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A cohort study to assess various safety outcomes of interest in users of aliskiren using US claims data

REDACTED STUDY REPORT

Author [redacted]

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Research questions and objectives	This non-interventional study aimed to assess whether, under real-world conditions, aliskiren – either as monotherapy or in combination (especially with ACE inhibitors or angiotensin receptor blockers) – may be associated with a risk increase of certain outcomes of interest as identified in the ALTITUDE study compared to other antihypertensive drugs. The primary objective was to quantify associations between aliskiren and the occurrence of selected clinical outcomes. This involved quantification of incidence rates and relative risks of (i) cerebrovascular accidents, (ii) transient ischemic attack (TIA), (iii) myocardial infarction, (iv) heart failure leading to hospitalization, (v) acute renal failure (ARF), (vi) end stage renal disease (ESRD) in users of aliskiren compared to users of other antihypertensive drugs.

	Secondary objectives included quantifying associations between aliskiren and the occurrence of hyperkalemia, hypotension, and death. This secondary objective involved separately assessing the incidence rates and relative risks of (i) hyperkalemia, (ii) hypotension, and (iii) death in users of other antihypertensive drugs.
Country (-ies) of study	United States
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1 Abstract

Title

A cohort study to assess various safety outcomes in aliskiren initiators using US claims data

Date: 17 March 2014 (version 1.0)

Author, affiliation: [redacted]

Keywords

Cohort study; secondary use of data; claims database; safety; aliskiren; hypertension

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, in addition to angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as compared to ACEI or ARB therapy together with placebo 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 an 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 aimed to assess whether in a routine care setting, aliskiren – either as monotherapy or in combination with other antihypertensives (especially with ACEIs or ARBs) – may be associated with an increased risk of certain outcomes of interest as identified in the ALTITIUDE study compared to other antihypertensive drugs. The study objectives were as follows:

Primary objective: To quantify associations between aliskiren and the occurrence of selected clinical outcomes. This involved the quantification of incidence rates and relative risks of (i) cerebrovascular accidents, (ii) transient ischemic attack (TIA), (iii) myocardial infarction, (iv) heart failure leading to hospitalization, (v) acute renal failure (ARF), (vi) end stage renal disease (ESRD) in users of aliskiren compared to users of other antihypertensive drugs.

Secondary objective: To quantify associations between aliskiren and the occurrence of hyperkalemia, hypotension, and death. This involved separately assessing the incidence rates and relative risks of (i) hyperkalemia, (ii) hypotension, and (iii) death in aliskiren initiators compared to initiators of other antihypertensive drugs.

Study design

This cohort study involved secondary use of data from two United States (U.S.)-based health insurance claims databases (i.e. UnitedHealth and MarketScan). Three sets of propensity-score matched cohorts (up to a 1:4 ratio of aliskiren to comparator) were formed after limiting to adults (18+ years) who had a baseline diagnosis of hypertension: 1) Cohort 1 were new users of aliskiren or other antihypertensive medications; 2) Cohort 2 were new users of aliskiren or other antihypertensive medications as add-on to ACEIs or ARBs; 3) Cohort 3 were new users of aliskiren or other antihypertensive medications as add-on to calcium channel blockers (CCBs).

Setting

This study was conducted in parallel in UnitedHealth data and in MarketScan data, involving patients who used antihypertensive medications between March 2007 and June 2012. Patients from the two databases were analyzed separately and also pooled together for the pooled analyses (primary outcomes).

Subjects and study size, including dropouts

Cohort 1 (any new use): From the United data source, there were 16,244 aliskiren new users matched to 64,817 new users of other antihypertensive medications. From the MarketScan data source there were 67,557 aliskiren new users matched to 269,586 new users of other antihypertensive medications.

Cohort 2 (new use as add-on to ACEIs or ARBs): 5,748 aliskiren new users matched to 22,813 new users of other antihypertensive medications from the United data source; 29,813 aliskiren new users matched to 116,757 new users of other antihypertensive medications from the MarketScan data source.

Cohort 3 (new use as add-on to CCBs): 4,149 aliskiren new users matched to 16,438 new users of other antihypertensive medications from the United data source; 19,092 aliskiren new users matched to 75,912 new users of other antihypertensive medications from the MarketScan data source.

Variables and data sources

The primary exposure variable was whether the patient initiated aliskiren or a comparator antihypertensive medication.

There were nine primary outcome variables identified within the follow-up time of the study cohorts. Each of these required a hospitalization with appropriate codes:

- Cerebrovascular accident (CVA)
- Stroke
- Ischemic stroke
- Hemorrhagic stroke
- Transient Ischemic Attack (TIA)
- Myocardial infarction
- Heart Failure (HF)
- Acute Renal Failure (ARF)
- End-Stage Renal Disease (ESRD)

Along with the primary outcomes, there were three secondary outcomes identified in the study follow-up time: hyperkalemia, hypotension, and mortality.

There were numerous covariates and stratification variables including various comorbidities and comedications. Please see the appropriate sections of the report for a complete list.

Results

Below are the intent-to-treat (ITT) results of the primary outcomes of interest presented as hazard ratios (HRs) with corresponding 95% confidence intervals for each outcome pooled over both data sources. Other analyses can be found in the results section of the report.

Outcome	Cohort 1	Cohort 2	Cohort 3
Cerebrovascular accidents	1.07 (0.99 - 1.15)	1.02 (0.92 - 1.14)	0.86 (0.76 - 0.98)
Stroke	1.02 (0.96 - 1.08)	0.97 (0.89 - 1.05)	0.91 (0.83 - 1.00)
Ischemic stroke	1.01 (0.95 - 1.06)	0.96 (0.88 - 1.04)	0.91 (0.83 - 1.00)
Hemorrhagic stroke	1.23 (1.03 - 1.46)	1.14 (0.88 - 1.48)	0.87 (0.63 - 1.20)
Transient ischemic attack	1.05 (0.95 - 1.16)	1.08 (0.92 - 1.25)	1.02 (0.86 - 1.21)
Myocardial infarction	0.91 (0.84 - 0.99)	0.88 (0.78 - 1.00)	0.85 (0.74 - 0.98)
Heart failure	0.87 (0.82 - 0.92)	0.81 (0.74 - 0.87)	0.84 (0.77 - 0.92)

Outcome	Cohort 1	Cohort 2	Cohort 3
Acute renal failure	0.96 (0.92 - 0.99)	0.93 (0.89 - 0.98)	0.95 (0.90 - 1.01)
End-stage renal disease	0.89 (0.83 - 0.95)	0.87 (0.79 - 0.96)	0.85 (0.77 - 0.94)

Discussion

This large real-world, non-interventional study of patients receiving aliskiren and comparator antihypertensive medication in settings of routine care found no increased risk for a range of outcomes. The finding of an increased risk of hemorrhagic stroke was inconsistent across the analyses conducted and is based on small numbers of outcomes, making non-causal mechanisms (chance, bias, or confounding) more plausible. The high degree of balance between compared groups across the 3 cohorts achieved by propensity score matching makes it difficult to interpret the finding of a consistently decreased risk of heart failure along with myocardial infarction and the renal outcomes, although these findings may represent non-causal associations mediated through unmeasured baseline confounding or differential changes in health status during follow-up. Overall, this study provides fairly strong evidence from routine care that there is not a substantially increased risk of several cardiovascular and renal outcomes associated with aliskiren during routine care. This is because the precision of the findings as shown in 95% confidence intervals is such that a substantial increase in risk would have been readily apparent. However, a smaller increase in risk (perhaps around 10% or 20%) would not be so apparent due to imprecision in the estimate along with the increased plausability of bias and confounding as alternate explanations that comes with a smaller increase in risk.

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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
CVA	Cerebrovascular Accident
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
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 Investigators

4 Other responsible parties

Not applicable.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	15 February 2013	15 February 2013	Not applicable
End of data collection	30 June 2013	30 June 2013	Not applicable
Registration in the EU PAS	08 February 2013	01 March 2013	Delay due to operational problems with registration
Final report of study results	March 2014	17 March 2014	Not applicable

6 Rationale and background

In December 2011, the European Medicines Agency (EMA) requested from Novartis to perform an epidemiological study to further investigate the signal of harm for aliskiren based on results of an interim analysis of the 'Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints' (ALTITUDE), particularly concentrating on outcomes when aliskiren is used in combination with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).

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 (Angeli et al 2012) 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) (Parving et al 2009).

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 the aliskiren group
- Excess of creatinine >50% increase

7 Research question and objectives

This non-interventional study aimed to assess whether, under real-world conditions, aliskiren – either as monotherapy or in combination (especially with ACEIs or ARBs) – may be associated with a risk increase of certain outcomes of interest as identified in the ALTITUDE study compared to other antihypertensive drugs. The study objectives were as follows:

7.1 Primary objectives

The primary objective was to quantify associations between aliskiren and the occurrence of selected clinical outcomes. This involved quantification of incidence rates and relative risks of (i) cerebrovascular accidents, (ii) transient ischemic attack (TIA), (iii) myocardial infarction, (iv) heart failure leading to hospitalization, (v) acute renal failure (ARF), (vi) end stage renal disease (ESRD) in users of aliskiren compared to users of other antihypertensive drugs.

These outcomes were considered as acute events and therefore would represent incident events even if patients have experienced them prior to cohort entry.

7.2 Secondary objectives

Secondary objectives included quantifying associations between aliskiren and the occurrence of hyperkalemia, hypotension, and death. This study separately assessed the incidence rates and relative risks of (i) hyperkalemia, (ii) hypotension, and (iii) death in users of aliskiren compared to users of other antihypertensive drugs.

8 Amendments and updates to the protocol

Not applicable.

9 Research methods

9.1 Study design

This was a cohort study with secondary use of data based on two United States (US) longitudinal healthcare claims databases (i.e. MarketScan® and UnitedHealth Research Database, see also Section 9.5 for more details). This design provides direct estimates of risk (as incidence) for study outcomes, facilitates comparison across exposure groups along with adjustment through propensity score (PS) techniques, and permits straight-forward subgroup analyses, all of which are of interest in this study.

The study identified contemporaneous cohorts of aliskiren and other antihypertensive medication initiators within the databases and identified outcomes that occurred during the follow-up of the cohorts. Comparisons of outcomes among aliskiren users to those among other antihypertensive medication users were the focus of analyses that involved control for confounding through propensity scores and several pre-specified subgroup analyses and pre-specified exposure measures, including intent-to-treat (ITT), as-treated, and cumulative dose analyses. The ITT analysis mimics the analytic approach used in ALTITUDE and therfore, provides for the most direct comparison to it, while as-treated and cumulative dose analyses provide alternate exposure measurements that reflect actual use and assess the effect of aliskiren exposure more directly.All analyses were 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 for primary outcomes were also pooled over the databases with an indicator of the database added as a pre-defined covariate for adjustment in the final outcome model.

This study was approved by the [redacted] IRB and registered in the EU PAS register (ENCEPP/SDPP/3577).

9.2 Setting

The study population was selected from two US data sources: (1) US MarketScan® Commercial Claims and Encounters database and Medicare Supplement provided by Novartis and (2) UnitedHealth Research Database provided by [redacted] (for more details on data sources, see also Section 9.5) as patients who had a first-time recorded dispensing between 1 March 2007 and 30 June 2012 for aliskiren (aliskiren cohort) or another antihypertensive drug (comparison cohort).

For the detailed list of antihypertensive drugs, see Annex 2-Table 2-1.

9.3 Subjects

9.3.1 Inclusion criteria

Patients were required to have the following:

- At least one prescription for aliskiren or another antihypertensive drug between 1 March 2007 and 30 June 2012
- 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)

- At least 18 years old at the time of the first prescription for aliskiren or other antihypertensive drug
- Valid data for age and sex
- At least one inpatient or outpatient ICD-9 diagnosis code of hypertension (401.xx - 405.xx) during the baseline period

9.3.2 Exclusion criteria

Patients not meeting inclusion criteria were excluded; no separate additional exclusion criteria were applied.

9.4 Variables

9.4.1 Exposure

There were three cohorts formed from the eligible study population (detailed below). Primary analyses included patients with a diagnosis code of hypertension (HTN) during the baseline period while a secondary analysis included patients with or without HTN diagnosis (obtained by expanding the initial study selection criteria). For all cohorts, the index exposure and index date were defined based on the first prescription for an antihypertensive drug of interest (aliskiren or a comparator) such that there were no prescriptions for an antihypertensive of the same type in the 6 months prior (but there may have been prescriptions for other antihypertensives during that period).

9.4.1.1 Details of three study cohorts

Cohort 1 – Any new use of aliskiren

This cohort includes all patients initiating aliskiren or another antihypertensive for any indication. The comparison is 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, but not limited to ACEIs, ARBs, and CCBs both as free- or fixed-dose combination). Patients from Cohort 2 and 3 are also included in this cohort. The comparator exposure is initiation of another antihypertensive, including monotherapy as well as concomitant therapy of two or more antihypertensives.

Cohort 2 – Any new use of aliskiren as add-on to ACEI or ARB

This cohort consists 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) is 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.

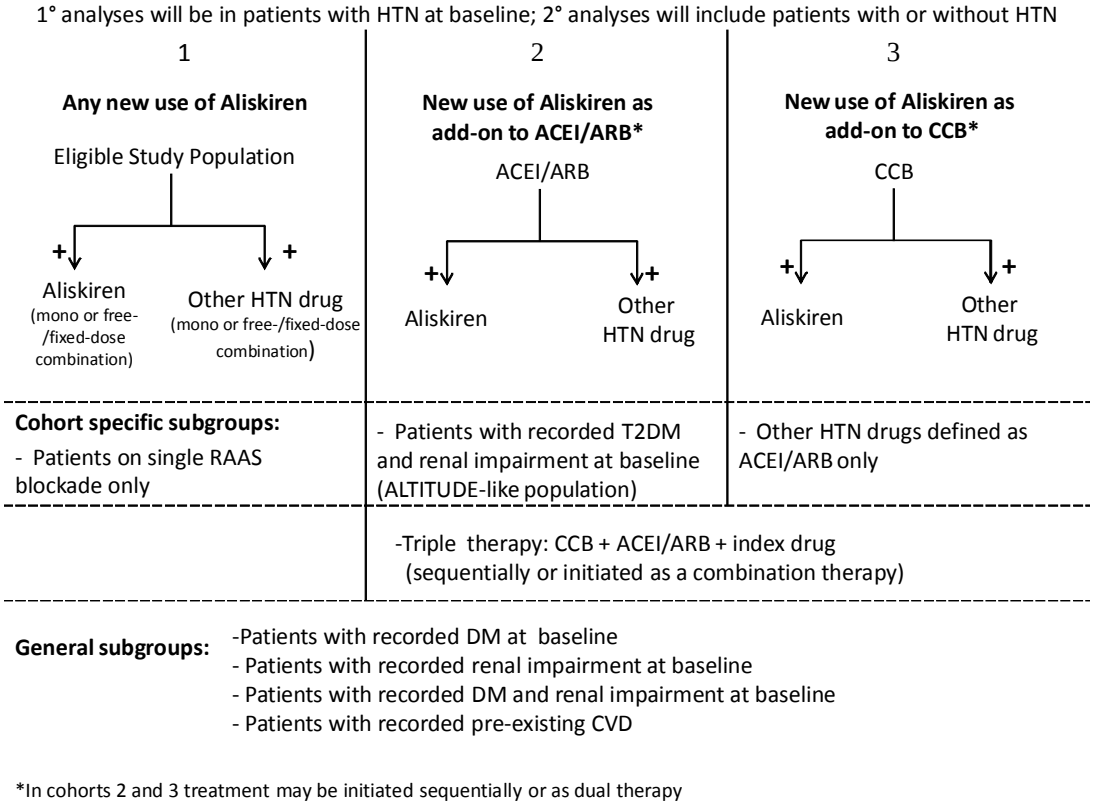
Cohort 3 – Any new use of aliskiren as add-on to calcium channel blockers (CCB)

This cohort consists of patients initiating aliskiren for any indication in addition to a CCB compared to patients initiating any other antihypertensive in addition to a CCB. Addition is

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.

A graphical representation of the three study cohorts is displayed in Figure 9-1.

Figure 9-1 Three aliskiren exposure groups and comparison groups in the cohort study



9.4.2 Subgroups

The following sub-populations were considered in all three cohorts. These subgroup variables (for details including codes – see Annex 2-Table 2-2) were ascertained at baseline and identified potential effect modifiers considered.

- Patients with recorded diabetes mellitus (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).

In addition:

- For Cohort 1 (any new use of aliskiren), a subset of patients on single RAAS blockade therapy was formed by excluding patients on double RAAS blockade (any combination of aliskiren, ACEI, or ARB) on index date.
- For Cohort 2 (new use of aliskiren as an add-on to ACEI/ARB), a subset with a baseline diagnosis of T2DM and renal impairment formed the "ALTITUDE-like" population.
- For Cohort 3 (new use of aliskiren as an add-on to a CCB), patients initiating aliskiren were compared with patients initiating ACEI/ARB as a subgroup of other antihypertensive drug.
- For Cohorts 2 and 3, a subset of patients on triple therapy ACEI/ARB + CCB + index exposure drug (either aliskiren or a comparator antihypertensive) formed the triple therapy subgroup. These therapies could be initiated either sequentially or at the same time; however, the therapies initiated prior to the index date were required to have days' supply spanning the index date, representing concomitant use.

Additional exploratory analyses included stratifying by subgroups of age (≥ 65 versus < 65 years), sex, and quintiles of the estimated propensity to receive aliskiren. Quintile 1 is the lowest quintile of the propensity score, quintile 5 is the highest, meaning that quintile 1 is populated with aliskiren recipients and comparators who are empirically least similar to the typical aliskiren initiator, while quintile 5 contains patients (initiators of aliskiren and comparators) who are empirically the most typical aliskiren initiators.

9.4.3 Other variables

For additional variables, see Section 9.5.3 (covariates) and Section 9.5.5 (outcomes).

9.5 Data sources and measurement

9.5.1 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 Truven Health Analytics™ 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).

The Medicare Supplemental and Coordination-of-benefits (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 is 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).

9.5.2 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 United Healthcare insurance.

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

9.5.3 Measurements – covariates

The pre-defined covariates were ascertained on the basis of enrollment information and claims during the 6 months preceding (and including the date of) the index dispensing and included demographic characteristics (e.g., age, sex, region, plan type), coexisting medical conditions (e.g., heart diseases such as coronary artery disease, hypertension, heart failure, arrthythmia; metabolic disorders including diabetes, hyperlipidemia; cerebrovascular disorders; renal impairment, etc.), prior medications (e.g., antihypertensives, antiplatelets, anticoagulants, antidiabetics, etc.), and health care utilization (e.g., number of hospitalizations, number of physician visits, number of laboratory tests ordered, etc.). See Annex 2-Table 2-2 for the full list of pre-defined covariates and their definitions.

The diagnosis-based covariate definitions were intended to reflect a reasonable balance of sensitive and specific measurement. This is contrary to the more specific definitions used for the study endpoints (Schneeweiss and Avorn 2005). Throughout this document, these variables are referred to as the “pre-defined” covariates. These variables were also used for

building the propensity scores, and they were of primary interest when assessing the comparability of aliskiren patients versus comparator patients.

9.5.4 Measurements – follow-up

Patients were 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 (30 June 2012), whichever came first. For the as-treated analysis, an additional end of follow-up occurred with discontinuation of the drug exposure at cohort entry. In Cohorts 2 and 3 where the cohort entry required a concomitant antihypertensive drug (ACEI/ARB or CCB) in addition to aliskiren or a comparator, follow-up ended on the day when at least one of the required drugs was discontinued. Medication discontinuation was defined as a 30-day gap with no prescriptions for the index medication following the end of the days' supply for the previous prescription.

Patients were not censored at the occurrence of other outcome events besides the outcome of interest; for example, in the analysis of ESRD, patients were not censored for stroke, TIA, MI, etc.

9.5.5 Measurements – outcomes

The primary safety outcomes include treatment emergent:

- Cerebrovascular accidents
- Stroke (both hemorrhagic and ischemic)
- Ischemic stroke
- Hemorrhagic stroke
- TIA
- MI
- Heart failure hospitalization
- ARF
- ESRD – defined as initiation of persistent dialysis or renal transplantation

The outcomes of stroke and TIA were identified and analyzed separately since the performance characteristics (sensitivity, specificity, positive predictive value [PPV]) of diagnosis codes for these two outcomes differ substantially (Holick et al 2009). The outcome of cerebrovascular accident was defined on the basis of a validated algorithm (Roumie et al 2008), while the outcomes ischemic stroke and hemorrhagic stroke were defined using different algorithms (see Annex 2-Table 2-3). The outcome stroke is the sum of ischemic and hemorrhagic strokes, and since the algorithms differ, the variable stroke is not equal to the variable cerebrovascular accident. The variable ESRD was used to identify patients who developed renal failure. This is also in line with the primary renal event of the ALTITUDE study (ESRD 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 concentration, sustained for at least a month). However, this study does not assess renal death or doubling of baseline serum creatinine concentration as these events are not included in the health insurance claims databases.

The secondary safety endpoints of interest include treatment emergent:

- Hyperkalemia
- Hypotension
- Death

These outcomes are considered secondary due to the potential for them to be incompletely captured within the data sources used for this study. In medical claims databases, laboratory-based adverse events (AEs) along with those based on symptoms are incompletely captured, and similarly death is incompletely captured, primarily coming from hospital discharge status (including Emergency Department discharge). In the United database, death was identified through linkage to Social Security Death Master in addition to hospital discharge status and therefore, two separate outcomes, Death from any cause and Death from any cause in a hospital, were assessed. For MarketScan data, only the outcome of Death from any cause in a hospital was evaluated.

Details on coding of primary and secondary outcomes of interest can be found in Annex 2-Table 2-3.

9.6 Bias

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. A large number of potential confounders was identified (see Section 9.5.3) that were assessed at baseline (6 months leading up to and including the date of index dispensing) in the claims data sources.

9.7 Study size

Combining the MarketScan and UnitedHealth data was expected to provide approximately 95,000 aliskiren users, of whom 25,000 would be age 65 or older, and approximately 5,000 were expected to match the ALTITUDE population. The duration of follow-up among these groups was expected to vary by analysis, and power was assessed by assuming an average follow-up of 6 months.

The full aliskiren population of 95,000 across the two databases was expected to include some patients who would not enter into analyses due to application of exclusion criteria or the process of PS-matching. To account for this, the study was expected to retain approximately 90% power for identifying a relative risk of outcomes even if only 70% of the aliskiren patients were retained in the analyses (~ 67,000 aliskiren users), and they were expected to contribute close to 34,000 person-years [PYs] of aliskiren exposure. These assumptions meant that the study was expected to provide approximately 90% power to detect a relative risk of 1.30 for an infrequently occurring outcome such as MI (expected incidence 5/1,000 PYs), and considerably higher power for more frequently occurring outcomes. Among the subset of patients older than 65 years, a similar set of assumptions (including 70% matching) meant that there would be approximately 17,500 aliskiren users who would contribute close to 9,000 PYs of aliskiren exposure, which would provide close to 80% power to detect a relative risk of 1.50 for MI among this subgroup.

The actual study accrual numbers and average follow-up exceeded projections, so the study met the *a priori* power expectations. A more direct assessment of study power for a completed study can be seen in the width of the confidence intervals of effect estimates, and the narrow confidence intervals around study effect measures for this study indicates suitable power for identifying relative risks of the size anticipated (relative risk of 1.3 to 1.5).

9.8 Data transformation

The source data for this study are the health insurance transactions between two large health insurers and providers of healthcare services. These transactional records are routinely conducted for reimbursement of healthcare services. The source data are transformed from raw insurance claims to a series of indicator variables (yes/no) for the presence or absence of patient characteristics (covariates) on a given date or in the 6-month period leading up to a given date. During follow-up, the occurrence of a claim for an outcome condition is taken as the occurrence of the outcome on the date corresponding to the claim according to Section 9.5.5.

9.9 Statistical methods

The statistical methods applied in this study are appropriate for observational follow-up studies (cohort studies). Patients in the study cohorts contribute person-time at risk of outcomes and outcomes that are observed are counted in the appropriate cohort.

9.9.1 Main summary measures

This study estimates the relative incidence (as a hazard ratio [HR]) of each outcome comparing patients initiating aliskiren to patients initiating other antihypertensive medications.

9.9.2 Main statistical methods

Confounding by indication is an important threat to the validity in non-randomized studies of treatment effects (Walker 1996). All analyses were conducted in PS-matched cohorts (see Section 9.9.2.1) to achieve a high degree of multivariate confounding control (Schneeweiss and Avorn 2005, Schneeweiss 2010). In addition, counts and incidence rates (IRs) are reported in the population of patients that are exposed to aliskiren but who could not be matched to comparable non-users of aliskiren. However, a formal comparison of this group of patients was not performed since a valid comparison group could not be identified.

In addition, although many analyses on the outcomes were performed, no adjustment was formally done for multiple comparisons. Rather than conducting formal hypothesis testing, this study aims to estimate the association of aliskiren with study outcomes relative to comparison treatments across numerous exposures and exposure subgroups. Estimates and 95% confidence intervals (CIs) for each comparison are presented without adjustment for multiplicity, and these 95% CIs can be interpreted independently as including the true association value approximately 95% of the time, even where multiple comparisons have been made.

9.9.2.1 Propensity score matching

Balance in patient characteristics was 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. The primary propensity score was estimated for each patient using a logistic regression model that included all pre-defined covariates as well as interactions between subgroup indicators and major confounders (Rassen et al 2012a). The major confounders were limited to age, sex, and the top 3 confounders as ranked by the high-dimensional propensity score (hdPS) algorithm (see Section 9.9.4.1 for hdPS details) with respect to their potential for bias. One primary propensity score was estimated in each of the 3 cohorts.

Matching was performed using variable-ratio nearest-neighbor matching with a maximum match ratio of 1:4 (Rassen et al 2012b), which has been shown to preserve the intrinsic advantages of cohort matching combined with the efficiency of using a large comparator group. We limited the caliper to 0.025 on the propensity score, so that comparator patients were matched to an aliskiren user only if their propensity score differed by no more than 2.5% (Austin 2011).

To assess balance on patient characteristics through matching, all pre-defined covariates were compared in aliskiren and comparator drug exposed matched patients. The standardized difference was not greater than 0.1 on any major confounder (Austin 2008), so further measures such as re-matching patients using a narrower propensity score caliper or re-estimating the propensity score model were not considered.

9.9.2.2 Primary and secondary analyses

The primary analysis was conducted with exposure defined analogously to an intent-to-treat analysis (ITT) in a randomized controlled trial. In this analysis, the exposure at cohort entry was carried forward until a patient had an event, disenrollment from the database, or the end of the study period was reached.

Secondary analyses defined exposure on an as-treated basis, so that exposure to the index medication was terminated if the patient discontinued 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 were censored at the end of the first such gap.

In each of these analyses, for the propensity score matched population, we identified the occurrence of each of the specified outcomes and tabulated the results as counts of events for each outcome and the number of people and person-years at risk for each outcome. We developed IRs (counts of events divided by person-time) along with 95% CIs. The relative risk (expressed as HR) with 95% CIs was estimated among initiators of aliskiren relative to initiators of comparator agents using Cox regression models that account for matching by stratifying on the matching ratio.

All analyses were 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 for primary outcomes were also pooled over the databases with an indicator of the database added as a pre-defined covariate for adjustment in the final outcome model.

9.9.2.3 Subgroups

For each subgroup (see Section 9.4.2), we identified patients within the matched populations that satisfied the subgroup inclusion criteria and repeated the checks of balance to assess whether the overall balance of the cohorts was retained in the subgroups. There were a few variables that were out of balance in specific subgroups, but no individual variables that were consistently out of balance across subgroups, so the propensity score (a summary of each individual variable) was included in outcome Cox proportional hazards models within subgroups as a continuous variable.

9.9.3 Missing values

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

Each of the other study variables (exposure, covariates, and outcomes) was considered present where represented by an appropriate code (NDC, ICD-9, CPT, or death indicator). Thus, lack of a code represented non-presence of the variable rather than missing. This coding approach is appropriate for comprehensive health insurance databases (such as the ones that form the basis for this study) (Schneeweiss and Avorn 2005).

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

9.9.4 Sensitivity analyses

Several sensitivity analyses were conducted:

9.9.4.1 High-dimensional propensity score (HdPS)

This approach seeks 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 (Schneeweiss et al 2009, Rassen et al 2011). These empirically identified confounders were combined with the pre-defined covariates (from Section 9.5.3) to improve confounding adjustment. Such hdPS approaches have been shown to improve validity in longitudinal claims data studies, particularly when combined with pre-specified covariates (Patorno et al 2010, Huybrechts et al 2011, Rassen and Schneeweiss 2012, Garbe et al 2013) as well as in simulation studies (Myers et al 2012, Rassen et al 2012c). In each of the three cohorts, the hdPS incorporated the pre-defined covariates and their interactions as well as numerous empirically identified patient characteristics. In each cohort, we matched patients based on this hdPS and assessed the result relative to that obtained using the propensity score development and matching specified in Section 9.9.2.1.

9.9.4.2 ITT stratified by duration of follow-up

To explore time-varying treatment effects within the ITT analysis, we conducted an exploratory analysis that stratified the duration of follow-up into 6-month intervals (0-6, 7-12, 13-18, > 18 months). In this analysis, we estimated separate HRs for each 6-month interval of follow-up time. Patients that were censored or had an event prior to the beginning of an interval did not contribute information to the HR estimate for that interval.

9.9.4.3 ITT stratified by cumulative exposure

To explore variation in treatment effects with varying cumulative exposure within the ITT analysis, we conducted an exploratory analysis that was stratified based on the cumulative exposure to the index medication. Cumulative exposure was measured as the total days covered with the index medication during follow-up and was calculated on as-treated basis regardless of breaks in therapy. Person-time was calculated on ITT basis. After examination of cumulative exposure in both exposure groups, the following categories were evaluated: cumulative exposure < 6 months (183 days), cumulative exposure from 6 months to 18 months, and cumulative exposure > 18 months. A separate HR was estimated in each category. The analyses for 2nd and 3rd categories were additionally adjusted for propensity score, which was added as a continuous variable to the outcome model.

9.9.4.4 Laboratory results assessment

In addition, although limited in its ability to identify laboratory-based outcomes, the study assessed the association of aliskiren relative to other antihypertensive medications on outpatient laboratory test results (focusing on potassium and serum creatinine). These test results were available for a subset of cohort members (approximately 25% of the United Health patients). Laboratory test results were analyzed during baseline period (the test closest to the index date was used) to assess baseline balance obtained through propensity score matching. The frequency of these tests performed during the first year of follow-up for those patients who had them available at baseline was analyzed to assess the intensity of surveillance during follow-up.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 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 were used for this study represent adjudicated claims that have been further processed for usability and for assurance of patient confidentiality.

Under stewardship of the [redacted], the data reside on a Linux-based computer cluster in Partners Healthcare System's state-of-the-art data center located in a secure location in the Boston area. This facility houses clinical systems and electronic medical records for [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] Security, 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 Department of Defense standard for data security, and are stored in a locked facility.

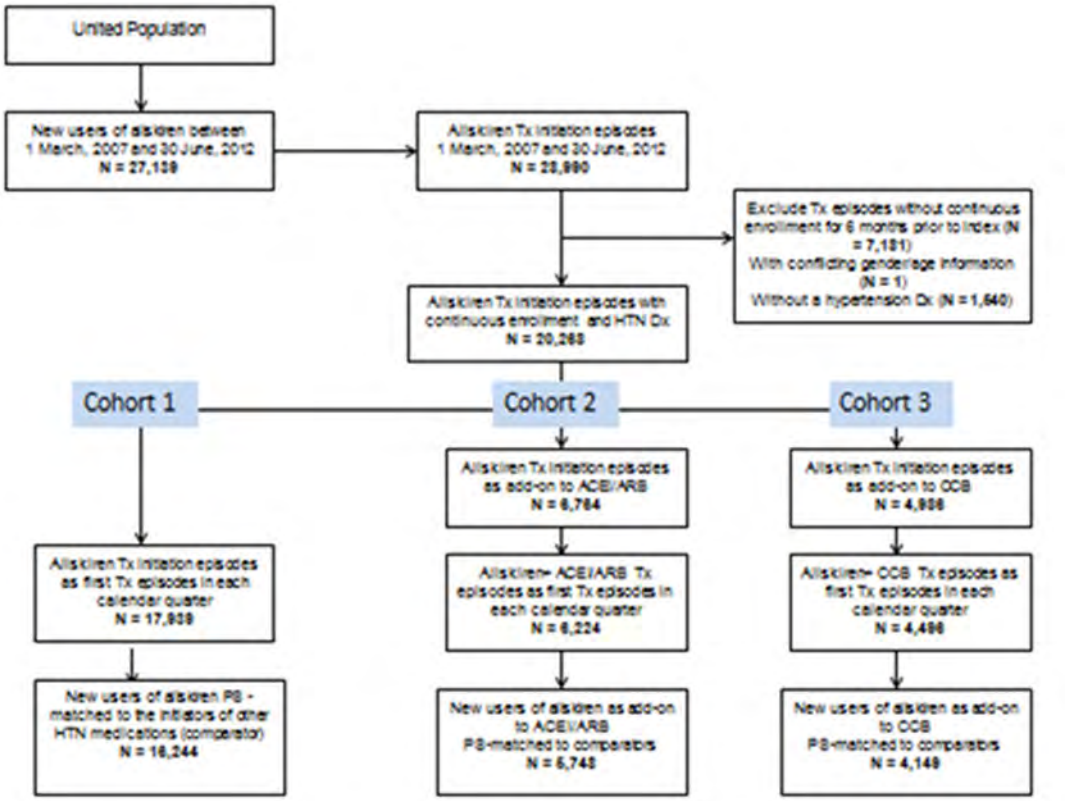
All aspects of data analysis were conducted according to standard procedures of the [redacted]. Programming for this project was conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing and analysis steps, the validation analyst reviewed the program along with input and output data sets, and for select steps of the project employed double programming techniques to reduce the potential for programming errors.

10 Results

10.1 Participants

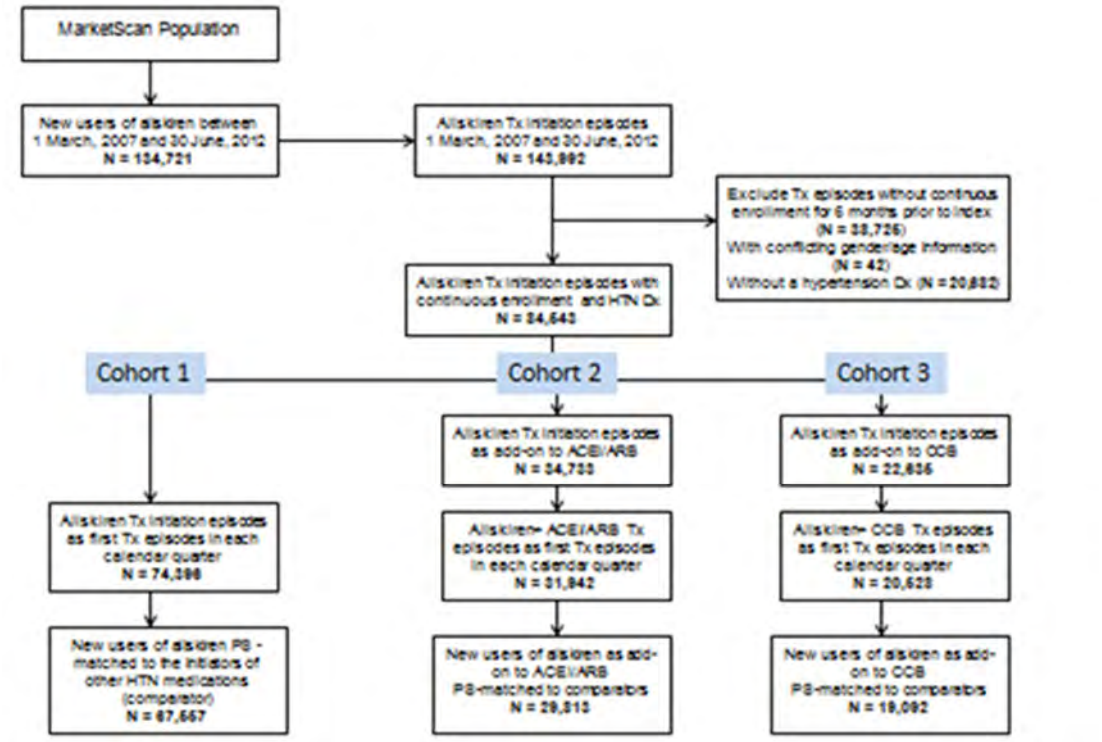
The patient flow chart in each database and the final number of aliskiren and comparator patients in each cohort is shown in the following figures.

Figure 10-1 Patient flow chart for aliskiren patients – United database



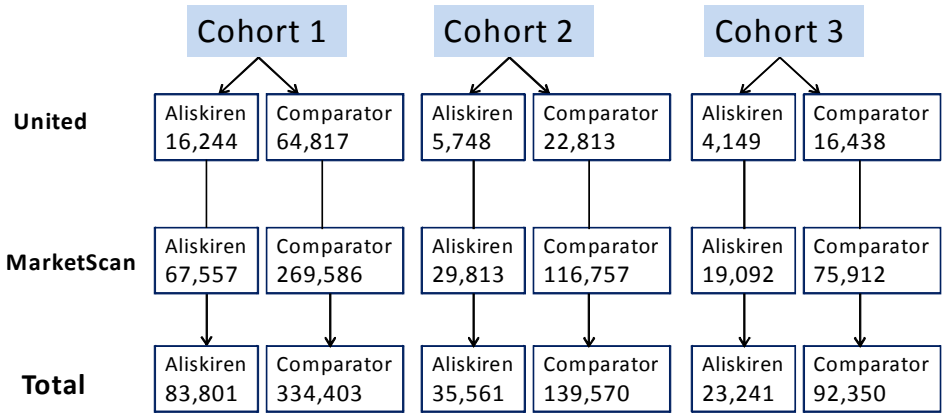
ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Dx = diagnosis; HTN = hypertension; PS = propensity score; Tx = treatment

Figure 10-2 Patient flow chart for aliskiren patients – MarketScan database



ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Dx = diagnosis; HTN = hypertension; PS = propensity score; Tx = treatment

Figure 10-3 Number of patients in each cohort and exposure group, stratified by database and overall



Overall, 83,801 aliskiren-exposed patients were included from United and MarketScan in Cohort 1 together with 334,403 PS-matched comparator patients exposed to other antihypertensive drugs.

10.2 Descriptive data

Table 10-1 presents selected baseline characteristics of PS-matched patients pooled over the two databases from each cohort. As can be seen from the table, PS-matching resulted in very similar patient populations exposed to aliskiren and comparator antihypertensive drugs across the three cohorts with respect to demographic characteristics, as well as frequency of comorbid conditions, prior medications, and health care utilization.

For full pooled patient characteristic information, see Annex 2-Table 2-4.

Table 10-1 Baseline characteristics of each cohort, stratified by exposure group (data pooled from both databases)

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Demographics	**%**	**%**	**%**	**%**	**%**	**%**
Age: 18-39	8.2	8.2	5.3	5.4	3.7	3.7
Age: 40-54	37.4	37.5	27.3	27.2	24.8	24.5
Age: 55-64	37.9	37.8	36.8	36.6	36.1	36.3
Age: 65+	16.6	16.5	30.6	30.8	35.4	35.5
Male	56.5	56.6	53.0	53.1	52.9	52.9
Coexisting medical conditions						
Atherosclerosis	13.1	13.0	16.2	16.4	17.0	17.2

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Heart failure (CHF)	2.9	2.9	4.3	4.4	4.4	4.4
Cardiovascular disease	26.7	26.5	31.6	31.8	34.9	34.9
Diabetes	27.5	27.4	32.9	33.1	33.8	33.5
Diabetes and renal impairment	4.2	4.1	4.8	4.8	5.3	5.3
Hemorrhagic stroke	1.5	1.5	1.9	1.9	2.2	2.3
Hyperkalemia	0.9	0.9	1.1	1.2	1.6	1.5
Hyperlipidemia	43.2	43.4	44.6	44.6	43.8	43.9
Ischemic stroke	1.5	1.5	1.9	2.0	2.5	2.5
Previous MI	0.7	0.7	1.0	1.0	1.0	1.0
Previous TIA	1.6	1.6	1.8	1.9	2.1	2.2
Renal impairment	8.1	8.0	11.0	11.0	12.9	12.8
Type 2 diabetes	26.2	26.2	31.3	31.6	32.2	31.9
Prior medications						
Alpha blocker	3.6	3.6	4.4	4.5	5.7	5.7
Combined alpha and beta blocker	9.4	9.2	11.8	11.9	12.0	11.7
ACE inhibitor	21.0	21.0	39.1	39.1	29.4	29.7
Aliskiren	0.0	1.0	0.0	1.4	0.0	1.9
Anti-arrhythmic drug	1.6	1.5	2.2	2.1	2.4	2.4
ARB	20.1	19.7	38.2	37.7	25.8	25.2
Aspirin	0.1	0.0	0.1	0.1	0.1	0.1
Aspirin/dipyridamole	0.4	0.4	0.5	0.5	0.6	0.6
Beta blocker	30.1	30.2	34.9	35.1	37.2	37.5
Calcium channel blocker	31.3	31.2	38.1	38.1	88.6	88.4
Clopidogrel	7.0	7.1	8.8	9.0	9.9	9.9
Diabetes medications	23.4	23.4	28.1	28.3	28.5	28.4
Insulin	8.3	8.2	11.0	11.0	11.3	11.0
Loop diuretic	13.4	13.2	18.9	18.8	18.8	18.5
NSAIDs	19.2	19.2	19.5	19.4	19.9	19.9
Oral anticoagulants	4.2	4.2	5.7	5.7	6.3	6.3
Other hypertension medications	11.0	10.8	14.0	14.0	18.0	17.8
Other lipid-lowering drugs	16.7	16.8	18.9	18.8	19.8	19.6
Potassium sparing agents/aldosterone antagonists	6.5	6.6	7.6	7.5	8.3	8.1
Potassium supplements	11.4	11.3	14.1	14.2	16.9	16.9
Statin	43.2	43.2	49.1	49.4	50.2	50.5
Thiazide diuretic	43.1	42.9	39.1	39.3	51.0	50.9
Health Care Utilization	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of medications	7.9 (5.3)	7.8 (4.9)	8.4 (5.9)	8.4 (5.4)	9.6 (5.5)	9.5 (5.1)

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Number of hospitalizations	0.1 (0.4)	0.1 (0.3)	0.2 (0.5)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Number of physician office visits	5.9 (4.4)	5.8 (4.2)	6.4 (4.7)	6.3 (4.4)	6.6 (4.8)	6.6 (4.5)
Number of cardiologist visits	0.8 (1.8)	0.8 (1.4)	0.9 (2.0)	0.9 (1.6)	1.0 (2.2)	1.0 (1.7)
Number of laboratory tests ordered	2.7 (3.0)	2.7 (2.5)	2.9 (3.3)	2.9 (2.8)	2.9 (3.5)	2.9 (2.9)

Details of baseline characteristics of Cohort 1, stratified by database can be found in Annex 2-Table 2-5; for Cohort 2 in Annex 2-Table 2-6; and for Cohort 3 in Annex 2-Table 2-7.

10.3 Outcome data

See Section 10.4 for counts of outcomes within the study cohorts.

10.4 Main results

Main results are presented in tabular form below and described subsequently.

In ITT analyses for Cohort 1, hemorrhagic stroke was the only outcome associated with an increased relative risk in users of aliskiren versus comparators (HR 1.23; 95% CI: 1.0-1.46), while the remaining outcomes showed no risk increase or even a risk decrease (MI, heart failure, ARF, ESRD) in association with aliskiren exposure. Relative risk estimates were similar for Cohorts 2 and 3. Primary outcomes of interest from the ITT analysis are displayed in Table 10-2 for all three cohorts.

Table 10-2 Hazard ratios of primary outcomes in each cohort, ITT analysis

Outcome	Events	Rate per 1,000 person-yrs	Events	Rate per 1,000 person-yrs	HR (95% CI)
Cohort 1	**Aliskiren (N = 83,801)**		**Comparator (N = 334,403)**		
Cerebrovascular accidents	951	6.0	3,481	5.6	1.07 (0.99 - 1.15)
Stroke	1,546	9.8	5,940	9.6	1.02 (0.96 - 1.08)
Ischemic stroke	1,456	9.2	5,671	9.1	1.01 (0.95 - 1.06)
Hemorrhagic stroke	166	1.0	530	0.8	1.23 (1.03 - 1.46)
Transient ischemic attack	457	2.9	1,702	2.7	1.05 (0.95 - 1.16)
Myocardial infarction	657	4.1	2,820	4.5	0.91 (0.84 - 0.99)
Heart failure	1,395	8.8	6,240	10.1	0.87 (0.82 - 0.92)
Acute renal failure	3,878	24.9	15,872	26.0	0.96 (0.92 - 0.99)
End-stage renal disease	931	5.9	4,092	6.6	0.89 (0.83 - 0.95)
Cohort 2	**Aliskiren (N = 35,561)**		**Comparator (N = 139,570)**		
Cerebrovascular accidents	442	7.2	1,675	7.1	1.02 (0.92 - 1.14)
Stroke	737	12.1	2,949	12.5	0.97 (0.89 - 1.05)
Ischemic stroke	698	11.5	2,820	12.0	0.96 (0.88 - 1.04)
Hemorrhagic stroke	73	1.2	251	1.1	1.14 (0.88 - 1.48)
Transient ischemic attack	209	3.4	756	3.2	1.08 (0.92 - 1.25)

Outcome	Events	Rate per 1,000 person-yrs	Events	Rate per 1,000 person-yrs	HR (95% CI)
Myocardial infarction	307	5.0	1,339	5.7	0.88 (0.78 - 1.00)
Heart failure	744	12.2	3,555	15.2	0.81 (0.74 - 0.87)
Acute renal failure	2,019	34.0	8,315	36.3	0.93 (0.89 - 0.98)
End-stage renal disease	540	8.8	2,367	10.0	0.87 (0.79 - 0.96)
Cohort 3	**Aliskiren (N = 23,241)**		**Comparator (N = 92,350)**		
Cerebrovascular accidents	294	6.9	1,311	7.9	0.86 (0.76 - 0.98)
Stroke	530	12.4	2,246	13.6	0.91 (0.83 - 1.00)
Ischemic stroke	506	11.9	2,148	13.0	0.91 (0.83 - 1.00)
Hemorrhagic stroke	46	1.1	205	1.2	0.87 (0.63 - 1.20)
Transient ischemic attack	163	3.8	620	3.7	1.02 (0.86 - 1.21)
Myocardial infarction	237	5.5	1,077	6.5	0.85 (0.74 - 0.98)
Heart failure	561	13.2	2,557	15.5	0.84 (0.77 - 0.92)
Acute renal failure	1,589	38.5	6,453	40.3	0.95 (0.90 - 1.01)
End-stage renal disease	448	10.5	2,031	12.3	0.85 (0.77 - 0.94)

In the as-treated analyses, none of the outcomes in Cohort 1 showed any relative risk increase in association with aliskiren use, while heart failure, ARF, and ESRD again showed a decreased risk in patients exposed to aliskiren versus comparators, as already seen in the ITT analysis. In Cohort 2, hemorrhagic stroke was associated with an increased risk in users of aliskiren (HR 1.61 95% CI: 1.00-2.58), while otherwise results were comparable to those seen in Cohort 1. Results seen in Cohort 3 also were comparable with those from Cohort 1 (for details on the as-treated analyses, see Table 10-3).

Table 10-3 Hazard ratios of primary outcomes in each cohort, as-treated analysis

Outcome	Events	Rate per 1,000 person-yrs	Events	Rate per 1,000 person-yrs	HR (95% CI)
Cohort 1	**Aliskiren (N = 83,801)**		**Comparator (N = 334,403)**		
Cerebrovascular accidents	300	4.9	1,143	5.0	1.00 (0.88 - 1.13)
Stroke	507	8.4	2,019	8.9	0.95 (0.86 - 1.05)
Ischemic stroke	485	8.0	1,918	8.5	0.96 (0.87 - 1.06)
Hemorrhagic stroke	44	0.7	186	0.8	0.90 (0.65 - 1.25)
Transient ischemic attack	149	2.5	580	2.6	0.98 (0.82 - 1.17)
Myocardial infarction	221	3.6	936	4.1	0.88 (0.76 - 1.02)
Heart failure	458	7.6	2,380	10.5	0.73 (0.66 - 0.81)
Acute renal failure	1,485	24.6	6,125	27.2	0.91 (0.86 - 0.97)
End-stage renal disease	281	4.6	1,516	6.7	0.70 (0.62 - 0.79)
Cohort 2	**Aliskiren (N = 35,561)**		**Comparator (N = 139,570)**		
Cerebrovascular accidents	133	6.5	448	6.5	1.04 (0.86 - 1.26)
Stroke	218	10.6	807	11.7	0.94 (0.81 - 1.09)
Ischemic stroke	205	10.0	775	11.3	0.92 (0.79 - 1.07)
Hemorrhagic stroke	25	1.2	55	0.8	1.61 (1.00 - 2.58)
Transient ischemic attack	63	3.1	191	2.8	1.17 (0.88 - 1.56)
Myocardial infarction	87	4.2	326	4.7	0.92 (0.72 - 1.16)
Heart failure	219	10.6	1,085	15.8	0.71 (0.62 - 0.82)

Outcome	Events	Rate per 1,000 person-yrs	Events	Rate per 1,000 person-yrs	HR (95% CI)
Acute renal failure	686	33.5	2,651	38.8	0.89 (0.82 - 0.97)
End-stage renal disease	153	7.4	673	9.8	0.79 (0.67 - 0.95)
Cohort 3	**Aliskiren (N = 23,241)**		**Comparator (N = 92,350)**		
Cerebrovascular accidents	66	5.1	332	7.2	0.72 (0.56 - 0.94)
Stroke	133	10.4	598	13.1	0.81 (0.67 - 0.98)
Ischemic stroke	128	10.0	567	12.4	0.82 (0.68 - 1.00)
Hemorrhagic stroke	7	0.5	52	1.1	0.50 (0.23 - 1.11)
Transient ischemic attack	37	2.9	149	3.3	0.92 (0.64 - 1.32)
Myocardial infarction	62	4.8	245	5.3	0.90 (0.68 - 1.19)
Heart failure	154	12.0	783	17.1	0.72 (0.61 - 0.86)
Acute renal failure	463	36.2	2,046	45.1	0.83 (0.75 - 0.92)
End-stage renal disease	114	8.9	597	13.0	0.71 (0.58 - 0.86)

See Annex 2-Table 2-8, Annex 2-Table 2-9, Annex 2-Table 2-10 for ITT analyses, and Annex 2-Table 2-11, Annex 2-Table 2-12, Annex 2-Table 2-13 for as-treated analyses for Cohorts 1, 2, and 3, respectively, stratified by database.

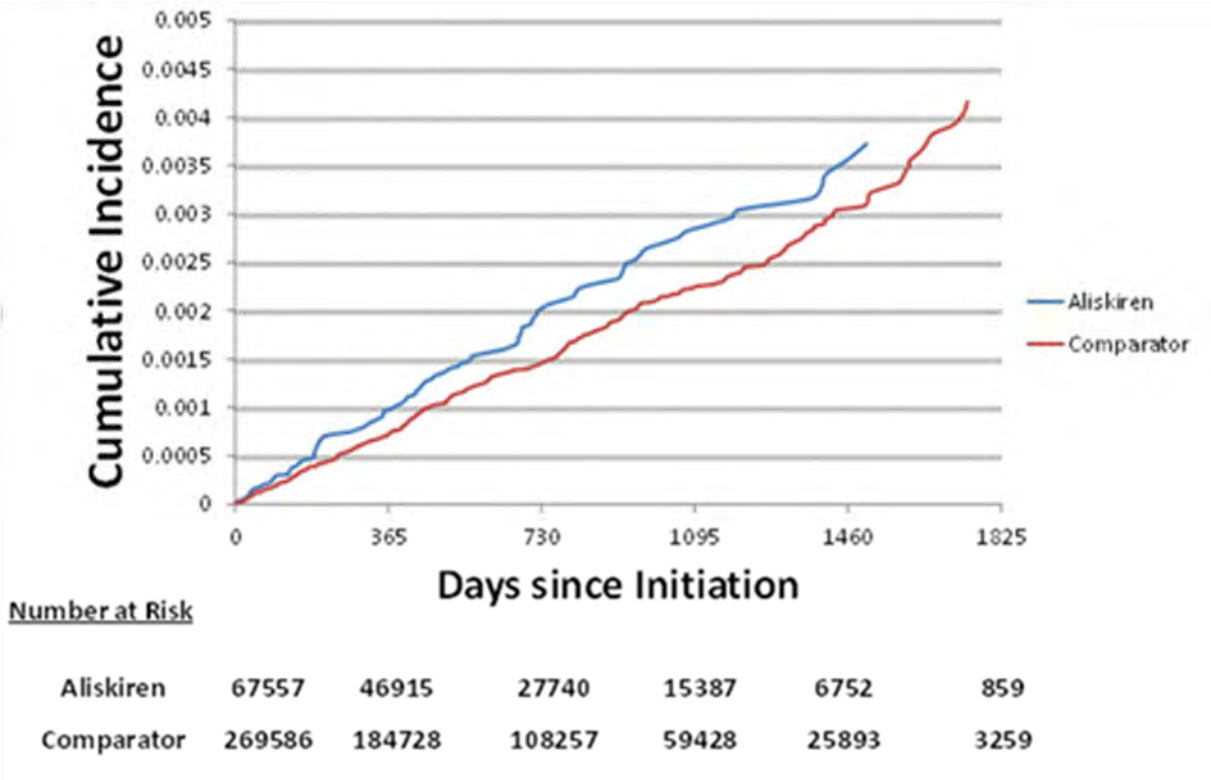
Figures of cumulative incidence curves for each outcome (ITT analysis) are presented in Annex 2.5.1, Annex 2-Figure 2-1 to Annex 2-Figure 2-54 (stratified by cohorts and databases).

10.4.1 Cohort 1 – any new use of aliskiren

Across the outcomes of CVA, stroke, ischemic stroke and TIA, the HRs were close to 1.0 with narrow confidence intervals that include 1.0, a pattern consistent with neither increase nor decrease in risk for these outcomes (for details, see Table 10-2 for ITT and Table 10-3 for as-treated analyses).

Hemorrhagic stroke: This outcome presents considerable heterogeneity. While the main ITT analyses in either pooled data (HR = 1.23, 95% CI: 1.03-1.46; Table 10-2) or the MarketScan subset (HR = 1.31, 95% CI 1.07-1.61; see Annex 2-Table 2-8) suggest an increased risk, the as-treated pooled anylsis does not (HR = 0.90, 95% CI: 0.65-1.25; Table 10-3) and the subset of data derived from United does not (HR for ITT= 1.04, 95% CI: 0.75-1.44, see Annex 2-Table 2-8). The comparison of the cumulative incidence in the MarketScan ITT analysis (see Figure 10-4) reveals that the increased incidence among aliskiren users becomes more apparent after approximately 6 months of follow-up (which is the average follow-up in the as-treated analysis).

Figure 10-4 Cumulative incidence of hemorrhagic stroke in Cohort 1 – MarketScan patients (ITT analysis)



The outcomes myocardial infarction, heart failure, acute renal failure, and end-stage renal disease have HRs below 1.0 with narrow confidence intervals that exclude 1.0 (except for MI 'as-treated'), a pattern consistent with a decrease in risk for these outcomes. In the context of this study (designed to address a potential increase in risk among study outcomes), these results are consistent with no increase in risk (for details, see Table 10-2 for ITT and Table 10-3 for as-treated analyses).

10.4.2 Cohort 2 – any new use of aliskiren as add-on to ACEI or ARB

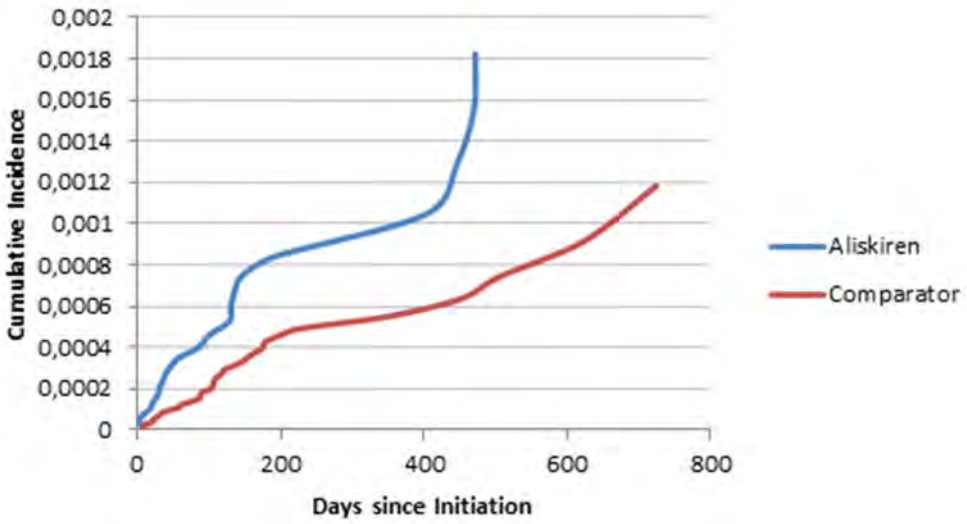
As in Cohort 1, the outcomes of CVA, stroke, ischemic stroke and TIA in cohort 2 resulted in HRs close to 1.0 with narrow confidence intervals that include 1.0, a pattern consistent with neither increase nor decrease in risk for these outcomes (for details, see Table 10-2 for ITT and Table 10-3 for as-treated analyses).

Hemorrhagic stroke: As seen for Cohort 1, the results show considerable heterogeneity. While the main ITT analyses in the pooled data (ITT: HR = 1.14, 95% CI: 0.88-1.48; Table 10-2) is consistent with a chance finding, the as-treated analysis (HR = 1.61; 95% CI: 1.00-2.58; Table 10-3) suggests an increased risk, primarily driven by the increased risk seen in MarketScan (HR = 2.08; 95% CI: 1.21-3.58; Annex 2-Table 2-12) in MarketScan while United data do not suggest an increased risk (HR = 0.75; 95% CI: 0.26-2.18; Annex 2-Table 2-12).

In order to focus on the hemorrhagic stroke outcome more closely among the MarketScan data within Cohort 2, the cumulative incidence figure for the as-treated analysis is presented below in Figure 10-5. This figure provides the timing of the outcomes relative to cohort entry

and indicates survival curves that are similar to one another (given the small numbers of events as indicated by the y-axis scale) until approximately one year into follow-up. After one year, the curves diverge rapidly, but this divergence is based on small numbers of events. Indeed, the absolute risk difference between cohorts is 0.2 events per 1,000 person-years.

Figure 10-5 Cumulative incidence of hemorrhagic stroke in Cohort 2 – MarketScan patients (as-treated analysis)



In a post-hoc analysis (not specified in the protocol), we examined the chronologic claims profiles of the patients who had hemorrhagic stroke outcomes (in Figure 10-5). The definition of the outcome includes both intracerebral and subdural hemorrhage and most of the patients in each group (90.5% of aliskiren and 85.7% of comparator patients) had the former. Out of the patients who experienced the event, 28.6% of aliskiren as compared to 11.4% of comparators had at least one dispensing of an oral anticoagulant within 3 months prior to an event, and 14.3% of aliskiren patients vs 11.4% of comparators were on an oral antiplatelet drug. The imbalances in these risk factors for hemorrhagic stroke were not present at the start of follow-up (see Annex 2-Table 2-6 for baseline characteristics of Cohort 2 patients) and its development may provide some insight into the mechanism underlying this finding of an elevated hemorrhagic stroke risk among aliskiren users.

Also similar to Cohort 1 results, the outcomes myocardial infarction, heart failure, acute renal failure, and end-stage renal disease all have HRs below 1.0 with somewhat wider confidence intervals that mostly exclude 1.0 (again, except for MI), a pattern consistent with a decrease in risk for these outcomes. In the context of this study (designed to address a potential increase in risk among study outcomes), these results are consistent with no increase in risk (for details, see Table 10-2 for ITT and Table 10-3 for as-treated analyses).

10.4.3 Cohort 3 – any new use of aliskiren as add-on to calcium channel blockers (CCBs)

Cohort 3 results differ slightly from those of cohorts 1 & 2 in that the HR for more outcomes (CVA, stroke, Ischemic stroke, MI, heart failure, ARF, and ESRD) are below 1.0, many with confidence intervals excluding 1.0. In the context of this study (designed to address a potential

increase in risk among study outcomes), these results are consistent with no increase in risk. The HR for the outcome TIA is close to 1.0 with confidence intervals that include 1.0, suggesting neither increase nor decrease in risk for this outcome.

Hemorrhagic stroke: This outcome is not observed to be increased among aliskiren initiators in Cohort 3. Main analyses in pooled data do not suggest an increased risk (ITT: HR = 0.87, 95% CI: 0.63-1.20 (Table 10-2), as-treated: HR: 0.50, 95% CI: 0.23-1.11 (Table 10-3)), as neither do analyses in the MarketScan subset or United (see Annex 2-Table 2-10 for the ITT analysis and Annex 2-Table 2-13 for the as-treated analysis).

10.4.4 Subgroups

The subgroup analyses are represented graphically for ease of identifying treatment effect heterogeneity across the strata formed by the subgroups in Annex 2.5.2, Annex 2-Figure 2-55 to Annex 2-Figure 2-72 for Cohort 1, Annex 2-Figure 2-73 to Annex 2-Figure 2-90 for Cohort 2 and Annex 2-Figure 2-91 to Annex 2-Figure 2-108 for Cohort 3.

More detailed information on the number of patients in each subgroup category, as well as number of events, IRs and HRs with 95% CIs stratified by database are presented in Annex 2-Table 2-14 to Annex 2-Table 2-31 (Cohort 1), Annex 2-Table 2-32 to Annex 2-Table 2-49 (Cohort 2), and Annex 2-Table 2-50 to Annex 2-Table 2-67 (Cohort 3) both for ITT and as-treated analyses. The most notable pattern observed over a range of outcomes is the progression of the HR across strata of propensity score quintiles, with the greatest difference generally seen between quintiles 1 and 5. It appears the greatest risk is in quintile 1, while the lowest risk is in quintile 5, suggesting no increase in risk with aliskiren when it is prescribed to the typical aliskiren patient, and progressively more risk when aliskiren is prescribed to less typical candidates.

The figures below show the treatment effect in subgroups for the outcome of hemorrhagic stroke in Cohort 1 MarketScan patients, where an increased risk was observed in the ITT analysis (Figure 10-6) and Cohort 2 MarketScan patients, where an increased risk was observed in the as-treated analysis (Figure 10-7). For the corresponding tables please see Annex 2-Table 2-21 and Annex 2-Table 2-39. Annex 2-Figure 2-61 and Annex 2-Figure 2-79 along with Annex 2-Table 2-20 and Annex 2-Table 2-38 show the treatment effect in subgroups of United patients for Cohort 1 and 2.

Figure 10-6 Hazard ratios of hemorrhagic stroke in Cohort 1 MarketScan patients, ITT and as-treated analyses

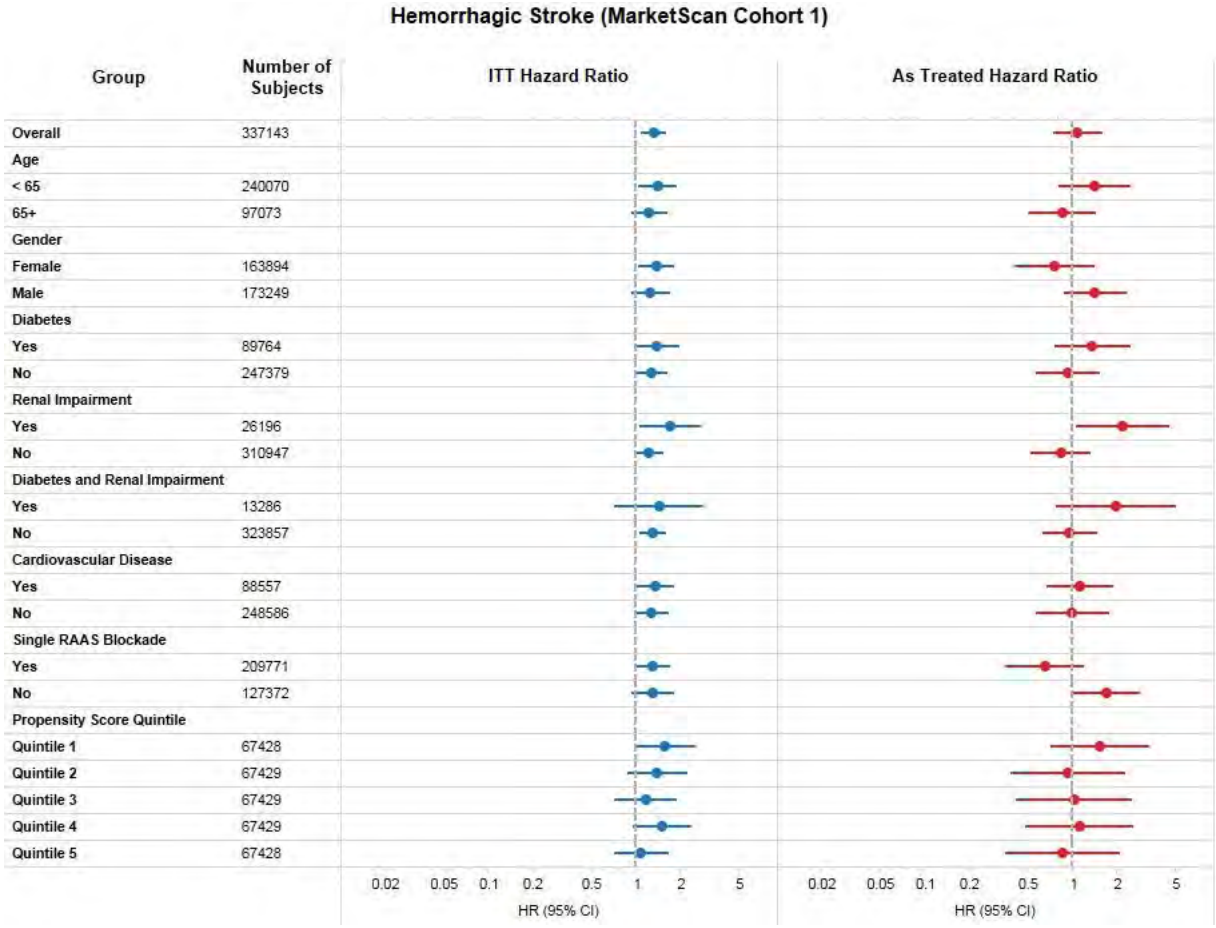


Figure 10-6 indicates little treatment effect heterogeneity among subgroups in the ITT analysis, but some potential heterogeneity across certain subgroups in the as-treated analysis. A higher risk may be present among younger patients and patients with renal impairment at baseline.

Figure 10-7 Hazard ratios of hemorrhagic stroke in Cohort 2 MarketScan patients, ITT and as-treated analyses

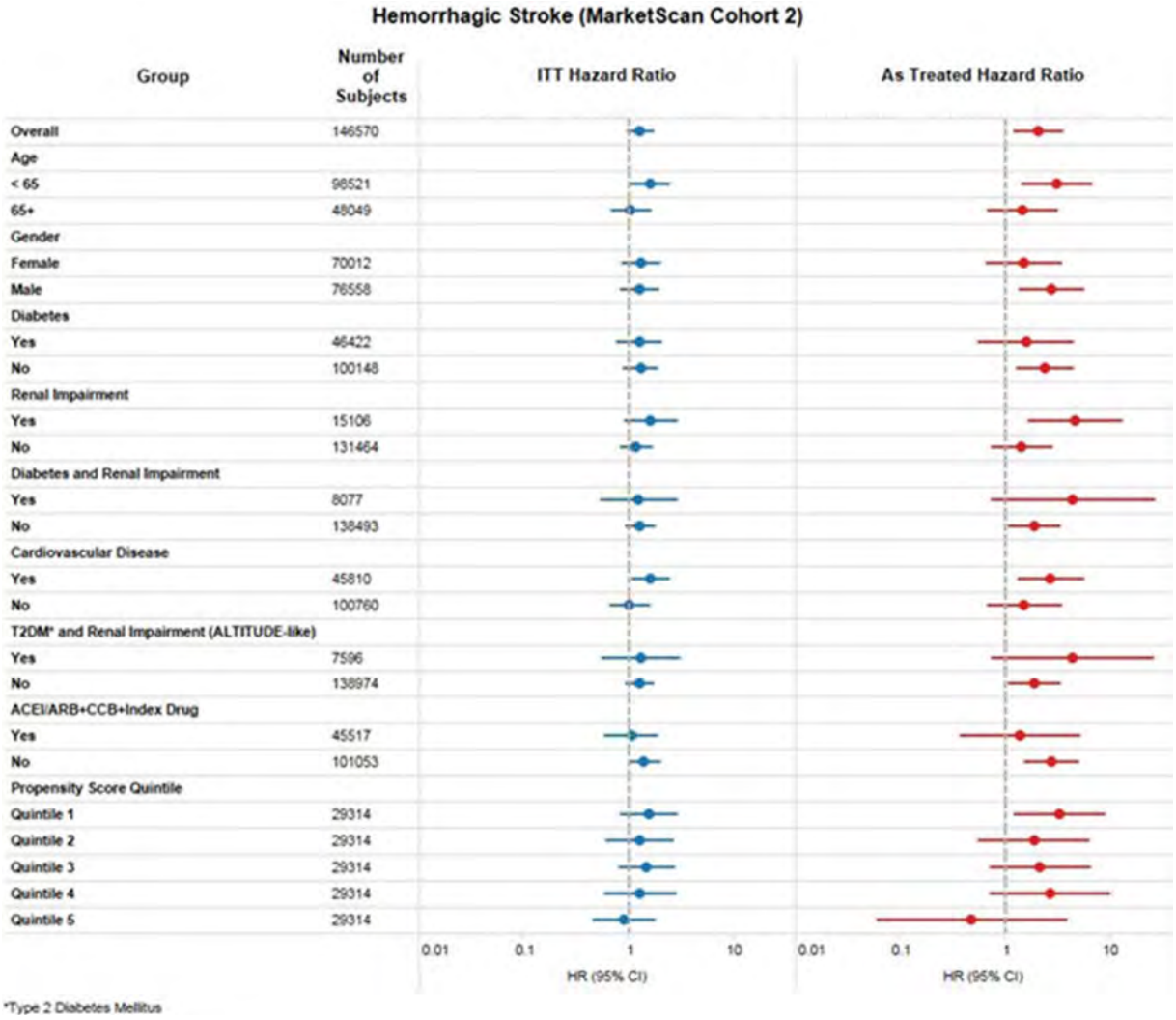


Figure 10-7 for the outcome of hemorrhagic stroke among subgroups in Cohort 2 MarketScan as-treated analysis (see Annex 2-Table 2-39) indicates an increased risk in many subgroups: e.g. those younger than 65 years of age, males, patients with no diabetes at baseline, patients with renal impairment at baseline, and patients with CVD at baseline. The ITT results for hemorrhagic stroke were consistent with no overall effect, but the subgroups of patients <65 years of age and patients with CVD at baseline may be at increased risk.

10.4.4.1 ALTITUDE-like population

The ALTITUDE-like subset was formed as a subset of Cohort 2, specifically the subset of patients who had both T2DM and renal impairment at baseline. The study outcomes among this subset are presented below in Table 10-4. The small size of this subset leads to wide confidence intervals for effect estimates, which in turn limits the strength of inferences that can be drawn. However, the HRs for most outcomes are close to 1.0, with the most notable exceptions being hemorrhagic stroke in the as-treated MarketScan portion of this table, an

elevated result that illustrates the effect of the small numbers (HR = 4.35, 95% CI: 0.72-26.13).

Table 10-4 Hazard ratios of primary outcomes in ALTITUDE-like patients

Outcome	Events	PYs	IR*	Events	PYs	IR*	HR (95% CI)
United	**Aliskiren (N = 470)**			**Comparator (N = 1,766)**			
ITT analysis							
Cerebrovascular accidents	18	767	23.5	67	2,787	24.0	0.99 (0.59 - 1.67)
Stroke	22	762	28.9	85	2,772	30.7	0.95 (0.59 - 1.52)
Ischemic stroke	22	762	28.9	82	2,774	29.6	0.98 (0.61 - 1.57)
Hemorrhagic stroke	2	779	2.6	7	2,847	2.5	1.09 (0.23 - 5.27)
Transient ischemic attack	15	758	19.8	46	2,807	16.4	1.21 (0.67 - 2.16)
Myocardial infarction	9	771	11.7	42	2,809	15.0	0.79 (0.39 - 1.63)
Heart failure	54	712	75.9	244	2,558	95.4	0.80 (0.60 - 1.08)
Acute renal failure	91	666	136.6	411	2,369	173.5	0.81 (0.64 - 1.01)
End-stage renal disease	50	721	69.4	260	2,546	102.1	0.71 (0.53 - 0.96)
As-treated							
Cerebrovascular accidents	3	224	13.4	17	790	21.5	0.63 (0.18 - 2.15)
Stroke	4	223	17.9	20	789	25.3	0.70 (0.24 - 2.05)
Ischemic stroke	4	223	17.9	20	789	25.3	0.70 (0.24 - 2.05)
Hemorrhagic stroke	0	224	0.0	1	796	1.3	-
Transient ischemic attack	3	223	13.4	14	791	17.7	0.79 (0.23 - 2.77)
Myocardial infarction	1	224	4.5	9	794	11.3	0.34 (0.04 - 2.68)
Heart failure	17	221	77.0	80	781	102.4	0.76 (0.45 - 1.28)
Acute renal failure	31	219	141.4	166	763	217.4	0.68 (0.46 - 0.99)
End-stage renal disease	20	221	90.4	72	784	91.8	1.00 (0.61 - 1.64)
MarketScan	**Aliskiren (N = 1,579)**			**Comparator (N = 6,017)**			
ITT analysis							
Cerebrovascular accidents	29	2,635	11.0	116	9,715	11.9	0.91 (0.61 - 1.37)
Stroke	56	2,603	21.5	253	9,561	26.5	0.82 (0.61 - 1.09)
Ischemic stroke	53	2,609	20.3	242	9,563	25.3	0.80 (0.60 - 1.08)
Hemorrhagic stroke	7	2,657	2.6	20	9,821	2.0	1.30 (0.55 - 3.07)
Transient ischemic attack	11	2,650	4.2	44	9,763	4.5	0.93 (0.48 - 1.79)
Myocardial infarction	34	2,629	12.9	134	9,697	13.8	0.94 (0.64 - 1.36)
Heart failure	96	2,542	37.8	472	9,202	51.3	0.75 (0.60 - 0.93)
Acute renal dfailure	355	2,258	157.2	1271	8,246	154.1	1.03 (0.91 - 1.16)
End-stage renal disease	179	2,455	72.9	783	8,889	88.1	0.84 (0.72 - 0.99)
As-treated							
Cerebrovascular accidents	8	813	9.8	24	2,672	9.0	1.14 (0.51 - 2.55)
Stroke	16	810	19.8	63	2,656	23.7	0.86 (0.49 - 1.49)
Ischemic stroke	14	810	17.3	62	2,656	23.3	0.76 (0.43 - 1.37)
Hemorrhagic stroke	3	817	3.7	2	2,675	0.8	4.35 (0.72 - 26.13)
Transient ischemic attack	2	817	2.5	13	2,670	4.9	0.50 (0.11 - 2.25)
Myocardial infarction	13	815	16.0	39	2,668	14.6	1.12 (0.60 - 2.09)
Heart failure	32	811	39.5	151	2,631	57.4	0.71 (0.48 - 1.04)
Acute renal failure	132	792	166.7	455	2,567	177.2	0.98 (0.81 - 1.19)
End-stage renal disease	59	800	73.8	237	2,614	90.7	0.86 (0.65 - 1.15)

PYs = person-years; IR = Incidence rate
*IR – incidence rate per 1,000 person-years

10.5 Other analyses

10.5.1 Sensitivity analyses – Cohort 1

10.5.1.1 High dimensional propensity score results

The hdPS results are closely similar to the results obtained using the protocol-specified propensity score variables (Annex 2-Table 2-68). For example, the hdPS-based United ITT analysis for CVA yielded a HR of 1.05 (0.91-1.20) compared to the protocol specified PS-based United ITT analysis of CVA, which yielded a HR of 1.05 (0.91-1.20). Similarly, the hdPS-based MarketScan ITT analysis for CVA yielded a HR of 1.04 (0.95-1.13) compared to the protocol specified PS-based MarketScan ITT analysis for CVA, which yielded a HR of 1.08 (0.99-1.17). As hdPS algorithm evaluates thousands of diagnoses, procedures and pharmacy claims codes to empirically identify and prioritize confounders (see Section 9.9.4.1 for more details on hdPS), the closeness of the results between the hdPS and protocol-specified PS suggests that the study ascertains and accounts for measured confounding to the extent the data sources permit.

