Observational Study Protocol MB102-110 ST

COMPARISON OF THE RISK OF ACUTE KIDNEY INJURY BETWEEN PATIENTS WITH TYPE 2 DIABETES EXPOSED TO DAPAGLIFLOZIN AND THOSE EXPOSED TO OTHER ANTIDIABETIC TREATMENTS

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SYNOPSIS

Observational Study Protocol MB102-110 ST

Title of Study: Comparison of the Risk of Acute Kidney Injury Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments

Department: AstraZeneca Epidemiology

Study Objectives

Primary Objective: To compare, by insulin use at the index date, the incidence of hospitalization for acute kidney injury (AKI) among patients with type 2 diabetes mellitus who are new users of dapagliflozin with those who are new users of antidiabetic drugs (ADs) in classes other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

Secondary Objective #1: To compare, by insulin use at the index date, baseline patient characteristics of patients with type 2 diabetes mellitus who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy and to identify important prognostic variables that should be balanced between the study groups.

Secondary Objective #2: To examine potential risk factors for AKI if new users of dapagliflozin are found to be at greater risk for this outcome than new users of other ADs.

Study Design: This will be a cohort study that will be conducted with data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK) and the HealthCore Integrated Research Database (HIRD^{SM}) and Medicare database in the United States of America (US). The study will compare the incidence of hospitalizations for AKI among new users of dapagliflozin with incidence of hospitalizations among those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The planned study duration is 5 years; however, duration will depend on the market uptake of dapagliflozin.

Study Population: Patients will be eligible for inclusion in this study if they meet all of the following criteria: (1) receive newly prescribed dapagliflozin (with or without other ADs) or receive a newly prescribed AD (with or without other ADs) in a class other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy; (2) do not have any diagnostic code indicating type1 diabetes; (3) are aged 18 years or older at the index date for CPRD patients, 18-64 years for HIRD^{SM} patients, or 65 years or older for Medicare patients; and (4) have been enrolled in the data source for at least 180 days before the first prescription or dispensing dapagliflozin or eligible index comparator AD. Patients with a previous diagnosis of chronic kidney failure will be excluded. Patients with a history of diabetic nephropathy will be included, and this history will be accounted for in the analysis. In the HIRD^{SM}, all available eligible comparator patients will be used in the analysis. In the CPRD and Medicare, it may be necessary to select a subsample of AD users before propensity score estimation if all available data cannot be used. If used, the subsample will be identified by frequency matching eligible comparator patients to dapagliflozin patients by 5-year age groups, sex, geographic region, and calendar year of the index date in at least a 6:1 ratio in the CPRD and 15:1 in Medicare.

Data Collection Methods

Data Sources: The CPRD contains electronic medical records including outpatient diagnoses and prescriptions from general practitioner (GP) practices in the UK and mentions of diagnoses associated with hospitalizations. The HIRD^{SM} contains health insurance claims from the largest commercially insured population in the US. Medicare data include health insurance claims from the federally sponsored health insurance program for individuals in the US aged 65 years or older and individuals with permanent disabilities.

Exposures: New use of dapagliflozin will be defined to begin on the date of first dapagliflozin prescription or dispensing recorded in the relevant data source. New use of an AD in a class eligible for inclusion will be defined to begin on the date of first prescription or dispensing for these medications in the relevant data source.

Outcomes: The primary outcome in this study will be hospital admission for AKI. To validate the identified cases or a sample of electronically identified cases, in the CPRD, additional clinical details will be obtained via a questionnaire sent to the GP. In the HIRD^{SM} and Medicare cohorts, individuals with health insurance claims for hospitalization for AKI will be identified as potential cases; for a subset of potential cases, the medical

records for that hospitalization will be abstracted to confirm the diagnosis and diagnosis date of AKI. If the electronic algorithm for identifying potential cases is associated with positive predictive value less than 0.80, then the case ascertainment algorithm will be modified.

Follow-up: Follow-up will begin on the day after the index date, which is the day a patient is first prescribed or dispensed dapagliflozin or a comparator AD. Follow-up time for a given exposure category will continue until hospitalization for AKI; death; the end of study data or study period; initiation of an SGLT2 inhibitor other than dapagliflozin; or the end of the risk window for the index AD, defined as 30 days after the estimated discontinuation of dapagliflozin or the index comparator AD, whichever occurs first. Sensitivity analyses will involve each of the following variations, one at a time: (1) the risk window will be extended to 90 days after the estimated discontinuation of the index AD, (2) follow-up will end if new use of any study AD is added, and (3) comparator cohorts be limited to new users of study drug classes.

Data Analyses: Descriptive statistics will be generated to compare baseline characteristics (e.g., demographic information, comorbidities, and medication use at the index date) between dapagliflozin initiators and comparator AD initiators, by insulin use at the index date. Propensity scores will be estimated by logistic regression analyses, incorporating measured potential predictors of therapy and calendar year of the index date as independent variables in the regression model and with exposure group (dapagliflozin group vs. comparator group) as the outcome. Duration of lookback time and timing of information on key covariates will be included in the model. Incidence rates of AKI will be determined in each cohort. Propensity score–stratified analysis will be used to estimate unadjusted and adjusted incidence rate ratios (IRRs) (with 95% confidence intervals) of the outcome of interest in dapagliflozin initiators versus other AD initiators. If necessary, further adjustment for therapies added during follow-up will be performed via time-dependent Cox proportional hazards regression. Analyses will be conducted in each data source, and a pooled estimate will be calculated if deemed appropriate.

Study Size/Power: A weighted average of the rates of AKI in the general diabetes population across the three data sources is 14.8 per 1,000 person-years. It is currently projected that at the end of 5 years, there will be a total of 91,927 person-years of exposure to dapagliflozin across the three data sources (CPRD: 3,600 person-years; HIRD^{SM}: 42,473 person-years; and Medicare: 45,854 person-years). This includes approximately 73,542 person-years among those not on insulin at the index date and 18,385 person-years among those on insulin at the index date. Using these estimates and assuming that the true dapagliflozin:comparator IRR is 1.0 and there are 73,000 person-years of dapagliflozin follow-up among new users of dapagliflozin not on insulin at the index date, there will be an 81% probability that the upper 95% confidence limit of the observed IRR will be less than 1.1.

Limitations/Strengths: The UK is an ideal setting for population-based studies of diabetes because diabetes care is largely coordinated by the GP, and information about metabolic parameters, cardiovascular risk factors, diabetes comorbidities, and disease outcomes are collected electronically. In addition, this population-based data source provides data entered by GP practices without any awareness of the hypothesis or of an ongoing study. Furthermore, clinical guidelines in the UK facilitate consistency in patterns of care. However, there are still limitations. In the CPRD, there may be inaccuracies in the recorded dates of hospitalization and information about care by specialists may be missing. Patient-specific variability in the availability of laboratory data and medical records, misclassification of exposures and outcome, and limitations in the numbers of available of study patients are the major potential limitations of this study**.**

In the HIRD^{SM} and Medicare cohorts, the health insurance claims database includes claims for all medical services for cohort members during the study period. The Medicare data cover a very large proportion of US residents aged 65 years or older, and the HIRD^{SM} covers a large proportion of the US population younger than 65 years of age. Information on potentially important confounders such as high body mass index and smoking is virtually nonexistent unless treatment for either is detectable through claims. Therefore, an evaluation of the impact of missing confounders is planned.

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1 INTRODUCTION

Dapagliflozin (BMS-512148) is a highly potent, selective, and reversible inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin is the first approved drug in its class. It lowers plasma glucose by inhibiting the renal reabsorption of glucose, thereby promoting urinary excretion of glucose, making it a member of an emerging therapeutic class in the treatment of type 2 diabetes mellitus (T2DM) (Bristol-Myers Squibb [BMS] and AstraZeneca [AZ], 2011).

Epidemiology of Acute Kidney Injury

Acute kidney injury (AKI) is characterized by a sudden (i.e., hours to days) impairment of kidney function. In a study of health care encounters for acute renal failure conducted in the General Practice Research Database (GPRD) in the United Kingdom (UK), now the Clinical Practice Research Datalink (CPRD), incidence was 198 per 100,000 person-years among patients with T2DM and 27 per 100,000 patient-years among those without T2DM in multivariate analyses adjusting for various comorbidities (adjusted hazard ratio for acute renal failure in T2DM vs. no T2DM was 2.5; 95% confidence interval [CI], 2.2-2.7) (Girman et al., 2012). The change in the incidence ratio after adjusting for confounding suggests that there was substantial confounding. Risk factors that raised the incidence by more than 50% were age, obesity, history of congestive heart failure, hypertension, past renal failure, history of chronic kidney disease, and Charlson comorbidity index of 1 or higher. Among the individuals with acute renal failure, 65% were identified via a referral or hospitalization for acute renal failure. Therefore, we estimate that the expected incidence of hospitalizations for acute renal failure is about 65% of 198 per 100,000 person-years, or about 1.3 per 1,000 person-years in patients with T2DM. Two studies have used large administrative and/or claims databases to examine secular trends in the epidemiology of AKI in the United States of America (US). Xue et al. (2006) used inpatient claims data from a 5% sample of US Medicare beneficiaries; among the general population of Medicare enrollees, the incidence of AKI rose from 15 to 36 per 1,000 discharges between 1992 and 2001. Using the same ICD-9-CM[1] codes to identify AKI in a similar and partially overlapping study population, Waikar et al. (2006) examined the Nationwide Inpatient Sample, a nationally representative database of hospital discharges in the US; between 1988 and 2002, the incidence of AKI rose from 4 to 27 per 1,000 discharges. The study estimated the incidence of AKI to be 288 per 100,000 US population in 2002. The incidence of AKI requiring dialysis was estimated to be 27 per 100,000 population.

Some of the most robust data relating to the development of diabetic nephropathy in a population of predominantly white patients with T2DM was reported from the United Kingdom Prospective Diabetes Study, which compared the efficacy of different treatment regimens (e.g., diet, hypoglycemics, insulin, antihypertensive agents, varying blood pressure goals, and other interventions) on glycemic control and the complications of diabetes (including kidney failure) in newly diagnosed patients with T2DM (Adler et al., 2003). Among 5,100 patients with T2DM, at 10 years following diagnosis, the prevalence of microalbuminuria was 25%; macroalbuminuria,

[1] ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*.

5%; and either an elevated plasma creatinine concentration (defined as ≥ 175 µmol/L [2.0 mg/dL]) or a requirement for renal replacement therapy, 0.8%. Further, the percentage of patients that progressed each year from diagnosis to microalbuminuria was 2.0%; from microalbuminuria to macroalbuminuria, 2.8%; and from macroalbuminuria to an elevated plasma creatinine concentration or renal replacement therapy, 2.3%.

In the US, a study conducted within a single Veterans Affairs facility among 3,679 patients with diabetes, predominantly men, showed that incidence of hospitalization for AKI was 2.8 per 100 person-years; the mean age was 61.7 years (Thakar et al., 2011).

Few studies have evaluated the risk of AKI associated with antidiabetic medications. One nested case-control study using data from the GPRD (now the CPRD) found a moderately strong association between acute renal failure and current insulin use (adjusted odds ratio, 2.5; 95% CI, 0.8-7.8), but only a weak association with current use of other antidiabetic drugs (ADs) (adjusted odds ratio, 1.3; 95% CI, 0.5-3.1) (Huerta et al., 2005).

Challenges in the Identification of Acute Kidney Injury

Medical administrative and claims databases afford investigators the opportunity to study AKI in vast numbers of patients admitted over multiple years to a wide spectrum of hospitals, including those not ordinarily represented in prospective cohort studies. The major limitation of claims-based administrative databases is the lack of detailed clinical and laboratory information. In the GPRD (now the CPRD), studies of acute renal failure have validated the potential cases and reported positive predictive values (PPVs) ranging from 8.5% (García Rodríguez et al., 1997) to 48% (García Rodríguez et al., 2008a). In the more recent García Rodríguez and colleagues (2008a) study, 717 potential cases were identified from the standard electronic data, and patient profiles (listings of all available health care encounters, mostly with the general practitioner [GP], and prescriptions) for these cases were available for review. For 462 of these patients, additional free-text fields from the GP records were obtained and reviewed; 35 cases were judged to require further follow-up from the GP, and that follow-up was obtained for 29 cases, 14 of which were confirmed cases of acute renal failure. The screening criteria that identified the original 717 potential cases were not described.

Changes in estimated glomerular filtration rate (eGFR) or urine output are more difficult to assess than changes in serum creatinine as they might not always be performed, and baseline values might not be available. For epidemiologic studies, one approach is to use changes in serum creatinine from baseline, which in turn reflect the change in eGFR (Bellomo et al., 2004). An increase in serum creatinine of 1.5 times the baseline value indicates risk of kidney dysfunction, 2 times baseline indicates injury to the kidney, and 3 times baseline indicates failure of kidney function.

The definition of acute renal failure in epidemiological studies has been based on absolute increases of serum creatinine from normal values (1.7 and 2 times the upper limit of normal [ULN]) or change from baseline (20% to 50%) or both (García Rodríguez et al., 2008a; García Rodríguez et al., 2008b; Goettsch et al., 2006; Griffin et al., 2000, Huerta et al., 2005; Pérez-Gutthann et al., 1996).

1.1 Study Rationale

The dapagliflozin clinical development program reported small mean decreases in eGFR (estimated by the Modification of Diet in Renal Disease [MDRD] equation) from baseline in dapagliflozin-treated patients at week 1 in the short-term plus long-term Placebo-controlled Pool of clinical trial experience. Following this initial drop in eGFR, there was a gradual return to baseline without evidence of progressive renal dysfunction. These early decreases in renal function assessments, although small, were dose-dependent, and may reflect early, dynamic, autoregulatory changes related to the mild proximal tubular diuretic effect of dapagliflozin. There was minimal change from baseline in serum creatinine, and changes in blood urea nitrogen during the short-term double-blind treatment period were not clinically relevant (BMS and AZ, 2011).

This post-authorization safety study is being conducted as part of the BMS/AZ Dapagliflozin Risk Management Plan to monitor the safety of dapagliflozin in real-world use. Because of the mechanism of action for dapagliflozin, there is interest in evaluating whether individuals who use it are at increased risk of AKI. This protocol describes a cohort study to be conducted in the CPRD (UK) and two US data sources: the HealthCore Integrated Research Database (HIRD^{SM}) and Centers for Medicare and Medicaid Services (CMS) Medicare data. The study will compare the incidence of hospitalization for AKI among new users of dapagliflozin with the incidence among those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

1.2 Research Question

What is the risk of hospitalization for AKI for patients with T2DM who are new users of dapagliflozin compared with those who are new users of other AD treatments?

