TITLE: **Assessment of cardiovascular effects of non-insulin glucose-lowering agents.**

Major cardiovascular events in new users of non-insulin glucose-lowering agents: observational longitudinal study in the Catalan population-based electronic health record database, SIDIAP, 2010-2015.

STUDY REFERENCE NUMBER:

AUTHORS: Raquel Herrera Comoglio, Xavier Vidal Guitart, Luisa Ibáñez Mora, Mònica Sabaté Gallego, Pili Ferrer Argelés, Maria Elena Ballarin Alins, Jean-Luc Faillie

ABSTRACT:

Background:

Cardiovascular (CV) risk is the leading cause of morbidity and mortality in T2DM population. The effect of control serum glucose levels on macrovascular complications remains uncertain. Glucose-lowering agents are currently marketed based on results of clinical trials with subrogate variables, mainly the percentage of glycated haemoglobin and other glucose markers. In 2007, concerns about CV safety of rosiglitazone led to regulatory recommendations regarding CV risk of new hypoglycemic agents, which are in force since 2008 (FDA, US) and 2012 (EMA, EU). In order to fulfill these recommendations, since 2008 a number of large randomized clinical trials have been designed and conducted, with a non-inferiority design as basis. Among those, three recently published large RCTs showed beneficial effects on cardiovascular mortality, meanwhile five large RCTs have failed to demonstrate any beneficial effect on CV outcomes. Other ten large RCTs, on-going or recently completed, are currently assessing the CV effect of seven marketed agents–and are foreseen to be completed up to 2020- are currently unavailable. In spite of enrolling a large number of diabetic patients with established or at high risk of CVD and having long follow-up periods, these studies are not free of limitations of RCTs. In addition, concerns have risen about the effect of some therapeutic groups or agents on heart failure (HF).

Electronic healthcare data, collected in the course of actual clinical practice by physicians can provide information of drugs effects in a real-world setting. Electronic medical records (EMRs) contain demographic and clinical information tests, and can be linked with other databases (hospitalization or deaths). An increasing number of population-based observational research focuses on effect of glucose-lowering agents on CV outcomes in large cohorts of patients. Up to date, no such studies have been performed in Spain. The Catalan general practitioners (GP) database SIDIAP contains pharmacoepidemiological data of 80 % of the total regional population.

Aim: to evaluate the effect of currently marketed non-insulin glucose-lowering agents on major CV outcomes in cohorts of Spanish population based on records of population-based EMR SIDIAP.

Design: Longitudinal retrospective observational cohort study, period of observation of six years (1st January 2010- 31st Dec 2015)

Material and Methods: Cohorts of patients aged 18 yrs. or older registered in the Catalan general practitioners (GP) database (SIDIAP), diagnosed of type 2 diabetes mellitus, and treated with approved glucose-lowering agents since their first prescription. Patients will be stratified by demographic and clinical variables. The

incidence rate of the first major cardiovascular event will be calculated. The primary outcome (PCO) is the composite of CV death, non-fatal myocardium infarction (MI) and non-fatal stroke. Secondary outcomes are: composite (SCO) of CV death, a non-fatal myocardium infarction (MI), non-fatal stroke and hospitalization due to unstable angina or coronary revascularization procedures; individual components of SCO, hospitalization due to HF (HHF) and all-cause mortality.

Strengths and limitations: Analysis of these databases could provide an estimation of the effect of currently marketed glucose-lowering agents on CV outcomes in a sample of non-selected population. New-users design prevents survivors bias. Limitations are mainly derived from its observational design (no randomization and confounding by indication). Concerning exposure data, some more recently marketed agents will not reach a number of prescriptions or follow-up periods appropriate to make valid comparisons with older agents. Concerning outcomes data, CV fatal outcomes not occurring in healthcare setting can be missclassified. Concerning completeness of data, missing data about a number of patients have been reported in other studies with SIDIAP database. The study period (6 years, from 2010 to 2015), which has been chosen according to availability of prescription/dispensing data, results in a follow-up can be not enough long for new diagnosed T2DM patients or patients not at high cardiovascular risk.

Expected results: For the drugs and period's study, adjusted results should be similar to those obtained in large randomized controlled trials evaluating the effect of glucose-lowering agents on cardiovascular outcomes. Thus, up to a 10% reduction in cardiovascular morbidity and mortality compared with the use of reference non-insulin glucose-lowering agents, metformin and sulphonylureas (SU) can be expected.

LIST OF ABBREVIATIONS

Acronym	Text
AHT	Arterial hypertension
AMI	Acute myocardial infarction
BL	Baseline
BMI	Body mass index
BNP	Brain natriuretic peptide
BNP	Brain natriuretic peptide
CABG	Coronary arterial by-pass graft
CHF	Congestive Heart Failure
CKD	Chronic kidney disease
CV	cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase - 4
DPP-4i	Dipeptidyl peptidase – 4 inhibitor
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food&Drug Administration
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
GLP-1 RA	Glucagon-like peptide 1 receptor analogue
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein colesterol

HF	Heart failure
HHF	Hospitalization for heart failure
LDL-C	Low-density lipoprotein colesterol
LV	Left ventriculum, left ventricular
MACE	Major adverse cardiovascular events
MET	metformin
MI	Myocardial infarction
N-BNP	N-terminal pro-Brain natriuretic peptide
PAOD	Peripheral arterial occlusive disease
PCO	Primary composite outcome
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SCO	Secondary composite outcome
SGLT-2	sodium glucose co-transporter-2
SIDIAP	Information System for the Development of Research in Primary Care
SU	Sulphonylurea
T2DM	Type 2 Diabetes Mellitus
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
UA	Unstable angina
US	United States
VLDL-C	Very low-density lipoprotein colesterol
WHO	World Health Organization

Introduction

Diabetes mellitus affects more than 422 million people; by 2035 its prevalence is foreseen to rise to 592 million, being the number of people with diabetes increased almost 4-fold from 1980 to 2014[1]. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (1 every 12 people). [1,2]

Diabetes mellitus Type 2 (T2DM) accounts or around 90% of all diabetes cases worldwide.[2] Diagnosed type 2 diabetes mellitus' prevalence has been estimated to increase more than twice between 2000 and 2013 in UK, up to 5.32%.[3] In Catalonia diagnosed T2DM prevalence was 7.6% in 2009, being 3-fold higher in patients aged 75 yr. or older, [4] which is consistent with data reporting a 25% of US population aged ≥65 years having diabetes.[5]

Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation[1], WHO projects that diabetes will be the 7th leading cause of death in 2030 [1], and it has been estimated that diabetes caused 4.9 million deaths in 2014.[2] The greatest number of people with diabetes is between 40 and 59 years of age.

Diabetes-related microvascular complications can lead to significant morbidity and premature mortality; however, the greatest cause of death in people with diabetes is for cardiovascular disease (CVD).[6] It has long been recognized that diabetes is an independent risk factor for CVD, affecting all components of the cardiovascular system: microvasculature, larger arteries, the heart, as well as the kidneys; and imparting a 2- to 4-fold risk of CVD. In addition, many diabetic patients often have other risk factors for CVD, such as obesity, hypertension and dyslipemia.[7] Patients with diabetes have twice the risk of incident myocardial infarction and stroke as that of the general population, many don't survive their first event, or their mortality rate is generally greater than that of the general population. As many as 80% of patients with type 2 diabetes mellitus will develop and possibly die of macrovascular disease. [8,9] Older adults with diabetes are at substantial risk for both acute and chronic microvascular and cardiovascular complications of the disease, althought cardiovascular disease prevalence is not affected by older-age onset diabetes. [5]

Heart failure doesn't fit clearly into the traditional, binary classification of diabetes complications as either microvascular or macrovascular; its pathogenesis includes not only coronary artery disease but also hypertension and diabetic cardiomyopathy causing it.[10] In the Framingham study, that has found that in non-diabetic patients the incidence rate of heart failure was greater for men than for women,[11] it has been estimated that in diabetic patients treated with insulin, diabetes confers more tan a two-fold increase in risk of heart failure in men and five-fold higher risk in women. [12] As with stroke and myocardial infarction, in a heart-failure setting in patients with diabetes, mortality rates are about twice that of the non-diabetic population; individuals with diabetes aged 45–54 years are almost 9-fold more likely to develop heart failure, and the relative risk falls to 1·8 for those aged 75–84 years.[10] Results of 4 yrs. follow-up of an international registry found that diabetes mellitus was associated with a 33% greater risk of hospitalization for heart failure. In patients with diabetes mellitus, heart failure at baseline was independently associated with cardiovascular death, increasing fatal oucome 2.5 fold.[13]

Marked reductions in cardiovascular disease mortality were seen in the last decades as a result of new therapies and proactive diagnosis, however, this decline has been smaller

in diabetic patients. A study found that adults with diabetes have experienced a 50% reduction in the rate of incident CVD, although remaining at a consistent, approximate 2-fold excess for CVD events compared with those without diabetes.[14] Average annual healthcare costs associated with patients with type 2 diabetes are substantially more expensive (72.4%) compared with non-diabetic subjects, and are higher among diabetic patients with poor glycaemic control and macrovascular complications.[15]

Dysglycemia and diabetes complications

In spite of the extensive clinical research devoted to, diabetes is still defined by its features (elevated fasting plasma glucose, glycated haemoglobin, hiperglucemia and glucosuria) and complications, the pathogenesis of type 2 diabetes and its complications remains unknown. [16] Haemoglobin binds irreversibly with glucose: glycated haemoglobin (HbA1c), which indicates the glycemic level during the previous 3-months – the lifespan time of red blood cells-, is the surrogate marker that has been the gold standard outcome in diabetic trials for more than 40 yrs. [17]

