Patient characteristics and cardiovascular and mortality outcomes in patients with high cardiovascular risk and type 2 diabetes mellitus initiating treatment with sodium-glucose co-transporter-2 inhibitors and other antidiabetic medications

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients at high CV risk with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors and other selected groups of antidiabetic medicines. The study will use observational data from several databases and countries including UK (CPRD, THIN), US (Humedica, MarketScan) and the Nordic countries.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutical Chemical Classification system
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase-4 inhibitors
GLP-1	Glucagon-like peptide-1 receptor agonists
HF	Heart failure
ICD	International Classification of Diseases
MI	Myocardial infarction
SGLT-2	Sodium glucose cotransporter-2 inhibitor
SOC	Standard of care
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

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PROTOCOL SYNOPSIS

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients at high CV risk with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors and other selected groups of antidiabetic medicines. The study will use observational data from several databases and countries including UK (CPRD, THIN), US (Humedica, MarketScan) and the Nordic countries (Sweden).

Background/Rationale: In September 2015 the EMPA-REG trial presented data on positive effects of empagliflozin, a SGLT-2 inhibitor on CV outcomes. This has created a need for data on how this class of medicines affect CV event rates when used in clinical practice. An observational study can never replicate a RCT study since neither placebo treatment nor randomisation is part of clinical practice. An observational study will instead use an active comparator group. To provide a good comparison, the groups should be used in a similar way and ideally be exchangeable alternatives to each other with similar patient characteristics and baseline risk of the users. For medication classes recently introduced on the market it may be more difficult to find a suitable comparator and the number of patients exposed and length of exposure may be limited. This is the case for SGLT-2s, therefore this study has two steps. Step 1 will assess the number of patients initiating use with this class of medicines and their length of follow up as well as describe characteristics of new users of SGLT-2s and several groups of potential comparators. If Step 1 shows that a suitable comparator group is available and if there is power to conduct a comparative analysis a comparative analysis will be conducted in Step 2.

Objectives and Hypotheses: To describe patient characteristics and co-morbidities and estimate incidence rate of CVD and mortality rate among new users of SGLT-2 and DPP-4, SU, GLP-1 and other standard of care treatments as well as a group of matched comparators, respectively in clinical practice for all patients as well as a subset with established CVD.

Methods:

    Study design: Cohort study (Section 3.1)

    Data Source(s): CPRD, THIN, Humedica, MarketScan and Sweden (the DAISY cohort) (Section 3.1.1)

    Study Population: New users of SGLT-2 and DPP-4, SU, GLP-1 and other standard of care treatments as well as a group of matched comparators initiating diabetes medication (Section3.2)

Exposure(s): SGLT-2 and DPP-4, SU, GLP-1 and other diabetes medications (Section 4.1)

Outcome(s): Hospitalisation for specific CV events (heart failure, myocardial infarction, stroke, TIA, unstable angina and multi-vessel coronary artery disease), all-cause mortality (with the exception of Humedica database) and CV mortality. (Section 4.2)

Sample Size Estimations: This is a descriptive study assessing number of patients in the groups with established CVD and their follow up time to provide a basis on whether a comparative study of hospitalisation for specific CV events for SGLT-2 users and a suitable comparator class is possible. The number of individuals exposed to SGLT-2s in each database range from 3000 up to almost 60000 individuals as described in Section 3.2. Sample sizes required in a comparative analysis are outlined in section 5.3.

Statistical Analysis: Since the first part is a descriptive study (step 1), the primary aim is not to conduct any formal statistical comparisons between SGLT-2 users and users of other diabetes medications. Rather, the event rates and baseline characteristics for each treatment group will be summarized descriptively. Propensity scores will be calculated to assess comparability between SGLT-2 users and the groups of potential comparators. This is described in detail in Section 5. Once the treatment, comparator, and primary outcome have been identified in step 1, the primary objective of step 2 is to provide a formal statistical comparison between the treatment and comparator group with respect to the outcome of interest using a hazard ratio (or other appropriate measure).

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
	N/A	

MILESTONES

Date	Milestone
Q4 2016	Development of Study Concept Sheet
Q4 2016	Final Protocol
November 17 2015	Development of Study Concept Sheet
December 16 2015	Internal scientific review of protocol
December 31 2015	Approval of protocol
January 30, 2016	Development of core SAP
	Database/EC/IRB approvals
February 17, 2016	– CPRD (ISAC approval)
March 2, 2016	– CPRD+THIN
	Core data sets set up
April 27, 2016	– CPRD only
May 4, 2016	– CPRD+THIN
February 28, 2016	– Humedica
April 30, 2016	– MarketScan
February 15, 2016	– Sweden
	Final results tables step 1
June 2, 2016	– CPRD only
July 13, 2016	– CPRD+THIN
March 31, 2016	– Humedica
May 31, 2016	– MarketScan
March 31, 2016	– Sweden
	Final report for step 1
July 7, 2016	– CPRD only
August 17, 2016	– CPRD+THIN
April 30, 2016	– Humedica
June 30, 2016	– MarketScan
April 30, 2016	– Sweden
	Final Manuscript draft

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, myocardial infarction (MI) or stroke was reported from the first three placebo-controlled trials involving the dipeptidyl peptidase-4 inhibitors, DPP-4, saxagliptin (i.e. SAVOR-TIMI53)2 and alogliptin (i.e. EXAMINE) and sitagliptin (i.e. TECOS).3-5 In the SAVOR-TIMI 53 trial, an unexpected excess rate of hospitalization for heart failure in the saxagliptin group was observed. This was not confirmed in the recent US real world retrospective observational study comparing the risk for hospitalisation for heart failure in new users of SUs and DPP-4s. 6 Furthermore a non significant numerical unbalance in hospitalization for HF was reported in the alogliptin group in the EXAMINE trial3, in contrast to TECOS5 where the rates of hospitalization for heart failure did not differ between the two groups. Observational studies from several European countries7,8,9 and Asia10 comparing the risk of CV events and CV death among users of DPP-4 inhibitors compared to users of SUs have reported higher risk for CV among those on SU compared to those on DPP-4s in line with the study by Fu et al6. For GLP-1 agonists several RCT studies assessing different CV outcomes are ongoing including LEADER on liraglutide and EXSCEL for exenatide as well as the FIGHT study assess effect of liraglutide on CV death and hospitalisation in patients with heart failure.

Sodium glucose cotransporter-2 (SGLT-2) inhibitors 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 (UGE).11 Currently three drugs in this class are approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA): canagliflozin, dapagliflozin and empagliflozin.12-22 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-2 inhibitors. In a meta-analysis from the dapagliflozin trial programme23 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.24 In this analysis, 201 4-point MACE occurred in 9632 patients. The overall HR was 0.91 (95% 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 inhibitor (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.[25] This was a placebo controlled randomised trial where patients with established CVD were randomised to either empagliflozin or placebo on top of standard of care (SOC). 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-4 inhibitors and 3% used a GLP-1 analogue. Two major CVOT with SGLT2i are ongoing: CANVAS, in patients treated with canagliflozin, that should complete by mid-2017 and DECLARE, conducted with dapagliflozin, planned to read data by 2019.