2 STUDY OBJECTIVES

2.1 Primary Objective

To compare, by insulin use at the index date, the incidence of hospitalization for AKI among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.

2.2 Secondary Objective #1

To compare, by insulin use at the index date, baseline patient characteristics of patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy and to identify important prognostic variables that should be balanced between the study groups.

2.3 Secondary Objective #2

To examine potential risk factors for hospitalization for AKI if patients taking dapagliflozin are found to be at greater risk for this outcome than patients newly starting other ADs.

2.4 Exploratory Objectives

Not applicable.

3 STUDY DESIGN

3.1 Overview of Study Design

This cohort study will compare the incidence of hospitalization for AKI among new users of dapagliflozin with the incidence of hospitalization for AKI among new users of ADs in classes other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The source study populations are the UK and the US. A cohort design will allow direct estimation of the incidence and risk of the outcome of interest associated with dapagliflozin. Further, the cohort design permits assessment of the outcome at multiple time points. The planned study duration is 5 years; however, duration will depend on the actual market uptake of dapagliflozin.

The index date for each patient will be defined as the date the patient is newly prescribed or dispensed either dapagliflozin (single-entity dapagliflozin or the fixed-dose combination of dapagliflozin and metformin) or an eligible comparator AD after the beginning of the study observation period, according to the time of approval of dapagliflozin in each country. The lookback time, all available data before the index date, will be used to evaluate patient characteristics among the exposure groups and the potential for confounding. The follow-up time, which begins the day after the index date, will be used to evaluate the incidence of AKI and will be used to identify other confounders, effect modifiers, and exposures not controlled at baseline or that change during follow-up. Propensity scores will be estimated at each planned data cut and will be adjusted by calendar year. Multiple logistic regression models will be used to compute propensity scores, and adjusted incidence rate ratios (IRRs) will be derived by propensity score stratification. Other analytic methods that do not control for intermediate variables to evaluate and adjust for added concomitant AD during follow-up will be considered.

3.2 Study Population

During the conduct of the study, patients will be identified at selected intervals. Study populations of patients with T2DM will be identified using data on GP diagnoses and prescriptions in the CPRD in the UK and health insurance claims for outpatient medication dispensings in the HIRD^{SM} and Medicare databases of the US. These patients will be new users of dapagliflozin or other selected ADs, as detailed in Section 3.2.1, Inclusion Criteria.

3.2.1 Inclusion Criteria

Patients are eligible for the study if they meet *all* of the following criteria:

- Were newly prescribed or dispensed dapagliflozin (with or without other ADs) or newly prescribed or dispensed an AD (with or without other ADs) in a class other than SGLT2

inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy (see Appendix 4)

- Were enrolled in the data source for at least 180 days before the first prescription or dispensing for dapagliflozin or other AD qualifying for the comparator group
- Were aged (at the index date)
  - 18 years or older in the CPRD
  - 18-64 years in the HIRD^{SM} or
  - 65 years or older in Medicare and were participants only in the fee-for-service program (i.e., were not in a managed care program); were enrolled in Parts A, B, and D of the Medicare program for at least 180 days before entering the study (follow-up will be censored if Part D coverage was discontinued); had a residence in a US state or District of Columbia; and Medicare eligibility was not due to end-stage renal disease.

Our rationale for comparing new users of dapagliflozin with new users of ADs *in a class other than SGLT2 inhibitors* is to ensure that we do not miss potentially important associations that are due to the SGLT2 class after more such compounds become available. Analysis results in each cohort will be evaluated by insulin use at the index date because insulin use is clinically considered to be associated with a longer history of diabetes.

Our rationale for excluding new users of either metformin monotherapy or sulfonylurea monotherapy is that patients diagnosed with T2DM are likely to be prescribed these medications early in the course of the disease following diagnosis—e.g., following guidelines of the UK National Institute for Health and Clinical Excellence (2015) and the American Diabetes Association (2014)—whereas dapagliflozin is expected to be used after initial treatment with these therapies. In addition, the long history of availability of sulfonylureas and metformin could result in misclassification of new use when these medications are started again after an interruption of treatment.

Further, in clinical practice, patients may be newly prescribed dapagliflozin or another AD with or without other ADs already prescribed as part of their regimen (i.e., patients may have new AD medications added on or they may switch agents). Therefore, we plan to include patients, regardless of whether or not they are taking other ADs at the time they are newly prescribed either dapagliflozin or an eligible AD. In addition, we will collect information on whether patients received prior AD therapy and/or if they were "added on" or "switched to" dapagliflozin or other ADs at the time of inclusion in the study.

3.2.2 Exclusion Criteria

Patients will be excluded if they meet *any* of the following criteria before entering the cohort:

- AKI was experienced by a patient within 180 days before the index date.
- A diagnosis of chronic kidney disease is recorded on or before the index date.
- The patient was prescribed a non-dapagliflozin SGLT2 inhibitor on or before the index date.
- The patient initiated metformin or sulfonylurea as AD monotherapy at the index date.
- The patient initiated insulin monotherapy at the index date.

- The patient had evidence of type 1 diabetes before cohort entry or first recorded AD is insulin monotherapy.

3.2.3 Selection of Patients

Eligible study patients will be selected from the study data sources separately. All eligible patients in each data source who meet inclusion and exclusion criteria and are new users of dapagliflozin will be selected for inclusion. In the HIRD^{SM}, all available eligible comparator patients will be used in the analysis. In the CPRD and Medicare, it may be necessary to select a subsample of AD users before propensity score estimation if it is not feasible to use all available data. If used, the subsample will be identified by frequency matching eligible comparator patients with eligible comparator episodes to dapagliflozin new users by 5-year age groups, sex, geographic region, and calendar year of the index date in at least a 6:1 ratio in the CPRD and at least a 15:1 ratio in Medicare. The rationale for selecting at least 6 comparator AD new users for each dapagliflozin new user in the CPRD and at least 15 comparator AD new users in Medicare is to ensure that we have sufficient numbers of patients to develop the propensity score and to conduct secondary analyses, as needed.

Patients will enter the study cohort based on the first new use of a qualifying study medication after all inclusion criteria are met. However, inclusion in the study cohort as a new user of dapagliflozin or one of the comparator AD medications does not preclude the patient from being included as a new user of another study medication if the criteria for inclusion in the study cohort are met.

3.2.4 Follow-up of Patients

Follow-up will begin on the day after, but not including, the index date, which is the day after a patient is newly prescribed or dispensed dapagliflozin or a comparator AD. Since AKI could occur soon after exposure to a medication, we assume that patients prescribed dapagliflozin or comparator AD could be at risk for the study outcome the day after the index date.

Follow-up time in a given exposure category will continue until hospitalization for AKI, death, the end of study data or study period, or the end of the risk window for the index AD, whichever occurs first. Discontinuation will be defined as no further prescription 30 or more days after the end of days' supply of the last consecutive prescription in the index exposure episode (assigned to be 30 days if days' supply is missing). Follow-up will be censored at the addition of a non-dapagliflozin SGLT2 inhibitor in either group. Follow-up will *not* be censored if other ADs are prescribed in addition to dapagliflozin or the comparator AD after the index date. If a patient develops type 1 diabetes during follow-up (physician diagnosis in the CPRD or fulfillment of a claims definition in the HIRD^{SM} or Medicare), follow-up time will be censored at the date of diagnosis.

3.2.5 Exposure and Time at Risk

We assume that the potential increased risk of AKI related to medication use could occur at the beginning of therapy, be maintained at an increased level during the duration of treatment, and decrease gradually to the background risk after stopping treatment. Therefore, the time window

of risk relating to use of the index drug will start at the index date and will end 30 days after the end of the last prescription's days' supply (assigned to be 30 days if days' supply is missing) for the index drug.

For most patients, the risk window will end 60 days after the last prescription date (assuming last prescription was a 30-day supply) for the index AD. Adding 30 days to days of supply after the estimated end of supply will capture a potential effect after stopping therapy and any delay in the detection of and hospitalization for AKI. For sensitivity analyses, the risk window for the index drug will extend to 90 days after the end of the last prescription's days' supply for the index AD. This sensitivity assessment will allow exploration of any further potential delay in effect. We selected 90 days because this period is long enough to account for noncompliant and extended use of the discontinued index exposure and a delay in effect.

If a comparator initiator starts on dapagliflozin, that patient will switch to the dapagliflozin group. See Appendix 2 for a description of how switching study exposure groups and the assignment of person-time will be handled under various AD initiation scenarios. If any patient discontinues the index AD and starts on another AD that qualifies as a study exposure, there will be some person-time at risk that pertains both to the tailing off of the first AD and to the startup of the second AD. Person-time during follow-up with combined exposure to dapagliflozin and a comparator AD will be grouped into a combined exposure category and analyzed separately from the person-time of exposure to only dapagliflozin.

3.3 Data Sources/Data Collection Process

This study requires data sources that longitudinally capture inpatient and outpatient diagnoses and procedures, capture prescription and dispensing information, and allow validation of data source listings of AKI. This study will be conducted using three sources of longitudinal data: the CPRD in the UK and the HIRD^{SM} and Medicare in the US. A detailed summary of the available data fields and other characteristics of the data in each data source is provided in Appendix 3.

3.3.1 Clinical Practice Research Datalink – UK

In the UK, GPs are the gatekeepers for the health care of the patients registered with them. In practices that contribute information to the CPRD, common software is used to create the electronic medical record that GPs keep for the clinical follow-up of their patients (http://www.cprd.com/intro.asp). The CPRD includes information on patient demographics, lifestyle factors (admittedly not complete for all patients), outpatient diagnoses (documented to be complete), additional clinical information (completeness dependent upon the type of information), referrals, prescriptions issued by GPs (complete), and other information that GPs consider important for clinical care (e.g., results from complementary exams, procedures, hospitalizations, and reports from specialists—these generally require validation). In addition, validation of outcomes can be implemented by surveying the GP. Approximately 65% of the English practices contributing to the CPRD have consented to have their patient information linked, via a trusted third party, to other health care data sets (including Hospital Episode Statistics [HES] data) via the patient's National Health Service number, sex, date of birth, and

postal code. English practices represent approximately 75% of all practices contributing to the CPRD; therefore, approximately half of the total CPRD practices can be linked to HES data if needed. Previous experience with linkage of data from the CPRD and the HES suggests that the hospitalization dates listed in the CPRD may be up to 120 days later than the actual hospital admission date. The CPRD has information on 5.1 million individuals (active contributors), which represents approximately 8% of the UK population.

The CPRD contains lifestyle factors with a variable proportion of missing values. For example, data on body weight and height, smoking, and alcohol use were available for approximately 70% of patients in the CPRD (Gelfand et al., 2005). In contrast, the pharmaceutical exposures and comorbidities are expected to be based on outpatient prescriptions and to be complete. Although information on race is not available, other user characteristics of interest are likely to be captured. In particular, the diagnosis of T2DM, after excluding individuals with type 1 diabetes diagnoses, has been validated in the CPRD and found to have a high PPV: 98.6% (95% CI, 92.2%-99.7.0%, calculated using Episheet [Rothman, 2012]) (Van Staa and Abenhaim, 1994).

The UK is an ideal setting for population-based studies of diabetes because diabetes care is largely coordinated by the GP, and metabolic parameters, cardiovascular risk factors, diabetes comorbidities, and disease outcomes are collected electronically. Furthermore, clinical guidelines in the UK facilitate consistency in patterns of care (Rubino et al., 2007). The prevalence of diabetes has increased in the UK from 2.8% in 1996 to 4.3% in 2005. The incidence of diabetes has increased from 2.7 per 1,000 person-years in 1996 to 4.4 per 1,000 person-years in 2005. During the period 1996-2005, a change in AD use has occurred, from sulfonylureas to metformin (González et al., 2009).

3.3.2 HealthCore Integrated Research Database – US

HealthCore, Inc., (hereafter, HealthCore) is a wholly owned subsidiary of Anthem, Inc. Anthem is the largest health benefits company in the US in terms of medical membership. Anthem is an independent licensee of the Blue Cross and Blue Shield Association and serves its members as the Blue Cross licensee in 14 states and through UniCare. Anthem is also the parent of Health Management Corporation, a preventive health and disease management company.

The HIRD^{SM} contains fully adjudicated paid claims from the largest commercially insured population in the US, with dates of service for all noncapitated ambulatory, emergency department, inpatient, and outpatient encounters (including administrative claims for laboratory tests) for members with eligibility at the time of service. It also includes claims for outpatient dispensings of prescription pharmaceuticals from pharmacies. The full HIRD^{SM} dates back to 01 January 2006. The majority of data can be accessed from that time period through the most recent update. Data are updated monthly, with an approximate 3-month time lag for up to 95% full capture of paid medical claims. The lag for pharmacy data is shorter, with approximately 99% paid within 30 days. As of January 2014, the HIRD^{SM} contained claims information for approximately 35.8 million lives available for research. In addition, HealthCore has the ability to redact or abstract inpatient and outpatient medical records for the health plan members represented in the HIRD^{SM}, identify and contact providers and members for survey research

through vendor relationships, and link data to national vital records. The HIRD^{SM} enables rapid access to US population-based health care data resources representing all major geographic regions and health care settings and varied clinical indications that permit long-term longitudinal patient follow-up. The specific geographic regions represented in the HIRD^{SM} are the Northeast, Mid-Atlantic, Southeast, Midwest, Central, and West regions of the US. The HIRD^{SM} has been used as a data source in multiple studies related to safety outcomes and validation.

Health plans contributing data to the HIRD^{SM} include several different lines of business such as health maintenance organizations, point-of-service plans, preferred provider organizations, and indemnity plans.

Data on patient enrollment, medical care (professional and facility claims), outpatient prescription drug use, laboratory test result data, and health care utilization may be tracked for patients in the database. Diagnoses and procedures are identified by ICD-9-CM or ICD-10-CM,[1] Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes for both outpatient visits and inpatient stays. Drug claims are captured by National Drug Codes (NDCs), which can be translated to broader, more meaningful classification systems such as Generic Product Identifier codes. Standard Logical Observation Identifiers Names and Codes are used to define specific laboratory test result data. Physician, specialist, and emergency department visits, as well as hospital stays, are captured through CPT codes, uniform billing (UB-92) revenue codes (e.g., room and board), and place-of-service codes. Information on physician specialty is also retained in the database.

Patients aged 65 years or older will be excluded from this data source to avoid any duplication with Medicare data. In addition, patients in the HIRD^{SM} will be censored during follow-up the day before their 65th birthday.

