Retrospective Observational Database Study Protocol

Drug Substance	Saxagliptin
Study Code	*<<Matrix D Number>>*
Date	2/23/2015

Study Comparing Risk of Hospitalization for Heart Failure Between Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Health Economics and Outcomes Research Therapeutic area: Diabetes

Name of Requester(s): Jack Sheehan PhD, MBA, RPh

Sponsor:

Name and address of RWE Engagement Lead: Iftekhar Kalsekar, PhD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Name and address of RWE Design and Analytics core member (s):

John Sheehan, PhD, MBA, RPh; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Iftekhar Kalsekar, PhD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Ameen Ghannam, MD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Katherine Tsai, PhD, MPH; 101 Orchard Ridge Drive, Gaithersburg, MD 20878; MedImmune, LLC.

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	**Date of Amendment**		

Administrative Change No.	Date of Administrative Change		

Please follow the International Society of Pharmacoepidemiology Guidelines for good pharmacoepidemiology Practices when completing this protocol.

These guidelines can be accessed via the following link:

http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Comparative Effectiveness Studies should also follow the GRACE Principles. These guidelines can be accessed via the following link: http://www.graceprinciples.org/

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Outcomes Research Practices are consensus documents on key outcomes research methods, including for database analyses, and can be found here: http://www.ispor.org/workpaper/practices_index.asp.

This protocol template should be completed for retrospective observational studies that use pre-collected ***anonymous*** data from electronic databases, such as health insurance claims data, hospital administrative data, and electronic medical records.

Observational studies that collect data prospectively (including Patient Reported Outcomes) and other Non-Interventional Studies **SHOULD NOT** use this protocol template.

PROTOCOL SYNOPSIS

Study Comparing Risk of Hospitalization for Heart Failure Between Dipeptidyl Peptidase-4 Inhibitors and Sulfonylureas

Principal Investigator

John Sheehan, PhD, MBA, RPh; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Co-Investigators

Stephen Johnston, MA; 7700 Old Georgetown Rd, Ste 650, Bethesda, MD 20814, USA; Truven Health Analytics, Inc.

Iftekhar Kalsekar, PhD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Ameen Ghannam, MD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Katherine Tsai, PhD, MPH; 101 Orchard Ridge Drive, Gaithersburg, MD 20878; MedImmune, LLC.

Alex Z. Fu, PhD; 3300 Whitehaven St NW, Suite 4100, Washington, DC 20007, USA; Georgetown University Medical Center.

Objectives

Primary objective:

To compare the risk of hospitalization for heart failure (hHF) between patients with type 2 diabetes mellitus (T2DM) treated with dipeptidyl peptidase-4 inhibitors (DPP-4is) vs. sulfonylureas (SUs)

Secondary objectives:

1. To compare the risk of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF between patients with T2DM treated with DPP-4is vs. SUs

2. To compare the risk of hHF between patients with T2DM treated with saxagliptin vs. sitagliptin or linagliptin
3. To compare the risk of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF between patients with T2DM treated with saxagliptin vs. sitagliptin or linagliptin

Study design

This will be a retrospective, observational cohort study. This study will use as its methodological foundation, as closely as possible and appropriate, the approach that is outlined in the Mini-Sentinel protocol for active surveillance of AMI in association with use of anti-diabetic agents.

Databases to be used

The study data source will be U.S. administrative claims data extracted from the *Truven Health MarketScan® Commercial Claims and Encounters* (Commercial) and *Medicare Supplemental and Coordination of Benefits* (Medicare Supplemental) databases.

Target subject population

The population to be studied is adult patients with T2DM newly-initiating a DPP-4i or an SU. Patients selected to address the study's primary objective and secondary objective #1 will be new initiators of either DPP-4is or SUs (including fixed dose combinations containing any medication from these classes) during the *patient selection period* lasting from August 1, 2010 (one year after the U.S. Food and Drug Administration [FDA] approval of saxagliptin), through August 30, 2013 (the date on which the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus [SAVOR]—Thrombolysis in Myocardial Infarction [TIMI] 53) results were initially presented). The analysis in which DPP4is are compared to SUs will henceforth be referred to as the *interclass comparison*.

A study *index date* will be set as the first observed outpatient prescription claim for a DPP-4i or an SU during the patient selection period, and the medication to which the first observed outpatient prescription claim corresponds will be designated the *index therapy*. Patients will be required to have continuous enrollment in medical and prescription benefits for the 365-day period prior to the index date, a period which will be designated the *baseline period*. Patients will be required to have no outpatient prescription claims for either DPP-4is or SUs during the baseline period. Patients will also be required to meet various other selection criteria, primarily intended to isolate patients with T2DM.

Patients selected to address the study's secondary objectives #2 and #3 will be new initiators of saxagliptin, sitagliptin, or linagliptin (including fixed dose combinations containing any of these medications) during the patient selection period lasting from August 1, 2010 (May 1, 2012 for linagliptin – *see main protocol text for rationale*), through August 30, 2013. The analysis in which saxagliptin is compared to sitagliptin or linagliptin will henceforth be referred to as the *intra-class comparison*. All selection criteria and study design elements

applied to the patients selected for the interclass comparison (e.g., setting of the index date and baseline period) will also apply to the intra-class comparison, with the exception that patients included in the intra-class comparison will be allowed to have outpatient prescription claims for SUs during the baseline period.

Exposures of Interest

The exposure variable for the primary objective and secondary objective #1 is membership in the DPP4-i or SU cohort; the exposure variable for secondary objectives #2 and #3 is membership in the saxagliptin, sitagliptin, or linagliptin cohorts.

Outcomes of Interest

The primary outcome of hHF as well as the secondary outcomes of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF will be measured during the *follow-up period* and analyzed as time-to-event variables.

For all analyses, the follow-up period will be variable-length, will begin on the day after the index date, and will end at the first occurrence of one of the following censoring events: (1) cessation of index therapy; (2) filling a prescription claim for an SU (applicable to DPP-4i cohort only), a DPP-4i (applicable to SU cohort only), or a non-index DPP-4i (applicable to the saxagliptin, sitagliptin, and linagliptin cohorts only); (3) beginning of a >31 day gap in continuous enrollment in health insurance benefits; (4) inpatient death; or (5) reaching the study end date of 8/30/2013. For the purposes of calculating time to a given outcome event, follow-up will be terminated at the first occurrence of an event or censoring at one of the aforementioned censoring events.

Statistical methods

In the interclass comparison, the DPP-4i cohort will be matched to the SU cohort using a propensity score (propensity for treatment with DPP-4is vs. SUs; nearest neighbour technique and enforcing a caliper of 0.01 [on the probability scale]) derived from a logistic regression model including a wide variety of demographic, insurance, utilization, and clinical variables measured during the baseline period. The intra-class comparison will also use the aforementioned propensity score matching techniques to match the saxagliptin cohort to the sitagliptin cohort, and separately match the saxagliptin cohort to the linagliptin cohort. Outcomes will be compared using bivariate Cox proportional hazards models (i.e., using the exposure of interest [cohort membership indicator] as the only independent variable) applied to the propensity score matched cohorts. In a sensitivity analysis for only the primary outcome of hHF, hHF will be compared using multivariable Cox proportional hazards models applied to the cohorts before matching. All statistical analyses will be separately conducted in patients with prior cardiovascular disease vs. patients without prior cardiovascular disease.

Based on previously-published information and the results of power calculations (*details in Section 13.2*), we expect that the probability of censoring in the analyses of patients with prior cardiovascular disease will be approximately 97.0%, and will therefore require a total sample

size of 12,869 patients. We expect that the probability of censoring in the analyses of patients without prior cardiovascular disease will be approximately 99.5%, and therefore expect to need a total sample size of 77,209 patients. Any analyses with samples that do not meet these pre-specified sample size and power criteria may not be conducted.

A total of six one-way sensitivity analyses (*details in Section 13*) will be conducted. All one-way sensitivity analyses focus on the primary outcome of hHF and will be conducted on the propensity score matched samples only. All applicable statistical methods and approaches described above will apply to the one-way sensitivity analyses.

Limitations

- Administrative claims data are not collected for research purposes and the diagnostic and procedure coding on administrative claims is recorded by physicians to support reimbursement. Codes on claims may be recorded incorrectly or not recorded at all, thereby potentially introducing measurement error with respect to code-based variables.

- The Medicare Supplemental database includes both the Medicare-paid and supplemental-paid components of reimbursed administrative claims. There are some services that are fully covered by Medicare without need for additional supplemental payments. Such services are not captured in the Medicare Supplemental database but are uncommon, unlikely to vary by index therapy, and therefore unlikely to systematically bias the study results.

- The administrative claims data that will be used for this study lack some useful clinical information, including severity and duration of T2DM.

- This study is limited to only those individuals with commercial or Medicare supplemental health insurance. Consequently, results of this analysis may not be generalizable to individuals with other insurance such as Medicaid or individuals without health insurance coverage. Furthermore, the patients in the Medicare Supplemental database have supplemental insurance paid for by their current or former employers, and therefore may not be representative of individuals with only primary Medicare coverage and no supplemental insurance coverage.

- Patients who change employers or opt for insurance coverage outside of their employer are lost to follow-up.

- Multivariable adjustment cannot correct for unmeasured confounding.

TABLE OF CONTENTS PAGE

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event (see definition in Section 14).
AMI	Acute myocardial infarction
CAROLINA	Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes
CABG	Coronary artery bypass graft
CPT-4	Current Procedural Technology 4th edition
CVD	Cardiovascular disease
DPP-4i	Dipeptidyl-peptidase 4 inhibitor
EXAMINE	EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome
FDA	U.S. Food and Drug Administration
GLP-1RA	Glucagon-like peptide-1 receptor agonists
GRACE	Good Research for Comparative Effectiveness
GPP	Good Pharmacoepidemiology Practice
HCPCS	Healthcare Common Procedure Coding System
hHF	Hospitalization for heart failure
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
NDC	National Drug Code
SAE	Serious adverse event (see definition in Section 14).
SAVOR	The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SU	Sulfonylurea
TZD	Thiazolidinediones
T2DM	Type 2 diabetes mellitus

1. STUDY INVESTIGATORS

1.1 Investigator name, title, degree, address, and affiliation

John Sheehan, PhD, RPh; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Stephen Johnston, MA; 7700 Old Georgetown Rd, Ste 650, Bethesda, MD 20814, USA; Truven Health Analytics, Inc.