10.5.1.2 Duration of exposure and cumulative dose

Assessing potential heterogeneity of effect by either duration of exposure or cumulative dose allows the study to address hypotheses related to timing and dose. However, in this study results do not vary extensively with respect to either duration of follow-up or cumulative exposure. As an example, based on duration of follow-up, the United ITT analysis for CVA produced a HR of 1.03 (95% CI 0.80-1.33) in the first six months (0-6 months) of follow-up, a HR of 1.08 (95% CI 0.78-1.49) in the second six months (7-12 months), and a HR of 1.40 (95% CI 1.02-1.92) in the third six months (13-18 months), and a HR of 0.96 (95% CI 0.62-1.48) in the fourth six month block (19-24 months), with a HR of 0.88 (95% CI 0.66-1.17) for all follow-up time beyond that (25+ months). These point estimates are all consistent with one another and reflect greater precision in the first two 6-month blocks. Using the same example, but based on cumulative exposure the HR is 1.05 (95% CI 0.89-1.25) for up to 6 months of cumulative exposure, 1.13 (95% CI 0.85-1.49) for up to 18 months of cumulative exposure, and 0.90 (95% CI 0.61-1.33) for cumulative exposures beyond 18 months.

For more details, see Annex 2-Table 2-71 (ITT stratified by duration of follow-up, Cohort 1 – United), Annex 2-Table 2-72 (ITT stratified by duration of follow-up, Cohort 1 – MarketScan), Annex 2-Table 2-73 (ITT stratified by cumulative exposure duration, Cohort 1 – United), Annex 2-Table 2-74 (ITT stratified by cumulative exposure Cohort 1 – MarketScan).

The stratification by follow-up in MarketScan also illustrates heterogeneity for the hemorrhagic stroke outcome, with the period from 7 months to 12 months suggesting an increased risk (HR = 1.72; 95% CI 1.10-2.71), and other periods not suggesting an increased risk (see Annex 2-Table 2-72). The cumulative exposure stratification in MarketScan suggested an increased risk of hemorrhagic stroke for patients with exposure < 6 months (HR = 1.42; 95% CI 1.09-1.84) – additional analyses revealed that most of those events occurred

after patients had discontinued aliskiren or the comparator medication (data not shown). There was no increased hemorrhagic stroke risk in patients with cumulative exposure > 6 months (see Annex 2-Table 2-74).

10.5.2 Sensitivity analyses – Cohort 2

10.5.2.1 High dimensional propensity score results

Cohort 2 sensitivity analyses and subgroup results lead to inferences that are largely similar to those derived from Cohort 1: Results from hdPS-matching are consistent with protocol-specified PS-matching (for details, see Annex 2-Table 2-69).

10.5.2.2 Duration of exposure and cumulative dose

There is little evidence of heterogeneity across groups defined by either duration of follow-up or cumulative exposure. There seems to be an increased risk of hemorrhagic stroke in MarketScan patients during the first 6 months of follow-up in ITT analysis (HR 1.73, 95% CI (1.02-2.92); however, no increased risk was observed in the subsequent follow-up periods or in cumulative exposure analyses. For more details on ITT analyses by duration of follow-up, and by cumulative exposure, see Annex 2-Table 2-75 (ITT stratified by duration of follow-up, Cohort 2 – United), Annex 2-Table 2-76 (ITT stratified by duration of follow-up, Cohort 2 – MarketScan), Annex 2-Table 2-77 (ITT stratified by cumulative exposure duration, Cohort 2 – United), Annex 2-Table 2-78 (ITT stratified by cumulative exposure Cohort 2 – MarketScan).

10.5.3 Sensitivity analyses – Cohort 3

10.5.3.1 High dimensional propensity score results

Cohort 3 sensitivity analyses results lead to inferences that are largely similar to those derived from Cohort 1: Results from hdPS-matching are again consistent with protocol-specified PS-matching (for details, see Annex 2-Table 2-70).

10.5.3.2 Duration of exposure and cumulative dose

There is little evidence of heterogeneity across groups defined by duration of follow-up or cumulative exposure.

For more details on ITT analyses by duration of follow-up, and by cumulative exposure, see Annex 2-Table 2-79 (ITT stratified by duration of follow-up, Cohort 3 – United), Annex 2-Table 2-80 (ITT stratified by duration of follow-up, Cohort 3 – MarketScan), Annex 2-Table 2-81 (ITT stratified by cumulative exposure duration, Cohort 3 – United), Annex 2-Table 2-82 (ITT stratified by cumulative exposure Cohort 3 – MarketScan).

10.5.4 Secondary outcomes

No increase in risk is seen across the secondary outcomes (i.e. hyperkalemia, hypotension, death) in any of the three cohorts, stratified by database, neither in the ITT nor the as-treated analyses.

For details, see Annex 2-Table 2-83 (Cohort 1), Annex 2-Table 2-84 (Cohort 2), and Annex 2-Table 2-85 (Cohort 3).

10.5.5 Analyses in patients with or without hypertension diagnosis

Expanding the study cohorts by not requiring a baseline HTN diagnosis resulted in largely similar results to the main study results (which required a baseline HTN diagnosis). For example, with baseline HTN, the United ITT results for CVA are: HR = 1.05 (95% CI 0.91-1.20), while not requiring a baseline HTN diagnosis led to HR = 1.03 (95% CI 0.90-1.18). The greater size of the cohorts obtained when not requiring a baseline HTN diagnosis lead to more events and narrower confidence intervals, but no substantial difference in effect estimates or in the inferences that might be drawn from them.

For details, see: Annex 2-Table 2-86 (hazard ratios of primary outcomes in Cohort 1 patients with or without hypertension diagnosis at baseline, stratified by database, ITT and as-treated); Annex 2-Table 2-87 (Cohort 2); Annex 2-Table 2-88 (Cohort 3).

10.5.6 Laboratory results

Since laboratory results were not available for all people who entered the study cohorts (and not available at all for the MarketScan cohorts), measures based on them could not be incorporated into the propensity scores. However, it is plausible to consider laboratory results as potential confounders of the association between aliskiren and each of the study outcomes. If either serum creatinine or potassium levels differ at baseline for the matched cohorts, this difference could represent an alternate explanation for an observed association between aliskiren and a study outcome. As a check on the plausibility of laboratory results to confound associations observed, we present laboratory results for the subset of the United cohorts that have laboratory data. A similar sized subset of each group (aliskiren or comparator) have laboratory results (approximately 25%), and the average creatinine level was 1.10 mg/dL in the aliskiren group and 1.13 mg/dL in the comparator group, while the mean potassium was 4.2 mEq/L in the aliskiren group and 4.2 mEq/L in the comparator group. The similarity of these laboratory results in the matched cohorts when the cohorts were not specifically matched on these test results suggests that the insurance claims data included adequate proxies to balance the laboratory values. A second aspect to the laboratory testing is that people who have more laboratory tests performed during follow-up have more opportunities to record an elevated result that could trigger a medical evaluation, during which an outcome may be identified. To assess this potential differential surveillance, we tabulated the frequency of laboratory testing that produced results over the first year of follow-up in patients who had such results available at baseline. The closeness of the matched cohorts with respect to intensity of laboratory surveillance (1.3 tests per year for each cohort and each test) suggests a similar level of surveillance in each cohort.

For details, see: Annex 2-Table 2-89, and Annex 2-Table 2-90 (Cohort 1), Annex 2-Table 2-91, and Annex 2-Table 2-92 (Cohort 2), Annex 2-Table 2-93, and Annex 2-Table 2-94 (Cohort 3).

10.5.7 Aliskiren patients who were not matched

The baseline characteristics of the aliskiren patients not matched to a comparator in each of the 3 cohorts are shown in Annex 2-Table 2-95 (Cohort 1), Annex 2-Table 2-96 (Cohort 2), and Annex 2-Table 2-97 (Cohort 3). Except for calendar year (reflecting the usage characteristics of aliskiren) there do not appear to be characteristics among these unmatched patients that are substantially different from the matched patients, such as an upward distribution with respect to age categories. For the outcomes among these unmatched patients for Cohort 1, the incidence rate of CVA among the United cohort was 13.0 (95% CI 9.2-18.4) events/1,000 PYs compared to 8.7 events/1,000 PYs among the matched United aliskiren Cohort 1 patients. Similarly, the incidence of CVA among the unmatched MarketScan Cohort 1 patients was 7.9 (95% CI 6.4-9.8) events/1,000 PYs compared to 4.5 events/1,000 PYs. In each of these cases (and for other outcomes), the unmatched patients exhibit a higher absolute incidence of outcomes suggesting higher baseline risk consistent with older age and corresponding comorbidities. These patients were not matched because they were different with respect to baseline characteristics, and this difference translates into a higher event rate. Even though the matching process leads to the exclusion of these aliskiren recipients, their removal improves the validity of study comparisons since the different characteristics and high outcome risk means that their inclusion would require statistical adjustment and corresponding assumptions.

For details on incidence rates, see Annex 2-Table 2-98 (incidence rates of primary outcomes in not PS-matched aliskiren patients, all 3 cohorts).

10.6 Adverse events and adverse reactions

As this was a non-interventional study with secondary use of data retrieved from two US health claims databases, safety monitoring and safety reporting on an individual case level is not applicable.

11 Discussion

11.1 Key results

This study identified large numbers of aliskiren new users (> 83,000) within two different US health insurer databases and followed them for the occurrence of a number of health outcomes. The study employed inclusion criteria that differed across the 3 cohorts (any new use, add-on to ACEI/ARB and add-on to CCB) in a way that reflects aliskiren use in routine clinical care and formed PS-matched comparator groups within each of the 3 cohorts in order to improve the ability of the analyses to identify an increased risk of any of the study outcomes under a range of assumptions about the time-course of exposure on the occurrence of outcomes. The main finding is that aliskiren does not increase the risk of the overall stroke outcome or the ischemic stroke outcome or TIA relative to the different comparison group in the three cohorts studied. For the outcomes of MI, heart failure, ARF and ESRD, the finding of a decreased risk for aliskiren in several of the analyses can be interpreted as evidence of no increase in risk. The numerous analyses that were conducted to support this study indicate that the results are robust to variations in exposure definition and to covariate construction as well as being consistent across most study subgroups.

For the outcome of hemorrhagic stroke, some of the analyses suggest an increased risk while others do not in a pattern that seems inconsistent with a direct causal effect (elevated in one database and not the other, sometimes in the ITT analysis, other times in the as-treated analysis).

11.2 Limitations

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. As a comprehensive insurance database, essentially all billable medical services result in claims for reimbursement, so that certainty of capture is tied to likelihood of a claim being submitted to the insurer (Schneeweiss and Avorn 2005). Misclassification of prescription drug exposure is generally considered less than in other exposure assessment approaches, including physician prescribing notes and patient self-reporting (Stergachis 1988, West et al 1994, West et al 1995). 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 (Kelsey et al 1996).

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, would result in incomplete control of such confounders and ultimately to residual confounding bias (Greenland 1980, Greenland et al 1999). 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.

Health claims databases such as the ones used for this study do not provide information on blood pressure values. Therefore, this study assumes that patients compared across cohorts have comparable blood pressure values. This assumption rests on the extensive covariate balancing methods that were applied (propensity scores including empirical covariate identification). By balancing on numerous covariates through the propensity score, an unmeasured characteristic (such as blood pressure) that is at least partially represented by other variables (such as comorbidities or co-medications) through proxy may also be balanced. Therefore, although blood pressure values are not evaluated, the study comparisons may have been balanced on blood pressure. However, this remains an untested assumption that could represent an alternate explanation for study findings.

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, along with generalizability to those older than 65 with Medicare supplement insurance. Since they were not directly studied, patients without commercial health insurance (such as the poor, the wealthy, and those over age 65 without Medicare supplement insurance) may have a different effect from aliskiren than the patients who were studied. However, it remains unclear how the effect of aliskiren would be altered by health insurance coverage unless the different coverage represented a marker for differences in healthcare delivery that affect both use of aliskiren and likelihood of a study outcome.

Although formal adjustment for multiple comparisons has not been conducted, it is important to consider the large number of analyses performed and comparisons made when drawing conclusions from the study. Instead of testing specific hypotheses, this study aims to estimate the association between aliskiren exposure and a range of study outcomes relative to comparison treatments across three different cohorts and numerous exposure subgroups, along with the uncertainty in these estimated associations (precision). These associations are quantified through hazard ratios and the precision quantified through 95% CIs, and these 95% CIs can be interpreted independently as including the true hazard ratio approximately 95% of the time (accurate estimates of precision), even where multiple comparisons have been made. However, across the large number of 95% CIs that have been estimated 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, is greater than 5%. Further, in contrast to an efficacy trial where adjustment for multiple comparisons is standard to protect against false positive findings, safety studies (such as this) have a different standard such that protection against false negative findings is more important. In addition, type I errors cannot decrease (the whole point of adjustments for multiple comparisons) without inflating type II errors (the probability of accepting the null hypothesis when the alternative is true) (Rothman 1990, Perneger 1998, Rothman 2014).

11.3 Interpretation

These study findings should indicate that aliskiren does not increase the risk of a range of health outcomes studied and across numerous ways of conducting the analyses. Results from Cohort 1, which compared aliskiren initiators (as naive, switch, or add-on therapy) to initiators of a broad basket of other medications for hypertension provides the most generalizable results and thereby the results most applicable to public health concerns. In particular, the as-treated analysis of Cohort 1 provides the most direct contrast of aliskiren exposure to alternate antihypertensive medication exposure in routine care across a broad population of users, and the pooled analysis reduces variability across databases. This pooled Cohort 1, as-treated analysis produced the following (HRs , 95% CIs): CVA (1.00, 0.88-1.13); Stroke (0.95, 0.86-1.05); Ischemic stroke (0.96, 0.87-1.06); Hemorrhagic stroke (0.90, 0.65-1.25); TIA (0.98, 0.82-1.17); MI (0.88, 0.76-1.02); HF (0.73, 0.66-0.81); ARF (0.91, 0.86-0.97); ESRD (0.70, 0.62-0.79). These results are consistent with no substantial increase in risk for any of these outcomes associated with aliskiren. The finding that aliskiren was associated with an increased risk of hemorrhagic stroke in certain cohort analyses and subgoups is in contrast to the other study outcomes that all were consistent in showing no increase (or even a decrease) in risk.

Interpretation of these study results should also be made within the context of the ALTITUDE study, which randomized 8,561 patients with T2DM or kidney disease to treatment with either aliskiren or placebo as adjunct to ACEI or ARB. Followed for up to 4 years for a range of cardiovascular and renal outcomes, the study was stopped early due to a trend of increased risk for the primary composite outcome (HR 1.08, 95% CI 0.98-1.20) and a similar trend for secondary outcomes. For the outcome of MI, there was a HR of 1.04 (0.83-1.31), which contrasts with the ITT analysis for MI in Cohort 2 of this study (i.e. the population with any new use of aliskiren as add-on to ACEI or ARB and correspodning comparators) (HR = 0.88, 95% CI: 0.78-1.00). The study population of Cohort 2 however was not specifically restricted to patients with T2DM and renal impairment (as the ALTITUDE study was), which represents an additional source for potential differences between the studies. The subgroup analysis of this study of ALTITUDE-like patients included few patients and outcomes so that the confidence intervals for estimated HRs are wide. A comparison of the absolute incidence rates of MI in ALTITUDE can be made with this study. There were 147 MI events among 4274 aliskiren patients contributing approximately 11,700 PY for an incidence rate of 12.5 per 1000 PY, while this study had an incidence rate for MI of 5.0 per 1000 PY. The average age in ALTITUDE (65 years) relative to the average age in this study (58 years) could account for the difference in incidence, while the heterogeneity in effect with age could account for the difference in HR observed. We observed some treatment effect heterogeneity with those younger than 65 years old sometimes having an increased HR relative to those over 65, although this finding varied by outcome.

11.4 Generalizability

Since the study data is derived from compiled health insurer claims that are captured in the conduct of routine care among patients across the US, the study results should be broadly generalizable within the US. The study is based on people with commercial health insurance (with some Medicare supplement data) so the results are most generalizable to such people and under-represent the elderly (who tend to have Medicare) and do not capture people without commercial health insurance (particularly the unemployed). Very little evidence was found for heterogeneity of aliskiren effect according to demographic characteristics, so it is plausible to expect the study results to generalize to a broader population. To the extent that the results reflect biological effects rather than manifestations of the commercial healthcare system, the results are generalizable beyond the specific patients in the study, including the elderly, unemployed, and non-US patients. Although not directly assessed for feasibility in the context of this report, European data sources appear unlikely to provide a large enough population of aliskiren users to estimate the association with study outcomes, so the application of a US data source to the question represents a reasonable tradeoff between precision and generalizability.

12 Other information

This study was designed to evaluate the association between aliskiren and the selected outcomes as thoroughly as feasible using routine care data. To address the nature of the data source, a number of design elements have been included that provide robustness and redundancy in the estimates of effect obtained. This cohort study begins follow-up with the initiation of a new medication (either aliskiren or a comparator), which addresses potential

bias that could arise from mixing together patients who had been using the medications for different amounts of time (prevalent users and new users).

13 Conclusion

This large study of patients receiving aliskiren and comparator antihypertensive medication in settings of routine care found no increased risk of a range of outcomes. The propensity score matching produced a high degree of balance between compared groups across the 3 cohorts, which makes it difficult to interpret findings either increased or decreased risk as a result of confounding. The finding of an increased risk of hemorrhagic stroke was inconsistent across the analyses conducted and is based on small numbers of outcomes, enhancing the plausibility of non-causal mechanisms (chance, bias, or confounding). The outcomes with decreased risk among aliskiren users (heart failure along with myocardial infarction and the renal outcomes) may represent non-causal associations mediated through unmeasured baseline confounding or differential changes in the cohorts during follow-up since they were not observed in the ALTITUDE study. The ALTITUDE-like subset in this study was the fairly small (2,039 aliskiren patients and 7,783 comparators) subset of patients with both T2DM and renal impairment at baseline. These patients are at high risk of outcomes, and results in this subset are within the 95% CIs of the results from ALTITUDE largely due to the small size of the subset and correspondingly wide confidence intervals for effect estimates. The effect estimates for most outcomes in this ALTITUDE-like subset are close to 1.0, with the most notable exceptions being hemorrhagic stroke in the as-treated MarketScan portion of this table, an elevated result that illustrates the effect of the small numbers (HR = 4.35, 95% CI: 0.72-26.13).

Overall, this study provides fairly strong evidence from routine care that there is not a substantially increased risk of several cardiovascular and renal outcomes associated with aliskiren during routine care. This is because the precision of the findings as shown in the 95% confidence intervals is such that a substantial increase in risk would have been readily apparent. However, a smaller increase in risk (perhaps around 10% or 20%) would not be so apparent due to the imprecision in the estimate along with the increased plausibility of bias and confounding as alternate explanations that comes with a smaller increase in risk.

14 References

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Appendices

Annex 1 - List of stand-alone documents

Not applicable

Annex 2 - Additional information

Annex 2.1 Comparison medications

Annex 2-Table 2-1 Comparison cohort antihypertensive medications

Therapeutic class	Individual drugs (oral forms only)
ACE inhibitors (ACEIs)	Benazepril
	Captopril
	Enalapril
	Enalaprilat
	Enalaprilat Dihydrate
	Fosinopril
	Lisinopril
	Moexipril
	Perindopril
	Quinapril
	Ramipril
	Trandolapril
Angiotensin II receptor blockers (ARBs)	Azilsartan
	Candesartan
	Eprosartan
	Irbesartan
	Losartan
	Olmesartan
	Telmisartan
	Valsartan
Calcium channel blockers (CCBs)	**Nondihydropyridines**
	Diltiazem
	Verapamil
	Dihydropyridines
	Amlodipine
	Bepridil
	Clevidipine
	Felodipine
	Isradipine
	Nicardipine
	Nifedipine
	Nimodipine
	Nisoldipine
Diuretics	**Thiazides**
	Bendroflumethiazide
	Benzthiazide
	Chlorothiazide
	Chlorothiazide Sodium
	Chlorthalidone
	Cyclothiazide
	Hydrochlorothiazide
	Hydroflumethiazide
	Indapamide

Therapeutic class	Individual drugs (oral forms only)
	Methyclothiazide
	Metolazone
	Polythiazide
	Quinethazone
	Trichlormethiazide
	Potassium-Sparing Agents
	Amiloride Hydrochloride
	Triamterene
	Aldosterone antagonists
	Eplerenone
	Spironolactone
Alpha blockers (ABs)	Doxazosin
	Prazosin
	Terazosin
Beta blockers (BBs)	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 2.2 Patient characteristics/pre-defined covariates

Annex 2-Table 2-2 Patient characteristics of interest/pre-defined covariates

Covariate	Definition	Comments
Demographics		
Age	By year	
	By category (18-39, 40-54, 55-64, 65+)	
Sex	Female, Male	
Census region	Northeast: CT, ME, MA, NH, NJ, NY, PA, RI, VT	
	South: AR, AL, DE, DC, FL, GA, KY, LA, MD, MS, NC, OK, SC,TN, TX,VA, WV	
	Midwest: IN, IL, IA, KS, MI, MN, MO, NE, ND, OH, SD, WI	
	West: AZ, AK, CA, CO, HI, ID, NM, MT, NV, OR, WA, WY	

Covariate	Definition	Comments
State	US state of residence as present in the data	Determine 4 largest (in terms of users) states and list them individually, 5th category – "others"
Plan type	Commercial, Medicare Advantage	
Calendar quarter	1-2 q2007, 3q07, 4q07, etc until 2q2012	Combine 1st and 2nd quarter of 2007 (Jan-June), and then each quarter
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		Ionic contrast media
Hypertension	At least 1 Dx of ICD-9 Dx 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,	

Covariate	Definition	Comments
	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 Dx 250.x0, 250.x2)) OR 1 hospital discharge Dx of T2DM OR 1 diagnosis of T2DM plus an oral antidiabetic dispensing	
Hyperlipidemia	ICD-9Dx: 272.0, 272.2, 272.4	
Atherosclerosis	ICD-9 Dx: 440.9 (arteriosclerosis) 414.X (other forms of chronic ischemic heart disease) 429.2 (ASCVD)	
Heart failure (CHF)	1 inpatient or 2 outpatient claims with any of ICD-9 Dx codes : 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	
Hemorrhagic stroke	1 inpatient or 2 outpatient claims with any of IDC-9 Dx codes 430.x – 433.x	
Ischemic stroke	1 inpatient or 2 outpatient claims with any of ICD-9 Dx codes: 434.x, 436.x, 437.1, 438.x	
Other stroke effects	1 inpatient or 2 outpatient claims with any of ICD-9 Dx codes: 438.x	
Previous TIA	ICD-9 Dx 435.xx	
Previous (old) MI	ICD-9 Dx 412.x	
Recent MI	ICD-9 Dx 410.x	
Renal impairment	ICD-9 Dx: 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)	
DM and renal impairment	Diabetes AND renal impairment (see	

Covariate	Definition	Comments
	individual components for definitions)	
CVD	ICD-9 Dx: 410.xx – 414.xx 420.xx – 429.xx	
Hyperkalemia	ICD-9 Dx 276.7	
Prior medications		
Aliskiren		Not including the index date
ARB		Not including the index date
ACE inhibitor		Not including the index date
Beta blocker		Not including the index date
Calcium channel blocker		Not including the index date
Alpha blocker		Not including the index date
Combined alpha and beta blocker		
Loop diuretic		Not including the index date
Thiazide diuretic		Not including the index date
Potassium sparing agents/aldosterone antagonists		Not including the index date
Other hypertension medications		Not including the index date
Aspirin		
Aspirin/dipyridamole		
Clopidogrel		
Prasugrel		
Ticagrelor		
Other antiplatelet agent	Cilostazol, ticlopidine	
Oral anticoagulants	Apixaban, dabigatran, rivaroxaban, warfarin	
Anti-arrhythmic drug		
NSAIDs		
Potassium supplements		
Statin		
Other lipid-lowering drugs		
Diabetes medications, excl insulin		
Insulin		
Concurrent Tx		
Monotherapy	Exposure to only 1 antihypertensive on index date	
Dual therapy	Exposure to 2 antihypertensives on index date	
Multiple therapy	Exposure to > 2 antihypertensives on index date	
Single RAAS blockade	Therapy on only one of the following drugs on index date: Aliskiren, ACEI, ARB	
Health care utilization		
Number of medications	Count of distinct medications dispensed in prior 6 months	Including the index date (not including the index medication)
Number of hospitalizations	Count of hospitalizations in prior 6 months	
Number of hospital days	Sum of hospital days in prior 6 months	

Covariate	Definition	Comments
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 (Y/N)	
Number of laboratory tests ordered	CPT-4: 80048-80076, 81000-81099, 82000- 87999	Count of laboratory tests in prior 6 months
Number of lipid tests ordered	CPT-4: 80061 82465 83701 83704 83718 83721 84478 82172	Count of lipid-related laboratory tests in prior 6 months
Number of creatinine tests ordered	CPT-4: 82565	Count of creatinine levels obtained in prior 6 months

Annex 2.3 Outcomes of interest

Annex 2-Table 2-3 Codes used to identify primary and secondary outcomes of interest

Outcome	Hospital discharge code(s)	Comments
Primary outcomes		
Cerebrovascular accidents	**ICD-9 primary discharge diagnosis (Dx):** 430.x Subarachnoid hemorrhage (SAH) 431.x Intracranial hemorrhage (West et al 1994) 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events	In Tennessee Medicaid enrollees aged 50-84, the algorithm had PPV of 97% for primary discharge diagnoses and 89% for primary and secondary (Roumie et al 2008)
Ischemic stroke	**ICD-9 Dx:** 433.x1 Occlusion and stenosis of precerebral arteries with cerebral infarction 434.x1 Occlusion and stenosis of cerebral arteries with cerebral infarction	PPV 95.5% in commercially-insured population (Wahl et al 2010)
Hemorrhagic stroke	**As primary ICD-9 discharge diagnosis (Dx):** 430.x Subarachnoid hemorrhage (SAH) 431.x Intracranial hemorrhage (West et al 1994)	Median PPV 96% (86% if all discharge diagnoses) for ICH based on 2 validation studies; PPV 93% (80% if all discharge diagnoses) for SAH based on 2 validation studies (Andrade et al 2012)
Transient ischemic attack (TIA)	**ICD-9 Dx:** 435.xx Transient cerebral ischemia as the principal (primary) discharge diagnosis	PPV of 89% (primary Dx) and 77% (primary and secondary) in 1992 study (Benesch et al 1997) and 70% (primary only in Canadian database) (Kokotailo and Hill 2005) have been reported.
Myocardial infarction	**ICD-9 Dx:** 410.x Acute myocardial infarction, excluding 410.x2 as the principal (primary) or the next (secondary) discharge diagnosis AND	PPV 94% in Medicare claims data (Kiyota et al 2004) PPV 88.4% in commercially-insured population (Wahl et al 2010)

Outcome	Hospital discharge code(s)	Comments
	a length of stay between 3-180 days, or death if LOS is < 3 days	
Heart failure hospitalization	**ICD-9 Dx:** 428.x Heart failure as the principal (primary) discharge diagnosis	Validation studies that included primary discharge diagnosis of ICD-9 code 428.x had PPV in the 85%-100% range (mini-sentinel report) (Saczynski et al 2012)
Acute renal failure (ARF)	**ICD-9 Dx:** 584.xx Acute Renal Failure Or ESRD (see ESRD for codes)	Validation studies indicated low sensitivity but high specificity and moderate PPV (Waikar et al 2006)
End stage renal disease (ESRD)	**ICD-9 procedure:** 39.95 Hemodialysis 54.98 Peritoneal dialysis V45.1Renal dialysis status V56.0 Extracorporeal dialysis V56.8 Peritoneal dialysis 55.6x Renal transplant V42.0 Kidney replaced by transplant **CPT-4:** 90935 – 90993, 99512, 99559	
Secondary outcomes		
Hyperkalemia	276.7 Hyperpotassemia	Any position
Hypotension	458.9 Hypotension, unspecified	Any position
Death from any cause	Identified through linkage to Social Security Death Master and hospital discharge status	United only
Death from any cause in a hospital	Identified through hospital discharge status	

Annex 2.4 Results tables

Annex 2-Table 2-4 Full patient characteristics (pooled data) in the three cohorts

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Demographics	**%**	**%**	**%**	**%**	**%**	**%**
Age: 18-39	8.2	8.2	5.3	5.4	3.7	3.7
Age: 40-54	37.4	37.5	27.3	27.2	24.8	24.5
Age: 55-64	37.9	37.8	36.8	36.6	36.1	36.3
Age: 65+	16.6	16.5	30.6	30.8	35.4	35.5
Male	56.5	56.6	53.0	53.1	52.9	52.9
Region: Midwest	15.6	15.6	23.8	23.7	26.2	26.4
Northeast	8.3	8.3	11.3	11.2	10.9	10.8
South	63.4	63.6	49.2	49.4	47.4	47.1
West	12.7	12.6	15.8	15.7	15.6	15.7
Plan type: commercial	76.6	76.5	72.4	72.3	68.5	68.3
Monotherapy on index date	30.4	30.1	N/A	N/A	N/A	N/A

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Dual therapy on index date	37.1	38.2	32.3	32.1	22.4	22.1
Multiple therapy on index date	32.6	31.6	67.7	67.9	77.6	78.0
Coexisting medical conditions						
Atrial fibrillation/flutter	4.3	4.3	5.9	5.8	6.8	6.8
Atherosclerosis	13.1	13.0	16.2	16.4	17.0	17.2
Coronary artery bypass graft, old or new	0.9	0.9	1.2	1.2	1.2	1.2
Coronary artery disease (CAD)	14.7	14.6	18.0	18.2	18.9	19.0
Carotid endarterectomy	0.1	0.1	0.2	0.2	0.2	0.2
Carotid stent	0.0	0.0	0.0	0.0	0.0	0.0
Heart failure (CHF)	2.9	2.9	4.3	4.4	4.4	4.4
Conduction disorders	1.3	1.3	1.6	1.7	1.9	1.8
Coronary stent	0.5	0.5	0.8	0.8	0.8	0.8
CVD	26.7	26.5	31.6	31.8	34.9	34.9
Diabetes	27.5	27.4	32.9	33.1	33.8	33.5
Diabetes and renal impairment	4.2	4.1	4.8	4.8	5.3	5.3
Hemorrhagic stroke	1.5	1.5	1.9	1.9	2.2	2.3
Hyperkalemia	0.9	0.9	1.1	1.2	1.6	1.5
Hyperlipidemia	43.2	43.4	44.6	44.6	43.8	43.9
Ischemic stroke	1.5	1.5	1.9	2.0	2.5	2.5
Other stroke effects	0.4	0.4	0.6	0.6	0.7	0.7
Previous MI	0.7	0.7	1.0	1.0	1.0	1.0
Previous TIA	1.6	1.6	1.8	1.9	2.1	2.2
Pre-diabetes	1.9	1.9	1.9	1.9	2.0	2.0
Percutaneous transluminal coronary angioplasty (PTCA)	0.5	0.5	0.7	0.7	0.7	0.7
Peripheral vascular disease or PVD surgery	1.4	1.4	1.7	1.7	2.1	2.2
Radiographic procedures requiring contrast media	7.5	7.5	8.5	8.4	9.3	9.4
Recent MI	0.7	0.7	1.0	1.0	1.0	1.1
Renal impairment	8.1	8.0	11.0	11.0	12.9	12.8
Type 2 diabetes	26.2	26.2	31.3	31.6	32.2	31.9
Ventricular arrhythmia	2.0	2.0	2.5	2.5	2.7	2.7
Prior medications						
Alpha blocker	3.6	3.6	4.4	4.5	5.7	5.7
Combined alpha and beta blocker	9.4	9.2	11.8	11.9	12.0	11.7
ACE inhibitor	21.0	21.0	39.1	39.1	29.4	29.7

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	Aliskiren	Comparator	Aliskiren	Comparator	Aliskiren	Comparator
	N = 83,801	N = 334,403	N = 35,561	N = 139,570	N = 23,241	N = 92,350
Aliskiren	0.0	1.0	0.0	1.4	0.0	1.9
Anti-arrhythmic drug	1.6	1.5	2.2	2.1	2.4	2.4
ARB	20.1	19.7	38.2	37.7	25.8	25.2
Aspirin	0.1	0.0	0.1	0.1	0.1	0.1
Aspirin/dipyridamole	0.4	0.4	0.5	0.5	0.6	0.6
Beta blocker	30.1	30.2	34.9	35.1	37.2	37.5
Calcium channel blocker	31.3	31.2	38.1	38.1	88.6	88.4
Clopidogrel	7.0	7.1	8.8	9.0	9.9	9.9
Diabetes medications	23.4	23.4	28.1	28.3	28.5	28.4
Insulin	8.3	8.2	11.0	11.0	11.3	11.0
Loop diuretic	13.4	13.2	18.9	18.8	18.8	18.5
NSAIDs	19.2	19.2	19.5	19.4	19.9	19.9
Oral anticoagulants	4.2	4.2	5.7	5.7	6.3	6.3
Other antiplatelet agent	0.5	0.5	0.5	0.6	0.7	0.7
Other hypertension medications	11.0	10.8	14.0	14.0	18.0	17.8
Other lipid-lowering drugs	16.7	16.8	18.9	18.8	19.8	19.6
Potassium sparing agents/aldosterone antagonists	6.5	6.6	7.6	7.5	8.3	8.1
Potassium supplements	11.4	11.3	14.1	14.2	16.9	16.9
Prasugrel	0.1	0.1	0.2	0.2	0.2	0.2
Statin	43.2	43.2	49.1	49.4	50.2	50.5
Thiazide diuretic	43.1	42.9	39.1	39.3	51.0	50.9
Health care utilization	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of medications	7.9 (5.3)	7.8 (4.9)	8.4 (5.9)	8.4 (5.4)	9.6 (5.5)	9.5 (5.1)
Number of hospitalizations	0.1 (0.4)	0.1 (0.3)	0.2 (0.5)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Number of hospital days	0.7 (3.1)	0.7 (1.5)	0.9 (3.9)	0.9 (2.0)	1.1 (4.5)	1.1 (2.4)
Number of physician office visits	5.9 (4.4)	5.8 (4.2)	6.4 (4.7)	6.3 (4.4)	6.6 (4.8)	6.6 (4.5)
Number of cardiologist visits	0.8 (1.8)	0.8 (1.4)	0.9 (2.0)	0.9 (1.6)	1.0 (2.2)	1.0 (1.7)
Number of neurologist visits	0.1 (0.6)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)
Hospitalization in 30 days prior	0.0 (0.2)	0.0 (0.1)	0.0 (0.2)	0.0 (0.1)	0.1 (0.2)	0.1 (0.1)
Number of laboratory tests ordered	2.7 (3.0)	2.7 (2.5)	2.9 (3.3)	2.9 (2.8)	2.9 (3.5)	2.9 (2.9)
Number of lipid tests ordered	0.6 (0.8)	0.6 (0.7)	0.6 (0.8)	0.6 (0.7)	0.6 (0.8)	0.6 (0.7)
Number of creatinine tests ordered	0.1 (0.4)	0.1 (0.2)	0.1 (0.4)	0.1 (0.2)	0.1 (0.4)	0.1 (0.2)

Annex 2-Table 2-5 Baseline characteristics of Cohort 1 patients, stratified by database

Characteristic	United		MarketScan	
	Aliskiren	Comparator	Aliskiren	Comparator
	N = 16,244	N = 64,817	N = 67,557	N = 269,586
Demographics	**%**	**%**	**%**	**%**
Age: 18-39	8.2	8.2	6.3	6.3
40-54	37.4	37.5	29.9	29.9
55-64	37.9	37.8	35.1	35.0
65+	16.6	16.5	28.7	28.8
Index year: 2007	17.0	17.0	13.5	13.5
2008	24.1	24.1	21.1	21.1
2009	21.5	21.5	20.0	20.0
2010	19.4	19.4	24.3	24.3
2011	15.5	15.5	19.0	19.0
2012	2.4	2.4	2.2	2.2
Male	56.5	56.6	51.4	51.4
Region: Midwest	15.6	15.6	25.8	25.9
Northeast	8.3	8.3	11.5	11.3
South	63.4	63.6	48.0	48.4
West	12.7	12.6	14.7	14.4
Plan type: commercial	99.9	99.9	70.9	70.8
Medicare	0.1	0.1	29.1	29.2
Monotherapy on index date	30.4	30.1	23.7	23.7
Dual therapy on index date	37.1	38.2	37.8	37.5
Multiple therapy on index date	32.6	31.6	38.6	38.8
Coexisting medical conditions				
Atrial fibrillation/flutter	3.8	3.8	4.4	4.4
Atherosclerosis	13.9	13.8	13.0	12.8
Coronary artery bypass graft, old or new	1.3	1.4	0.7	0.7
Coronary artery disease (CAD)	15.5	15.4	14.6	14.4
Carotid endarterectomy	0.1	0.1	0.2	0.1
Carotid stent	0.0	0.0	0.0	0.0
Heart failure (CHF)	2.8	2.8	2.9	2.9
Conduction disorders	1.3	1.3	1.3	1.3
Coronary stent	0.5	0.4	0.5	0.6
CVD	27.7	27.3	26.4	26.3
Diabetes	30.6	30.5	26.7	26.7
Diabetes and renal impairment	5.0	4.9	4.0	3.9
Hemorrhagic stroke	1.5	1.4	1.5	1.5
Hyperkalemia	1.3	1.3	0.9	0.8
Hyperlipidemia	61.1	61.7	38.9	38.9
Ischemic stroke	1.4	1.3	1.6	1.5
Other stroke effects	0.4	0.4	0.4	0.4
Old MI	1.0	1.0	0.7	0.7
Previous TIA	1.5	1.4	1.6	1.6
Pre-diabetes	2.8	2.8	1.6	1.7

Characteristic	United		MarketScan	
	Aliskiren N = 16,244	Comparator N = 64,817	Aliskiren N = 67,557	Comparator N = 269,586
Percutaneous transluminal coronary angioplasty (PTCA)	0.4	0.4	0.5	0.5
Peripheral vascular disease or PVD surgery	1.7	1.7	1.3	1.3
Radiographic procedures requiring contrast media	6.6	6.5	7.8	7.8
Recent MI	0.7	0.6	0.7	0.7
Renal impairment	9.2	9.0	7.9	7.8
Type 2 diabetes	29.5	29.3	25.4	25.4
Ventricular arrhythmia	1.9	2.0	2.0	2.0
Prior medications				
Alpha blocker	3.2	3.1	3.7	3.7
Combined alpha and beta blocker	8.5	7.9	9.7	9.5
ACE inhibitor	20.2	20.5	21.2	21.1
Aliskiren	0.0	0.5	0.0	1.1
Anti-arrhythmic drug	1.3	1.3	1.6	1.6
ARB	18.7	18.1	20.4	20.1
Aspirin	0.0	0.0	0.1	0.1
Aspirin/dipyridamole	0.3	0.3	0.4	0.4
Beta blocker	27.5	27.2	30.8	30.9
Calcium channel blocker	30.8	30.1	31.4	31.5
Clopidogrel	5.7	5.8	7.3	7.3
Diabetes medications	24.1	24.1	23.3	23.2
Insulin	9.0	9.0	8.1	8.0
Loop diuretic	11.3	10.9	13.9	13.8
NSAIDs	17.9	17.9	19.5	19.5
Oral anticoagulants	3.5	3.5	4.3	4.4
Other antiplatelet agent	0.4	0.3	0.5	0.5
Other hypertension medications	10.1	9.5	11.2	11.1
Other lipid-lowering drugs	16.7	16.9	16.7	16.8
Potassium sparing agents/aldosterone antagonists	6.1	6.2	6.6	6.7
Potassium supplements	10.3	9.8	11.7	11.7
Prasugrel	0.1	0.1	0.1	0.2
Statin	42.4	42.8	43.4	43.3
Thiazide diuretic	42.8	41.9	43.1	43.2
Ticagrelor	0.0	0.0	0.0	0.0
Health care utilization	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of medications	7.5 (5.2)	7.4 (4.7)	8.0 (5.3)	7.9 (5.0)
Number of hospitalizations	0.2 (0.5)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)
Number of hospital days	0.7 (3.2)	0.6 (1.5)	0.7 (3.1)	0.7 (1.6)
Number of physician office visits	5.5 (4.0)	5.4 (3.9)	6.0 (4.5)	5.9 (4.3)
Number of cardiologist visits	0.8 (1.8)	0.8 (1.4)	0.8 (1.9)	0.8 (1.4)
Number of neurologist visits	0.1 (0.6)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)
Hospitalization in 30 days prior	0.0 (0.2)	0.0 (0.1)	0.0 (0.2)	0.0 (0.1)
Number of laboratory tests ordered	2.7 (2.7)	2.7 (2.4)	2.7 (3.1)	2.7 (2.6)
Number of lipid tests ordered	0.7 (0.8)	0.7 (0.7)	0.6 (0.8)	0.6 (0.7)
Number of creatinine tests ordered	0.0 (0.2)	0.0 (0.1)	0.1 (0.4)	0.1 (0.2)

Annex 2-Table 2-6 Baseline characteristics of Cohort 2 patients, stratified by database

Characteristic	United		MarketScan	
	Aliskiren	Comparator	Aliskiren	Comparator
	N = 5,748	N = 22,813	N = 29,813	N = 116,757
Demographics	**%**	**%**	**%**	**%**
Age: 18-39	5.9	5.8	5.2	5.3
40-54	31.9	31.7	26.4	26.4
55-64	41.1	40.6	35.9	35.8
65+	21.1	21.9	32.5	32.5
Index year: 2007	12.5	12.5	9.3	9.3
2008	17.8	17.8	13.8	13.8
2009	18.0	18.0	14.6	14.6
2010	28.3	28.3	37.4	37.4
2011	20.8	20.8	22.9	22.9
2012	2.5	2.5	2.0	2.0
Male	56.8	56.9	52.3	52.4
Region: Midwest	15.5	15.5	25.4	25.3
Northeast	7.9	8.0	11.9	11.8
South	63.4	63.4	46.5	46.7
West	13.3	13.1	16.2	16.2
Plan type: commercial	99.8	99.9	67.1	67.0
Medicare	0.2	0.1	32.9	33.0
Monotherapy on index date	0.0	0.0	0.0	0.0
Dual therapy on index date	33.1	32.4	32.2	32.1
Multiple therapy on index date	66.9	67.6	67.8	67.9
Coexisting medical conditions				
Atrial fibrillation/flutter	6.0	5.7	5.9	5.8
Atherosclerosis	18.9	19.2	15.6	15.9
Coronary artery bypass graft, old or new	2.2	2.1	1.0	1.0
Coronary artery disease (CAD)	20.6	21.0	17.5	17.7
Carotid endarterectomy	0.2	0.2	0.2	0.2
Carotid stent	0.0	0.0	0.0	0.0
Heart failure (CHF)	5.1	5.2	4.1	4.2
Conduction disorders	1.8	1.9	1.6	1.6
Coronary stent	0.7	0.7	0.8	0.8
CVD	35.1	35.1	30.9	31.1
Diabetes	39.2	39.7	31.6	31.8
Diabetes and renal impairment	0.6	0.6	5.6	5.6
Hemorrhagic stroke	2.0	2.0	1.9	1.9
Hyperkalemia	1.7	1.6	1.0	1.1
Hyperlipidemia	66.4	66.4	40.4	40.5
Ischemic stroke	2.1	2.1	1.9	2.0
Other stroke effects	0.7	0.8	0.6	0.6
Old MI	1.5	1.5	0.9	0.9
Previous TIA	1.9	1.9	1.8	1.9
Pre-diabetes	3.1	3.0	1.7	1.7

Characteristic	United		MarketScan	
	Aliskiren N = 5,748	Comparator N = 22,813	Aliskiren N = 29,813	Comparator N = 116,757
Percutaneous transluminal coronary angioplasty (PTCA)	0.6	0.7	0.7	0.7
Peripheral vascular disease or PVD surgery	2.0	2.1	1.6	1.6
Radiographic procedures requiring contrast media	7.2	7.2	8.7	8.6
Recent MI	1.1	1.1	1.0	1.0
Renal impairment	14.3	13.9	10.4	10.4
Type 2 diabetes	37.8	38.2	30.1	30.3
Ventricular arrhythmia	2.7	2.8	2.4	2.4
Prior medications				
Alpha blocker	4.4	4.5	4.4	4.5
Combined alpha and beta blocker	11.8	11.6	11.8	11.9
ACE inhibitor	42.7	43.7	38.5	38.2
Aliskiren	0.0	1.0	0.0	1.5
Anti-arrhythmic drug	2.0	2.1	2.2	2.2
ARB	40.2	39.9	37.8	37.3
Aspirin	0.1	0.1	0.1	0.1
Aspirin/dipyridamole	0.4	0.4	0.5	0.5
Beta blocker	33.8	34.1	35.1	35.3
Calcium channel blocker	39.6	39.9	37.8	37.8
Clopidogrel	8.1	8.2	9.0	9.2
Diabetes medications	31.9	32.5	27.4	27.5
Insulin	13.5	13.4	10.5	10.6
Loop diuretic	18.2	18.1	19.0	18.9
NSAIDs	18.0	18.4	19.8	19.6
Oral anticoagulants	5.6	5.8	5.7	5.7
Other antiplatelet agent	0.4	0.5	0.6	0.6
Other hypertension medications	13.6	13.3	14.1	14.1
Other lipid-lowering drugs	20.2	20.2	18.6	18.6
Potassium sparing agents/aldosterone antagonists	7.6	7.6	7.6	7.5
Potassium supplements	13.8	13.9	14.1	14.3
Prasugrel	0.2	0.2	0.2	0.2
Statin	51.1	51.7	48.7	48.9
Thiazide diuretic	38.0	38.4	39.4	39.4
Ticagrelor	0.0	0.0	0.0	0.0
Health care utilization	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of medications	9.0 (5.6)	9.0 (5.0)	8.3 (5.9)	8.3 (5.5)
Number of hospitalizations	0.2 (0.7)	0.2 (0.4)	0.2 (0.5)	0.2 (0.3)
Number of hospital days	1.0 (4.3)	1.0 (2.2)	0.9 (3.8)	0.9 (2.0)
Number of physician office visits	6.0 (4.4)	6.0 (4.1)	6.4 (4.7)	6.3 (4.5)
Number of cardiologist visits	1.1 (2.1)	1.1 (1.7)	0.9 (2.0)	0.9 (1.5)
Number of neurologist visits	0.1 (0.5)	0.1 (0.2)	0.1 (0.6)	0.1 (0.3)
Hospitalization in 30 days prior	0.0 (0.2)	0.0 (0.1)	0.0 (0.2)	0.0 (0.1)
Number of laboratory tests ordered	2.9 (3.1)	3.0 (2.8)	2.9 (3.3)	2.9 (2.8)
Number of lipid tests ordered	0.7 (0.8)	0.7 (0.8)	0.6 (0.8)	0.6 (0.7)

Characteristic	United		MarketScan	
	Aliskiren	Comparator	Aliskiren	Comparator
	N = 5,748	N = 22,813	N = 29,813	N = 116,757
Number of creatinine tests ordered	0.0 (0.3)	0.0 (0.1)	0.1 (0.4)	0.1 (0.2)

Annex 2-Table 2-7 Baseline characteristics of Cohort 3 patients, stratified by database

Characteristic	United		MarketScan	
	Aliskiren	Comparator	Aliskiren	Comparator
	N = 4,149	N = 16,438	N = 19,092	N = 75,912
Demographics	**%**	**%**	**%**	**%**
Age: 18-39	4.5	4.7	3.5	3.4
40-54	31.5	31.5	23.4	22.9
55-64	40.3	40.6	35.2	35.4
65+	23.6	23.2	37.9	38.2
Index year: 2007	15.9	15.9	12.8	12.8
2008	21.6	21.6	19.7	19.7
2009	21.6	21.6	18.9	18.9
2010	19.3	19.3	22.2	22.2
2011	18.7	18.7	23.4	23.4
2012	3.0	3.0	3.0	3.0
Male	58.8	58.4	51.6	51.7
Region: Midwest	17.8	18.0	28.0	28.2
Northeast	7.7	7.2	11.6	11.6
South	60.5	61.1	44.5	44.1
West	14.0	13.7	15.9	16.2
Plan type: commercial	99.8	99.8	61.7	61.4
Medicare	0.2	0.2	38.3	38.6
Monotherapy on index date	0.0	0.0	0.0	0.0
Dual therapy on index date	25.8	25.7	21.7	21.3
Multiple therapy on index date	74.2	74.3	78.3	78.7
Coexisting medical conditions				
Atrial fibrillation/flutter	6.4	6.1	6.8	6.9
Atherosclerosis	19.1	18.9	16.6	16.8
Coronary artery bypass graft, old or new	1.9	2.0	1.0	1.0
Coronary Artery Disease (CAD)	20.7	20.6	18.5	18.7
Carotid endarterectomy	0.1	0.2	0.2	0.3
Carotid stent	0.0	0.0	0.0	0.0
Heart failure (CHF)	4.5	4.3	4.3	4.4
Conduction disorders	2.0	1.8	1.8	1.8
Coronary stent	0.6	0.6	0.8	0.8
CVD	37.0	36.5	34.5	34.6
Diabetes	38.9	38.6	32.6	32.4
Diabetes and renal impairment	0.7	0.7	6.3	6.3
Hemorrhagic stroke	2.4	2.3	2.2	2.3
Hyperkalemia	2.4	2.4	1.4	1.3
Hyperlipidemia	65.5	65.4	39.1	39.3

Characteristic	United		MarketScan	
	Aliskiren N = 4,149	Comparator N = 16,438	Aliskiren N = 19,092	Comparator N = 75,912
Ischemic stroke	2.5	2.4	2.5	2.5
Other stroke effects	0.6	0.5	0.7	0.8
Old MI	1.5	1.4	0.9	0.9
Previous TIA	1.8	1.8	2.2	2.3
Pre-diabetes	3.4	3.5	1.7	1.7
Percutaneous transluminal coronary angioplasty (PTCA)	0.5	0.5	0.8	0.8
Peripheral vascular disease or PVD surgery	2.7	2.7	2.0	2.1
Radiographic procedures requiring contrast media	7.7	7.7	9.6	9.8
Recent MI	0.8	1.0	1.1	1.1
Renal impairment	15.3	15.1	12.3	12.3
Type 2 diabetes	37.6	37.3	31.0	30.8
Ventricular arrhythmia	2.7	2.9	2.7	2.6
Prior medications				
Alpha blocker	5.6	5.3	5.7	5.8
Combined alpha and beta blocker	12.1	11.9	12.0	11.7
ACE inhibitor	29.2	29.4	29.5	29.8
Aliskiren	0.0	1.4	0.0	2.0
Anti-arrhythmic drug	1.9	1.9	2.5	2.5
ARB	24.4	23.9	26.1	25.5
Aspirin	0.0	0.0	0.1	0.1
Aspirin/dipyridamole	0.6	0.5	0.6	0.6
Beta blocker	34.9	35.3	37.6	38.0
Calcium channel blocker	91.1	91.0	88.0	87.8
Clopidogrel	8.2	7.8	10.3	10.4
Diabetes medications	30.3	30.0	28.1	28.0
Insulin	12.8	12.5	11.0	10.6
Loop diuretic	17.8	17.3	19.0	18.7
NSAIDs	18.7	19.1	20.2	20.1
Oral anticoagulants	5.3	5.2	6.5	6.5
Other antiplatelet agent	0.6	0.6	0.7	0.7
Other hypertension medications	17.5	16.9	18.1	18.0
Other lipid-lowering drugs	19.8	19.9	19.7	19.6
Potassium sparing agents/aldosterone antagonists	8.5	8.2	8.2	8.1
Potassium supplements	16.1	16.1	17.1	17.0
Prasugrel	0.2	0.2	0.2	0.2
Statin	50.5	50.8	50.2	50.5
Thiazide diuretic	52.6	52.6	50.6	50.5
Ticagrelor	0.0	0.0	0.0	0.0
Health care utilization	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of medications	9.3 (5.3)	9.3 (5.0)	9.6 (5.5)	9.6 (5.1)
Number of hospitalizations	0.2 (0.6)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Number of hospital days	1.1 (4.8)	1.1 (2.5)	1.1 (4.4)	1.1 (2.3)
Number of physician office visits	6.2 (4.4)	6.1 (4.1)	6.7 (4.8)	6.7 (4.5)
Number of cardiologist visits	1.1 (2.1)	1.0 (1.6)	1.0 (2.2)	1.0 (1.7)

Characteristic	United		MarketScan	
	Aliskiren N = 4,149	Comparator N = 16,438	Aliskiren N = 19,092	Comparator N = 75,912
Number of neurologist visits	0.1 (0.5)	0.1 (0.3)	0.1 (0.6)	0.1 (0.3)
Hospitalization in 30 days prior	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)
Number of laboratory tests ordered	2.9 (3.0)	2.9 (2.7)	2.9 (3.6)	2.9 (2.9)
Number of lipid tests ordered	0.7 (0.8)	0.7 (0.8)	0.6 (0.8)	0.6 (0.7)
Number of creatinine tests ordered	0.0 (0.3)	0.0 (0.1)	0.1 (0.4)	0.1 (0.2)

Annex 2-Table 2-8 Hazard ratios of primary outcomes in Cohort 1 patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 16,244)**			**Comparator (N = 64,817)**			
Cerebrovascular accidents	258	29,687	8.7	951	115,314	8.3	1.05 (0.91-1.20)
Stroke	285	29,653	9.6	1,076	115,155	9.3	1.02 (0.90-1.17)
Ischemic stroke	262	29,673	8.8	992	115,252	8.6	1.02 (0.89-1.17)
Hemorrhagic stroke	45	29,933	1.5	167	116,213	1.4	1.04 (0.75-1.44)
Transient ischemic attack	167	29,775	5.6	619	115,616	5.4	1.05 (0.88-1.24)
Myocardial infarction	103	29,840	3.5	443	115,836	3.8	0.90 (0.73-1.12)
Heart failure	386	29,510	13.1	1,742	114,257	15.3	0.86 (0.77-0.96)
Acute renal failure	715	29,141	24.5	2,973	112,982	26.3	0.93 (0.85-1.01)
End-stage renal disease	194	29,718	6.5	854	115,403	7.4	0.88 (0.75-1.03)
MarketScan	**Aliskiren (N = 67,557)**			**Comparator (N = 269,586)**			
Cerebrovascular accidents	693	129,564	5.4	2,530	508,943	5.0	1.08 (0.99-1.17)
Stroke	1,261	128,860	9.8	4,864	505,937	9.6	1.02 (0.96-1.08)
Ischemic stroke	1,194	128,908	9.3	4,679	506,098	9.3	1.00 (0.94-1.07)
Hemorrhagic stroke	121	130,285	0.9	363	511,593	0.7	1.31 (1.07-1.61)
Transient ischemic attack	290	129,974	2.2	1,083	510,317	2.1	1.05 (0.92-1.20)
Myocardial infarction	554	129,743	4.3	2,377	509,007	4.7	0.91 (0.83-1.00)
Heart failure	1,009	129,084	7.8	4,498	506,345	8.9	0.88 (0.82-0.94)
Acute renal failure	3,163	126,550	25.0	12,899	497,070	26.0	0.96 (0.92-1.00)
End-stage renal disease	737	129,546	5.7	3,238	508,155	6.4	0.89 (0.82-0.96)

Annex 2-Table 2-9 Hazard ratios of primary outcomes in Cohort 2 patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 5,748)**			**Comparator (N = 22,813)**			
Cerebrovascular accidents	107	9,732	11.0	433	37,611	11.5	0.96 (0.78-1.18)
Stroke	122	9,712	12.6	509	37,525	13.6	0.93 (0.76-1.13)
Ischemic stroke	113	9,718	11.6	467	37,574	12.4	0.94 (0.76-1.15)

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
Hemorrhagic stroke	19	9,834	1.9	86	37,996	2.3	0.86 (0.52-1.42)
Transient ischemic attack	67	9,766	6.9	268	37,767	7.1	0.98 (0.75-1.28)
Myocardial infarction	54	9,788	5.5	206	37,836	5.4	1.00 (0.74-1.35)
Heart failure	195	9,611	20.3	949	36,929	25.7	0.79 (0.68-0.92)
Acute renal failure	344	9,419	36.5	1,448	36,428	39.8	0.92 (0.81-1.03)
End-stage renal disease	114	9,714	11.7	524	37,483	14.0	0.83 (0.68-1.02)
MarketScan	**Aliskiren (N = 29,813)**			**Comparator (N = 116,757)**			
Cerebrovascular accidents	335	51,514	6.5	1,242	199,112	6.2	1.05 (0.93-1.18)
Stroke	615	51,182	12.0	2,440	197,743	12.3	0.98 (0.89-1.07)
Ischemic stroke	585	51,201	11.4	2,353	197,800	11.9	0.96 (0.88-1.05)
Hemorrhagic stroke	54	51,854	1.0	165	200,396	0.8	1.28 (0.94-1.74)
Transient ischemic attack	142	51,723	2.8	488	199,905	2.4	1.13 (0.94-1.36)
Myocardial infarction	253	51,620	4.9	1,133	199,261	5.7	0.86 (0.75-0.99)
Heart failure	549	51,179	10.7	2,606	197,207	13.2	0.81 (0.74-0.89)
Acute renal failure	1,675	49,981	33.5	6,867	192,549	35.7	0.94 (0.89-0.99)
End-stage renal disease	426	51,388	8.3	1,843	198,346	9.3	0.88 (0.79-0.98)

Annex 2-Table 2-10 Hazard ratios of primary outcomes in Cohort 3 patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 4,149)**			**Comparator (N = 16,438)**			
Cerebrovascular accidents	85	7,397	11.5	333	28,274	11.8	0.98 (0.77-1.24)
Stroke	100	7,384	13.5	381	28,215	13.5	1.01 (0.81-1.25)
Ischemic stroke	94	7,389	12.7	351	28,253	12.4	1.03 (0.82-1.29)
Hemorrhagic stroke	16	7,468	2.1	60	28,603	2.1	1.03 (0.59-1.78)
Transient ischemic attack	63	7,413	8.5	197	28,429	6.9	1.23 (0.92-1.63)
Myocardial infarction	43	7,428	5.8	147	28,509	5.2	1.11 (0.79-1.56)
Heart failure	162	7,288	22.2	698	27,831	25.1	0.88 (0.74-1.05)
Acute renal failure	301	7,129	42.2	1,168	27,285	42.8	0.98 (0.86-1.11)
End-stage renal disease	98	7,365	13.3	389	28,205	13.8	0.97 (0.77-1.21)
MarketScan	**Aliskiren (N = 19,092)**			**Comparator (N = 75,912)**			
Cerebrovascular accidents	209	35,480	5.9	978	137,996	7.1	0.83 (0.71-0.96)
Stroke	430	35,208	12.2	1,865	136,860	13.6	0.89 (0.80-0.99)
Ischemic stroke	412	35,218	11.7	1,797	136,900	13.1	0.89 (0.80-0.99)
Hemorrhagic stroke	30	35,705	0.8	145	139,038	1.0	0.80 (0.54-1.19)
Transient ischemic attack	100	35,590	2.8	423	138,563	3.1	0.92 (0.74-1.15)
Myocardial infarction	194	35,491	5.5	930	138,007	6.7	0.81 (0.69-0.94)
Heart failure	399	35,270	11.3	1,859	136,803	13.6	0.83 (0.74-0.92)
Acute renal failure	1,288	34,164	37.7	5,285	132,892	39.8	0.95 (0.89-1.01)

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
End-stage renal disease	350	35,332	9.9	1,642	137,219	12.0	0.82 (0.73-0.92)

Annex 2-Table 2-11 Hazard ratios of primary outcomes in Cohort 1 patients, stratified by database, as-treated analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 16,244)**			**Comparator (N = 64,817)**			
Cerebrovascular accidents	82	10,741	7.6	347	42,277	8.2	0.93 (0.73-1.18)
Stroke	94	10,736	8.8	406	42,245	9.6	0.91 (0.73-1.14)
Ischemic stroke	88	10,736	8.2	370	42,265	8.8	0.94 (0.74-1.18)
Hemorrhagic stroke	10	10,772	0.9	68	42,408	1.6	0.58 (0.30-1.12)
Transient ischemic attack	56	10,744	5.2	228	42,304	5.4	0.97 (0.72-1.29)
Myocardial infarction	33	10,765	3.1	150	42,375	3.5	0.86 (0.59-1.26)
Heart failure	130	10,722	12.1	706	42,133	16.8	0.73 (0.60-0.87)
Acute renal failure	265	10,662	24.9	1,202	41,968	28.6	0.86 (0.75-0.98)
End-stage renal disease	70	10,751	6.5	348	42,320	8.2	0.79 (0.61-1.02)
MarketScan	**Aliskiren (N = 67,557)**			**Comparator (N = 269,586)**			
Cerebrovascular accidents	218	49,967	4.4	796	184,899	4.3	1.03 (0.88-1.19)
Stroke	413	49,869	8.3	1,613	184,541	8.7	0.96 (0.86-1.07)
Ischemic stroke	397	49,873	8.0	1,548	184,568	8.4	0.96 (0.86-1.07)
Hemorrhagic stroke	34	50,048	0.7	118	185,214	0.6	1.08 (0.74-1.59)
Transient ischemic attack	93	49,988	1.9	352	185,047	1.9	0.99 (0.78-1.24)
Myocardial infarction	188	49,994	3.8	786	184,954	4.3	0.89 (0.76-1.04)
Heart failure	328	49,906	6.6	1,674	184,533	9.1	0.73 (0.65-0.83)
Acute renal failure	1,220	49,630	24.6	4,923	183,408	26.8	0.92 (0.87-0.98)
End-stage renal disease	211	49,977	4.2	1,168	184,874	6.3	0.67 (0.58-0.78)

Annex 2-Table 2-12 Hazard ratios of primary outcomes in Cohort 2 patients, stratified by database, as-treated analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 5,748)**			**Comparator (N = 22,813)**			
Cerebrovascular accidents	30	2,983	10.1	123	11,018	11.2	0.91 (0.61-1.36)
Stroke	36	2,981	12.1	144	11,008	13.1	0.94 (0.65-1.35)
Ischemic stroke	34	2,981	11.4	132	11,012	12.0	0.97 (0.66-1.41)
Hemorrhagic stroke	4	2,991	1.3	20	11,052	1.8	0.75 (0.26-2.18)
Transient ischemic attack	23	2,983	7.7	66	11,036	6.0	1.32 (0.82-2.12)
Myocardial infarction	14	2,989	4.7	52	11,048	4.7	0.97 (0.53-1.75)

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
Heart failure	62	2,974	20.9	320	10,968	29.2	0.72 (0.55-0.95)
Acute renal failure	118	2,957	39.9	512	10,934	46.8	0.86 (0.70-1.05)
End-stage renal disease	35	2,983	11.7	145	11,026	13.2	0.90 (0.62-1.30)
MarketScan	**Aliskiren (N = 29,813)**			**Comparator (N = 116,757)**			
Cerebrovascular accidents	103	17,629	5.8	325	57,932	5.6	1.09 (0.87-1.36)
Stroke	182	17,593	10.3	663	57,827	11.5	0.94 (0.80-1.11)
Ischemic stroke	171	17,596	9.7	643	57,830	11.1	0.91 (0.77-1.08)
Hemorrhagic stroke	21	17,665	1.2	35	58,030	0.6	2.08 (1.21-3.58)
Transient ischemic attack	40	17,638	2.3	125	57,972	2.2	1.09 (0.77-1.56)
Myocardial infarction	73	17,650	4.1	274	57,966	4.7	0.90 (0.70-1.17)
Heart failure	157	17,612	8.9	765	57,797	13.2	0.71 (0.60-0.84)
Acute renal failure	568	17,532	32.4	2,139	57,485	37.2	0.90 (0.82-0.99)
End-stage renal disease	118	17,636	6.7	528	57,906	9.1	0.77 (0.63-0.94)

Annex 2-Table 2-13 Hazard ratios of primary outcomes in Cohort 3 patients, stratified by database, as-treated analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 4,149)**			**Comparator (N = 16,438)**			
Cerebrovascular accidents	17	2,193	7.8	105	8,178	12.8	0.61 (0.37-1.02)
Stroke	21	2,192	9.6	121	8,176	14.8	0.66 (0.41-1.04)
Ischemic stroke	20	2,192	9.1	107	8,180	13.1	0.71 (0.44-1.14)
Hemorrhagic stroke	2	2,199	0.9	24	8,207	2.9	0.32 (0.08-1.34)
Transient ischemic attack	13	2,192	5.9	59	8,193	7.2	0.83 (0.46-1.51)
Myocardial infarction	11	2,197	5.0	37	8,204	4.5	1.06 (0.54-2.08)
Heart failure	51	2,183	23.4	250	8,154	30.7	0.77 (0.57-1.05)
Acute renal failure	99	2,175	45.5	406	8,118	50.0	0.92 (0.74-1.15)
End-stage renal disease	29	2,192	13.2	131	8,183	16.0	0.84 (0.56-1.26)
MarketScan	**Aliskiren (N = 19,092)**			**Comparator (N = 75,912)**			
Cerebrovascular accidents	49	10,667	4.6	227	37,654	6.0	0.78 (0.57-1.06)
Stroke	112	10,643	10.5	477	37,583	12.7	0.85 (0.69-1.04)
Ischemic stroke	108	10,644	10.2	460	37,586	12.2	0.85 (0.69-1.04)
Hemorrhagic stroke	5	10,694	0.5	28	37,729	0.7	0.67 (0.26-1.73)
Transient ischemic attack	24	10,681	2.3	90	37,695	2.4	0.97 (0.62-1.53)
Myocardial infarction	51	10,680	4.8	208	37,681	5.5	0.88 (0.64-1.19)
Heart failure	103	10,663	9.7	533	37,571	14.2	0.70 (0.57-0.86)
Acute renal failure	364	10,602	34.3	1,640	37,300	44.0	0.81 (0.72-0.90)
End-stage renal disease	85	10,671	8.0	466	37,609	12.4	0.67 (0.53-0.84)

Annex 2-Table 2-14 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	258	29,687	8.7	1.05 (0.91 - 1.20)	16,244	82	10,741	7.6	0.93 (0.73 - 1.18)
Comparator	64,817	951	115,314	8.3		64,817	347	42,277	8.2	
Stratified by age										
<65 – Aliskiren	13,554	179	24,729	7.2	1.16 (0.99 - 1.38)	13,554	58	8,643	6.7	1.08 (0.81 - 1.44)
<65 - Comparator	54,163	594	96,367	6.2		54,163	214	34,743	6.2	
65+ - Aliskiren	2,690	79	4,958	15.9	0.84 (0.66 - 1.08)	2,690	24	2,098	11.4	0.65 (0.42 - 1.01)
65+ - Comparator	10,654	357	18,947	18.8		10,654	133	7,534	17.7	
Stratified by gender										
Female - Aliskiren	7,063	121	12,959	9.3	1.06 (0.87 - 1.30)	7,063	42	4,535	9.3	1.07 (0.76 - 1.50)
Female - Comparator	28,134	441	50,042	8.8		28,134	151	17,289	8.7	
Male – Aliskiren	9,181	137	16,727	8.2	1.03 (0.85 - 1.25)	9,181	40	6,207	6.4	0.81 (0.58 - 1.14)
Male - Comparator	36,683	510	65,273	7.8		36,683	196	24,988	7.8	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	128	8,819	14.5	1.07 (0.88 - 1.31)	4,976	38	3,287	11.6	0.85 (0.60 - 1.20)
Diabetes - Comparator	19,746	451	33,731	13.4		19,746	174	12,694	13.7	
No diabetes - Aliskiren	11,268	130	20,867	6.2	1.01 (0.83 - 1.23)	11,268	44	7,454	5.9	1.01 (0.72 - 1.40)
No diabetes - Comparator	45,071	500	81,583	6.1		45,071	173	29,583	5.9	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	54	2,495	21.7	1.15 (0.85 - 1.57)	1,497	21	915	22.9	1.17 (0.72 - 1.90)
Renal impairment - Comparator	5,818	177	9,438	18.8		5,818	71	3,672	19.3	
No renal impairment - Aliskiren	14,747	204	27,192	7.5	1.02 (0.87 - 1.19)	14,747	61	9,826	6.2	0.86 (0.65 - 1.13)
No renal impairment - Comparator	58,999	774	105,876	7.3		58,999	276	38,605	7.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	36	1,319	27.3	1.10 (0.76 - 1.61)	813	12	486	24.7	1.01 (0.53 - 1.90)
Diabetes and renal impairment - Comparator	3,128	119	4,912	24.2		3,128	46	1,932	23.8	
No diabetes and renal impairment - Aliskiren	15,431	222	28,367	7.8	1.03 (0.89 - 1.20)	15,431	70	10,255	6.8	0.91 (0.70 - 1.18)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes and renal impairment - Comparator	61,689	832	110,402	7.5		61,689	301	40,345	7.5	
Stratified by CVD										
CVD - Aliskiren	4,507	120	8,112	14.8	1.00 (0.82 - 1.23)	4,507	43	3,070	14.0	0.91 (0.65 - 1.27)
CVD - Comparator	17,682	455	30,920	14.7		17,682	179	11,614	15.4	
No CVD - Aliskiren	11,737	138	21,575	6.4	1.07 (0.89 - 1.30)	11,737	39	7,671	5.1	0.91 (0.64 - 1.29)
No CVD - Comparator	47,135	496	84,395	5.9		47,135	168	30,663	5.5	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	170	21,020	8.1	1.12 (0.94 - 1.32)	11,208	51	7,277	7.0	0.97 (0.72 - 1.32)
Single RAAS - Comparator	45,872	614	84,373	7.3		45,872	221	30,683	7.2	
No single RAAS - Aliskiren	5,036	88	8,666	10.2	0.90 (0.71 - 1.14)	5,036	31	3,465	9.0	0.81 (0.55 - 1.21)
No single RAAS - Comparator	18,945	337	30,942	10.9		18,945	126	11,594	10.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	58	5,380	10.8	1.48 (1.09 - 2.00)	3,242	16	1,839	8.7	1.11 (0.64 - 1.94)
Quintile 1 - Comparator	12,970	154	21,119	7.3		12,970	59	7,619	7.7	
Quintile 2 - Aliskiren	3,243	45	5,885	7.7	1.15 (0.82 - 1.59)	3,243	15	1,993	7.5	1.07 (0.61 - 1.89)
Quintile 2 - Comparator	12,969	157	23,538	6.7		12,969	58	8,401	6.9	
Quintile 3 - Aliskiren	3,242	38	5,945	6.4	0.93 (0.65 - 1.32)	3,242	12	2,119	5.7	0.87 (0.47 - 1.63)
Quintile 3 - Comparator	12,971	158	22,928	6.9		12,971	55	8,434	6.5	
Quintile 4 - Aliskiren	3,243	56	6,145	9.1	1.14 (0.85 - 1.54)	3,243	18	2,262	8.0	1.02 (0.61 - 1.70)
Quintile 4 - Comparator	12,969	189	23,766	8.0		12,969	70	9,005	7.8	
Quintile 5 - Aliskiren	3,274	61	6,332	9.6	0.77 (0.58 - 1.01)	3,274	21	2,528	8.3	0.72 (0.45 - 1.15)
Quintile 5 - Comparator	12,938	293	23,965	12.2		12,938	105	8,817	11.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-15 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	693	129,564	5.4	1.08 (0.99 - 1.17)	218	67,557	49,967	4.4	1.03 (0.88 - 1.19)
Comparator	269,586	2,530	508,943	5.0		796	269,586	184,899	4.3	
Stratified by age										
<65 - Aliskiren	48,191	297	88,775	3.4	1.07 (0.95 - 1.22)	48,191	88	33,715	2.6	1.06 (0.84 - 1.34)
<65 - Comparator	191,879	1,085	349,815	3.1		191,879	317	127,644	2.5	
65+ - Aliskiren	19,366	396	40,789	9.7	1.07 (0.96 - 1.20)	19,366	130	16,252	8.0	0.97 (0.80 - 1.17)
65+ - Comparator	77,707	1,445	159,127	9.1		77,707	479	57,255	8.4	
Stratified by gender										
Female - Aliskiren	32,853	369	63,643	5.8	1.09 (0.97 - 1.22)	32,853	98	23,838	4.1	0.89 (0.72 - 1.12)
Female - Comparator	131,041	1,334	250,582	5.3		131,041	401	86,241	4.7	
Male - Aliskiren	34,704	324	65,921	4.9	1.06 (0.94 - 1.20)	34,704	120	26,129	4.6	1.15 (0.94 - 1.41)
Male - Comparator	138,545	1,196	258,360	4.6		138,545	395	98,658	4.0	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	281	33,020	8.5	1.08 (0.95 - 1.24)	18,044	88	13,062	6.7	1.06 (0.84 - 1.35)
Diabetes - Comparator	71,720	1,003	127,355	7.9		71,720	308	47,631	6.5	
No diabetes - Aliskiren	49,513	412	96,543	4.3	1.06 (0.95 - 1.19)	49,513	130	36,906	3.5	1.00 (0.82 - 1.21)
No diabetes - Comparator	197,866	1,527	381,587	4.0		197,866	488	137,268	3.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	112	9,392	11.9	1.19 (0.96 - 1.47)	5,327	45	3,592	12.5	1.57 (1.10 - 2.22)
Renal impairment - Comparator	20,869	358	35,749	10.0		20,869	105	13,155	8.0	
No renal impairment - Aliskiren	62,230	581	120,172	4.8	1.05 (0.96 - 1.15)	62,230	173	46,376	3.7	0.93 (0.79 - 1.10)
No renal impairment - Comparator	248,717	2,172	473,193	4.6		248,717	691	171,744	4.0	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	66	4,622	14.3	1.29 (0.97 - 1.70)	2,695	26	1,774	14.7	1.77 (1.11 - 2.83)
Diabetes and renal impairment - Comparator	10,591	195	17,541	11.1		10,591	53	6,386	8.3	
No diabetes and Renal impairment –	64,862	627	124,941	5.0	1.05 (0.97 - 1.15)	64,862	192	48,193	4.0	0.97 (0.82 - 1.13)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren										
No diabetes and renal impairment – Comparator	258,995	2,335	491,402	4.8		258,995	743	178,513	4.2	
Stratified by CVD										
CVD – Aliskiren	17,832	324	34,465	9.4	1.09 (0.96 - 1.23)	17,832	109	13,486	8.1	1.05 (0.85 - 1.30)
CVD – Comparator	70,725	1,144	131,628	8.7		70,725	374	47,771	7.8	
No CVD – Aliskiren	49,725	369	95,099	3.9	1.05 (0.94 - 1.18)	49,725	109	36,481	3.0	0.98 (0.79 - 1.21)
No CVD – Comparator	198,861	1,386	377,315	3.7		198,861	422	137,128	3.1	
Stratified by single RAAS										
Single RAAS – Aliskiren	41,269	400	83,675	4.8	1.05 (0.95 - 1.18)	41,269	115	29,876	3.9	0.97 (0.79 - 1.18)
Single RAAS - Comparator	168,502	1,539	336,283	4.6		168,502	479	119,290	4.0	
No single RAAS - Aliskiren	26,288	293	45,889	6.4	1.09 (0.96 - 1.25)	26,288	103	20,091	5.1	1.07 (0.86 - 1.34)
No single RAAS - Comparator	101,084	991	172,660	5.7		101,084	317	65,609	4.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	116	22,731	5.1	1.20 (0.97 - 1.47)	13,486	38	8,483	4.5	1.16 (0.81 - 1.66)
Quintile 1 - Comparator	53,942	388	90,625	4.3		53,942	130	33,541	3.9	
Quintile 2 - Aliskiren	13,485	153	26,579	5.8	1.29 (1.08 - 1.55)	13,485	48	9,704	5.0	1.19 (0.86 - 1.65)
Quintile 2 - Comparator	53,944	468	104,975	4.5		53,944	156	37,226	4.2	
Quintile 3 - Aliskiren	13,485	136	26,724	5.1	1.13 (0.94 - 1.37)	13,485	40	10,107	4.0	1.01 (0.72 - 1.44)
Quintile 3 - Comparator	53,944	473	105,091	4.5		53,944	149	37,942	3.9	
Quintile 4 - Aliskiren	13,488	138	26,378	5.2	1.04 (0.86 - 1.25)	13,488	44	10,521	4.2	0.93 (0.66 - 1.29)
Quintile 4 - Comparator	53,941	521	103,455	5.0		53,941	172	37,874	4.5	
Quintile 5 - Aliskiren	13,613	150	27,151	5.5	0.85 (0.71 - 1.01)	13,613	48	11,152	4.3	0.89 (0.65 - 1.22)
Quintile 5 - Comparator	53,815	680	104,796	6.5		53,815	189	38,316	4.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-16 Hazard ratios of stroke in subgroups of Cohort 1 – United

