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ORIGINAL RESEARCH ARTICLE

Impact of Second-Line Combination Treatment for Type 2 Diabetes Mellitus on Disease Control: A Population-Based Cohort Study

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Abstract

Background Type 2 diabetes mellitus is a chronic disease affecting millions of people worldwide. Achieving and maintaining glycemic control is essential to prevent or delay complications and different strategies are available as second-line treatment options for patients with type 2 diabetes who do not achieve glycemic control with metformin monotherapy.

Objective The aim of this work is to describe the impact of initiating a combination treatment to reduce glycated hemoglobin in patients with type 2 diabetes with insufficient glycemic control.

Methods We included patients with a type 2 diabetes diagnosis between 2015 and 2020 at the Information System for Research in Primary Care (SIDIAP) database in Catalonia, Spain. The primary outcome was the time to glycated hemoglobin control ($\leq 7\%$) during the first 720 days, expressed as the restricted mean survival time. Adjusted differences of the restricted mean survival time were compared to analyze the performance of each treatment versus the combination with a sulfonylurea. Adherence was calculated as the medication possession ratio using an algorithm to model treatment exposure.

Results A total of 28,425 patients were analyzed. The most frequent combinations were those with sulfonylureas and dipeptidyl peptidase-4 inhibitors. All treatments reduced glycated hemoglobin and the restricted mean survival time for the sulfonylurea treatment was 455 (451–459) days although combinations with glucagon-like peptide-1 and insulin reached glycemic control earlier, − 126 days (− 152 to − 100, $p < 0.001$) and − 69 days (− 88 to − 50, $p < 0.001$), respectively. Adherence was high in all groups apart from the insulin combination and had a significant effect in reducing glycated hemoglobin except in sodium-glucose cotransporter type 2 inhibitors and insulin. Glucagon-like peptide-1 and sodium-glucose cotransporter type 2 inhibitors showed significant reductions in weight.

Conclusions Patients achieved the glycated hemoglobin goal with second-line treatments. Glucagon-like peptide-1 and insulin combinations achieved the goal earlier than sulfonylurea combinations. Adherence significantly reduced the time to glycated hemoglobin control except for the combination with sodium-glucose cotransporter type 2 inhibitors.

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Key Points

Second-line combination treatments of metformin with glucagon-like peptide-1 and insulin achieved earlier glycated hemoglobin control than metformin and sulfonylurea combinations.

Adherence to medication significantly reduced the time to glycated hemoglobin control for most treatments, except for the combination with sodium-glucose cotransporter type 2 inhibitors.

Metformin with glucagon-like peptide-1 or with sodium-glucose cotransporter type 2 inhibitors showed significant reductions in weight.

1 Introduction

Type 2 diabetes mellitus (DM2) is a disease that affects many people in our society [1]. Although it can initially be controlled with a good diet and healthy habits, most patients will require treatment for glycemic control [2, 3].

Throughout their lives, patients diagnosed with DM2 may receive different treatments to treat their condition and control glycemia [4]. In general, it is recommended to maintain glycated hemoglobin (HbA1c) below 7%, individualizing this target value according to the patient's needs and characteristics, such as comorbidities or age [5–8]. Initially, if a patient shows a satisfactory response to treatment, HbA1c levels tend to reduce, especially during the first months of treatment, and they are unlikely to return to baseline [9].

Type 2 diabetes can be managed with a range of pharmacological treatments, with metformin and lifestyle modifications being the recommended first-line therapy, although initiation with other alternatives is considered in some situations, such as other antidiabetic drugs in combination therapy [10] if patients do not achieve adequate HbA1c control with metformin monotherapy [11, 12] or in patients with an established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, when the treatment regimen should include agents that reduce the cardiorenal risk [10]. These combination therapies include sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose cotransporter type 2 inhibitors (SGLT2i), glucagon-like peptide-1 (GLP1) receptor antagonists, other hypoglycemic agents (others), and insulins [13–15].

A recently published meta-analysis, including 36,746 adults in 68 randomized clinical trials, concluded that all classes of oral antidiabetic drugs result in similar reductions in HbA1c levels when added to metformin, although SGLT2i showed an additional benefit on body weight reduction [16]. Despite the availability of many classes of medication in the DM2 field, medication adherence is poor [17]. When the target is not achieved with single metformin therapy, the second line should add a medication class that considers adherence and persistence to achieve good glycemic control for the patient in the long term. In this study, we aimed to measure and compare the impact of the different combination treatments for DM2 on the reduction in HbA1c, patient adherence, and patient weight after their addition.

2 Methods

2.1 Study Design and Population

We conducted a population-based cohort study including all adult patients with an active DM2 diagnosis and metformin prescription between 2015 and 2020 in Catalonia, Spain. The main inclusion criteria were: initial treatment of metformin monotherapy followed by a combination therapy; at least two measures of HbA1c; HbA1c measure $>7\%$ 90 days before the second-line addition; and one or more HbA1c values at least 90 days after the start of the combination therapy. All International Classification of Diseases, Tenth Revision [18] and Anatomical Therapeutic Chemical classification system [19] codes included in the study are shown in Table 1 of the Electronic Supplementary Material (ESM).

2.2 Data Source

The study data source is the Information System for Research in Primary Care (SIDIAP) [20], which captures clinical information of approximately 5.8 million people from Catalonia, Spain (around 80% of the Catalan population). This information is pseudonymized, originating from different data sources: (1) ECAP (electronic health records in primary healthcare of the Catalan Health Institute); including sociodemographic characteristics, residents in nursing homes/long-term facilities, comorbidities registered as International Classification of Diseases, Tenth Revision codes, specialist referrals, clinical parameters, unhealthy habits, sickness leave, date of death, laboratory test data, and drug prescriptions issued in primary healthcare, registered in the Anatomical Therapeutic Chemical classification system; (2) pharmacy claims data corresponding to the primary healthcare drug prescriptions; and (3) the database of diagnoses at hospital discharge [21, 22].

