Glycemic Control after Treatment Intensification in Patients with Type 2 Diabetes

Uncontrolled on Two or More Non-Insulin Antidiabetic Drugs in a Real-World Setting

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Running title:
HbA1c after intensification in T2DM already on 2 or more antidiabetics

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ABSTRACT

**Aims:** To assess glycaemic control after treatment intensification in patients with type 2 diabetes uncontrolled on ≥2 non-insulin antidiabetic drugs (NIADS).

**Methods:** Retrospective cohort study, using electronic health records from the SIDIAP database (2010-2014). Intensification was defined as the prescription of any new antidiabetic drug in patients treated with ≥2 NIADS and HbA1c >7%. The primary outcome was the absolute change in HbA1c 6 to 12 months after any intensification. Secondary analyses included the percentage of patients reaching HbA1c <7%, HbA1c <8%, and a reduction of HbA1c >1% after the first intensification.

**Results:** There were 21,241 intensifications in 15,205 patients with a mean (SD) HbA1c of 9.02% (±1.35). Insulin and DPP4-inhibitors were the most frequently added therapies. The mean baseline-adjusted HbA1c reduction was 0.78% (95% CI, -0.80 to -0.76), varying from -0.69% with DPP4-inhibitors to -0.85% with GLP1 receptor agonists while the addition of insulin was associated with a reduction >1%.

After the first intensification, 48.9% of patients achieved a HbA1c <8%, 16.2% HbA1c <7%, and 43.1% a reduction >1%. High previous HbA1c was positively associated with the reduction of HbA1c >1% (odds ratio [OR] 2.13 [95% CI: 2.05-2.21]), but inversely associated with the attainment of HbA1c <7% (OR 0.64 [0.61-0.67]) or <8% (OR 0.63 [0.60-0.65]). Older age, male gender, higher Charlson index, and short diabetes duration were associated with achievement of HbA1c <7%.

**Conclusions:** Despite intensification, most patients failed the glycaemic goal of HbA1c <7%. The reduction depended mainly on pre-intensification HbA1c values, with small differences between drugs.

**Keywords:** type 2 diabetes mellitus, glycaemic control, intensification, observational
INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health problem worldwide.\textsuperscript{1} Both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) propose a stepwise approach for T2DM treatment that involves lifestyle recommendations and metformin as the first-line therapy.\textsuperscript{2} When glycaemic control is not achieved, it is recommended to add a second oral antidiabetic agent or an injectable drug as second-line therapy. If glycaemic control is still not acceptable, the recommendations are to add three or more agents.\textsuperscript{3,4} The second drug introduced after metformin is usually a sulfonylurea (SU) because of its glucose-lowering efficacy and low cost despite the higher hypoglycaemia-associated risk compared to other drugs.\textsuperscript{3,4} Likewise, the most common third-line agent in T2DM therapy is insulin being the most effective drug for reducing glycaemic levels in an advanced stage of the disease.\textsuperscript{3} However, new types of antidiabetic drugs have become available in the last 20 years, including glitazones, glucagon-like peptide-1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium glucose co-transporter 2 inhibitors (SGLT2i). All of them have demonstrated safety and similar efficacy and, in some cases, cardiovascular benefits.\textsuperscript{4,5}

While there are a significant number of randomised clinical trials (RCTs) and real-world studies showing the efficacy of different therapeutic agents in the second-line treatment for T2DM, data for the third- or fourth-line therapies remain scarce.\textsuperscript{6} Moreover, intensification is usually delayed in the third step because of the barriers to insulin treatment.\textsuperscript{7} As a consequence, patients may persist with poor glycaemic control for long periods of time (months to years),\textsuperscript{8} which is in turn associated with poor long term outcomes.\textsuperscript{9} Indeed, our group previously reported that, among T2DM patients inadequately controlled when treated with two or more non-insulin antidiabetic drugs (NIADs), a new NIAD was added at a mean glycated haemoglobin (HbA1c) value of 8.7\% and insulin at a mean value of 9.4\%.\textsuperscript{10} To our knowledge, few real-world studies have assessed the efficacy of the different agents used as the third or even fourth step of treatment, and even
fewer have compared the use of insulin versus other antidiabetic drugs. In this study, we aimed to describe, in a real-world setting, the magnitude of HbA1c reduction after the addition of a new antidiabetic agent in T2DM patients with inadequate glycaemic control treated with two or more NIADs. The secondary outcomes were to determine, after six to 12 months of the first intensification, the percentage of patients who attained an absolute reduction of HbA1c greater than 1%, and the proportion who achieved target HbA1c goals <7% (53 mmol/mol) or <8% (64 mmol/mol). Finally, we analysed factors associated with the achievement of the HbA1c targets.

