

## Article

# Variability in the Control of Type 2 Diabetes in Primary Care and Its Association with Hospital Admissions for Vascular Events. The APNA Study.

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**Abstract:** Type 2 diabetes (T2D) is associated with increased cardiovascular morbidity, mortality, and hospital admissions. There is variability in clinical practice. The objectives are to analyze the variability in the control of Blood Pressure (BP), HbA1c, and LDL-C in T2D patients and its influence on admissions due to cardiovascular events (CVE) Methods: We analyzed the electronic records in Primary Care Health centers in Navarra (Spain) and hospital admission for CVE. We follow 480637 people from 2012 to 2016. We calculated indicators of control of patients with T2D for each year, percentage with: HbA1c < 7%; HbA1c  $\geq$  9%; BP <140/90 mmHg; LDL-C <100 mg/dl. We used logistic and Cox regression. Results: Patients in the best control GP practices cluster are 2.5 times more likely to have HbA1c <7% [OR: 2.46 (95% CI: 2.29-3.64)]. Poor HbA1c control  $\geq$  9% is more likely in the worst control cluster [OR: 1.73 (95% CI:1.63-1.83)]. The probability of admission for CVE increases with age, being male, low income, obesity, history of CVE, having HbA1c  $\geq$  9%, and belonging to a GP practice in the cluster of HbA1c  $\geq$  9% worst control. In contrast, it decreases in patients with HbA1c <7%, BP<140/90 mmHg and LDL <100 mg/dl.

**Keywords:** Healthcare Disparities; Diabetes Mellitus, Type 2; Vascular Diseases; Primary Health Care; Cohort

## 1. Introduction

Type 2 diabetes (T2D) is a highly prevalent disease associated with increased cardiovascular morbidity and mortality and subsequent hospital admissions [1–3]. Cardiovascular risk factors in patients with T2D are mostly common to the general population. It could be divided into those that are modifiable (glycemic control, smoking, obesity, and hypertension and dyslipidemia)[4,5] and non-modifiable (family history of cardiovascular disease, years of T2D evolution, race, gender, age, age at T2D debut, and history of cardiovascular event) [6]. An association has also been found between low socioeconomic status and higher mortality in diabetic patients [7–13].

Glycosylated hemoglobin (HbA1c) is a widely used marker in detecting and monitoring diabetes. It is linearly related to the risk of vascular complications in both patients with diabetes and nondiabetic patients [14]. There is also evidence that elevated HbA1c predicts cardiovascular (CV) events [15]. Despite pharmacological advances and new devices

for treating and controlling T2D, the clinical practice still has variability. Optimal control levels of HbA1c <7% are achieved in approximately only half of the population [16–18]. Two other valuable parameters in evaluating T2D follow-up are BP control and LDL-C due to their association with CVE [19]. Various guidelines recommend maintaining BP <140/90 mg/dl and LDL-C levels <100 mg/dl [2,4].

In Spain, primary health care centers (PHCC) carry out the care of T2D patients. In complex patients, PHCCs work in coordination with their referral hospital or outpatient Endocrinology services. Interventions in health centers aim to treat and control the disease and act on modifiable factors, following the recommendations of the different scientific societies [2,4,20]. Compliance with these recommendations is not as adequate as it could be, and there is significant variability depending on the different countries, regions, and even on the characteristics of the physician who monitors these patients [21–23]. How patients are cared for influences risk factors control, and treatment adherence [23,24]. The evolution of quality indicators in patients with T2D has been evaluated [25], including complications such as foot ulcers, amputations, and retinopathy [26]. However, little has been studied on their influence on the development of CVE. Is for that, it is interesting to know the level of compliance achievable in clinical practice. Achieving full compliance with the indicators does not depend solely on measures proposed by doctors. There are variables that they cannot control and that sometimes rely on their patients' adherence to treatment or others.

In Navarra, a computerized medical record is employed in primary care. It was implemented in 2000, and it was in general use since 2008. Our study is part of a series of studies included under the acronym "APNA Study" (Navarra Primary Care Study) that analyze data from the computerized medical record registry of Navarra, with different purposes. Many studies are done with the data from this registry that endorse the data quality in terms of T2D [27–30].

The objectives of our present study are to analyze the variability in the control of HbA1c, BP, and LDL-C in type 2 diabetic patients with T2D and its influence on admissions for cardiovascular events.

