BMJ Open

Glycemic Control and Antidiabetic Treatment Trends in Primary Care Centers in Patients with Type 2 Diabetes During 2007-2013 in Catalonia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012463
Article Type:	Research
Date Submitted by the Author:	29-Apr-2016
Complete List of Authors:	Mata-Cases, Manuel; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salu Franch-Nadal, Josep; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut Real, Jordi; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Universitat Internacional de Catalunya, Epidemiologia i Salut Pública Mauricio, Didac ; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	antidiabetics, prescription, glycemic control, Type 2 diabetes mellitus, PRIMARY CARE

Glycemic Control and Antidiabetic Treatment Trends in Primary Care Centers in Patients with Type 2 Diabetes During 2007-2013 in Catalonia

Manel Mata-Cases,[1,2,3] Josep Franch-Nadal,[1,2,4] Jordi Real,[1,5] Dídac Mauricio,[1,2,6]

[1]DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain

[2]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Spain

[3]Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Sant Adrià de Besòs, Spain

[4]Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Barcelona, Spain

[5]Universitat Internacional de Catalunya, Epidemiologia i Salut Pública, Sant Cugat, Spain

[6]Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Corresponding author:

Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol

Carretera del Canyet s/n

08916 Badalona, Barcelona, Spain

Phone: +34 934978860

Fax: +34 934978497

Email: didacmauricio@gmail.com

Keywords: antidiabetics, prescription, glycemic control, diabetes, primary care

Main body of the text word count: 3,575

ABSTRACT

Objectives: To assess trends in prescribing practices of antidiabetic agents and glycemic control in patients with type 2 diabetes (T2DM).

Design: Cross-sectional analysis using yearly clinical data and antidiabetic treatments prescribed obtained from an electronic population database.

Setting: Primary health care centers, including the entire population attended by the Institut Català de la Salut in Catalonia, Spain, from 2007 to 2013.

Participants: Patients aged 31 to 90 years with a diagnosis of T2DM.

Results: The total number of T2DM registered patients in the database was 257,072 in 2007, increasing up to 343,969 in 2013. Between 2007 and 2013, the proportion of patients not pharmacologically treated decreased progressively (28.1% to 19.4%), while there was a gradual increase in the percentage of patients on monotherapy (31.8% to 36.2%), combination therapy (22.6% to 25.4%), and insulin alone or in combination (17.5% to 20%). The use of metformin and DPP4 inhibitors increased gradually, and the use of sulfonylureas, glitazones, and alpha-glucosidase inhibitors decreased. The use of glinides remained stable, and the use of GLP-1 receptor agonists was still marginal. Regarding glycemic control, there were no relevant differences across years: mean HbA1c value was around 7.2%; the percentage of patients reaching a HbA1c ≤7% target ranged between 52.2% and 55.6%; and those attaining their individualized target from 72.8% to 75.7%.

Conclusions: Although the proportion of patients under pharmacological treatment increased substantially over time and there was an increase in the use of combination therapies, there have not been relevant changes in glycemic control during the 2007-2013 period in Catalonia.

ARTICLE SUMMARY

Strengths and limitations of the study

- The main strength of the study is the use of a large outpatients database that is indicative of the trends of general practitioners' practices in a real-life clinical setting.
- However, this was a retrospective study subject to errors in data recording or missing values.
- We were not able to assess whether the change in prescribed treatments over time was driven by patients' needs and characteristics (e.g. prior low tolerability or effectiveness), and we cannot therefore claim a causal effect.
- We could not assess whether doses of pharmacological treatments were appropriately chosen, and we did not consider data on prescriptions within the same therapeutic class.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic disease at risk of chronic micro- and macrovascular complications when glycemic control is suboptimal. [1] Although diet and lifestyle changes are initially effective, most patients will need an oral glucose-lowering agent to better control blood-glucose levels, and most will eventually need multiple therapies as the disease progresses.[2] The pharmacological armamentarium to treat hyperglycemia in T2DM has changed substantially over the last twenty years with the development of new therapeutic agents, such as insulin secretagogues (glinides), thiazolidinediones, incretins (glucagon-like peptide-1 receptor agonists [GLP-1ra] and dipeptidyl peptidase-IV inhibitors [DPP4i]), sodium-glucose transporter-2 inhibitors, fixed-dose combinations, and also with the advent of insulin analogs.[3] This, together with changing treatment recommendations advocating for an intense glycemic control in early stages of the disease,[4 5] makes drug choice increasingly challenging, and it has driven substantial changes in current prescribing practices with wide variations between countries depending on each therapeutic class.[6-17]

General practice databases are a reliable and rich source of information from the general population, and therefore a valuable tool to study medical practice in the community.[18] In Catalonia, Spain, such an electronic general practice database is available for researchers (Information System for the Development of Research in Primary Care [SIDIAP]), and it has been previously used to conduct several observational studies to assess different aspects of the natural history and treatment of T2DM in our autonomous region.[19-26]

In the present study we aimed to examine prescribing patterns for antidiabetic treatment in primary care in Catalonia between 2007 and 2013 using SIDIAP data, and how changes impacted the degree of attained glycemic control over time.

MATERIALS AND METHODS

Design

This was a cross-sectional, retrospective study using the SIDIAP database, which started in 2006 and stores data from electronic medical records. The database contains anonymized longitudinal patient information obtained from the electronic clinical records using specific software (Electronic Clinical station in Primary Care; eCAP) developed by the institution and

used since 2001 by all of the 274 primary care centers pertaining to the Catalan Health Institute (ICS), which attends 80% of the total population (about 5.835 million patients) in Catalonia.

Data Extraction

Data from patients aged 31 to 90 years with a diagnosis of T2DM (by means of the International Classification of Diseases codes [ICD-10] codes E11 or E14) was obtained from the SIDIAP database for the years 2007 to 2013. Registered variables included: age; gender; time since diagnosis; the presence of comorbidities (ICD-10 codes); and the most recent value for each year of body mass index (BMI) and mean glycated hemoglobin (HbA1c). Before 1st January 2010, between 50% and 70% of laboratories in Spain expressed HbA1c values using the Japanese Diabetes Society/Japanese Society for Clinical Chemistry criteria (JDS/JCC; normal range 3.9%-5.7%),[27] and these values were not converted to the internationally defined Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP) calibration criteria (normal range 4%-6%). All values from 1st January 2010 onwards were expressed using DCCT/NGSP criteria.

The prescribed antidiabetic treatments for each patient and year were extracted from prescription- and pharmacy-invoicing data provided by the CatSalut (Catalan Health Service), which are yearly incorporated into the SIDIAP database. Glucose lowering agents included the use of insulin and non-insulin antidiabetic drugs (NIADs) marketed in Spain during the study period, namely metformin, sulfonylureas, glinides, glitazones, DPP-4i, GLP-1ra, and alpha-glucosidase inhibitors (AGI). The first DPP-4i marketed in Spain was sitagliptin (2007) followed by vildagliptin (2007), saxagliptin (2010) and linagliptin (2012). For GLP-1ra, daily exenatide appeared in 2007, and liraglutide in 2011. Steps of treatment were categorized as no pharmacological treatment, a NIAD in monotherapy, NIADs in combination, insulin alone, or insulin in combination with NIADs.

This study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol.

Statistical analysis

Descriptive analyses by year are presented as mean and standard deviation for continuous variables, and percentages for categorical variables. We used 3 different criteria for adequate glycemic control: mean HbA1c ≤7%, as widely recommended and accepted; HbA1c ≤8%, as recommended by our institution during the study period (ICS);[28 29] and individualized goals based on age, duration of the disease, and presence of serious complications or comorbidities, as proposed by the Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud 2014 (Red-GDPS).[30] All statistical calculations were performed using StataCorp 2009 (Stata Statistical Software: Release 11. College Station, TX: StataCorp, LP).

RESULTS

Patients' characteristics

The total number of T2DM registered patients in our database was 257,072 in 2007, increasing up to 343,969 in 2013 (a total increase of 86,897 cases) (**Table 1**). The patients' mean age did not vary substantially over the years (67.7-68.9 years), nor did the mean BMI or the number of obese subjects, but we observed a small progressive increase in the proportion of male patients (from 52.2% in 2007 to 54.3% in 2013), and also a gradual increase in the mean duration of the disease (from 5.4 years in 2007 to 7.8 years in 2013).

Table 1. Demographic, clinical characteristics, and degree of glycemic control of patients with T2DM by year

	2007 N = 257,072	2008 N = 271,690	2009 N = 286,019	2010 N = 301,144	2011 N = 317,215	2012 N = 331,317	2013 N = 343,969
Age, mean (SD), years	67.7 (11.7)	67.9 (11.8)	68.1 (11.8)	68.2 (11.9)	68.4 (12.0)	68.6 (12.1)	68.9 (12.1)
Males, %	52.2	52.7	53.2	53.6	53.9	54.1	54.3
T2DM duration, mean (SD), years	5.4 (5.3)	5.9 (5.3)	6.3 (5.3)	6.7 (5.4)	7.0 (5.5)	7.4 (5.6)	7.8 (5.6)
BMI, mean (SD), kg/m^2	30.1 (5.0)	30.1 (5.0)	30.1 (5.0)	30.1 (5.0)	30.1 (5.1)	30.0 (5.1)	30.0 (5.1)
Obesity (BMI >30 kg/m^2), %	45.6	45.5	45.3	45.7	45.3	45.1	45.1
HbA1c*, mean (SD), %	7.16 (1.46)	7.23 (1.48)	7.25 (1.47)	7.19 (1.40)	7.20 (1.36)	7.30 (1.35)	7.24 (1.35)
HbA1c ≤7%, %	54.9	52.8	52.2	55.1	55.6	52.6	55.2
HbA1c ≤8%, ** **%**	78.9	77.8	77.9	79.3	79.6	78.4	79.6
Individualized HbA1c target*, %	75.4	73.2	72.8	74.8	75.4	73.7	75.7

*Cut-off stated by the Institut Català de la Salut (ICS); **Based on the 2014 algorithm of the Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud (Red-GDPS)
BMI, body mass index; SD, standard deviation; T2DM, type 2 diabetes

Prescribing pattern of antidiabetic drugs

The proportion of patients not receiving antidiabetic drugs decreased from 28.1% in 2007 to 19.4% in 2013, while the percentage of patients receiving pharmacological antidiabetic treatment was 71.9% in 2007, and this proportion increased annually between 1.7-2.1% until 2012, and 0.3% between 2012 and 2013 (81.6% in the last year of the study), showing an overall 9.7% increase over the study period. The proportion of patients receiving each type of therapy across the time period 2007-2013 is shown in **Figure 1**. The most frequent prescription was a NIAD in monotherapy, the use of which increased from 31.8% in 2007 to 36.2% in 2013, followed by NIADs in combination (increasing from 22.6% to 25.4%), and insulin alone or in combination (increasing from 17.5 to 20%). Among NIADs, the most frequently used drugs were metformin and sulfonylureas, although the prescription rate of metformin increased notably across time (from 48.5% in 2007 to 68% in 2013), whereas it decreased gradually in the case of sulfonylureas (from 33.8% to 25.6% in 2013) (**Figure 2**). As for the use of the rest of the available options, only the prescription of DPP4i increased substantially up to a 13.2% in 2013, while the use of glitazones, glinides, AGI, and GLP-1ra remained low: in the case of glitazones and AGI, prescriptions even decreased with time (from 3.9% to 1.2% in 2013, and from 3.6% to 0.7%, respectively), and glinides and GLP-1ra only increased slightly over time (overall increase 0.8% and 0.9%, respectively).