METHODS

Study design and data source

This was a sub-study of a previously described retrospective cohort study conducted to assess therapeutic inertia in patients with T2DM treated with ≥2 NIADs and inadequate glycaemic control in primary care. Briefly, data were obtained from the SIDIAP electronic database, covering the period between January 2010 and December 2014.

Catalonia is a Mediterranean region in north-eastern Spain and has a public health system. The main health provider in the region is the Catalan Health Institute (ICS), which operates around 280 primary health care centres (PCCs) with >3500 general practitioners (GP) that provide medical cover to 5.8 million subjects (which represent 80% of the region’s population and 10% of the Spain’s population). All GPs pertaining to the ICS record demographic and clinical information, laboratory test results, prescriptions, and referrals of their patients into common electronic medical records (eCAP). These data, together with the dispensed treatments extracted from pharmacy-invoicing data provided by the Catalan Health Service (CatSalut), are further incorporated into an anonymized electronic general practice database available for researchers, the SIDIAP database (Information System for the Development of Research in Primary Care), which started in 2005. Since the SIDIAP database was established, a number
of observational studies have assessed the validity of its information, and it has been shown to be highly representative of the population of Catalonia regarding geographical (both urban and rural areas), age and sex distributions.\textsuperscript{11,13-15}

The inclusion criteria for the entry in the cohort was an inadequate glycaemic control defined as one HbA1c value >7% during 2010 (recruitment phase).\textsuperscript{10,16} Intensification was defined as the prescription of a new antidiabetic drug during follow-up.

When the HbA1c value at the time of intensification was missing or <7%, patients were excluded. Since a patient could receive more than one new antidiabetic agent during the follow-up period, each intensification was considered independently for the absolute HbA1c reduction assessment. For the secondary outcomes, we only included patients receiving the first intensification.

**Study variables**

The main study variables were the HbA1c values before and after intensification and the electronic prescriptions of antidiabetic treatment during the follow-up period, including: insulin, metformin, sulfonylureas, glinides, glitazones, GLP-1RAs, and DPP-4i. SGLT-2i were not included in the study because the first marketed drug of this group, dapagliflozin, was not available in Spain until the beginning of 2014. The following HbA1c values were assessed: a) last measurement up to 1 year before intensification, and b) the first available measurement after the addition of a new antidiabetic treatment, allowing a window-frame between 6 and 12 months. The thresholds considered for the evaluation of outcomes were: HbA1c <7%, HbA1c <8% and a reduction of HbA1c >1 point (i.e., >1%). Clinical and demographic data included age; gender; duration of diabetes; body mass index (BMI); estimated glomerular filtration rate (eGFR) using the Modified Diet in Renal Disease (MDRD) formula; presence of cardiovascular disease, including coronary artery disease, and peripheral artery disease; presence of microvascular complications (i.e., diabetic retinopathy, nephropathy or neuropathy); presence of...
heart failure; and Charlson comorbidity index score (abbreviated version) at baseline. “We calculated the baseline Charlson Comorbidity Index (CCI) score in its abbreviated version using the 8 categories of comorbidity (as recorded in the eCAP software) to create a score that reflects a cumulative increased likelihood of 1-year mortality.”

Poor glycaemic control was defined as an HbA1c value ≥7% as recommended by international and local guidelines, and also ≥8% according to the pay-per-performance indicator of our institution (Catalan Institute of Health; ICS) in force during that period.