## 2. Materials and Methods

We analyzed the care of patients with T2D from 2012 to 2016 in Navarra, a region located in northern Spain, where access to health care is universal. In Primary Care, Health centers work with family physicians. In all primary care health centers, a population group called "GP practice" or "quota" is assigned to a team formed by a family physician and a nurse responsible for their care. We studied 385 GP practices with a mean population of 1420 people (SD 342) with a range between 508 and 2165 at the end of cohort follow-up.

We analyzed the electronic records that show the clinical variables that doctors or nurses record in coded form during patients visits. We also collected the analytical results that are included electronically in the clinical history from the laboratories. We extracted from the hospital discharge registration system the date of the first hospital admission with a CVE as the main reason for admission during the follow-up period recorded as ischemic heart disease (ICD codes: 410-414; ICD10: I20-I25) or cerebrovascular disease (ICD: 430-438; ICD10: I60-I69). Patients were followed up until an event occurred or until 31 December 2016.

### 2.1. Study variables:

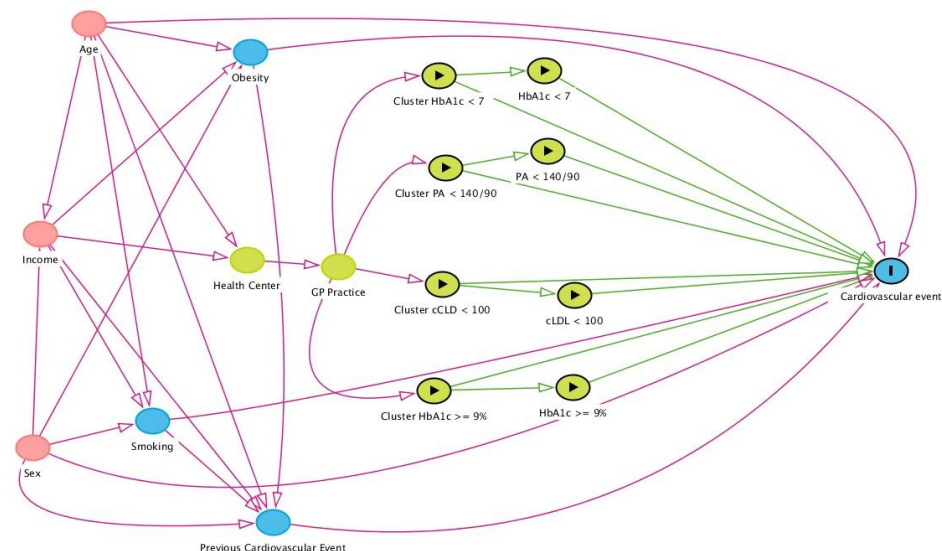
We collected each year of the cohort, age, sex, health center, GP practice, date of T2D diagnoses made by physicians. The low-income status < 18,000 euros/year, used in Spain to

establish the pharmaceutical co-payment, is also identified. Clinical variables: the following variables were used: weight (kilograms), height (meters), Body Mass Index (BMI) (weight/height<sup>2</sup>), systolic and diastolic BP (mmHg), HbA1c %, LDL-C (mg/dl), and smoker during the follow-up period. Based on BMI, obese patients were identified as those with a BMI >30. The values of the clinical variables before admission were collected. In the case of non-admission, the first value of the year was collected. The history of CVE is also recorded. The data were anonymized. The Clinical Research Ethics Committee of Navarra (CEIC) approved the study with the number 3/2014 on 26 March 2014.

## 2.2. Statistical methods:

We calculated four indicators of control of patients with T2D for each year: percentage with HbA1c < 7%; percentage with HbA1c  $\geq$  9%; percentage with BP <140/90 mmHg; percentage LDL-C <100 mg/dl. We analyzed the mean values of each indicator during the years of follow-up. To compare the prevalence between GP practices, we directly standardized rates by age, taking the population of Navarra as a reference. We show the % compliance and the coefficient of variation (CV) to identify the variability between GP practices in compliance with the control indicators. We present the % compliance and the coefficient of variation (CV). In addition, using a non-hierarchical K-means cluster analysis, we classified GP practices into two clusters according to the level of compliance. We consider clusters representing less than 3% of the GP practices as outliers and excludes those GP practices from the analysis.

