Therapeutic inertia in patients treated with two or more antidiabetics in primary care: Factors predicting intensification of treatment

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Aims: To determine the patterns and predictors of treatment intensification in patients with type 2 diabetes on ≥2 non-insulin antidiabetic drugs (NIADs) and inadequate glycaemic control in primary care in Catalonia, Spain.

Material and Methods: This was a retrospective analysis using electronic medical records from patients with HbA1c ≥7% and a first prescription for a new NIAD or insulin recorded from January 2010 to December 2014. Therapeutic inertia was defined as no intensification if HbA1c was ≥8% at baseline or during follow-up. Time to first intensification was evaluated by time-to-event analysis, and factors predicting intensification through a competing-risk regression model.

Results: Among 23,678 patients with HbA1c ≥7%, 26.2% were censored without treatment intensification after a median follow up of 4.2 years. Among the 12,730 patients in the subgroup with HbA1c ≥8% at baseline or during follow-up, therapeutic inertia was present in 18.1% of cases. In the overall cohort, mean HbA1c at initiation of insulin and NIAD were 9.4%±1.5% and 8.7%±1.3%, respectively. Median time to first intensification was 17.1 months in patients with HbA1c 8.0% to 9.9%, and 10.1 months in those with HbA1c >10%. Variables strongly associated with intensification were HbA1c values 8.0% to 9.9% (sub-hazard ratio [SHR], 1.7; 95% CI, 1.65-1.78) and >10% (SHR, 2.5; 95% CI, 2.37-2.68); diabetes duration ≥20 years (SHR, 1.25; 95% CI, 1.11-1.41) and, to a lesser extent, female gender, presence of comorbidities, chronic kidney disease and microvascular complications.

Conclusions: Intensification was not undertaken in 1 in 5 patients. Both HbA1c thresholds and time until therapy intensification exceeded current recommendations.

KEYWORDS
antidiabetic drug, intensification, type 2 diabetes, population study, primary care

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1 | INTRODUCTION

Therapeutic inertia is the failure to initiate or intensify therapy in a well-timed and proper manner in patients who have chronic conditions such as hypertension, dyslipidaemia, or hyperglycaemia or, as most recently stated, failure to close the gap between the most appropriate practice and the patient’s usual level of care. In the particular case of type 2 diabetes (T2DM), clinical guidelines for management recommend early and continued adequate glucose control in order to avoid prolonged exposure to hyperglycaemia, which is associated with micro- and macrovascular complications. Nevertheless, over half of patients fail to achieve therapeutic target glycaemic control even with therapy at maximal doses, therefore requiring addition of oral or injectable therapies. The glycated hemoglobin (HbA1c) value at which treatment intensification is recommended varies between 6.5% and 8.0% in international and national guidelines, and it is 8% for incentivization purposes in our institution (Catalan Institute of Health; ICS). However, some advocate for an individualized approach, with stringent HbA1c goals (6.0%-6.5%) in selected healthy subjects and a relaxed goal (7.5%-8%) in those with health complications and those without sufficient empowerment, resources or social support. Regarding the appropriate interval to medication adjustment, some recommend intensifying therapy whenever HbA1c exceeds the individualized target, and others when the patient is not maintained at his/her target for an interval of 3 months. Literature reviews investigating patterns of antidiabetic treatment related to initiation and intensification of both non-insulin antidiabetic drugs (NIADs) and insulin therapy in real-world settings have documented therapeutic inertia as a factor contributing to suboptimal glycaemic management globally. Of note, all studies reported that HbA1c levels far exceed acceptable thresholds at the time of treatment intensification, regardless of the sequential therapeutic step considered. In Spain, studies conducted in primary healthcare services reported that the lack of intensification in patients with poor glycaemic control (HbA1c ≥ 7%) varies between 32.2% and 52.5%. The longest delays in treatment intensification are known to occur among patients receiving 2 or more NIADs. On the one hand, for patients with glycaemic levels between 7% and 8%, the term “therapeutic inertia” may not always apply if it is more appropriate to not to intensify, based on established individualized targets and to avoid overtreatment. On the other hand, patients with glycaemic levels ≥8% are those most likely to benefit from timely intensification in order to avoid sustained hyperglycaemia.

