DAP_Cat
Grup de Recerca Epidemiològica en Diabetis des de l´Atenció Primària

POST-AUTHORIZATION STUDY PROTOCOL

Study information

Title	Study about the results of the addition of a sulfonylurea, DPP4 inhibitors or SGLT2 inhibitors as a second antidiabetic drug in patients with diabetes mellitus type 2 in treatment with metformin and insufficient glycemic control. (eControl Met +)
Ethical committee protocol number	P17-205
Internal code:	DAP-MET-2018-01
ESR code	ESR-16-12628
Protocol version identifier	2.0
Date of the last version of protocol	15/02/2018
EU Post Authorization Study (PAS) register number	Study not yet registered
Active substance	Metformin (A10BA02) Sulphonylureas (A10BB) and fixed-dose combinations with metformin DPP-4i(A10BH) and fixed-dose combinations with metformin SGLT-2i (A10BK) and fixed-dose combinations with metformin
Research question and objectives	To compare the proportion of patients that achieve the reduction of HbA1c of at least 0.5%, and weight reduction of at least 3%, after the addition of a sulfonylurea, an DPP-4i or an SGLT-2i to the treatment with metformin in patients with T2DM and insufficient glycemic control up to a maximum of 24-month follow-up period

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SIGNATURE OF THE PROTOCOL

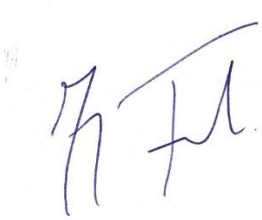
For the study titled: "*Study about the results of the addition of a sulfonylurea, DPP4 inhibitors or SGLT2 inhibitors as a second antidiabetic drug in patients with diabetes mellitus type 2 in treatment with metformin and insufficient glycemic control. (eControl Met +)*"

I confirm that I agree to carry out the study according to the protocol.

I acknowledge being responsible for the overall conduct of the study.

I agree to carry it out personally or supervise the conduct of the study described.

I agree to ensure that all researchers and associates involved in the study are informed of their obligations and that there are mechanisms in place to ensure that the staff at each participating center receives the appropriate information throughout the study.



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LIST OF ABBREVIATIONS

Abbreviation	Definition
T2DM	Type 2 Diabetes Mellitus
DPP-4i	Inhibitors dipeptidyl peptidase-4
ISGTL2	Inhibitors sodium/glucose cotransporter 2
SU	Sulfonilurea
HB1Ac	Glycated hemoglobin
CVD	Cardio Vascular Diseases
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
SBP/DBP	Systolic blood pressure/ diastolic blood pressure
GLP -1	Glucagon-like peptide-1
ICD-10	International Statistical Classification of Diseases and Related Health Problems
BMI	Body mass index
ICS	Institut Català de la Salut
ECAP	Estació clínica d'atenció primària
SAP	Statistical analysis plan
MPR	Medication possession ratios
BP	Blood pressure

RESPONSIBLE PARTIES

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ABSTRACT

Main objective:

To compare the proportion of patients that achieve the reduction of HbA1c of at least 0.5%, and weight reduction of at least 3%, after the addition of a sulfonylurea, an DPP-4i or an SGLT-2i to the treatment with metformin in patients with T2DM and insufficient glycemic control up to a maximum of 24-month follow-up period.

Methodology:

Retrospective longitudinal cohort study with a maximum of 24-month follow-up period. Data will be collected from SIDIAP databases, which obtains data from electronic health care records of 75% of the Catalonia population attended in Primary Care facilities. We define as study population; patients diagnosed with type 2 diabetes mellitus on treatment with metformin and insufficient glycemic control that initiate treatment with a sulphonylurea, a DPP-4i or a SGLT-2i as a second antidiabetic drug during 2010-2015. The 3 cohorts will be formed and matched by propensity score technique according to age, sex, HbA1c and weight at the time of inclusion. Main determinations: Weight and Hb1Ac during 6, 12 and 24 months of follow-up and baseline characteristics for demographic variables and comorbidities related to their addition to the prescribed treatment. Statistical analysis: For the main analysis it will be used, the regression model of the mixed effects line and the COX models for the estimation of incidence and risk rates. Each dependent variable will be adjusted for baseline demographic factors and for predictive factors.

Expected results:

The data obtained from this study will improve the knowledge about the effects of the addition of a second oral antidiabetic.

Relevance: There is a need for a large-scale observational study to know the effects of the three most common strategies for the second therapeutic choice for T2DM in real practice conditions.

Keywords: Complications; glycemic control; type 2 diabetes mellitus; treatment.

AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Version 2.0	15/02/2018	Substantial	Objectives	Change of the order of objectives , secondary objective "To compare the proportion of patients achieving the reduction in HbA1c values of at least 0.5%, a weight reduction of at least 3%, after the addition of a SU, an DPP-4i or an SGLT-2i to the treatment with metformin in patients with T2DM and insufficient glycemic control in the medium-long term, up to a maximum of 24 months of follow-up" become principal objective	Scientific relevance
Version 2.0	15/02/2018	Substantial	Study size sample	Additional information about study size sample	Scientific relevance

MILESTONES

Milestone	Planned date
Presentation of the study protocol to the scientific committee of SIDIAP	*17/10/2017*
Protocol approval from ethical committee	*25/10/2017*
<Registration in the EU PAS register>	*March 2018*
Start of data collection, study variables operational definition	*Abril 2018*
End of data collection (data management and extraction)	*July 2018*
Statistical analysis	*August -October 2018*
Final study report	*November2018*
Article submission for publication in open access international journal	*December 2018*

RATIONALE AND BACKGROUND

Type 2 diabetes mellitus (T2DM) is a clinical disease with progressive deterioration of the glycemic control that usually makes necessary the combination with several antidiabetic drugs with different mechanism of action. In the Spanish population according to data from the di@bet.es study (1), the prevalence is estimated to be around 13.8% in adults 18 years or older. It is the main cause of blindness, amputations and terminal kidney disease (2). Additionally, T2DM carries a significant risk for cardiovascular diseases (CVD), both by itself and due to its association with other risk factors, such as hypertension and dyslipidemia (3).

The final goal of T2DM treatment is to reduce morbidity, mortality and to improve the quality of life of people who suffer from this disease. Although it should contemplate the control of all risk factors, generally the aim of hypoglycemic agents is to reduce hyperglycemia, which is clearly associated with microvascular morbidity (4) (5), and to reduce the degree of macrovascular morbidity and mortality (6).

Current guidelines recommend the use of metformin as monotherapy as a first-line treatment to reduce glucose, except in cases where it is contraindicated or not tolerated (3) (7) (8) (9). In real clinical practice, there is a very frequent situation where a patient under treatment with metformin in monotherapy and an insufficient glycemic control, needs an addition of a second antidiabetic drug. This happens generally, due to that fact that, the increase in the dose of metformin usually does not result in large reductions in HbA1c level, but just increase of gastrointestinal side effects (10). The current prescription data for the second antidiabetic agent differ between studied populations, but shows a preferred use of oral antidiabetics such as sulfonylureas (SU), dipeptidyl peptidase 4 inhibitors (DPP-4i) or sodium-glucose cotransporter type 2 inhibitors of (SGLT-2ii) as main therapeutic options.

In the selection of the second antidiabetic drug, there are important challenges that have not been resolved by the recently published clinical trials. Usually, that published data come from clinical trials in patients with strict inclusion criteria and do not represent the population heterogeneity and the real healthcare conditions (real-world data evidence). The Canadian Agency for Drugs and Technologies in Health (CADTH) in 2017 published a systematic review and meta-analysis of all the randomized clinical trials available in that period, to assess the use of second-line antidiabetic therapies after inadequate control with monotherapy with metformin. All classes of antidiabetic drugs added to metformin achieved similar, statistically significant reductions in HbA1c, but with an important conclusion that indicates the general lack of evidence regarding of the effect of these drugs on clinically important long-term complications of diabetes such as blindness, amputations and terminal kidney disease (11).

A recently published meta-analysis by Mishriky et al. (12), which includes studies comparing DPP-4i and SU in patients with T2DM treated with metformin alone, suggests that both DPP-4i and SU effectively reduce HbA1c when they are added to metformin. The

reduction in HbA1c was significantly higher in the group of SU plus metformin (-0.7%) in a short treatment period (12 weeks) compared to the group of DPP-4i plus metformin (-0.5%) but without significant differences for 52 and 104 weeks of treatment period. The incidence of hypoglycemia was significantly higher in the SU group. On the other hand, the meta-analysis of Clar et al. that includes randomized controlled trials of inhibitors of SGLT2 receptors compared to placebo or active comparator in T2DM in combination therapy, observed that SGLT2 inhibitors are effective similarly to SU for reduction of HbA1c in the short term period, and it seems to be safe (13). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in 2013 started a large clinical trial of comparative effectiveness between the four main classes of hypoglycemic drugs in patients with T2DM and treated with metformin (GRADE) (14). The end of this clinical trial it is expected in 2020 and therefore we still do not have these results.

- The sulfonylureas have a strong hypoglycemic effect, acting on the pancreatic beta cell by stimulating insulin secretion, and a chronic hypoglycemic effect mediated by the intensification of the action of insulin through an increase in the number of receptors for insulin or it´s binding to receptors sensitive tissues (15). The metformin+SU combination is the combination of oral antidiabetic drugs with the greatest experience of use and traditionally has been the most used combination in Catalonia, after the failure of monotherapy with metformin. Due to the low cost, it is currently recommended in the Pautes d'harmonització del tractament de la diabetis. However, there are important doubts about its safety, especially because of the risk of hypoglycemia (16), or the lack of studies on cardiovascular safety (17). Its use is not recommended in fragile patients or patients with ischemic heart disease or heart failure (5).

- DPP-4i (also known as gliptins) potentiates postprandial insulin secretion and suppresses glucagon secretion by temporarily blocking the degradation of incretins (glucagon-like peptide [GLP]-1.) These drugs offer a good safety profile, without increased risk of hypoglycemia, weight gain and cardiovascular events compared to placebo (18) (19) (20). They are increasingly used in the treatment of T2DM as an alternative to SU, or as additional therapy with other oral antidiabetics, especially in the presence of kidney disease or in elderly patients (21).