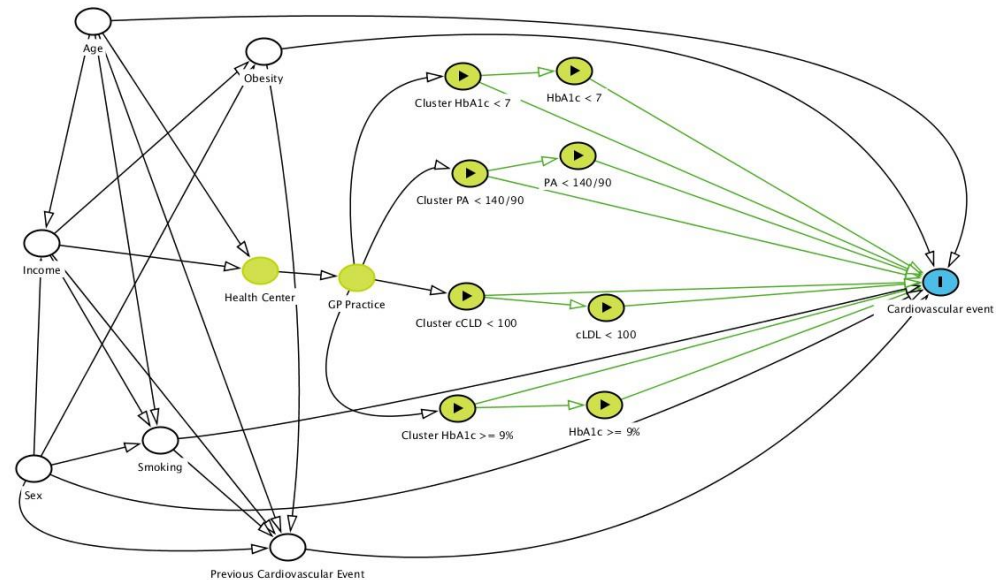
Using the Directed Acyclic Graph (DAG) [31] (Figure 1), we studied the relationship of exposure cluster of HbA1c  $\geq$  9% with CVE and potential confounding factors: sex, age, low income, obesity, smoking, and CVE antecedent.



**Figure 1.** Directed Acyclic Graph (DAG) of the effect of Cluster of HbAc  $\geq$ 9% (exposure) on Cardiovascular event (outcome). Ancestors of exposure and outcome (red) ancestors of Outcome (Blue), ancestors of exposure (green), exposure (green & ►) Outcome (Blue & !). Based on DAGitty version 3.0.

The DAG shows that age and income determine where people live and influence the health center they are linked to and the GP practice they belong to. Age and sex were related to the appearance of CVE and influenced antecedents of CVE, obesity, and current smoking. We observed that the cluster directly affects CVE and the control measure that

affects the outcomes. The software indicated that to study the effects of cluster and controls in the outcome was necessary to adjust by sex, age, income, obesity, and current smoking (Figure 2).



**Figure 2.** Adjusted Directed Acyclic Graph (DAG) of the effect of Cluster of HbAc  $\geq 9\%$  (exposure) on Cardiovascular event (outcome). Adjusted variables (white color), ancestors of exposure (green), exposure (green & ►) Outcome (Blue & !). Based on DAGitty version 3.0.

To calculate the probability of a patient meeting an indicator above the 5-year follow-up average, we used logistic regression calculating Odds Ratios, with 95% confidence intervals, between patients included in the GP practices group with the highest level in each indicator versus the lowest group. We adjusted the models for age, sex, low-income status, and a previous CVE

Finally, we used Cox regression to estimate the excess risk of admission for a CVE associated with T2D control and belonging to the GP practices cluster with the highest score in the control indicators, adjusted for age, sex, low income, obesity, current smoking, and history of a CVE before admission.

