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Analysis of the effectiveness of second oral glucose-lowering therapy in routine clinical practice from the mediterranean area: A retrospective cohort study

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ABSTRACT

Aim: To compare the changes in HbA1c, the effect on body weight or both combined after the addition of a DPP-4i, SGLT-2i, or sulfonylureas (SU) to metformin in real-world condition.

Methods: We used a primary care SIDIAP database. The included subjects were matched by propensity score according to baseline age, sex, HbA1c, weight, inclusion date, diabetes duration, and kidney function.

Results: Mean absolute HbA1c reduction was: 1.28% for DPP4i, 1.29% for SGLT2i and 1.26% for SU. Mean weight reduction was: 1.21 kg for DPP4i, 3.47 kg for SGLT2i and 0.04 kg for SU. The proportion of patients who achieved combined target HbA1c (≥0.5%) and weight (≥3%) reductions after the addition of DPP-4i, SGLT-2i or SU, was: 24.2%, 41.3%, and 15.2%, respectively. Small differences in systolic blood pressure reduction (1.07, 3.10 and 0.96 mmHg, respectively) were observed in favour of SGLT-2i. Concerning the lipids, we

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observed small differences, with an HDL-cholesterol increase with SGLT-2i.
Conclusion: Our real-world study showed that the addition of SGLT-2i to metformin was associated with greater reductions in weight and the combination target of weight-HbA1c compared to SU and DPP4 inhibitors. However, similar hypoglycaemic effectiveness was observed among the three-drug classes.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous condition characterized by progressive deterioration of glycaemic control that with time usually requires the combination of several antidiabetic drugs with different mechanisms of action. Additionally, T2DM carries a high risk for cardiovascular diseases (CVD) due to cardiovascular risk factors including overweight, hypertension, smoking, family history of premature coronary disease, chronic kidney disease, albuminuria and dyslipidaemia [1].

Most current clinical guidelines recommend metformin as the drug of choice for the initial pharmacological treatment of T2DM. However, the recommendations for second-line therapy in case of contraindications or intolerance to metformin are less specific, and the selection of a drug class is usually based on patient-specific treatment goals and preferences, presence of comorbidities, drug efficacy, and safety profile [1–3]. In clinical practice, there is often a need for the addition of second-line therapies to improve glycaemic control and to reduce risks from macrovascular and microvascular complications. Three classes of oral antidiabetics, namely dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and sulfonylureas (SU) are the most widely prescribed second-line oral therapy options as add-on therapy to metformin [1,4].

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 SGLT-2i showed the additional benefit on body weight reduction [5]. However, subjects included in randomized clinical trials are not representative of the population heterogeneity and the real healthcare conditions (real-world data evidence) due to the strict eligibility criteria [6,7]. Moreover, health policy variations across countries (e.g., national reimbursement strategies), local professional expertise, physician's and patient's personal choice, and study settings may be associated with different patterns of prescription of second-line treatment [8–10]. In view of these limitations, routine data from primary healthcare databases could provide relevant information on the effectiveness of intensification with a second antidiabetic drug.

The primary objective of the current study was to compare the changes in glycated haemoglobin (HbA1c) and the effect on body weight following the addition of DPP-4i, SGLT-2i, or SU as second-line therapies to metformin in a primary care population with T2DM.

2. Material and methods

2.1. Study design and setting

We designed a matched retrospective cohort study with a follow-up period of up to 24-months. Data were obtained for the period between January 1st, 2010, and December 31st, 2017. We used the primary care SIDIAP (The Information System for the development of Primary Care Research) database [11], which contains anonymized data from electronic medical records of the people attending 279 Primary Health Care Centres (Spain) of the Institut Català de la Salut (ICS). SIDIAP database has been extensively used for national and international epidemiologic and pharmacoepidemiological studies and has been validated in primary care [12,13].

2.2. Inclusion and exclusion criteria

Subjects were included if they were 18 years and older, had been diagnosed with T2DM (ICD-10 codes E11), and had HbA1c values $\geq$ 7% (53 mmol/mol). The inclusion date for each cohort was defined by the day of the addition of second-line therapy for the first time to metformin. We excluded subjects with a code for other types of diabetes (such as diabetes mellitus type 1, gestational or secondary; ICD-10 codes: E8, E9, E10, O24, E13), as well as those with missing baseline values of HbA1c or weight. The users in each cohort were followed for 24 months or up to premature discontinuation of the study, defined as death, treatment switch, the addition of a third antidiabetic treatment, transfer to non-ICS centres or end date 31/12/2017. No minimum follow-up time was established.

