Non-Interventional Study Protocol	
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Patient characteristics and cardiovascular and mortality outcomes in patients with type 2 diabetes mellitus initiating treatment with sodium-glucose co-transporter-2 inhibitors and other antidiabetic medications in Finland

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors and other diabetes medications (other glucose lowering drugs). The study will analyze the risk of hospitalization for heart failure (HF), other CV outcomes, severe hypoglycemia, kidney disease (KD), and all-cause mortality in T2DM patients who initiate use or treatment with SGLT-2s compared to patients initiating other glucose lowering drugs (GLD) in Finland.

This study protocol refers to the Finland part of the global study titled "Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL; ClinicalTrials.gov identifier: NCT02993614)"

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutical Chemical Classification system
AE	Adverse event
AF	Atrial fibrillation
CANVAS	Canagliflozin Cardiovascular Assessment Study
CI	Confidence interval
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
DPP-4	Dipeptidyl peptidase-4 inhibitor
FDA	Food and drug administration
GLD	Glucose lowering drug
GLP-1	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
HR	Hazard ratio
ICD	International Classification of Diseases
KD	Kidney disease
MACE	Major Adverse Cardiovascular Event
MI	Myocardial infarction
NCSP	NOMESCO Classification of Surgical Procedures
SGLT-2	Sodium glucose cotransporter-2 inhibitor
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
US	United States

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PROTOCOL SYNOPSIS

This observational study will describe patient characteristics and rate of CV and mortality outcomes in patients with T2DM who are initiating treatment with SGLT-2s as a class, and dapagliflozin separately, or other glucose lowering drugs (other GLDs). The study will analyze the risk of hospitalization for HF, other CV outcomes, severe hypoglycemia, KD, all-cause mortality and health care resource utilization in patients with T2DM who initiate treatment with SGLT-2s as a class, and dapagliflozin separately compared to patients initiating other GLDs in Finland.

Background/Rationale: In September 2015, the EMPA-REG cardiovascular outcomes trial (CVOT) presented data on a reduction in CV events in patients exposed to empagliflozin, a SGLT-2, compared to placebo on top of standard of care. This has created a need for data on how the SGLT-2 class of medicines affect CV event rates when used in clinical practice. The main objective of this study is to provide this kind of evidence based on real world experience from a broad multinational population of T2DM patients. For medication classes recently introduced on the market it may be challenging to find a suitable comparator and the number of patients exposed as well as the length of exposure may be limited. This study will assess the number of patients initiating SGLT-2 use as a class and dapagliflozin separately, and their length of follow up. The study will describe the characteristics of new users of SGLT-2 as a class, and dapagliflozin separately, and a matched group of potential comparators including dipeptidyl peptidase-4 inhibitors (DPP-4s) and/or other GLDs.

Objectives and Hypotheses: The primary objective of this study is to compare the risk for hospitalization for HF, in patients with T2DM who are new users of SGLT-2s as a class or dapagliflozin separately, versus an active comparison group including patients with T2DM who are new users of other GLD. The secondary objective is to compare all-cause death using similar methods. The exploratory objectives are to conduct corresponding comparisons for hospitalization for major adverse cardiovascular events (MACE) and its sub-components CV mortality, acute myocardial infarction (MI) and stroke, as well as atrial fibrillation (AF), unstable angina, coronary revascularization, severe hypoglycemia, kidney disease (KD) and health care resource utilization in both treatment groups.

Methods:

Study design: A retrospective observational database linkage cohort study using patient level data from different nationwide registers in Finland. (Section 3.1)

Data Source(s): The Finnish Prescription Register, The Finnish Causes of Death Register, The Finnish Care Register for Health Care (HILMO) and The Finnish Register for Primary Health Care Visits.

Study Population: New users of SGLT-2s, dapagliflozin, DPP-4s, and other GLD. (Section 3.2)

Exposure(s): SGLT-2s as a class, dapagliflozin separately, DPP-4s as a class and other GLD. (Section 4.1)

Outcome(s): Hospitalisation for HF, all-cause mortality, MACE and its sub-components CV mortality, acute MI, stroke, unstable angina**,** coronary revascularization**,** AF, severe hypoglycaemia, KD and health care resource utilization (Section 4.2)

Sample Size Estimations: Sample size considerations for the comparative analysis are outlined in section 5.3.

Statistical Analysis: The event rates and baseline characteristics for each treatment group will be summarized descriptively. Propensity scores (PS) will be calculated to assess comparability between SGLT-2 users, dapagliflozin users, and the groups of matched comparators (DPP-4 and other GLD users). This is described in detail in Section 5. The primary objective is to provide a formal statistical comparison between the treatment and comparator group with respect to hospitalizations for HF using a hazard ratio (HR) (or other appropriate measure).