2.3 Outcome Measures

The primary outcome is the time (in days) to HbA1c normalization (≤7%) after initiating the hypoglycemic combined treatment. Different secondary outcomes were considered: (1) to assess the impact of combination therapy adherence on HbA1c levels; (2) impact on weight after initiation of the combination therapy; (3) distribution of combination therapy over time; (4) duration of the single metformin treatment (number of days between the first therapy and the combination therapy); and (5) duration of the combination therapy (number of days between the first and last prescription). The follow-up time for all the outcomes started at the day of the hypoglycemic combined treatment initiation and ended at one of the following censoring events: end of study period (720 days) or disenrollment from the database or death.

2.4 Modeling Drug Exposure to Combination Treatment

We have used the records from electronic prescriptions and dispensations in pharmacies for drug exposure. Prescriptions are recorded with the exact date but invoice data from the pharmacy are recorded by month-year and not linked to the prescription. To assess this linkage, we used the smooth algorithm, developed in our group, which automatically determines at a patient level the most probable treatment (monotherapy or combination) throughout the study period [23]. The smooth algorithm was used to model the drug exposure in both prescriptions and dispensations, to obtain the exact moment of addition of combination therapy, the period exposed to that treatment, and the compliance or adherence.

The adherence was calculated as an approximation of the medication possession ratio (MPR). It was calculated as the ratio between the total days covered by the packages dispensed at the pharmacy, the numerator, and the total days of active prescriptions for that treatment, the denominator. We used a threshold of 80% to classify patients into adherents and non-adherents.

2.5 Statistical Analysis

Results are presented as percentages, means and standard deviations, or median and interquartile range (IQR). In addition, a bivariate baseline analysis was performed. Comparisons between groups in baseline variables were performed by the analysis of variance test for continuous variables and the χ^2 test for categorical variables (exact Fisher test with observed frequencies < 5). In the primary outcome, the time in days was calculated until the first time the HbA1c was below the threshold (≤7%). Those patients who did not achieve HbA1c control during the follow-up period were censored at the date of the last HbA1c sample.

To assess the impact of each combination treatment on HbA1c, a survival analysis was carried out using the Kaplan–Meier and restricted mean survival time (RMST) methods [24–26]. Comparison between the survival curves was undertaken using the log-rank test. Regression models were used to estimate the RMST and its standard error using the delta method [27] and we compared the difference of each RMST with the combination of metformin with sulfonylurea, our reference treatment. The RMST was adjusted by the patient's characteristics using relevant covariates and truncated to 720 days (the follow-up time). Differences between RMSTs were calculated using the identity link and reported with 95% confidence intervals (CIs) along with their p values. For the weight reduction analyses, we fitted a logistic regression model to estimate the odds ratio (OR) of losing more than 5% of weight after the combination treatment versus the same reference group. The ORs were adjusted by the same covariates, and the 95% CI and p values were calculated using classic methods. All analyses were performed with the R statistical package version 4.2 [28, 29] or above under a significant level of 0.05.

3 Results

3.1 Study Participants

From the 43,068 patients starting with a metformin treatment, a total of 28,425 individuals had an addition of a combination therapy during the 720 days of follow-up, and at least two measures of HbA1c: one HbA1c ≥7% before the addition and at least another HbA1c result after 90 days (Fig. 1). The demographic and clinical characteristics of the population at baseline show differences between the study groups (Table 1). Overall baseline HbA1c was 8.63% [70.78 mmoL/mol] (standard deviation [SD] = 1.34), but higher in patients with a combination with insulin, 10.83% [94.86 mmoL/mol] (SD = 2.09). The mean age was 63.63 years (SD = 11.38), a total of 38.1% were women, and the average weight of the population was 83.64 kg (SD = 16.64). Patients with a combination therapy of GLP1 were more frequently observed in women, 52.1%, a higher weight, 107.26 kg (SD = 20.52), and were diagnosed with DM2 3.33 (SD = 3.99) years ago. Clinical characteristics were homogeneous between groups, the mean glomerular filtration rate (as CKDEPI) was 81.12 (SD = 12.92) mL/min/1.73 m^2, and the main comorbidities in the population were hypertension, 19,866 (69.9%), obesity, 18,311 (64.4%), and dyslipidemia, 17,814 (62.7%).

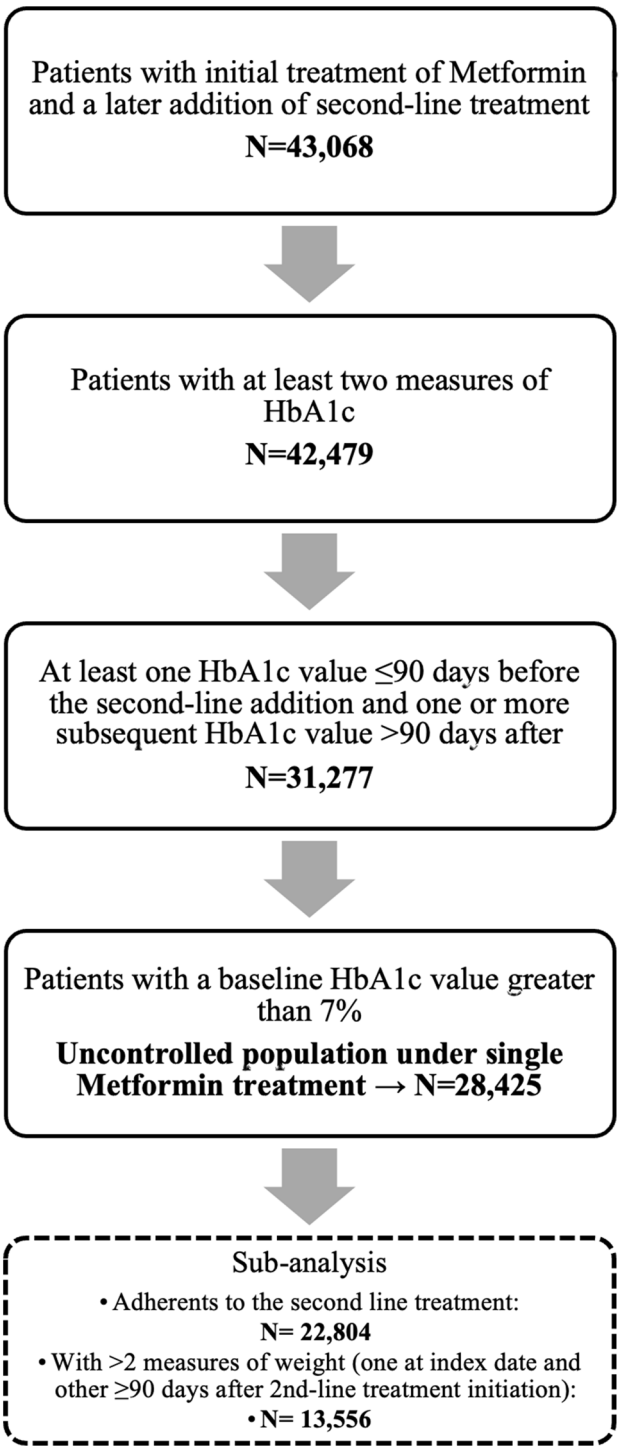

Fig. 1 Study population flowchart: participant selection and exclusion. *HbA1c* glycated hemoglobin