2.3. Study variables

Baseline clinical and medication data were extracted for the inclusion date or, failing this, for the nearest date prior to the inclusion (maximum of 12 months apart). We collected information on (1) demographic characteristics, including age, gender, and smoking habit; (2) the presence of comorbidities, including heart failure, peripheral vascular disease, ischemic heart disease, hypertension, hyperlipidaemia, acute/chronic pancreatitis, chronic kidney disease, relevant liver diseases, chronic obstructive pulmonary disease (COPD), diabetic neuropathy, diabetic retinopathy, and relevant mental disorders; (3) variables related to T2DM, including diabetes duration and HbA1c value; and (4) additional clinical variables such as body weight, BMI, blood pressure (BP), lipid profile,

estimated glomerular filtration rate (eGFR; CDK-EPI equation), and albumin/creatinine ratio.

2.4. Study outcomes

For each cohort (i.e., addition of DPP-4i, SGLT-2i, or SU), we defined the primary study outcomes as the percentage of patients with a reduction of HbA1c of at least 0.5% (5.5 mmol/-mol), a weight reduction of at least 3%, or both (main composite binary outcome). The reductions in the HbA1c value and body weight were calculated as change between the baseline and after three months following the addition of second-line therapy (with a maximum of 24 months of follow-up); we calculated percentage of users reaching target of HbA1c below 7% (53 mmol/mol). Secondary outcomes included changes in systolic and diastolic blood pressure (SBP and DBP) and lipid profile.

2.5. Statistical analysis

2.5.1. Propensity score matching

The basal characteristics of the three groups were assessed for homogeneity and, based on the observed differences; they were matched to ensure the balance of covariates. Baseline weight, HbA1c, sex, age, diabetes duration, year of inclusion, and kidney function were used as the matching variables. Since the SGLT-2i group was the least represented cohort, for each user in this group we selected participants from the other two cohorts. This was done in two steps, firstly matching against the DPP-4i group, and thereafter against the SU group. Matching was done by the "Nearest Neighbor algorithm" (caliper = 0.01), using the "MatchIt" library of the R (v3.6.1) statistical package [14,15].

2.5.2. Main analysis

Mean, median, and standard deviation for continuous variables, frequency and percentage for categorical variables, were used to describe the baseline characteristics of the cohorts. We calculated the average changes from baseline as well as the proportion of patients that achieved the reduction of HbA1c $\geq$ 0.5% or weight reduction $\geq$ 3%. The composite outcome (reduction in both HbA1c $\geq$ 0.5% and weight $\geq$ 3%) was analysed using logistic regression and the findings summarized as absolute percentage risk differences and odds ratios (ORs), with confidence intervals (CI). As a sensitivity analysis, adjusted estimates were calculated with multivariate models (multivariate logistic for the binary outcome and linear regression models for continuous response) including the following baseline variables: weight, HbA1c, age, diabetes duration, year of inclusion, eGFR and number of comorbidities. All pairwise comparisons were conducted between groups (i.e., no reference group), where the significance individual level was prefixed at α = 0.017 (familywise significance level = 5%) and individual confidence level at 0.98 (familywise confidence level = 95%). The statistical analyses were performed using R3.6.1 (https://www.r-project.org/).

2.5.3. Missing data and sensitivity analysis

Incomplete cases during the follow-up period were handled using multiple imputation cases analysis (MICA). For this, we draw 10 resamples with the "mice-package" for the R3.6.0 statistical software [16]. The estimates of the parameters for each imputed data set were combined using Rubin's rules [15]. We then conducted a sensitivity analysis comparing the results obtained with only subjects who had all variables observed (complete cases analysis [CCA]) vs those obtained with the MICA approach.

2.5.4. Effect size estimate

To assess the magnitude of the effect of each treatment on the outcomes, we calculated the effect size through the standardized mean differences between drug classes. This analysis was conducted with "parameters"[17] and "effect size"[18] for the R3.6.1 statistical software.

2.6. Ethical review

The study was approved by the Ethics Committee of the Primary Health Care University Research Institute (IDIAP) Jordi Gol, Barcelona (P17/205).

3. Results

The flow chart of the study is shown in Supplementary Fig. 1. A total of 75,808 patients with T2DM initiating a second treatment in addition to metformin during the study period met the study inclusion criteria: 27,878 (36.7%) initiated a DPP-4i, 2,198 (2.89%) an SGLT-2i and 45,732 (60.3%) a SU. After the matching procedure for baseline variables, the three treatment groups were well balanced (Supplementary Fig. 2), with 6,310 subjects available overall for comparisons and follow-up: 2,124 for DPP-4i, 2,124 for SGLT-2i and 2,062 for SU. Table 1 provides the baseline characteristics of the study population. Across treatment groups, the mean age ranged between 60.5 and 61.2 years, the mean T2DM duration between 7.28 and 7.89 years, and the mean HbA1c before treatment addition varied between 8.75% and 8.78%. The average length of follow-up was similar between treatment groups, with a median of 350, 472, and 381 days for DPP-4i users, SGLT-2i users, and SU users, respectively (Supplementary Table 1). In combination to metformin, the most frequently prescribed DPP-4i was sitagliptin (45.0%), and for SGLT-2i it was dapagliflozin (25.4%), while for SU it was gliclazide (83.2%) (Supplementary Table 5).