3.3.3 Medicare – US

Medicare is a federally sponsored health insurance program in the US that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with a permanent disability (Cubanski et al., 2010). Most adults become eligible for Medicare when they reach 65 years of age, although younger adults can qualify if they are permanently disabled. Medicare beneficiaries make up approximately 15% of the total US population and include more than 98% of the US population aged 65 years or older (Research Data Assistance Center, 2013). In 2012, 11.2 million people aged 65 years or older had been diagnosed with diabetes (Centers for Disease Control and Prevention, 2014), and most would have Medicare coverage. Therefore, Medicare data are particularly useful for the current study.

Medicare consists of Part A, which is hospitalization insurance; Part B, which covers physician services and outpatient care; and Part D, which is outpatient prescription drug coverage. Parts B and D are optional, and enrollees must pay a monthly premium for this coverage. Part D coverage has been available since 2006 and is purchased by beneficiaries through private

[1] ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification.*

insurance companies approved by Medicare. As of 2010, about 60% of Medicare beneficiaries were enrolled in Part D.

Analytic files on claims contain information collected by Medicare to pay for health care services provided to Medicare beneficiaries. Data are available for each claim type: institutional (inpatient, outpatient, skilled nursing facility, hospice, or home health agency) and noninstitutional (physician and durable medical equipment providers). Similar to the HIRD^{SM}, diagnoses and procedures are identified by ICD-9-CM or ICD-10-CM, CPT, and HCPCS codes for both outpatient visits and inpatient stays. Additionally, the Part D data claims file contains information on prescription drug fills, including product codes (NDCs), quantity dispensed, and days' supply.

There is currently a 2-year lag in accessing Medicare Part D data. Generally, Medicare releases Part D data each January. Therefore, if the first interim analysis occurs in January 2018, Medicare data would be available through the end of 2015.

3.4 Definitions of Study Variables

3.4.1 Outcomes/Endpoint Variables

In each data source, electronically available diagnosis data will be utilized to screen for potential cases of AKI. After all potential cases are identified, a validation effort will be implemented to obtain more detail to classify potential cases. Depending upon the total number of potential cases in each data source, the validation process may be initiated for all potential cases. If the number of potential cases is relatively large, e.g., more than 125 potential cases in any single data source, validation of a potential algorithm will be implemented for a sample of potential cases. Resampling and validation may be required if the algorithm requires modification (for criteria, see Section 3.4.1.2, Case Validation via Medical Record Review).

3.4.1.1 Electronic Case Identification

Acute kidney injury will be identified as any record of hospitalization for acute kidney injury (see Appendix 1 for Read, ICD-9-CM, and CPT codes; ICD-10[1] codes will be included in the statistical analysis plan).

Potential cases of AKI will be identified as follows:

- In the CPRD, via GP mentions of hospitalizations associated with a hospital discharge code for renal injury or acute kidney injury. To identify hospitalizations that may be missing from the CPRD and to confirm dates of hospitalizations within the CPRD, we will link to HES data to identify hospitalizations with relevant diagnoses during follow-up and up to 120 days after the end of follow-up. Linkage to the HES data is currently limited to approximately 55% of GP practices in England (Gallagher et al., 2011).
- In HIRD^{SM} and Medicare data: via claims for hospitalization discharge diagnosis code for acute kidney failure or a procedure code associated with dialysis.

[1] ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision.*

3.4.1.2 Case Validation via Medical Record Review

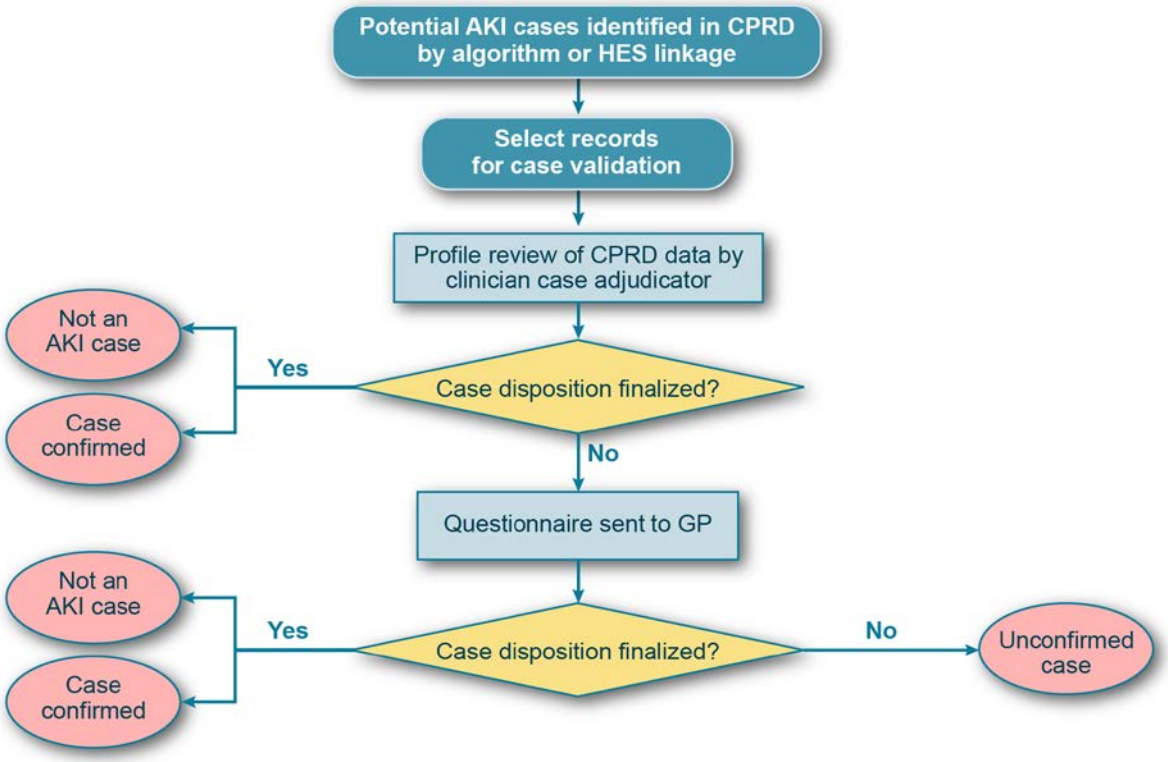
The process for validation for each data source will be detailed in the validation plan, to be developed in the future. In summary, the medical records for up to 125 potential cases will be requested and abstracted to assess the accuracy of algorithms based on codes for identifying confirmed cases. The resulting medical record data will be reviewed by endpoint adjudicators with relevant clinical expertise. We aim to develop an electronic algorithm of codes that results in a positive predictive value greater than 80% for medical record–confirmed outcomes.

If the lower bound of the 95% CI for the positive predictive value of the coding algorithm for AKI is found to be below 80% in one or more of the data sources, we will modify the coding algorithm for that outcome to achieve a higher positive predictive value; if necessary, we will draw a second sample of medical records to validate the revised algorithm. The algorithm development process will be described in the validation plan.

CPRD

The process for case validation in the CPRD is shown in Figure 1. A random sample of potential AKI cases identified from the CPRD will be evaluated further through review of the patient profiles. Guidelines in the UK recommend that serum creatinine be measured annually for individuals with T2DM (National Collaborating Centre for Chronic Conditions, 2008). For patients for whom available clinical data in the CPRD cannot rule out AKI, including those for whom no HES linkage is available, we will further attempt to validate the AKI diagnosis by collecting the relevant clinical information, i.e., serum creatinine levels and their timing, through a questionnaire sent to the GP. Final confirmation of cases will be conducted independently by clinical experts identified by RTI Health Solutions (RTI-HS) who will be blinded to exposure to medications.

Figure 1: Case Validation in the Clinical Practice Research Datalink

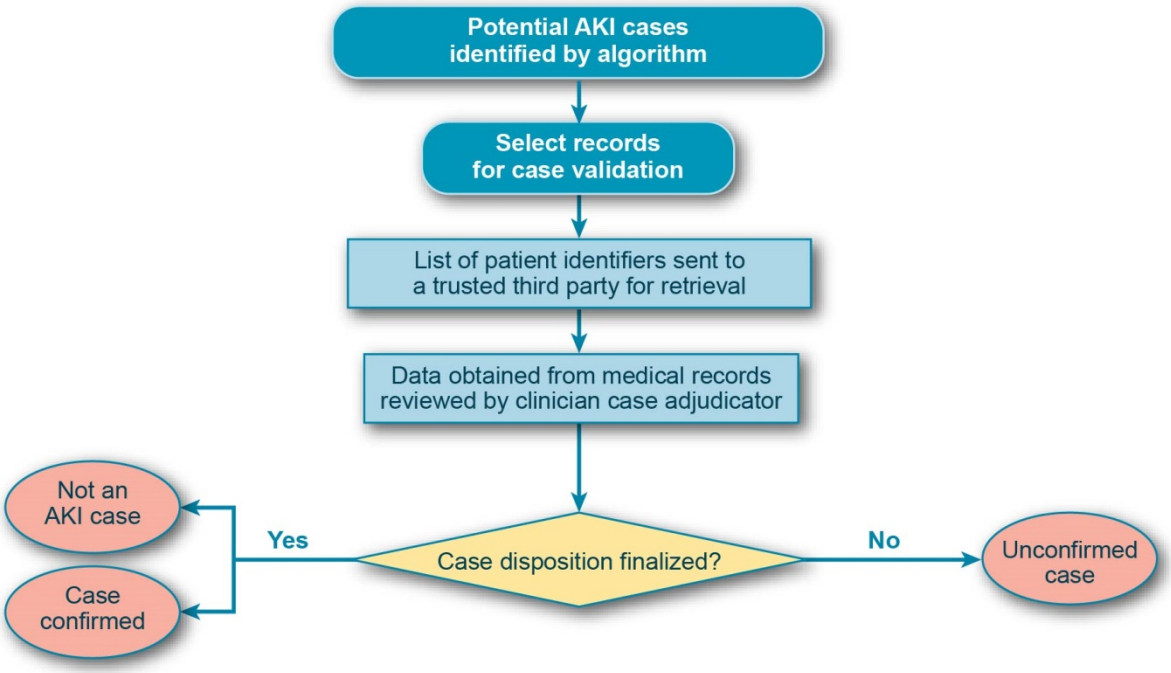


AKI = acute kidney injury; CPRD = Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics.

Medicare/ HIRD^{SM}

The process for case validation in Medicare data and the HIRD^{SM} is shown in Figure 2. Patient identifiers (name, date of birth, and social security number) are included in the Medicare files and can be used for further data abstraction. Additionally, individual and institutional providers have a unique identification number that is used to identify specific providers. Patients meeting the outcome definition of AKI based on diagnosis codes associated with hospital claims will be identified, and information about the individual provider for these patients, will be collected. Relevant potential cases will be identified from each cohort, and a list will be sent to separate individual trusted third parties for Medicare and for HIRD^{SM}. Each third party will contact the individual provider to obtain the required information from relevant medical records. For patients in the Medicare database, details from the medical record will be obtained by record abstraction. For patients in the HIRD^{SM}, redacted copies of the medical records will be obtained. Structured forms for abstraction of Medicare data and for guiding the copying of relevant records for HIRD^{SM} patients will be used to collect the relevant information to confirm the outcome (forms will be provided as part of the study report). Final confirmation of cases will be conducted independently by endpoint adjudicators who will be blinded to exposure to medications and will be identified by RTI-HS and HealthCore.

Figure 2: Case Validation in Medicare and HIRD^{SM} Data



AKI = acute kidney injury; CMS = Centers for Medicare and Medicaid Services.

3.4.1.3 Case Definition via Medical Record Review

Confirmed cases of AKI require all three of the following criteria. These criteria are based on prior epidemiological research and on a subset of the RIFLE criteria proposed by the Acute Dialysis Quality Initiative (Bellomo et al., 2004):

- A diagnosis of renal injury or acute renal injury recorded as a hospital discharge diagnosis (see Appendix 1 for diagnosis codes)

AND

- An increase in serum creatinine at hospital admission or within 72 hours of hospital admission from the lowest baseline value recorded during the 365 days before the index date, ascertained from the medical record or from database laboratory test results, when available) as follows:
  - In patients with normal baseline renal function (≤ ULN), at least a 2-fold increase from the baseline value to a value greater than the ULN
  - In patients with baseline renal insufficiency (defined as > ULN), an increase from the baseline value to at least twice the ULN

AND

- Absence of a recorded diagnosis of chronic kidney disease at any time before the index date

We restricted the study definition of confirmed AKI to involve changes in serum creatinine because it is specific to renal function and is routinely measured in clinical practice and therefore available in medical records. Because serum creatinine levels are required to validate the AKI classification, we wish to select a period of time for assessing baseline serum creatinine levels that will avoid immortal time bias (inclusion of patients who cannot be a case because they do not have a baseline serum creatinine level).

In the event that the necessary serum creatinine levels are frequently not available for documenting a change in serum creatinine, the case adjudicator may determine from the clinical details that AKI is likely, and such individuals will be classified as cases.

3.4.2 Exposure/Independent Variables of Interest

For this study, we plan to identify the study medications of interest among eligible patients from GP prescriptions in the CPRD and from outpatient pharmacy claims in the HIRD^{SM} and Medicare data. New use of dapagliflozin will be defined as the date of first dapagliflozin prescription (CPRD) or dispensing (HIRD^{SM} and Medicare) in the data source. New use of an AD in a class other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy will be defined as the date of first prescription or dispensing for these medications in the data source. As illustrated in Appendix 2, more than one treatment episode within the person-time of a patient can be selected as comparator exposures if a qualifying drug is initiated at a point in time after the first eligible treatment episode ends and is a different drug than the first. Potential comparators are eligible to enter the pool of patients from which comparators can be selected multiple times (i.e., if they qualify with drug A and then later switch to drug B, which also qualifies as a new comparator drug, they can enter both times). Follow-up will not be censored with addition of any other antidiabetic drug (other than a non-dapagliflozin SGLT2 inhibitor) during the index risk window.

The index medication is the dapagliflozin or comparator AD exposure that qualifies the patient to enter the study. When the episodes (time windows at risk) of study medications overlap, only one of medications will be used as the index medication. If the overlapping episodes include dapagliflozin, then dapagliflozin will be the index medication. If the overlapping episodes do not include dapagliflozin, then the first episode will be used as the index medication. If the episodes of two or more comparator AD episodes start at the same date, we will randomly choose one as the index medication and the exposure will be classified as index combined therapy.

Initiators of the antidiabetic medications listed in Appendix 4 will be included in the comparison group.