Most studies assessing real-life patterns of treatment intensification in diabetes have been conducted in the USA and the UK, with a marked absence of studies covering regions in the Mediterranean area. The aim of the present study was to evaluate real-life patterns of treatment intensification beyond 2 concurrent NIADs in patients with T2DM in primary care in Catalonia (Spain). Our aims were to determine the frequency of intensification at the end of the follow-up period, the duration of time to therapy intensification, and the factors associated with the likelihood of medication escalation.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design and data source

This was a retrospective, cohort study using the SIDIAP (System for the Development of Research in Primary Care) electronic database which contains anonymized, longitudinal data on clinical history and active prescriptions from primary care records, obtained through specific software (the Electronic Clinical station in Primary Care; eCAP). The database includes information from all of the 274 primary care centres pertaining to the Catalan Health Institute (ICS), which cares for 5835 million patients (80% of the total population of Catalonia). Data were obtained from the SIDIAP database covering the period between January 2010 and December 2014.

Poor glycaemic control was defined as an HbA1c value ≥7% (53 mmol/mol) as recommended by international and local guidelines and also ≥8% (64 mmol/mol) according to the pay-per-performance indicator recommended by our institution, the Catalan Institute of Health (ICS).

2.2 | Inclusion and exclusion criteria

Patients aged 31 to 90 years with a diagnosis of T2DM (International Classification of Diseases [ICD-10] codes E11.0-E11.9, E14 or E14.0-E14.9) were included in the study if they had, on January 1, 2010, active prescriptions in the eCAP database, 2 or more concomitant active NIADs, and had one recorded HbA1c measurement ≥7% during 2010 (index date for intensification follow-up) (Figure S1. Appendix S1). For analyses of therapeutic inertia, subjects with HbA1c levels ≥8% at baseline or during follow-up were chosen. Subjects already receiving insulin, with a diagnosis code for type 1 diabetes, gestational diabetes or secondary diabetes, without basal HbA1c or with less than 1 year of follow-up were excluded.

2.3 | Study variables

Clinical and demographic variables extracted at baseline included: age; gender; duration of diabetes; body mass index (BMI); estimated glomerular filtration rate (eGFR) using the Modified Diet in Renal Disease (MDRD) formula; albumin to creatinine ratio (UACR); presence of cardiovascular disease, including coronary artery disease (ICD-10 codes I20-I24), stroke (ICD-10 codes I63, I64, G45 or G46), and peripheral artery disease (ICD-10 code I73.9); presence of microvascular complications (ie, diabetic retinopathy, nephropathy or neuropathy); liver dysfunction (except non-alcoholic steatosis), defined as transaminases more than 10 times the upper limit of normal; chronic pulmonary obstructive disease; and hypertension. Additionally, we calculated the baseline Charlson Comorbidity Index (CCI) score in its abbreviated version, which uses 8 categories of comorbidity to calculate a score that reflects a cumulative increased likelihood of 1-year mortality.

Prescribed antidiabetic treatments were also extracted from the SIDIAP database. NIADs marketed in Spain during the study period were: metformin; sulfonylureas, glinides, glitazones, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4
inhibitors (DPP-4i), and alpha-glucosidase inhibitors (AGI). Sodium glucose cotransporter-2 inhibitors (SGLT-2i) were censored (or not included) in the analysis as the first drug of this group, dapagliflozin, was not available until the beginning of 2014, was prescribed to very few patients and, consequently, during a shorter period of time in comparison to other medications. Fixed-dose combinations were considered as 2 different NIADs.

The following HbA1c values during the study period were extracted and analysed: (1) the first value during 2010 (baseline HbA1c or index date for intensification follow-up); and (2) HbA1c prior to intensification, defined as the available value immediately (up to 1 year) preceding treatment intensification.

Treatment intensification was defined as the first recorded prescription of any antidiabetic drug (addition of either insulin or an NIAD of a different therapeutic class) to the index regimen during the 5-year observation period. Data on dose changes were not available and thus not considered as a form of treatment intensification.

No intensification was defined as the absence of a new drug prescription from another therapeutic class during follow-up in the entire cohort. Additionally, therapeutic inertia was considered when this occurred in patients with a glycaemic value ≥8% at baseline or during follow-up.