Evolution of the degree of glycemic control

The mean standardized HbA1c value was around 7.2%, with no clinically relevant differences across years. Moreover, the proportion of patients attaining a glycemic target of HbA1c ≤7% ranged from 52.2% to 55.6%, and the ICS target ≤8% ranged from 77.8% and 79.6%, with no remarkable changes across years (**Table 1**). Moreover, the percentage of patients attaining their individualized HbA1c target ranged from 72.8% to 75.7% (**Table 1**). Finally, the analysis of the evolution of the attained glycemic control according to different HbA1c intervals also showed that there were no noticeable changes among years in any case (**Figure 3**). Of note, the group of patients who were less likely to achieve the corresponding glycemic target were those younger than 65 years old, without comorbidities, and duration of T2DM ≤15 years (range 50.8%-55.1%) (**Supplementary Table 1**).

The evolution of the mean Hb1Ac levels according to each step of treatment and duration of T2DM is shown in **Figure 4**. Considering all antidiabetic treatments, there was a progressive worsening of HbA1c levels as the disease duration increased, but this worsening was in fact only observed among patients treated with insulin alone or in combination with NIADs. Conversely, glycemic values in patients not pharmacologically treated or on NIADs improved as T2DM duration increased, with no substantial differences across the study period.

DISCUSSION

This cross-sectional, descriptive study is, to the best of our knowledge, the first to assess trends in the prescribing practices of antidiabetic drugs in relation to the level of attained glycemic control between 2007 and 2013 in a primary health care setting in Spain.

The proportion of patients receiving pharmacological treatment for T2DM increased annually up to 81.6% at the end of the study, with an absolute 9.7% increase, and this was paralleled by a substantial decrease in the proportion of patients not receiving drugs. This gradual increase in the prescription of antidiabetic agents has been previously reported in Spain [16 17] and in studies conducted worldwide throughout the same or overlapping years as in our study.[6-8 10-12 31 32] The proportion of patients in all therapeutic steps increased gradually across years, with NIADs in monotherapy the most prescribed, followed by NIADs in combination, and insulin alone or in combination. An increase in the use of combinations of oral antidiabetic drugs (OAD) has been consistently observed in several studies from different countries,[6 7 9 11 17 31] but the trends in its use as monotherapy vary among reports, with some describing an overall increase over time,[11 13 32] and others a progressive decrease.[6 9 31] Moreover, while the number of prescriptions of insulin in combination with an OAD has been shown to increase with time,[6 7 11] the use of insulin alone has been reported to remain stable [17 33], to decrease,[6 11 31] or even to increase.[32] Differences between drug schemes and studies may be attributable to health policy variations across countries, local professional expertise, physician's personal choice, study setting (e.g. hospital vs. primary care or insurance claims vs. national database), or inclusion of both type 1 and type 2 DM patients in some cases.

Metformin and sulfonylureas accounted for the vast majority of NIAD prescriptions across the study period. However, the trend in prescriptions of both drugs differed: while the number of patients who were prescribed metformin increased notably throughout the follow-up, there was a progressive decline in the use of sulfonylureas. Both an increase in the use of metformin and a decrease in the use of sulfonylureas have been consistently reported by other groups.[6-9 11-13 15 17 31-33] This decline could be related to the recent recommendation of cautionary use in the elderly,[34] their worse safety profile, associated weight gain, unclear role in reducing long-term complications, and/or to the availability of safer new therapeutic options.[5] With regards to the prescription pattern of other NIADs in our study, the use of glinides remained low but stable (about 5%), the use of AGIs and glitazones decreased gradually from 2008 to less than 1% of prescriptions in 2013, the use of GLP-1ar was marginal, and the use of DPP4i increased immediately after 1 year of availability (2007) in our market, increasing up to a 13.2% at the end of the study. Although a decrease in both glinides and AGIs use has been reported in Spain, Japan and in the UK,[11 15 17 33] in our study the number of glinides' prescriptions remained stable, which could be explained by the fact that in spite of their risk of hypoglycemia,[5] they are the most used therapeutic class in patients with chronic kidney disease.[25]

The decrease in AGIs might be explained by the high frequency of gastrointestinal side effects that led to the recommendation to only use them in people unable to use other oral glucose-lowering medications.[35] The decrease in the use of glitazones has been consistently documented in several studies that included data after 2007,[8 9 11-13 15 17 31-33] when the first regulatory warnings and the results of a meta-analysis alerted clinicians to cardiovascular risk associated with rosiglitazone,[36 37] and to a risk of bladder cancer with pioglitazone in 2011.[38] Both side effects have been recently ruled out,[37 39] but the influence of these alarms, together with weight gain, the risk of heart failure and the increased risk of bone fractures in women observed with this class of drugs has limited its use. The marginal use of GLP-1ra in our study is similar to a recent study conducted in the UK,[15] but in contrast with a substantial increase documented in another region of Spain,[17] Ireland, and the US.[9 13] The administrative restrictions and negative economic incentives of our institution (ICS) for the prescription of GLP-1ar may have contributed to the limited use of this

therapeutic class. Finally, DPP-4i were the newly introduced NIADs that had the greatest increase in use, which is in agreement with other reports conducted worldwide.[9 11-13 17 31-33] This rapid adoption, mainly as an alternative to sulfonylureas, may respond to the lower risk of hypoglycemia, its neutral effects on body weight, and also the greater convenience of an oral treatment instead of the need of injections for GLP-1ar or insulin.[40]

When we assessed the attained glycemic control based on the treatment step, we found that patients on NIADs in combination or on insulin with or without a NIAD were the ones with the highest HbA1c levels. This is in line with the results of several studies showing a delay in treatment intensification in patients already on combination therapies whose control of blood glucose remained or became inadequate.[35 41] Moreover, we found that about half of the patients had HbA1c levels ≤7% as recommended by clinical guidelines, about 80% below the 8% recommended by our institution (ICS), and about 75% below the individualized goal recommended by the Red-GDPS. Our figures are slightly worse than the ones reported by a study conducted in the Basque country in Spain for patients achieving HbA1c levels ≤7% (about 64.1% of them), but similar to their 85.5% of patients achieving an ≤8% target.[42] Finally, and confirming previous analyses, the subgroup with the highest proportion of patients attaining appropriate individualized glycemic control was the one of patients older than 75 years,[23] while subjects younger than 65 years without comorbidities or serious complications and T2DM duration ≤15 years were less likely to achieve the corresponding individualized glycemic control target. This could be explained by a higher proportion of obesity among younger patients, a longer survival among adequately controlled older patients, or by an easier to reach glycemic goal in the elderly (≤8% versus ≤7%). More importantly, our results confirm that an individualized therapeutic approach considerably increases the chances of attaining an adequate glycemic control and provides effective T2DM care.[43] However, one of the most striking findings of our study was that there were no relevant changes across years, meaning that in spite of the overall observed gradual increase in pharmacological treatments along the study there was no obvious trend towards an increase in the proportion of subjects with an adequate HbA1c target whatever the used cut-off, and the mean HbA1c values did not significantly change over time regardless the treatment step. There are few reports on how the evolution in the prescription pattern of

antidiabetic drugs affects the level of attained glycemic control, but our results are in contrast with a study conducted in Japan showing that the rate of patients achieving the ≤7% goal significantly improved together with the progressive increase in the proportion of pharmacological treatments.[11] However, a very recent study conducted in Canada reported that the mean HbA1c values in older subjects even slightly increased over a 5-year period in spite of the overall increase in the use of antidiabetic treatment.[14] Our results seriously question the ICS threshold to maintain HbA1c levels ≤8% for all patients, giving general practitioners financial incentives if this goal is attained, without taking into account age, diabetes duration or the presence of comorbidities. This threshold was established to avoid overtreatment -especially in the elderly- but can be counterproductive in younger patients. Certainly, about 25% of patients had HbA1c between 7.1% and 8%, and were therefore at potential risk of suboptimal management or undertreatment until they reach this value, especially in people under 65 years. Thus, this institutional policy potentially contributes to therapeutic inertia, defined as a delay in treatment intensification among patients with poor glycemic control. Clinical inertia has been documented in primary care settings [44 45], and a study conducted in Catalonia in 2007 in a sample of 2,783 T2DM patients reported that therapeutic inertia was present in 33.2% of cases, and treatment intensification was implemented in patients with a mean HbA1c of 8.4%,[41] which is far above the 8% threshold established by the institution. On the other hand, the next step in patients treated with NIAD combinations includes insulin and GLP-1ar, which are less convenient for patients and more time consuming for health care givers, so that therapeutic inertia is more frequent at this stage. Finally, in the most advanced therapies (insulin plus NIADs) patients had mean HbA1c values around 8%, so that most of them probably need some optimization with multiple insulin doses or the combination of GLP-1ar with insulin. In these circumstances most family physicians find these patients difficult to manage or have reasonable safety concerns, facilitating an inadequate glycemic control in the long term.

Our results show a global negative effect of T2DM duration on glycemic control that did not change substantially across the study period. A progressive worsening of mean Hb1Ac values within each sequential evaluation might be expected because the proportion of patients with a disease duration >10 years increased, but this could have been counteracted

by an intensified management in all treatment steps, eventually leading to steady mean HbA1c levels along the study. This is a possible explanation if we take into account that patients in lowest treatment steps (i.e. no drugs, and NIADs in monotherapy or combined) and a disease duration >10 years had lower HbA1c values than those with a disease duration lower than <2 years, as those on poor glycemic control were probably switched to the next superior treatment step. In contrast, glycemic control among patients on insulin (alone or in combination) worsened as the duration of disease increased, probably because they are at the last treatment step and only intensive management with multiple insulin doses under endocrinologist supervision may improve control.

The present study has strengths and limitations worth mentioning. The main strength is that we used a large outpatients database that, although not completely representative of other areas of Spain, is indicative of the trends of general practitioners' practices in a real-life clinical setting. However, this was a retrospective study subject to errors in data recording or a high percentage of missing values (e.g. 35% of HbA1c values were missing in 2007 decreasing to 25% in 2013), although this would apply to all the study period equally, therefore not affecting the conclusions of the study. Moreover, we were not able to assess whether the change in prescribed treatments over time was driven by patients' needs and characteristics (e.g. prior low tolerability or effectiveness), and we cannot therefore claim a causal effect. Finally, we could not assess whether doses were appropriately chosen, and we did not consider data on prescriptions within the same therapeutic class.

CONCLUSIONS

Although the intensity of pharmacological antidiabetic treatment of T2DM increased substantially during 2007-2013 in Catalonia, there was no evidence that this was accompanied by a positive change in the degree of glycemic control. This reveals shortcomings in the primary health care system that could be tackled through more intensive educational programs for physicians oriented to the individualization of glycemic goals and prioritizing more intensive treatments in the younger patients.

ACKNOWLEDGEMENTS

We acknowledge Mònica Gratacòs and Amanda Prowse for providing support in the manuscript preparation and editing. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) is an initiative from Instituto de Salud Carlos III.