The most prescribed combination therapy were sulfonylureas, 13,216 (46.5%) and DPP4i, 12,000 (42.2%). The rest of the therapies were observed in 17.3% of the patients, with SGLT2i the least prescribed with only 837 (2.9%) patients. Distribution was constant over time, although the sulfonylurea prescriptions as a combination treatment showed a negative trend, with DPP4i becoming the most prescribed from 2017 (Fig. 1 of the ESM).

3.2 Primary Outcome

On average, all treatments had a positive impact on HbA1c with a mean reduction of 1.82% (SD = 1.44, Table 2). Independently of the baseline level, we observed an exponential decay of HbA1c during the first 3–6 months after the addition of second-line treatment. Then, the HbA1c reaches its minimum before entering a slow recovery phase but without returning to baseline values (Fig. 2 of the ESM).

More than a half of the patients, 65.4%, reached the HbA1c goal during the follow-up. In the group treated with GLP1, the percentage of controlled patients was higher, 236 (81.4%), followed by insulins, 61.7%, sulfonylureas, 65.8%, DPP4i, 65.4%, and other hypoglycemic agents, 63.2%.

The efficacy on controlling HbA1c was measured using the RMST. The combination that reached the HbA1c target earlier was the GLP1 with a RMST of 330 days (95% CI 304–357), whereas intensification with other hypoglycemic agents needed more time to reach the HbA1c target, 483 days (95% CI 469–498). In patients with a combination treatment of sulfonylurea (our reference group), the RMST was 455 days (95% CI 451–459), 447 days (95% CI 442–452) in DPP4i, 452 days (95% CI 435–469) in combinations with insulins, and 457 (95% CI 440–457) in SGLT2i (Table 2).

At 720 days, the adjusted difference of RMST to the combination treatment with sulfonylureas was statistically different in all treatments except for SGLT2i ($p = 0.549$). Patients receiving GLP1 and insulins reached the HbA1c goal earlier, − 126.26 (95% CI − 152.49 to − 100.03) and − 69.18 (95% CI − 88.07 to − 50.30) days, respectively. While those receiving a combination treatment with other hypoglycemic agents and DPP4i needed more days to reduce the HbA1c levels, 39.01 (95% CI 24.08–53.95) and 14.81 (95% CI 8.61–21.01) days (Fig. 2).

3.3 Effect of Adherence

The MPR and frequency of adherent patients to each combination treatment were also calculated (Table 2). The mean MPR for the entire cohort was 87.76% (SD = 23.6), with a total of 80.2% adherents. The combination treatments with more adherent patients were DPP4i, 10,540 (87.8%) and sulfonylurea, 10,143 (76.7%), whereas patients prescribed with a combination with insulin were less adherent to the treatment, 465 (48.8%).

The effect of adherence on the primary outcome is shown in Table 3. At 2 years, the adjusted differences in RMST between adherent and non-adherent patients was significantly different ($p < 0.001$). Overall, adherent patients

Table 1 Demographic and clinical characteristics of the study population according to its second-line treatment