3.1. Changes from baseline in HbA1c value and body weight

The composite main outcome (HbA1c reduction of at least 0.5%, weight reduction of at least 3%, or both) was achieved more frequently by SGLT-2i users (41.3%) than by DPP-4i users (24.2%) and SU users (15.2%) (Fig. 1 and Supplementary Table 2). When comparing the drug cohorts, we observed that the likelihood of achieving this composite outcome was 2.2-fold higher among SGLT-2i users compared to DPP-4i users

Table 1 – Baseline characteristics of the study population for users initiating second add-on treatment to metformin with DPP-4i, an SGLT-2i, or an SU.

Characteristic	MET + DPP-4i (n = 2124)	MET + SGLT-2i (n = 2124)	MET + SU (n = 2062)
Age, mean (SD), years	61.2 (12.1)	60.5 (11.1)	60.6 (12.0)
Gender, n (%)			
Female	892 (42.0)	924 (43.5)	868 (42.1)
Male	1232 (58.0)	1200 (56.5)	1194 (57.9)
Smoking habit, n (%)			
Non-smoker	1010 (47.9)	957 (45.3)	996 (48.5)
Ex-smoker	700 (33.2)	758 (35.9)	616 (30.0)
Smoker	398 (18.9)	398 (18.8)	440 (21.4)
Clinical variables			
Diabetes duration, mean (SD), years	7.64 (7.12)	7.89 (6.67)	7.28 (5.89)
HbA1c, mean (SD), %	8.78 (1.48)	8.77 (1.49)	8.75 (1.39)
HbA1c, mean (SD), (mmol/mol)	72.3 (15.9)	72.5 (16.2)	72.4 (16.2)
Weight, mean (SD), kg	89.2 (18.5)	91.4 (17.5)	89.5 (18.2)
BMI, mean (SD), kg/m^2	32.8 (5.72)	33.9 (5.80)	32.8 (5.87)
Blood pressure, mean (SD), mmHg			
SBP	134 (14.4)	133 (13.8)	134 (13.5)
DBP	78.8 (10.2)	78.0 (9.55)	79.4 (9.46)
Renal function			
Albumin / creatinine ratio, mean (SD)	57.1 (217)	72.0 (254)	43.4 (145)
eGFR, mean (SD), mL/min/1.73 m^2	81.2 (13.4)	81.0 (13.0)	82.2 (12.9)
eGFR groups (mL/min/1.73 m^2), n (%)			
<30	5 (0.24)	6 (0.28)	10 (0.48)
30–44	31 (1.46)	36 (1.69)	34 (1.65)
45–59	182 (8.57)	155 (7.30)	140 (6.79)
≥60	1871 (88.1)	1892 (89.1)	1845 (89.5)
Lipid profile, mean (SD), mg/dL			
Total Cholesterol	191 (45.2)	186 (44.2)	193 (41.4)
HDL-cholesterol	46.7 (11.3)	46.2 (12.1)	46.9 (11.5)
LDL-cholesterol	106 (33.3)	102 (34.1)	108 (33.0)
Triglycerides	207 (152)	216 (180)	207 (167)
Number of comorbidities, mean (SD)	1.86 (1.22)	2.05 (1.25)	1.76 (1.16)
Comorbidities, n (%)			
Heart failure	89 (4.19)	104 (4.90)	73 (3.54)
Peripheral vascular disease	79 (3.72)	116 (5.46)	77 (3.73)
Stroke	125 (5.89)	156 (7.34)	99 (4.80)
Ischemic heart disease	205 (9.65)	334 (15.7)	164 (7.95)
Hypertension	1426 (67.1)	1527 (71.9)	1363 (66.1)
Hyperlipidaemia	1220 (57.4)	1318 (62.1)	1193 (57.9)
Diabetic neuropathy	77 (3.63)	155 (7.30)	42 (2.04)
Diabetic retinopathy	179 (8.43)	350 (16.5)	116 (5.63)
Acute/chronic pancreatitis	29 (1.37)	53 (2.50)	19 (0.92)
COPD	160 (7.53)	167 (7.86)	136 (6.60)
Renal failure	159 (7.49)	140 (6.59)	124 (6.01)
Relevant liver disease (excluding steatosis)	75 (3.53)	86 (4.05)	47 (2.28)
Major Mental disorders	431 (20.3)	422 (19.9)	375 (18.2)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CDK-EPI formula); HbA1c, glycated haemoglobin A1c; SBP, systolic blood pressure; SD, standard deviation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; COPD, chronic obstructive pulmonary disease.

(OR2.23, 98% CI: 1.7, 2.9) and 3.9-fold higher than in SU users (OR0.25, 98% CI 0.4, 0.8), and it was 1.7 -fold higher in DPP-4i users than in SU users (OR0.56, 98% CI: 0.2, 0.3) (Fig. 1).