2.4 | Statistical methods

Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range (IQR) where appropriate, and categorical variables as absolute numbers and percentages. Descriptive analyses were performed on the entire dataset overall and were also stratified according to the presence of treatment intensification and by age subgroups (<75 years and ≥75 years), diabetes duration (<5 years, 5-10 years, 11-20 years and >20 years), and presence of obesity (BMI ≥ 30 or <30 kg/m²). Three different HbA1c levels of glycaemic control were used: 7% to 7.9% (53-63 mmol/mol); 8% to 9.9% (64-85 mmol/mol); and ≥10% (86 mmol/mol). Pharmacological treatments were grouped as NIADs and insulin. GLP-1RA was not grouped together with insulin as "injectable therapies" because local guidelines recommend them only when intensification is not possible with insulin, and because its use in our health region is very low (0.9% of patients).14,24

Time to first treatment intensification with any new antidiabetic treatment, any new NIAD and insulin was evaluated by time-to-event analysis with a competing-risks regression using the method of Fine and Gray,25 and considering death as the competing event precluding the likelihood of intensification during follow-up. The competing-risk regression model was also used to test for factors associated with the probability of having intensified at end of follow-up. The variables assessed in the model were those statistically significantly associated (P < .05) in the univariate analysis and those considered clinically relevant. Potential predictors included the following baseline variables: gender, age, diabetes duration, BMI, Charlson comorbidity score, treatment at baseline, kidney disease, presence of micro- or macrocomplications, heart failure, and smoking status.

Parameter estimates were expressed as subhazard ratios (SHR) and 95% confidence intervals (95% CI). Statistical calculations were performed using StataCorp 2009 (Stata Statistical Software: Release 11, College Station, Texas: StataCorp LP).

3 | RESULTS

Among the 301 144 patients with T2DM registered in the database on January 1, 2010, a total of 23 678 patients treated with ≥2 concurrent NIADs and with HbA1c values ≥7% were included in the study (Figure S1, Appendix S1). Median follow-up was 4.2 years (IQR, 0.03-4.98). At baseline, mean age of the overall population was 66.7 ± 10.5 years and diabetes duration was 8.0 (±5.2) years (Table 1). The mean HbA1c value was 8.4% (±1.2), and 53.8% (n = 12 730) of patients had an HbA1c value ≥8%. The most commonly prescribed treatment regimen was the combination of 2 NIADs (86.0%), which in most cases was metformin and sulfonylurea (72.4%), while 13.5% and 0.5% of patients were receiving 3 or 4 NIADs, respectively (Table 1).

3.1 | Treatment intensification in the overall cohort

Among the overall cohort (patients with HbA1c ≥ 7% at baseline), 73.8% received treatment intensification, while 26.2% (n = 6213) were censored without any drug escalation (Table 1 and Figure S3, Appendix S1). The mean HbA1c value at baseline among intensified patients was 8.6%, and 8.0% among those not intensified (Table 1 and Figure S4, Appendix S1). Most of the intensified patients (59.8%) had an HbA1c value ≥8%, while the majority of not-intensified patients (63%) had an HbA1c value <8% (Table 1). By glycaemic subgroup, the highest proportion of not-intensified patients had a baseline HbA1c between 7.0% and 7.9% (35%), and this percentage decreased to 19.8% and 11.5% in the 2 subgroups with higher levels (8.0%-9.9% and ≥10%, respectively) (Figure S3, Appendix S1) (P < .001).

3.2 | Therapeutic inertia in patients with HbA1c > 8% at baseline or during follow-up

In the subgroup of patients with HbA1c values ≥8% at baseline or during follow-up (n = 12 730), treatment was not intensified (therapeutic inertia) in 18.1% of cases (n = 2299) (Figure S5, Appendix S1), and they had a mean HbA1c value of 8.7% (±0.97), while those who
**TABLE 1** Demographic and clinical characteristics of and recorded treatment for T2DM patients treated with ≥2 NIADs and with HbA1c ≥ 7% (53 mmol/mol) at baseline included in the study