1.2   Rationale

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 need to compare against an active comparator and disease severity as well as prescriber preferences influence the choice of treatment. This may introduce differences in patient characteristics associated with the treatment choice as well as the outcome and is referred to as confounding by indication or channelling bias. The choice of comparator in observational studies requires careful selection and consideration in order to find a comparator with as similar patient characteristics regarding demographics and disease progression as possible. Patients with T2DM include a large span of disease severity which is important to account for; one marker of this is insulin use. As seen in the EMPA-REG population insulin use is common in T2DM patients with established CVD. The SGLT-2 class is relatively recently introduced on the market in both Europe and the US, introduced in November 2012 and March 2013, respectively. Thus both the number of patients exposed to this class of drugs and their follow up time on the medicines are limited.

The current study will therefore be carried out in two steps of which the first is a descriptive study of patient characteristics in T2DM patients prescribed a SGLT-2 inhibitor or other possible comparator drugs. The rationale for conducting this descriptive study is to gain more insight into the patient characteristics of patients at high baseline CV risk initiating use with SGLT-2s, and specifically dapagliflozin, and four potential comparator groups (DPP-4, SU, GLP-1 and other standard of care treatments) in the different countries (US, UK and Sweden). In addition the descriptive study will also assess the overall rate of CV and mortality outcomes in the target study population. This protocol primarily concerns the first descriptive step. Since SGLT-2s were recently marketed little is known on the patient characteristics of users of these medications in comparison with patient characteristics of users of other medication classes but it is likely that they differ since SGLT-2s have primarily been recommended as third line treatment in many countries. Previous studies have reported some differences in patient characteristics between new users of DPP-4 inhibitors compared to SU concerning age, diabetes duration and concomitant medication use.7[,8,10] More 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 assess several potential comparator groups to find a suitable comparison group.

The results from the first part of this study (step 1) is descriptive and will help inform whether it will be feasible to conduct a comparative effectiveness study, assessing the effects of SGLT-2s (and potentially dapagliflozin separately) versus an active comparator, on CV and mortality outcomes (step 2). Such a study will require adequate power and relevant data for cohort selection and outcomes and to perform required statistical modelling to address channelling bias. A potential 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 first SGLT-2 inhibitor CV outcomes trial.[25]

2.   OBJECTIVES AND HYPOTHESES

2.1   Primary Objective(s) & Hypothesis(es)

This study is divided in two steps where step 1 will assess the study population length and follow up as well as comparability between SGLT-2 users and users of other diabetes medication groups. Step 2 will only be conducted given that step 1 shows that a comparative analysis is feasible according to the criteria outlined below. Step 2 is a comparative analysis of the risk for CV events between SGLT-2 users and a group of active comparators.

The descriptive study (step 1) has six objectives, for each of these we will stratify by insulin use at the time of initiating use of the treatment of interest:

1) To describe the characteristics, including cardiovascular medications and morbidity, of patients with T2DM initiating use of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments as well as a group of matched comparators, respectively in clinical practice to identify baseline variables that are different between the treatment groups

2) To describe the characteristics, including cardiovascular medications and morbidity, of patients with T2DM at high baseline risk for CV outcomes initiating use of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments as well as a group of matched comparators, respectively, in clinical practice to identify baseline variables that are different between the treatment groups

3) To describe the distribution of characteristics of patients, including cardiovascular medications and morbidity, by different diabetes medications in the group of other standard of care treatments and matched comparators

4) To describe which diabetes medications patient initiating SGLT-2 used when initiating SGLT-2 use

5) To describe the incidence of hospitalisation for CV events (including heart failure) and the mortality rate for both all-causes death and for CV related death, respectively, among patients with T2DM who initiate treatment with SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments as well as the group of matched comparators by baseline risk for CV outcomes

6) To calculate the propensity scores for the groups (new users of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments and the group of matched comparators respectively) and evaluate the possibilities for matching comparators

For all the objectives in step 1 dapagliflozin, canagliflozin and empagliflozin will be described and propensity scores calculated and assessed both separately and together as a class of SGLT-2s to assess the feasibility of an analysis of dapagliflozin separately. Differences in disease progression and patient characteristics are expected in patients on oral versus insulin at treatment initiation (index date), thus the descriptions of characteristics in all aims will be stratified by insulin use at treatment initiation.

Step 2 has one objective and will only be conducted given that a comparative analysis is feasible based on the results from step 1. Feasibility will be determined by the following requirements a) the study population has enough length of follow up, required variables of interest, and size to have sufficient power to assess the outcome of interest according to the power calculations presented in Section 5.3 and b) a suitable comparator group is identified in step 1. Suitability of comparator groups will be assessed based on the propensity score matching by applying normal requirements to assess sufficient match between different groups. This process will be outlined in more detail in the SAP. Step 1 will also inform whether analysis needs to be done on SGLT-2 class level or dapagliflozin separately applying the above-mentioned criteria. If step 2 is to be conducted, a protocol amendment will be created to outline the analysis in detail including the specifics about the treatment group, comparator group, and primary outcome, as determined in step 1. The overall objective of step 2 is:

1) To compare the risk for hospitalization for specific CV events (including heart failure) and mortality, both all-cause mortality and CV related mortality between patients with T2DM treated with SGLT-2 inhibitors as a class or a specific SGLT-2 substance versus an active comparison group. The comparator group will be determined in step 1.

Since different characteristics and previous morbidity is expected in patients who use SGLT-2 as an add-on to metformin and those who use it as an add-on to insulin separate comparisons with different comparator groups may be needed for these groups. If assessed possible in step 1, within class comparisons will be conducted.

2.2   Secondary Objective(s) & Hypothesis(es)

This study has three secondary objectives.

1) To describe the proportion of patients switching to another diabetic medication class during follow up and the time from index date to the switch in new users of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments as well as matched comparators, respectively.

2) To describe the characteristics of patients with T2DM initiating use of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments as well as a group of matched comparators, for patients with concomitant use of metformin to identify baseline variables that are different between the treatment groups

3) To calculate the propensity scores for the groups (new users of SGLT-2s and DPP-4, SU, GLP-1 and other standard of care treatments and the group of matched comparators respectively) with concomitant use of metformin and evaluate the possibilities for matching comparators

2.3   Exploratory Objective(s) & Hypothesis(es)

1) To describe subpopulation by incremental CV risk profiles (comorbidities) at baseline and their evolution over the FU period
2) To describe over the follow up period any addition or change in the treatments, including within class changes, and rate of different combinations use

3.   METHODOLOGY

3.1   Study Design – General Aspects

This is a cohort study of patients with T2DM who are new users of SGLT-2 inhibitors and DPP-4, SU, GLP-1 and other standard of care treatments, respectively, in Sweden, United Kingdom and United States. In addition a group consisting of new users of different diabetic medications matched by index day and baseline characteristics will be included. This will be a mixed bag of different diabetic medications.

The study period will range from launch of the first SGLT-2 in each of the countries (November 2012 for Nordics and UK, March 2013 for US) and end at latest available data in each data source (during 2015 for UK and US databases and 2014 for Sweden). Dapagliflozin was the first SGLT-2 granted marketing approval by the European Commission (EC) for the treatment of T2DM in Europe in November 2012. The US Food and Drug Administration (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.[26]

A new user of SGLT-2, DPP-4, SU or GLP-1 is defined as an individual receiving a prescription or filling a prescription of the mentioned diabetes medication classes with no issued/dispensed prescriptions of that medicine class during the preceding year. New users of the mixed group of other standard of care treatments as well as mixed group of matched comparators will be defined as those receiving a prescription or filling a prescription of a specific drug with no issued/dispensed prescriptions of that drug during the preceding year. Those initiating metformin monotherapy use are not included in these groups.