### 3. Results

#### 3.1. Descriptive statistics

The mean population of the dynamic cohort from 2012 to 2016 was 480637 (243129 females and 237508 males). **Table S1** shows the descriptive indicators of the studied population. In 2012 the prevalence of T2D was 4.14%, increasing to 5.05% in 2016, being all years higher in men. The mean age of patients with T2D during 2012-2016 was 67.59 years, compared to 48.73 years in nondiabetic patients. The age-standardized prevalence of T2D in  $\geq 18$  years reached in 2016 was 5.05% (women: 4.30% and men: 5.83%). The proportion of people with low income in 2012 in nondiabetic patients was 3.68%. In patients with diabetes, it was 4.57%. This proportion was progressively increased in the two groups during the follow-up years to 4.01% and 5.26%, respectively, in 2016. In all years, the proportion of women with low income is higher. The proportion of obese people without T2D was 25.15% in 2012. This proportion was slightly decreasing to 23.96% in 2016. On the contrary, the prevalence of obesity in patients with diabetes increased from 46.04 to 48.08%. The

proportion of smokers in nondiabetic patients was 24.75% in 2012, experiencing a decrease to 23.57%. The proportion of patients with TD2 smokers in 2012 was 17.01%, experiencing a slight reduction at the end of the period to 16.85%. The age group with the highest prevalence of T2D was 75-84 years old (15.96% in 2016). The highest increase in the prevalence of diabetes was in persons over 85 years of age. Diabetes prevalence has increased in this age group from 7.44% in 2012 to 14.86% in 2016 (an 89.5% increase).

The DAG shows the relations between variables. Age and socioeconomic status influence on domicile and Health center. GP practices associated with preventive measures clusters. It also shows the effects of obesity, smoking, and antecedents of CVE on the occurrence of CVE (Figure 1,2)

### 3.2. Multivariate cluster analysis of GP practices

The prevalence adjusted in multivariate analysis is 65.6% higher in males [(OR 1.658 (95% CI: 1.610-1.702)]. People who have suffered an admission for a CVE are 27.6% more likely to have diabetes [OR: 1.276 (95% CI: 1.211-1.344)]. Belonging to a cluster of GP practices with a higher level of detection is associated with being diagnosed with T2D 40.2% more, compared to GP practices with a lower level of diagnosis [OR: 1.402 (95% CI:1.363-1.411)] (Table 1).

**Table 1** Variability of control indicators by GP Practices

Variable	Mean	Number of highest and lowest scoring clusters	Mean of clusters with the highest score	Mean of clusters with the lowest score	Coefficient Variation between general practices
Standardized prevalence (2016)	5.74†	101/327	8.20†	4.83†	42.32
HbA1c <7% *	47.34	360/72	52.14	23.34	31.72
HbA1c ≥9%*	15.65	210/222	21.42	10.12	47.41
PA <140/90 mmHg *	52.52	243/188	61.18	41.39	25.45
LDL-C <100 mg/dl*	46.16	180/252	57.36	38.15	28.12

\* Average value of % compliance by general practices over the five years. †Age-standardized prevalence. (4 General practices were eliminated due to high outlier values.)

Patients in the best control GP practices cluster are 2.5 times more likely to have HbA1c <7% [OR: 2.457 (95% CI: 2.291-3.636)]. Poor HbA1c control ≥ 9% is 72.9% more likely in GP practices in the worst control cluster [OR: 1.729 (95% CI:1.631-1.834)]. BP control <140/90 mmHg is somewhat better in women, worsens slightly with age, low-income level, and persons who have suffered an admission for a vascular event. The probability of meeting the indicator is 83.3% higher in patients in the best control cluster GP practices [OR: 1.833 (95% CI: 1.757-1.913)]. Control of LDL <100 mg/dL is 40.8% higher in men [OR: 1.408 (95% CI: 1.348-1.469)], increases slightly with age, and there are no differences according to income level. (Table 2)

**Table 2:** Odds Ratios of having met the indicator above the 5-year mean.

Variables	Sex **	Age	Low Income	Hospital admission for CV event	General practices cluster†
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Standardized prevalence (2016)	1.656 (1.614-1.700)	1.056 (1.055-1.057)	2.111 (1.992-2.237)	1.276 (1.211-1.344)	1.402 (1.363-1.411)
HbA1c <7%*	1.099 (1.053-1.148)	1.001 (0.999-1.002)	0.801 (0.721-0.890)	0.529 (0.490-0.571)	2.457 (2.291-3.636)
HbA1c ≥9%*	0.951 (0.896-1.009)	0.980 (0.978-0.982)	1.447 (1.279-1.637)	1.354 (1.227-1.495)	1.729 (1.631-1.834)
PA<140/90 mmHg *	0.909 (0.871-0.949)	0.979 (0.978-0.981)	0.865 (0.780-0.961)	0.920 (0.855-0.990)	1.833 (1.757-1.913)
LDL-C <100 mg/dl *	1.408 (1.348-1.469)	1.006 (1.004-1.007)	1.009 (0.909-1.121)	0.880 (0.818-0.947)	1.728 (1.657-1.802)