COMPETING INTERESTS. None declared

FUNDING

This study was funded by Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), and an unrestricted grant provided by Astra Zeneca. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

AUTHOR'S CONTRIBUTIONS

MM-C and JF-N wrote the manuscript and contributed equally to this study; JR managed the data base, performed the statistical analyses and contributed to the discussion; and JF-N, MM-C, and DM designed and conducted the study, reviewed/edited the manuscript and contributed to the discussion. MM-C had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis.

DATA SHARING

No additional unpublished data are available.

FIGURE LEGENDS

Figure 1. Percentage of T2DM patients in each step of antidiabetic treatment

Figure 2. Percentage of patients having non-insulin antidiabetic drug prescriptions (alone or in combination)

Figure 3. Percentage of patients achieving glycemic control according to HbA1c intervals

Figure 4. Evolution of mean HbA1c according to the different steps of antidiabetic treatment and T2DM duration

REFERENCES

1. *International Diabetes Federation. IDF Diabetes Atlas, 6th edn.* Brussels, Belgium: International Diabetes Federation, 2013.

2. Turner RC, Cull CA, Frighi V*, et al.* Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281(21):2005-12.

3. Bailey CJ. The Current Drug Treatment Landscape for Diabetes and Perspectives for the Future. *Clin Pharmacol Ther* 2015;98(2):170-84.

4. Holman RR, Paul SK, Bethel MA*, et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359(15):1577-89.

5. Inzucchi SE, Bergenstal RM, Buse JB*, et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38(1):140-9.

6. Baviera M, Monesi L, Marzona I*, et al.* Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: a large population-based study. *Diabetes Res Clin Pract* 2011;93(1):123-30.

7. Chang CH, Jiang YD, Chung CH*, et al.* National trends in anti-diabetic treatment in Taiwan, 2000-2009. *J Formos Med Assoc* 2012;111(11):617-24.

8. Leal I, Romio SA, Schuemie M*, et al.* Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. *Br J Clin Pharmacol* 2013;75(3):861-8.

9. Turner LW, Nartey D, Stafford RS, *et al.* Ambulatory treatment of type 2 diabetes in the U.S., 1997-2012. *Diabetes Care* 2014;37(4):985-92.

10. Strom H, Selmer R, Birkeland KI, *et al.* No increase in new users of blood glucose-lowering drugs in Norway 2006-2011: a nationwide prescription database study. *BMC Public Health* 2014;14:520.

11. Oishi M, Yamazaki K, Okuguchi F, *et al.* Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). *J Diabetes Investig* 2014;5(5):581-7.

12. Hampp C, Borders-Hemphill V, Moeny DG, *et al.* Use of antidiabetic drugs in the U.S., 2003-2012. *Diabetes Care* 2014;37(5):1367-74.

13. Zaharan NL, Williams D, Bennett K. Prescribing of antidiabetic therapies in Ireland: 10-year trends 2003-2012. *Ir J Med Sci* 2014;183(2):311-8.

14. Clemens KK, Liu K, Shariff S, *et al.* Secular trends in antihyperglycemic medication prescriptions in older adults with diabetes and chronic kidney disease: 2004-2013. *Diabetes Obes Metab* 2016

15. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6(1):e010210.

16. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Utilización de medicamentos antidiabéticos en España durante el periodo 2000-2014. Available from http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/antidiabeticos-2000-2014.pdf. Accessed 21 March 2016.

17. Mancera-Romero J, Hormigo-Pozo A, Fernandez-Arquero J*, et al.* [Use of glucose-lowering drugs in a primary care setting in Malaga during the years 2008-2012]. *Semergen* 2014;40(1):4-11.

18. Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. *J Public Health Med* 1999;21(3):299-304.

19. Vinagre I, Mata-Cases M, Hermosilla E*, et al.* Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). *Diabetes Care* 2012;35(4):774-9.

20. Mata-Cases M, Mauricio D, Vinagre I*, et al.* Treatment of Hyperglycaemia in Type 2 Diabetic Patients in a Primary Care Population Database in a Mediterranean Area (Catalonia, Spain). *J Diabetes Metab* 2014;5:338.

21. Franch-Nadal J, Mata-Cases M, Vinagre I*, et al.* Differences in the Cardiometabolic Control in Type 2 Diabetes according to Gender and the Presence of Cardiovascular Disease: Results from the eControl Study. *Int J Endocrinol* 2014;2014:131709.

22. Rodriguez-Poncelas A, Miravet-Jimenez S, Casellas A*, et al.* Prevalence of diabetic retinopathy in individuals with type 2 diabetes who had recorded diabetic retinopathy from retinal photographs in Catalonia (Spain). *Br J Ophthalmol* 2015;99(12):1628-33.

23. Barrot-de la Puente J, Mata-Cases M, Franch-Nadal J*, et al.* Older type 2 diabetic patients are more likely to achieve glycaemic and cardiovascular risk factors targets than younger patients: analysis of a primary care database. *Int J Clin Pract* 2015;69(12):1486-95.

24. Mata-Cases M, Casajuana M, Franch-Nadal J*, et al.* Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. *Eur J Health Econ* 2015

25. Ruiz-Tamayo I, Franch-Nadal J, Mata-Cases M, *et al.* Noninsulin Antidiabetic Drugs for Patients with Type 2 Diabetes Mellitus: Are We Respecting Their Contraindications? *J Diabetes Res* 2016;2016:7502489.

26. Mata-Cases M, Mauricio D, Franch-Nadal J. Clinical characteristics of type 2 diabetic patients on basal insulin therapy with adequate fasting glucose control that do not achieve glycated hemoglobin targets. *J Diabetes* 2016

27. Goberna R, Aguilar-Diosdado M, Santos-Rey K, *et al.* Consensus document for the harmonization of HbA1c results in Spain. *Av Diabetol* 2009;25:35-37.

28. Mata-Cases M, Cos-Claramunt FX, Morros R, *et al.* Abordatge de la diabetis mellitus tipus 2 [online]. 2010; Guies de pràctica clínica, num 15. http://www.gencat.cat/ics/professionals/guies/diabetis/diabetis.htm (accessed 27 June 2014).

29. Avilés F, L. MB, Coma Redon E, *et al.* Sistema de Información de los Servicios de Atención Primaria (SISAP). La experiencia 2006 - 2009 del Institut Català de la Salut (ICS). *RISAI* 2010;2(1):1-17.

30. Alemán JJ, Artola S, Franch J, *et al.* Recomendaciones para el tratamiento de la diabetes mellitus tipo 2: control glucémico. *Diabetes Práctica* 2014;5(1):1-48.

31. Clemens KK, Shariff S, Liu K, *et al.* Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002-2013. *PLoS ONE* 2015;10(9):e0137596.

32. Rafaniello C, Arcoraci V, Ferrajolo C, *et al.* Trends in the prescription of antidiabetic medications from 2009 to 2012 in a general practice of Southern Italy: a population-based study. *Diabetes Res Clin Pract* 2015;108(1):157-63.

33. Kohro T, Yamazaki T, Sato H, *et al.* Trends in antidiabetic prescription patterns in Japan from 2005 to 2011. *Int Heart J* 2013;54(2):93-7.

34. Sinclair AJ, Paolisso G, Castro M, *et al.* European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011;37 Suppl 3:S27-38.

35. NICE (National Institute for Health and Clinical Excellence). Clinical guideline CG87. Type 2 diabetes: the management of type 2 diabetes. Last updated December 2014. Available from: http://guidance.nice.org.uk/CG87/NiceGuidance/pdf/English. Accessed March 2014

36. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356(24):2457-71.

37. FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines. Issued on December 16, 2015. [Retrieved 30 March 2016]. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm. Accessed March 2014

38. Lewis JD, Ferrara A, Peng T, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34(4):916-22.

39. Ryder RE. Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. *Diabet Med* 2015;32(3):305-13.

40. Karagiannis T, Paschos P, Paletas K, *et al.* Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ* 2012;344:e1369.

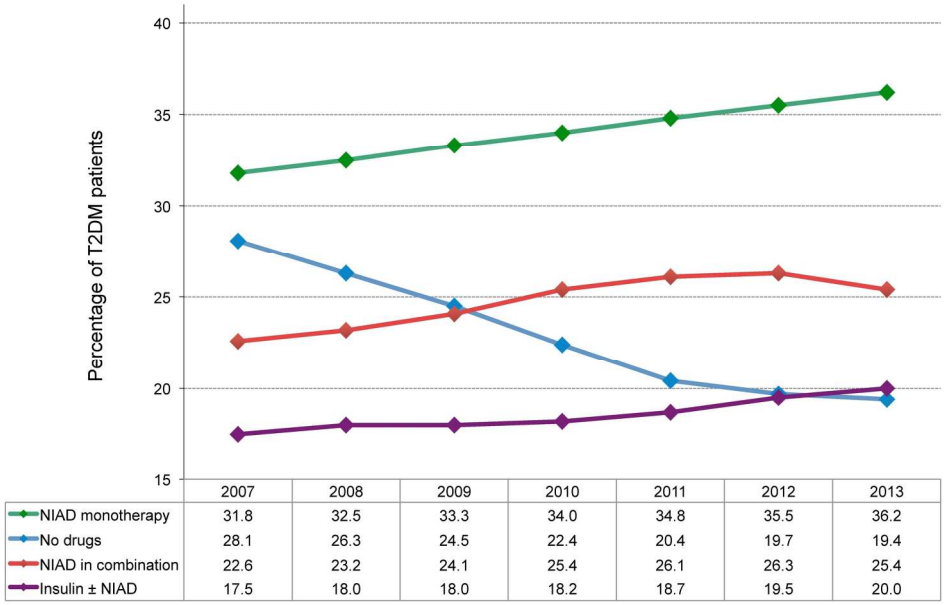
41. Mata-Cases M, Benito-Badorrey B, Roura-Olmeda P*, et al.* Clinical inertia in the treatment of hyperglycemia in type 2 diabetes patients in primary care. *Curr Med Res Opin* 2013;29(11):1495-502.

42. Alonso-Morán E, Orueta JF, Esteban JIF*, et al.* Prevalence and quality of care indicators of type 2 diabetes in the population of the Basque Country (Spain). *Av Diabetol* 2015;31(2):72-79.

43. Subramanian S, Hirsch IB. Personalized Diabetes Management: Moving from Algorithmic to Individualized Therapy. *Diabetes Spectr* 2014;27(2):87-91.

44. Khunti K, Wolden ML, Thorsted BL*, et al.* Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013;36(11):3411-7.

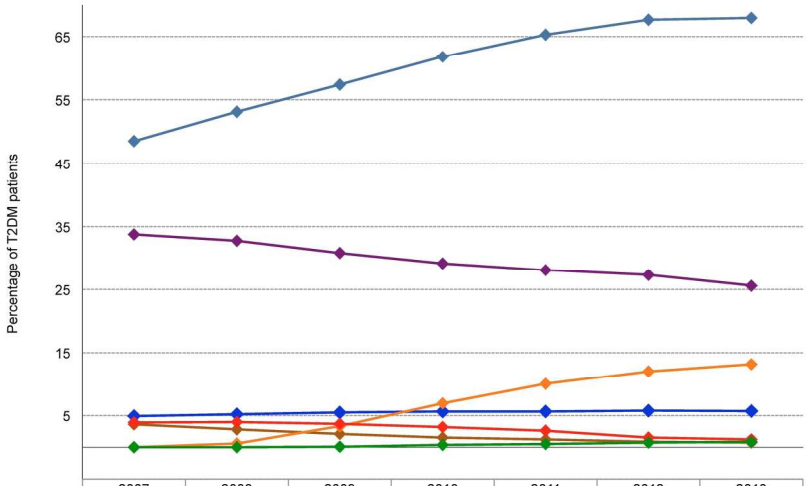
45. Khunti K, Nikolajsen A, Thorsted BL*, et al.* Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab* 2016;18(4):401-9.