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
None	None	None

MILESTONES

Date	Milestone
November 2017	Approval of Study Protocol
December 2017	Ethical approval
January 2018	Data permits
January 2018	Data analysis done
March 2018	Study results report

1. BACKGROUND AND RATIONALE

1.1 Background

The potential effect of glucose lowering interventions on CV risk might ultimately be dependent on the mode of action of the drug in terms of which CV pathway(s) are being modulated. However, to date, the potential effects of specific glucose-lowering agents on CV events in patients with T2DM remain uncertain (1). Recently, a neutral effect for the composite CV death, MI or stroke was reported from the first three placebo-controlled trials involving the DPP-4s saxagliptin (i.e. SAVOR-TIMI53) (2) and alogliptin (i.e. EXAMINE) and sitagliptin (i.e. TECOS) (3, 4, 5). In the SAVOR-TIMI 53 trial, an unexpected excess rate of hospitalization for HF in the saxagliptin group was observed. This was not confirmed in the recent United States (US) real world retrospective observational study comparing the risk for hospitalisation for HF in new users of sitagliptin versus saxagliptin (6). Furthermore a non-significant numerical unbalance in hospitalization for HF was reported in the alogliptin group in the EXAMINE trial (3), in contrast to TECOS (5) where the rates of hospitalization for HF did not differ between the two groups. Observational studies from several European countries (7, 8, 9), United States (6) and Asia (10) have reported higher risk for CV among those on SU compared to those on DPP-4s. For glucacon-like peptide-1 receptor agonists (GLP-1RAs) recent CVOT have reported mixed results with a reduction in major CV events in the GLP-1 arm observed in the LEADER trial on liraglutide (11) and corresponding neutral findings but with a reduction in all cause death in the EXSCEL trial for exenatide (12).

SGLT-2s are a new class of glucose-lowering agents that reduce hyperglycaemia in patients with T2DM by reducing renal glucose re-absorption; as a result, they increase urinary glucose excretion (13). Currently three drugs in this class are approved by US Food and Drug Administration (FDA) and European Medicines Agency: canagliflozin, dapagliflozin and empagliflozin (14-24). While anticipating the results of the ongoing outcome trials, several analyses with pooled data from shorter term trials have been conducted to explore the CV safety profiles of the SGLT-2s. In a meta-analysis from the dapagliflozin trial programme (25) including 21 phase 2b/3 studies, of which two trials with high CV risk patients pre-specified 4-point MACE has been used. In this analysis, 178 events occurred in 9339 patients analysed. The HR was 0.81 (0.59, 1.09). In a similar pooled analysis from canagliflozin trials 4-point MACE were accrued from one phase 2 and seven phase 3 trials with between 12 and 104 weeks duration and one interim analysis of the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) trial (26). In this analysis, 201 4-point MACE occurred in 9632 patients. The overall HR was 0.91 (95% confidence interval (CI): 0.68, 1.22), while the HR for the interim results of CANVAS, which contributed 80% of the overall number of events (n = 161), was 1.00 (95% CI: 0.72, 1.39). The limitation of these analyses is that the pooled data of limited number of CV events was from heterogeneous, short-term follow-up studies that were neither adequately powered nor designed to address CV outcomes.

The first CV outcomes trial with an SGLT-2 (EMPA-REG) demonstrated CV risk reduction in patients with T2DM and at high risk of a CV event, driven by an unprecedented reduction in CV mortality (27). This was a placebo controlled randomised trial where patients with established CV disease were randomised to either empagliflozin or placebo on top of standard

of care. Standard of care included both use with oral diabetes medicines as well as insulin. At baseline, 29% of the population in EMPA-REG had monotherapy and 48% dual therapy of diabetes medications. Three out of four (74%) in the study population used metformin at baseline, 48% used insulin, 43% used SU, 11% used DPP-4s and 3% used a GLP-1. Recently similar findings with regard to MACE was observed in the CANVAS trial in patients treated with canagliflozin (28). The corresponding CVOT for dapagliflozin, the DECLARE trial is planned to read out in 2019.

1.2 Rationale

Carefully conducted and properly designed observational studies addressing comparative effectiveness may complement the CVOTs. An observational study cannot replicate the design and results of a placebo-controlled randomised clinical trial since neither randomisation nor placebo treatment are part of clinical practice. An observational study will compare against an active comparator (comparative effectiveness) and disease severity as well as prescriber preferences may influence the choice of treatment. This may introduce differences between the groups to be compared regarding patient characteristics associated with the treatment choice as well as the outcome and is referred to as confounding by indication or channelling bias. This is a major potential source of bias in comparative effectiveness studies that needs to be evaluated and taken into account in design as well as in the interpretation of the findings. Patients with T2DM is a heterogeneous patient population with multiple treatment options. The SGLT-2 class is relatively recently introduced on the market in Europe, the US and Asia. It was launched in Finland in 2012 and has been reimbursed since 2013. Thus, information on patient characteristics, concomitant treatment and available follow up time in patients initiated on SGLT-2s is limited in most countries.