\* Average value of % compliance by general practices over the five years \*\*Male over female †Adjusted for sex, age, low income

### 3.3. Cox regression.

The probability of admission for a CVE increases with age, male sex, low income, previous history of a CVE obesity, having HbA1c ≥ 9%, and the patient belonging to a GP practice in the cluster of HbA1C ≥ 9% worst control. In contrast, it decreases in those patients with HbA1c <7%, BP<140/90 mmHg, and LD-C <100 mg/dl. There is no significant difference between GP practices clusters by HbA1c <7%, BP 140/90, LDL-C<100 mg/dl, or being a smoker (Table 3).

**Table 3** Cox regression model to analyze the risk of admission for a cardiovascular event in patients with type 2 Diabetes

Variable	HR	95% CI	p
Age	1.339	1.189-1.507	<0.001
Sex*	1.034	1.028-1.040	<0.001
Low Income	1.484	1.129-1.950	0.005
History of cardiovascular event prior to admission	17.885	15.499-20.638	<0.001
HbA1c < 7%**	0.670	0.579-0.775	<0.001
HbA1c ≥ 9%**	1.665	1.339-2.070	<0.001
BP <140/90 mmHg**	0.794	0.682-0.924	0.003
LDL-C <100 mg/dl**	0.844	0.737-0.967	0.015
Cluster indicator HbA1c < 7%	1.091	0.927-1.283	0.293
Cluster indicator HbA1c ≥ 9%	1.147	1.030-1.277	0.012
Cluster indicator PA <140/90 mmHg	1.082	0.968-1.210	0.166
Cluster indicator LDL-C <100 mg/dl	0.919	0.824-1.026	0.132
Current smoker	1.043	0.935-1.164	0.451
Obesity (BMI >30)	1.190	1.026-1.381	0.022

\* Male over female \*\* Average 5-year compliance

## 4. Discussion

### 4.1. Strengths and limitations

Our study had several strengths. First, we study the entire population of Navarra, an area in the north of Spain with more than 600.000 inhabitants. This fact minimizes the selection risk of bias. We have used cluster analysis to classify GP practices on compliance with the indicators rather than other methods. It identifies clusters in which intragroup variability is minimal and maximizes extra group variability. Thus, the individuals in each cluster are very similar and different from the other clusters. This analysis allows us to correct the drawbacks of more straightforward methods such as deciles or quartiles, and others that include individuals with outliers may bias.

Our population is so large that slight differences, without clinical relevance, can be significant. Therefore, using the Hazard Ratio or Odds Ratio to measure the association's strength allows us to visualize better the most clinically relevant differences between the different GP practices in compliance with the quality indicators.

In this study, we do not know how many years the general practitioner was in a GP practice, so it would be interesting to analyze the continuity of the same physician in each GP practice in other studies.

Our study has been carried out based on the electronic records of health professionals during patient care, being a faithful reflection of clinical practice. This is one of the strengths of this type of study. But they may have biases due to limitations in the quality of the records. Studies with large administrative databases often show high accuracy in the diagnostic and treatment aspects. Still, they are subject to misclassification problems related to underreporting of lifestyle that affect the outcome of interest. In contrast, in many traditional "ad hoc" epidemiological studies, there is a great deal of information on risk factors, but the clinical data is incomplete or of lower quality.

Administrative databases may be insufficient to obtain reliable estimates of the effects of preventive actions due to unmeasured confounding factors [32,33]. This can occur in both longitudinal and cross-sectional studies [34]. There may be an underreporting of

our study's lifestyle or clinical examination data, such as smoking, BP, and weight measurements. Compared with the literature, the percentage of smokers in T2D and obese patients is similar to previous studies in Spain [18,35–38]. Laboratory data are collected automatically, so they accurately reflect what has been requested from each patient. The registry of Navarra was rated as the highest quality among the 17 Regional Health Services in Spain in patients with T2D [39]. In Navarra, studies have shown the usefulness of electronic records for assessing the quality of care of patients with T2D [7,27–29]. This study could only access data on hospital admissions for cardiovascular CVE but not mortality data. Future studies would be of great interest to analyze the risk of cardiovascular mortality in patients with T2D. [35]