Ameen Ghannam, MD; 601 Office Center Dr, Suite 200, Fort Washington, PA 19034, USA; AstraZeneca Pharmaceuticals, LP.

Katherine Tsai, PhD, MPH; 101 Orchard Ridge Drive, Gaithersburg, MD 20878; MedImmune, LLC.

Alex Z. Fu, PhD; 3300 Whitehaven St NW, Suite 4100, Washington, DC 20007, USA; Georgetown University Medical Center.

1.2 List of collaborating institutions

AstraZeneca Pharmaceuticals, LP

Truven Health Analytics, Inc

MedImmune, LLC

Georgetown University Medical Center

2. INTRODUCTION

2.1 Background

Among the randomized trials investigating the cardiovascular safety of individual dipeptidyl-peptidase 4 inhibitors (DPP-4is), two are completed (for saxagliptin and alogliptin) and three are ongoing (for sitagliptin and linagliptin).

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) 53 trial evaluated the cardiovascular safety and efficacy of saxagliptin versus placebo in patients with type 2 diabetes mellitus (T2DM) who were at risk for cardiovascular events.[1] In this trial, the primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke; the secondary end point included the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina. In this trial, saxagliptin did not increase or decrease the rate of ischemic events; however, the rate of hospitalization for heart failure (hHF) – which was neither a primary nor secondary endpoint – was increased for saxagliptin relative to the placebo group (3.5% versus 2.8 %, according to two-year Kaplan-Meier estimates; hazard ratio, 1.27; 95% CI, 1.07 to 1.51).[1] This imbalance in hHF was unexpected and interpreted cautiously within the context of multiple testing and the risk of a false positive result.

The EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) trial evaluated the long-term cardiovascular safety of alogliptin versus placebo in patients with T2DM and recent acute coronary syndrome.[2] In post-hoc analyses of this trial's data, alogliptin had no effect – relative to placebo – on either a composite cardiovascular endpoint including hHF (within-composite rate of hHF = 3.1% alogliptin vs. 2.9% placebo; hazard ratio, 1.07; 95% CI, 0.79 to 1.46) or hHF as a standalone endpoint (3.9% alogliptin vs. 3.3% placebo; hazard ratio, 1.19; 95% CI, 0.90 to 1.58).[3]

Experimental data on the risk of hHF with sitagliptin (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin [TECOS]) or linagliptin (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes [CAROLINA]; CArdiovascular safety and Renal Microvascular outcomE with LINAgliptin in patients with Type 2 Diabetes mellitus at high vascular risk [CARMELINA]) are forthcoming, with TECOS data scheduled for earlier presentation in 2015.[4,5,6]

2.2 Scientific and Business Rationale and Significance

The study described herein will provide real world evidence regarding the comparative cardiovascular safety of DPP-4is vs. sulfonylureas (SUs) and saxagliptin vs. sitagliptin or linagliptin, with a primary focus on hHF.

The rationale for this study is that there is uncertainty in the clinical community regarding whether or not the hHF observation from SAVOR-TIMI represents a false positive result due

to multiple testing. Furthermore, if the result is a true positive, there is uncertainty regarding whether the risk of hHF differs across the class of DPP-4is. The present study will address both of these uncertainties by: (1) assessing the risk of hHF with DPP-4is as compared to SUs, which are known to be used in patients that are relatively similar to patients receiving DPP-4is and which have long-standing experience in the clinical community; and (2) by assessing the risk of hHF for saxagliptin in comparison to other DPP-4is where there is sufficient administrative claims data for a valid comparison.

Although prior pharmacoepidemiology studies have examined the association between incretin-based treatments – such as DPP-4is and glucagon-like peptide-1 receptor agonists (GLP-1RAs) – and the risk of hHF, these studies have produced mixed results and none of have compared the risk of hHF between agents within the class of DPP-4is.[7,8,9,10,11,12,13,14] Thus, there is a lack of real world evidence regarding the comparative safety of saxagliptin relative to other DPP-4is.

Finally, in the absence of the direct, head-to-head comparative data that will generated by the present study, any understanding of within-DPP-4i-class differences in cardiovascular safety would be based upon indirect comparisons of the various clinical trials that have been completed or are underway. These trials differ substantially with respect to design, enrollment criteria, geographic region, follow-up time, sample size, and order of hierarchical testing.

3. STUDY OBJECTIVES

3.1 Primary objective

To compare the risk of hHF between patients with T2DM treated with DPP-4is vs. SUs

3.2 Secondary objectives

1. To compare the risk of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF between patients with T2DM treated with DPP-4is vs. SUs
2. To compare the risk of hHF between patients with T2DM treated with saxagliptin vs. sitagliptin or linagliptin
3. To compare the risk of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF between patients with T2DM treated with saxagliptin vs. sitagliptin or linagliptin

4. STUDY PLAN AND PROCEDURES

4.1 Overall study design and flow chart

This will be a retrospective, observational cohort study using U.S. administrative insurance claims data drawn from the *Truven Health MarketScan® Commercial Claims and Encounters* (Commercial) and *Medicare Supplemental and Coordination of Benefits* (Medicare Supplemental) databases (*details in Section 6*). This study will use as its methodological foundation, as closely as possible and appropriate, the approach that is outlined in the Mini-Sentinel protocol for active surveillance of AMI in association with use of anti-diabetic agents.[15]

Precise detail on the study design and variable definitions is provided within the sections below; however, patients selected to address the study's primary objective and secondary objective #1 will be new initiators of either DPP-4is or SUs (including fixed dose combinations containing any medication from these classes) during the *patient selection period* lasting from August 1, 2010 (one year after the U.S. Food and Drug Administration [FDA] approval of saxagliptin; May 1, 2012 for linagliptin [*see Section 5 for rationale*]), through August 30, 2013 (the date on which the SAVOR-TIMI results were initially presented). The analysis in which DPP4is are compared to SUs will henceforth be referred to as the *interclass comparison*.

A study *index date* will be set as the first observed outpatient prescription claim for a DPP-4i or an SU during the patient selection period, and the medication to which the first observed outpatient prescription claim corresponds will be designated the *index therapy*. Patients will be required to have continuous enrollment in medical and prescription benefits for the 365-day period prior to the index date, a period which will be designated the *baseline period*. Patients will be required to have no outpatient prescription claims for either DPP-4is or SUs during the baseline period. Patients will also be required to meet various other selection criteria, primarily intended to isolate patients with T2DM (*details in Section 7*).

Patients selected to address the study's secondary objectives #2 and #3 will be new initiators of saxagliptin, sitagliptin, or linagliptin (including fixed dose combinations containing any of these medications) during the patient selection period lasting from August 1, 2010, through August 30, 2013. The analysis in which saxagliptin is compared to sitagliptin or linagliptin will henceforth be referred to as the *intra-class comparison*. All selection criteria and study design elements applied to the patients selected for the interclass comparison (e.g., setting of the index date and baseline period) will also apply to the intra-class comparison, with the exception that patients included in the intra-class comparison will allowed to have outpatient prescription claims for SUs during the baseline period.

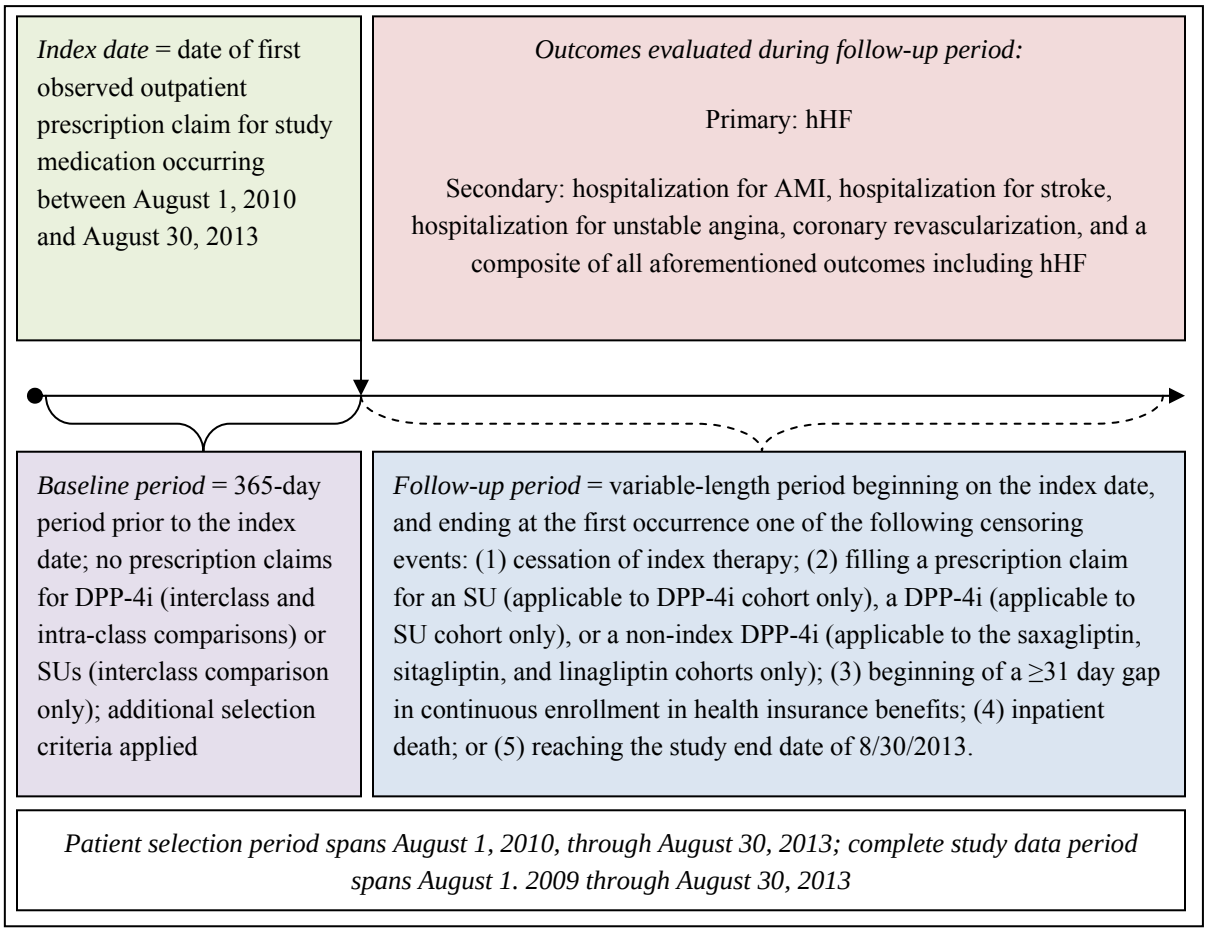
For all analyses, the follow-up period will be variable-length, will begin on the day after the index date, and will end at the first occurrence of one of the following censoring events (*details in Section 9*): (1) cessation of index therapy; (2) filling a prescription claim for an SU (applicable to DPP-4i cohort only), a DPP-4i (applicable to SU cohort only), or a non-index DPP-4i (applicable to the saxagliptin, sitagliptin, and linagliptin cohorts only); (3) beginning