The beneficial effect of intensive therapy on microvascular outcomes have been established for insulin-dependant diabetes mellitus in 1993, showing a direct relationship between increased glycemic levels and microvascular complications.[18] The observational study UKPD 35 found that in type 2 diabetic patients, previous hyperglycemia was strongly associated with microvascular and macrovascular complications, being any reduction in HbA(1c) likely to reduce the risk of complications, with the lowest risk being in those with HbA(1c) values in the normal range (<6.0%). Each 1% reduction in updated mean HbA1c was associated with reductions in risk of macrovascular and microvascular complications: (non significant) 14% for myocardial infarction and (significant) 37% for microvascular complications. [19]

Several mechanisms have been proposed to explain hyperglycemia to increased cardiovascular morbidity and mortality. It has been suggested that hyperglycemia may produce advanced glycation end products in diabetic patiens and even in those who are prone to developing diabetes before diabetes onset, contributing to endothelial dysfunction, atherosclerosis and microangiopathy, relevant factors to CVD and heart failure. [20,21]

Since the publication of UKPDS 33 in 1998,[22] the beneficial effect of blood glucose-lowering agents on microvascular complications of diabetes mellitus has been almost unanimously acknowledged by most published statements (77%–100%) and guidelines (95%).[23] However, their effect on macrovascular complications, such as coronary, cerebral and peripheral macroangiopathy, remains uncertain.[8,24,25] A metaanalysis analysing 16 guidelines and 328 statements found that this evidence reported no significant impact of tight glycemic control on the risk of dialysis/transplantation/renal death, blindness, or neuropathy, and a consistent 15% relative risk reduction of nonfatal myocardial infarction, with no significant effect on allcause mortality, cardiovascular mortality, or stroke.[23] These results are consistent with a previous meta-analysis of more-intensive vs. less intensive glucose control found the same risk reduction of 15% for MI favouring the more intensive control. Exploratory analysis in this MA also suggested that participants with no history of macrovascular disease achieved benefit, whereas those with prior macrovascular disease did not.[26]

Epidemiological studies and meta-analyses have clearly shown a direct relationship between HbA1c and CVD, but the potential of intensive glycemic control to reduce

CVD events has been less clearly defined.[6] A meta-analysis of clinical trials [Selvin et al.], showed that, after adjustment for other risk factors, an increase of 1% in the glycated hemoglobin level is associated with an increase of 18% in the risk of cardiovascular events.[27] The observational UKPDS 35 study found an increase of 14% in the risk of death, and an increase of 37% in the risk of retinopathy or renal failure.[18] These increased risks have been confirmed with more or less consistent results in studies using secondary data from healthcare databases. [28,29] It also has been suggested that in no diabetic patients the relation between glycated haemoglobin and cardiovascular events would have a linear association in non-extreme values. [30] The Heart Outcomes Prevention Evaluation (HOPE) found that in diabetic participants, a 1% absolute rise in the updated HbA1c predicted future CVevents after adjusting for confounders and treatment, and the analysis of diabetic and non diabetic patients showed that a 1 mmol/l rise in fasting plasma glucose was related to an increased risk of CV outcomes, after adjusting for presence or abscense of diabetes, thus indicating an independent progressive relationship between indices of glycaemia and incident CV events, renal disease and death.[31]

It also has been suggested that the current target of the current target of HBA1c level does not predict a better coronary microcirculatory function in T2DM patients and a possible link between coronary microvascular disease and LV diastolic function in Type2 diabetic patients.[32,33]

Effect of glucose-lowering therapies on CV outcomes

A number of trials assessed the effects of glucose-lowering therapies on CV outcomes.

The Diabetes Control and Complications Trial (DCCT, 1993)[19] randomly assigned 1441 patients with insulin-dependent diabetes mellitus to receive intensive therapy or standard therapy with insulin. In this study, tight glycemic control in type 1 diabetes patients significantly reduced the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.[19] Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study. The risk of the primary composite CVD outcome was reduced by 42% in the original and that of fatal or nonfatal MI or stroke (MACE) by 57% in the intensive vs. The control group, but the very small number of patients with events (12) is inadequate to draw conclusions. [34]

The United Kingdom Prospective Diabetes Study (UKPDS 33, 1998) was designed in order to assess micro and macrovascular complications of diabetes in 3867 newly diagnosed patients with type 2 diabetes, median age 54 years patients with standard therapy (diet, it was allowed to give patients pharmacological therapy only if they had hyperglycemic symptoms or FPG was higher than 15 mm/L) or pharmacological therapy based on sulphonylureas (chlorpropamide, glibenclamide and glipizide) or with insulin in order to maintain FPG < 6.0 mm/L, with a stepwise addition of other hypoglycaemic agents (metformin or insulin) when the glycaemic goals were not met (patients assigned to any of the three sulphonylureas could be given metformin, and these oral agents could later be replaced by insulin). Patients were followed for 10 years. Haemoglobin A1c (HbA1c) was 7.0% in the intensive group compared with 7.9% in the conventional group--an 11% reduction, with no difference in HbA1c among agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% lower for the composite of any diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal

myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction); 10% lower for any diabetes-related death (death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death); and 6% lower for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction.[22]

In the United Kingdom Prospective Diabetes Study (UKPDS 34, 1998), 753 overweight patients were included in a randomised controlled trial, and were followed for 10·7 years. 411 patients were allocated in standard treatment, primarily with diet alone, and 342 patients were allocated in pharmacological treatment with metformin, aiming for FPG below 6 mmol/L. A secondary analysis compared the 342 patients allocated metformin with 951 overweight patients allocated intensive blood-glucose control with chlorpropamide (n=265), glibenclamide (n=277), or insulin (n=409). Metformin have found to have beneficial effects on cardiovascular outcomes in overweight patients, 34% reduction; sulfonylureas showed a non-significant reduction in risk of myocardial infarction (MI). [35] UKPDS 34 also found a significant 60% higher death rate in patients given metformin plus sulfonylurea compared with those given sulfonylurea alone.[35] It has been noted that these results were obtained in a randomised subgroup of obese patients (342 patients in the metformin group and 411 in the conventional group) and have never been reproduced, suggesting design and methodological drawbacks.[36]

A post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes: 3277 patients were followed through clinical visits or anual questionnaires for 5 years, with no intervention to maintain their previously assigned therapies all patients in years 6 to 10 were assessed through questionnaires. Although differences in glycated hemoglobin levels were lost after the first year, relative reduction in risk of microvascular outcomes persisted at 10 years and reduction in risk on some CV outcomes emerged. In the sulfonylurea-insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) and microvascular disease (24%, P=0.001), risk reductions for myocardial infarction (15%, P=0.01) and death from any cause (13%, P=0.007) emerged over time. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002). [37]

The PROActive trial (2005) assessed the effect of pioglitazone on secondary prevention of macrovascular events in in 5238 patients with type 2 diabetes, who were randomly assigned to receive pioglitazone (titrated from 15 mg to 45 mg) or placebo in addition to their glucose-lowering drugs and other medications. Primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle); no significant results were achieved for the primary endpoint (HR, 0.90). The secondary endpoint (composite of all-cause mortality, MI and stroke) was significantly less frequent in the pioglitazone group (HR, 0.84), meanwhile the incidence of heart failure hospitalizations was higher in the pioglitazone group.[38]

In the Veterans Affairs Diabetes Trial, (VADT, 2009) no significant effect on the rates of major cardiovascular events, death, or microvascular complications - with the exception of progression of albuminuria- was obtained through an intensive glucose control in patients with poorly controlled type 2 diabetes. In this study, 1791 military

veterans (mean age, 60.4 years, mean time of diagnosis of diabetes 11.5, yrs, 40% with history of previous cardiovascular event) were randomly assigned to receive intensive vs. standard pharmacological therapy, and followed during a median of 5.6 yrs.The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. Both groups patients were given metformin plus rosiglitazone if they had a BMI of 27 or more, and those with a BMI of less than 27 were started on glimepiride plus rosiglitazone. Intensive therapy started at maximal doses, and standard therapy started at half of maximal doses. [39] In the follow-up extension of VADT trial, after 9.8 years of follow-up, patients with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had fewer major cardiovascular events than those assigned to standard therapy, but no improvement was seen in the rate of overall survival (VADT follow-up, 2015).[40]

In the ADVANCE trial (2008), in which 11,140 patients with type 2 diabetes were allocated to receive either standard glucose control or intensive glucose control, defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less, there were no significant effects of the type of glucose control on major macrovascular events (HR with intensive control, 0.94; 95% CI, 0.84 to 1.06; P=0.32), death from cardiovascular causes (HR with intensive control, 0.88; 95% CI, 0.74 to 1.04; P=0.12), or death from any cause (HR with intensive control, 0.93; 95% CI, 0.83 to 1.06; P=0.28).[41]