Previous studies have reported some differences in patient characteristics between new users of DPP-4s compared to SU concerning age, diabetes duration and concomitant medication use (7, 8, 10). Moreover, differences have been reported between SU users and GLP-1 users in age, treatment duration and concomitant medications used (8). This stresses the importance to carefully assess potential comparator groups (other GLD users) in comparative effectiveness studies involving SGLT-2s. Recently, a similar approach was used to compare new users of SGLT-2s to new users of other GLD in Denmark, Norway and Sweden (29) and in the United States, Denmark, Norway, Sweden, Germany and the United Kingdom (30), resulting in comparable cohorts. Also in (31) matching of SGLT-2s with DPP-4s in Denmark, Norway and Sweden, resulted in comparable cohorts.

A comparative effectiveness study could fill a current knowledge gap for SGLT-2s as a class and dapagliflozin specifically in light of the result from the SGLT-2 inhibitor CVOTs so far presented (27, 28).

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective(s) & Hypothesis(es)

The Primary objectives of the study are

1) To compare the risk for hospitalization for HF between
    a. patients with T2DM who are new users of SGLT-2s as a class versus patients with T2DM who are new users of other GLD
    b. patients with T2DM who are new users of dapagliflozin patients with T2DM who are new users of other GLD
    c. patients with T2DM who are new users of dapagliflozin patients with T2DM who are new users of DPP-4

The secondary of objectives of this study are

2) To compare all-cause mortality between
    a. patients with T2DM who are new users of SGLT-2s as a class versus patients with T2DM who are new users of other GLD.
    b. patients with T2DM who are new users of dapagliflozin versus patients with T2DM who are new users of other GLD.
    c. patients with T2DM who are new users of dapagliflozin patients with T2DM who are new users of DPP-4

The exploratory objectives of this study are

3) To compare the risk for hospitalization for MACE, CV mortality, acute MI, stroke, unstable angina, coronary revascularization, AF, severe hypoglycemia and KD, and to compare health care resource utilization between
    a. patients with T2DM who are new users of SGLT-2s as a class versus patients with T2DM who are new users of other GLD.
    b. patients with T2DM who are new users of dapagliflozin versus patients with T2DM who are new users of other GLD.
    c. patients with T2DM who are new users of dapagliflozin patients with T2DM who are new users of DPP-4

3. METHODOLOGY

3.1 Study Design – General Aspects

This is a cohort study of patients with T2DM in Finland, who are new users of SGLT-2s as a class, dapagliflozin separately, DPP-4s as a class, and of other GLD, respectively.

Dapagliflozin was the first SGLT-2 inhibitor granted marketing approval by the European Commission for the treatment of T2DM in Europe in November 2012. The FDA approved canagliflozin as the first SGLT-2 for treatment of T2DM in March 2013, followed by dapagliflozin in January 2014 and empagliflozin in August 2014 (32). The study follow-up period will be 2013-2015 in Finland, since the first SGLT-2 (dapagliflozin) received the reimbursement status only in 2013.

A new user of SGLT-2 (or dapagliflozin) is defined as an individual filling a prescription of SGLT-2 (or dapagliflozin) with no filled prescriptions of SGLT-2s during the preceding year. New users of other GLD will be defined as those filling a prescription of a specific drug class with no filled prescriptions of that drug class during the preceding year, i.e., a new user of DPP-4 has no DPP-4 filled prescription in the previous year.

The date of the first filled prescription of the investigated medication classes (index medication group) during the study period will be denoted as the index date. Patients will be followed from index date (inclusive) to the earliest of year of immigration, end of 2015, death date or date of outcome. In 'on treatment' analyses patients will in addition be censored at the end of use of the index medication class.

Baseline characteristics including demographic and clinical characteristics will be captured for patients in the year before the index date.

The class SGLT-2s include dapagliflozin, canagliflozin and empagliflozin users. Since SGLT-2s are relatively recently introduced on the market the population size and follow-up time is limited. During the study follow-up period 2013-2015 there were no canagliflozin users in Finland (Finnish Prescription Register).

3.1.1 Data Source(s)

The study will include information via linkage of four national Finnish registries, with full coverage of the Finnish population: 1) The Finnish Prescription Register covering filled drug prescriptions 2) The Finnish Care Register for Health Care (HILMO) 3) The Finnish Register for Primary Health Care Visits (AvoHILMO) 3) The Finnish Causes of Death Registry.

Register	**Register holder**	**Content**	**Data period**
Finnish Prescription Register	Social Insurance Institution	Drug purchases Reimbursement statuses Place of domicile *	1996-2015 -2015 2011-2015
Finnish Care Register for Health	National Institute for Health and Welfare	In- and outpatient diagnoses	-2015

Care (HILMO)		Hospitalization periods	
Finnish Register for Primary Health Care Visits (avoHILMO)	National Institute for Health and Welfare	Primary care diagnoses	-2015
Finnish Causes of Death Registry	Statistics Finland	Time of death Cause of death	-2015

* To account for migration during the study period.

3.2 Study Population

The broad study population from Finland will include all T2DM patients defined as follows: A filled prescription of a GLD (Anatomical Therapeutical Chemical Classification system (ATC) code A10) during 1998-2015, from which patients with reimbursement for diabetes mellitus with a diagnose type 1 diabetes mellitus (International Classification of Diseases (ICD)-9: 250.xB or ICD-10: E10) or other specific non-T2DM diagnosis (250.xC, E12, E13, E14, E89.1) without a T2DM (250.xA, E11) diagnosis are excluded.