The date of the first issued /filled prescription of the investigated medication classes (index medication group) during the study period will be denoted the index date. Patients will be followed from index date (inclusive) to the earliest of end of use of the index medication group, migration/leaving the practice/leaving the database, last date of data collection, death date or date of outcome. The availability of some of this information differs between databases and a definition for each database will be described in Section 3.5.

Baseline characteristics including demographic and clinical characteristics will be captured for patients in the year before the index date. Insulin use before index date will be assessed during three months preceding the index date.

3.1.1   Data Source(s)

Several observational data sources will be included in this study to obtain a large enough population. These databases include databases from the United Kingdom including the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). It also includes databases from the Nordic countries (Sweden) as well as the United States (MarketScan, Humedica). AstraZeneca has access to several of these databases in-house. The databases are described below.

The contents and coverage of different variables vary between databases, therefore a set of core variables for both patient characteristics and CV events and mortality will be developed which will be described in all databases. In addition, specific variables of interest including baseline characteristics and CV events and mortality available in a limited number of the databases will also be described where appropriate.

CPRD:
CPRD holds anonymised longitudinal primary care patient records collected from over 680 general practices across the UK including more than 15 million patients. It includes diagnoses, issued drug prescriptions, clinical measures taken within the general practice, lab tests, and referrals to specialist care. Hospitalisation information and specialist care notes are generally recorded by the general practitioner (GP) into the primary care patient records. CPRD may be linked to the Hospital Episode Statistics (HES) dataset, with detailed hospitalisation information (excluding drug use) on all hospitalisation episodes in England. Accident and Emergency visits are not well recorded in HES, unless it concludes with a hospital admission. Overall approximately 58% of all CPRD practices can be linked to HES. About 58% of the CPRD population may also be linked to death certificates to derive estimates of all-cause and cause-specific mortality (Office of National Statistics, ONS). CPRD may be linked to several other datasets to provide important geographic and socioeconomic information such as the aggregate socioeconomic Townsend score. There is an approximate lag of 6 weeks from data availability and last date of data collection. For HES and ONS the end dates are March 31st, 2015 and 30th April 2015. CPRD covers approximately 8% of the UK population. The Read code system is used for coding of diagnoses in CPRD while the ICD-10 system is used in HES. This study will use CPRD, HES, ONS and Townsend.

THIN:

THIN holds similar data as CPRD and some of the general practices providing data to CPRD are also providing data to THIN. Therefore, there is an overlap and a potential to combine the two databases in order to increase patient numbers. THIN includes data from approximately 600 practices and last date of data collection is May 15th, 2015. Approximately 160 English practices have HES linkage and HES end date is March 31st, 2014. All THIN practices are linked to the Townsend Deprivation Score at the patient's postal code level. The linkage is done at the practice site. THIN covers approximately 7% of the UK population. This study will use THIN and HES and will assess the overlap between THIN and CPRD to exclude overlapping patients.[27]

Sweden:
The DAISY database includes information from linkage of three national Swedish registries will full coverage of the Swedish population: the Prescribed Drug Register (PDR) July 1, 2005 to December 2013, covering all drug prescriptions filled using Anatomical Therapeutic Chemical (ATC) codes; the Cause of Death Register 1961–2013; and the National Patient Register covering all hospital admissions and discharge diagnoses in 1987–2013, discharge diagnoses, and open patient clinic visits in 2001–2013. Diagnoses are recorded according to the ICD-system. An update of the DAISY database is ongoing with data up to 2014 expected to be incorporated by the end of 2015. All three registers are held by the Swedish National Board of Health and Welfare (NBHW). Norway, Denmark and Finland have similar registry infra structure as Sweden and corresponding databases are being set up for each of these countries during the first half of 2016. These will however not be included in the descriptive part.

Humedica
Humedica's dataset is derived from dozens of large healthcare organizations treating approximately 46 million patients living throughout the 50 United States and Puerto Rico. The data is certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules, and managed according to Humedica's customer data use agreements. Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory electronic health records (EHRs), practice management systems and numerous other internal systems; and is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Humedica's data elements include demographics; medications prescribed and administered; immunizations; allergies; lab results (including microbiology); vital signs and other observable measurements; clinical and inpatient stay administrative data and coded diagnoses and procedures. Diagnoses are coded according to ICD-9 classification system.

Market Scan:
Truven Health MarketScan® Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases. These databases comprise enrolment information, demographic information, and inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from over 300 large self-insured U.S. employers and over 25 U.S. health plans. The Commercial database includes information for individuals who are under the age of 65 and are the primary insured or a spouse or dependent thereof. The Medicare Supplemental database includes information

for individuals who are Medicare-eligible and have a supplemental insurance paid for by their current or former employer. The Medicare Supplemental database includes both the Medicare-paid and supplemental-paid components of reimbursed administrative claims. The study databases contain data for over 70 million unique individuals during the study period. Diagnoses are coded according to ICD-9 classification system.

3.2   Study Population

New users will be defined as an individual with T2DM either receiving or filling a prescription of a SGLT-2 or DPP-4, SU, GLP-1 and other standard of care treatments during the study period. Individuals with a previous issued/filled prescription of that medicine class during the preceding year (i.e. 365 before the index date) are not regarded as new users. The date of the first issued /filled prescription of the included medication classes during the study period will be denoted the index date. The group consisting of other standard of care treatments is a mixed bag of diabetes medications initiated which is likely to have different composition in different countries and depending on whether the patient was on oral diabetes medication only or on oral diabetes medication and insulin. This group will include all diabetes medicines, allowing combinations and monotherapy use with the exception of metformin monotherapy and use of SGLT-2s. The class SGLT-2s include dapagliflozin, canagliflozin and empagliflozin. The group including comparators matched on baseline characteristics will be matched on a 1:10 ratio with 10 matched comparators for each SGLT-2 user. These will be matched on age at index date, gender, previous MI, previous stroke, previous heart failure, and use of CV-/glucose lowering drug treatment (e.g. ACE inhibitors or ARBs, high ceiling (LOOP) diuretics, diuretics, aldosteron antagonists, beta-blockers, SU, DPP-4i, and GLP-1 agonists) before the index date. There may be other variables included in the matching process as well.

In order to assess differences in patient characteristics by those on oral diabetes medication and those with insulin add-on, stratification will be done by insulin use at index date described as in the exposure variable section.

High baseline CV risk is defined as a diagnosis of MI, unstable angina, stroke, evidence of multi-vessel coronary artery disease, evidence of single-vessel coronary artery disease, or occlusive peripheral artery disease before the index date. ICD-codes for these are provided in Table 8.1 in section 8. Other CV risk factors that will be included where possible include obesity, dyslipidemias (hypercolesterolmia), hypertension, end stage renal disease and low socioeconomic status.

Since dapagliflozin and SGLT-2s are relatively recently introduced the population sizes are limited. Thus the main assessment of eligibility and comparability will be conducted on medication class level to ensure a large enough population. Current numbers of SGLT-2 users are described below, dapagliflozin accounts for 80-100% of the patients on SGLT-2 in included European databases and 25-40% in the included US databases.

The current number of SGLT users and dapagliflozin users in each of the databases.

