

Control of Glycemia and Cardiovascular Risk Factors in Patients With Type 2 Diabetes in Primary Care in Catalonia (Spain)

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OBJECTIVE—The objective of this study was to analyze the clinical characteristics and levels of glycemic and cardiovascular risk factor control in patients with type 2 diabetes that are in primary health care centers in Catalonia (Spain).

RESEARCH DESIGN AND METHODS—This was a cross-sectional study of a total population of 3,755,038 individuals aged 31–90 years at the end of 2009. Clinical data were obtained retrospectively from electronic clinical records.

RESULTS—A total of 286,791 patients with type 2 diabetes were identified (7.6%). Fifty-four percent were men, mean (SD) age was 68.2 (11.4) years, and mean duration of disease was 6.5 (5.1) years. The mean (SD) A1C value was 7.15 (1.5)%, and 56% of the patients had A1C values $\leq 7\%$. The mean (SD) blood pressure (BP) values were 137.2 (13.8)/76.4 (8.3) mmHg, mean total cholesterol concentration was 192 (38.6) mg/dL, mean HDL cholesterol concentration was 49.3 (13.2) mg/dL, mean LDL cholesterol (LDL-C) concentration was 112.5 (32.4) mg/dL, and mean BMI was 29.6 (5) kg/m². Thirty-one percent of the patients had BP values $\leq 130/80$ mmHg, 37.9% had LDL-C values ≤ 100 mg/dL, and 45.4% had BMI values ≤ 30 kg/m². Twenty-two percent were managed exclusively with lifestyle changes. Regarding medicated diabetic patients, 46.9, 22.9, and 2.8% were prescribed one, two, or three antidiabetic drugs, respectively, and 23.4% received insulin therapy.

CONCLUSIONS—The results from this study indicate a similar or improved control of glycemia, lipids, and BP in patients with type 2 diabetes when compared with previous studies performed in Spain and elsewhere.

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Type 2 diabetes is a chronic disease with a prevalence of 13.8% in people over 18, with up to 6% of the population remaining undiagnosed, according to a recent Spanish study (1). Because diabetic patients have a higher risk of

developing microvascular disease and a two- to fourfold higher risk of developing macrovascular disease than the general population, type 2 diabetes is considered to be among the top conditions with the greatest health and economic impact (2).

Many studies have shown that the occurrence of these complications depends largely on the degree of glycemic control and intensive control of cardiovascular risk factors (CVRFs) (3–5).

In the last few decades, a consensus toward the implementation of a multidisciplinary approach to prevention and control of patients with type 2 diabetes in primary care has been reached. Since 1993, the Spanish Group of Study of Diabetes in Primary Health Care (Gedaps) has published up-to-date guidelines with the main recommendations for diagnosis, control, and treatment of diabetes. The Catalan Health Institute has subsequently incorporated these recommendations into its own guidelines (6). Current targets include an A1C value $\leq 7\%$, blood pressure (BP) values $\leq 130/80$ mmHg, a total cholesterol (TC) value ≤ 200 mg/dL, and an LDL cholesterol (LDL-C) value ≤ 100 mg/dL (7).

Despite scientific evidence and the publication of international (8,9) and national guidelines (6,7), adequate control of these patients' health remains beset with challenges. A number of observational studies performed in Spain (10–14) and elsewhere (15–22) have shown that there is a gap between recommendations and daily clinical practice. Several studies have indicated that only 7–9% of diabetic patients achieve optimal control of all CVRFs (11,13,23). The current generalization of electronic clinical records systems in Spain allowed us to access the data of the entire diabetic population registered in the public health care system for our study, unlike previous studies that were based on population samples. The analyses of these data more accurately reflect the actual control of patients with type 2 diabetes in our setting. Previous publications on population registers in other countries have indicated the relevance of these types of data (15–22). Consequently, this cross-sectional study aimed to determine the clinical features and the glycemic and CVRF control of patients with type 2 diabetes in primary care centers of the Catalan Health Institute in Catalonia (Spain).