of a ≥31 day gap in continuous enrollment in health insurance benefits; (4) inpatient death; or (5) reaching the study end date of 8/30/2013. For the purposes of calculating time to a given outcome event, follow-up will be terminated at the first occurrence of an event or censoring at one of the aforementioned censoring events (*details in Section 10*).

The primary outcome of hHF as well as the secondary outcomes of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF will be measured during the follow-up period and analyzed as time-to-event variables (*details in Section 10*).

Figure 1 depicts the key elements of the study design.

Figure 1 Study flow chart



In the interclass comparison, the DPP-4i cohort will be matched to the SU cohort using a propensity score (propensity for treatment with DPP-4is vs. SUs) derived from a logistic regression model including a wide variety of demographic, insurance, utilization, and clinical variables measured during the baseline period (*details in Section 13*). The intra-class comparison will also use the aforementioned propensity score matching techniques to match the saxagliptin cohort to the sitagliptin cohort, and separately match the saxagliptin cohort to

the linagliptin cohort. Outcomes will be compared using bivariate (i.e., using the exposure of interest [cohort membership indicator] as the only independent variable) Cox proportional hazards models applied to the propensity score matched cohorts. In a sensitivity analysis for only the primary outcome of hHF, hHF will be compared using multivariable Cox proportional hazards models applied to the cohorts before matching. All statistical analyses will be separately conducted in patients with prior cardiovascular disease vs. patients without prior cardiovascular disease (*details in Section 13*).

Table 1. Study Timelines and Milestone Chart

Kickoff	Completion of draft protocol	Completion of protocol review	Completion of analytic file build	Completion of bivariate analyses	Completion of multivariable analyses	Completion of draft final report
January 12, 2015	January 16, 2015	January 30, 2015	March 27, 2015	April 17, 2015	May 29, 2015	June 26, 2015

5. STUDY DESIGN SELECTION AND RATIONALE

5.1 Rationale for study design

This study will use as its methodological foundation, as closely as possible and appropriate, the approach that is outlined in the Mini-Sentinel protocol for active surveillance of AMI in association with use of anti-diabetic agents, particularly saxagliptin compared with: sitagliptin, pioglitazone, and long-acting or combination insulin.[15] The rationale for this approach is that the Mini-Sentinel protocol was developed by governmental, academic, and commercial stakeholders for the exact purpose of evaluating the risk of a cardiovascular safety event among patients treated with saxagliptin vs. various other antidiabetes medications. Thus, using this approach is likely to be viewed as being valid and unbiased.

The patient selection period will last from August 1, 2010 (one year after the FDA approval of saxagliptin), through August 30, 2013 (the date on which the SAVOR-TIMI results were initially presented). The rationale for using August 1, 2010 as the beginning of this period is that within the first year after approval, market access for a medication may be limited and such limitations could potentially bias prescribing patterns. Beginning the patient selection period one year after the FDA approval of saxagliptin may help to reduce the impact of such biases. Similarly, for patients who are treated with linagliptin, the patient selection period will begin one year after FDA approval of linagliptin (May 1, 2012). In all comparisons, only patients who initiate on or after the beginning of the comparator's patient selection window will be considered for analysis. The rationale for using August 30, 2013 as the end of the patient selection period as well as the end of follow-up is that physicians may have altered their prescribing patterns for saxagliptin after learning of the hHF results in SAVOR-TIMI.

5.2 Rationale for selection of comparators

The rationale for selection of SUs as the comparator in the interclass comparison is that, after metformin, SUs are the most commonly used antidiabetes medication in the U.S.[16] Moreover, both DPP-4is and SUs are most commonly used as second-line treatment after, or in addition to, metformin. The rationale for selection of sitagliptin and linagliptin as the comparators in the intra-class comparison is that these are two of the four drugs, currently approved by the FDA for treatment of T2DM in the U.S., that the DPP-4i class comprises (i.e., alogliptin, linagliptin, saxagliptin, and sitagliptin). The rationale for exclusion of alogliptin from the intra-class comparison is that the sample size will be too small for comparative effectiveness analysis of a rare endpoint such as hHF given its date of FDA approval (January 2013) relative to the end of the patient selection (August 2013). Before application of any other study selection criteria, the MarketScan Commercial and Medicare Supplemental claims databases contained data on only 450 patients treated with alogliptin during the patient selection period.

6. DATABASE(S) TO BE USED

The study data source will be U.S. administrative claims data extracted from the *Truven Health MarketScan® Commercial Claims and Encounters* (Commercial) and *Medicare Supplemental and Coordination of Benefit*s (Medicare Supplemental) databases.

These databases comprise enrollment information, demographic information, and inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from over 300 large self-insured U.S. employers and over 25 U.S. health plans. The Commercial database includes information for individuals who are under the age of 65 and are the primary insured or a spouse or dependent thereof. The Medicare Supplemental database includes information for individuals who are Medicare-eligible and have a supplemental insurance paid for by their current or former employer. The Medicare Supplemental database includes both the Medicare-paid and supplemental-paid components of reimbursed administrative claims. The study databases contain data for over 70 million unique individuals during the study period.

The rationale for using these databases for this study is that: (1) they represent the largest proprietary non-probability administrative claims database available for research in the U.S.; and (2) they comprise a wide variety of health plan types and formularies, thereby being more generalizable than single payer databases, which may have systematic prescribing biases related to saxagliptin or other DPP-4is.

As described in greater detail below, study variables were measured from the database using enrollment records, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, Current Procedural Technology 4th edition (CPT-4®) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs), as appropriate.

7. SELECTION OF STUDY POPULATION

7.1 Population to be studied

The population to be studied is adult patients with T2DM newly-initiating a DPP-4i or an SU. Two populations will be studies, those qualifying for the interclass comparison and those qualifying for the intra-class comparison. Detailed participant eligibility criteria are provided below.

NOTE: See Appendix A, Table 1 for codes and medications used for selection of study population

7.2 Participant eligibility

7.2.1 Inclusion criteria for interclass comparison

Patients must fulfill all of the following criteria to be eligible for the interclass comparison:

1. ≥1 outpatient prescription claim for a DPP-4i[*] (saxagliptin, saxagliptin/metformin, sitagliptin, sitagliptin/metformin, sitagliptin/simvastatin, linagliptin, linagliptin/metformin) or an SU[†] between 8/1/2010 (5/1/2012 for linagliptin) - 8/30/2013; the date of the first of such claims is designated the *index date*; the medication to which the first observed outpatient prescription claim corresponds will be designated the *index therapy*

2. ≥1 day of follow-up

3. ≥18 years of age on the index date

4. 365 days of continuous enrollment (no gaps >31 days) in medical and pharmacy benefits immediately prior to the index date; this period is designated the *baseline period*

5. ≥1 outpatient prescription claim for an antidiabetes medication or ≥1 medical claim with an ICD-9-CM diagnosis code for T2DM during the baseline period

7.2.2 Exclusion criteria for interclass comparison

Any of the following is regarded as a criterion for exclusion from the comparison:

6. More than one type of DPP-4i, more than one type of SU, or a DPP-4i and an SU on the index date

7. ≥1 outpatient prescription claim for saxagliptin, saxagliptin/metformin, sitagliptin, sitagliptin/metformin, sitagliptin/simvastatin, linagliptin, linagliptin/metformin, alogliptin, alogliptin/metformin, alogliptin/pioglitazone, or an SU during the baseline period

8. hHF in the 60-day period before the index date (*see Section 10 for detailed definition of hHF*)

9. ≥1 non-diagnostic (i.e., not linked to laboratory tests, radiology, or other services that are often used to rule out the presence of a health condition) medical claim with ICD-9-CM, CPT, or HCPCS codes indicative of pregnancy or gestational diabetes during the baseline period or from the index date through the earliest of the end of continuous enrollment or the end of available data

[*] Alogliptin was approved in January of 2013 and therefore after extending the patient selection window to begin one year after the approval of alogliptin it does not fall within this study's periods of interest.
[†] Patients using sulfonylureas co-formulated with metformin or a TZD will be included in the sample.