	CPRD	THIN	Humedica	MarketScan	Sweden
SGLT-2 users	6684	4381	38,928	58,925	~3,000
Dapagliflozin	5281	3790[*]	9,565	24,211	~3,000
Updated to	15/08/15[***]	~01/06/ 15	31/03/15	31/12/14	2014

*a more recent count for dapagliflozin in THIN revealed: ~4,400 patients from data updated approx Sep/2015 ** Not available *** 15/6/15 (dapa)

3.3　　　Inclusion Criteria

Inclusion criteria are:
– New user receiving or dispensed prescription of SGLT-2 medication or DPP-4, SU, GLP-1 and other standard of care treatments, oral as well as injectable, including fixed-dose combination (FDC) products containing these medication groups
– T2DM diagnosis on or prior to the index date defined by ICD9 codes 250.X0, 250.X2 or ICD10 codes E11 and 024.1. Read codes for T2DM are presented in Table 8.2 in section 8.
– ≥ 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 T1DM diagnosis (ICD9 codes 250.x1, 250.X3 or ICD 10 codes E10 and O24.0, read codes for T1DM are presented in Table 8.2) on or prior to index date and only insulin use in the year prior to index date.
– Patients with a gestational diabetes (ICD9 codes648.8 ; ICD10: O24.4; read codes L180811 and L180900) within 1 year before index date
– Initiation of metformin monotherapy use

3.5　　　Participant Follow-up (Optional)

Participants will be followed from the index date until end of use of the index treatment or migration/leaving the practice/leaving the database, last date of data collection, death date (Sweden, UK) or date of outcome.

4.　　　VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1　　　Exposures

The exposure of interest is use of SGLT-2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) or DPP-4, SU, GLP-1 or other standard of care treatments. Other standard of care treatment will include other diabetes medicines than SGLT-2 inhibitors excluding monotherapy of metformin. 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. Insulin use in the three months preceding index date will be assessed and descriptions of characteristics will be conducted by insulin use before index date.

An individual will be considered exposed to the medication of interest from the index date and until the last day with medication available (either last day of the last filled prescription (Sweden, Humedica, MarketScan) or last day of the last issued prescription (CPRD)) plus a grace period of 30 days.

The SGLT-2 class is defined as the medications dapagliflozin (ATC code A10BX09, A10BD15), canagliflozin (A10BX11, A10BD16) and empagliflozin (A10BX12, A10BD19). DPP-4 includes all available medicines in the ATC category A10BH and the substances A10BD07,08,10,11,13, 18 (combinations with metformin). SU include the ATC-category A10BB. GLP-1 analogues are defined as products with the ATC codes A10BX04, A10BX07, A10BX10, A10BX13. Combination of SGLT-2 and DPP-4 including linagliptin and empagliflozin (A10BD19), DPP-4 and TZDs including pioglitazone and alogliptin (A10BD09) and pioglitazone and sitagliptin (A10BD12) as well as SU and TZD including glimepiride and pioglitazone (A10BD06) will be looked into separately. Diabetes medications are classified as ATC group A10A and A10B. Brand names used in the US of the medication groups are outlined in Table 8.3 in section 8 appendix.

4.2   Outcomes

The core CV outcomes described in all databases are hospitalisation for specific CV events (heart failure (ICD-9 code 428.xx, ICD-10 code I50), myocardial infarction (ICD-9:410.xx, ICD-10:I21-I22) , stroke (ICD-9: 430, 431, 432.xx, 433.xx, 434.xx, 436, ICD-10: I60-64 , G45), TIA (ICD-9: 435.9, ICD-10:G45), unstable angina (ICD-9:411.1x, ICD-10:I20.0) and multi-vessel coronary artery disease) and all-cause mortality (with the exception of Humedica database). Read codes will be listed separately.

In addition fatal CV events will be described in a limited number of the included databases where this information is available (CPRD, Sweden).

4.3   Other Variables and Covariates

Covariates will be measured to describe baseline characteristics of the study population. A set of core covariates will be determined where data is available in all databases, in the lists below these are marked with an *. Additional covariates will be described where available, [1] indicates Sweden/DAISY, [2] Humedica, [3] MarketScan, [4] CPRD, and [5] THIN. The list of covariates may not all be present in the considered databases. However, the availability of these covariates should be one of the key considerations when selecting study data source. These will be measured prior to the index date (age will be on index date) and by clinical coding from either primary or secondary care records. Therapies will be assessed in the twelve months before the index date.

Demographics
   –   Age at index date*

- Gender*
- Ethnicity or country of birth [1, 4]
- Socioeconomic indicators
  - Townsend deprivation score [4]

Therapies
- Diabetes medications defined as medications in the ATC-groups A10A and A10B *
  - Including α-glucosidase inhibitors, dipeptidyl peptidase-IV (DPP-IV) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, insulin, metformin, meglitinides, sulfonylureas, thiazolidinediones, other
- Hypertension medications*
  - ACE inhibitors (ATC-group C09A), ARB blockers (C09C), renin antagonists (C09X), beta blockers (C07), dihydropyridine calcium channel blockers (C08CA), low ceiling diuretics (thiazides) (C03A)
- Aldosterone agonists (C03DA)*
- High-ceiling diuretics (loop-diuretics) (C03C)*
- Statins (C10AA)*
- Anti-platelets (B01A)*
- Aspirin (B01AC06 (low dose))*
- Weight loss drugs (A08A)*
- Hormone replacement therapy (G03C, G03D, G03F)

For a complete list of US brands please see Table 8.3

Co-morbidities (incl. variables to be used for defining CV risk)
ICD-9 and ICD-10 codes for previous CVD is presented in Table 8.1
- Myocardial infarction (MI) *
- Stroke (ischemic or hemorrhagic) *
- Transient Ischemic Attack (TIA)*
- Unstable angina*
- Single-vessel coronary artery disease*
- Multi-vessel coronary artery disease incl. *percutaneous coronary intervention* (*PCI*), Coronary artery bypass grafting (*CABG*), percutaneous transluminal coronary angioplasty (PCTA) *
- Peripheral Artery Disease (PAD) – including limb angioplasty, PCI, PCTA, CABG, or limb or foot/ toe amputation or ankle brachial <0.9 in ≥1 ankle *
- Heart Failure*
- Atrial fibrillation
- Angina pectoris
- Hypertension [2,4,5]
- Hyperlipidemia [2,4,5]
- Neuropathy [1,2,3,4,5]
- Nephropathy [1,2,3,4,5]
- Retinopathy [1,2,3,4,5]
- Obesity [2,4,5]
- Depression

  − Cancer*
  − End stage renal disease*
  − Microalbuminuria [2,4, 5]
  − and other relevant co-morbidities

Tests/clinical measures
  − Angiography (coronary or multi-slice computed tomography) – for evidence of multi-vessel coronary artery disease i.e. in ≥2 major coronary arteries or the left main coronary artery
  − Non-invasive stress test for ischemia
  − Height last value recorded within 12 months before the index date [2,4,5]
  − Weight/body mass index (BMI) last value recorded within 12 months before the index date [2,4,5]
  − Glycosylated haemoglobin (HbA1c) last value recorded within 12 months before the index date [2,4,5]
  − Systolic and diastolic blood pressure (BP) last value recorded within 12 months before the index date [2,4,5]
  − Total cholesterol last value recorded within 12 months before the index date [2,4,5]
  − Low density lipoprotein last value recorded within 12 months before the index date [2,4,5]
  − High density lipoprotein last value recorded within 12 months before the index date [2,4,5]
  − Serum Creatinine last value recorded within 12 months before the index date [2,4,5]
  − Estimated glomerular filtration rate (eGFR) last value recorded within 12 months before the index date [2,4,5]

Other variables
  − Smoking status last value recorded within 12 months before the index date [2,4,5]
  − Duration of T2DM at index date [2,4,5]
  − Duration of observation in database prior to the index date
  − Duration of observation in database after the index date (inclusive) i.e. follow up time

5.   STATISTICAL ANALYSIS PLAN

5.1   Statistical Methods – General Aspects

The first part of this protocol is a descriptive study which will describe the baseline characteristics separately by diabetes medication class/agent and the incidence/mortality of outcomes in the whole target population. The proportion of all users of SGLT-2 and DPP-4, SU, GLP-1, and other standard of care treatments fulfilling the criteria of high baseline CV risk will be assessed and the distribution of patient characteristics within this group will be assessed. As this study is descriptive in nature, no formal statistical comparisons between the treatment groups will be performed. Rather, the intent of this study is to generate data from an exploratory perspective in order to help inform a future formal comparative statistical analysis.