- SGLT-2i (also known as gliflozins), is a new pharmacological class of drugs with glucosuric effect. They inhibit the reabsorption of glucose in the proximal tube and, therefore, promote glycosuria, an effect independent of insulin. By reducing hyperglycemia, SGLT-2i reduces glycotoxicity, which indirectly results in an improvement of both beta cell function and peripheral insulin sensitivity (22). In a clinical trial (EMPAREG), empagliflozin has shown a reduction in cardiovascular morbidity / mortality and slow the progression of diabetic nephropathy in patients with established vascular disease (23) (24). Another SGLT-2i, canagliflozin, in the CANVAS clinical trial, has shown that patients treated with this drug had a lower risk

of cardiovascular events than those who received placebo but a greater risk of amputations and fractures (25).

The aim of the present study is to obtain comparative efficacy and safety data after the addition of an SU, a DPP-4i or an SGLT-2i to patients with T2DM and insufficient glycemic control, treated with metformin under real clinical conditions. Secondarily, we will study the possibility to define clinical profiles of the patients for each drug combination group and determinate where greater benefit or mayor risk of side effects could occur.

Research question and objectives

Pre-specified hypotheses

After addition of an SU, an DPP-4i or an SGLT-2i to the metformin treatments as monotherapy in patients with T2DM and poor glycemic control, there will be differences in the intensity of the reduction of HbA1c, depending on the treatment prescribed; the reduction of weight in the medium-long term (up to 24 months) and the appearance of adverse effects. We expect a similar reduction in HbA1c with the three pharmacological groups, but a greater weight reduction between the patients treated with SGLT-2i.

* According to data from the CADTH therapeutic review (26), it was observed an average reduction of HbA1c of 0.70% and a mean weight gain of 2.11 kg in the SU cohort. An average reduction of HbA1c of 0.58% and weight of 0.18 kg in the DPP-4i cohort, and an average reduction of HbA1c of 0.67% and 2.21kg in the SGLT-2i cohort, respect to the average baseline HbA1c and weight in the medium-long term (up to 24 months).

The primary objective

• To compare the proportion of patients achieving the reduction in HbA1c values of at least 0.5%, a weight reduction of at least 3%, after the addition of a SU, an DPP-4i or an SGLT-2i to the treatment with metformin in patients with T2DM and insufficient glycemic control in the medium-long term, up to a maximum of 24 months of follow-up.

Secondary objectives*:

• To estimate the mean reduction of HbA1c and body weight separately after the addition of an SU, a DPP-4i or an SGLT-2i in patients with DM2 treated with metformin and insufficient glycemic control (up to 24 months).
• To assess the average reduction in systolic blood pressure after the addition of an SU, a DPP-4i or an SGLT-2i in patients with DM2 treated with metformin and insufficient glycemic control.
• To assess the evolution of lipid profile (mean total cholesterol, HDL, LDL, and triglycerides) after the addition of an SU, a DPP-4i or an SGLT-2i in patients with DM2 treated with metformin and insufficient control glycemic.

• To assess the adherence to treatment after the addition of an SU, a DPP-4i or an SGLT-2i in patients with DM2 treated with metformin and insufficient glycemic control.
• To assess the percentage of suspensions/dropouts of treatment at 6, 12 and 24 months (persistence of treatment).
• To describe the relevant adverse reactions produced after the addition of an SU, an DPP-4i or an SGLT-2i in patients with DM2 treated with metformin and insufficient glycemic control.
• To describe the comorbidity profile and baseline clinical characteristics of patients with DM2 and insufficient control with metformin in monotherapy after addition of a treatment with SU, DPP-4i or SGLT-2i.
• To describe the clinical characteristics of patients who have the best efficacy results (patients with a reduction of HbA1c of more than 0.5% and a weight reduction of at least 3% before the end of follow-up).

***the changes will be evaluated up to 12 months and a maximum of 24 months after the addition of the treatment or end of follow-up.**

RESEARCH METHODS

Study design

Retrospective longitudinal study with a follow-up of three cohorts of patients matched for: age, sex, diabetes duration, HbA1c , body mass index (BMI), hypertension diagnosis, dyslipidemia diagnosis (hypercholesterolemia, hypertrigliceridemia, or both), renal function (CKD-epi), macrovascular complications, heart failure, microvascular complications (retinopathy, albuminuria) at the time of inclusion. The study will be based on secondary data collection.

Study cohorts

• Cohort A: patients with T2DM and insufficient glycemic control (HbA1c ≥ 7%), treated with metformin as monotherapy who switch to dual combinational therapy with sulphonylureas during the study period.

• Cohort B: patients with T2DM and insufficient glycemic control (HbA1c ≥ 7%), treated with metformin in monotherapy who switch to dual combinational therapy with DPP-4i during the study period.

• Cohort C: patients with T2DM and insufficient glycemic control (HbA1c ≥ 7%), treated with metformin in monotherapy who switch to dual combinational therapy with SGLT-2i during the study period.