Subgroup	ITT	As treated

	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	285	29,653	9.6	1.02 (0.90 - 1.17)	16,244	94	10,736	8.8	0.91 (0.73 - 1.14)
Comparator	64,817	1,076	115,155	9.3		64,817	406	42,245	9.6	
Stratified by age										
<65 - Aliskiren	13,554	191	24,706	7.7	1.12 (0.95 - 1.32)	13,554	66	8,639	7.6	1.09 (0.83 - 1.44)
<65 - Comparator	54,163	660	96,277	6.9		54,163	240	34,728	6.9	
65+ - Aliskiren	2,690	94	4,947	19.0	0.86 (0.69 - 1.08)	2,690	28	2,097	13.4	0.61 (0.41 - 0.91)
65+ - Comparator	10,654	416	18,878	22.0		10,654	166	7,517	22.1	
Stratified by gender										
Female - Aliskiren	7,063	134	12,946	10.4	1.04 (0.86 - 1.25)	7,063	46	4,531	10.2	1.00 (0.72 - 1.38)
Female - Comparator	28,134	502	49,973	10.1		28,134	177	17,275	10.3	
Male - Aliskiren	9,181	151	16,707	9.0	1.01 (0.85 - 1.21)	9,181	48	6,204	7.7	0.84 (0.61 - 1.14)
Male - Comparator	36,683	574	65,182	8.8		36,683	229	24,970	9.2	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	140	8,801	15.9	1.05 (0.87 - 1.26)	4,976	44	3,282	13.4	0.87 (0.63 - 1.21)
Diabetes - Comparator	19,746	507	33,674	15.1		19,746	196	12,685	15.5	
No diabetes - Aliskiren	11,268	145	20,853	7.0	0.99 (0.83 - 1.19)	11,268	50	7,454	6.7	0.94 (0.69 - 1.28)
No diabetes - Comparator	45,071	569	81,481	7.0		45,071	210	29,560	7.1	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	63	2,485	25.4	1.08 (0.82 - 1.44)	1,497	26	913	28.5	1.15 (0.74 - 1.78)
Renal impairment - Comparator	5,818	221	9,391	23.5		5,818	89	3,667	24.3	
No renal impairment - Aliskiren	14,747	222	27,169	8.2	1.00 (0.87 - 1.16)	14,747	68	9,822	6.9	0.83 (0.64 - 1.08)
No renal impairment - Comparator	58,999	855	105,764	8.1		58,999	317	38,578	8.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	813	41	1,313	31.2	1.03 (0.72 - 1.46)	813	14	484	28.9	0.94 (0.52 - 1.69)
Diabetes and renal impairment – Comparator	3,128	147	4,883	30.1		3,128	57	1,929	29.6	
No diabetes and renal impairment – Aliskiren	15,431	244	28,340	8.6	1.02 (0.88 - 1.17)	15,431	80	10,251	7.8	0.90 (0.70 - 1.14)
No diabetes and renal impairment –	61,689	929	110,272	8.4		61,689	349	40,316	8.7	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator										
Stratified by CVD										
CVD – Aliskiren	4,507	135	8,094	16.7	0.98 (0.81 - 1.19)	4,507	49	3,066	16.0	0.89 (0.65 - 1.21)
CVD – Comparator	17,682	524	30,843	17.0		17,682	211	11,598	18.2	
No CVD – Aliskiren	11,737	150	21,560	7.0	1.05 (0.88 - 1.26)	11,737	45	7,669	5.9	0.91 (0.66 - 1.26)
No CVD – Comparator	47,135	552	84,312	6.6		47,135	195	30,646	6.4	
Stratified by single RAAS										
Single RAAS – Aliskiren	11,208	182	21,006	8.7	1.06 (0.90 - 1.24)	11,208	58	7,273	8.0	0.96 (0.72 - 1.27)
Single RAAS - Comparator	45,872	694	84,274	8.2		45,872	256	30,665	8.4	
No single RAAS - Aliskiren	5,036	103	8,647	11.9	0.93 (0.75 - 1.16)	5,036	36	3,462	10.4	0.80 (0.56 - 1.15)
No single RAAS - Comparator	18,945	382	30,881	12.4		18,945	150	11,579	13.0	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	63	5,375	11.7	1.44 (1.08 - 1.93)	3,242	20	1,837	10.9	1.17 (0.71 - 1.93)
Quintile 1 - Comparator	12,970	171	21,083	8.1		12,970	70	7,614	9.2	
Quintile 2 - Aliskiren	3,243	49	5,879	8.3	1.12 (0.82 - 1.54)	3,243	18	1,993	9.0	1.10 (0.65 - 1.84)
Quintile 2 - Comparator	12,969	175	23,516	7.4		12,969	68	8,392	8.1	
Quintile 3 - Aliskiren	3,242	42	5,938	7.1	0.93 (0.66 - 1.30)	3,242	14	2,117	6.6	0.84 (0.47 - 1.49)
Quintile 3 - Comparator	12,971	175	22,906	7.6		12,971	67	8,430	8.0	
Quintile 4 - Aliskiren	3,243	62	6,140	10.1	1.07 (0.81 - 1.42)	3,243	19	2,260	8.4	0.94 (0.57 - 1.55)
Quintile 4 - Comparator	12,969	223	23,741	9.4		12,969	80	9,000	8.9	
Quintile 5 - Aliskiren	3,274	69	6,320	10.9	0.77 (0.59 - 1.00)	3,274	23	2,528	9.1	0.69 (0.44 - 1.08)
Quintile 5 - Comparator	12,938	332	23,910	13.9		12,938	121	8,810	13.7	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-17 Hazard ratios of stroke in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren	67,557	1,261	128,860	9.8	1.02 (0.96 - 1.08)	67,557	413	49,869	7.6	0.96 (0.86 - 1.07)
Comparator	269,586	4,864	505,937	9.6		269,586	1,613	184,541	8.2	
Stratified by age										
<65 - Aliskiren	48,191	535	88,499	6.1	1.02 (0.93 - 1.12)	48,191	161	33,682	6.7	0.93 (0.79 - 1.11)
<65 - Comparator	191,879	2,057	348,594	5.9		191,879	653	127,505	6.2	
65+ - Aliskiren	19,366	726	40,361	18.0	1.01 (0.93 - 1.10)	19,366	252	16,187	11.4	0.94 (0.82 - 1.08)
65+ - Comparator	77,707	2,807	157,343	17.8		77,707	960	57,036	17.7	
Stratified by gender										
Female - Aliskiren	32,853	683	63,226	10.8	1.03 (0.94 - 1.12)	32,853	204	23,788	9.3	0.87 (0.75 - 1.02)
Female - Comparator	131,041	2,620	248,899	10.5		131,041	852	86,042	8.7	
Male - Aliskiren	34,704	578	65,634	8.8	1.01 (0.92 - 1.10)	34,704	209	26,081	6.4	1.04 (0.89 - 1.21)
Male - Comparator	138,545	2,244	257,037	8.7		138,545	761	98,499	7.8	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	501	32,754	15.3	1.00 (0.90 - 1.10)	18,044	170	13,024	11.6	1.00 (0.84 - 1.18)
Diabetes - Comparator	71,720	1,946	126,159	15.4		71,720	631	47,505	13.7	
No diabetes - Aliskiren	49,513	760	96,106	7.9	1.03 (0.95 - 1.11)	49,513	243	36,845	5.9	0.93 (0.81 - 1.07)
No diabetes - Comparator	197,866	2,918	379,778	7.7		197,866	982	137,036	5.9	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	200	9,300	21.5	0.97 (0.83 - 1.14)	5,327	74	3,575	22.9	1.12 (0.86 - 1.45)
Renal impairment - Comparator	20,869	777	35,272	22.0		20,869	243	13,109	19.3	
No renal impairment - Aliskiren	62,230	1,061	119,560	8.9	1.02 (0.95 - 1.09)	62,230	339	46,294	6.2	0.92 (0.82 - 1.03)
No renal impairment - Comparator	248,717	4,087	470,665	8.7		248,717	1,370	171,433	7.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	118	4,570	25.8	1.01 (0.82 - 1.23)	2,695	45	1,765	24.7	1.26 (0.90 - 1.78)
Diabetes and renal impairment – Comparator	10,591	443	17,264	25.7		10,591	130	6,362	23.8	
No diabetes and renal impairment – Aliskiren	64,862	1,143	124,289	9.2	1.01 (0.95 - 1.08)	64,862	368	48,104	6.8	0.92 (0.82 - 1.04)
No diabetes and renal impairment -	258,995	4,421	488,673	9.1		258,995	1,483	178,179	7.5	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator										
Stratified by CVD										
CVD – Aliskiren	17,832	579	34,130	17.0	0.98 (0.89 - 1.07)	17,832	206	13,435	14.0	0.94 (0.81 - 1.10)
CVD – Comparator	70,725	2,267	130,223	17.4		70,725	787	47,591	15.4	
No CVD - Aliskiren	49,725	682	94,730	7.2	1.04 (0.95 - 1.13)	49,725	207	36,434	5.1	0.94 (0.81 - 1.10)
No CVD - Comparator	198,861	2,597	375,714	6.9		198,861	826	136,950	5.5	
Stratified by single RAAS										
Single RAAS - Aliskiren	41,269	716	83,253	8.6	1.00 (0.92 - 1.09)	41,269	220	29,828	7.0	0.93 (0.81 - 1.08)
Single RAAS - Comparator	168,502	2,906	334,429	8.7		168,502	950	119,086	7.2	
No single RAAS - Aliskiren	26,288	545	45,607	12.0	1.02 (0.93 - 1.13)	26,288	193	20,041	9.0	0.96 (0.81 - 1.12)
No single RAAS - Comparator	101,084	1,958	171,508	11.4		101,084	663	65,455	10.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	218	22,621	9.6	1.17 (1.00 - 1.36)	13,486	75	8,469	8.7	1.11 (0.86 - 1.44)
Quintile 1 - Comparator	53,942	747	90,194	8.3		53,942	267	33,468	7.7	
Quintile 2 - Aliskiren	13,485	241	26,474	9.1	1.09 (0.95 - 1.26)	13,485	77	9,688	7.5	1.00 (0.78 - 1.28)
Quintile 2 - Comparator	53,944	869	104,427	8.3		53,944	298	37,161	6.9	
Quintile 3 - Aliskiren	13,485	240	26,596	9.0	1.05 (0.91 - 1.21)	13,485	75	10,091	5.7	0.96 (0.75 - 1.24)
Quintile 3 - Comparator	53,944	900	104,555	8.6		53,944	296	37,874	6.5	
Quintile 4 - Aliskiren	13,488	254	26,231	9.7	0.96 (0.84 - 1.11)	13,488	84	10,505	8.0	0.90 (0.71 - 1.15)
Quintile 4 - Comparator	53,941	1,034	102,820	10.1		53,941	340	37,816	7.8	
Quintile 5 - Aliskiren	13,613	308	26,939	11.4	0.90 (0.80 - 1.02)	13,613	102	11,116	8.3	0.86 (0.70 - 1.07)
Quintile 5 - Comparator	53,815	1,314	103,941	12.6		53,815	412	38,221	11.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-18 Hazard ratios of ischemic stroke in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren	16,244	262	29,673	8.8	1.02 (0.89 - 1.17)	16,244	88	10,736	8.2	0.94 (0.74 - 1.18)
Comparator	64,817	992	115,252	8.6		64,817	370	42,265	8.8	
Stratified by age										
<65 - Aliskiren	13,554	172	24,725	7.0	1.10 (0.93 - 1.30)	13,554	61	8,639	7.1	1.12 (0.85 - 1.49)
<65 - Comparator	54,163	606	96,340	6.3		54,163	216	34,745	6.2	
65+ - Aliskiren	2,690	90	4,948	18.2	0.89 (0.71 - 1.12)	2,690	27	2,097	12.9	0.64 (0.42 - 0.96)
65+ - Comparator	10,654	386	18,912	20.4		10,654	154	7,520	20.5	
Stratified by gender										
Female - Aliskiren	7,063	127	12,951	9.8	1.06 (0.87 - 1.29)	7,063	45	4,532	9.9	1.06 (0.76 - 1.47)
Female - Comparator	28,134	465	50,017	9.3		28,134	163	17,283	9.4	
Male - Aliskiren	9,181	135	16,722	8.1	0.98 (0.81 - 1.19)	9,181	43	6,205	6.9	0.83 (0.60 - 1.15)
Male - Comparator	36,683	527	65,235	8.1		36,683	207	24,982	8.3	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	131	8,810	14.9	1.04 (0.86 - 1.26)	4,976	40	3,282	12.2	0.85 (0.61 - 1.20)
Diabetes - Comparator	19,746	477	33,707	14.2		19,746	182	12,695	14.3	
No diabetes - Aliskiren	11,268	131	20,863	6.3	0.99 (0.82 - 1.20)	11,268	48	7,454	6.4	1.01 (0.74 - 1.39)
No diabetes - Comparator	45,071	515	81,545	6.3		45,071	188	29,570	6.4	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	60	2,486	24.1	1.08 (0.81 - 1.45)	1,497	24	913	26.3	1.11 (0.70 - 1.74)
Renal impairment - Comparator	5,818	210	9,398	22.4		5,818	85	3,667	23.2	
No renal impairment - Aliskiren	14,747	202	27,187	7.4	1.00 (0.86 - 1.17)	14,747	64	9,823	6.5	0.87 (0.66 - 1.14)
No renal impairment - Comparator	58,999	782	105,854	7.4		58,999	285	38,598	7.4	
Stratified by diabetes and renal impairment										
Diabetes and denal impairment - Aliskiren	813	40	1,314	30.4	1.02 (0.72 - 1.45)	813	13	484	26.9	0.89 (0.48 - 1.62)
Diabetes and renal impairment - Comparator	3,128	144	4,886	29.5		3,128	56	1,929	29.0	
No diabetes and renal impairment - Aliskiren	15,431	222	28,358	7.8	1.01 (0.87 - 1.18)	15,431	75	10,252	7.3	0.93 (0.72 - 1.20)
No diabetes and renal impairment - Comparator	61,689	848	110,366	7.7		61,689	314	40,336	7.8	
Stratified by CVD										
CVD - Aliskiren	4,507	123	8,100	15.2	0.97 (0.80 - 1.18)	4,507	44	3,067	14.4	0.88 (0.63 - 1.22)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
CVD - Comparator	17,682	484	30,886	15.7		17,682	191	11,606	16.5	
No CVD - Aliskiren	11,737	139	21,573	6.4	1.06 (0.87 - 1.27)	11,737	44	7,669	5.7	0.97 (0.69 - 1.34)
No CVD - Comparator	47,135	508	84,367	6.0		47,135	179	30,659	5.8	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	166	21,022	7.9	1.03 (0.87 - 1.23)	11,208	55	7,274	7.6	0.98 (0.73 - 1.31)
Single RAAS - Comparator	45,872	648	84,330	7.7		45,872	237	30,677	7.7	
No single RAAS - Aliskiren	5,036	96	8,651	11.1	0.97 (0.77 - 1.21)	5,036	33	3,462	9.5	0.83 (0.56 - 1.21)
No single RAAS - Comparator	18,945	344	30,922	11.1		18,945	133	11,588	11.5	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	56	5,383	10.4	1.39 (1.02 - 1.88)	3,242	20	1,837	10.9	1.26 (0.77 - 2.09)
Quintile 1 - Comparator	12,970	158	21,092	7.5		12,970	65	7,616	8.5	
Quintile 2 - Aliskiren	3,243	48	5,879	8.2	1.18 (0.86 - 1.63)	3,243	17	1,993	8.5	1.12 (0.65 - 1.91)
Quintile 2 - Comparator	12,969	162	23,532	6.9		12,969	63	8,397	7.5	
Quintile 3 - Aliskiren	3,242	36	5,944	6.1	0.90 (0.62 - 1.29)	3,242	11	2,118	5.2	0.76 (0.40 - 1.45)
Quintile 3 - Comparator	12,971	155	22,937	6.8		12,971	58	8,438	6.9	
Quintile 4 - Aliskiren	3,243	58	6,143	9.4	1.08 (0.80 - 1.44)	3,243	18	2,261	8.0	0.95 (0.57 - 1.58)
Quintile 4 - Comparator	12,969	208	23,758	8.8		12,969	75	9,001	8.3	
Quintile 5 - Aliskiren	3,274	64	6,323	10.1	0.77 (0.59 - 1.01)	3,274	22	2,528	8.7	0.73 (0.46 - 1.16)
Quintile 5 - Comparator	12,938	309	23,934	12.9		12,938	109	8,814	12.4	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-19 Hazard ratios of ischemic stroke in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	1,194	128,908	9.3	1.00 (0.94 - 1.07)	67,557	397	49,873	8.0	0.96 (0.86 - 1.07)
Comparator	269,586	4,679	506,098	9.3		269,586	1,548	184,568	8.4	
Stratified by age										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
<65 - Aliskiren	48,191	504	88,522	5.7	1.00 (0.91 - 1.11)	48,191	153	33,685	4.5	0.92 (0.77 - 1.10)
<65 - Comparator	191,879	1,971	348,669	5.7		191,879	629	127,516	4.9	
65+ - Aliskiren	19,366	690	40,385	17.1	0.99 (0.91 - 1.08)	19,366	244	16,187	15.1	0.95 (0.82 - 1.09)
65+ - Comparator	77,707	2,708	157,429	17.2		77,707	919	57,052	16.1	
Stratified by gender										
Female - Aliskiren	32,853	644	63,253	10.2	1.00 (0.92 - 1.09)	32,853	199	23,790	8.4	0.88 (0.76 - 1.03)
Female - Comparator	131,041	2,523	248,982	10.1		131,041	822	86,050	9.6	
Male - Aliskiren	34,704	550	65,655	8.4	1.00 (0.91 - 1.10)	34,704	198	26,083	7.6	1.03 (0.88 - 1.21)
Male - Comparator	138,545	2,156	257,115	8.4		138,545	726	98,519	7.4	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	476	32,770	14.5	0.97 (0.88 - 1.08)	18,044	162	13,025	12.4	0.98 (0.83 - 1.17)
Diabetes - Comparator	71,720	1,890	126,206	15.0		71,720	610	47,513	12.8	
No diabetes - Aliskiren	49,513	718	96,137	7.5	1.01 (0.93 - 1.10)	49,513	235	36,848	6.4	0.94 (0.81 - 1.08)
No diabetes - Comparator	197,866	2,789	379,891	7.3		197,866	938	137,055	6.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	189	9,309	20.3	0.95 (0.81 - 1.12)	5,327	69	3,576	19.3	1.09 (0.83 - 1.43)
Renal impairment - Comparator	20,869	750	35,292	21.3		20,869	233	13,115	17.8	
No renal impairment - Aliskiren	62,230	1,005	119,599	8.4	1.00 (0.94 - 1.07)	62,230	328	46,297	7.1	0.93 (0.82 - 1.04)
No renal impairment - Comparator	248,717	3,929	470,806	8.4		248,717	1,315	171,453	7.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	113	4,576	24.7	1.00 (0.81 - 1.23)	2,695	42	1,765	23.8	1.25 (0.88 - 1.78)
Diabetes and renal impairment - Comparator	10,591	427	17,278	24.7		10,591	123	6,367	19.3	
No diabetes and renal impairment - Aliskiren	64,862	1,081	124,332	8.7	1.00 (0.93 - 1.07)	64,862	355	48,107	7.4	0.93 (0.82 - 1.04)
No diabetes and renal impairment - Comparator	258,995	4,252	488,820	8.7		258,995	1,425	178,202	8.0	
Stratified by CVD										
CVD - Aliskiren	17,832	550	34,146	16.1	0.96 (0.88 - 1.06)	17,832	195	13,436	14.5	0.93 (0.79 - 1.09)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
CVD - Comparator	70,725	2,188	130,297	16.8		70,725	755	47,606	15.9	
No CVD - Aliskiren	49,725	644	94,762	6.8	1.02 (0.94 - 1.11)	49,725	202	36,437	5.5	0.96 (0.82 - 1.12)
No CVD - Comparator	198,861	2,491	375,800	6.6		198,861	793	136,963	5.8	
Stratified by single RAAS										
Single RAAS - Aliskiren	41,269	674	83,285	8.1	0.98 (0.90 - 1.07)	41,269	213	29,829	7.1	0.95 (0.81 - 1.10)
Single RAAS - Comparator	168,502	2,798	334,525	8.4		168,502	909	119,102	7.6	
No single RAAS - Aliskiren	26,288	520	45,623	11.4	1.02 (0.92 - 1.12)	26,288	184	20,044	9.2	0.94 (0.80 - 1.11)
No single RAAS - Comparator	101,084	1,881	171,572	11.0		101,084	639	65,466	9.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	206	22,631	9.1	1.15 (0.98 - 1.34)	13,486	70	8,471	8.3	1.10 (0.84 - 1.43)
Quintile 1 - Comparator	53,942	717	90,230	8.0		53,942	253	33,476	7.6	
Quintile 2 - Aliskiren	13,485	227	26,484	8.6	1.08 (0.93 - 1.25)	13,485	73	9,689	7.5	1.00 (0.78 - 1.30)
Quintile 2 - Comparator	53,944	831	104,470	8.0		53,944	280	37,170	7.5	
Quintile 3 - Aliskiren	13,485	229	26,608	8.6	1.04 (0.90 - 1.20)	13,485	73	10,091	7.2	0.97 (0.75 - 1.26)
Quintile 3 - Comparator	53,944	868	104,575	8.3		53,944	284	37,876	7.5	
Quintile 4 - Aliskiren	13,488	239	26,239	9.1	0.94 (0.81 - 1.08)	13,488	82	10,505	7.8	0.92 (0.72 - 1.17)
Quintile 4 - Comparator	53,941	1,002	102,845	9.7		53,941	326	37,824	8.6	
Quintile 5 - Aliskiren	13,613	293	26,945	10.9	0.89 (0.79 - 1.02)	13,613	99	11,116	8.9	0.85 (0.68 - 1.06)
Quintile 5 - Comparator	53,815	1,261	103,978	12.1		53,815	405	38,222	10.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-20 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	45	29,933	1.5	1.04 (0.75 - 1.44)	16,244	10	10,772	0.9	0.58 (0.30 - 1.12)
Comparator	64,817	167	116,213	1.4		64,817	68	42,408	1.6	
Stratified by age										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
<65 - Aliskiren	13,554	33	24,886	1.3	1.18 (0.80 - 1.74)	13,554	7	8,666	0.8	0.64 (0.29 - 1.41)
<65 - Comparator	54,163	108	96,910	1.1		54,163	44	34,814	1.3	
65+ - Aliskiren	2,690	12	5,047	2.4	0.77 (0.41 - 1.43)	2,690	3	2,106	1.4	0.43 (0.13 - 1.45)
65+ - Comparator	10,654	59	19,303	3.1		10,654	24	7,595	3.2	
Stratified by gender										
Female - Aliskiren	7,063	17	13,082	1.3	0.94 (0.55 - 1.60)	7,063	2	4,554	0.4	0.31 (0.07 - 1.30)
Female - Comparator	28,134	69	50,483	1.4		28,134	25	17,348	1.4	
Male - Aliskiren	9,181	28	16,851	1.7	1.11 (0.73 - 1.68)	9,181	8	6,217	1.3	0.74 (0.35 - 1.57)
Male - Comparator	36,683	98	65,730	1.5		36,683	43	25,061	1.7	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	16	8,954	1.8	0.88 (0.51 - 1.52)	4,976	5	3,296	1.5	0.74 (0.28 - 1.92)
Diabetes - Comparator	19,746	68	34,153	2.0		19,746	26	12,759	2.0	
No diabetes - Aliskiren	11,268	29	20,979	1.4	1.14 (0.75 - 1.72)	11,268	5	7,475	0.7	0.47 (0.19 - 1.19)
No diabetes - Comparator	45,071	99	82,061	1.2		45,071	42	29,649	1.4	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	10	2,540	3.9	1.42 (0.69 - 2.94)	1,497	3	921	3.3	1.18 (0.32 - 4.29)
Renal impairment - Comparator	5,818	27	9,590	2.8		5,818	10	3,704	2.7	
No renal impairment - Aliskiren	14,747	35	27,393	1.3	0.96 (0.67 - 1.40)	14,747	7	9,851	0.7	0.47 (0.21 - 1.02)
No renal impairment - Comparator	58,999	140	106,623	1.3		58,999	58	38,704	1.5	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	6	1,351	4.4	1.45 (0.57 - 3.71)	813	1	489	2.1	0.78 (0.09 - 6.68)
Diabetes and renal impairment – Comparator	3,128	16	5,012	3.2		3,128	5	1,951	2.6	
No diabetes and renal impairment - Aliskiren	15,431	39	28,582	1.4	1.00 (0.70 - 1.42)	15,431	9	10,283	0.9	0.55 (0.28 - 1.11)
No diabetes and renal impairment - Comparator	61,689	151	111,201	1.4		61,689	63	40,458	1.6	
Stratified by CVD										
CVD - Aliskiren	4,507	24	8,221	2.9	1.12 (0.71 - 1.77)	4,507	8	3,086	2.6	0.90 (0.42 - 1.94)
CVD - Comparator	17,682	81	31,331	2.6		17,682	34	11,693	2.9	
No CVD - Aliskiren	11,737	21	21,712	1.0	0.95 (0.59 - 1.53)	11,737	2	7,686	0.3	0.23 (0.06 - 0.97)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No CVD - Comparator	47,135	86	84,882	1.0		47,135	34	30,715	1.1	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	32	21,180	1.5	1.30 (0.87 - 1.93)	11,208	5	7,294	0.7	0.53 (0.21 - 1.34)
Single RAAS - Comparator	45,872	99	84,971	1.2		45,872	40	30,769	1.3	
No single RAAS - Aliskiren	5,036	13	8,753	1.5	0.65 (0.36 - 1.18)	5,036	5	3,477	1.4	0.58 (0.23 - 1.52)
No single RAAS - Comparator	18,945	68	31,242	2.2		18,945	28	11,640	2.4	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	10	5,430	1.8	1.56 (0.75 - 3.25)	3,242	1	1,842	0.5	0.46 (0.06 - 3.62)
Quintile 1 - Comparator	12,970	25	21,258	1.2		12,970	9	7,642	1.2	
Quintile 2 - Aliskiren	3,243	4	5,940	0.7	0.62 (0.22 - 1.77)	3,243	3	2,002	1.5	1.14 (0.32 - 4.07)
Quintile 2 - Comparator	12,969	26	23,672	1.1		12,969	11	8,429	1.3	
Quintile 3 - Aliskiren	3,242	11	5,970	1.8	1.59 (0.79 - 3.21)	3,242	4	2,121	1.9	1.23 (0.40 - 3.77)
Quintile 3 - Comparator	12,971	27	23,085	1.2		12,971	13	8,453	1.5	
Quintile 4 - Aliskiren	3,243	10	6,196	1.6	1.14 (0.56 - 2.31)	3,243	1	2,271	0.4	0.33 (0.04 - 2.54)
Quintile 4 - Comparator	12,969	34	23,946	1.4		12,969	12	9,030	1.3	
Quintile 5 - Aliskiren	3,274	10	6,397	1.6	0.67 (0.34 - 1.31)	3,274	1	2,536	0.4	0.15 (0.02 - 1.13)
Quintile 5 - Comparator	12,938	55	24,251	2.3		12,938	23	8,854	2.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-21 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	121	130,285	0.9	1.31 (1.07 - 1.61)	67,557	34	50,048	0.7	1.08 (0.74 - 1.59)
Comparator	269,586	363	511,593	0.7		269,586	118	185,214	0.6	
Stratified by age										
<65 - Aliskiren	48,191	60	89,066	0.7	1.40 (1.04 - 1.88)	48,191	17	33,743	0.5	1.42 (0.81 - 2.48)
<65 - Comparator	191,879	169	350,911	0.5		191,879	46	127,773	0.4	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
65+ - Aliskiren	19,366	61	41,218	1.5	1.23 (0.92 - 1.64)	19,366	17	16,305	1.0	0.85 (0.50 - 1.44)
65+ - Comparator	77,707	194	160,681	1.2		77,707	72	57,441	1.3	
Stratified by gender										
Female - Aliskiren	32,853	65	64,016	1.0	1.37 (1.03 - 1.82)	32,853	12	23,873	0.5	0.75 (0.41 - 1.40)
Female - Comparator	131,041	187	251,975	0.7		131,041	59	86,389	0.7	
Male - Aliskiren	34,704	56	66,269	0.9	1.25 (0.93 - 1.69)	34,704	22	26,175	0.8	1.43 (0.87 - 2.33)
Male - Comparator	138,545	176	259,618	0.7		138,545	59	98,825	0.6	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	41	33,310	1.2	1.37 (0.96 - 1.96)	18,044	15	13,094	1.2	1.36 (0.75 - 2.46)
Diabetes - Comparator	71,720	116	128,443	0.9		71,720	41	47,762	0.9	
No diabetes - Aliskiren	49,513	80	96,975	0.8	1.28 (1.00 - 1.65)	49,513	19	36,955	0.5	0.93 (0.56 - 1.54)
No diabetes - Comparator	197,866	247	383,150	0.6		197,866	77	137,453	0.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	24	9,496	2.5	1.70 (1.05 - 2.75)	5,327	12	3,609	3.3	2.17 (1.05 - 4.49)
Renal impairment - Comparator	20,869	53	36,093	1.5		20,869	19	13,192	1.4	
No renal impairment - Aliskiren	62,230	97	120,789	0.8	1.23 (0.98 - 1.55)	62,230	22	46,439	0.5	0.83 (0.52 - 1.32)
No renal impairment - Comparator	248,717	310	475,500	0.7		248,717	99	172,022	0.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	11	4,681	2.4	1.44 (0.72 - 2.88)	2,695	7	1,783	3.9	1.98 (0.78 - 5.06)
Diabetes and renal impairment - Comparator	10,591	29	17,754	1.6		10,591	12	6,403	1.9	
No diabetes and renal impairment - Aliskiren	64,862	110	125,604	0.9	1.30 (1.05 - 1.61)	64,862	27	48,265	0.6	0.96 (0.63 - 1.46)
No diabetes and renal impairment - Comparator	258,995	334	493,838	0.7		258,995	106	178,811	0.6	
Stratified by CVD										
CVD - Aliskiren	17,832	55	34,811	1.6	1.35 (0.99 - 1.83)	17,832	19	13,522	1.4	1.13 (0.67 - 1.89)
CVD - Comparator	70,725	157	132,802	1.2		70,725	61	47,916	1.3	
No CVD - Aliskiren	49,725	66	95,474	0.7	1.27 (0.96 - 1.68)	49,725	15	36,526	0.4	1.00 (0.57 - 1.77)
No CVD - Comparator	198,861	206	378,790	0.5		198,861	57	137,298	0.4	
Stratified by single RAAS										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Single RAAS - Aliskiren	41,269	74	84,102	0.9	1.31 (1.01 - 1.70)	41,269	12	29,914	0.4	0.65 (0.35 - 1.20)
Single RAAS - Comparator	168,502	228	337,931	0.7		168,502	74	119,495	0.6	
No single RAAS - Aliskiren	26,288	47	46,182	1.0	1.30 (0.93 - 1.81)	26,288	22	20,134	1.1	1.71 (1.02 - 2.86)
No single RAAS - Comparator	101,084	135	173,661	0.8		101,084	44	65,719	0.7	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	24	22,828	1.1	1.56 (0.98 - 2.50)	13,486	9	8,492	1.1	1.54 (0.71 - 3.33)
Quintile 1 - Comparator	53,942	62	90,948	0.7		53,942	23	33,591	0.7	
Quintile 2 - Aliskiren	13,485	23	26,741	0.9	1.40 (0.87 - 2.25)	13,485	6	9,726	0.6	0.93 (0.38 - 2.26)
Quintile 2 - Comparator	53,944	65	105,485	0.6		53,944	25	37,283	0.7	
Quintile 3 - Aliskiren	13,485	21	26,883	0.8	1.16 (0.71 - 1.89)	13,485	6	10,122	0.6	1.03 (0.42 - 2.53)
Quintile 3 - Comparator	53,944	71	105,614	0.7		53,944	22	38,003	0.6	
Quintile 4 - Aliskiren	13,488	26	26,516	1.0	1.50 (0.96 - 2.36)	13,488	7	10,539	0.7	1.12 (0.48 - 2.61)
Quintile 4 - Comparator	53,941	68	103,987	0.7		53,941	23	37,950	0.6	
Quintile 5 - Aliskiren	13,613	27	27,317	1.0	1.08 (0.71 - 1.66)	13,613	6	11,169	0.5	0.86 (0.35 - 2.11)
Quintile 5 - Comparator	53,815	97	105,559	0.9		53,815	25	38,388	0.7	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-22 Hazard ratios of transient ischemic attack in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	167	29,775	5.6	1.05 (0.88 - 1.24)	16,244	56	10,744	5.2	0.97 (0.72 - 1.29)
Comparator	64,817	619	115,616	5.4		64,817	228	42,304	5.4	
Stratified by age										
<65 - Aliskiren	13,554	120	24,791	4.8	1.18 (0.96 - 1.45)	13,554	38	8,654	4.4	1.15 (0.80 - 1.66)
<65 - Comparator	54,163	396	96,545	4.1		54,163	131	34,761	3.8	
65+ - Aliskiren	2,690	47	4,985	9.4	0.80 (0.58 - 1.09)	2,690	18	2,090	8.6	0.68 (0.41 - 1.12)
65+ - Comparator	10,654	223	19,071	11.7		10,654	97	7,543	12.9	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by gender										
Female - Aliskiren	7,063	91	12,978	7.0	1.08 (0.86 - 1.37)	7,063	30	4,532	6.6	0.99 (0.66 - 1.48)
Female - Comparator	28,134	325	50,157	6.5		28,134	116	17,295	6.7	
Male - Aliskiren	9,181	76	16,797	4.5	1.00 (0.78 - 1.29)	9,181	26	6,212	4.2	0.92 (0.60 - 1.41)
Male - Comparator	36,683	294	65,460	4.5		36,683	112	25,009	4.5	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	78	8,879	8.8	1.13 (0.88 - 1.45)	4,976	22	3,288	6.7	0.85 (0.53 - 1.35)
Diabetes - Comparator	19,746	263	33,898	7.8		19,746	100	12,712	7.9	
No diabetes - Aliskiren	11,268	89	20,896	4.3	0.98 (0.78 - 1.23)	11,268	34	7,456	4.6	1.04 (0.71 - 1.52)
No diabetes - Comparator	45,071	356	81,719	4.4		45,071	128	29,592	4.3	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	34	2,497	13.6	1.20 (0.82 - 1.77)	1,497	11	914	12.0	0.99 (0.51 - 1.93)
Renal impairment - Comparator	5,818	106	9,500	11.2		5,818	43	3,683	11.7	
No renal impairment - Aliskiren	14,747	133	27,278	4.9	1.00 (0.82 - 1.21)	14,747	45	9,829	4.6	0.93 (0.67 - 1.29)
No renal impairment - Comparator	58,999	513	106,116	4.8		58,999	185	38,621	4.8	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	24	1,323	18.1	1.29 (0.81 - 2.06)	813	5	488	10.3	0.70 (0.27 - 1.83)
Diabetes and renal impairment - Comparator	3,128	68	4,963	13.7		3,128	27	1,936	14.0	
No diabetes and renal impairment - Aliskiren	15,431	143	28,452	5.0	1.00 (0.83 - 1.20)	15,431	51	10,256	5.0	0.98 (0.72 - 1.33)
No diabetes and renal impairment - Comparator	61,689	551	110,654	5.0		61,689	201	40,368	5.0	
Stratified by CVD										
CVD - Aliskiren	4,507	83	8,141	10.2	1.04 (0.82 - 1.33)	4,507	27	3,071	8.8	0.86 (0.57 - 1.31)
CVD - Comparator	17,682	305	31,037	9.8		17,682	119	11,624	10.2	
No CVD - Aliskiren	11,737	84	21,634	3.9	1.04 (0.82 - 1.33)	11,737	29	7,673	3.8	1.04 (0.69 - 1.56)
No CVD - Comparator	47,135	314	84,580	3.7		47,135	109	30,680	3.6	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	107	21,089	5.1	1.03 (0.83 - 1.27)	11,208	32	7,276	4.4	0.90 (0.62 - 1.32)
Single RAAS - Comparator	45,872	423	84,545	5.0		45,872	150	30,696	4.9	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No single RAAS - Aliskiren	5,036	60	8,686	6.9	1.07 (0.80 - 1.43)	5,036	24	3,468	6.9	1.04 (0.66 - 1.64)
No single RAAS - Comparator	18,945	196	31,072	6.3		18,945	78	11,608	6.7	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	36	5,395	6.7	1.44 (0.98 - 2.11)	3,242	9	1,838	4.9	0.90 (0.44 - 1.85)
Quintile 1 - Comparator	12,970	98	21,162	4.6		12,970	41	7,623	5.4	
Quintile 2 - Aliskiren	3,243	26	5,912	4.4	1.06 (0.69 - 1.63)	3,243	5	2,001	2.5	0.56 (0.22 - 1.42)
Quintile 2 - Comparator	12,969	99	23,568	4.2		12,969	37	8,410	4.4	
Quintile 3 - Aliskiren	3,242	23	5,957	3.9	0.82 (0.52 - 1.29)	3,242	11	2,117	5.2	1.41 (0.71 - 2.81)
Quintile 3 - Comparator	12,971	108	22,998	4.7		12,971	31	8,440	3.7	
Quintile 4 - Aliskiren	3,243	33	6,169	5.4	0.93 (0.64 - 1.36)	3,243	14	2,267	6.2	1.08 (0.60 - 1.94)
Quintile 4 - Comparator	12,969	137	23,811	5.8		12,969	52	9,010	5.8	
Quintile 5 - Aliskiren	3,274	49	6,342	7.7	1.05 (0.76 - 1.44)	3,274	17	2,520	6.8	0.90 (0.53 - 1.54)
Quintile 5 - Comparator	12,938	177	24,078	7.4		12,938	67	8,822	7.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-23 Hazard ratios of transient ischemic attack in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	290	129,974	2.2	1.05 (0.92 - 1.20)	67,557	93	49,988	1.9	0.99 (0.78 - 1.24)
Comparator	269,586	1,083	510,317	2.1		269,586	352	185,047	1.9	
Stratified by age										
<65 - Aliskiren	48,191	111	88,968	1.3	1.01 (0.82 - 1.25)	48,191	28	33,734	0.8	0.82 (0.54 - 1.23)
<65 - Comparator	191,879	431	350,492	1.2		191,879	128	127,721	1.0	
65+ - Aliskiren	19,366	179	41,006	4.4	1.07 (0.91 - 1.26)	19,366	65	16,253	4.0	1.05 (0.79 - 1.38)
65+ - Comparator	77,707	652	159,825	4.1		77,707	224	57,326	3.9	
Stratified by gender										
Female - Aliskiren	32,853	172	63,806	2.7	1.06 (0.90 - 1.25)	32,853	59	23,834	2.5	1.07 (0.80 - 1.43)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Female - Comparator	131,041	639	251,155	2.5		131,041	201	86,285	2.3	
Male - Aliskiren	34,704	118	66,168	1.8	1.04 (0.85 - 1.27)	34,704	34	26,153	1.3	0.85 (0.59 - 1.24)
Male - Comparator	138,545	444	259,162	1.7		138,545	151	98,761	1.5	
Stratified by Diabetes										
Diabetes - Aliskiren	18,044	100	33,204	3.0	0.95 (0.76 - 1.18)	18,044	31	13,075	2.4	0.93 (0.62 - 1.37)
Diabetes - Comparator	71,720	408	127,971	3.2		71,720	122	47,702	2.6	
No diabetes - Aliskiren	49,513	190	96,771	2.0	1.11 (0.94 - 1.30)	49,513	62	36,913	1.7	1.01 (0.76 - 1.34)
No diabetes - Comparator	197,866	675	382,346	1.8		197,866	230	137,345	1.7	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	34	9,484	3.6	1.13 (0.77 - 1.66)	5,327	6	3,610	1.7	0.62 (0.26 - 1.49)
Renal impairment - Comparator	20,869	114	35,992	3.2		20,869	34	13,182	2.6	
No renal impairment - Aliskiren	62,230	256	120,491	2.1	1.03 (0.90 - 1.19)	62,230	87	46,378	1.9	1.01 (0.80 - 1.28)
No renal impairment - Comparator	248,717	969	474,324	2.0		248,717	318	171,865	1.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	22	4,668	4.7	1.35 (0.83 - 2.21)	2,695	5	1,783	2.8	1.00 (0.37 - 2.69)
Diabetes and renal impairment - Comparator	10,591	62	17,696	3.5		10,591	18	6,399	2.8	
No diabetes and renal impairment - Aliskiren	64,862	268	125,307	2.1	1.03 (0.90 - 1.18)	64,862	88	48,205	1.8	0.98 (0.77 - 1.24)
No diabetes and renal impairment – Comparator	258,995	1,021	492,621	2.1		258,995	334	178,648	1.9	
Stratified by CVD										
CVD – Aliskiren	17,832	145	34,650	4.2	1.10 (0.92 - 1.33)	17,832	50	13,480	3.7	1.05 (0.77 - 1.44)
CVD – Comparator	70,725	501	132,197	3.8		70,725	172	47,835	3.6	
No CVD – Aliskiren	49,725	145	95,324	1.5	0.98 (0.82 - 1.18)	49,725	43	36,508	1.2	0.89 (0.64 - 1.24)
No CVD – Comparator	198,861	582	378,120	1.5		198,861	180	137,212	1.3	
Stratified by single RAAS										
Single RAAS – Aliskiren	41,269	161	83,910	1.9	0.99 (0.83 - 1.18)	41,269	51	29,886	1.7	0.98 (0.72 - 1.33)
Single RAAS - Comparator	168,502	662	337,174	2.0		168,502	210	119,389	1.8	
No single RAAS - Aliskiren	26,288	129	46,065	2.8	1.13 (0.93 - 1.38)	26,288	42	20,102	2.1	0.98 (0.70 - 1.39)
No single RAAS - Comparator	101,084	421	173,143	2.4		101,084	142	65,657	2.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	53	22,785	2.3	1.35 (0.99 - 1.85)	13,486	15	8,487	1.8	0.99 (0.56 - 1.75)
Quintile 1 - Comparator	53,942	156	90,776	1.7		53,942	60	33,559	1.8	
Quintile 2 - Aliskiren	13,485	51	26,686	1.9	1.04 (0.77 - 1.42)	13,485	19	9,709	2.0	1.06 (0.64 - 1.77)
Quintile 2 - Comparator	53,944	193	105,272	1.8		53,944	69	37,260	1.9	
Quintile 3 - Aliskiren	13,485	60	26,827	2.2	1.09 (0.82 - 1.45)	13,485	18	10,119	1.8	1.02 (0.60 - 1.71)
Quintile 3 - Comparator	53,944	216	105,342	2.1		53,944	67	37,971	1.8	
Quintile 4 - Aliskiren	13,488	51	26,472	1.9	0.87 (0.64 - 1.18)	13,488	17	10,528	1.6	0.90 (0.53 - 1.53)
Quintile 4 - Comparator	53,941	230	103,693	2.2		53,941	69	37,920	1.8	
Quintile 5 - Aliskiren	13,613	75	27,204	2.8	1.00 (0.78 - 1.30)	13,613	24	11,145	2.2	0.96 (0.61 - 1.51)
Quintile 5 - Comparator	53,815	288	105,234	2.7		53,815	87	38,337	2.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-24 Hazard ratios of myocardial infarction in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	103	29,840	3.5	0.90 (0.73 - 1.12)	16,244	33	10,765	3.1	0.86 (0.59 - 1.26)
Comparator	64,817	443	115,836	3.8		64,817	150	42,375	3.5	
Stratified by age										
<65 - Aliskiren	13,554	56	24,843	2.3	0.72 (0.54 - 0.96)	13,554	14	8,663	1.6	0.57 (0.32 - 1.00)
<65 - Comparator	54,163	301	96,632	3.1		54,163	98	34,793	2.8	
65+ - Aliskiren	2,690	47	4,997	9.4	1.25 (0.90 - 1.75)	2,690	19	2,102	9.0	1.27 (0.75 - 2.15)
65+ - Comparator	10,654	142	19,204	7.4		10,654	52	7,582	6.9	
Stratified by gender										
Female - Aliskiren	7,063	44	13,053	3.4	1.03 (0.74 - 1.44)	7,063	15	4,551	3.3	0.99 (0.56 - 1.75)
Female - Comparator	28,134	165	50,346	3.3		28,134	57	17,334	3.3	
Male - Aliskiren	9,181	59	16,786	3.5	0.82 (0.62 - 1.09)	9,181	18	6,214	2.9	0.77 (0.46 - 1.27)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Male - Comparator	36,683	278	65,489	4.2		36,683	93	25,042	3.7	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	61	8,888	6.9	1.02 (0.77 - 1.36)	4,976	21	3,291	6.4	1.13 (0.70 - 1.84)
Diabetes - Comparator	19,746	227	33,954	6.7		19,746	72	12,744	5.7	
No diabetes - Aliskiren	11,268	42	20,952	2.0	0.76 (0.55 - 1.06)	11,268	12	7,474	1.6	0.60 (0.33 - 1.11)
No diabetes - Comparator	45,071	216	81,882	2.6		45,071	78	29,632	2.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	22	2,528	8.7	0.78 (0.50 - 1.24)	1,497	6	920	6.5	0.64 (0.27 - 1.51)
Renal impairment - Comparator	5,818	106	9,491	11.2		5,818	38	3,696	10.3	
No renal impairment - Aliskiren	14,747	81	27,312	3.0	0.93 (0.73 - 1.18)	14,747	27	9,845	2.7	0.93 (0.61 - 1.42)
No renal impairment - Comparator	58,999	337	106,344	3.2		58,999	112	38,679	2.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	813	17	1,342	12.7	0.82 (0.48 - 1.39)	813	5	488	10.2	0.69 (0.27 - 1.79)
Diabetes and renal impairment – Comparator	3,128	75	4,944	15.2		3,128	29	1,943	14.9	
No diabetes and renal impairment – Aliskiren	15,431	86	28,498	3.0	0.90 (0.71 - 1.14)	15,431	28	10,277	2.7	0.90 (0.59 - 1.35)
No diabetes and renal impairment – Comparator	61,689	368	110,892	3.3		61,689	121	40,432	3.0	
Stratified by CVD										
CVD – Aliskiren	4,507	52	8,170	6.4	0.97 (0.71 - 1.31)	4,507	16	3,082	5.2	0.81 (0.47 - 1.39)
CVD – Comparator	17,682	204	31,172	6.5		17,682	74	11,670	6.3	
No CVD – Aliskiren	11,737	51	21,670	2.4	0.83 (0.61 - 1.12)	11,737	17	7,683	2.2	0.89 (0.52 - 1.50)
No CVD – Comparator	47,135	239	84,663	2.8		47,135	76	30,705	2.5	
Stratified by single RAAS										
Single RAAS – Aliskiren	11,208	59	21,129	2.8	0.83 (0.63 - 1.10)	11,208	18	7,292	2.5	0.81 (0.49 - 1.35)
Single RAAS - Comparator	45,872	286	84,713	3.4		45,872	94	30,744	3.1	
No Single RAAS - Aliskiren	5,036	44	8,711	5.1	0.97 (0.69 - 1.35)	5,036	15	3,474	4.3	0.88 (0.49 - 1.55)
No Single RAAS - Comparator	18,945	157	31,123	5.0		18,945	56	11,632	4.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	20	5,413	3.7	1.35 (0.81 - 2.24)	3,242	6	1,841	3.3	1.29 (0.52 - 3.24)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 1 - Comparator	12,970	58	21,205	2.7		12,970	19	7,637	2.5	
Quintile 2 - Aliskiren	3,243	17	5,917	2.9	0.84 (0.50 - 1.41)	3,243	3	2,002	1.5	0.52 (0.16 - 1.72)
Quintile 2 - Comparator	12,969	81	23,622	3.4		12,969	24	8,427	2.9	
Quintile 3 - Aliskiren	3,242	11	5,972	1.8	0.53 (0.28 - 1.00)	3,242	2	2,121	0.9	0.27 (0.06 - 1.11)
Quintile 3 - Comparator	12,971	80	23,023	3.5		12,971	30	8,445	3.6	
Quintile 4 - Aliskiren	3,243	20	6,182	3.2	0.90 (0.55 - 1.46)	3,243	4	2,271	1.8	0.61 (0.21 - 1.74)
Quintile 4 - Comparator	12,969	86	23,857	3.6		12,969	26	9,024	2.9	
Quintile 5 - Aliskiren	3,274	35	6,356	5.5	0.96 (0.66 - 1.39)	3,274	18	2,531	7.1	1.24 (0.72 - 2.12)
Quintile 5 - Comparator	12,938	138	24,129	5.7		12,938	51	8,843	5.8	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-25 Hazard ratios of myocardial infarction in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	554	129,743	4.3	0.91 (0.83 - 1.00)	67,557	188	49,994	3.8	0.89 (0.76 - 1.04)
Comparator	269,586	2,377	509,007	4.7		269,586	786	184,954	4.3	
Stratified by age										
<65 – Aliskiren	48,191	247	88,825	2.8	0.95 (0.83 - 1.09)	48,191	73	33,725	2.2	0.81 (0.63 - 1.04)
<65 - Comparator	191,879	1,017	349,820	2.9		191,879	338	127,650	2.7	
65+ - Aliskiren	19,366	307	40,917	7.5	0.88 (0.78 - 0.99)	19,366	115	16,269	7.1	0.92 (0.75 - 1.12)
65+ - Comparator	77,707	1,360	159,186	8.5		77,707	448	57,305	7.8	
Stratified by gender										
Female - Aliskiren	32,853	259	63,752	4.1	0.96 (0.84 - 1.10)	32,853	87	23,846	3.7	0.93 (0.73 - 1.18)
Female - Comparator	131,041	1,055	250,850	4.2		131,041	337	86,281	3.9	
Male - Aliskiren	34,704	295	65,990	4.5	0.87 (0.77 - 0.99)	34,704	101	26,148	3.9	0.85 (0.69 - 1.06)
Male - Comparator	138,545	1,322	258,156	5.1		138,545	449	98,674	4.6	
Stratified by diabetes										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes - Aliskiren	18,044	230	33,074	7.0	0.87 (0.75 - 1.00)	18,044	83	13,069	6.4	0.88 (0.69 - 1.12)
Diabetes - Comparator	71,720	1,023	127,387	8.0		71,720	345	47,653	7.2	
No diabetes - Aliskiren	49,513	324	96,668	3.4	0.94 (0.83 - 1.06)	49,513	105	36,926	2.8	0.89 (0.72 - 1.10)
No diabetes - Comparator	197,866	1,354	381,620	3.6		197,866	441	137,302	3.2	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	105	9,410	11.2	0.86 (0.69 - 1.06)	5,327	37	3,602	10.3	0.87 (0.61 - 1.24)
Renal impairment - Comparator	20,869	464	35,658	13.0		20,869	156	13,158	11.9	
No renal impairment - Aliskiren	62,230	449	120,333	3.7	0.92 (0.83 - 1.02)	62,230	151	46,392	3.3	0.89 (0.74 - 1.06)
No renal impairment - Comparator	248,717	1,913	473,348	4.0		248,717	630	171,797	3.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	75	4,609	16.3	1.08 (0.84 - 1.40)	2,695	29	1,777	16.3	1.23 (0.81 - 1.88)
Diabetes and renal impairment - Comparator	10,591	261	17,532	14.9		10,591	85	6,388	13.3	
No diabetes and renal impairment - Aliskiren	64,862	479	125,134	3.8	0.89 (0.80 - 0.98)	64,862	159	48,217	3.3	0.84 (0.71 - 1.00)
No diabetes and renal impairment - Comparator	258,995	2,116	491,475	4.3		258,995	701	178,567	3.9	
Stratified by CVD										
CVD - Aliskiren	17,832	244	34,546	7.1	0.77 (0.67 - 0.88)	17,832	80	13,494	5.9	0.70 (0.55 - 0.88)
CVD - Comparator	70,725	1,207	131,522	9.2		70,725	411	47,796	8.6	
No CVD - Aliskiren	49,725	310	95,197	3.3	1.04 (0.92 - 1.18)	49,725	108	36,500	3.0	1.08 (0.87 - 1.33)
No CVD - Comparator	198,861	1,170	377,485	3.1		198,861	375	137,158	2.7	
Stratified by single RAAS										
Single RAAS - Aliskiren	41,269	318	83,773	3.8	0.88 (0.78 - 0.99)	41,269	98	29,882	3.3	0.83 (0.67 - 1.03)
Single RAAS - Comparator	168,502	1,476	336,229	4.4		168,502	478	119,314	4.0	
No single RAAS - Aliskiren	26,288	236	45,970	5.1	0.96 (0.83 - 1.10)	26,288	90	20,112	4.5	0.94 (0.74 - 1.18)
No single RAAS - Comparator	101,084	901	172,777	5.2		101,084	308	65,641	4.7	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	108	22,724	4.8	1.22 (0.98 - 1.52)	13,486	34	8,484	4.0	1.13 (0.77 - 1.65)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 1 - Comparator	53,942	353	90,614	3.9		53,942	119	33,565	3.6	
Quintile 2 - Aliskiren	13,485	89	26,656	3.3	0.87 (0.69 - 1.09)	13,485	27	9,718	2.8	0.79 (0.52 - 1.19)
Quintile 2 - Comparator	53,944	407	105,060	3.9		53,944	132	37,236	3.5	
Quintile 3 - Aliskiren	13,485	98	26,804	3.7	0.81 (0.65 - 1.01)	13,485	26	10,115	2.6	0.56 (0.37 - 0.85)
Quintile 3 - Comparator	53,944	474	105,086	4.5		53,944	174	37,940	4.6	
Quintile 4 - Aliskiren	13,488	97	26,415	3.7	0.77 (0.62 - 0.96)	13,488	36	10,529	3.4	0.79 (0.55 - 1.14)
Quintile 4 - Comparator	53,941	493	103,432	4.8		53,941	166	37,883	4.4	
Quintile 5 - Aliskiren	13,613	162	27,144	6.0	0.96 (0.80 - 1.13)	13,613	65	11,148	5.8	1.15 (0.87 - 1.52)
Quintile 5 - Comparator	53,815	650	104,814	6.2		53,815	195	38,330	5.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-26 Hazard ratios of heart failure in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	386	29,510	13.1	0.86 (0.77 - 0.96)	16,244	130	10,722	12.1	0.73 (0.60 - 0.87)
Comparator	64,817	1,742	114,257	15.3		64,817	706	42,133	16.8	
Stratified by age										
<65 - Aliskiren	13,554	206	24,654	8.4	0.80 (0.69 - 0.93)	13,554	61	8,647	7.1	0.63 (0.48 - 0.82)
<65 - Comparator	54,163	998	95,754	10.4		54,163	384	34,659	11.1	
65+ - Aliskiren	2,690	180	4,856	37.1	0.91 (0.77 - 1.07)	2,690	69	2,075	33.3	0.77 (0.59 - 1.00)
65+ - Comparator	10,654	744	18,503	40.2		10,654	322	7,474	43.1	
Stratified by gender										
Female - Aliskiren	7,063	186	12,873	14.5	0.97 (0.82 - 1.14)	7,063	64	4,529	14.1	0.92 (0.70 - 1.21)
Female - Comparator	28,134	739	49,682	14.9		28,134	265	17,232	15.4	
Male - Aliskiren	9,181	200	16,637	12.0	0.76 (0.66 - 0.89)	9,181	66	6,193	10.7	0.59 (0.46 - 0.76)
Male - Comparator	36,683	1,003	64,575	15.5		36,683	441	24,901	17.7	
Stratified by diabetes										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes - Aliskiren	4,976	217	8,710	24.9	0.82 (0.70 - 0.94)	4,976	78	3,270	23.9	0.74 (0.58 - 0.94)
Diabetes - Comparator	19,746	1,003	33,023	30.4		19,746	406	12,602	32.2	
No diabetes - Aliskiren	11,268	169	20,800	8.1	0.89 (0.75 - 1.05)	11,268	52	7,451	7.0	0.68 (0.51 - 0.92)
No diabetes - Comparator	45,071	739	81,235	9.1		45,071	300	29,530	10.2	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	135	2,389	56.5	0.93 (0.77 - 1.13)	1,497	48	904	53.1	0.82 (0.60 - 1.12)
Renal impairment - Comparator	5,818	553	8,955	61.8		5,818	233	3,613	64.5	
No renal impairment - Aliskiren	14,747	251	27,121	9.3	0.81 (0.70 - 0.92)	14,747	82	9,817	8.4	0.67 (0.53 - 0.84)
No renal impairment - Comparator	58,999	1,189	105,302	11.3		58,999	473	38,520	12.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	96	1,235	77.7	0.95 (0.76 - 1.19)	813	36	475	75.7	0.89 (0.62 - 1.27)
Diabetes and renal impairment - Comparator	3,128	382	4,588	83.3		3,128	158	1,897	83.3	
No diabetes and renal impairment - Aliskiren	15,431	290	28,275	10.3	0.82 (0.72 - 0.93)	15,431	94	10,246	9.2	0.66 (0.53 - 0.83)
No diabetes and renal impairment - Comparator	61,689	1,360	109,670	12.4		61,689	548	40,235	13.6	
Stratified by CVD										
CVD - Aliskiren	4,507	261	7,927	32.9	0.87 (0.76 - 1.00)	4,507	96	3,044	31.5	0.71 (0.57 - 0.89)
CVD - Comparator	17,682	1,143	30,008	38.1		17,682	511	11,492	44.5	
No CVD - Aliskiren	11,737	125	21,583	5.8	0.80 (0.66 - 0.97)	11,737	34	7,677	4.4	0.68 (0.47 - 0.98)
No CVD - Comparator	47,135	599	84,250	7.1		47,135	195	30,641	6.4	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	217	20,956	10.4	0.81 (0.70 - 0.93)	11,208	64	7,268	8.8	0.62 (0.48 - 0.81)
Single RAAS - Comparator	45,872	1,087	83,684	13.0		45,872	434	30,572	14.2	
No single RAAS - Aliskiren	5,036	169	8,554	19.8	0.87 (0.73 - 1.03)	5,036	66	3,454	19.1	0.79 (0.60 - 1.03)
No single RAAS - Comparator	18,945	655	30,573	21.4		18,945	272	11,561	23.5	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	3,242	86	5,347	16.1	1.56 (1.22 - 2.00)	3,242	25	1,834	13.6	1.14 (0.73 - 1.77)
Quintile 1 - Comparator	12,970	217	21,016	10.3		12,970	90	7,614	11.8	
Quintile 2 - Aliskiren	3,243	49	5,873	8.3	0.78 (0.57 - 1.05)	3,243	16	1,996	8.0	0.59 (0.35 - 1.00)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	12,969	252	23,407	10.8		12,969	112	8,392	13.4	
Quintile 3 - Aliskiren	3,242	55	5,929	9.3	0.72 (0.54 - 0.96)	3,242	18	2,114	8.5	0.61 (0.37 - 1.00)
Quintile 3 - Comparator	12,971	297	22,797	13.0		12,971	118	8,411	14.0	
Quintile 4 - Aliskiren	3,243	67	6,120	11.0	0.73 (0.56 - 0.95)	3,243	22	2,258	9.7	0.68 (0.43 - 1.07)
Quintile 4 - Comparator	12,969	354	23,539	15.0		12,969	129	8,974	14.4	
Quintile 5 - Aliskiren	3,274	129	6,241	20.7	0.77 (0.64 - 0.93)	3,274	49	2,520	19.5	0.69 (0.51 - 0.93)
Quintile 5 - Comparator	16,244	386	29,510	13.1	0.86 (0.77 - 0.96)	16,244	130	10,722	12.1	0.73 (0.60 - 0.87)

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-27 Hazard ratios of heart failure in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	1,009	129,084	7.8	0.88 (0.82 - 0.94)	67,557	328	49,906	6.6	0.73 (0.65 - 0.83)
Comparator	269,586	4,498	506,345	8.9		269,586	1,674	184,533	9.1	
Stratified by age										
<65 - Aliskiren	48,191	373	88,652	4.2	0.95 (0.85 - 1.06)	48,191	124	33,708	3.7	0.82 (0.68 - 1.00)
<65 - Comparator	191,879	1,541	349,116	4.4		191,879	569	127,561	4.5	
65+ - Aliskiren	19,366	636	40,432	15.7	0.84 (0.77 - 0.91)	19,366	204	16,198	12.6	0.66 (0.57 - 0.77)
65+ - Comparator	77,707	2,957	157,229	18.8		77,707	1,105	56,972	19.4	
Stratified by gender										
Female - Aliskiren	32,853	522	63,373	8.2	0.92 (0.84 - 1.02)	32,853	150	23,798	6.3	0.69 (0.58 - 0.82)
Female - Comparator	131,041	2,227	249,357	8.9		131,041	803	86,081	9.3	
Male - Aliskiren	34,704	487	65,710	7.4	0.83 (0.75 - 0.92)	34,704	178	26,108	6.8	0.77 (0.65 - 0.90)
Male - Comparator	138,545	2,271	256,987	8.8		138,545	871	98,451	8.9	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	517	32,672	15.8	0.87 (0.79 - 0.96)	18,044	185	13,018	14.2	0.79 (0.67 - 0.92)
Diabetes - Comparator	71,720	2,315	125,673	18.4		71,720	875	47,401	18.5	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	49,513	492	96,411	5.1	0.88 (0.80 - 0.97)	49,513	143	36,889	3.9	0.67 (0.56 - 0.80)
No diabetes - Comparator	197,866	2,183	380,672	5.7		197,866	799	137,132	5.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	271	9,174	29.5	0.83 (0.73 - 0.95)	5,327	97	3,571	27.2	0.68 (0.54 - 0.84)
Renal impairment - Comparator	20,869	1,252	34,658	36.1		20,869	535	12,985	41.2	
No renal impairment - Aliskiren	62,230	738	119,910	6.2	0.89 (0.82 - 0.96)	62,230	231	46,335	5.0	0.75 (0.65 - 0.87)
No renal impairment - Comparator	248,717	3,246	471,687	6.9		248,717	1,139	171,548	6.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	173	4,472	38.7	0.80 (0.68 - 0.95)	2,695	64	1,757	36.4	0.67 (0.52 - 0.88)
Diabetes and renal impairment – Comparator	10,591	822	16,790	49.0		10,591	350	6,263	55.9	
No diabetes and renal impairment - Aliskiren	64,862	836	124,612	6.7	0.89 (0.82 - 0.96)	64,862	264	48,149	5.5	0.74 (0.65 - 0.85)
No diabetes and renal impairment – Comparator	258,995	3,676	489,555	7.5		258,995	1,324	178,270	7.4	
Stratified by CVD										
CVD – Aliskiren	17,832	666	33,969	19.6	0.81 (0.75 - 0.88)	17,832	235	13,417	17.5	0.68 (0.59 - 0.78)
CVD – Comparator	70,725	3,132	129,085	24.3		70,725	1,258	47,392	26.5	
No CVD – Aliskiren	49,725	343	95,115	3.6	0.99 (0.88 - 1.11)	49,725	93	36,489	2.6	0.83 (0.66 - 1.04)
No CVD – Comparator	198,861	1,366	377,260	3.6		198,861	416	137,141	3.0	
Stratified by single RAAS										
Single RAAS - Aliskiren	41,269	510	83,509	6.1	0.80 (0.73 - 0.88)	41,269	143	29,850	4.8	0.62 (0.52 - 0.74)
Single RAAS - Comparator	168,502	2,607	334,781	7.8		168,502	940	119,083	7.9	
No single RAAS - Aliskiren	26,288	499	45,575	11.0	0.95 (0.86 - 1.05)	26,288	185	20,056	9.2	0.83 (0.70 - 0.97)
No single RAAS - Comparator	101,084	1,891	171,564	11.0		101,084	734	65,450	11.2	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	196	22,619	8.7	1.41 (1.20 - 1.66)	13,486	61	8,474	7.2	0.97 (0.73 - 1.29)
Quintile 1 - Comparator	53,942	557	90,362	6.2		53,942	248	33,501	7.4	
Quintile 2 - Aliskiren	13,485	146	26,580	5.5	0.82 (0.68 - 0.98)	13,485	46	9,705	4.7	0.62 (0.46 - 0.85)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	53,944	707	104,791	6.8		53,944	286	37,188	7.7	
Quintile 3 - Aliskiren	13,485	180	26,680	6.8	0.89 (0.76 - 1.05)	13,485	58	10,095	5.8	0.78 (0.59 - 1.03)
Quintile 3 - Comparator	53,944	792	104,703	7.6		53,944	284	37,880	7.5	
Quintile 4 - Aliskiren	13,488	205	26,256	7.8	0.82 (0.70 - 0.95)	13,488	70	10,506	6.7	0.74 (0.58 - 0.96)
Quintile 4 - Comparator	53,941	986	102,796	9.6		53,941	348	37,792	9.2	
Quintile 5 - Aliskiren	13,613	282	26,949	10.5	0.74 (0.65 - 0.84)	13,613	93	11,125	8.4	0.64 (0.51 - 0.80)
Quintile 5 - Comparator	53,815	1,456	103,693	14.0		53,815	508	38,172	13.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-28 Hazard ratios of acute renal failure in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	715	29,141	24.5	0.93 (0.85 - 1.01)	16,244	265	10,662	24.9	0.86 (0.75 - 0.98)
Comparator	64,817	2,973	112,982	26.3		64,817	1,202	41,968	28.6	
Stratified by age										
<65 – Aliskiren	13,554	451	24,401	18.5	0.90 (0.81 - 1.00)	13,554	153	8,612	17.8	0.81 (0.68 - 0.96)
<65 - Comparator	54,163	1,921	94,722	20.3		54,163	738	34,541	21.4	
65+ - Aliskiren	2,690	264	4,740	55.7	0.95 (0.83 - 1.09)	2,690	112	2,050	54.6	0.86 (0.70 - 1.06)
65+ - Comparator	10,654	1,052	18,260	57.6		10,654	464	7,427	62.5	
Stratified by gender										
Female - Aliskiren	7,063	299	12,779	23.4	0.96 (0.85 - 1.09)	7,063	107	4,514	23.7	0.87 (0.70 - 1.07)
Female - Comparator	28,134	1,198	49,182	24.4		28,134	465	17,179	27.1	
Male - Aliskiren	9,181	416	16,362	25.4	0.90 (0.81 - 1.00)	9,181	158	6,148	25.7	0.83 (0.70 - 0.99)
Male - Comparator	36,683	1,775	63,800	27.8		36,683	737	24,788	29.7	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	400	8,478	47.2	0.93 (0.83 - 1.04)	4,976	150	3,236	46.4	0.83 (0.70 - 0.99)
Diabetes - Comparator	19,746	1,627	32,353	50.3		19,746	685	12,499	54.8	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	11,268	315	20,662	15.3	0.91 (0.80 - 1.03)	11,268	115	7,427	15.5	0.86 (0.71 - 1.06)
No diabetes - Comparator	45,071	1,346	80,630	16.7		45,071	517	29,469	17.5	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	261	2,242	116.4	0.89 (0.78 - 1.02)	1,497	113	882	128.1	0.81 (0.66 - 1.00)
Renal impairment - Comparator	5,818	1,108	8,290	133.7		5,818	542	3,501	154.8	
No renal impairment - Aliskiren	14,747	454	26,898	16.9	0.93 (0.84 - 1.03)	14,747	152	9,780	15.5	0.88 (0.74 - 1.05)
No renal impairment - Comparator	58,999	1,865	104,692	17.8		58,999	660	38,467	17.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	171	1,144	149.4	0.90 (0.76 - 1.07)	813	79	463	170.6	0.85 (0.67 - 1.09)
Diabetes and renal impairment - Comparator	3,128	706	4,189	168.5		3,128	357	1,819	196.3	
No diabetes and renal impairment - Aliskiren	15,431	544	27,996	19.4	0.92 (0.84 - 1.01)	15,431	186	10,199	18.2	0.84 (0.72 - 0.99)
No diabetes and renal impairment - Comparator	61,689	2,267	108,793	20.8		61,689	845	40,149	21.1	
Stratified by CVD										
CVD - Aliskiren	4,507	361	7,817	46.2	0.92 (0.82 - 1.03)	4,507	142	3,024	47.0	0.80 (0.67 - 0.96)
CVD - Comparator	17,682	1,487	29,730	50.0		17,682	673	11,452	58.8	
No CVD - Aliskiren	11,737	354	21,323	16.6	0.92 (0.82 - 1.03)	11,737	123	7,639	16.1	0.90 (0.74 - 1.10)
No CVD - Comparator	47,135	1,486	83,253	17.9		47,135	529	30,516	17.3	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	429	20,729	20.7	0.93 (0.84 - 1.03)	11,208	151	7,232	20.9	0.87 (0.73 - 1.03)
Single RAAS - Comparator	45,872	1,859	82,828	22.4		45,872	730	30,487	23.9	
No single RAAS - Aliskiren	5,036	286	8,412	34.0	0.87 (0.76 - 0.99)	5,036	114	3,430	33.2	0.76 (0.62 - 0.94)
No single RAAS - Comparator	18,945	1,114	30,154	36.9		18,945	472	11,481	41.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	120	5,340	22.5	1.29 (1.05 - 1.58)	3,242	31	1,830	16.9	0.81 (0.55 - 1.19)
Quintile 1 - Comparator	12,970	366	20,921	17.5		12,970	157	7,591	20.7	
Quintile 2 - Aliskiren	3,243	109	5,827	18.7	1.05 (0.85 - 1.30)	3,243	41	1,992	20.6	1.06 (0.75 - 1.49)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	12,969	415	23,239	17.9		12,969	161	8,376	19.2	
Quintile 3 - Aliskiren	3,242	100	5,859	17.1	0.78 (0.63 - 0.96)	3,242	36	2,107	17.1	0.78 (0.55 - 1.12)
Quintile 3 - Comparator	12,971	498	22,578	22.1		12,971	183	8,385	21.8	
Quintile 4 - Aliskiren	3,243	139	6,040	23.0	0.84 (0.70 - 1.01)	3,243	53	2,239	23.7	0.81 (0.60 - 1.09)
Quintile 4 - Comparator	12,969	639	23,217	27.5		12,969	259	8,926	29.0	
Quintile 5 - Aliskiren	3,274	247	6,075	40.7	0.87 (0.76 - 1.00)	3,274	104	2,493	41.7	0.82 (0.66 - 1.02)
Quintile 5 - Comparator	12,938	1,055	23,027	45.8		12,938	442	8,690	50.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-29 Hazard ratios of acute renal failure in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	3,163	126,550	25.0	0.96 (0.92 - 1.00)	67,557	1,220	49,630	24.6	0.92 (0.87 - 0.98)
Comparator	269,586	12,899	497,070	26.0		269,586	4,923	183,408	26.8	
Stratified by age										
<65 - Aliskiren	48,191	1,426	87,431	16.3	0.98 (0.92 - 1.04)	48,191	527	33,580	15.7	0.88 (0.80 - 0.97)
<65 - Comparator	191,879	5,707	344,436	16.6		191,879	2,236	126,932	17.6	
65+ - Aliskiren	19,366	1,737	39,119	44.4	0.94 (0.89 - 0.99)	19,366	693	16,050	43.2	0.92 (0.84 - 1.00)
65+ - Comparator	77,707	7,192	152,634	47.1		77,707	2,687	56,477	47.6	
Stratified by gender										
Female - Aliskiren	32,853	1,527	62,214	24.5	1.02 (0.97 - 1.08)	32,853	551	23,680	23.3	0.93 (0.85 - 1.02)
Female - Comparator	131,041	5,884	245,306	24.0		131,041	2,144	85,660	25.0	
Male - Aliskiren	34,704	1,636	64,336	25.4	0.91 (0.86 - 0.96)	34,704	669	25,950	25.8	0.90 (0.83 - 0.98)
Male - Comparator	138,545	7,015	251,763	27.9		138,545	2,779	97,748	28.4	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	1,547	31,445	49.2	0.97 (0.91 - 1.02)	18,044	613	12,888	47.6	0.91 (0.83 - 0.99)
Diabetes - Comparator	71,720	6,217	121,258	51.3		71,720	2,495	46,853	53.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	49,513	1,616	95,105	17.0	0.95 (0.90 - 1.00)	49,513	607	36,742	16.5	0.92 (0.84 - 1.01)
No diabetes - Comparator	197,866	6,682	375,812	17.8		197,866	2,428	136,556	17.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	944	8,315	113.5	0.95 (0.88 - 1.02)	5,327	402	3,482	115.5	0.86 (0.77 - 0.96)
Renal impairment - Comparator	20,869	3,828	31,607	121.1		20,869	1,727	12,583	137.3	
No renal impairment - Aliskiren	62,230	2,219	118,235	18.8	0.96 (0.91 - 1.00)	62,230	818	46,148	17.7	0.94 (0.87 - 1.01)
No renal impairment - Comparator	248,717	9,071	465,462	19.5		248,717	3,196	170,825	18.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	581	3,957	146.8	0.97 (0.89 - 1.07)	2,695	258	1,700	151.8	0.92 (0.80 - 1.05)
Diabetes and renal impairment - Comparator	10,591	2,293	15,032	152.5		10,591	1,029	6,052	170.0	
No diabetes and renal impairment - Aliskiren	64,862	2,582	122,594	21.1	0.95 (0.91 - 0.99)	64,862	962	47,930	20.1	0.91 (0.85 - 0.98)
No diabetes and renal impairment – Comparator	258,995	10,606	482,038	22.0		258,995	3,894	177,356	22.0	
Stratified by CVD										
CVD – Aliskiren	17,832	1,562	32,903	47.5	0.93 (0.88 - 0.98)	17,832	634	13,291	47.7	0.88 (0.81 - 0.96)
CVD – Comparator	70,725	6,459	125,528	51.5		70,725	2,586	47,011	55.0	
No CVD – Aliskiren	49,725	1,601	93,647	17.1	0.98 (0.93 - 1.03)	49,725	586	36,339	16.1	0.93 (0.85 - 1.01)
No CVD – Comparator	198,861	6,440	371,542	17.3		198,861	2,337	136,398	17.1	
Stratified by single RAAS										
Single RAAS – Aliskiren	41,269	1,671	82,063	20.4	0.94 (0.89 - 0.99)	41,269	592	29,710	19.9	0.91 (0.83 - 0.99)
Single RAAS - Comparator	168,502	7,301	329,312	22.2		168,502	2,645	118,524	22.3	
No single RAAS - Aliskiren	26,288	1,492	44,487	33.5	0.96 (0.91 - 1.02)	26,288	628	19,920	31.5	0.88 (0.81 - 0.97)
No single RAAS - Comparator	101,084	5,598	167,758	33.4		101,084	2,278	64,884	35.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	520	22,278	23.3	1.19 (1.08 - 1.31)	13,486	207	8,441	24.5	1.19 (1.02 - 1.39)
Quintile 1 - Comparator	53,942	1,753	89,281	19.6		53,942	687	33,379	20.6	
Quintile 2 - Aliskiren	13,485	514	26,177	19.6	0.98 (0.89 - 1.08)	13,485	202	9,660	20.9	1.02 (0.87 - 1.19)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	53,944	2,070	103,207	20.1		53,944	764	37,010	20.6	
Quintile 3 - Aliskiren	13,485	538	26,248	20.5	0.92 (0.84 - 1.01)	13,485	198	10,044	19.7	0.89 (0.76 - 1.04)
Quintile 3 - Comparator	53,944	2,295	103,074	22.3		53,944	842	37,695	22.3	
Quintile 4 - Aliskiren	13,488	660	25,689	25.7	0.93 (0.85 - 1.01)	13,488	249	10,450	23.8	0.82 (0.72 - 0.94)
Quintile 4 - Comparator	53,941	2,800	100,804	27.8		53,941	1,107	37,532	29.5	
Quintile 5 - Aliskiren	13,613	931	26,159	35.6	0.89 (0.83 - 0.96)	13,613	364	11,036	33.0	0.83 (0.74 - 0.93)
Quintile 5 - Comparator	67,557	3,163	126,550	25.0	0.96 (0.92 - 1.00)	67,557	1,220	49,630	24.6	0.92 (0.87 - 0.98)