The ACCORD trial (2008), which was designed to assess the effect of intensive therapy vs. glucose-lowering standard on 10,251 patients (mean age, 62.2 years, 38% women, 35% with history of cardiovascular event) with a median glycated hemoglobin level of 8.1%. The target of the intensive therapy group was a glycated hemoglobin level below 6.0%, and the standard therapy target from 7.0 to 7.9%. After a follow-up of 3.5 yrs., the intensive group therapy was discontinued because of a higher mortality (HR ratio, 1.22; 95% CI, 1.01 to 1.46; P = 0.04). The primary outcome - a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes- was no significant reduced in the intensive therapy group (HR, 0.90; [CI], 0.78 to 1.04; P = 0.16). This result was due to a lower rate of nonfatal MI in the intensive group than in the standard-therapy group (3.6% vs. 4.6%; HR, 0.76; 95% CI, 0.62 to 0.92; P = 0.004), and a higher rate of death from cardiovascular causes in the intensive group (2.6% vs. 1.8%; hazard ratio, 1.35; 95% CI, 1.04 to 1.76; P = 0.02); with no significant difference in the rate of nonfatal stroke (1.3% vs. 1.2%; HR, 1.06; 95% CI, 0.75 to 1.50; P = 0.74). Of note, rates of the primary outcome began to separate in the two study groups after 3 years.[42]. After the intensive therapy was discontinuated, the target for glycated hemoglobin level was set from 7 to 7.9% for all participants, and the median HbA1c in thisgroup rose from 6.4% to 7.2%, and the use of glucose lowering medications and rates of severe hypoglycemia were similar in the two groups. The follow-up continued until the planned end of the trial (5 yrs). The trends in CV mortality and MI persisted during the entire follow-up period (HR for death, 1.19; 95% CI, 1.03 to 1.38; and HR for nonfatal myocardial infarction, 0.82; 95% CI, 0.70 to 0.96).[43]

Before the ACCORD trial, a majority of statements declared valuable to achieve tight glycemic control to prevent macrovascular complications (47%–59%). After its publication in 2008, only 21% of statements favored tight glycemic control in 2009.[23]

Cardiovascular safety and regulatory recommendation for new non-insulin glucose-lowering agents

FDA issued the marketing authorization for rosiglitazone in late May 1999 and European authorities did so in July 2000, but required a post-approval clinical outcome trial, known as the RECORD (rosiglitazone evaluated for cardiovascular outcomes and regulation of glycemia in diabetes) trial. In a meta-analysis (MA) published in 2007, Nissen et al. suggested increased CV risk for patients treated with rosiglitazone, with an odds ratio for myocardial infarction of 1.43 (95% confidence interval: 1.03 to 1.98, p = 0.03) and a border-line significant increase of the risk of CV mortality.[44] Interim results from the the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD study), published in 2007, reported that rosiglitazone was associated with a small, nonsignificant increase in the risk of the primary outcome of all hospitalizations and deaths from CV cause (HR, 1.08; 95% [CI], 0.89 to 1.31), and for the fatal or nonfatal myocardial infarction outcome, the HR ratio was 1.16 (95% CI, 0.75 to 1.81). [45] A manufacturer's MA with data similar to that by Nissen and Wolski had been provided to the FDA and the European Medicines Agency in August 2006, and prompted the information was included in product labels in Europe two months later.[46] Observational research using health care database added evidence about the increased risk of congestive heart failure, acute myocardial infarction, and mortality associated with rosiglitazone. [47]

In December 2008, the US Food and Drug Administration (FDA) issued a Guidance for Industry recommending that, "in order to establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk". At the time of NDA submission, all applicants have to compare the incidence of important CV events occurring with their investigational agent to the incidence of the same types of events in the control group. At least three major cardiovascular events (MACE) should be prospectively adjudicated: CV death, non-fatal myocardial infarction and non-fatal stroke, and can include other endpoints. This assessment can be accomplished through a meta-analysis of phase 2 and phase 3 clinical trials and/or throughout a single, large safety trial.[24]

In response to concerns regarding rosiglitazone's CV safety, in September 2010 US FDA significantly restricted the use of rosiglitazone to patients who cannot control their Type 2 diabetes on other medications, and required that GSK develop a restricted access program for Avandia (rosiglitazone) under a risk evaluation and mitigation strategy, or REMS available to new patients only if they are unable to achieve glucose control on other medications and are unable to take pioglitazone, the only other drug in the class of thiazolinedediones.[48] FDA performed a re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, and decided to modify the rosiglitazone REMS program requirements in November 2013.[49] Rosiglitazone was withdrawn from the EU market in September 2010; the marketing authorisation for Avandia (Rosiglitazone) expired on 11 July 2015 following the decision of the marketing authorisation holder,[50] Smithkline Beecham Ltd., not to apply for a renewal of the marketing authorisation.[51]

In 2012, the EMA issued a guidance stating that a new glucose-lowering agent should preferably show a neutral or beneficial effect on parameters associated with cardiovascular risk(e.g. body weight, blood pressure, lipid levels), recommending that

"the emphasis will be on major cardiovascular events (MACE) (CV death, non-fatal myocardial infarction and stroke) but hospitalization for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. Other events such as revascularization and/or worsening of heart failure will also be evaluated (…).[25]

Following regulatory recommendations, a number of large randomized controlled trials have been designed and conducted in order to assess the impact of non-insulin glucose-lowering agents on major cardiovascular outcomes. Out of them, five large RCTs (one terminated at an interim analysis) showed neutral results on cardiovascular outcomes (SAVOR-TIMI 53 [sitagliptin], EXAMINE, (alogliptin) AleCardio [aleglitazar], TECOS[sitagliptin], ELIXA, [lixisenatide]), and three studies, (EMPA-REG [empagliflozin], LEADER [liraglutide] and SUSTAIN-6 [semaglutide] showed beneficial results for the primary composite outcome. Apart from other studies terminated because of safety concerns (fasiglifam) and some others finished (ACE [acarbose]) or terminated (omarigliptin, taspoglutide) with not-published results, currently ten large RCT are on-going and assess the effect of seven agents on CV outcomes: CARMELINA and CAROLINA [linagliptin], HARMONY [albiglutide], REWIND [dulaglutide], EXCEL and ITCA [exenatide], CANVAS and CREDENCE [canagliflozin], dapagliflozin [DECLARE-TIMI] and ertugliflozin.

These large double-blind, randomized, event-driven RCTs have adopted a non-inferiority design – superiority is sometimes included as secondary outcome. Investigational products are compared to placebo in addition to standard care. These studies enroll high CV risk T2DM patients, or patients with established CV disease (CVD), in order to achieve the goal of showing absence of negative CV outcomes in the shortest possible time.[52,53]

So far, empagliflozin is the only one agent that received a US FDA approval for a new indication: to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease prevention, decision made based on the decrease on CV mortality in the EMPA-REG study, which is probably related with the body water depletion and subsequent effect on heart failure occurrence or worsening.[54]

EMA is reviewing its 'Guideline on clinical investigation of medicinal products in the 10 treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1). Recommendations state that "A dedicated cardiovascular outcome trial might be necessary when an increased cardiovascular risk has not been excluded in a meta-analysis of the phase II/III studies. A dedicated cardiovascular outcome trial might also be favored whenever a cardiovascular "off-target" risk is intrinsic in the molecule or mechanism of action, or when cardiovascular signals have been observed in the pre-clinical studies (…) and have an adequate control arm, and if an active control is used this should preferably be one for which the cardiovascular risk, or absence thereof, is already well characterized".[55]

Evidence from clinical research

Due to randomized allocation and double blind design, well designed and conducted RCTs are considered the "gold standard" for scientific evidence: every patient in a study has a known (usually equal) chance of receiving each of the treatments, the selection bias is minimized and both known (and unknown) confounding factors are likely to be distributed in an unbiased manner between the groups. Random assignment of a large number of subjects into treatment groups usually leads to a good balance of observed and unobserved risk factors in all groups. Nevertheless, randomized controlled trials

have major limitations when they are used to assess the role of medications in the etiology and management of chronic diseases. The main limitations arise from selected populations, the long time required from trial design to completion, the relatively short duration of exposure, and under representativeness of frail elderly patients. Results obtained from trials can be misleading if generalized to the general population because effect sizes, baseline risks, and comorbidity have been shown to differ between trial populations and the broader population not represented in trials. [56] Although longer, with larger sample sizes, and including older patients, CV outcomes large trials for hypoglycemic agents are not completely free of these limitations, in particular selected populations (i.e., patients at high cardiovascular risk, exclusion of patients at end stage of renal chronic disease, good treatment compliance).

RCTs include selected populations, with defined risks, and are followed in conditions different from the clinical practice. In addition, many of RCTs designed to fulfill regulatory requirements are still ongoing and foreseen to be completed in the next years; results are foreseen to be published since 2017 up to 2020, being currently unavailable.

FDA's guidance reccommended that outcomes in RCTs evaluating glucose-lowering agents for T2DM should include "cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints".[24] Being death the most important clinical event it has a very low expected rate in T2DM trials, and the event rate of the rest of CV outcomes are foreseen to be low, even in high CV risk populations. Then, in order to reduce the sample size and the length of the study, these RCTs have a primary composite outcome (PCO) of three or four individual components: cardiovascular death, and non-fatal events of similar clinical importance. However, analysis, interpretation and reporting of COs are complex and can be even misleading.[57]

Up to 2016 five large (RCTs) failed to show any beneficial effect on CV outcomes of three dipeptidy-peptidase 4 inhibitors (saxagliptin, alogliptin, sitagliptin), the short-acting glucagon-like peptide 1 analogue lixisenatide the dual agonist of peroxisome proliferator-activated receptors, and aleglitazar (study terminated because of futility of effects and adverse effects). It has been suggested that the lack of evidence of a cardioprotective effect can be due to patients' charateristics (extensive aterosclerosis and long-standing diabetes) or because a very long duration of exposure would be required to be achieved before beneficial effects on CV outcomes could manifest.[58] Additionally, concerns arose from two large dipeptidyl peptidase inhibitors trials (saxagliptin and alogliptin) because of increased rates of heart failure in patients treated with these agents.[59] Three more recently published trials showed beneficial effects on cardiovascular outcomes of two long-acting GLP-1 analogues, liraglutide and semaglutide, and of the sodium-glucose transporters inhibitor (SGLT-2), empagliflozin.