**Statistical analysis**

Continuous variables were summarised using mean and standard deviation (SD), and categorical variables as absolute numbers and percentages. Logistic regression models were fitted to identify those variables associated with the achievement of glycaemic targets. Multivariate models were adjusted with ENTER method by variables clinically associated with achievement of glycaemic goals, namely pre-intensification HbA1c, gender, age, BMI, intensification type (insulin vs. NIADs), Charlson index, presence of micro- and macrovascular complications, presence of cardiac failure, and categories of T2DM duration. Adjusted changes in HbA1c were estimated by weighted linear regression model considering basal HbA1c. The relationship between baseline HbA1c and subsequent change in HbA1c was explored by different functional forms (i.e., linear, non-linear with quadratic terms, and smoothing splines). Finally, we conducted a sensitivity analysis based on multiple imputation (MI) using Rubin’s rules to compare the results obtained with complete cases (i.e., with available data at baseline and also after intervention) and results including subjects with missing data. Estimates of the changes, differences of HbA1c, and odds ratios (OR) were reported with their corresponding 95% confidence intervals (CI) with the statistically significant level set at 5%. All statistical analyses were performed using Stata 15® (Stata Corp, College Station, TX, USA) and R version 3.5.1.
RESULTS

The cohort included 15,205 patients, 53.5% of them male, with a mean age of 67.5 years (SD=10.4), and a mean T2DM duration of 9.7 years (SD=5.4) (Table 1). Micro- and macrovascular comorbidities were present in 27.5% and 15.3% of patients, respectively. The majority of patients were previously treated with metformin and a SU (83.8%) or metformin and a DPP4i (14.4%). During follow-up, 54.2% received insulin and 66.9% a NIAD. There were 21,241 intensifications in total: 9809 of them were insulin, 7922 a DPP4i, 1404 a SU/glinide, 743 a glitazone, 814 a GLP-1RA, and 549 metformin.

Mean HbA1c before intensification was 9.02% (SD=1.35). The changes in HbA1c per treatment group and stratified by pre-intensification HbA1c levels are shown in Figure 1 and Supplementary Table 1. In 18,407 intensifications with pre- and post- HbA1c values available, the mean overall magnitude of HbA1c decrease was 0.79% (95% CI, -0.82 to -0.77). The maximum mean reduction was obtained after adding insulin (-1.12%), and the minimum after adding a DPP4i (-0.56%). However, these differences were reduced after adjusting for baseline HbA1c levels (9.02%): -0.85% with a GLP-1RA, -0.84% with metformin, -0.81% with insulin, 0.76% with pioglitazone -0.74% with a SU/glinide and -0.69% with a DPP4i. In the same line, the largest reductions were obtained when pre-intensification HbA1c values were ≥10%: -2.13% with insulin, followed by metformin (-1.77%), SU/glinides (-1.71%), GLP-1RA (-1.70 %), DPP4i (-1.54%) and glitazones (-1.50%).

The achievement of objectives by pharmacological groups is shown in Figure 2 and Supplementary Table 2. Overall, there were no major differences between the different NIAD class groups, although the reduction of >1% was slightly more frequent among insulin (52.1%) and GLP-1RA (49.2%) users than among those on oral agents. Conversely, the achievement of the other two glycaemic targets (HbA1c <7% or <8%) was inferior with insulin.
Target achievements by subgroups of patients after the first intensification are shown in [Supplementary Table 3](#). Attainment of the HbA1c <8% goal was observed in 48.9% of cases, attainment of HbA1c <7% goal in 16.2% of cases, and a reduction of >1% in HbA1c in 43.1% of cases. Results were slightly lower in women and in those younger than 75 years. Results did not differ when stratifying by BMI and T2DM duration, with the exception of patients with a T2DM duration over 20 years, with a slightly lower proportion of patients achieved a HbA1c reduction of >1% than those with a T2DM duration between 5 and 20 years (40.4% vs. 42.4%-43.5%).