10. ≥1 non-diagnostic medical claim with an ICD-9-CM diagnosis code for type 1 diabetes mellitus during the baseline period or from the index date through the earliest of the end of continuous enrollment or the end of available data

7.2.3 Inclusion criteria for intra-class comparison

Patients must fulfil all of the following criteria to be eligible for the intra-class comparison:

1. ≥1 outpatient prescription claim for saxagliptin (including saxagliptin/metformin), sitagliptin (including sitagliptin/metformin and sitagliptin/simvastatin), or linagliptin (including linagliptin/metformin) between 8/1/2010 (5/1/2012 for linagliptin) - 8/30/2013; the date of the first of such claims is designated the *index date*; the DPP-4i component of the medication to which the first observed outpatient prescription claim corresponds will be designated the *index therapy* (i.e., saxagliptin, sitagliptin, or linagliptin)

2. ≥1 day of follow-up

3. ≥18 years of age on the index date

4. 365 days of continuous enrollment (no gaps >31 days) in medical and pharmacy benefits immediately prior to the index date; this period is designated the *baseline period*

5. ≥1 outpatient prescription claim for an antidiabetes medication or ≥1 medical claim with an ICD-9-CM diagnosis code for T2DM during the baseline period

7.2.4 Exclusion criteria for intra-class comparison

Any of the following is regarded as a criterion for exclusion from the intra-class comparison:

11. More than one type of DPP-4i on the index date

12. ≥1 outpatient prescription claim for saxagliptin, saxagliptin/metformin, sitagliptin, sitagliptin/metformin, sitagliptin/simvastatin, linagliptin, linagliptin/metformin, alogliptin, alogliptin/metformin, alogliptin/pioglitazone during the baseline period

13. hHF in the 60-day period before the index date (see Section 10 for detailed definition of hHF)

14. ≥1 non-diagnostic medical claim with ICD-9-CM, CPT, or HCPCS codes indicative of pregnancy or gestational diabetes during the baseline period or from the index date through the earliest of the end of continuous enrollment or the end of available data

15. ≥1 non-diagnostic medical claim with an ICD-9-CM diagnosis code for type 1 diabetes mellitus during the baseline period or from the index date through the earliest of the end of continuous enrollment or the end of available data.

8. EXPOSURES OF INTEREST

8.1 Drug-specific exposure/treatment

The exposure variable for the primary objective and secondary objective #1 is membership in the DPP4-i or SU cohort; the exposure variable for secondary objectives #2 and #3 is membership in the saxagliptin, sitagliptin, or linagliptin cohorts. Patients are classified into their respective index therapy cohorts as described above in Section 7.

8.2 Treatment Compliance

As described in greater detail within Section 9 below, patients must remain compliant to their treatment to the extent that follow-up will be censored at cessation of treatment.

9. PARTICIPANT FOLLOW-UP

For all analyses, the follow-up period will be variable-length, will begin on the day after the index date, and will end at the first occurrence one of the following censoring events:

(i) Cessation of index therapy (defined in next paragraph);

(ii) Filling a prescription claim for: an SU (applicable to DPP-4i cohort); a DPP-4i (applicable to SU cohort); a non-index DPP-4i (applicable to the saxagliptin, sitagliptin, and linagliptin cohorts)

(iii) Beginning of a >31 day gap in continuous enrollment in health insurance benefits;

(iv) Inpatient death;

(v) Reaching the study end date of 8/30/2013

Cessation of index therapy is defined as a gap in days' supply for the index therapy that is equal to 1/3 of the days' supply of the most recent prescription of the index therapy. Gaps in days' supply of less than 10 days are not considered cessation regardless of the days' supply of the most recent prescription of the index therapy. Table 2 provides an example of the gaps in days' supply that will designate cessation of index therapy.

Table 2. Example of gaps in days' supply that will designate cessation of index therapy

Days' supply of the most recent prescription of the index therapy	Example of allowable gap / day of censoring
1-32 days	10 days / 11th day
45 days	15 days / 16th day
100 days	33 days / 34th day

In calculating days' supply of the index therapy, "stockpiling" (wherein a given prescription is filled "early" [i.e., before exhaustion of the previous prescription's days' supply]) will be accounted for by adding any remaining days' supply from the previous prescription to the days supply of the "early" prescription. The maximum number of allowable "stockpiled" days' supply will be 120.

Additionally, for the DPP-4i vs. SU comparison only, individual agents within the index therapy's class will be considered interchangeable. For example, if a patient in the DPP-4i cohort initiates index therapy on saxagliptin and subsequently switches treatment to sitagliptin, they will be considered as having remained exposed to the index therapy, as long as no other censoring event occurs between the last saxagliptin prescription and first sitagliptin prescription. In cases wherein the prescription for the within-class agent to which a patient switched is filled "early," as described above, the remaining days' supply from the previous prescription will be "stockpiled."

10. DEFINITIONS OF OUTCOME VARIABLES

NOTE: See Appendix A, Table 2 for codes used for measurement of outcome variables

10.1 Primary outcome variables

The primary outcome is hHF during exposure to index therapy. hHF will be measured and analyzed as a time-to-event variable.

hHF events will be defined as inpatient admission with a principal discharge diagnosis for heart failure. This definition has been validated and the ICD-9-CM coding is consistent with the definition provided for heart failure within the Mini-Sentinel protocol.[15,17] Time to hHF will be defined as the number of days from the index date until the first occurrence of the date of admission for an hHF event or censoring at the end of exposure to index therapy.

10.2 Secondary outcome variables (and other outcome variables, if applicable)

The secondary outcomes are hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all outcomes together including hHF during exposure to index therapy. Each of the secondary outcomes will be analyzed separately and each will be measured and analyzed as a time-to-event variable.

Hospitalization for AMI will be defined as an inpatient admission with a principal discharge diagnosis for AMI. This definition has been validated but differs from the Mini-Sentinel definition due to lack of information on mortality outside of the inpatient setting.[18] Time to hospitalization for AMI will be defined as the number of days from the index date until the

first occurrence of the date of admission for a hospitalization for AMI or censoring at the end of exposure to index therapy.

Hospitalization for stroke will be defined as an inpatient admission with a principal discharge diagnosis for stroke. This definition has been validated and the ICD-9-CM coding is consistent with the definition provided for stroke ("narrow") within the Mini-Sentinel protocol.[15,19] Time to hospitalization for stroke will be defined as the number of days from the index date until the first occurrence of the date of admission for a hospitalization for stroke or censoring at the end of exposure to index therapy.

Hospitalization for unstable angina will be defined as an inpatient admission with a principal discharge diagnosis for unstable angina. This definition has been validated and the ICD-9-CM coding is consistent with the definition provided for unstable angina within the Mini-Sentinel protocol.[15,20] Time to hospitalization for unstable angina will be defined as the number of days from the index date until the first occurrence of the date of admission for a hospitalization for unstable angina or censoring at the end of exposure to index therapy.

Coronary revascularization will be defined as an inpatient admission or outpatient encounter with a procedure code for coronary revascularization in any position (i.e., primary or non-primary). Although this definition has not, to our knowledge, been validated, procedure codes are distinct from diagnosis codes in that they are less likely to be coded erroneously than diagnosis codes. Time to coronary revascularization will be defined as the number of days from the index date until the first occurrence of the date of a procedure for coronary revascularization or censoring at the end of exposure to index therapy.

Composite outcome events will be defined as having experienced any of the primary or secondary outcomes. Time to the composite outcome will be defined as the minimum time-to-event value taken from among the time-to-event values for the primary and secondary outcomes.

11. DEFINITIONS OF OTHER VARIABLES

11.1 Demographic variables

Demographic variables will be measured on the index date using insurance enrollment information contained in the study databases.

- Age in years
- Sex (male vs. female)
- Insurance plan type (basic/major medical, comprehensive, exclusive provider organization, health maintenance organization, point-of-service, point-of-service

with capitation, preferred provider organization, consumer-directed health plan, high-deductible health plan, unknown)

- Payer (commercial vs. Medicare)
- Index year (2010, 2011, 2012, 2013)
- Geographic region (Northeast, North Central, South, West, Unknown)
- Population density (urban, rural, unknown)

11.2 Potential confounder and effect modifier variables

Potential confounder variables will be measured during the baseline period (including the index date) unless otherwise noted. The effect modifier variable of primary interest is prior cardiovascular disease versus no prior cardiovascular disease; all analyses will be stratified by this variable. Section 13 presents additional groups of patients and alternative definitions of follow-up which have been chosen for one-way sensitivity analyses. Potential confounder and effect modifier variables will include all variables from the Mini-Sentinel protocol Tables 3 and 4 plus additional covariates that have been included in observational analyses of hHF.[10]

NOTE: See Appendix A, Table 3 for codes used for measurement of prior cardiovascular disease; see Appendix A, Table 4 for codes and medications used for measurement of other effect modifiers and potential confounders

11.2.1 Effect modifier variables

- Prior cardiovascular disease vs. no prior cardiovascular disease: defined as a ≥1 non-diagnostic medical claim with ICD-9-CM, CPT, or HCPCS codes indicative of any of the following incurred during the baseline period:
  - Prior heart failure
  - Prior hHF (>60 days before index date)
  - Prior AMI
  - Other ischemic heart disease
  - Other heart disease
  - Stroke (narrow)
  - Stroke (broad)
  - Peripheral artery disease

- Coronary revascularization procedures
  - Coronary artery bypass graft
  - Percutaneous coronary intervention
- Carotid revascularization procedures
  - Carotid endarterectomy, stenting, angioplasty, or atherectomy
  - Carotid bypass
- Lower extremity revascularization procedures
  - Lower extremity endarterectomy, stenting, angioplasty, or atherectomy
  - Lower extremity bypass
  - Lower extremity amputation

11.2.2 Potential confounder variables: baseline healthcare utilization

- Hospitalization in 30 days pre-index
- Hospitalization in 31-365 days pre-index
- Emergency room visit in 30 days pre-index
- Emergency room visit in 31-365 days pre-index
- Number of outpatient visits during 1-year baseline
- Number of unique medications during 1-year baseline
- Residence in nursing home or stay in other non-hospital institution during 1-year baseline
- Cardiologist visit
- Creatinine test ordered
- HbA1c test ordered

11.2.3 Potential confounder variables: baseline comorbid conditions

Comorbid conditions will be defined as ≥1 non-diagnostic medical claim with ICD-9-CM, CPT, or HCPCS codes indicative of any of the following incurred during the baseline period:

- Asthma
- Cancer (excluding non-melanoma skin cancer)
- Chronic kidney disease (excluding end stage renal disease)
- Chronic obstructive pulmonary disease
- Dementia
- Depression
- End stage renal disease
- Fracture
- Human immunodeficiency virus/acquired immune deficiency syndrome
- Hyperlipidemia or lipid disorder
- Hypertension
- Hypoglycemia
- Liver disease
- Microvascular complications of diabetes
  - Nephropathy
  - Retinopathy
  - Peripheral neuropathy
- Obesity (or weight gain)
- Osteoporosis
- Tobacco use

11.2.4 Potential confounder variables: baseline medications

Baseline medication use will be defined as ≥1 outpatient prescription claim for of any of the medications listed below. Two sets of flags will be created, one based on outpatient prescription claims incurred during the baseline period and one based on outpatient prescription claims incurred during the 6-month period immediately preceding the index date (referred to as "current at baseline" in the Mini-Sentinel protocol).