| Characteristic                        | Overall population (N = 23 678) | Patients with treatment intensified (N = 17 465) | Patients not intensified (censored) N = (6213) |
|--------------------------------------|---------------------------------|-------------------------------------------------|------------------------------------------------|
| **Age, mean (SD), years**            | 66.7 (10.5)                     | 65.8 (10.3)                                     | 68.7 (10.5)                                     |
| <75 years, n (%)                     | 18 416 (77.8)                   | 14 043 (80.4)                                   | 4373 (70.4)                                     |
| ≥75 years, n (%)                     | 5262 (22.2)                     | 3422 (19.6)                                     | 1810 (27.5)                                     |
| Gender, males, n (%)                 | 12 675 (53.5)                   | 9319 (53.4)                                     | 3356 (54.0)                                     |
| Diabetes duration, mean (SD), years  | 8.0 (5.2)                       | 8.0 (5.2)                                       | 8.1 (5.1)                                       |
| <5 years, n (%)                      | 6164 (26.0)                     | 4572 (26.2)                                     | 1592 (25.6)                                     |
| 5 to 10 years, n (%)                 | 12 514 (52.9)                   | 9258 (53.0)                                     | 3256 (52.4)                                     |
| 11 to 20 years, n (%)                | 4448 (18.8)                     | 3219 (18.4)                                     | 1229 (19.8)                                     |
| >20 years, n (%)                     | 542 (2.2)                       | 407 (23.3)                                      | 135 (2.2)                                       |
| HbA1c, mean, % (SD) [mmol/mol]       | 8.4 (1.2) [68]                  | 8.6 (1.3) [70]                                  | 8.0 (1.0) [64]                                  |
| HbA1c by category, % (mmol/mol), n (%)|                                 |                                                |                                                |
| 7.0% to 7.9% (53-63)                 | 10 948 (46.2)                   | 7034 (40.3)                                     | 3914 (63.0)                                     |
| 8.0% to 9.9% (64-85)                 | 10 016 (42.3)                   | 8029 (46.0)                                     | 1987 (32.0)                                     |
| ≥10 (86)                             | 2714 (11.5)                     | 2402 (13.8)                                     | 312 (5.0)                                       |
| HbA1c ≥8% (64 mmol/mol), n (%)       | 12 730 (53.8)                   | 10 431 (59.7)                                   | 2299 (37.0)                                     |
| BMI, mean (SD), kg/m²                | 30.2 (5.0)                      | 30.4 (5.1)                                      | 29.9 (4.7)                                      |
| Obesity (BMI ≥30 kg/m²), n (%)       | 9599 (46.5)                     | 7233 (47.6)                                     | 2366 (43.5)                                     |
| Charlson index score, median (IQR)   | 1 (1–2)                         | 1 (1–2)                                         | 1 (1–2)                                         |
| Low comorbidity (score = 1), n (%)   | 15 207 (64.2)                   | 11 227 (64.3)                                   | 3980 (64.1)                                     |
| Average comorbidity (score = 2), n (%)| 5286 (22.3)                     | 3688 (22.1)                                     | 1418 (22.8)                                     |
| High comorbidity (score = 3), n (%)  | 2145 (9.1)                      | 1601 (9.2)                                      | 544 (8.8)                                       |
| Very high comorbidity (score ≥ 4), n (%)| 1040 (4.4)                     | 769 (4.4)                                       | 271 (4.4)                                       |
| Microvascular complications⁴, n (%)  | 6382 (27.0)                     | 4862 (27.8)                                     | 1520 (24.5)                                     |
| Macrovascular complications⁵, n (%)  | 3760 (15.9)                     | 2737 (15.7)                                     | 1023 (16.5)                                     |
| Heart failure, n (%)                 | 590 (2.5)                       | 422 (2.4)                                       | 168 (2.7)                                       |
| Chronic kidney disease, n %          |                                 |                                                |                                                |
| Moderate (eGFR 30-60 mL/min)         | 4000 (16.9)                     | 2874 (16.5)                                     | 1126 (18.1)                                     |
| Severe (eGFR <30 mL/min)             | 107 (0.5)                       | 96 (0.6)                                        | 11 (0.2)                                        |
| Combined antidiabetic treatment      |                                  |                                                |                                                |
| 2 NIADs, n (%)                       | 20 371 (86.0)                   | 14 873 (85.2)                                   | 5498 (88.5)                                     |
| Met + SU⁶                            | 17 136 (72.4)                   | 11 995 (68.7)                                   | 5141 (82.8)                                     |
| Met + DPP4i                          | 1517 (6.4)                      | 1310 (7.5)                                      | 207 (3.3)                                       |
| Other 2-drug combinations            | 1718 (7.3)                      | 1568 (8.9)                                      | 150 (2.4)                                       |
| 3 NIADs, n (%)                       | 3187 (13.5)                     | 2493 (14.3)                                     | 694 (11.2)                                      |
| Met + SU + DPP4i                     | 1516 (6.4)                      | 1080 (6.2)                                      | 436 (7.0)                                       |
| Met + SU + glitazone                 | 1167 (4.9)                      | 994 (5.7)                                       | 173 (2.8)                                       |
| Other 3-drug combinations            | 504 (2.3)                       | 419 (2.4)                                       | 85 (1.4)                                        |
| 4 NIADs, n (%)                       | 119 (0.5)                       | 98 (0.6)                                        | 21 (0.3)                                        |
| Met + SU + glitazone + DPP4i         | 77 (0.3)                        | 64 (0.4)                                        | 13 (0.2)                                        |
| Other 4-drug combinations            | 42 (0.2)                        | 34 (0.2)                                        | 8 (0.1)                                         |