	2007	2008	2009	2010	2011	2012	2013
NIAD monotherapy	31.8	32.5	33.3	34.0	34.8	35.5	36.2
No drugs	28.1	26.3	24.5	22.4	20.4	19.7	19.4
NIAD in combination	22.6	23.2	24.1	25.4	26.1	26.3	25.4
Insulin ± NIAD	17.5	18.0	18.0	18.2	18.7	19.5	20.0

Figure 1. Percentage of T2DM patients in each step of antidiabetic treatment

190x142mm (300 x 300 DPI)



	2007	2008	2009	2010	2011	2012	2013
Metformin	48.5	53.1	57.4	61.8	65.3	67.7	68.0
Sulfonylureas	33.8	32.8	30.8	29.2	28.1	27.3	25.6
Glinides	4.9	5.2	5.5	5.6	5.6	5.8	5.7
AGI	3.6	2.8	2.1	1.5	1.2	0.9	0.7
DPP4i	0.0	0.6	3.3	6.9	10.0	12.0	13.2
Glitazones	3.9	4.0	3.7	3.2	2.6	1.5	1.2
GLP-1ra	0.0	0.0	0.1	0.4	0.5	0.7	0.9

Figure 2. Percentage of patients having non-insulin antidiabetic drug prescriptions (alone or in combination)

190x142mm (300 x 300 DPI)

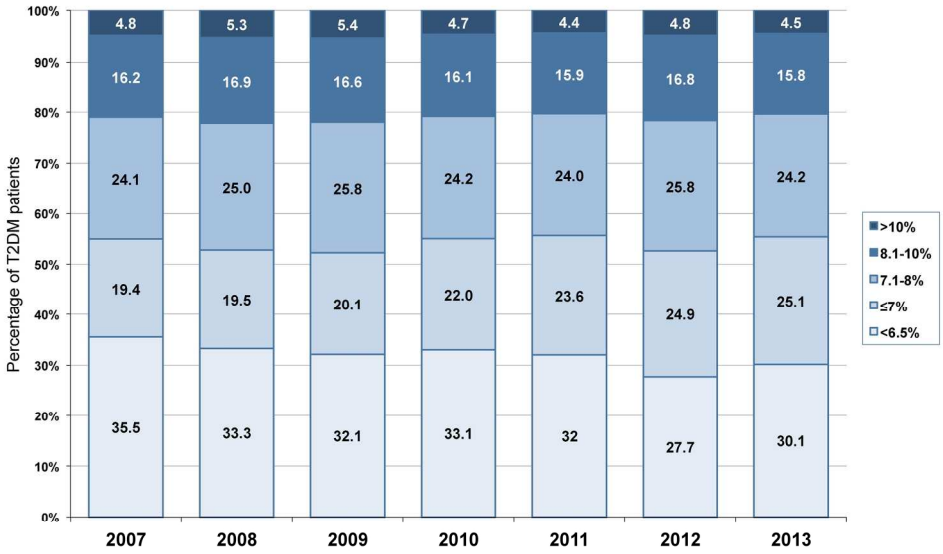


Figure 3. Percentage of patients achieving glycemic control according to HbA1c intervals

190x142mm (300 x 300 DPI)

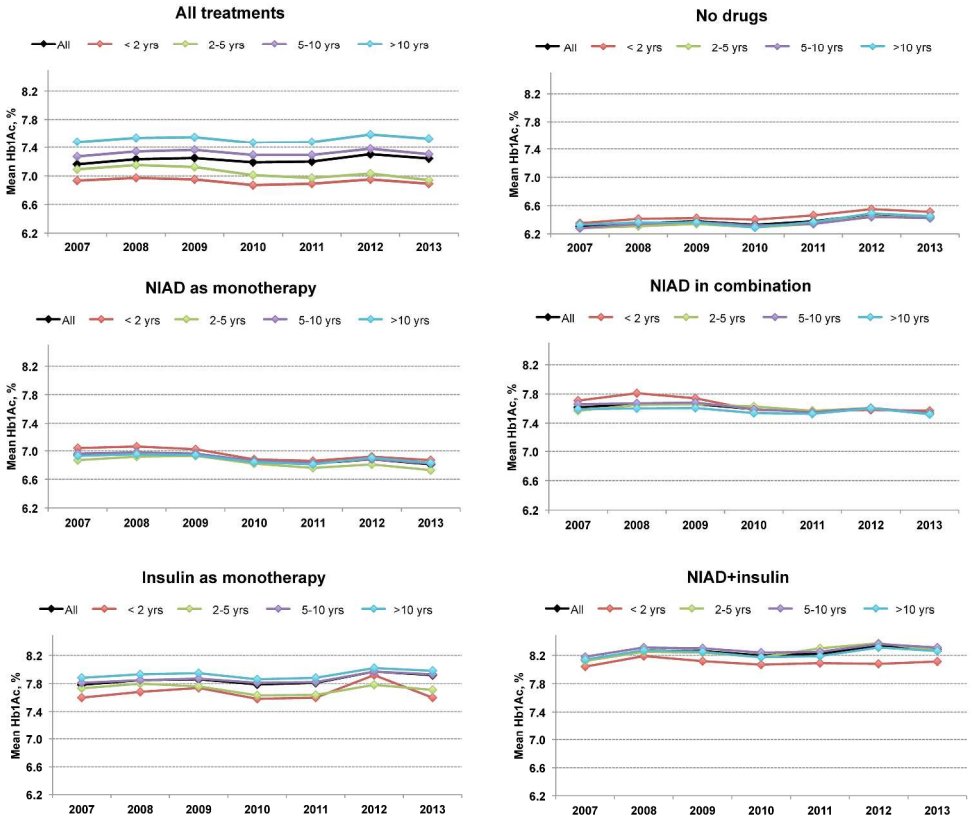


Figure 4. Evolution of mean HbA1c according to the different steps of antidiabetic treatment and T2DM duration

355x420mm (300 x 300 DPI)

Supplementary Table 1. Percentage of patients reaching individualized glycemic targets based on age, duration of T2DM, and presence of comorbidities (Red-GDPS criteria)

	HbA1c glycemic target	2007	2008	2009	2010	2011	2012	2013
Patients with HbA1c values, N		166,388	177,291	193,467	209,022	226,452	241,664	255,553
Age >75 years	≤8.5%	88.7	88.1	88.2	89.2	89.6	88.2	89.0
Age 66-75 years								
With comorbidities or serious complications	≤8.5%	84.7	84.3	83.5	84.7	84.5	83.3	84.1
Without comorbidities or serious complications; T2DM duration >15 years	≤8.0%	73.4	70.9	71.1	73.0	73.2	71.3	72.6
Without comorbidities or serious complications; T2DM duration ≤15 years	≤7.0%	58.8	56.4	56.2	59.6	60.6	57.9	61.5
Age ≤65 years								
Duration >15 years, or <15 years with complications or serious comorbidities	≤8.0%	69.7	67.9	67.4	68.7	68.3	67.0	68.1
Duration <15 years without comorbidities or serious complications	≤7.0%	53.4	51.6	50.8	53.9	55.1	52.7	54.9

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1 & 2 1 & 2 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			4
Objectives	3	State specific objectives, including any prespecified hypotheses			4
Methods					
Study Design	4	Present key elements of study design early in the paper			4 & 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			5
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the		RECORD 6.1: The methods of study population selection (such as codes or	5

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	 NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			5
Bias	9	Describe any efforts to address potential sources of bias			5
Study size	10	Explain how the study size was			NA

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			5
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	5
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	NA

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	6
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			6 & 7
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			7
Main results	16	(a) Give unadjusted estimates			7-9

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			7-9
Discussion					
Key results	18	Summarise key results with reference to study objectives			9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results			13

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Provided during the submission process

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Glycemic Control and Antidiabetic Treatment Trends in Primary Care Centers in Patients with Type 2 Diabetes During 2007-2013 in Catalonia: a Population-Based Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012463.R1
Article Type:	Research
Date Submitted by the Author:	03-Aug-2016
Complete List of Authors:	Mata-Cases, Manuel; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salu Franch-Nadal, Josep; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut Real, Jordi; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Universitat Internacional de Catalunya, Epidemiologia i Salut Pública Mauricio, Didac ; DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol); Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	antidiabetics, prescription, glycemic control, Type 2 diabetes mellitus, PRIMARY CARE

Glycemic Control and Antidiabetic Treatment Trends in Primary Care Centers in Patients with Type 2 Diabetes During 2007-2013 in Catalonia: a Population-Based Study

Manel Mata-Cases,[1,2,3] Josep Franch-Nadal,[1,2,4] Jordi Real,[1,5] Dídac Mauricio,[1,2,6]

[1]DAP-Cat group. Unitat de Suport a la Recerca Barcelona Ciutat, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain

[2]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Spain

[3]Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Sant Adrià de Besòs, Spain

[4]Primary Health Care Center Raval Sud, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Barcelona, Spain

[5]Universitat Internacional de Catalunya, Epidemiologia i Salut Pública, Sant Cugat, Spain

[6]Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol, Badalona, Spain

Corresponding author:

Dídac Mauricio

Department of Endocrinology & Nutrition, Health Sciences Research Institute & Hospital Universitari Germans Trias i Pujol

Carretera del Canyet s/n

08916 Badalona, Barcelona, Spain

Phone: +34 934978860

Fax: +34 934978497

Email: didacmauricio@gmail.com

Keywords: antidiabetics, prescription, glycemic control, diabetes, primary care

Main body of the text word count: 3,575

ABSTRACT

Objectives: To assess trends in prescribing practices of antidiabetic agents and glycemic control in patients with type 2 diabetes (T2DM).

Design: Cross-sectional analysis using yearly clinical data and antidiabetic treatments prescribed obtained from an electronic population database.

Setting: Primary health care centers, including the entire population attended by the Institut Català de la Salut in Catalonia, Spain, from 2007 to 2013.

Participants: Patients aged 31 to 90 years with a diagnosis of T2DM.

Results: The number of registered T2DM patients in the database was 257,072 in 2007, increasing up to 343,969 in 2013. The proportion of patients not pharmacologically treated decreased by 9.7% (95%CI=-9.48 to -9.92), while there was an increase in the percentage of patients on monotherapy (4.4% increase; 95%CI=4.16 to 4.64), combination therapy (2.8% increase; 95%CI=2.58 to 3.02), and insulin alone or in combination (increasing 2.5%; 95%CI=2.2 to 2.8). The use of metformin and DPP4 inhibitors increased gradually, while sulfonylureas, glitazones, and alpha-glucosidase inhibitors decreased. The use of glinides remained stable, and the use of GLP-1 receptor agonists was still marginal. Regarding glycemic control, there were no relevant differences across years: mean HbA1c value was around 7.2%; the percentage of patients reaching a HbA1c ≤7% target ranged between 52.2% and 55.6%; and those attaining their individualized target from 72.8% to 75.7%.