Results of the multivariate analysis for the first intensification are shown in [Figure 3](#) and [Supplementary Table 4](#). Pre-intensification HbA1c levels were inversely associated with both the achievement of HbA1c <8% and <7%. Moreover, the pre-intensification HbA1c value was the most relevant variable associated with the reduction of HbA1c >1% (OR=2.13 per unit increase; 95% CI=2.05-2.21, p<0.001), and was inversely related with the probability to attain HbA1c values <7% (OR=0.64 per unit increase; 95% CI=0.61-0.67; p<0.001) or <8% (OR=0.63 per unit increase; 95% CI=0.60-0.65; p<0.001). Older age, male gender, high Charlson index, and short diabetes duration were the main factors related to a HbA1c <7% target achievement, while the addition of insulin (in comparison to intensification with NIADs) was specifically associated with a reduction of HbA1c >1% (OR=1.17; 95% CI=1.08-1.27; p<0.001).

The sensitivity analysis showed that the changes in HbA1c per treatment group and stratified by pre-intensification HbA1c levels, and also the variables associated with the achievement of glycaemic objectives after the first intensification, were similar to the results from the analyses only considering complete cases ([Supplementary Tables 1 and 4](#)).

DISCUSSION

There is limited real-world evidence exploring the changes in HbA1c levels in triple- or fourth-line therapy in people with T2DM. In the present study, the most frequently added antidiabetic
drugs during the follow-up were insulin and a DPP4i. Our results point out that the magnitude of the reduction in HbA1c levels in patients treated with ≥2 NIADs is closely associated with the HbA1c levels prior to the intensification, a finding reported previously.\textsuperscript{20} In our study, when HbA1c levels prior to intensification were ≥10\%, the observed HbA1c decline was larger regardless of the prescribed drug, although insulin was the most potent drug. Indeed, intensification with insulin was associated with the highest proportion of patients reducing HbA1c levels >1\%, and with the least probability of reaching target glycaemic goals (both <7\% and <8\%) compared with all other studied drugs. The latter was probably due to the fact that patients on insulin had the highest baseline HbA1c values. However, when adjusted for baseline HbA1c levels, the reductions were quite similar and the drugs which lead to a major HbA1c decline were GLP-1RA, instead of insulin. As patients receiving insulin have higher HbA1c levels and longer T2DM duration than those starting a NIAD, they are probably in a more advanced stage of the disease. In these situations, the decision to start insulin treatment should depend more on the characteristics and preferences of the patients than the theoretically superior reductions in HbA1c attributable to insulin.

Our results also showed that, when pre-intensification HbA1c levels were below 8\%, the improvement in glycaemic control after intensification was not clinically relevant. This highlights the need for the individualization of glycaemic objectives considering the patient’s characteristics and their preferences.\textsuperscript{5} Therefore, a targeted approach appears particularly important among those poorly controlled and treated with ≥2 NIADs.

Regarding the achievement of HbA1c goals, we did not observe major differences between the different groups based on the glucose-lowering agent after baseline adjustment, as has been observed with the addition of a second antidiabetic in other population-based studies.\textsuperscript{21,22} Indeed, adjustment for baseline Hb1c levels was crucial to better compare the effects of the different drugs as already done in these studies.\textsuperscript{21,22} Conversely, the achievement of the other two goals (HbA1c <7\% or <8\%) was inferior with insulin and GLP-1RA, probably because of the
higher pre-intensification HbA1c levels in these two groups (9.4% for insulin and 9.1% for GLP-1RA vs. 8.7-9.0%). Our results are in line with those of a recent meta-analysis of 43 RCTs (overall 16,590 participants) assessing the effects of the addition of a third drug after failure of dual therapy. The authors concluded that rapid-acting insulin added to metformin and SUs resulted in the largest reduction in HbA1c after 24 to 36 weeks (1.6% vs. placebo), followed by GLP-1RA (1.0%), basal insulin (0.8%), and SGLT-2i and DPP4i (both 0.7%). A great number of treatment options show notable efficacy in RCTs, but their impact on glycaemic control in real-world clinical practice is usually less than expected. It has been suggested that poor adherence is the key factor explaining the gap between results from real-world studies and RCTs. Indeed, a recent real-world study showed that HbA1c reductions at 12 months in patients who initiated a GLP-1RA or DPP4i in the US were similar (0.52% vs. 0.51%, respectively), whereas in a meta-analysis of 11 RCTs, a greater efficacy of both drugs was observed, with a striking superiority of GLP-1RA in comparison to DPP4i (1.30% vs. 0.68%, respectively). The main limitation of this real-world study was the small sample size (only 221 patients on a GLP-1RA and 652 on a DPP4i). In our study, 7922 and 814 patients received a DPP4i or a GLP-1RA, respectively, and the absolute reductions after baseline adjustment were 0.56% and 0.91%, respectively. Compared to the ones observed in the US real-world study, these figures are quite similar in the case of DPP4i, but much larger in the case of GLP-1RA, but still inferior to the reductions achieved in RCTs.