Study drugs definition cohorts (ATC* / DDD**)

Cohort A	Metformin (A10BA02) + Sulfonylurea (A10BB)/ or fixed-dose combinations (A10BD02)
Cohort B	Metformin (A10BA02) + DPP-4i (A10BH) or fixed-dose combinations (A10BD07 to A10BD13) (except A10BD09 and A10BD12)
Cohort C	Metformin (A10BA02) + SGLT-2i (A10BK) fixed-dose combinations (A10BD15, A10BD16 and A10BD20)

* Anatomical Therapeutic Chemical (ATC) classification system

**Defined daily dose

The cohorts will be formed using matching techniques (Nearest-Neighbor algorithm) to ensure balance in terms of baseline characteristics (age, sex, HbA1c and weight at the index date). The "MatchIt" library of the R statistical package will be used (v3.0.1) the previous feasibility study and the availability of data will determine the population finally analyzed.

If there is no possibility for matching between the three groups, matching will be done between two groups (Cohort B and Cohort C or Cohort A or Cohort C).

Enrollment and follow-up period

The recruitment period is defined from January 1, 2010, to December 31, 2015. The follow-up period is defined as 24 months since the recruitment (index date).

Definition of index date

Index date is defined as date fulfilling the inclusion criteria and first prescription/dispensation of one of the study drugs (SU, DPP-4i or SGLT-2i) for each cohort during the study period between 2010 and 2015. Checkings will be made to ensure that the patients have never received before the index date any of the study drugs (SU, DPP-4i or SGLT-2i).

Definition of follow-up period and premature discontinuation

The follow-up period for each patient is defined between the index date and up to 24 months or premature discontinuation from the study.

Premature discontinuation from the study is defined as death, the switch or addition of a new antidiabetic treatment, last billing of study drugs before 24 months after prescription, or transfers to non-ICS centers.

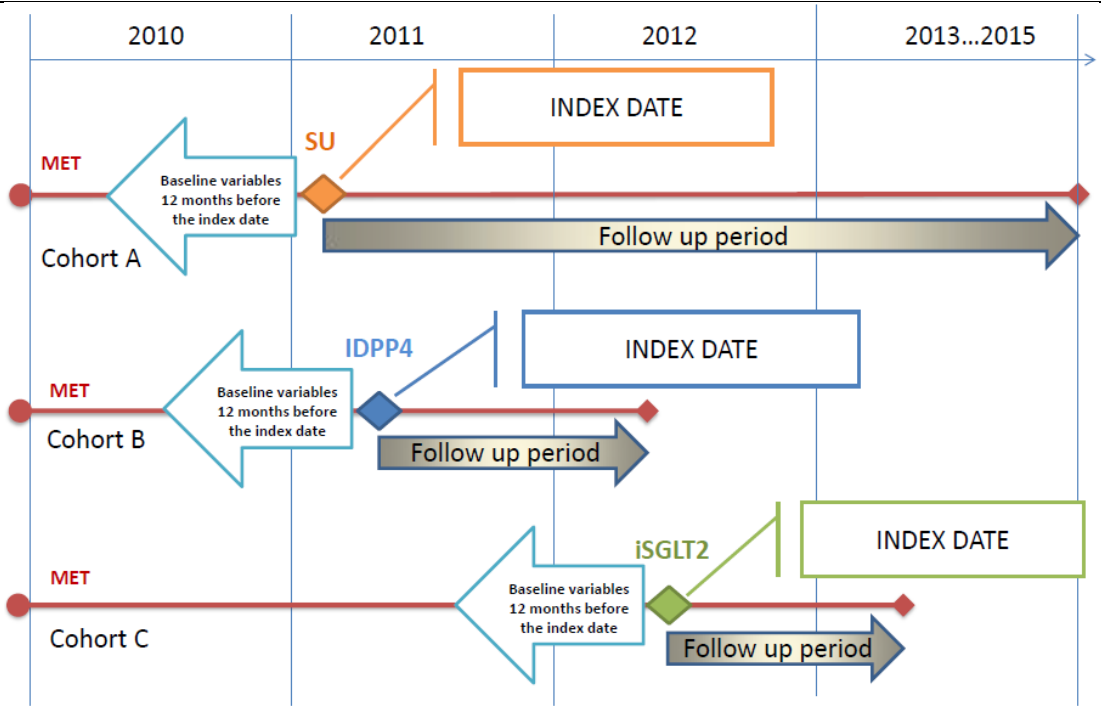

Figure 1: Index date definition and follow up period

Inclusion criteria

At the index date (date when the second antidiabetic drug is added to metformin):

- Patients with T2DM (ICD-10: E11) 18 years and older.
- Patients with HbA1C values equal to or greater than 7% (*last registry of this determination during year prior to the index date)
- Patients who are on antidiabetic treatment with metformin in monotherapy and start a second line therapy as combinational therapy from the group of sulfonylureas, DPP-4i or SGLT-2i during the inclusion period (2010-2015).

Exclusion criteria

Assessed at baseline*/index date

- Patients with diabetes mellitus type 1, gestational or secondary (ICD-10: E8, E9, E10, O24, E13).