In the first step, the incidence rate of CV outcomes after the index date will be estimated for the whole study population of new users of the medication groups of interest together as well as specifically for those with high CV risk. These incidence rates will be summarized by index treatment group.

In the second step, once the treatment group, the comparator group, and the outcome have been determined from the first step, the incidence rates will be formally compared between the treatment groups using hazard ratios (or some other appropriate measure) and corresponding 95% confidence intervals. In this ratio, either dapagliflozin or SGLT-2 as a class will be considered the reference treatment.

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 each of the medication classes of interest as well as dapagliflozin separately. These baseline characteristics can include age, gender, duration of diabetes, HbA1c, geographic region of residence, medical conditions, concomitant medications, and certain lifestyle/ health care utilization variables, as data permit. These lifestyle/ health care utilization variables can include body mass index, smoking history, alcohol use, socioeconomic status, race/ethnicity, number of outpatient visits, number of hospitalizations, number of emergency department visits, and number of specialty care visits. These characteristics will be assessed for all patients fulfilling the inclusion/exclusion criteria and for patients at high baseline CV risk, respectively.

Continuous and count variables will be described using mean (± standard deviation [SD], 95% confidence intervals (95%CI), median (quartiles), and minimum and maximum values. The proportion of patients falling above/below certain weight/BMI and HbA1c thresholds will be derived.

The data from the observational databases may be integrated and combined prior to the analyses, if feasible from a logistic perspective as in terms of comparability between health care systems, and the inclusion/exclusion criteria will be applied to determine the eligible patients for analysis. Analyses will be performed using the statistical software SAS.

To assess the possible imbalances in baseline covariates between treatment groups which may result in confounding, a propensity score approach will be utilized. Propensity scores will be calculated after the relevant inclusion/exclusion criteria are applied for each outcome. The propensity score for each subject is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. Variables that are unrelated to the treatment exposure but are related to the outcome of interest will be included in the calculation of the propensity score. The inclusion of these variables increases the precision of the estimated treatment effect without increasing bias. The variables to be considered for the estimation of the propensity score include age at index date, gender, duration of lookback time, indicator variable for calendar year of the index date, indicator variable for whether the

index medication was an add-on or switch from the previous medication, medical conditions, indicators of diabetes severity (including duration of diabetes), short or long term insulin use, other concomitant medications, lifestyle/ socioeconomic status indicators, and indicators of health care utilization. Patients will then be grouped into categories such that patients within a certain category should have similar propensity scores. To determine whether there is balance in key covariates between treatment groups, the covariate distribution between the treatment groups will be compared within each propensity score stratum by creating a table with the frequency distribution of each key covariate by index drug use.

Incidence analyses of cardiovascular outcomes/mortality events will be conducted by treatment group and stratified by baseline insulin use. 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 display). Incident events will be summed across all patients within each treatment group in each stratification category. 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 in each stratification category. 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 1000 person-years with 95% exact confidence intervals.

There are certain covariates that will vary over time and these time-varying covariates may be adjusted for using marginal structural models or structural nested models. A key time-varying covariate is treatment change, including switching of one therapy to another, the add-on of other therapies (including insulin), dose changes, etc. Indicator variables will be created to account for treatment changes after the index date and will be incorporated into the statistical models. This process will be described in further detail in the SAP.

As the objective of step 1 in this study is descriptive in nature, missing data will not be imputed. For step 2, this will be described in a separate protocol amendment based on the findings in step 1.

5.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

The secondary objectives are all descriptive and data will be presented in the same way as for the descriptive primary objectives.

5.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

The explorative objectives are all descriptive and data will be presented in the same way as for the descriptive primary objectives.

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 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 will be used to adjust for potential covariate differences between the treatment groups. Matching the patients in the treatment and comparator groups by the propensity score 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

Not applicable

5.2.3   Strengths and Limitations

This first step will inform the possible second step of comparative analyses on limitations. In the first step the following limitations apply:
-    The set of core outcomes and variables will be limited to ensure an as large as possible population
-    The data in selected (to be selected) databases reflects everyday health care and is collected for non-research purposes. Therefore, clinical values are captured as part of routine clinical practice and there is considerable variation in the timing and completeness of measurements
-    Some databases reports issued prescriptions only. In these cases, no information may be available as to whether the patient collected the prescription and used the product. However, if a product is repeatedly issued this most likely indicate that the medication is used.
-    The index prescription i.e. the first prescription of a SGLT-2 medicine may not be the first ever SGLT-2 prescription for the patient in GP based EMR databases. For example, the first prescription may have been initiated by a consultant but then the general practitioner will usually continue the care which could be a scenario in databases like CPRD and THIN.
-    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

Limitations that will be further investigated in step 1 to provide further information on these aspects for evaluation of a possible step 2
- Patient may have limited length of follow-up time in the databases and this could impact the likelihood of observing the outcomes
- Comparators will likely have earlier index dates to larger extent than SGLT-2 users and thus may have longer follow up
- Users of comparators may have different CV risk profiles at baseline compared to SGLT-2 users
- 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 randomised clinical trial because this is an observational study

5.3 Sample Size and Power Calculations

This is a descriptive study and all patients initiating SGLT-2 or DPP-4, SU, GLP-1, and other standard of care treatments should be considered for the analyses.

As this study will help inform whether a comparative study is feasible, power calculations are included here to inform what potential minimum number of patients treated with dapagliflozin will be needed from the respective databases. A comparative study would need to be able to conduct propensity score matching or other relevant methods to adjust for covariate differences between the treatment arms and also taking missing data into consideration unless imputation is conducted. The required sample size below was calculated based on the EMPA-REG study thus referring to a population with T2DM and high CV risk (based on power=80% and α=0.05).[30]

Power calculation for comparison of two rates (based in EMPA-REG relative risk reduction in outcome[1]) in a high CV risk population

Outcomes	EMPA rate per 100 person years	Placebo rate per 100 person year	Person years required per group
Hospitalization for heart failure	0.94	1.45	7,204
MACE*	3.74	4.39	15,086
All cause death	1.94	2.86	4,446
CV death	1.24	2.02	4,201

*MACE: Major Cardiovascular Events (from EMPA-REG[25])

Considering a general dapagliflozin population (non-high risk), the number needed per patient group in real world data for the outcome of all cause mortality would be
10,192 patient years per group (based on power=80% and α=0.05) based on a mortality estimate of 8.4/1000 person years observed in CPRD patients receiving dapagliflozin.

