REDACTED PROTOCOL

Title	A Cohort Study to Assess Various Safety Outcomes of Interest in Users of Aliskiren Using Claims Data
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Marketing authorization holder	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
Joint PASS	No
Research question and objectives	With this non-interventional study we would like to assess whether under real-world conditions [redacted] The study objectives are as follows: Primary: [redacted] Secondary: [redacted].
Country of study	USA
Author	[redacted]

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1 Table of contents

List of tables and figures

2 List of abbreviations

AB	Alpha Blockers
ACEI	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AES	Advanced Encryption Standard
ALTITUDE	Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints
ARB	Angiotensin Receptor Blocker
ARF	Acute Renal Failure
BB	Beta Blocker
CCB	Calcium Channel Blocker
CI	Confidence Interval
CPT	Current Procedural Terminology
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DRG	Diagnosis-Related Group
Dx	Diagnosis
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESRD	End Stage Renal Disease
EU PAS	European Union Post-Authorization Studies
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
hdPS	High-Dimensional Propensity Score
HF	Heart Failure
HR	Hazard Ratio
HTN	Hypertension
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IR	Incidence Rate
IRB	Institutional Review Board
ITT	Intent-to-treat

MAH	Marketing Authorization Holder
MI	Myocardial Infarction
NDC	National Drug Code
NIS	Non-interventional Study
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PASS	Post-Authorization Safety Study
PPV	Positive Predictive Value
PY	Person-Year
RAAS	Renin-angiotensin-aldosterone System
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TIA	Transient Ischemic Attack
US	United States

3 Responsible parties

Principal Investigator (PI):

Author:

Marketing authorization contact:

4 Abstract

Title: A Cohort Study to Assess Various Safety Outcomes of Interest in Users of Aliskiren Using Claims Data

Rationale and background: The 'Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints (ALTITUDE)', a randomized trial to assess cardiovascular and renal morbidity and mortality among patients with type 2 diabetes mellitus (T2DM) at high risk for cardiovascular and renal events treated with aliskiren, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) included approximately 8,600 patients. An interim analysis from this study indicated a higher incidence of serious adverse events of renal concern (creatinine >50% increase), cerebrovascular accidents, hyperkalemia, hypotension, falls, and deaths among patients treated with aliskiren.

Based on the interim analysis, the European Medicines Agency (EMA) requested from Novartis to develop "an epidemiological study to further investigate the signal of harm for aliskiren from the ALTITUDE study, particularly concentrating on outcomes when aliskiren is used in combination with either ACEI or an ARB".

Research question and objectives:

This non-interventional study aims to assess whether under real-world conditions [redacted] The study objectives are as follows:

Primary:

[redacted]

Secondary: [redacted].

Study design: This will be a retrospective cohort study conducted within two U.S.-based healthcare claims databases.

The study will identify contemporaneous cohorts of aliskiren and other antihypertensive medication users within the databases and identify outcomes that occur during the follow-up of the cohorts. Comparisons of outcomes among aliskiren users to those among other antihypertensive medication users will be the focus of analyses that will involve control for confounding through propensity scores and several pre-specified subgroup analyses and pre-specified exposure measures, including intent-to-treat, as-treated, and cumulative dose analyses. All analyses will be conducted in parallel in each data source, providing separate estimates of the association between aliskiren and each outcome within each of the data sources, and combined if appropriate, based on homogeneity of treatment effect.

Population: The population is derived from two US health claims databases (see Data sources).

Patients will have a first-time dispensing of aliskiren (aliskiren cohort) or another antihypertensive drug (comparison cohort) between 1 March 2007 and 31 December 2011 (or latest available). They must have been continuously enrolled for at least 6 months prior to the first prescription for aliskiren or other antihypertensive drug, be at least 18 years old, have valid data for age and sex, and have a diagnosis code for HTN at baseline.

The primary exposure will be aliskiren both as monotherapy (with no other antihypertensive agents) as well as aliskiren dosed with other antihypertensives (ACEIs, ARBs, calcium channel blockers [CCBs], diuretics, or beta-blockers both as free- or fixed-dose combination) in patients with documented hypertension at baseline. A specific group of interest will be patients with treatment regimes consisting of concomitant exposure to aliskiren and an ACEI, ARB, or CCB, compared against patients with treatment regimes containing non-aliskiren antihypertensive drugs combined with an ACEI, ARB, or CCB.

In secondary analyses, we will loosen the requirement of documented HTN diagnosis at baseline and will include patients with or without recorded HTN.

Data sources: The two data sources involve both commercial and Medicare claims.

1) US MarketScan®: This data source is derived from health insurer transactions (claims) involving more than 25 million lives annually. The database includes both inpatient and outpatient diagnoses, along with standard pharmacy and mail order prescription records.

The number of aliskiren users 18 years or older with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) in MarketScan-Medicare from 2007 to April 2012 was a total of 75,853 users, of which 22,617 were > 65 years of age. This corresponds to approximately 25% of the overall aliskiren users 18 years of age or older. This is markedly lower than the ~50% seen in ALTITUDE, likely reflecting the age structure of in this commercial US health claims database with under-representation of people above 65 years.

2) UnitedHealth Research Database: This data source is derived from patients with United Healthcare insurance, with approximately 14 million members annually (4%-5% of US population). Claims are coded in a similar manner to the MarketScan® data.

In the United data (18 years or older, 6 months continuous enrollment prior to use), there were a total of 19,685 aliskiren users, of whom 3,276 (16.6%) were > 65 years of age.

Study size: This study will involve two separate databases, and the numbers may be combined in a pooled analysis if appropriate, based on homogeneity of treatment effect. Combining the MarketScan and UnitedHealth data will provide approximately 95,000 aliskiren users, of whom 25,000 are age 65 or older, and approximately 5,000 are expected to match the characteristics of the ALTITUDE population. The duration of follow-up among these groups will vary by analysis, and all power projections assume an average follow-up of 6 months.

The full aliskiren population of 95,000 will include some patients who may not enter into analyses due to exclusion criteria or propensity score matching. If 70% are included in the study, then there will be ~67,000 aliskiren users in analyses, and they will contribute close to 34,000 person-years [PY] of aliskiren exposure. This study size will provide approximately 90% power to detect a relative risk of 1.30 for an infrequently-occurring outcome such as MI (expected incidence 5/1000 PY), and considerably higher power for more frequently occurring outcomes. If a similar 70% of patients older than 65 years are included in study analyses, there will be

17,500 aliskiren users, and they will contribute close to 9,000 PY of aliskiren exposure so that there will be close to 80% power to detect a relative risk of 1.50 for MI among this subgroup.

Data analysis: Analyses will be conducted with exposure defined on an intent-to-treat basis (exposure at cohort entry carried forward) and also on an as-treated basis (exposure status updates during follow-up). In addition, analyses based on duration of follow-up (in 6 month blocks) and cumulative dose will be conducted.

The primary safety outcomes include treatment emergent:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The secondary safety endpoints of interest include treatment emergent:

- [redacted]
- [redacted]
- [redacted]

We will seek to address confounding through the development and use of a propensity score that will incorporate numerous patient characteristics. Balance in patient characteristics will be obtained through matching of the cohorts with respect to this propensity score. And effect modification will be assessed.

Measures and Statistical methods

We will identify the first occurrence of each of the specified outcomes and tabulate the results. We will develop incidence rates (counts of first events divided by person-time) along with 95% confidence intervals (CIs). The relative risk (expressed as a hazard ratio [HR]) with 95% CIs will be estimated among users of aliskiren relative to non-users of aliskiren using Cox regression models. Since the Cox regression will be conducted within the propensity score matched cohorts, potential channeling and confounding will be largely mitigated through the matching.

Subgroup analyses will be conducted in the following sub-populations:

- Patients with recorded DM at baseline
- Patients with recorded renal impairment at baseline
- Patients with recorded DM and renal impairment at baseline [the ALTITUDE-like population will be formed by limiting this subgroup to patients with T2DM and renal impairment at baseline]
- Patients with recorded pre-existing cardiovascular disease

Analyses will also be stratified by subgroups of age (stratification at 65 yrs), sex, and propensity to receive aliskiren.

Milestones:

Table 1 Milestones planned dates

Milestone	Planned Date
Start of data collection (extraction)	15 February 2013
End of data collection (analytic dataset available)	30 June 2013
Registration in the EU PAS register	01 March 2013
Final report of study results	30 November 2013

5 Amendments and updates

None

6 Milestones

Milestone	Planned date
Start of data collection (extraction)	15 February 2013
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Registration in the EU PAS register	01 March 2013
Final report of study results	30 November 2013

7 Rationale and background

Aliskiren is the first known representative of a new class of non-peptide orally active renin inhibitors that blocks the renin-angiotensin-aldosterone-system (RAAS) at its rate-limiting step. It induces a net reduction in plasma renin activity, angiotensin II and aldosterone levels. Aliskiren is effective in reducing blood pressure and overall is well tolerated. The incidence of adverse events and the number of study discontinuations as a result of adverse events during aliskiren treatment were relatively low and generally similar to placebo.[1] Aliskiren (Rasilez®, Tekturna®) was first registered for hypertension in the United States (US) in March 2007 and was approved in the European Union in August 2007.