Our results also suggest that the best glycaemic control is achieved in the elderly and in patients with comorbid conditions, whereas the worst control was observed among women. In general, data regarding older and comorbid patients remain scarce because these patients are usually excluded from clinical trials. A previous study also found that elderly T2DM patients had better glycaemic control irrespective of the duration of the disease. Our results demonstrate that vulnerable patients (those older and with more comorbidities) achieve better glycaemic control, which could be an illustration of overtreatment in this vulnerable population. Overtreatment in older diabetic patients is quite common and should
be avoided in order to prevent harmful consequences such as falls due to hypoglycaemia.\textsuperscript{28} In line with the concept of quaternary prevention -avoidance of overmedicalisation in at-risk populations-,\textsuperscript{29} the definition of adequate glycaemic control should be revised in those vulnerable patients along with the promotion of safest drugs, instead of insulin or SUs. In our study, we excluded patients with pre-intensification HbA1c values <7% to minimize the possibility overtreatment. Moreover, our results showed that the benefits in patients with HbA1c values between 7% and 8% we quite limited, so that a threshold of HbA1c of 8% for intensification in the third step of treatment would be a reasonable cut-off for certain individuals to avoid overtreatment, in particular among older patients.

Our study also suggested that female gender was associated with poorer glycaemic control after intensification. Gender differences have been largely studied in the pathophysiology of T2DM,\textsuperscript{30} and both biological factors (e.g., women are frequently more obese and hypertensive than men) and psychosocial factors (e.g., emotional distress and wellbeing) could explain the observed differences.\textsuperscript{31,32}

The major strength of the present study is the use of the SIDIAP database, which includes prescribed medications and clinical data from the majority of patients from Catalonia; these data might better reflect the effects in T2DM patients than the results from clinical trials, which are less representative of patients managed in the real-world setting.\textsuperscript{25} Indeed, clinical trials contribute to the major scientific evidence, but observational studies using real-world data can complement the scientific evidence by adding new data of patients that are not necessarily included in the clinical trials.

Our study also adds new data on the reductions according to the antidiabetic drugs in patients already receiving a second-line non-insulin treatment based on the HbA1c levels before the intensification. However, this study has some limitations too. Some limitations are inherent to its observational nature, such as the lack of randomization and the resulting selection bias.
amongst patients treated with different regimens. Other limitations include the non-availability of other relevant variables (e.g., adherence, hypoglycaemic episodes, weight changes, side effects of the medications, drug interactions, etc.), and residual confounding, which are common in observational retrospective studies using real-world databases. In addition, since medication doses were not identifiable from the routine data, we did not account for dose titration of existing treatments when we assessed treatment intensification. Missing data can as well be a source of confounding bias, although the sensitivity analysis showed that the results were comparable to the ones obtained using only complete cases. Changes in weight or other cardiovascular risk factors are additional benefits of some drugs like GLP-1RA, but were not considered in this study. Moreover, we only considered changes on the first HbA1c value for the secondary outcomes but no further values, so this precluded the possibility to detect improvements or deterioration of the glycaemic control in the long term. Finally, changes in HbA1c levels could be partly due to other causes than the prescription itself (e.g., changes in lifestyle, improvement in the adherence to previous drugs, the natural history of the disease, among others).

In conclusion, our study, based on real-world data, showed that the effects on glycaemic control with the intensification in T2DM patients who are poorly controlled and treated with at least 2 NIADs depends mainly on pre-intensification HbA1c values. There were no relevant differences between the studied drugs in terms of HbA1c decline when results were adjusted for baseline HbA1c. Therefore, intensification with a NIAD as a third drug prior to insulin therapy seems a reasonable and efficacious option in at least half of the patients, as now recommended in the Standards of Care of the ADA. Moreover, and again in agreement with current recommendations, in those patients with very high HbA1c levels, insulin remains the best option. However, it is important to stress that, despite the availability of different therapeutic drugs for T2DM, many patients still do not reach an adequate glycaemic control after intensification, even after insulin initiation.