6.   STUDY CONDUCT AND REGULATORY DETAILS

6.1   Data Management

6.1.1   Study Flow Chart and Plan

This study will be carried out internally to the largest extent possible. We will utilize the internal AZ access to Humedica, MarketScan and CPRD databases. Combining THIN and CPRD data will require the analysis to be conducted by a contractor, this affects the timelines as well (see below).
A new tool (DRIVE) using a common data model for data extraction and analyses of internally accessible databases is currently being developed and will be launched in different phases in Q1 2016 expected to be functioning fully in early March 2016. This will be used where possible to ensure that analyses are done in a uniform way. The Swedish data (DAISY) will be updated with data for 2014 which will be available in December 2015. The Nordic/Baltic MC has access to the DAISY database and will conduct the analyses of Swedish data.

Key Opinion Leaders (KOL) involvement
Involvement of external KOLs will be considered during when commencing step 1 to ensure their feedback during the study development. A formal Scientific Committee would be set up for a possible comparative study (step 2).

6.1.2   Quality Control

All analyses will be conducted with the Statistical software SAS version 9.3 or higher. Quality control of coding and programming will be done according to the procedures applied for each database.

6.2   Protection of Human Subjects

Governance
Respective databases may have governance requirements in place to be allowed to use their data and publish the study results. This may require approval of the study protocol by external scientific bodies. For example the CPRD database studies will require Independent Scientific Advisory Committee (ISAC) approval and THIN database studies will require Scientific Committee Review (SCR) approval. The protocol will undergo internal scientific review by the Diabetes ORT and require sign off by the GCL.

The final protocol of the Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

6.2.1 Subject Informed Consent

Not applicable since this is a secondary data study.

6.2.2 Confidentiality of Study/Subject Data

NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

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 (SAE)

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 (ADR)

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

An internal advisory committee will be set up for the project with the aim to facilitate dissemination of information and open for a direct communication with key stakeholders and to have a forum for discussion on the project. The committee will include the project leads, internal high level key stakeholders from global functions including Global Medical Affairs, Clinical Operations, Patient Safety, Commercial as well as the European Region Leads for medical and commercial, and key marketing companies including US Business, UK MC and Nordic/Baltic MC.

6.4.1 Publication Plan

After completion of final analyses of step 1, results will be presented to the Global Product Team for dapagliflozin. This will be done in a stepwise manner as step 1 results are ready from the databases in a sequential manner. Based on the results for step 1, a decision will be made together with the Global Product Team on whether it is feasible to start step 2 analyses or not.

A Non-Interventional Study Report will be prepared within 12 months after completion of the final analytic dataset as described in the Milestones section. If step 2 is conducted the Non-Interventional Study Report will incorporated both steps.

External publications including both full-length articles and abstracts to relevant scientific conferences will be prepared for the Step 1 results from each database. If step 2 is conducted external publications will be prepared in the same way.

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

6.4.2 Compliance with Study Registration and Results Posting Requirements

The study will be registered on clincialtrials.gov in accordance with AZ International Procedure 8-P43-cv-X, Disclosure of Trial Information on Public Websites.

Step 1 is not a PASS-study. The status in relation to PASS- studies of step 2 needs to be assessed. If considered a PASS study it will be registered in the EU_PAS register on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) web page.

6.4.3   Compliance with Financial Disclosure Requirements

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

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8. APPENDICES

Table 8.1: Codes used for measurement of prior cardiovascular disease

Category	ICD-9 codes	ICD-10 codes
Prior AMI	ICD-9-CM Dx: 410.xx	I21-I22, I25
Other ischemic heart disease	ICD-9-CM Dx: 411.xx-414.xx	I20.0, I20.9, I25.1, I25.2, Z95
Other heart disease	ICD-9-CM Dx: 402.01, 402.11, 402.91, 420.xx-429.xx, 440.xx	
Stroke	ICD-9-CM Dx: 430, 431, 432.xx, 433.x1, 434.x1, 436	I60-I64, G45
PAD	ICD-9-CM Dx: 443.9	I70-79
Coronary revascularization procedures	*See subcategories*	
CABG	ICD-9-CM Px: 36.1x CPT: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, HCPCS: S2205-S2209	
PCI	ICD-9-CM Px: 0.66, 17.55, 36.06, 36.07 CPT: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996 HCPCS: C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608, G0290, G0291	
Carotid revascularization procedures	*See subcategories*	
Carotid endarterectomy, stenting, angioplasty, or atherectomy	ICD-9-CM Px: 00.61, 00.63, 38.11, 38.12 CPT: 35301, 35390, 37215, 37216	
Carotid bypass	ICD-9-CM Px: 39.28 CPT: 35501, 35601	
Hospitalization for heart failure	ICD-9-CM Dx: 428.xx	I50

Hospitalization for acute myocardial infarction	ICD-9-CM Dx: 410.xx	I21-I22
Hospitalization for stroke	ICD-9-CM Dx: 430.xx, 431.xx, 433.x1, 434.x1, 436.xx	I60-I64, G45
Hospitalization for unstable angina	ICD-9-CM Dx:411.1x	I20.0
Coronary revascularization	ICD-9-CM Px: 00.66, 17.55, 36.06, 36.07, 36.1x CPT: 33510-33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, 92980-92984, 92920 92921, 92928, 92929, 92995, 92996, 92924, 92925, 92933, 92934, 92937, 92938, 92941, 92943, 92944 HCPCS: S2205-S2209, G0290, G0291, C9600-C9608	Z95
Lower extremity revascularization procedures	*See subcategories*	
Lower extremity endarterectomy, stenting, angioplasty, or atherectomy	ICD9-CM: 17.56, 38.18, 39.50, 39.90 CPT: 35302, 35303, 35304, 35305, 35306, 35351, 35355, 35361, 35363, 35371, 35372, 35454, 35456, 35458, 35459, 35460, 35470, 35473, 35474, 35475, 35476, 35482, 35483, 35484, 35485, 35492, 35493, 35494, 35495, 37205, 37206, 37207, 37208, 37220, 37221, 37222, 37223, 37224, 37225, 37226, 37227, 37228, 37229, 37230, 37231, 37232, 37233, 37234, 37235, 0237T, 0238T	
Lower extremity bypass	ICD-9-CM Px: 39.25, 39.29 CPT: 34520, 34530, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661,	

	35663, 35665, 35666, 35671, 35681, 35682, 35683, 35879	
Lower extremity amputation	ICD-9-CM Px: 84.1x CPT: 27290, 27295, 27590, 27591, 27592, 27596, 27598, 27880, 27881, 27882, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825	

