (Median/SD) mmHg	129.7/20.9	
Diastolic blood pressure (Median/SD) mmHg	77.5/9.8	

[a] Standard deviation, [b] High-density lipoproteins, [c] Low-density lipoproteins.

Table 4. Anti-diabetic drugs and co-medication of 112 patients studied at the Hospital San Pedro y San Pablo in La Virginia, Risaralda, 2016-2018.

Variable	N	%
Non-pharmacological treatment	107	95.5
DPP4 inhibitor[a]	112	100.0
Sitagliptin tablet 100 mg	84	75.0
Once a day	76	90.5
Twice a day	8	9.5
Dosage mg/day (mean)	109.5	
Vildagliptin tablet 50 mg	17	15.2
Once a day	4	23.5
Twice a day	13	76.5
Dosage mg/day (Median)	88.2	
Linagliptin tablet 5 mg	11	9.8
Once a day	11	100.0
Dosage mg/day (Median)	5.0	
Metformin	91	81.3
Dosage mg/day (Median/SD[b])	2274.1/461.4	
Glibenclamide	44	39.3
Dosage mg/day (Median/SD)	10.4/2.8	
Insulin	17	15.2
Crystalline	12	10.7
NPH	6	5.4
Lispro	1	0.9
Co-medication		
Hypolipemics	88	78.6
Antihypertensives	83	74.1
Platelet antiaggregants	35	31.3
NSAIDs [c]	10	8.9
Antiulcer	7	6.3

[a] Dipeptidyl Peptidase-4 inhibitor, [b] Standard deviation, [c] Non steroidal anti-inflammatory drugs.

The analysis of the HbA1c reduction for each DPP4 inhibitor, individually, showed a decrease of 0.25% for those treated with sitagliptin (mean of 204.0 ± 132.4 days between the first and second measurement) and 0.5% for those treated with vildagliptin (mean of 132.0 days ± 62.5 days between the first and second measurement). In the case of patients prescribed with linagliptin, there was an increase in HbA1c of 0.54% (mean of 255.6 ± 108.6 days between the first and second measurement). Table 5 describes the prescription of DPP4 inhibitors and their effect on HbA1c in patients included in the study.

Table 5. Prescription of DPP4 inhibitor and reduction of HbA1c in 112 patients treated at Hospital San Pedro y San Pablo in La Virginia, Risaralda, 2016-2018.

Variable	N	%
DPP4 inhibitor[a] prescription adjusted to GPC recommendation	35	31.3
Patients with HbA1c reduction[b]	68	60.7
First consultation		
HbA1c % (Median/SD[c])	7.0/1.9	
Patients with metabolic control	51	45.5
Follow-up consultation		
HbA1c % (Median/SD)	6.7/1.7	
Patients with metabolic control	56	50.0
Number of follow-up consultations per patient during the study period (Median/SD)	3.4/1.8	

[a] Dipeptidyl Peptidase -4 inhibitor, [b] Glycosylated hemoglobin, [c] Standard deviation

Multivariate analysis

Logistic regression found that patients with a first-degree relative with history of DM (OR: 5.617; 95%CI: 1.033-30.532; p=0.046) were more likely to receive a prescription outside the GPC recommendations. There were no variables associated with a reduction of this probability.

Discussion

The objective of determining whether DPP4 inhibitors were being used in accordance with GPC recommendations and their effect on HbA1c was achieved. The implementation of this GPC brought about a substantial change in management, since a high percentage of DM2 patients require a second drug to achieve good metabolic control. The application of these recommendations, besides generating changes in therapeutic behaviors of primary care physicians, has become a challenge for the health system considering the difference of cost between glibenclamide (the second most commonly used therapeutic option previously)[7-13] and DPP4 inhibitors, which could be a significant barrier to applying these guidelines in daily clinical practice. In our study, of 207 patients prescribed DPP4 inhibitor, 60 (28.9%) did not have access to the drug. This limitation may be even greater in municipalities far from large cities, where the delivery of drugs such as DPP4 inhibitors or sodium glucose co-transporter type 2 (SGLT2) inhibitors, recommended by the GPC, may be almost utopian; however, reports confirming this statement have not been published.

The population included in this study had an overall reduction of HbA1c lower than expected (0.21%), while only 5.0% of patients achieved the goal of this parameter after the addition of DPP4 inhibitors, with vildagliptin being the most effective. Most studies demonstrate a reduction between 0.5-1.0% in HbA1c with DPP4 inhibitors, either as a second option following metformin use[13,14] or as adjunct therapy in patients already receiving insulin[7-12]. These results reveal a limitation for the population that requires significant reductions in HbA1c to meet the goals set by the treating physician based on age and comorbidities[13].

To the best of our knowledge, there are no controlled clinical trials comparing the efficacy of glibenclamide versus DPP4 inhibitors; however, when comparing sulfonylurea monotherapy with a placebo, the reduction in HbA1c is about 1.5%[15]. In that sense, the use of glibenclamide should not be completely ruled out as a therapeutic option in DM2, taking into account its effectiveness and easy access. Its main indication continues to be for patients under the age of 65, without associated heart or kidney disease, ideally with normal body mass index, and preferably along with metformin[15].

In this study, it was striking to find that the use of linagliptin was related to the increase of HbA1c. This increase could be explained by the reduced number of patients who had it formulated and a greater number of days between follow-ups, compared to the other DPP4 inhibitors, thus preventing a more rigorous statistical analysis. A clinical trial conducted at 45 sites in six European countries showed a reduction of 0.13% in patients treated with linagliptin who had HbA1c less than 8% at the beginning of the treatment, and up to 0.87% in those who began with HbA1c greater than 9%, which is similar to the efficacy previously demonstrated by other DPP4 inhibitors[14].