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RESEARCH DESIGN AND METHODS

A cross-sectional study that included all patients with type 2 diabetes treated at the Catalan Health Institute was conducted in Catalonia, a Mediterranean region in northeastern Spain. Catalonia has a public health system in which primary care is organized in primary care centers. Every citizen is registered with an individual general practitioner (GP) and a nurse in one of these centers. The main health provider in the region is the Catalan Health Institute, a publicly funded health care system that operates 279 health care centers with >3,500 GPs and 5.8 million patients (80% of the region's population). All GPs in the Catalan Health Institute use the same specific software called ECAP to record clinical information of their patients. Prescribed medication is sold in private pharmacies and registered in a general database (CatSalut database).

Health care and all diagnostic procedures are free of charge to patients. Most patients pay 40% of the cost of medications, which is free for retired, severely ill, or handicapped people. Antidiabetic drugs are almost completely free of charge. Strips for blood glucose monitoring are provided free of charge according to local guidelines.

On average, 70% of patients contacted their primary care team in a given year, although this rate varied according to socioeconomic status. Over three consecutive years, this figure rose to an average of 85% of patients.

The source of information used in this study is the SIDIAP, a computerized database containing anonymized patient records for the 5.8 million people registered with a GP in the Catalan Health Institute. The SIDIAP includes data from ECAP (demographics, consultations with GPs, diagnoses, clinical variables, prescriptions, and referrals), laboratory test results, and medications obtained from the pharmacists (provided by the CatSalut database). The SIDIAP contains all data entered into the ECAP database since it was first introduced in some practices in 1998. In 2005, the system was generalized and used systematically in every Catalan Health Institute practice. Data on laboratory test results and medications sold were available beginning in 2005. Since the SIDIAP database was established, different studies have assessed the validity of its information. This study also contributes to its validation.

All patients aged 31–90 years with a diagnosis of type 2 diabetes (International Classification of Diseases 10 [ICD-10] codes E11 and E14) before 1 July 2009 were

included. All variables registered at the end of 2009 were collected. The following data were available for each patient: age; sex; number of visits with the primary care team (physician or nurse) in the previous 12 months; time since diagnosis; and A1C values, using the last value of the previous 15 months. Values expressed in Japan Diabetes Society/Japan Society of Clinical Chemistry (JDS/JSCC) units were converted to the National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial (NGSP/DCCT) units using the NGSP equation (24).

Data pertaining to chronic complications were also available, including diabetic retinopathy (ICD-10 codes E11.3 and H36.0), diabetic nephropathy (using the most recent value of albumin/creatinine ratio of the study period), and impaired renal function (using the last recorded value of the estimated glomerular filtration rate [GFR] with the MDRD [modification of diet in renal disease] formula in the last 15 months). In addition, data were available for coronary artery disease (ICD-10 codes I20, I21, I22, I23, and I24), stroke (codes I63, I64, G45, and G46), peripheral artery disease (code I73.9), and heart failure (code I50). Information on other CVRFs was available, such as BMI, using the most recent weight value of the last 24 months; blood lipids (TC, LDL-C, and HDL cholesterol [HDL-C]), using the most recent value of the last 15 months; BP (systolic and diastolic BP with the mean value of the last 12 months); and smoking status, according to the last condition registered. CVRF diagnostic criteria were hypertension (ICD-10 code I10) or BP $\geq 140/90$ mmHg, TC ≥ 250 mg/dL, triglycerides (TGs) ≥ 150 mg/dL, BMI ≥ 30 kg/m², and a current or former smoking habit.

To assess the degree of control, we used the current local guideline targets: A1C value $\leq 7\%$, BP $\leq 130/80$ mmHg, TC ≤ 200 mg/dL, and LDL-C ≤ 100 mg/dL for secondary prevention and LDL-C ≤ 130 mg/dL for primary prevention (7). Furthermore, we assessed the same variables according to the pay-for-performance thresholds established by our institution: A1C $< 8\%$, BP $\leq 140/90$ mmHg, and an LDL-C ≤ 100 mg/dL; however, this LDL-C threshold was used for secondary-prevention patients.

At this stage, we also collected basic data on glucose-lowering medication. For this purpose, drug treatment data for 2009 were obtained from the CatSalut prescription drug pharmacy invoice database. Subjects were considered to have received

antidiabetic medication when they had purchased from the pharmacy sufficient medication to cover at least 80% of the total theoretical minimum dose needed during the study period. Patients were considered to be untreated if they had not purchased any drugs. Patients who did not meet the criteria described above, such as those on sporadic treatment or those affected by potential invoicing errors, were considered “unclassifiable”. Supplementary Table 1 describes the minimum dose used and the percentage of “unclassifiable” diabetic patients for each antidiabetic drug ($< 5\%$ of all patients).