The proportion of patients achieving a reduction in HbA1c ≥ 0.5%, considered as a single outcome, was very similar across drug classes (71.6% for DPP-4i and 72.5% for SGLT-2i, and 74.1% for SU; Fig. 1 and Supplementary Table 2). Similar tendency across the cohorts was observed for users reaching target of HbA1c < 7%. The mean in HbA1c values were similar across the cohorts with a reduction of 1.28%, 1.29%, and 1.26% for DPP-4i, SGLT-2i, and SU, respectively (Fig. 2A; Supplementary Table 2). As such, we did not observe significant differences between drug classes when we compared the likelihood of a reduction of ≥ 0.5% in HbA1c from baseline or for users reaching target of HbA1c < 7% (Fig. 1; Supplementary Table 3).

Regarding body weight as a secondary outcome, SGLT-2i was the drug class that was associated with the greatest proportion of patients achieving a ≥ 3% reduction (53.6%; Fig. 1; Supplementary Table 2) and also the drug associated with the greatest decrease from baseline (−3.47 kg) (Fig. 2B). In contrast, the mean change in weight with DPP-4i was −1.21 kg

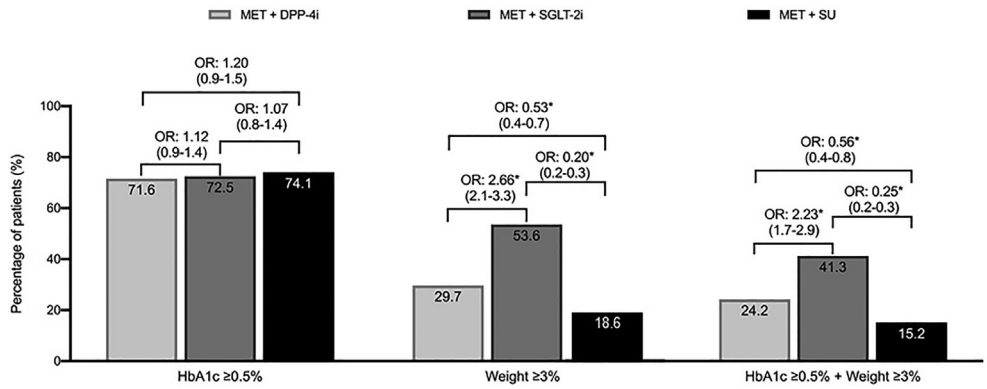

Fig. 1 – Percentage of patients that achieved the main outcomes for each treatment group and adjusted comparisons (odds ratio [OR] and 98% CI) between drug classes. *Statistically significant p-value after multiple testing correction (<0.017) HbA1c, glycated haemoglobin; IDPP4, inhibitors dipeptidyl peptidase-4; MET, metformin; SGLT-2i, inhibitors sodium/glucose cotransporter 2; SU, sulphonylureas.