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-30 Hazard ratios of end-stage renal disease in subgroups of Cohort 1 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	16,244	194	29,718	6.5	0.88 (0.75 - 1.03)	16,244	70	10,751	6.5	0.79 (0.61 - 1.02)
Comparator	64,817	854	115,403	7.4		64,817	348	42,320	8.2	
Stratified by age										
<65 – Aliskiren	13,554	147	24,721	6.0	0.87 (0.73 - 1.04)	13,554	50	8,651	5.8	0.77 (0.57 - 1.04)
<65 - Comparator	54,163	655	96,240	6.8		54,163	258	34,744	7.4	
65+ - Aliskiren	2,690	47	4,997	9.4	0.89 (0.65 - 1.23)	2,690	20	2,100	9.5	0.79 (0.49 - 1.28)
65+ - Comparator	10,654	199	19,163	10.4		10,654	90	7,576	11.9	
Stratified by gender										
Female - Aliskiren	7,063	83	12,994	6.4	0.97 (0.76 - 1.23)	7,063	32	4,544	7.0	0.86 (0.58 - 1.26)
Female - Comparator	28,134	337	50,179	6.7		28,134	145	17,315	8.4	
Male - Aliskiren	9,181	111	16,724	6.6	0.82 (0.67 - 1.00)	9,181	38	6,206	6.1	0.73 (0.52 - 1.04)
Male - Comparator	36,683	517	65,224	7.9		36,683	203	25,005	8.1	
Stratified by diabetes										
Diabetes - Aliskiren	4,976	123	8,815	14.0	0.88 (0.72 - 1.07)	4,976	43	3,286	13.1	0.77 (0.55 - 1.06)
Diabetes - Comparator	19,746	536	33,630	15.9		19,746	218	12,697	17.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	11,268	71	20,903	3.4	0.86 (0.67 - 1.11)	11,268	27	7,465	3.6	0.80 (0.53 - 1.21)
No diabetes - Comparator	45,071	318	81,773	3.9		45,071	130	29,623	4.4	
Stratified by renal impairment										
Renal impairment - Aliskiren	1,497	145	2,347	61.8	0.80 (0.67 - 0.96)	1,497	57	902	63.2	0.73 (0.55 - 0.97)
Renal impairment - Comparator	5,818	691	8,781	78.7		5,818	307	3,600	85.3	
No renal impairment - Aliskiren	14,747	49	27,371	1.8	1.13 (0.82 - 1.56)	14,747	13	9,849	1.3	1.22 (0.66 - 2.29)
No renal impairment - Comparator	58,999	163	106,622	1.5		58,999	41	38,720	1.1	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	813	89	1,238	71.9	0.79 (0.63 - 0.99)	813	36	480	75.0	0.72 (0.50 - 1.02)
Diabetes and renal impairment - Comparator	3,128	429	4,530	94.7		3,128	195	1,885	103.5	
No diabetes and renal impairment - Aliskiren	15,431	105	28,480	3.7	0.94 (0.76 - 1.17)	15,431	34	10,271	3.3	0.85 (0.59 - 1.24)
No diabetes and renal impairment - Comparator	61,689	425	110,873	3.8		61,689	153	40,436	3.8	
Stratified by CVD										
CVD - Aliskiren	4,507	107	8,087	13.2	0.96 (0.77 - 1.18)	4,507	44	3,071	14.3	0.84 (0.61 - 1.17)
CVD - Comparator	17,682	432	30,909	14.0		17,682	198	11,639	17.0	
No CVD - Aliskiren	11,737	87	21,631	4.0	0.78 (0.62 - 0.98)	11,737	26	7,680	3.4	0.67 (0.44 - 1.01)
No CVD - Comparator	47,135	422	84,494	5.0		47,135	150	30,681	4.9	
Stratified by single RAAS										
Single RAAS - Aliskiren	11,208	98	21,076	4.7	0.84 (0.67 - 1.04)	11,208	33	7,283	4.5	0.79 (0.54 - 1.14)
Single RAAS - Comparator	45,872	478	84,501	5.7		45,872	178	30,717	5.8	
No single RAAS - Aliskiren	5,036	96	8,642	11.1	0.86 (0.69 - 1.08)	5,036	37	3,467	10.7	0.68 (0.47 - 0.97)
No single RAAS - Comparator	18,945	376	30,902	12.2		18,945	170	11,603	14.7	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,242	30	5,400	5.6	1.34 (0.88 - 2.02)	3,242	11	1,836	6.0	1.00 (0.52 - 1.94)
Quintile 1 - Comparator	12,970	89	21,198	4.2		12,970	45	7,632	5.9	
Quintile 2 - Aliskiren	3,243	30	5,906	5.1	1.41 (0.93 - 2.14)	3,243	10	2,001	5.0	1.12 (0.56 - 2.25)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	12,969	85	23,601	3.6		12,969	37	8,419	4.4	
Quintile 3 - Aliskiren	3,242	17	5,952	2.9	0.53 (0.32 - 0.88)	3,242	7	2,120	3.3	0.62 (0.28 - 1.37)
Quintile 3 - Comparator	12,971	125	22,981	5.4		12,971	45	8,450	5.3	
Quintile 4 - Aliskiren	3,243	35	6,168	5.7	0.72 (0.50 - 1.03)	3,243	11	2,268	4.9	0.54 (0.29 - 1.02)
Quintile 4 - Comparator	12,969	189	23,777	8.0		12,969	80	9,014	8.9	
Quintile 5 - Aliskiren	3,274	82	6,292	13.0	0.84 (0.66 - 1.07)	3,274	31	2,526	12.3	0.79 (0.54 - 1.17)
Quintile 5 - Comparator	12,938	366	23,847	15.4		12,938	141	8,804	16.0	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-31 Hazard ratios of end-stage renal disease in subgroups of Cohort 1 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	67,557	737	129,546	5.7	0.89 (0.82 - 0.96)	67,557	211	49,977	4.2	0.67 (0.58 - 0.78)
Comparator	269,586	3,238	508,155	6.4		269,586	1,168	184,874	6.3	
Stratified by age										
<65 – Aliskiren	48,191	1,426	87,431	16.3	0.98 (0.92 - 1.04)	48,191	527	33,580	15.7	0.88 (0.80 - 0.97)
<65 - Comparator	191,879	5,707	344,436	16.6		191,879	2,236	126,932	17.6	
65+ - Aliskiren	19,366	1,737	39,119	44.4	0.94 (0.89 - 0.99)	19,366	693	16,050	43.2	0.92 (0.84 - 1.00)
65+ - Comparator	77,707	7,192	152,634	47.1		77,707	2,687	56,477	47.6	
Stratified by gender										
Female - Aliskiren	32,853	1,527	62,214	24.5	1.02 (0.97 - 1.08)	32,853	551	23,680	23.3	0.93 (0.85 - 1.02)
Female - Comparator	131,041	5,884	245,306	24.0		131,041	2,144	85,660	25.0	
Male - Aliskiren	34,704	1,636	64,336	25.4	0.91 (0.86 - 0.96)	34,704	669	25,950	25.8	0.90 (0.83 - 0.98)
Male - Comparator	138,545	7,015	251,763	27.9		138,545	2,779	97,748	28.4	
Stratified by diabetes										
Diabetes - Aliskiren	18,044	1,547	31,445	49.2	0.97 (0.91 - 1.02)	18,044	613	12,888	47.6	0.91 (0.83 - 0.99)
Diabetes - Comparator	71,720	6,217	121,258	51.3		71,720	2,495	46,853	53.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	49,513	1,616	95,105	17.0	0.95 (0.90 - 1.00)	49,513	607	36,742	16.5	0.92 (0.84 - 1.01)
No diabetes - Comparator	197,866	6,682	375,812	17.8		197,866	2,428	136,556	17.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	5,327	944	8,315	113.5	0.95 (0.88 - 1.02)	5,327	402	3,482	115.5	0.86 (0.77 - 0.96)
Renal impairment - Comparator	20,869	3,828	31,607	121.1		20,869	1,727	12,583	137.3	
No renal impairment - Aliskiren	62,230	2,219	118,235	18.8	0.96 (0.91 - 1.00)	62,230	818	46,148	17.7	0.94 (0.87 - 1.01)
No renal impairment - Comparator	248,717	9,071	465,462	19.5		248,717	3,196	170,825	18.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	2,695	581	3,957	146.8	0.97 (0.89 - 1.07)	2,695	258	1,700	151.8	0.92 (0.80 - 1.05)
Diabetes and renal impairment - Comparator	10,591	2,293	15,032	152.5		10,591	1,029	6,052	170.0	
No diabetes and renal impairment - Aliskiren	64,862	2,582	122,594	21.1	0.95 (0.91 - 0.99)	64,862	962	47,930	20.1	0.91 (0.85 - 0.98)
No diabetes and renal impairment - Comparator	258,995	10,606	482,038	22.0		258,995	3,894	177,356	22.0	
Stratified by CVD										
CVD – Aliskiren	17,832	1,562	32,903	47.5	0.93 (0.88 - 0.98)	17,832	634	13,291	47.7	0.88 (0.81 - 0.96)
CVD - Comparator	70,725	6,459	125,528	51.5		70,725	2,586	47,011	55.0	
No CVD - Aliskiren	49,725	1,601	93,647	17.1	0.98 (0.93 - 1.03)	49,725	586	36,339	16.1	0.93 (0.85 - 1.01)
No CVD - Comparator	198,861	6,440	371,542	17.3		198,861	2,337	136,398	17.1	
Stratified by single RAAS										
Single RAAS - Aliskiren	41,269	1,671	82,063	20.4	0.94 (0.89 - 0.99)	41,269	592	29,710	19.9	0.91 (0.83 - 0.99)
Single RAAS - Comparator	168,502	7,301	329,312	22.2		168,502	2,645	118,524	22.3	
No single RAAS - Aliskiren	26,288	1,492	44,487	33.5	0.96 (0.91 - 1.02)	26,288	628	19,920	31.5	0.88 (0.81 - 0.97)
No single RAAS - Comparator	101,084	5,598	167,758	33.4		101,084	2,278	64,884	35.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	13,486	520	22,278	23.3	1.19 (1.08 - 1.31)	13,486	207	8,441	24.5	1.19 (1.02 - 1.39)
Quintile 1 - Comparator	53,942	1,753	89,281	19.6		53,942	687	33,379	20.6	
Quintile 2 - Aliskiren	13,485	514	26,177	19.6	0.98 (0.89 - 1.08)	13,485	202	9,660	20.9	1.02 (0.87 - 1.19)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	53,944	2,070	103,207	20.1		53,944	764	37,010	20.6	
Quintile 3 - Aliskiren	13,485	538	26,248	20.5	0.92 (0.84 - 1.01)	13,485	198	10,044	19.7	0.89 (0.76 - 1.04)
Quintile 3 - Comparator	53,944	2,295	103,074	22.3		53,944	842	37,695	22.3	
Quintile 4 - Aliskiren	13,488	660	25,689	25.7	0.93 (0.85 - 1.01)	13,488	249	10,450	23.8	0.82 (0.72 - 0.94)
Quintile 4 - Comparator	53,941	2,800	100,804	27.8		53,941	1,107	37,532	29.5	
Quintile 5 - Aliskiren	13,613	931	26,159	35.6	0.89 (0.83 - 0.96)	13,613	364	11,036	33.0	0.83 (0.74 - 0.93)
Quintile 5 - Comparator	53,815	3,981	100,704	39.5		53,815	1,523	37,792	40.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-32 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	107	9,732	11.0	0.96 (0.78 - 1.18)	5,748	30	2,983	10.1	0.91 (0.61 - 1.36)
Comparator	22,813	433	37,611	11.5		22,813	123	11,018	11.2	
Stratified by age										
<65 – Aliskiren	4,535	67	7,595	8.8	0.95 (0.73 - 1.24)	4,535	18	2,257	8.0	0.83 (0.50 - 1.39)
<65 - Comparator	17,815	271	29,060	9.3		17,815	81	8,443	9.6	
65+ - Aliskiren	1,213	40	2,137	18.7	0.99 (0.70 - 1.40)	1,213	12	726	16.5	1.05 (0.55 - 1.99)
65+ - Comparator	4,998	162	8,551	19.0		4,998	42	2,575	16.3	
Stratified by gender										
Female - Aliskiren	2,485	55	4,245	12.96	1.04 (0.77 - 1.39)	2,485	19	1,246	15.3	1.47 (0.86 - 2.51)
Female - Comparator	9,851	207	16,380	12.6		9,851	47	4,419	10.6	
Male - Aliskiren	3,263	52	5,487	9.5	0.89 (0.66 - 1.20)	3,263	11	1,737	6.3	0.55 (0.29 - 1.04)
Male - Comparator	12,962	226	21,231	10.6		12,962	76	6,599	11.5	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	60	3,840	15.6	0.96 (0.72 - 1.27)	2,255	17	1,165	14.6	0.96 (0.57 - 1.63)
Diabetes - Comparator	9,023	240	14,669	16.36		9,023	69	4,485	15.4	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	3,493	47	5,892	8.0	0.95 (0.69 - 1.31)	3,493	13	1,818	7.2	0.86 (0.47 - 1.58)
No diabetes - Comparator	13,790	193	22,942	8.4		13,790	54	6,533	8.3	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	31	1,356	22.9	1.15 (0.77 - 1.73)	821	11	405	27.1	1.63 (0.80 - 3.33)
Renal impairment - Comparator	3,138	101	5,042	20.0		3,138	24	1,387	17.3	
No renal impairment - Aliskiren	4,927	76	8,377	9.07	0.89 (0.69 - 1.14)	4,927	19	2,577	7.4	0.72 (0.44 - 1.18)
No renal impairment - Comparator	19,675	332	32,569	10.2		19,675	99	9,631	10.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment – Comparator	125	5	225	22.2		125	1	58	17.2	
No diabetes and renal impairment - Aliskiren	5,716	107	9,681	11.1	0.97 (0.78 - 1.19)	5,716	30	2,969	10.1	0.91 (0.61 - 1.36)
No diabetes and renal impairment – Comparator	22,688	428	37,386	11.45		22,688	122	10,959	11.1	
Stratified by CVD										
CVD – Aliskiren	2,020	63	3,450	18.3	1.08 (0.82 - 1.43)	2,020	20	1,044	19.2	1.08 (0.66 - 1.78)
CVD – Comparator	8,014	228	13,377	17.0		8,014	69	3,867	17.8	
No CVD – Aliskiren	3,728	44	6,282	7.0	0.82 (0.59 - 1.14)	3,728	10	1,939	5.2	0.69 (0.35 - 1.36)
No CVD – Comparator	14,799	205	24,234	8.5		14,799	54	7,151	7.6	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	18	767	23.5	0.99 (0.59 - 1.67)	470	3	224	13.4	0.63 (0.18 - 2.15)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	67	2,787	24.0		1,766	17	790	21.5	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	89	8,966	9.9	0.94 (0.75 - 1.19)	5,278	27	2,759	9.8	0.95 (0.62 - 1.45)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	366	34,824	10.5		21,047	106	10,227	10.4	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	42	2,981	14.1	1.06 (0.75 - 1.48)	1,770	5	807	6.2	0.49 (0.19 - 1.23)
ACEI/ARB+CCB+Index drug – Comparator	7,418	165	12,335	13.4		7,418	39	2,959	13.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No ACEI/ARB+CCB+Index drug – Aliskiren	3,978	65	6,751	9.6	0.91 (0.69 - 1.19)	3,978	20	1,969	10.2	1.02 (0.62 - 1.67)
No ACEI/ARB+CCB+Index drug – Comparator	15,395	268	25,276	10.6		15,395	74	7,417	10.0	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	1,142	18	1,962	9.2	0.97 (0.58 - 1.62)	1,142	4	484	8.3	0.80 (0.27 - 2.32)
Quintile 1 – Comparator	4,570	73	7,711	9.5		4,570	21	2,182	9.6	
Quintile 2 - Aliskiren	1,143	25	1,938	12.9	1.30 (0.83 - 2.05)	1,143	7	575	12.2	1.26 (0.54 - 2.96)
Quintile 2 - Comparator	4,569	75	7,580	9.9		4,569	21	2,098	10.0	
Quintile 3 - Aliskiren	1,142	21	1,834	11.5	0.85 (0.53 - 1.36)	1,142	7	585	12.0	0.93 (0.41 - 2.14)
Quintile 3 - Comparator	4,571	99	7,321	13.5		4,571	28	2,211	12.7	
Quintile 4 - Aliskiren	1,144	19	1,956	9.7	0.99 (0.60 - 1.64)	1,144	4	664	6.0	0.70 (0.24 - 2.06)
Quintile 4 - Comparator	4,568	73	7,415	9.85		4,568	20	2,192	9.1	
Quintile 5 - Aliskiren	1,177	24	2,042	11.8	0.80 (0.51 - 1.24)	1,177	8	675	11.9	0.87 (0.40 - 1.89)
Quintile 5 - Comparator	4,535	113	7,585	14.9		4,535	33	2,335	14.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-33 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	335	51,514	6.5	1.05 (0.93 - 1.18)	29,813	103	17,629	5.8	1.09 (0.87 - 1.36)
Comparator	116,757	1,242	199,112	6.2		116,757	325	57,932	5.6	
Stratified by age										
<65 – Aliskiren	20,132	133	32,453	4.1	1.03 (0.85 - 1.25)	20,132	44	11,561	3.8	1.16 (0.82 - 1.63)
<65 - Comparator	78,389	495	125,131	4.0		78,389	133	38,165	3.5	
65+ - Aliskiren	9,681	202	19,061	10.6	1.05 (0.90 - 1.23)	9,681	59	6,069	9.7	1.03 (0.77 - 1.38)
65+ - Comparator	38,368	747	73,981	10.1		38,368	192	19,768	9.7	
Stratified by gender										
Female - Aliskiren	14,233	186	25,034	7.4	1.12 (0.95 - 1.32)	14,233	53	8,218	6.5	1.04 (0.76 - 1.42)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Female - Comparator	55,779	647	97,154	6.7		55,779	169	26,060	6.5	
Male - Aliskiren	15,580	149	26,480	5.6	0.97 (0.81 - 1.16)	15,580	50	9,411	5.3	1.13 (0.82 - 1.56)
Male - Comparator	60,978	595	101,958	5.8		60,978	156	31,872	4.9	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	153	16,106	9.5	1.17 (0.97 - 1.40)	9,429	38	5,410	7.0	1.04 (0.72 - 1.49)
Diabetes - Comparator	36,993	511	62,089	8.2		36,993	129	18,331	7.0	
No diabetes - Aliskiren	20,384	182	35,408	5.1	0.97 (0.82 - 1.14)	20,384	65	12,219	5.3	1.14 (0.86 - 1.51)
No diabetes - Comparator	79,764	731	137,023	5.3		79,764	196	39,601	5.0	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	61	5,298	11.5	1.06 (0.79 - 1.40)	3,086	25	1,625	15.4	1.72 (1.06 - 2.79)
Renal impairment - Comparator	12,020	219	20,323	10.8		12,020	49	5,431	9.0	
No renal impairment - Aliskiren	26,727	274	46,215	5.9	1.04 (0.91 - 1.19)	26,727	78	16,004	4.9	0.97 (0.75 - 1.25)
No renal impairment - Comparator	104,737	1,023	178,789	5.7		104,737	276	52,501	5.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	36	2,790	12.9	1.06 (0.73 - 1.54)	1,670	10	852	11.7	1.37 (0.66 - 2.86)
Diabetes and renal impairment - Comparator	6,407	126	10,461	12.0		6,407	25	2,853	8.8	
No diabetes and renal impairment - Aliskiren	28,143	299	48,724	6.1	1.04 (0.92 - 1.18)	28,143	93	16,777	5.5	1.06 (0.84 - 1.34)
No diabetes and renal impairment - Comparator	110,350	1116	188,651	5.9		110,350	300	55,080	5.5	
Stratified by CVD										
CVD - Aliskiren	9,223	184	16,538	11.1	1.20 (1.02 - 1.41)	9,223	60	5,388	11.1	1.35 (1.00 - 1.82)
CVD - Comparator	36,587	598	64,432	9.3		36,587	152	17,782	8.6	
No CVD - Aliskiren	20,590	151	34,976	4.3	0.91 (0.76 - 1.08)	20,590	43	12,241	3.5	0.86 (0.61 - 1.20)
No CVD - Comparator	80,170	644	134,680	4.8		80,170	173	40,150	4.3	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	29	2,635	11	0.91 (0.61 - 1.37)	1,579	8	813	9.8	1.14 (0.51 - 2.55)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	116	9,715	11.9		6,017	24	2,672	9.0	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	306	48,878	6.3	1.06 (0.93 - 1.20)	28,234	95	16,816	5.7	1.08 (0.86 - 1.36)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	1,126	189,397	6.0		110,740	301	55,261	5.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	117	16,347	7.2	0.97 (0.79 - 1.19)	9,070	19	4,476	4.3	0.67 (0.41 - 1.09)
ACEI/ARB+CCB+Index drug - Comparator	36,447	486	64,938	7.5		36,447	102	14,936	6.8	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	218	35,166	6.2	1.10 (0.95 - 1.28)	20,743	73	11,963	6.1	1.29 (0.99 - 1.69)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	756	134,174	5.6		80,310	195	39,579	4.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	79	10,179	7.8	1.24 (0.96 - 1.59)	5,863	23	2,893	8.0	1.26 (0.78 - 2.01)
Quintile 1 - Comparator	23,451	253	40,299	6.3		23,451	69	10,859	6.4	
Quintile 2 - Aliskiren	5,864	73	10,038	7.3	1.22 (0.94 - 1.59)	5,864	21	3,322	6.3	1.13 (0.69 - 1.85)
Quintile 2 - Comparator	23,450	235	39,549	5.9		23,450	63	11,310	5.6	
Quintile 3 - Aliskiren	5,862	68	10,152	6.7	1.06 (0.81 - 1.38)	5,862	24	3,562	6.7	1.13 (0.71 - 1.80)
Quintile 3 - Comparator	23,452	252	39,687	6.4		23,452	71	11,513	6.2	
Quintile 4 - Aliskiren	5,863	60	10,051	6.0	1.03 (0.77 - 1.36)	5,863	23	3,673	6.3	1.17 (0.73 - 1.89)
Quintile 4 - Comparator	23,451	233	40,067	5.8		23,451	67	11,979	5.6	
Quintile 5 - Aliskiren	6,361	55	11,095	5.0	0.74 (0.55 - 0.99)	6,361	12	4,180	2.9	0.69 (0.37 - 1.30)
Quintile 5 - Comparator	22,953	269	39,509	6.8		22,953	55	12,272	4.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-34 Hazard ratios of stroke in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	122	9,712	12.6	0.93 (0.76 - 1.13)	5,748	36	2,981	12.1	0.94 (0.65 - 1.35)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator	22,813	509	37,525	13.6		22,813	144	11,008	13.1	
Stratified by age										
<65 – Aliskiren	4,535	72	7,583	9.5	0.91 (0.71 - 1.18)	4,535	21	2,256	9.3	0.88 (0.55 - 1.42)
<65 - Comparator	17,815	303	29,021	10.4		17,815	89	8,439	10.6	
65+ - Aliskiren	1,213	50	2,129	23.5	0.97 (0.72 - 1.33)	1,213	15	726	20.7	1.01 (0.57 - 1.79)
65+ - Comparator	4,998	206	8,504	24.2		4,998	55	2,569	21.4	
Stratified by gender										
Female - Aliskiren	2,485	60	4,236	14.2	0.93 (0.70 - 1.24)	2,485	21	1,245	16.9	1.24 (0.76 - 2.04)
Female - Comparator	9,851	250	16,329	15.3		9,851	62	4,411	14.1	
Male - Aliskiren	3,263	62	5,476	11.3	0.93 (0.70 - 1.22)	3,263	15	1,736	8.6	0.70 (0.40 - 1.21)
Male - Comparator	12,962	259	21,195	12.2		12,962	82	6,597	12.4	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	68	3,827	17.8	0.94 (0.72 - 1.22)	2,255	20	1,164	17.2	0.98 (0.60 - 1.61)
Diabetes - Comparator	9,023	280	14,621	19.15		9,023	80	4,480	17.9	
No diabetes - Aliskiren	3,493	54	5,885	9.2	0.92 (0.68 - 1.24)	3,493	16	1,818	8.8	0.90 (0.52 - 1.56)
No diabetes - Comparator	13,790	229	22,903	10.0		13,790	64	6,527	9.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	37	1,350	27.4	1.08 (0.75 - 1.56)	821	13	405	32.1	1.47 (0.77 - 2.81)
Renal impairment - Comparator	3,138	129	5,020	25.7		3,138	31	1,385	22.4	
No renal Impairment - Aliskiren	4,927	85	8,362	10.2	0.87 (0.69 - 1.10)	4,927	23	2,577	8.9	0.77 (0.49 - 1.20)
No renal Impairment - Comparator	19,675	380	32,504	11.7		19,675	113	9,623	11.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment - Comparator	125	6	225	26.7		125	1	58	17.2	
No diabetes and renal impairment - Aliskiren	5,716	122	9,661	12.6	0.94 (0.77 - 1.14)	5,716	36	2,968	12.1	0.94 (0.65 - 1.36)
No diabetes and renal impairment - Comparator	22,688	503	37,300	13.5		22,688	143	10,950	13.1	
Stratified by CVD										
CVD – Aliskiren	2,020	72	3,439	20.9	1.06 (0.82 - 1.38)	2,020	23	1,043	22.1	1.11 (0.70 - 1.76)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
CVD – Comparator	8,014	267	13,324	20.0		8,014	78	3,862	20.2	
No CVD – Aliskiren	3,728	50	6,273	8.0	0.79 (0.58 - 1.07)	3,728	13	1,938	6.7	0.74 (0.41 - 1.35)
No CVD - Comparator	14,799	242	24,201	10.0		14,799	66	7,146	9.2	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	22	762	28.9	0.95 (0.59 - 1.52)	470	4	223	17.9	0.70 (0.24 - 2.05)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	85	2,772	30.7		1,766	20	789	25.3	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	100	8,950	11.2	0.92 (0.74 - 1.14)	5,278	32	2,758	11.6	0.97 (0.66 - 1.43)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	424	34,753	12.2		21,047	124	10,219	12.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	50	2,977	16.8	1.08 (0.79 - 1.47)	1,770	6	807	7.4	0.52 (0.22 - 1.22)
ACEI/ARB+CCB+Index drug - Comparator	7,418	193	12,309	15.7		7,418	45	2,956	15.2	
No ACEI/ARB+CCB+Index drug - Aliskiren	3,978	72	6,735	10.7	0.85 (0.66 - 1.10)	3,978	25	1,968	12.7	1.06 (0.68 - 1.65)
No ACEI/ARB+CCB+Index drug - Comparator	15,395	316	25,216	12.5		15,395	89	7,411	12.0	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	21	1,956	10.7	0.97 (0.60 - 1.57)	1,142	5	483	10.4	0.79 (0.30 - 2.05)
Quintile 1 - Comparator	4,570	85	7,698	11.0		4,570	27	2,178	12.4	
Quintile 2 - Aliskiren	1,143	26	1,936	13.4	1.15 (0.74 - 1.77)	1,143	8	575	13.9	1.31 (0.59 - 2.93)
Quintile 2 - Comparator	4,569	89	7,559	11.8		4,569	23	2,098	11.0	
Quintile 3 - Aliskiren	1,142	21	1,834	11.5	0.76 (0.48 - 1.22)	1,142	7	585	12.0	0.87 (0.38 - 1.97)
Quintile 3 - Comparator	4,571	110	7,310	15.1		4,571	31	2,210	14.0	
Quintile 4 - Aliskiren	1,144	25	1,951	12.8	1.08 (0.70 - 1.69)	1,144	7	664	10.5	0.99 (0.43 - 2.28)
Quintile 4 - Comparator	4,568	88	7,397	11.9		4,568	25	2,191	11.4	
Quintile 5 - Aliskiren	1,177	29	2,035	14.3	0.80 (0.54 - 1.20)	1,177	9	674	13.4	0.87 (0.42 - 1.80)
Quintile 5 - Comparator	4,535	137	7,560	18.1		4,535	38	2,332	16.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-35 Hazard ratios of stroke in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	335	51,514	6.5	1.05 (0.93 - 1.18)	29,813	103	17,629	5.8	1.09 (0.87 - 1.36)
Comparator	116,757	1,242	199,112	6.2		116,757	325	57,932	5.6	
Stratified by age										
<65 – Aliskiren	20,132	133	32,453	4.1	1.03 (0.85 - 1.25)	20,132	44	11,561	3.8	1.16 (0.82 - 1.63)
<65 - Comparator	78,389	495	125,131	4.0		78,389	133	38,165	3.5	
65+ - Aliskiren	9,681	202	19,061	10.6	1.05 (0.90 - 1.23)	9,681	59	6,069	9.7	1.03 (0.77 - 1.38)
65+ - Comparator	38,368	747	73,981	10.1		38,368	192	19,768	9.7	
Stratified by gender										
Female - Aliskiren	14,233	186	25,034	7.4	1.12 (0.95 - 1.32)	14,233	53	8,218	6.5	1.04 (0.76 - 1.42)
Female - Comparator	55,779	647	97,154	6.7		55,779	169	26,060	6.5	
Male - Aliskiren	15,580	149	26,480	5.6	0.97 (0.81 - 1.16)	15,580	50	9,411	5.3	1.13 (0.82 - 1.56)
Male - Comparator	60,978	595	101,958	5.8		60,978	156	31,872	4.9	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	153	16,106	9.5	1.17 (0.97 - 1.40)	9,429	38	5,410	7.0	1.04 (0.72 - 1.49)
Diabetes - Comparator	36,993	511	62,089	8.2		36,993	129	18,331	7.0	
No diabetes - Aliskiren	20,384	182	35,408	5.1	0.97 (0.82 - 1.14)	20,384	65	12,219	5.3	1.14 (0.86 - 1.51)
No diabetes - Comparator	79,764	731	137,023	5.3		79,764	196	39,601	5.0	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	61	5,298	11.5	1.06 (0.79 - 1.40)	3,086	25	1,625	15.4	1.72 (1.06 - 2.79)
Renal impairment - Comparator	12,020	219	20,323	10.8		12,020	49	5,431	9.0	
No renal impairment - Aliskiren	26,727	274	46,215	5.9	1.04 (0.91 - 1.19)	26,727	78	16,004	4.9	0.97 (0.75 - 1.25)
No renal impairment - Comparator	104,737	1,023	178,789	5.7		104,737	276	52,501	5.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,670	36	2,790	12.9	1.06 (0.73 - 1.54)	1,670	10	852	11.7	1.37 (0.66 - 2.86)
Diabetes and renal impairment - Comparator	6,407	126	10,461	12.0		6,407	25	2,853	8.8	
No diabetes and renal impairment -	28,143	299	48,724	6.1	1.04 (0.92 - 1.18)	28,143	93	16,777	5.5	1.06 (0.84 - 1.34)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren										
No diabetes and renal impairment - Comparator	110,350	1116	188,651	5.9		110,350	300	55,080	5.5	
Stratified by CVD										
CVD – Aliskiren	9,223	184	16,538	11.1	1.20 (1.02 - 1.41)	9,223	60	5,388	11.1	1.35 (1.00 - 1.82)
CVD – Comparator	36,587	598	64,432	9.3		36,587	152	17,782	8.6	
No CVD – Aliskiren	20,590	151	34,976	4.3	0.91 (0.76 - 1.08)	20,590	43	12,241	3.5	0.86 (0.61 - 1.20)
No CVD - Comparator	80,170	644	134,680	4.8		80,170	173	40,150	4.3	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	29	2,635	11.0	0.91 (0.61 - 1.37)	1,579	8	813	9.8	1.14 (0.51 - 2.55)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	116	9,715	11.9		6,017	24	2,672	9.0	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	306	48,878	6.3	1.06 (0.93 - 1.20)	28,234	95	16,816	5.7	1.08 (0.86 - 1.36)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	1,126	189,397	6.0		110,740	301	55,261	5.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	117	16,347	7.2	0.97 (0.79 - 1.19)	9,070	19	4,476	4.3	0.67 (0.41 - 1.09)
ACEI/ARB+CCB+Index drug - Comparator	36,447	486	64,938	7.5		36,447	102	14,936	6.8	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	218	35,166	6.2	1.10 (0.95 - 1.28)	20,743	73	11,963	6.1	1.29 (0.99 - 1.69)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	756	134,174	5.6		80,310	195	39,579	4.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	79	10,179	7.8	1.24 (0.96 - 1.59)	5,863	23	2,893	8.0	1.26 (0.78 - 2.01)
Quintile 1 - Comparator	23,451	253	40,299	6.3		23,451	69	10,859	6.4	
Quintile 2 - Aliskiren	5,864	73	10,038	7.3	1.22 (0.94 - 1.59)	5,864	21	3,322	6.3	1.13 (0.69 - 1.85)
Quintile 2 - Comparator	23,450	235	39,549	5.9		23,450	63	11,310	5.6	
Quintile 3 - Aliskiren	5,862	68	10,152	6.7	1.06 (0.81 - 1.38)	5,862	24	3,562	6.7	1.13 (0.71 - 1.80)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Comparator	23,452	252	39,687	6.4		23,452	71	11,513	6.2	
Quintile 4 - Aliskiren	5,863	60	10,051	6.0	1.03 (0.77 - 1.36)	5,863	23	3,673	6.3	1.17 (0.73 - 1.89)
Quintile 4 - Comparator	23,451	233	40,067	5.8		23,451	67	11,979	5.6	
Quintile 5 - Aliskiren	6,361	55	11,095	5.0	0.74 (0.55 - 0.99)	6,361	12	4,180	2.9	0.69 (0.37 - 1.30)
Quintile 5 - Comparator	22,953	269	39,509	6.8		22,953	55	12,272	4.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-36 Hazard ratios of ischemic stroke in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	113	9,718	11.6	0.94 (0.76 - 1.15)	5,748	34	2,981	11.4	0.97 (0.66 - 1.41)
Comparator	22,813	467	37,574	12.4		22,813	132	11,012	12.0	
Stratified by age										
<65 – Aliskiren	4,535	64	7,589	8.4	0.89 (0.68 - 1.16)	4,535	19	2,256	8.4	0.87 (0.53 - 1.43)
<65 - Comparator	17,815	277	29,053	9.5		17,815	82	8,443	9.7	
65+ - Aliskiren	1,213	49	2,129	23.0	1.04 (0.76 - 1.42)	1,213	15	726	20.7	1.11 (0.62 - 1.97)
65+ - Comparator	4,998	190	8,521	22.3		4,998	50	2,569	19.5	
Stratified by gender										
Female - Aliskiren	2,485	57	4,238	13.5	0.97 (0.72 - 1.29)	2,485	21	1,245	16.9	1.36 (0.82 - 2.24)
Female - Comparator	9,851	230	16,351	14.1		9,851	57	4,415	12.9	
Male - Aliskiren	3,263	56	5,479	10.2	0.91 (0.68 - 1.22)	3,263	13	1,736	7.5	0.66 (0.37 - 1.19)
Male - Comparator	12,962	237	21,223	11.2		12,962	75	6,597	11.4	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	64	3,830	16.7	0.92 (0.70 - 1.21)	2,255	18	1,164	15.5	0.95 (0.57 - 1.58)
Diabetes - Comparator	9,023	268	14,634	18.3		9,023	75	4,481	16.7	
No diabetes - Aliskiren	3,493	49	5,887	8.3	0.96 (0.70 - 1.31)	3,493	16	1,818	8.8	1.02 (0.58 - 1.77)
No diabetes - Comparator	13,790	199	22,940	8.7		13,790	57	6,532	8.7	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by renal impairment										
Renal impairment - Aliskiren	821	35	1,351	25.9	1.08 (0.74 - 1.57)	821	12	405	29.7	1.39 (0.71 - 2.72)
Renal impairment - Comparator	3,138	122	5,027	24.3		3,138	30	1,385	21.7	
No renal impairment - Aliskiren	4,927	78	8,366	9.3	0.88 (0.69 - 1.12)	4,927	22	2,577	8.5	0.82 (0.51 - 1.29)
No renal impairment - Comparator	19,675	345	32,547	10.6		19,675	102	9,627	10.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment - Comparator	125	5	227	22.0		125	1	58	17.2	
No diabetes and renal impairment - Aliskiren	5,716	113	9,667	11.7	0.95 (0.77 - 1.16)	5,716	34	2,968	11.5	0.97 (0.67 - 1.42)
No diabetes and renal impairment - Comparator	22,688	462	37,347	12.4		22,688	131	10,954	12.0	
Stratified by CVD										
CVD – Aliskiren	2,020	65	3,444	18.9	1.05 (0.80 - 1.38)	2,020	21	1,043	20.1	1.13 (0.69 - 1.84)
CVD – Comparator	8,014	244	13,351	18.3		8,014	70	3,866	18.1	
No CVD – Aliskiren	3,728	48	6,274	7.7	0.82 (0.60 - 1.12)	3,728	13	1,938	6.7	0.79 (0.43 - 1.44)
No CVD - Comparator	14,799	223	24,223	9.2		14,799	62	7,146	8.7	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	22	762	28.9	0.98 (0.61 - 1.57)	470	4	223	17.9	0.70 (0.24 - 2.05)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	82	2,774	29.6		1,766	20	789	25.3	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	91	8,955	10.2	0.92 (0.73 - 1.15)	5,278	30	2,758	10.9	1.01 (0.68 - 1.51)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	385	34,800	11.1		21,047	112	10,223	11.0	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	46	2,978	15.4	1.07 (0.77 - 1.48)	1,770	6	807	7.4	0.59 (0.25 - 1.39)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
ACEI/ARB+CCB+Index drug - Comparator	7,418	179	12,322	14.5		7,418	40	2,956	13.5	
No ACEI/ARB+CCB+Index drug - Aliskiren	3,978	67	6,739	9.9	0.87 (0.67 - 1.14)	3,978	23	1,968	11.7	1.06 (0.67 - 1.68)
No ACEI/ARB+CCB+Index drug - Comparator	15,395	288	25,253	11.4		15,395	82	7,415	11.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	21	1,956	10.7	1.09 (0.67 - 1.76)	1,142	5	483	10.4	0.90 (0.34 - 2.35)
Quintile 1 - Comparator	4,570	76	7,706	9.9		4,570	24	2,182	11.0	
Quintile 2 - Aliskiren	1,143	25	1,936	12.9	1.18 (0.76 - 1.85)	1,143	7	575	12.2	1.20 (0.51 - 2.81)
Quintile 2 - Comparator	4,569	83	7,571	11.0		4,569	22	2,098	10.5	
Quintile 3 - Aliskiren	1,142	20	1,834	10.9	0.80 (0.49 - 1.29)	1,142	7	585	12.0	0.93 (0.40 - 2.12)
Quintile 3 - Comparator	4,571	100	7,321	13.7		4,571	29	2,210	13.1	
Quintile 4 - Aliskiren	1,144	22	1,953	11.3	1.06 (0.66 - 1.70)	1,144	7	664	10.5	1.07 (0.46 - 2.50)
Quintile 4 - Comparator	4,568	79	7,408	10.7		4,568	23	2,192	10.5	
Quintile 5 - Aliskiren	1,177	25	2,039	12.3	0.73 (0.48 - 1.12)	1,177	8	674	11.9	0.86 (0.40 - 1.87)
Quintile 5 - Comparator	4,535	129	7,567	17.1		4,535	34	2,332	14.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-37 Hazard ratios of ischemic stroke in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	585	51,201	11.4	0.96 (0.88 - 1.05)	29,813	171	17,596	9.7	0.91 (0.77 - 1.08)
Comparator	116,757	2,353	197,800	11.9		116,757	643	57,830	11.1	
Stratified by age										
<65 – Aliskiren	20,132	223	32,355	6.9	0.95 (0.82 - 1.10)	20,132	69	11,552	6.0	0.94 (0.72 - 1.23)
<65 - Comparator	78,389	905	124,673	7.3		78,389	256	38,127	6.7	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
65+ - Aliskiren	9,681	362	18,846	19.2	0.97 (0.86 - 1.09)	9,681	102	6,045	16.9	0.88 (0.71 - 1.09)
65+ - Comparator	38,368	1,448	73,127	19.8		38,368	387	19,703	19.6	
Stratified by gender										
Female - Aliskiren	14,233	318	24,856	12.8	0.98 (0.86 - 1.10)	14,233	87	8,202	10.6	0.85 (0.67 - 1.07)
Female - Comparator	55,779	1,266	96,423	13.1		55,779	344	26,004	13.2	
Male - Aliskiren	15,580	267	26,344	10.1	0.95 (0.83 - 1.08)	15,580	84	9,395	8.9	0.98 (0.77 - 1.25)
Male - Comparator	60,978	1,087	101,377	10.7		60,978	299	31,827	9.4	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	263	15,966	16.5	1.01 (0.88 - 1.16)	9,429	72	5,393	13.4	0.95 (0.73 - 1.23)
Diabetes - Comparator	36,993	1007	61,525	16.4		36,993	265	18,289	14.5	
No diabetes - Aliskiren	20,384	322	35,235	9.1	0.93 (0.82 - 1.05)	20,384	99	12,203	8.1	0.90 (0.72 - 1.12)
No diabetes - Comparator	79,764	1,346	136,275	9.9		79,764	378	39,541	9.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	99	5,255	18.8	0.86 (0.70 - 1.08)	3,086	32	1,622	19.7	0.97 (0.65 - 1.43)
Renal impairment - Comparator	12,020	437	20,070	21.8		12,020	113	5,411	20.9	
No renal impairment - Aliskiren	26,727	486	45,946	10.6	0.98 (0.89 - 1.09)	26,727	139	15,975	8.7	0.89 (0.74 - 1.08)
No renal impairment - Comparator	104,737	1,916	177,730	10.8		104,737	530	52,419	10.1	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	60	2,763	21.7	0.85 (0.64 - 1.13)	1,670	16	849	18.8	0.85 (0.49 - 1.46)
Diabetes and renal impairment - Comparator	6,407	263	10,298	25.5		6,407	65	2,837	22.9	
No diabetes and renal impairment - Aliskiren	28,143	525	48,438	10.8	0.97 (0.89 - 1.07)	28,143	155	16,747	9.3	0.92 (0.77 - 1.09)
No diabetes and renal impairment - Comparator	110,350	2090	187,502	11.2		110,350	578	54,994	10.5	
Stratified by CVD										
CVD - Aliskiren	9,223	302	16,376	18.4	0.98 (0.86 - 1.11)	9,223	91	5,367	17.0	0.95 (0.75 - 1.20)
CVD - Comparator	36,587	1,206	63,728	18.9		36,587	329	17,724	18.6	
No CVD - Aliskiren	20,590	283	34,825	8.1	0.95 (0.84 - 1.08)	20,590	80	12,230	6.5	0.87 (0.68 - 1.11)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No CVD - Comparator	80,170	1,147	134,072	8.6		80,170	314	40,107	7.8	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment – Aliskiren	1,579	53	2,609	20.3	0.80 (0.60 - 1.08)	1,579	14	810	17.3	0.76 (0.43 - 1.37)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	242	9,563	25.3		6,017	62	2,656	23.3	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	532	48,592	11.0	0.98 (0.89 - 1.08)	28,234	157	16,786	9.4	0.92 (0.77 - 1.10)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	2,111	188,237	11.2		110,740	581	55,174	10.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	225	16,218	13.9	0.99 (0.85 - 1.14)	9,070	45	4,465	10.1	0.76 (0.55 - 1.05)
ACEI/ARB+CCB+Index drug - Comparator	36,447	913	64,427	14.2		36,447	210	14,912	14.1	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	360	34,983	10.3	0.95 (0.85 - 1.07)	20,743	108	11,944	9.0	0.96 (0.77 - 1.19)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	1,440	133,373	10.8		80,310	389	39,518	9.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	139	10,098	13.8	1.12 (0.92 - 1.35)	5,863	39	2,886	13.5	1.06 (0.74 - 1.51)
Quintile 1 - Comparator	23,451	493	40,002	12.3		23,451	141	10,835	13.0	
Quintile 2 - Aliskiren	5,864	104	10,005	10.4	0.95 (0.77 - 1.18)	5,864	30	3,318	9.0	0.90 (0.60 - 1.34)
Quintile 2 - Comparator	23,450	429	39,312	10.9		23,450	116	11,296	10.3	
Quintile 3 - Aliskiren	5,862	115	10,105	11.4	0.95 (0.78 - 1.17)	5,862	32	3,559	9.0	0.75 (0.51 - 1.11)
Quintile 3 - Comparator	23,452	472	39,423	12.0		23,452	141	11,488	12.3	
Quintile 4 - Aliskiren	5,863	117	9,967	11.7	1.01 (0.83 - 1.24)	5,863	38	3,665	10.4	1.05 (0.73 - 1.51)
Quintile 4 - Comparator	23,451	463	39,840	11.6		23,451	125	11,961	10.5	
Quintile 5 - Aliskiren	6,361	110	11,026	10.0	0.79 (0.65 - 0.98)	6,361	32	4,169	7.7	0.82 (0.55 - 1.22)
Quintile 5 - Comparator	22,953	496	39,222	12.7		22,953	120	12,250	9.8	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-38 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	19	9,834	1.9	0.86 (0.52 - 1.42)	5,748	4	2,991	1.3	0.75 (0.26 - 2.18)
Comparator	22,813	86	37,996	2.3		22,813	20	11,052	1.8	
Stratified by age										
<65 – Aliskiren	4,535	14	7,648	1.8	1.08 (0.60 - 1.96)	4,535	3	2,262	1.3	0.81 (0.23 - 2.83)
<65 - Comparator	17,815	50	29,304	1.7		17,815	14	8,465	1.7	
65+ - Aliskiren	1,213	5	2,186	2.3	0.56 (0.22 - 1.43)	1,213	1	729	1.4	0.63 (0.08 - 5.24)
65+ - Comparator	4,998	36	8,692	4.1		4,998	6	2,587	2.3	
Stratified by gender										
Female - Aliskiren	2,485	8	4,291	1.9	0.74 (0.35 - 1.58)	2,485	1	1,251	0.8	0.45 (0.06 - 3.62)
Female - Comparator	9,851	42	16,570	2.5		9,851	8	4,435	1.8	
Male - Aliskiren	3,263	11	5,543	2.0	0.97 (0.50 - 1.88)	3,263	3	1,740	1.7	0.96 (0.27 - 3.42)
Male - Comparator	12,962	44	21,426	2.1		12,962	12	6,617	1.8	
Stratified by diabetes										
Diabetes – Aliskiren	2,255	8	3,893	2.1	1.12 (0.51 - 2.45)	2,255	2	1,168	1.7	0.87 (0.19 - 4.02)
Diabetes - Comparator	9,023	28	14,898	1.9		9,023	9	4,506	2.0	
No diabetes - Aliskiren	3,493	11	5,941	1.9	0.74 (0.39 - 1.41)	3,493	2	1,824	1.1	0.66 (0.15 - 2.97)
No diabetes - Comparator	13,790	58	23,098	2.5		13,790	11	6,546	1.7	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	7	1,379	5.1	1.66 (0.68 - 4.04)	821	2	408	4.9	3.62 (0.51 - 25.84)
Renal impairment - Comparator	3,138	16	5,133	3.1		3,138	2	1,394	1.4	
No renal impairment - Aliskiren	4,927	12	8,455	1.4	0.67 (0.37 - 1.24)	4,927	2	2,583	0.8	0.43 (0.10 - 1.83)
No renal impairment - Comparator	19,675	70	32,864	2.1		19,675	18	9,658	1.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment - Comparator	125	1	230	4.4		125	0	59	0.0	
No diabetes and renal impairment - Aliskiren	5,716	19	9,783	1.9	0.87 (0.53 - 1.43)	5,716	4	2,978	1.3	0.75 (0.26 - 2.19)
No diabetes and renal impairment - Comparator	22,688	85	37,766	2.3		22,688	20	10,994	1.8	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by CVD										
CVD – Aliskiren	2,020	14	3,504	4.0	1.22 (0.67 - 2.23)	2,020	4	1,049	3.8	1.25 (0.40 - 3.87)
CVD – Comparator	8,014	45	13,555	3.3		8,014	12	3,885	3.1	
No CVD – Aliskiren	3,728	5	6,330	0.8	0.48 (0.19 - 1.20)	3,728	0	1,943	0.0	–
No CVD - Comparator	14,799	41	24,442	1.7		14,799	8	7,167	1.1	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	2	779	2.6	1.09 (0.23 - 5.27)	470	0	224	0.0	–
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	7	2,847	2.5		1,766	1	796	1.3	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	17	9,055	1.9	0.84 (0.50 - 1.43)	5,278	4	2,767	1.5	0.79 (0.27 - 2.33)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	79	35,150	2.3		21,047	19	10,256	1.9	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	9	3,023	3.0	1.45 (0.68 - 3.10)	1,770	0	808	0.0	–
ACEI/ARB+CCB+Index drug - Comparator	7,418	26	12,482	2.1		7,418	8	2,966	2.7	
No ACEI/ARB+CCB+Index drug - Aliskiren	3,978	10	6,811	1.5	0.63 (0.32 - 1.23)	3,978	4	1,974	2.0	1.28 (0.41 - 3.99)
No ACEI/ARB+CCB+Index drug - Comparator	15,395	60	25,514	2.4		15,395	12	7,440	1.6	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	0	1,979	0.0	–	1,142	0	484	0.0	–
Quintile 1 - Comparator	4,570	21	7,773	2.7		4,570	4	2,190	1.8	
Quintile 2 - Aliskiren	1,143	4	1,961	2.0	0.98 (0.33 - 2.92)	1,143	3	576	5.2	2.73 (0.61 - 12.19)
Quintile 2 - Comparator	4,569	16	7,647	2.1		4,569	4	2,105	1.9	
Quintile 3 - Aliskiren	1,142	3	1,854	1.6	0.63 (0.19 - 2.14)	1,142	0	588	0.0	–
Quintile 3 - Comparator	4,571	19	7,408	2.6		4,571	3	2,221	1.4	
Quintile 4 - Aliskiren	1,144	5	1,974	2.5	1.36 (0.49 - 3.78)	1,144	0	665	0.0	–
Quintile 4 - Comparator	4,568	14	7,481	1.9		4,568	3	2,194	1.4	
Quintile 5 - Aliskiren	1,177	7	2,067	3.4	1.70 (0.70 - 4.13)	1,177	1	677	1.5	0.61 (0.07 - 5.07)
Quintile 5 - Comparator	4,535	16	7,687	2.1		4,535	6	2,342	2.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-39 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	54	51,854	1.0	1.28 (0.94 - 1.74)	29,813	21	17,665	1.2	2.08 (1.21 - 3.58)
Comparator	116,757	165	200,396	0.8		116,757	35	58,030	0.6	
Stratified by age										
<65 – Aliskiren	20,132	29	32,587	0.9	1.58 (1.03 - 2.43)	20,132	12	11,577	1.0	3.07 (1.42 - 6.65)
<65 - Comparator	78,389	72	125,618	0.6		78,389	14	38,203	0.4	
65+ - Aliskiren	9,681	25	19,267	1.3	1.05 (0.67 - 1.63)	9,681	9	6,087	1.5	1.45 (0.66 - 3.17)
65+ - Comparator	38,368	93	74,778	1.2		38,368	21	19,826	1.1	
Stratified by gender										
Female - Aliskiren	14,233	28	25,216	1.1	1.30 (0.85 - 2.00)	14,233	8	8,237	1.0	1.50 (0.65 - 3.45)
Female - Comparator	55,779	84	97,832	0.9		55,779	18	26,108	0.7	
Male - Aliskiren	15,580	26	26,638	1.0	1.26 (0.81 - 1.97)	15,580	13	9,428	1.4	2.74 (1.33 - 5.64)
Male - Comparator	60,978	81	102,565	0.8		60,978	17	31,921	0.5	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	20	16,255	1.2	1.25 (0.76 - 2.07)	9,429	5	5,427	0.9	1.58 (0.55 - 4.55)
Diabetes - Comparator	36,993	63	62,622	1.0		36,993	11	18,369	0.6	
No diabetes - Aliskiren	20,384	34	35,600	1.0	1.30 (0.88 - 1.91)	20,384	16	12,238	1.3	2.36 (1.25 - 4.45)
No diabetes - Comparator	79,764	102	137,774	0.7		79,764	24	39,660	0.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	15	5,349	2.8	1.62 (0.89 - 2.96)	3,086	9	1,633	5.5	4.66 (1.65 - 13.14)
Renal impairment - Comparator	12,020	36	20,527	1.8		12,020	6	5,439	1.1	
No renal impairment - Aliskiren	26,727	39	46,505	0.8	1.18 (0.82 - 1.68)	26,727	12	16,032	0.8	1.44 (0.73 - 2.83)
No renal impairment - Comparator	104,737	129	179,869	0.7		104,737	29	52,590	0.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,670	7	2,822	2.5	1.24 (0.53 - 2.93)	1,670	3	857	3.5	4.42 (0.74 - 26.56)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes and renal impairment – Comparator	6,407	21	10,576	2.0		6,407	2	2,857	0.7	
No diabetes and renal impairment – Aliskiren	28,143	47	49,032	1.0	1.28 (0.92 - 1.77)	28,143	18	16,808	1.1	1.91 (1.08 - 3.40)
No diabetes and Renal impairment – Comparator	110,350	144	189,821	0.8		110,350	33	55,173	0.6	
Stratified by CVD										
CVD – Aliskiren	9,223	30	16,735	1.8	1.62 (1.06 - 2.47)	9,223	13	5,410	2.4	2.71 (1.32 - 5.59)
CVD – Comparator	36,587	73	65,079	1.1		36,587	17	17,831	1.0	
No CVD – Aliskiren	20,590	24	35,119	0.7	1.02 (0.65 - 1.59)	20,590	8	12,255	0.7	1.53 (0.66 - 3.51)
No CVD – Comparator	80,170	92	135,318	0.7		80,170	18	40,199	0.5	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	7	2,657	2.6	1.30 (0.55 - 3.07)	1,579	3	817	3.7	4.35 (0.72 - 26.13)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	20	9,821	2.0		6,017	2	2,675	0.8	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	47	49,198	1.0	1.27 (0.91 - 1.76)	28,234	18	16,848	1.1	1.91 (1.08 - 3.40)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	145	190,575	0.8		110,740	33	55,354	0.6	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	14	16,467	0.9	1.06 (0.59 - 1.90)	9,070	3	4,485	0.7	1.40 (0.37 - 5.27)
ACEI/ARB+CCB+Index drug - Comparator	36,447	54	65,453	0.8		36,447	8	14,960	0.5	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	40	35,387	1.1	1.38 (0.96 - 1.99)	20,743	18	11,984	1.5	2.76 (1.49 - 5.12)
No ACEI/ARB+CCB+Index drug – Comparator	80,310	111	134,943	0.8		80,310	23	39,635	0.6	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	5,863	13	10,267	1.3	1.56 (0.82 - 2.96)	5,863	7	2,900	2.4	3.27 (1.18 - 9.01)
Quintile 1 – Comparator	23,451	33	40,548	0.8		23,451	8	10,876	0.7	
Quintile 2 – Aliskiren	5,864	9	10,109	0.9	1.27 (0.60 - 2.68)	5,864	4	3,331	1.2	1.88 (0.55 - 6.45)
Quintile 2 – Comparator	23,450	28	39,817	0.7		23,450	7	11,332	0.6	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 – Aliskiren	5,862	14	10,224	1.4	1.48 (0.80 - 2.73)	5,862	5	3,567	1.4	2.15 (0.70 - 6.60)
Quintile 3 - Comparator	23,452	37	39,946	0.9		23,452	8	11,536	0.7	
Quintile 4 - Aliskiren	5,863	8	10,104	0.8	1.28 (0.58 - 2.83)	5,863	4	3,680	1.1	2.69 (0.72 - 10.06)
Quintile 4 - Comparator	23,451	25	40,312	0.6		23,451	5	12,003	0.4	
Quintile 5 - Aliskiren	6,361	10	11,150	0.9	0.90 (0.45 - 1.80)	6,361	1	4,187	0.2	0.48 (0.06 - 3.93)
Quintile 5 - Comparator	22,953	42	39,773	1.1		22,953	7	12,283	0.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-40 Hazard ratios of transient ischemic attack in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	67	9,766	6.9	0.98 (0.75 - 1.28)	5,748	23	2,983	7.7	1.32 (0.82 - 2.12)
Comparator	22,813	268	37,767	7.1		22,813	66	11,036	6.0	
Stratified by age										
<65 - Aliskiren	4,535	43	7,612	5.7	1.00 (0.71 - 1.39)	4,535	12	2,257	5.3	1.23 (0.64 - 2.36)
<65 - Comparator	17,815	167	29,173	5.7		17,815	37	8,457	4.4	
65+ - Aliskiren	1,213	24	2,154	11.1	0.96 (0.61 - 1.49)	1,213	11	725	15.2	1.41 (0.70 - 2.82)
65+ - Comparator	4,998	101	8,594	11.8		4,998	29	2,579	11.2	
Stratified by gender										
Female - Aliskiren	2,485	37	4,247	8.7	1.07 (0.74 - 1.53)	2,485	10	1,247	8.0	1.63 (0.77 - 3.45)
Female - Comparator	9,851	135	16,450	8.2		9,851	22	4,432	5.0	
Male - Aliskiren	3,263	30	5,519	5.4	0.88 (0.59 - 1.31)	3,263	13	1,736	7.5	1.14 (0.62 - 2.12)
Male - Comparator	12,962	133	21,317	6.2		12,962	44	6,604	6.7	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	33	3,860	8.6	0.90 (0.62 - 1.31)	2,255	11	1,165	9.4	1.12 (0.58 - 2.20)
Diabetes - Comparator	9,023	142	14,759	9.6		9,023	39	4,493	8.7	
No diabetes - Aliskiren	3,493	34	5,906	5.8	1.05 (0.72 - 1.53)	3,493	12	1,818	6.6	1.60 (0.81 - 3.15)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Comparator	13,790	126	23,007	5.5		13,790	27	6,543	4.1	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	18	1,354	13.3	1.09 (0.65 - 1.84)	821	6	406	14.8	1.21 (0.48 - 3.07)
Renal impairment - Comparator	3,138	63	5,079	12.4		3,138	18	1,388	13.0	
No renal impairment - Aliskiren	4,927	49	8,411	5.8	0.93 (0.68 - 1.27)	4,927	17	2,576	6.6	1.36 (0.78 - 2.37)
No renal impairment - Comparator	19,675	205	32,688	6.3		19,675	48	9,648	5.0	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment – Comparator	125	2	231	8.7		125	0	59	0.0	
No diabetes and renal impairment – Aliskiren	5,716	67	9,715	6.9	0.98 (0.75 - 1.28)	5,716	23	2,969	7.8	1.31 (0.82 - 2.11)
No diabetes and renal impairment – Comparator	22,688	266	37,536	7.1		22,688	66	10,978	6.0	
Stratified by CVD										
CVD – Aliskiren	2,020	40	3,468	11.5	0.99 (0.70 - 1.40)	2,020	13	1,045	12.4	1.07 (0.58 - 1.98)
CVD – Comparator	8,014	159	13,406	11.9		8,014	46	3,874	11.9	
No CVD – Aliskiren	3,728	27	6,298	4.3	0.96 (0.63 - 1.47)	3,728	10	1,938	5.2	1.93 (0.90 - 4.14)
No CVD – Comparator	14,799	109	24,361	4.5		14,799	20	7,162	2.8	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	15	758	19.8	1.21 (0.67 - 2.16)	470	3	223	13.4	0.79 (0.23 - 2.77)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	46	2,807	16.4		1,766	14	791	17.7	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	52	9,008	5.8	0.91 (0.68 - 1.24)	5,278	20	2,759	7.3	1.46 (0.87 - 2.45)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	222	34,959	6.4		21,047	52	10,245	5.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug – Aliskiren	1,770	25	2,997	8.3	1.15 (0.74 - 1.79)	1,770	7	807	8.7	1.33 (0.56 - 3.15)
ACEI/ARB+CCB+Index drug – Comparator	7,418	91	12,403	7.3		7,418	20	2,963	6.8	
No ACEI/ARB+CCB+Index drug – Aliskiren	3,978	42	6,769	6.2	0.89 (0.64 - 1.25)	3,978	14	1,970	7.1	1.21 (0.67 - 2.22)
No ACEI/ARB+CCB+Index drug – Comparator	15,395	177	25,364	7.0		15,395	44	7,430	5.9	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	19	1,954	9.7	1.60 (0.94 - 2.72)	1,142	4	481	8.3	1.88 (0.58 - 6.04)
Quintile 1 - Comparator	4,570	47	7,720	6.1		4,570	10	2,189	4.6	
Quintile 2 - Aliskiren	1,143	8	1,955	4.1	0.75 (0.35 - 1.59)	1,143	2	576	3.5	0.85 (0.18 - 3.94)
Quintile 2 - Comparator	4,569	42	7,617	5.5		4,569	9	2,101	4.3	
Quintile 3 - Aliskiren	1,142	13	1,843	7.1	0.84 (0.46 - 1.54)	1,142	7	586	11.9	1.85 (0.75 - 4.59)
Quintile 3 - Comparator	4,571	61	7,363	8.3		4,571	14	2,219	6.3	
Quintile 4 - Aliskiren	1,144	13	1,959	6.6	0.94 (0.51 - 1.72)	1,144	8	662	12.1	2.12 (0.88 - 5.14)
Quintile 4 - Comparator	4,568	53	7,437	7.1		4,568	13	2,190	5.9	
Quintile 5 - Aliskiren	1,177	14	2,054	6.8	0.83 (0.47 - 1.48)	1,177	2	677	3.0	0.36 (0.08 - 1.54)
Quintile 5 - Comparator	4,535	65	7,630	8.5		4,535	20	2,337	8.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-41 Hazard ratios of transient ischemic attack in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	142	51,723	2.8	1.13 (0.94 - 1.36)	29,813	40	17,638	2.3	1.09 (0.77 - 1.56)
Comparator	116,757	488	199,905	2.4		116,757	125	57,972	2.2	
Stratified by age										
<65 - Aliskiren	20,132	49	32,560	1.5	1.04 (0.76 - 1.43)	20,132	15	11,574	1.3	1.05 (0.58 - 1.88)
<65 - Comparator	78,389	180	125,474	1.4		78,389	47	38,184	1.2	
65+ - Aliskiren	9,681	93	19,163	4.9	1.18 (0.94 - 1.49)	9,681	25	6,064	4.1	1.10 (0.70 - 1.73)
65+ - Comparator	38,368	308	74,431	4.1		38,368	78	19,788	3.9	
Stratified by gender										
Female - Aliskiren	14,233	85	25,125	3.4	1.21 (0.95 - 1.54)	14,233	25	8,222	3.0	1.15 (0.73 - 1.81)
Female - Comparator	55,779	275	97,551	2.8		55,779	72	26,077	2.8	
Male - Aliskiren	15,580	57	26,597	2.1	1.03 (0.77 - 1.38)	15,580	15	9,417	1.6	0.99 (0.56 - 1.76)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Male - Comparator	60,978	213	102,354	2.1		60,978	53	31,895	1.7	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	60	16,192	3.7	1.02 (0.77 - 1.36)	9,429	15	5,413	2.8	1.05 (0.59 - 1.86)
Diabetes - Comparator	36,993	228	62,397	3.7		36,993	50	18,345	2.7	
No diabetes - Aliskiren	20,384	82	35,530	2.3	1.23 (0.96 - 1.57)	20,384	25	12,225	2.1	1.13 (0.72 - 1.78)
No diabetes - Comparator	79,764	260	137,508	1.9		79,764	75	39,627	1.9	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	17	5,348	3.2	0.88 (0.52 - 1.49)	3,086	3	1,633	1.8	0.58 (0.17 - 1.99)
Renal impairment - Comparator	12,020	74	20,444	3.6		12,020	17	5,433	3.1	
No renal impairment - Aliskiren	26,727	125	46,374	2.7	1.17 (0.96 - 1.43)	26,727	37	16,005	2.3	1.17 (0.81 - 1.71)
No renal impairment - Comparator	104,737	414	179,461	2.3		104,737	108	52,539	2.1	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	11	2,816	3.9	0.86 (0.45 - 1.66)	1,670	2	857	2.3	0.51 (0.11 - 2.28)
Diabetes and renal impairment – Comparator	6,407	48	10,511	4.6		6,407	13	2,851	4.6	
No diabetes and renal impairment – Aliskiren	28,143	131	48,907	2.7	1.16 (0.95 - 1.41)	28,143	38	16,781	2.3	1.16 (0.80 - 1.68)
No diabetes and renal impairment - Comparator	110,350	440	189,394	2.3		110,350	112	55,121	2.0	
Stratified by CVD										
CVD - Aliskiren	9,223	71	16,659	4.3	1.18 (0.90 - 1.54)	9,223	21	5,388	3.9	1.21 (0.73 - 1.99)
CVD - Comparator	36,587	235	64,840	3.6		36,587	60	17,801	3.4	
No CVD - Aliskiren	20,590	71	35,064	2.0	1.08 (0.83 - 1.41)	20,590	19	12,250	1.6	0.98 (0.59 - 1.64)
No CVD - Comparator	80,170	253	135,065	1.9		80,170	65	40,171	1.6	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	11	2,650	4.2	0.93 (0.48 - 1.79)	1,579	2	817	2.5	0.50 (0.11 - 2.25)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	44	9,763	4.5		6,017	13	2,670	4.9	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	131	49,072	2.7	1.15 (0.95 - 1.40)	28,234	38	16,821	2.3	1.16 (0.80 - 1.68)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	444	190,142	2.3		110,740	112	55,302	2.0	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug – Aliskiren	9,070	58	16,404	3.5	1.28 (0.95 - 1.71)	9,070	10	4,479	2.2	1.03 (0.51 - 2.08)
ACEI/ARB+CCB+Index drug – Comparator	36,447	183	65,267	2.8		36,447	34	14,953	2.3	
No ACEI/ARB+CCB+Index drug – Aliskiren	20,743	84	35,319	2.4	1.05 (0.83 - 1.34)	20,743	28	11,966	2.3	1.14 (0.74 - 1.75)
No ACEI/ARB+CCB+Index drug – Comparator	80,310	305	134,638	2.3		80,310	84	39,598	2.1	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	5,863	36	10,242	3.5	1.69 (1.15 - 2.50)	5,863	12	2,894	4.2	1.88 (0.94 - 3.76)
Quintile 1 - Comparator	23,451	84	40,479	2.1		23,451	24	10,865	2.2	
Quintile 2 - Aliskiren	5,864	25	10,087	2.5	0.99 (0.64 - 1.54)	5,864	6	3,325	1.8	0.91 (0.37 - 2.23)
Quintile 2 - Comparator	23,450	99	39,699	2.5		23,450	24	11,322	2.1	
Quintile 3 - Aliskiren	5,862	24	10,214	2.4	1.00 (0.64 - 1.57)	5,862	5	3,566	1.4	0.78 (0.30 - 2.07)
Quintile 3 - Comparator	23,452	93	39,867	2.3		23,452	22	11,529	1.9	
Quintile 4 - Aliskiren	5,863	28	10,071	2.8	1.04 (0.69 - 1.58)	5,863	9	3,671	2.5	1.08 (0.51 - 2.28)
Quintile 4 - Comparator	23,451	107	40,197	2.7		23,451	29	11,990	2.4	
Quintile 5 - Aliskiren	6,361	29	11,110	2.6	1.02 (0.67 - 1.54)	6,361	8	4,182	1.9	0.94 (0.42 - 2.09)
Quintile 5 - Comparator	22,953	105	39,663	2.7		22,953	26	12,266	2.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-42 Hazard ratios of myocardial infarction in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren	5,748	54	9,788	5.5	1.00 (0.74 - 1.35)	5,748	14	2,989	4.7	0.97 (0.53 - 1.75)
Comparator	22,813	206	37,836	5.4		22,813	52	11,048	4.7	
Stratified by age										
<65 – Aliskiren	4,535	28	7,625	3.7	0.81 (0.54 - 1.22)	4,535	4	2,261	1.8	0.45 (0.16 - 1.27)
<65 - Comparator	17,815	132	29,205	4.5		17,815	34	8,464	4.0	
65+ - Aliskiren	1,213	26	2,163	12.0	1.37 (0.88 - 2.15)	1,213	10	728	13.7	1.86 (0.84 - 4.10)
65+ - Comparator	4,998	74	8,632	8.6		4,998	18	2,584	7.0	
Stratified by gender										
Female - Aliskiren	2,485	34	4,268	8.0	1.71 (1.14 - 2.57)	2,485	8	1,250	6.4	1.84 (0.78 - 4.35)
Female - Comparator	9,851	75	16,513	4.5		9,851	15	4,436	3.4	
Male - Aliskiren	3,263	20	5,520	3.6	0.59 (0.37 - 0.95)	3,263	6	1,739	3.5	0.60 (0.25 - 1.42)
Male - Comparator	12,962	131	21,324	6.1		12,962	37	6,612	5.6	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	32	3,860	8.3	0.89 (0.60 - 1.31)	2,255	9	1,166	7.7	0.91 (0.44 - 1.90)
Diabetes - Comparator	9,023	135	14,766	9.14		9,023	37	4,501	8.2	
No diabetes - Aliskiren	3,493	22	5,928	3.7	1.18 (0.73 - 1.91)	3,493	5	1,823	2.7	1.20 (0.44 - 3.30)
No diabetes - Comparator	13,790	71	23,070	3.1		13,790	15	6,547	2.3	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	12	1,373	8.7	0.71 (0.38 - 1.32)	821	1	408	2.5	0.23 (0.03 - 1.73)
Renal impairment - Comparator	3,138	63	5,080	12.4		3,138	14	1,391	10.1	
No renal impairment - Aliskiren	4,927	42	8,415	5.0	1.13 (0.80 - 1.60)	4,927	13	2,581	5.0	1.26 (0.67 - 2.36)
No renal impairment - Comparator	19,675	143	32,757	4.4		19,675	38	9,657	3.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	32	0	51	0.0	–	32	0	14	0.0	–
Diabetes and renal impairment - Comparator	125	3	226	13.3		125	0	59	0.0	
No diabetes and renal impairment - Aliskiren	5,716	54	9,737	5.6	1.01 (0.75 - 1.37)	5,716	14	2,975	4.7	0.96 (0.53 - 1.75)
No diabetes and renal impairment - Comparator	22,688	203	37,611	5.4		22,688	52	10,989	4.7	
Stratified by CVD										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
CVD - Aliskiren	2,020	33	3,475	9.5	1.04 (0.71 - 1.54)	2,020	10	1,047	9.6	1.12 (0.55 - 2.31)
CVD - Comparator	8,014	120	13,461	8.9		8,014	31	3,884	8.0	
No CVD - Aliskiren	3,728	21	6,312	3.3	0.93 (0.58 - 1.50)	3,728	4	1,942	2.1	0.72 (0.25 - 2.09)
No CVD - Comparator	14,799	86	24,376	3.5		14,799	21	7,164	2.9	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	9	771	11.7	0.79 (0.39 - 1.63)	470	1	224	4.5	0.34 (0.04 - 2.68)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	42	2,809	15.0		1,766	9	794	11.3	
No type 2 diabetes mellitus and renal impairment – Aliskiren	5,278	45	9,016	5.0	1.05 (0.75 - 1.46)	5,278	13	2,765	4.7	1.10 (0.59 - 2.04)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	164	35,027	4.7		21,047	43	10,253	4.2	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	22	3,004	7.3	1.20 (0.75 - 1.94)	1,770	6	807	7.4	1.69 (0.64 - 4.46)
ACEI/ARB+CCB+Index drug - Comparator	7,418	76	12,408	6.1		7,418	13	2,965	4.4	
No ACEI/ARB+CCB+Index drug - Aliskiren	3,978	32	6,784	4.7	0.87 (0.59 - 1.28)	3,978	7	1,974	3.6	0.64 (0.28 - 1.48)
No ACEI/ARB+CCB+Index drug - Comparator	15,395	130	25,429	5.1		15,395	37	7,437	5.0	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	11	1,965	5.6	1.16 (0.59 - 2.28)	1,142	2	484	4.1	0.75 (0.17 - 3.40)
Quintile 1 - Comparator	4,570	37	7,734	4.8		4,570	11	2,192	5.0	
Quintile 2 - Aliskiren	1,143	5	1,958	2.6	0.63 (0.25 - 1.62)	1,143	0	576	0.0	–
Quintile 2 - Comparator	4,569	31	7,643	4.1		4,569	7	2,104	3.3	
Quintile 3 - Aliskiren	1,142	11	1,846	6.0	1.19 (0.61 - 2.33)	1,142	1	588	1.7	0.38 (0.05 - 2.93)
Quintile 3 - Comparator	4,571	37	7,381	5.0		4,571	10	2,220	4.5	
Quintile 4 - Aliskiren	1,144	9	1,967	4.6	0.81 (0.39 - 1.66)	1,144	2	664	3.0	0.50 (0.11 - 2.21)
Quintile 4 - Comparator	4,568	42	7,438	5.7		4,568	14	2,192	6.4	
Quintile 5 - Aliskiren	1,177	18	2,051	8.8	1.11 (0.65 - 1.89)	1,177	9	676	13.3	2.92 (1.17 - 7.28)
Quintile 5 - Comparator	4,535	59	7,641	7.7		4,535	10	2,340	4.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-43 Hazard ratios of myocardial infarction in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	253	51,620	4.9	0.86 (0.75 - 0.99)	29,813	73	17,650	4.1	0.90 (0.70 - 1.17)
Comparator	116,757	1,133	199,261	5.7		116,757	274	57,966	4.7	
Stratified by age										
<65 – Aliskiren	20,132	107	32,492	3.3	0.86 (0.70 - 1.06)	20,132	30	11,574	2.6	0.87 (0.58 - 1.30)
<65 - Comparator	78,389	476	125,129	3.8		78,389	118	38,175	3.1	
65+ - Aliskiren	9,681	146	19,128	7.6	0.86 (0.72 - 1.03)	9,681	43	6,076	7.1	0.92 (0.65 - 1.29)
65+ - Comparator	38,368	657	74,132	8.9		38,368	156	19,792	7.9	
Stratified by gender										
Female - Aliskiren	14,233	124	25,100	4.9	0.95 (0.78 - 1.15)	14,233	32	8,229	3.9	0.89 (0.60 - 1.32)
Female - Comparator	55,779	508	97,313	5.2		55,779	117	26,083	4.5	
Male - Aliskiren	15,580	129	26,519	4.9	0.79 (0.65 - 0.96)	15,580	41	9,421	4.4	0.91 (0.65 - 1.29)
Male - Comparator	60,978	625	101,947	6.1		60,978	157	31,884	4.9	
Stratified by diabetes										
Diabetes – Aliskiren	9,429	118	16,132	7.3	0.85 (0.69 - 1.03)	9,429	38	5,418	7.0	0.97 (0.68 - 1.39)
Diabetes - Comparator	36,993	538	62,093	8.7		36,993	136	18,339	7.4	
No diabetes - Aliskiren	20,384	135	35,488	3.8	0.88 (0.73 - 1.06)	20,384	35	12,232	2.9	0.87 (0.60 - 1.25)
No diabetes - Comparator	79,764	595	137,168	4.3		79,764	138	39,627	3.5	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	49	5,321	9.2	0.73 (0.54 - 0.99)	3,086	14	1,631	8.6	0.74 (0.42 - 1.33)
Renal impairment - Comparator	12,020	257	20,271	12.7		12,020	65	5,427	12.0	
No renal impairment - Aliskiren	26,727	204	46,299	4.4	0.90 (0.77 - 1.05)	26,727	59	16,019	3.7	0.95 (0.71 - 1.27)
No renal impairment - Comparator	104,737	876	178,990	4.9		104,737	209	52,539	4.0	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	36	2,792	12.9	0.90 (0.63 - 1.30)	1,670	13	855	15.2	1.07 (0.58 - 2.01)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes and renal impairment - Comparator	6,407	150	10,434	14.4		6,407	41	2,849	14.4	
No diabetes and renal impairment - Aliskiren	28,143	217	48,828	4.4	0.85 (0.73 - 0.99)	28,143	60	16,795	3.6	0.87 (0.66 - 1.16)
No diabetes and renal impairment - Comparator	110,350	983	188,827	5.2		110,350	233	55,117	4.2	
Stratified by CVD										
CVD – Aliskiren	9,223	117	16,610	7.0	0.75 (0.61 - 0.91)	9,223	37	5,398	6.9	0.77 (0.54 - 1.11)
CVD – Comparator	36,587	607	64,468	9.4		36,587	163	17,795	9.2	
No CVD – Aliskiren	20,590	136	35,010	3.9	0.99 (0.82 - 1.19)	20,590	36	12,252	2.9	1.09 (0.75 - 1.59)
No CVD - Comparator	80,170	526	134,793	3.9		80,170	111	40,171	2.8	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	34	2,629	12.9	0.94 (0.64 - 1.36)	1,579	13	815	16.0	1.12 (0.60 - 2.09)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	134	9,697	13.8		6,017	39	2,668	14.6	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	219	48,990	4.5	0.85 (0.73 - 0.98)	28,234	60	16,835	3.6	0.87 (0.65 - 1.15)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	999	189,563	5.3		110,740	235	55,298	4.3	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	103	16,370	6.3	0.85 (0.69 - 1.05)	9,070	20	4,480	4.5	0.73 (0.45 - 1.19)
ACEI/ARB+CCB+Index drug - Comparator	36,447	482	64,973	7.4		36,447	95	14,943	6.4	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	150	35,249	4.3	0.87 (0.73 - 1.04)	20,743	49	11,976	4.1	1.04 (0.75 - 1.43)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	651	134,287	4.9		80,310	161	39,595	4.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	57	10,221	5.6	1.24 (0.92 - 1.67)	5,863	10	2,900	3.5	0.77 (0.39 - 1.52)
Quintile 1 - Comparator	23,451	181	40,387	4.5		23,451	49	10,869	4.5	
Quintile 2 - Aliskiren	5,864	45	10,070	4.5	0.80 (0.58 - 1.10)	5,864	17	3,326	5.1	1.12 (0.65 - 1.93)
Quintile 2 - Comparator	23,450	222	39,602	5.6		23,450	53	11,319	4.7	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Aliskiren	5,862	44	10,184	4.3	0.71 (0.52 - 0.98)	5,862	16	3,563	4.5	0.93 (0.53 - 1.61)
Quintile 3 - Comparator	23,452	241	39,697	6.1		23,452	57	11,520	5.0	
Quintile 4 - Aliskiren	5,863	49	10,053	4.9	0.88 (0.65 - 1.20)	5,863	14	3,676	3.8	0.92 (0.51 - 1.66)
Quintile 4 - Comparator	23,451	221	40,092	5.5		23,451	51	11,995	4.3	
Quintile 5 - Aliskiren	6,361	58	11,091	5.2	0.78 (0.58 - 1.03)	6,361	16	4,184	3.8	0.79 (0.46 - 1.37)
Quintile 5 - Comparator	22,953	268	39,483	6.8		22,953	64	12,263	5.2	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-44 Hazard ratios of heart failure in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	195	9,611	20.3	0.79 (0.68 - 0.92)	5,748	62	2,974	20.9	0.72 (0.55 - 0.95)
Comparator	22,813	949	36,929	25.7		22,813	320	10,968	29.2	
Stratified by age										
<65 - Aliskiren	4,535	93	7,541	12.3	0.68 (0.55 - 0.85)	4,535	29	2,253	12.9	0.65 (0.44 - 0.96)
<65 - Comparator	17,815	518	28,712	18.0		17,815	163	8,420	19.4	
65+ - Aliskiren	1,213	102	2,070	49.3	0.94 (0.76 - 1.16)	1,213	33	720	45.8	0.77 (0.53 - 1.12)
65+ - Comparator	4,998	431	8,217	52.5		4,998	157	2,548	61.6	
Stratified by gender										
Female - Aliskiren	2,485	92	4,189	22.0	0.88 (0.70 - 1.11)	2,485	28	1,243	22.5	0.79 (0.53 - 1.19)
Female - Comparator	9,851	397	16,156	24.6		9,851	127	4,409	28.8	
Male - Aliskiren	3,263	103	5,422	19.0	0.72 (0.58 - 0.88)	3,263	34	1,731	19.6	0.66 (0.46 - 0.95)
Male - Comparator	12,962	552	20,772	26.6		12,962	193	6,559	29.4	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	117	3,759	31.1	0.77 (0.64 - 0.95)	2,255	41	1,158	35.4	0.83 (0.59 - 1.16)
Diabetes - Comparator	9,023	577	14,205	40.6		9,023	193	4,459	43.3	
No Diabetes - Aliskiren	3,493	78	5,851	13.3	0.81 (0.64 - 1.04)	3,493	21	1,815	11.6	0.60 (0.38 - 0.94)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No Diabetes - Comparator	13,790	372	22,723	16.4		13,790	127	6,510	19.5	
Stratified by renal impairment										
Renal Impairment - Aliskiren	821	81	1,287	63.0	0.88 (0.69 - 1.12)	821	26	401	64.8	0.82 (0.54 - 1.26)
Renal Impairment - Comparator	3,138	344	4,730	72.7		3,138	112	1,368	81.9	
No Renal Impairment - Aliskiren	4,927	114	8,324	13.7	0.72 (0.59 - 0.88)	4,927	36	2,572	14.0	0.64 (0.45 - 0.91)
No Renal Impairment - Comparator	19,675	605	32,198	18.8		19,675	208	9,600	21.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	3	48	63.1	0.84 (0.23 - 3.05)	32	0	14	0.0	–
Diabetes and renal impairment – Comparator	125	14	210	66.8		125	5	56	89.9	
No diabetes and renal impairment – Aliskiren	5,716	192	9,563	20.1	0.79 (0.67 - 0.92)	5,716	62	2,960	21.0	0.73 (0.56 - 0.96)
No diabetes and renal impairment – Comparator	22,688	935	36,719	25.5		22,688	315	10,913	28.9	
Stratified by CVD										
CVD – Aliskiren	2,020	144	3,343	43.1	0.81 (0.68 - 0.97)	2,020	50	1,033	48.4	0.79 (0.58 - 1.07)
CVD – Comparator	8,014	683	12,753	53.6		8,014	239	3,821	62.5	
No CVD – Aliskiren	3,728	51	6,268	8.1	0.72 (0.54 - 0.98)	3,728	12	1,941	6.2	0.54 (0.29 - 0.98)
No CVD – Comparator	14,799	266	24,176	11.0		14,799	81	7,147	11.3	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	54	712	75.9	0.80 (0.60 - 1.08)	470	17	221	77.0	0.76 (0.45 - 1.28)
Type 2 diabetes mellitus and renal impairment – Comparator	1,766	244	2,558	95.4		1,766	80	781	102.4	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	141	8,899	15.9	0.76 (0.64 - 0.92)	5,278	45	2,753	16.4	0.69 (0.50 - 0.95)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	705	34,370	20.5		21,047	240	10,187	23.6	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index dug – Aliskiren	1,770	85	2,925	29.1	0.90 (0.71 - 1.14)	1,770	28	803	34.9	0.87 (0.58 - 1.32)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
ACEI/ARB+CCB+Index drug - Comparator	7,418	389	12,006	32.4		7,418	123	2,941	41.8	
No ACEI/ARB+CCB+Index drug – Aliskiren	3,978	110	6,686	16.5	0.71 (0.58 - 0.87)	3,978	30	1,966	15.3	0.61 (0.42 - 0.91)
No ACEI/ARB+CCB+Index drug – Comparator	15,395	560	24,922	22.5		15,395	177	7,400	23.9	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	1,142	38	1,931	19.7	1.08 (0.75 - 1.54)	1,142	10	479	20.9	0.90 (0.45 - 1.78)
Quintile 1 - Comparator	4,570	139	7,599	18.3		4,570	48	2,183	22.0	
Quintile 2 - Aliskiren	1,143	27	1,925	14.0	0.78 (0.52 - 1.18)	1,143	6	575	10.4	0.50 (0.21 - 1.17)
Quintile 2 - Comparator	4,569	135	7,515	18.0		4,569	45	2,094	21.5	
Quintile 3 - Aliskiren	1,142	32	1,815	17.6	0.71 (0.49 - 1.04)	1,142	7	587	11.9	0.39 (0.18 - 0.85)
Quintile 3 - Comparator	4,571	178	7,218	24.7		4,571	68	2,204	30.9	
Quintile 4 - Aliskiren	1,144	46	1,925	23.9	0.82 (0.60 - 1.13)	1,144	20	662	30.2	0.94 (0.57 - 1.54)
Quintile 4 - Comparator	4,568	211	7,251	29.1		4,568	74	2,173	34.1	
Quintile 5 - Aliskiren	1,177	52	2,014	25.8	0.67 (0.50 - 0.90)	1,177	19	670	28.3	0.78 (0.47 - 1.29)
Quintile 5 - Comparator	4,535	286	7,345	38.9		4,535	85	2,314	36.7	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-45 Hazard ratios of heart failure in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	549	51,179	10.7	0.81 (0.74 - 0.89)	29,813	157	17,612	8.9	0.71 (0.60 - 0.84)
Comparator	116,757	2,606	197,207	13.2		116,757	765	57,797	13.2	
Stratified by age										
<65 – Aliskiren	20,132	195	32,387	6.0	0.81 (0.69 - 0.95)	20,132	68	11,561	5.9	0.84 (0.65 - 1.10)
<65 - Comparator	78,389	915	124,511	7.4		78,389	281	38,116	7.4	
65+ - Aliskiren	9,681	354	18,792	18.8	0.81 (0.72 - 0.91)	9,681	89	6,051	14.7	0.62 (0.50 - 0.78)
65+ - Comparator	38,368	1,691	72,696	23.3		38,368	484	19,681	24.6	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by gender										
Female - Aliskiren	14,233	289	24,833	11.6	0.85 (0.75 - 0.97)	14,233	75	8,206	9.1	0.68 (0.53 - 0.87)
Female - Comparator	55,779	1,319	96,183	13.7		55,779	371	26,005	14.3	
Male - Aliskiren	15,580	260	26,346	9.9	0.77 (0.67 - 0.88)	15,580	82	9,407	8.7	0.73 (0.58 - 0.93)
Male - Comparator	60,978	1,287	101,024	12.7		60,978	394	31,792	12.4	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	295	15,903	18.6	0.80 (0.71 - 0.91)	9,429	102	5,392	18.9	0.86 (0.69 - 1.06)
Diabetes - Comparator	36,993	1412	60,865	23.2		36,993	420	18,236	23.0	
No diabetes - Aliskiren	20,384	254	35,276	7.2	0.82 (0.72 - 0.94)	20,384	55	12,220	4.5	0.55 (0.41 - 0.73)
No diabetes - Comparator	79,764	1,194	136,342	8.8		79,764	345	39,561	8.7	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	153	5,155	29.7	0.77 (0.64 - 0.91)	3,086	47	1,622	29.0	0.71 (0.52 - 0.97)
Renal impairment - Comparator	12,020	768	19,575	39.2		12,020	227	5,375	42.2	
No renal impairment - Aliskiren	26,727	396	46,025	8.6	0.83 (0.74 - 0.92)	26,727	110	15,990	6.9	0.71 (0.58 - 0.87)
No renal impairment - Comparator	104,737	1,838	177,632	10.4		104,737	538	52,422	10.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,670	104	2,695	38.6	0.75 (0.61 - 0.93)	1,670	34	850	40.0	0.71 (0.49 - 1.03)
Diabetes and renal impairment - Comparator	6,407	512	9,910	51.7		6,407	161	2,808	57.3	
No diabetes and renal impairment – Aliskiren	28,143	445	48,485	9.2	0.82 (0.74 - 0.91)	28,143	123	16,762	7.3	0.70 (0.58 - 0.86)
No diabetes and renal impairment - Comparator	110,350	2094	187,298	11.2		110,350	604	54,989	11.0	
Stratified by CVD										
CVD – Aliskiren	9,223	387	16,240	23.8	0.80 (0.71 - 0.89)	9,223	123	5,369	22.9	0.73 (0.60 - 0.89)
CVD – Comparator	36,587	1,879	62,764	29.9		36,587	583	17,660	33.0	
No CVD – Aliskiren	20,590	162	34,940	4.6	0.85 (0.72 - 1.01)	20,590	34	12,243	2.8	0.62 (0.43 - 0.90)
No CVD - Comparator	80,170	727	134,443	5.4		80,170	182	40,137	4.5	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	96	2,542	37.8	0.75 (0.60 - 0.93)	1,579	32	811	39.5	0.71 (0.48 - 1.04)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	472	9,202	51.3		6,017	151	2,631	57.4	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	453	48,637	9.3	0.82 (0.74 - 0.91)	28,234	125	16,801	7.4	0.70 (0.58 - 0.85)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	2,134	188,005	11.4		110,740	614	55,166	11.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	222	16,206	13.7	0.83 (0.72 - 0.96)	9,070	56	4,473	12.5	0.79 (0.59 - 1.06)
ACEI/ARB+CCB+Index drug - Comparator	36,447	1066	64,107	16.6		36,447	252	14,891	16.9	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	327	34,974	9.4	0.81 (0.72 - 0.91)	20,743	89	11,953	7.5	0.67 (0.54 - 0.84)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	1,540	133,101	11.6		80,310	458	39,513	11.6	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	100	10,153	9.9	0.87 (0.70 - 1.08)	5,863	29	2,891	10.0	0.76 (0.51 - 1.14)
Quintile 1 - Comparator	23,451	455	40,049	11.4		23,451	146	10,834	13.5	
Quintile 2 - Aliskiren	5,864	96	9,999	9.6	0.83 (0.67 - 1.03)	5,864	25	3,320	7.5	0.67 (0.44 - 1.03)
Quintile 2 - Comparator	23,450	455	39,254	11.6		23,450	135	11,299	12.0	
Quintile 3 - Aliskiren	5,862	113	10,081	11.2	0.88 (0.72 - 1.07)	5,862	32	3,558	9.0	0.75 (0.51 - 1.11)
Quintile 3 - Comparator	23,452	505	39,363	12.8		23,452	145	11,502	12.6	
Quintile 4 - Aliskiren	5,863	113	9,964	11.3	0.77 (0.63 - 0.94)	5,863	33	3,667	9.0	0.71 (0.49 - 1.03)
Quintile 4 - Comparator	23,451	582	39,583	14.7		23,451	161	11,950	13.5	
Quintile 5 - Aliskiren	6,361	127	10,983	11.6	0.74 (0.61 - 0.90)	6,361	38	4,176	9.1	0.66 (0.46 - 0.94)
Quintile 5 - Comparator	22,953	609	38,958	15.6		22,953	178	12,211	14.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-46 Hazard ratios of acute renal failure in subgroups of Cohort 2 – United