	Overall	Metformin + sulfonylurea	Metformin + GLP1	Metformin + DPP4i	Metformin + insulin	Metformin + SGLT2i	Metformin + others
N	28,425	13,216	290	12,000	952	837	1130
HbA1c at index date [mean (SD)]	8.6 (1.34)	8.6 (1.28)	8.6 (1.31)	8.5 (1.18)	10.8 (2.09)	8.5 (1.28)	8.6 (1.21)
HbA1c (mmoL/mol) at index date [mean (SD)]	70.78 (14.70)	70.86 (14.05)	70.08 (14.34)	68.93 (12.98)	94.86 (22.89)	69.83 (14.01)	70.15 (13.27)
Years since DM2 diagnosis [mean (SD)]	5.88 (4.64)	5.77 (4.53)	3.33 (3.99)	6.14 (4.70)	5.01 (4.72)	5.10 (4.35)	6.33 (5.12)
Women (%)	10,831 (38.1)	4956 (37.5)	151 (52.1)	4588 (38.2)	359 (37.7)	326 (38.9)	451 (39.9)
Age, years [mean (SD)]	63.63 (11.38)	62.64 (11.10)	54.92 (10.87)	64.98 (11.22)	62.81 (13.47)	60.10 (10.68)	66.27 (12.03)
Smoking habit (%)							
Non-smoker	12,195 (42.9)	5579 (42.2)	99 (34.1)	5310 (44.2)	349 (36.7)	330 (39.4)	528 (46.7)
Ex-smoker	4997 (17.6)	2384 (18.0)	61 (21.0)	1992 (16.6)	203 (21.3)	178 (21.3)	179 (15.8)
Current smoker	11,233 (39.5)	5253 (39.7)	130 (44.8)	4698 (39.1)	400 (42.0)	329 (39.3)	423 (37.4)
Weight [mean (SD)]	83.64 (16.64)	84.13 (16.38)	107.26 (20.52)	82.34 (16.01)	81.09 (18.23)	90.53 (18.43)	82.70 (16.28)
BMI [mean, kg (SD)], missing 52.4%	31.39 (5.30)	31.44 (5.17)	39.81 (6.45)	31.02 (5.07)	30.42 (5.98)	34.54 (5.96)	30.95 (5.05)
BMI ≥ 30 (%)	7626 (26.8)	3705 (28.0)	123 (42.4)	2949 (24.6)	240 (25.2)	315 (37.6)	294 (26.0)
CKDEPI [mean, mL/min/1.73 m^2 (SD)]	81.12 (12.92)	82.12 (12.02)	83.87 (12.22)	80.38 (13.25)	79.39 (15.07)	83.24 (10.92)	76.56 (16.71)
MDRD [mean, mL/min/1.73 m^2 (SD)], missing 0.8%	59.19 (3.52)	59.40 (2.98)	59.06 (4.18)	59.11 (3.62)	58.51 (5.03)	59.58 (2.57)	57.79 (5.86)
Comorbidities, *N* (%)							
Ischemic stroke	443 (1.6)	212 (1.6)	1 (0.3)	176 (1.5)	17 (1.8)	9 (1.1)	28 (2.5)
Atherosclerosis	1994 (7.0)	909 (6.9)	12 (4.1)	836 (7.0)	97 (10.2)	51 (6.1)	89 (7.9)
Cerebrovascular disease	1644 (5.8)	750 (5.7)	17 (5.9)	698 (5.8)	65 (6.8)	36 (4.3)	78 (6.9)
Cancer	4351 (15.3)	1946 (14.7)	33 (11.4)	1907 (15.9)	165 (17.3)	104 (12.4)	196 (17.3)
Ischemic heart disease	3394 (11.9)	1547 (11.7)	25 (8.6)	1388 (11.6)	137 (14.4)	143 (17.1)	154 (13.6)
Dyslipidemia	17,814 (62.7)	8237 (62.3)	171 (59.0)	7617 (63.5)	546 (57.4)	520 (62.1)	723 (64.0)
Atrial fibrillation	2191 (7.7)	949 (7.2)	23 (7.9)	947 (7.9)	97 (10.2)	51 (6.1)	124 (11.0)
Hypertension	19,866 (69.9)	9219 (69.8)	208 (71.7)	8365 (69.7)	642 (67.4)	572 (68.3)	860 (76.1)
Heart failure	1465 (5.2)	615 (4.7)	17 (5.9)	623 (5.2)	89 (9.3)	44 (5.3)	77 (6.8)
Chronic respiratory diseases	3076 (10.8)	1234 (9.3)	21 (7.2)	1419 (11.8)	117 (12.3)	46 (5.5)	239 (21.2)
COPD	2464 (8.7)	1114 (8.4)	22 (7.6)	1020 (8.5)	123 (12.9)	77 (9.2)	108 (9.6)
Obesity	18,311 (64.4)	8753 (66.2)	283 (97.6)	7339 (61.2)	557 (58.5)	658 (78.6)	721 (63.8)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *DM2* type 2 diabetes mellitus, *DPP4i* dipeptidyl peptidase-4 inhibitors, *GLP1* glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *MDRD* Modification of Diet in Renal Disease, *SD* standard deviation, *SGLT2i* sodium-glucose cotransporter type 2 inhibitors

reached the HbA1c goal 42 days earlier (95% CI 34–49) than non-adherent patients. A similar effect was observed in combination therapies with sulfonylureas 54 (95% CI 44–64) days earlier, GLP1 66 days (9–122), DPP4i 54 days (40–68), and other hypoglycemic agents 50 days (18–82). In contrast, the time to HbA1c control was not statistically different in patients with the insulin and SGLT2i combination treatment.

We also performed the main analysis using only adherent patients and did not find significant changes. As seen with the entire population, the adjusted difference of RMST was

Table 2 Effects of second-line combination therapies on HbA1c control, adherence, and weight loss

	Overall	Metformin + sulfonylurea	Metformin + GLP1	Metformin + DPP4i	Metformin + insulin	Metformin + SGLT2i	Metformin + others
N	28,425	13,216	290	12,000	952	837	1130
HbA1c changes							
Absolute decrease from baseline [mean (SD)]	− 1.82 (1.44)	− 1.84 (1.37)	− 2.13 (1.30)	− 1.66 (1.30)	− 3.90 (2.24)	− 1.64 (1.36)	− 1.73 (1.32)
At 180 days [mean (SD)], missing 28.2%	− 1.66 (1.47)	− 1.65 (1.40)	− 1.99 (1.34)	− 1.51 (1.33)	− 3.76 (2.29)	− 1.54 (1.37)	− 1.55 (1.36)
≥ 0.5 decrease at 180 days (%)	17,312 (60.9)	8229 (62.3)	206 (71.0)	7018 (58.5)	676 (71.0)	505 (60.3)	678 (60.0)
Reached HbA1c goal (%)	18,594 (65.4)	8702 (65.8)	236 (81.4)	7854 (65.4)	587 (61.7)	501 (59.9)	714 (63.2)
Time to HbA1c control (≤ 7%)							
Days to HbA1c normalization (median [IQR])	362.00 [187.00, 772.00]	376.50 [186.00, 868.00]	235.50 [160.00, 378.75]	349.00 [188.00, 700.00]	342.00 [186.00, 770.50]	338.00 [176.00, 595.00]	427.50 [203.00, 907.25]
Median survival time from K–M curves (95% CI)	443 (430–457)	463 (441–486)	245 (228–270)	425 (411–441)	365 (38.3)	476 (413–538)	567 (504–637)
RMST truncated at 720 days (95% CI)	–	455 (451–459)	330 (304–357)	447 (442–452)	452 (435–469)	457 (440–475)	483 (469–498)
Duration of treatment							
Days exposed to initial metformin (median [IQR])	701.0 [375.0, 1156.0]	630.0 [335.0, 1051.0]	560.5 [288.8, 973.0]	812.0 [430.0, 1252.3]	554.5 [307.0, 1042.5]	741.0 [361.0, 1293.0]	698.00 [377.25, 1116.75]
At least 1 year (%)	21,492 (75.6)	9475 (71.7)	196 (67.6)	9668 (80.6)	662 (69.5)	626 (74.8)	865 (76.5)
Days exposed to second-line treatment (median [IQR])	679.0 [362.0, 720.0]	733.0 [380.0, 720.0]	512.0 [300.0, 720.0]	666.0 [364.0, 720.0]	557.0 [279.3, 720.0]	423.0 [219.0, 720.0]	620.5 [315.0, 720.0]
At least 1 year (%)	21,235 (74.7)	10,150 (76.8)	190 (65.5)	8989 (74.9)	630 (66.2)	482 (57.6)	794 (70.3)
Adherence							
MPR [mean (SD)]	87.76 (23.57)	85.75 (24.46)	80.04 (31.09)	92.23 (19.72)	70.17 (30.59)	85.39 (26.78)	82.37 (26.76)
Adherents, MPR ≥ 80% (%)	22,804 (80.2)	10,143 (76.7)	204 (70.3)	10,540 (87.8)	465 (48.8)	646 (77.2)	806 (71.3)