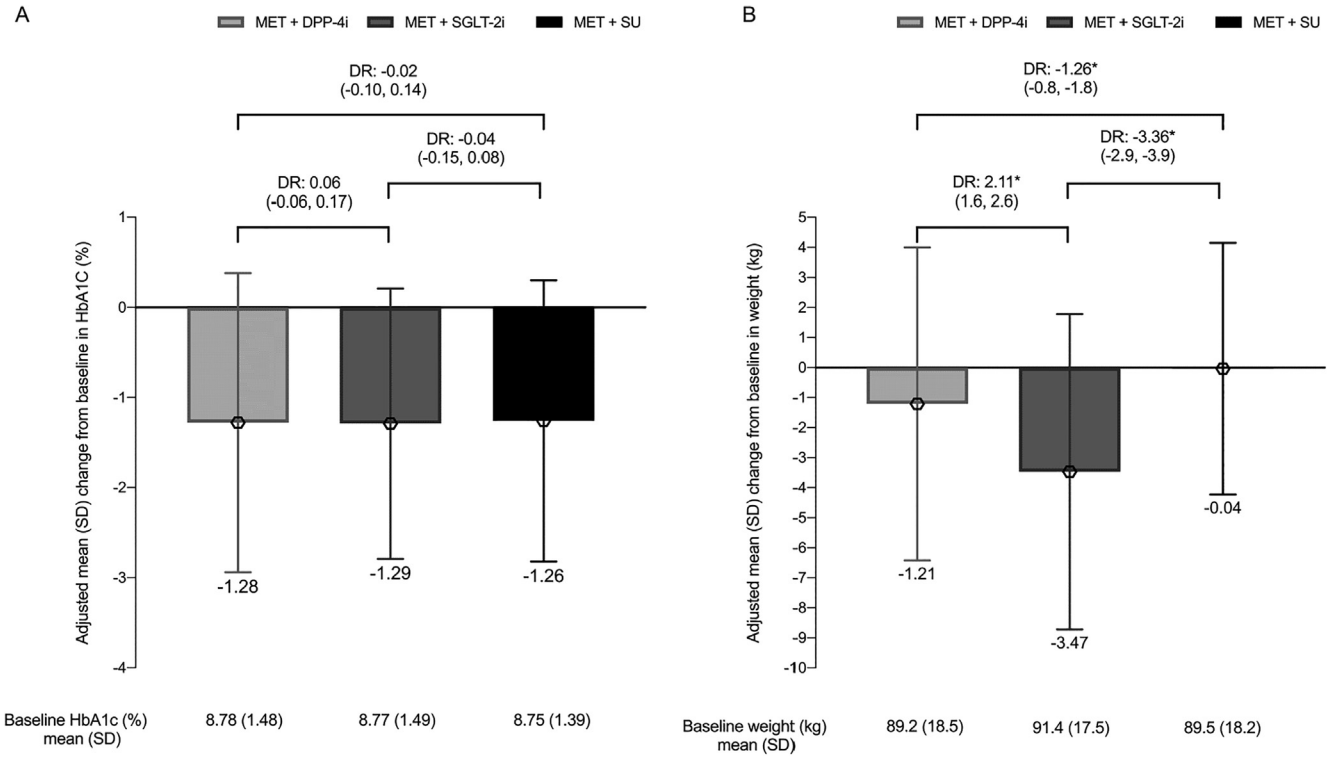

Fig. 2 – Adjusted mean changes from baseline by treatment group and differences in the reduction (DR and 98% CI) between drug classes in HbA1c values (A) and body weight (B). *Statistically significant p-value after multiple testing correction (<0.017). HbA1c, glycated haemoglobin; IDPP4, inhibitors dipeptidyl peptidase-4; MET, metformin; SGLT-2i, inhibitors sodium/glucose cotransporter 2; SU, sulphonylureas.

(29.7% of patients achieving ≥ 3% reduction) and only −0.04 kg with SU (18.6% of patients with ≥ 3% weight loss). When comparing the drug cohorts, patients who initiated add-on therapy with SGLT-2i were 2.7 times more likely to achieve weight loss ≥ 3% compared to DPP-4i users (OR2.66, 98% CI 2.1, 3.3) and 5.0 times more likely than SU users (OR0.2, 98% CI 0.2,0.3) (Fig. 1). Overall there was a 2.11 kg (98% CI: 1.6, 2.6) reduction in weight in those initiated on SGLT-2i compared to those initiated on DPP-4i and a 3.36 kg (98% CI: 2.9, 3.9) weight loss compared to those initiated on an SU (Fig. 2 B; Supplementary Table 4). Patients initiated on DPP-4i users had a mean of 1.26 kg (98% CI: 0.8, 1.8) reduction in weight compared to SU users.

The median time to achieve the reduction in HbA1c and weight was shorter for DPP-4i users (277 days and 295 days, respectively) compared to SGLT-2i users (343 days and 348 days, respectively) and SU users (286.5 and 301 days, respectively) (Supplementary Table 1).

3.2. *Reduction of blood pressure and lipid parameters*

Regarding SBP, There was a mean reduction in SBP of 3.10 mmHg (±15.0), 1.07 mmHg (±15.5), and 0.96 mmHg (±15.2) in those initiated on SGLT-2i, DPP-4i and SU respectively (Supplementary Table 2). Comparable changes were observed for DBP, with reductions of 1.75 mmHg (±9.94), 0.63 mmHg (±9.86), and 0.53 mmHg (±9.41) for SGLT-2i, DPP-4i, and SU, respectively.

Regarding the effects in the lipid profile (Supplementary Table 2), SU users had the greatest average reductions in total cholesterol 10.4 mg/dL (±36.2) triglycerides 29.7 mg/dL (±159) and LDL cholesterol 5.68 mg/dL (±27.5). In contrast, those initiated on an SGLT-2i had a mean increase for HDL cholesterol 2.36 mg/dL (±7.42). This effect on HDL was confirmed when we compared the differences between the SGLT-2i and the DPP-4i cohort, as SGLT-2i users experienced an average HDL additional increase of 2.33 mg/dL (98% CI: −3.14,-1.52) (Supplementary Table 4).

3.3. *Effect size analysis*

The clinical relevance of the observed differences between treatments was assessed through the effect sizes. The results are shown in Fig. 3 and summarized in Table 2. The effect of SGLT-2i compared to DPP-4i was moderate regarding the composite reduction of HbA1c $\geq$ 0.5% and weight $\geq$ 3%, but it was large compared to SU. Moreover, SGLT-2i had a large effect on weight reduction of $\geq$ 3% compared to both DPP-4i and SU. As per blood pressure, there was a small effect favouring SGLT-2i compared to DPP-4i and SU. The only non-trivial differences in the lipid profile were a small benefit of SGLT-2i over SU in total cholesterol decrease, and a moderate effect of SGLT-2i in HDL increase compared to both DPP-4i and SU.