Subgroup	ITT	As treated

	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	344	9,419	36.5	0.92 (0.81 - 1.03)	5,748	118	2,957	39.9	0.86 (0.70 - 1.05)
Comparator	22,813	1,448	36,428	39.8		22,813	512	10,934	46.8	
Stratified by age										
<65 – Aliskiren	4,535	217	7,395	29.4	0.89 (0.77 - 1.04)	4,535	60	2,245	26.7	0.68 (0.52 - 0.90)
<65 - Comparator	17,815	920	28,277	32.5		17,815	323	8,387	38.5	
65+ - Aliskiren	1,213	127	2,025	62.7	0.96 (0.79 - 1.17)	1,213	58	713	81.4	1.09 (0.81 - 1.47)
65+ - Comparator	4,998	528	8,150	64.8		4,998	189	2,547	74.2	
Stratified by gender										
Female - Aliskiren	2,485	140	4,134	33.9	0.89 (0.74 - 1.07)	2,485	52	1,237	42.0	0.86 (0.63 - 1.17)
Female - Comparator	9,851	596	15,912	37.5		9,851	213	4,392	48.5	
Male - Aliskiren	3,263	204	5,285	38.6	0.93 (0.80 - 1.09)	3,263	66	1,720	38.4	0.83 (0.64 - 1.09)
Male - Comparator	12,962	852	20,516	41.5		12,962	299	6,542	45.7	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	204	3,627	56.3	0.88 (0.75 - 1.02)	2,255	71	1,144	62.0	0.86 (0.67 - 1.11)
Diabetes - Comparator	9,023	894	13,925	64.2		9,023	318	4,434	71.7	
No diabetes - Aliskiren	3,493	140	5,793	24.2	0.97 (0.80 - 1.16)	3,493	47	1,813	25.9	0.84 (0.61 - 1.16)
No diabetes - Comparator	13,790	554	22,502	24.6		13,790	194	6,500	29.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	137	1,215	112.8	0.81 (0.67 - 0.98)	821	45	401	112.3	0.66 (0.48 - 0.91)
Renal impairment - Comparator	3,138	615	4,405	139.6		3,138	237	1,338	177.2	
No renal impairment - Aliskiren	4,927	207	8,204	25.2	0.96 (0.83 - 1.12)	4,927	73	2,557	28.6	0.98 (0.76 - 1.27)
No renal impairment - Comparator	19,675	833	32,023	26.0		19,675	275	9,596	28.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	3	44	67.8	0.46 (0.11 - 2.04)	32	2	13	155.0	0.65 (0.07 - 6.47)
Diabetes and renal impairment - Comparator	125	20	202	99.1		125	5	56	89.7	
No diabetes and renal impairment - Aliskiren	5,716	341	9,375	36.4	0.92 (0.82 - 1.03)	5,716	116	2,944	39.4	0.84 (0.69 - 1.03)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes and renal impairment - Comparator	22,688	1428	36,226	39.4		22,688	507	10,878	46.6	
Stratified by CVD										
CVD – Aliskiren	2,020	198	3,257	60.8	0.95 (0.81 - 1.11)	2,020	75	1,024	73.3	0.91 (0.70 - 1.17)
CVD – Comparator	8,014	808	12,662	63.8		8,014	312	3,821	81.7	
No CVD – Aliskiren	3,728	146	6,163	23.7	0.87 (0.73 - 1.04)	3,728	43	1,934	22.2	0.77 (0.55 - 1.07)
No CVD - Comparator	14,799	640	23,766	26.9		14,799	200	7,113	28.1	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	470	91	666	136.6	0.81 (0.64 - 1.01)	470	31	219	141.4	0.68 (0.46 - 0.99)
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	411	2,369	173.5		1,766	166	763	217.4	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	253	8,753	28.9	0.94 (0.82 - 1.08)	5,278	87	2,738	31.8	0.92 (0.73 - 1.16)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	1,037	34,058	30.5		21,047	346	10,171	34.0	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,770	139	2,860	48.6	0.94 (0.78 - 1.13)	1,770	42	802	52.4	0.89 (0.64 - 1.25)
ACEI/ARB+CCB+Index drug - Comparator	7,418	610	11,800	51.7		7,418	180	2,934	61.4	
No ACEI/ARB+CCB+Index drug - Aliskiren	3,978	205	6,559	31.3	0.89 (0.76 - 1.04)	3,978	68	1,950	34.9	0.84 (0.65 - 1.10)
No ACEI/ARB+CCB+Index drug - Comparator	15,395	838	24,627	34.0		15,395	291	7,374	39.5	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	1,142	48	1,929	24.9	1.10 (0.80 - 1.51)	1,142	13	481	27.0	0.91 (0.50 - 1.65)
Quintile 1 - Comparator	4,570	173	7,585	22.8		4,570	61	2,181	28.0	
Quintile 2 - Aliskiren	1,143	51	1,895	26.9	0.94 (0.69 - 1.28)	1,143	21	569	36.9	1.07 (0.66 - 1.74)
Quintile 2 - Comparator	4,569	213	7,434	28.7		4,569	73	2,090	34.9	
Quintile 3 - Aliskiren	1,142	65	1,775	36.6	1.05 (0.80 - 1.37)	1,142	20	583	34.3	0.79 (0.49 - 1.27)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Comparator	4,571	250	7,153	35.0		4,571	97	2,202	44.1	
Quintile 4 - Aliskiren	1,144	75	1,885	39.8	0.86 (0.67 - 1.11)	1,144	23	658	34.9	0.69 (0.44 - 1.09)
Quintile 4 - Comparator	4,568	327	7,114	46.0		4,568	113	2,162	52.3	
Quintile 5 - Aliskiren	1,177	105	1,936	54.2	0.80 (0.65 - 0.99)	1,177	41	666	61.6	0.85 (0.61 - 1.20)
Quintile 5 - Comparator	4,535	485	7,142	67.9		4,535	168	2,299	73.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-47 Hazard ratios of acute renal failure in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	29,813	1,675	49,981	33.5	0.94 (0.89 - 0.99)	29,813	568	17,532	32.4	0.90 (0.82 - 0.99)
Comparator	116,757	6,867	192,549	35.7		116,757	2,139	57,485	37.2	
Stratified by age										
<65 – Aliskiren	20,132	720	31,847	22.6	0.91 (0.84 - 0.99)	20,132	250	11,523	21.7	0.84 (0.73 - 0.97)
<65 - Comparator	78,389	2,999	122,206	24.5		78,389	1,007	37,949	26.5	
65+ - Aliskiren	9,681	955	18,134	52.7	0.95 (0.89 - 1.02)	9,681	318	6,009	52.9	0.93 (0.82 - 1.06)
65+ - Comparator	38,368	3,868	70,343	55.0		38,368	1,132	19,535	58.0	
Stratified by gender										
Female - Aliskiren	14,233	812	24,317	33.4	0.98 (0.90 - 1.05)	14,233	262	8,181	32.0	0.90 (0.78 - 1.03)
Female - Comparator	55,779	3,195	94,159	33.9		55,779	955	25,883	36.9	
Male - Aliskiren	15,580	863	25,664	33.6	0.90 (0.83 - 0.97)	15,580	306	9,351	32.7	0.89 (0.79 - 1.01)
Male - Comparator	60,978	3,672	98,390	37.3		60,978	1,184	31,601	37.5	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	872	15,285	57.1	0.96 (0.89 - 1.03)	9,429	297	5,357	55.4	0.94 (0.83 - 1.07)
Diabetes - Comparator	36,993	3494	58,548	59.7		36,993	1,091	18,089	60.3	
No diabetes - Aliskiren	20,384	803	34,696	23.1	0.91 (0.85 - 0.99)	20,384	271	12,175	22.3	0.87 (0.76 - 0.99)
No diabetes - Comparator	79,764	3,373	134,001	25.2		79,764	1,048	39,395	26.6	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	581	4,670	124.4	1.01 (0.92 - 1.11)	3,086	217	1,590	136.5	0.97 (0.84 - 1.13)
Renal impairment - Comparator	12,020	2,210	17,827	124.0		12,020	767	5,253	146.0	
No renal impairment - Aliskiren	26,727	1094	45,310	24.1	0.90 (0.84 - 0.96)	26,727	351	15,942	22.0	0.86 (0.76 - 0.97)
No renal impairment - Comparator	104,737	4,657	174,722	26.7		104,737	1,372	52,232	26.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	378	2,394	157.9	1.02 (0.91 - 1.15)	1,670	138	831	166.1	0.97 (0.80 - 1.18)
Diabetes and renal impairment – Comparator	6,407	1,376	8,841	155.6		6,407	486	2,743	177.2	
No diabetes and renal impairment – Aliskiren	28,143	1,297	47,586	27.3	0.91 (0.85 - 0.96)	28,143	430	16,702	25.8	0.88 (0.79 - 0.97)
No diabetes and renal impairment – Comparator	110,350	5491	183,707	29.9		110,350	1,653	54,742	30.2	
Stratified by CVD										
CVD – Aliskiren	9,223	877	15,711	55.8	0.92 (0.86 - 0.99)	9,223	305	5,338	57.1	0.89 (0.79 - 1.01)
CVD – Comparator	36,587	3,666	60,825	60.3		36,587	1,161	17,538	66.2	
No CVD – Aliskiren	20,590	798	34,269	23.3	0.95 (0.88 - 1.02)	20,590	263	12,194	21.6	0.90 (0.78 - 1.03)
No CVD – Comparator	80,170	3,201	131,724	24.3		80,170	978	39,946	24.5	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	355	2,258	157.2	1.03 (0.91 - 1.16)	1,579	132	792	166.7	0.98 (0.81 - 1.19)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	1,271	8,246	154.1		6,017	455	2,567	177.2	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	1,320	47,723	27.7	0.91 (0.85 - 0.96)	28,234	436	16,740	26.0	0.87 (0.79 - 0.97)
No type 2 diabetes mellitus and renal impairment - Comparator	110,740	5,596	184,303	30.4		110,740	1,684	54,917	30.7	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	714	15,637	45.7	1.00 (0.92 - 1.08)	9,070	184	4,448	41.4	0.91 (0.77 - 1.07)
ACEI/ARB+CCB+Index drug –	36,447	2842	62,138	45.7		36,447	710	14,808	48.0	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator										
No ACEI/ARB+CCB+Index drug – Aliskiren	20,743	961	34,344	28.0	0.90 (0.84 - 0.97)	20,743	331	11,910	27.8	0.87 (0.77 - 0.98)
No ACEI/ARB+CCB+Index drug – Comparator	80,310	4,025	130,411	30.9		80,310	1,296	39,313	33.0	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	5,863	281	9,969	28.2	1.02 (0.89 - 1.16)	5,863	93	2,881	32.3	1.03 (0.82 - 1.29)
Quintile 1 - Comparator	23,451	1,092	39,409	27.7		23,451	343	10,798	31.8	
Quintile 2 - Aliskiren	5,864	321	9,762	32.9	1.06 (0.94 - 1.20)	5,864	98	3,308	29.6	0.88 (0.70 - 1.09)
Quintile 2 - Comparator	23,450	1,194	38,486	31.0		23,450	391	11,243	34.8	
Quintile 3 - Aliskiren	5,862	325	9,891	32.9	0.92 (0.81 - 1.03)	5,862	105	3,542	29.7	0.81 (0.65 - 1.00)
Quintile 3 - Comparator	23,452	1,377	38,367	35.9		23,452	437	11,418	38.3	
Quintile 4 - Aliskiren	5,863	328	9,726	33.7	0.89 (0.79 - 1.00)	5,863	116	3,651	31.8	0.85 (0.70 - 1.04)
Quintile 4 - Comparator	23,451	1,464	38,626	37.9		23,451	460	11,885	38.7	
Quintile 5 - Aliskiren	6,361	420	10,632	39.5	0.85 (0.76 - 0.95)	6,361	156	4,151	37.6	0.94 (0.78 - 1.12)
Quintile 5 - Comparator	22,953	1740	37,660	46.2		22,953	508	12,140	41.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-48 Hazard ratios of end-stage renal disease in subgroups of Cohort 2 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	5,748	114	9,714	11.7	0.83 (0.68 - 1.02)	5,748	35	2,983	11.7	0.90 (0.62 - 1.30)
Comparator	22,813	524	37,483	14.0		22,813	145	11,026	13.2	
Stratified by age										
<65 – Aliskiren	4,535	87	7,550	11.5	0.81 (0.64 - 1.02)	4,535	25	2,256	11.1	0.84 (0.54 - 1.30)
<65 - Comparator	17,815	407	28,891	14.1		17,815	109	8,445	12.9	
65+ - Aliskiren	1,213	27	2,164	12.5	0.91 (0.60 - 1.39)	1,213	10	727	13.8	0.99 (0.49 - 2.00)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
65+ - Comparator	4,998	117	8,592	13.6		4,998	36	2,581	14.0	
Stratified by gender										
Female - Aliskiren	2,485	51	4,238	12.03	0.91 (0.67 - 1.23)	2,485	17	1,249	13.6	0.93 (0.55 - 1.60)
Female - Comparator	9,851	213	16,380	13.0		9,851	63	4,427	14.2	
Male - Aliskiren	3,263	63	5,476	11.5	0.77 (0.59 - 1.01)	3,263	18	1,735	10.4	0.84 (0.51 - 1.40)
Male - Comparator	12,962	311	21,104	14.7		12,962	82	6,600	12.4	
Stratified by diabetes										
Diabetes - Aliskiren	2,255	70	3,820	18.3	0.77 (0.60 - 1.00)	2,255	25	1,164	21.5	1.10 (0.70 - 1.71)
Diabetes - Comparator	9,023	345	14,541	23.7		9,023	88	4,492	19.6	
No diabetes - Aliskiren	3,493	44	5,894	7.5	0.95 (0.68 - 1.32)	3,493	10	1,819	5.5	0.61 (0.31 - 1.19)
No diabetes - Comparator	13,790	179	22,942	7.8		13,790	57	6,535	8.7	
Stratified by renal impairment										
Renal impairment - Aliskiren	821	92	1,276	72.1	0.81 (0.64 - 1.01)	821	31	401	77.3	0.87 (0.58 - 1.28)
Renal impairment - Comparator	3,138	429	4,618	92.9		3,138	127	1,365	93.1	
No renal impairment - Aliskiren	4,927	22	8,438	2.6	0.87 (0.55 - 1.38)	4,927	4	2,582	1.6	0.83 (0.28 - 2.44)
No renal impairment - Comparator	19,675	95	32,865	2.9		19,675	18	9,662	1.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	32	3	44	67.8	0.89 (0.26 - 3.13)	32	1	14	74.1	0.46 (0.04 - 5.03)
Diabetes and renal impairment – Comparator	125	17	214	79.5		125	6	56	106.7	
No diabetes and renal impairment – Aliskiren	5,716	111	9,670	11.5	0.83 (0.68 - 1.02)	5,716	34	2,970	11.5	0.89 (0.61 - 1.30)
No diabetes and renal impairment – Comparator	22,688	507	37,270	13.6		22,688	139	10,970	12.7	
Stratified by CVD										
CVD – Aliskiren	2,020	66	3,429	19.3	0.87 (0.67 - 1.14)	2,020	25	1,042	24.0	1.08 (0.69 - 1.68)
CVD – Comparator	8,014	292	13,236	22.1		8,014	88	3,874	22.7	
No CVD – Aliskiren	3,728	48	6,285	7.6	0.78 (0.57 - 1.06)	3,728	10	1,941	5.2	0.62 (0.32 - 1.21)
No CVD – Comparator	14,799	232	24,248	9.6		14,799	57	7,153	8.0	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment	470	50	721	69.4	0.71 (0.53 - 0.96)	470	20	221	90.4	1.00 (0.61 - 1.64)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
- Aliskiren										
Type 2 diabetes mellitus and renal impairment - Comparator	1,766	260	2,546	102.1		1,766	72	784	91.8	
No type 2 diabetes mellitus and renal impairment - Aliskiren	5,278	64	8,993	7.1	0.93 (0.71 - 1.22)	5,278	15	2,762	5.4	0.75 (0.43 - 1.30)
No type 2 diabetes mellitus and renal impairment - Comparator	21,047	264	34,938	7.6		21,047	73	10,242	7.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug – Aliskiren	1,770	52	2,966	17.5	0.81 (0.60 - 1.09)	1,770	14	804	17.4	0.96 (0.53 - 1.73)
ACEI/ARB+CCB+Index drug – Comparator	7,418	264	12,191	21.7		7,418	56	2,957	18.9	
No ACEI/ARB+CCB+Index drug – Aliskiren	3,978	62	6,748	9.2	0.85 (0.65 - 1.13)	3,978	20	1,972	10.1	1.00 (0.61 - 1.64)
No ACEI/ARB+CCB+Index drug – Comparator	15,395	260	25,292	10.3		15,395	73	7,431	9.8	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	1,142	18	1,964	9.2	1.74 (1.00 - 3.04)	1,142	6	483	12.4	1.81 (0.70 - 4.73)
Quintile 1 – Comparator	4,570	41	7,745	5.3		4,570	14	2,192	6.4	
Quintile 2 – Aliskiren	1,143	14	1,939	7.2	1.00 (0.56 - 1.80)	1,143	6	576	10.4	1.38 (0.54 - 3.52)
Quintile 2 - Comparator	4,569	55	7,617	7.2		4,569	16	2,103	7.6	
Quintile 3 - Aliskiren	1,142	20	1,834	10.9	0.97 (0.60 - 1.59)	1,142	5	587	8.5	0.79 (0.30 - 2.07)
Quintile 3 - Comparator	4,571	82	7,332	11.2		4,571	24	2,215	10.8	
Quintile 4 - Aliskiren	1,144	29	1,943	14.9	0.81 (0.54 - 1.21)	1,144	10	664	15.1	0.77 (0.39 - 1.54)
Quintile 4 - Comparator	4,568	136	7,334	18.5		4,568	43	2,187	19.7	
Quintile 5 - Aliskiren	1,177	33	2,034	16.2	0.57 (0.40 - 0.83)	1,177	8	674	11.9	0.59 (0.28 - 1.25)
Quintile 5 - Comparator	4,535	210	7,456	28.2		4,535	48	2,330	20.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-49 Hazard ratios of end-stage renal disease in subgroups of Cohort 2 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Aliskiren	29,813	426	51,388	8.3	0.88 (0.79 - 0.98)	29,813	118	17,636	6.7	0.77 (0.63 - 0.94)
Comparator	116,757	1,843	198,346	9.3		116,757	528	57,906	9.1	
Stratified by age										
<65 – Aliskiren	20,132	257	32,309	8.0	0.86 (0.75 - 0.99)	20,132	74	11,560	6.4	0.76 (0.59 - 0.98)
<65 - Comparator	78,389	1,131	124,306	9.1		78,389	336	38,129	8.8	
65+ - Aliskiren	9,681	169	19,078	8.9	0.91 (0.77 - 1.07)	9,681	44	6,076	7.2	0.77 (0.56 - 1.08)
65+ - Comparator	38,368	712	74,040	9.6		38,368	192	19,777	9.7	
Stratified by gender										
Female - Aliskiren	14,233	181	25,013	7.2	0.87 (0.74 - 1.02)	14,233	43	8,228	5.2	0.60 (0.44 - 0.84)
Female - Comparator	55,779	794	96,964	8.2		55,779	238	26,057	9.1	
Male - Aliskiren	15,580	245	26,374	9.3	0.88 (0.77 - 1.02)	15,580	75	9,409	8.0	0.91 (0.70 - 1.17)
Male - Comparator	60,978	1,049	101,382	10.4		60,978	290	31,849	9.1	
Stratified by diabetes										
Diabetes - Aliskiren	9,429	261	15,978	16.3	0.91 (0.79 - 1.04)	9,429	70	5,407	13.0	0.86 (0.66 - 1.11)
Diabetes - Comparator	36,993	1105	61,399	18.0		36,993	287	18,300	15.7	
No diabetes - Aliskiren	20,384	165	35,410	4.7	0.85 (0.72 - 1.01)	20,384	48	12,229	3.9	0.68 (0.50 - 0.93)
No diabetes - Comparator	79,764	738	136,947	5.4		79,764	241	39,605	6.1	
Stratified by renal impairment										
Renal impairment - Aliskiren	3,086	311	4,979	62.5	0.82 (0.72 - 0.92)	3,086	101	1,603	63.0	0.74 (0.60 - 0.92)
Renal impairment - Comparator	12,020	1,450	18,750	77.3		12,020	474	5,318	89.1	
No renal impairment - Aliskiren	26,727	115	46,409	2.5	1.11 (0.90 - 1.36)	26,727	17	16,033	1.1	1.03 (0.59 - 1.78)
No renal impairment - Comparator	104,737	393	179,597	2.2		104,737	54	52,588	1.0	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	1,670	198	2,595	76.3	0.85 (0.72 - 0.99)	1,670	61	838	72.8	0.82 (0.62 - 1.08)
Diabetes and renal impairment - Comparator	6,407	875	9,526	91.9		6,407	262	2,789	93.9	
No diabetes and renal impairment - Aliskiren	28,143	228	48,792	4.7	0.90 (0.78 - 1.04)	28,143	57	16,798	3.4	0.74 (0.55 - 0.98)
No diabetes and renal impairment -	110,350	968	188,821	5.1		110,350	266	55,117	4.8	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator										
Stratified by CVD										
CVD - Aliskiren	9,223	221	16,480	13.4	0.85 (0.73 - 0.98)	9,223	75	5,387	13.9	0.86 (0.67 - 1.11)
CVD - Comparator	36,587	998	63,925	15.6		36,587	304	17,757	17.1	
No CVD - Aliskiren	20,590	205	34,908	5.9	0.92 (0.79 - 1.07)	20,590	43	12,249	3.5	0.64 (0.46 - 0.89)
No CVD - Comparator	80,170	845	134,422	6.3		80,170	224	40,149	5.6	
Stratified by type 2 diabetes mellitus and renal impairment (ALTITUDE-like)										
Type 2 diabetes mellitus and renal impairment - Aliskiren	1,579	179	2,455	72.9	0.84 (0.72 - 0.99)	1,579	59	800	73.8	0.86 (0.65 - 1.15)
Type 2 diabetes mellitus and renal impairment - Comparator	6,017	783	8,889	88.1		6,017	237	2,614	90.7	
No type 2 diabetes mellitus and renal impairment - Aliskiren	28,234	247	48,933	5.1	0.89 (0.77 - 1.02)	28,234	59	16,837	3.5	0.70 (0.53 - 0.93)
No type 2 diabetes mellitus and renal impairment – Comparator	110,740	1,060	189,458	5.6		110,740	291	55,292	5.3	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,070	208	16,219	12.8	0.86 (0.74 - 1.00)	9,070	49	4,474	11.0	0.74 (0.55 - 1.01)
ACEI/ARB+CCB+Index drug - Comparator	36,447	956	64,356	14.9		36,447	238	14,914	16.0	
No ACEI/ARB+CCB+Index drug - Aliskiren	20,743	218	35,169	6.2	0.93 (0.80 - 1.07)	20,743	59	11,973	4.9	0.79 (0.60 - 1.06)
No ACEI/ARB+CCB+Index drug - Comparator	80,310	887	133,990	6.6		80,310	253	39,578	6.4	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	5,863	77	10,196	7.6	1.30 (1.01 - 1.68)	5,863	23	2,896	7.9	1.18 (0.74 - 1.89)
Quintile 1 - Comparator	23,451	234	40,301	5.8		23,451	73	10,859	6.7	
Quintile 2 - Aliskiren	5,864	72	10,036	7.2	0.99 (0.76 - 1.28)	5,864	14	3,328	4.2	0.61 (0.34 - 1.07)
Quintile 2 - Comparator	23,450	287	39,532	7.3		23,450	83	11,315	7.3	
Quintile 3 - Aliskiren	5,862	67	10,142	6.6	0.75 (0.58 - 0.97)	5,862	23	3,561	6.5	0.77 (0.49 - 1.21)
Quintile 3 - Comparator	23,452	349	39,563	8.8		23,452	103	11,506	9.0	
Quintile 4 - Aliskiren	5,863	94	10,007	9.4	0.94 (0.75 - 1.17)	5,863	24	3,676	6.5	0.77 (0.49 - 1.19)
Quintile 4 - Comparator	23,451	400	39,883	10.0		23,451	111	11,983	9.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 5 - Aliskiren	6,361	116	11,006	10.5	0.71 (0.58 - 0.87)	6,361	34	4,176	8.1	0.66 (0.46 - 0.97)
Quintile 5 - Comparator	22,953	573	39,067	14.7		22,953	158	12,242	12.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-50 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	85	7,397	11.5	0.98 (0.77 - 1.24)	4,149	17	2,193	7.8	0.61 (0.37 - 1.02)
Comparator	16,438	333	28,274	11.8		16,438	105	8,178	12.8	
Stratified by age										
<65 - Aliskiren	3,170	59	5,606	10.5	1.16 (0.87 - 1.55)	3,170	10	1,620	6.2	0.71 (0.36 - 1.40)
<65 - Comparator	12,642	197	21,648	9.1		12,642	53	6,247	8.5	
65+ - Aliskiren	979	26	1,791	14.5	0.71 (0.47 - 1.09)	979	7	573	12.2	0.47 (0.22 - 1.04)
65+ - Comparator	3,796	136	6,627	20.5		3,796	52	1,931	26.9	
Stratified by gender										
Female - Aliskiren	1,711	39	3,090	12.6	0.96 (0.68 - 1.36)	1,711	8	846	9.5	0.64 (0.30 - 1.36)
Female - Comparator	6,862	158	11,858	13.3		6,862	46	3,102	14.8	
Male - Aliskiren	2,438	46	4,307	10.7	1.00 (0.72 - 1.39)	2,438	9	1,348	6.7	0.58 (0.29 - 1.16)
Male - Comparator	9,576	175	16,416	10.7		9,576	59	5,076	11.6	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	49	2,834	17.3	0.99 (0.72 - 1.36)	1,613	8	851	9.4	0.48 (0.23 - 1.00)
Diabetes - Comparator	6,319	185	10,584	17.5		6,319	63	3,201	19.7	
No diabetes - Aliskiren	2,536	36	4,562	7.9	0.95 (0.66 - 1.37)	2,536	9	1,343	6.7	0.82 (0.40 - 1.68)
No diabetes - Comparator	10,119	148	17,690	8.4		10,119	42	4,977	8.4	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	29	997	29.1	1.25 (0.82 - 1.91)	633	5	288	17.4	0.60 (0.23 - 1.56)
Renal impairment - Comparator	2,462	89	3,935	22.6		2,462	31	1,167	26.6	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No renal impairment - Aliskiren	3,516	56	6,400	8.8	0.87 (0.65 - 1.16)	3,516	12	1,905	6.3	0.59 (0.32 - 1.09)
No renal impairment - Comparator	13,976	244	24,339	10.0		13,976	74	7,011	10.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	30	2	52	38.8	3.50 (0.46 - 26.53)	30	0	14	0.0	–
Diabetes and renal impairment – Comparator	113	3	202	14.8		113	0	54	0.0	
No diabetes and renal impairment – Aliskiren	4,119	83	7,345	11.3	0.96 (0.76 - 1.23)	4,119	17	2,179	7.8	0.61 (0.36 - 1.01)
No diabetes and renal impairment – Comparator	16,325	330	28,072	11.8		16,325	105	8,123	12.9	
Stratified by CVD										
CVD – Aliskiren	1,534	47	2,737	17.2	0.95 (0.69 - 1.31)	1,534	8	809	9.9	0.47 (0.22 - 0.97)
CVD – Comparator	5,980	187	10,314	18.1		5,980	63	2,898	21.7	
No CVD – Aliskiren	2,615	38	4,660	8.2	1.00 (0.70 - 1.44)	2,615	9	1,384	6.5	0.81 (0.39 - 1.66)
No CVD - Comparator	10,458	146	17,960	8.1		10,458	42	5,279	8.0	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	85	7,397	11.5	1.10 (0.82 - 1.47)	4,149	17	2,193	7.8	0.67 (0.38 - 1.20)
Comparator (ACEI/ARB)	5,694	100	9,603	10.4		5,694	35	3,121	11.2	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug – Aliskiren	1,791	42	3,035	13.8	0.99 (0.71 - 1.40)	1,791	5	810	6.2	0.39 (0.15 - 0.98)
ACEI/ARB+CCB+Index drug – Comparator	6,490	155	11,133	13.9		6,490	42	2,625	16.0	
No ACEI/ARB+CCB+Index drug – Aliskiren	2,358	43	4,361	9.9	0.96 (0.69 - 1.35)	2,358	9	1,246	7.2	0.63 (0.31 - 1.27)
No ACEI/ARB+CCB+Index drug – Comparator	9,948	178	17,141	10.4		9,948	58	4,888	11.9	
Stratified by PS quintiles										
Quintile 1 – Aliskiren	824	18	1,330	13.5	1.26 (0.74 - 2.14)	824	5	342	14.6	1.15 (0.43 - 3.10)
Quintile 1 – Comparator	3,293	56	5,192	10.8		3,293	18	1,513	11.9	
Quintile 2 – Aliskiren	823	17	1,457	11.7	1.41 (0.81 - 2.46)	823	3	424	7.1	0.88 (0.25 - 3.09)
Quintile 2 – Comparator	3,295	46	5,554	8.3		3,295	13	1,582	8.2	
Quintile 3 – Aliskiren	823	17	1,494	11.4	1.09 (0.64 - 1.87)	823	1	442	2.3	0.25 (0.03 - 1.92)
Quintile 3 – Comparator	3,294	60	5,683	10.6		3,294	15	1,632	9.2	
Quintile 4 – Aliskiren	824	10	1,526	6.6	0.53 (0.27 - 1.03)	824	1	523	1.9	0.12 (0.02 - 0.89)
Quintile 4 - Comparator	3,294	73	5,863	12.5		3,294	30	1,731	17.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 5 - Aliskiren	855	23	1,590	14.5	0.89 (0.56 - 1.40)	855	7	462	15.1	0.91 (0.40 - 2.07)
Quintile 5 - Comparator	3,262	98	5,981	16.4		3,262	29	1,719	16.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-51 Hazard ratios of cerebrovascular accidents in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	209	35,480	5.9	0.83 (0.71 - 0.96)	19,092	49	10,667	4.6	19,092
Comparator	75,912	978	137,996	7.1		75,912	227	37,654	6.0	75,912
Stratified by age										
<65 – Aliskiren	11,849	67	20,679	3.2	0.68 (0.52 - 0.88)	11,849	14	6,386	2.2	11,849
<65 - Comparator	46,878	383	80,666	4.8		46,878	100	22,847	4.4	46,878
65+ - Aliskiren	7,243	142	14,801	9.6	0.92 (0.77 - 1.11)	7,243	35	4,281	8.2	7,243
65+ - Comparator	29,034	595	57,330	10.4		29,034	127	14,807	8.6	29,034
Stratified by gender										
Female - Aliskiren	9,242	106	17,450	6.1	0.79 (0.64 - 0.97)	9,242	19	4,927	3.9	9,242
Female - Comparator	36,717	517	67,645	7.6		36,717	99	17,044	5.8	36,717
Male - Aliskiren	9,850	103	18,031	5.7	0.87 (0.70 - 1.08)	9,850	30	5,740	5.2	9,850
Male - Comparator	39,195	461	70,351	6.6		39,195	128	20,610	6.2	39,195
Stratified by diabetes										
Diabetes - Aliskiren	6,232	86	11,057	7.8	0.83 (0.65 - 1.04)	6,232	16	3,446	4.6	6,232
Diabetes - Comparator	24,459	400	42,549	9.4		24,459	93	12,061	7.7	24,459
No diabetes - Aliskiren	12,860	123	24,423	5.0	0.82 (0.68 - 1.00)	12,860	33	7,221	4.6	12,860
No diabetes - Comparator	51,453	578	95,447	6.1		51,453	134	25,593	5.2	51,453
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	35	4,111	8.5	0.75 (0.52 - 1.08)	2,354	10	1,213	8.3	2,354
Renal impairment - Comparator	9,313	178	15,660	11.4		9,313	33	4,300	7.7	9,313

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No renal impairment - Aliskiren	16,738	174	31,370	5.6	0.84 (0.71 - 0.99)	16,738	39	9,454	4.1	16,738
No renal impairment - Comparator	66,599	800	122,336	6.5		66,599	194	33,354	5.8	66,599
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	17	2,011	8.5	0.64 (0.39 - 1.08)	1,207	3	617	4.9	1,207
Diabetes and renal impairment - Comparator	4,723	101	7,711	13.1		4,723	16	2,091	7.7	4,723
No diabetes and renal impairment - Aliskiren	17,885	192	33,469	5.7	0.85 (0.72 - 0.99)	17,885	46	10,050	4.6	17,885
No diabetes and renal impairment - Comparator	71,189	877	130,284	6.7		71,189	211	35,563	5.9	71,189
Stratified by CVD										
CVD - Aliskiren	6,585	109	12,436	8.8	0.83 (0.67 - 1.02)	6,585	28	3,601	7.8	6,585
CVD - Comparator	26,218	506	47,725	10.6		26,218	114	12,263	9.3	26,218
No CVD - Aliskiren	12,507	100	23,045	4.3	0.82 (0.66 - 1.02)	12,507	21	7,066	3.0	12,507
No CVD - Comparator	49,694	472	90,271	5.2		49,694	113	25,391	4.5	49,694
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	209	35,480	5.9	0.92 (0.77 - 1.10)	19,092	49	10,667	4.6	19,092
Comparator (ACEI/ARB)	25,378	291	45,342	6.4		25,378	75	13,723	5.5	25,378
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	117	16,733	7.0	0.89 (0.73 - 1.09)	9,303	23	4,556	5.1	9,303
ACEI/ARB+CCB+Index drug - Comparator	32,502	467	59,905	7.8		32,502	90	12,990	6.9	32,502
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	92	18,747	4.9	0.75 (0.60 - 0.94)	9,789	24	5,272	4.6	9,789
No ACEI/ARB+CCB+Index drug - Comparator	43,410	511	78,091	6.5		43,410	122	21,297	5.7	43,410
Stratified by PS quintiles										
Quintile 1 – Aliskiren	3,800	45	6,467	7.0	0.98 (0.71 - 1.36)	3,800	11	1,839	6.0	3,800
Quintile 1 - Comparator	15,200	180	25,263	7.1		15,200	46	7,184	6.4	15,200
Quintile 2 - Aliskiren	3,800	53	6,735	7.9	1.09 (0.81 - 1.48)	3,800	14	2,000	7.0	3,800
Quintile 2 - Comparator	15,201	192	26,664	7.2		15,201	50	7,485	6.7	15,201
Quintile 3 - Aliskiren	3,800	40	7,009	5.7	0.92 (0.65 - 1.29)	3,800	7	2,177	3.2	3,800
Quintile 3 - Comparator	15,201	172	27,664	6.2		15,201	41	7,532	5.4	15,201
Quintile 4 - Aliskiren	3,799	30	7,213	4.2	0.60 (0.41 - 0.88)	3,799	8	2,252	3.6	3,799
Quintile 4 - Comparator	15,202	195	28,121	6.9		15,202	33	7,671	4.3	15,202

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 5 - Aliskiren	3,893	41	8,057	5.1	0.63 (0.45 - 0.88)	3,893	9	2,399	3.8	3,893
Quintile 5 - Comparator	15,108	239	30,284	7.9		15,108	57	7,782	7.3	15,108

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-52 Hazard ratios of stroke in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	100	7,384	13.5	1.01 (0.81 - 1.25)	4,149	21	2,192	9.6	0.66 (0.41 - 1.04)
Comparator	16,438	381	28,215	13.5		16,438	121	8,176	14.8	
Stratified by age										
<65 - Aliskiren	3,170	65	5,599	11.6	1.17 (0.88 - 1.54)	3,170	13	1,619	8.0	0.81 (0.44 - 1.47)
<65 - Comparator	12,642	216	21,620	10.0		12,642	61	6,246	9.8	
65+ - Aliskiren	979	35	1,785	19.6	0.79 (0.55 - 1.14)	979	8	573	14.0	0.47 (0.23 - 0.99)
65+ - Comparator	3,796	165	6,595	25.0		3,796	60	1,930	31.1	
Stratified by gender										
Female - Aliskiren	1,711	46	3,083	14.9	1.01 (0.73 - 1.39)	1,711	9	846	10.6	0.71 (0.35 - 1.45)
Female - Comparator	6,862	178	11,839	15.0		6,862	47	3,103	15.2	
Male - Aliskiren	2,438	54	4,301	12.6	1.01 (0.75 - 1.37)	2,438	12	1,346	8.9	0.62 (0.33 - 1.13)
Male - Comparator	9,576	203	16,376	12.4		9,576	74	5,073	14.6	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	57	2,827	20.2	1.03 (0.77 - 1.39)	1,613	10	849	11.8	0.53 (0.27 - 1.02)
Diabetes - Comparator	6,319	207	10,553	19.6		6,319	72	3,201	22.5	
No diabetes - Aliskiren	2,536	43	4,558	9.4	0.97 (0.69 - 1.35)	2,536	11	1,343	8.2	0.86 (0.45 - 1.65)
No diabetes - Comparator	10,119	174	17,662	9.9		10,119	49	4,975	9.9	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	32	993	32.2	1.12 (0.75 - 1.66)	633	7	287	24.4	0.73 (0.33 - 1.65)
Renal impairment - Comparator	2,462	110	3,910	28.1		2,462	36	1,166	30.9	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No renal impairment - Aliskiren	3,516	68	6,392	10.6	0.95 (0.73 - 1.24)	3,516	14	1,905	7.4	0.61 (0.34 - 1.07)
No renal impairment - Comparator	13,976	271	24,305	11.2		13,976	85	7,009	12.1	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	2	51	39.3	5.90 (0.51 - 67.71)	30	1	14	70.4	–
Diabetes and renal impairment - Comparator	113	2	203	9.9		113	0	54	0.0	
No diabetes and renal impairment - Aliskiren	4,119	98	7,334	13.4	0.99 (0.79 - 1.24)	4,119	20	2,178	9.2	0.62 (0.39 - 1.00)
No diabetes and renal impairment - Comparator	16,325	379	28,012	13.5		16,325	121	8,122	14.9	
Stratified by CVD										
CVD - Aliskiren	1,534	58	2,727	21.3	1.02 (0.76 - 1.36)	1,534	11	808	13.6	0.56 (0.30 - 1.06)
CVD - Comparator	5,980	216	10,275	21.0		5,980	72	2,897	24.9	
No CVD - Aliskiren	2,615	42	4,658	9.0	0.98 (0.70 - 1.38)	2,615	10	1,384	7.2	0.77 (0.39 - 1.53)
No CVD - Comparator	10,458	165	17,940	9.2		10,458	49	5,279	9.3	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	100	7,384	13.5	1.16 (0.88 - 1.52)	4,149	21	2,192	9.6	0.71 (0.42 - 1.21)
Comparator (ACEI/ARB)	5,694	112	9,593	11.7		5,694	41	3,121	13.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	50	3,029	16.5	1.00 (0.73 - 1.37)	1,791	6	810	7.4	0.42 (0.18 - 0.98)
ACEI/ARB+CCB+Index drug - Comparator	6,490	182	11,111	16.4		6,490	47	2,625	17.9	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	50	4,356	11.5	1.01 (0.74 - 1.37)	2,358	12	1,245	9.6	0.74 (0.40 - 1.37)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	199	17,104	11.6		9,948	66	4,887	13.5	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	19	1,328	14.3	1.13 (0.68 - 1.87)	824	6	341	17.6	1.18 (0.48 - 2.92)
Quintile 1 - Comparator	3,293	66	5,184	12.7		3,293	21	1,513	13.9	
Quintile 2 - Aliskiren	823	22	1,454	15.1	1.62 (0.98 - 2.66)	823	4	424	9.4	0.95 (0.32 - 2.84)
Quintile 2 - Comparator	3,295	52	5,548	9.4		3,295	16	1,582	10.1	
Quintile 3 - Aliskiren	823	21	1,490	14.1	1.17 (0.72 - 1.91)	823	1	442	2.3	0.22 (0.03 - 1.65)
Quintile 3 - Comparator	3,294	69	5,665	12.2		3,294	17	1,631	10.4	
Quintile 4 - Aliskiren	824	13	1,524	8.5	0.64 (0.36 - 1.15)	824	2	523	3.8	0.22 (0.05 - 0.92)
Quintile 4 - Comparator	3,294	79	5,854	13.5		3,294	33	1,731	19.1	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 5 - Aliskiren	855	25	1,588	15.8	0.82 (0.53 - 1.27)	855	8	462	17.3	0.89 (0.41 - 1.93)
Quintile 5 - Comparator	3,262	115	5,964	19.3		3,262	34	1,719	19.8	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-53 Hazard ratios of stroke in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	430	35,208	12.2	0.89 (0.80 - 0.99)	19,092	112	10,643	10.5	0.85 (0.69 - 1.04)
Comparator	75,912	1,865	136,860	13.6		75,912	477	37,583	12.7	
Stratified by age										
<65 - Aliskiren	11,849	160	20,564	7.8	0.89 (0.75 - 1.05)	11,849	42	6,377	6.6	0.75 (0.54 - 1.05)
<65 - Comparator	46,878	702	80,276	8.7		46,878	205	22,815	9.0	
65+ - Aliskiren	7,243	270	14,644	18.4	0.90 (0.78 - 1.02)	7,243	70	4,267	16.4	0.91 (0.70 - 1.18)
65+ - Comparator	29,034	1,163	56,584	20.6		29,034	272	14,768	18.4	
Stratified by gender										
Female - Aliskiren	9,242	221	17,307	12.8	0.84 (0.72 - 0.97)	9,242	48	4,918	9.8	0.70 (0.51 - 0.95)
Female - Comparator	36,717	1019	66,994	15.2		36,717	243	17,006	14.3	
Male - Aliskiren	9,850	209	17,901	11.7	0.96 (0.83 - 1.12)	9,850	64	5,725	11.2	1.00 (0.76 - 1.31)
Male - Comparator	39,195	846	69,866	12.1		39,195	234	20,577	11.4	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	188	10,940	17.2	0.92 (0.79 - 1.08)	6,232	52	3,433	15.2	0.89 (0.66 - 1.20)
Diabetes - Comparator	24,459	785	42,056	18.7		24,459	210	12,030	17.5	
No diabetes - Aliskiren	12,860	242	24,267	10.0	0.87 (0.75 - 1.00)	12,860	60	7,210	8.3	0.81 (0.61 - 1.08)
No diabetes - Comparator	51,453	1080	94,804	11.4		51,453	267	25,553	10.5	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	76	4,074	18.7	0.75 (0.59 - 0.97)	2,354	24	1,208	19.9	0.97 (0.62 - 1.52)
Renal impairment - Comparator	9,313	383	15,419	24.8		9,313	91	4,288	21.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No renal impairment - Aliskiren	16,738	354	31,134	11.4	0.92 (0.82 - 1.04)	16,738	88	9,435	9.3	0.82 (0.65 - 1.03)
No renal impairment - Comparator	66,599	1,482	121,440	12.2		66,599	386	33,295	11.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	45	1,986	22.7	0.77 (0.56 - 1.05)	1,207	15	614	24.4	1.10 (0.62 - 1.97)
Diabetes and renal impairment - Comparator	4,723	223	7,572	29.5		4,723	49	2,086	23.5	
No diabetes and renal impairment - Aliskiren	17,885	385	33,222	11.6	0.91 (0.81 - 1.01)	17,885	97	10,029	9.7	0.81 (0.65 - 1.02)
No diabetes and renal impairment - Comparator	71,189	1642	129,288	12.7		71,189	428	35,498	12.1	
Stratified by CVD										
CVD - Aliskiren	6,585	225	12,291	18.3	0.88 (0.76 - 1.01)	6,585	65	3,587	18.1	0.91 (0.69 - 1.20)
CVD - Comparator	26,218	990	47,116	21.0		26,218	253	12,229	20.7	
No CVD - Aliskiren	12,507	205	22,917	9.0	0.91 (0.78 - 1.06)	12,507	47	7,056	6.7	0.76 (0.56 - 1.05)
No CVD - Comparator	49,694	875	89,744	9.8		49,694	224	25,354	8.8	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	430	35,208	12.2	0.99 (0.87 - 1.12)	19,092	112	10,643	10.5	0.95 (0.74 - 1.21)
Comparator (ACEI/ARB)	25,378	552	45,000	12.3		25,378	152	13,699	11.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	234	16,602	14.1	0.94 (0.82 - 1.09)	9,303	54	4,544	11.9	0.84 (0.62 - 1.14)
ACEI/ARB+CCB+Index drug - Comparator	32,502	884	59,381	14.9		32,502	187	12,964	14.4	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	196	18,606	10.5	0.83 (0.72 - 0.97)	9,789	53	5,264	10.1	0.86 (0.64 - 1.15)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	981	77,478	12.7		43410	257	21,264	12.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	88	6,426	13.7	1.01 (0.80 - 1.27)	3,800	23	1,835	12.5	1.07 (0.67 - 1.70)
Quintile 1 - Comparator	15,200	342	25,067	13.6		15,200	84	7,171	11.7	
Quintile 2 - Aliskiren	3,800	90	6,694	13.4	1.04 (0.83 - 1.31)	3800	26	1,996	13.0	1.04 (0.67 - 1.60)
Quintile 2 - Comparator	15,201	342	26,472	12.9		15,201	95	7,475	12.7	
Quintile 3 - Aliskiren	3,800	88	6,945	12.7	1.04 (0.82 - 1.31)	3,800	22	2,172	10.1	0.89 (0.56 - 1.42)
Quintile 3 - Comparator	15,201	336	27,466	12.2		15,201	89	7,518	11.8	
Quintile 4 - Aliskiren	3,799	64	7,166	8.9	0.68 (0.52 - 0.89)	3,799	15	2,251	6.7	0.62 (0.36 - 1.07)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 4 - Comparator	15,202	367	27,892	13.2		15202	86	7,653	11.2	
Quintile 5 - Aliskiren	3,893	100	7,976	12.5	0.78 (0.63 - 0.97)	3,893	26	2,389	10.9	0.71 (0.46 - 1.08)
Quintile 5 - Comparator	15,108	478	29,963	16.0		15,108	123	7,766	15.8	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-54 Hazard ratios of ischemic stroke in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	94	7,389	12.7	1.03 (0.82 - 1.29)	4,149	20	2,192	9.1	0.71 (0.44 - 1.14)
Comparator	16,438	351	28,253	12.4		16,438	107	8,180	13.1	
Stratified by age										
<65 - Aliskiren	3,170	60	5,604	10.7	1.16 (0.87 - 1.55)	3,170	12	1,619	7.4	0.79 (0.43 - 1.48)
<65 - Comparator	12,642	200	21,636	9.2		12,642	57	6,248	9.1	
65+ - Aliskiren	979	34	1,786	19.0	0.85 (0.59 - 1.23)	979	8	573	14.0	0.56 (0.27 - 1.19)
65+ - Comparator	3,796	151	6,617	22.8		3,796	50	1,932	25.9	
Stratified by gender										
Female - Aliskiren	1,711	43	3,085	13.9	1.01 (0.72 - 1.41)	1,711	8	846	9.5	0.73 (0.34 - 1.56)
Female - Comparator	6,862	166	11,856	14.0		6,862	40	3,104	12.9	
Male - Aliskiren	2,438	51	4,304	11.9	1.05 (0.77 - 1.44)	2,438	12	1,346	8.9	0.68 (0.37 - 1.26)
Male - Comparator	9,576	185	16,397	11.3		9,576	67	5,075	13.2	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	55	2,830	19.4	1.07 (0.79 - 1.45)	1,613	10	849	11.8	0.59 (0.30 - 1.15)
Diabetes - Comparator	6,319	193	10,570	18.3		6,319	64	3,202	20.0	
No diabetes - Aliskiren	2,536	39	4,559	8.6	0.97 (0.68 - 1.37)	2,536	10	1,343	7.5	0.89 (0.45 - 1.76)
No diabetes - Comparator	10,119	158	17,683	8.9		10,119	43	4,978	8.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	31	993	31.2	1.16 (0.78 - 1.74)	633	6	287	20.9	0.67 (0.28 - 1.60)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Renal impairment - Comparator	2,462	103	3,918	26.3		2,462	34	1,168	29.1	
No renal impairment - Aliskiren	3,516	63	6,397	9.9	0.96 (0.73 - 1.27)	3,516	14	1,905	7.4	0.70 (0.40 - 1.24)
No renal impairment - Comparator	13,976	248	24,335	10.2		13,976	73	7,012	10.4	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment – Aliskiren	30	2	51	39.3	6.41 (0.55 - 74.55)	30	1	14	70.4	–
Diabetes and renal impairment - Comparator	113	1	205	4.9		113	0	54	0.0	
No diabetes and renal impairment – Aliskiren	4,119	92	7,339	12.5	1.01 (0.80 - 1.27)	4,119	19	2,178	8.7	0.66 (0.41 - 1.08)
No diabetes and renal impairment - Comparator	16,325	350	28,048	12.5		16,325	107	8,125	13.2	
Stratified by CVD										
CVD - Aliskiren	1,534	55	2,728	20.2	1.05 (0.78 - 1.41)	1,534	10	808	12.4	0.60 (0.31 - 1.16)
CVD - Comparator	5,980	200	10,298	19.4		5,980	62	2,899	21.4	
No CVD - Aliskiren	2,615	39	4,661	8.4	0.99 (0.70 - 1.41)	2,615	10	1,384	7.2	0.84 (0.42 - 1.67)
No CVD - Comparator	10,458	151	17,955	8.4		10,458	45	5,281	8.5	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	94	7,389	12.7	1.15 (0.87 - 1.52)	4,149	20	2,192	9.1	0.71 (0.42 - 1.22)
Comparator (ACEI/ARB)	5,694	106	9,605	11.0		5,694	39	3,122	12.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	46	3,031	15.2	1.00 (0.72 - 1.38)	1,791	6	810	7.4	0.47 (0.20 - 1.10)
ACEI/ARB+CCB+Index drug - Comparator	6,490	169	11,130	15.2		6,490	42	2,625	16.0	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	48	4,359	11.0	1.06 (0.77 - 1.45)	2,358	12	1,245	9.6	0.84 (0.45 - 1.56)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	182	17,123	10.6		9948	58	4,890	11.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	18	1,330	13.5	1.15 (0.68 - 1.95)	824	6	341	17.6	1.47 (0.58 - 3.73)
Quintile 1 - Comparator	3,293	61	5,194	11.8		3,293	17	1,515	11.2	
Quintile 2 - Aliskiren	823	21	1,455	14.4	1.78 (1.06 - 2.99)	823	4	424	9.4	1.25 (0.40 - 3.87)
Quintile 2 - Comparator	3,295	45	5,557	8.1		3,295	12	1,582	7.6	
Quintile 3 - Aliskiren	823	20	1,490	13.4	1.15 (0.70 - 1.90)	823	0	442	0.0	–
Quintile 3 - Comparator	3,294	67	5,669	11.8		3,294	16	1,631	9.8	
Quintile 4 - Aliskiren	824	11	1,526	7.2	0.59 (0.31 - 1.10)	824	2	523	3.8	0.24 (0.06 - 1.01)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 4 - Comparator	3,294	73	5,861	12.5		3294	30	1,731	17.3	
Quintile 5 - Aliskiren	855	24	1,588	15.1	0.87 (0.56 - 1.35)	855	8	462	17.3	0.95 (0.44 - 2.06)
Quintile 5 - Comparator	3,262	105	5,972	17.6		3,262	32	1,719	18.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-55 Hazard ratios of ischemic stroke in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	412	35,218	11.7	0.89 (0.80 - 0.99)	19,092	108	10,644	10.2	0.85 (0.69 - 1.04)
Comparator	75,912	1,797	136,900	13.1		75,912	460	37,586	12.2	
Stratified by age										
<65 - Aliskiren	11,849	155	20,568	7.5	0.90 (0.75 - 1.07)	11,849	42	6,377	6.6	0.78 (0.56 - 1.09)
<65 - Comparator	46,878	673	80,299	8.4		46,878	197	22,817	8.6	
65+ - Aliskiren	7,243	257	14,650	17.5	0.88 (0.77 - 1.01)	7,243	66	4,267	15.5	0.89 (0.68 - 1.16)
65+ - Comparator	29,034	1,124	56,600	19.9		29,034	263	14,770	17.8	
Stratified by gender										
Female - Aliskiren	9,242	215	17,311	12.4	0.84 (0.73 - 0.98)	9,242	48	4,918	9.8	0.72 (0.53 - 0.98)
Female - Comparator	36,717	985	67,014	14.7		36,717	236	17,008	13.9	
Male - Aliskiren	9,850	197	17,907	11.0	0.94 (0.81 - 1.10)	9,850	60	5,725	10.5	0.97 (0.73 - 1.30)
Male - Comparator	39,195	812	69,885	11.6		39,195	224	20,579	10.9	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	180	10,946	16.4	0.92 (0.78 - 1.08)	6,232	50	3,433	14.6	0.89 (0.65 - 1.21)
Diabetes - Comparator	24,459	756	42,073	18.0		24,459	202	12,031	16.8	
No diabetes - Aliskiren	12,860	232	24,272	9.6	0.86 (0.75 - 1.00)	12,860	58	7,211	8.0	0.81 (0.61 - 1.08)
No diabetes - Comparator	51,453	1041	94,826	11.0		51,453	258	25,555	10.1	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	72	4,077	17.7	0.75 (0.58 - 0.97)	2,354	23	1,208	19.0	0.96 (0.61 - 1.53)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Renal impairment - Comparator	9,313	365	15,428	23.7		9,313	88	4,288	20.5	
No renal impairment - Aliskiren	16,738	340	31,141	10.9	0.92 (0.82 - 1.04)	16,738	85	9,436	9.0	0.82 (0.65 - 1.04)
No renal impairment - Comparator	66,599	1,432	121,472	11.8		66,599	372	33,298	11.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	44	1,988	22.1	0.79 (0.57 - 1.10)	1,207	15	614	24.4	1.15 (0.64 - 2.05)
Diabetes and renal impairment - Comparator	4,723	211	7,580	27.8		4,723	47	2,086	22.5	
No diabetes and renal impairment - Aliskiren	17,885	368	33,230	11.1	0.90 (0.80 - 1.01)	17,885	93	10,030	9.3	0.81 (0.65 - 1.01)
No diabetes and renal impairment - Comparator	71,189	1586	129,320	12.3		71,189	413	35,501	11.6	
Stratified by CVD										
CVD - Aliskiren	6,585	215	12,297	17.5	0.86 (0.74 - 1.00)	6,585	62	3,588	17.3	0.90 (0.68 - 1.18)
CVD - Comparator	26,218	963	47,135	20.4		26,218	245	12,231	20.0	
No CVD - Aliskiren	12,507	197	22,921	8.6	0.92 (0.79 - 1.07)	12,507	46	7,056	6.5	0.78 (0.57 - 1.07)
No CVD - Comparator	49,694	834	89,765	9.3		49,694	215	25,356	8.5	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	412	35,218	11.7	0.98 (0.86 - 1.11)	19,092	108	10,644	10.2	0.95 (0.74 - 1.21)
Comparator (ACEI/ARB)	25,378	535	45,010	11.9		25,378	147	13,699	10.7	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	227	16,605	13.7	0.95 (0.82 - 1.10)	9,303	52	4,545	11.4	0.84 (0.62 - 1.15)
ACEI/ARB+CCB+Index drug - Comparator	32,502	852	59,397	14.3		32,502	180	12,967	13.9	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	185	18,613	9.9	0.82 (0.70 - 0.96)	9,789	51	5,264	9.7	0.86 (0.63 - 1.16)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	945	77,503	12.2		43410	247	21,265	11.6	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	83	6,431	12.9	0.99 (0.77 - 1.25)	3,800	22	1,835	12.0	1.09 (0.68 - 1.74)
Quintile 1 - Comparator	15,200	329	25,077	13.1		15,200	79	7,172	11.0	
Quintile 2 - Aliskiren	3,800	89	6,695	13.3	1.05 (0.83 - 1.32)	3800	25	1,996	12.5	1.00 (0.64 - 1.55)
Quintile 2 - Comparator	15,201	336	26,476	12.7		15,201	95	7,475	12.7	
Quintile 3 - Aliskiren	3,800	83	6,949	11.9	1.02 (0.80 - 1.30)	3,800	21	2,173	9.7	0.89 (0.55 - 1.44)
Quintile 3 - Comparator	15,201	321	27,471	11.7		15,201	85	7,518	11.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 4 - Aliskiren	3,799	61	7,167	8.5	0.68 (0.52 - 0.89)	3,799	14	2,251	6.2	0.60 (0.34 - 1.05)
Quintile 4 - Comparator	15,202	351	27,905	12.6		15202	83	7,655	10.8	
Quintile 5 - Aliskiren	3,893	96	7,977	12.0	0.78 (0.62 - 0.97)	3,893	26	2,389	10.9	0.73 (0.48 - 1.13)
Quintile 5 - Comparator	19,092	412	35,218	11.7	0.89 (0.80 - 0.99)	19,092	108	10,644	10.2	0.85 (0.69 - 1.04)