3.4.3 Other Covariates/Control Variables

Information to characterize the cohorts at the time of study drug initiation will be collected from the period ending on the index date, using all available information in the data source. Because all patients in the study are required to have at least 180 days of data before the index date, there will be a minimum of 180 days of data from which to evaluate covariate values. For some patients, more information will be available, and all information will be considered to reduce misclassification of covariate information. During development of propensity scores, use of

indicator variables for the duration of lookback time and timing of information on key covariates will address possible differential availability of information on covariates by exposure group, as well as control for associations that vary by time of recorded information. Exclusion diagnoses will be identified based on recorded GP diagnoses (CPRD) or claims diagnoses (HIRD^{SM} and Medicare) during the lookback period. Data on likely predictors of AKI (Table 1) will be identified for all patients prior to and including the index date. Although severity of T2DM may be a predictor for AKI, indicators for severity, e.g., glycated hemoglobin (HbA1c) value, will be available only in the CPRD and approximately 30% of patients in the HIRD^{SM}. All of these variables, as much as available, and additional variables that could potentially differ by exposure (e.g., history of urinary tract infections; see Appendix 5) will be included in a logistic regression model that will be used to generate propensity scores for the final analysis. The propensity scores will quantify the probability of receiving dapagliflozin at the time of the index date.

Table 1: Variables of Interest to be Collected for Propensity Score Development

Demographic or Lifestyle	Medications
Age Sex Calendar year of index date Duration of lookback time Body mass index > 30 (CPRD only) or obesity surgery Smoking history (CPRD only) History of alcohol abuse (CPRD) Socioeconomic status: index of multiple socioeconomic deprivation, quintiles–first least deprived to fifth most deprived (CPRD only) Geographic region of residence	Antihypertensives, diuretics including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, calcium-channel blockers, other antihypertensives, antiarrhythmics, digoxin, nitrates NSAIDs (nonsteroidal anti-inflammatory drugs) Opioids Statins, fibrates Oral steroids Zoledronic acid Lipid-modifying agents Other: acetaminophen, antibiotics (penicillins, sulfa),, anticonvulsants, antifungals, antituberculars, chemotherapeutic agents, methotrexate, aspirin and other antiplatelets (e.g., clopidogrel, ticlopidine, prasugrel), systemic antivirals, anticoagulants Concomitant antidiabetics (including specification of add-on or switch)

Medical Comorbidities[a]	Indicators of Diabetes Severity
Hospitalization for a serious condition that requires intensive care in the 180 days before the index date Length of hospitalization High blood pressure Heart failure Chronic renal disease or renal dialysis Liver disease Peripheral artery disease Pregnancy in the 180 days before and including the index date	Renal insufficiency or diabetic nephropathy Retinopathy Peripheral neuropathy Peripheral vascular disease Coronary heart disease Cerebrovascular disease Amputations Time since first diagnosis of type 2 diabetes mellitus, if available (CPRD only)

CPRD = Clinical Practice Research Datalink.

[a] Additional medical comorbidities that may be included can be found in Appendix 5.

Other variables to include in the propensity score models will be indicators of health care utilization in the 180 days before but not including the index date. These variables are number of outpatient visits, number of hospitalizations, number of emergency department visits, and number of specialty care visits.

Another variable to be examined will be whether, at the time of the index date, patients “added on” dapagliflozin or new use of another AD, that is, whether prescriptions or dispensings for the ADs that the patient was receiving in the 90 days before the prescription or dispensing for dapagliflozin or the newly initiated AD are continued in the 90 days after the index date (i.e., at least one more prescription is recorded). Patients will be classified as having “switched to”

dapagliflozin or new use of another AD if there is a prescription or dispensing for the medication recorded in the 90 days before the index date and no prescriptions or dispensings for that medication are recorded from the index date to 90 days after the index date. Days' supply will be used to determine the calculated end of previous AD therapy or will be assumed to be 30 days if missing.

To explore the impact of addition of ADs other than the index exposure, we will determine the rates of new AD use during the person-time of the index exposure episode among dapagliflozin initiators and comparator AD initiators (see Section 4.1.3). The additional drug could be any AD that was not a part of the initial treatment episode, including insulin. To be considered exposed to an added AD during follow-up (i.e., added after the index date), one prescription or dispensing for the medication must be added to the regimen during follow-up (recorded as yes/no for whether an AD was prescribed).

Variables other than the addition of other ADs, both fixed and time dependent, that could represent possible confounders and effect modifiers will be identified, if deemed necessary and feasible, and classified during follow-up time. The degree to which we can pursue analyses of these variables is contingent on the number of events within each outcome.

The approaches to handling concomitant ADs in the analyses are summarized in Table 2.

Table 2: Approaches to Handling Concomitant Antidiabetic Drugs

Timing and Type of Antidiabetic Drug Dispensing or Prescription	Analysis Approach
At index date, any AD taken during baseline that is not the new prescription and is not eligible to be a study exposure	Include in propensity score
At index date, any AD taken during baseline that is not the new prescription and is eligible to be a study exposure	Include in propensity score
Designation whether the AD initiated at the index date is an add-on to current medication or a switch to a different medication	Include in propensity score
Insulin at the index date	Conduct descriptive and comparative analyses separately by insulin use at index date (Yes or No)
ADs that have been used in the past added during follow-up	Consider use of time-varying covariate methods
Potential bias from new use, by exposure status, of a drug class	Sensitivity analysis excluding all individuals not new to the index drug class—e.g., a new user of saxagliptin (comparator group) will be included in the sensitivity analysis only if he/she was not treated with any DPP-4 inhibitor during the baseline time period
SGLT2 inhibitor other than dapagliflozin added during follow-up	End follow-up and censor

AD = antidiabetic drug; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-glucose cotransporter 2.

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

In the following analyses, descriptive analyses (i.e. secondary objective #1) will be done before other analyses. Specifics of variable definitions will be described in the statistical analysis plan, to be developed after finalization of the protocol.

All conversion of the original data to analysis variables will be performed using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Data management for CPRD and Medicare will be carried out in accordance with RTI-HS standard operating procedures. Routine procedures include checking electronic files, maintaining security and data confidentiality, following the statistical analysis plan, and performing quality-control checks of all programs. Data extraction programming for creating the study population from the HIRD^{SM} and creating the analytic file will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction and data development methods that are referenced in HealthCore standard operating procedures.

4.1.1 Propensity Score Approach

Demographic, medical, and clinical factors that may be associated with the decision to begin therapy with any particular AD may also be associated with the outcome. However, the number of outcomes will likely be small, limiting the number of variables that could be included in a regression model that predicts these outcomes (Cepeda et al., 2003). To address this difficulty, we will summarize the set of confounding variables into a single propensity score, based on the literature on potential confounding variables associated with the outcome. The propensity score is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates (Braitman and Rosenbaum, 2002; D'Agostino, 1998; Perkins et al., 2000).

Within each data source, propensity scores will be estimated by conducting logistic regression modeling and incorporating measured potential predictors of therapy as independent variables and exposure group status (dapagliflozin group vs. comparator group) as the outcome. The variables listed in Table 1 and Appendix 5, if available in the data source, will be assessed on the index date or, for chronic conditions, before the exposure index date, and will be considered for inclusion in the propensity score model.

If matching is performed, the propensity score models will be fitted after matching. The propensity score models will be developed for patients within each data source and will adjust for calendar year of the index date as a continuous variable to allow for changing prescription patterns for dapagliflozin from the time it is first available through the date of receipt of the data. As prescription patterns change, the confounding influence of the determinants of the prescription may also change. During development of propensity scores, indicator variables for the duration of lookback time and timing of information on key covariates will be included. Descriptive analyses will be stratified by data source and propensity score deciles and will be conducted at each scheduled data cut.

For data sources for which it is not feasible to obtain data on all eligible comparator cohort members in the data source, propensity scores will be obtained after selection of the comparator cohort through matching. For all analyses, we will exclude patients who have estimated propensity scores outside the range that is common to both exposed and comparator cohorts. This process is known as "trimming." Trimming occurs at both ends of the propensity score scale. At the bottom end, we will exclude all patients, exposed or unexposed, who have a propensity score below the 2.5 percentile value of the distribution of scores among the exposed group. At the upper end, we will exclude all patients, exposed and unexposed, with scores greater than the 97.5 percentile of scores among the comparator patients. This trimming will be performed separately for each index year–specific set of propensity scores.

Within each propensity score analysis, after trimming, the data will be stratified into deciles of propensity scores based on the distribution among dapagliflozin initiators. Within each of these 10 propensity score–based strata, we will investigate the extent to which covariates are balanced between the two treatment groups by use of the absolute standardized difference to assess the balance of measured baseline covariates between the dapagliflozin group and the comparator AD group before and after propensity stratification (Austin, 2009). Any imbalance will be addressed by either revising the propensity score model or by making adjustments in the final outcome model (Braitman and Rosenbaum, 2002; Perkins et al., 2000). We will report the number of patients trimmed from the analysis because of nonoverlap of propensity scores. If using deciles to create strata results in strata that are too small, it may be necessary to combine adjacent deciles.

4.1.2 Primary Objective

The incidence rate of hospitalizations for AKI among dapagliflozin initiators and among the comparator group will be estimated. The number of new hospitalized cases of AKI during follow-up will be determined using the validated algorithm. Person-time for each patient will be determined as the time between the date of first prescription or dispensing for either dapagliflozin or comparator ADs and the end of time at risk. The total person-time of observation among individuals at risk will then be calculated. The incidence rate of AKI will be estimated by insulin use at the index date in each cohort. Within each data source, crude and adjusted rates will be calculated as the number of new cases of AKI during the observation period divided by the total person-time of observation among individuals at risk. Incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% CIs.

The following incidences and comparisons will be generated:

- Crude incidence rate, by insulin use at the index date, among dapagliflozin initiators versus among the entire comparator group
- Summary IRRs after adjusting for propensity score decile, calendar year, and data source, estimated by categories of insulin use at the index date, among dapagliflozin initiators versus the entire comparator group

- Summary IRRs after adjusting for propensity score decile, calendar year, and data source, estimated by categories of insulin use at the index date, among dapagliflozin initiators versus initiators of the most commonly used classes of ADs (each class separately)

The adjusted IRRs will be the primary endpoint. In CPRD and Medicare data, crude IRRs will facilitate comparison with the adjusted IRRs to provide an indication of the degree of confounding. Follow-up time that includes exposure to more than one index AD, e.g., first 30 days after patients switch from dapagliflozin exposure group and selection into the comparator group, will be assigned to a separate category for multiple exposures.

Adjusted incidence rates and IRRs will be calculated by standardizing to the dapagliflozin person-time distribution: weighting the incidence or IRR in each stratum (defined by propensity score decile, calendar year, and data source) by the amount of dapagliflozin person-time within the stratum. More details on the analysis methods will be included in the statistical analysis plan.

4.1.3 Secondary Objectives

4.1.3.1 Secondary Objective #1

For each data source, descriptive statistics, by insulin use at the index date, will be generated to compare baseline characteristics between dapagliflozin initiators and comparator AD initiators. Categorical variables will be summarized by frequencies and proportions, and continuous variables will be summarized by means and standard deviations or medians and interquartile ranges. The following variables will be characterized:

- Age stratified by sex
- Body mass index (CPRD only)
- Duration of lookback time prior to index date
- Prescription or dispensing of each specific non-dapagliflozin AD at index date
- Switch versus add-on initiation of study exposure (dapagliflozin or other AD) at index date
- History of diabetic nephropathy diagnosis
- History of cardiovascular disease diagnosis
- History of hypertension diagnosis
- HbA1c at index date (most recent measurement on or before the index date) (CPRD only)
- History of alcoholism or liver disease diagnosis (CPRD only)
- History of hyperlipidemia diagnosis or treatment
- History of chronic obstructive pulmonary disease or asthma diagnosis
- History of malignancy diagnosis
- History of peripheral vascular disease diagnosis
- History of vasculitis, scleroderma, or lupus diagnosis
- History of trauma diagnosis in last 6 months
- History of neuropathy diagnosis
- History of heart failure diagnosis

Results of the descriptive analyses will be used to inform subsequent analyses.

4.1.3.2 Secondary Objective #2

Other variables (both fixed and time dependent) will be classified during follow-up time, and analyses stratifying exposure time by level of these variables will be performed to explore potential effect modification and confounding by these variables on the relative incidence rates and rate ratios for AKI hospitalization. Some of the stratification variables will include index year, HbA1c level (when available in the CPRD and HIRD^{SM}), whether patients were "added on" or "switched to" dapagliflozin or other ADs, each specific concomitant AD medication class added during follow-up, and prescription for a medication associated with AKI during follow-up. Also, variables for which close balance was not achieved within propensity score strata will be further examined.

We will calculate the following statistics:

- Incidence rates by exposure category stratified by potential effect modifiers or confounders and data source
- IRRs stratified by potential effect modifiers or confounders and data source

To explore the impact of differential addition of ADs or factors associated with the need for an additional AD by exposure, we will compare rates of new AD use among dapagliflozin initiators and comparator AD initiators. If necessary, further adjustment for therapies added during follow-up will be performed via time-dependent Cox proportional hazards regression. Techniques to pool the data will be applied to combine IRR estimates across data sources, if appropriate (see Section 4.1.7).

4.1.4 Imputation of Missing Values

We expect that relatively few key variables will have notable missing values. Variables such as smoking and alcohol consumption levels, body mass index, and HbA1c level will be unavailable or have high levels of missing values. The pharmaceutical exposures and comorbidities are expected to be based on outpatient prescriptions and dispensings and to be complete. If there are considerable missing data for lifestyle covariates, multiple imputation will be used to fill in missing values for the propensity score creation and multivariable analyses. The decision to use multiple imputation will depend on the strength of the association between the variable and treatment and the extent of missing data. Based on information from the observations with nonmissing values, we will impute five simulated versions of the data set. The imputed data sets will be used for creation of propensity scores and in the multivariable analyses, with the results being combined appropriately to generate final point estimates and CIs. In theory, this should give point estimates with equal or less bias than those that would be obtained if we had limited the sample to those with complete data, and it should give greater precision because of the larger number of patients that will be included using this method as opposed to restricting the analysis to observations with complete data. The specific approach will be detailed in the statistical analysis plan.

We have selected the multiple imputation approach because existing methods for imputation penalize the standard errors when imputing data and multiple imputation allows for better bias correction than most alternatives, including the complete-case approach, for many, although not all, applications. The complete-case approach can be very costly of information in a body of high-dimensional data, since the proportion of complete cases will decline with the increase in the number of variables.

4.1.5 Exploratory Objectives

Not applicable.