3.4. *Sensitivity analysis*

The magnitude of the results of sensitivity analysis with the multiple missing imputations approach was similar to those from the analyses only considering complete cases. SGLT-2i remained as the drug class with the highest percentage of patients achieving the composite outcome (i.e., HbA1c reduction of at least 0.5% and weight reduction of at least 3%) (Supplementary Table 2) and the drug with the highest probability of such achievements compared to the two other treatments (Supplementary Table 3). In addition, SGLT-2i was the drug class that was associated with the greatest mean weight loss from baseline, although the difference in reduction was only

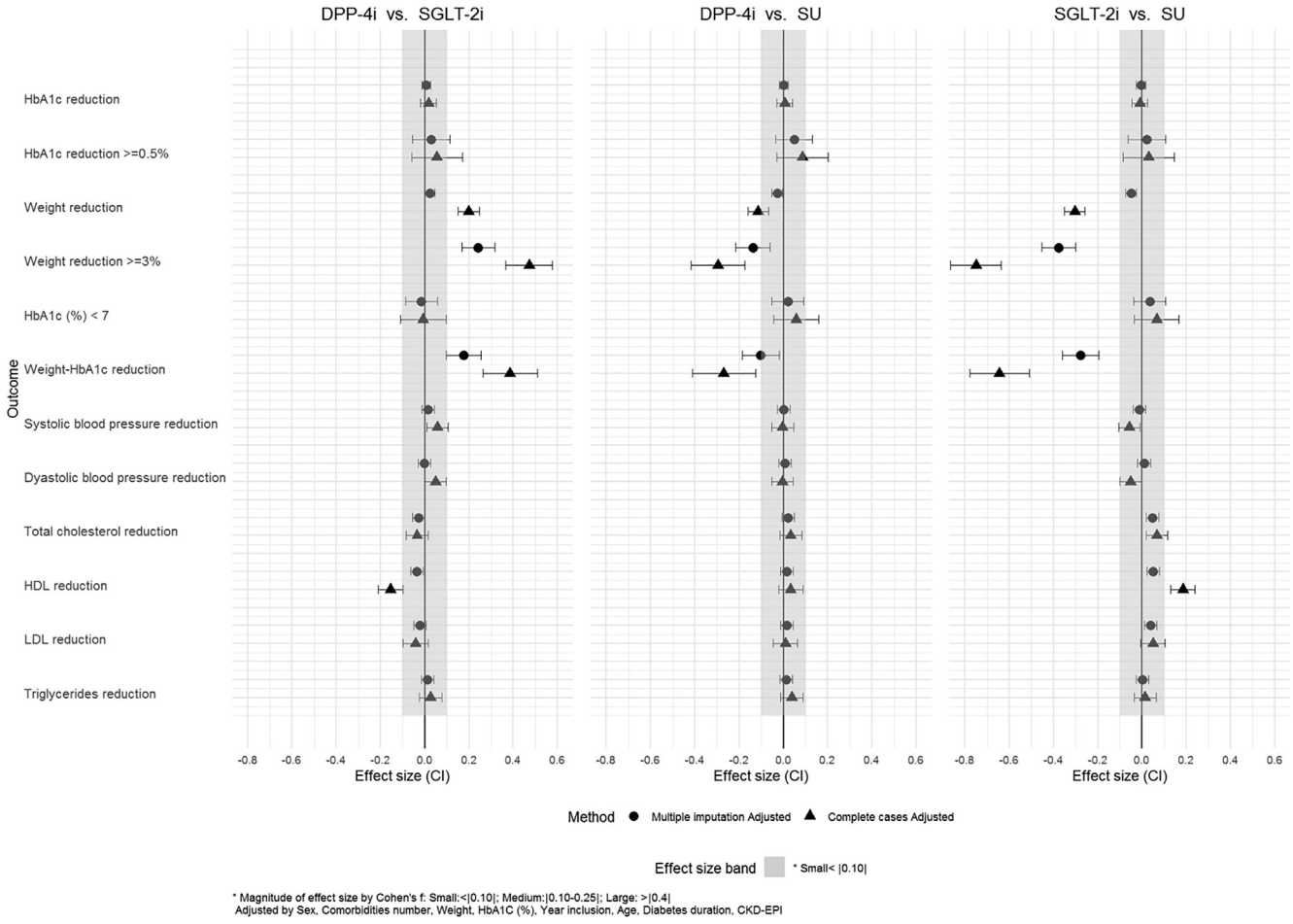

Fig. 3 – Forest plot of the standardized mean differences (effect sizes) between the different drug classes. HbA1c, glycated haemoglobin; IDPP4, inhibitors dipeptidyl peptidase-4; MET, metformin; SGLT-2i, inhibitors sodium/glucose cotransporter 2; SU, sulphonylureas.

Table 2 – Magnitude of the effect sizes between treatments for the different outcomes.