The study population will be constructed from the broad study population with the following inclusion and exclusion criteria.

3.3 Inclusion Criteria

Inclusion criteria are:

- New user of SGLT-2 medication or other GLD treatments oral as well as injectable, including fixed-dose combination products containing these medication groups during 2012-2015
- ≥ 18 years old at index date
- > 1 year data history prior to the index date

3.4 Exclusion Criteria

Exclusion criteria are:

- Patients with a type 1 diabetes mellitus diagnosis (ICD-9 codes 250.xB or ICD-10 codes E10) or other specific non-T2DM diagnosis (250.xC, E12, E13, E14, E89.1) without a T2DM (250.xA, E11) diagnosis on or prior to index date*
- Patients with only insulin use in the year prior to index date.
- Patients with a gestational diabetes (ICD-10: O24.4, O24.9) within 1 year before index date

*diagnosis based on in- and outpatient hospital visits and primary care visits

3.5 Participant Follow-up

Participants will be followed from the index date until year of emigration, end of 2015, death date, or date of outcome. In analyses of 'on treatment' patients will also be censored at the end of use of the index treatment.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

The exposure of interest is use of SGLT-2s (dapagliflozin, canagliflozin, empagliflozin and other agents in this drug class) or other GLDs (Table 4-1). Other GLD treatment will include any other diabetes medicines than SGLT-2s. An individual will be defined as a user on the index therapy for the duration of subsequent prescriptions with no gaps between prescriptions exceeding 45 days. An individual will only be included if he or she is a new user of one of the mentioned medicine groups. The majority of SGLT-2 users in Finland (over 85% in 2015) were dapagliflozin users, therefore dapagliflozin exposure will be considered also as a separate exposure group.

An individual will be considered exposed to the medication of interest from the index date and until the last day with medication available (last day covered by the last filled prescription) plus a grace period of 30 days.

Table 4-1 ATC codes for GLD classes considered as exposure (including combinations with metformin)

Drug classes	**ATC codes**
Metformin/Biguanides	A10BA
SGLT-2	A10BX09, A10BX12 or A10BD15
dapagliflozin	A10BX09, A10BD15
canagliflozin	Not available during study period
empagliflozin	A10BX12 (No combination available during study period)
DPP-4	A10BH, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13
SU	A10BB
GLP-1	A10BX04, A10BX07, A10BX10
TZD	A10BG, A10BD05
Insulin	A10A
Short-acting	A10AB
Intermediate-acting	A10AC
Premixed insulin	A10AD
Long-acting	A10AE

Combination of DPP-4 and thiazolidinedione including pioglitazone and alogliptin (A10BD09) will be looked into separately.

4.2 Outcomes

The following table (Table 4-2) presents the study outcomes together with the ICD-10/ NOMESCO Classification of Surgical Procedures (NCSP) codes.

Table 4-2 Study outcomes and corresponding medical codes

Outcome	**ICD-10/NCSP code**
Primary outcome	
Hospitalization for HF	I50
Secondary outcomes	
All-cause mortality	n/a
Exploratory outcomes	
MACE	Hospitalizations: I21-I22, I60-I64, G45 Deaths: I00-99
CV mortality	I00-99
Hospitalization for acute MI	I21-I22
Hospitalization for Stroke: Hemorrhagic, Ischemic, Transitory ischemic attack	I60-I64, G45
Hospitalization for Unstable angina	I20.0
Hospitalization for coronary revascularization	NCSP codes; CABG (FNA-FNE) and PCI with stent (FNG)
Hospitalization for AF	I48
Hospitalization for Severe hypoglycaemia/Diabetic Coma	E10.0, E11.0, E12.0, E13.0, E14.0, E11.6A, E16.0-2
Hospitalization for KD	N17-N19
Health care utilization	Number of inpatient hospitalizations, Number of outpatient visits, Number of primary care visits, costs of

	GLDs, costs of diabetes/CV related drugs

4.3 Other Variables and Covariates

Covariates will be measured to describe baseline characteristics of the study population. In addition, some key co-variates may be evaluated also across the follow-up time if available. These will be measured prior to the index date by clinical coding from either primary care records, secondary care records and medical records. Current therapies will be assessed in the twelve months before the index date. The main study variables / variable categories of interest are summarised in Table 4-3. And the surgical codes of interest are provided in Table 8-4.