Table 2 (continued)

	Overall	Metformin + sulfonylurea	Metformin + GLP1	Metformin + DPP4i	Metformin + insulin	Metformin + SGLT2i	Metformin + others
Impact on weight (kg)							
Absolute difference at 720 days [mean (SD)], missing 52.3%	− 4.10 (5.84)	− 3.86 (5.61)	− 10.40 (11.53)	− 4.17 (5.57)	− 3.12 (6.80)	− 6.83 (7.18)	− 3.74 (5.63)
Reduced > 5% in weight (%), missing 52.3%	5370 (39.6)	2434 (37.4)	82 (64.1)	2245 (41.0)	171 (35.3)	233 (56.7)	205 (36.8)
Reduction > 5% of weight compared to metformin + sulfonylurea ($N = 13{,}556$)							
aOR (95% CI)[b]		Ref	2.63 (1.8–3.84)[a]	1.28 (1.19–1.38)[a]	0.95 (0.77–1.17)	2.27 (1.85–2.8)[a]	0.94 (0.79–1.14)

BMI body mass index, *CI* confidence interval, *DM2* type 2 diabetes mellitus, *DPP4i* dipeptidyl peptidase-4 inhibitors, *GLP1* glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *IQR* interquartile interval, *K-M* Kaplan–Meier, *MPR* medication possession ratio, *OR* odds ratio, *ref* reference, *RMST* restricted mean survival time, *SD* standard deviation, *SGLT2i* sodium-glucose cotransporter type 2 inhibitors

[a]Significant ($p < 0.001$)

[b]Adjusted by days under second-line treatment, baseline weight, days exposed to initial metformin treatment, years with DM2, age, smoking habits, weight, CKDEPI, cancer, ischemic heart disease, chronic respiratory failure, and obesity

significantly different in all therapies except for SGLT2i. The adherence is reducing the time to reach the HbA1c goal but is not changing the results in the comparison with sulfonylureas (Table 3).

3.4 Secondary Outcomes

During the first 2 years, we observed a weight loss (reduction > 5% respect to baseline) in 5370 (39.6%) of the patients. The combination of metformin and a sulfonylurea reached this reduction in 2434 (37.4%) patients, which was the same for other hypoglycemic agents and insulin combinations, although the percentages were higher in the other treatments. The odds of losing more than 5% of weight were significantly higher in combinations with GLP1, OR = 2.63 (95% CI 1.8–3.84), DPP4i, OR = 1.28 (1.19–1.38), and SGLT2i, OR = 2.27 (1.85–2.8) (Table 2).

The duration of previous single metformin treatment was a median 701 (IQR = 375, 1156) days and 75.6% were treated during at least 1 year before the addition. No significant differences between treatments were observed (Table 2). Regarding the exposition period after the second-line therapy, the median number of days was, overall, 679 days (IQR = 362, 720). The sulfonylurea prescriptions were longer, 733 days (IQR = 380, 720), while patients receiving SGLT2i maintained the combined treatment for less time compared with the other treatments, 423 days (IQR = 219, 720).

The average impact on weight was also positive regardless of treatment (Table 2). The overall mean weight reduction at 720 days was 4.10 kg (SD = 5.84) higher in GLP1 and SGLT2i combinations with a mean reduction of 10.40 (SD = 11.5) and 6.83 (SD = 7.2) kg, respectively.

4 Discussion

We analyzed the impact of second-line treatments in HbA1c and weight in 28,425 patients with diabetes and compared them with the combination of metformin and sulfonylureas. In our population, patients receiving metformin and any combination therapy achieved control for HbA1c in less than a year (in median), and GLP1 and insulin combinations reached the control earlier than the combination with sulfonylureas.

The effect of adherence on HbA1c control was also measured for all type of combinations comparing adherent versus non-adherent patients. For all groups except insulins and SGLT2i, adherent patients reached the HbA1c goal earlier than non-adherent patients. Overall, the adherence to antidiabetic drugs was high, which could be explained by the patient perception of disease as we focused on patients with HbA1c uncontrolled DM2 [32]. This was not true with insulins, which includes rapid/short- and intermediate-acting insulins, and their use differs from long-acting insulins. Not having a fixed-dose use is underestimating the measure of adherence [33].

	Median survival (CI 95%)*	RMST (CI 95%)*	Difference RMST (CI 95%)	P-value	Adjusted difference RMST** (CI 95%)	P-value
Metformin+Sulfonylurea	463 (441 to 486)	455 (451 to 459)	ref	-	ref	-
Metformin+GLP1	245 (228 to 270)	330 (304 to 357)	-120.91 (-147.02, -94.81)	<.001	-126.26 (-152.49, -100.03)	<.001
Metformin+DPP4i	425 (411 to 441)	447 (442 to 452)	-0.80 (-7.05, 5.44)	0.801	14.81 (8.61, 21.01)	<.001
Metformin+Insulin	446 (382 to 537)	452 (435 to 469)	-80.3 (-99.54,-61.07)	<.001	-69.18 (-88.07,-50.3)	<.001
Metformin+SGLT2i	476 (413 to 538)	457 (440 to 475)	7.49 (-10.60, 25.58)	0.417	5.42 (-12.32, 23.16)	0.549
Metformin+others	567 (504 to 637)	483 (469 to 498)	31.08 (16.15, 46.01)	<.001	39.01 (24.08, 53.95)	<.001

** From the Kaplan-Meier curves*

*** Adjusted by Days under 2nd-line treatment, Baseline HbA1c, Days under previous metformin treatment, Years with DM2, Age, Smoking habits, Weight, CKDEPI, Cancer, Ischemic heart disease, Chronic respiratory failure and Obesity*