Conclusions: Although the proportion of patients under pharmacological treatment increased substantially over time and there was an increase in the use of combination therapies, there have not been relevant changes in glycemic control during the 2007-2013 period in Catalonia.

ARTICLE SUMMARY

Strengths and limitations of the study

- The main strength of the study is the use of a large outpatients database that is indicative of the trends of general practitioners' practices in a real-life clinical setting.
- However, this was a retrospective study subject to errors in data recording or missing values.
- We were not able to assess whether the change in prescribed treatments over time was driven by patients' needs and characteristics (e.g. prior low tolerability or effectiveness), and we cannot therefore claim a causal effect.
- We could not assess whether doses of pharmacological treatments were appropriately chosen, and we did not consider data on prescriptions within the same therapeutic class.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic disease at risk of chronic micro- and macrovascular complications when glycemic control is suboptimal. [1] Although diet and lifestyle changes are initially effective, most patients will need an oral glucose-lowering agent to better control blood-glucose levels, and most will eventually need multiple therapies as the disease progresses.[2] The pharmacological armamentarium to treat hyperglycemia in T2DM has changed substantially over the last twenty years with the development of new therapeutic agents, such as insulin secretagogues (glinides), thiazolidinediones, incretins (glucagon-like peptide-1 receptor agonists [GLP-1ra] and dipeptidyl peptidase-IV inhibitors [DPP4i]), sodium-glucose transporter-2 inhibitors, fixed-dose combinations, and also with the advent of insulin analogs.[3] This, together with changing treatment recommendations advocating for an intense glycemic control in early stages of the disease,[4, 5] makes drug choice increasingly challenging, and it has driven substantial changes in current prescribing practices with wide variations between countries depending on each therapeutic class.[6-17]

General practice databases are a reliable and rich source of information from the general population, and therefore a valuable tool to study medical practice in the community.[18] In Catalonia, Spain, such an electronic general practice database is available for researchers (Information System for the Development of Research in Primary Care [SIDIAP]), and it has been previously used to conduct several observational studies to assess different aspects of the natural history and treatment of T2DM in our autonomous region.[19-26]

In the present study we aimed to examine prescribing patterns for antidiabetic treatment in primary care in Catalonia between 2007 and 2013 using SIDIAP data, and how changes impacted the degree of attained glycemic control over time.

MATERIALS AND METHODS

Design

This was a cross-sectional, retrospective study using the SIDIAP database, which started in 2006 and stores data from electronic medical records. The database contains anonymized longitudinal patient information obtained from the electronic clinical records using specific software (Electronic Clinical station in Primary Care; eCAP) developed by the institution and

used since 2001 by all of the 274 primary care centers pertaining to the Catalan Health Institute (ICS), which attends 80% of the total population (about 5.835 million patients) in Catalonia.

Data Extraction

Data from patients aged 31 to 90 years with a diagnosis of T2DM (by means of the International Classification of Diseases codes [ICD-10] codes E11 or E14) was obtained from the SIDIAP database for the years 2007 to 2013. Data were extracted for patients for each particular year. As a dynamic database, new patients enter when a new diagnosis of T2DM is recorded, and patients are withdrawn when a death occurs or the subject moves to another health care region not served by the Catalonian Health Institute. Registered variables included: age; gender; time since diagnosis; the presence of comorbidities (ICD-10 codes); and the most recent value for each year of body mass index (BMI) and mean glycated hemoglobin (HbA1c). Before 1st January 2010, between 50% and 70% of laboratories in Spain expressed HbA1c values using the Japanese Diabetes Society/Japanese Society for Clinical Chemistry criteria (JDS/JCC; normal range 3.9%-5.7%),[27] and these values were not converted to the internationally defined Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program (DCCT/NGSP) calibration criteria (normal range 4%-6%). All values from 1st January 2010 onwards were expressed using DCCT/NGSP criteria.

The prescribed antidiabetic treatments for each patient and year were extracted from prescription- and pharmacy-invoicing data provided by the CatSalut (Catalan Health Service), which are yearly incorporated into the SIDIAP database. Glucose lowering agents included the use of insulin and non-insulin antidiabetic drugs (NIADs) marketed in Spain during the study period, namely metformin, sulfonylureas, glinides, glitazones, DPP-4i, GLP-1ra, and alpha-glucosidase inhibitors (AGI). The first DPP-4i marketed in Spain was sitagliptin (2007) followed by vildagliptin (2007), saxagliptin (2010) and linagliptin (2012). For GLP-1ra, daily exenatide appeared in 2007, and liraglutide in 2011. Treatment steps of were categorized as non-pharmacological treatment, a NIAD in monotherapy, NIADs in combination (2 or more without insulin), insulin alone or insulin in combination with NIADs.

This study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol.

Statistical analysis

Descriptive analyses by year are presented as mean and standard deviation for continuous variables, and percentages for categorical variables. Changes across the study period were evaluated through the absolute overall increase and the 95% confidence intervals (95%CI) using the normal approximation. We used 3 different criteria for adequate glycemic control: mean HbA1c ≤7%, as widely recommended and accepted; HbA1c ≤8%, as recommended by our institution during the study period (ICS);[28, 29] and individualized goals based on age, duration of the disease, and presence of serious complications or comorbidities, as proposed by the Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud 2014 (Red-GDPS).[30] All statistical calculations were performed using StataCorp 2009 (Stata Statistical Software: Release 11. College Station, TX: StataCorp, LP).

RESULTS

Patients' characteristics

The total number of T2DM registered patients in our database was 257,072 in 2007, increasing up to 343,969 in 2013 (a total increase of 86,897 cases) (**Table 1**). The patients' mean age did not vary substantially over the years (overall increase 1.20 years; 95%CI=1.14 to 1.26), nor did the mean BMI or the number of obese subjects (overall decrease 0.08 kg/m^2; 95%CI=-0.11 to -0.05; overall 0.043% decrease of obese subjects; 95%CI=-0.12 to -0.74), but we observed a small progressive increase in the proportion of male patients (overall increase 2.15%; 95%CI=1.90 to 2.40), and also a gradual increase in the mean duration of the disease (overall increase 2.40 years; 95%CI= 2.37 to 2.43).

Table 1. Demographic, clinical characteristics, and degree of glycemic control of patients with T2DM by year

	2007	2008	2009	2010	2011	2012	2013	Change 2007-2013
	N = 257,072	N = 271,690	N = 286,019	N = 301,144	N = 317,215	N = 331,317	N = 343,969	(95%CI)
Age, mean (SD), years	67.7 (11.7)	67.9 (11.8)	68.1 (11.8)	68.2 (11.9)	68.4 (12.0)	68.6 (12.1)	68.9 (12.1)	1.20 (1.14 to 1.26)
Males, %	52.2	52.7	53.2	53.6	53.9	54.1	54.3	2.15 (1.90 to 2.40)
T2DM duration, mean (SD), years	5.4 (5.3)	5.9 (5.3)	6.3 (5.3)	6.7 (5.4)	7.0 (5.5)	7.4 (5.6)	7.8 (5.6)	2.40 (2.37 to 2.43)
BMI, mean (SD), kg/m^2	30.1 (5.0)	30.1 (5.0)	30.1 (5.0)	30.1 (5.0)	30.1 (5.1)	30.0 (5.1)	30.0 (5.1)	-0.08 (-0.11 to -0.05)
Obesity (BMI >30 kg/m^2), %	45.6	45.5	45.3	45.7	45.3	45.1	45.1	-0.043 (-0.12 to -0.74)
HbA1c*, mean (SD), %	7.16 (1.46)	7.23 (1.48)	7.25 (1.47)	7.19 (1.40)	7.20 (1.36)	7.30 (1.35)	7.24 (1.35)	0.08 (0.07 to 0.09)
HbA1c ≤7%, %	54.9	52.8	52.2	55.1	55.6	52.6	55.2	0.29 (-0.02 to 0.60)†
HbA1c ≤8%*, %	78.9	77.8	77.9	79.3	79.6	78.4	79.6	0.64 (0.39 to 0.89)
Individualized HbA1c target, %**	75.4	73.2	72.8	74.8	75.4	73.7	75.7	1.15 (0.88 to 1.42)

*Cut-off stated by the Institut Català de la Salut (ICS); **Based on the 2014 algorithm of the Red de Grupos de Estudio de la Diabetes en Atención Primaria de la Salud (Red-GDPS); †The CI contains the null change (0) and therefore it is not statistically significant
BMI, body mass index; SD, standard deviation; T2DM, type 2 diabetes

Prescribing pattern of antidiabetic drugs

The proportion of patients not receiving antidiabetic drugs decreased by 9.7% (95%CI=-9.48 to -9.92) from 2007 to 2013, while the percentage of patients receiving pharmacological antidiabetic treatment was 71.9% in 2007, and this proportion increased annually and was 81.6% in the last year of the study, showing an overall 9.7% increase over the study period. The proportion of patients receiving each type of therapy across the time period 2007-2013 is shown in **Figure 1**. The most frequent prescription was a NIAD in monotherapy, the use of which increased 4.4% (95%CI= 4.16 to 4.64) from 2007 to 2013, followed by NIADs in combination (increasing 2.8%; 95%CI=2.58 to 3.02), and insulin alone or in combination (increasing 2.5%; 95%CI= 2.2 to 2.8). Among NIADs, the most frequently used drugs were metformin and sulfonylureas, although the prescription rate of metformin increased notably across time (19.5%; 95%CI=19.25 to 19.75), whereas it decreased gradually in the case of sulfonylureas (8.20%; 95%CI=-7.97 to -8.43) (**Figure 2**). As for the use of the rest of the available options, only the prescription of DPP4i increased substantially up to a 13.2% in 2013 (95%CI=13.09 to 13.31), while the use of glitazones, glinides, AGI, and GLP-1ra remained low. Glitazones and AGI prescriptions even decreased with time: glitazones an overall 2.9% (95%CI=-2.82 to -2.98) and AGI 2.70% (95%CI=-2.62 to -2,78). Finally glinides and GLP-1ra only increased slightly over time: 0.8% in the case of glinides (95%CI= 0.69 to 0.91) and 0.9% in the case of GLP-1ra (95%CI=0.87 to 0.93).

Evolution of the degree of glycemic control

The mean standardized HbA1c value was around 7.2%, with no clinically relevant differences across years (**Table 1**). Moreover, the proportion of patients attaining a glycemic target of HbA1c ≤7% ranged from 52.2% to 55.6% (overall change 0.29%; 95%CI=-0.02 to 0.60), and the ICS target ≤8% ranged from 77.8% and 79.6% (overall change 0.64%; 95%CI=0.39 to 21.42), with no clinically relevant changes across years (**Table 1**). Moreover, the percentage of patients attaining their individualized HbA1c target ranged increased only 1.15% (95%CI= 0.88 to 1.42) (**Table 1**). Finally, the analysis of the evolution of the attained glycemic control according to different HbA1c intervals also showed that there were no remarkable changes among years in any case (**Figure 3**). Of note, the group of patients who were less likely to achieve the corresponding glycemic target were those younger than 65 years old, without

comorbidities, and duration of T2DM ≤15 years (range 50.8%-55.1%) (**Supplementary Table 1**).