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate using the Modified Diet in Renal Disease (MDRD) formula; DPP-4i, dipeptidyl peptidase-4 (DPP-4) inhibitors; HbA1c, glycated hemoglobin; IQR, interquartile range; Met, metformin; NIAD, non-insulin antidiabetic; SD, standard deviation; SU, sulfonylureas.

⁴ Includes coronary heart disease, stroke and peripheral artery disease.

⁵ Available for 23 666 patients.

⁶ Includes retinopathy, nephropathy (urine albumin/creatinine ratio > 30 mg/g; available for 20 528 patients) and neuropathy.

⁷ Includes sulfonylureas and glinides.
were intensified had a mean value of 9.0% (±1.16) (Figure S4, Appendix S1).

### 3.3 | HbA1c levels prior to intensification

The mean HbA1c value prior to any treatment escalation was 9.0% (±1.4), 8.7% (±1.3) before the first added NIAD and 9.4% (±1.5) among those who were intensified with insulin (Figure S4, Appendix S1). In the subgroup of patients with HbA1c levels ≥8% at baseline or at any time during the study period, the mean value prior to any treatment intensification was 9.4% (±1.24), 9.2% (±1.1) before the first added NIAD and 9.7% (±1.3) among those who received insulin (Figure S4, Appendix S1). Based on HbA1c categories prior to treatment intensification, a new NIAD was the most frequent addition among patients with HbA1c levels 7.0% to 7.9% (69.3%), either a new NIAD or insulin among patients with 8.0% to 9.9% levels (50.8% and 49.2%, respectively), and insulin among patients with ≥10% levels (66.3%).

### 3.4 | Time to treatment intensification

In the overall population, the median time to first intensification (addition of any new antidiabetic agent regardless of type, ie, an NIAD or insulin) was 22.6 months (IQR, 6.9-59.9), and less with progressive increase in HbA1c levels (Table 2 and Figure 1A): from 35.3 months (P25-P75: 11.1 to > 60) in patients with baseline HbA1c 7.0% to 7.9%, to 10.1 months (IQR, 1.6-25.1) in patients with HbA1c ≥10%. Similarly, the probability of intensification at the end of follow-up was 73.8%; this increased in parallel with the increase in HbA1c levels, from 64.3% when HbA1c was 7.9% to 7.9% to 88.5% among those with levels ≥10%.

Among all intensified patients, the relative proportion that was intensified with a new NIAD as the first change to the index regimen was higher than the proportion that received insulin as the first change (63.8% vs 36.2%) (Table 2). However, the probability of receiving insulin increased gradually and in parallel with the increase in HbA1c levels (Table 2 and Figure 1B and C). For instance, 30.5% of patients with HbA1c levels 7.0% to 7.9% received insulin as the first change (19.6% probability), but this increased up to 49.9% (43.4% probability) when HbA1c levels were ≥10%.

### 3.5 | Factors predicting intensification

Covariate analysis showed that the probability of having treatment intensified decreased with increasing age beyond 65 years (66-75 years, SHR, 0.93 [95% CI, 0.88-0.99]; >75 years, SHR, 0.73 [95% CI, 0.69-0.79]) and was lower among patients treated at baseline with 3 or 4 NIADs compared to 2 NIADs (SHR, 0.87 [95% CI, 0.82-0.93]) (Figure 2 and Table S1, Appendix S1). Conversely, covariates associated with a higher probability of treatment intensification were