- Antidiabetic medications
  - Alpha-glucosidase inhibitors
  - Amylin analogs
  - Biguanides (metformin)
  - GLP-1 RAs
  - Insulin
  - Meglitinides
  - SGLT2 inhibitors
  - Sulfonylureas
  - Thiazolidinedioines
  - Any antidiabetic medication
  - Number of antidiabetic medications
- Antihypertensive medications
  - Angiotensin-converting-enzyme inhibitors
  - Alpha-beta blockers
  - Angiotensin II receptor blocker
  - Beta-blockers
  - Calcium channel blockers
  - Central alpha-2 receptor agonists
  - Direct renin inhibitors
  - Direct vasodilators
  - Loop diuretics
  - Potassium sparing diuretics
  - Thiazide diuretics

  - Any antihypertensive medication

- Lipid lowering medications
- Other medications/medication classes
  - Digoxin (cardiac glycoside)
  - Anticoagulants
  - Antiplatelets
  - Opioids
  - Oral corticosteroids

12. DATA MANAGEMENT

12.1 Confidentiality of study data

The study databases satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the Health Insurance Portability and Accountability Act of 1996 privacy rule regarding the determination and documentation of statistically de-identified data. Because this study used only de-identified patient records and does not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study was not necessary.

12.2 Data storage and retention

The study databases will be stored on secured and encrypted Truven Health Analytics servers and will be retained indefinitely.

12.3 Data access procedures

Only authorized Truven Health Analytics staff will have access to the study data.

12.4 Quality control and management procedures

Truven Health Analytics has specific standard practices to ensure programming quality and accuracy. These practices comprise the following steps:

(i) Clinical Code Review: All diagnosis (ICD-9-CM), procedure (ICD-9-CM, CPT), and pharmacy (NDC) coding will be created by the Analyst in conjunction with the Project Manager and Truven Health Analytics' nosologists. The codes will be

catalogued in the project specification and reviewed by the principal SAS Programmer/Analyst.

(ii) Programming Code review: All SAS code will be reviewed, during its creation, by the principal SAS Programmer/Analyst. Diagnostics from the analytic file will be distributed by the SAS Programmer/Analyst and reviewed by the entire Project Team. Code Review will be conducted by a second, SAS Programmer/Analyst per Truven Health Analytics' Code Review Standard Operating Procedure.

(iii) The statistical methods utilized by the Statistician and the output of all models will be reviewed by the Sr. Statistician in conjunction with the entire project team.

(iv) The statistical methods utilized and the output of the models will be created according to the Statistical Analysis Plan. The document will be modified according to group consensus among Pfizer and Truven Health Analytics. Results will be generated by Truven Health Analytics' Sr. Statistician and reviewed by the entire project team.

(v) All SAS output will initially be reviewed by the SAS Programmer/Analyst for reasonability. Diagnostic and results output will then be reviewed by the entire project team. Additional reports will be run by the SAS programmer, as needed, to ensure validation of SAS output. Finally, a SAS Programmer/Analyst is assigned as the Code Reviewer who also independently reviews program code, logs, and output.

(vi) All SAS log files will be cross referenced to ensure that all patient counts are consistent across file development modules.

(vii) All tables will be generated directly from SAS and output into Excel tables so no manual data entry will be required. As the SAS programming and output will have already been validated as described above, Excel tables will be spot checked against the SAS output to ensure accurate generation of production tables.

Truven Health Analytics certifies that all of the above steps will be taken.

13. STATISTICAL METHODS AND SAMPLE SIZE

13.1 Statistical evaluation – general aspects

13.1.1 Primary groups to be analyzed

The statistical evaluation will involve bivariate/unadjusted, propensity score matched, and multivariable analyses. A total of 6 groups will be subjected to analysis for the primary outcome of hHF, as displayed in Table 3. The same 6 groups will be subjected to analysis for the secondary outcomes of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF. In keeping with the Mini-Sentinel protocol, no multiplicity adjustments will be made for hypothesis testing. In all analyses described below, a $P \leq 0.05$ will be considered the threshold for statistical significance when testing hypotheses.

Table 3. Primary groups and outcomes to be analyzed

Comparison	Stratification	Outcome analyzed					
		hHF	AMI	Stroke	UA	CR	Comp.
DPP-4i vs. SU	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X
Saxagliptin vs. sitagliptin	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X
Saxagliptin vs. linagliptin	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X

Comp. = composite; CR = coronary revascularization; CVD = cardiovascular disease; UA = unstable angina

13.1.2 Bivariate/unadjusted analyses

In the bivariate/unadjusted analyses, all study outcomes, demographic variables, and potential confounder variables will be tabulated in Microsoft Excel tables that are stratified (i.e., column stratifications) by the specific comparator cohorts of interest to each group. Categorical variables will be presented as the count and percentage of patients in each category. Continuous variables will be summarized by providing the means, standard deviations, minimums, maximums, and medians. The outcome events will be summarized by providing number and percent of individuals experiencing the outcome event and the mean, standard deviation, and median values of the time-to outcome event distribution. Additionally, the outcome events will be summarized according to the incidence rate of the outcome, which is calculated by summing the number patients experiencing the outcome in a given cohort and dividing that number by the sum of each patients' time-to the outcome in the cohort.

13.1.3 Propensity score matching

In all comparisons, only patients who initiate on or after the beginning of the comparator's patient selection window will be considered for analysis or matching. The propensity score matching procedure will involve a total of 6 logistic regressions from which propensity score will be estimated, one for each of the 6 groups displayed in Table 3. Each logistic regression's dependent variable will be a binary variable for membership in the DPP-4i or saxagliptin cohort, as appropriate to the comparison. All logistic regressions will use an independent variable specification that is selected *a priori* and includes the demographic variables (Section 11.1), baseline healthcare utilization variables (Section 11.2.2), baseline comorbid condition variables (Section 11.2.3), and baseline medication variables (Section 11.2.4). Regressions fitted among the stratification of patients with prior cardiovascular disease will additionally include the individual cardiovascular variables which the prior cardiovascular disease variable comprises (Section 11.2.1).

From each logistic regression, a predicted probability of the outcome will be retained as the propensity score. Separately for each of the 6 groups, patients from each comparator cohort will be matched to one-another using the nearest neighbour technique and enforcing a caliper of 0.01 (on the probability scale). Patients from the DPP-4i or saxagliptin cohorts who cannot be matched to a comparator will be excluded from subsequent analyses involving the propensity score matched samples.

The discriminative accuracy of the propensity score models will be reported using the area under the receiver operating characteristic curve, also known as the C-statistic. The balance achieved by the propensity score matching will be reported by comparing the post-match distributions of the independent variables included in the propensity score model via the standardized difference, which is a measure of balance that is not sensitive to study sample sizes and therefore less susceptible than t-tests and chi-squared tests to Type I (Type II) error in the presence of large (small) samples.[21] A standardized difference value of less than 10 is considered to be evidence of adequate covariate balance.[22]

13.1.4 Analyses of the primary outcome

The primary analyses of the primary outcome of hHF will be conducted through bivariate Cox proportional hazards models, applied to propensity score matched samples, in which the failure variable is the hHF event variable and the time variable is the time-to hHF variable.[23] For these and all models described below, the Schoenfeld test will be used to assess whether the models' independent variable meets the proportionality assumption of the Cox proportional hazards modeling approach.[24] If evidence of non-proportionality is found, time-segmented Cox regression will be conducted, with the choice of segments informed by visual inspection of Kaplan Meier plots.[25] For these primary analyses, a total of 6 Cox proportional hazards models will be fitted, one for each of the 6 groups displayed in Table 3.

Furthermore, the Kaplan Meier method of survival analysis will be used to visually depict the distribution of time-to hHF. For these primary analyses, a total of 6 Kaplan Meier plots will be created, one for each of the 6 groups displayed in Table 3.

In a sensitivity analysis for only the primary outcome of hHF, multivariable Cox proportional hazards models, adjusting for the independent variables used in the propensity score analyses, will be applied to the cohorts before matching. The variance inflation factor will be used to assess multi-collinearity of the models' independent variables.[26] For these sensitivity analyses, a total of 6 Cox proportional hazards models will be fitted and a total of 6 (unadjusted) Kaplan Meier plots will be created, one for each of the 6 groups displayed in Table 3.

13.1.5 Analyses of the secondary outcomes

Analyses of the secondary outcomes of hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all aforementioned outcomes including hHF will be conducted through bivariate Cox proportional hazards models, applied to propensity score matched samples, in which the failure variable is the given event variable and the time variable is the given time-to event variable.

Furthermore, the Kaplan Meier method of survival analysis will be used to visually depict the distribution of time-to each secondary outcome. For these analyses, a total of 24 Cox proportional hazards models will be fitted and a total of 24 Kaplan Meier plots will be created, one for each secondary outcome by the 6 groups displayed in Table 3.

13.2 Sample size

This study will use all patients who meet the study selection criteria and therefore will not cease 'enrollment' of patients once a certain minimum goal is met. Table 4 displays the number of patients meeting the full study selection criteria.

Table 4. Number of patients meeting study selection criteria

Medication	**N**
Interclass comparison	
SU-naïve DPP-4i	121,492
DPP-4i-naïve SU	194,704
Intra-class comparison	
Saxagliptin	56,452
Sitagliptin	148,233
Linagliptin	12,696

Table 5 displays the minimum required sample sizes to detect a hazard ratio of 1.33 by varying probabilities of censoring. The hazard ratio threshold of 1.33 was chosen based on the Mini-Sentinel protocol, in which it is noted that the sequential analysis plan is designed to have 80% statistical power to detect a relative risk of 1.33 over the surveillance period.