- Patients missing any baseline HbA1c, weight, age or sex.

***(Patients with previous registry of other type of diabetes then T2DM in medical history would be excluded from the study)**

Variables

Definition of exposures

As exposure, we define all the patients diagnosed with T2DM on metformin treatment who during the study period have first add-on prescription/dispensation of any of the study drugs: SU, DPP-4i or SGLT-2i.

Definition of outcomes

As outcomes, we define the reduction of HbA1c of at least 0.5%, reduction of a weight of at least 3%, as well as occurrence of different side effects after index date for each cohort.

Characteristics at the index date:

Sociodemographic variables: age, gender, toxic habits

Table 1: Sociodemographic variables

Variable	Role	Source	Operational definition
Age	Baseline characteristics	SIDIAP	Birth date (month/year)
Gender	Baseline characteristics	SIDIAP	Male / female
Toxic habits	Baseline characteristics	SIDIAP	Alcohol consumers (no, moderate, risk) Tobacco consumers (Yes / No)

Basal comorbidity variables: heart failure, peripheral vascular diseases, ischemic heart disease, hypertension, acute /chronic pancreatitis, renal failure, liver cirrhosis, etc.

Table 2: Baseline comorbidity variables

Variable	Role	Source	Operational definition ICD-10
Heart failure	Baseline characteristics	SIDIAP	I50
Peripheral vascular diseases	Baseline characteristics	SIDIAP	I73.8, I73.9
Ischemic heart disease	Baseline characteristics	SIDIAP	I20 , I25
Hypertension	Baseline characteristics	SIDIAP	I10-I15
Acute / chronic pancreatitis	Baseline characteristics	SIDIAP	K85
Renal insufficiency	Baseline characteristics	SIDIAP	N17– N19
Relevant liver disease (excluding steatosis	Baseline characteristics	SIDIAP	K70–K77 (except K76)
Mental disorders due to known physiological conditions	Baseline characteristics	SIDIAP	F01 ;F02 ; F03 ; F06.7 ; G30/ F00.9 ; G31.8 ;

Clinical variables related to T2DM: diabetes duration (years from T2DM diagnosis), HbA1c value, weight and BMI, BP, lipid profile, GFR, albumin/creatinine ratio at the time of addition of the second antidiabetic drug. In the case of no available determination at the index date for laboratory parameters as well as values for weight, BMI, blood pressure, these will be collected from a closest determination available, up to 1 year previous of the index date.

Table 3: Clinical variables related to T2DM

Variable	Role	Source	Operational definition ICD-10
Diabetes duration	Baseline characteristics	SIDIAP	years since diagnosis of DM2
HbA1c	Baseline characteristics	SIDIAP	HbA1c value
BMI	Baseline characteristics	SIDIAP	BMI
Weight	Baseline characteristics	SIDIAP	Weight
Blood pressure	Baseline characteristics	SIDIAP	SBP/DBP
Lipid profile	Baseline characteristics	SIDIAP	Triglycerides (mg / dL) Total cholesterol (mg / dL) HDL cholesterol (mg / dL) LDL cholesterol (mg / dL)
Glomerular filtration	Baseline characteristics	SIDIAP	Glomerular filtration estimated by CKD-epi (mL / min / 1.73m ^ 2)
albumin / creatinine ratio	Baseline characteristics	SIDIAP	albumin / creatinine (mg / g)

Variables related to the efficacy of treatment during follow-up changes in HbA1c, BMI, BP, lipid profile, GFR, albumin / creatinine ratio. The variables will be collected every 6, 12, 24 (with time window ± 3 months for each collection period) or, in the case they were not available values for those periods the last determination within 3-24 months from the index date will be collected. Patients with known factors that affect the mechanism of action of study treatments such as history of pancreatitis or eGFR level< 30 ml/min/1.73m2), will be excluded from analysis for efficacy of treatment during follow-up.

Table 4: Variables related to treatment efficacy

Variable	Role	Source	Operational definition ICD-10
HbA1c	follow-up characteristics	SIDIAP	HbA1c value during follow-up
BMI	follow-up characteristics	SIDIAP	BMI during follow-up
Weight	follow-up characteristics	SIDIAP	Weight during follow-up
Blood pressure	follow-up characteristics	SIDIAP	SBP/DBP during follow-up
Lipid profile	follow-up characteristics	SIDIAP	Triglycerides (mg / dL) Total cholesterol (mg / dL) HDL cholesterol (mg / dL) LDL cholesterol (mg / dL) during follow-up
Glomerular filtration	follow-up characteristics	SIDIAP	Glomerular filtration estimated by CKD-epi (mL / min / 1.73m ^ 2) during follow-up
albumin / creatinine ratio	follow-up characteristics	SIDIAP	albumin / creatinine (mg / g) during follow-up

Variables related to drug safety during the follow-up period or until premature discontinuation, data will be collected for adverse reaction such as pancreatitis, neoplasms, bone fractures, urogenital infections, digestive intolerance, peripheral amputations, hospital admissions due to acute decompensation, hypoglycemia recorded in the clinical history, etc.