#### 4.2. Prevalence of diabetes

The prevalence of T2D increased over the years studied from 4.14% to 5.05%. It was higher in men in all years. The mean standardized prevalence achieved in 2016 in the highest and lowest diagnosed GP practices clusters was 8.20% and 4.83%, respectively. Several studies with different methodologies have analyzed the prevalence and degree of control of patients with T2D in Spain [40,41]. One of the main findings in the literature is that most of the studies conducted in Spain do not provide prevalence figures [20,41–44]. An exception is the epidemiological study Di@bet.es, with data from a population-based sample of 5,072 participants aged  $\geq 18$  years and identified a prevalence of T2D of 13.8%. (CI 95% 12.8- 14.7), being unknown by patients in 6.0% (CI 95% 5.4-6.7) [36]. In our investigation, the prevalence detected is lower in both the highest and lowest detection clusters with patient visit data. In Catalonia (Spain), a study with electronic records of patient visits on a population of 3,755,038 inhabitants between 31 and 90 years of age found a prevalence of 7.6% of patients with diabetes. Although this figure is higher than our GP practices average is like the cluster with higher detection.

According to the 2014 European Health Survey, the prevalence of self-reported T2D is 6.82% (7.25% in men and 6.4% in women), higher than detected in our study but lower than detected by the highest detection cluster [45]. The European health survey in Spain 2017 points out that the prevalence of T2D had doubled from 1993 (4.1%) to 2017 (7.8%) [46]. Results from the 2017-2018 age-adjusted NAHNES survey conducted in the US among US adults 18 years and older showed a prevalence of 7.5 % among non-Hispanic whites[47]. Our standardized prevalence for the population of Navarra is 5.74% (8.2% higher cluster and 4.83 lower cluster).

#### 4.3. Risk factors for cardiovascular disease

There is a relationship between the duration of the evolution of T2D and the deterioration of lipid control [43]. In Navarra, a cross-sectional study showed that women were less likely than men to achieve HbA1c (59 vs. 61%), LDL (35 vs. 45%), and HDL (58 vs. 78%) control targets and that patients under 65 years of age had worse control than older age groups. [27] Data from our study agree with these results given that men had an OR of 1.099 for HbA1c<7% and 1.408 for LDL-C<100mg/dl, however, BP control was better in women (OR 0.909). Another multicenter cross-sectional study found that patients with T2D had a high prevalence of cardiovascular risk factors in Spain. Control of glycemia, smoking, BP, and LDL-C was not optimal [44]. Our study observed that, on average, less than half of the patients with T2D had HbA1c <7% or LDL-C<100 mg/dl in the five years of follow-up. As for BP, the percentage of control is somewhat higher, 52%. In a cohort study conducted in primary care in the Community of Madrid, cardiovascular complications were: 6.2% coronary heart disease, 3.2% peripheral vascular disease, and 2.8% stroke. In addition, it detected retinopathy in 5.9% of patients [42].

#### 4.4. Variability in control indicators

We used only four quality indicators of T2D control, which different guidelines have proposed. The indicators were percentage of people with T2D per GP practice with HbA1c <7; percentage of people with T2D per GP practice with HbA1c  $\geq$  9, percentage of people with T2D per GP practice with LDL-C <100 mg/dl, and percentage of patients per GP practice with BP < 140/90 mmHg [1,4].

HbA1c is a marker of average blood glucose concentration that is linearly related to the risk of vascular complications. HbA1c is very useful for the diagnosis of diabetes. Its value is increasingly discussed for treatment because the average glucose and blood glucose range is becoming critical [48]. Although HbA1c level is continuously associated with cardiovascular risk, different guidelines have recommended an HbA1c <7% as the cut-off point for establishing recommendations for managing T2D [1,4]. Analysis of electronic HbA1c records helps predict increased emergency department visits and hospital admissions [49]. Being in the cluster of GP practices with the best control multiplies by 2.5, the probability of having HbA1c controlled. Being in a GP practice in the worst control cluster increases the likelihood of having HbA1c  $\geq$  9% by 73%. This is a cause for concern due to the inequity involved. The American Diabetes Association (ADA) has revised its overall BP targets for patients with T2D, placing it at <140/90 mmHg [50,51]. In our study, the probability of control in the best control cluster is almost double. According to the recommendations of the clinical guidelines, we have taken LDL-C <100 mg/dl as a reference for lipid control [2,4]. Again, we detected significant differences between the clusters, with almost double the probability of having controlled LDL-C in the best-controlled cluster.