The probabilities of censoring in Table 5 are based upon observed rates of hHF in the SAVOR-TIMI trial (3.5%) and in an observational analysis which included patients treated with DPP-4i conducted by Kim et al. (2014) (3.0% among patients with baseline cardiovascular disease; 0.8% among all patients).[1,10]

We expect that the probability of censoring in the analyses of patients with prior cardiovascular disease will be approximately 97.0%, and will therefore require a total sample size of 12,869 patients. We expect that the probability of censoring in the analyses of patients without prior cardiovascular disease will be approximately 99.5%, and therefore expect to need a total sample size of 77,209 patients. Any analyses with samples that do not meet these pre-specified sample size and power criteria may not be conducted. If a primary (propensity score matched) analysis does not meet the power criteria, the sensitivity analyses associated with that comparison will not be conducted.

Table 5. Minimum required sample sizes to detect a hazard ratio of 1.33 by varying probabilities of censoring

Probability of censoring / % of patients with observed hHF	**Total required sample size**
99.75 (0.25%)	154,417
99.5% (0.5%)	77,209
99.0% (1.0%)	38,605
98.0% (2.0%)	19,303
97.0% (3.0%)	12,869
96.0% (4.0%)	9,652

13.2.1 One-way sensitivity analyses

Table 6 displays the one-way sensitivity analyses that are planned for this study. All one-way sensitivity analyses focus on the primary outcome of hHF and will be conducted on the propensity score matched samples only. All applicable statistical methods and approaches described above will apply to the one-way sensitivity analyses.

The first sensitivity analysis will subset the sample to patients who are age 65 years or older; this analysis will require 6 propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. The rationale for the first sensitivity analysis is that patients who are age 65 years or older are a population of interest due to their greater baseline cardiovascular risk and their coverage by Medicare insurance.

The second sensitivity analysis will allow a gap in days' supply of ≤45 days before triggering cessation of therapy; this sensitivity analysis will require no additional propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. The rationale for the second sensitivity analysis is that under the primary criteria for cessation of therapy, follow-up may be limited due to relatively short periods of non-persistence.

The third sensitivity analysis will extend the period during which hHF is identified to up-to 30 days beyond the last point at which hHF is identified for the primary analysis; this sensitivity analysis will require no additional propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. . The rationale for the third sensitivity analysis is that it is plausible that some patients may be proactively discontinued from therapy if their physician detects symptoms which may be indicative of increased risk for hHF.

The fourth sensitivity analysis will subset the sample to patients who meet criteria which roughly approximate the cardiovascular risk criteria of SAVOR-TIMI 53; this sensitivity analysis will require 6 additional propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. The rationale for the fourth sensitivity analysis is that it is important to examine hHF risks specifically among patients who are similar to those that participated in SAVOR-TIMI 53. Patients who are selected for this analysis must meet one of the following two sets of criteria:

- Age 40+ AND one of the following conditions/procedures during the baseline period: atherosclerosis, AMI, stroke (based on the narrow definition), heart failure, unstable angina, percutaneous coronary intervention, or coronary artery bypass graft
- Age 55+ (male) or 60+ (female) AND one of the following conditions during the baseline period: dyslipidemia, hypertension, or tobacco use disorder

The fifth sensitivity analysis will subset the sample to patients who have no baseline or follow-up use of TZDs; this sensitivity analysis will require 6 additional propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. The rationale for the fifth sensitivity analysis is that TZDs, which increase the risk of heart failure, may be added to

DPP-4i-containing regimens at a greater rate than SUs-containing regimens due to the comparatively lower risks of adverse effects when a TZD is used with a DPP-4i vs. an SU.

The sixth and final sensitivity analysis will subset the sample to patients who have no baseline use of loop diuretics; this sensitivity analysis will require 6 additional propensity score matches, 6 Cox proportional hazards models, and 6 Kaplan Meier plots. The rationale for the sixth sensitivity analysis is that loop diuretics are used in the treatment of heart failure. Excluding patients with baseline use of these medications may result in a lower-risk and potentially more homogenous sample for evaluation of the risk of hHF.

Table 6. One-way sensitivity analyses

Comparison	Stratification	Outcome = hHF					
		Age 65+	45-day gap	30-day extend	SAVOR-TIMI 53	TZD	Loop diuretic
DPP-4i vs. SU	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X
Saxagliptin vs. sitagliptin	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X
Saxagliptin vs. linagliptin	Prior CVD	X	X	X	X	X	X
	No prior CVD	X	X	X	X	X	X

CVD = cardiovascular disease; TZD = Thiazolidinediones

13.3 Interim analyses (if applicable)

Not applicable

14. STRENGTH AND LIMITATIONS

14.1 Strengths

- Administrative claims data are well-suited for measuring the primary outcome of hHF as well as the secondary outcomes.
- This study answers a previously-unaddressed question that is relevant to patients, healthcare providers, and payers.
- Comparators consist only of active comparators of oral antidiabetic medications commonly used as second-line antidiabetic medications.

- During the enrollment and study follow-up windows, heart failure was not considered a risk for any of the treatments being compared, thereby minimizing the risk of confounding specifically related to hHF.

- This study's observational results will reflect the experience of patients with T2DM outside of the limits of a clinical trial environment, thereby presenting insight into everyday clinical practice and experience.

- hHF events in SAVOR occurred relatively early in the 2.5 year study. Although the Mini-Sentinel approach does not adjust for concomitant use of medications during the follow-up period, if the real-world risk of hHF follows the pattern observed in SAVOR, this will mitigate the risk of bias from long-term exposure to medications that are newly-initiated initiated during the follow-up period.

- Rather than focusing on one center or limited population, this study will use a large database representing the experience of hundreds of thousands of patients with T2DM.

- This study will use as its methodological foundation, as closely as possible and appropriate, the approach that is outlined in the Mini-Sentinel protocol for active surveillance of AMI in association with use of anti-diabetic agents. The rationale for this approach is that the Mini-Sentinel protocol was developed by governmental, academic, and commercial stakeholders for the exact purpose of evaluating the risk of a cardiovascular safety event among patients treated with saxagliptin vs. various other antidiabetes medications. Thus, using this approach is likely to be viewed as being valid and unbiased.

- This study's new-user cohort design, with a start to follow-up clearly anchored to medication exposure, is the default methodology recommended by Agency for Healthcare Quality and Research for observational comparative effectiveness research.

- The study databases represent the largest proprietary non-probability administrative claims database available for research in the U.S.

- The study databases comprise a wide variety of health plan types and formularies, thereby being more generalizable than single payer databases, which may have systematic prescribing biases related to saxagliptin or other DPP-4is.

- The study will use validated definitions for its primary and nearly all of its secondary endpoints.

14.2 Limitations

- Administrative claims data are not collected for research purposes and the diagnostic and procedure coding on administrative claims is recorded by physicians

to support reimbursement. Codes on claims may be recorded incorrectly or not recorded at all, thereby potentially introducing measurement error with respect to code-based variables.

- The Medicare Supplemental database includes both the Medicare-paid and supplemental-paid components of reimbursed administrative claims. There are some services that are fully covered by Medicare without need for additional supplemental payments. Such services are not captured in the Medicare Supplemental database but are uncommon and unlikely to systematically bias the study results.

- The administrative claims data that will be used for this study lack some useful clinical information, including severity and duration of T2DM.

- This study is limited to only those individuals with commercial or Medicare supplemental health insurance. Consequently, results of this analysis may not be generalizable to individuals with other insurance such as Medicaid or individuals without health insurance coverage. Furthermore, the patients in the Medicare Supplemental database have supplemental insurance paid for by their current or former employers, and therefore may not be representative of individuals with only primary Medicare coverage and no supplemental insurance coverage.

- Patients who change employers or opt for insurance coverage outside of their employer are lost to follow-up.

- Multivariable adjustment cannot correct for unmeasured confounding.

15. ETHICAL CONSIDERATION

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Epidemiology Practices and applicable regulatory requirements.

16. ADVERSE EVENT REPORTING

A serious adverse event is an AE occurring during any study phase and fulfils one or more of the following criteria:

- results in death

- is immediately life-threatening

- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

16.1 Definition of Adverse Drug Reactions (ADR)

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

All AEs collected will be reported in aggregate in the final study report. No individual or expedited reporting is required.

17. COMMUNICATION PLAN

Study reports and manuscripts should adhere to the STROBE Guidelines (http://www.strobe-statement.org/) and the GRACE principles (http://www.graceprinciples.org/).

We plan to submit study results to a scientific congress and to develop a study manuscript. Authorship will be determined in keeping with the International Committee of Medical Journal Editors authorship guidelines.

18. CHANGES TO THE PROTOCOL

Study procedures will not be changed without the agreement of AstraZeneca RWE sponsors.

Any amendments, new versions, or administrative changes must be approved by AstraZeneca sponsors.