The 'Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints' (ALTITUDE) was a randomized, double-blind, placebo-controlled, parallel-group study to determine whether in patients with type 2 diabetes mellitus (T2DM) at high risk for cardiovascular and renal events, aliskiren, on top of conventional treatment – including either an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) – reduces cardiovascular and renal morbidity and mortality. The primary endpoint was the first event of the following composite primary endpoint: cardiovascular death, resuscitated sudden death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, onset of end-stage renal disease or renal death (death attributable to kidney failure, need for renal replacement therapy with no dialysis or transplantation available or applied) or doubling of baseline serum creatinine.

Key inclusion criteria were: T2DM, > 35 years of age with at least one of the following (i) macroalbuminuria and estimated glomerular filtration rate (eGFR) >30 ml/min; (ii) microalbuminuria and eGFR >30 ml/min and <60 ml/min; (iii) cardiovascular disease history (previous myocardial infarction, stroke, hospitalization for heart failure, documented coronary artery disease and eGFR >30 ml/min and <60 ml/min).[2]

The study included approximately 8,600 patients (mean age of 65 years, 68% male, and 56.6% Caucasians; other anti-hypertensive drugs used with aliskiren: ACEI 44%, ARB 56%, calcium channel blocker 61%, β-blocker 50%, loop/thiazide diuretics 63%); an interim analysis was performed with 1,123 adjudicated primary events.

Following the results of this interim analysis, the data monitoring committee (DMC) identified the following points of concerns:

- Excess in serious adverse events (SAEs) of

- Renal concern
- Cerebrovascular accidents
- Hyperkalemia
- Hypotension
- Fall

- More deaths in aliskiren group
- Excess of creatinine >50% increase

Based on the results from the ALTITUDE interim analysis, the European Medicines Agency (EMA) asked Novartis to "propose an outline for an epidemiological study to further investigate the signal of harm for aliskiren from the ALTITUDE study, particularly concentrating on outcomes when aliskiren is used in combination with either ACEI or an ARB".

8 Research questions and objectives

This non-interventional study aims to assess [redacted]. The study objectives are as follows:

8.1 Primary objectives

[redacted]

8.2 Secondary objectives

[redacted]

9 Research methods

9.1 Study design

This will be a retrospective cohort study conducted within two U.S.-based longitudinal healthcare claims databases (i.e. MarketScan® and UnitedHealth Research Database, see also Section 9.4. for more details). This design will provide direct estimates of risk (as incidence) for study outcomes, facilitates comparison across exposure groups along with adjustment through propensity score techniques, and permits straight-forward subgroup analyses, all of which are of interest in this study.

The study will identify contemporaneous cohorts of aliskiren and other antihypertensive medication initiators within the databases and identify outcomes that occur during the follow-up of the cohorts. Comparisons of outcomes among aliskiren users to those among other antihypertensive medication users will be the focus of analyses that will involve control for confounding through propensity scores and several pre-specified subgroup analyses and pre-specified exposure measures, including intent-to-treat, as-treated, and cumulative dose analyses. All analyses will be conducted in parallel in each data source, providing separate estimates of the association between aliskiren and each outcome within each of the data sources. The numbers may be combined in a pooled analysis if appropriate, based on homogeneity of treatment effect (see Section 9.2)

9.2 Setting

We will select a study population from two U.S. data sources: (1) US MarketScan® Commercial Claims and Encounters database and Medicare Supplement provided by Novartis and (2) UnitedHealth Research Database provided by Brigham and Women's Hospital as patients who have a first-time recorded dispensing between 1 March 2007 and 31 December 2011 (or latest available from each data source) for aliskiren (aliskiren cohort) or another antihypertensive drug (comparison cohort; see Annex 3.3 for the list of drugs).

The population will be members of the data sources (derived from residents of the U.S.) between March 2007 and December 2011. We will initially select cohorts and perform all analyses separately within each database and check for heterogeneity of effect across data sources. Heterogeneity will be assessed by comparing the treatment effect point estimates across data sources. Assessment of heterogeneity will not rely on a statistical test of heterogeneity, since the large study size may indicate significant heterogeneity ($p<0.05$) even if not clinically meaningful and this assessment of heterogeneity is intended only for determining whether it is reasonable to combine data sources. It is expected that there is no heterogeneity of treatment effects as the databases are very comparable with regard to patient composition and information content. If appropriate, this study will involve a combined analysis that pools data from both databases. This pooled analysis will be identical to those described within each database, except that an indicator of the database will be added as an additional pre-defined covariate for adjustment.

9.2.1 Inclusion criteria

Patients are required to

- Have at least one prescription for aliskiren or another antihypertensive drug
- Have at least 6 months of continuous enrollment prior to (and inclusive of the date of) the first prescription for aliskiren or another antihypertensive drug (to form the baseline period)
- Be at least 18 years old at the time of the first prescription for aliskiren or other antihypertensive drug
- Have valid data for age and sex
- Have at least one inpatient or outpatient ICD-9 diagnosis code of hypertension (401.xx - 405.xx) during the baseline period

9.2.2 Exclusion criteria

Patients not meeting inclusion criteria will be excluded and no separate exclusion criteria will be applied. A CONSORT-like patient flow diagram will be produced.[3]

9.3 Variables

9.3.1 Exposure

There will be 3 cohorts formed from the eligible study population. Primary analyses will include patients with a diagnosis code of hypertension (HTN) during the baseline period while secondary analyses will include patients with or without HTN diagnosis. For all cohorts, the index exposure and index date will be defined based on the first prescription for an antihypertensive drug of interest (aliskiren or a comparator) such that there are no prescriptions for an antihypertensive of the same type in the 6 months prior (but there may be prescriptions for other antihypertensives during this period).

I. ***Any new use of aliskiren***. This cohort will include all patients initiating aliskiren or another antihypertensive for any indication. The comparison will be between initiation of any exposure to aliskiren, including aliskiren as monotherapy (with no other antihypertensive agents) as well as aliskiren dosed with other antihypertensives (including ACEIs, ARBs, and CCBs both as free- or fixed-dose combination). Patients from cohort I and II will also be included in this cohort. The comparator exposure will be initiation of another antihypertensive, including monotherapy as well as concomitant therapy of two or more antihypertensives.

II. ***Any new use of aliskiren as add-on to ACEI or ARB***. This cohort will consist of patients initiating aliskiren for any indication in addition to ACEI/ARB compared to patients initiating another antihypertensive drug in addition to ACEI/ARB. Addition of an antihypertensive drug (dual/concomitant therapy) will be defined as initiation of dual therapy with ACEI/ARB on the index date (both as free- or fixed-dose combination) or a prior prescription for ACEI/ARB that extends beyond the index date.

III. ***Any new use of aliskiren as add-on to calcium channel blockers (CCB)***. This cohort will consist of patients initiating aliskiren for any indication in addition to CCB compared to patients initiating any other antihypertensive in addition to CCB. Addition will be defined as initiation of dual therapy with CCB on the index date (both as free-or fixed-dose combination) or a prior prescription for CCB that extends beyond the index date.

Figure 1 illustrates the 3 study cohorts.