Table 4-3 Demographics, main comorbidities and main drug classes considered in the study

Variable	**Definition**
Demographics	
Age	Defined at index date
Gender	
Duration of T2DM at index date	Time since first A10 medication filling or date of reimbursement decision
Duration of observation in database prior to the index date	Time since 1998 or time of immigration
Duration of observation in database after the index date (inclusive) i.e. follow up time	Evaluated until date of death or date of emigration
Comorbidities	
Cardiovascular diseases	Appendix 1: Table 8-1
Cerebrovascular diseases	Appendix 1: Table 8-1
Kidney diseases	Appendix 1: Table 8-1
Endocrinological diseases	Appendix 1: Table 8-1
Gastrointestinal diseases	Appendix 1: Table 8-1
Other comorbidities	Appendix 1: Table 8-1
Specified diabetic complications	Appendix 1: Table 8-2
Medications	
Glucose lowering drugs	Appendix 1: Table 8-3

Anticoagulants/thrombotics	Appendix 1: Table 8-3
Cardiovascular medication	Appendix 1: Table 8-3
Cholesterol lowering medication	Appendix 1: Table 8-3
Medication for HF	Appendix 1: Table 8-3
Other medications	Appendix 1: Table 8-3

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

The baseline characteristics will be described separately for all users of SGLT-2 as a class, dapagliflozin users separately, other GLD, and DPP-4 users, and the incidence/mortality of outcomes will be presented for these groups.

The incidence rates will be formally compared between the treatment groups (SGLT-2 vs other GLD, dapagliflozin vs other GLD, and dapagliflozin vs DPP-4) using HRs and corresponding 95% CIs. In this ratio, either SGLT-2 as a class or dapagliflozin separately will be considered the 'exposure' treatment.

Health care utilization (counts and costs) for the treatment groups (SGLT-2, dapagliflozin, DPP-4, other GLD) will be presented using cumulative counts/costs during follow-up.

Details of the statistical analyses are outlined below. A more detailed description is provided in the statistical analysis plan.

5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

Frequencies and percentages of categorical baseline characteristics (covariates) will be described for all users of SGLT-2 as a class, and dapagliflozin users separately, other GLDs, and DPP-4 as a class. These baseline characteristics include age, gender, duration of diabetes, medical conditions, concomitant medications, and certain health care utilization variables, as data permit. These health care utilization variables include number of outpatient hospital visits, number of hospitalizations and costs of drugs one year before index and during follow-up.

Continuous and count variables will be described using mean (± standard deviation, 95% CI), median (quartiles), and minimum and maximum values.

To assess the possible imbalances in baseline covariates between treatment groups which may result in confounding, a PS approach will be utilized. PSs will be calculated after the relevant inclusion/exclusion criteria. The PS for each subject is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. A non-parsimonious PS will be calculated including a large set of relevant variables. The variables to be considered for the estimation of the PS include age at index date, gender, calendar year of the index date, index medication, comorbidities, indicators of diabetes severity (including duration of diabetes treatment), drug treatment, and indicators of health care utilization. PS distributions for new users of SGLT-2s, dapagliflozin, other GLDs, and DPP-4s, respectively will be compared. Provided there is sufficient, overlap in these distributions patients in the SGLT-2 group will be matched 1:1 (and 1:3 for sensitivity analysis) with patients in the other GLD group. For matching the nearest neighbor, caliper width of 0.20 multiplied by the standard deviation of the PS distribution will be applied (33). To determine whether there is balance in key covariates between treatment groups after the matching on PSs, the covariate distribution between the treatment groups will be compared using standardized differences >10%. A similar comparison will be performed using the subgroup of patients with dapagliflozin as index drug and their matched comparisons in other GLDs. A separate matching will be performed for new users of dapagliflozin and new users of DPP-4 class.

Crude incidence rates of cardiovascular outcomes/mortality events will be calculated for the treatment groups (SGLT-2 users or dapagliflozin users) and their comparison groups. Only the first episode of the CV event will be included in the incidence analyses (however, the subsequent CV events within a subject will be summarized descriptively in a separate table). Person-time at risk for each patient will be the length of the index exposure episode, defined as the number of days from the day after the index prescription start date to the last day of follow-up. Person-time will be summed across all patients within each treatment group. For each outcome of interest, the crude incidence rate in each index exposure group is the number of incident events divided by the total number of person-years at risk and will be expressed per 100 person-years with 95% exact CIs.

Comparative analyses

Comparative analyses of hospitalizations for the primary outcome, hospitalization for HF, will be conducted by treatment groups (SGLT-2 users or dapagliflozin users, and their comparator groups). Only the first episode of the event will be included in the incidence analyses (however, the subsequent events within a subject will be summarized descriptively in a separate table). The unadjusted and adjusted incidence rates for the new users of SGLT-2 group, new users of dapagliflozin and the comparator (other GLD) groups will be compared using a HR or a relative risk and corresponding 95% CI. This analysis will be performed using Cox proportional hazards regression or some other suitable method if the assumptions for the Cox model are not met.

An 'on treatment' approach will be used for the primary analysis to account for additions or switches to the index assigned treatment. A grace period of the duration of last issued prescription will be applied. As a sensitivity analysis, an intent-to-treat approach will also be applied in which subjects will be analyzed according to the treatment they were originally assigned to, regardless of whether there were any subsequent treatment changes. Further details regarding both these approaches, including the censoring rules, potentially allowing for time varying factors and imputation of missing data, is provided in the statistical analysis plan. Similar analysis will be performed for secondary and exploratory outcomes.