4.1.6 Sensitivity Analyses

The following sensitivity analyses will be conducted:

- Estimate IRRs for dapagliflozin compared with comparator group by applying the risk window extended from 30 to 90 days in the exposed follow-up time for dapagliflozin initiators and for comparator initiators.
- Assess the effect of unmeasured confounders on the association between dapagliflozin use and AKI hospitalization by assuming a plausible range of values for those confounders (Lash et al., 2009).
- Estimate the crude incidence rate without stratification by insulin categories at the index date, among dapagliflozin initiators versus among the entire comparator group.
- Estimate summary IRRs after adjusting for propensity score decile, calendar year, and data source without stratification by insulin categories at the index date, among dapagliflozin initiators versus the entire comparator group.
- Estimate summary IRRs after adjusting for propensity score decile, calendar year, and data source without stratification by insulin categories at the index date, among dapagliflozin initiators versus initiators of the most commonly used classes of ADs (each class separately).
- Estimate summary IRRs after adjusting for propensity score, calendar year, and data source after excluding individuals not new to the index AD drug class

4.1.7 Pooled Analysis

The results of two or more data sources with similar results for the primary outcome (i.e., plausibly differing only from sampling variability), will be pooled. The pooled analysis will be designed to estimate the effect of the exposure while controlling for confounding using the data stratified on propensity scores. The data source will be retained as a stratification variable, so the effect within each data source can be estimated.

Mantel-Haenszel techniques will be used to pool the data from each data source and calculate overall adjusted incidence rate ratios. This analysis is designed to estimate the effect of the exposure while controlling for confounding by using the data source–specific propensity score stratification.

If residual confounding is suspected in any of the data sources (for example, due to lack of information on one or more confounding variables), external adjustment can be used to assess the impact of unidentified confounders and to reduce the amount of such confounding (see Section 4.1.6) (Lash et al., 2009).

4.1.8 Power/Sample Size

The observed study size will depend upon the market uptake of dapagliflozin in the US and UK. We estimate a total of 91,927 person-years of follow-up among new users of dapagliflozin across all three data sources. The derivation of this total follows.

Currently, we estimate that in the CPRD, approximately 3,600 person-years of follow-up will be available among all new users of dapagliflozin during the 5 years of the study; including approximately 2,900 person-years among those not on insulin at the index date and 700 person-years among those on insulin at the index date. These estimates are based on the following assumptions: number of patients aged 18 years and older with a newly prescribed AD in the CPRD per year is 23,970 (CPRD data as of 31 December 2011); the proportion of new users starting dapagliflozin among patients who meet inclusion criteria will be 1% during year 1, 2% during year 2, 3% during year 3, 4% during year 4, and 5% during year 5 of the study; on average, each new user will contribute 12 months of person-time; and approximately 20% of new dapagliflozin users will be on insulin at the index date (derived from Hall et al., 2012).

In the US data sources, we estimate that there will be approximately 88,327 person-years of follow-up available among all new users of dapagliflozin (HIRD^{SM}: 42,473 person-years; Medicare: 45,854 person-years). This exposure would include approximately 70,662 person-years among those not on insulin at the index date and 17,665 person-years among those on insulin at the index date. These estimates are based on the following assumptions: (1) the age distribution among oral AD users is 61.9% aged 18-64 years and 37.7% aged 65 years or older (Boccuzzi et al., 2001), (2) 34.15% coverage rate for Medicare Part D among Medicare beneficiaries, (3) the HIRD^{SM} database covers 6% of the US population aged 64 years or younger, (4) each new dapagliflozin user will contribute 12 months of exposed person-time, and (5) approximately 20% of new dapagliflozin users will be on insulin at the index date (Hall et al., 2012).

To provide precision estimates in relation to the total projected study size, we first estimated the background AKI hospitalization incidence rate in T2DM from the literature. The incidence of AKI associated with referral or hospitalization in the general diabetes population in the UK has been estimated to be approximately 1.3 per 1,000 person-years (Girman et al., 2012). The incidence of hospitalization for AKI is much higher in older patients. In the US, the rate of hospitalization for AKI among older patients with diabetes has been estimated at 28 per 1,000 person-years (Thakar et al., 2011). If we apply this rate to new users of dapagliflozin not on insulin at the index date in Medicare and the rate of 1.3 per 1,000 person-years to HIRD^{SM}/CPRD, we would expect to observe approximately 5,375 events if the 73,542 person-years we anticipate are accrued among this group. Table 3 shows the expected number of AKI events among all cohort members by study data source.

Table 3: Estimated Number of Events for Acute Kidney Injury Among All Cohort Members

	HIRD[SM]	Medicare	CPRD	Total
Total sample cohort[a]	212,366	229,270	18,000	459,636
Average length of follow-up	1 year	1 year	1 year	1 year
Exposed person-years	42,473	45,854	3,600	91,927
Rate of acute renal injury (per 1,000 person-years)	1.3	28	1.3	
Estimated number of events	276	6,420	23	6,719

CPRD = Clinical Practice Research Datalink; HIRD[SM] = HealthCore Integrated Research Database.

[a] Assumes 34.15% population coverage rate for Medicare enrollment criteria and 6% population coverage for HIRD[SM].

To estimate the anticipated magnitude of the upper 95% confidence limit, we calculated a weighted average of the two expected background incidence rates (1.3 per 1,000 and 28 per 1,000), based on the age distributions and the distribution of person-years in each data source. We estimated the precision of the study under various scenarios using this weighted incidence rate. Table 4 shows the probability that the upper 95% confidence limit around the observed IRR will be less than the specified IRRs for dapagliflozin users not on insulin, assuming that the true IRR is 1.0 and a 1:4 dapagliflozin:comparator person-year ratio. For example, a study size of 73,000 person-years of follow-up among new users of dapagliflozin not on insulin at the index date will provide an 81% probability that the upper 95% confidence limit of the IRR will be less than 1.1.

Table 4: Probability That the Upper 95% Confidence Limit of the IRR Estimate is Below the Specified Value, Assuming IRR in Population = 1.0

Dapagliflozin Exposed Person-years	Upper 95% Confidence Limit of IRR for Dapagliflozin Versus Comparator				
	1.05	1.1	1.2	1.3	1.4
20,000	0.11	0.32	0.81	0.98	1.00
50,000	0.22	0.65	0.99	1.00	1.00
60,000	0.26	0.73	1.00	1.00	1.00
73,000	0.30	0.81	1.00	1.00	1.00
85,000	0.35	0.86	1.00	1.00	1.00
90,000	0.36	0.88	1.00	1.00	1.00

IRR = incidence rate ratio.

Note: Assuming a weighted average of 14.8 per 1,000 person-years is the AKI rate associated with hospitalization among patients not exposed to dapagliflozin, a 1:4 dapagliflozin:comparator person-year ratio, and population IRR = 1.0. This table was calculated using Episheet (Rothman, 2012).

4.2 Milestones

For the purpose of periodic regulatory reporting, one descriptive analysis, one interim comparative analyses, and one final comparative analysis are planned. The descriptive analysis, which includes comparison of baseline characteristics for each cohort and total case counts will be performed after dapagliflozin has been on the market in the US for approximately 30 months. The interim comparative analysis will be performed after dapagliflozin has been available in the US for approximately 48 months, and the final analysis will be conducted after dapagliflozin has been available for 60 months. The interim comparative analysis will be performed if at least two outcome events are observed in the entire study cohort (dapagliflozin and comparator AD cohorts combined).

The proposed timeline for analyses is shown in Table 5.

Table 5: Milestones

Report	Data Cut (Time After Dapagliflozin is Available to Patients in the US) Anticipated Month/Year[a]
Interim descriptive analysis	24 months January 2016 (includes only CPRD and HIRD^{SM})
Interim comparative analysis	48 months January 2018 (includes all data sources)
Final analysis	60 months January 2019 (includes all data sources)

[a] Due to data source lags, which are typically 4-6 months in HIRD^{SM} and CPRD, the 24-month report will likely include data from the first 18 months of dapagliflozin use in the HIRD^{SM} and CPRD, the 48-month report will include data through the first 42 months of dapagliflozin use in the HIRD^{SM} and CPRD and 18 months of dapagliflozin use in Medicare, and the 60-month report will include data through the first 54 months of dapagliflozin use in the CPRD and HIRD^{SM} and 30 months of dapagliflozin use in Medicare.

5 STUDY LIMITATIONS/STRENGTHS

5.1 Confounding

All potential confounding variables for which there are data will be controlled to the extent possible, primarily through the use of propensity scores. Potential unidentified confounding conditions are those that cannot be identified in this manner and that are differentially distributed between the exposure groups, related to the outcome, and largely uncorrelated with the measurable characteristics.

In the CPRD, the lack of specialist prescriptions may result in lack of information on the early prescriptions for some medications, before prescribing is transferred to the GP. Some variables, such as use of over-the-counter medication, will remain unmeasured in all data sources.

Confounding by indication (or channeling bias) is a common bias in observational pharmacoepidemiology studies whereby the indication for therapy may be associated with both the treatment and the outcome. Since patients who receive a particular drug therapy may have more severe disease or a perceived higher risk (due to self-selection or physician preference)

compared with patients not on the medication, selection of treatment can be confounded with clinical and nonclinical patient factors that may be related to the outcomes of interest. New medications may be prescribed differentially to healthier patients whom physicians believe could tolerate a product with a lesser-known safety profile or to patients who have more severe disease, have failed previous treatment regimens, or have contraindications to other drugs (e.g., thiazolidinediones are not recommended for use in patients with heart failure). New medications may also be prescribed differentially by physicians who are "early adopters" of new technologies. As much as possible, such considerations are taken into account by the propensity score, but some aspects may remain unmeasured and could result in residual confounding. Specifically, dapagliflozin could be preferentially prescribed to patients with more severe diabetes or who have failed other therapies. In the CPRD, HbA1c levels are likely to be available for most patients with T2DM, so such bias may be assessed and adjusted for in analysis. However, this variable is available for only 30% of individuals in the HIRD^{SM} and is not available in Medicare data. Comparisons of adjusted IRRs from the CPRD with those assessed in HIRD^{SM} and Medicare data can facilitate assessment of such uncontrolled confounding in the claims-based data sources. Dapagliflozin could also be preferentially prescribed to patients with fewer risk factors for AKI. These channeling patterns could bias the IRR toward or away from the null.

To assess the effect of unmeasured confounders on the association between dapagliflozin use and AKI, we will conduct sensitivity analyses to estimate the degree of possible bias that might be present by assuming a plausible range of values for those confounders.

5.2 Other Biases

Misclassification bias can result if study patients are not categorized correctly with regard to exposure or outcome. We expect minimal misclassification with respect to exposure, since this will be determined from prescribing records. However, actual adherence to instructions for taking dapagliflozin or other ADs cannot be confirmed. Further, misclassification as to whether the patient is a new user could exist if providers supplied samples of dapagliflozin or comparator ADs for varying duration to patients, at no cost, and with no record in the respective data source. Because of the newness of dapagliflozin, we expect little misclassification of dapagliflozin initiators. However, initiators of older ADs will be more likely to be misclassified as new users if they used the medication of interest before the patients' data were included in the data sources.

Classification of type 2 versus type 1 diabetes mellitus may also be a source if misclassification. Potential patients with evidence of type 1 diabetes mellitus (T1DM) are to be excluded. However, with the repeated health care that individuals with T1DM or T2DM require, we anticipate that accuracy of classification of diabetes type will be improved from the relative frequency of the use of these two diagnoses in individual patients.

Misclassification of the outcome will be reduced by evaluating AKI that is associated with hospitalization and using medical records and laboratory data, if available, to confirm clinical diagnoses of the outcome. Misclassification of whether AKI resulted in a hospitalization or was hospital-acquired is possible and could affect study results. However, by obtaining serum

creatinine levels prior to the hospitalization of interest, and through information from questionnaires sent to the GPs, we expect to identify the timing of onset relative to the hospitalization date. Medical chart review for a sample of potential cases ascertained in the HIRD[SM] and Medicare data can also be used to validate the date of onset.

5.3 Study Size

The ability to meet the sample size projections depends upon the uptake of dapagliflozin. It is currently projected that at the end of 5 years, the study will yield 91,927 person-years of exposure to dapagliflozin; approximately 73,542 among those not on insulin at the index date and 18,385 among those on insulin at the index date.

As discussed in the study size section, with 73,542 person-years accrued among those taking dapagliflozin and not on insulin, we will have an 81% probability that the upper 95% confidence limit of the IRR will be less than 1.1 (assuming that the true IRR is 1.0 and a 1:4 dapagliflozin:comparator person-year ratio); however, among smaller subgroups of interest (e.g., dapagliflozin initiators on insulin at baseline) the probability under the same assumptions will be lower (29%). However, we will still have substantial power in this subgroup—e.g., a 77% probability that the upper 95% confidence limit of the IRR will be less than 1.2.

If the uptake of dapagliflozin is less than expected, we still expect to have good precision. For example, if the use of dapagliflozin among patients not taking insulin is one-fourth of that expected, then the final study size from this data source will be 18,385 person-years, with a 77% probability that the upper 95% confidence limit will be less than 1.2 under the null hypothesis of no association.

5.4 Generalizability

Use of the CPRD and US claims data sources provides data entered or submitted by pharmacies, general medical practices, and US clinics and hospitals without any awareness of the hypothesis of studies that may use these data. The study results will be generalizable to UK patients with T2DM meeting the inclusion and exclusion criteria. Results from the Medicare data will be generalizable to US patients with T2DM aged 65 years or older and not in a residential care facility. Results from HIRD[SM] data are generalizable to patients with claims-identified T2DM among the employable US population.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2015) and applicable regulatory requirements. As with all research at RTI International that involves human patients or data on human patients, RTI-HS will request review of the protocol by the RTI International[1] institutional review board (IRB), and we anticipate that the IRB will agree to exemption because we will not have any patient identifiers.

[1] RTI Health Solutions is a business unit of RTI International, a not-for-profit research organization.

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

6.1.1.1 CPRD

RTI-HS will prepare the request and submit the study protocols to the CPRD's Independent Scientific Advisory Committee (ISAC) (http://www.CPRD.com/isac) for approval. The CPRD has obtained ethical approval from a Multicenter Research Ethics Committee (MREC) for all observational research using CPRD data without patient involvement; however, ISAC may recommend that the MREC review the study documentation if any ethical issues arise.

6.1.1.2 HIRD^{SM}

This component of the overall study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. There is no active enrollment or active follow-up of study patients, and no data will be collected directly from individuals.

HealthCore maintains Data Sharing Agreements and Business Associate Agreements with all covered entities who provide data to the HIRD^{SM}. HealthCore's access, use, and disclosure of protected health information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR Part 160 and Subparts A and E of Part 164). HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (e.g., a HIPAA Waiver of Authorization from an IRB). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

As PHI must be accessed in order to acquire medical records to validate electronic case-finding algorithms, a HIPAA Waiver of Authorization will be applied for from an IRB. HealthCore will submit the protocol to a central IRB for review and approval. Approval is typically provided within 2 to 3 weeks of submission. Once IRB approval is obtained, HealthCore's vendor will proceed with the conduct of medical record acquisition. If changes to the protocol are required, HealthCore will submit an amendment to the IRB. As the IRB is independent, HealthCore cannot control the approval or whether there are conditions for the approval.