The evolution of the mean Hb1Ac levels according to each step of treatment and duration of T2DM is shown in **Figure 4** and **Supplementary Table 2**. Considering all antidiabetic treatments, there was a progressive worsening of HbA1c levels as the disease duration increased, but this worsening was in fact only observed among patients treated with insulin alone or in combination with NIADs. Conversely, glycemic values in patients not pharmacologically treated or on NIADs improved as T2DM duration increased, with no substantial differences across the study period.

DISCUSSION

This cross-sectional, descriptive study is, to the best of our knowledge, the first to assess trends in the prescribing practices of antidiabetic drugs in relation to the level of attained glycemic control between 2007 and 2013 in a primary health care setting in Spain.

A gradual increase in the prescription of antidiabetic agents has been previously reported in Spain [16, 17] and in studies conducted worldwide throughout the same or overlapping years as in our study.[6-8, 10-12, 31, 32] An increase in the use of combinations of oral antidiabetic drugs (OAD) has been consistently observed in several studies from different countries,[6, 7, 9, 11, 17, 31] but the trends in its use as monotherapy vary among reports, with some describing an overall increase over time,[11, 13, 32] and others a progressive decrease.[6, 9, 31] Moreover, while the number of prescriptions of insulin in combination with an OAD has been shown to increase with time,[6, 7, 11] the use of insulin alone has been reported to remain stable [17, 33], to decrease,[6, 11, 31] or even to increase.[32] Differences between drug schemes and studies may be attributable to health policy variations across countries, local professional expertise, physician's personal choice, study setting (e.g. hospital vs. primary care or insurance claims vs. national database), or inclusion of both type 1 and type 2 DM patients in some cases.

Both an increase in the use of metformin and a decrease in the use of sulfonylureas have been consistently reported by other groups.[6-9, 11-13, 15, 17, 31-33] This decline could be related to the recent recommendation of cautionary use in the elderly,[34] their worse safety

profile, associated weight gain, unclear role in reducing long-term complications, and/or to the availability of safer new therapeutic options.[5] Although a decrease in both glinides and AGIs use has been reported in Spain, Japan and in the UK,[11, 15, 17, 33] in our study the number of glinides' prescriptions remained stable, which could be explained by the fact that in spite of their risk of hypoglycemia,[5] they are the most used therapeutic class in patients with chronic kidney disease.[25] The decrease in AGIs might be explained by the high frequency of gastrointestinal side effects that led to the recommendation to only use them in people unable to use other oral glucose-lowering medications.[35] The decrease in the use of glitazones has been consistently documented in several studies that included data after 2007,[8, 9, 11-13, 15, 17, 31-33] when the first regulatory warnings and the results of a meta-analysis alerted clinicians to cardiovascular risk associated with rosiglitazone,[36, 37] and to a risk of bladder cancer with pioglitazone in 2011.[38] Both side effects have been recently ruled out,[37, 39] but the influence of these alarms, together with weight gain, the risk of heart failure and the increased risk of bone fractures in women observed with this class of drugs has limited its use. The marginal use of GLP-1ra in our study is similar to a recent study conducted in the UK,[15] but in contrast with a substantial increase documented in another region of Spain,[17] Ireland, and the US.[9, 13] The administrative restrictions and negative economic incentives of our institution (ICS) for the prescription of GLP-1ar may have contributed to the limited use of this therapeutic class. Finally, DPP-4i were the newly introduced NIADs that had the greatest increase in use, which is in agreement with other reports conducted worldwide.[9, 11-13, 17, 31-33] This rapid adoption, mainly as an alternative to sulfonylureas, may respond to the lower risk of hypoglycemia, its neutral effects on body weight, and also the greater convenience of an oral treatment instead of the need of injections for GLP-1ar or insulin.[40] In summary, although a plethora of hypoglycemic agents are currently available with a substantially comparable effect in terms of glycemic control, physician's choice should be personalized based on patient's characteristics such as age, risk factors, and comorbidities.

When we assessed the attained glycemic control based on the treatment step, we found that patients on NIADs in combination or on insulin with or without a NIAD were the ones with the highest HbA1c levels. This is in line with the results of several studies showing a delay in treatment intensification in patients already on combination therapies whose control of blood

glucose remained or became inadequate.[35, 41] Moreover, we found that about half of the patients had HbA1c levels ≤7% as recommended by clinical guidelines, about 80% below the 8% recommended by our institution (ICS), and about 75% below the individualized goal recommended by the Red-GDPS. Our figures are slightly worse than the ones reported by a study conducted in the Basque country in Spain for patients achieving HbA1c levels ≤7% (about 64.1% of them), but similar to their 85.5% of patients achieving an ≤8% target.[42] Finally, and confirming previous analyses, the subgroup with the highest proportion of patients attaining appropriate individualized glycemic control was the one of patients older than 75 years,[23] while subjects younger than 65 years without comorbidities or serious complications and T2DM duration ≤15 years were less likely to achieve the corresponding individualized glycemic control target. This could be explained by a higher proportion of obesity among younger patients, a longer survival among adequately controlled older patients, or by an easier to reach glycemic goal in the elderly (≤8% versus ≤7%). More importantly, our results confirm that an individualized therapeutic approach considerably increases the chances of attaining an adequate glycemic control and provides effective T2DM care.[43] However, one of the most striking findings of our study was that there were no relevant changes across years, meaning that in spite of the overall observed gradual increase in pharmacological treatments along the study there was no obvious trend towards an increase in the proportion of subjects with an adequate HbA1c target whatever the used cut-off, and the mean HbA1c values did not significantly change over time regardless the treatment step. There are few reports on how the evolution in the prescription pattern of antidiabetic drugs affects the level of attained glycemic control, but our results are in contrast with a study conducted in Japan showing that the rate of patients achieving the ≤7% goal significantly improved together with the progressive increase in the proportion of pharmacological treatments.[11] However, a very recent study conducted in Canada reported that the mean HbA1c values in older subjects even slightly increased over a 5-year period in spite of the overall increase in the use of antidiabetic treatment.[14] Our results seriously question the ICS threshold to maintain HbA1c levels ≤8% for all patients, giving general practitioners financial incentives if this goal is attained, without taking into account age, diabetes duration or the presence of comorbidities. This threshold was established to avoid

overtreatment -especially in the elderly- but can be counterproductive in younger patients. Certainly, about 25% of patients had HbA1c between 7.1% and 8%, and were therefore at potential risk of suboptimal management or undertreatment until they reach this value, especially in people under 65 years. Thus, this institutional policy potentially contributes to therapeutic inertia, defined as a delay in treatment intensification among patients with poor glycemic control. Clinical inertia has been documented in primary care settings [44, 45], and a study conducted in Catalonia in 2007 in a sample of 2,783 T2DM patients reported that therapeutic inertia was present in 33.2% of cases, and treatment intensification was implemented in patients with a mean HbA1c of 8.4%,[41] which is far above the 8% threshold established by the institution. On the other hand, most family physicians find that patients treated with NIAD combination but needing intensification with insulin or GLP-1ar, and those already on insulin needing optimization with multiple insulin doses or the addition of a GLP-1ar, are difficult to manage or they have reasonable safety concerns. In these cases, clinical inertia is a major factor that contributes to inadequate glycemic control in the long term.

Our results show a global negative effect of T2DM duration on glycemic control that did not change substantially across the study period. A progressive worsening of mean Hb1Ac values within each sequential evaluation might be expected because the proportion of patients with a disease duration >10 years increased, but this could have been counteracted by an intensified management in all treatment steps, eventually leading to steady mean HbA1c levels along the study. This is a possible explanation if we take into account that patients in lowest treatment steps (i.e. no drugs, and NIADs in monotherapy or combined) and a disease duration >10 years had lower HbA1c values than those with a disease duration lower than <2 years, as those on poor glycemic control were probably switched to the next superior treatment step. In contrast, glycemic control among patients on insulin (alone or in combination) worsened as the duration of disease increased, probably because they are at the last treatment step and only intensive management with multiple insulin doses under endocrinologist supervision may improve control.

The present study has strengths and limitations worth mentioning. The main strength is that we used a large outpatients database that, although not completely representative of other areas of Spain, is indicative of the trends of general practitioners' practices in a real-life

clinical setting. However, this was a retrospective study subject to errors in data recording or a high percentage of missing values (e.g. 35% of HbA1c values were missing in 2007 decreasing to 25% in 2013), although this would apply to all the study period equally, therefore not affecting the conclusions of the study. Moreover, we were not able to assess whether the change in prescribed treatments over time was driven by patients' needs and characteristics (e.g. prior low tolerability or effectiveness), and we cannot therefore claim a causal effect. Finally, we could not assess whether doses were appropriately chosen, and we did not consider data on prescriptions within the same therapeutic class.

CONCLUSIONS

Although the intensity of pharmacological antidiabetic treatment of T2DM increased substantially during 2007-2013 in Catalonia, there was no evidence that this was accompanied by a positive change in the degree of glycemic control. This reveals shortcomings in the primary health care system that could be tackled through more intensive educational programs for physicians oriented to the individualization of glycemic goals and prioritizing more intensive treatments in the younger patients.

ACKNOWLEDGEMENTS

We acknowledge Mònica Gratacòs and Amanda Prowse for providing support in the manuscript preparation and editing. CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) is an initiative from Instituto de Salud Carlos III.

COMPETING INTERESTS. None declared

FUNDING

This study was funded by Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), and an unrestricted grant provided by Astra Zeneca. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

AUTHOR'S CONTRIBUTIONS

MM-C and JF-N wrote the manuscript and contributed equally to this study; JR managed the data base, performed the statistical analyses and contributed to the discussion; and JF-N, MM-C, and DM designed and conducted the study, reviewed/edited the manuscript and contributed to the discussion. MM-C had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis.

DATA SHARING STATEMENT

No additional unpublished data are available.

FIGURE LEGENDS

Figure 1. Percentage of T2DM patients in each step of antidiabetic treatment

Figure 2. Percentage of patients having non-insulin antidiabetic drug prescriptions (alone or in combination)

Figure 3. Percentage of patients achieving glycemic control according to HbA1c intervals

Figure 4. Evolution of mean HbA1c according to the different steps of antidiabetic treatment and T2DM duration

REFERENCES

1. *International Diabetes Federation. IDF Diabetes Atlas, 6th edn.* Brussels, Belgium: International Diabetes Federation, 2013.

2. Turner RC, Cull CA, Frighi V*, et al.* Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281:2005-12.

3. Bailey CJ. The Current Drug Treatment Landscape for Diabetes and Perspectives for the Future. *Clin Pharmacol Ther* 2015;98:170-84.

4. Holman RR, Paul SK, Bethel MA*, et al.* 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.

5. Inzucchi SE, Bergenstal RM, Buse JB*, et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140-9.

6. Baviera M, Monesi L, Marzona I*, et al.* Trends in drug prescriptions to diabetic patients from 2000 to 2008 in Italy's Lombardy Region: a large population-based study. *Diabetes Res Clin Pract* 2011;93:123-30.