Meta-analysis

Similar studies are being performed in several other countries with the goal is to combine the country specific results from the Finnish study results with these in a meta-analysis. A meta-analysis approach, based on the Der Simonian and Laird method (34), will be used where the HR point estimates for each country are pooled together to obtain an overall summary weighted point estimate. In this approach, random-effects models with inverse variance weighting for each country will be implemented.

Up to now, similar studies have been conducted in the United States, Denmark, Norway, Sweden, Germany and the United Kingdom and the results for hospitalization for HF have been combined in a meta-analysis (26, 27, 28).

5.2 Bias

5.2.1 Methods to Minimize Bias

As this is an observational study, it is important to address and minimize potential sources of bias which may affect the validity and interpretation of study results. One such bias that may occur is channelling bias which occurs when patients with certain baseline characteristics are more likely to be prescribed a certain treatment over another treatment. Hence, this may lead to differences in baseline characteristics between the treatment groups which may confound the relationship between the treatment group and the outcome, especially if the baseline characteristics are known to be correlated with the outcome. To address this potential source of bias, propensity scoring matching will be used to take into account covariate differences between the treatment groups. Matching the patients in the treatment and comparator groups by the PS should minimize the potential confounding by these covariates. If the propensity scoring is not deemed a suitable method to control for potential confounding variables, other methods may be considered.

5.2.2 Adjustment for Multiple Comparisons

Will not be applied.

5.2.3 Strengths and Limitations

- This study results will include be interpreted in a meta-analysis together with results from studies from multiple countries in order to increase the power and the generalizability of the results
- Because of the real world observational data, the population of this study will be more diverse compared to a randomized controlled trial and the results of this study will be more generalizable to a broader diabetes population.
- This study will provide some insight on the potential cardiovascular benefits of SGLT-2/dapagliflozin ahead of the DECLARE study results.
- Will not be possible to define the outcome exactly equivalent to EMPA-REG as the databases will most likely not have all the required tests recorded
- Comparators will likely have earlier index dates to larger extent than SGLT-2 users and thus may have longer follow up
- Combination use of several of the classes of interest or a history of use of several of the classes of interest will occur and a classification of this will be assessed
- Patients may have limited persistence with their SGLT-2 treatment
- Cannot interpret statistical analyses from this study in the same way as could be done with a randomized clinical trial because this is an observational study
- The 1:3 treatment allocation ratio of SGLT-2:other GLD patients may reduce the representativeness of the SGLT-2 patients selected for this study compared to the overall SGLT-2 patient population

5.3 Sample Size and Power Calculations

This study is one of several similar studies conducted in multiple countries. To increase the power of the study the results from the individual studies will be combined in a meta-analysis According to the power calculation (presented below in Table 5-1) 730 events was sufficient to obtain sufficient power (85%) for a 20% reduction in the primary outcome. As then number of events was higher than 730, a meta-analysis for the primary outcome was conducted by Kosiborod et al (27) (961 hospitalization for HF). The inclusion of results from this Finnish study will further increase the power.

Power calculations

For the comparative analyses, the primary endpoint is hospitalization for HF. For 85% power to detect a risk reduction of 20% with a two-sided alpha level of 0.05, and up to 1:3 treatment allocation of SGLT-2 to the comparator arm, a total of 970 events will be needed across both treatment groups after the matched SGLT-2 and control groups have been created (Table 5-1). This calculation assumes the background rate of hospitalization for HF in the standard of care group is 0.625 events per 100 person-years and assuming a 20% reduction a rate of 0.5 events per 100 person years in the SGLT-2 group. For 1:1 treatment allocation, approximately 64,889 person-years will be needed in the SGLT-2 group and 129,778 person-years will be needed in

the control group. However, the key driver for the power and the analysis is the number of events. The sample size is merely an approximation of how many person-years might produce the required number of events based on the assumed event rates. In summary, as long as a total of 730 events are achieved, the analysis will be sufficiently powered.

As there may not be enough statistical power for a standalone analysis in any of the individual country databases, a meta-analysis approach will be used to conduct the treatment comparison by pooling the results from studies in several countries (27).

Table 5-1 displays the target number of events and total exposure time (in person-years) needed for the SGLT-2 and control groups under different estimates for risk reduction, power, and SGLT-2: control treatment allocation ratios.

Table 5-1 Exposure time needed for hospitalization for HF (person-years) if SGLT-2 rate is 0.5 events/100 patient-years.