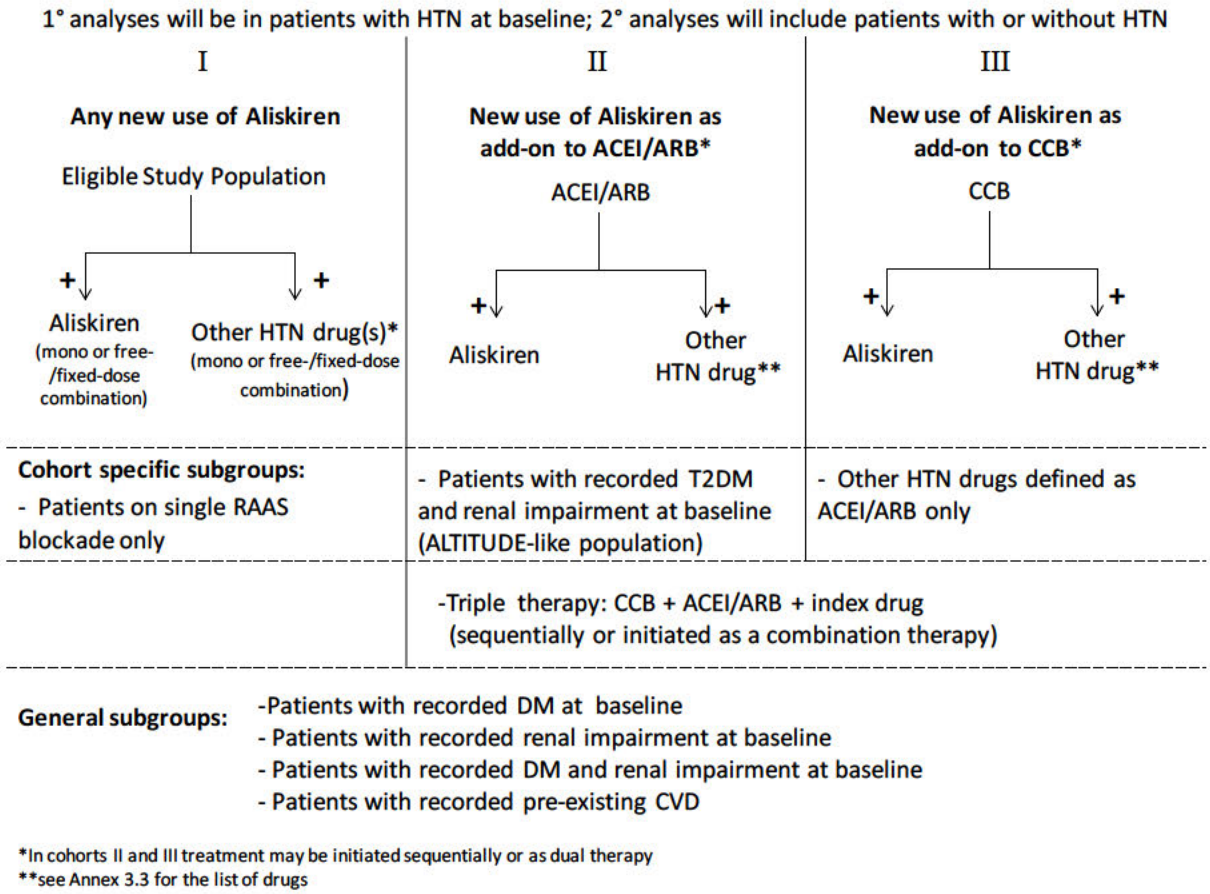

Figure 1 **Three aliskiren exposure groups and comparison groups in the cohort study**

9.3.1.1 Subgroups

The following sub-populations will be considered in all three cohorts. These subgroup variables identify the potential effect modifiers that will be considered.

- Patients with recorded DM at baseline
- Patients with recorded renal impairment at baseline
- Patients with recorded DM and renal impairment at baseline
- Patients with recorded pre-existing cardiovascular disease, defined as MI, angina, ischemic heart disease, pericarditis, endocarditis, myocarditis, and other diseases of either pericardium or endocardium (excluding rheumatic), cardiomyopathy, conduction disorders and cardiac dysrhythmias, and heart failure (for codes, see Annex 3.4).

In addition,

- For cohort I (any new use of aliskiren), we will form a subset of patients on single RAAS blockade therapy by excluding patients on double RAAS blockade (any combination of aliskiren, ACEI, or ARB)
- For cohort II (new use of aliskiren as an add-on to ACEI/ARB), a subset with a baseline diagnosis of T2DM and renal impairment will form the "ALTITUDE-like" population
- For cohort III (new use of aliskiren as an add-on to CCB), we will also look into comparing patients initiating aliskiren with patients initiating ACEI/ARB as a subgroup of other HTN drug

- For cohorts II and III, a subset of patients on triple therapy ACEI/ARB + CCB + index exposure drug (either aliskiren or a comparator antihypertensive) will form the triple therapy subgroup. These therapies can be initiated either sequentially or at the same time; however, the therapies initiated prior to the index date have to have days' supply spanning the index date

9.3.1.2 Follow-up

Patients will be followed up from the day after the index date (index date defined by the date of the first dispensing for aliskiren or the comparison antihypertensive drug until the first occurrence of the outcome of interest, disenrollment from the database, or the end of the study period will be reached (i.e. 31 December 2011 or latest available data), whichever comes first. For the as-treated analysis, an additional end of follow-up will occur with discontinuation of the drug exposure at cohort entry. Patients will not be censored at the occurrence of other outcome events besides the outcome of interest; for example, in the analysis of ESRD, patients will not be censored for stroke, TIA, MI, etc.

9.3.2 Outcomes

The primary safety outcomes include treatment emergent:

The secondary safety endpoints of interest include treatment emergent:

These outcomes are considered secondary due to potential incompleteness of capture in the data sources used for this study. In medical claims databases, laboratory-based adverse events (AEs) are incompletely captured, and similarly death is incompletely captured, primarily coming from hospital discharge status (including Emergency Department discharge).

Table 3 and 4 below display the ICD-9 codes to be used for identification of events of the primary and secondary outcomes of interest along with some information on previous validation work and positive predictive values (PPVs).

Table 3 Primary Outcomes

Outcome	Hospital Discharge Code(s)	Comments
[redacted]	[redacted]	[redacted]

	[redacted]	

Table 4 Secondary Outcomes

Outcome	Hospital Discharge Code(s)	Comments
[redacted]	[redacted]	[redacted]

9.3.3 Other variables – Patient demographics/other baseline characteristics

The following pre-defined covariates will be assessed on the basis of enrollment information and claims during the 6 months preceding (and including the date of) the index dispensing. The diagnosis-based covariate definitions are intended to reflect a reasonable balance of sensitive and specific measurement. This is contrary to the more specific definitions used for the study endpoints.[13] Throughout this document, we refer to the variables listed below as the "pre-defined" covariates. These variables will be used for building the propensity scores, and they will be of primary interest when assessing the comparability of aliskiren patients versus comparator patients (see Section 9.7.3).

Table 5 Patient demographics/other baseline characteristics

Covariate	Definition	Comments
Demographics		
Age	By year By category (18-39, 40-54, 55-64, 65+)	
Sex	Female, Male	
Census Region	Northeast Southeast Midwest West	
State	US state of residence	As present in the data
Plan type	Commercial, Medicare Advantage	
Coexisting medical conditions		
Coronary Artery Disease (CAD)	ICD-9 Dx: 410.x-414.x, 429.2 V45.81	
Coronary artery bypass graft (CABG), old or new	CPT-4: 33510-33545; ICD-9 Dx: V45.81 or V15.1 (old CABG) ICD-9 procedure: 36.1x, 36.2x DRG: 106, 107, 109, 547, 549, 550	
Percutaneous transluminal coronary angioplasty (PTCA)	CPT-4: 92982-92984, 92995, 92997 ICD-9 procedure: 00.66, 36.03, 36.09 DRG: 112, 555	1 inpatient or 2 outpatient claims

Coronary stent	CPT-4: 92980, 92981 ICD-9 procedure: 36.06, 36.07 DRG: 556, 557, 558	1 inpatient or 2 outpatient claims
Carotid endarterectomy	ICD-9 procedure: 00.61, 38.12	1 inpatient or 2 outpatient claims
Carotid stent	ICD-9 procedure: 00.63	1 inpatient or 2 outpatient claims
Radiographic procedures requiring contrast media	See Annex 3.5 for codes	Ionic contrast media
Hypertension	At least 1 Dx of ICD-9 codes 401.x – 405.x	
Atrial fibrillation/flutter	ICD-9 Dx: 427.3x	
Ventricular arrhythmia	ICD-9 Dx: 427.1x – paroxysmal ventricular tachycardia 427.4x – ventricular fibrillation and flutter 427.5x – cardiac arrest 427.9x – cardiac dysrhythmia, unspecified	
Conduction disorders	ICD-9 Dx 426.xx	
Peripheral Vascular disease or PVD surgery	1 inpatient or 2 outpatient claims with any of the following codes: ICD9 diagnosis: 440.20 - 440.24, 440.29 – 440.32, 440.3, 443.9 ICD9 procedure: 38.08, 38.09, 38.18, 38.48, 38.49, 39.25, 39.5, 39.9, 84.10 - 84.17 HCPCs: 35256, 35286, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35621, 35623, 35641, 35646, 35647, 35650, 35651, 35654, 35656, 35661, 35663, 35666, 35671, 27590, 27591, 27592, 27594, 27596, 27880, 27881, 27882, 27884, 27886, 27888	
Pre-diabetes	ICD-9 Dx: 790.29	
Diabetes	At least 2 outpatient diagnoses of DM (ICD-9 250.X (diabetes)) OR 1 hospital discharge Dx of DM OR 1 diagnosis of DM plus an insulin or oral antidiabetic dispensing	
T2DM	At least 2 outpatient diagnoses of T2DM (ICD-9 250.x0 - type II or unspecified, not stated as uncontrolled, ICD-9 250.x2 – type II or unspecified, uncontrolled)) OR 1 hospital discharge Dx of T2DM OR 1 diagnosis of T2DM plus an oral antidiabetic dispensing	
Hyperlipidemia	ICD-9 272.0, 272.2, 272.4	
Atherosclerosis	ICD-9 440.9 (arteriosclerosis) ICD-9 414.X (other forms of chronic ischemic heart disease) ICD-9 429.2 (ASCVD)	
Heart failure (CHF)	1 inpatient or 2 outpatient claims with any of ICD-9 codes : 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	Validated in Medicare algorithm: Hospital discharge ICD-9

		codes: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 PPV 0.97, Spec. 0.97, Sens. 0.76[14]
Hemorrhagic stroke	1 inpatient or 2 outpatient claims with any of 430.x – 433.x	
Ischemic stroke	1 inpatient or 2 outpatient claims with any of ICD-9 codes: 434.x, 436.x, 437.1, 438.x	
Other Stroke Effects	1 inpatient or 2 outpatient claims with any of ICD-9 codes: 438.x	
Previous TIA	ICD-9 435.xx	
Previous MI	ICD-9 412.x	Separate variables for recent MI (ICD-9 410) and old MI (ICD-9 412)
Renal impairment	580.xx acute glomerulonephritis 581.xx nephrotic syndrome 582.xx chronic glomerulonephritis 583.xx nephritis and nephropathy not specified as acute or chronic 584.xx acute renal failure 585.xx chronic kidney disease (CKD) 586.xx renal failure, unspecified ICD-9 procedure: 39.95 hemodialysis 54.98 peritoneal dialysis V45.1Renal dialysis status V56.0 extracorporeal dialysis V56.8 peritoneal dialysis CPT-4: 90935 – 90993, 99512, 99559 (corresponding to dialysis services)	
Prior medications		
ARB		Identified by product-specific NDC-codes
ACE inhibitor		Identified by product-specific NDC codes
Beta blocker		Identified by product-specific NDC codes
Calcium channel blocker		Identified by product-specific NDC codes
Alpha blocker		Identified by product-specific NDC codes
Loop diuretic		Identified by product-specific NDC codes
Thiazide diuretic		Identified by product-specific NDC codes
Potassium sparing agents/aldosterone antagonists		Identified by product-specific NDC codes
Other hypertension medications		Identified by product-specific NDC codes?
Aspirin		Identified by product-specific NDC codes
Aspirin/dipyridamole		Identified by product-specific NDC codes