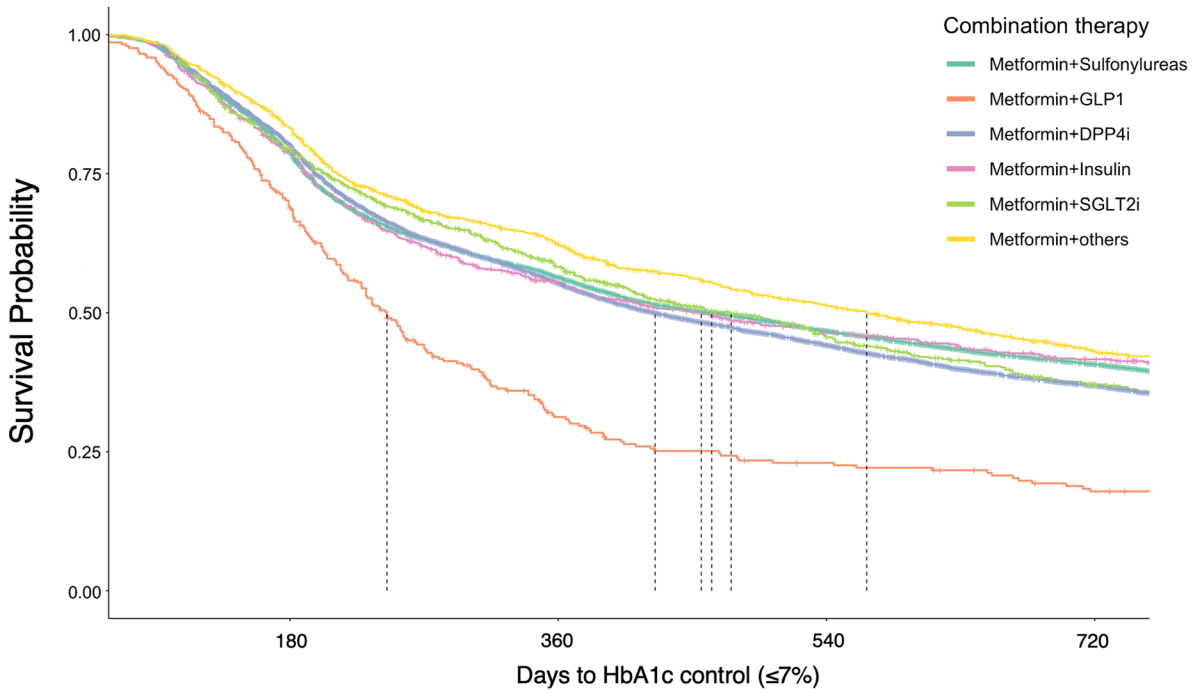

Fig. 2 Kaplan–Meier and restricted mean survival time (RMST) for the time to glycated hemoglobin (HbA1c) control (≤7%) by combination treatment over 2 years. *CI* confidence interval, *DM2* type 2 diabetes mellitus, *DPP4i* dipeptidyl peptidase-4 inhibitors, *GLP1* glucagon-like peptide-1, *ref* reference, *SGLTi* sodium-glucose cotransporter type 2 inhibitors

In adherent patients, all combinations showed an earlier achievement of the HbA1c goal except for the SGLT2i group compared to sulfonylureas. However, this combination together with GLP1 and DPP4i groups had higher probabilities to reduce more than 5% of the weight.

4.1 Bibliography Comparison

Vlacho et al. found a trivial effect in HbA1c reductions between groups [30]. Although in our study comparative effect sizes have not been assessed, we highlighted that all groups, except for the SGLT2i, reached HbA1c control faster than those receiving the sulfonylurea combination. The *N* from our study (43,068) differs drastically from the study by Vlacho et al. (75,808) probably owing to differences in the study design and periods selected, as our study analyses more recent data, and this could explain the discordances found. The proportion of patients who reached the HbA1c goal was higher in our study but the proportion of patients with a decrease ≥0.5 at 180 days was lower. In both studies, the sulfonylurea group had a higher proportion of users reaching the target of HbA1c below 7%. Days to HbA1c normalization were similar in both studies, and significant weight reductions were found for DPP4i and SGLT2i groups [30].

Regarding adherence to second-line therapy, Sicras-Mainar et al. conducted an analysis in 2008–9 but this was not comparable to our study because of the population characteristics, methods, and differences between period studies [31]. In Vlacho et al., they also found high MPR levels but lower than in our study [3]. The sulfonylurea group had the lowest proportion of adherent patients (MPR > 80%), and the time exposed to second-line treatment or persistence in our study was higher in all groups. These differences can be related

Table 3 RSMT to HbA1c control by adherence and second-line combination therapy

Adherent vs non-adherent patients ($N = 28,189$)	RMST (95% CI)[a]		Adjusted diff RMST (95% CI)[b]	*P*-value
	Adherents	Non-adherents		
All patients	438 (434–441)	507 (500–514)	−41.89 (−49.34, −34.45)	< 0.001
Metformin + sulfonylurea ($N = 13,117$)	437 (432–442)	511 (502–520)	−54.29 (−64.43, −44.14)	< 0.001
Metformin + GLP1 ($N = 289$)	306 (277–336)	388 (335–442)	−65.6 (−122.1, −9.09)	0.023
Metformin + DPP4i ($N = 11,901$)	437 (432–442)	520 (508–533)	−54.09 (−67.71, −40.47)	< 0.001
Metformin + insulin ($N = 938$)	456 (432–479)	454 (430–477)	5.15 (−28.68, 38.98)	0.765
Metformin + SGLT2i ($N = 830$)	445 (425–465)	491 (455–527)	−21.31 (−61.02, 18.41)	0.293
Metformin + others ($N = 1114$)	468 (451–486)	523 (496–550)	−49.73 (−81.85, −17.61)	0.002
Only adherent patients ($N = 22,804$)	*N*	RMST (95% CI)[a]	Adjusted diff RMST (95% CI)[b]	*P* value
Metformin+sulfonylurea	10,143	438 (433–443)	Ref	–
Metformin+GLP1	204	305 (276–335)	−129.73 (−159.46, −100.01)	< 0.001
Metformin+DPP4i	10,540	437 (432–442)	19.5 (12.67, 26.32)	< 0.001
Metformin+insulin	465	455 (431–479)	−63.63 (−89.16, −38.1)	< 0.001
Metformin+SGLT2i	646	446 (426–466)	12.59 (−7.79, 32.97)	0.226
Metformin+others	806	468 (450–485)	36.97 (19.5, 54.43)	< 0.001