We labeled the patient as undergoing double or triple antidiabetic therapy when 1) the criteria for continuous treatment were met for each of the components and 2) either a combination or a fixed-dose combination of two or three antidiabetic drugs was given at least for 2 months, according to the prescription drug pharmacy invoices. This study was approved by the Ethics Committee of the Primary Health Care University Research Institute Jordi Gol.

Analysis

We estimated the prevalence of type 2 diabetes stratified by age for binomial events. Means with SDs and proportions were calculated for all variables (clinical characteristics, diabetes-related complications, treatment, and therapeutic goals). We always provide the value over the total number of patients, excluding those with missing values. The Pearson χ^2 test was used to compare categorical data according to sex and age (< 65 vs. ≥ 65 years), and an unpaired Student *t* test was used to compare continuous variables. All statistical analyses were conducted according to the complete-case principle. A two-tailed value of $P < 0.05$ was considered statistically significant. Statistical calculations were performed using Stata Statistical Software Release 11 (StataCorp, LP, College Station, TX).

RESULTS—Of a total population of 3,755,038 individuals between ages 31 and 90 years, 286,791 people were diagnosed with type 2 diabetes, which corresponds to a prevalence of 7.6%. The prevalence increases to 22.4% in patients > 70 years of age. Fifty-four percent of the patients were men. Clinical and laboratory characteristics are summarized in Table 1.

During 2009, 96% of patients with type 2 diabetes consulted their GP, and blood tests, which included A1C measurements, were performed on 75% of patients. The mean (SD) A1C value was 7.15 (1.5)%.

Table 1—Clinical characteristics of the study population

	Total = 286,791	Men (n = 153,987)	Women (n = 132,804)
Age (years)	68.2 (11.4)	66.4 (11.3)	70.3 (11.1)
Diabetes duration (years)	6.5 (5.1)	6.2 (4.8)	6.9 (5.3)
A1C (%) (n = 214,867; women = 102,063)	7.15 (1.46)	7.16 (1.48)	7.14 (1.44)
Hypertension (%)	77.8	76.3	79.9
Systolic BP (mmHg) (n = 243,092; women = 114,606)	137.2 (13.8)	136.9 (13.6)	137.5 (14.0)
Diastolic BP (mmHg) (n = 242,942; women = 114,548)	76.4 (8.3)	76.6 (8.5)	76.2 (8.1)
TGs (mg/dL) (n = 195,285; women = 91,627)	156.2 (104.9)	158.5 (117.3)	153.5 (88.7)
TC (mg/dL) (n = 221,623; women = 105,249)	192.0 (38.6)	186.2 (38.2)	198.4 (38.0)
HDL-C (mg/dL) (n = 176,021; women = 83,666)	49.3 (13.2)	46.2 (12.3)	52.7 (13.4)
LDL-C (mg/dL) (n = 199,586; women = 95,426)	112.5 (32.4)	109.7 (32.2)	115.6 (32.3)
Obesity (%) (n = 202,451; women = 94,777)	45.4	39	52.7
BMI (kg/m ²) (n = 202,451; women = 94,777)	29.6 (5.0)	28.8 (4.3)	30.5 (5.6)
Smoking habit (%) (n = 218,068; women = 96,716)			
Current smoker	15.4	24.0	6.0
Ex-smoker	18.7	30.9	5.3

Data are mean (SD) or percent. Where indicated, the *n* value denotes the number of study subjects with available data. All comparisons between men and women showed a significant difference, *P* < 0.005.

Fifty-six percent of the patients achieved the optimal A1C target ($\leq 7\%$), a result more frequently observed in patients >65 years of age (*P* < 0.001). Eighty-five percent of the patients had at least one BP measurement during the study period. Of these patients, 65% had a systolic BP measurement <140 mmHg, and 36.2% were <130 mmHg, whereas 92.5% had a diastolic BP measurement <90 mmHg, with up to 69.5% of the patients <80 mmHg. Total cholesterol was measured in 77.3% of patients, and overall, women had higher values than men. Ninety-three percent had TC