Notwithstanding receipt of approval from a central IRB, in some instances, individual institutions may require approval from their local IRB, which would require a separate protocol submission and, in some cases, additional fees. In these cases, HealthCore, RTI-HS, and AZ will need to agree whether or not to proceed with chart acquisition from these institutions.

HealthCore will provide the vendor only the minimum amount of patient information that is necessary to execute the medical record acquisition. HealthCore uses only vendors that follow federal and state laws and regulations, including but not limited to privacy and security rules such as HIPAA.

At no time during the conduct of this study will HealthCore provide patient- or provider-identifying information to RTI-HS, BMS, or AZ. Only aggregated data will be reported to RTI-HS, BMS, and AZ.

6.1.1.3 Medicare

For use of Medicare data, the CMS requires that IRB review and approval be obtained before use of Medicare data for research can be approved. This protocol will be reviewed by the RTI International IRB before applying to use Medicare data and will undergo a continuing IRB review at least once per year.

Under the Privacy Rule (under 45 CFR 164.512), CMS may disclose protected health information for research without documentation of individual authorization only if an IRB or a CMS Privacy Board has approved a waiver of research. Such a waiver must be provided to CMS.

Data requests for research identifiable data must be reviewed by the CMS Privacy Board to ensure that any study patient's privacy is protected and the need for identifiable data is justified.

6.2 Responsibilities Within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by AZ.

6.2.1 Sponsor Roles and Responsibilities

The sponsor, AZ, is responsible for providing reasonable resources for study implementation and to assure study progress. They are also responsible for communicating with regulatory agencies about the study protocol, the progress of the study, and study findings.

6.2.2 Investigator Roles and Responsibilities

The study investigators at RTI-HS and HealthCore share responsibility with AZ for the design of the study. The investigators at RTI-HS are responsible for conducting the CPRD and Medicare components in a manner that meets regulatory and methodologic standards, conducting analyses, and preparing scientific reports. The investigators at HealthCore are responsible for designing analysis in the HIRD^{SM} in a manner that meets regulatory standards, conducting analyses, and preparing scientific reports.

The study shall be conducted as described in the approved protocol. The authors will not develop or implement any deviation or change to the protocol without prior review by AZ.

6.3 Confidentiality of Study Data

The confidentiality of records that could identify patients within the individual data sources must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Data that could directly identify the patient will not be collected in the "study database."

6.4 Quality Control

Experienced US-based RTI-HS programmers will perform all analyses for the CPRD and Medicare data. To ensure the integrity and quality of the study results, RTI-HS will follow the programming validation life cycle process for all analyses. This includes quality-checking programs, logs, and output for accuracy according to relevant standard operating procedures. All programs will be independently reviewed by a second programmer/analyst.

This project will be guided by a written plan to ensure that all collaborators conduct quality-control checks of all aspects of data manipulation and analysis and preparation of study deliverables. The plan will specify that all collaborators will establish and maintain adequate documentation of performance of major tasks. The RTI-HS Office of Quality Assurance will conduct periodic audits during the study period to ensure that such documentation meets the necessary standards, especially the completion of these quality-control checks, according to the plan.

HealthCore's quality system is organized around the Quality Manual, the quality checks with the project life cycle, and the standard operating procedures. HealthCore performs internal audits to ensure adherence to the quality system according to a formal procedure and has procedures for retention of PHI and project data. The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established multiple layers of quality assurance throughout the project life cycle:

- Role-Based Control Checks: Each member of the team is responsible for performing thorough quality assurance checks on his or her work. In addition, the Project Director in collaboration with the Lead Epidemiologist is also accountable for quality of all deliverables.
- Quality Check Points: Centralized "check points" have been implemented during the data management cycle to help ensure accurate translation of programming requests.
- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project life cycle.
- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

HealthCore's research team documents the progress and scientific and quality review of all study activities and deliverables (e.g., protocol, reports, and manuscripts) in a project log. The project log provides documentation of the major study tasks related to a specific study activity performed by the research team, to develop and execute the requirements of the protocol or other guiding document for a HealthCore research project. In addition, the project log documents the quality assurance measures performed for each study activity during the conduct of the research project. Also, any research team and/or sponsor interaction resulting in a change to study specifications (e.g., protocol, study database, variables in the analytic files) is described in the project log. This is necessary to ensure that such communications are appropriately documented, that the most up-to-date versions of relevant documents are readily identifiable, and that affected documents are clearly tracked in the project log.

6.5 Database Retention and Archiving of Study Documents

Each investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period

specified by the sponsor, whichever is longer. Investigators must contact the study sponsor prior to destroying any records associated with the study. The location of the study database and supporting documentation will be outlined in the final observational study report.

6.6 Registration of Study on Public Website

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS Register (ENCePP, 2016) and ClinTrials.gov before the first data cut. The research team and study sponsor adhere to the general principles of transparency and independence in the ENCePP code of conduct (ENCePP, 2014).

6.7 Plans for Disseminating and Communicating Study Results

In accordance with the Guidelines for Good Pharmacoepidemiology Practices (ISPE, 2015), there is an ethical obligation to disseminate findings of potential scientific or public health importance, e.g., results pertaining to the safety of a marketed medication. The Consolidated Standards of Reporting Trials (CONSORT) statement refers to randomized studies, but also provides useful guidance applicable to nonrandomized studies (Moher et al., 2001). A well-developed publication strategy is encouraged in the Guideline on Good Pharmacovigilance Practices, module VIII, section B.7 (European Medicines Agency, 2016).

Reports will be provided after each of the analyses, i.e., the descriptive analysis and the comparative analyses. RTI-HS personnel will work with HealthCore to submit the results from any of these analyses for publication and, indeed, commits that they will, at least, publish the final results. The authorship of publications shall be in accordance with standards as described in the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* by the International Committee of Medical Journal Editors (2016).

7 ADVERSE EVENT REPORTING

7.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A nonserious AE is any AE that is not classified as serious.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see Note below)

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

Suspected transmission of an infectious agent, pathogenic or nonpathogenic, via the AZ product under study is an SAE.

An ***overdose*** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events are handled as SAEs.

Note: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event).
- Elective surgery, planned prior to signing consent.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reasons).

7.2 Adverse Event Collection and Reporting

All AEs collected will be reported in aggregate in the final study report.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Not applicable.

8.2 List of Abbreviations

Term	Definition
AD	antidiabetic drug
AE	adverse event
AKI	acute kidney injury
AZ	AstraZeneca Pharmaceuticals LP
BMS	Bristol-Myers Squibb
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services

Term	Definition
CONSORT	Consolidated Standards of Reporting Trials (statement)
CPRD	Clinical Practice Research Datalink
CPT	Current Procedural Terminology
eGFR	estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GP	general practitioner
GPRD	General Practice Research Database
HCPCS	Healthcare Common Procedure Coding System
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability and Accountability Act
HIRD^{SM}	HealthCore Integrated Research Database
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IRB	institutional review board
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
MDRD	Modification of Diet in Renal Disease
MREC	Multicenter Research Ethics Committee
NDC	National Drug Code
NEC	not elsewhere classified
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
PHI	protected health information
PPV	positive predictive value
RIFLE	criteria for defining and classifying acute renal failure; acronym indicates Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function; and End-stage kidney disease (Bellomo et al., 2004)
RTI-HS	RTI Health Solutions
SAE	serious adverse event
SGLT2	sodium-glucose cotransporter 2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UK	United Kingdom
ULN	upper limit of normal
US	United States of America

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APPENDIX 1. DIAGNOSIS CODES USED IN THE STUDY

Table 1-1: Electronic Algorithm ICD-9-CM and CPT Codes for Acute Kidney Injury in the US Data Sources

Code	Type	Description
584.x	ICD-9-CM	ACUTE RENAL FAILURE
584.5	ICD-9-CM	LOWER NEPHRON NEPHROSIS
584.6	ICD-9-CM	AC RENAL FAIL, CORT NECR
584.7	ICD-9-CM	AC REN FAIL, MEDULL NECR
584.8	ICD-9-CM	AC RENAL FAILURE NEC
584.9	ICD-9-CM	ACUTE RENAL FAILURE NOS
90945	CPT	DIALYSIS PROCEDURE; SINGLE PHYSICIAN EVAL.
90947	CPT	DIALYSIS PROCEDURE; REPEATED EVALS.
90989	CPT	DIALYSIS TRAINING OF PATIENT; COMPLETED
90993	CPT	DIALYSIS TRAINING OF PATIENT; INCOMPLETE
90997	CPT	HEMOPERFUSION
90999	CPT	DIALYSIS PROCEDURE NOS; INPATIENT OR OUTPATIENT
99601	CPT	HOME INFUSION; DIALYSIS
90920	CPT	END-STAGE RENAL DISEASE SERVICES; FULL MONTH; AGE 12-19
90921	CPT	END-STAGE RENAL DISEASE SERVICES; FULL MONTH; AGE 20+
90924	CPT	END-STAGE RENAL DISEASE SERVICES; LESS THAN FULL MONTH; AGE 12-19
90925	CPT	END-STAGE RENAL DISEASE SERVICES; LESS THAN FULL MONTH; AGE 20+
39.95	ICD-9_PX	HEMODIALYSIS
90935	CPT	HEMODIALYSIS PROCEDURE; SINGLE PHYSICIAN EVAL.
90937	CPT	HEMODIALYSIS PROCEDURE; REPEATED EVALS.
90940	CPT	HEMODIALYSIS ACCESS FLOW STUDY

CPT = Current Procedural Terminology; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; NEC = not elsewhere classified; NOS = not otherwise specified; US = United States of America.

ICD-9-CM codes will be mapped to ICD-10 codes.

Table 1-2: Electronic Algorithm Read Codes for Acute Kidney Injury in the CPRD

Code	Type	Description
K04..00	READ	ACUTE RENAL FAILURE
K040.00	READ	ACUTE RENAL TUBULAR NECROSIS
K041.00	READ	ACUTE RENAL CORTICAL NECROSIS

Code	Type	Description
K042.00	READ	ACUTE RENAL MEDULLARY NECROSIS
K042.11	READ	NECROTISING RENAL PAPILLITIS
K043.00	READ	ACUTE DRUG-INDUCED RENAL FAILURE
K044.00	READ	ACUTE RENAL FAIL URIN OBSTRUCT
K04y.00	READ	OTHER ACUTE RENAL FAILURE
K04z.00	READ	ACUTE RENAL FAILURE NOS
14V2.00	READ	H/O: RENAL DIALYSIS
14V2.11	READ	H/O: KIDNEY DIALYSIS
7L1A.00	READ	COMPENSATION FOR RENAL FAILURE
7L1A.11	READ	DIALYSIS FOR RENAL FAILURE
7L1A000	READ	RENAL DIALYSIS
7L1A011	READ	THOMAS INTRAVASCULAR SHUNT FOR DIALYSIS
7L1Ay00	READ	OTHER SPECIFIED COMPENSATION FOR RENAL FAILURE
7L1Az00	READ	COMPENSATION FOR RENAL FAILURE NOS
ZV45100	READ	[V]RENAL DIALYSIS STATUS
ZV56.00	READ	[V]AFTERCARE INVOLVING INTERMITTENT DIALYSIS
ZV56000	READ	[V]AFTERCARE INVOLVING EXTRACORPOREAL DIALYSIS
ZV56011	READ	[V]AFTERCARE INVOLVING RENAL DIALYSIS NOS
ZV56100	READ	[V]PREPARATORY CARE FOR DIALYSIS
ZV56y00	READ	[V]OTHER SPECIFIED AFTERCARE INVOLVING INTERMITTENT DIALYSIS
ZV56y11	READ	[V]AFTERCARE INVOLVING PERITONEAL DIALYSIS
ZV56z00	READ	[V]UNSPECIFIED AFTERCARE INVOLVING INTERMITTENT DIALYSIS
ZVu3G00	READ	[X]OTHER DIALYSIS
K0D..00	READ	END-STAGE RENAL DISEASE
7L1A200	READ	HAEMODIALYSIS NEC
7L1A300	READ	HAEMOFILTRATION
7L1A700	READ	HAEMOPERFUSION
K06..00	READ	RENAL FAILURE UNSPECIFIED
K06..11	READ	URAEMIA NOS
K060.00	READ	RENAL IMPAIRMENT
K060.11	READ	IMPAIRED RENAL FUNCTION
Kyu2000	READ	[X]OTHER ACUTE RENAL FAILURE
A160200	READ	TUBERCULOUS PYELONEPHRITIS
G500400	READ	ACUTE PERICARDITIS - URAEMIC

Code	Type	Description
K101000	READ	ACUTE PYELONEPHRITIS WITHOUT MEDULLARY NECROSIS
K101100	READ	ACUTE PYELONEPHRITIS WITH MEDULLARY NECROSIS
7L1A100	READ	PERITONEAL DIALYSIS
7L1A400	READ	AUTOMATED PERITONEAL DIALYSIS
7L1A500	READ	CONTINUOUS AMBULATORY PERITONEAL DIALYSIS
7L1A600	READ	PERITONEAL DIALYSIS NEC
14S2.00	READ	H/O: KIDNEY RECIPIENT
7B00.00	READ	TRANSPLANTATION OF KIDNEY
7B00000	READ	AUTOTRANSPLANT OF KIDNEY
7B00100	READ	TRANSPLANTATION OF KIDNEY FROM LIVE DONOR
7B00111	READ	ALLOTRANSPLANTATION OF KIDNEY FROM LIVE DONOR
7B00200	READ	TRANSPLANTATION OF KIDNEY FROM CADAVER
7B00211	READ	ALLOTRANSPLANTATION OF KIDNEY FROM CADAVER
7B00300	READ	ALLOTRANSPLANTATION OF KIDNEY FROM CADAVER, HEART-BEATING
7B00400	READ	ALLOTRANSPLANTATION KIDNEY FROM CADAVER, HEART NON-BEATING
7B00500	READ	ALLOTRANSPLANTATION OF KIDNEY FROM CADAVER NEC
7B00y00	READ	OTHER SPECIFIED TRANSPLANTATION OF KIDNEY
7B00z00	READ	TRANSPLANTATION OF KIDNEY NOS
ZV42000	READ	[V]KIDNEY TRANSPLANTED
44J3.00	READ	SERUM CREATININE
44J3000	READ	SERUM CREATININE ABNORMAL
44J3300	READ	SERUM CREATININE RAISED
44J3z00	READ	SERUM CREATININE NOS
4512.00	READ	RENAL FUNCTION TESTS ABNORMAL
4519.00	READ	DETERIORATING RENAL FUNCTION
7B00212	READ	CADAVERIC RENAL TRANSPLANT
7B00600	READ	XENOGRAFT RENAL TRANSPLANT
7B0F100	READ	PRE-TRANSPLANTATION OF KIDNEY WORK-UP, RECIPIENT
7B0F200	READ	PRE-TRANSPLANTATION OF KIDNEY WORK-UP, LIVE DONOR
7B0F300	READ	POST-TRANSPLANTATION OF KIDNEY EXAMINATION, RECIPIENT
7B0F400	READ	POST-TRANSPLANTATION OF KIDNEY EXAMINATION, LIVE DONOR
K04..11	READ	ARF - ACUTE RENAL FAILURE
K04..11	READ	ARF - ACUTE RENAL FAILURE
K04..12	READ	ACUTE KIDNEY INJURY