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-56 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	16	7,468	2.1	1.03 (0.59 - 1.78)	4,149	2	2,199	0.9	0.32 (0.08 - 1.34)
Comparator	16,438	60	28,603	2.1		16,438	24	8,207	2.9	
Stratified by age										
<65 - Aliskiren	3,170	14	5,649	2.5	1.57 (0.85 - 2.92)	3,170	2	1,622	1.2	1.10 (0.23 - 5.30)
<65 - Comparator	12,642	35	21,842	1.6		12,642	7	6,260	1.1	
65+ - Aliskiren	979	2	1,819	1.1	0.29 (0.07 - 1.21)	979	0	577	0.0	–
65+ - Comparator	3,796	25	6,761	3.7		3,796	17	1,947	8.7	
Stratified by gender										
Female - Aliskiren	1,711	9	3,118	2.9	1.31 (0.62 - 2.79)	1,711	2	848	2.4	0.63 (0.14 - 2.83)
Female - Comparator	6,862	27	12,017	2.3		6,862	12	3,113	3.9	
Male - Aliskiren	2,438	7	4,350	1.6	0.81 (0.36 - 1.83)	2,438	0	1,351	0.0	–
Male - Comparator	9,576	33	16,586	2.0		9,576	12	5,094	2.4	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	8	2,881	2.8	1.01 (0.47 - 2.21)	1,613	1	853	1.2	0.29 (0.04 - 2.25)
Diabetes - Comparator	6,319	30	10,764	2.8		6,319	13	3,218	4.0	
No diabetes - Aliskiren	2,536	8	4,587	1.7	1.04 (0.48 - 2.27)	2,536	1	1,346	0.7	0.35 (0.05 - 2.74)
No diabetes - Comparator	10,119	30	17,840	1.7		10,119	11	4,989	2.2	
Stratified by renal impairment										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Renal impairment - Aliskiren	633	5	1,023	4.9	1.30 (0.47 - 3.60)	633	1	290	3.5	0.82 (0.09 - 7.32)
Renal impairment - Comparator	2,462	15	4,013	3.7		2,462	4	1,175	3.4	
No renal impairment - Aliskiren	3,516	11	6,444	1.7	0.94 (0.49 - 1.81)	3,516	1	1,909	0.5	0.19 (0.03 - 1.38)
No renal impairment - Comparator	13,976	45	24,590	1.8		13,976	20	7,032	2.8	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	1	52	19.1	3.27 (0.20 - 53.69)	30	0	14	0.0	–
Diabetes and renal impairment - Comparator	113	2	203	9.9		113	0	54	0.0	
No diabetes and renal impairment - Aliskiren	4,119	15	7,415	2.0	1.00 (0.57 - 1.77)	4,119	2	2,185	0.9	0.32 (0.08 - 1.34)
No diabetes and renal impairment - Comparator	16,325	58	28,400	2.0		16,325	24	8,153	2.9	
Stratified by CVD										
CVD - Aliskiren	1,534	9	2,775	3.2	1.03 (0.49 - 2.16)	1,534	1	812	1.2	0.23 (0.03 - 1.72)
CVD - Comparator	5,980	33	10,499	3.1		5,980	16	2,915	5.5	
No CVD - Aliskiren	2,615	7	4,693	1.5	1.01 (0.44 - 2.33)	2,615	1	1,387	0.7	0.47 (0.06 - 3.77)
No CVD - Comparator	10,458	27	18,105	1.5		10,458	8	5,292	1.5	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	16	7,468	2.1	1.56 (0.75 - 3.25)	4,149	2	2,199	0.9	0.54 (0.10 - 2.77)
Comparator (ACEI/ARB)	5,694	13	9,700	1.3		5,694	5	3,131	1.6	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	11	3,074	3.6	1.50 (0.74 - 3.03)	1,791	0	811	0.0	–
ACEI/ARB+CCB+Index drug - Comparator	6,490	27	11,289	2.4		6,490	8	2,633	3.0	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	5	4,394	1.1	0.60 (0.24 - 1.55)	2,358	0	1,251	0.0	–
No ACEI/ARB+CCB+Index drug - Comparator	9,948	33	17,314	1.9		9948	15	4,907	3.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	1	1,342	0.8	0.36 (0.05 - 2.80)	824	0	345	0.0	–
Quintile 1 - Comparator	3,293	11	5,242	2.1		3,293	6	1,514	4.0	
Quintile 2 - Aliskiren	823	2	1,470	1.4	0.85 (0.18 - 3.91)	823	0	426	0.0	–
Quintile 2 - Comparator	3,295	9	5,594	1.6		3,295	5	1,587	3.2	
Quintile 3 - Aliskiren	823	5	1,505	3.3	2.73 (0.87 - 8.60)	823	1	442	2.3	1.83 (0.17 - 20.18)
Quintile 3 - Comparator	3,294	7	5,753	1.2		3,294	2	1,640	1.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 4 - Aliskiren	824	3	1,535	2.0	0.84 (0.24 - 2.93)	824	0	523	0.0	–
Quintile 4 - Comparator	3,294	14	5,943	2.4		3294	6	1,740	3.5	
Quintile 5 - Aliskiren	855	5	1,617	3.1	1.02 (0.38 - 2.73)	855	1	463	2.2	0.83 (0.10 - 7.15)
Quintile 5 - Comparator	3,262	19	6,071	3.1		3,262	5	1,726	2.9	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-57 Hazard ratios of hemorrhagic stroke in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	30	35,705	0.8	0.80 (0.54 - 1.19)	19,092	5	10,694	0.5	0.67 (0.26 - 1.73)
Comparator	75,912	145	139,038	1.0		75,912	28	37,729	0.7	
Stratified by age										
<65 - Aliskiren	11,849	12	20,741	0.6	0.65 (0.35 - 1.20)	11,849	1	6,390	0.2	0.35 (0.05 - 2.71)
<65 - Comparator	46,878	72	81,056	0.9		46,878	11	22,879	0.5	
65+ - Aliskiren	7,243	18	14,964	1.2	0.96 (0.57 - 1.60)	7,243	4	4,304	0.9	0.85 (0.29 - 2.52)
65+ - Comparator	29,034	73	57,982	1.3		29,034	17	14,849	1.1	
Stratified by gender										
Female - Aliskiren	9,242	10	17,567	0.6	0.50 (0.26 - 0.97)	9,242	0	4,940	0.0	–
Female - Comparator	36,717	77	68,197	1.1		36,717	13	17,075	0.8	
Male - Aliskiren	9,850	20	18,138	1.1	1.14 (0.69 - 1.88)	9,850	5	5,753	0.9	1.26 (0.46 - 3.46)
Male - Comparator	39,195	68	70,841	1.0		39,195	15	20,654	0.7	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	11	11,142	1.0	0.72 (0.38 - 1.37)	6,232	2	3,454	0.6	0.61 (0.14 - 2.70)
Diabetes - Comparator	24,459	59	42,959	1.4		24,459	12	12,090	1.0	
No diabetes - Aliskiren	12,860	19	24,563	0.8	0.84 (0.51 - 1.39)	12,860	3	7,240	0.4	0.71 (0.21 - 2.42)
No diabetes - Comparator	51,453	86	96,078	0.9		51,453	16	25,638	0.6	
Stratified by renal impairment										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Renal impairment - Aliskiren	2,354	4	4,140	1.0	0.45 (0.16 - 1.26)	2,354	1	1,217	0.8	0.74 (0.09 - 6.35)
Renal impairment - Comparator	9,313	34	15,836	2.2		9,313	5	4,307	1.2	
No renal impairment - Aliskiren	16,738	26	31,565	0.8	0.90 (0.59 - 1.39)	16,738	4	9,477	0.4	0.64 (0.22 - 1.86)
No renal impairment - Comparator	66,599	111	123,202	0.9		66,599	23	33,421	0.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	1	2,026	0.5	0.19 (0.03 - 1.39)	1,207	0	619	0.0	–
Diabetes and renal impairment - Comparator	4,723	20	7,813	2.6		4,723	2	2,096	1.0	
No diabetes and renal impairment - Aliskiren	17,885	29	33,679	0.9	0.90 (0.60 - 1.34)	17,885	5	10,075	0.5	0.72 (0.27 - 1.86)
No diabetes and renal impairment - Comparator	71,189	125	131,225	1.0		71,189	26	35,633	0.7	
Stratified by CVD										
CVD - Aliskiren	6,585	15	12,551	1.2	0.89 (0.51 - 1.57)	6,585	4	3,619	1.1	1.25 (0.40 - 3.86)
CVD - Comparator	26,218	65	48,287	1.4		26,218	12	12,301	1.0	
No CVD - Aliskiren	12,507	15	23,154	0.7	0.73 (0.42 - 1.27)	12,507	1	7,075	0.1	0.23 (0.03 - 1.75)
No CVD - Comparator	49,694	80	90,751	0.9		49,694	16	25,428	0.6	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	30	35,705	0.8	0.85 (0.53 - 1.34)	19,092	5	10,694	0.5	0.61 (0.21 - 1.75)
Comparator (ACEI/ARB)	25,378	45	45,638	1.0		25,378	11	13,750	0.8	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	13	16,849	0.8	0.78 (0.43 - 1.43)	9,303	3	4,569	0.7	0.95 (0.26 - 3.47)
ACEI/ARB+CCB+Index drug - Comparator	32,502	59	60,404	1.0		32,502	10	13,013	0.8	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	17	18,856	0.9	0.83 (0.50 - 1.40)	9,789	2	5,279	0.4	0.46 (0.11 - 1.99)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	86	78,634	1.1		43410	18	21,336	0.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	10	6,512	1.5	1.40 (0.68 - 2.87)	3,800	1	1,843	0.5	0.49 (0.06 - 3.95)
Quintile 1 - Comparator	15,200	28	25,448	1.1		15,200	8	7,196	1.1	
Quintile 2 - Aliskiren	3,800	2	6,793	0.3	0.38 (0.09 - 1.60)	3800	1	2,011	0.5	1.94 (0.18 - 21.38)
Quintile 2 - Comparator	15,201	21	26,881	0.8		15,201	2	7,510	0.3	
Quintile 3 - Aliskiren	3,800	6	7,055	0.9	0.82 (0.34 - 1.96)	3,800	2	2,179	0.9	1.14 (0.23 - 5.68)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Comparator	15,201	29	27,841	1.0		15,201	6	7,544	0.8	
Quintile 4 - Aliskiren	3,799	5	7,241	0.7	0.63 (0.25 - 1.63)	3,799	1	2,253	0.4	1.20 (0.12 - 11.56)
Quintile 4 - Comparator	15,202	31	28,319	1.1		15202	3	7,681	0.4	
Quintile 5 - Aliskiren	3,893	7	8,105	0.9	0.72 (0.32 - 1.63)	3,893	0	2,408	0.0	–
Quintile 5 - Comparator	15,108	36	30,549	1.2		15,108	9	7,798	1.2	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-58 Hazard ratios of transient ischemic attack in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	63	7,413	8.5	1.23 (0.92 - 1.63)	4,149	13	2,192	5.9	0.83 (0.46 - 1.51)
Comparator	16,438	197	28,429	6.9		16,438	59	8,193	7.2	
Stratified by age										
<65 - Aliskiren	3,170	45	5,615	8.0	1.68 (1.18 - 2.38)	3,170	9	1,620	5.6	1.12 (0.53 - 2.36)
<65 - Comparator	12,642	104	21,748	4.8		12,642	31	6,253	5.0	
65+ - Aliskiren	979	18	1,798	10.0	0.73 (0.44 - 1.21)	979	4	572	7.0	0.50 (0.18 - 1.43)
65+ - Comparator	3,796	93	6,680	13.9		3,796	28	1,941	14.4	
Stratified by gender										
Female - Aliskiren	1,711	33	3,089	10.7	1.21 (0.82 - 1.79)	1,711	6	843	7.1	0.92 (0.38 - 2.25)
Female - Comparator	6,862	106	11,918	8.9		6,862	24	3,107	7.7	
Male - Aliskiren	2,438	30	4,324	6.9	1.26 (0.84 - 1.91)	2,438	7	1,349	5.2	0.76 (0.34 - 1.72)
Male - Comparator	9,576	91	16,510	5.5		9,576	35	5,087	6.9	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	40	2,846	14.1	1.60 (1.10 - 2.31)	1,613	8	851	9.4	0.95 (0.44 - 2.05)
Diabetes - Comparator	6,319	95	10,678	8.9		6,319	32	3,209	10.0	
No diabetes - Aliskiren	2,536	23	4,567	5.0	0.88 (0.56 - 1.38)	2,536	5	1,341	3.7	0.69 (0.27 - 1.80)
No diabetes - Comparator	10,119	102	17,750	5.8		10,119	27	4,984	5.4	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by renal impairment										
Renal impairment - Aliskiren	633	17	1,002	17.0	1.47 (0.84 - 2.57)	633	5	289	17.3	0.95 (0.36 - 2.55)
Renal impairment - Comparator	2,462	46	3,980	11.6		2,462	20	1,170	17.1	
No renal impairment - Aliskiren	3,516	46	6,411	7.2	1.15 (0.83 - 1.60)	3,516	8	1,903	4.2	0.76 (0.35 - 1.62)
No renal impairment - Comparator	13,976	151	24,448	6.2		13,976	39	7,023	5.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	0	53	0.0	–	30	0	14	0.0	–
Diabetes and renal impairment - Comparator	113	0	205	0.0		113	0	54	0.0	
No diabetes and renal impairment - Aliskiren	4,119	63	7,360	8.6	1.23 (0.93 - 1.63)	4,119	13	2,178	6.0	0.83 (0.45 - 1.51)
No diabetes and renal impairment - Comparator	16,325	197	28,223	7.0		16,325	59	8,139	7.3	
Stratified by CVD										
CVD - Aliskiren	1,534	35	2,746	12.8	1.19 (0.81 - 1.73)	1,534	7	811	8.6	0.76 (0.34 - 1.71)
CVD - Comparator	5,980	113	10,395	10.9		5,980	34	2,907	11.7	
No CVD - Aliskiren	2,615	28	4,667	6.0	1.28 (0.84 - 1.97)	2,615	6	1,382	4.3	0.92 (0.38 - 2.25)
No CVD - Comparator	10,458	84	18,034	4.7		10,458	25	5,286	4.7	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	63	7,413	8.5	1.39 (0.97 - 1.98)	4,149	13	2,192	5.9	0.96 (0.47 - 1.94)
Comparator (ACEI/ARB)	5,694	58	9,651	6.0		5,694	19	3,128	6.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	27	3,046	8.9	1.15 (0.75 - 1.78)	1,791	7	809	8.7	1.19 (0.50 - 2.81)
ACEI/ARB+CCB+Index drug - Comparator	6,490	87	11,223	7.8		6,490	20	2,626	7.6	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	36	4,367	8.2	1.30 (0.89 - 1.89)	2,358	6	1,245	4.8	0.71 (0.30 - 1.69)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	110	17,206	6.4		9948	34	4,903	6.9	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	16	1,326	12.1	1.90 (1.05 - 3.46)	824	4	344	11.6	2.07 (0.62 - 6.89)
Quintile 1 - Comparator	3,293	33	5,227	6.3		3,293	8	1,515	5.3	
Quintile 2 - Aliskiren	823	8	1,467	5.5	1.45 (0.64 - 3.27)	823	1	426	2.4	0.45 (0.06 - 3.60)
Quintile 2 - Comparator	3,295	21	5,577	3.8		3,295	8	1,586	5.0	
Quintile 3 - Aliskiren	823	10	1,496	6.7	0.83 (0.42 - 1.64)	823	1	438	2.3	0.30 (0.04 - 2.31)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Comparator	3,294	46	5,705	8.1		3,294	12	1,633	7.4	
Quintile 4 - Aliskiren	824	11	1,533	7.2	0.96 (0.49 - 1.85)	824	2	523	3.8	0.43 (0.10 - 1.85)
Quintile 4 - Comparator	3,294	44	5,894	7.5		3294	17	1,735	9.8	
Quintile 5 - Aliskiren	855	18	1,591	11.3	1.30 (0.76 - 2.23)	855	5	462	10.8	1.37 (0.49 - 3.80)
Quintile 5 - Comparator	3,262	53	6,026	8.8		3,262	14	1,724	8.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-59 Hazard ratios of transient ischemic attack in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	100	35,590	2.8	0.92 (0.74 - 1.15)	19,092	24	10,681	2.3	0.97 (0.62 - 1.53)
Comparator	75,912	423	138,563	3.1		75,912	90	37,695	2.4	
Stratified by age										
<65 - Aliskiren	11,849	36	20,699	1.7	1.00 (0.70 - 1.45)	11,849	9	6,387	1.4	0.97 (0.47 - 2.03)
<65 - Comparator	46,878	141	80,946	1.7		46,878	34	22,866	1.5	
65+ - Aliskiren	7,243	64	14,891	4.3	0.88 (0.67 - 1.15)	7,243	15	4,294	3.5	0.97 (0.55 - 1.72)
65+ - Comparator	29,034	282	57,617	4.9		29,034	56	14,830	3.8	
Stratified by gender										
Female - Aliskiren	9,242	59	17,497	3.4	0.92 (0.70 - 1.23)	9,242	15	4,933	3.0	1.04 (0.59 - 1.85)
Female - Comparator	36,717	249	67,903	3.7		36,717	51	17,057	3.0	
Male - Aliskiren	9,850	41	18,093	2.3	0.92 (0.66 - 1.30)	9,850	9	5,748	1.6	0.86 (0.42 - 1.77)
Male - Comparator	39,195	174	70,659	2.5		39,195	39	20,639	1.9	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	31	11,106	2.8	0.71 (0.48 - 1.04)	6,232	7	3,446	2.0	0.67 (0.30 - 1.50)
Diabetes - Comparator	24,459	170	42,759	4.0		24,459	38	12,076	3.2	
No diabetes - Aliskiren	12,860	69	24,484	2.8	1.07 (0.82 - 1.40)	12,860	17	7,235	2.4	1.20 (0.69 - 2.07)
No diabetes - Comparator	51,453	253	95,804	2.6		51,453	52	25,620	2.0	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	16	4,125	3.9	1.01 (0.58 - 1.76)	2,354	1	1,217	0.8	0.33 (0.04 - 2.55)
Renal impairment - Comparator	9,313	59	15,780	3.7		9,313	11	4,303	2.6	
No renal impairment - Aliskiren	16,738	84	31,464	2.7	0.90 (0.71 - 1.14)	16,738	23	9,464	2.4	1.06 (0.67 - 1.69)
No renal impairment - Comparator	66,599	364	122,783	3.0		66,599	79	33,392	2.4	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	7	2,021	3.5	0.67 (0.30 - 1.50)	1,207	0	619	0.0	–
Diabetes and renal impairment - Comparator	4,723	39	7,776	5.0		4,723	5	2,094	2.4	
No diabetes and renal impairment - Aliskiren	17,885	93	33,569	2.8	0.95 (0.76 - 1.19)	17,885	24	10,062	2.4	1.03 (0.65 - 1.62)
No diabetes and renal impairment - Comparator	71,189	384	130,787	2.9		71,189	85	35,602	2.4	
Stratified by CVD										
CVD - Aliskiren	6,585	54	12,490	4.3	1.01 (0.75 - 1.36)	6,585	11	3,611	3.1	0.87 (0.45 - 1.68)
CVD - Comparator	26,218	207	48,040	4.3		26,218	45	12,288	3.7	
No CVD - Aliskiren	12,507	46	23,100	2.0	0.84 (0.61 - 1.15)	12,507	13	7,071	1.8	1.06 (0.57 - 1.97)
No CVD - Comparator	49,694	216	90,523	2.4		49,694	45	25,408	1.8	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	100	35,590	2.8	1.05 (0.80 - 1.36)	19,092	24	10,681	2.3	0.93 (0.55 - 1.56)
Comparator (ACEI/ARB)	25,378	122	45,513	2.7		25,378	34	13,731	2.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	58	16,786	3.5	1.05 (0.78 - 1.40)	9,303	11	4,562	2.4	0.91 (0.46 - 1.80)
ACEI/ARB+CCB+Index drug - Comparator	32,502	200	60,169	3.3		32,502	35	13,004	2.7	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	42	18,804	2.2	0.78 (0.56 - 1.09)	9,789	12	5,275	2.3	1.09 (0.57 - 2.05)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	223	78,394	2.8		43410	46	21,315	2.2	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	24	6,496	3.7	1.26 (0.80 - 2.00)	3,800	4	1,841	2.2	0.98 (0.33 - 2.92)
Quintile 1 - Comparator	15,200	74	25,377	2.9		15,200	16	7,189	2.2	
Quintile 2 - Aliskiren	3,800	19	6,774	2.8	0.84 (0.52 - 1.39)	3800	4	2,010	2.0	0.56 (0.20 - 1.60)
Quintile 2 - Comparator	15,201	89	26,779	3.3		15,201	27	7,498	3.6	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Aliskiren	3,800	12	7,041	1.7	0.59 (0.32 - 1.08)	3,800	5	2,177	2.3	1.17 (0.42 - 3.21)
Quintile 3 - Comparator	15,201	80	27,747	2.9		15,201	15	7,538	2.0	
Quintile 4 - Aliskiren	3,799	17	7,223	2.4	0.85 (0.50 - 1.44)	3,799	5	2,252	2.2	0.93 (0.35 - 2.49)
Quintile 4 - Comparator	15,202	78	28,250	2.8		15,202	19	7,675	2.5	
Quintile 5 - Aliskiren	3,893	28	8,056	3.5	1.05 (0.69 - 1.60)	3,893	6	2,401	2.5	1.64 (0.62 - 4.33)
Quintile 5 - Comparator	15,108	102	30,409	3.4		15,108	13	7,795	1.7	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-60 Hazard ratios of myocardial infarction in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	43	7,428	5.8	1.11 (0.79 - 1.56)	4,149	11	2,197	5.0	1.06 (0.54 - 2.08)
Comparator	16,438	147	28,509	5.2		16,438	37	8,204	4.5	
Stratified by age										
<65 - Aliskiren	3,170	24	5,635	4.3	1.04 (0.66 - 1.63)	3,170	4	1,621	2.5	0.76 (0.26 - 2.24)
<65 - Comparator	12,642	89	21,778	4.1		12,642	19	6,258	3.0	
65+ - Aliskiren	979	19	1,793	10.6	1.20 (0.71 - 2.01)	979	7	576	12.2	1.25 (0.52 - 3.03)
65+ - Comparator	3,796	58	6,731	8.6		3,796	18	1,946	9.3	
Stratified by gender										
Female - Aliskiren	1,711	18	3,107	5.8	0.97 (0.57 - 1.63)	1,711	4	848	4.7	0.61 (0.20 - 1.84)
Female - Comparator	6,862	69	11,965	5.8		6,862	20	3,108	6.4	
Male - Aliskiren	2,438	25	4,320	5.8	1.23 (0.79 - 1.93)	2,438	7	1,349	5.2	1.67 (0.69 - 4.06)
Male - Comparator	9,576	78	16,544	4.7		9,576	17	5,096	3.3	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	30	2,850	10.5	1.19 (0.79 - 1.81)	1,613	9	851	10.6	1.26 (0.58 - 2.72)
Diabetes - Comparator	6,319	93	10,701	8.7		6,319	25	3,216	7.8	
No diabetes - Aliskiren	2,536	13	4,578	2.8	0.93 (0.51 - 1.70)	2,536	2	1,346	1.5	0.62 (0.14 - 2.76)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Comparator	10,119	54	17,808	3.0		10,119	12	4,988	2.4	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	11	1,018	10.8	0.95 (0.49 - 1.84)	633	3	290	10.4	0.87 (0.24 - 3.15)
Renal impairment - Comparator	2,462	45	3,986	11.3		2,462	12	1,174	10.2	
No renal impairment - Aliskiren	3,516	32	6,409	5.0	1.19 (0.80 - 1.77)	3,516	8	1,907	4.2	1.17 (0.53 - 2.59)
No renal impairment - Comparator	13,976	102	24,524	4.2		13,976	25	7,029	3.6	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	0	53	0.0	–	30	0	14	0.0	–
Diabetes and renal impairment - Comparator	113	6	199	30.2		113	1	54	18.5	
No diabetes and renal impairment - Aliskiren	4,119	43	7,374	5.8	1.16 (0.82 - 1.63)	4,119	11	2,183	5.0	1.08 (0.55 - 2.13)
No diabetes and renal impairment - Comparator	16,325	141	28,310	5.0		16,325	36	8,150	4.4	
Stratified by CVD										
CVD - Aliskiren	1,534	24	2,750	8.7	0.97 (0.62 - 1.52)	1,534	6	810	7.4	0.84 (0.34 - 2.08)
CVD - Comparator	5,980	92	10,446	8.8		5,980	24	2,912	8.2	
No CVD - Aliskiren	2,615	19	4,678	4.1	1.34 (0.80 - 2.26)	2,615	5	1,387	3.6	1.64 (0.58 - 4.66)
No CVD - Comparator	10,458	55	18,063	3.0		10,458	13	5,291	2.5	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	43	7,428	5.8	1.37 (0.89 - 2.10)	4,149	11	2,197	5.0	1.49 (0.63 - 3.53)
Comparator (ACEI/ARB)	5,694	41	9,679	4.2		5,694	10	3,131	3.2	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	21	3,055	6.9	1.07 (0.66 - 1.74)	1,791	6	810	7.4	1.24 (0.47 - 3.26)
ACEI/ARB+CCB+Index drug - Comparator	6,490	72	11,249	6.4		6,490	14	2,631	5.3	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	22	4,372	5.0	1.17 (0.73 - 1.88)	2,358	4	1,250	3.2	0.77 (0.26 - 2.26)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	75	17,260	4.4		9,948	20	4,907	4.1	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	7	1,336	5.2	1.71 (0.70 - 4.16)	824	1	344	2.9	0.69 (0.08 - 5.71)
Quintile 1 - Comparator	3,293	16	5,240	3.1		3,293	6	1,514	4.0	
Quintile 2 - Aliskiren	823	10	1,462	6.8	1.72 (0.82 - 3.64)	823	0	426	0.0	–
Quintile 2 - Comparator	3,295	22	5,584	3.9		3,295	4	1,588	2.5	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 3 - Aliskiren	823	9	1,501	6.0	1.39 (0.65 - 3.00)	823	2	441	4.5	1.88 (0.34 - 10.27)
Quintile 3 - Comparator	3,294	24	5,733	4.2		3,294	4	1,639	2.4	
Quintile 4 - Aliskiren	824	7	1,526	4.6	0.79 (0.35 - 1.79)	824	3	523	5.7	1.45 (0.37 - 5.64)
Quintile 4 - Comparator	3,294	34	5,926	5.7		3294	7	1,739	4.0	
Quintile 5 - Aliskiren	855	10	1,602	6.2	0.72 (0.37 - 1.43)	855	5	463	10.8	1.05 (0.38 - 2.89)
Quintile 5 - Comparator	3,262	51	6,026	8.5		3,262	16	1,724	9.3	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-61 Hazard ratios of myocardial infarction in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	194	35,491	5.5	0.81 (0.69 - 0.94)	19,092	51	10,680	4.8	0.88 (0.64 - 1.19)
Comparator	75,912	930	138,007	6.7		75,912	208	37,681	5.5	
Stratified by age										
<65 - Aliskiren	11,849	67	20,664	3.2	0.67 (0.52 - 0.87)	11,849	20	6,385	3.1	0.90 (0.55 - 1.46)
<65 - Comparator	46,878	388	80,664	4.8		46,878	82	22,863	3.6	
65+ - Aliskiren	7,243	127	14,827	8.6	0.90 (0.74 - 1.09)	7,243	31	4,295	7.2	0.83 (0.56 - 1.24)
65+ - Comparator	29,034	542	57,343	9.5		29,034	126	14,818	8.5	
Stratified by gender										
Female - Aliskiren	9,242	94	17,454	5.4	0.89 (0.71 - 1.11)	9,242	22	4,937	4.5	0.83 (0.52 - 1.33)
Female - Comparator	36,717	406	67,734	6.0		36,717	88	17,049	5.2	
Male - Aliskiren	9,850	100	18,037	5.5	0.74 (0.60 - 0.92)	9,850	29	5,743	5.1	0.89 (0.59 - 1.34)
Male - Comparator	39,195	524	70,273	7.5		39,195	120	20,632	5.8	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	81	11,058	7.3	0.70 (0.55 - 0.89)	6,232	20	3,450	5.8	0.72 (0.45 - 1.17)
Diabetes - Comparator	24,459	444	42,474	10.5		24,459	98	12,066	8.1	
No diabetes - Aliskiren	12,860	113	24,434	4.6	0.91 (0.74 - 1.11)	12,860	31	7,231	4.3	1.00 (0.67 - 1.49)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Comparator	51,453	486	95,533	5.1		51,453	110	25,615	4.3	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	44	4,103	10.7	0.70 (0.50 - 0.96)	2,354	7	1,216	5.8	0.49 (0.22 - 1.09)
Renal impairment - Comparator	9,313	241	15,593	15.5		9,313	50	4,297	11.6	
No renal impairment - Aliskiren	16,738	150	31,388	4.8	0.84 (0.71 - 1.01)	16,738	44	9,464	4.7	0.99 (0.71 - 1.39)
No renal impairment - Comparator	66,599	689	122,413	5.6		66,599	158	33,384	4.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	28	1,999	14.0	0.69 (0.46 - 1.03)	1,207	5	618	8.1	0.60 (0.23 - 1.55)
Diabetes and renal impairment - Comparator	4,723	155	7,674	20.2		4,723	29	2,089	13.9	
No diabetes and renal impairment - Aliskiren	17,885	166	33,492	5.0	0.83 (0.70 - 0.98)	17,885	46	10,062	4.6	0.91 (0.66 - 1.26)
No diabetes and renal impairment - Comparator	71,189	775	130,332	6.0		71,189	179	35,591	5.0	
Stratified by CVD										
CVD - Aliskiren	6,585	97	12,442	7.8	0.74 (0.59 - 0.92)	6,585	22	3,613	6.1	0.63 (0.40 - 0.99)
CVD - Comparator	26,218	504	47,733	10.6		26,218	119	12,269	9.7	
No CVD - Aliskiren	12,507	97	23,050	4.2	0.89 (0.71 - 1.11)	12,507	29	7,067	4.1	1.19 (0.78 - 1.81)
No CVD - Comparator	49,694	426	90,274	4.7		49,694	89	25,412	3.5	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	194	35,491	5.5	0.83 (0.69 - 1.00)	19,092	51	10,680	4.8	0.88 (0.61 - 1.26)
Comparator (ACEI/ARB)	25,378	289	45,335	6.4		25,378	72	13,730	5.2	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	103	16,758	6.2	0.87 (0.70 - 1.08)	9,303	18	4,567	3.9	0.70 (0.42 - 1.16)
ACEI/ARB+CCB+Index drug - Comparator	32,502	424	59,916	7.1		32,502	78	12,997	6.0	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	91	18,734	4.9	0.75 (0.60 - 0.93)	9,789	26	5,269	4.9	0.98 (0.64 - 1.50)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	506	78,091	6.5		43410	107	21,313	5.0	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	35	6,489	5.4	0.85 (0.59 - 1.23)	3,800	7	1,838	3.8	0.61 (0.28 - 1.36)
Quintile 1 - Comparator	15,200	160	25,279	6.3		15,200	45	7,184	6.3	
Quintile 2 - Aliskiren	3,800	25	6,752	3.7	0.59 (0.39 - 0.89)	3800	7	2,009	3.5	0.75 (0.33 - 1.69)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	15,201	169	26,708	6.3		15,201	35	7,500	4.7	
Quintile 3 - Aliskiren	3,800	36	7,016	5.1	0.83 (0.58 - 1.19)	3,800	11	2,177	5.1	1.11 (0.56 - 2.18)
Quintile 3 - Comparator	15,201	171	27,638	6.2		15,201	35	7,537	4.6	
Quintile 4 - Aliskiren	3,799	38	7,200	5.3	0.76 (0.53 - 1.07)	3,799	8	2,252	3.6	0.81 (0.38 - 1.76)
Quintile 4 - Comparator	15,202	196	28,125	7.0		15202	35	7,672	4.6	
Quintile 5 - Aliskiren	3,893	60	8,034	7.5	0.96 (0.73 - 1.28)	3,893	18	2,405	7.5	1.02 (0.60 - 1.74)
Quintile 5 - Comparator	15,108	234	30,257	7.7		15,108	58	7,787	7.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-62 Hazard ratios of heart failure in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	162	7,288	22.2	0.88 (0.74 - 1.05)	4,149	51	2,183	23.4	0.77 (0.57 - 1.05)
Comparator	16,438	698	27,831	25.1		16,438	250	8,154	30.7	
Stratified by age										
<65 - Aliskiren	3,170	81	5,554	14.6	0.81 (0.64 - 1.03)	3,170	23	1,617	14.2	0.70 (0.45 - 1.08)
<65 - Comparator	12,642	382	21,399	17.9		12,642	128	6,231	20.5	
65+ - Aliskiren	979	81	1,734	46.7	0.95 (0.75 - 1.22)	979	28	566	49.5	0.82 (0.54 - 1.23)
65+ - Comparator	3,796	316	6,431	49.1		3,796	122	1,924	63.4	
Stratified by gender										
Female - Aliskiren	1,711	73	3,031	24.1	0.95 (0.73 - 1.23)	1,711	28	842	33.3	0.98 (0.64 - 1.49)
Female - Comparator	6,862	295	11,701	25.2		6,862	106	3,091	34.3	
Male - Aliskiren	2,438	89	4,257	20.9	0.83 (0.66 - 1.04)	2,438	23	1,341	17.2	0.61 (0.39 - 0.94)
Male - Comparator	9,576	403	16,130	25.0		9,576	144	5,063	28.4	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	107	2,763	38.7	0.91 (0.73 - 1.12)	1,613	35	847	41.4	0.84 (0.58 - 1.21)
Diabetes - Comparator	6,319	441	10,239	43.1		6,319	159	3,181	50.0	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	2,536	55	4,525	12.2	0.82 (0.62 - 1.10)	2,536	16	1,337	12.0	0.67 (0.39 - 1.14)
No diabetes - Comparator	10,119	257	17,591	14.6		10,119	91	4,974	18.3	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	69	949	72.7	1.04 (0.80 - 1.36)	633	23	283	81.1	0.80 (0.51 - 1.25)
Renal impairment - Comparator	2,462	262	3,717	70.5		2,462	115	1,148	100.2	
No renal impairment - Aliskiren	3,516	93	6,339	14.7	0.80 (0.64 - 1.00)	3,516	28	1,900	14.7	0.77 (0.51 - 1.16)
No renal impairment - Comparator	13,976	436	24,113	18.1		13,976	135	7,006	19.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	3	50	60.4	0.92 (0.26 - 3.28)	30	0	14	0.0	–
Diabetes and renal impairment - Comparator	113	15	189	79.3		113	6	52	114.6	
No diabetes and renal impairment - Aliskiren	4,119	159	7,238	22.0	0.88 (0.74 - 1.05)	4,119	51	2,169	23.5	0.79 (0.59 - 1.07)
No diabetes and renal impairment - Comparator	16,325	683	27,641	24.7		16,325	244	8,102	30.1	
Stratified by CVD										
CVD - Aliskiren	1,534	117	2,640	44.3	0.89 (0.73 - 1.09)	1,534	40	798	50.1	0.78 (0.55 - 1.10)
CVD - Comparator	5,980	494	9,940	49.7		5,980	190	2,873	66.1	
No CVD - Aliskiren	2,615	45	4,648	9.7	0.85 (0.61 - 1.17)	2,615	11	1,385	7.9	0.71 (0.37 - 1.35)
No CVD - Comparator	10,458	204	17,890	11.4		10,458	60	5,282	11.4	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	162	7,288	22.2	1.02 (0.83 - 1.26)	4,149	51	2,183	23.4	1.12 (0.77 - 1.62)
Comparator (ACEI/ARB)	5,694	201	9,501	21.2		5,694	63	3,115	20.2	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	87	2,979	29.2	0.98 (0.77 - 1.24)	1,791	29	805	36.0	0.94 (0.62 - 1.42)
ACEI/ARB+CCB+Index drug - Comparator	6,490	326	10,935	29.8		6,490	105	2,619	40.1	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	75	4,309	17.4	0.78 (0.61 - 1.00)	2,358	19	1,241	15.3	0.62 (0.38 - 1.00)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	372	16,896	22.0		9948	124	4,881	25.4	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	27	1,312	20.6	1.02 (0.67 - 1.56)	824	9	342	26.3	0.85 (0.42 - 1.75)
Quintile 1 - Comparator	3,293	104	5,133	20.3		3,293	43	1,507	28.5	
Quintile 2 - Aliskiren	823	31	1,436	21.6	1.22 (0.81 - 1.82)	823	5	425	11.8	0.58 (0.23 - 1.50)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Comparator	3,295	98	5,507	17.8		3,295	32	1,583	20.2	
Quintile 3 - Aliskiren	823	28	1,481	18.9	0.93 (0.61 - 1.40)	823	9	440	20.5	0.83 (0.40 - 1.70)
Quintile 3 - Comparator	3,294	116	5,633	20.6		3,294	41	1,630	25.2	
Quintile 4 - Aliskiren	824	30	1,495	20.1	0.82 (0.55 - 1.21)	824	11	516	21.3	0.80 (0.42 - 1.56)
Quintile 4 - Comparator	3,294	142	5,781	24.6		3294	48	1,730	27.7	
Quintile 5 - Aliskiren	855	46	1,564	29.4	0.71 (0.51 - 0.97)	855	17	459	37.0	0.74 (0.44 - 1.24)
Quintile 5 - Comparator	3,262	238	5,776	41.2		3,262	86	1,705	50.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-63 Hazard ratios of heart failure in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	399	35,270	11.3	0.83 (0.74 - 0.92)	19,092	103	10,663	9.7	0.70 (0.57 - 0.86)
Comparator	75,912	1,859	136,803	13.6		75,912	533	37,571	14.2	
Stratified by age										
<65 - Aliskiren	11,849	134	20,608	6.5	0.84 (0.70 - 1.01)	11,849	39	6,380	6.1	0.76 (0.54 - 1.08)
<65 - Comparator	46,878	616	80,359	7.7		46,878	180	22,828	7.9	
65+ - Aliskiren	7,243	265	14,662	18.1	0.82 (0.72 - 0.94)	7,243	64	4,283	14.9	0.65 (0.50 - 0.85)
65+ - Comparator	29,034	1,243	56,445	22.0		29,034	353	14,742	23.9	
Stratified by gender										
Female - Aliskiren	9,242	216	17,305	12.5	0.91 (0.78 - 1.05)	9,242	50	4,923	10.2	0.68 (0.50 - 0.92)
Female - Comparator	36,717	920	67,090	13.7		36,717	262	16,996	15.4	
Male - Aliskiren	9,850	183	17,964	10.2	0.75 (0.64 - 0.88)	9,850	53	5,740	9.2	0.71 (0.53 - 0.95)
Male - Comparator	39,195	939	69,713	13.5		39,195	271	20,574	13.2	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	215	10,895	19.7	0.89 (0.76 - 1.03)	6,232	63	3,434	18.3	0.81 (0.62 - 1.07)
Diabetes - Comparator	24,459	930	41,804	22.3		24,459	280	12,011	23.3	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No diabetes - Aliskiren	12,860	184	24,374	7.6	0.76 (0.65 - 0.90)	12,860	40	7,229	5.5	0.57 (0.40 - 0.79)
No diabetes - Comparator	51,453	929	95,000	9.8		51,453	253	25,560	9.9	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	126	4,002	31.5	0.79 (0.65 - 0.95)	2,354	35	1,206	29.0	0.66 (0.46 - 0.95)
Renal impairment - Comparator	9,313	607	15,149	40.1		9,313	193	4,256	45.4	
No renal impairment - Aliskiren	16,738	273	31,267	8.7	0.84 (0.74 - 0.96)	16,738	68	9,457	7.2	0.71 (0.55 - 0.92)
No renal impairment - Comparator	66,599	1,252	121,655	10.3		66,599	340	33,315	10.2	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	77	1,942	39.7	0.84 (0.66 - 1.08)	1,207	22	611	36.0	0.70 (0.44 - 1.10)
Diabetes and renal impairment - Comparator	4,723	350	7,394	47.3		4,723	112	2,070	54.1	
No diabetes and renal impairment - Aliskiren	17,885	322	33,328	9.7	0.82 (0.73 - 0.93)	17,885	81	10,052	8.1	0.69 (0.54 - 0.88)
No diabetes and renal impairment - Comparator	71,189	1509	129,410	11.7		71,189	421	35,501	11.9	
Stratified by CVD										
CVD - Aliskiren	6,585	266	12,244	21.7	0.81 (0.71 - 0.93)	6,585	75	3,598	20.9	0.70 (0.54 - 0.89)
CVD - Comparator	26,218	1,256	46,760	26.9		26,218	384	12,190	31.5	
No CVD - Aliskiren	12,507	133	23,026	5.8	0.85 (0.70 - 1.03)	12,507	28	7,065	4.0	0.66 (0.44 - 0.99)
No CVD - Comparator	49,694	603	90,043	6.7		49,694	149	25,380	5.9	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	399	35,270	11.3	0.93 (0.82 - 1.06)	19,092	103	10,663	9.7	0.88 (0.69 - 1.14)
Comparator (ACEI/ARB)	25,378	531	45,053	11.8		25,378	146	13,705	10.7	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	237	16,573	14.3	0.89 (0.77 - 1.03)	9,303	59	4,556	13.0	0.73 (0.55 - 0.98)
ACEI/ARB+CCB+Index drug - Comparator	32,502	943	59,221	15.9		32,502	242	12,947	18.7	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	162	18,696	8.7	0.73 (0.62 - 0.87)	9,789	36	5,265	6.8	0.61 (0.43 - 0.87)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	916	77,582	11.8		43410	244	21,264	11.5	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	67	6,449	10.4	0.87 (0.67 - 1.14)	3,800	23	1,835	12.5	0.94 (0.60 - 1.49)
Quintile 1 - Comparator	15,200	300	25,142	11.9		15,200	95	7,173	13.2	

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 2 - Aliskiren	3,800	85	6,693	12.7	1.11 (0.87 - 1.41)	3800	13	2,007	6.5	0.58 (0.33 - 1.04)
Quintile 2 - Comparator	15,201	304	26,545	11.5		15,201	85	7,491	11.4	
Quintile 3 - Aliskiren	3,800	64	6,977	9.2	0.77 (0.59 - 1.00)	3,800	18	2,176	8.3	0.69 (0.42 - 1.15)
Quintile 3 - Comparator	15,201	328	27,423	12.0		15,201	93	7,516	12.4	
Quintile 4 - Aliskiren	3,799	78	7,162	10.9	0.80 (0.62 - 1.01)	3,799	18	2,249	8.0	0.54 (0.33 - 0.89)
Quintile 4 - Comparator	15,202	382	27,858	13.7		15202	117	7,640	15.3	
Quintile 5 - Aliskiren	3,893	105	7,988	13.1	0.71 (0.58 - 0.88)	3,893	31	2,396	12.9	0.73 (0.49 - 1.08)
Quintile 5 - Comparator	15,108	545	29,836	18.3		15,108	143	7,751	18.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-64 Hazard ratios of acute renal failure in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	301	7,129	42.2	0.98 (0.86 - 1.11)	4,149	99	2,175	45.5	0.92 (0.74 - 1.15)
Comparator	16,438	1,168	27,285	42.8		16,438	406	8,118	50.0	
Stratified by age										
<65 - Aliskiren	3,170	178	5,454	32.6	0.93 (0.79 - 1.10)	3,170	49	1,614	30.4	0.78 (0.58 - 1.07)
<65 - Comparator	12,642	728	20,991	34.7		12,642	238	6,206	38.4	
65+ - Aliskiren	979	123	1,675	73.4	1.05 (0.86 - 1.28)	979	50	561	89.2	1.05 (0.76 - 1.43)
65+ - Comparator	3,796	440	6,293	69.9		3,796	168	1,913	87.8	
Stratified by gender										
Female - Aliskiren	1,711	125	2,993	41.8	1.04 (0.86 - 1.27)	1,711	43	841	51.1	1.04 (0.74 - 1.46)
Female - Comparator	6,862	466	11,483	40.6		6,862	154	3,082	50.0	
Male - Aliskiren	2,438	176	4,135	42.6	0.95 (0.80 - 1.12)	2,438	56	1,334	42.0	0.85 (0.63 - 1.13)
Male - Comparator	9,576	702	15,801	44.4		9,576	252	5,036	50.0	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	183	2,669	68.6	0.98 (0.84 - 1.16)	1,613	60	839	71.5	0.88 (0.67 - 1.17)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes - Comparator	6,319	694	9,921	70.0		6,319	258	3,160	81.7	
No diabetes - Aliskiren	2,536	118	4,460	26.5	0.97 (0.79 - 1.18)	2,536	39	1,335	29.2	1.00 (0.70 - 1.42)
No diabetes - Comparator	10,119	474	17,364	27.3		10,119	148	4,959	29.8	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	123	894	137.6	0.99 (0.81 - 1.21)	633	45	280	160.9	0.90 (0.65 - 1.25)
Renal impairment - Comparator	2,462	482	3,433	140.4		2,462	201	1,131	177.7	
No renal impairment - Aliskiren	3,516	178	6,235	28.6	0.98 (0.83 - 1.15)	3,516	54	1,895	28.5	0.96 (0.71 - 1.30)
No renal impairment - Comparator	13,976	686	23,851	28.8		13,976	205	6,987	29.3	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	2	49	41.0	0.44 (0.10 - 1.91)	30	2	14	141.5	1.04 (0.21 - 5.17)
Diabetes and renal impairment - Comparator	113	23	180	127.6		113	8	53	151.0	
No diabetes and renal impairment - Aliskiren	4,119	299	7,080	42.2	0.99 (0.87 - 1.13)	4,119	97	2,160	44.9	0.92 (0.74 - 1.15)
No diabetes and renal impairment - Comparator	16,325	1145	27,104	42.2		16,325	398	8,066	49.4	
Stratified by CVD										
CVD - Aliskiren	1,534	165	2,592	63.7	0.94 (0.79 - 1.12)	1,534	60	797	75.3	0.88 (0.67 - 1.17)
CVD - Comparator	5,980	660	9,730	67.8		5,980	250	2,867	87.2	
No CVD - Aliskiren	2,615	136	4,537	30.0	1.03 (0.85 - 1.24)	2,615	39	1,378	28.3	0.97 (0.68 - 1.38)
No CVD - Comparator	10,458	508	17,554	28.9		10,458	156	5,251	29.7	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	301	7,129	42.2	1.17 (1.00 - 1.37)	4,149	99	2,175	45.5	1.23 (0.94 - 1.61)
Comparator (ACEI/ARB)	5,694	325	9,347	34.8		5,694	112	3,104	36.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	140	2,920	48.0	0.95 (0.79 - 1.15)	1,791	40	804	49.7	0.80 (0.56 - 1.12)
ACEI/ARB+CCB+Index drug - Comparator	6,490	536	10,655	50.3		6,490	166	2,606	63.7	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	161	4,209	38.3	0.99 (0.83 - 1.18)	2,358	54	1,235	43.7	1.06 (0.78 - 1.43)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	632	16,629	38.0		9948	202	4,862	41.6	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	44	1,292	34.1	0.97 (0.70 - 1.35)	824	17	341	49.9	1.02 (0.60 - 1.74)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Quintile 1 - Comparator	3,293	179	5,071	35.3		3,293	69	1,499	46.0	
Quintile 2 - Aliskiren	823	52	1,410	36.9	1.18 (0.87 - 1.61)	823	16	420	38.1	1.01 (0.58 - 1.75)
Quintile 2 - Comparator	3,295	170	5,414	31.4		3,295	61	1,574	38.8	
Quintile 3 - Aliskiren	823	63	1,439	43.8	1.17 (0.88 - 1.55)	823	23	436	52.7	1.35 (0.84 - 2.18)
Quintile 3 - Comparator	3,294	208	5,512	37.7		3,294	64	1,622	39.5	
Quintile 4 - Aliskiren	824	55	1,474	37.3	0.83 (0.62 - 1.11)	824	15	521	28.8	0.57 (0.33 - 0.99)
Quintile 4 - Comparator	3,294	254	5,640	45.0		3294	91	1,722	52.8	
Quintile 5 - Aliskiren	855	87	1,514	57.5	0.90 (0.71 - 1.13)	855	28	457	61.3	0.86 (0.57 - 1.30)
Quintile 5 - Comparator	3,262	357	5,648	63.2		3,262	121	1,702	71.1	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-65 Hazard ratios of acute renal failure in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	1,288	34,164	37.7	0.95 (0.89 - 1.01)	19,092	364	10,602	34.3	0.81 (0.72 - 0.90)
Comparator	75,912	5,285	132,892	39.8		75,912	1,640	37,300	44.0	
Stratified by age										
<65 - Aliskiren	11,849	522	20,117	26.0	0.91 (0.83 - 1.00)	11,849	159	6,351	25.0	0.77 (0.65 - 0.91)
<65 - Comparator	46,878	2,228	78,458	28.4		46,878	761	22,679	33.6	
65+ - Aliskiren	7,243	766	14,047	54.5	0.97 (0.90 - 1.05)	7,243	205	4,251	48.2	0.83 (0.71 - 0.96)
65+ - Comparator	29,034	3,057	54,434	56.2		29,034	879	14,621	60.1	
Stratified by gender										
Female - Aliskiren	9,242	627	16,786	37.4	1.01 (0.92 - 1.10)	9,242	170	4,896	34.7	0.82 (0.69 - 0.97)
Female - Comparator	36,717	2,421	65,488	37.0		36,717	738	16,902	43.7	
Male - Aliskiren	9,850	661	17,378	38.0	0.89 (0.82 - 0.97)	9,850	194	5,706	34.0	0.79 (0.68 - 0.92)
Male - Comparator	39,195	2,864	67,404	42.5		39,195	902	20,397	44.2	
Stratified by diabetes										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Diabetes - Aliskiren	6,232	654	10,365	63.1	0.96 (0.89 - 1.05)	6,232	196	3,412	57.4	0.81 (0.70 - 0.95)
Diabetes - Comparator	24,459	2,610	39,882	65.4		24,459	872	11,862	73.5	
No diabetes - Aliskiren	12,860	634	23,799	26.6	0.92 (0.84 - 1.00)	12,860	168	7,190	23.4	0.79 (0.67 - 0.93)
No diabetes - Comparator	51,453	2,675	93,009	28.8		51,453	768	25,438	30.2	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	453	3,599	125.9	0.95 (0.86 - 1.05)	2,354	147	1,188	123.7	0.78 (0.65 - 0.93)
Renal impairment - Comparator	9,313	1,821	13,577	134.1		9,313	686	4,133	166.0	
No renal impairment - Aliskiren	16,738	835	30,565	27.3	0.94 (0.87 - 1.01)	16,738	217	9,414	23.1	0.82 (0.71 - 0.95)
No renal impairment - Comparator	66,599	3,464	119,315	29.0		66,599	954	33,166	28.8	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	271	1,724	157.2	0.95 (0.83 - 1.08)	1,207	88	605	145.4	0.74 (0.59 - 0.93)
Diabetes and renal impairment - Comparator	4,723	1,082	6,479	167.0		4,723	417	1,992	209.4	
No diabetes and renal impairment - Aliskiren	17,885	1,017	32,440	31.4	0.94 (0.88 - 1.01)	17,885	276	9,997	27.6	0.82 (0.72 - 0.93)
No diabetes and renal impairment - Comparator	71,189	4,203	126,413	33.3		71,189	1,223	35,308	34.6	
Stratified by CVD										
CVD - Aliskiren	6,585	706	11,702	60.3	0.97 (0.89 - 1.05)	6,585	212	3,564	59.5	0.84 (0.73 - 0.98)
CVD - Comparator	26,218	2,812	44,999	62.5		26,218	899	12,074	74.5	
No CVD - Aliskiren	12,507	582	22,461	25.9	0.92 (0.84 - 1.00)	12,507	152	7,038	21.6	0.74 (0.62 - 0.88)
No CVD - Comparator	49,694	2,473	87,893	28.1		49,694	741	25,225	29.4	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	1,288	34,164	37.7	1.07 (1.00 - 1.16)	19,092	364	10,602	34.3	1.06 (0.92 - 1.22)
Comparator (ACEI/ARB)	25,378	1,506	43,954	34.3		25,378	437	13,636	32.1	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	731	16,014	45.7	1.00 (0.92 - 1.08)	9,303	183	4,534	40.4	0.82 (0.70 - 0.97)
ACEI/ARB+CCB+Index drug - Comparator	32,502	2,624	57,248	45.8		32,502	674	12,880	52.3	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	557	18,150	30.7	0.87 (0.80 - 0.96)	9,789	155	5,239	29.6	0.78 (0.66 - 0.92)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	2,661	75,643	35.2		43410	819	21,138	38.8	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	215	6,302	34.1	0.98 (0.84 - 1.14)	3,800	60	1,831	32.8	0.82 (0.62 - 1.08)
Quintile 1 - Comparator	15,200	860	24,601	35.0		15,200	288	7,132	40.4	
Quintile 2 - Aliskiren	3,800	202	6,562	30.8	0.91 (0.78 - 1.06)	3800	60	1,998	30.0	0.82 (0.62 - 1.08)
Quintile 2 - Comparator	15,201	881	25,905	34.0		15,201	278	7,451	37.3	
Quintile 3 - Aliskiren	3,800	229	6,763	33.9	0.93 (0.80 - 1.07)	3,800	68	2,153	31.6	0.84 (0.64 - 1.09)
Quintile 3 - Comparator	15,201	978	26,758	36.6		15,201	293	7,459	39.3	
Quintile 4 - Aliskiren	3,799	249	6,927	36.0	0.90 (0.79 - 1.04)	3,799	69	2,238	30.8	0.74 (0.57 - 0.96)
Quintile 4 - Comparator	15,202	1,078	27,044	39.9		15202	332	7,600	43.7	
Quintile 5 - Aliskiren	3,893	393	7,609	51.7	0.99 (0.89 - 1.11)	3,893	107	2,382	44.9	0.81 (0.65 - 1.00)
Quintile 5 - Comparator	15,108	1,488	28,582	52.1		15,108	449	7,658	58.6	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-66 Hazard ratios of end-stage renal disease in subgroups of Cohort 3 – United

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	4,149	98	7,365	13.3	0.97 (0.77 - 1.21)	4,149	29	2,192	13.2	0.84 (0.56 - 1.26)
Comparator	16,438	389	28,205	13.8		16,438	131	8,183	16.0	
Stratified by age										
<65 - Aliskiren	3,170	69	5,575	12.4	0.89 (0.68 - 1.16)	3,170	20	1,617	12.4	0.76 (0.47 - 1.22)
<65 - Comparator	12,642	300	21,507	14.0		12,642	102	6,237	16.4	
65+ - Aliskiren	979	29	1,789	16.2	1.20 (0.79 - 1.83)	979	9	575	15.6	1.05 (0.50 - 2.23)
65+ - Comparator	3,796	89	6,699	13.3		3,796	29	1,946	14.9	
Stratified by gender										
Female - Aliskiren	1,711	45	3,070	14.7	1.26 (0.90 - 1.77)	1,711	16	845	18.9	1.28 (0.72 - 2.25)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Female - Comparator	6,862	139	11,885	11.7		6,862	47	3,105	15.1	
Male - Aliskiren	2,438	53	4,294	12.3	0.80 (0.60 - 1.08)	2,438	13	1,347	9.7	0.59 (0.33 - 1.06)
Male - Comparator	9,576	250	16,321	15.3		9,576	84	5,077	16.5	
Stratified by diabetes										
Diabetes - Aliskiren	1,613	65	2,819	23.1	0.93 (0.71 - 1.22)	1,613	17	852	20.0	0.84 (0.50 - 1.42)
Diabetes - Comparator	6,319	263	10,478	25.1		6,319	78	3,203	24.4	
No diabetes - Aliskiren	2,536	33	4,545	7.3	1.03 (0.70 - 1.51)	2,536	12	1,340	9.0	0.85 (0.45 - 1.59)
No diabetes - Comparator	10,119	126	17,728	7.1		10,119	53	4,980	10.6	
Stratified by renal impairment										
Renal impairment - Aliskiren	633	84	926	90.8	1.02 (0.80 - 1.30)	633	27	283	95.5	0.88 (0.58 - 1.34)
Renal impairment - Comparator	2,462	321	3,630	88.4		2,462	118	1,148	102.8	
No renal impairment - Aliskiren	3,516	14	6,439	2.2	0.77 (0.43 - 1.37)	3,516	2	1,909	1.1	0.58 (0.13 - 2.55)
No renal impairment - Comparator	13,976	68	24,575	2.8		13,976	13	7,035	1.9	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	30	4	44	90.6	1.08 (0.35 - 3.31)	30	2	12	160.5	1.21 (0.23 - 6.32)
Diabetes and renal impairment - Comparator	113	19	183	103.6		113	6	53	114.2	
No diabetes and renal impairment - Aliskiren	4,119	94	7,320	12.8	0.98 (0.78 - 1.22)	4,119	27	2,180	12.4	0.83 (0.55 - 1.25)
No diabetes and renal impairment - Comparator	16,325	370	28,022	13.2		16,325	125	8,130	15.4	
Stratified by CVD										
CVD - Aliskiren	1,534	55	2,713	20.3	0.92 (0.69 - 1.24)	1,534	20	806	24.8	0.92 (0.56 - 1.50)
CVD - Comparator	5,980	229	10,263	22.3		5,980	80	2,901	27.6	
No CVD - Aliskiren	2,615	43	4,652	9.2	1.02 (0.73 - 1.43)	2,615	9	1,386	6.5	0.67 (0.33 - 1.36)
No CVD - Comparator	10,458	160	17,943	8.9		10,458	51	5,282	9.7	
Aliskiren compared to ACEI/ARB										
Aliskiren	4,149	98	7,365	13.3	1.12 (0.85 - 1.47)	4,149	29	2,192	13.2	0.97 (0.60 - 1.55)
Comparator (ACEI/ARB)	5,694	111	9,588	11.6		5,694	42	3,122	13.5	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	1,791	49	3,028	16.2	0.98 (0.71 - 1.34)	1,791	14	808	17.3	1.05 (0.58 - 1.91)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
ACEI/ARB+CCB+Index drug - Comparator	6,490	183	11,090	16.5		6,490	45	2,630	17.1	
No ACEI/ARB+CCB+Index drug - Aliskiren	2,358	49	4,337	11.3	0.94 (0.69 - 1.29)	2,358	12	1,247	9.6	0.67 (0.36 - 1.23)
No ACEI/ARB+CCB+Index drug - Comparator	9,948	206	17,115	12.0		9,948	72	4,892	14.7	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	824	20	1,319	15.2	1.13 (0.69 - 1.86)	824	5	343	14.6	0.63 (0.25 - 1.62)
Quintile 1 - Comparator	3,293	70	5,186	13.5		3,293	32	1,511	21.2	
Quintile 2 - Aliskiren	823	15	1,455	10.3	0.92 (0.52 - 1.61)	823	7	425	16.5	0.99 (0.43 - 2.28)
Quintile 2 - Comparator	3,295	63	5,543	11.4		3,295	27	1,583	17.1	
Quintile 3 - Aliskiren	823	22	1,485	14.8	1.54 (0.94 - 2.53)	823	4	442	9.1	0.97 (0.32 - 2.90)
Quintile 3 - Comparator	3,294	55	5,694	9.7		3,294	16	1,637	9.8	
Quintile 4 - Aliskiren	824	15	1,516	9.9	0.74 (0.42 - 1.28)	824	5	523	9.6	0.70 (0.27 - 1.84)
Quintile 4 - Comparator	3,294	80	5,854	13.7		3,294	26	1,734	15.0	
Quintile 5 - Aliskiren	855	26	1,590	16.4	0.80 (0.52 - 1.22)	855	8	460	17.4	1.00 (0.46 - 2.18)
Quintile 5 - Comparator	3,262	121	5,930	20.4		3,262	30	1,718	17.5	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-67 Hazard ratios of end-stage renal disease in subgroups of Cohort 3 – MarketScan

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
All										
Aliskiren	19,092	350	35,332	9.9	0.82 (0.73 - 0.92)	19,092	85	10,671	8.0	0.67 (0.53 - 0.84)
Comparator	75,912	1,642	137,219	12.0		75,912	466	37,609	12.4	
Stratified by age										
<65 - Aliskiren	11,849	209	20,511	10.2	0.86 (0.74 - 0.99)	11,849	57	6,371	9.0	0.70 (0.53 - 0.93)
<65 - Comparator	46,878	949	79,988	11.9		46,878	301	22,803	13.2	
65+ - Aliskiren	7,243	141	14,822	9.5	0.78 (0.65 - 0.93)	7,243	28	4,300	6.5	0.60 (0.40 - 0.89)
65+ - Comparator	29,034	693	57,231	12.1		29,034	165	14,806	11.1	
Stratified by gender										

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Female - Aliskiren	9,242	156	17,382	9.0	0.90 (0.76 - 1.07)	9,242	37	4,928	7.5	0.66 (0.46 - 0.93)
Female - Comparator	36,717	668	67,473	9.9		36,717	201	17,020	11.8	
Male - Aliskiren	9,850	194	17,951	10.8	0.77 (0.66 - 0.90)	9,850	48	5,744	8.4	0.67 (0.50 - 0.92)
Male - Comparator	39,195	974	69,745	14.0		39,195	265	20,589	12.9	
Stratified by diabetes										
Diabetes - Aliskiren	6,232	214	10,921	19.6	0.84 (0.73 - 0.97)	6,232	54	3,440	15.7	0.73 (0.55 - 0.98)
Diabetes - Comparator	24,459	979	41,840	23.4		24,459	268	12,021	22.3	
No diabetes - Aliskiren	12,860	136	24,412	5.6	0.79 (0.66 - 0.95)	12,860	31	7,231	4.3	0.57 (0.39 - 0.83)
No diabetes - Comparator	51,453	663	95,378	7.0		51,453	198	25,588	7.7	
Stratified by renal impairment										
Renal impairment - Aliskiren	2,354	266	3,829	69.5	0.78 (0.69 - 0.90)	2,354	78	1,196	65.2	0.70 (0.55 - 0.89)
Renal impairment - Comparator	9,313	1,278	14,280	89.5		9,313	410	4,193	97.8	
No renal impairment - Aliskiren	16,738	84	31,503	2.7	0.88 (0.70 - 1.12)	16,738	7	9,475	0.7	0.46 (0.21 - 1.00)
No renal impairment - Comparator	66,599	364	122,939	3.0		66,599	56	33,415	1.7	
Stratified by diabetes and renal impairment										
Diabetes and renal impairment - Aliskiren	1,207	164	1,840	89.1	0.82 (0.69 - 0.97)	1,207	50	606	82.5	0.78 (0.57 - 1.05)
Diabetes and renal impairment - Comparator	4,723	758	6,889	110.0		4,723	229	2,033	112.7	
No diabetes and renal impairment - Aliskiren	17,885	186	33,493	5.6	0.81 (0.69 - 0.95)	17,885	35	10,065	3.5	0.54 (0.38 - 0.77)
No diabetes and renal impairment - Comparator	71,189	884	130,330	6.8		71,189	237	35,576	6.7	
Stratified by CVD										
CVD - Aliskiren	6,585	197	12,337	16.0	0.83 (0.71 - 0.97)	6,585	50	3,604	13.9	0.66 (0.49 - 0.90)
CVD - Comparator	26,218	909	47,301	19.2		26,218	273	12,231	22.3	
No CVD - Aliskiren	12,507	153	22,996	6.7	0.81 (0.68 - 0.96)	12,507	35	7,067	5.0	0.66 (0.46 - 0.94)
No CVD - Comparator	49,694	733	89,918	8.2		49,694	193	25,378	7.6	
Aliskiren compared to ACEI/ARB										
Aliskiren	19,092	350	35,332	9.9	0.92 (0.80 - 1.06)	19,092	85	10,671	8.0	0.89 (0.68 - 1.18)

Subgroup	ITT					As treated				
	N	Events	PYs	IR*	HR (95% CI)	N	Events	PYs	IR*	HR (95% CI)
Comparator (ACEI/ARB)	25,378	471	45,098	10.4		25,378	123	13,713	9.0	
ACEI/ARB+CCB+Index drug										
ACEI/ARB+CCB+Index drug - Aliskiren	9,303	210	16,612	12.6	0.96 (0.83 - 1.12)	9,303	49	4,558	10.8	0.87 (0.63 - 1.19)
ACEI/ARB+CCB+Index drug - Comparator	32,502	775	59,507	13.0		32,502	175	12,975	13.5	
No ACEI/ARB+CCB+Index drug - Aliskiren	9,789	140	18,721	7.5	0.67 (0.56 - 0.80)	9,789	29	5,272	5.5	0.50 (0.34 - 0.73)
No ACEI/ARB+CCB+Index drug - Comparator	43,410	867	77,711	11.2		43,410	242	21,276	11.4	
Stratified by PS quintiles										
Quintile 1 - Aliskiren	3,800	75	6,435	11.7	1.22 (0.94 - 1.58)	3,800	28	1,837	15.2	1.41 (0.92 - 2.18)
Quintile 1 - Comparator	15,200	242	25,232	9.6		15,200	77	7,177	10.7	
Quintile 2 - Aliskiren	3,800	57	6,728	8.5	0.82 (0.62 - 1.09)	3,800	16	2,008	8.0	0.67 (0.40 - 1.15)
Quintile 2 - Comparator	15,201	274	26,588	10.3		15,201	91	7,490	12.2	
Quintile 3 - Aliskiren	3,800	58	6,999	8.3	0.79 (0.60 - 1.05)	3,800	16	2,172	7.4	0.63 (0.37 - 1.07)
Quintile 3 - Comparator	15,201	289	27,529	10.5		15,201	93	7,521	12.4	
Quintile 4 - Aliskiren	3,799	53	7,178	7.4	0.68 (0.51 - 0.92)	3,799	5	2,253	2.2	0.24 (0.10 - 0.58)
Quintile 4 - Comparator	15,202	303	28,007	10.8		15,202	78	7,657	10.2	
Quintile 5 - Aliskiren	3,893	107	7,992	13.4	0.74 (0.60 - 0.91)	3,893	20	2,402	8.3	0.53 (0.33 - 0.85)
Quintile 5 - Comparator	15,108	534	29,863	17.9		15,108	127	7,764	16.4	

CVD = Cardiovascular Disease; HR = Hazard Ratio; *IR = incidence rate (per 1,000 person-years); ITT = intent-to-treat; N = Number of patients; PYs = Person-Years; RAAS = Renin-Angiotensin-Aldosterone System; PS = Propensity Score

Annex 2-Table 2-68 Hazard ratios of primary outcomes in Cohort 1 hdPS-matched patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 16,125)**			**Comparator (N = 64,193)**			
Cerebrovascular accidents	257	29,490	8.7	952	115,196	8.3	1.05 (0.91-1.20)
Stroke	282	29,455	9.6	1,070	115,034	9.3	1.02 (0.90-1.17)
Ischemic stroke	258	29,477	8.8	988	115,112	8.6	1.01 (0.88-1.16)
Hemorrhagic stroke	47	29,734	1.6	164	116,099	1.4	1.10 (0.79-1.52)
Transient ischemic attack	169	29,576	5.7	573	115,518	5.0	1.15 (0.97-1.37)
Myocardial infarction	102	29,640	3.4	418	115,783	3.6	0.95 (0.76-1.18)
Heart failure	383	29,325	13.1	1,646	114,235	14.4	0.90 (0.80-1.00)
Acute renal failure	705	28,963	24.3	2,783	112,993	24.6	0.98 (0.90-1.07)
End-stage renal disease	195	29,529	6.6	819	115,285	7.1	0.92 (0.79-1.08)
MarketScan	**Aliskiren (N = 67,184)**			**Comparator (N = 266,480)**			
Cerebrovascular accidents	687	128,953	5.3	2,578	505,022	5.1	1.04 (0.95-1.13)
Stroke	1,241	128,260	9.7	4,919	502,015	9.8	0.98 (0.92-1.05)
Ischemic stroke	1,170	128,312	9.1	4,749	502,162	9.5	0.96 (0.90-1.02)
Hemorrhagic stroke	121	129,674	0.9	349	507,794	0.7	1.35 (1.10-1.66)
Transient ischemic attack	284	129,376	2.2	1,081	506,564	2.1	1.02 (0.90-1.16)
Myocardial infarction	553	129,131	4.3	2,240	505,358	4.4	0.96 (0.88-1.06)
Heart failure	1,004	128,486	7.8	4,225	502,750	8.4	0.93 (0.86-0.99)
Acute renal failure	3,148	125,997	25.0	12,517	493,336	25.4	0.98 (0.94-1.02)
End-stage renal disease	743	128,933	5.8	2,953	504,662	5.9	0.98 (0.90-1.06)

CI = confidence interval; hdPS = high density propensity score; HR = hazard ratio; ITT = intent-to-treat; yrs = years

Annex 2-Table 2-69 Hazard ratios of primary outcomes in Cohort 2 hdPS-matched patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 5,731)**			**Comparator (N = 22,370)**			
Cerebrovascular accidents	105	9,719	10.8	420	37,035	11.3	0.94 (0.76-1.17)
Stroke	119	9,699	12.3	480	36,961	13.0	0.94 (0.77-1.15)
Ischemic stroke	110	9,704	11.3	437	36,998	11.8	0.95 (0.77-1.17)
Hemorrhagic stroke	18	9,819	1.8	75	37,448	2.0	0.92 (0.55-1.53)
Transient ischemic attack	66	9,750	6.8	245	37,216	6.6	1.02 (0.78-1.34)

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Myocardial infarction	48	9,778	4.9	198	37,311	5.3	0.92 (0.67-1.27)
Heart failure	192	9,601	20.0	924	36,449	25.4	0.77 (0.66-0.90)
Acute renal failure	332	9,423	35.2	1,444	35,810	40.3	0.86 (0.76-0.97)
End-stage renal disease	113	9,701	11.7	450	36,992	12.2	0.95 (0.78-1.17)
MarketScan	**Aliskiren (N =29,626)**			**Comparator (N = 113,757)**			
Cerebrovascular accidents	331	51,217	6.5	1,240	195,301	6.4	1.03 (0.91-1.16)
Stroke	613	50,889	12.1	2,391	193,939	12.3	0.98 (0.90-1.07)
Ischemic stroke	582	50,909	11.4	2,323	193,983	12.0	0.96 (0.87-1.05)
Hemorrhagic stroke	56	51,552	1.1	157	196,565	0.8	1.35 (1.00-1.84)
Transient ischemic attack	139	51,430	2.7	556	195,907	2.8	0.96 (0.79-1.15)
Myocardial infarction	252	51,323	4.9	1,061	195,441	5.4	0.90 (0.78-1.03)
Heart failure	540	50,895	10.6	2,383	193,740	12.3	0.86 (0.78-0.94)
Acute renal failure	1,654	49,695	33.3	6,675	188,962	35.3	0.93 (0.88-0.98)
End-stage renal disease	425	51,093	8.3	1,656	194,754	8.5	0.97 (0.87-1.08)

CI = confidence interval; hdPS = high density propensity score; HR = hazard ratio; ITT = intent-to-treat; yrs = years

Annex 2-Table 2-70 Hazard ratios of primary outcomes in Cohort 3 hdPS-matched patients, stratified by database, ITT analysis