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**TABLE 2** Median time and probability of treatment intensification during follow-up (N = 23 678)

| HbA1c category | First drug added | Any (NIAD or insulin) | NIAD | Insulin |
|----------------|------------------|-----------------------|------|---------|
| All ≥ 7% (53 mmol/mol) | | | | |
| N | 17 465 | 11 144 | 6321 |
| Relative % of patients | 100% | 63.8% | 36.2% |
| Median time to intensification (P25-P75), months | 22.6 (6.9-59.9) | – | – |
| Probability of treatment intensification | 73.8% | 47.1% | 26.7% |
| 7.0% to 7.9% (53-63 mmol/mol) | | | | |
| N | 7034 | 4891 | 2143 |
| Relative % of patients | 100% | 69.6% | 30.5% |
| Median time (P25-P75), months | 35.3 (11.1- > 60) | – | – |
| Probability of treatment intensification | 64.3% | 44.7% | 19.6% |
| HR (95% CI) | 1 | 1 | 1 |
| 8.0% to 9.9% (64-85 mmol/mol) | | | | |
| N | 8029 | 5029 | 3000 |
| Relative % of patients | 100% | 62.6% | 37.4% |
| Median time (P25-P75), months | 17.1 (4.9 to >60) | – | – |
| Probability of treatment intensification | 80.2% | 50.2% | 30% |
| HR (95% CI) | 1.7 (1.7-1.8) | 1.3 (1.2-1.32) | 1.73 (1.63-1.83) |
| ≥10% (86 mmol/mol) | | | | |
| N | 2402 | 1224 | 1178 |
| Relative % of patients | 100% | 50.1% | 49.9% |
| Median time (P25-P75), months | 10.1 (1.6-25.1) | – | – |
| Probability of treatment intensification | 88.5% | 45.1% | 43.4% |
| HR (95% CI) | 2.6 (2.4-2.7) | 1.1 (1.04-1.2) | 3.05 (2.82-3.29) |

Abbreviations: NIAD, noninsulin antidiabetic drug; P25, 25th percentile; P75, 75th percentile.

a Less than 50% of patients intensified treatment.
mainly the highest HbA1c values compared to values between 7.0% and 7.9% (8.0%-9.9%; SHR, 1.72 [95% CI, 1.65-1.78]; ≥10%; SHR, 2.52 [95% CI: 2.37-2.68]) and, to a lesser extent, female gender (SHR, 1.10 [95% CI, 1.05-1.13]); diabetes duration longer than 5 years (5-10 years, SHR, 1.05 [95% CI, 1.00-1.09] and >20 years, SHR, 1.25 [95% CI, 1.11-1.41]); a high number of comorbid conditions vs only 1 condition (ie, Charlson score = 3; SHR, 1.11 [95% CI, 1.04-1.18]); chronic kidney disease (SHR, 1.10 [95% CI, 1.02-1.13]) and the presence of microvascular complications (SHR, 1.07 [95% CI, 1.03-1.12]).

4 | DISCUSSION

This population-based retrospective analysis of adult patients with T2DM concomitantly treated with ≥2 NIADs showed that 26.2% of patients with a baseline HbA1c level ≥7% were not intensified during 5 years of follow-up, and therapeutic inertia was present in up to 18% of patients with HbA1c levels ≥8%. Therapy escalation occurred following a significant deterioration in glycaemic levels, and it was delayed far beyond the 3 to 6 months typically advocated by clinical guidelines. Finally, the transition to new treatment regimens was least frequent among older patients and those with complex regimens, and occurred most frequently among those with HbA1c levels >8% and those with long-standing disease, kidney disease or high comorbidity.