Clopidogrel		Identified by product-specific NDC codes
Prasugrel		Identified by product-specific NDC codes
Ticagrelor		Identified by product-specific NDC codes
Other antiplatelet agent	Cilostazol, ticlopidine	Identified by product-specific NDC codes
Oral anticoagulants	Apixaban, dabigatran, rivaroxaban, warfarin	
Anti-arrhythmic drug		Identified by product-specific NDC codes
NSAIDs		Identified by product-specific NDC codes
Potassium supplements		Identified by product-specific NDC codes
Statin		Identified by product-specific NDC codes
Other lipid-lowering drugs		Identified by product-specific NDC codes
Diabetes medications		Identified by product-specific NDC codes
Health Care Utilization		
Number of Medications	Count of distinct medications dispensed in prior 6 months	
Number of Hospitalizations	Count of hospitalizations in prior 6 months	
Number of hospital days	Sum of hospital days in prior 6 months	
Number of Physician Office visits	Count of physician office visits in prior 6 months	
Number of cardiologist visits	Count of cardiologist office visits in prior 6 months	
Number of neurologist visits	Count of neurologist office visits in prior 6 months	
Hospitalization in 30 days prior to treatment initiation	Indicator of recent hospitalization	
Number of laboratory tests ordered	Count of laboratory tests in prior 6 months	
Number of lipid tests ordered	Count of lipid-related laboratory tests in prior 6 months	
Number of creatinine tests ordered	Count of creatinine levels obtained in prior 6 months	

9.3.4 Potential confounding factors

Numerous potential confounding variables are plausible for this study, since many patient characteristics that might be prognostic of the primary or secondary outcomes could be part of the selection of patients to one or another antihypertensive medication. We have identified a large number of potential confounders (see previous Section 9.3.3) that are measured and can be assessed at baseline (6 months leading up to and including the date of index dispensing) in the claims data sources.

9.4 Data sources

9.4.1 Data source 1 – US MarketScan® Commercial Claims and Encounters database and Medicare Supplement

US MarketScan® Commercial Claims and Encounters database and Medicare Supplement are covering more than 25 million lives annually. The database comprises longitudinal claims data, which are provided to [redacted]™ by payers, e.g., self-insured employers. The database includes both inpatient and outpatient diagnoses, that have been coded using International Classification of Diseases, Ninth Revision, Clinical Modification codes (ICD-9-CM), and procedures codes (i.e. Current Procedural Terminology [CPT-4]). Both standard pharmacy and mail order prescription records allow for longitudinal tracking of medication refill patterns and changes in medications using National Drug Code (NDC) and include other features of dispensing (drug name, dosage, drug strength, fill date, days of supply, cost information, and de-identified patient and prescriber codes).

In a feasibility assessment, the number of aliskiren users 18 years or older with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) in MarketScan-Medicare from 2007 to April 2012 was identified. A total of 75,853 users were identified of which 22,617 were > 65 years of age. This corresponds to approximately 30% of the overall aliskiren population 18 years of age or older. This is markedly lower as compared to the ~50% seen in ALTITUDE, but most probably reflects the age structure of a hypertensive population in this US health claims database with under-representation of the age group above 65 years.

The Medicare Supplemental and COB Database contains eligible retirees, 65 years or older, with employer-sponsored Medicare Supplemental plans. This database contains predominantly fee-for-service plan data. The Medicare Database table structure is identical to the Commercial Claims and Encounters table structure; the data of this database will be combined into one file for analysis (hereafter referred to as MarketScan in this document).
Importantly for this analysis that covers dosing with antihypertensives and clinically significant outcomes that result in hospitalization, the database includes both inpatient and outpatient diagnoses, that have been coded using diagnosis (ICD-9-CM codes), and procedures codes (ICD-9 procedure codes, HCPCS codes, or CPT-4 codes).

9.4.2 Data source 2 – UnitedHealth Research Database

The UnitedHealth Research Database covers more than 14 million lives annually and readily allows for the identification of large numbers of exposed patients with lag time of about 6 month from the occurrence of the service (medication dispensing) and availability of the claims for research. This data source has an open formulary with tiered copayment structure so that use of medications is guided more by physician-patient interactions than by health insurer policies. This feature of the data source means that newly-marketed medications will be observed within it in relation to their use among the physicians who accept patients with [redacted].
The database includes both inpatient and outpatient diagnoses, that have been coded using ICD-9-CM codes, and procedures codes (i.e. CPT-4).
The database also includes both standard and mail order prescription records allowing for longitudinal tracking of medication refill patterns and changes in medications for up to 44 months. This information includes data on:

- National Drug Code (NDC)
- Drug name

- Dosage form
- Drug strength
- Fill date
- Days of supply
- Cost information
- De-identified patient and prescriber codes

In a feasibility assessment, the number of aliskiren users 18 years or older with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) from 2007 through December 2011 was identified. A total of 19,685 users were identified of which 3,276 were > 65 years of age

9.5 Study size

Combining the MarketScan and UnitedHealth data will provide approximately 95,000 aliskiren users, of whom 25,000 are age 65 or older, and approximately 5,000 are expected to match the ALTITUDE population. The duration of follow-up among these groups will vary by analysis, and all power projections assume an average follow-up of 6 months.

The full aliskiren population of approximately 95,000 will include some patients who may not enter into analyses due to exclusion criteria or propensity score matching. If 70% are included in the study, then there will be ~67,000 aliskiren users in analyses, and they will contribute close to 34,000 person-years [PY] of aliskiren exposure. This study size will provide approximately 90% power to detect a relative risk of 1.30 for an infrequently-occurring outcome such as MI (expected incidence 5/1000 PY), and considerably higher power for more frequently occurring outcomes. If a similar 70% of patients older than 65 years are included in study analyses, there will be 17,500 aliskiren users, and they will contribute close to 9,000 PY of aliskiren exposure so that there will be close to 80% power to detect a relative risk of 1.50 for MI among this subgroup. (Figure 2) The Figure allows for power assessments under a range of variations in eligible person-years and relative risks to detect.

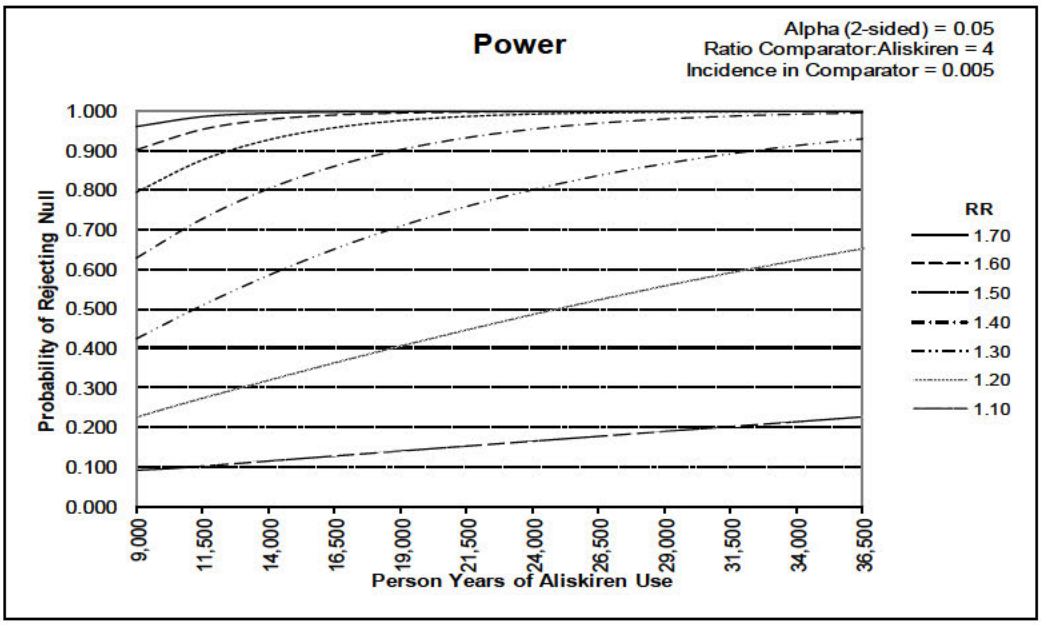

Figure 2 **Power for the study to detect a range of relative risks with varying amounts of observed follow-up**

9.6 Data management

All analyses will be done using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC).