7. Chang CH, Jiang YD, Chung CH*, et al.* National trends in anti-diabetic treatment in Taiwan, 2000-2009. *J Formos Med Assoc* 2012;111:617-24.

8. Leal I, Romio SA, Schuemie M*, et al.* Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. *Br J Clin Pharmacol* 2013;75:861-8.

9. Turner LW, Nartey D, Stafford RS, *et al.* Ambulatory treatment of type 2 diabetes in the U.S., 1997-2012. *Diabetes Care* 2014;37:985-92.

10. Strom H, Selmer R, Birkeland KI, *et al.* No increase in new users of blood glucose-lowering drugs in Norway 2006-2011: a nationwide prescription database study. *BMC Public Health* 2014;14:520.

11. Oishi M, Yamazaki K, Okuguchi F, *et al.* Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). *J Diabetes Investig* 2014;5:581-7.

12. Hampp C, Borders-Hemphill V, Moeny DG, *et al.* Use of antidiabetic drugs in the U.S., 2003-2012. *Diabetes Care* 2014;37:1367-74.

13. Zaharan NL, Williams D, Bennett K. Prescribing of antidiabetic therapies in Ireland: 10-year trends 2003-2012. *Ir J Med Sci* 2014;183:311-8.

14. Clemens KK, Liu K, Shariff S, *et al.* Secular trends in antihyperglycaemic medication prescriptions in older adults with diabetes and chronic kidney disease: 2004-2013. *Diabetes Obes Metab* 2016;18:607-14.

15. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6:e010210.

16. Pornet C, Bourdel-Marchasson I, Lecomte P, *et al.* Trends in the quality of care for elderly people with type 2 diabetes: the need for improvements in safety and quality (the 2001 and 2007 ENTRED Surveys). *Diabetes Metab* 2011;37:152-61.

17. Mancera-Romero J, Hormigo-Pozo A, Fernandez-Arquero J*, et al.* [Use of glucose-lowering drugs in a primary care setting in Malaga during the years 2008-2012]. *Semergen* 2014;40:4-11.

18. Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. *J Public Health Med* 1999;21:299-304.

19. Vinagre I, Mata-Cases M, Hermosilla E*, et al.* Control of glycemia and cardiovascular risk factors in patients with type 2 diabetes in primary care in Catalonia (Spain). *Diabetes Care* 2012;35:774-9.

20. Mata-Cases M, Mauricio D, Vinagre I*, et al.* Treatment of Hyperglycaemia in Type 2 Diabetic Patients in a Primary Care Population Database in a Mediterranean Area (Catalonia, Spain). *J Diabetes Metab* 2014;5:338.

21. Franch-Nadal J, Mata-Cases M, Vinagre I*, et al.* Differences in the Cardiometabolic Control in Type 2 Diabetes according to Gender and the Presence of Cardiovascular Disease: Results from the eControl Study. *Int J Endocrinol* 2014;2014:131709.

22. Rodriguez-Poncelas A, Miravet-Jimenez S, Casellas A*, et al.* Prevalence of diabetic retinopathy in individuals with type 2 diabetes who had recorded diabetic retinopathy from retinal photographs in Catalonia (Spain). *Br J Ophthalmol* 2015;99:1628-33.

23. Barrot-de la Puente J, Mata-Cases M, Franch-Nadal J*, et al.* Older type 2 diabetic patients are more likely to achieve glycaemic and cardiovascular risk factors targets than younger patients: analysis of a primary care database. *Int J Clin Pract* 2015;69:1486-95.

24. Mata-Cases M, Casajuana M, Franch-Nadal J*, et al.* Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. *Eur J Health Econ* 2015

25. Ruiz-Tamayo I, Franch-Nadal J, Mata-Cases M, *et al.* Noninsulin Antidiabetic Drugs for Patients with Type 2 Diabetes Mellitus: Are We Respecting Their Contraindications? *J Diabetes Res* 2016;2016:7502489.

26. Mata-Cases M, Mauricio D, Franch-Nadal J. Clinical characteristics of type 2 diabetic patients on basal insulin therapy with adequate fasting glucose control that do not achieve glycated hemoglobin targets. *J Diabetes* 2016

27. Goberna R, Aguilar-Diosdado M, Santos-Rey K, *et al.* Consensus document for the harmonization of HbA1c results in Spain. *Av Diabetol* 2009;25:35-37.

28. Mata-Cases M, Cos-Claramunt FX, Morros R, *et al.* Abordatge de la diabetis mellitus tipus 2 [online]. 2010; Guies de pràctica clínica, num 15. http://www.gencat.cat/ics/professionals/guies/diabetis/diabetis.htm (accessed 27 June 2014).

29. Avilés F, L. MB, Coma Redon E, *et al.* Sistema de Información de los Servicios de Atención Primaria (SISAP). La experiencia 2006 - 2009 del Institut Català de la Salut (ICS). *RISAI* 2010;2:1-17.

30. Alemán JJ, Artola S, Franch J, *et al.* Recomendaciones para el tratamiento de la diabetes mellitus tipo 2: control glucémico. *Diabetes Práctica* 2014;5:1-48.

31. Clemens KK, Shariff S, Liu K, *et al.* Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002-2013. *PLoS ONE* 2015;10:e0137596.

32. Rafaniello C, Arcoraci V, Ferrajolo C, *et al.* Trends in the prescription of antidiabetic medications from 2009 to 2012 in a general practice of Southern Italy: a population-based study. *Diabetes Res Clin Pract* 2015;108:157-63.

33. Kohro T, Yamazaki T, Sato H, *et al.* Trends in antidiabetic prescription patterns in Japan from 2005 to 2011. *Int Heart J* 2013;54:93-7.

34. Sinclair AJ, Paolisso G, Castro M, *et al.* European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011;37 Suppl 3:S27-38.

35. NICE (National Institute for Health and Clinical Excellence). Clinical guideline CG87. Type 2 diabetes: the management of type 2 diabetes. Last updated December 2014. Available from: http://guidance.nice.org.uk/CG87/NiceGuidance/pdf/English. 2014

36. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71.

37. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. *Diabetes Care* 2009;32 Suppl 2:S253-9.

38. Lewis JD, Ferrara A, Peng T, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916-22.

39. Ryder RE. Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. *Diabet Med* 2015;32:305-13.

40. Karagiannis T, Paschos P, Paletas K, *et al.* Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. *BMJ* 2012;344:e1369.

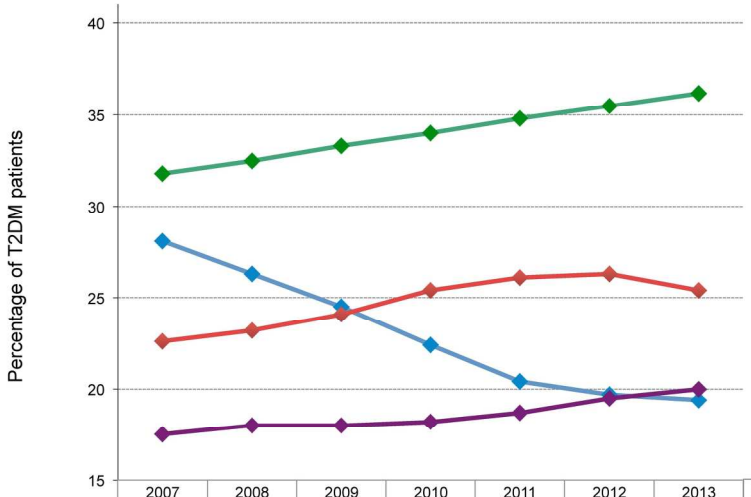
41. Mata-Cases M, Benito-Badorrey B, Roura-Olmeda P, *et al.* Clinical inertia in the treatment of hyperglycemia in type 2 diabetes patients in primary care. *Curr Med Res Opin* 2013;29:1495-502.

42. Alonso-Morán E, Orueta JF, Esteban JIF*, et al.* Prevalence and quality of care indicators of type 2 diabetes in the population of the Basque Country (Spain). *Av Diabetol* 2015;31:72-79.

43. Subramanian S, Hirsch IB. Personalized Diabetes Management: Moving from Algorithmic to Individualized Therapy. *Diabetes Spectr* 2014;27:87-91.

44. Khunti K, Wolden ML, Thorsted BL*, et al.* Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care* 2013;36:3411-7.

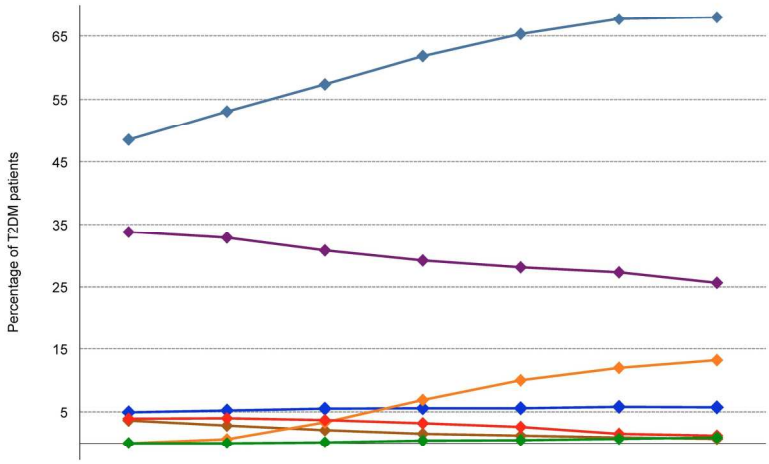
45. Khunti K, Nikolajsen A, Thorsted BL*, et al.* Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab* 2016;18:401-9.



	2007	2008	2009	2010	2011	2012	2013	Change 2007-2013 (95% CI)
NIAD monotherapy	31.8	32.5	33.3	34.0	34.8	35.5	36.2	4.40 (4.16 to 4.64)
No drugs	28.1	26.3	24.5	22.4	20.4	19.7	19.4	-9.70 (-9.48 to -9-92)
NIAD in combination	22.6	23.2	24.1	25.4	26.1	26.3	25.4	2.80 (2.58 to 3.02)
Insulin ± NIAD	17.5	18.0	18.0	18.2	18.7	19.5	20.0	2.5 (2.2 to 2.8)

Figure 1. Percentage of T2DM patients in each step of antidiabetic treatment

190x142mm (300 x 300 DPI)



	2007	2008	2009	2010	2011	2012	2013	Change 2007-2013 (95% CI)
Metformin	48.5	53.1	57.4	61.8	65.3	67.7	68.0	19.50 (19.25 to 19.75)
Sulfonylureas	33.8	32.8	30.8	29.2	28.1	27.3	25.6	-8.20 (-7.97 to -8.43)
Glinides	4.9	5.2	5.5	5.6	5.6	5.8	5.7	0.00 (0.09 to 0.91)
AGI	3.6	2.8	2.1	1.5	1.2	0.9	0.7	-2.90 (-2.82 to -2.98)
DPP4i	0.0	0.6	3.3	6.9	10.0	12.0	13.2	13.20 (13.09 to 13.31)
Glitazones	3.9	4.0	3.7	3.2	2.6	1.5	1.2	-2.70 (-2.62 to -2.78)
GLP-1ra	0.0	0.0	0.1	0.4	0.5	0.7	0.9	0.90 (0.8 to 0.93)

Figure 2. Percentage of patients having non-insulin antidiabetic drug prescriptions (alone or in combination)