Table 8.1: Read codes to define T1DM and T2DM

	Read codes
T1DM	66An.00, 66At000, 66At011, 8Hj3.00, 8Hj4.00, 8Hj5.00, 8I82.00, 8I83.00, 8I84.00, 9NiC.00, 9NiD.00, 9NiE.00, 9OLG.00, 9OLH.00, 9OLJ.00, 9OLK.00, 9OLL.00, C100011, C101000, C102000, C103000, C104000, C105000, C106000, C107000, C107300, C108.00, C108.11, C108.12, C108.13, C108000, C108011, C108012, C108100, C108112, C108200, C108211, C108212, C108300, C108400, C108411, C108412, C108500, C108511, C108512, C108600, C108700, C108711, C108712, C108800, C108811, C108812, C108900, C108911, C108912, C108A00, C108A11, C108B00, C108B11, C108C00, C108D00,C108D11, C108E00, C108E11, C108E12, C108F00, C108F11, C108G00, C108H00, C108H11, C108J00, C108J11, C108J12, C10C.12, C10E.00, C10E.11, C10E.12, C10E000, C10E012, C10E100, C10E111, C10E112, C10E200, C10E212, C10E300, C10E311, C10E312, C10E400, C10E411, C10E412, C10E500, C10E511, C10E512, C10E600, C10E611, C10E700, C10E711, C10E712, C10E800, C10E812, C10E900, C10E911, C10E912, C10EA00, C10EA11, C10EA12, C10EB00, C10EC00, C10EC11, C10EC12, C10ED00, C10ED12, C10EE00, C10EE12, C10EF00, C10EF12, C10EG00, C10EH00, C10EJ00, C10EK00, C10EL00, C10EL11, C10EM00, C10EM11, C10EN00, C10EN11, C10EP00, C10EP11, C10EQ00, C10z000, L180500
T2DM	66A4.00, 66Ao.00, 66At100, 66At111, 66AV.00, C100100, C100111, C100112, C101100, C102100, C103100, C104100, C105100, C106100, C107100, C107200, C107400, C109.00, C109.11, C109.12, C109.13, C109000, C109011, C109012, C109100, C109111, C109112, C109200, C109211, C109212, C109300, C109400, C109411, C109412, C109500, C109511, C109512, C109600, C109611, C109612, C109700, C109711, C109712, C109900, C109A00, C109A11, C109B00, C109B11, C109C00, C109C11, C109C12, C109D00, C109D11, C109D12, C109E00, C109E11, C109E12, C109F00, C109F11, C109F12,C109G00, C109G11, C109G12, C109H00, C109H11, C109H12, C109J00, C109J11, C109J12, C109K00, C10C.11, C10D.00, C10D.11, C10F.00, C10F.11, C10F000, C10F011, C10F100, C10F111, C10F200, C10F211, C10F300, C10F311, C10F400, C10F411, C10F500, C10F511, C10F600, C10F611, C10F700, C10F711, C10F900, C10F911, C10FA00, C10FA11, C10FB00, C10FB11, C10FC00, C10FC11, C10FD00, C10FD11, C10FE00, C10FE11, C10FF00, C10FF11, C10FG00, C10FG11, C10FH00, C10FJ00, C10FJ11, C10FK00, C10FL00, C10FL11, C10FM00, C10FM11, C10FN00, C10FP00, C10FQ00, C10FR00, C10K.00, C10K000, C10z100, L180600

Table 8.3: Codes and medications used for measurement of other effect modifiers and potential confounders

Category	Codes/Medications
Lab Tests Ordered	*See subcategories*
BUN	CPT: 80047, 80048, 80053, 80069, 84520, 84525, 84540 , 84545
Creatinine	CPT: 80047, 80048, 80053, 80069, 82565, 82570, 82575
HbA1c	CPT: 83036, 83037
Asthma	ICD-9-CM Dx: 493.xx
Cancer (excluding non-melanoma skin cancer)	ICD-9-CM Dx: 140.xx-172.xx, 174.xx-209.3x, 209.7x
Chronic Kidney Disease (excluding End Stage Renal Disease)	ICD-9-CM Dx: 585.1-585.4 HCPCS: G0420, G0421
Chronic Obstructive Pulmonary Disease	ICD-9-CM Dx: 491.xx, 492.xx, 496
Dementia	ICD-9-CM Dx: 290.0 , 290.1x, 290.2x, 290.3, 290.4x, 290.8, 290.9, 291.2, 292.82, 294.0, 294.1x, 294.2x, 294.8, 331.0 , 331.1x, 331.2, 331.7, 331.8x, 331.9, 797
Depression	ICD-9-CM Dx: 296.2x, 296.3x, 300.4, 311
ESRD	ICD-9-CM Px: 38.95, 39.27, 39.42, 39.95, 54.98, 55.52, 55.53, 55.54, 55.69, ICD-9-CM Dx: 285.21, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 458.21, 584.5, 584.6, 584.7, 584.8, 584.9, 585.5, 585.6, 586, 792.5, 996.56, 996.68, 996.73, 996.81, V42.0, V45.1x, V56.xx, E879.1, CPT: 36145, 36800–36815, 36825–36833, 50340, 50370, 76776, 76778, 90918–90999, 93990, 99512, 0505F, 0507F, 4052F, 4053F, 4054F, 4055F HCPCS: A4690, E1510, E1590, E1592, E1594, E1630, E1632, E1635, G0257, G0320, G0321, G0322, G0323, G0324, G0325, G0326, G0327, G8075, G8076, G8081, G8082, G8085, G8488, J0636, J0881, J0882, J0885, J0886, Q4054, Q4055, S9335, S9339 UB-04: 0304, 0367, 080x, 082x, 083x, 084x, 085x, 086x, 087x, 088x
Fracture	ICD-9-CM Dx: 733.1, 733.93-733.98, 805.xx-807.4x, 808.xx-825.xx, 827.xx, V54.13, V54.23

	ICD-9CM Px: 79.01,79.02, 79.05, 79.06, 79.11, 79.12, 79.15, 79.16, 79.21, 79.22, 79.25, 79.26, 79.31, 79.32, 79.35, 79.36, 79.61, 79.62, 79.65, 79.6, 81.65, 81.66
Human immunodeficiency virus/acquired immune deficiency syndrome	ICD-9-CM Dx: 042, 043, 044, 795.71, V08, 079.53
Hyperlipidemia or lipid disorder	ICD-9-CM Dx: 272.0-272.2, 272.4
Hypertension	ICD-9-CM Dx: 401.xx, 402.00, 402.1, 402.10, 402.90, 403.xx-405.xx
Hypoglycemia	ICD-9-CM Dx: 250.8x, 251.0-251.2
Liver disease	ICD-9-CM Dx: 570, 571.xx, 572.xx, 573.xx
Microvascular complications of diabetes	*See subcategories*
Nephropathy	ICD-9-CM Dx: 250.4x
Retinopathy	ICD-9-CM Dx: 250.5x, 362.0x
Peripheral neuropathy	ICD-9-CM Dx: 250.6x, 337.1, 354.xx, 355.xx, 357.2
Obesity (or weight gain)	ICD-9-CM Dx: 278.0x, 793.91, V85.3x, V85.4x, 783.1
Osteoporosis	ICD-9-CM Dx: 733.0x
Tobacco use	ICD-9-CM Dx: 305.1, V15.82
Andiabetes medications	*See subcategories*
Alpha-glucosidase inhibitors	Acarbose, Miglitol
Amylin analogs	Pramlintide Acetate
Biguanides (metformin)	Metformin Hcl
DPP-4 inhibitors	Alogliptin Benzoate, Linagliptin, Saxagliptin Hcl, Sitagliptin Phosphate
GLP-1 RAs	Exenatide, Liraglutide
Insulin	*See subcategories*
Long-acting and combination	Insulin Aspart Protamine Human/Insulin Aspart, Insulin Detemir, Insulin Glargine, Human Recombinant Analog, Insulin Lispro Protamine & Insulin Lispro, Insulin Nph Human Semi-Syn, Insulin Nph Human Semi-Syn/Insulin Reg Human Semi-Syn, Insulin Zinc Extend Human Rec, Insulin Zinc Human Rec, Insulin Zinc Human Semi-Syn, Nph, Human Insulin Isophane, Nph, Human Insulin Isophane/Insulin Regular, Human
Short-acting	Insulin Aspart, Insulin Glulisine, Insulin Lispro, Insulin Reg Human Semi-Syn, Insulin Reg, Hum S-S Buff, Insulin Regular, Human, Insulin Regular, Human/Insulin Release Unit, Insulin Regular, Human/Insulin Release Unit/Chamber/Inhaler, Insulin Regular,Human Buffered