9.7 Data analysis

All analyses will be performed by th [redacted].

9.7.1 Analysis of the objectives

We will identify the first occurrence of each outcome event during follow-up. Time until the event of interest is defined as the number of days from the day after the index date to the date of the event. As defined earlier, these outcome events include:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Similar analyses will be conducted for the secondary outcomes [redacted]).

9.7.2 Statistical hypothesis, model, and methods of analysis

This study will seek to estimate the [redacted].

Confounding by indication is an important threat to the validity in non-randomized studies of treatment effects.[15] All analyses will be conducted in propensity score matched cohorts (see the next section) to achieve a high degree of multivariate confounding control.[13, 16] In addition, we will report counts and incidence rates (IRs) in the population of patients that are exposed to aliskiren but who cannot be matched to comparable non-users of aliskiren. However, we will not perform a formal comparison of this group of patients since a valid comparison group could not be identified.

In addition, although many analyses on the outcomes will be performed, we will not formally adjust for multiple comparisons. Rather than hypothesis testing, this study aims to [redacted]. Estimates and 95% confidence intervals (CIs) for each

comparison will be presented without adjustment for multiplicity, and these 95% CIs can be interpreted individually as including the true association value approximately 95% of the time, even where multiple comparisons have been made.

In each of the three cohorts defined above, we will conduct several analyses.

- **ITT**: The primary analysis will be conducted with exposure defined analogous to an intent-to-treat analysis in a randomized controlled trial. In this analysis, the exposure at cohort entry is carried forward until a patient has an event, disenrollment from the database, or the end of the study period will be reached.
- **As-treated**: Secondary analyses will define exposure on an as-treated basis, so that exposure to the index medication is terminated if the patient discontinues that medication, defined as a 30-day gap with no prescriptions for the index medication following the end of the days supply for the previous prescription. In the as-treated analysis, patients will be censored at the end of the first such gap. Combination treatment will discontinue with the first such gap for any medication in the combination.
- **ITT stratified by duration of follow-up**: To explore time-varying treatment effects within the ITT analysis, we will conduct an exploratory analysis that stratifies the duration of follow-up into 6-month blocks. In this analysis, we estimate a separate HR for each 6-month interval of follow-up time. Patients that are censored or have an event prior to the beginning of an interval do not contribute information to the HR estimate for that interval.
- **ITT stratified by cumulative exposure**: To explore variation in treatment effects with varying cumulative exposure within the ITT analysis, we will conduct an exploratory analysis that is stratified based on the cumulative exposure to the index medication. Cumulative exposure is measured as the total days covered with the index medication during follow-up. We will categorize cumulative exposure based on the tertiles of total days covered. In this analysis, we estimate a separate HR within each category of cumulative exposure. We will not analyze cumulative dose, since there is uncertainty regarding dose equivalency across antihypertensive agents.

In each of these analyses, for the propensity score matched population, we will identify the first occurrence of each of the specified outcomes and tabulate the results as counts of first events for each outcome and the number of people and person-years at risk for each outcome. We will develop IRs (counts of first events divided by person-time) along with 95% CIs. The relative risk (expressed as HR) with 95% CIs will be estimated among users of aliskiren relative to non-users of aliskiren using Cox regression models that account for the matching by stratifying on the matched sets. See Table 6 for an example of how these calculations will be reported for each analysis.

Table 6 Example analysis table after multivariate propensity score matching

Outcome	Aliskiren Exposed				Exposed to comparator agent				HR* (95% CI)
	Events	Patients	Person-years	IR* (95% CI)	Events	Patients	Person-years	IR* (95% CI)	

* IR = incidence rate; HR = hazard ratio; CI = confidence interval

9.7.3 Potential confounding

Balance in patient characteristics will be obtained through matching aliskiren-exposed patients with those exposed to the respective comparator agent in each cohort with respect to the propensity score. The propensity score is the predicted probability of initiating aliskiren (as opposed to a comparator drug), given all measured covariates. We will estimate the primary propensity score for each patient using a logistic regression model that includes all pre-defined covariates (from Section 9.3.3) as well as interactions between subgroup indicators and major confounders.[17] We will limit the major confounders to age, sex, and the top 3 confounders as ranked by the high-dimensional propensity score (hdPS) algorithm (see below) with respect to their potential for bias. There will be no further variable selection. We will estimate one primary propensity score in each of the 3 cohorts.

Matching will be performed using variable-ratio nearest-neighbor matching with a maximum match ratio of 1:4,[18] which has been shown to preserve the intrinsic advantages of cohort matching combined with the efficiency of using a large comparator group. We will limit the caliper to 0.025 on the propensity score, so that comparator patients will be matched to an aliskiren user only if their propensity score differs by no more than 2.5%.[19]

To assess balance on patient characteristics through matching, we will compare all pre-defined covariates (from Section 9.3.3) in exposed and unexposed matched patients. For categorical covariates, we will report the number and % of patients in each category; for continuous covariates, we will report the mean and standard deviation (Table 7). We will calculate both the absolute difference in prevalences or difference in means between exposed and unexposed patients, as well as the standardized difference (the absolute difference divided by the within group standard deviation). To make these comparisons while accounting for the variable matching ratio, we will calculate the % or mean for the unexposed patients first within each matched set and then average across the matched sets. To calculate standard deviation accounting for the matching, we will calculate the standard deviation first within each matched set (the mean squared distance from the overall mean), and then average across the matched sets.

We will also report these patient characteristics for the entire exposed and unexposed cohort prior to matching, as well as for patients that were exposed to aliskiren but were not matched, but we will not compare the balance for these groups.

Table 7 Example balance table

Covariate	Aliskiren Exposed		Unexposed*		Absolute Difference	Standardized Difference**
	Mean / %	SD / N	Mean / %	SD / N		

* accounted for the variable matching ratio by computing means within matching set.
** absolute difference divided by the within group standard deviation

We will evaluate these patient characteristics to assess the balance achieved through matching. If the standardized difference is greater than 0.1 on any major confounder,[20] we will consider further measures such as re-matching patients using a narrower propensity score caliper or re-estimating the propensity score model.

As a secondary analysis, we will seek to address confounding in the primary ITT analysis through extensive empirical identification and modeling of characteristics associated with dispensing of aliskiren relative to the other antihypertensive medications. The hdPS algorithm evaluates thousands of diagnoses, procedures, and pharmacy claim codes, including their frequency and proximity to the index exposure, to identify and prioritize those covariates that serve as proxies for unmeasured confounders.[21-22] These empirically identified confounders are combined with the pre-defined covariates (from Section 9.3.3) to improve confounding adjustment. hdPS approaches have been shown to improve validity in longitudinal claims data studies, particularly when combined with pre-specified covariates,[23-26] as well as in simulation studies.[27-28]

In each of the three cohorts, this process will lead to the development of a hdPS that will incorporate the pre-defined covariates and their interactions as well as numerous empirically identified patient characteristics. In each cohort, we will match patients based on the respective hdPS.

9.7.4 Handling of missing values/censoring/discontinuations

Patient demographics (age and sex) may be missing in the source data, but since their presence is a criterion for study inclusion, they will not be missing for any of the study subjects in the analyses.

Each of the other study variables (exposure, covariates, and outcomes) will be considered present where represented by an appropriate code (NDC, ICD-9, CPT, or death indicator). Thus, lack of a code will represent non-presence of the variable rather than missing. This coding approach is appropriate for comprehensive health insurance databases (such as the ones that will form the basis for this study).[13]

Censoring will be handled through the use of a Cox proportional hazards regression model to analyze outcomes. This model accommodates differential follow-up times across patients by accounting for time-varying risks in outcome events.

9.7.5 Subgroup analyses

Subgroup analyses conducted in all three cohorts will include:

- Patients with recorded DM at baseline
- Patients with recorded renal impairment at baseline
- Patients with recorded DM and renal impairment at baseline
- Patients with recorded pre-existing cardiovascular disease

In addition, analyses conducted within subgroups identified in section 9.3.1.1 will be conducted.

Additional explorative analyses will also stratify by subgroups of age (≥ 65 years versus < 65), sex, and quintiles of the estimated propensity to receive aliskiren.

For each subgroup, we will identify all patients within the matched populations that are in the subgroup and repeat the checks of balance. If balance is acceptable (as defined in Section 9.7.3), we will proceed with the primary analysis in this population. If balance does not meet the

specified criteria, we will consider alternative approaches, such as re-estimating the propensity score within the subgroup and rematch before estimating treatment effects in the subgroup.

The number of analyses and subgroup analyses imply a large number of tables for presenting the results. We will seek economies of presentation where feasible in designing tabular presentation (such as combining multiple results into a table).