19. APPENDIX CODES AND MEDICATIONS USED FOR MEASUREMENT OF VARIABLES

Table A1: Codes and medications used for selection of study population

Category	Codes/Medications
Dipeptidyl-peptidase 4 inhibitors*	*See table A4 below*
Sulfonylurea	*See Table A4 below*
Type 2 diabetes mellitus	ICD-9-CM Dx: 250.x0, 250.x2
Hospitalization for heart failure	*See Table A2 below*
Pregnancy	ICD-9-CM Px: 72.xx-75.xx ICD-9-CM Dx: 630.xx-648.7x, 648.9x-679.xx, V22.xx-V23.xx, V27.xx, V28.xx, V61.6x-V61.7x, V72.42, V91.xx MS-DRG: 765-770, 774, 775, 777-779 CPT: 57022, 58605, 58611, 59000-59899, 76801-76828, 76941, 83661-83664, S0612, S0613, S2400-S2405, S2409, S2411, S8055, 01965, 01966, 0500F, 0501F, 0503F
Gestational diabetes	ICD-9-CM Dx: 648.8x
Type 1 diabetes mellitus	ICD-9-CM Dx: 250.x1, 250.x3

Note that alogliptin and co-formulations thereof are not used for intra-class comparison

Table A2: Codes used for measurement of outcome variables

Category	Codes
Hospitalization for heart failure	ICD-9-CM Dx: 428.xx
Hospitalization for acute myocardial infarction	ICD-9-CM Dx: 410.xx
Hospitalization for stroke	ICD-9-CM Dx: 430.xx, 431.xx, 433.x1, 434.x1, 436.xx
Hospitalization for unstable angina	ICD-9-CM Dx:411.1x
Coronary revascularization	ICD-9-CM Px: 00.66, 17.55, 36.06, 36.07, 36.1x CPT: 33510-33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, 92980-92984, 92920 92921, 92928, 92929, 92995, 92996, 92924, 92925, 92933, 92934, 92937, 92938, 92941, 92943, 92944 HCPCS: S2205-S2209, G0290, G0291, C9600-C9608

Table A3: Codes used for measurement of prior cardiovascular disease

Category	Codes
Prior AMI	ICD-9-CM Dx: 410.xx
Other ischemic heart disease	ICD-9-CM Dx: 411.xx-414.xx
Other heart disease	ICD-9-CM Dx: 402.01, 402.11, 402.91, 420.xx-429.xx, 440.xx
Stroke (narrow)	ICD-9-CM Dx: 430, 431, 433.x1, 434.x1, 436
Stroke (broad)	ICD-9-CM Dx: 430, 431, 432.xx, 433.xx, 434.xx, 436
PAD	ICD-9-CM Dx: 443.9
Coronary revascularization procedures	*See subcategories*
CABG	ICD-9-CM Px: 36.1x CPT: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, HCPCS: S2205-S2209
PCI	ICD-9-CM Px: 0.66, 17.55, 36.06, 36.07 CPT: 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996 HCPCS: C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608, G0290, G0291
Carotid revascularization procedures	*See subcategories*
Carotid endarterectomy, stenting, angioplasty, or atherectomy	ICD-9-CM Px: 00.61, 00.63, 38.11, 38.12 CPT: 35301, 35390, 37215, 37216
Carotid bypass	ICD-9-CM Px: 39.28 CPT: 35501, 35601
Lower extremity revascularization procedures	*See subcategories*
Lower extremity endarterectomy, stenting, angioplasty, or atherectomy	ICD9-CM: 17.56, 38.18, 39.50, 39.90 CPT: 35302, 35303, 35304, 35305, 35306, 35351, 35355, 35361, 35363, 35371, 35372, 35454, 35456, 35458, 35459, 35460, 35470, 35473, 35474, 35475, 35476, 35482, 35483, 35484, 35485, 35492, 35493, 35494, 35495, 37205, 37206, 37207, 37208, 37220, 37221, 37222, 37223, 37224, 37225, 37226, 37227, 37228, 37229, 37230, 37231, 37232, 37233, 37234,

	37235, 0237T, 0238T
Lower extremity bypass	ICD-9-CM Px: 39.25, 39.29 CPT: 34520, 34530, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35683, 35879
Lower extremity amputation	ICD-9-CM Px: 84.1x CPT: 27290, 27295, 27590, 27591, 27592, 27596, 27598, 27880, 27881, 27882, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825

Table A4: Codes and medications used for measurement of other effect modifiers and potential confounders

Category	**Codes/Medications**
Lab Tests Ordered	*See subcategories*
BUN	CPT: 80047, 80048, 80053, 80069, 84520, 84525, 84540 , 84545
Creatinine	CPT: 80047, 80048, 80053, 80069, 82565, 82570, 82575
HbA1c	CPT: 83036, 83037
Asthma	ICD-9-CM Dx: 493.xx
Cancer (excluding non-melanoma skin cancer)	ICD-9-CM Dx: 140.xx-172.xx, 174.xx-209.3x, 209.7x
Chronic Kidney Disease (excluding End Stage Renal Disease)	ICD-9-CM Dx: 585.1-585.4 HCPCS: G0420, G0421
Chronic Obstructive Pulmonary Disease	ICD-9-CM Dx: 491.xx, 492.xx, 496
Dementia	ICD-9-CM Dx: 290.0 , 290.1x, 290.2x, 290.3, 290.4x, 290.8, 290.9, 291.2, 292.82, 294.0, 294.1x, 294.2x, 294.8, 331.0 , 331.1x, 331.2, 331.7, 331.8x, 331.9, 797
Depression	ICD-9-CM Dx: 296.2x, 296.3x, 300.4, 311
ESRD	ICD-9-CM Px: 38.95, 39.27, 39.42, 39.95, 54.98, 55.52, 55.53, 55.54, 55.69, ICD-9-CM Dx: 285.21, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 458.21, 584.5, 584.6, 584.7, 584.8, 584.9, 585.5, 585.6, 586, 792.5, 996.56, 996.68, 996.73, 996.81, V42.0, V45.1x, V56.xx,

	E879.1, CPT: 36145, 36800–36815, 36825–36833, 50340, 50370, 76776, 76778, 90918–90999, 93990, 99512, 0505F, 0507F, 4052F, 4053F, 4054F, 4055F HCPCS: A4690, E1510, E1590, E1592, E1594, E1630, E1632, E1635, G0257, G0320, G0321, G0322, G0323, G0324, G0325, G0326, G0327, G8075, G8076, G8081, G8082, G8085, G8488, J0636, J0881, J0882, J0885, J0886, Q4054, Q4055, S9335, S9339 UB-04: 0304, 0367, 080x, 082x, 083x, 084x, 085x, 086x, 087x, 088x
Fracture	ICD-9-CM Dx: 733.1, 733.93-733.98, 805.xx-807.4x, 808.xx-825.xx, 827.xx, V54.13, V54.23 ICD-9CM Px: 79.01,79.02, 79.05, 79.06, 79.11, 79.12, 79.15, 79.16, 79.21, 79.22, 79.25, 79.26, 79.31, 79.32, 79.35, 79.36, 79.61, 79.62, 79.65, 79.6, 81.65, 81.66
Human immunodeficiency virus/acquired immune deficiency syndrome	ICD-9-CM Dx: 042, 043, 044, 795.71, V08, 079.53
Hyperlipidemia or lipid disorder	ICD-9-CM Dx: 272.0-272.2, 272.4
Hypertension	ICD-9-CM Dx: 401.xx, 402.00, 402.1, 402.10, 402.90, 403.xx-405.xx
Hypoglycemia	ICD-9-CM Dx: 250.8x, 251.0-251.2
Liver disease	ICD-9-CM Dx: 570, 571.xx, 572.xx, 573.xx
Microvascular complications of diabetes	*See subcategories*
Nephropathy	ICD-9-CM Dx: 250.4x
Retinopathy	ICD-9-CM Dx: 250.5x, 362.0x
Peripheral neuropathy	ICD-9-CM Dx: 250.6x, 337.1, 354.xx, 355.xx, 357.2
Obesity (or weight gain)	ICD-9-CM Dx: 278.0x, 793.91, V85.3x, V85.4x, 783.1
Osteoporosis	ICD-9-CM Dx: 733.0x
Tobacco use	ICD-9-CM Dx: 305.1, V15.82
Andiabetes medications	*See subcategories*
Alpha-glucosidase inhibitors	Acarbose, Miglitol
Amylin analogs	Pramlintide Acetate
Biguanides (metformin)	Metformin Hcl
DPP-4 inhibitors	Alogliptin Benzoate, Linagliptin, Saxagliptin Hcl, Sitagliptin Phosphate
GLP-1 RAs	Exenatide, Liraglutide
Insulin	*See subcategories*

Long-acting and combination	Insulin Aspart Protamine Human/Insulin Aspart, Insulin Detemir, Insulin Glargine, Human Recombinant Analog, Insulin Lispro Protamine & Insulin Lispro, Insulin Nph Human Semi-Syn, Insulin Nph Human Semi-Syn/Insulin Reg Human Semi-Syn, Insulin Zinc Extend Human Rec, Insulin Zinc Human Rec, Insulin Zinc Human Semi-Syn, Nph, Human Insulin Isophane, Nph, Human Insulin Isophane/Insulin Regular, Human
Short-acting	Insulin Aspart, Insulin Glulisine, Insulin Lispro, Insulin Reg Human Semi-Syn, Insulin Reg, Hum S-S Buff, Insulin Regular, Human, Insulin Regular, Human/Insulin Release Unit, Insulin Regular, Human/Insulin Release Unit/Chamber/Inhaler, Insulin Regular,Human Buffered
Meglitinides	Nateglinide, Repaglinide
SGLT2 inhibitors	Canagliflozin, Dapagliflozin Propanediol, Empagliflozin
Sulfonylureas	Acetohexamide, Chlorpropamide, Glimepiride, Glipizide, Glyburide, Nateglinide, Repaglinide, Tolazamide, Tolbutamide
Thiazolidinedioines	Pioglitazone Hcl, Rosiglitazone Maleate, Troglitazone
Antihypertensive medications	*See subcategories*
ACE inhibitors	Benazepril Hcl, Captopril, Enalapril Maleate, Fosinopril Sodium, Lisinopril, Moexipril Hcl, Perindopril Erbumine, Quinapril Hcl, Ramipril, Trandolapril
Alpha-blockers	Doxazosin Mesylate, Phenoxybenzamine Hcl, Prazosin Hcl, Terazosin Hcl
ARBs	Azilsartan Medoxomil, Candesartan Cilexetil, Eprosartan Mesylate, Irbesartan, Losartan Potassium, Olmesartan Medoxomil, Telmisartan, Valsartan
Beta-blockers	Acebutolol Hcl, Atenolol, Betaxolol Hcl, Bisoprolol Fumarate, Carteolol Hcl, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Nebivolol Hcl, Penbutolol Sulfate, Pindolol, Propranolol Hcl, Timolol Maleate
CCBs	Amlodipine Besylate, Diltiazem Hcl, Diltiazem Malate, Felodipine, Isradipine, Mibefradil Di-Hcl, Nicardipine Hcl, Nifedipine, Nimodipine, Nisoldipine, Verapamil Hcl
Direct Vasodilators	Hydralazine Hcl, Isosorbide Dinitrate/Hydralazine Hcl, Minoxidil
Direct Renin Inhibitors	Aliskiren Hemifumarate
Diuretics	*See subcategories*