Meglitinides	Nateglinide, Repaglinide
SGLT2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Sulfonylureas	Acetohexamide, Chlorpropamide, Glimepiride, Glipizide, Glyburide, Nateglinide, Repaglinide, Tolazamide, Tolbutamide
Thiazolidinedioines	Pioglitazone Hcl, Rosiglitazone Maleate, Troglitazone
Antihypertensive medications	*See subcategories*
ACE inhibitors	Benazepril Hcl, Captopril, Enalapril Maleate, Fosinopril Sodium, Lisinopril, Moexipril Hcl, Perindopril Erbumine, Quinapril Hcl, Ramipril, Trandolapril
Alpha-blockers	Doxazosin Mesylate, Phenoxybenzamine Hcl, Prazosin Hcl, Terazosin Hcl
ARBs	Azilsartan Medoxomil, Candesartan Cilexetil, Eprosartan Mesylate, Irbesartan, Losartan Potassium, Olmesartan Medoxomil, Telmisartan, Valsartan
Beta-blockers	Acebutolol Hcl, Atenolol, Betaxolol Hcl, Bisoprolol Fumarate, Carteolol Hcl, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Nebivolol Hcl, Penbutolol Sulfate, Pindolol, Propranolol Hcl, Timolol Maleate
CCBs	Amlodipine Besylate, Diltiazem Hcl, Diltiazem Malate, Felodipine, Isradipine, Mibefradil Di-Hcl, Nicardipine Hcl, Nifedipine, Nimodipine, Nisoldipine, Verapamil Hcl
Direct Vasodilators	Hydralazine Hcl, Isosorbide Dinitrate/Hydralazine Hcl, Minoxidil
Direct Renin Inhibitors	Aliskiren Hemifumarate
Diuretics	*See subcategories*
Aldosterone antagonists	Eplerenone, Spironolactone
Loop diuretics	Bumetanide, Ethacrynic Acid, Furosemide, Torsemide
Potassium sparing diuretics	Amiloride Hcl, Triamterene
Thiazide diuretics	Bendroflumethiazide, Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Trichlormethiazide
Lipid lowering medications	Amlodipine Besylate/Atorvastatin Calcium, Aspirin (Calcium Carb & Magnesium Buffers)/Pravastatin, Atorvastatin Calcium, Cerivastatin Sodium, Cholestyramine (With Sugar), Cholestyramine/Aspartame, Clofibrate, Colesevelam Hcl, Colestipol Hcl, Dextrothyroxine Sodium, Docosahexanoic Acid/Eicosapentaenoic Acid,

	Ezetimibe, Ezetimibe/Atorvastatin Calcium, Ezetimibe/Simvastatin, Fenofibrate, Fenofibrate Nanocrystallized, Fenofibrate,Micronized, Fenofibric Acid, Fenofibric Acid (Choline), Fish Oil/Omega-3 Fatty Acids/Dl-Vit E/Folic Acid/B6-B12, Fluvastatin Sodium, Gemfibrozil, Icosapent Ethyl, Inositol/Choline/Multivitamin, Lomitapide Mesylate, Lovastatin, Methionine/Inositol/Choline/Folic Acid, Mipomersen Sodium, Niacin, Niacin/Lovastatin, Niacin/Simvastatin, Omega-3 Acid Ethyl Esters, Omega-3 Fatty Acids/Dha/Epa/Other Omega-3S/Fish Oil, Omega-3/Dha/Epa/Marine Phospholipids/Astaxanthin/Krill Oil, Phytosterol/Omega-3 Fatty Acids/Dha/Epa/Fish Oil, Pitavastatin Calcium, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin
Digoxin (cardiac glycoside)	Digoxin
Anticoagulants	Anisindione, Apixaban, Dabigatran Etexilate Mesylate, Dicumarol, Rivaroxaban, Warfarin Sodium
Anti-platelets	Anagrelide Hcl, Aspirin/Dipyridamole, Cilostazol, Clopidogrel Bisulfate, Dipyridamole, Prasugrel Hcl, Ticagrelor, Ticlopidine Hcl, Vorapaxar Sulfate
Opioids	Acetaminophen With Codeine Phosphate, Aspirin/Codeine Phosphate, Buprenorphine, Butalbital/Acetaminophen/Caffeine/Codeine Phosphate, Butorphanol Tartrate, Codeine Phosphate, Codeine Phosphate/Butalbital/Aspirin/Caffeine, Codeine Phosphate/Carisoprodol/Aspirin, Codeine Sulfate, Codeine/Aspirin/Salicylamide/Acetaminophen/Caffeine, Dihydrocodeine Bitartrate/Acetaminophen/Caffeine, Dihydrocodeine Bitartrate/Aspirin/Caffeine, Dihydrocodeine/Aspirin/Caffeine, Fentanyl, Fentanyl Citrate, Hydrocodone Bitartrate, Hydrocodone Bitartrate/Acetaminophen, Hydrocodone Bitartrate/Acetaminophen/Dietary Supplement #11, Hydrocodone Bitartrate/Aspirin, Hydrocodone/Ibuprofen, Hydromorphone Hcl, Ibuprofen/Oxycodone Hcl, Levomethadyl Acetate Hcl, Levorphanol Tartrate, Meperidine Hcl, Meperidine Hcl/Promethazine Hcl, Methadone Hcl, Morphine Sulfate, Morphine Sulfate/Naltrexone Hcl, Oxycodone Hcl, Oxycodone Hcl/Acetaminophen, Oxycodone Hcl/Aspirin, Oxycodone Hcl/Oxycodone Terephthalate/Aspirin, Oxycodone/Aspirin, Oxymorphone Hcl, Pentazocine Hcl/Acetaminophen, Pentazocine Hcl/Aspirin, Pentazocine Hcl/Naloxone Hcl, Propoxyphene Hcl, Propoxyphene Hcl/Acetaminophen, Propoxyphene

	Hcl/Aspirin/Caffeine, Propoxyphene Napsylate, Propoxyphene Napsylate/Acetaminophen, Tapentadol Hcl, Tramadol Hcl, Tramadol Hcl/Acetaminophen, Tramadol Hcl/Dietary Supplement,Misc. Cb.11, Tramadol Hcl/Glucosamine Sulfate
Oral corticosteroids	Betamethasone, Cortisone Acetate, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone, Hydrocortisone Cypionate, Methylprednisolone, Prednisolone, Prednisolone Acetate, Prednisolone Sod Phosphate, Prednisolone Sodium Phosphate/Peak Flow Meter, Prednisone, Triamcinolone, Triamcinolone Diacetate

9.   ATTACHMENTS

10.   SIGNATURES

ASTRAZENECA SIGNATURE(S)

This observational study will describe patient characteristics and rate of cardiovascular (CV) and mortality outcomes in patients at high CV risk with type 2 diabetes mellitus (T2DM) who are initiating use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors and other selected groups of antidiabetic medicines. The study will use observational data from several databases and countries including UK (CPRD, THIN), US (Humedica, MarketScan) and the Nordic countries (Sweden).

<<This NIS Protocol >> <<has/have>> been subjected to an internal AstraZeneca review>>
I agree to the terms of this Non-Interventional Study protocol.

AstraZeneca representative

Peter Fenici, Medical Affairs Lead *Medical Evidence Director/ Delegate/ Medical Director/Delegate/ NIS Study Leader* *peter.fenici@astrazeneca.com, +44 7818 524220*	Date (Day Month Year)

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

AstraZeneca representative

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AstraZeneca representative

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