#### *4.5. Variability. The risk of admission for a CVE*

The most frequent complication leading to hospitalization of T2D is stroke (34.7%), followed by ischemic heart disease (28.7%) [3]. Our study provides information on the risk of admission for [35] stroke and ischemic heart disease in patients with T2D. However, it has the limitation that it does not include deaths due to these causes. Still, it allows adjusting the risk of admission by age, sex, and low income, including the variability of the physician providing the care. Our study found that the risk of cardiovascular admission increases by 3.4% with each year of age. Other studies report a similar annual risk of fatal and nonfatal CVE between 2-5% [52,53]. The risk of admission was lower in those patients with HbA1c <7% (HR: 0.67) and increased if HbA1c had elevated values  $\geq$  9% (HR: 1.665). Our results coincide with other studies indicating an increased CVE risk with elevated HbA1c levels [54-56].

Similarly, lipid and BP control were protective factors. There was no difference in admissions between patients whose GP was in the higher control cluster of HbA1c <7% and those in the lower cluster. The same happened with BP <140/90 mmHg and LDL-C <100 mg/dl clusters. Differences were found between clusters with a higher proportion of patients with poor control of HbA1c  $\geq$  9%. A GP practice located in a poorly controlled cluster entails an additional risk of admission for a CVE of 14.7%, and this risk is independent of the risk that the patients may have when their HbA1c  $\geq$  9% is uncontrolled.

#### *4.6. Implications for research and practice*

Variability in clinical practice is a factor that influences the health of the population. It has been studied how professionals' knowledge and interest in specific pathologies influence the control of different health indicators [21,22,24]. On the other hand, another factor that influences care is continuity of care. Previous studies have shown that having a primary care physician that knows their patients for many years is a protective factor in admissions and mortality [57,58]. We have not evaluated this item because it does not appear in the database analyzed.

With a small number of indicators, our study provides information on the technical quality achieved in clinical practice in the care of patients with T2D, identifying variability

among primary care providers. Cluster analysis allows us to obtain homogeneous groups of GP practices by identifying those who achieve better or worse results in routine clinical practice. Odds ratios quantify the differences between clusters, showing compliance with the indicators between the different GP practices. We detected a significant equity problem according to the health care providers and socio-economic level.

The methodology used would be helpful to establish incentives through benchmarking strategies that introduce a comparative evaluation with the best and most efficient practices. This type of strategy is a method of continuous improvement in various business sectors, including the health sector [59–61]

**Supplementary Materials:** The following is available online at <http://www.mdpi.com/> Table S1: Descriptive indicators of the population of Navarra, cohort 2012 to 2016 (>=18 years) stratified by sex.

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**Author Contributions:** Conceptualization, SGA, ABL, LF; methodology, SGA, ABL; data curation ABL, LF; writing—original draft preparation, SGA, ABL; writing—review and editing, SGA, IAO, ABL, LF, FGG, LGA; visualization, FGG, IAO, LGA; supervision, ABL, LF; funding acquisition, LF. All authors have read and agreed to the published version of the manuscript.

**Institutional Review Board Statement:** The APNA study received approvals from the Spanish Agency for Medicines and Health Products of the Ministry of Health, Social Services, and Equality under code ABL-MET-2013-01 on 9 December 2013 and from the Clinical Research Ethics Committee of the Government of Navarra. (CEIC) number 3/2014 on 26 March 2014 and number 83/2014 on 30 September 2014.

**Informed Consent Statement:** The database is an administrative database of Navarra Health Service. Clinical Records were collected routinely during attendance in primary health care and hospitals. All users of Navarra Health Services know that their clinical records are registered, and that can be used for epidemiological research. According to Data Protection Law, they have the right to the cancellation of their records.

**Data Availability Statement:** The datasets generated for this study are unavailable due to the data protection law.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role neither in study design nor in the collection, analyses, interpretation of data, manuscript writing, or in the decision to publish the results”.

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