Table 5: Variables related to safety

Variable	Role	Source	Operational definition ICD-10
Metabolic adverse reactions	follow-up characteristics	SIDIAP /CMBD	Hypoglycemia (ICD 10: E16.0 ICD 9: 250.8)

			Acute decompensation (ICD-9: 250.2 -250.3) Diabetic ketoacidosis (ICD10: E11.1 ICD9: 250.1 *)
Gastrointestinal adverse reactions	follow-up characteristics	SIDIAP	Diarrhea R19.7 nausea R11.0 flatulence R14 Vomiting R11.1 K85 pancreatitis Gastrointestinal neoplasms C15-C26 abdominal pain R10, epigastric R10.1
Hepatic adverse reactions	follow-up characteristics	SIDIAP	Elevation of liver enzymes (three times above the upper limit of normal> 150 U / L) R74.0 Toxic liver disease (ICD10: K71.6) Hepatic insufficiency, not classified under another concept (ICD10: K72.9
Kidney adverse reactions	follow-up characteristics	SIDIAP	Acute renal failure and chronic kidney disease (N17-N19) Kidney transplant Z94.0
musculoskeletal system adverse reactions	follow-up characteristics	SIDIAP/ CMBD	Injury of unspecified body region bone fractures (ICD 10: S00-S99 T14 peripheral amputations (Absence acquired from member ICD10: Z89.4, 89.5, 89.6,) ICD9: 800-829; 895-897.
Dermatological	follow-up	SIDIAP	Angioedema: T78.3

adverse reactions	characteristics		Skin rash Skin rash and other nonspecific skin rashes: R21 Hives: L50; T78.4 pruritus: L29.9 Cutaneous vasculitis: I77.6 erythema multiforme and Steven-Johnson syndrome: L51
Hematological adverse reactions	follow-up characteristics	SIDIAP	Megaloblastic anemia: D53.1
Urogenital adverse reactions	follow-up characteristics	SIDIAP	Urinary infections: N30.0; N39.0 Genital infections: B37.3 N51.2; N48.1
Death	follow-up characteristics	SIDIAP/CMBD SIDIAP	Death for any reason CIE 10: R99 / CIE 9: 798
Treatment suspensions (patients with premature termination)	follow-up characteristics		Time between the index date and date of treatment suspension

Variables related to safety, concomitant drugs would be collected on the index date and follow-up period. For the safety analysis, the possible adverse reactions caused by the concomitant drugs will be taken into account. The analysis would be adjusted by potential confounder variables.

Table 5.1: Concomitant drugs during the inclusion period

Variable	Role	Source	Operational definition
Drugs with hyperglycemic effect	Baseline / follow-up characteristics	SIDIAP	Glucocorticoids H02AB
Drugs that induce pancreatitis	Baseline / follow-up characteristics	SIDIAP	Metronidazole A01AB17 Tetracycline's J01AA Valproic Acid N03AG01
Drugs that induce cirrhosis	Baseline / follow-up characteristics	SIDIAP	Amiodarone C01BD01
Drugs that cause acute hepatitis	Baseline / follow-up characteristics	SIDIAP	Amoxicillin-Clavulanic Acid J01CR02
Other hepatotoxic drugs	Baseline / follow-up characteristics	SIDIAP	Fluconazole J02AC01 Itraconazole J02AC02 Ketoconazole J02AB02

Variables related to therapeutic adherence

The therapeutic adherence will be assessed through pharmacy invoice data (drug dispensing) from patients who initiate with combinational therapy during 2010-2015. For each patient who has a metformin prescription in combination with an SU or an DPP-4i or an iSGLT, two dates will be determined. The date of the first dispensation (first billing data) of the combination of two drugs, and the date of the last dispensation. The medication possession ratio (MPR) will be calculated using the following formula:

$$\boldsymbol{MPR = \frac{Total\ days\ of\ supply}{Elapsed\ days(including\ the\ last\ prescription)} \times 100}$$

"Total days of supply" is the sum of the days of supply of the drugs between the date of the first dispensation and the last dispensation (including the last dispensation)."Elapsed days" is the number of days between the date of the first prescription and the date of the last prescription during the period of follow-up or until the premature termination.

Table 6: Variables related to therapeutic adherence

Variable	Role	Source	Operational definition
adherence	follow-up characteristics	SIDIAP	Good adherence (> 80%) Low adherence (<80%)

Data sources

To investigate the reduction of HbA1c and weight for each study cohorts requires an efficient means to identify a sufficient number of the patients taking these drugs. At present, the largest and most readily accessible drug utilization data come from automated databases that record prescriptions, diagnoses, and procedures on an individual-patient basis. Such databases accumulate records longitudinally so that patient experience can be observed before and after prescription of a drug of interest.

The Information System for the development of Primary Care Research (SIDIAP) will be used to obtain the data of the people attended in the 279 Primary Care Teams of the Institut Català de la Salut (ICS) with an assigned population of 5,835,000 patients (75% of the Catalan population). The SIDIAP contains anonymized clinical information that originates from different data sources: 1) eCAP™ (electronic medical records in Primary Care of the Institut Català de la Salut [ICS]); which includes information since 2006 on sociodemographic characteristics, health conditions registered as ICD10 codes, General Practitioners' prescriptions, clinical parameters and toxic habits. 2) Laboratory data. 3) Prescriptions and their corresponding pharmacy invoice data; available since 2005contain information on all pharmaceutical products dispensed by community pharmacies with Catalan Health System prescriptions, by ATC codes.