CI confidence interval, *diff* difference, *DM2* type 2 diabetes mellitus, *DPP4i* dipeptidyl peptidase-4 inhibitors, *GLP1* glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *RMST* restricted mean survival time, *SGLT2i* sodium-glucose cotransporter type 2 inhibitors

[a]Estimation from Kaplan–Meier curves

[b]Adjusted by days under second-line treatment, baseline Hb1Ac, days exposed to initial metformin treatment, years with DM2, age, smoking habits, weight, CKDEPI, cancer, ischemic heart disease, chronic respiratory disease, and obesity

to divergences in the methodology but, independently on how this was measured, a higher adherence was associated with greater glycemic control [34–36], lower ratios on some micro-macrovascular outcomes [37], and with lower health-care costs [38, 39].

In our database, adherent patients reduced the time to reach HbA1c control with the GLP1 combination followed by insulins. This is in line with the clinical guidelines, as GLP1 is indicated for an uncontrolled obese population with diabetes while insulins are for general uncontrolled patients with diabetes [15].

4.2 Limitations and Strengths

Among the limitations, the GLP1 group in our context is a pharmacological treatment indicated in combination with metformin and reimbursed only for patients with obesity in the Spanish Health Service. It is a non-comparable group because of the selecting bias, but our aim was to show the general practice in our context. Insulin-treated patients may not be comparable either, as they are usually patients with poor glycemic control. The sulfonylurea group is the second-line gold standard treatment clinically, thus it was chosen as the reference group for the statistical comparison [15]. Another limitation of our study is that we were unable to consider hypoglycemic events because of poor recording in the Catalonia primary care system. Given the high prevalence of sulfonylureas in our study population, which are known to carry a risk of hypoglycemia, it is important to interpret our results with this limitation in mind. The strengths of our study are the large number of patients, complete sociodemographic data, and adherence to each treatment group.

We have used the smooth algorithm to determine the electronic drug records. It allowed us to automate the data management step and model different aspects of drug exposure. With the algorithm, we obtained all patients who had received the second-line combination treatment, determined treatment initiation, its duration, possible treatment changes or interruptions, and calculated the adherence.

Adherence in databases like SIDIAP is difficult to assess. We have pharmacy invoice records that are not linked to electronic prescriptions, and extra work is required to link both databases. We described a process to easily calculate an approximation to the MPR that is consistent with the official data reported in our region but different to the MRP levels reported by Vlacho et al. [3]. This is a common example of how, in pharmacoepidemiologic studies with similar characteristics, each research team has a unique method to assess drug exposure that may induce biases and less comparable results. We tried to overcome this by using an automatic algorithm that brings additional value to our study [23]. Future research should include a longer follow-up time and focus the analysis on

adverse effects such as bleeding or ictus after the addition of second-line treatment.

5 Conclusions

Second-line treatments reached the HbA1c goal for most of the patients and GLP1 and insulin combinations reached the control earlier than the combination with sulfonylureas. Adherence had a significant effect on reducing the time to HbA1c control in all combinations except for SGLT2i. Weight reduction was also achieved earlier in GLP1 therapy and the SGLT2i combination was able to achieve significant reductions in weight.

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Declarations

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Conflict of interest Dan Ouchi, Carles Vilaplana-Carnerero, Ramon Monfà, Maria Giner-Soriano, Ana Garcia-Sangenís, Ferran Torres, and Rosa Morros have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study was approved by the Primary Care Research and Ethics Committee of the Research Institute IDIAP Jordi Gol, Barcelona, Spain (reference number, 21/026-P, 24 February, 2021).

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors contributed to the study design. R.Mon., C.V., A.G., M.G.S., and R.Mor. conceived the study. M.G.S., R.Mon., C.V., and D.O. collected the data. D.O. performed the statistical analyses. D.O., A.G., R.Mon., C.V., M.G.S., and R.Mor. were involved in the interpretation of the data. D.O. and C.V. wrote the manuscript and designed the tables and figures. All authors critically revised the report and approved the final version to be submitted for publication. The corresponding author confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al KJ. Epidemiology of type 2 diabetes: global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020;10(1):107.
2. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). Endocrinologist. 1999;9(6):503.
3. Vlacho B, Mata-Cases M, Mundet-Tudurí X, Vallès-Callol JA, Real J, Farre M, et al. Analysis of the adherence and safety of second oral glucose-lowering therapy in routine practice from the Mediterranean area: a retrospective cohort study. Front Endocrinol (Lausanne). 2021;12(Jul):1–8.
4. Lind M, Pivodic A, Cea-Soriano L, Nerman O, Pehrsson NG, Garcia-Rodriguez LA. Changes in HbA1c and frequency of measuring HbA1c and adjusting glucose-lowering medications in the 10 years following diagnosis of type 2 diabetes: a population-based study in the UK. Diabetologia. 2014;57(8):1586–94.
5. Huang ES, Davis AM. Glycemic control in older adults with diabetes mellitus. JAMA. 2015;314:1509–10.
6. Care D, Supp SS. 6. Glycemic targets: standards of medical care in diabetes: 2022. Diabetes Care. 2022;45(1):83–96.
7. Type 2 diabetes in adults: management. London: National Institute for Health and Care Excellence (NICE); 2022. (NICE Guideline, No. 28.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK553486/.
8. Mata M, Cos FX, Morros R, Diego L, Barrot J, Berengué M, et al. Pautes per a l'harmonització del tractament farmacològic de la diabetis mellitus tipus 2. Barcelona: Servei Català de la Salut. Departament de Salut. Generalitat de Catalunya; 2017. (Programa d'harmonització farmacoterapèutica de medicaments en l'àmbit de l'atenció primària i comunitària del Servei Català de la Salut; 01/2017).
9. Xu Y, Yang Z, Lin H, Shen P, Wang H, Zhan S. Long-term patterns of antidiabetic medication use in patients with type 2 diabetes. Med Sci Monit. 2018;24:8707.
10. Care D, Suppl SS. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes: 2022. Diabetes Care. 2022;45(Jan):S125–43.
11. Mamza J, Mehta R, Donnelly R, Idris I. Important differences in the durability of glycaemic response among second-line treatment options when added to metformin in type 2 diabetes: a retrospective cohort study. Ann Med. 2016;48(4):224–34.
12. McIntosh B, Cameron C, Singh SR, Yu C, Dolovich L, Houlden R. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. Open Med. 2012;6(2):e62.
13. New Drugs for Type 2 Diabetes: Second-Line Therapy — Science Report [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017. (CADTH Therapeutic Review, No. 4.1b.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK531904/.