values <250 mg/dL, and 61.3% had values <200 mg/dL. HDL-C values were >40 mg/dL in 79.04% of men and >50 mg/dL in 70.1% of women. TG values were <200 mg/dL in 79.7% of patients with type 2 diabetes, with a mean value of 156.2 mg/dL. Obesity was more frequent in women, whereas smoking was more frequent in men (*P* < 0.005 for both comparisons). The control of target CVRFs is summarized in Table 2. The complete set of data for all three main control criteria (A1C, LDL-C, and BP) was available for 179,915 (63%) patients. Of the patients on primary prevention,

only 12.9% had met all targets (A1C $\leq 7\%$, BP $\leq 130/80$ mmHg, and LDL-C <130 mg/dL), whereas in patients on secondary prevention, this number was similar at 12.1% (A1C $\leq 7\%$, BP $\leq 130/80$ mmHg, and LDL-C <100 mg/dL).

Chronic complications of the patients with type 2 diabetes are shown in Table 3. Diabetic retinopathy, impaired renal function (but not albuminuria), and ischemic heart disease were more frequent in women than in men (*P* < 0.001 for all comparisons).

With regard to antidiabetic treatment, we analyzed only those patients considered

Table 2—Results of individual or combined (primary and secondary cardiovascular prevention) treatment goals achieved for the total population and also stratified according to sex and age

	Total	Men	Women	Age <65 years	Age ≥ 65 years
A1C $\leq 7\%$ (n = 214,867; women = 102,063; ≥ 65 years = 139,161)	56.1	55.8	56.5	51.8	58.5
A1C $\leq 8\%$	79.6	79.1	80.1	74.2	82.5
A1C >10%	5	5.2	4.7	8	3.3
BP $\leq 130/80$ mmHg (n = 242,842; women = 114,493; ≥ 65 years = 159,838)	31.7	32.0	31.4	33.3	30.9
BP $\leq 140/90$ mmHg	63.5	63.5	63.1	66.6	61.9
TC <200 mg/dL (n = 221,623; women = 91,627; ≥ 65 years = 126,014)	61.3	67.3	54.6	55.4	63.4
LDL-C <100 mg/dL (n = 199,586; women = 95,426; ≥ 65 years = 130,529)	37.9	41.3	34.2	32.8	40.6
LDL-C <130 mg/dL	72.4	75.2	69.4	67.2	75.2
TGs <150 mg/dL (n = 195,285; women = 91,627; ≥ 65 years = 126,014)	39.6	38.8	40.4	47.2	35.4
BMI <30 kg/m ² (n = 202,451; women = 94,777; ≥ 65 years = 130,851)	45.4	39.0	52.7	51.5	42.1
Nonsmoker (n = 195,632; women = 96,716; ≥ 65 years = 138,247)	65.9	45.1	88.8	51.2	73.7
Primary prevention: A1C $\leq 7\%$, BP $\leq 130/80$ mmHg, and LDL-C <130 mg/dL (n = 145,605; women = 71,246; ≥ 65 years = 91,689)	12.9	13.3	12.7	12.2	13.3
Secondary prevention: A1C $\leq 7\%$, BP $\leq 130/80$ mmHg, and LDL-C <100 mg/dL (n = 34,310; women = 12,200; ≥ 65 years = 27,386)	12.1	13.3	9.9	11.9	12.1

Data are percentages. The primary and secondary prevention treatment goals were defined according to the local guidelines. The percentages are from the study subjects with available data for each variable. All variables showed significant differences between sex (*P* < 0.005) and age groups (*P* < 0.001).

Table 3—Prevalence of diabetes-related micro- and macroangiopathic complications, as assessed by ICD code records and laboratory data

	Total = 286,791	Men (n = 153,987)	Women (n = 132,804)
Retinopathy (%)	5.8	5.6	6.1
Impaired renal function (%) (n = 174,571; women = 82,440)			
GFR: 30–59 mL/min	18.6	14.5	23.9
GFR: 15–30 mL/min	1.2	0.9	1.5
GFR <15 mL/min	0.2	0.3	0.2
Albuminuria (%) (n = 171,063; women = 80,983)			
Microalbuminuria	14.9	18.4	11.1
Macroalbuminuria	1.8	2.4	1.2
Ischemic heart disease (%)	11.3	14.3	7.8
Cerebral vascular disease (%)	6.5	7.1	5.9
Peripheral vascular disease (%)	2.9	4.2	1.5

Where indicated, the *n* value denotes the number of study subjects with available data. GFR was assessed using the MDRD formula. Micro- and macroalbuminuria were defined as an albumin/creatinine ratio of 30–300 and >300 mg/g, respectively. All comparisons between men and women showed a significant difference, *P* < 0.001.

to be taking continuous medication. Twenty-two percent of all patients studied were managed by lifestyle measures. Most medicated patients were prescribed oral antidiabetic treatments: 46.9, 22.9, and 2.8% were taking one, two, and three antidiabetic drugs, respectively. A total of 23.4% of the patients on continuous antidiabetic drug therapy received insulin, ~10% as monotherapy, whereas 13.4% combined insulin with oral agents.