Clinical outcome	DPP-4i vs. SGLT-2i	DPP-4i vs. SU	SGLT-2i vs SU
HbA1c Reduction	Trivial effect	Trivial effect	Trivial effect
Weight reduction	Medium effect favouring **SGLT-2i**	Medium-small effect favouring **DPP4i**	Medium effect favouring **SGLT-2i**
HbA1c ≥0.5% Reduction	Trivial effect	Trivial effect	Trivial effect
Weight reduction of ≥3%	Large effect favouring **SGLT-2i**	Medium effect favouring **DPP4i**	Large effect favouring **SGLT-2i**
HbA1c ≥0.5% + weight reduction ≥3%	Medium effect favouring **SGLT-2i**	Medium effect favouring **DPP4i**	Large effect favouring **SGLT-2i**
Users reaching target of HbA1c < 7%	Trivial effect	Trivial effect	Trivial effect
SBP and DBP decrease	Small effect favouring **SGLT-2i**	Trivial effect	Small effect favouring **SGLT-2i**
Total Cholesterol decrease	Trivial effect	Trivial effect	Small effect favouring **SU**
HDL increase	Medium effect favouring **SGLT-2i**	Trivial effect	Medium effect favouring **SGLT-2i**
LDL decrease	Trivial effect	Trivial effect	Trivial effect
Triglycerides decrease	Trivial effect	Trivial effect	Trivial effect

HbA1c, glycated haemoglobin; DPP4i, inhibitors dipeptidyl peptidase-4; MET, metformin; SGLT-2i, inhibitors sodium/glucose cotransporter 2; SU, sulphonylureas.
Magnitude of effect size by Cohen´s f: Small < 0.10; Medium 0.10–0.25; Large > 0.4.

significant when compared to SU users (Supplementary Table 4). Finally, the magnitude and direction of the effect sizes did not change when assessed with the multiple imputation approach (Fig. 3).

4. Discussion

This real-world study based on a large representative cohort of people with type 2 diabetes from Spain suggests that SGLT2i, DPP4i, and SU had similar effectiveness in terms of HbA1c reduction, but significant differences for weight reductions and the composite outcome of HbA1c and weight reduction in favour of SGLT-2i.

The important reduction in HbA1c, when compared to the one usually found in clinical trials (1.29% greater in our study), may be related to the higher baseline HbA1c values when second-line therapies are initiated in clinical practice [19]. This is in line with the findings of a meta-analysis by DeFronzo et al., which reported a positive relationship between baseline HbA1c values and the magnitude of the HbA1c change across 10 categories of glucose-lowering therapies, irrespective of the class or mode of action [20]. In our study, treatment intensification with second-line therapy occurred at a mean HbA1c level of 8.8% (72.3 mmol/mol), which is far from the HbA1c > 7% threshold recommended in current guidelines, thus confirming the delay in intensification observed in previous similar real-world studies [21–24]. The high HbA1c level at the time of treatment intensification suggests the need to tackle therapeutic inertia, in particular in early disease, with the addition of a second antidiabetic drug [25]. We have recently addressed the issue of clinical inertia in a previous study using the same database in which we found a lack of treatment intensification in a relevant proportion of subjects type 2 diabetes with HbA1c values over 8% at baseline [26]. Indeed, the NICE guidelines suggest adding the second antidiabetic drug when HbA1c is above 6.5% [3]. The recent data suggest that early combination glucose-lowering therapy provides greater and durable long term benefits [27]. Furthermore, this has recently been also recommended in primary care position statement [27].

Similar retrospective studies have been recently published using data collected from electronic medical records from the UK, US, Denmark, and Germany on patients who initiate add-on therapy to metformin [23,24,28–31], where the prescription patterns for these three antidiabetic combinations are different. The data in our study are quite similar to those observed in the UK, where the most common add-on treatment to metformin were sulfonylureas, then DPP-4i and SGLT-2i [23,28,29]. Conversely, the addition of SU was rarely chosen in Germany (4.4%) [28]. The use of SU in our study was superior to the rest of drugs probably due to the in-force CatSalut local current guidelines during that period that recommend the use of SU as the second line therapy of choice [32].

Comparing the baseline characteristics of our study with others, there were similarities in terms of age, gender, and baseline HbA1c at the time of intensification with the second-line therapy. For instance, baseline HbA1c was higher in the UK study (9.0%) [23] than the US cohort (8.4%) [24], while in our study the average baseline HbA1c values between the cohorts were slightly different, i.e. 8.8% for all drug classes investigated. These HbA1c values are too high and far from those recommended by current guidelines as the level for timely intensification of treatment in daily clinical practice [1–4].

In general, and before the propensity score matching procedure, the SGLT-2i group was younger, more obese, and with a longer duration of diabetes compared to the rest of the groups. Moreover, these patients had the worst comorbidity profile, notably mainly cardiovascular disease. Similar results were observed in the US study where users intensified with SGLT2i were younger, more likely to be female, and obese, as compared with those who initiated dual therapy with DPP-4i, or SU [24]. The higher presence of the CVD comorbidity among these users could be explained by the recommendations issued in guidelines that SGLT2i should be used in patients with established CVD or at high cardiovascular risk [1]. Moreover, previous clinical trials have demonstrated cardio-renal benefits of these drugs in patients with T2DM and established cardiovascular disease [33–35] or high cardiovascular risk [34] that seems independent of the reduction on the HbA1c.