Published RCTs:

SAVOR-TIMI 53:

Saxagliptin is a potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP-4) inhibitor approved in July 2009 in US and in October 2009 in EU. The SAVOR-TIMI 53 trial was designed as a superiority trial, with a closed testing hierarchy to preserve the alpha level that prespecified that a test for noninferiority with

respect to the primary composite end point should be performed first and a test for superiority performed thereafter**.** [60]

In this trial, 16,492 patients with type 2 diabetes (glycated hemoglobin level of 6.5% to 12.0%), and either a history of established cardiovascular disease (78%) or multiple risk factors for vascular disease were randomized to receive saxagliptin 5 mg (2.5 mg for patients with GFR ≤50 mL/min) or placebo and were followed for a median of 2.1 years. To meet the criteria for established cardiovascular disease, patients had to be at least 40 years old and have a history of a clinical event associated with aterosclerosis involving the coronary, cerebrovascular, or peripheral vascular system. To meet the criteria for the multiple risk factors, patients had to be at least 55 years of age (men) or 60 years of age (women) with at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking.

Results showed neutral effects of saxagliptin on primary end point, a composite of 3-point MACE (cardiovascular death, myocardial infarction, or ischemic stroke) (HR, 1.00; 95% confidence interval [CI], 0.89 to 1.12) as well on the major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure (hazard ratio, 1.02; 95% CI, 0.94 to 1.11; P = 0.66). However, hospitalization for heart failure was more frequent in the saxagliptin group than in the placebo group (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51). [61]

These results were consistent irrespective of renal function. Overall, the risk of hospitalization for heart failure among the three eGFR groups of patients (>50 mL/min, 30-50 mL/min and < 30 mL/min) was 2.2% (referent), 7.4% (adjusted HR 2.38), and 13.0% (adjusted HR 4.59), respectively. The relative risk of hospitalization for heart failure with saxagliptin was similar in patients with eGFR >50 mL/min/1.73 m^2 (HR 1.23 [95% CI 0.99-1.55]), eGFR 30-50 mL/min/1.73 m(2) (HR 1.46 [95% CI 1.07-2.00]), and in patients with eGFR <30 (HR 0.94 [95% CI 0.52-1.71]). Patients with renal impairment achieved reductions in microalbuminuria with saxagliptin that were similar to those of the overall trial population.[62] The change in albumin/creatinin ratio (ACR) did not correlate with that in HbA1c.[63]

In the SAVOR TIMI 53 trial, baseline HbA1c≥7% was associated with increased risk of cardiovascular death, myocardial infarction, or ischemic stroke (adjusted hazard ratio [HR(adj)] 1.35; 95% confidence interval [CI], 1.17-1.58) but not hospitalization for heart failure (HR(adj) 1.09; 95% CI, 0.88-1.36). Saxagliptin neither increased nor decreased the risk of cardiovascular death, myocardial infarction, or ischemic stroke in patients with HbA1c <7% , 7%-<8%, 8%-<9% , ≥9%. Baseline HbA1c is associated with increased risk of macrovascular events but not hospitalization for heart failure. There was no heterogeneity in the effect of saxagliptin on cardiovascular events by baseline HbA1c, with cardiovascular death, myocardial infarction, or ischemic stroke neither increased nor decreased across the spectrum of baseline HbA1c values.[64]

EXAMINE:

Alogliptin is a selective inhibitor of dipeptidyl peptidase 4 (DPP-4), approved for the treatment of type 2 diabetes in January 2013 in US and in September 2013 in EU. Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE study) was a non inferiority trial with a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [65]

In the EXAMINE trial, 5380 type 2 diabetes patients with and acute coronary syndrome (ACS) - either an acute myocardial infarction or unstable angina requiring hospitalization - within the previous 15 to 90 days were randomized to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. Fort he PCO, the HR was 0.96. Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points).[66]

The exploratory extended MACE endpoint (all-cause mortality, non-fatal myocardial infarction, nonfatal stroke, urgent revascularisation due to unstable angina, and hospital admission for heart failure**)** was seen in 16·0% patients assigned to alogliptin and in 16·5% assigned to placebo (hazard ratio [HR] 0·98, 95% CI 0·86–1·12). Hospital admission for heart failure was the first event in 3·1% patients taking alogliptin compared with 2·9% taking placebo (HR 1·07, 95% CI 0·79–1·46).[65] Alogliptin had no effect on composite events of cardiovascular death and hospital admission for heart failure in the post hoc analysis (HR 1·00, 95% CI 0·82–1·21) and results did not differ by baseline BNP concentration. Patients with history of heart failure at baseline were older, more frequently women, and had higher baseline BNP concentrations and lower eGFR values, than patients with no history of heart failure. HbA1c concentrations were, overall, significantly lower in the alogliptin group than in the placebo group at the end of the trial.[67]

TECOS:

Sitagliptin is a dipeptidyl-peptidase inhibitor approved by the US FDA in October 2006; the European Commission granted a marketing authorisation valid throughout the European Union in March 2007. The TECOS was a a non-inferiority design trial that evaluated long-term effects on cardiovascular outcomes of sitagliptin, or placebo added to existing therapy. The trial enrolled 14,671 patients aged ≥50 years with T2DM (glycated hemoglobin level, 6.5 to 8.0%), established cardiovascular disease and no severe renal insufficiency, and the median follow-up was 3 yrs. Patients were eligible if their diabetes had been managed with stable-dose monotherapy or dual combination therapy with metformin, pioglitazone, or a sulfonylurea for ≥3 months prior to enrollment or insulin (with or without metformin). In the TECOS Study, sitagliptin was non-inferior to placebo for the primary composite cardiovascular outcome of CV death, MI, stroke and hospitalization for unstable angina. (HR, 0.98;5% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00). The statistical analysis plan prespecified that the following hypotheses be tested in a sequential manner: noninferiority for the primary composite cardiovascular outcome (per-protocol analysis), noninferiority for the secondary composite cardiovascular outcome (per-protocol analysis), superiority for the primary composite cardiovascular outcome in the intention-to-treat analysis, and superiority for the secondary composite cardiovascular outcome in the intention-to-treat analysis. [68]

AleCardio: Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and expected favorable effects on lipid profiles. This large RCT enrolled 7226 patients hospitalized for ACS (myocardial infarction or unstable angina) with T2DM, (90% had DM for an average of 8 years before enrollment) who were randomized in a 1:1 ratio to receive aleglitazar 150 µg or placebo daily. The planned follow-up – at least 2.5 years until 950 primary end point events were positively adjudicated – was terminated after a median of 104 weeks, upon recommendation of the data and safety monitoring board due to futility for efficacy and increased rates of safety end points (hospitalization due to heart failure and changes in renal function). The primary end point - time to cardiovascular death, nonfatal

myocardial infarction, or nonfatal stroke - occurred in 9.5% in the aleglitazar group and 10.0% in the placebo group (HR 0.96). Rates of serious adverse events, including heart failure (3.4% for aleglitazar vs 2.8% for placebo, P= .14), gastrointestinal hemorrhages (2.4% for aleglitazar vs 1.7% for placebo, P=.03), and renal dysfunction (7.4% for aleglitazar vs 2.7% for placebo, P< .001) were increased. Some of these adverse effects are related to class effects. Heart failure is an established risk of PPAR-γ activators and thought to be due to fluid retention. The increased risk for heart failure associated with aleglitazar in the AleCardio trial (HR, 1.22) was similar to that attributed to pioglitazone in a meta-analysis (HR, 1.41) and to that observed with an unrelated diabetes agent, saxagliptin, in SAVOR-TIMI 53 trial (HR, 1.27) Increased serum creatinine is also a known effect of PPAR-α activators and was associated with aleglitazar in this trial. Increased serum creatinine with aleglitazar, reversible upon drug discontinuation, is thought to be due to decreased glomerular filtration rate.[59]

ELIXA: Lixisenatide is a close analogue of human glucagon like peptide 1 (GLP-1), with an i.v. half-life of 30 min and a half-life of 2–3 h after s.c. administration;[69] it was appoved in EU in 2013. The ELIXA study was designed as a non-inferiority as well as superiority to placebo trial for the primary composite end point of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. The trial included 6068 T2DM with acute coronary syndrome [ACS] (defined as history of myocardial infarction or hospitalization for unstable angina within the previous 180 days) who were randomized 1:1 to receive lixisenatide or placebo once daily in addition to standards therapy, and who were followed for 2.1 years. The intervention showed neutral results on the primary composite outcome (HR, 1.02) , showing the noninferiority of lixisenatide to placebo (P<0.001) but failing to show superiority (P = 0.81). The frequency of each separate cardiovascular components of the primary end point was similar in the two study groups: CV death (HR, 0.98;95% CI, 0.78 to 1.22), fatal or nonfatal myocardial infarction (HR, 1.03; 95% CI, 0.87 to 1.22), fatal or non-fatal stroke (hazard ratio, 1.12; 95% CI, 0.79 to 1.58), hospitalization for unstable angina (HR, 1.11;95% CI, 0.47 to 2.62). No significant between-group differences in the rate of hospitalization for heart failure (hazard ratio in the lixisenatide group, 0.96; 95% CI, 0.75 to 1.23) or the rate of death (hazard ratio, 0.94; 95% CI, 0.78 to 1.13). Slightly less number of deaths from any cause occurred in the liraglutide group HR, 0.94; 95% CI, 0.78 to 1.13). Effect of lixesenatide on percentage change in the urinary albumin-to creatinine ratio from baseline until week 108 was neutral after adjustment for the glycated hemoglobin level as measured at baseline and at 3 months after randomization.[70] No results about retinophatic events were published, althougth published results in www.clinicaltrials.gov report a higher number of events in the lixisenatide group.