CONCLUSIONS—In Spain, where the current prevalence of diabetes is 13.8% (of which 6% corresponds to unknown diabetes) (1), type 2 diabetic patients are mainly treated by the primary care public health system. In recent years, several studies have analyzed the characteristics and degree of control of patients with type 2 diabetes in our country, but these studies were characterized by great differences in methods and sample size (2,10–14,23,25). The major strength of our study is the inclusion of every patient with type 2 diabetes from a total population database of 3,755,038 people over age 30. With data from 286,791 diabetic patients and a prevalence of diabetes of 7.6%, this is the largest study ever undertaken in Europe. The observed prevalence of type 2 diabetes is close to the reported prevalence of 7.8% for known diabetes in the Spanish population (1), even though our study analyzed only type 2 diabetes in people >30, with the main purpose to avoid the inclusion of patients with type 1 diabetes. Although we did not have access to the data of every patient in

Catalonia, we considered this prevalence to be a precise estimate because the Catalan Health Institute provides health care to 80% of the Catalan population (7 million patients in 2009). Moreover, 96% of the patients with type 2 diabetes had contacted the health care system at least once during the year of study. The frequent use and quality of this registry make the SIDIAP an ideal reference database for surveillance of the prevalence and risk factor control of type 2 diabetes in our region. With regard to methodology, the accuracy of the results is strengthened by the existing link between primary care clinical records and prescriptions obtained from the pharmacy database, thus reducing the possible gap between physician prescription and patient adherence.

Study subject characteristics, such as mean age and degree of obesity, were similar to previously published data from other Spanish studies (34–50% patients were obese), though we found a slightly higher proportion of men and a slightly shorter duration of the disease (6.5 years). This could have been the result of the computerization of clinical records that took place between 2000 and 2004 at our institution, which required active registration of the date of diagnosis by the health care professional. The registration in some cases could have been set by default as the date of the first visit.

Likewise, the degree of glycemic control, as measured by the mean A1C at a cutoff of 7.15%, is comparable to that of other studies that have found values between 6.8

and 7.3%. However, the proportion of patients with good control (56.1% with A1C ≤7%) was lower than in other Spanish studies, most likely because of the previous lack of standardization of A1C measurement. The lack of A1C standardization affects the proportion of patients with good control. In fact, the Japanese kit (JDS/JSCC method) yields lower values of A1C than the DCCT kit, and standardization has led to a slight increase in the A1C values (6.85 vs. 7.15%) and a decrease in the percentage of patients with A1C ≤7% (65 vs. 56.1%). We considered this difference to be the main reason for the differences observed between Spanish studies and those in other countries, such as the U.S., where DCCT values were more widely used. Indeed, in the American study of Saaddine et al. (16), carried out between 1988 and 2002, only 42.3% of patients had A1C values ≤7%, whereas in 2005, a study in Italy showed that 59.9% of patients had A1C values ≤7% (19), a result very similar to ours. This relatively good result can be explained by early diagnosis and treatment aimed at achieving the control targets. The implementation of a target-based management system for chronic diseases includes financial incentives for Catalan Health Institute professionals, who receive an annual financial incentive based on the percentage of patients that achieve glycemic (55% with A1C <8%), hypertension (55% with BP <140/90 mmHg), and lipid control (40% with LDL-C <100 mg/dL) during the previous year.

In our current study, 79.6% of the patients had A1C values ≤8%, a result above the proposed target. The effect of pay for performance on quality in primary care was recently evaluated in England (20). In that study, the proportion of patients who achieved the target A1C value (≤7.5%) increased from 59.1 to 66.7%, the proportion that achieved the target BP (≤145/85 mmHg) increased from 70.9 to 80.2%, and the proportion that achieved the target TC value (≤5 mmol/L) increased from 72.6 to 83.6%.