9.7.6 Analysis of other objectives

9.7.6.1 Laboratory results

Although limited in its ability to identify laboratory-based outcomes, the study will also assess the association of aliskiren relative to other antihypertensive medications on outpatient laboratory test results (focusing on potassium and serum creatinine). These test results will be available for a subset of cohort members (approximately 20-30% of the United Health enrollees) and will be analyzed as available (both during baseline and follow-up). These laboratory assessments will not be included in the propensity score matching, since they are only available for a subset of the cohort, but they can serve as an assessment of baseline balance and intensity of surveillance during follow-up, assessing the balance obtained through propensity score matching.[29-30]

9.8 Quality control

Since the data sources for this study begin with routine clinical interactions and processes for reimbursement of patient care, the data sources each apply their own sets of proprietary data integrity procedures to reduce the potential for fraudulent billing. The commercially-available data sources that will be used for this study represent adjudicated claims that have been further processed for usability and for assurance of patient confidentiality.

[redacted]. Entry into the computer room requires passing through staffed building security, a successful palm scan, and then passing through staffed computer room security. All entries and exits are logged. We maintain 26 TB of redundant NetApp storage for maximal data integrity and high-speed data access. We also exclusively use a 96 TB of database storage on a Netezza 96 CPU parallel computer. The computers and data files are only accessible via a local area network which is overseen by [redacted], who apply the same standards used for the hospital's electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current [redacted] standard for data security, and are stored in a locked facility.

All aspects of data analysis will be conducted according to standard procedures of the [redacted]. Programming for this project will be conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst will review the program along with input and output data sets, and

for select steps of the project will employ double programming techniques to reduce the potential for programming errors.

9.9 Limitations of the research methods

As a non-interventional study, there are inherent limitations with respect to potential for alternate explanations for any observed association. The source claims data include limitations with respect to certainty of capture of exposure, covariates, and outcomes. There are a number of covariates, such as race, BMI, and smoking, that are not directly assessed in a health insurer database. Further, some covariates that can be directly assessed through diagnosis and procedure codes (such as renal impairment) have uncertain sensitivity, specificity, and predictive value. Although duration of diabetes may represent a risk factor for study outcomes, this covariate will be incompletely captured since the patient history in the dataset is relatively short (at least 6 months, and an average of approximately 2 years), and a first claim within the database may not represent diabetes onset.
As a comprehensive insurance database, essentially all billable medical services will result in claims for reimbursement, so that certainty of capture is tied to likelihood of a claim being submitted to the insurer.[13] Misclassification of prescription drug exposure is generally considered less than in other exposure assessment approaches, including physician prescribing notes and patient self reporting.[31-33] Misclassification of outcomes is a potential source of bias that we seek to reduce by selecting validated code combinations that have shown high specificity. High specificity will lead to less biased or unbiased relative risk estimates, even if sensitivity is far lower than 100%, assuming non-differential misclassification.[34]

Non-differential misclassification of confounding factors, which can be caused by under-coding of an existing condition that leads to its non-existence in the research database, will lead to incomplete control of such confounders and ultimately to residual confounding bias.[35-36] Adjusting for many proxies of the relevant confounding constructs using hdPS adjustment is hoped to minimize this issue (see above), however, it cannot be fully ruled out. Although certain potential confounding variables are not available in a claims data source, including race, socioeconomic status, and lifestyle factors (alcohol use, smoking, exercise), the data sources exhibit reduced ranges in some of these variables relative to what might be expected in the general population (e.g. as an employed data source, high and low extremes of income are removed), so that the potential confounding due to the variable is reduced.

The data sources for this study are commercial US data sources (based on employed people and their dependents), so they tend to over-represent working-age people. However they are supplemented with elderly through patients with certain types of Medicare coverage (Medicare Advantage). Elderly with Medicare Advantage might differ from elderly with other types of Medicare as they tend to be healthier and more likely to still be employed. These features of the data may limit the generalizability in that the results will be most generalizable to US people who are employed. The effect of aliskiren observed in this study may differ from the patients with different forms of health insurance coverage, particularly if the effect of aliskiren is altered by non-employment status.

Although we will not formally adjust for multiple comparisons, it is important to consider the large number of analyses performed and comparisons made when drawing conclusions from the study. Instead of testing a specific hypothesis, this study aims to estimate the association

between aliskiren exposure and a range of study outcomes relative to comparison treatments across numerous exposures and exposure subgroups, along with the uncertainty in these estimated associations. This information is quantified through hazard ratios and 95% CIs, and these 95% CIs can be interpreted independently as including the true hazard ratio approximately 95% of the time, even where multiple comparisons have been made. However, across the dozens of 95% CIs that will be created in this study, the chance that at least one of those CIs does not contain the true value is greater than 5%. Conversely, the chance that at least one 95% CI does not include the null hazard ratio of 1.0, even if the true treatment effect in that analysis is 1.0, will be greater than 5%.

In addition, it should be kept in mind that we have no control over patient follow-up in the study. We assume a follow-up of 6 months on average; however, if the observed follow-up is shorter and the number of outcomes is lower than anticipated, the power of the study to assess a given risk will be affected as it depends on the incidence of study outcomes.

9.10 Other aspects

None

10 Protection of human subjects

As a non-interventional study, by definition no interventions will be made to patients under study. The patients on whom this study is based will be de-identified by the data owner prior to transfer to the [redacted] for processing and analysis, reducing the potential for loss of patient privacy at any stage of the research. This study will be submitted to an appropriate IRB for review.

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected; consistent with the principles that have their origin in the Declaration of Helsinki; and that the study data are credible and responsibly reported.

11 Management and reporting of adverse events/adverse reactions

Not Applicable.

12 Plans for disseminating and communicating study results

Upon study completion and finalization of the study report, manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences.

Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	13
1.1.2 End of data collection[2]	X	☐	☐	13
1.1.3 Study progress report(s)	X	☐	☐	13
1.1.4 Interim progress report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS register	X	☐	☐	13
1.1.6 Final report of study results.	X	☐	☐	13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	13-14
2.1.2 The objective(s) of the study?	X	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	15-17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	X	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	X	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	X	☐	☐	14

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	26

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	X	☐	☐	23-24
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	X	☐	☐	15
4.2.2 Age and sex?	X	☐	☐	15-16
4.2.3 Country of origin?	X	☐	☐	15
4.2.4 Disease/indication?	X	☐	☐	15
4.2.5 Co-morbidity?	X	☐	☐	15-17
4.2.6 Seasonality?	☐	☐	X	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	15

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	X	☐	☐	16-17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	X	☐	☐	31
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	X	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	X	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	X	☐	☐	27

Comments:

Exposure classified based on a drug initiated. New users are compared

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	X	☐	☐	18-20
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	18-20

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	X	☐	☐	28
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	X	☐	☐	29

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	X	☐	☐	24-25
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	X	☐	☐	24-25
8.1.3 Covariates?	X	☐	☐	24-25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	24-25
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	24-25
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	X	☐	☐	24-25
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	X	☐	☐	24-25
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	X	☐	☐	24-25
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	X	☐	☐	24-25
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

No linkage for patients required

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	X	☐	☐	25

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	X	☐	☐	26-27
10.2 Is the choice of statistical techniques described?	X	☐	☐	26-27
10.3 Are descriptive analyses included?	X	☐	☐	26-27
10.4 Are stratified analyses included?	X	☐	☐	29
10.5 Does the plan describe methods for adjusting for confounding?	X	☐	☐	28
10.6 Does the plan describe methods addressing effect modification?	X	☐	☐	29

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	X	☐	☐	29
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	30
11.3 Are methods of quality assurance described?	X	☐	☐	30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	X	☐	☐	31
11.5 Is there a system in place for independent review of study results?	☐	☐	X	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	X	☐	☐	28
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases,	X	☐	☐	28

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	25
12.3 Does the protocol address other limitations?	X	☐	☐	31

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	32
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	32

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	X	☐	☐	13

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	32
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	32

Comments:

[redacted]

Annex 3. Additional information

Annex 3.1. Relevant counts in the MarketScan database

Table A1 Aliskiren users in MarketScan-Medicare from 2007 to April 2012, 18 years or older with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) and having either a recorded diagnosis of DM, or hypertension or renal disease at or prior to the start of aliskiren

All patients (N=75,853)									
					Number of prescriptions				
					1-3	4-6	7-10	11-15	>15
DM	HTN	Ren Dis	n	%	n	n	n	n	n
any	any	any							
No	No	No	12,287	16.2	4,326	2,144	2,017	1,715	2,085
No	No	Yes	483	0.6	159	86	98	71	69
No	Yes	No	40,853	53.9	14,385	7,160	6,735	5,508	7,065
No	Yes	Yes	2,201	2.9	822	394	337	306	342
Yes	No	No	4,700	6.2	1,512	926	874	637	751
Yes	No	Yes	458	0.6	145	92	84	64	73
Yes	Yes	No	12,893	17.0	4,419	2,409	2,220	1,819	2,026
Yes	Yes	Yes	1,978	2.6	755	395	376	222	230

DM= diabetes mellitus: At least 2 diagnoses of diabetes; HTN=hypertension: at least 2 diagnoses of hypertension; Ren Dis=renal disease: At least 2 diagnoses of chronic kidney disease, acute renal failure, or use of dialysis (hemo, peritoneal) or hemofiltration