EMPA-REG outcomes:

Empagliflozin is a sodium-glucose co-transporter type 2 (SGLT2) inhibitor, approved in US and in EU in 2014. The EMPA-REG study assessed the effect of empagliflozin, a selective sodium–glucose cotransporter 2 in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care. The study had a four-step hierchical design (noninferiority for the primary outcome, noninferiority for the key secondary outcome, superiority for the primary outcome, and superiority for the key secondary oucome) and analyzed in the pooled empagliflozin group versus the placebo group. The primary outcome was a composite of death from cardiovascular causes,

nonfatal myocardial infarction, or nonfatal stroke, The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.[71,72]

The study randomized 7020 patients assigned to receive 10 mg or 25 mg of empagliflozin or placebo once daily, the median follow-up time was 3.1 yrs. Rates of death from cardiovascular causes (HR, 0.62), hospitalization for heart failure (hazard ratio, 0.65), and death from any cause (hazard ratio, 0.68), were significantly lower in the empagliflozin pooled group, with no reduction in the rates of fatal and non-fatal myocardial infarction (hazard ratio, 0.87) or fatal and non-fatal stroke (hazard ratio, 1.18). Silent myocardial infarction (hazard ratio, 1.28) and non-fatal stroke (hazard ratio, 1.24) had non-significant higher rates in the empagliflozin group. There was some heterogeneity among sub-groups in the primary composite outcome, but the benefit on cardiovascular death was consistent across all groups. After 12 weeks (with unchanged glucose-lowering therapy) glycemic control showed a dose-related response in the empagliflozin group (adjusted mean differences in the glycated hemoglobin level in patients receiving empagliflozin 10 mg. were −0.54 percentage points and −0.60 percentage points in the 25-mg group), and this difference declined over time. Althought small dose–response effect for the 10-mg dose of empagliflozin versus placebo and the 25-mg dose versus placebo has been documented for metabolic responses, the two dose groups had similar hazard rates on cardiovascular outcomes. Adverse effects related to empagliflozin were genital infections and urosepsis, with similar proportions of diabetic ketoacidosis, volumen depletion, thromboembolic events, and bone fracture in the empagliflozin groups and the placebo group.[72]

706 patients (10.1%) had heart failure at baseline. The composite of heart failure hospitalization or cardiovascular death [hazard ratio, HR: 0.66 (95% confidence interval: 0.55–0.79)], hospitalization for heart failure [HR: 0.65 (95% CI: 0.5–0.85)], cardiovascular death [HR: 0.62 (95% CI: 0.49–0.77)], and all-cause mortality [HR: 0.68 (95% CI: 0.57–0.82)], occurred in a lower percentage of patients treated with empagliflozin than with placebo, but in a lesser extend and non significantly in patients with HF at baseline. These effects were consistently observed across subgroups defined by baseline characteristics, including patients with vs. without heart failure, and across categories of medications to treat diabetes and/or heart failure.[73]

Both an increase of hematocrit and a non-significant increase in the risk of stroke have been reported in the EMPAREG study.[74] The hematocrit increases during treatment with SGLT2 inhibitors, which have a diuretic effect but do not cause sufficient hemoconcentration to increase the risk of cerebral infarction. Elevation of the hematocrit during SGLT2 inhibitor therapy is presumed to involve enhancement of erythropoiesis in addition to hemoconcentration.[75] The increase in the hematocrit and an HR of 1.33 for stroke have been found in a metaanalysis of RCTs with SGLT2 inhibitors.[74,76]

LEADER:

Liraglutide is a GLP-1 analogue with an i.v. half-life of 8−10 h and 13−15 h after s.c. administration, making it suitable for once daily administration,[77] approved in EU in 2010. The LEADER was a double-blind, randomized, placebo-controlled trial, assessing the effect of liraglutide on cardiovascular outcomes, with a non-inferiority design regarding the primary outcome (CV death, non-fatal infarction and non-fatal stroke). 9340 Type 2 diabetic patients with a glycated hemoglobin level of 7.0% or more and established CVD or with risk factors for CVD were randomized 1:1 to receive liraglutide 1,8 mg. or placebo. The median follow-up was 3.8 years. The primary

outcome for liraglutide group was significant lower (HR, 0.87), mainly due to a lower rate in CV death in the liraglutide group (hazard ratio, 0.78). Non-fatal MI and non-fatal stroke were non-statistically lower in the liraglutide group: HR, 0.88 and HR, 0.89 respectively. The rate of death from any cause was lower in the liraglutide group (HR, 0.85). Hospitalization for heart failure (HHF) was non-significantly reduced in the liraglutide arm (HR, 0.87) .The rate of composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (hazard ratio, 0.84), driven by a lower rate of nephropathy events in the liraglutide group (hazard ratio, 0.78), retinopathy events were non significantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR, 1.15).[78]

SUSTAIN-6: The SUSTAIN study was a non-inferiority large RCT assessing the effect of semaglutide, a long acting glucagon-like peptide 1 (GLP-1) analogue with an extended half-life of approximately 1 week, on cardiovascular outcomes vs. placebo 3297 Type 2 diabetic patients. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome occurred in 6.6% in the semaglutide group and in 8.9% in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P = 0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P = 0.04). Rates of death from cardiovascular causes were similar in the two groups.[79]

On-going studies, design and rationale published:

CAROLINA: Linagliptin effect on cardiovascular outcomes in subjects with early type 2 diabetes and increased cardiovascular risk or established complications is also assessed in an on-going randomized trial, CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (NCT01243424). The study will determine the long-term cardiovascular impact of linagliptin versus the sulphonylurea glimepiride, with a design of non-inferiority by comparing the upper limit of the two-sided 95% confidence interval as being below 1.3 for a given hazard ratio, withfive subsequent hierarchical testing for superiority.[80]

CANVAS is a double-blind, placebo-controlled trial designed to evaluate the effects of canagliflozin on the risk of cardiovascular disease and to assess safety and tolerability in patients with inadequately controlled T2DM and increased cardiovascular risk. The first of 2 planned phases randomized 4,330 individuals to placebo, canagliflozin 100 or 300 mg (1:1:1) with planned follow-up of about 2 years to substantiate potential cardiovascular protection by assessing key biomarkers and to achieve initial safety objectives. By the end of mid-September 2012, a total of 7174 patient-years of follow-up were accrued.The intended primary objectives of the study were 2- fold—the first being to determine the effects of canagliflozin compared to placebo (against a background of standard of care) on the risk of cardiovascular disease, and the second being to provide data on safety and tolerability. The primary null hypothesis to be tested was that there would be no difference in the risk of cardiovascular disease between patients treated with canagliflozin compared to patients treated with placebo.[81]

The ACE trial is a randomized, placebo-controlled, double-blind, secondary-prevention trial in 7500 patients with coronary heart disease (defined as prior myocardial infarction

[MI], unstable angina or current stable angina), who also have impaired glucose tolerance (IGT) and are≥50 years old. Randomization is the 1:1 addition to optimized usual cardiovascular disease care of acarbose 50 mg or matching placebo TID. Exclusions include a history of diabetes, cardiovascular event within the last 3 months, New York Heart Association class III/IV heart failure, severe hepatic disease, and severe renal impairment. [82]

Diabetes in Spain

In Spain, the prevalence of diagnosed diabetes has been estimated in 13,8% of the general population aged 18 and older (of which 6% corresponds to unknown diabetes), with 41.3% and 37.4% of men aged 75 years and older.[83]

A cross-sectional study performed in the SIDIAP database in 2009, found a prevalence of 7.6%. of people diagnosed with type 2 diabetes, which corresponds to 286.800 people between 31-90 yrs., mean age 68 yr, duration of disease 6.5 yrs., 54% were men. The prevalence increases to 22.4% in patients.70 years of age.[4]

A cross-sectional study performed in the Catalan primary care electronic database SIDIAP, analyzing data of patients registered in general practitioner charts during 2011, found a total of 318,020 subjects aged 30 yrs and older with a diagnosis of T2DM (53.8% men), with a mean age of 68.8 years; mean age at diagnosis 61.6 years, and a median disease duration of 6.7 years. 38.0% of subjects were ≤65 (62.9% males); 29.4% were 66–75 (54.3% males); 25.8% were 76–85 (45% males); and 6.8% were > 85 years (33.4% males). Among this population, about 22.5% with diagnosed Type 2 diabetes had no pharmacological treatment. [84] The proportion of overweighted or obese among diabetic patients has been estimated in 23,6% in 2009. [85]

Glucose-lowering agents' utilization in Spain:

According to a report from the Spanish Medicines Agency, metformin and the sulphonyurea glimepiride were the most used oral antidiabetic in Spain in 2006, with defined daily dose/1.000 inhabitants (DDD/1.000) of 13,5 DHD for metformin (24 % of all hypoglycemic agents including insulins), 10,32 for glimepiride (18.5%) and 7,03 for glibenclamide (12.6%). The use of glibenclamide decreased since 2000 and the use of metformin has continuously increased since 1998, date of the publication of the UKPDS33. The ratio ot use of non-insulin glucose-lowering agents vs. insulin was 2,18 in 1992 to 3,12 en 2006, [86] this ratio was also observed between 2010-2014.[87]

During 2008-2014, new non-insulin glucose-lowering agents have been marketed in Spain: sitagliptin and vildagliptin (2008), exenatide (2009), liraglutide (2011), linagliptin (2012) o lixisenatida (2013), dapagliflozin (2013) and fixed-dose combinations: metformin-vildagliptin and metformin-pioglitazone (2008), metformin-sitagliptin (2009), glimepiride-pioglitazone (2010) saxagliptin-metformin (2012) and linagliptin-metformin- (2013). Clorpropamide (2011) y rosiglitazone (2010) are not longer marketed. Fixed-dose combinations more used in Spain in 2014 were combinaciones a dosis fijas más utilizadas en 2014 fueron vildagliptin-metformin and sitagliptin-metformin (4,2 and 5,1 DHD respectively). [87]