Study size

All subjects that meet the inclusion criteria during the study period will be included. The number of subjects available in the SIDIAP database will determine the study size. We currently know that for the period between 2010 and 2016, we have about 189,776 potential subjects who have some dispensation registry of SU, DPP-4i, thiazolidinediones/gliflozins in addition to a dispensation registry of metformin.

According to the data of the study "Glycemic control and antidiabetic treatment trends in primary care centers in patients with type 2 diabetes mellitus during 2007- 2013 in Catalonia" (27), the proportion of patients in combined therapy in each year studied did not exceed more than 26%. By pharmacological groups, the treatment with SGLT-2i is clearly lower (2.6%) compared with patients taking DPP-4i (17%) or a sulphonylurea (19%), since they are relatively newer drugs.

According to this distribution (treatment with SGLT-2i of 2.6%) in a potential population of 189,776 subjects, the group with the lowest frequency could have approximately 5000 diabetic patients treated with metformin + SGLT-2i (cohort C). If the study includes 5000 subjects per group, would be obtained a power greater than 99% to detect differences in the contrast of the null hypothesis Ho: p1 = p2 by means of a bilateral χ^2 test for two independent samples. Taking into account that the level of significance is 5%, and assuming that 46% of the subjects will achieve the combined goal (HbA1c and weight) in the IDPP4 or SU group and 67.7% of subjects in the SGLT-2i group according to the recent literature (28, 29). The estimation of study size was done through the Ene 2.0 program (http://www.ene-ctm.com).

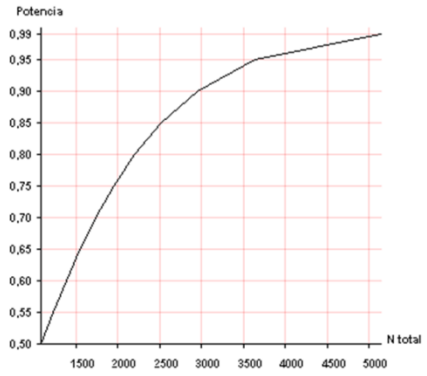

Figure 2: Power estimation for approximately 5000 diabetic patients treated with metformin + SGLT-2i

Data management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks. SIDIAP database will maintain any patient-identifying information securely on site according to internal standard operating procedures.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except authorized study staff.

Appropriate data storage and archiving procedures will be followed (i.e., storage on CD-ROM or DVD), with a periodic backup of files to tape.

Data analysis

Descriptive statistics (Minimum, maximum, mean, standard deviation, frequency, and percentage) of each of the registered variables will be used to describe and evaluate the baseline characteristics of the cohorts. To evaluate the homogeneity of the groups, it will be calculated the differences between the means and standard deviation with respect to one of the groups pre and post matching. And homogeneity for categorical variables would be done by comparison of the frequency distribution across levels of the variable.

For the main analysis, generalized linear mixed models (GLMM) will be used to evaluate changes in clinical parameters between groups during follow-up. Average changes or reductions in average means per temporal unit will be estimated after treatment. COX regression models will be used to estimate the risk of achieving the combined objective

(reduction of HbA1c of at least 0.5%, weight reduction of at least 3% or both) during follow-up. The estimates will also be adjusted for the baseline demographic factors and the predictive factors for each dependent variable. As a sensitivity analysis, the unadjusted estimates will also be calculated in different adjustment scenarios for the potentially confusing variables. Between all the cohorts (A vs B, A vs C and B vs C), 2X2 comparison will be performed indistinctly, where the global significance level (alpha = 0.05) will be adjusted by multiple test and prefixed to 0.017.

Outcome variables will be assessed by protocol (complete cases) and intention-to-treat approach (incomplete cases).

Treatment of missing values: Patients with missing values in the main determinations during follow-up will be treated according to the following scenarios: (a) Analysis including only patients with complete data during follow-up (at least one subsequent determination), (b) Estimates using multiple imputation techniques of missing's, and (c) For event type variables (combined objective), censoring at the time of cohort migration. The traceability of the information cuts will be safeguarded with the data analyzed as well as the programs for data management, analysis, and results. The statistical analysis will be performed using R3.4.0 and SPSS-IBM PC v19 and the level of significance will be 5% bilateral, corrected by adjustment by multiple comparisons with the Bonferroni method.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Quality control

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All programming written by one study analyst will be reviewed independently by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality control review, senior scientific review, and editorial review.

Limitations of the research methods

This is an observational study with data obtained from an electronic database. Therefore, it is subject to certain inherent limitations in all these studies, such as collecting non-random data, missing or incomplete information and potential confounders as well as coding errors, which may negatively influence in the validity of the results and the conclusions obtained by the study.