Number of controls per SGLT-2 patient	Number of events			Total exposure time (SGLT-2 + control)			SGLT-2 exposure time		
30% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	255	290	340	42000	47765	56000	21000	23882	28000
3	340	380	460	51459	57514	69622	12865	14378	17405
5	470	545	610	69263	80316	89895	11544	13386	14982
25% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	385	440	515	66000	75429	88286	33000	37714	44143
3	520	600	700	83200	96000	112000	20800	24000	28000
5	710	790	940	111130	123652	147130	18522	20609	24522
20% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	635	730	850	112889	129778	151111	56444	64889	75556
3	850	970	1160	143158	163368	195368	35789	40842	48842
5	1160	1350	1520	192000	223448	251586	32000	37241	41931
15% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	1195	1370	1600	219622	251784	294054	109811	125892	147027
3	1620	1870	2120	286130	330286	374442	71532	82571	93610
5	2220	2500	2900	387077	435897	505641	64513	72650	84274

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Data Management

6.1.1 Study Flow Chart and Plan

R language (www.r-project.org, read 25 Sep 2014) will be used for in data management for creating the analysis database and in statistical analysis for creating tabulations and graphics

as well as in all statistical modelling. R language is described more detailed in report "R: Regulatory Compliance and Validation Issues: A Guidance Document for the Use of R in Regulated Clinical Trial Environments" (www.rproject.org/doc/R-FDA.pdf, read 25 Sep 2014). Full audit trail starting from raw data obtained from register holders, and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for five years after publication of results.

6.1.2 Quality Control

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the sponsor, the principal investigator and the co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to register holders.

The study may be inspected by the sponsor's independent representative(s), study scientific committee, or by the competent authorities. Supporting documents will be retained for five years after the report finalization and then destroyed. As the register holder of the study register EPID Research is responsible of deleting the data. The study data will be retained and destroyed according to the timelines specified in the data permits by the data holders. Secure archives will be maintained for the orderly storage and retrieval of all study-related material. Access to the study data cannot be given to any third parties, neither the study data can be used to other purposes than prescribed in this protocol. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.

6.2 Protection of Human Subjects

This is a fully register-based study and patients will not be contacted in any phase of the study. The study does not affect the treatment of the patients.

The protocol will be subjected to Ethics Committee of Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study registers will be sent to the Office of the Data Protection Ombudsman

6.2.1 Subject Informed Consent

Not applicable since this is a secondary data study.

6.2.2 Confidentiality of Study/Subject Data

EPID Research will process pseudonymized data including study identification numbers only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the register holders). The study registers are formed on the basis

mentioned in the Personal Data Act (523/1999) §12 and the data is handled as described in §14 therein. The sponsor will not have access to the patient level data.

6.3 Management and Report of Adverse Events/Adverse Drug Reactions

6.3.1 Definition of Adverse Events (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.3.2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

6.3.3 Definition of Adverse Drug Reactions

An ADR is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

No reporting of adverse event data will take place in this study since it is based on secondary data.

6.4 Communication Plan

The principal and co-investigators will write a study report. The study report is delivered to the Sponsor and to the data permit holders according to the data permits. Within three months following the study report, an abstract of the study findings will be made available to the public through the EU PAS register.

6.4.1 Publication Plan

The principal and co-investigators will write the study report. The report is delivered to the Sponsor. Based on these results the principal and co-investigators will co-author scientific manuscript(s) of the results to be published. The study Sponsor is entitled to view the final results and interpretations thereof prior to submission for publication and to comment in advance of submission as agreed in the research contract and without unjustifiably delaying the publication.

All publications will adhere to the guidelines on publications in biomedical journals established by the International Committee of Medical Journal Editors and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.

6.4.2 Compliance with Study Registration and Results Posting Requirements

The main study CVD REAL has been registered on clincialtrials.gov in accordance with AstraZeneca International Procedure 8-P43-cv-X, Disclosure of Trial Information on Public Websites. Unique identifier NCT02993614.

This local study is conducted by following the ENCePP code of conduct (35) as well as the Guidelines for GPP (36). EPID Research, the Sponsor and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study will be registered into ENCePP's European Union electronic Register of Post-Authorisation Studies (EU PAS register).

6.4.3 Compliance with Financial Disclosure Requirements

The AstraZeneca Standard Operating Procedures will be adhered to when engaging healthcare professionals or institutions in the project.

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8. APPENDICES

APPENDIX 1

Table 8-1 ICD-10 codes for main comorbidities of interest

Diagnoses	**ICD 10 code**
Diabetes	E10-E14
Type 1	E10
Type 2	E11
Other	E13-E14
Cardiovascular disease	I00-I99
Myocardial infarction	I21-I22
STEMI	I21.0-3/I22.0-1
NSTEMI	I21.4/I21.9/I22.9
Unstable angina	I20.0
Angina pectoris	I20.9/I25.1
Old myocardial infarction	I25.2
Coronary revascularisation	Z95
Heart failure	I50
Severe ischemic arrhythmias	I46-I49
Atrial fibrillation	I48
Cerebrovascular disease	
Hemorrhagic/embolic stroke	I60-I64, G45
Embolic stroke	I63-I64
Hemorrhagic stroke	I60-I62
Transitoric ischemic attack	G45
Peripheral artery disease	I70-I79
Kidney disease	
Glomerular dysfunction	N08.3
Chronic kidney disease	N18
Unspecified kidney disease	N19
Acute kidney disease	N17
Dialysis	Y82.4/Z49
Endocrinological diseases	
Hypertension	I10
Hypercholesterolemia	E78
Hypothyreosis	E03
Diabetic counselling	Z71.3
Gastrointestinal disease	K00-K99