190x142mm (300 x 300 DPI)

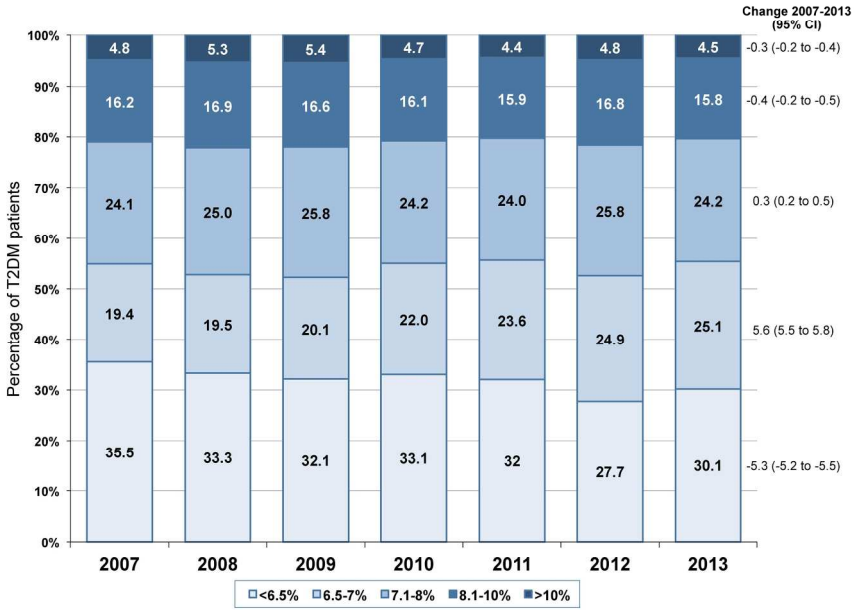


Figure 3. Percentage of patients achieving glycemic control according to HbA1c intervals

190x142mm (300 x 300 DPI)

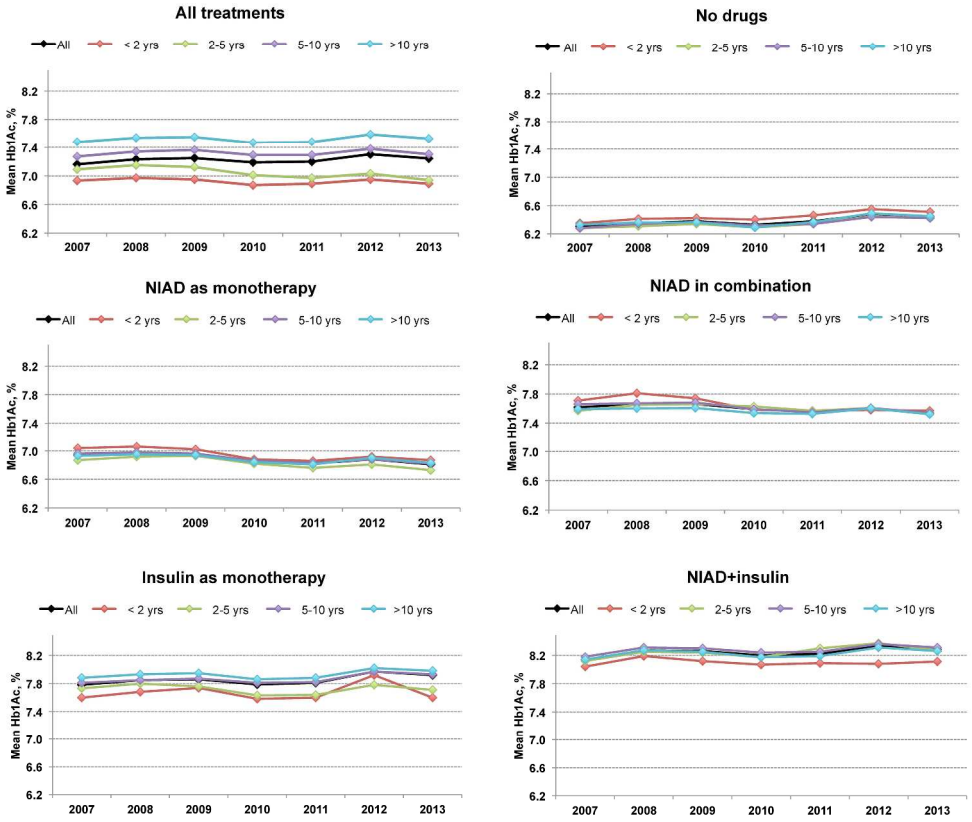


Figure 4. Evolution of mean HbA1c according to the different steps of antidiabetic treatment and T2DM duration

355x420mm (300 x 300 DPI)

Supplementary Table 1. Percentage of patients reaching individualized glycemic targets based on age, duration of T2DM, and presence of comorbidities (Red-GDPS criteria)

	HbA1c glycemic target	2007	2008	2009	2010	2011	2012	2013	Change 2007-2013 (95% CI)
Patients with HbA1c values, N		166,388	177,291	193,467	209,022	226,452	241,664	255,553	
Age >75 years	≤8.5%	88.7	88.1	88.2	89.2	89.6	88.2	89.0	0.30 (-0.06 to 0.66)*
Age 66-75 years									
*With comorbidities or serious complications***	≤8.5%	84.7	84.3	83.5	84.7	84.5	83.3	84.1	-0.60 (-1.39 to 0.19)*
Without comorbidities or serious complications; T2DM duration >15 years	≤8.0%	73.4	70.9	71.1	73.0	73.2	71.3	72.6	-0.80 (-3.32 to 1.72)*
Without comorbidities or serious complications; T2DM duration ≤15 years	≤7.0%	58.8	56.4	56.2	59.6	60.6	57.9	61.5	2.70 (2.01 to 3.39)
Age ≤65 years									
Duration >15 years, or <15 years with comorbidities or serious complications	≤8.0%	69.7	67.9	67.4	68.7	68.3	67.0	68.1	-1.69 (-0.70 to -2.69)
Duration <15 years without comorbidities or serious complications	≤7.0%	53.4	51.6	50.8	53.9	55.1	52.7	54.9	1.50 (0.97 to 2.03)

*The CI contains the null change (0) and therefore it is not statistically significant
** The following conditions were considered as comorbidities or serious complications:

- Ischemic heart disease (ICD codes I20-25
- Cerebral vascular accident (ICD-10 codes I63, I64, I67, I69, G45, and G46)
- Peripheral vascular disease (ICD-10 codes I70.2, I73, I73.8, and I73.9)
- Hear failure (ICD-10 codes I50, I11.0, I13.0, and I13.2)
- Diabetic retinopathy (ICD-10 codes E11.3, E14.3, and H36.0)
- Cardiovascular procedures such as coronary revascularization, or revascularization or non-traumatic amputation of lower extremity
- Severe renal failure (patients with estimated glomerular filtration rate <30 ml/min)

Supplementary Table 2. Change in the evolution of mean HbA1c according to the different steps of antidiabetic treatment and T2DM duration (95% CI)

	2007 Mean (SD)	2013 Mean (SD)	Change 2007-2013 (95% CI)
All treatments			
All years	7.16 (1.46)	7.24 (1.35)	0.08 (0.07 to 0.09)
< 2 yrs	6.93 (1.52)	6.89 (1.28)	-0.04 (-0.06 to -0.02)
2-5 yrs	7.09 (1.42)	6.94 (1.23)	-0.15 (-0.17 to -0.14)
5-10 yrs	7.27 (1.45)	7.30 (1.35)	0.03 (0.01 to 0.05)
>10 yrs	7.48 (1.47)	7.30 (1.38)	0.05 (0.03 to 0.07)
No drugs			
All years	6.31 (0.99)	6.45 (0.81)	0.14 (0.13 to 0.15)
< 2 yrs	6.35 (1.03)	6.51 (0.76)	0.16 (0.14 to 0.18)
2-5 yrs	6.28 (0.95)	6.42 (0.77)	0.140 (0.12 to 0.16)
5-10 yrs	6.28 (0.96)	6.42 (0.86)	0.14 (0.11 to 0.17)
>10 yrs	6.33 (1.06)	6.45 (0.91)	0.12 (0.07 to 0.17)
NIAD Monotherapy			
All years	6.94 (1.28)	6.81 (0.99)	-0.13 (-0.12 to -0.14)
< 2 yrs	7.04 (1.49)	6.87 (1.17)	-0.17 (-0.16 to -0.2)
2-5 yrs	6.87 (1.20=	6.73 (0.94)	-0.14 (-0.12 to -0.16)
5-10 yrs	6.96 (1.19)	6.82 (0.95)	-0.14 (-0.12 to -0.16)
>10 yrs	6.93 (1.19)	6.83 (0.93)	-0.10 (-0.07 to -0.13)
NIAD in combination			
All years	7.62 (1.47)	7.54 (1.33)	-0.08 (-0.07 to -0.2)
< 2 yrs	7.71 (1.76)	7.57 (1.73)	-0.14 (-0.08 to -0.2)
2-5 yrs	7.57 (1.44)	7.54 (1.43)	-0.03 (-0.061 to -0.001)

	2007 Mean (SD)	2013 Mean (SD)	Change 2007-2013 (95% CI)
5-10 yrs	7.66 (1.44)	7.54 (1.31)	-0.12 (-0.10 to -0.15)
>10 yrs	7.59 (1.37)	7.52 (1.24)	-0.07 (-0.04 to -0.1)
NIAD + Insulin			
All years	8.14 (1.59)	8.28 (1.56)	0.140 (0.11 to 0.17)
< 2 yrs	8.04 (1.91)	8.11 (2.24)	0.07 (-0.08 to 0.22)*
2-5 yrs	8.12 (1.61)	8.27 (1.82)	0.15 (0.07 to 0.23)
5-10 yrs	8.18 (1.56)	8.31 (1.55)	0.13 (0.08 to 0.18)
>10 yrs	8.14 (1.49)	8.26 (1.46)	0.12 (0.08 to 0.17)
Insulin monotherapy			
All	7.78 (1.60)	7.92 (1.56)	0.14 (0.10 to 0.18)
< 2 yrs	7.60 (1.87)	7.60 (2.04)	0.000 (-0.19 to 0.19)*
2-5 yrs	7.73 (1.58)	7.71 (1.75)	-0.02 (-0.14 to 0.1)*
5-10 yrs	7.81 (1.58)	7.93 (1.56)	0.12 (0.05 to 0.19)
>10 yrs	7.88 (1.52)	7.98 (1.46)	0.10 (0.03 to 0.17)

*The CI contains the null change (0) and therefore it is not statistically significant

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1 & 2 1 & 2 NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			4
Objectives	3	State specific objectives, including any prespecified hypotheses			4
Methods					
Study Design	4	Present key elements of study design early in the paper			4 & 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			5
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the		RECORD 6.1: The methods of study population selection (such as codes or	5

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	 NA NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			5
Bias	9	Describe any efforts to address potential sources of bias			5
Study size	10	Explain how the study size was			NA

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			5
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	5
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	NA

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	6
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			6 & 7
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			7
Main results	16	(a) Give unadjusted estimates			7-9

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			7-9
Discussion					
Key results	18	Summarise key results with reference to study objectives			9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results			13

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			14
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Provided during the submission process

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.