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 4,134)**			**Comparator (N = 16,067)**			
Cerebrovascular accidents	86	7,401	11.6	310	27,485	11.3	1.02 (0.80-1.29)
Stroke	101	7,388	13.7	349	27,445	12.7	1.06 (0.85-1.33)
Ischemic stroke	95	7,393	12.9	329	27,473	12.0	1.06 (0.85-1.34)
Hemorrhagic stroke	16	7,470	2.1	50	27,797	1.8	1.18 (0.67-2.08)
Transient ischemic attack	58	7,425	7.8	178	27,623	6.4	1.18 (0.88-1.59)
Myocardial infarction	163	7,286	22.4	661	27,031	24.5	0.90 (0.76-1.07)
Heart failure	292	7,134	40.9	1,065	26,599	40.0	1.00 (0.88-1.14)
Acute renal failure	41	7,431	5.5	152	27,680	5.5	0.99 (0.70-1.40)
End-stage renal disease	100	7,358	13.6	361	27,386	13.2	1.03 (0.82-1.28)
MarketScan	**Aliskiren (N = 18,945)**			**Comparator (N = 74,265)**			
Cerebrovascular accidents	218	35,098	6.2	955	135,889	7.0	0.87 (0.75-1.01)
Stroke	428	34,837	12.3	1,809	134,869	13.4	0.91 (0.82-1.01)
Ischemic stroke	410	34,847	11.8	1,742	134,921	12.9	0.90 (0.81-1.01)
Hemorrhagic stroke	30	35,342	0.9	149	136,855	1.1	0.77 (0.52-1.14)
Transient ischemic	97	35,233	2.8	389	136,436	2.9	0.97 (0.77-1.21)

Outcome	Events	Person-Years	Rate Per 1,000 person-yrs	Events	Person-Years	Rate Per 1,000 person-yrs	HR (95% CI)
attack							
Myocardial infarction	197	35,122	5.6	836	135,966	6.2	0.91 (0.78-1.06)
Heart failure	405	34,891	11.6	1,692	134,865	12.6	0.92 (0.82-1.02)
Acute renal failure	1,282	33,816	37.9	5,023	130,961	38.4	0.97 (0.91-1.03)
End-stage renal disease	362	34,952	10.4	1,425	135,318	10.5	0.96 (0.86-1.08)

CI = confidence interval; hdPS = high density propensity score; HR = hazard ratio; ITT = intent-to-treat; yrs = years

Annex 2-Table 2-71 ITT stratified by duration of follow-up, Cohort 1 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	75	16,244	7,323	10.2	287	64,817	29,094	9.9	1.03 (0.80-1.33)
Stroke	88	16,244	7,320	12.0	340	64,817	29,083	11.7	1.02 (0.81-1.30)
Ischemic stroke	81	16,244	7,321	11.1	310	64,817	29,089	10.7	1.03 (0.81-1.32)
Hemorrhagic stroke	12	16,244	7,338	1.6	55	64,817	29,151	1.9	0.86 (0.46-1.61)
TIA	48	16,244	7,329	6.6	172	64,817	29,117	5.9	1.11 (0.80-1.52)
Myocardial infarction	28	16,244	7,333	3.8	118	64,817	29,135	4.1	0.93 (0.62-1.41)
Heart failure	114	16,244	7,314	15.6	664	64,817	28,990	22.9	0.68 (0.56-0.83)
Acute renal failure	219	16,244	7,289	30.0	1,043	64,817	28,901	36.1	0.82 (0.71-0.95)
ESRD	65	16,244	7,322	8.9	342	64,817	29,081	11.8	0.75 (0.58-0.98)
Follow-up from 7 to 12 months									
CVA	47	13,443	5,951	7.9	170	53,082	23,442	7.3	1.08 (0.78-1.49)
Stroke	51	13,432	5,945	8.6	201	53,040	23,416	8.6	0.99 (0.73-1.35)
Ischemic stroke	48	13,438	5,948	8.1	192	53,063	23,428	8.2	0.98 (0.71-1.34)
Hemorrhagic stroke	7	13,492	5,979	1.2	31	53,264	23,548	1.3	0.88 (0.39-2.01)
TIA	24	13,464	5,964	4.0	133	53,160	23,476	5.7	0.71 (0.46-1.09)
Myocardial infarction	21	13,478	5,970	3.5	93	53,197	23,502	4.0	0.89 (0.56-1.43)
Heart failure	82	13,408	5,925	13.8	317	52,747	23,261	13.6	1.01 (0.79-1.29)
Acute renal failure	135	13,321	5,874	23.0	535	52,455	23,091	23.2	0.98 (0.82-1.19)
ESRD	34	13,446	5,951	5.7	165	53,021	23,415	7.1	0.79 (0.55-1.15)
Follow-up from 13 to 18 months									
CVA	52	10,802	4,740	11.0	144	42,174	18,395	7.8	1.40 (1.02-1.92)
Stroke	58	10,790	4,733	12.3	158	42,115	18,368	8.6	1.42 (1.05-1.92)
Ischemic stroke	53	10,797	4,737	11.2	141	42,139	18,382	7.7	1.45 (1.06-1.99)
Hemorrhagic stroke	10	10,869	4,779	2.1	29	42,421	18,522	1.6	1.32 (0.64-2.70)
TIA	25	10,834	4,758	5.3	97	42,244	18,434	5.3	1.00 (0.64-1.55)
Myocardial infarction	13	10,848	4,768	2.7	51	42,309	18,469	2.8	0.99 (0.54-1.82)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Heart failure	64	10,742	4,713	13.6	237	41,792	18,211	13.0	1.03 (0.78-1.36)
Acute renal failure	120	10,635	4,653	25.8	416	41,420	18,013	23.1	1.11 (0.91-1.37)
ESRD	22	10,812	4,751	4.6	113	42,138	18,381	6.2	0.75 (0.47-1.18)
Follow-up 19 to 24 months									
CVA	26	8,368	3,644	7.1	104	32,409	14,046	7.4	0.96 (0.62-1.48)
Stroke	26	8,356	3,637	7.2	112	32,358	14,023	8.0	0.89 (0.58-1.36)
Ischemic stroke	22	8,364	3,641	6.0	101	32,392	14,039	7.2	0.83 (0.53-1.32)
Hemorrhagic stroke	7	8,452	3,682	1.9	19	32,675	14,178	1.3	1.42 (0.60-3.38)
TIA	13	8,411	3,662	3.6	54	32,492	14,093	3.8	0.91 (0.50-1.67)
Myocardial infarction	13	8,426	3,669	3.5	59	32,577	14,125	4.2	0.85 (0.47-1.55)
Heart failure	30	8,314	3,619	8.3	166	32,057	13,891	12.0	0.69 (0.47-1.02)
Acute renal failure	70	8,198	3,562	19.7	341	31,658	13,689	24.9	0.79 (0.61-1.02)
ESRD	24	8,397	3,655	6.6	83	32,394	14,052	5.9	1.11 (0.70-1.74)
Follow-up 25+ Months									
CVA	58	6,409	8,029	7.2	246	24,598	30,337	8.1	0.88 (0.66-1.17)
Stroke	62	6,399	8,018	7.7	265	24,555	30,266	8.8	0.87 (0.66-1.15)
Ischemic stroke	58	6,408	8,026	7.2	248	24,584	30,314	8.2	0.87 (0.65-1.16)
Hemorrhagic stroke	9	6,479	8,155	1.1	33	24,858	30,815	1.1	1.01 (0.48-2.11)
TIA	57	6,442	8,062	7.1	163	24,701	30,496	5.4	1.33 (0.99-1.80)
Myocardial infarction	28	6,457	8,100	3.5	122	24,744	30,604	4.0	0.86 (0.57-1.30)
Heart failure	96	6,366	7,939	12.1	358	24,303	29,904	12.0	1.00 (0.80-1.26)
Acute renal failure	171	6,259	7,762	22.0	638	23,903	29,288	21.8	1.00 (0.84-1.18)
ESRD	49	6,425	8,039	6.1	151	24,625	30,474	5.0	1.23 (0.89-1.70)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-72 ITT stratified by duration of follow-up, Cohort 1 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	163	67,557	30,965	5.3	649	269,586	122,881	5.3	1.00 (0.84-1.18)
Stroke	325	67,557	30,927	10.5	1,354	269,586	122,712	11.0	0.95 (0.84-1.08)
Ischemic stroke	309	67,557	30,931	10.0	1,300	269,586	122,723	10.6	0.94 (0.83-1.07)
Hemorrhagic stroke	28	67,557	30,996	0.9	97	269,586	123,013	0.8	1.15 (0.75-1.75)
TIA	72	67,557	30,981	2.3	283	269,586	122,963	2.3	1.01 (0.78-1.31)
Myocardial infarction	131	67,557	30,973	4.2	632	269,586	122,884	5.1	0.82 (0.68-0.99)
Heart failure	254	67,557	30,938	8.2	1,461	269,586	122,649	11.9	0.69 (0.60-0.79)
Acute renal failure	888	67,557	30,796	28.8	4,073	269,586	122,030	33.4	0.86 (0.80-0.93)
ESRD	204	67,557	30,951	6.6	1,106	269,586	122,761	9.0	0.73 (0.63-0.84)
Follow-up from 7 to 12 months									
CVA	145	57,557	25,757	5.6	464	227,593	101,624	4.6	1.23 (1.02-1.49)
Stroke	245	57,425	25,679	9.5	929	226,995	101,259	9.2	1.04 (0.90-1.20)
Ischemic stroke	230	57,436	25,687	9.0	893	227,032	101,278	8.8	1.02 (0.88-1.17)
Hemorrhagic stroke	27	57,674	25,831	1.1	62	228,051	101,909	0.6	1.72 (1.10-2.71)
TIA	54	57,634	25,806	2.1	218	227,861	101,778	2.1	0.97 (0.72-1.31)
Myocardial infarction	104	57,585	25,776	4.0	442	227,589	101,625	4.4	0.92 (0.75-1.14)
Heart failure	201	57,478	25,705	7.8	855	226,855	101,207	8.5	0.92 (0.79-1.07)
Acute renal failure	625	56,953	25,389	24.6	2,425	224,797	100,006	24.3	1.01 (0.93-1.10)
ESRD	144	57,520	25,740	5.6	652	227,190	101,401	6.4	0.86 (0.72-1.03)
Follow-up from 13 to 18 months									
CVA	107	46,972	20,787	5.2	412	184,999	81,603	5.1	1.02 (0.83-1.26)
Stroke	196	46,778	20,679	9.5	786	184,148	81,148	9.7	0.98 (0.84-1.14)
Ischemic stroke	183	46,795	20,686	8.9	755	184,197	81,173	9.3	0.95 (0.81-1.12)
Hemorrhagic stroke	22	47,163	20,887	1.1	60	185,684	81,973	0.7	1.44 (0.88-2.34)
TIA	42	47,095	20,847	2.0	174	185,349	81,789	2.1	0.95 (0.68-1.33)
Myocardial infarction	92	47,028	20,811	4.4	374	185,008	81,603	4.6	0.97 (0.77-1.21)
Heart failure	167	46,857	20,721	8.1	651	184,090	81,162	8.0	1.01 (0.85-1.19)
Acute renal failure	496	46,108	20,316	24.4	1,881	181,358	79,761	23.6	1.03 (0.94-1.14)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
ESRD	102	46,945	20,773	4.9	466	184,548	81,395	5.7	0.85 (0.69-1.06)
Follow-up 19 to 24 months									
CVA	88	37,145	16,032	5.5	303	145,381	62,679	4.8	1.13 (0.89-1.44)
Stroke	150	36,924	15,924	9.4	547	144,423	62,221	8.8	1.07 (0.89-1.28)
Ischemic stroke	143	36,939	15,932	9.0	528	144,473	62,243	8.5	1.06 (0.88-1.27)
Hemorrhagic stroke	17	37,355	16,139	1.1	48	146,159	63,063	0.8	1.38 (0.79-2.40)
TIA	23	37,262	16,096	1.4	106	145,780	62,879	1.7	0.85 (0.54-1.33)
Myocardial infarction	75	37,186	16,056	4.7	239	145,372	62,688	3.8	1.22 (0.94-1.58)
Heart failure	108	36,993	15,961	6.8	464	144,509	62,272	7.5	0.91 (0.73-1.12)
Acute renal failure	343	36,164	15,558	22.1	1,388	141,615	60,889	22.8	0.96 (0.86-1.09)
ESRD	72	37,116	16,028	4.5	330	145,025	62,528	5.3	0.85 (0.66-1.10)
Follow-up 25+ Months									
CVA	190	28,006	36,024	5.3	702	109,328	140,156	5.0	1.05 (0.90-1.23)
Stroke	345	27,791	35,650	9.7	1,248	108,456	138,597	9.0	1.07 (0.95-1.21)
Ischemic stroke	329	27,808	35,672	9.2	1,203	108,500	138,680	8.7	1.06 (0.94-1.20)
Hemorrhagic stroke	27	28,221	36,432	0.7	96	110,098	141,635	0.7	1.11 (0.72-1.69)
TIA	99	28,150	36,244	2.7	302	109,744	140,907	2.1	1.27 (1.01-1.60)
Myocardial infarction	152	28,065	36,126	4.2	690	109,367	140,207	4.9	0.86 (0.72-1.02)
Heart failure	279	27,865	35,759	7.8	1,067	108,562	139,054	7.7	1.01 (0.89-1.16)
Acute renal failure	811	27,100	34,491	23.5	3,132	105,849	134,384	23.3	1.01 (0.93-1.09)
ESRD	215	28,018	36,054	6.0	684	109,081	140,070	4.9	1.21 (1.04-1.41)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-73 ITT stratified by cumulative exposure duration, Cohort 1 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	161	16,244	16,794	9.6	612	64,817	67,538	9.1	1.05 (0.89-1.25)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Stroke	180	16,244	16,781	10.7	695	64,817	67,457	10.3	1.04 (0.88-1.22)
Ischemic stroke	168	16,244	16,793	10.0	631	64,817	67,503	9.4	1.07 (0.90-1.26)
Hemorrhagic stroke	27	16,244	16,914	1.6	118	64,817	67,973	1.7	0.91 (0.60-1.38)
TIA	103	16,244	16,832	6.1	376	64,817	67,694	5.6	1.09 (0.88-1.36)
Myocardial infarction	63	16,244	16,858	3.7	275	64,817	67,770	4.1	0.92 (0.70-1.20)
Heart failure	251	16,244	16,685	15.0	1,167	64,817	66,967	17.4	0.86 (0.75-0.98)
Acute renal failure	430	16,244	16,533	26.0	1,923	64,817	66,340	29.0	0.89 (0.80-0.99)
ESRD	132	16,244	16,794	7.9	619	64,817	67,507	9.2	0.85 (0.71-1.03)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	64	7,544	8,696	7.4	218	30,060	33,437	6.5	1.13 (0.85-1.49)
Stroke	71	7,535	8,680	8.2	251	30,040	33,391	7.5	1.08 (0.83-1.41)
Ischemic stroke	66	7,537	8,683	7.6	239	30,060	33,419	7.2	1.06 (0.81-1.39)
Hemorrhagic stroke	11	7,567	8,772	1.3	30	30,189	33,716	0.9	1.39 (0.70-2.77)
TIA	36	7,554	8,732	4.1	171	30,118	33,521	5.1	0.81 (0.57-1.16)
Myocardial infarction	30	7,561	8,741	3.4	116	30,158	33,605	3.5	1.00 (0.67-1.49)
Heart failure	91	7,532	8,645	10.5	407	29,907	33,085	12.3	0.82 (0.65-1.03)
Acute renal failure	195	7,488	8,516	22.9	697	29,748	32,677	21.3	1.05 (0.90-1.23)
ESRD	42	7,544	8,700	4.8	176	30,064	33,454	5.3	0.88 (0.63-1.24)
Cumulative exposure > 547 days									
CVA	33	2,977	4,197	7.9	121	11,187	14,340	8.4	0.90 (0.61-1.33)
Stroke	34	2,972	4,192	8.1	130	11,173	14,306	9.1	0.86 (0.59-1.26)
Ischemic stroke	28	2,975	4,197	6.7	122	11,182	14,330	8.5	0.75 (0.50-1.14)
Hemorrhagic stroke	7	2,998	4,247	1.7	19	11,264	14,524	1.3	1.25 (0.52-2.97)
TIA	28	2,989	4,212	6.7	72	11,202	14,402	5.0	1.34 (0.86-2.07)
Myocardial infarction	10	2,997	4,241	2.4	52	11,239	14,461	3.6	0.65 (0.33-1.28)
Heart failure	44	2,974	4,180	10.5	168	11,094	14,205	11.8	0.88 (0.63-1.22)
Acute renal failure	90	2,934	4,091	22.0	353	11,001	13,965	25.3	0.84 (0.66-1.06)
ESRD	20	2,993	4,223	4.7	59	11,219	14,442	4.1	1.12 (0.67-1.86)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease

*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-74 ITT stratified by cumulative exposure duration, Cohort 1 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	392	67,557	66,522	5.9	1,500	269,586	284,129	5.3	1.12 (1.00-1.25)
Stroke	717	67,557	66,197	10.8	2,928	269,586	282,720	10.4	1.04 (0.96-1.13)
Ischemic stroke	674	67,557	66,222	10.2	2,814	269,586	282,796	10.0	1.02 (0.94-1.11)
Hemorrhagic stroke	75	67,557	66,835	1.1	227	269,586	285,297	0.8	1.42 (1.09-1.84)
TIA	156	67,557	66,728	2.3	674	269,586	284,691	2.4	0.99 (0.83-1.18)
Myocardial infarction	313	67,557	66,557	4.7	1,401	269,586	284,053	4.9	0.95 (0.84-1.08)
Heart failure	561	67,557	66,237	8.5	2,786	269,586	282,767	9.9	0.85 (0.77-0.93)
Acute renal failure	1,721	67,557	65,127	26.4	7,789	269,586	278,550	28.0	0.93 (0.88-0.98)
ESRD	466	67,557	66,385	7.0	2,142	269,586	283,422	7.6	0.91 (0.83-1.01)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	203	36,428	41,387	4.9	711	136,069	152,225	4.7	1.05 (0.90-1.22)
Stroke	368	36,357	41,173	8.9	1,379	135,694	151,252	9.1	0.98 (0.87-1.10)
Ischemic stroke	351	36,364	41,187	8.5	1,326	135,721	151,301	8.8	0.97 (0.86-1.09)
Hemorrhagic stroke	32	36,499	41,623	0.8	96	136,395	153,127	0.6	1.23 (0.82-1.83)
TIA	90	36,461	41,516	2.2	289	136,242	152,730	1.9	1.14 (0.90-1.44)
Myocardial infarction	163	36,467	41,463	3.9	663	136,112	152,289	4.4	0.90 (0.76-1.07)
Heart failure	294	36,408	41,273	7.1	1,223	135,703	151,397	8.1	0.88 (0.77-1.00)
Acute renal failure	982	36,184	40,365	24.3	3,569	134,517	148,250	24.1	1.00 (0.93-1.07)
ESRD	203	36,448	41,404	4.9	817	135,942	152,011	5.4	0.89 (0.76-1.04)
Cumulative exposure > 547 days									
CVA	98	15,328	21,654	4.5	319	54,741	72,589	4.4	1.02 (0.82-1.28)
Stroke	176	15,254	21,490	8.2	557	54,441	71,965	7.7	1.05 (0.88-1.24)
Ischemic stroke	169	15,260	21,499	7.9	539	54,458	72,000	7.5	1.04 (0.88-1.24)
Hemorrhagic stroke	14	15,399	21,827	0.6	40	55,021	73,169	0.6	1.17 (0.64-2.15)
TIA	44	15,362	21,730	2.0	120	54,894	72,895	1.7	1.22 (0.86-1.72)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Myocardial infarction	78	15,374	21,723	3.6	313	54,815	72,665	4.3	0.83 (0.65-1.06)
Heart failure	154	15,315	21,574	7.1	489	54,550	72,181	6.8	1.04 (0.86-1.24)
Acute renal failure	460	15,111	21,059	21.8	1,541	53,626	70,269	21.9	0.98 (0.88-1.09)
ESRD	68	15,373	21,757	3.1	279	54,784	72,722	3.8	0.80 (0.61-1.04)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease

*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-75 ITT stratified by duration of follow-up, Cohort 2 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	31	5,748	2,612	11.9	136	22,813	10,247	13.3	0.90 (0.61-1.33)
Stroke	39	5,748	2,610	14.9	160	22,813	10,241	15.6	0.96 (0.68-1.36)
Ischemic stroke	37	5,748	2,611	14.2	146	22,813	10,244	14.3	1.00 (0.70-1.43)
Hemorrhagic stroke	4	5,748	2,618	1.5	23	22,813	10,275	2.2	0.69 (0.24-1.99)
TIA	21	5,748	2,613	8.0	69	22,813	10,263	6.7	1.21 (0.74-1.97)
Myocardial infarction	15	5,748	2,615	5.7	59	22,813	10,265	5.8	0.97 (0.55-1.71)
Heart failure	61	5,748	2,606	23.4	344	22,813	10,188	33.8	0.69 (0.53-0.91)
Acute renal failure	113	5,748	2,593	43.6	554	22,813	10,137	54.7	0.80 (0.65-0.97)
ESRD	36	5,748	2,609	13.8	190	22,813	10,237	18.6	0.74 (0.52-1.06)
Follow-up from 7 to 12 months									
CVA	25	4,798	2,115	11.8	103	18,733	8,253	12.5	0.95 (0.61-1.47)
Stroke	29	4,791	2,111	13.7	120	18,716	8,241	14.6	0.94 (0.63-1.42)
Ischemic stroke	28	4,792	2,111	13.3	109	18,726	8,247	13.2	1.00 (0.66-1.52)
Hemorrhagic stroke	3	4,818	2,128	1.4	18	18,826	8,308	2.2	0.66 (0.19-2.23)
TIA	14	4,805	2,119	6.6	61	18,786	8,279	7.4	0.90 (0.51-1.62)
Myocardial infarction	10	4,809	2,123	4.7	42	18,790	8,287	5.1	0.93 (0.47-1.86)
Heart failure	48	4,771	2,098	22.9	195	18,540	8,146	23.9	0.94 (0.69-1.30)
Acute renal failure	82	4,727	2,069	39.6	268	18,384	8,070	33.2	1.19 (0.93-1.52)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
ESRD	23	4,791	2,112	10.9	102	18,674	8,228	12.4	0.87 (0.55-1.37)
Follow-up from 13 to 18 months									
CVA	21	3,812	1,657	12.7	74	14,775	6,350	11.7	1.09 (0.67-1.78)
Stroke	23	3,802	1,653	13.9	81	14,746	6,334	12.8	1.10 (0.69-1.74)
Ischemic stroke	21	3,804	1,654	12.7	76	14,762	6,343	12.0	1.07 (0.66-1.73)
Hemorrhagic stroke	4	3,843	1,674	2.4	22	14,905	6,414	3.4	0.70 (0.24-2.04)
TIA	3	3,823	1,665	1.8	49	14,833	6,377	7.7	0.24 (0.07-0.76)
Myocardial infarction	7	3,831	1,668	4.2	40	14,856	6,389	6.3	0.66 (0.30-1.47)
Heart failure	31	3,765	1,635	19.0	142	14,553	6,241	22.8	0.84 (0.57-1.23)
Acute renal failure	59	3,703	1,600	36.9	215	14,392	6,158	34.9	1.05 (0.79-1.40)
ESRD	10	3,808	1,657	6.0	84	14,733	6,331	13.3	0.45 (0.23-0.87)
Follow-up 19 to 24 months									
CVA	13	2,855	1,194	10.9	43	10,839	4,533	9.5	1.14 (0.62-2.13)
Stroke	13	2,848	1,191	10.9	49	10,807	4,517	10.9	1.01 (0.55-1.86)
Ischemic stroke	12	2,851	1,192	10.1	44	10,825	4,526	9.7	1.04 (0.55-1.96)
Hemorrhagic stroke	3	2,892	1,212	2.5	8	10,976	4,597	1.7	1.44 (0.38-5.42)
TIA	10	2,877	1,204	8.3	28	10,899	4,560	6.1	1.37 (0.67-2.82)
Myocardial infarction	9	2,877	1,204	7.5	21	10,927	4,572	4.6	1.65 (0.75-3.59)
Heart failure	14	2,818	1,181	11.9	93	10,634	4,439	21.0	0.57 (0.32-0.99)
Acute renal failure	31	2,745	1,146	27.1	140	10,463	4,361	32.1	0.82 (0.56-1.22)
ESRD	20	2,862	1,199	16.7	40	10,805	4,520	8.9	1.82 (1.06-3.12)
Follow-up 25+ Months									
CVA	17	1,986	2,154	7.9	77	7,552	8,228	9.4	0.84 (0.49-1.42)
Stroke	18	1,981	2,148	8.4	99	7,522	8,192	12.1	0.69 (0.42-1.14)
Ischemic stroke	15	1,984	2,150	7.0	92	7,537	8,215	11.2	0.62 (0.36-1.07)
Hemorrhagic stroke	5	2,020	2,202	2.3	15	7,675	8,401	1.8	1.29 (0.47-3.54)
TIA	19	2,000	2,165	8.8	61	7,598	8,288	7.4	1.20 (0.72-2.01)
Myocardial infarction	13	2,006	2,177	6.0	44	7,617	8,324	5.3	1.12 (0.60-2.08)
Heart failure	41	1,962	2,091	19.6	175	7,356	7,915	22.1	0.89 (0.63-1.25)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Acute renal failure	59	1,899	2,012	29.3	271	7,203	7,701	35.2	0.84 (0.63-1.11)
ESRD	25	1,992	2,136	11.7	108	7,530	8,167	13.2	0.88 (0.57-1.35)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease;
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-76 ITT stratified by duration of follow-up, Cohort 2 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	88	29,813	13,669	6.4	363	116,757	53,148	6.8	0.95 (0.75-1.20)
Stroke	170	29,813	13,651	12.5	762	116,757	53,052	14.4	0.87 (0.73-1.02)
Ischemic stroke	158	29,813	13,653	11.6	737	116,757	53,055	13.9	0.83 (0.70-0.99)
Hemorrhagic stroke	20	29,813	13,686	1.5	46	116,757	53,225	0.9	1.73 (1.02-2.92)
TIA	32	29,813	13,682	2.3	146	116,757	53,194	2.7	0.86 (0.59-1.26)
Myocardial infarction	61	29,813	13,676	4.5	285	116,757	53,163	5.4	0.83 (0.63-1.10)
Heart failure	160	29,813	13,650	11.7	918	116,757	52,989	17.3	0.68 (0.57-0.80)
Acute renal failure	529	29,813	13,569	39.0	2,283	116,757	52,656	43.4	0.90 (0.82-0.99)
ESRD	138	29,813	13,657	10.1	626	116,757	53,072	11.8	0.86 (0.71-1.03)
Follow-up from 7 to 12 months									
CVA	75	25,440	11,288	6.6	248	98,466	43,581	5.7	1.18 (0.91-1.52)
Stroke	131	25,371	11,246	11.7	497	98,145	43,391	11.5	1.03 (0.85-1.24)
Ischemic stroke	123	25,378	11,250	10.9	485	98,162	43,399	11.2	0.99 (0.81-1.20)
Hemorrhagic stroke	11	25,503	11,329	1.0	25	98,730	43,738	0.6	1.72 (0.85-3.50)
TIA	27	25,489	11,317	2.4	88	98,629	43,675	2.0	1.20 (0.78-1.84)
Myocardial infarction	55	25,465	11,301	4.9	237	98,526	43,600	5.4	0.90 (0.67-1.20)
Heart failure	113	25,379	11,249	10.1	504	97,968	43,287	11.6	0.86 (0.70-1.06)
Acute renal failure	333	25,075	11,075	30.1	1,391	96,875	42,636	32.6	0.91 (0.81-1.03)
ESRD	80	25,399	11,267	7.1	384	98,244	43,441	8.8	0.80 (0.63-1.02)
Follow-up from 13 to 18 months									

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
CVA	53	20,428	8,919	5.9	193	78,676	34,204	5.6	1.06 (0.79-1.44)
Stroke	90	20,324	8,861	10.2	373	78,233	33,978	11.0	0.93 (0.74-1.17)
Ischemic stroke	84	20,335	8,866	9.5	362	78,250	33,986	10.7	0.89 (0.70-1.13)
Hemorrhagic stroke	9	20,536	8,972	1.0	22	79,054	34,403	0.6	1.58 (0.73-3.43)
TIA	19	20,507	8,954	2.1	82	78,906	34,326	2.4	0.89 (0.54-1.46)
Myocardial infarction	56	20,467	8,932	6.3	176	78,720	34,229	5.1	1.22 (0.90-1.64)
Heart failure	83	20,345	8,874	9.4	381	78,032	33,877	11.3	0.83 (0.66-1.06)
Acute renal failure	266	19,945	8,658	30.7	1,028	76,553	33,115	31.0	0.99 (0.86-1.13)
ESRD	53	20,394	8,901	6.0	258	78,385	34,066	7.6	0.77 (0.57-1.04)
Follow-up 19 to 24 months									
CVA	37	15,553	6,366	5.8	151	59,443	24,437	6.2	0.93 (0.65-1.33)
Stroke	71	15,440	6,314	11.3	275	58,989	24,217	11.4	0.99 (0.76-1.28)
Ischemic stroke	70	15,450	6,318	11.1	257	59,004	24,226	10.6	1.04 (0.80-1.36)
Hemorrhagic stroke	6	15,661	6,419	0.9	30	59,865	24,638	1.2	0.79 (0.33-1.89)
TIA	15	15,621	6,402	2.3	48	59,698	24,561	2.0	1.21 (0.68-2.16)
Myocardial infarction	29	15,569	6,379	4.6	138	59,490	24,463	5.6	0.81 (0.54-1.21)
Heart failure	61	15,458	6,320	9.7	259	58,792	24,141	10.7	0.91 (0.68-1.20)
Acute renal failure	183	15,025	6,118	29.9	768	57,240	23,389	32.8	0.90 (0.77-1.06)
ESRD	47	15,514	6,354	7.4	190	59,197	24,328	7.8	0.92 (0.67-1.27)
Follow-up 25+ Months									
CVA	82	10,343	11,272	7.3	287	39,957	43,742	6.6	1.11 (0.87-1.42)
Stroke	153	10,242	11,110	13.8	533	39,545	43,105	12.4	1.12 (0.93-1.34)
Ischemic stroke	150	10,250	11,112	13.5	512	39,562	43,134	11.9	1.14 (0.95-1.37)
Hemorrhagic stroke	8	10,442	11,448	0.7	42	40,340	44,392	1.0	0.74 (0.35-1.58)
TIA	49	10,415	11,368	4.3	124	40,204	44,150	2.8	1.53 (1.10-2.14)
Myocardial infarction	52	10,373	11,331	4.6	297	40,001	43,807	6.8	0.67 (0.50-0.90)
Heart failure	132	10,241	11,087	11.9	544	39,377	42,914	12.7	0.94 (0.77-1.13)
Acute renal failure	364	9,874	10,561	34.5	1,397	37,923	40,753	34.3	1.00 (0.89-1.12)
ESRD	108	10,318	11,208	9.6	385	39,739	43,439	8.9	1.07 (0.86-1.33)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-77 ITT stratified by cumulative exposure duration, Cohort 2 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	72	5,748	6,546	11.0	338	22,813	26,179	12.9	0.85 (0.66-1.10)
Stroke	85	5,748	6,537	13.0	398	22,813	26,120	15.2	0.86 (0.68-1.08)
Ischemic stroke	80	5,748	6,541	12.2	363	22,813	26,151	13.9	0.88 (0.69-1.13)
Hemorrhagic stroke	11	5,748	6,605	1.7	71	22,813	26,422	2.7	0.63 (0.33-1.19)
TIA	47	5,748	6,557	7.2	199	22,813	26,276	7.6	0.96 (0.70-1.31)
Myocardial infarction	36	5,748	6,571	5.5	148	22,813	26,317	5.6	0.96 (0.66-1.38)
Heart failure	133	5,748	6,461	20.6	720	22,813	25,726	28.0	0.73 (0.61-0.88)
Acute renal failure	239	5,748	6,351	37.6	1,059	22,813	25,382	41.7	0.89 (0.78-1.03)
ESRD	89	5,748	6,522	13.7	408	22,813	26,049	15.7	0.86 (0.69-1.09)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	29	2,162	2,463	11.8	70	8,077	8,769	8.0	1.50 (0.97-2.31)
Stroke	31	2,158	2,454	12.6	78	8,068	8,750	8.9	1.44 (0.95-2.18)
Ischemic stroke	29	2,158	2,455	11.8	73	8,072	8,766	8.3	1.44 (0.94-2.21)
Hemorrhagic stroke	6	2,170	2,496	2.4	10	8,124	8,881	1.1	2.13 (0.78-5.87)
TIA	17	2,166	2,480	6.9	51	8,100	8,811	5.8	1.20 (0.69-2.08)
Myocardial infarction	17	2,169	2,483	6.9	44	8,107	8,836	5.0	1.36 (0.78-2.39)
Heart failure	48	2,158	2,447	19.6	171	8,010	8,603	19.9	0.97 (0.71-1.34)
Acute renal failure	84	2,144	2,378	35.3	289	7,998	8,494	34.0	1.01 (0.79-1.29)
ESRD	19	2,160	2,467	7.7	89	8,087	8,772	10.2	0.74 (0.45-1.22)
Cumulative exposure > 547 days									
CVA	6	619	723	8.3	25	2,327	2,663	9.4	0.90 (0.37-2.20)
Stroke	6	617	721	8.3	33	2,324	2,655	12.4	0.67 (0.28-1.60)
Ischemic stroke	4	617	721	5.6	31	2,327	2,658	11.7	0.47 (0.17-1.34)
Hemorrhagic stroke	2	625	734	2.7	5	2,346	2,694	1.9	1.52 (0.29-7.84)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
TIA	3	623	729	4.1	18	2,338	2,680	6.7	0.61 (0.18-2.05)
Myocardial infarction	1	625	734	1.4	14	2,342	2,684	5.2	0.26 (0.03-2.00)
Heart failure	14	615	703	19.9	58	2,305	2,600	22.3	0.88 (0.49-1.58)
Acute renal failure	21	608	691	30.4	100	2,289	2,551	39.2	0.77 (0.48-1.23)
ESRD	6	622	725	8.3	27	2,339	2,663	10.1	0.74 (0.30-1.82)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-78 ITT stratified by cumulative exposure duration, Cohort 2 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	212	29,813	31,937	6.6	906	116,757	135,535	6.7	0.99 (0.85-1.15)
Stroke	396	29,813	31,763	12.5	1,801	116,757	134,675	13.4	0.93 (0.83-1.04)
Ischemic stroke	373	29,813	31,776	11.7	1,736	116,757	134,713	12.9	0.91 (0.81-1.02)
Hemorrhagic stroke	38	29,813	32,119	1.2	125	116,757	136,315	0.9	1.30 (0.90-1.87)
TIA	89	29,813	32,070	2.8	366	116,757	135,996	2.7	1.03 (0.82-1.30)
Myocardial infarction	167	29,813	31,981	5.2	771	116,757	135,643	5.7	0.92 (0.78-1.08)
Heart failure	348	29,813	31,747	11.0	1,934	116,757	134,303	14.4	0.75 (0.67-0.84)
Acute renal failure	1,076	29,813	31,057	34.7	4,930	116,757	131,381	37.5	0.91 (0.85-0.97)
ESRD	313	29,813	31,814	9.8	1,412	116,757	134,936	10.5	0.92 (0.82-1.04)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	94	13,662	14,783	6.4	270	44,881	48,527	5.6	1.18 (0.93-1.49)
Stroke	167	13,627	14,666	11.4	512	44,732	48,150	10.6	1.09 (0.92-1.30)
Ischemic stroke	159	13,629	14,672	10.8	495	44,739	48,164	10.3	1.08 (0.90-1.29)
Hemorrhagic stroke	13	13,695	14,892	0.9	31	45,020	48,885	0.6	1.39 (0.73-2.67)
TIA	45	13,675	14,836	3.0	95	44,965	48,771	2.0	1.59 (1.12-2.27)
Myocardial infarction	70	13,677	14,821	4.7	274	44,924	48,539	5.6	0.85 (0.65-1.10)
Heart failure	155	13,634	14,679	10.6	525	44,676	48,009	10.9	0.98 (0.82-1.18)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Acute renal failure	448	13,521	14,299	31.3	1,492	44,292	46,712	31.9	0.98 (0.88-1.09)
ESRD	86	13,656	14,763	5.8	341	44,836	48,344	7.1	0.83 (0.66-1.05)
Cumulative exposure > 547 days									
CVA	29	4,356	4,794	6.1	66	13,729	15,050	4.4	1.38 (0.89-2.14)
Stroke	52	4,332	4,753	10.9	127	13,655	14,917	8.5	1.28 (0.93-1.77)
Ischemic stroke	53	4,334	4,753	11.2	122	13,657	14,923	8.2	1.36 (0.98-1.88)
Hemorrhagic stroke	3	4,380	4,844	0.6	9	13,819	15,197	0.6	1.04 (0.28-3.84)
TIA	8	4,361	4,817	1.7	27	13,778	15,138	1.8	0.94 (0.43-2.08)
Myocardial infarction	16	4,365	4,817	3.3	88	13,770	15,079	5.8	0.57 (0.33-0.97)
Heart failure	46	4,343	4,754	9.7	147	13,646	14,895	9.9	0.96 (0.69-1.34)
Acute renal failure	151	4,283	4,625	32.7	445	13,437	14,456	30.8	1.05 (0.87-1.26)
ESRD	27	4,368	4,811	5.6	90	13,760	15,067	6.0	0.91 (0.59-1.41)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-79 ITT stratified by duration of follow-up, Cohort 3 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	22	4,149	1,877	11.7	119	16,438	7,358	16.2	0.71 (0.45-1.12)
Stroke	28	4,149	1,876	14.9	136	16,438	7,353	18.5	0.80 (0.53-1.20)
Ischemic stroke	26	4,149	1,877	13.9	124	16,438	7,357	16.9	0.81 (0.53-1.24)
Hemorrhagic stroke	5	4,149	1,880	2.7	23	16,438	7,381	3.1	0.86 (0.33-2.27)
TIA	16	4,149	1,878	8.5	66	16,438	7,371	9.0	0.94 (0.54-1.62)
Myocardial infarction	11	4,149	1,878	5.9	34	16,438	7,379	4.6	1.23 (0.62-2.43)
Heart failure	55	4,149	1,868	29.4	268	16,438	7,312	36.7	0.80 (0.60-1.07)
Acute renal failure	100	4,149	1,858	53.8	440	16,438	7,273	60.5	0.88 (0.71-1.10)
ESRD	30	4,149	1,874	16.0	145	16,438	7,347	19.7	0.81 (0.55-1.21)
Follow-up from 7 to 12 months									

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
CVA	18	3,435	1,502	12.0	58	13,373	5,855	9.9	1.20 (0.71-2.04)
Stroke	22	3,430	1,499	14.7	75	13,361	5,845	12.8	1.14 (0.71-1.84)
Ischemic stroke	22	3,431	1,500	14.7	71	13,370	5,850	12.1	1.21 (0.75-1.95)
Hemorrhagic stroke	0	3,449	1,511	0.0	9	13,457	5,903	1.5	0.00 (0.00-.)
TIA	11	3,440	1,505	7.3	33	13,421	5,883	5.6	1.28 (0.65-2.54)
Myocardial infarction	8	3,443	1,508	5.3	38	13,450	5,894	6.5	0.83 (0.39-1.77)
Heart failure	31	3,407	1,487	20.9	123	13,249	5,794	21.2	0.97 (0.66-1.44)
Acute renal failure	55	3,370	1,465	37.6	230	13,109	5,709	40.3	0.92 (0.69-1.24)
ESRD	21	3,426	1,495	14.1	87	13,353	5,842	14.9	0.94 (0.59-1.52)
Follow-up from 13 to 18 months									
CVA	14	2,685	1,173	11.9	47	10,453	4,517	10.4	1.15 (0.63-2.09)
Stroke	18	2,679	1,169	15.4	53	10,431	4,507	11.8	1.32 (0.77-2.25)
Ischemic stroke	17	2,680	1,170	14.5	50	10,443	4,513	11.1	1.32 (0.76-2.29)
Hemorrhagic stroke	2	2,712	1,186	1.7	8	10,559	4,570	1.8	0.98 (0.21-4.59)
TIA	9	2,696	1,177	7.7	25	10,511	4,545	5.5	1.41 (0.66-3.02)
Myocardial infarction	4	2,699	1,181	3.4	18	10,530	4,555	4.0	0.83 (0.28-2.47)
Heart failure	25	2,653	1,155	21.6	97	10,324	4,450	21.8	1.00 (0.64-1.55)
Acute renal failure	35	2,605	1,132	30.9	162	10,132	4,353	37.2	0.83 (0.57-1.19)
ESRD	11	2,675	1,169	9.4	62	10,421	4,504	13.8	0.68 (0.36-1.28)
Follow-up 19 to 24 months									
CVA	11	2,067	900	12.2	33	7,846	3,376	9.8	1.27 (0.64-2.51)
Stroke	10	2,059	897	11.2	39	7,826	3,367	11.6	0.98 (0.49-1.95)
Ischemic stroke	8	2,061	898	8.9	37	7,836	3,372	11.0	0.82 (0.38-1.77)
Hemorrhagic stroke	4	2,093	913	4.4	6	7,950	3,428	1.8	2.53 (0.72-8.98)
TIA	7	2,075	904	7.8	23	7,901	3,401	6.8	1.16 (0.50-2.70)
Myocardial infarction	6	2,080	907	6.6	16	7,920	3,411	4.7	1.43 (0.56-3.65)
Heart failure	15	2,031	884	17.0	60	7,715	3,315	18.1	0.92 (0.52-1.63)
Acute renal failure	36	1,993	863	41.7	105	7,516	3,224	32.6	1.26 (0.86-1.84)
ESRD	15	2,062	899	16.7	32	7,817	3,366	9.5	1.71 (0.92-3.16)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up 25+ Months									
CVA	20	1,572	1,945	10.3	76	5,924	7,168	10.6	0.98 (0.60-1.61)
Stroke	22	1,569	1,943	11.3	78	5,907	7,143	10.9	1.04 (0.65-1.68)
Ischemic stroke	21	1,573	1,945	10.8	69	5,917	7,162	9.6	1.13 (0.70-1.85)
Hemorrhagic stroke	5	1,596	1,977	2.5	14	6,025	7,321	1.9	1.31 (0.47-3.64)
TIA	20	1,578	1,950	10.3	50	5,968	7,228	6.9	1.51 (0.90-2.53)
Myocardial infarction	14	1,584	1,955	7.2	41	5,990	7,269	5.6	1.26 (0.68-2.30)
Heart failure	36	1,544	1,893	19.0	150	5,812	6,960	21.6	0.86 (0.60-1.24)
Acute renal failure	75	1,501	1,812	41.4	231	5,634	6,726	34.3	1.19 (0.92-1.55)
ESRD	21	1,567	1,927	10.9	63	5,906	7,146	8.8	1.23 (0.75-2.02)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-80 ITT stratified by duration of follow-up, Cohort 3 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Follow-up from 0 to 6 months									
CVA	50	19,092	8,724	5.7	277	75,912	34,375	8.1	0.71 (0.52-0.96)
Stroke	109	19,092	8,711	12.5	559	75,912	34,310	16.3	0.77 (0.62-0.94)
Ischemic stroke	106	19,092	8,711	12.2	542	75,912	34,314	15.8	0.77 (0.62-0.95)
Hemorrhagic stroke	5	19,092	8,736	0.6	36	75,912	34,430	1.1	0.55 (0.22-1.41)
TIA	22	19,092	8,731	2.5	109	75,912	34,413	3.2	0.80 (0.51-1.26)
Myocardial infarction	52	19,092	8,726	6.0	231	75,912	34,383	6.7	0.89 (0.66-1.21)
Heart failure	104	19,092	8,714	11.9	595	75,912	34,281	17.4	0.69 (0.56-0.85)
Acute renal failure	375	19,092	8,652	43.3	1,743	75,912	33,982	51.3	0.84 (0.75-0.94)
ESRD	107	19,092	8,712	12.3	546	75,912	34,302	15.9	0.77 (0.63-0.95)
Follow-up from 7 to 12 months									
CVA	41	16,171	7,151	5.7	169	63,321	27,893	6.1	0.94 (0.67-1.32)
Stroke	79	16,123	7,122	11.1	339	63,080	27,750	12.2	0.90 (0.71-1.16)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Ischemic stroke	74	16,126	7,124	10.4	326	63,091	27,755	11.8	0.88 (0.69-1.14)
Hemorrhagic stroke	10	16,211	7,174	1.4	26	63,528	28,010	0.9	1.48 (0.71-3.07)
TIA	11	16,196	7,167	1.5	70	63,456	27,966	2.5	0.61 (0.32-1.15)
Myocardial infarction	35	16,167	7,152	4.9	173	63,357	27,900	6.2	0.78 (0.54-1.12)
Heart failure	79	16,126	7,124	11.1	371	63,043	27,725	13.4	0.82 (0.64-1.05)
Acute renal failure	251	15,901	6,990	35.9	975	62,114	27,199	35.9	0.99 (0.87-1.14)
ESRD	71	16,121	7,124	10.0	343	63,101	27,751	12.4	0.80 (0.62-1.04)
Follow-up from 13 to 18 months									
CVA	32	12,872	5,621	5.7	142	50,010	21,786	6.5	0.87 (0.59-1.27)
Stroke	77	12,796	5,578	13.8	273	49,685	21,614	12.6	1.09 (0.84-1.40)
Ischemic stroke	74	12,801	5,579	13.3	263	49,696	21,619	12.2	1.08 (0.84-1.40)
Hemorrhagic stroke	4	12,931	5,650	0.7	22	50,274	21,925	1.0	0.71 (0.25-2.06)
TIA	23	12,914	5,637	4.1	66	50,178	21,870	3.0	1.36 (0.85-2.19)
Myocardial infarction	28	12,879	5,623	5.0	161	50,012	21,776	7.4	0.68 (0.45-1.01)
Heart failure	62	12,814	5,589	11.1	273	49,620	21,584	12.7	0.87 (0.66-1.15)
Acute renal failure	207	12,491	5,414	38.2	778	48,454	20,999	37.1	1.03 (0.89-1.20)
ESRD	49	12,811	5,588	8.8	234	49,679	21,623	10.8	0.80 (0.59-1.09)
Follow-up 19 to 24 months									
CVA	30	9,931	4,290	7.0	108	38,374	16,610	6.5	1.06 (0.71-1.59)
Stroke	50	9,841	4,249	11.8	209	38,020	16,438	12.7	0.93 (0.68-1.26)
Ischemic stroke	47	9,844	4,251	11.1	202	38,035	16,445	12.3	0.90 (0.66-1.24)
Hemorrhagic stroke	5	9,993	4,323	1.2	17	38,673	16,757	1.0	1.14 (0.42-3.08)
TIA	6	9,960	4,310	1.4	57	38,557	16,694	3.4	0.41 (0.18-0.95)
Myocardial infarction	26	9,933	4,295	6.1	103	38,351	16,603	6.2	0.98 (0.64-1.51)
Heart failure	44	9,861	4,259	10.3	171	37,977	16,424	10.4	0.99 (0.71-1.38)
Acute renal failure	131	9,496	4,084	32.1	536	36,781	15,847	33.8	0.94 (0.78-1.14)
ESRD	31	9,869	4,269	7.3	171	38,067	16,482	10.4	0.70 (0.48-1.03)
Follow-up 25+ Months									
CVA	56	7,543	9,694	5.8	282	29,190	37,332	7.6	0.77 (0.57-1.02)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Stroke	115	7,463	9,549	12.0	485	28,847	36,749	13.2	0.91 (0.74-1.11)
Ischemic stroke	111	7,467	9,552	11.6	464	28,858	36,767	12.6	0.92 (0.75-1.13)
Hemorrhagic stroke	6	7,612	9,821	0.6	44	29,487	37,915	1.2	0.52 (0.22-1.22)
TIA	38	7,591	9,745	3.9	121	29,355	37,620	3.2	1.22 (0.85-1.75)
Myocardial infarction	53	7,553	9,695	5.5	262	29,181	37,346	7.0	0.77 (0.57-1.04)
Heart failure	110	7,477	9,583	11.5	449	28,820	36,790	12.2	0.93 (0.76-1.15)
Acute renal failure	324	7,157	9,024	35.9	1,253	27,704	34,865	35.9	0.99 (0.88-1.12)
ESRD	92	7,510	9,639	9.5	348	28,955	37,059	9.4	0.99 (0.79-1.25)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease
*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-81 ITT stratified by cumulative exposure duration, Cohort 3 – United

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	56	4,149	4,766	11.8	255	16,438	19,218	13.3	0.88 (0.66-1.18)
Stroke	65	4,149	4,762	13.7	293	16,438	19,180	15.3	0.89 (0.68-1.16)
Ischemic stroke	60	4,149	4,763	12.6	276	16,438	19,194	14.4	0.87 (0.66-1.15)
Hemorrhagic stroke	11	4,149	4,801	2.3	35	16,438	19,439	1.8	1.28 (0.65-2.51)
TIA	45	4,149	4,771	9.4	157	16,438	19,305	8.1	1.15 (0.83-1.61)
Myocardial infarction	31	4,149	4,775	6.5	105	16,438	19,379	5.4	1.19 (0.80-1.78)
Heart failure	109	4,149	4,698	23.2	525	16,438	18,918	27.8	0.83 (0.67-1.01)
Acute renal failure	203	4,149	4,598	44.2	859	16,438	18,561	46.3	0.94 (0.81-1.10)
ESRD	70	4,149	4,734	14.8	295	16,438	19,163	15.4	0.95 (0.73-1.24)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	18	1,600	1,880	9.6	59	6,016	6,848	8.6	1.13 (0.66-1.91)
Stroke	23	1,599	1,875	12.3	68	6,010	6,829	10.0	1.25 (0.78-2.01)
Ischemic stroke	23	1,601	1,877	12.3	57	6,015	6,849	8.3	1.50 (0.93-2.44)
Hemorrhagic stroke	2	1,610	1,907	1.1	20	6,059	6,925	2.9	0.36 (0.08-1.55)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
TIA	13	1,603	1,887	6.9	32	6,039	6,895	4.6	1.53 (0.80-2.92)
Myocardial infarction	9	1,608	1,895	4.8	34	6,049	6,898	4.9	0.96 (0.46-2.00)
Heart failure	39	1,593	1,850	21.1	140	5,993	6,740	20.8	1.02 (0.71-1.45)
Acute renal failure	65	1,583	1,810	35.9	234	5,940	6,611	35.4	1.00 (0.76-1.31)
ESRD	21	1,604	1,877	11.2	75	6,028	6,830	11.0	1.02 (0.63-1.65)
Cumulative exposure > 547 days									
CVA	11	540	751	14.7	19	1,827	2,208	8.6	1.77 (0.84-3.72)
Stroke	12	537	748	16.0	20	1,824	2,206	9.1	1.76 (0.86-3.63)
Ischemic stroke	11	537	749	14.7	18	1,825	2,210	8.2	1.80 (0.84-3.84)
Hemorrhagic stroke	3	543	760	4.0	5	1,842	2,239	2.2	1.84 (0.44-7.72)
TIA	5	540	755	6.6	8	1,836	2,229	3.6	1.89 (0.62-5.82)
Myocardial infarction	3	541	758	4.0	8	1,837	2,232	3.6	1.09 (0.29-4.12)
Heart failure	14	534	740	18.9	33	1,808	2,173	15.2	1.24 (0.66-2.32)
Acute renal failure	33	528	721	45.8	75	1,784	2,113	35.5	1.26 (0.84-1.91)
ESRD	7	540	753	9.3	19	1,829	2,212	8.6	1.15 (0.48-2.74)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease

*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-82 ITT stratified by cumulative exposure duration, Cohort 3 – MarketScan

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Cumulative exposure ≤ 182 days									
CVA	145	19,092	21,596	6.7	718	75,912	91,459	7.9	0.86 (0.72-1.02)
Stroke	288	19,092	21,429	13.4	1,348	75,912	90,760	14.9	0.90 (0.79-1.02)
Ischemic stroke	277	19,092	21,436	12.9	1,294	75,912	90,794	14.3	0.90 (0.79-1.03)
Hemorrhagic stroke	22	19,092	21,703	1.0	115	75,912	92,071	1.3	0.82 (0.52-1.30)
TIA	67	19,092	21,635	3.1	295	75,912	91,816	3.2	0.97 (0.75-1.27)
Myocardial infarction	123	19,092	21,579	5.7	638	75,912	91,455	7.0	0.82 (0.68-0.99)
Heart failure	256	19,092	21,450	11.9	1,347	75,912	90,699	14.9	0.80 (0.70-0.91)

Outcome	Aliskiren				Comparator				HR (95% CI)
	Events	Patients	Person-Years	IR*	Events	Patients	Person-Years	IR*	
Acute renal failure	850	19,092	20,815	40.8	3,759	75,912	88,312	42.6	0.95 (0.88-1.02)
ESRD	249	19,092	21,438	11.6	1,184	75,912	90,923	13.0	0.88 (0.77-1.01)
183 days ≤ Cumulative exposure ≤ 547 days									
CVA	44	8,348	9,753	4.5	199	29,347	33,860	5.9	0.76 (0.55-1.05)
Stroke	99	8,319	9,679	10.2	398	29,238	33,545	11.9	0.86 (0.69-1.07)
Ischemic stroke	95	8,320	9,682	9.8	389	29,242	33,550	11.6	0.85 (0.68-1.06)
Hemorrhagic stroke	4	8,379	9,831	0.4	22	29,462	34,159	0.6	0.61 (0.21-1.77)
TIA	29	8,372	9,802	3.0	97	29,414	33,997	2.9	1.04 (0.69-1.57)
Myocardial infarction	53	8,373	9,780	5.4	217	29,381	33,871	6.4	0.84 (0.62-1.13)
Heart failure	106	8,348	9,699	10.9	382	29,242	33,547	11.4	0.95 (0.77-1.18)
Acute renal failure	330	8,255	9,363	35.3	1,138	28,885	32,449	35.1	1.00 (0.89-1.14)
ESRD	84	8,360	9,744	8.6	367	29,298	33,635	10.9	0.78 (0.61-0.98)
Cumulative exposure > 547 days									
CVA	20	3,011	4,131	4.8	61	9,768	12,677	4.8	0.99 (0.60-1.65)
Stroke	43	3,000	4,100	10.5	119	9,708	12,555	9.5	1.09 (0.77-1.55)
Ischemic stroke	40	3,000	4,100	9.8	114	9,708	12,555	9.1	1.06 (0.74-1.52)
Hemorrhagic stroke	4	3,027	4,172	1.0	8	9,838	12,809	0.6	1.54 (0.46-5.10)
TIA	4	3,015	4,153	1.0	31	9,813	12,750	2.4	0.40 (0.14-1.12)
Myocardial infarction	18	3,013	4,132	4.4	75	9,786	12,681	5.9	0.72 (0.43-1.21)
Heart failure	37	3,006	4,120	9.0	130	9,724	12,557	10.4	0.87 (0.60-1.25)
Acute renal failure	108	2,940	3,986	27.1	388	9,528	12,130	32.0	0.84 (0.68-1.04)
ESRD	17	3,017	4,150	4.1	91	9,768	12,660	7.2	0.55 (0.33-0.92)

CVA=cerebrovascular accidents; TIA=transient ischemic attack, ESRD=End-stage renal disease

*IR – incidence rate per 1,000 person-years

Annex 2-Table 2-83 Hazard ratios of secondary outcomes in Cohort 1 patients, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 16,244)**			**Comparator (N = 64,817)**			

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
ITT analysis							
Hyperkalemia	156	29,783	5.2	740	115,516	6.4	0.83 (0.70-0.99)
Hypotension	215	29,716	7.2	962	115,285	8.3	0.88 (0.76-1.02)
Death from any cause*	212	29,922	7.1	1,078	116,120	9.3	0.76 (0.66-0.88)
Death from any cause in a hospital	81	29,949	2.7	320	116,314	2.8	0.98 (0.77-1.25)
As treated							
Hyperkalemia	55	10,751	5.1	253	42,329	6.0	0.86 (0.64-1.15)
Hypotension	66	10,738	6.2	366	42,299	8.7	0.71 (0.54-0.92)
Death from any cause*	50	10,769	4.6	294	42,416	6.9	0.68 (0.50-0.91)
Death from any cause in a hospital	17	10,771	1.6	86	42,428	2.0	0.78 (0.47-1.32)
MarketScan	**Aliskiren (N = 67,557)**			**Comparator (N = 269,586)**			
ITT analysis							
Hyperkalemia	609	129,681	4.7	2,146	509,539	4.2	1.11 (1.02-1.22)
Hypotension	683	129,603	5.3	2,878	508,559	5.7	0.93 (0.86-1.01)
Death from any cause in a hospital	394	130,346	3.0	1,860	511,698	3.6	0.83 (0.74-0.92)
As treated							
Hyperkalemia	212	49,989	4.2	789	184,983	4.3	1.00 (0.86-1.16)
Hypotension	235	49,974	4.7	1,012	184,861	5.5	0.87 (0.75-1.00)
Death from any cause in a hospital	104	50,049	2.1	564	185,218	3.1	0.68 (0.55-0.84)

*Death from any cause was obtained through linkage to Social Security Death Master file and was only available in the United database

Annex 2-Table 2-84 Hazard ratios of secondary outcomes in Cohort 2 patients, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 5,748)**			**Comparator (N = 22,813)**			
ITT analysis							
Hyperkalemia	82	9,747	8.4	343	37,678	9.1	0.92 (0.72-1.17)
Hypotension	96	9,729	9.9	416	37,629	11.1	0.89 (0.72-1.11)
Death from any cause*	104	9,824	10.6	467	37,990	12.3	0.85 (0.69-1.06)

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Death from any cause in a hospital	33	9,837	3.4	153	38,052	4.0	0.82 (0.56-1.20)
As treated							
Hyperkalemia	24	2,984	8.0	112	12,355	9.1	0.88 (0.56-1.36)
Hypotension	21	2,985	7.0	139	12,349	11.3	0.62 (0.39-0.98)
Death from any cause*	20	2,991	6.7	91	11,053	8.2	0.81 (0.50-1.32)
Death from any cause in a hospital	6	2,991	2.0	35	11,056	3.2	0.60 (0.25-1.44)
MarketScan	**Aliskiren (N = 29,813)**			**Comparator (N = 116,757)**			
ITT analysis							
Hyperkalemia	339	51,513	6.6	1,290	199,083	6.5	1.02 (0.90-1.15)
Hypotension	334	51,559	6.5	1,479	198,818	7.4	0.87 (0.77-0.98)
Death from any cause in a hospital	200	51,878	3.9	939	200,407	4.7	0.83 (0.71-0.96)
As treated							
Hyperkalemia	112	17,644	6.4	372	57,939	6.4	1.02 (0.82-1.26)
Hypotension	108	17,640	6.1	432	57,924	7.5	0.86 (0.69-1.06)
Death from any cause in a hospital	55	17,666	3.1	182	58,024	3.1	1.03 (0.76-1.40)

*Death from any cause was obtained through linkage to Social Security Death Master file and was only available in the United database

Annex 2-Table 2-85 Hazard ratios of secondary outcomes in Cohort 3 patients, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 4,149)**			**Comparator (N = 16,438)**			
ITT analysis							
Hyperkalemia	71	7,389	9.6	304	28,286	10.8	0.88 (0.68-1.14)
Hypotension	89	7,372	12.1	326	28,278	11.5	1.04 (0.82-1.31)
Death from any cause*	86	7,463	11.5	401	28,565	14.0	0.81 (0.64-1.03)
Death from any cause in a hospital	30	7,471	4.0	114	28,635	4.0	1.02 (0.68-1.53)
As treated							
Hyperkalemia	26	2,193	11.9	90	8,192	11.0	1.10 (0.71-1.70)
Hypotension	26	2,189	11.9	93	8,189	11.4	1.04 (0.67-1.61)

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Death from any cause*	15	2,199	6.8	76	8,209	9.3	0.76 (0.44-1.32)
Death from any cause in a hospital	3	2,200	1.4	27	8,212	3.3	0.43 (0.13-1.42)
MarketScan	**Aliskiren (N = 18,945)**			**Comparator (N = 74,265)**			
ITT analysis							
Hyperkalemia	252	35,429	7.1	1,009	138,000	7.3	0.97 (0.85-1.12)
Hypotension	242	35,454	6.8	982	137,980	7.1	0.96 (0.83-1.11)
Death from any cause in a hospital	159	35,707	4.5	700	139,092	5.0	0.89 (0.75-1.05)
As treated							
Hyperkalemia	60	10,681	5.6	315	37,647	8.4	0.70 (0.53-0.93)
Hypotension	69	10,677	6.5	263	37,666	7.0	0.97 (0.75-1.27)
Death from any cause in a hospital	30	10,692	2.8	143	37,726	3.8	0.75 (0.51-1.12)

*Death from any cause was obtained through linkage to Social Security Death Master file and was only available in the United database

Annex 2-Table 2-86 Hazard ratios of primary outcomes in Cohort 1 patients with or without hypertension diagnosis at baseline, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 17,370)**			**Comparator (N = 69,422)**			
ITT analysis							
Cerebrovascular accidents	269	31,566	8.5	1,018	123,525	8.2	1.03 (0.90-1.18)
Stroke	297	31,532	9.4	1,147	123,370	9.3	1.01 (0.89-1.15)
Ischemic stroke	274	31,551	8.7	1,039	123,479	8.4	1.03 (0.90-1.18)
Hemorrhagic stroke	47	31,825	1.5	194	124,488	1.6	0.95 (0.69-1.31)
Transient ischemic attack	180	31,648	5.7	604	123,902	4.9	1.17 (0.99-1.38)
Myocardial infarction	111	31,716	3.5	456	124,167	3.7	0.95 (0.78-1.17)
Heart failure	409	31,370	13.0	1,792	122,469	14.6	0.89 (0.80-0.99)
Acute renal failure	748	30,997	24.1	3,034	121,196	25.0	0.96 (0.89-1.05)
End-stage renal disease	200	31,612	6.3	938	123,509	7.6	0.84 (0.72-0.97)
As treated							

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Cerebrovascular accidents	84	11,315	7.4	350	45,215	7.7	0.96 (0.76-1.22)
Stroke	95	11,311	8.4	394	45,189	8.7	0.97 (0.77-1.21)
Ischemic stroke	89	11,311	7.9	355	45,201	7.9	1.00 (0.80-1.27)
Hemorrhagic stroke	10	11,349	0.9	72	45,347	1.6	0.56 (0.29-1.08)
Transient ischemic attack	60	11,319	5.3	194	45,281	4.3	1.24 (0.93-1.65)
Myocardial infarction	35	11,341	3.1	162	45,302	3.6	0.86 (0.60-1.24)
Heart failure	141	11,297	12.5	725	45,071	16.1	0.77 (0.65-0.93)
Acute renal failure	277	11,239	24.7	1,193	44,909	26.6	0.92 (0.81-1.05)
End-stage renal disease	69	11,328	6.1	370	45,237	8.2	0.75 (0.58-0.96)
MarketScan	**Aliskiren (N = 82,943)**			**Comparator (N = 331,702)**			
ITT analysis							
Cerebrovascular accidents	843	161,831	5.2	3,247	633,382	5.1	1.02 (0.94-1.10)
Stroke	1,528	160,971	9.5	6,009	629,992	9.5	1.00 (0.94-1.05)
Ischemic stroke	1,444	161,027	9.0	5,768	630,190	9.2	0.98 (0.93-1.04)
Hemorrhagic stroke	146	162,744	0.9	465	636,731	0.7	1.23 (1.02-1.48)
Transient ischemic attack	358	162,346	2.2	1,285	635,328	2.0	1.09 (0.97-1.22)
Myocardial infarction	711	162,009	4.4	2,952	633,608	4.7	0.94 (0.87-1.02)
Heart failure	1,284	161,202	8.0	5,712	630,128	9.1	0.88 (0.83-0.93)
Acute renal failure	3,888	158,103	24.6	15,790	618,698	25.5	0.97 (0.93-1.00)
End-stage renal disease	862	161,864	5.3	3,803	632,674	6.0	0.89 (0.82-0.96)
As treated							
Cerebrovascular accidents	266	61,586	4.3	1,011	228,650	4.4	0.99 (0.86-1.13)
Stroke	491	61,471	8.0	1,959	228,235	8.6	0.94 (0.85-1.04)
Ischemic stroke	470	61,476	7.7	1,889	228,261	8.3	0.93 (0.84-1.03)
Hemorrhagic stroke	42	61,691	0.7	129	229,042	0.6	1.22 (0.86-1.73)
Transient ischemic attack	111	61,620	1.8	419	228,850	1.8	0.99 (0.81-1.23)
Myocardial infarction	236	61,627	3.8	957	228,736	4.2	0.92 (0.80-1.06)
Heart failure	413	61,517	6.7	2,110	228,131	9.3	0.74 (0.66-0.82)
Acute renal failure	1,474	61,180	24.1	6,022	226,785	26.6	0.92 (0.87-0.97)

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
End-stage renal disease	236	61,623	3.8	1,267	228,654	5.5	0.70 (0.61-0.81)

Annex 2-Table 2-87 Hazard ratios of primary outcomes in Cohort 2 patients with or without hypertension diagnosis at baseline, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 7,423)**			**Comparator (N = 29,604)**			
ITT analysis							
Cerebrovascular accidents	126	12,167	10.4	477	46,803	10.2	1.02 (0.84-1.24)
Stroke	143	12,143	11.8	558	46,702	12.0	0.99 (0.82-1.19)
Ischemic stroke	131	12,154	10.8	519	46,738	11.1	0.97 (0.80-1.18)
Hemorrhagic stroke	23	12,289	1.9	82	47,239	1.7	1.08 (0.68-1.72)
Transient ischemic attack	88	12,198	7.2	291	46,995	6.2	1.16 (0.92-1.48)
Myocardial infarction	61	12,231	5.0	236	47,065	5.0	1.00 (0.75-1.32)
Heart failure	243	12,018	20.2	1,080	46,142	23.4	0.86 (0.75-0.99)
Acute renal failure	423	11,812	35.8	1,679	45,517	36.9	0.97 (0.87-1.08)
End-stage renal disease	135	12,158	11.1	566	46,659	12.1	0.92 (0.76-1.11)
As treated							
Cerebrovascular accidents	36	3,881	9.3	143	14,902	9.6	0.97 (0.67-1.40)
Stroke	44	3,880	11.3	172	14,894	11.6	0.98 (0.71-1.37)
Ischemic stroke	41	3,880	10.6	162	14,896	10.9	0.97 (0.69-1.37)
Hemorrhagic stroke	6	3,892	1.5	19	14,937	1.3	1.24 (0.49-3.10)
Transient ischemic attack	30	3,881	7.7	81	14,913	5.4	1.44 (0.95-2.19)
Myocardial infarction	15	3,889	3.9	68	14,922	4.6	0.84 (0.48-1.47)
Heart failure	86	3,868	22.2	373	14,841	25.1	0.89 (0.70-1.12)
Acute renal failure	145	3,849	37.7	601	14,793	40.6	0.93 (0.77-1.11)
End-stage renal disease	41	3,882	10.6	174	14,895	11.7	0.90 (0.64-1.26)
MarketScan	**Aliskiren (N = 36,892)**			**Comparator (N = 146,703)**			
ITT analysis							

Outcome	Events	Person-Years	Rate per 1,000 person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Cerebrovascular accidents	424	65,216	6.5	1,531	254,643	6.0	1.08 (0.97-1.21)
Stroke	764	64,820	11.8	2,921	253,015	11.5	1.02 (0.94-1.11)
Ischemic stroke	724	64,845	11.2	2,813	253,084	11.1	1.01 (0.93-1.09)
Hemorrhagic stroke	74	65,659	1.1	212	256,150	0.8	1.37 (1.05-1.78)
Transient ischemic attack	172	65,508	2.6	632	255,577	2.5	1.06 (0.90-1.26)
Myocardial infarction	342	65,339	5.2	1,403	254,747	5.5	0.95 (0.84-1.07)
Heart failure	706	64,848	10.9	3,252	252,430	12.9	0.84 (0.78-0.92)
Acute renal failure	2,076	63,324	32.8	8,540	246,861	34.6	0.94 (0.90-0.99)
End-stage renal disease	501	65,118	7.7	2,144	253,905	8.4	0.90 (0.82-0.99)
As treated							
Cerebrovascular accidents	131	21,968	6.0	393	73,392	5.4	1.16 (0.95-1.41)
Stroke	224	21,931	10.2	794	73,282	10.8	0.98 (0.84-1.14)
Ischemic stroke	210	21,935	9.6	769	73,286	10.5	0.95 (0.81-1.10)
Hemorrhagic stroke	30	22,008	1.4	46	73,508	0.6	2.29 (1.44-3.63)
Transient ischemic attack	46	21,981	2.1	155	73,454	2.1	1.03 (0.74-1.44)
Myocardial infarction	90	21,993	4.1	357	73,425	4.9	0.87 (0.69-1.09)
Heart failure	192	21,946	8.8	953	73,214	13.0	0.71 (0.61-0.83)
Acute renal failure	659	21,855	30.2	2,645	72,869	36.3	0.86 (0.78-0.93)
End-stage renal disease	136	21,977	6.2	585	73,367	8.0	0.80 (0.67-0.97)

Annex 2-Table 2-88 Hazard ratios of primary outcomes in Cohort 3 patients with or without hypertension diagnosis at baseline, stratified by database and type of analysis

Outcome	Events	Person-Years	Rate per 1,000 Person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
United	**Aliskiren (N = 5,332)**			**Comparator (N = 21,217)**			
ITT analysis							
Cerebrovascular accidents	98	9,193	10.7	423	35,742	11.8	0.90 (0.72-1.12)
Stroke	115	9,178	12.5	485	35,681	13.6	0.92 (0.75-1.13)
Ischemic stroke	107	9,188	11.7	454	35,710	12.7	0.92 (0.74-1.13)

Outcome	Events	Person-Years	Rate per 1,000 Person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Hemorrhagic stroke	20	9,272	2.2	57	36,163	1.6	1.38 (0.83-2.30)
Transient ischemic attack	71	9,214	7.7	255	35,896	7.1	1.08 (0.83-1.41)
Myocardial infarction	56	9,222	6.1	219	35,959	6.1	1.00 (0.75-1.34)
Heart failure	198	9,066	21.8	838	35,140	23.9	0.91 (0.78-1.06)
Acute renal failure	354	8,879	39.9	1,410	34,518	40.9	0.97 (0.86-1.09)
End-stage renal disease	124	9,148	13.6	479	35,600	13.5	1.01 (0.83-1.23)
As treated							
Cerebrovascular accidents	22	2,922	7.5	119	11,316	10.5	0.72 (0.46-1.14)
Stroke	27	2,919	9.3	140	11,313	12.4	0.75 (0.50-1.14)
Ischemic stroke	25	2,920	8.6	124	11,315	11.0	0.79 (0.51-1.21)
Hemorrhagic stroke	4	2,929	1.4	20	11,354	1.8	0.79 (0.27-2.31)
Transient ischemic attack	18	2,918	6.2	69	11,323	6.1	1.02 (0.61-1.71)
Myocardial infarction	18	2,926	6.2	68	11,341	6.0	1.03 (0.61-1.73)
Heart failure	66	2,910	22.7	295	11,281	26.2	0.86 (0.66-1.13)
Acute renal failure	111	2,900	38.3	521	11,206	46.5	0.82 (0.66-1.00)
End-stage renal disease	35	2,921	12.0	177	11,317	15.6	0.77 (0.54-1.10)
MarketScan	**Aliskiren (N = 22,835)**			**Comparator (N = 91,073)**			
ITT analysis							
Cerebrovascular accidents	272	43,185	6.3	1,161	168,597	6.9	0.91 (0.80-1.04)
Stroke	524	42,874	12.2	2,225	167,320	13.3	0.92 (0.83-1.01)
Ischemic stroke	502	42,884	11.7	2,149	167,373	12.8	0.91 (0.83-1.00)
Hemorrhagic stroke	42	43,495	1.0	154	169,806	0.9	1.07 (0.76-1.50)
Transient ischemic attack	125	43,348	2.9	450	169,330	2.7	1.09 (0.89-1.33)
Myocardial infarction	508	42,928	11.8	2,331	167,045	14.0	0.84 (0.77-0.93)
Heart failure	1,561	41,606	37.5	6,287	162,363	38.7	0.97 (0.92-1.02)
Acute renal failure	257	43,209	6.0	1,088	168,604	6.5	0.92 (0.81-1.06)
End-stage renal disease	427	43,029	9.9	1,955	167,546	11.7	0.85 (0.76-0.94)
As treated							
Cerebrovascular accidents	60	12,896	4.7	265	46,456	5.7	0.83 (0.63-1.10)

Outcome	Events	Person-Years	Rate per 1,000 Person-yrs	Events	Person-Years	Rate per 1,000 person-yrs	HR (95% CI)
Stroke	135	12,869	10.5	542	46,367	11.7	0.91 (0.75-1.10)
Ischemic stroke	130	12,870	10.1	522	46,370	11.3	0.91 (0.75-1.10)
Hemorrhagic stroke	9	12,922	0.7	32	46,545	0.7	1.03 (0.49-2.16)
Transient ischemic attack	29	12,908	2.3	105	46,497	2.3	1.02 (0.67-1.53)
Myocardial infarction	67	12,904	5.2	289	46,477	6.2	0.85 (0.65-1.10)
Heart failure	127	12,885	9.9	656	46,344	14.2	0.71 (0.59-0.86)
Acute renal failure	448	12,801	35.0	1,930	46,018	41.9	0.85 (0.77-0.94)
End-stage renal disease	102	12,898	7.9	558	46,394	12.0	0.68 (0.55-0.83)

Annex 2-Table 2-89 Baseline* serum creatinine and potassium values in Cohort 1 patients with laboratory tests results available in United database

Lab/exposure group	Number of patients	% of matched exposure group	Mean value	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	4,130	25.4	1.10	1.67	0.98	0.82-1.15
comparator	16,165	24.9	1.13	2.25	0.96	0.80-1.13
Potassium (mEq/L)						
aliskiren	4,090	25.2	4.2	0.5	4.2	3.9-4.5
comparator	16,000	24.7	4.2	0.5	4.2	3.9-4.5

SD=standard deviation

*assessed during the entire baseline period; the closest to the index date value is used

Annex 2-Table 2-90 Number of laboratory tests performed during 1 year of follow-up for Cohort 1 patients with laboratory tests results available in United database (intensity of surveillance)

Lab/exposure group	Number of patients	Person-Years	Mean number of tests	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	4,130	3,421	1.3	1.7	1	0 - 2
comparator	16,165	13,291	1.3	1.9	1	0 - 2
Potassium (mEq/L)						
aliskiren	4,090	3,389	1.3	1.8	1	0 - 2
comparator	16,000	13,156	1.3	1.9	1	0 - 2

SD=standard deviation

Annex 2-Table 2-91 Baseline* serum creatinine and potassium values in Cohort 2 patients with laboratory tests results available in United database

Lab/exposure group	Number of patients	% of matched exposure group	Mean value	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	1,520	26.4	1.12	0.57	1.00	0.85-1.20
comparator	5,817	25.5	1.17	1.56	0.99	0.81-1.20
Potassium (mEq/L)						
aliskiren	1,498	26.1	4.3	0.5	4.2	3.9-4.6
comparator	5,754	25.2	4.2	0.5	4.2	3.9-4.5