Oesophagitis	K20
Gastro-oesophageal reflux disease	K21
Other disease of oesophagus	K22
Peptic ulcers disease	K25-K28
Gastritis and duodenitis	K29
GI bleeding	K92.0, K92.1, K92.2
Dyspepsia	K30
Nausea	R11
Other diseases/conditions	
Obesity	E66
Gastric bypass	
Cancer	C00-C99
Chronic obstructive pulmonary disease	J44
Urinary infection	N39.0
Gout	M10
Pregnancy	Z32, Z33
Gestational diabetes	O24

Table 8-2 ICD-10 and NCSP codes for specified diabetic complications

Specified diabetic complications	**ICD-10**	**NCSP**
Eye		
Retinopathy	H36.0	CKC12, CKD65
Cataract	H28.0	
Glaucoma	H40.9	
Retinal oedema	H35.8	
Eye complications	E10.3, E11.3, E12.3, E13.3, E14.3	
Kidney		
Diabetic nephropathy	N08.3	
Diabetes with nephropathy	E10.2, E11.2, E12.2, E13.2, E14.2	
Neuropathy		
Diabetic mononeuropathy	G59.0	
Diabetic polyneuropathy	G63.2	
Autonomic neuropathy	G99.0	
Diabetes with neuropathy	E10.4, E11.4, E12.4, E13.4, E14.4	
Foot		
Diabetic artropathy	M14.2, M14.6	QDGX10
Peripheral angiopathy	I79.2	
Circulatory disturbance	E10.5, E11.5, E12.5, E13.5, E14.5	
Amputation knee and lower leg		NGQ 19, NGQ 99
Amputation ankle and foot		NHQ 1y, NHQ11, NHQ12, NHQ13, NHQ14, NHQ16, NHQ17, NHQ99
Other complications		
Hypoglycemia - Diabetic coma	E10.0, E11.0, E12.0, E13.0, E14.0, E16.0-E16.2	
Acidosis	E87.2	
Non-diabetes hypoglycemic coma	E15	
Ketoacidosis	E10.1, E11.1, E12.1, E13.1, E14.1	
Hypoglycemia	E16.0—2	
Diabetes with several complications	E10.7, E11.7, E12.7, E13.7, E14.7	
Diabetes with unspecified complications 250.9	E10.8, E11.8, E12.8, E13.8, E14.8	
Alzheimer	F00, G30	
Dementia in Parkinson disease	F02.3, G20.9	
Cognitive dysfunction	F01.9, F03.9	
Diabetes without complications	E10.9, E11.9, E12.9, E13.9, E14.9	

Table 8-3 ATC codes for study drugs by drug class

Drug class	**ATC**
drugs for acid related disorders	A02
propulsives	A03F
antiemetics and antinauseants	A04
intestinal antiinfectives	A07A
antiobesity preparations, excl. diet products	A08A
antidiabetic drugs	A10
antithrombotic agents	B01
cardiac therapy	C01
antihypertensives	C02
diuretics	C03
beta blocking agents	C07
calcium channel blockers	C08
agents acting on the renin-angiotensin system	C09
lipid modifying agents	C10
thyroid preparations	H03A
antibacterials for systemic use	J01
antimycotics for systemic use	J02
antimycobacterials	J04
antigout preparations	M04
benzodiazepine derivatives	N05CD
benzodiazepine related drugs	N05CF
antidepressants	N06A
drugs for obstructive airway diseases	R03

Table 8-4 Surgical codes for comorbidities and causes of death

Procedure	NCSP code
Coronary arteries	FN
Severe ischemic arrhythmia	FPE-FPG
Dialysis	KA_4
Lower limb amputations	NGQ, NFQ, NHQ

9. SIGNATURES

ASTRAZENECA SIGNATURE(S)

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 inhibitors (SGLT-2s) and other diabetes medications (other glucose lowering drugs). The study will analyze the risk of hospitalization for heart failure (HF), other CV outcomes, severe hypoglycemia, kidney disease (KD), all-cause mortality, and health care resource utilization in T2DM patients who initiate use or treatment with SGLT-2s compared to patients initiating other glucose lowering drugs (GLD) in Finland.

I agree to the terms of this Non-Interventional Study protocol.

AstraZeneca representative

13 Nov 2017
Date
(Day Month Year)

Niklas Lindarck
Medical Evidence Director
AstraZeneca AB, AstraZeneca Nordic-Baltic, 151 85 Södertälje, Sweden
niklas.lindarck@astrazeneca.com

PRINCIPAL INVESTIGATOR SIGNATURE

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 inhibitors (SGLT-2s) and other diabetes medications (other glucose lowering drugs). The study will analyze the risk of hospitalization for heart failure (HF), other CV outcomes, severe hypoglycemia, kidney disease (KD), all-cause mortality, and health care resource utilization in T2DM patients who initiate use or treatment with SGLT-2s compared to patients initiating other glucose lowering drugs (GLD) in Finland.

I approve this Non-Interventional Study protocol.

Fabian Hoti, PhD,
Head of RWE Statistics
EPID Research
fabian.hoti@epidresearch.com

13-Nov-2017
Date
(Day
Month
Year)