In a cross-sectional study performed in the Catalan SIDIAP database, in 2009, out of 216.868 T2DM patients, approximately 162,000 patients (74.6%) were treated with oral glucose-lowering agents: 46.9% with monotherapy, 22.9% with biotherapy, 2.8% with tritherapy and 2.0% with other combinations. An additional 10% out of 216,868 patients are treated with insulin plus oral non-insulin glucose-lowering agents. Only 2% of patients registered treatment changes.[4]

A cross-sectional study analyzing trends in diabetic treatments in Catalonia, found 257.072 registered patients with T2DM in the database SIDIAP in 2007; this number increased up to 343 969 in 2013. In the period 2007-2013, the proportion of patients not pharmacologically treated decreased by 9.7%, there was an increase in the percentage of patients on monotherapy (4.4% increase), combination therapy (2.8% increase), and insulin alone or in combination (increasing 2.5%). The use of metformin and dipeptidyl peptidase-IV inhibitors increased gradually, while sulfonylureas, glitazones and α-glucosidase inhibitors decreased. The use of glinides remained stable, and the use of glucagon-like peptide-1 receptor agonists was still marginal. Regarding glycaemic control, there were no relevant differences across years: mean glycated haemoglobin (HbA1c) value was around 7.2%; the percentage of patients reaching an HbA1c 17% target ranged between 52.2% and 55.6%; and those attaining their individualised target from 72.8% to 75.7%. [88]

Data Source:

Primary care data are a particularly suitable source for assessing cardiovascular risk in people in Spain since all the population is registered with a general practitioner. The Spanish National Health Service (NHS) is a state general tax funded system, divided into primary and secondary care, and provides universal healthcare. Primary care is the most accessible health-care level to the general population. In Spain, more than 95% of the population visit their GP at least once in every 5 years. [89]

SIDIAP:

The Information System for the Development of Research in Primary Care (SIDIAP database) has been created in 2010 by the Catalan Institute of Health (CIH) - the main provider of health services in Catalonia- and the Institut Jordi Gol. SIDIAP contains the primary care computerized medical records of more than 1,300 general practitioners (GPs) in Catalonia (North-East Spain), with information on a representative 80% of the population (> 5,5 million people). Currently, the SIDIAP database stores information corresponding to 279 primary health care centers of Catalonia, which represents the 74% of the total catalan population. Filtered and quality-controled data are representative of 1,900,000 people. [90-92]

It comprises the clinical and referral events registered by primary care health professionals (3,384 GPs and nurses) in electronic medical records, sociodemographic information, pharmacy invoicing data, as well as referrals to imaging, secondary care and their main outcomes. Only GPs who achieve coding quality standards can contribute to the SIDIAP database. Health professionals gather the information recorded in SIDIAP using ICD-10 codes, and structured forms designed for the standardized collection of variables relevant for primary health care, including lifestyle risk factors (smoking and alcohol drinking) and anthropometric measurements (height, weight and body mass index), among others.[90-92]

Available information from SIDIAP and related databases includes sociodemographics (date of birth, gender, country of origin), clinical information (GP visits, referrals,

vaccines, body mass index, blood pressure, spirometry, diseases coded by ICD-10 codes), subsidized drugs dispensed in community pharmacies, laboratory tests (creatinine, HbA1c, etc.), hospital admissions and date and cause of death, among other variables.[90-92]

Concerning dispensed medicines, SIDIAP database contains coded data of individual patients and prescribing health professional, medicine's National Code and ATC classification, description of presentation, number of units per package, daily dose, month of drug production, monthly number of packages dispensed and dates of start and end of prescription. [90, 93]

Code ICD-10 is available, as well dates of start and end of diagnosis. Values and record date of clinical parameters as systolicand diastolic blood pressure (SBP, DBP), SBP, weight, height, body mass index, (BMI), alcohol and cigarettes consumption. as well as laboratory tests, imaging diagnosing, and other tests can be accessed.

SIDIAP can be linked with Catalan hospital discharges' databases (CMBD-AH), which contain information of all hospital admissions in CIH hospitals, and with the mortality registry (date and cause of all deaths of Catalonia's residents). [91]

I. Research question:

Background:

Diabetes is an independent risk factor for CV disease. Cardiovascular disease has been estimated to be 2-4 fold higher in diabetic patients than non-diabetic, affecting a 80% of patients with type 2 diabetes. While the effect of effect of glucose-lowering agents on microvascular events has been established in different observational and interventional studies, the effect of glucose control on cardiovascular outcomes remains unclear. Metformin is currently the primary drug of choice for type 2 diabetes patients. Sulphonylureas (SU) have been associated with weight gain and an increased rate of myocardial infarction. A number of new drugs – including insulins- and new drug classes have been developed in order to achieve the glucose control in type 2 diabetic patients. Observational evidence of a potential increase of cardiovascular adverse events for rosiglitazone led regulatory agencies to require new glucose-lowering agents to show absence of cardiovascular toxicity. Large RCTs, designed and conducted in order to comply regulatory requirements, including populations at high cardiovascular risk, showed results varying from neutral effect to a decrease on CV primary outcome. Concerns have arisen because of an increased incidence of heart failure with the use of some agents, particularly some DPP-4 inhibitors (saxagliptin, alogliptin) and glitazones. Empagliflozin, a SGLT-2 inhibitor, showed to have a beneficial effect on all-cause mortality, cardiovascular mortality and myocardial infarction, but not on stroke incidence, and urinary and genital infections limit their tolerability. Among GLP-1 analogues, results of large RCT showed neutral effects on PCO for lixisenatide and beneficial effects on PCO for liraglutide and semaglutide. So far, empagliflozin is the only one agent that received a US FDA approval for reducing the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease prevention as a new indication; this based on the decrease on CV mortality in the EMPA-REG study, which is probably related with the body water depletion and subsequent effect on heart failure occurrence or worsening.

***Rationale*:** Effects of non-insulin glucose-lowering agents on cardiovascular outcomes in Type 2 diabetic patients is not well established Previous epidemiological research has obtained variable results different regarding the association between cardiovascular disease events and Type 2 diabetes. Three glucose-lowering agents demonstrated beneficial effect on MACE in large controlled-placebo trials conducted in high CV risk T2 diabetic patients. A number of published observational researches present different results in different settings.

The assessment of cardiovascular outcomes in cohorts of patients treated with hypoglycemic agents in clinical settings could provide useful information if adequately collected and analyzed, although it can be compromised by uncontrolled biases and confounding, in particular confounding by indication.

The aim of this study is to assess the effect in a clinical setting of non-insulin glucose-lowering agents on CV outcomes in cohorts of new users of Catalan general practitioners' databases, in the period between Jan 1st 2010 to Dec 31st 2015. This database can be linked with hospital discharges and mortality registries.

Research hypothesis: In the study period, non-insulin glucose-lowering agents introduced as add-on therapy to the diabetes best standard care don't provide a clinically relevant benefit defined as a 10% reduction in cardiovascular morbidity and mortality compared with the use of reference non-insulin glucose-lowering agents, metformin and sulphonylureas (SU).

II. Source and study populations

Setting: Catalonia (Spain)

Source population: All residents in Catalonia registered in the public Catalan Institut of Health, universal health care system, for at least one year, and recorded in the SIDIAP healthcare database.

The Catalan Institute of Health (CIH), the main provider of health services in Catalonia, manages 279 primary care teams (PCT) with data of 5.564.292 people, approximately 74% of the Catalan population. SIDIAP (Information System for the Development of Research in Primary Care) is a primary care population computerized database in Catalonia, Spain, containing anonymised patient's records for the 5.8 million people attended by general practitioners in the Catalan Health Institute. SIDIAP includes data on demographic variables, diagnoses, clinical variables, prescriptions, specialist referrals, laboratory test results, and medications withdrawn from pharmacist offices, obtained from the CatSalut general database.

Study population: Catalan population aged≥18, attending primary care practitioners registered in the SIDIAP, between January 1st 2010 to December 31st 2015 diagnosed of Type 2 diabetes mellitus and receiving a first prescription of a non-insulin glucose-lowering agent.

Study period: from January 1st 2010 until Dec 31 2015

Inclusion criteria (ICD-10 codes):

- all patients registered in the SIDIAP database for at least one year previous to the index date.
- aged ≥18,
- attending primary care practitioners registered in the SIDIAP, between January 1st 2010 to December 31st 2015
- diagnosed of Type 2 diabetes mellitus (Coded E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, and E11.9)
- receiving a first prescription of a non-insulin glucose-lowering agent. (*Patients with ICD 10 code Z79.84 [long term (current use) of oral antidiabetic drugs] can be included if receive a first prescription on another one non-insulin glucose lowering agent)*

Exclusion criteria (ICD-10 codes):

- people < 18 yrs,
- diagnosis of Type 1 diabetes mellitus, (Coded E10.0, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E11.8, and E11.9.)
- active prescription of the given non-insulin glucose-lowering agent in the 90 days previous to cohort entry.
- diabetes mellitus due to underlying condition, (E08)
- drug or chemical induced diabetes mellitus (E09)
- gestational diabetes (O24.4)
- post pancreatectomy diabetes mellitus (E13)
- postprocedural diabetes mellitus (E13)
- secondary diabetes mellitus NEC (E13)

III. Study Design:

Observational, retrospective, longitudinal, population-based cohorts study utilizing secondary data from electronic healthcare database (de-identified demographic, clinical, and prescription data of patients registered in general practitioner's medical health records linked with databases hospitalizations' records and death registries).

Primary objective is to compare the time from the first prescription of a given non-insulin glucose-lowering agent to the first occurrence of any component of a composite of major cardiovascular (CV) outcomes in cohorts of users of non-insulin glucose-lowering drugs.