The composite primary outcome of HbA1c and weight reduction was achieved in 41.3%% of subjects in the SGLT-2i group, followed by lower target achievement among DPP-4i (24.2%), and SU (15.2%) groups. Moreover, SGLT-2i users were more likely to achieve this outcome than DPP-4i and SU users, and the magnitude of this effect was estimated as large. The results observed in our study are in concordance with a similar study performed in the UK with an 18-month follow-up period, where the composite outcome was HbA1c reductions of $\geq$ 0.5% (5.5 mmol/mol), and body weight loss $\geq$ 2 kg; 36.5% of users intensified with SGLT-2i achieved this composite outcome, while this percentage was lower for DPP-4i (17.1%) and SU (9.6%) users [23].

Regarding outcomes individually, we did not find significant differences in terms of HbA1c reduction between the therapy cohorts, independently of the type of analysis (complete cases and imputation case analysis). However, we did observe significant differences in terms of weight changes among the cohorts (−1.21 kg for DPP-4i, −3.47 kg for SGLT-2i, and −0.04 kg for SU). As such, the effect size of the HbA1c reduction (and reduction $\geq$ 5%) was trivial between drug classes, while the effect on weight for SGLT-2i was large compared to both DPP-4i and SU regarding weight reduction $\geq$ 3%. Our real-world findings are consistent with a recent randomized clinical trials meta-analysis, in which all investigated glucose-lowering drugs lowered HbA1c to a similar extent when combined with metformin, but only SGLT-2i showed superiority in weight reduction [5,36].

Regarding changes in systolic blood pressure between the three therapy groups, results were in favour of the use of SGLT-2i compared to DPP4i or SUs (reductions of 3.10, 1.07, and 0.96 mmHg, respectively). When comparisons among the different cohorts were made, there were statistically significant differences in favour of SGLT-2i compared to the other 2 drug classes, although the magnitude of this effect was small. These findings are similar with those of a recently published study in a cohort study in UK primary care by Wilkinson et al, where the mean difference (mmHg) over 96 weeks of follow-up for SGLT2i users was −1.82 (95% CI −3.18, −0.45) compared to DPP4i and −3.06 (95% CI −4.43, −1.68) compared to SU [31].

Small numerical, although statistically significant differences were observed regarding lipid profile: an increase in HDL-cholesterol with SGLT-2i, a greater decrease in total and LDL-cholesterol with DPP4i and SU, and a greater decrease in triglycerides with SGLT-2i and SU. We only observed moderate beneficial effect of SGLT-2i in the increase of HDL-cholesterol compared to the other 2 drug classes.

The main strength of our study is a large number of subjects included and a population based representative (SIDIAP information comes from ICS, which manages >75% of the Catalan population) sample from primary care. However, there are some limitations in our study, typically inherent to observational studies using real-world databases such as the non-availability of some data. Despite this potential source of confounding bias, the sensitivity analysis showed that the results were comparable to the ones obtained using only complete cases. Another limitation is the possibility of indication bias or confounding by severity of disease. Using propensity matching, we could establish well-balanced groups and we would have minimized this possibility of this bias but not completely eliminated this. The time of follow-up was different in the cohorts, and this is mainly because the SGLT-2i were commercialized later in the study period in comparison with the other groups, but we may assume that there is no differential bias since the cohorts were matched for year of inclusion. We did not use BMI in the propensity matching due to quality of the variable and primary objective of our study. Despite this we obtained well balanced cohort groups for weight and BMI. This is an observational study; therefore, it shows associations but does not allow establishing a causal relationship that is exclusive of randomized clinical trials.

In summary, the present study showed similar effectiveness on HbA1c reduction among the different drug classes as second-line antidiabetic drug following metformin failure. However, SGLT-2i were associated with significantly greater reductions in weight or the combination target of weight-HbA1c compared to SU and DPP4 inhibitors. Moreover, our findings confirm the existence of far from optimal treatment intensification practice and suggest the need to overcome therapeutic inertia also in the early stages of treatment progression. There is a need for more studies on effectiveness in real-world conditions as they can help in better selection of treatment for poorly controlled T2DM patients.

Disclosures

M. M.-C. has received an advisory and or speaking fees from Astra-Zeneca, Bayer, 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, 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. KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly

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Data sharing statement

The data controller for SIDIAP does not allow the sharing of raw data. Statistical codes are available upon request from the corresponding authors (J.F.-N or D.M).

Author contributions

J.F.-N, M.M-C, J.R, D.M, X.M-T, JA.V, and B.V, conceived the research and participated in its design. J.R performed statistical analysis. B.V wrote the initial draft of the manuscript, which J.F.-N, M.M-C J.R, D.M, X.M-T, JA.V, M.F and K.K edited. All authors approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108616.

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