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Conflict of Interests

M. M-C. has received advisory honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received speaker honorarium from Astra-Zeneca, Bayer, Boehringer Ingelheim, GSK, Lilly, Menarini, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi.

J. F-N has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.

D. M. has received advisory and/or speaking fees from Astra-Zeneca, Ascensia, Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, and Sanofi; he has received research grants to the institution from Astra-Zeneca, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi, and Boehringer.
K. K. has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, and Merck Sharp & Dohme.

S.C, J. R., B. V., and M. G. have no conflicts of interest to declare.

Author contributions

S.C. and M.M-C wrote the manuscript. M.M-C., J.F-N., K.K., and D.M. contributed to study design. S.C., J.R., B.V., and M.G. were involved in data management and statistical analyses. All authors contributed to the analysis and interpretation of the data, provided critical input during the development of the manuscript and approved the final version for submission. 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 analyses.
References


Figure Legends

Figure 1. Changes in HbA1c per treatment group (A) and stratified by pre-intensification HbA1c levels (B)

Footnote:
DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagonlike peptide-1 receptor agonist;
HbA1c, glycated haemoglobin A1c

Figure 2. Achievement of objectives by pharmacological groups after the first intensification

Footnote:
DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagonlike peptide-1 receptor agonist;
HbA1c, glycated haemoglobin A1c

Figure 3. Variables associated with the achievement of glycaemic objectives after the first intensification in the multivariate analysis

Footnote:
*Baseline value
BMI, body mass index; CI, confidence interval; NIADs, non-insulin antidiabetic drugs; OR, odds ratio; T2DM, type 2 diabetes
Table 1. Characteristics of subjects whose treatment was intensified.

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<td>31.3 (5.5)</td>
<td>29.5 (4.4)</td>
<td>30.8 (5.1)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>All</td>
<td>Gender</td>
<td>Age (years)</td>
<td>T2DM duration (years)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>---------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>Men</td>
<td>≤75</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²), %</td>
<td>47.4</td>
<td>54.9</td>
<td>40.7</td>
<td>51.5</td>
</tr>
<tr>
<td>Charlson index, mean (SD)</td>
<td>1.54</td>
<td>1.49</td>
<td>1.58</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>(0.89)</td>
<td>(0.86)</td>
<td>(0.92)</td>
<td>(0.80)</td>
</tr>
<tr>
<td>Microvascular complications†, %</td>
<td>27.5</td>
<td>23.8</td>
<td>30.8</td>
<td>25.4</td>
</tr>
<tr>
<td>Macrovascular complications‡, %</td>
<td>15.3</td>
<td>9.2</td>
<td>20.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>2.3</td>
<td>2.6</td>
<td>2.0</td>
<td>1.38</td>
</tr>
<tr>
<td>Renal function (ml/min)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥60), %</td>
<td>83.7</td>
<td>79.5</td>
<td>87.3</td>
<td>89.4</td>
</tr>
<tr>
<td>Moderate failure (30–60), %</td>
<td>15.8</td>
<td>19.8</td>
<td>12.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Severe failure (&lt;30), %</td>
<td>0.5</td>
<td>0.7</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

BMI, body mass index; HbA1c, glycated haemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus

† Includes retinopathy, nephropathy (albuminuria >30 mg/g)
‡ Coronary heart disease, stroke, and peripheral arterial disease
§ Estimation of the glomerular filtration rate by the MDRD equation (Modification of the Diet in Renal Disease)
Author/s:
Canivell, S; Mata-Cases, M; Real, J; Franch-Nadal, J; Vlacho, B; Khunti, K; Gratacos, M; Mauricio, D

Title:
Glycaemic control after treatment intensification in patients with type 2 diabetes uncontrolled on two or more non-insulin antidiabetic drugs in a real-world setting

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