Primary outcome is a composite of three-components of mayor cardiovascular events (MACE): cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke.

Secondary objectives are to compare, in cohorts of users of non-insulin glucose-lowering drugs

1. the time from the first prescription of a A10B (ATC code) given agent to:
   - individual components of PCO:
     - CV death,
     - the first occurrence of non-fatal MI,
     - the first occurrence of non-fatal stroke
2. the time from the first prescription of a A10B (ATC code) given agent to:
   - the first occurrence of hospitalization for unstable angina (UA):
   - the first occurrence of hospitalization for heart failure (HF)
   - the first occurrence ofhospitalization for coronary revascularization procedures (coronary artery by-pass surgery grafting, CABP and percutaneous transluminal coronary angioplasty PTCA)
   - the first occurrence of incident diagnosis of intermittent claudication, worsening of intermittent claudication or revascularization procedures for peripheral vasculopathy.
   - the first occurrence of transient ischemic attack (TIA)
   - the time from the first prescription of a given A10B (ATC code) agent to first occurrence of MI, (fatal and non-fatal)
   - the time from the first prescription of a given A10B (ATC code)agent to the first occurrence of stroke (fatal and non-fatal)
3. to compare incidence of all-causes mortality in cohorts of users of non-insulin glucose-lowering drugs
4. the time from the first prescription of a given agent to the first occurrence of any of the components of the composite outcome (four-point MACE) CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina (UA) or coronary revascularization procedures.

Secondary outcomes:

Secondary Composite Outcome is a MACE of four components: CV death, non-fatal MI, non-fatal stroke and hospitalization due to unstable angina or coronary revascularization procedures.

Secondary Outcomes are:

- CV death,
- All-cause death

- first occurrence of any of the following events:
    - non-fatal MI,
    - non-fatal stroke
    - hospitalization due unstable angina or coronary revascularization procedures (coronary artery by-pass surgery grafting, CABP and percutaneous transluminal coronary angioplasty PTCA);
    - transient ischemic attack (TIA)
    - hospitalization for heart failure,
    - incident diagnosis of intermittent claudication, worsening of intermittent claudicationor hospitalization for peripheral revascularization procedures.

Measures of occurrence and association: Incidence rates of primary composite outcome (PCO), secondary composite outcome (SCO) and secondary outcomes (SOs) will be retrieved from SIDIAP database. Incidence rates for each cohort will be calculated from the index prescription (first dispensed prescription of a new non-insulin glucose-lowering agent) until the first event of the PCO, SCO, or events detailed in SOs, loss of follow-up or end of the observation period, whatever came first. Data will be censored at the date of the dispensed prescription of a new glucose-lowering treatment. Hazard ratios (HR) will be calculated for primary and secondary outcomes.

Follow-up period: from January 1st 2010 to December 31st 2015

IV. Data Sources

IV. 1. Clinical data for selecting study population

Selection of study population will be done on records of SIDIAP (Information System for the Development of Research in Primary Care),a primary care population computerized database. Data extraction and anonymization will be conducted by SIDIAP.

Demographic and clinical data extraction:

Selection of study population will be done on records of SIDIAP (Information System for the Development of Research in Primary Care).

Inclusion criteria:

- patients 18 years and older diagnosed with T2DM. ICD-10 (Codes E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, and E11.9)
- receiving a first prescription of a non-insulin glucose-lowering agent.

Exclusion criteria:

Patients with type 1 diabetes mellitus (Coded E10.0, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E11.8, and E11.9.)

- Patients with gestational diabetes
- Patients with diabetes mellitus due to underlying condition, (E08), drug or chemical induced diabetes mellitus (E09), post pancreatectomy diabetes mellitus (E13), postprocedural diabetes mellitus (E13), secondary diabetes mellitus NEC (E13)

Demographic data include:

- sex (men, women)
- age (further categorised into age subgroups: ≤45yrs, 46 to 55yrs, 56 to 65yrs; 66–75, 76–85, and > 85 years)
- MEDEA deprivation index for socio-economic inequalities in health [94]

Clinical variables include:

- Type 2-diabetes related:
  - standardised glycated haemoglobin (HbA1c) values; (registered at the index date [index prescription] ± 3 months)
  - diabetes duration (yrs) at the index date
  - insulin treatment at the index date
- body mass index (BMI);
- other cardiovascular risk factors
  - CV risk, according to REGICOR score
  - smoking status (past, current, never, according to the most recent information recorded in the medical history)
  - blood pressure (BP) (systolic [SBP] and diastolic [SBP]); (both SBP and DBP must be recorded in the same date in order to be included)
  - lipid levels including total cholesterol (TC), low-density lipoproteins or LDL cholesterol (LDLc), high-density lipoproteins or HDL cholesterol (HDLc) and triglycerides (TG) (TG, LDLc and HDLc must be recorded in the same date in order to be included)
- Creatinine levels at index date and during the follow-up period

Values of clinical variables will be those registered closest to the index date, and during the treatment.

Clinical history [ICD-10 codes]

Past morbidities include registered diagnosis previously to the index date of the following:

- Cardiovascular
  - Acute coronary syndrome (ACS) (I20, I24)
  - Myocardial infarction (I21)
  - Peripheric arteriopathy (excluding Buerger and Raynaud), intermittent claudication
  - Stroke (hospitalization for ischemic or haemorragic stroke, clinically evident transient ischemia) (I61, I62.9, I63, I64, I65, I66, I67, I69)
  - Hospitalization for heart failure, heart failure (I50, I51.7, I,51.9)
- Renal failure (N17-N19)

Concomitant medication [ATC codes]

Data for concomitant medication will be extracted, concerning use and period of use of:

- **Cardiovascular drugs**
  - Antihypertensives[C02, C03, C07, C08, C09]
  - Antithrombotic agents [B01A]
  - Lipid-modifying agents [C10]
- **Drugs that potentially affect cardiovascular risk**
  - Antidepressants [N06A]
  - NSAIDs [M01A]
- **Insulin and analogues** [A10A]

Concomitant medication is defined as every drug prescribed at the date of each prescription of a given glucose-lowering agent [index date] ± 1 month

IV.2 Exposure

IV.2.a. Exposure definition

Subjects are considered exposed if a given non-insulin glucose lowering agent is prescribed.

Exposure for a given agent starts on the date of prescription of a first new non-insulin glucose-lowering agent (index date) and ends 30 days after the prescription of the last recorded prescription.

When a given agent is added for the first time to a pre-existing glucose-lowering therapy (for instance, metformin or sulphonylurea), the exposure will be re-assigned to double-therapy (i.e., MET + X or SU + X). If a new agent is added to a double therapy, this addition will be compared to the existing double therapy, as an "add-on" therapy (i.e. "MET+SU+ X" will be compared to "MET+SU" OR "MET+SU+Y"

For cohorts of new users of metformin and SU, patients will be reassigned to if another hypoglycemic agent is prescribed.

Initial date of observations: January 1st 2010

Final date of observations: December 31st 2015

Patients will be considered exposed to a non-insulin glucose-lowering agent after the first prescription of any of the following:

Substance [ATC code] (date of EU approval)

- **Metformin**[A10BA02]
- **Sulphonylureas**[A10BB]
  - glibenclamide [A10BB01]
  - chlorpropamide [A10BB02]
  - tolbutamide [A10BB03]
  - glibornuride [A10BB04]
  - tolazamide [A10BB05]
  - carbutamide [A10BB06]
  - glipizide [A10BB07]

- gliquidone [A10BB08]
- gliclazide [A10BB09]
- metahexamide [A10BB10]
- glisoxepide [A10BB11]
- glimepiride [A10BB12]
- Acetohexamide [A10BB31]

- **Metiglinides**
  - Repaglinide [A10BX02](authorized in UE on August 17th 1998, authorized in Spain in 1999)
  - Nateglinide [A10BX03]] (authorized in UE on April 3rd 2001)
- **Alpha glucosidase inhibitors** [A10BF]
  - Acarbose[A10BF01](authorized in Spain in 1999)
  - Miglitol [A10BF02]
  - Voglibose [
- **DPP-4 inhibitors:**
  - vildagliptin [A10BH02] (authorized in EU in September 2007),
  - saxagliptin,[A10BH03] (approved in October 2009 in EU),
  - linagliptin[A10BH05] (approved in EU in August 2011),
  - alogliptin[A10BH04] (approved in September 2013 in EU).
  - sitagliptin [A10BH01] (approved in March 2007 in EU)
- **GLP-1 Receptor Analogues:**
  - exenatide [A10BJ01] (approved in 2005/2012),
  - liraglutide [A10BJ02] (approved in 2010);
  - lixisenatide[A10BJ03] (approved in EU in 2013),
  - albiglutide [A10BJ04] (approved in 2014)
  - dulaglutide [A10BJ05] (approved in 2014).

SGLT-2 inhibitors:

- dapagliflozin [A10BK01] (approved in EU in November 2012);
- canaglifozin [A10BK02] approved in November 2013 in EU;
- empagliflozin [A10BK03] (approved in EU in May 2014)

- **Thiazolidinediones:**
  - pioglitazone[A10BG03] (authorized in October 2000 in EU and 2000 in US
  - rosiglitazone [A10BG02] (authorized in EU in and suspended in EU in 2010)

Note: Semaglutide is not yet approved in EU or US FDA.

IV.2.b. Exposure data source and extraction

SIDIAP database contains coded data of individual patients and prescribing health professional, medicine's National Code and ATC classification, description of presentation, number of units per package, daily dose, month of drug dispensing, monthly number of packages dispensed and dates of start and end of prescription.