According to the data published by the Gedaps group in Catalonia, glycemic control has improved progressively, as demonstrated by A1C values that initially averaged 7.7% in 1993 and later reached 6.8% in 2007 (14). Because A1C values in the Gedaps study were not standardized to DCCT values, the 2007 result was actually similar to our result, which was 6.85% before standardization. Comparable positive trends have been observed in certain American Health Maintenance

Organizations, such as Kaiser Permanente, where the mean A1C value decreased from 8.3% in 1994 to 6.9% in 2003, and the mean LDL-C value decreased from 132 mg/dL in 1995 to 97 mg/dL in 2003 (22). The average LDL-C concentration in our study was 112.5 mg/dL, and 37.9% of patients had LDL-C \leq 100 mg/dL.

The mean values of BP control were similar to those observed in the Gedaps study in 2007 (137/77 mmHg and 66% of patients with BP \leq 140/90 mmHg) (14), better than those published in other Spanish studies (10,12,25). However, the American Behavioral Risk Factor Surveillance System (BRFSS) study (70.3% of patients with systolic BP <140 mmHg) (16) and the British pay-for-performance study (80.2% with BP \leq 145/85 mmHg) (20) achieved better control values than those observed in our study.

The results regarding chronic complications, such as macroangiopathy, are similar to those observed in other Spanish studies (14), whereas microvascular complications were probably underreported. We considered the impaired renal function values (MDRD <60 mL/min, 20%) reliable because they have been calculated by the MDRD formula, though this prevalence is slightly lower than that of other studies (14).

In general, the percentage of patients on pharmacological treatment (78%) was higher than that of other studies (15,17,18), even when only patients who were receiving continuous treatment with antidiabetic drugs were considered. Most patients receiving medication were managed with oral antidiabetic treatment (72.6%), whereas 23.4% were treated either with insulin alone or insulin combined with oral agents.

The current study has several limitations. The main limitation of this cross-sectional study is the missing data for a significant proportion of the patients studied. In some instances, the data were not recorded by the health care professionals, but in other cases, the heterogeneity of the variables recorded in the different centers precluded their use in the analysis. Although the data are consistent with previous findings, there is still a risk of bias in the results of this study, as underdiagnosis of type 2 diabetes or other associated conditions and underrecording of data may have occurred. These are common limitations of current primary-care, electronic-record databases and justify additional validation studies using external databases, the development of internal control algorithms, and the comparison of the results to other, similar studies. The present results

are comparable to those of previous publications. There is a need for further improvement of the quality of the data obtained in studies such as ours to strengthen their validity. Finally, some relevant diabetic patient-oriented outcomes, such as the mortality and quality of life, could not be addressed in this study. However, a future study on cardiovascular morbidity and mortality in this population is warranted.

The availability of the data on real-life clinical practice at the primary care level may have important implications for diabetes care. The information obtained should allow the current clinical practice to be assessed in terms of the outcomes of the process and the results of diabetes care. This possibility has several implications that should ultimately lead to improved patient care, including monitoring of diabetes indicators, identification of practice issues to be improved, potential introduction of changes in the health care plans, identification of appropriate targets for pay-for-performance incentives, and allocation of resources for this type of registry as a tool to aid decisions to improve diabetes care.

In conclusion, the results of this study, with regard to A1C value, dyslipidemia, and BP control in patients with type 2 diabetes are similar to those reported in other studies conducted in Spain and elsewhere. These results may be explained by early detection and adequate treatment by primary care professionals, which is enhanced by the target-based management system that includes financial incentives. The information provided by the current study might lead to the implementation of strategies to improve clinical care of type 2 diabetic patients. However, further improvement is necessary, and the SIDIAP database might be an optimal surveillance reference system for the prevalence and control of the disease. The impact of late complications in patients with type 2 diabetes deserves further analysis. To reduce the burden of this disease, policies that promote the optimal management of this condition and associated CVRFs should be implemented.

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I.V., M.M.-C., and R.M. wrote the manuscript and contributed to discussion. E.H. and F.F. researched the data and contributed to discussion. M.R. and C.C. contributed to discussion. J.F.-N., B.B., and D.M. designed and conducted the study, reviewed and edited the manuscript, and contributed to discussion. D.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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