However, thanks to the availability of a population sample and the ability to apply the matching methodology, we can configure a higher quality standard in the selection of the final participant, eliminating potential selection biases, forming more homogeneous groups, also in the distribution of missing values and infra registers.

The strengths of our study are a large number of patients included, the representativeness of the general population (SIDIAP information comes from ICS, which manages more than 80% of the Catalan population), complete demographic and clinical data records and clinical practice.

Periodic evaluations carried out on the basis of SIDIAP data make it possible to verify that the quality of the data has progressively increased in recent years (http://www.sidiap.org/index.php/en). Despite these limitations, the study has strong points such as a large number of people included, the representativeness of the general population and the real clinical practice environment.

It should also keep in mind that this study cannot establish a confirmatory demonstration of a hypothetical harmful or beneficial effect depending on the type of treatment studied in these cohorts since it is an observational study and does not allow establishing causal relationships. However, unlike clinical trials, the evaluation of the potential effectiveness and safety of treatments is carried out under the conditions of usual practice, not excluding those subjects or conditions that are not usually included in clinical trials (extreme ages, patients with high comorbidity, polypharmacy, etc ...). Unlike clinical trials, the allocation in the cohorts is not random, so the groups may not be comparable at baseline. The biases derived in the allocation to the cohorts will be controlled in the analysis of the data, at least for the factors known and/or collected in the study.

Another limitation is derived from the treatment decision in these patients. This can mean that, although the treatments we want to compare have similar effects, we cannot guarantee that the cohorts are fully comparable, so we intend to adjust for baseline differences in the risk factors between the two.

Other aspects

Relevance, Applicability

It will be the first study conducted under real clinical conditions of practice that analyzes the efficacy and safety of the different therapeutic options for the combined treatment for patients with type 2 diabetes mellitus treated with metformin in monotherapy, which is a very common situation in clinical practice. The conclusions obtained may be extrapolated to the total of people with type 2 diabetes in Catalonia who are in the same situation.

We believe that the applicability of the results obtained will be very important. On the one hand, we can compare in real practice situations the different therapeutic options usually used to achieve metabolic control (glycemia and other risk factors) as well as safety data. In addition, we can define patient profiles based on their response to different treatments, which can make specific recommendations for the best therapeutic option depending on the clinical characteristics, which undoubtedly will benefit the patient and the public health system.

PROTECTION OF HUMAN SUBJECTS

Ethical Conduct of the Study

The study will be conducted in accordance with the indications of this protocol, the regulatory requirements applicable to observational studies and with the requirements expressed in international standards related to the realization of epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences -CIOMS-, Geneva, 2009), as well as the Declaration of Helsinki (Fortaleza, Brasil,, October 2013).

This defines the principles that must be scrupulously respected by all the members involved in this investigation.

The treatment, communication, and transfer of personal data of all participating subjects will be in accordance with the provisions of Ley Orgánica 15/1999, of December 13, about the protection of personal data.

All the information registered in the SIDIAP database is anonymous and therefore does not include any information that allows knowing the identity of the patient.

This study will be classified by the Spanish Agency for Medicines and Sanitary Products (AEMPS) and reviewed and approved by an Ethics Committee before the study can begin.

Any change in the study protocol will be reflected in writing and communicated to the researchers involved and to the Clinical Research Ethics Committee that has evaluated the study, considering it as an amendment to the protocol.

Benefit-risk evaluation

The present study has no possibility of generating any risk, as it is a retrospective study without specific use of medication, which is limited to an anonymous data registry in a database that does not allow access to the patient's personal data.

Confidentiality of the data

All the information registered in the SIDIAP database is anonymous, so it does not include any data that allows knowing the identity of the patient.

Use of electronic means

The extraction of data from the study will be done automatically from the database in electronic SIDIAP format.

Monitoring and final reports

A report will be made in which the descriptive data will be presented, which will be reviewed and approved by the group of researchers of the IDIAP Jordi Gol. Intermediate reports are not planned.

The report must be made on the dates provided in the calendar and a copy of it will be sent to the Clinical Research Ethics Committee that has authorized the realization of the same.

Plans for disseminating, communicating study results and publication conditions

The results of this study will be comprehensively summarized in a final report. The publication of this retrospective observational study will be carried out in scientific journals with peer review and with mention of the corresponding Clinical Research Ethics Committee.

When the development and the result of the study are made public, in any case, the origin of the funds for its realization will be stated.

Neither the sponsor, nor the researchers will communicate any results of the study to third parties before the result of the analysis and its interpretation has been agreed upon.

The DAP_CAT group may independently prepare publications based on the study results irrespective of data ownership and publish the results accordance with the principles of scientific independence and transparency and respecting the criteria established in the Code of Conduct ENCePP.

CEIC that evaluates the project

The study was evaluated and approved by IDIAP Jordi Gol Clinical Research Ethics Committee on October 25th 2017. This protocol amendment will be notified to the same Ethics Committee.

Conflict of interests

Investigators declare that they don't have any conflict of interest.

Funding:

The company AstraZeneca will be responsible for funding of the project through a contract with the IDIAP Foundation - Jordi Gol.

Funding will always be independent of the results of the study.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None