In relation to cardiovascular risk, the literature does not report an increase in acute myocardial infarction or stroke beyond the expected incidence for a cohort of high-risk patients. A recent study on the effectiveness of major second-line drugs for the management of DM2 (after metformin) in major cardiovascular events showed no significant difference between DPP4 inhibitors, SGLT2 inhibitors and glucagon-like peptide-1 agonists (GLP-1), unlike sulfonylureas and insulin, which did increase the risk of cardiovascular events[16].

Other studies, such as the meta-analysis by Monami M *et al.*[17] published in 2013, even describes that treatment with DPP4 inhibitors reduces the risk of all-cause mortality in patients with DM2. More recently, the CARMELINA study evaluated the safety of linagliptin in patients with previous cardiovascular events, with a glomerular filtration rate (GFR) of less than 45 mL/min/1.73m^2 or macroalbuminuria, which is not inferior to a placebo in outcomes such as death, non-fatal myocardial infarction or non-fatal stroke, without showing any associated cardiovascular benefit[18]. In accordance with the results of the TECOS (sitagliptin) study, which was also designed to evaluate the safety of another DPP4 inhibitor, no increased risk of cardiovascular events was found[19].

It should be noted that this neutral effect on cardiovascular risk cannot be considered a class effect since the results of the SAVOR-TIMI 53 study by the Food and Drug Administration (FDA) published in 2016 warned about the possible association of saxagliptin with increased heart failure rate, being more likely in patients with pre-existing heart or kidney disease[20].

Despite their limited action on HbA1c, it is clear that DPP4 inhibitors are superior to sulfonylureas regarding cardiovascular safety. Fadini *et al.*[21] found that DPP4 inhibitors, with the exception of saxagliptin and alogliptin, were less associated with heart failure than sulfonylureas (OR: 0.78; 95%CI: 0.62-0.97). On the other hand, DPP4 inhibitors are associated with a lower risk for developing hypoglycemia than sulfonylureas with a number needed to harm (NNH) of 128 between these 2 groups of drugs[22]. The clinical significance of this data should be assessed to define whether it is a sufficient reason to prefer the use of DPP4 inhibitors over sulfonylureas in a general way.

When analyzing the complications developed by the patients in the study, nephropathy was the second most commonly found, which could be explained by the fact that DPP4 inhibitors can be used even in patients with a GFR of less than 30 mL/minute/1.73m^2 [23]. Due to its pharmacokinetic characteristics, linagliptin does not require dose adjustment in patients with chronic kidney disease (CKD)[24]. The other DPP4 inhibitors that are renally excreted have demonstrated over time that they can also be used when there is deterioration of the function of this organ. The TECOS study found that patients who have stage 4 CKD (GFR<30 ml/min/1.73m^2) or terminal CKD on hemodialysis, may receive 25 mg/day of sitagliptin[18]; this drug, in one of the sub-analyses conducted by Engels *et al.* on the TECOS study, also showed a reduction in microalbuminuria[25].

There is enough evidence to recommend the use of DPP4 inhibitors as a second-line treatment in patients with advanced stage CKD without negative cardiovascular impacts. However, the ADA, in its 2019 update[26], recommends SGLT2 inhibitors as the first option in second-line management of patients with DM2 and CKD, although its safety in patients with TFG <30 mL/ min/1.73m^2 is not clear yet. The EMPAREG (empagliflozine)[27] and CANVAS-R (canagliflozine)[28] studies did not include patients with these characteristics, and only 7% of cases in the DECLARE TIMI 58 (dapagliflozine)[29] trial had GFR<60 ml/min/1.73m^2, so new studies supporting the use of these drugs in patients with stage 4 or 5 CKD should be expected. It is important to bear in mind that, since 2016, the FDA updated the recommendations on the use of metformin considering the renal function of patients and contraindicating its use in those with GFR<30 ml/min/1.73 m^2 [30].

One of the limitations of this study is related to the origin of the information, which comes from clinical records that do not allow defining the reasons why doctors chose the drugs, the doses and the co-medication used; this is a common restriction of some observational studies. Additionally, a single HbA1c target was chosen, which may limit the number of patients who achieved metabolic control according to their cardiovascular risk and comorbidities and may require more lax goals. Being a retrospective analysis, it cannot be guaranteed that the patients fully complied with the medical recommendations or the daily doses of the medications, which could impact the results obtained. The results found are based on a greater number of prescriptions that did not follow the recommendations of the GPC (unadjusted prescription); however, the reports of this study show the behavior in the follow-up appointment of patients with DM2 in a primary care institution from Colombia, which may lead to improvements in control strategies aimed at patients with this condition in the country.

In conclusion, a limited effectiveness of DPP4 inhibitors to reduce HbA1c and achieve metabolic control in the patients studied is described, which is probably related to a prescription that was not adjusted to the recommendations of the Colombian GPC in more than half of the cases. While DPP4 inhibitors are a good option for the early management of some patients, such as those with CKD or the elderly, GPC's recommendation to use these inhibitors as the first option of a second-line treatment after metformin for all patients should be reviewed to consider one that individualizes drug choice taking into account comorbidities. New prospective studies are recommended to define the effectiveness of DPP4 inhibitors in the Colombian population, and a joint effort of all actors involved in the health system is required to guarantee comprehensive access to treatment.

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Ethical considerations

This research was approved by the Bioethics Committee of the Universidad Tecnológica de Pereira in the minimal risk category, respecting the principles established by the Declaration of Helsinki. In no case were personal

details of the patients taken into account. It did not receive specific grants from public sector agencies, the commercial sector, non-profit organizations, or the pharmaceutical industry.

Conflict of interest

The authors of this article declare that they have no conflict of interest.

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