Aldosterone antagonists	Eplerenone, Spironolactone
Loop diuretics	Bumetanide, Ethacrynic Acid, Furosemide, Torsemide
Potassium sparing diuretics	Amiloride Hcl, Triamterene
Thiazide diuretics	Bendroflumethiazide, Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Hydroflumethiazide, Indapamide, Methyclothiazide, Metolazone, Polythiazide, Trichlormethiazide
Lipid lowering medications	Amlodipine Besylate/Atorvastatin Calcium, Aspirin (Calcium Carb & Magnesium Buffers)/Pravastatin, Atorvastatin Calcium, Cerivastatin Sodium, Cholestyramine (With Sugar), Cholestyramine/Aspartame, Clofibrate, Colesevelam Hcl, Colestipol Hcl, Dextrothyroxine Sodium, Docosahexanoic Acid/Eicosapentaenoic Acid, Ezetimibe, Ezetimibe/Atorvastatin Calcium, Ezetimibe/Simvastatin, Fenofibrate, Fenofibrate Nanocrystallized, Fenofibrate,Micronized, Fenofibric Acid, Fenofibric Acid (Choline), Fish Oil/Omega-3 Fatty Acids/Dl-Vit E/Folic Acid/B6-B12, Fluvastatin Sodium, Gemfibrozil, Icosapent Ethyl, Inositol/Choline/Multivitamin, Lomitapide Mesylate, Lovastatin, Methionine/Inositol/Choline/Folic Acid, Mipomersen Sodium, Niacin, Niacin/Lovastatin, Niacin/Simvastatin, Omega-3 Acid Ethyl Esters, Omega-3 Fatty Acids/Dha/Epa/Other Omega-3S/Fish Oil, Omega-3/Dha/Epa/Marine Phospholipids/Astaxanthin/Krill Oil, Phytosterol/Omega-3 Fatty Acids/Dha/Epa/Fish Oil, Pitavastatin Calcium, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin
Digoxin (cardiac glycoside)	Digoxin
Anticoagulants	Anisindione, Apixaban, Dabigatran Etexilate Mesylate, Dicumarol, Rivaroxaban, Warfarin Sodium
Anti-platelets	Anagrelide Hcl, Aspirin/Dipyridamole, Cilostazol, Clopidogrel Bisulfate, Dipyridamole, Prasugrel Hcl, Ticagrelor, Ticlopidine Hcl, Vorapaxar Sulfate
Opioids	Acetaminophen With Codeine Phosphate, Aspirin/Codeine Phosphate, Buprenorphine, Butalbital/Acetaminophen/Caffeine/Codeine Phosphate, Butorphanol Tartrate, Codeine Phosphate, Codeine Phosphate/Butalbital/Aspirin/Caffeine, Codeine Phosphate/Carisoprodol/Aspirin, Codeine Sulfate, Codeine/Aspirin/Salicylamide/Acetaminophen/Caffeine, Dihydrocodeine Bitartrate/Acetaminophen/Caffeine, Dihydrocodeine Bitartrate/Aspirin/Caffeine,

	Dihydrocodeine/Aspirin/Caffeine, Fentanyl, Fentanyl Citrate, Hydrocodone Bitartrate, Hydrocodone Bitartrate/Acetaminophen, Hydrocodone Bitartrate/Acetaminophen/Dietary Supplement #11, Hydrocodone Bitartrate/Aspirin, Hydrocodone/Ibuprofen, Hydromorphone Hcl, Ibuprofen/Oxycodone Hcl, Levomethadyl Acetate Hcl, Levorphanol Tartrate, Meperidine Hcl, Meperidine Hcl/Promethazine Hcl, Methadone Hcl, Morphine Sulfate, Morphine Sulfate/Naltrexone Hcl, Oxycodone Hcl, Oxycodone Hcl/Acetaminophen, Oxycodone Hcl/Aspirin, Oxycodone Hcl/Oxycodone Terephthalate/Aspirin, Oxycodone/Aspirin, Oxymorphone Hcl, Pentazocine Hcl/Acetaminophen, Pentazocine Hcl/Aspirin, Pentazocine Hcl/Naloxone Hcl, Propoxyphene Hcl, Propoxyphene Hcl/Acetaminophen, Propoxyphene Hcl/Aspirin/Caffeine, Propoxyphene Napsylate, Propoxyphene Napsylate/Acetaminophen, Tapentadol Hcl, Tramadol Hcl, Tramadol Hcl/Acetaminophen, Tramadol Hcl/Dietary Supplement,Misc. Cb.11, Tramadol Hcl/Glucosamine Sulfate
Oral corticosteroids	Betamethasone, Cortisone Acetate, Dexamethasone, Fludrocortisone Acetate, Hydrocortisone, Hydrocortisone Cypionate, Methylprednisolone, Prednisolone, Prednisolone Acetate, Prednisolone Sod Phosphate, Prednisolone Sodium Phosphate/Peak Flow Meter, Prednisone, Triamcinolone, Triamcinolone Diacetate

20. REFERENCES

[1] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R,Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013 Oct 3;369(14):1317-26.

[2] White WB, Bakris GL, Bergenstal RM, Cannon CP, Cushman WC, Fleck P, Heller S, Mehta C, Nissen SE, Perez A, Wilson C, Zannad F. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011 Oct;162(4):620-626.e1.

[3] Zannad F, Cannon C, Cushman W, et al. Alogliptin in Patients With Type 2 Diabetes After Acute Coronary Syndromes: Heart Failure Outcomes and Cardiovascular Safety in Heart Failure Patients. J Am Coll Cardiol. 2014;63(12_S).

[4] Sitagliptin Cardiovascular Outcome Study (MK-0431-082) (TECOS). ClinicalTrials.gov Identifier: NCT00790205

[5] CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. ClinicalTrials.gov Identifier: NCT01243424

[6] Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA). ClinicalTrials.gov Identifier: NCT01897532

[7] Chen D, Wang S, Mao C, Tsai M, Lin Y, Chou C, Wen M, Wang C, Hsieh I, Hung K, Chen T. Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and AMI: A nationwide cohort study. Int J Cardiol. 2014 Dec 3;181C:200-206. doi: 10.1016/j.ijcard.2014.12.029. [Epub ahead of print]

[8] Clifton P. Do Dipeptidyl Peptidase IV (DPP-IV) Inhibitors Cause Heart Failure? Clin Ther. 2014 Dec 1;36(12):2072-9. doi: 10.1016/j.clinthera.2014.10.009. Epub 2014 Nov 13.

[9] Yu OH, Filion KB, Azoulay L, Patenaude V, Majdan A, Suissa S. Incretin-Based Drugs and the Risk of Congestive Heart Failure. Diabetes Care. 2014 Sep 9. pii: DC_141459. [Epub ahead of print]

[10] Kim SC, Glynn RJ, Liu J, Everett BM, Goldfine AB. Dipeptidyl peptidase-4 inhibitors do not increase the risk of cardiovascular events in type 2 diabetes: a cohort study. Acta Diabetol. 2014 Dec;51(6):1015-23. doi: 10.1007/s00592-014-0663-2. Epub 2014 Oct 14.

[11] Scheller NM, Mogensen UM, Andersson C, Vaag A, Torp-Pedersen C. All-cause mortality and cardiovascular effects associated with the DPP-IV inhibitor sitagliptin compared with metformin, a retrospective cohort study on the Danish population. Diabetes Obes Metab. 2014 Mar;16(3):231-6. doi: 10.1111/dom.12197. Epub 2013 Sep 10.

[12] Velez M, Peterson EL, Wells K, Swadia T, Sabbah HN, Williams LK, Lanfear DE. Association of antidiabetic medications targeting the glucagon-like Peptide 1 pathway and heart failure events in patients with diabetes. J Card Fail. 2015 Jan;21(1):2-8. doi: 10.1016/j.cardfail.2014.10.012. Epub 2014 Oct 28.

[13] Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen SJ, Yeh CM, Chen TJ, Lin SJ, Chiang CE. Sitagliptin and the risk of hospitalization for heart failure: A population-based study. Int J Cardiol. 2014 Nov 15;177(1):86-90. doi: 10.1016/j.ijcard.2014.09.038. Epub 2014 Sep 28.

[14] Weir DL, McAlister FA, Senthilselvan A, Minhas-Sandhu JK, Eurich DT. Sitagliptin use in patients with diabetes and heart failure: a population-based retrospective cohort study. JACC Heart Fail. 2014 Dec;2(6):573-82. doi: 10.1016/j.jchf.2014.04.005. Epub 2014 Jul 2.

[15] Selby J, et al. A protocol for active surveillance of AMI in association with use of anti-diabetic agents. Available at: http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_AMI-and-Anti-Diabetic-Agents_Protocol.pdf.

[16] Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care. 2014 May;37(5):1367-74.

[17] Lee DS, Donovan L, Austin PC, et al. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care* 2005; 43(2): 182–8.

[18] Metcalfe A, Neudam A, Forde S, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in-hospital mortality rates. Health Serv Res. 2013 Feb;48(1):290–318.

[19] Roumie CL, Mitchel E, Gideon PS, et al. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf. 2008 Jan;17(1):20-6.

[20] Varas-Lorenzo C, Castellsague J, Stang MR, et al. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. Pharmacoepidemiol Drug Saf. 2008 Aug;17(8):842-52.

[21] D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; 17(19): 2265–81.

[22] D'Agostino, R.B. Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998; 17: 2265–2281.

[23] Cox DR. Regression models and life tables. J R Stat Soc B. 1972;34:187-220.

[24] Hosmer DW, Lemeshow S, May S. Applied Survival Analysis: Regression Modeling of Time to Event Data, 2nd ed. Wiley, 2008.

[25] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc.1958; 53:457-81.

[26] Greene, WH. Econometric Analysis, 4th ed. Prentic-Hall, Upper Saddle River, New Jersey, 2000.