The baseline demographic characteristics of our study population, with a mean age above 65 years, more than half of the patients with mean HbA1c levels at baseline ≥8.0% and long-standing diabetes (mean of 8 years), largely reflect an advanced disease that progressively decreased the probability of maintaining adequate glycaemic control over time. Treatment was not intensified in 26.2% patients with HbA1c baseline values ≥7%, and the majority of patients who remained in the same index regimen had glycaemic levels between 7% and 7.9%. This could indicate that an HbA1c value <8%, considered as the threshold to avoid overtreatment in the elderly, as incentivization in our health care setting,15 and also the superior limit for individualized goals advocated by some clinical guidelines,11,14,26 is being implemented in part. Nonetheless, in patients with evident inadequate glycaemic control ≥8%, therapeutic inertia was present in 18.1% of cases, which is lower than that found in previous studies.27–30 The largest retrospective study published to date, conducted in >80 000 patients in the UK, reported that the probability of treatment intensification in patients receiving 2 or 3 oral antidiabetic drugs (OADs) at the end of a 7-year follow-up period was <50%, regardless of the cut-off considered (≥7.0, ≥7.5% or ≥8%).27 Our figures support previous findings from the few additional studies providing data on the subgroup of patients receiving ≥2 OADs, with clinical inertia values of 34.5% when poor glycaemic
control was defined as an HbA1c value >7%, between 18% and 51.3% when set to 8%,28–30 and 53.1% with a 9% cut-off.31 Variability among studies may be attributable to several factors, including type of health care setting (primary care, secondary care, private or public), duration of diabetes, treatment revision type (eg, OAD used for the first time, new OAD addition, switch to insulin, or all) and duration of the observational period. Last, but not least, it is also important to know if dose escalation was considered as a form of intensification, as prescribing an increased dose is more likely to take place among adherent patients still not reaching glycaemic targets compared with those who are not adherent;32 thus, therapeutic inertia may have been overestimated.

The mean HbA1c value prior to any treatment intensification was 9.0% in the overall population, and was higher (9.4%) in patients with values ≥8%. Moreover, mean glycaemic values were lower among subjects intensified by the addition of a new NIAD than by adding insulin. Our results support previous studies reporting that, in patients taking ≥2 OADs, the addition of a further oral medication takes place when HbA1c values are between 8.4% and 9.1%, and therapy is stepped up with insulin at when HbA1c values are between 9.2% and 9.9%.27,33–35 This reflects extremely poor glycaemic control, far above the recommended targets advocated in local14,15 and international10–12 guidelines. Finally, the third step has traditionally been addition of insulin,6,14 with the resultant patient and health care professional barriers. Patients often resist its use because of fear of injection, and primary care professionals are reluctant to prescribe it because of fear of weight gain or hypoglycaemia, time constrains or lack of educational resources, among others reasons.2,36

The median time spent before previous treatment was escalated with a new NIAD or insulin was far longer than the recommended 3 to 6 months for patients not meeting glycaemic targets before therapy is intensified.11,12,14,37 Our results are in line with previous studies reporting large delays in therapy escalation among patients receiving ≥2 OADs, and also reporting that the time lag is shorter among patients with the most poorly controlled glycaemic levels.
(>7 years in patients with levels ≥7%,27,33 and 4.9 to >7 years in patients with levels ≥8%).27,29 On the one hand, with the threshold for pay-per-performance indicators in our institution being HbA1c below 8%, it is reasonable to think that intensification may be delayed until this value is repeatedly exceeded. On the other hand, one may intuitively think that delays could also be linked partially to the implementation of relaxed personalized glycaemic goals in particular patients.

This multivariate analysis showed that patients older than 65 years who were treated at baseline with 3 or 4 NIADs were less likely to have their therapy stepped up, while increasing HbA1c values beyond 8%, especially when greater than 10%, and diabetes duration ≥20 years were the strongest independent predictors of medication intensification. Other factors also associated with greater odds, although to a lesser extent, were female gender, high Charlson index score, chronic kidney disease and presence of microvascular complications. All of these patient characteristics have been previously identified as being associated with the likelihood of, and/or time to, therapy intensification in the same direction as in our study.2,17-19,28-32,35,38-51 However, some studies have also reported decreased odds of treatment intensification or increased time to escalation with the presence of comorbid conditions.31,40,50,52,53

From the previous literature and our own results, it appears that the profile of the patient with the greatest odds of treatment escalation, if already receiving ≥2 NIADs, is younger than 65 years, with very poor glycaemic control, complex treatment regimens, long-standing diabetes and high comorbidity. This attitude potentially disregards the negative impact that cumulative glycaemic burden and delayed intervention has on long-term microvascular and cardiovascular complications3,4 in less severe cases. However, there may be many reasons behind a lack of intensification. In this study, we could not discern a failure to realize the probable need for therapy intensification from other situations such as medical conditions during which medication change is inappropriate; concerns about the risk of hypoglycaemic events (particularly among the elderly); gaps, lack of clarity or discrepancies in existing guidelines; or physician’s and patient’s preferences.20,54 In addition, for patients near their HbA1c goals, both care providers and the patients themselves may have agreed to implement other measures to improve self-management, such as lifestyle changes and dietary counseling, or education in engagement with treatment.