Table A2 Aliskiren users in MarketScan-Medicare from 2007 to April 2012, > 65 years of age with 6 months of continuous enrollment (prior to first aliskiren prescription) and having either a recorded diagnosis of DM, hypertension or renal disease at or prior to the start of aliskiren

Patients > 65 years (N=22,617)									
					Number of prescriptions				
					1-3	4-6	7-10	11-15	>15
T2DM	HTN	Ren Dis	n	%	n	n	n	n	n
any	any	any							
No	No	No	3,861	17.07	1,333	643	680	621	584
No	No	Yes	222	0.98	76	41	38	34	33
No	Yes	No	11,105	49.10	3,779	1,952	1,962	1,650	1,762
No	Yes	Yes	957	4.23	374	165	153	133	132
Yes	No	No	1,566	6.92	488	290	333	244	211
Yes	No	Yes	200	0.88	67	38	33	30	32
Yes	Yes	No	3,916	17.31	1,290	713	731	598	584
Yes	Yes	Yes	790	3.49	280	178	176	92	64

Annex 3.2. Relevant counts in the UnitedHealth database

Table A3 United Health data from 2007 to 2011, 18 years or older with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) and having either a recorded diagnosis of DM, or hypertension or renal disease at or prior to the start of aliskiren

All Patients (N=19,685)													
			All		1-3		4-6		7-10		11-15		>15	
DM	HTN	Renal Disease	**N 19,685**	**100%**	**N 8,323**	**100%**	**N 3,444**	**100%**	**N 2,769**	**100%**	**N 2,011**	**100%**	**N 3,138**	**100%**
No	No	No	2,161	10.98	954	11.46	390	11.32	281	10.15	206	10.24	330	10.52
No	No	Yes	47	0.24	24	0.29	11	0.32	4	0.14	2	0.1	6	0.19
No	Yes	No	10,562	53.66	4,454	53.51	1,784	51.8	1,479	53.41	1,092	54.3	1,753	55.86
No	Yes	Yes	668	3.39	300	3.6	142	4.12	93	3.36	60	2.98	73	2.33
Yes	No	No	439	2.23	189	2.27	85	2.47	64	2.31	45	2.24	56	1.78
Yes	No	Yes	39	0.2	19	0.23	7	0.2	4	0.14	3	0.15	6	0.19
Yes	Yes	No	4,880	24.79	1,992	23.93	851	24.71	714	25.79	522	25.96	801	25.53
Yes	Yes	Yes	889	4.52	391	4.7	174	5.05	130	4.69	81	4.03	113	3.6

DM= diabetes mellitus: At least 2 diagnoses of diabetes

HTN=hypertension: at least 2 diagnoses of hypertension
Ren Dis=renal disease: At least 2 diagnoses of chronic kidney disease, acute renal failure, or use of dialysis (hemo, peritoneal) or hemofiltration

Table A4 United Health data from 2007 through 2011, >65 years with 6 months of continuous enrollment (prior to the 1st aliskiren prescription) and having either a recorded diagnosis of DM, or hypertension or renal disease at or prior to the start of aliskiren

All Patients (N=3,276)

			All		1-3		4-6		7-10		11-15		>15	
DM	HTN	Renal Disease	**N=3,276**	**100%**	**N=1,268**	**100%**	**N=626**	**100%**	**N=475**	**100%**	**N=382**	**100%**	**N=525**	**100%**
No	No	No	374	11.42	131	10.33	82	13.1	51	10.74	38	9.95	72	13.71
No	No	Yes	5	0.15	1	0.08	1	0.16	1	0.21	1	0.26	1	0.19
No	Yes	No	1,553	47.41	607	47.87	276	44.09	215	45.26	189	49.48	266	50.67
No	Yes	Yes	165	5.04	66	5.21	37	5.91	25	5.26	16	4.19	21	4
Yes	No	No	75	2.29	28	2.21	16	2.56	10	2.11	14	3.66	7	1.33
Yes	No	Yes	13	0.4	6	0.47	2	0.32	1	0.21	1	0.26	3	0.57
Yes	Yes	No	871	26.59	337	26.58	163	26.04	135	28.42	106	27.75	130	24.76
Yes	Yes	Yes	220	6.72	92	7.26	49	7.83	37	7.79	17	4.45	25	4.76

DM= diabetes mellitus: At least 2 diagnoses of diabetes

HTN=hypertension: at least 2 diagnoses of hypertension
Ren Dis=renal disease: At least 2 diagnoses of chronic kidney disease, acute renal failure, or use of dialysis (hemo, peritoneal) or hemofiltration

Annex 3.3.Comparison medications (limited to oral forms)

Table A5 Comparison cohort antihypertensive medications

Therapeutic class	Individual drugs
ACE Inhibitors (ACEI)	Benazepril Captopril Enalapril Enalaprilat Enalaprilat Dihydrate Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril
Angiotensin II Receptor Blockers (ARB)	Azilsartan Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan
Calcium Channel Antagonists (CCB)	a. Nondihydropyridines Diltiazem Verapamil b. Dihydropyridines Amlodipine Bepridil Clevidipine Felodipine Isradipine Nicardipine Nifedipine Nimodipine Nisoldipine
Diuretics	a. Thiazides Bendroflumethiazide Benzthiazide Chlorothiazide Chlorothiazide Sodium Chlorthalidone Cyclothiazide Hydrochlorothiazide Hydroflumethiazide Indapamide

	Methyclothiazide Metolazone Polythiazide Quinethazone Trichlormethiazide b. Potassium-Sparing Agents Amiloride Hydrochloride Triamterene c. Aldosterone antagonists Eplerenone Spironolactone
Alpha Blockers (AB)	Doxazosin Prazosin Terazosin
Beta Blockers (BB)	Acebutolol Atenolol Betaxolol Bisoprolol Carteolol Esmolol Metoprolol Succinate Metoprolol Tartrate Nadolol Penbutolol Pindolol Propranolol Sotalol Timolol
Combined Alpha And Beta Blockers	Carvedilol Labetalol
Others	Clonidine Guanfacine Hydralazine

Annex 3.4. ICD-9 codes for cardiovascular disease conditions

410.xx –acute MI
411.xx – other acute and subacute forms of ischemic heart disease
412.xx – old MI
413.xx – angina pectoris
414.xx - other forms of chronic ischemic heart disease
420.xx – acute pericarditis (excl. rheumatic)
421.xx – acute and subacute endocarditis
422.xx – acute myocarditis (excl. rheumatic)
423.xx – other diseases of pericardium (excl. rheumatic)
424.xx – other diseases of endocardium (excl. rheumatic and bacterial)
425.xx – cardiomyopathy
426.xx – conduction disorders
427.xx – cardiac dysrhythmias
428.xx – heart failure
429.xx – ill-defined descriptions and complications of heart disease

Annex 3.5. List of CPT-4 codes for contrast agents

Code	DESCRIPTION
0042T	CEREBRAL PERFUSION ANALYSIS USING COMPUTED TOMOGRAPHY WITH CONTRAST ADMINISTRATION, INCLUDING POST-PROCESSING OF PARAMETRIC MAPS WITH
36598	CONTRAST INJECTION(S) FOR RADIOLOGIC EVALUATION OF EXISTING CENTRAL VENOUS ACCESS DEVICE, INCLUDING FLUOROSCOPY, IMAGE DOCUMENTATION AND
49427	INJECTION PROCEDURE (EG, CONTRAST MEDIA) FOR EVALUATION OF PREVIOUSLY PLACED PERITONEAL-VENOUS SHUNT
49465	CONTRAST INJECTION(S) FOR RADIOLOGICAL EVALUATION OF EXISTING GASTROSTOMY, DUODENOSTOMY, JEJUNOSTOMY, GASTRO-JEJUNOSTOMY, OR
51605	INJECTION PROC & PLACEMENT, CHAIN, CONTRAST &/OR CHAIN URETHROCYSTOGRAPHY URETHROCYSTOGRAPHY
58340	CATHETERIZATION AND INTRODUCTION OF SALINE OR CONTRAST MATERIAL FOR SALINE INFUSION SONOHYSTEROGRAPHY (SIS) OR HYSTEROSALPINGOGRAPHY
70015	CISTERNOGRAPHY, POSITIVE CONTRAST, RADIOLOGICAL S&I INTERPRETATION
70373	LARYNGOGRAPHY, CONTRAST, RADIOLOGICAL S&I
70460	CT SCAN, HEAD/BRAIN; W/CONTRAST MATL(S)
70481	CT SCAN, ORBIT/SELLA/POSTERIOR FOSSA/ OUTER, MIDDLE, INNER EAR; W/CONTRAST OR INNER EAR; WITH CONTRAST MATERIAL(S)
70482	CT SCAN, ORBIT/SELLA/POSTERIOR FOSSA/ OUTER, MIDDLE, INNER EAR; W/O CONTRAST, THEN W/CONTRAST OR INNER EAR; WITHOUT CONTRAST MATERIAL, FOLLOWED BY CONTRAST
70487	CT SCAN, MAXILLOFACIAL AREA; W/CONTRAST MATL(S)
70491	CT SCAN, SOFT TISSUE NECK; W/CONTRAST MATL(S)
70492	CT SCAN, NECK TISSUE; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS FOLLOWED BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
70496	CT ANGIOGRAPHY, HEAD, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S) W/IMAGE POST-PROCESSING INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE POSTPROCESSING
70498	CT ANGIOGRAPHY, NECK, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S), W/IMAGE POST-PROCESSING INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE POSTPROCESSING
71260	CT SCAN, THORAX; W/CONTRAST MATL(S)
71270	CT SCAN, THORAX; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS CONTRAST MATERIAL(S) AND FURTHER SECTIONS
71275	CT ANGIOGRAPHY, CHEST, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S), W/ IMAGE POST-PROCESSING MATERIAL(S), INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE
72126	CT SCAN, CERVICAL SPINE; W/CONTRAST
72127	CT SCAN, CERVICAL SPINE; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
72129	CT SCAN, THORACIC SPINE; W/CONTRAST
72130	CT SCAN, THORACIC SPINE; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
72132	CT SCAN, LUMBAR SPINE; W/CONTRAST
72133	CT SCAN, LUMBAR SPINE; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
72191	CT ANGIOGRAPHY, PELVIS, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S), W/IMAGE POST-PROCESSING INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE POSTPROCESSING
72193	CT SCAN, PELVIS; W/CONTRAST
72194	CT SCAN, PELVIS; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS CONTRAST MATERIAL(S) AND FURTHER SECTIONS
73201	CT SCAN, UPPER EXTREMITY; W/CONTRAST
73202	CT SCAN, UPPER EXTREMITY; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS FOLLOWED BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
73206	CT ANGIOGRAPHY, UPPR EXTREM, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S), W/IMAGE POST-PROC MATERIAL(S), INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE

73701	CT SCAN, LOWER EXTREMITY; W/CONTRAST
73702	CT SCAN, LOWER EXTREMITY; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS FOLLOWED BY CONTRAST MATERIAL(S) AND FURTHER SECTIONS
73706	CT ANGIOGRAPHY, LOWER EXTREMITY, W/O CONTRAST MATL(S), FOLLOWED CONTRST MATL(S), W/IMAG POST-PR0CESS MATERIAL(S), INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE
74160	CT SCAN, ABDOMEN; W/ CONTRAST
74170	CT SCAN, ABDOMEN; W/O CONTRAST, THEN W/CONTRAST & FURTHER SECTIONS CONTRAST MATERIAL(S) AND FURTHER SECTIONS
74174	COMPUTED TOMOGRAPHIC ANGIOGRAPHY, ABDOMEN AND PELVIS, WITH CONTRAST MATERIAL(S), INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE
74175	CT ANGIOGRAPHY, ABDOMEN, W/O CONTRAST MATL(S), FOLLOWED BY CONTRAST MATL(S) W/IMAGE POST-PROCESSING INCLUDING NONCONTRAST IMAGES, IF PERFORMED, AND IMAGE POSTPROCESSING
74177	COMPUTED TOMOGRAPHY, ABDOMEN AND PELVIS; WITH CONTRAST MATERIAL(S)
74470	RADIOLOGIC EXAM, RENAL CYST STUDY, TRANSLUMBAR, CONTRAST, RADIOLOGICAL S&I VISUALIZATION, RADIOLOGICAL SUPERVISION AND INTERPRETATION
75572	COMPUTED TOMOGRAPHY, HEART, WITH CONTRAST MATERIAL, FOR EVALUATION OF CARDIAC STRUCTURE AND MORPHOLOGY (INCLUDING 3D IMAGE POSTPROCESSING,
75573	COMPUTED TOMOGRAPHY, HEART, WITH CONTRAST MATERIAL, FOR EVALUATION OF CARDIAC STRUCTURE AND MORPHOLOGY IN THE SETTING OF CONGENITAL HEART
75574	COMPUTED TOMOGRAPHIC ANGIOGRAPHY, HEART, CORONARY ARTERIES AND BYPASS GRAFTS (WHEN PRESENT), WITH CONTRAST MATERIAL, INCLUDING 3D IMAGE
75635	COMPUTED TOMOGRAPHIC ANGIOGRAPHY, ABDOMINAL AORTA AND BILATERAL ILIOFEMORAL LOWER EXTREMITY RUNOFF, WITH CONTRAST MATERIAL(S),
75980	PERCUTANEOUS TRANSHEPATIC BILIARY DRAINAGE W/CONTRAST, RADIOLOGICAL S&I RADIOLOGICAL SUPERVISION AND INTERPRETATION
75984	PERCUTANEOUS DRAINAGE CATHETER CHANGE, W/CONTRAST, RADIOLOGICAL S&I MONITORING (EG, GENITOURINARY SYSTEM, ABSCESS), RADIOLOGICAL
76350	SUBTRACTION IN CONJUNCTION W/CONTRAST STUDIES

Annex 3.6. Shell tables

Table A6 Characteristics of Aliskiren and the comparator group cohorts (before matching)

Covariate	Aliskiren group N =	Comparator group N =
Demographics		
Age		
Sex		
Census Region		
State		
Plan type		
Coexisting medical conditions		
Coronary Artery Disease (CAD)		
Coronary artery bypass graft (CABG), old or new		
Percutaneous transluminal coronary angioplasty (PTCA)		
Coronary stent		
Carotid endarterectomy		
Carotid stent		
Radiographic procedures requiring contrast media		
Hypertension		
Atrial fibrillation/flutter		
Ventricular arrhythmia		
Conduction disorders		
Peripheral Vascular disease or PVD surgery		
Pre-diabetes		
Diabetes		
T2DM		
Hyperlipidemia		
Atherosclerosis		
Heart failure (CHF)		
Hemorrhagic stroke		
Ischemic stroke		
Other Stroke Effects		
Previous TIA		
Previous MI		
Renal impairment		
Prior medications		
ARB		
ACE inhibitor		
Beta blocker		
Calcium channel blocker		
Alpha blocker		
Loop diuretic		
Thiazide diuretic		
Potassium sparing agents/aldosterone antagonists		
Other hypertension medications		
Aspirin		
Aspirin/dipyridamole		
Clopidogrel		
Prasugrel		
Ticagrelor		

Other antiplatelet agent		
Oral anticoagulants		
Anti-arrhythmic drug		
NSAIDs		
Potassium supplements		
Statin		
Other lipid-lowering drugs		
Diabetes medications		
Health Care Utilization		
Number of Medications		
Number of Hospitalizations		
Number of hospital days		
Number of Physician Office visits		
Number of cardiologist visits		
Number of neurologist visits		
Hospitalization in 30 days prior to treatment initiation		
Number of laboratory tests ordered		
Number of lipid tests ordered		
Number of creatinine tests ordered		

This table will be repeated for all 3 cohorts

Table A7 Characteristics of Aliskiren and the comparator group cohorts (after matching)

Covariate	Aliskiren group N =	Comparator group N =	Unmatched Aliskiren N =
Demographics			
Age			
Sex			
Census Region			
State			
Plan type			
Coexisting medical conditions			
Coronary Artery Disease (CAD)			
Coronary artery bypass graft (CABG), old or new			
Percutaneous transluminal coronary angioplasty (PTCA)			
Coronary stent			
Carotid endarterectomy			
Carotid stent			
Radiographic procedures requiring contrast media			
Hypertension			
Atrial fibrillation/flutter			
Ventricular arrhythmia			
Conduction disorders			
Peripheral Vascular disease or PVD surgery			
Pre-diabetes			
Diabetes			
T2DM			
Hyperlipidemia			
Atherosclerosis			
Heart failure (CHF)			
Hemorrhagic stroke			
Ischemic stroke			
Other Stroke Effects			
Previous TIA			
Previous MI			
Renal impairment			
Prior medications			
ARB			
ACE inhibitor			
Beta blocker			
Calcium channel blocker			
Alpha blocker			
Loop diuretic			
Thiazide diuretic			
Potassium sparing agents/aldosterone antagonists			
Other hypertension medications			
Aspirin			
Aspirin/dipyridamole			
Clopidogrel			
Prasugrel			
Ticagrelor			

Other antiplatelet agent			
Oral anticoagulants			
Anti-arrhythmic drug			
NSAIDs			
Potassium supplements			
Statin			
Other lipid-lowering drugs			
Diabetes medications			
Health Care Utilization			
Number of Medications			
Number of Hospitalizations			
Number of hospital days			
Number of Physician Office visits			
Number of cardiologist visits			
Number of neurologist visits			
Hospitalization in 30 days prior to treatment initiation			
Number of laboratory tests ordered			
Number of lipid tests ordered			
Number of creatinine tests ordered			

This table will be repeated for all 3 exposure cohorts

Table A8 Follow-up and outcomes among matched cohorts

Outcome	Aliskiren Exposed				Unexposed				HR* (95% CI)
	Events	Patients	Person-years	IR* (95% CI)	Events	Patients	Person-years	IR* (95% CI)	
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
Secondary outcomes									
[redacted]									
[redacted]									
[redacted]									

IR = incidence rate; HR = hazard ratio; CI = confidence interval

Table A9 Follow-up and outcomes among non-matched aliskiren group

Outcome	Aliskiren Exposed			
	Events	Patients	Person-years	IR* (95% CI)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Secondary outcomes				
[redacted]				
[redacted]				
[redacted]				

IR = incidence rate; CI = confidence interval