14. Shin, JI. Second-line glucose-lowering therapy in type 2 diabetes mellitus. Curr Diab Rep. 2019;19:54. https://doi.org/10.1007/s11892-019-1171-0.
15. Fau E, Mata-Cases M, Morros R, Pellicer MA, Ricart W, Vallès JA, et al. Pautes per al tractament farmacològic de la diabetis mellitus tipus 2. Barcelona: Agència de Qualitat i Avaluació Sanitàries de Catalunya; 2013. https://hdl.handle.net/11351/1403.
16. Qian D, Zhang T, Zheng P, Liang Z, Wang S, Xie J, et al. Comparison of oral antidiabetic drugs as add-on treatments in patients with type 2 diabetes uncontrolled on metformin: a network meta-analysis. Diabetes Ther. 2018;9(5):1945–58.
17. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299–306.
18. WHO. ICD-10 version. Geneva: WHO; 2019.
19. Anonymous. WHO ATC/DDD Index 2020. WHO Collaborating Centre for Drugs Statistics Methodology. 2020.
20. Bolíbar B, Fina Avilés F, Morros R, Garcia-Gil Mdel M, Hermosilla E, Ramos R, Rosell M, Rodríguez J, Medina M, Calero S, Prieto-Alhambra D; Grupo SIDIAP. Base de datos SIDIAP: la historia clínica informatizada de Atención Primaria como fuente de información para la investigación epidemiológica [SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research]. Med Clin (Barc). 2012;138(14):617–21. Spanish. https://doi.org/10.1016/j.medcli.2012.01.020.
21. CatSalut. Servei Català de la Salut. Conjunt mínim bàsic de dades (CMBD). 2022. http://catsalut.gencat.cat/ca/proveidors-professionals/registres-catalegs/registres/cmbd/. Accessed 14 July 2022.
22. Catalan Agency for Health Quality and Evaluation (AQuAS). Updated SARS-CoV-2 data. 2022. https://aquas.gencat.cat/. Accessed 14 July 2022.
23. Ouchi D, Giner-Soriano M, Gómez-Lumbreras A, Vedia Urgell C, Torres F, Morros R. SMOOTH algorithm: an automatic method to estimate the most likely drug combination in electronic health records. Development and validation study. JMIR Preprints. 2022.
24. Kloecker DE, Davies MJ, Khunti K, Zaccardi F. Uses and limitations of the restricted mean survival time: Illustrative examples from cardiovascular outcomes and mortality trials in type 2 diabetes. Ann Intern Med. 2020;172(8):541–52.
25. A'Hern RP. Restricted mean survival time: an obligatory end point for time-to-event analysis in cancer trials? J Clin Oncol. 2016;34(28):3474–6.
26. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. 2011;30(19):2409–21.
27. Tian L, Zhao L, Wei LJ. Predicting the restricted mean event time with the subject's baseline covariates in survival analysis. Biostatistics. 2014;15(2):222–33.
28. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Development Core Team; 2017.
29. Dessau RB, Pipper CB. "R": project for statistical computing. Ugeskr Laeger. 2008.
30. Vlacho B, Mundet-Tudurí X, Mata-Cases M, Vallès-Callol JA, Real J, Farré M, et al. Analysis of the effectiveness of second oral glucose-lowering therapy in routine clinical practice from the Mediterranean area: a retrospective cohort study. Diabetes Res Clin Pract. 2021;171:1–10.
31. Sicras-Mainar A, Font-Ramos B, Roldán-Suárez C, Navarro-Artieda R, Ibáñez-Nolla J. Caracterización y costes asociados al perfil del paciente con diabetes tipo 2 en tratamiento con metformina al que se le añade un segundo fármaco antidiabético oral: estudio de base poblacional. Endocrinol Nutr. 2013;60(10):557–69.
32. Gil-Girbau M, Aznar-Lou I, Peñarrubia-María MT, Moreno-Peral P, Fernández A, Bellón JÁ, et al. Reasons for medication non-initiation: a qualitative exploration of the patients' perspective. Res Soc Admin Pharm. 2020;16(5):663–72.
33. Sarbacker GB, Urteaga EM. Adherence to insulin therapy. Diabetes Spectr. 2016;29(3):166–70.
34. Kim N, Agostini JV, Justice AC. Refill adherence to oral hypoglycemic agents and glycemic control in veterans. Ann Pharmacother. 2010;44(5):800–8. https://doi.org/10.1345/aph.1M570.
35. Ibrahim AO, Agboola SM, Elegbede OT, Ismail WO, Agbesanwa TA, Omolayo TA. Glycemic control and its association with sociodemographics, comorbid conditions, and medication adherence among patients with type 2 diabetes in southwestern Nigeria. J Int Med Res. 2021. https://doi.org/10.1177/03000605211044040.
36. Sánchez-Hernández MS, et al. Impact of adherence to Mediterranean diet and/or drug treatment on glycaemic control in type 2 diabetes mellitus patients: DM2-CUMCYL study. Prim Care Diab. 2020. https://doi.org/10.1016/j.pcd.2020.06.008.
37. Evans M, Engberg S, Faurby M, Fernandes JDDR, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: a systematic literature review. Diabetes Obes Metab. 2022;24(3):377–90. https://doi.org/10.1111/dom.14603.
38. Balkrishnan R, Rajagopalan R, Camacho FT, Huston SA, Murray FT, Anderson RT. Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. Clin Ther. 2003;25(11):2958–71. https://doi.org/10.1016/S0149-2918(03)80347-8.
39. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43(6):521–30. https://doi.org/10.1097/01.mlr.0000163641.86870.af.