Code	Type	Description
K043000	READ	ACUTE RENAL FAILURE DUE TO ACE INHIBITOR
K043100	READ	ACUTE RENAL FAILURE INDUCED BY AMINOGLYCOSIDE
K043300	READ	ACUTE RENAL FAILURE INDUCED BY CYCLOSPORIN A
K043400	READ	ACUTE RENAL FAILURE INDUCED BY NON-STEROID ANTI-INFLAMM DRUG
K045.00	READ	ACUTE RENAL FAILURE DUE TO NON-TRAUMATIC RHABDOMYOLYSIS
K046.00	READ	ACUTE RENAL FAILURE INDUCED BY TOXIN
K04B.00	READ	ACUTE RENAL FAILURE DUE TO TRAUMATIC RHABDOMYOLYSIS
K04C.00	READ	ACUTE KIDNEY INJURY STAGE 1
K04D.00	READ	ACUTE KIDNEY INJURY STAGE 2
K04E.00	READ	ACUTE KIDNEY INJURY STAGE 3
K060.11	READ	IMPAIRED RENAL FUNCTION
Kyu2.00	READ	[X]RENAL FAILURE
SP08E00	READ	ACUTE REJECTION OF RENAL TRANSPLANT - GRADE I
SP08F00	READ	ACUTE REJECTION OF RENAL TRANSPLANT - GRADE II
SP08G00	READ	ACUTE REJECTION OF RENAL TRANSPLANT - GRADE III
SP08H00	READ	ACUTE REJECTION OF RENAL TRANSPLANT
SP08R00	READ	RENAL TRANSPLANT REJECTION
SP08T00	READ	UROLOGICAL COMPLICATION OF RENAL TRANSPLANT
SP08V00	READ	VERY MILD ACUTE REJECTION OF RENAL TRANSPLANT
SP08W00	READ	VASCULAR COMPLICATION OF RENAL TRANSPLANT
SP15400	READ	RENAL FAILURE AS A COMPLICATION OF CARE
SP15411	READ	KIDNEY FAILURE AS A COMPLICATION OF CARE
TB00100	READ	KIDNEY TRANSPLANT WITH COMPLICATION, WITHOUT BLAME
TB00111	READ	RENAL TRANSPLANT WITH COMPLICATION, WITHOUT BLAME
TB11.00	READ	KIDNEY DIALYSIS WITH COMPLICATION, WITHOUT BLAME
TB11.11	READ	RENAL DIALYSIS WITH COMPLICATION, WITHOUT BLAME

CPRD = Clinical Practice Research Datalink; NEC = not elsewhere classified; NOS = not otherwise specified.

Source: Medical and product dictionary browsers, version 3.0. London: General Practice Research Database (now the CPRD); September 2015.

Table 1-3: ICD-9-CM Codes for Conditions to be Excluded from AKI

Code	Description
250.4	Diabetes with renal manifestations
403.x	Hypertensive chronic kidney disease
404.x	Hypertensive heart and chronic kidney disease
582.x	Chronic glomerulonephritis
585.x	Chronic kidney disease

ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*.

APPENDIX 2. ASSESSMENT OF INCIDENCE DURING CURRENT USE AND SWITCHING USE AND ESTIMATION OF PERSON-TIME

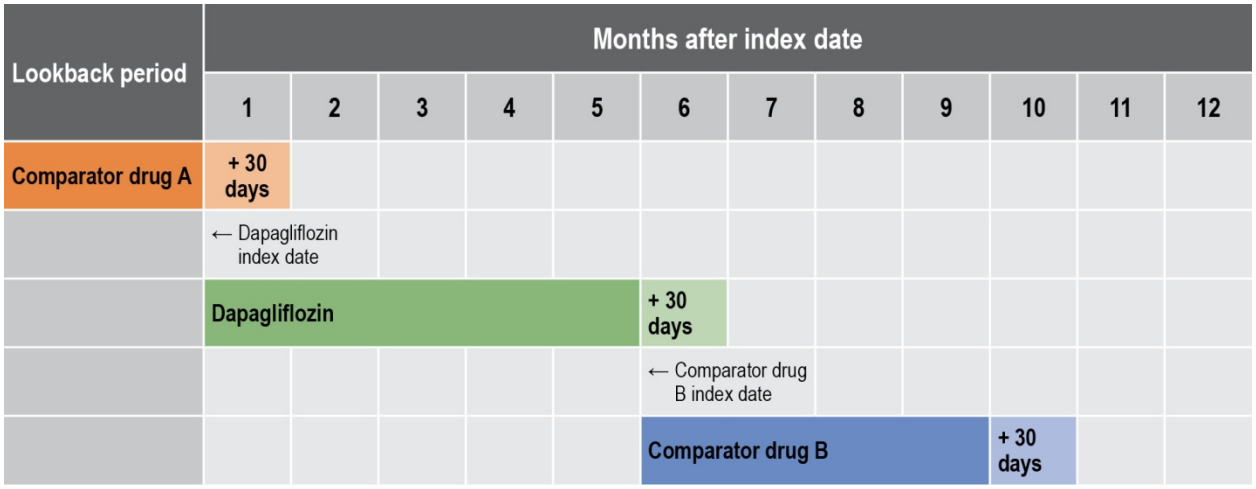
Example 1 through Example 6 on the following pages focus on assessment of incidence during dapagliflozin use compared with (1) use of other comparator antidiabetic drugs (ADs) as a group and (2) use of specific ADs.

- For calculation of crude incidence and incidence rate ratios (IRRs), the following comparisons can be made:
  - Incidence of AKI during any dapagliflozin-only exposed person-time can be compared with incidence during any comparator-exposed person-time.
  - Incidence of AKI during combined dapagliflozin-plus-comparator–exposed person-time can be compared with comparator-exposed person-time (see Example 1).
- For specific medication comparisons, e.g., comparing dapagliflozin to pioglitazone, the person-time and events during dapagliflozin person-time excluding any time overlapping with pioglitazone person-time can be compared with any non-dapagliflozin person-time in the pioglitazone group.
- For adjusted incidence, (1) propensity score will be used to adjust for concomitant medications at the index date, but only if not newly initiated at the time they were started, and (2) stratification or a multivariable model will be used to adjust for concomitant medications added during follow-up or switched at end of follow-up.

Example 1. Drug A was a medication newly initiated before the study period and is not an excluded AD. Drug A is not eligible to be a comparator drug as it was not newly initiated in the observation period; therefore the risk window for drug A is not evaluated, but use of drug A is controlled for in development of the propensity score.

The switch is from drug A, a comparator drug that was newly initiated but not during the observation period, to dapagliflozin and then from dapagliflozin to drug B, a newly initiated drug from the comparator group. At the initiation of drug B, the patient is eligible to be sampled for the comparator group.

Figure 2-1: Switch From a Potential Comparator Drug not in Exclusion Criteria to Dapagliflozin and then to a Different, New Comparator Drug



Risk window related to dapagliflozin = months 1-6; dapagliflozin categorized as “add-on” to drug A at the index date.

Risk window is further categorized into the following mutually exclusive categories:

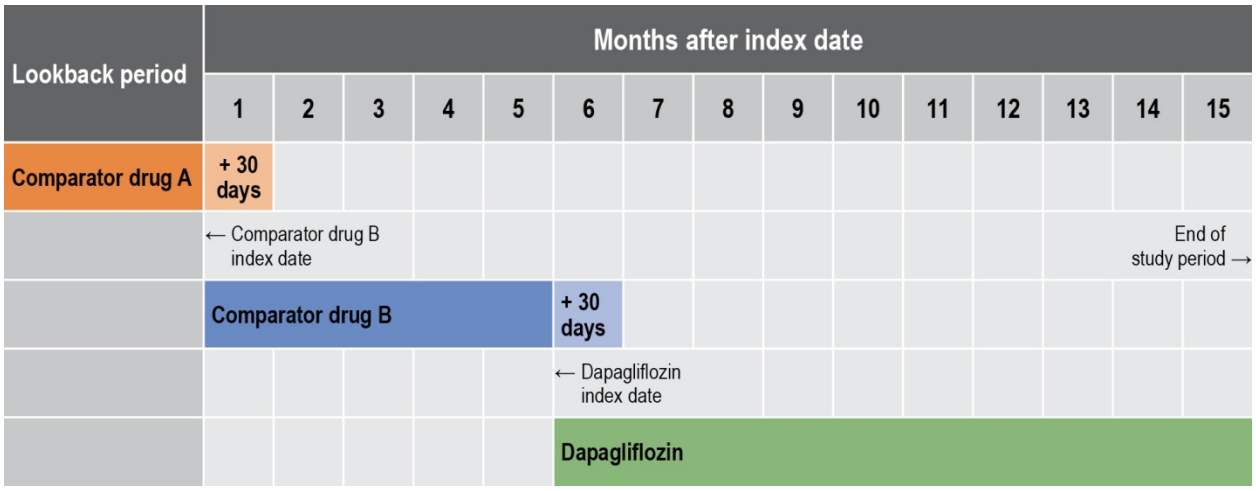
- Single exposure during follow-up: drug A: 0 months; dapagliflozin: months 2-5; drug B: months 7-10
- Multiple exposure during follow-up: months 1 and 6. Person-time in these months will be grouped into a “combined” exposure category and analyzed separately from the dapagliflozin-only exposure time and the comparator drug B–only exposure time.

Example 2. Drug A is not eligible to be a comparator drug; therefore the risk window for drug A is not evaluated, but use of drug A is controlled for in development of the propensity score.

Drug B is newly initiated and is eligible to be selected for the comparator cohort. If selected, follow-up starts at the beginning of month 1. Drug B risk window = months 1-6. Drug B is categorized as "add-on" to drug A at the index date.

When patient switches to dapagliflozin, person-time will be counted as "combined" exposure in month 6 and dapagliflozin-only exposed time in months 7-15. Person-time in months 1 and 6 will be grouped into a "combined" exposure category and analyzed separately from the dapagliflozin-only exposure time and the comparator drug B–only exposure time.

Figure 2-2: Switch From Comparator to Dapagliflozin



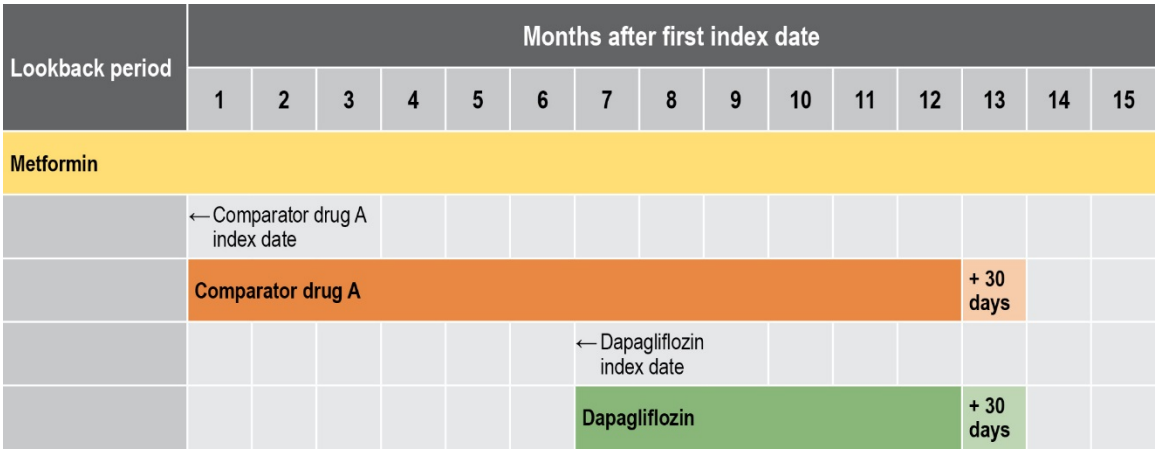
Example 3. Comparator drug A is initiated as an add-on to metformin, then dapagliflozin is added on in month 7 of follow-up. If dapagliflozin is added to a comparator drug treatment episode during follow-up, the person-time with combined exposure to dapagliflozin and comparator drug A (months 7-12) will be analyzed in a separate category of "combined exposure."

At the time of the addition of dapagliflozin (start of month 7), the patient is exposed to comparator drug A and dapagliflozin.

Risk window for drug A only = months 1-6.

Combined (dapagliflozin and comparator) exposure risk window = months 7-13.

Figure 2-3: Addition of Dapagliflozin to Comparator During Follow-up



Example 4. Comparator drug A is initiated as an add-on to metformin, then drug A is switched to comparator drug B, another newly initiated AD.

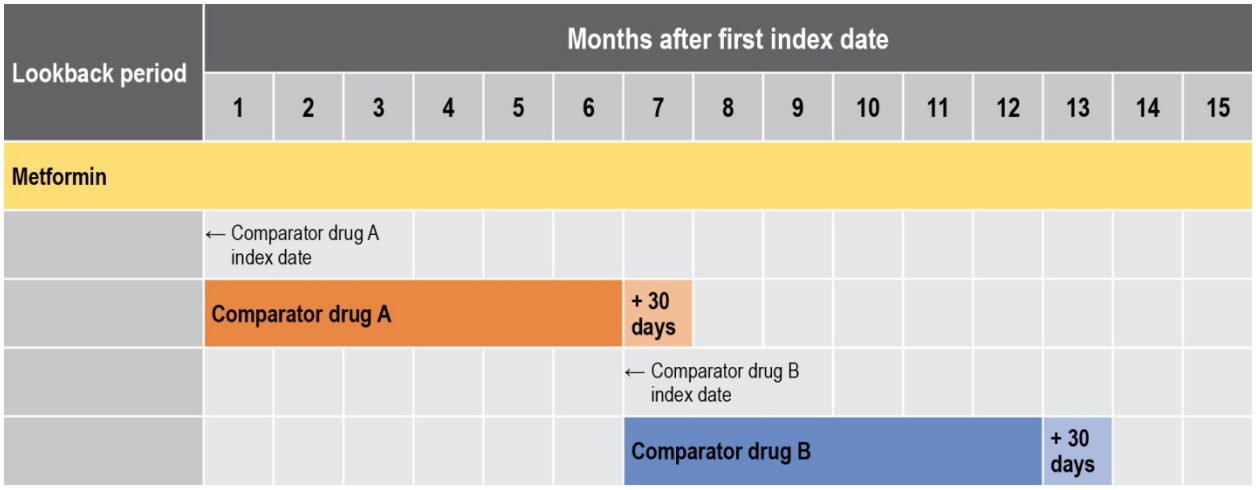
At the time of the switch (start of month 7), the patient is eligible to be selected into the comparator group (again).