Strengths of our study include the large sample size and the fact that it was conducted in a real-world setting that reflects routine clinical practice. However, the results of our study should be interpreted with potential limitations in mind. This was a retrospective analysis, intrinsically subject to incomplete documentation and loss of data concerning some of the studied variables; however, to minimize this limitation, subjects without basal HbA1c values or less than 1 year of follow-up were excluded. Furthermore, the study was conducted in an area that may not be completely representative of other areas inside or outside Spain, with different health care systems or prescription policies. Moreover, the censored nature of the study might have underestimated intensification times, although lack of intensification might be explained by sound reasons other than insufficient follow-up duration; for instance, a less stringent individualized approach was chosen, or other factors were taken into consideration, such as medication cost, inadequate patient adherence or risk of secondary effects. Also, although patients do not have financial barriers to adequate care, because they are treated at centres within the public healthcare system, the pay-per-performance model of our institution advises against the use of drug classes other than metformin, sulphonylureas or insulin, and prescription of the newest (and more expensive) drugs entails negative economic incentives for the physicians. In addition, we did not consider a dose increase within the same drug class as a form of therapy intensification, and intensification was defined as only an add-on, which precludes the distinction of an actual intensification from a treatment switch, all of which might have led to an overestimation of therapeutic inertia. Similarly, we considered fixed-dose combinations as 2 different NIADs, but they have been reported to be associated with greater adherence compared to the combination of separate pills,55 which may impact the need for treatment intensification in some cases. Moreover, differences between general practitioners and endocrinologists must be taken into account, as specialists are more likely to use insulin therapies (eg, in 8.6% and 1.7%, respectively, of patients with poor glycaemic control)56 and they tend to initiate insulin treatment sooner than primary care physicians.57 This probably reflects a referral bias, with specialists managing the most advanced and complex patients and, hence, those with the worst glycaemic control. Nevertheless, the SIDIAP database includes prescriptions from both specialists and primary care physicians, with no differentiation of origin. Finally, we did not have information concerning patient-related personal factors (eg, socio-economic status, level of education, urban vs rural location, or marital status), concerning organizational or structural differences among health care centres (eg, working conditions or lack of team-based care),20 drug dose escalations or additional predictors of a higher chance of treatment intensification, such as good adherence to treatment.28,32,41,45 more frequent and recent outpatient visits,20,41,44 specialist visits,49,51,57 high doses of OADs at baseline,28,44 or use of concomitant medications.51,44

In conclusion, the primary findings of this retrospective study showed that lack of treatment intensification was present in 1 in 5 patients with HbA1c values >8% at baseline, and that the time to introduction of a new NIAD or insulin exceeded that recommended before therapy is intensified. Overcoming therapeutic inertia should be an important goal for healthcare providers in the management of T2DM, and it could be minimized through more intense training and education or the development of practice-based interventions aimed at promoting early and well-timed medication adjustments.

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Conflict of interest

M. M-C has received honoraria for consulting and/or speaking for AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Esteve, Ferrer, GSK,
Lilly, Menarini, Merck, MSD, Novartis, Novo Nordisk, Sanofi and Servier. J. F-N has received honoraria for consulting and/or speaking from Abbott, AstraZeneca, Boehringer Ingelheim, Esteve, Ferrer, GlaxoSmithKline, Eli Lilly, Janssen, Menarini, Merck Sharp & Dohme, Novartis, Mylan, Novo Nordisk, and Sanofi. K. K. has received honoraria for consulting and/or speaking from Amgen, Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Sanofi, Boehringer Ingelheim, Roche and Servier. D. M. has received honoraria for consulting and/or speaking from Abbott, AstraZeneca, Boehringer Ingelheim, Ferrer, GlaxoSmithKline, Eli Lilly, Janssen, Medtronic, Menarini, Merck Sharp & Dohme, Novartis, Novo Nordisk, Praxxis Pharmaceutical and Sanofi. J. R., M. G. and F. L-S have no conflicts of interest to declare.

Author contributions
M.M-C and M.G. wrote the manuscript; J.R. managed the database, performed the statistical analyses and contributed to the discussion; and J.F-N, M.M-C., and D.M. designed and conducted the study, reviewed/editing the manuscript and contributed to the discussion. K.K. and F.L.S. contributed to the discussion. M.M-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.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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