IV.2.c. Exposure validation

The Catalan Health Institute (ServeiCatalà de la Salut [CatSalut]) manages a database which contains information about the dispensed drug, patient, prescriber and primary care center, and funds a percentage (for work active population) or the total amount of dispensed medicines (for retired people). SIDIAP prescription records are linked with CatSalut dispensing records.

In order to validate prescription, an aleatory sample of prescriptions will be matched with dispensing data. However, being a dispensed drug a proxy of administrated drug, treatment compliance could not be assessed.

IV. 3. Outcomes

IV. 3. a. Outcomes data source and coding

Data about outcomes will be retrieved from CMBD-AH ('minimum set of data at hospital discharge') which contains diagnoses coded with ICD-9 at hospital discharge from all hospitals in Catalonia, and can be linked to SIDIAP database. Linkage between databases is based on the CatSalut unique identifier code for each Catalonia resident. Incident CV events will be identified by ICD-9 for hospital data and ICD-10-CM for primary care data.

- myocardial infarction (I21) [410, 411]
- Hospitalization for unstable angina (I20) [413]
- stroke (I61. I62, I63, I64), [432, 433, 434, 435]
- hospitalization for coronary revascularization procedure
- hospitalization for peripheral revascularization procedure
- Hospitalization for heart failure (I50.0) [428]
- Onset or worsening of intermittent claudication (I73.9) [440.21]

SIDIAP database can be linked with Catalan mortality registry, which contains records of date and mortality causes for all Catalonia-residents' deaths. Linkage between databases is based on the CatSalut unique identifier code for each Catalonia resident. Cardiovascular death is defined as: [95]

- ICD-10 I46 code (cardiac arrest, I46.0, I46.1, I46.9) and
- any death occurred ≤ 30 days after following a recorded event of:
    - acute myocardial infarction (I21, I23),
    - stroke (I61. I62, I63),
    - cardiac arrhythmia (I49.9),
    - hearth failure,
    - cardiovascular procedure,
    - cardiovascular hemorrhage
        - non-stroke intracranial hemorrhage,
        - non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm),
        - or pulmonary hemorrhage from a pulmonary embolism

- other cardiovascular causes, such as pulmonary embolism or peripheral arterial disease.

IV. 3. b. Outcomes measurement

Incidence rates of primary composite outcome (PCO)and secondary composite outcome (SCO) and secondary outcomes (SOs) will be retrieved from SIDIAP database.

For each cohort, incidence rate will be calculated from the index prescription (first prescription of a new non-insulin glucose-lowering agent) until the first event of the PCO, SCO, or events detailed in SOs, loss of follow-up, subject transfer out of the area, end of the observation period, or death, whatever came first.

Loss of follow-up is defined as the absence of further medical, hospitalization or dispensing data (whatever was recorded later) for an individual for a period ≥ 1 yr after the last healthcare record (GP, hospital or dispensing). Patients lost to follow-up will be censored at the last record date (GP or hospitalization records or the last prescription of any drug, the later one that was recorded).

V. Biases and confounding

Data will be stratified according to patients' gender, age, renal status and cardiovascular risk at the index date. Patients' cardiovascular risk will be categorized by the REGICOR scores (adapted from Framingham scores).

Selection bias: SIDIAP includes data of the 80 % of total Catalan population. Since all new prescription of a non-insulin glucose-lowering agent defines selection, there is a low possibility of selection bias.

Differential misclassification of exposure in study and concomitant medications is unlikely due to the administrative nature of the system.

A possible outcomes' misclassification can occur if the event occurred out of the Catalan health system and it hasn't been recorded in GP records.

VI. Analysis plan

Descriptive statistics were used to summarize overall information.

Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (standard deviation) or median (interquartile range).

For each event, time to follow-up is defined as the time between the index date (first prescription of a new non-insulin glucose-lowering agent) entry and the event. Patients were followed up until the outcomes' occurrence, lost to follow-up or end of observation. Patients were also censored when they initiated a new non-insulin glucose-lowering treatment, because this is the entry in another cohort.

Incidence rates of primary and secondary composite outcomes events and secondary outcomes events will be estimated for each cohort during follow-up. Incident rates will be presented per 1000 patient-years and their corresponding 95% confidence intervals (CIs).

Hazard ratios of PCO, SCO and SO will be calculated between cohorts (treated vs. non-treated) for each therapeutic group and, secondarily, for each given agent. Data will be analysed with multivariate Cox proportional-hazard regression models, once verified proporcionality assumptions.

To control potential biases for confounding factors, the differences between exposed and non-exposed populations to the different hypoglycemic agents will be adjusted by estimating a propensity index using a logistic regression model. In order to control the effect of time-dependent confounders the use of marginal structural models will be also considered.

Analysis will be adjusted for the following socio-demographic characteristics and confounding and risk factors of each event:

- age,
- gender,
- socio-economic status,
- HbA1c at the index date
- co-morbidity,
- insulin therapy,
- renal status (according to creatinine clearance: ≤ 30, 31- 59, 60-89, ≥ 90 mL/min/ 1.73 m^2),
- cardiovascular medical treatment,
- other cardiovascular risk factors (smoking status, BMI, hypertension, serum lipid levels),
- high cardiovascular risk
- history of heart failure and
- calendar year of initiation of glucose-lowering therapy.

Subgroups analysis

For exploring heterogeneity treatment effect, descriptive subgroup analysis will be performed :

- good glycemic control (defined as a mean HbA1c ≤ 7%) vs. poor glycemic control (defined as a mean HbA1c >7%)
- new diagnosed T2DM vs T2DM ≥ 1 yr. and < 8 yrs. vs. diagnosed T2DM diagnosed ≥ 8 yrs,;
- patients with recent ACS (≤90 days) vs patients with no ACS vs. patients with history of ACS (> 90 days);
- heart failure and high cardiovascular risk vs. heart failure alone or high cardi
- ovascular risk alone.
- CKD and high cardiovascular risk vs. CKD alone vs. CKD, high CV risk and HF

Exploratory subgroup analysis will be derived from data.

Missing data

According to the magnitude and proportion of missing data, a multiple imputation technique will be considered. Each missing value will be replaced with a set of plausible values that represent the uncertainty about the right value to impute.

Cumulative mortality:

Cumulative mortality will be estimated by adjusted Kaplan-Meyer method for age, established cardiovascular disease, previous cardiac failure and analyzed according to the first monotherapy treatment, the last treatment and use of insulins.

Statistical analysis was performed with SAS (version 9.4; SAS Institute, Cary, NC)

VII. Quality assurance, feasibility and reporting

Quality assurance:

Data validation will be performed for outcomes. For exposure – defined according to prescriptions database - , CatSalut, as administrative database, performs its own validations.

Feasibility:

In order to conduct this study, an agreement has been already signed between Institut Jordi Gol and Catalan Institut of Pharmacologia,

Reporting:

Study protocol, design and results will be made published on www.clinicaltrials.govResults will be submitted to publication within one year after the final analysis of the study. Any relevant result will be conveyed to main Regulatory Agencies (Agencia Española del Medicamento, EMA and FDA) before publishing.

VIII. Strength & limitations of the study

Strengths

Healthcare data collected in clinical practice by physicians are representative of routine clinical practice in large populations. When used as a data source for observational pharmacoepidemiological research, and if data are properly collected and analyzed, results of this pharmacoepidemiological study could reflect the effect of treatment on relevant clinical outcomes.

Limitations

Limitations of the study are mainly those of observational research (no randomization and confounding, particularly confounding by indication and residual confounding).

Health care received by patients registered in these databases could be better than the one received by patients whose physicians don’t register their diagnoses, procedures and treatment in the healthcare database, and because of this, not fully representative of the whole population.

Another possible limitation of databases based on public healthcare systems in the period of the study is a possible relatively reduced number of patients treated with non-insulin glucose lowering agents that have been approved since 2008, especially for the newest agents (alogliptin, albiglutide, canaglifozin, empagliflozin, dapagliflozin). New users of rosiglitazone are expected to be recorded until 2010 (date of marketing suspension). These more recently marketed agents could not reach a number of prescriptions or follow-up periods appropriate to make valid comparisons with older agents

New-diagnosed T2DM are expected to have shorter DM duration and better clinical status. Effects of a given therapy on CV outcomes may not to manifest until the condition and related complications progress. The study period (6 years, from 2010 to 2015), which has been chosen according to availability of prescription/dispensing data, could result in a follow-up not enough long for new diagnosed T2DM patients or patients not at high cardiovascular risk.

Missing data about a number of patients have been reported in other studies with SIDIAP database.

IX. Ethical issues

The protocol will be submitted for evaluation/has been evaluated by the Clinical Investigations Ethics Review Board from the Investigation in Clinical Care Institut Jordi Gol. Local rules of confidentiality will be respected, according to the article 5, Ley Organica 15/1999, Regulación del Tratamiento de Datos de Carácter Personal. Since an existing Health Care Record will be used for data extraction, a Patient Informed Consent is considered not necessary**.**

Informed consent is considered not necessary due to data anonymization.

X. Amendments:

Amendments, if any, will be submitted to the Institut Jordi Gol Clinical Investigation Ethics Review Board

XI. Milestones:

Activity	**Responsible person/institution**	**Expected Date**
Project coordination	Raquel Herrera, Luisa Ibáñez, Xavier Vidal	March 2016- March 2018
Data Collection	SIDIAP	October 2016
Protocol drafting	All	March 2016-July 2016
Statistical plan and analysis	Raquel Herrera, Pili Ferrer, Jean-Luc Faille, Xavier Vidal	May 2016- December 2016
Registration in the EU PAS register	Raquel Herrera, Luisa Ibáñez, Xavier Vidal	March 2017
Preliminary reports	All	April 2017- May 2017
Publication and results reporting	All	October 2017- March 2018

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