Risk window for drug A only = months 1-6.

Risk window for drug A plus drug B (combined exposure) = month 7

Risk window for drug B, if selected into comparator group = months 8-13.

Figure 2-4: Add-on Drug A to Metformin, Then Switch to Drug B



Example 5. Sensitivity analysis with 60-day extended risk window

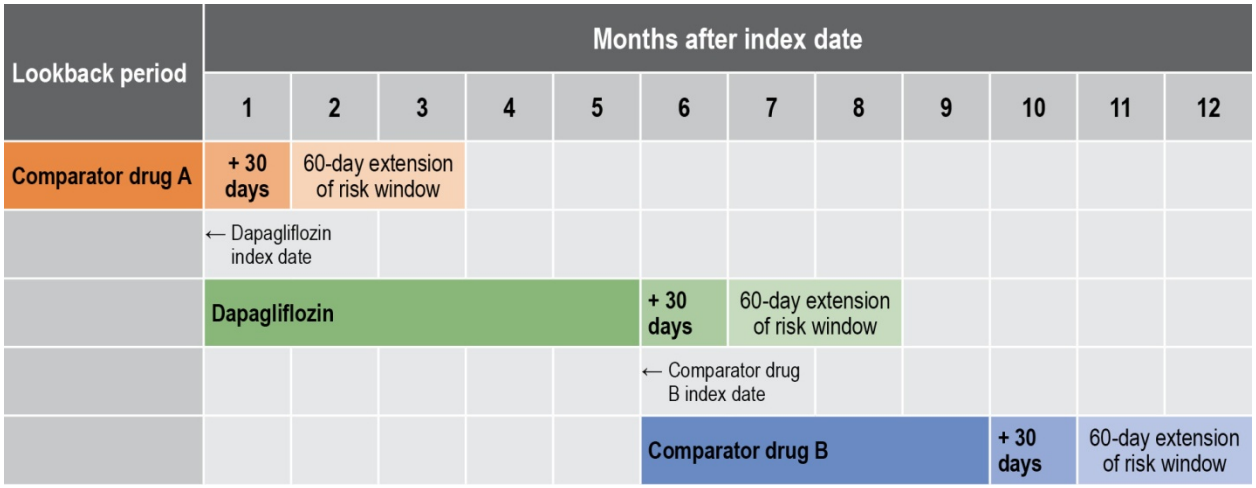
Drug A is not eligible to be a comparator drug; therefore the risk window for drug A is not evaluated, but use of drug A is controlled for in development of propensity score.

Risk window for dapagliflozin only = months 1-5.

Drug B is newly initiated by the patient, so patient is eligible to be selected for the comparator cohort; however, patient is not selected, so months 9-12 do not contribute to person-time exposure to drug B.

Risk window for dapagliflozin plus drug B (combined exposure) = months 6-8.

Figure 2-5: Sensitivity Analysis With Extended Risk Window



Example 6. Sensitivity analysis with exposure limited to only the index exposure episode

A sensitivity analysis will be performed that includes only the index exposure episodes. In Figure 2-6 and Figure 2-7 the follow-up time for the sensitivity analysis will be censored at the end of month 6 for each type of index exposure.

Risk window for dapagliflozin plus drug B (combined exposure) = month 6.

Figure 2-6: Sensitivity Analysis Including Only the Index Exposure Episode, Dapagliflozin

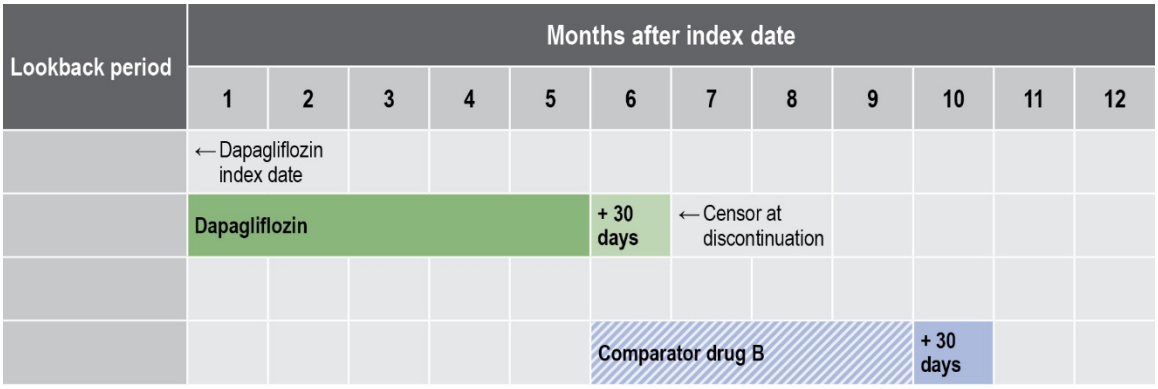
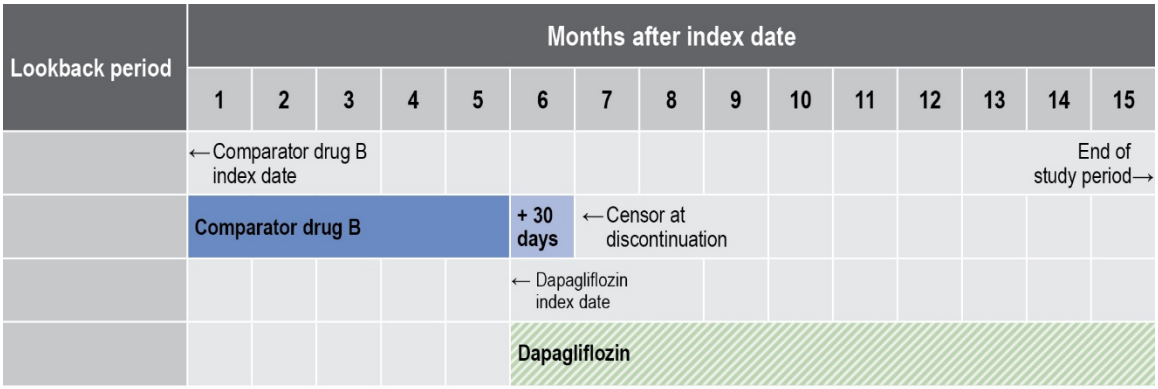


Figure 2-7: Sensitivity Analysis Including Only the Index Exposure Episode, Comparator



APPENDIX 3. OVERVIEW OF DATA SOURCE CHARACTERISTICS

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD℠, Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Database type	Primary-care electronic medical records of patients enrolled in practices contributing to the CPRD. Linkage to hospital data (Hospital Episode Statistics [HES]), mother-child data, practice-level socioeconomic data, death certificates (Office for National Statistics), cancer and cardiovascular disease registries, and others is possible. Linkage is available for a proportion of the practices.	Health insurance claims of patients enrolled in Anthem-affiliated health plans	Health insurance claims of patients enrolled in Medicare health insurance program; health insurance claims include pharmacy dispensings for those with Part D, hospital and outpatient claims, and procedure claims; medical record review is an option through a trusted third party
Database population (n)	5.1 million	35.8 million lives since 2006[a]	47 million
Population covered, description	Most UK residents are registered with a GP. Patients registered with practices that contribute to the CPRD are included. Prisoners and members of the armed forces are not included. The homeless are underrepresented.	United States residents who are enrolled in a covered employer-sponsored health plan	Federally sponsored health insurance program that offers health coverage to 47 million people, including 39 million people aged 65 years or older and 8 million nonelderly people with a permanent disability
Proportion of the country's population covered	8%	8%	60% of individuals aged 65 years or older and with Part D coverage
Representativeness of patients and practices	Age and sex of patients are representative of the UK population	Representative of all major geographic regions and health care settings for commercially insured US population aged less than 65 years	Considered to be representative of US population aged 65 years or older

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD℠, Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Demographics			
Lifestyle risk factors	Yes, but missing data. Marital status is updated, but there is no information on marital status at the time of a past event	None	None
Geographic location	First digits of physician's practice postal code	US	US
Medication information			
Source	All prescriptions issued by GPs. Repeat prescriptions may be implemented. There is a sequence number to know whether the prescription is new. The presence of a repeat prescription does not ensure that the prescription was picked up (of filled).	All claims submitted to Anthem, Inc.	All pharmacy claims submitted to Medicare
Drug dictionary codes/ therapeutic classification	Multilex/British National Formulary	National Drug Codes for outpatient prescriptions	National Drug Codes for outpatient prescriptions
Unique product code	Yes	Yes	Yes
Prescribed/dispensed drugs	GP prescriptions issued	Dispensed drugs at outpatient pharmacies	Dispensed drugs at outpatient pharmacies
Date drug prescribed/ dispensed	Yes, date the drug was prescribed	Yes, date dispensed	Yes, date dispensed
Dose	Yes, but it is not a mandatory field. The dose is a text code and requires some handling to be transformed into a number. This transformation may be performed by the researcher or by the CPRD.	Yes	Yes
Duration	There is a field to record duration, but it is highly incomplete. Duration can be derived from the number of prescriptions.	Days' supply	Days' supply is provided
Clinical indication	There is no field for indication. The user needs to assess diagnoses on the prescription. Prior diagnosis can be used as a proxy.	There is no field for indication. The user needs to assess diagnoses on the dispensing date. Prior diagnosis can be used as a proxy.	There is no field for indication. The user needs to assess diagnoses on the dispensing date. Prior diagnosis can be used as a proxy.

Characteristic	United Kingdom (Population, 62,435,709) Clinical Practice Research Datalink (CPRD)	United States HIRD℠, Aged 64 Years or Younger	United States Medicare, Aged 65 Years or Older
Inpatient medications	No	No	No
Specialist-prescribed medications	Only if the GP decided to include these in the medical record. GPs typically issue repeat prescriptions; there is a higher risk for not capturing the first specialist-initiated prescriptions than subsequent ones.	Available for many but not all outpatient pharmacy claims	Yes, if dispensed in outpatient setting
Diagnoses and procedures			
Coding system	Read	ICD-9-CM, ICD-10-CM, CPT, HCPCS	ICD-9-CM, ICD-10-CM, CPT, HCPCS
Outpatient visits	Yes, as entered by the GP	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Hospitalization data	Partial linkage to HES; as recorded by GPs	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Specialist visits	Information from referral letters	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Emergency room visits	As entered by the GP	Yes, one or more diagnoses on submitted claim	Yes, one or more diagnoses on submitted claim
Time period covered	Since 1987	Since 2006	Medicare Part D available since 2006
Updates	Quarterly	Monthly	Yearly
Approximate time lag	6-12 weeks	3-4 months	Up to 24 months
Access to medical records	GPs can be sent questionnaires via the CPRD for validation; also partial linkage to HES	Only through trusted a third party	Only through a trusted third party
Data transfer	Yes, third-party approval for standard data and linked databases. Data set will be delivered for analysis	No, data remain with at HIRD℠	Yes, after CMS protocol review
Approval process	ISAC approval of short protocol	Central institutional review board, possibly local institutional review board(s)	Local institutional review board, CMS Privacy Board

CMS = Centers for Medicare and Medicaid Services; CPRD = Clinical Practice Research Datalink; CPT = Current Procedural Terminology; GP = general practitioner; HCPCS = Healthcare Common Procedure Coding System; HES = Hospital Episode Statistics; HIRD^{SM} = HealthCore Integrated Research Database; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ISAC = Independent Scientific Advisory Committee; UK = United Kingdom; US = United States of America.

[a] HIRD^{SM} patients of any age enrolled in a qualifying health plan at any time between January 2006 and January 2014.

APPENDIX 4. ANTIDIABETIC DRUGS ELIGIBLE FOR INCLUSION IN THE COMPARATOR GROUP

Blood Glucose–Lowering Drugs (Excluding Insulin) by ATC Subgroup	Active Substance
A10BA, Biguanides	Metformin
A10BB, Sulfonamides, urea	Glibenclamide/glyburide
	Tolbutamide
	Gliclazide
	Glimepiride
	Carbutamide
	Chlorpropamide
	Tolazamide
	Glipizide
	Gliquidone
	Glyclopyramide
	Acetohexamide
A10BD, Combinations	Metformin/glibenclamide
	Metformin/rosiglitazone
	Rosiglitazone/glimepiride
	Pioglitazone/metformin hydrochloride
	Pioglitazone/glimepiride
	Sitagliptin/metformin hydrochloride
	Vildagliptin/metformin hydrochloride
	Pioglitazone/alogliptin
A10BF, Alpha glucosidase inhibitors	Acarbose
	Voglibose
	Miglitol
A10BG, Thiazolidinediones	Pioglitazone
A10BH, DPP-4 (dipeptidyl peptidase-4) inhibitors	Sitagliptin
	Vildagliptin
	Saxagliptin
	Linagliptin
	Alogliptin
A10BH, DPP-4 Combinations	Alogliptin/metformin
	Linagliptin/metformin

Blood Glucose–Lowering Drugs (Excluding Insulin) by ATC Subgroup	Active Substance
	Saxagliptin/metformin
A10BX, Other	Repaglinide
	Nateglinide
	Mitiglinide
	Exenatide
	Liraglutide
	Albiglutide
	Dulaglutide
	Lixisenatide

ATC = Anatomical Therapeutic Chemical (classification system).

Source: World Health Organization Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2015. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 30 October 2015.

APPENDIX 5. ADDITIONAL COVARIATES TO CONSIDER FOR INCLUSION IN THE PROPENSITY SCORE MODEL

Additional variables are provided in Table 1 in the body of the protocol.

Medical Comorbidities	
Other cardiovascular disease	Polymyalgia rheumatica
Autoimmune disease	Urinary infections (chronic or recurring)
Chronic obstructive pulmonary disease, emphysema, respiratory insufficiency	Kidney stones
	Bladder stones
Diffuse diseases of connective tissue	Colon polyps
Rheumatoid arthritis	Crohn's disease
Osteoarthrosis	Ulcerative colitis
	Pancreatitis
	Immunosuppressive diseases such as HIV/AIDS
	Peptic ulcer disease
	Dementia
	Asthma