SD=standard deviation

*assessed during the entire baseline period; the closest to the index date value is used

Annex 2-Table 2-92 Number of laboratory tests performed during 1 year of follow-up for Cohort 2 patients with laboratory tests results available in United database (intensity of surveillance)

Lab/exposure group	Number of patients	Person-Years	Mean number of tests	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	1,520	1,262	1.5	2.0	1	0 - 2
comparator	5,817	4,804	1.5	2.0	1	0 - 2
Potassium (mEq/L)						

Lab/exposure group	Number of patients	Person-Years	Mean number of tests	SD	Median	Interquartile range
aliskiren	1,498	1,244	1.3	1.8	1	0 - 2
comparator	5,754	4,752	1.3	1.9	1	0 - 2

SD=standard deviation

Annex 2-Table 2-93 Baseline* serum creatinine and potassium values in Cohort 3 patients with laboratory tests results available in United database

Lab/exposure group	Number of patients	% of matched exposure group	Mean value	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	1,023	24.7	1.15	0.57	1.02	0.87-1.26
comparator	3,940	24.0	1.25	1.50	1.00	0.85-1.28
Potassium (mEq/L)						
aliskiren	1,013	24.4	4.18	0.54	4.1	3.8-4.5
comparator	3,889	23.7	4.19	0.54	4.2	3.8-4.5

SD=standard deviation
*assessed during the entire baseline period; the closest to the index date value is used

Annex 2-Table 2-94 Number of laboratory tests performed during 1 year of follow-up for Cohort 3 patients with laboratory tests results available in United database (intensity of surveillance)

Lab/exposure group	Number of patients	Person-Years	Mean number of tests	SD	Median	Interquartile range
Serum creatinine (mg/dL)						
aliskiren	1,023	839	1.6	2.0	1	0-2
comparator	3,940	3,171	1.5	2.0	1	0-2
Potassium (mEq/L)						
aliskiren	1,013	829	1.6	2.0	1	0-2
comparator	3,889	3,131	1.5	2.0	1	0-2

SD=standard deviation

Annex 2-Table 2-95 Baseline characteristics of Cohort 1 not PS-matched aliskiren patients, stratified by database

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 1,695	N = 6,839
Demographics	***Count (%)***	***Count (%)***
Age: 18-39	109 (6.4)	299 (4.4)
40-54	572 (33.7)	1,741 (25.5)
55-64	680 (40.1)	2,469 (36.1)
65+	334 (19.7)	2,330 (34.1)
Index year: 2007	34 (2.0)	160 (2.3)
2008	250 (14.7)	844 (12.3)
2009	393 (23.2)	1,303 (19.1)
2010	460 (27.1)	1,968 (28.8)
2011	451 (26.6)	2,125 (31.1)
2012	107 (6.3)	439 (6.4)

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 1,695	N = 6,839
Male	952 (56.2)	3,386 (49.5)
Region: Midwest	234 (13.8)	1,741 (25.5)
Northeast	129 (7.6)	612 (8.9)
South	1,154 (68.1)	3,622 (53.0)
West	178 (10.5)	864 (12.6)
Plan type: commercial	1,694 (99.9)	4,462 (65.2)
Medicare	1 (0.1)	2,377 (34.8)
Monotherapy on index date	334 (19.7)	1,108 (16.2)
Dual therapy on index date	528 (31.2)	2,025 (29.6)
Multiple therapy on index date	833 (49.1)	3,706 (54.2)
Coexisting medical conditions		
Atrial fibrillation/flutter	76 (4.5)	369 (5.4)
Atherosclerosis	311 (18.4)	1,072 (15.7)
Coronary artery bypass graft, old or new	32 (1.9)	56 (0.8)
Coronary artery disease (CAD)	329 (19.4)	1,203 (17.6)
Carotid endarterectomy	4 (0.2)	8 (0.1)
Carotid stent	0 (0.0)	0 (0.0)
Heart failure (CHF)	82 (4.8)	276 (4.0)
Conduction disorders	30 (1.8)	93 (1.4)
Coronary stent	10 (0.6)	38 (0.6)
CVD	568 (33.5)	2,196 (32.1)
Diabetes	694 (40.9)	2,277 (33.3)
Diabetes and renal impairment	194 (11.5)	465 (6.8)
Hemorrhagic stroke	27 (1.6)	115 (1.7)
Hyperkalemia	36 (2.1)	75 (1.1)
Hyperlipidemia	1,105 (65.2)	2,696 (39.4)
Ischemic stroke	27 (1.6)	129 (1.9)
Other stroke effects	7 (0.4)	38 (0.6)
Old MI	18 (1.1)	57 (0.8)
Previous TIA	25 (1.5)	127 (1.9)
Pre-diabetes	44 (2.6)	117 (1.7)
Percutaneous transluminal coronary angioplasty (PTCA)	9 (0.5)	31 (0.5)
Peripheral vascular disease or PVD surgery	33 (2.0)	109 (1.6)
Radiographic procedures requiring contrast media	123 (7.3)	640 (9.4)
Recent MI	17 (1.0)	68 (1.0)
Renal impairment	290 (17.1)	843 (12.3)
Type 2 diabetes	656 (38.7)	2,160 (31.6)
Ventricular arrhythmia	43 (2.5)	157 (2.3)
Prior medications		
Alpha blocker	112 (6.6)	491 (7.2)
Combined alpha and beta blocker	285 (16.8)	1,267 (18.5)
ACE inhibitor	417 (24.6)	1,652 (24.2)
Aliskiren	0 (0.0)	0 (0.0)
Anti-arrhythmic drug	30 (1.8)	146 (2.1)

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 1,695	N = 6,839
ARB	438 (25.8)	1,863 (27.2)
Aspirin	0 (0.0)	7 (0.1)
Aspirin/dipyridamole	6 (0.4)	37 (0.5)
Beta blocker	572 (33.8)	2,544 (37.2)
Calcium channel blocker	693 (40.9)	2,920 (42.7)
Clopidogrel	151 (8.9)	653 (9.6)
Diabetes medications	528 (31.2)	1,904 (27.8)
Insulin	258 (15.2)	813 (11.9)
Loop diuretic	327 (19.3)	1,461 (21.4)
NSAIDs	320 (18.9)	1,319 (19.3)
Oral anticoagulants	73 (4.3)	342 (5.0)
Other antiplatelet agent	7 (0.4)	47 (0.7)
Other hypertension medications	399 (23.5)	1,659 (24.3)
Other lipid-lowering drugs	318 (18.8)	1,278 (18.7)
Potassium sparing agents/aldosterone antagonists	159 (9.4)	601 (8.8)
Potassium supplements	228 (13.5)	1,159 (17.0)
Prasugrel	3 (0.2)	19 (0.3)
Statin	812 (47.9)	3,125 (45.7)
Thiazide diuretic	704 (41.5)	3,111 (45.5)
Ticagrelor	0 (0.0)	0 (0.0)
Health Care Utilization	**Mean (SD)**	**Mean (SD)**
Number of medications	9.2 (5.7)	8.0 (5.3)
Number of hospitalizations	0.2 (0.6)	0.1 (0.4)
Number of hospital days	0.9 (4.1)	0.7 (3.1)
Number of physician office visits	6.2 (4.8)	6.0 (4.5)
Number of cardiologist visits	1.1 (2.2)	0.8 (1.9)
Number of neurologist visits	0.1 (0.5)	0.1 (0.6)
Hospitalization in 30 days prior	0.0 (0.2)	0.0 (0.2)
Number of laboratory tests ordered	3.0 (3.2)	2.7 (3.1)
Number of lipid tests ordered	0.7 (0.9)	0.6 (0.8)
Number of creatinine tests ordered	0.0 (0.3)	0.1 (0.4)

PS = propensity score

Annex 2-Table 2-96 Baseline characteristics of Cohort 2 not PS-matched aliskiren patients, stratified by database

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 476	N = 2,129
Demographics	**Count (%)**	**Count (%)**
Age: 18-39	21 (4.4)	77 (3.6)
40-54	140 (29.4)	470 (22.1)
55-64	185 (38.9)	780 (36.6)
65+	130 (27.3)	802 (37.7)
Index year: 2007	15 (3.2)	67 (3.1)

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 476	N = 2,129
2008	61 (12.8)	205 (9.6)
2009	95 (20.0)	328 (15.4)
2010	142 (29.8)	640 (30.1)
2011	143 (30.0)	753 (35.4)
2012	20 (4.2)	136 (6.4)
Male	268 (56.3)	1,074 (50.4)
Region: Midwest	60 (12.6)	530 (24.9)
Northeast	36 (7.6)	169 (7.9)
South	335 (70.4)	1,113 (52.3)
West	45 (9.5)	317 (14.9)
Plan type: commercial	476 (100.0)	1,317 (61.9)
Medicare	0 (0.0)	812 (38.1)
Monotherapy on index date	N/A	N/A
Dual therapy on index date	67 (14.1)	342 (16.1)
Multiple therapy on index date	409 (85.9)	1,787 (83.9)
Coexisting medical conditions		
Atrial fibrillation/flutter	27 (5.7)	156 (7.3)
Atherosclerosis	113 (23.7)	436 (20.5)
Coronary artery bypass graft, old or new	11 (2.3)	27 (1.3)
Coronary artery disease (CAD)	122 (25.6)	484 (22.7)
Carotid endarterectomy	0 (0.0)	1 (0.1)
Carotid stent	0 (0.0)	0 (0.0)
Heart failure (CHF)	37 (7.8)	124 (5.8)
Conduction disorders	11 (2.3)	37 (1.7)
Coronary stent	8 (1.7)	12 (0.6)
CVD	194 (40.8)	848 (39.8)
Diabetes	257 (54.0)	842 (39.6)
Diabetes and renal impairment	8 (1.7)	202 (9.5)
Hemorrhagic stroke	5 (1.1)	50 (2.4)
Hyperkalemia	9 (1.9)	38 (1.8)
Hyperlipidemia	332 (69.8)	877 (41.2)
Ischemic stroke	12 (2.5)	57 (2.7)
Other stroke effects	5 (1.1)	16 (0.8)
Old MI	7 (1.5)	25 (1.2)
Previous TIA	9 (1.9)	49 (2.3)
Pre-diabetes	9 (1.9)	36 (1.7)
Percutaneous transluminal coronary angioplasty (PTCA)	7 (1.5)	13 (0.6)
Peripheral vascular disease or PVD surgery	14 (2.9)	43 (2.0)
Radiographic procedures requiring contrast media	40 (8.4)	195 (9.2)
Recent MI	10 (2.1)	30 (1.4)
Renal impairment	120 (25.2)	375 (17.6)
Type 2 diabetes	241 (50.6)	802 (37.7)
Ventricular arrhythmia	16 (3.4)	71 (3.3)
Prior medications		

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 476	N = 2,129
Alpha blocker	58 (12.2)	230 (10.8)
Combined alpha and beta blocker	101 (21.2)	552 (25.9)
ACE inhibitor	246 (51.7)	927 (43.5)
Aliskiren	0 (0.0)	0 (0.0)
Anti-arrhythmic drug	9 (1.9)	61 (2.9)
ARB	257 (54.0)	1,098 (51.6)
Aspirin	1 (0.2)	5 (0.2)
Aspirin/dipyridamole	4 (0.8)	13 (0.6)
Beta blocker	219 (46.0)	962 (45.2)
Calcium channel blocker	299 (62.8)	1,239 (58.2)
Clopidogrel	55 (11.6)	273 (12.8)
Diabetes medications	192 (40.3)	712 (33.4)
Insulin	113 (23.7)	311 (14.6)
Loop diuretic	137 (28.8)	661 (31.1)
NSAIDs	85 (17.9)	411 (19.3)
Oral anticoagulants	35 (7.4)	147 (6.9)
Other antiplatelet agent	3 (0.6)	21 (1.0)
Other hypertension medications	160 (33.6)	717 (33.7)
Other lipid-lowering drugs	102 (21.4)	474 (22.3)
Potassium sparing agents/aldosterone antagonists	57 (12.0)	282 (13.3)
Potassium supplements	96 (20.2)	471 (22.1)
Prasugrel	4 (0.8)	9 (0.4)
Statin	279 (58.6)	1,150 (54.0)
Thiazide diuretic	210 (44.1)	993 (46.6)
Ticagrelor	0 (0.0)	0 (0.0)
Health Care Utilization	**Mean (SD)**	**Mean (SD)**
Number of medications	11.5 (6.2)	10.8 (6.5)
Number of hospitalizations	0.2 (0.7)	0.2 (0.4)
Number of hospital days	1.1 (3.7)	0.9 (3.4)
Number of physician office visits	7.2 (5.3)	7.8 (6.2)
Number of cardiologist visits	1.3 (2.0)	1.3 (2.5)
Number of neurologist visits	0.1 (0.5)	0.2 (1.4)
Hospitalization in 30 days prior	0.1 (0.2)	0.0 (0.2)
Number of laboratory tests ordered	3.4 (3.9)	3.2 (3.7)
Number of lipid tests ordered	0.8 (1.1)	0.6 (0.9)
Number of creatinine tests ordered	0.0 (0.3)	0.1 (0.4)

PS = propensity score

Annex 2-Table 2-97 Baseline characteristics of Cohort 3 not PS-matched aliskiren patients, stratified by database

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 347	N = 1,436
Demographics	**Count (%)**	**Count (%)**

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 347	N = 1,436
Age: 18-39	14 (4.0)	32 (2.2)
40-54	97 (28.0)	249 (17.3)
55-64	147 (42.4)	519 (36.1)
65+	89 (25.6)	636 (44.3)
Index year: 2007	13 (3.7)	51 (3.6)
2008	60 (17.3)	176 (12.3)
2009	79 (22.8)	292 (20.3)
2010	87 (25.1)	386 (26.9)
2011	95 (27.4)	447 (31.1)
2012	13 (3.7)	84 (5.8)
Male	220 (63.4)	750 (52.2)
Region: Midwest	58 (16.7)	405 (28.2)
Northeast	22 (6.3)	121 (8.4)
South	225 (64.8)	664 (46.2)
West	42 (12.1)	246 (17.1)
Plan type: commercial	347 (100.0)	788 (54.9)
Medicare	0 (0.0)	648 (45.1)
Monotherapy on index date	N/A	N/A
Dual therapy on index date	33 (9.5)	154 (10.7)
Multiple therapy on index date	314 (90.5)	1,282 (89.3)
Coexisting medical conditions		
Atrial fibrillation/flutter	26 (7.5)	117 (8.2)
Atherosclerosis	86 (24.8)	323 (22.5)
Coronary artery bypass graft, old or new	10 (2.9)	15 (1.0)
Coronary artery disease (CAD)	88 (25.4)	342 (23.8)
Carotid endarterectomy	1 (0.3)	6 (0.4)
Carotid stent	0 (0.0)	1 (0.1)
Heart failure (CHF)	27 (7.8)	92 (6.4)
Conduction disorders	5 (1.4)	27 (1.9)
Coronary stent	4 (1.2)	9 (0.6)
CVD	154 (44.4)	599 (41.7)
Diabetes	185 (53.3)	585 (40.7)
Diabetes and renal impairment	6 (1.7)	158 (11.0)
Hemorrhagic stroke	5 (1.4)	41 (2.9)
Hyperkalemia	12 (3.5)	15 (1.0)
Hyperlipidemia	246 (70.9)	577 (40.2)
Ischemic stroke	6 (1.7)	44 (3.1)
Other stroke effects	2 (0.6)	18 (1.3)
Old MI	4 (1.2)	10 (0.7)
Previous TIA	5 (1.4)	43 (3.0)
Pre-diabetes	10 (2.9)	27 (1.9)
Percutaneous transluminal coronary angioplasty (PTCA)	3 (0.9)	11 (0.8)
Peripheral vascular disease or PVD surgery	11 (3.2)	47 (3.3)
Radiographic procedures requiring contrast media	34 (9.8)	138 (9.6)

Characteristic	United	MarketScan
	Aliskiren	Aliskiren
	N = 347	N = 1,436
Recent MI	8 (2.3)	19 (1.3)
Renal impairment	82 (23.6)	296 (20.6)
Type 2 diabetes	175 (50.4)	560 (39.0)
Ventricular arrhythmia	7 (2.0)	36 (2.5)
Prior medications		
Alpha blocker	36 (10.4)	181 (12.6)
Combined alpha and beta blocker	88 (25.4)	361 (25.1)
ACE inhibitor	129 (37.2)	522 (36.4)
Aliskiren	0 (0.0)	0 (0.0)
Anti-arrhythmic drug	14 (4.0)	41 (2.9)
ARB	137 (39.5)	532 (37.1)
Aspirin	0 (0.0)	0 (0.0)
Aspirin/dipyridamole	1 (0.3)	10 (0.7)
Beta blocker	179 (51.6)	668 (46.5)
Calcium channel blocker	326 (94.0)	1,339 (93.3)
Clopidogrel	31 (8.9)	209 (14.6)
Diabetes medications	143 (41.2)	503 (35.0)
Insulin	78 (22.5)	212 (14.8)
Loop diuretic	89 (25.7)	407 (28.3)
NSAIDs	72 (20.8)	280 (19.5)
Oral anticoagulants	25 (7.2)	109 (7.6)
Other antiplatelet agent	2 (0.6)	14 (1.0)
Other hypertension medications	121 (34.9)	526 (36.6)
Other lipid-lowering drugs	83 (23.9)	342 (23.8)
Potassium sparing agents/aldosterone antagonists	32 (9.2)	170 (11.8)
Potassium supplements	72 (20.8)	344 (24.0)
Prasugrel	2 (0.6)	4 (0.3)
Statin	228 (65.7)	813 (56.6)
Thiazide diuretic	179 (51.6)	783 (54.5)
Ticagrelor	0 (0.0)	0 (0.0)
Health Care Utilization	**Mean (SD)**	**Mean (SD)**
Number of medications	11.4 (5.8)	11.4 (5.8)
Number of hospitalizations	0.2 (0.6)	0.2 (0.5)
Number of hospital days	0.7 (2.5)	1.0 (3.1)
Number of physician office visits	6.6 (4.5)	7.9 (6.0)
Number of cardiologist visits	1.6 (3.2)	1.4 (2.6)
Number of neurologist visits	0.1 (0.5)	0.2 (1.2)
Hospitalization in 30 days prior	0.0 (0.2)	0.0 (0.2)
Number of laboratory tests ordered	3.1 (3.1)	3.2 (4.0)
Number of lipid tests ordered	0.7 (0.8)	0.5 (0.8)
Number of creatinine tests ordered	0.0 (0.2)	0.1 (0.5)

PS = propensity score

Annex 2-Table 2-98 Incidence rates of primary outcomes in aliskiren patients not PS-matched to comparators, stratified by database and cohort

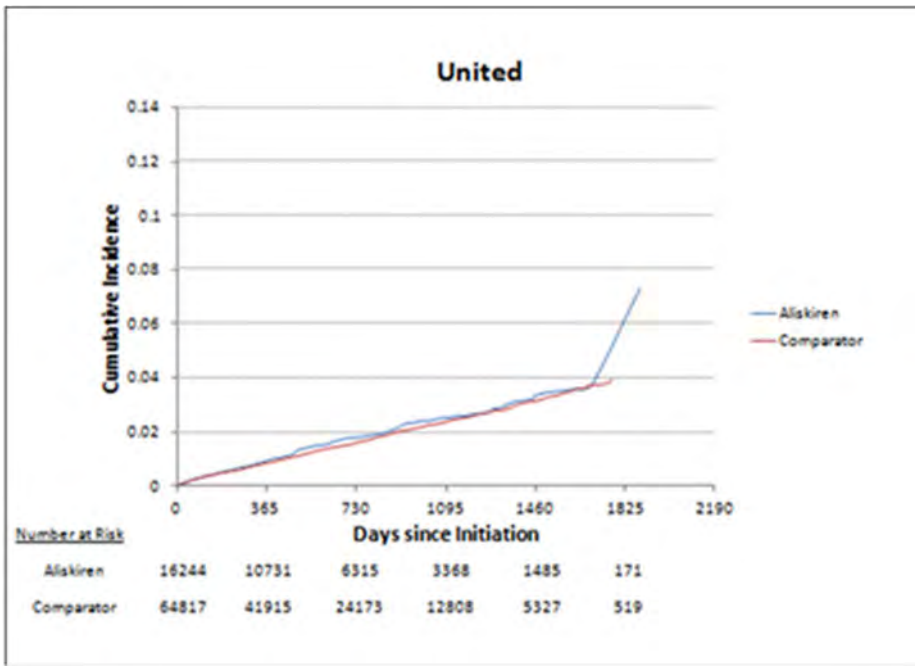
Outcome	Events	IR* (95% CI)	Events	IR* (95% CI)
Cohort 1	**United (N = 1,695)**		**MarketScan (N = 6,839)**	
Cerebrovascular accidents	32	13.0 (9.2-18.4)	84	7.9 (6.4-9.8)
Stroke	30	12.2 (8.5-17.4)	144	13.7 (11.6-16.1)
Ischemic stroke	28	11.4 (7.8-16.4)	135	12.8 (10.8-15.2)
Hemorrhagic stroke	6	2.4 (1.1-5.4)	9	0.8 (0.4-1.6)
Transient ischemic attack	14	5.7 (3.4-9.5)	29	2.7 (1.9-3.9)
Myocardial infarction	10	4.0 (2.2-7.5)	62	5.8 (4.6-7.5)
Heart failure	49	20.0 (15.2-26.5)	130	12.3 (10.4-14.6)
Acute renal failure	105	44.2 (36.5-53.5)	406	39.5 (35.8-43.5)
End-stage renal disease	41	16.7 (12.3-22.7)	97	9.2 (7.5-11.2)
Cohort 2	**United (N = 476)**		**MarketScan (N = 2,129)**	
Cerebrovascular accidents	3	4.4 (1.4-13.5)	38	12.1 (8.8-16.6)
Stroke	4	5.8 (2.2-15.5)	63	20.2 (15.8-25.8)
Ischemic stroke	4	5.8 (2.2-15.5)	62	19.8 (15.5-25.5)
Hemorrhagic stroke	0	-	3	1.0 (0.3-2.9)
Transient ischemic attack	5	7.3 (3.0-17.6)	12	3.8 (2.2-6.7)
Myocardial infarction	1	1.5 (0.2-10.3)	26	8.3 (5.6-12.1)
Heart failure	20	29.7 (19.2-46.1)	58	18.6 (14.4-24.0)
Acute renal failure	38	58.4 (42.5-80.3)	172	57.4 (49.5-66.7)
End-stage renal disease	13	19.2 (11.1-33.0)	47	15.0 (11.3-20.0)
Cohort 3	**United (N = 347)**		**MarketScan (N =1,436)**	
Cerebrovascular accidents	4	7.2 (2.7-19.3)	25	10.9 (7.4-16.2)
Stroke	4	7.2 (2.7-19.3)	45	19.8 (14.8-26.6)
Ischemic stroke	4	7.2 (2.7-19.3)	45	19.8 (14.8-26.6)
Hemorrhagic stroke	0	-	1	0.4 (0.1-3.1)
Transient ischemic attack	1	1.8 (0.3-12.8)	9	3.9 (2.0-7.5)
Myocardial infarction	1	1.8 (0.3-12.7)	23	10.1 (6.7-15.1)
Heart failure	14	25.9 (15.3-43.7)	42	18.5 (13.7-25.1)
Acute renal failure	23	43.5 (28.9-65.4)	125	57.6 (48.3-68.6)
End-stage renal disease	13	24.2 (14.1-41.7)	45	19.8 (14.8-26.6)

*IR – Incidence rate per 1,000 person-years of follow-up

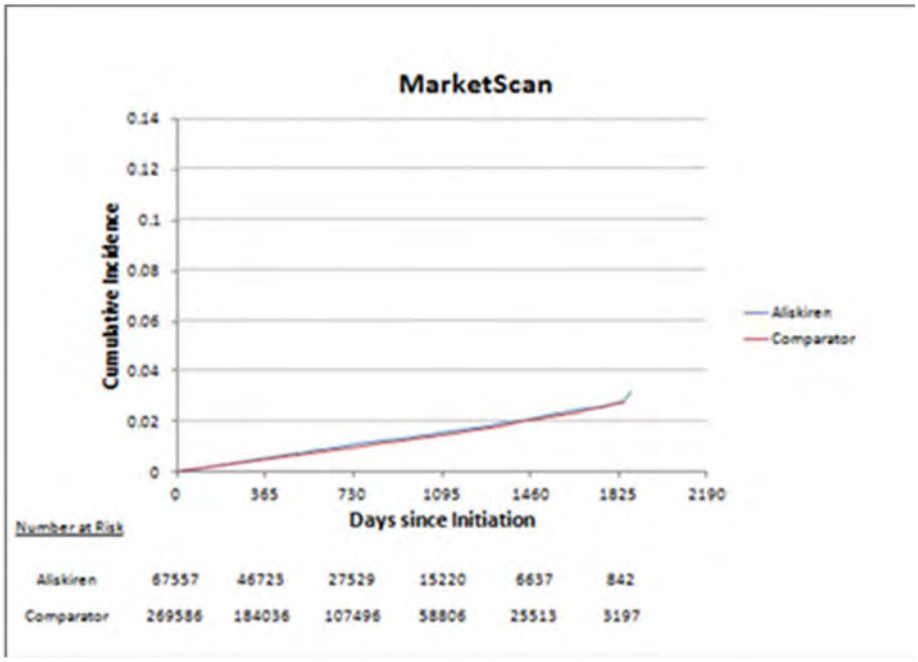
Annex 2.5 Results figures

Annex 2.5.1 Cumulative incidence figures

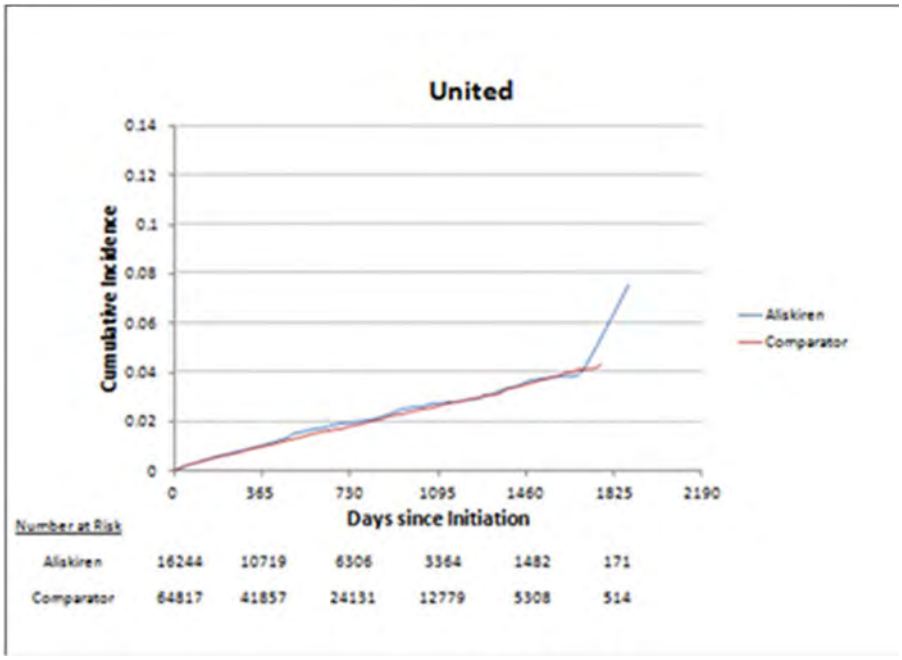
Annex 2-Figure 2-1 Cumulative incidence of cerebrovascular accidents in Cohort 1, ITT – United



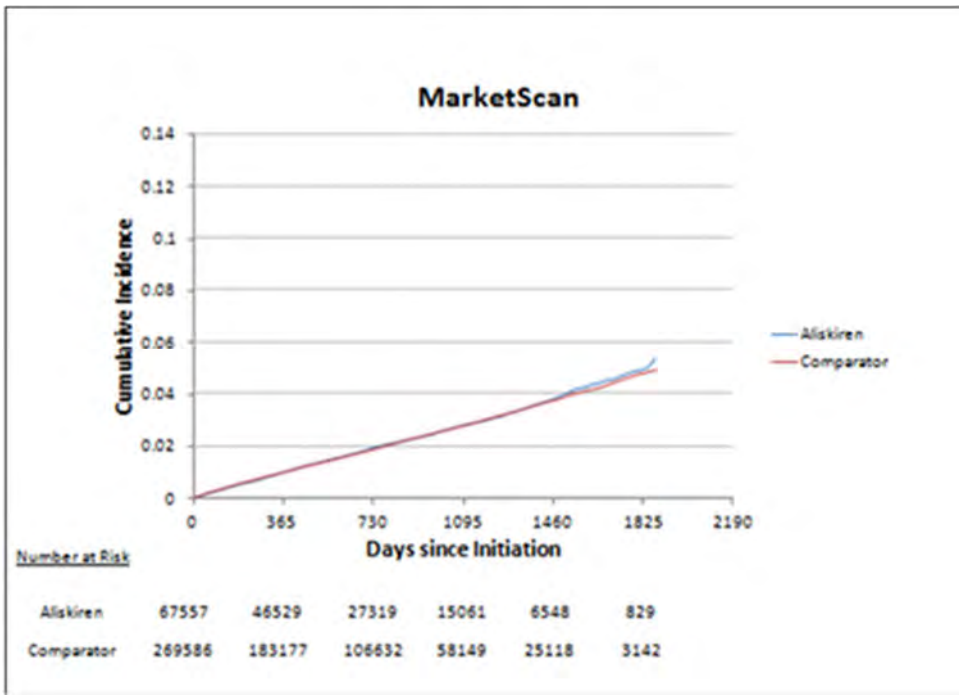
Annex 2-Figure 2-2 Cumulative incidence of cerebrovascular accidents in Cohort 1, ITT – MarketScan



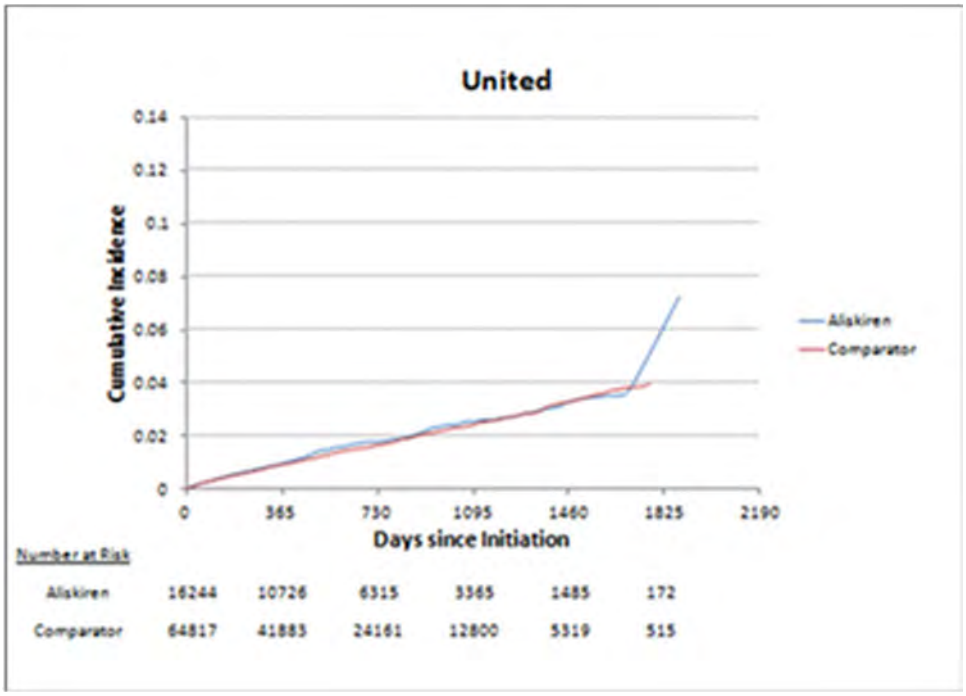
Annex 2-Figure 2-3 Cumulative incidence of stroke in Cohort 1, ITT – United



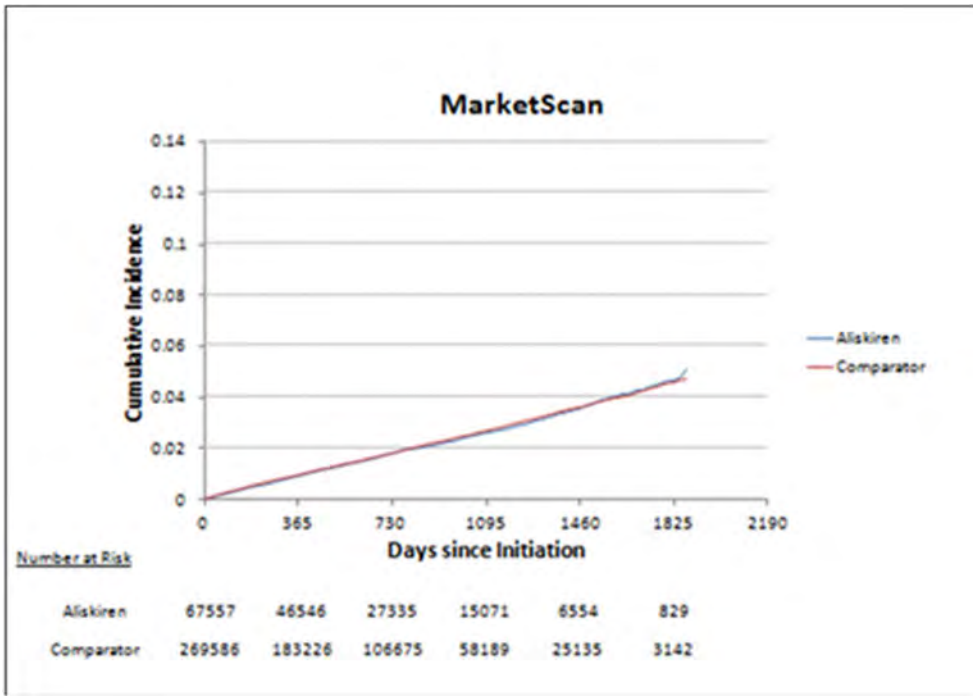
Annex 2-Figure 2-4 Cumulative incidence of stroke in Cohort 1, ITT – MarketScan



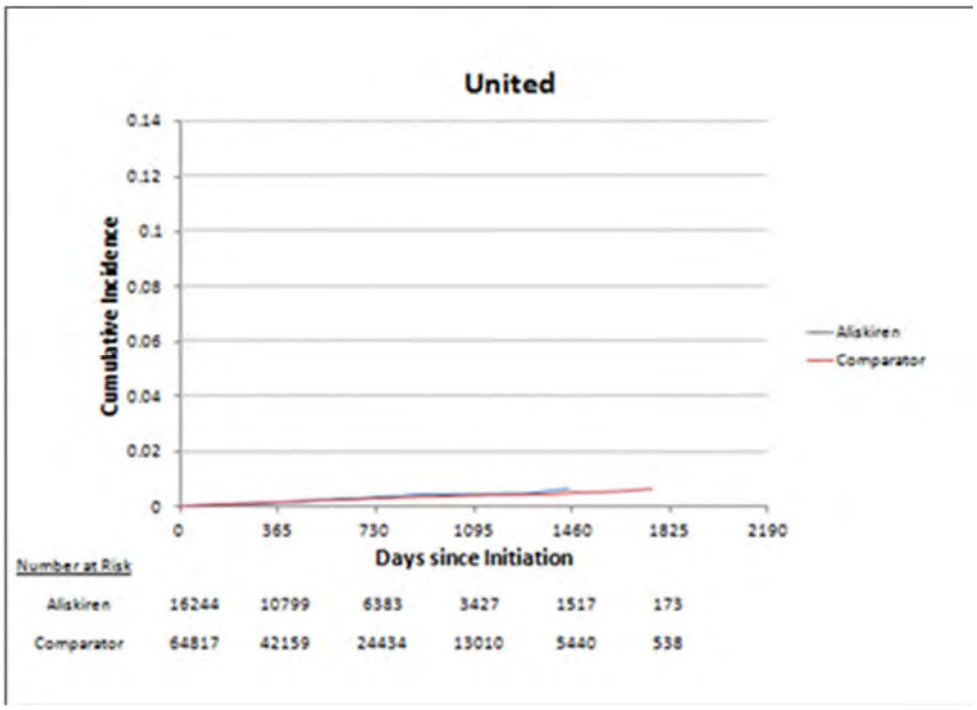
Annex 2-Figure 2-5 Cumulative incidence of ischemic stroke in Cohort 1, ITT – United



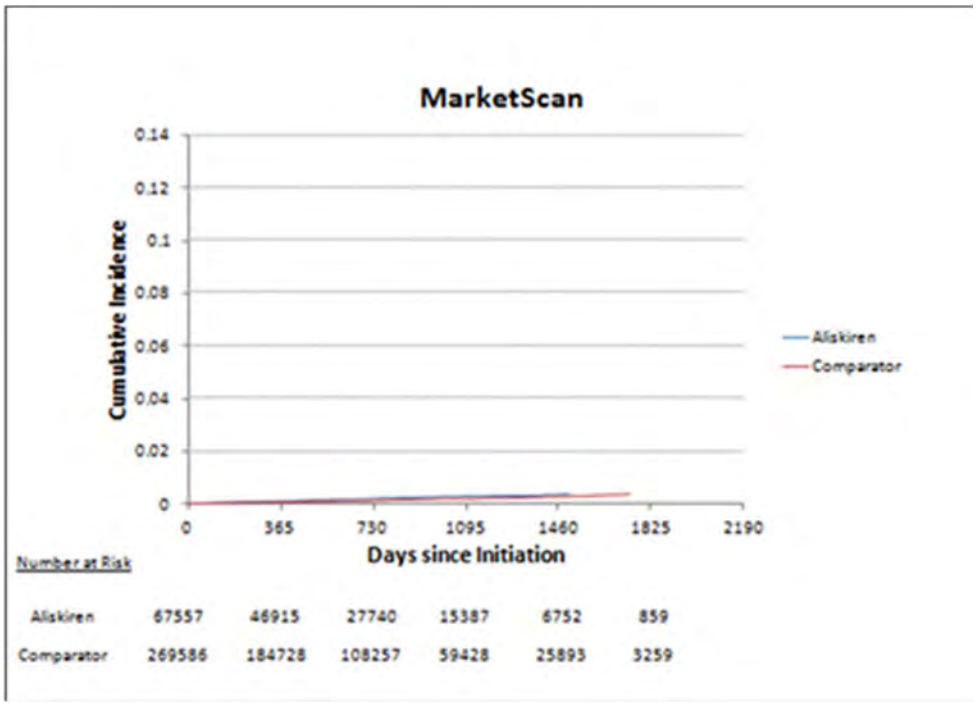
Annex 2-Figure 2-6 Cumulative incidence of ischemic stroke in Cohort 1, ITT – MarketScan



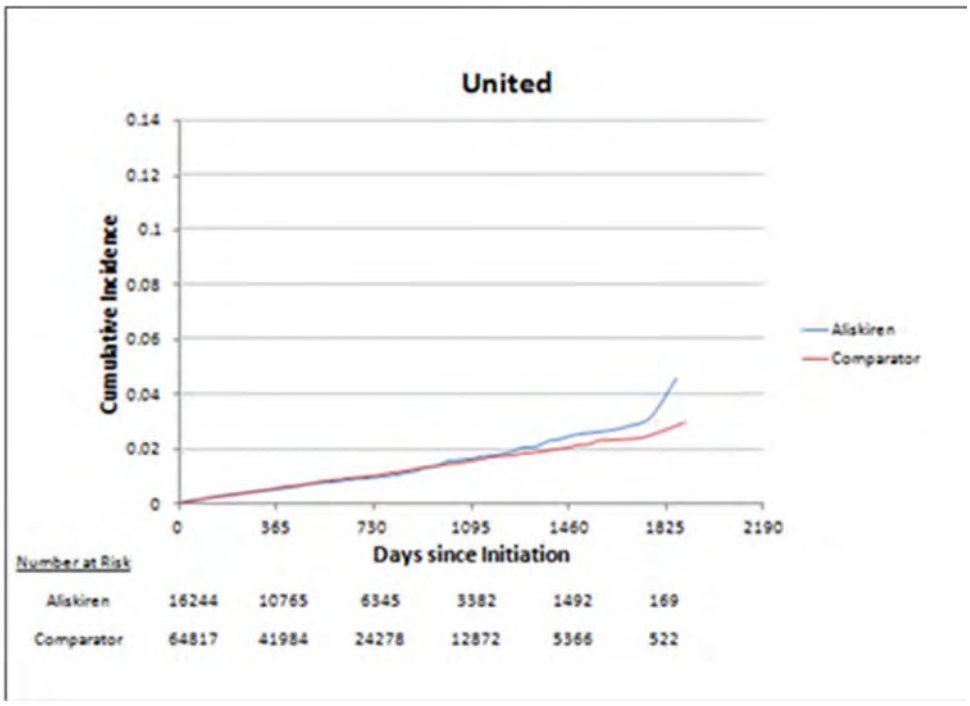
Annex 2-Figure 2-7 Cumulative incidence of hemorrhagic stroke in Cohort 1, ITT – United



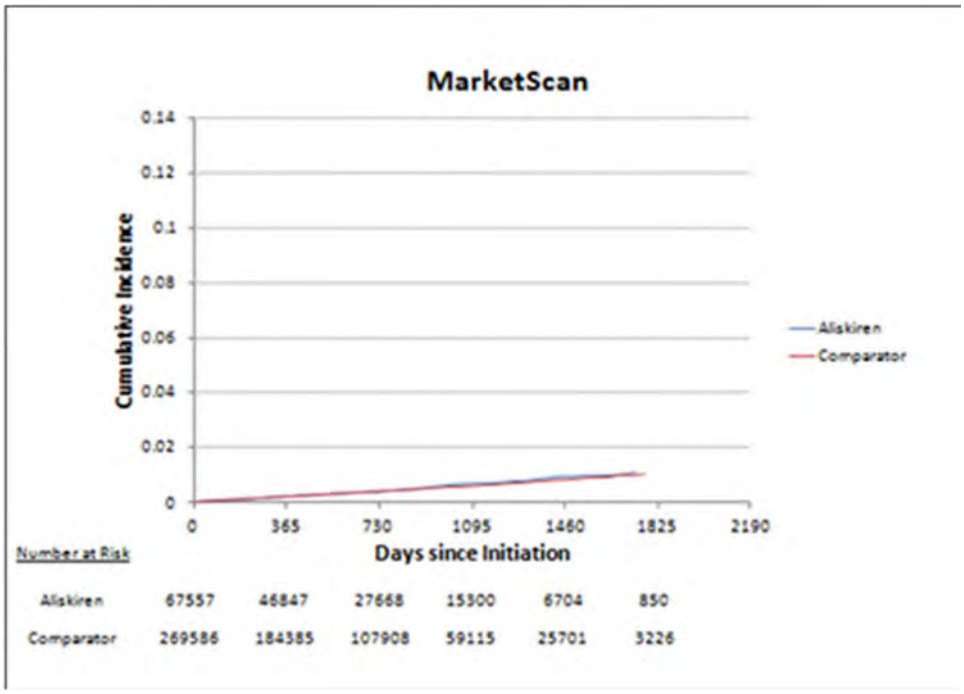
Annex 2-Figure 2-8 Cumulative incidence of hemorrhagic stroke in Cohort 1, ITT – MarketScan



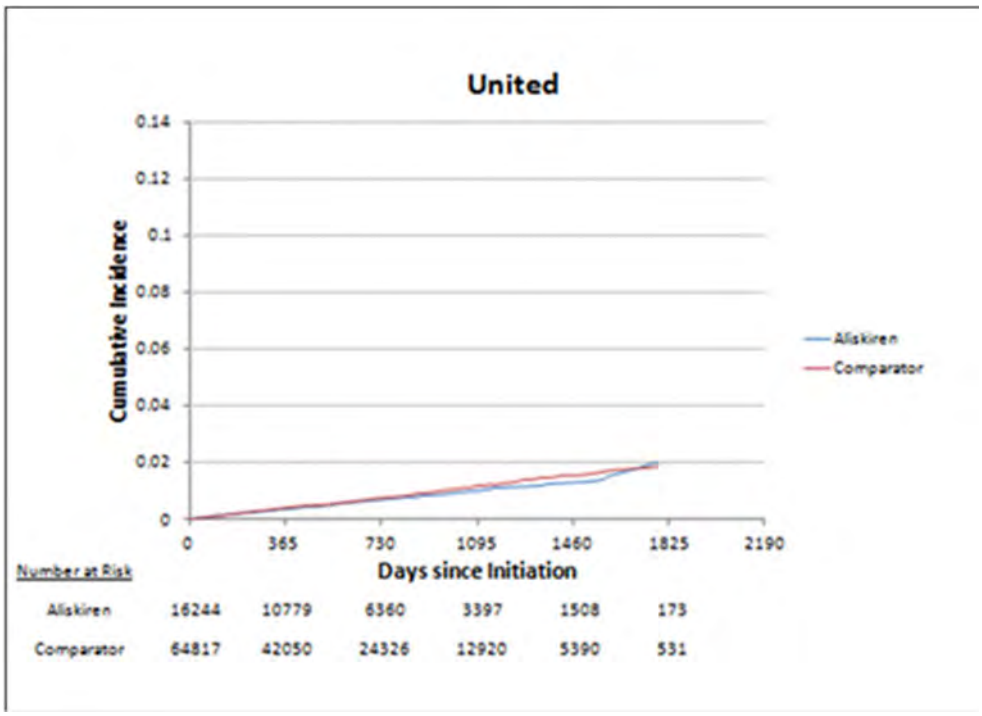
Annex 2-Figure 2-9 Cumulative incidence of transient ischemic attack in Cohort 1, ITT – United



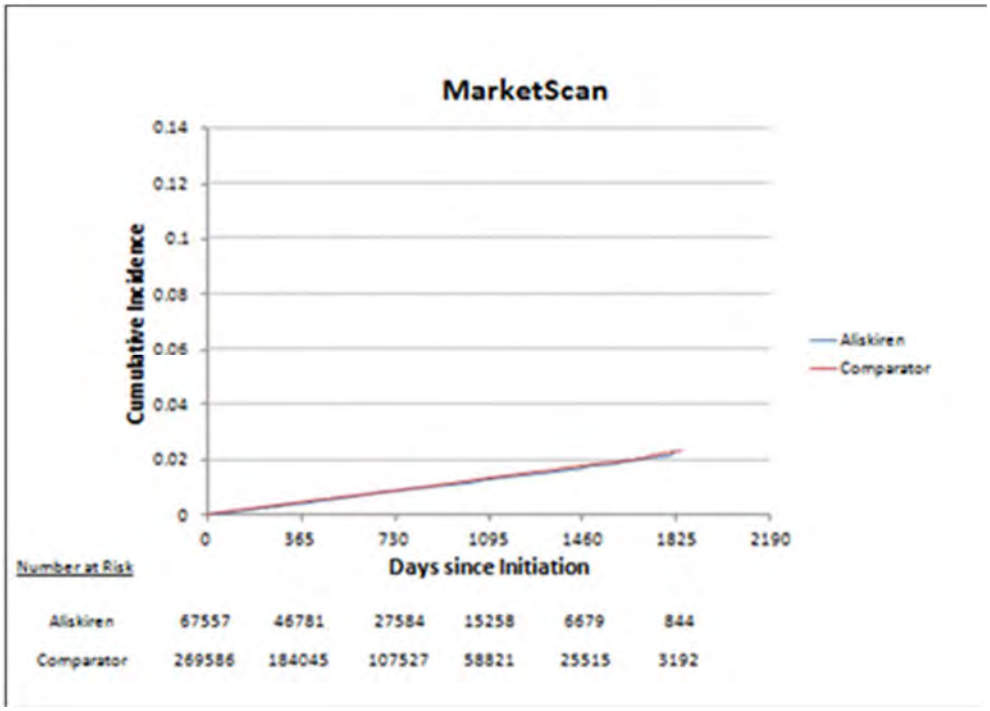
Annex 2-Figure 2-10 Cumulative incidence of transient ischemic attack in Cohort 1, ITT – MarketScan



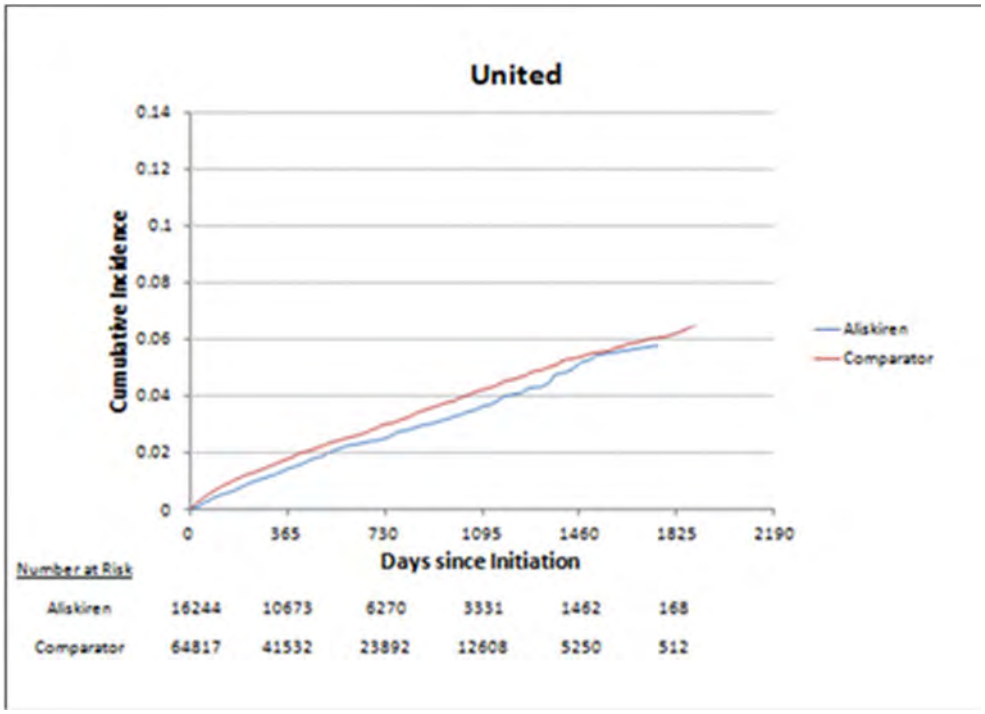
Annex 2-Figure 2-11 Cumulative incidence of myocardial infarction in Cohort 1, ITT – United



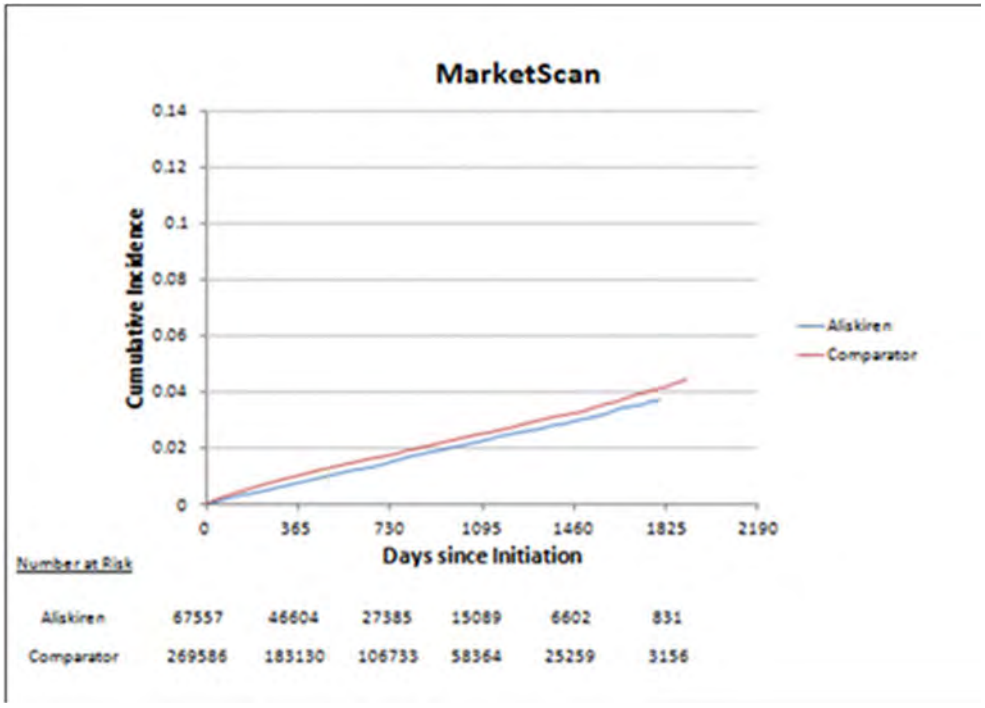
Annex 2-Figure 2-12 Cumulative incidence of myocardial infarction in Cohort 1, ITT – MarketScan



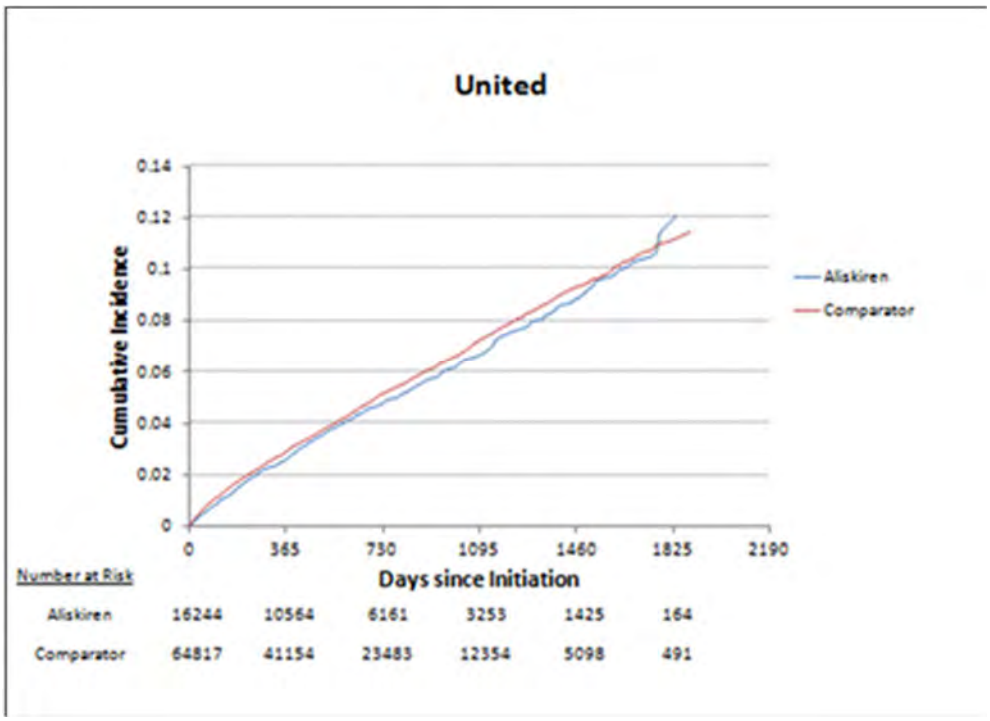
Annex 2-Figure 2-13 Cumulative incidence of heart failure in Cohort 1, ITT – United



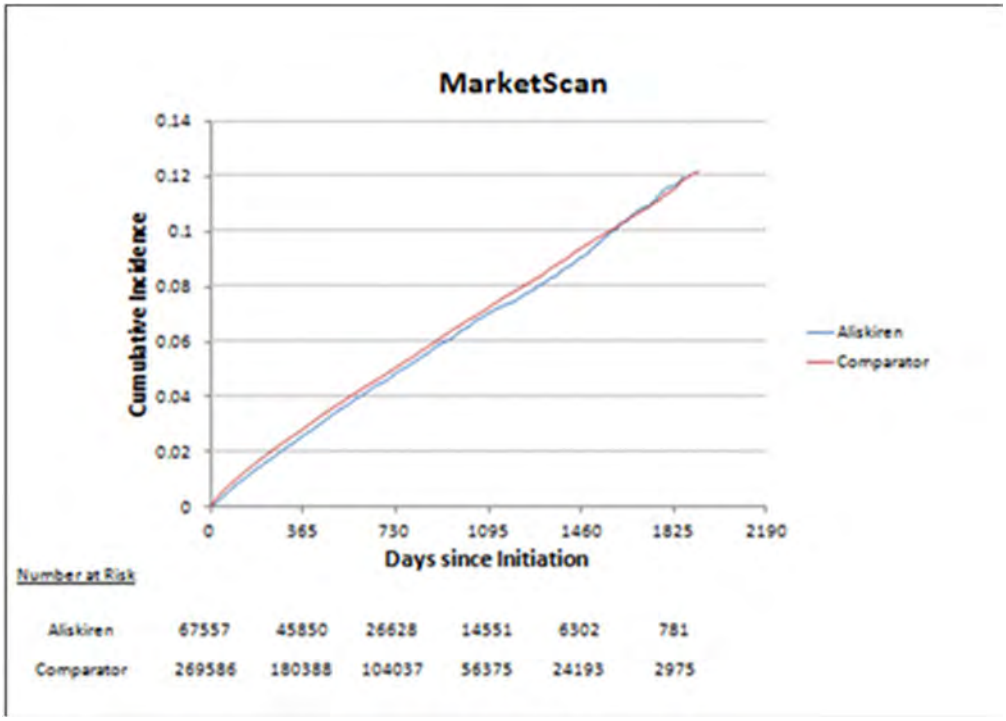
Annex 2-Figure 2-14 Cumulative incidence of heart failure in Cohort 1, ITT – MarketScan



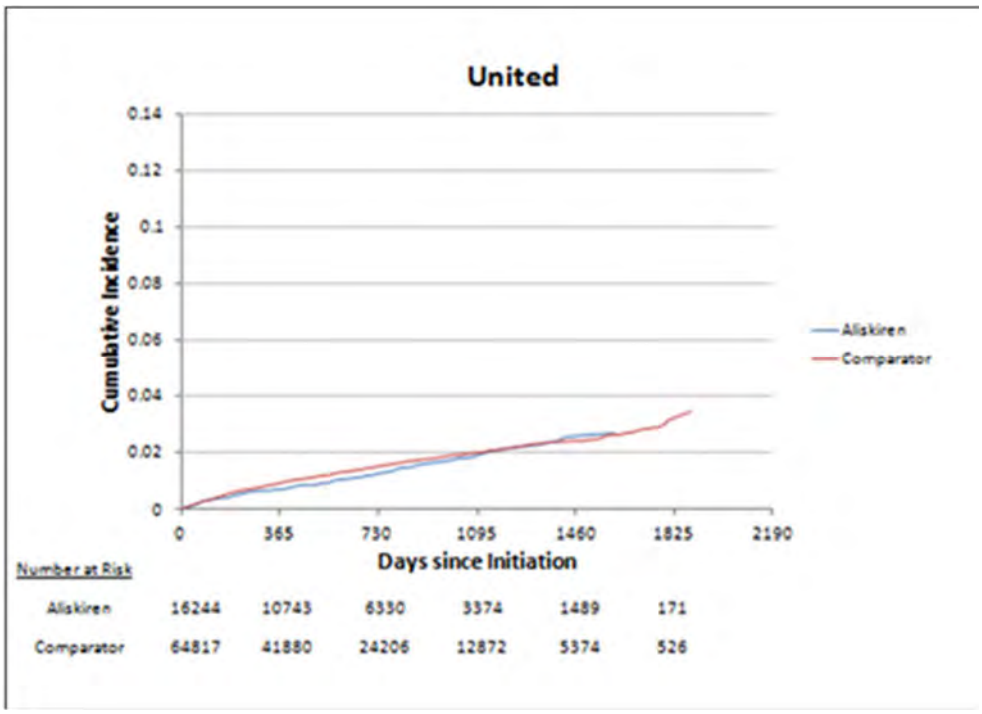
Annex 2-Figure 2-15 Cumulative incidence of acute renal failure in Cohort 1, ITT – United



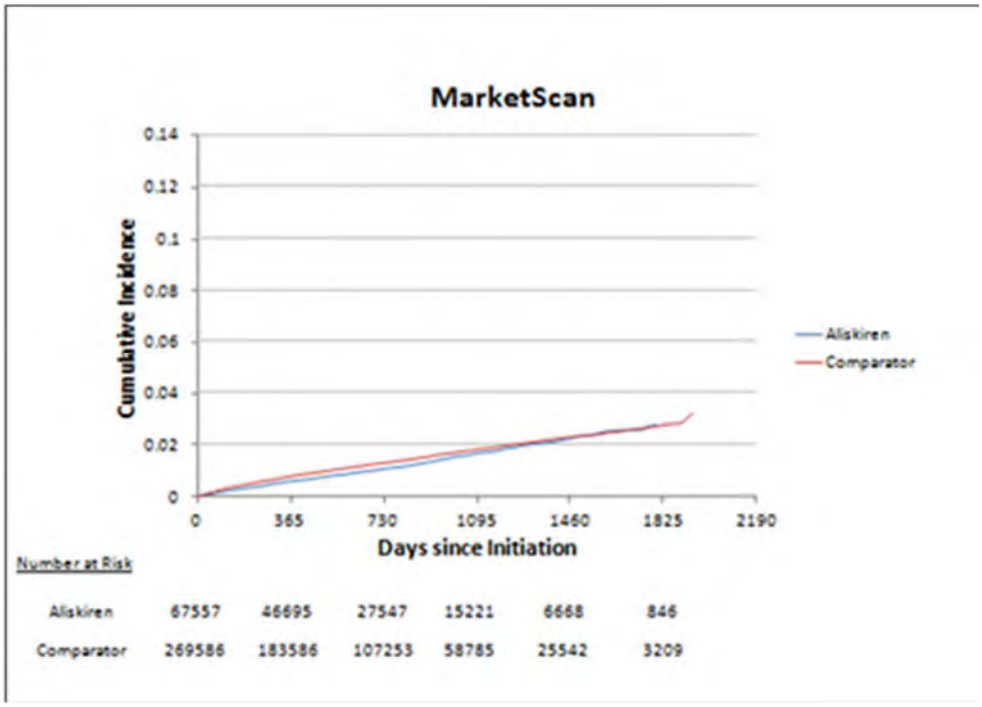
Annex 2-Figure 2-16 Cumulative incidence of acute renal failure in Cohort 1, ITT – MarketScan



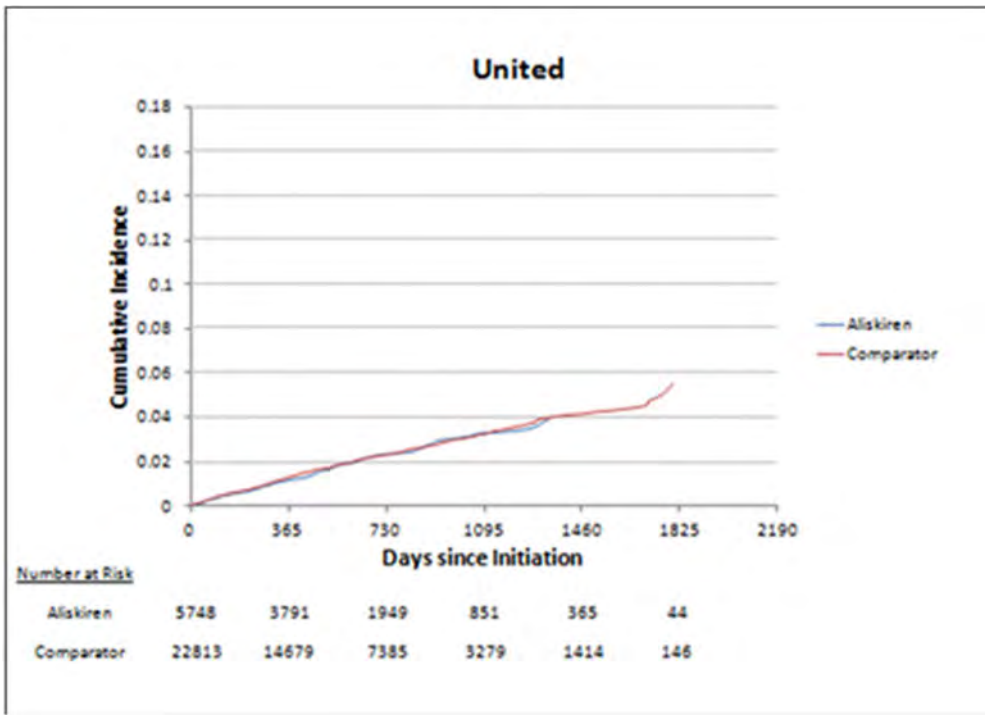
Annex 2-Figure 2-17 Cumulative incidence of end-stage renal disease in Cohort 1, ITT – United



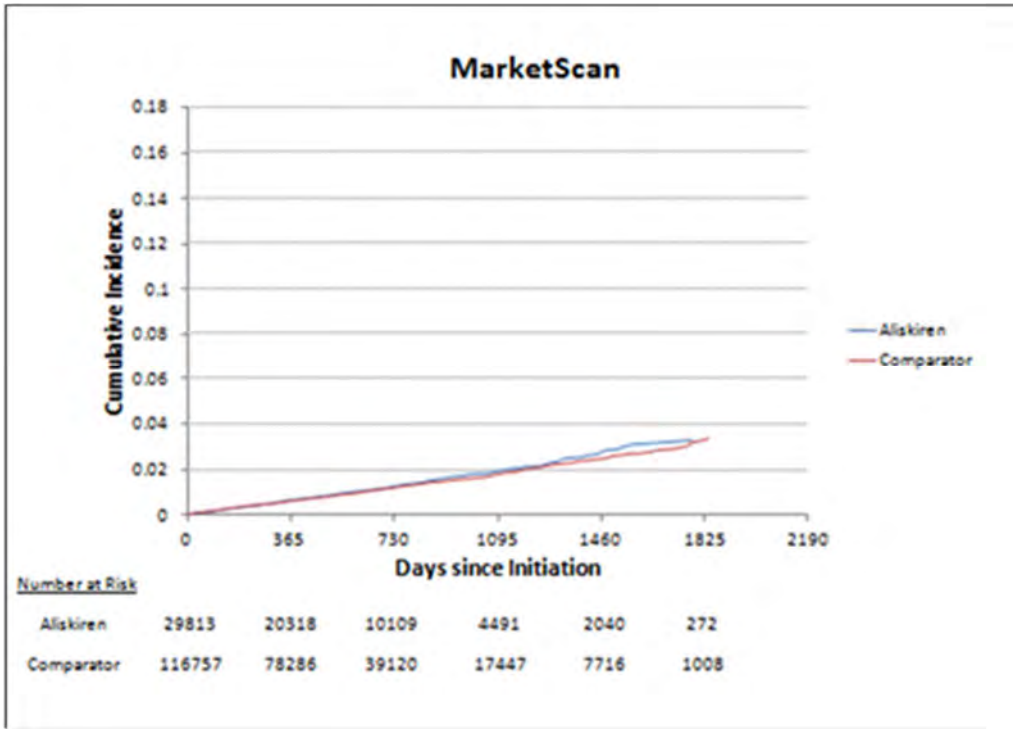
Annex 2-Figure 2-18 Cumulative incidence of end-stage renal disease in Cohort 1, ITT – MarketScan



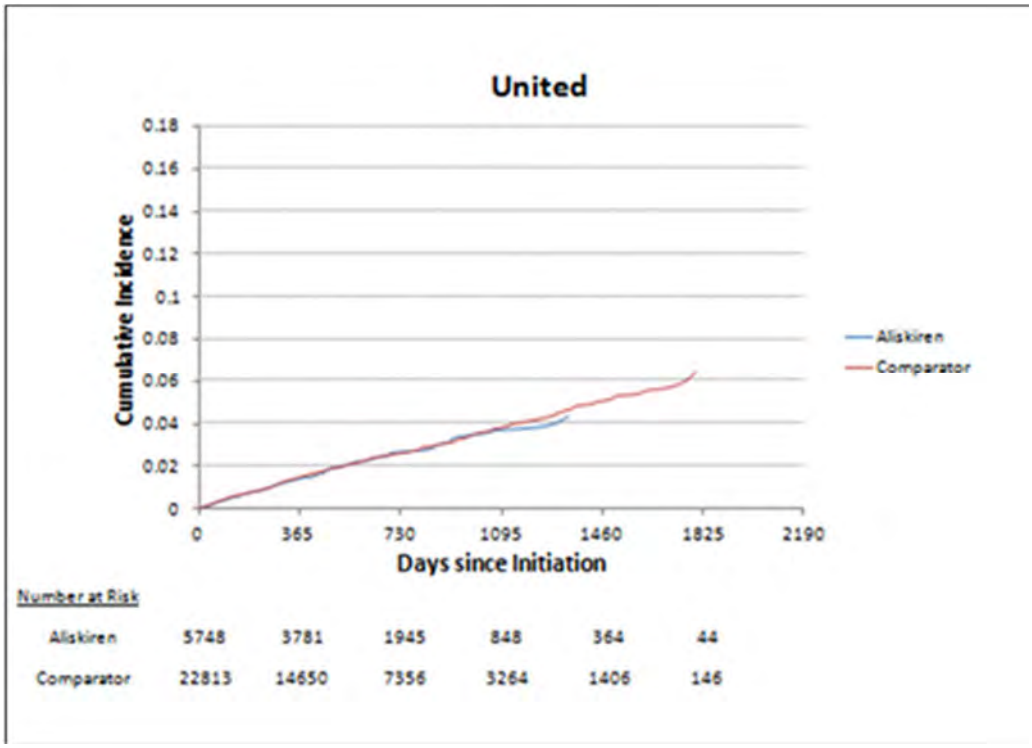
Annex 2-Figure 2-19 Cumulative incidence of cerebrovascular accidents in Cohort 2, ITT – United



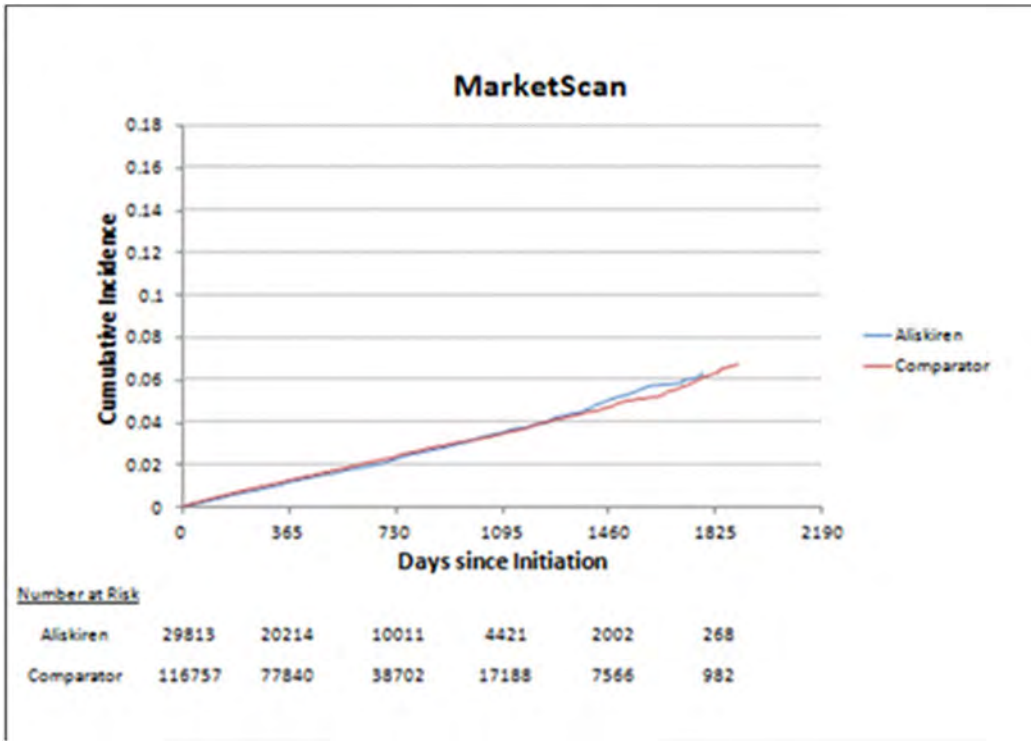
Annex 2-Figure 2-20 Cumulative incidence of cerebrovascular accidents in Cohort 2, ITT – MarketScan



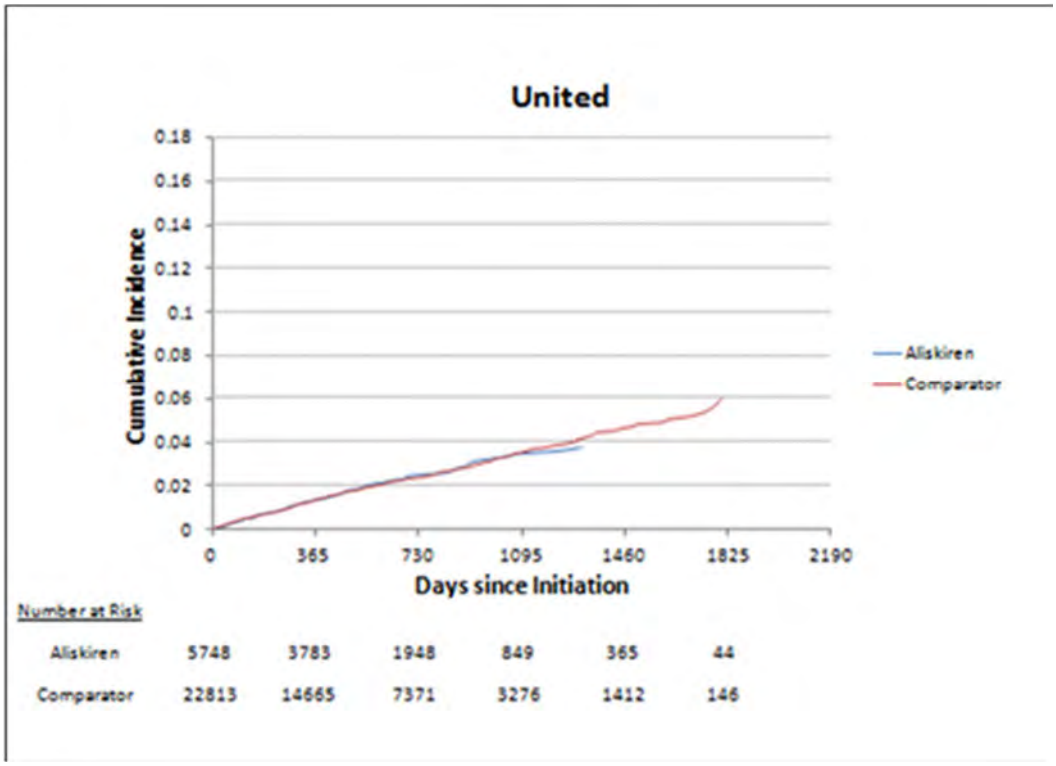
Annex 2-Figure 2-21 Cumulative incidence of stroke in Cohort 2, ITT – United



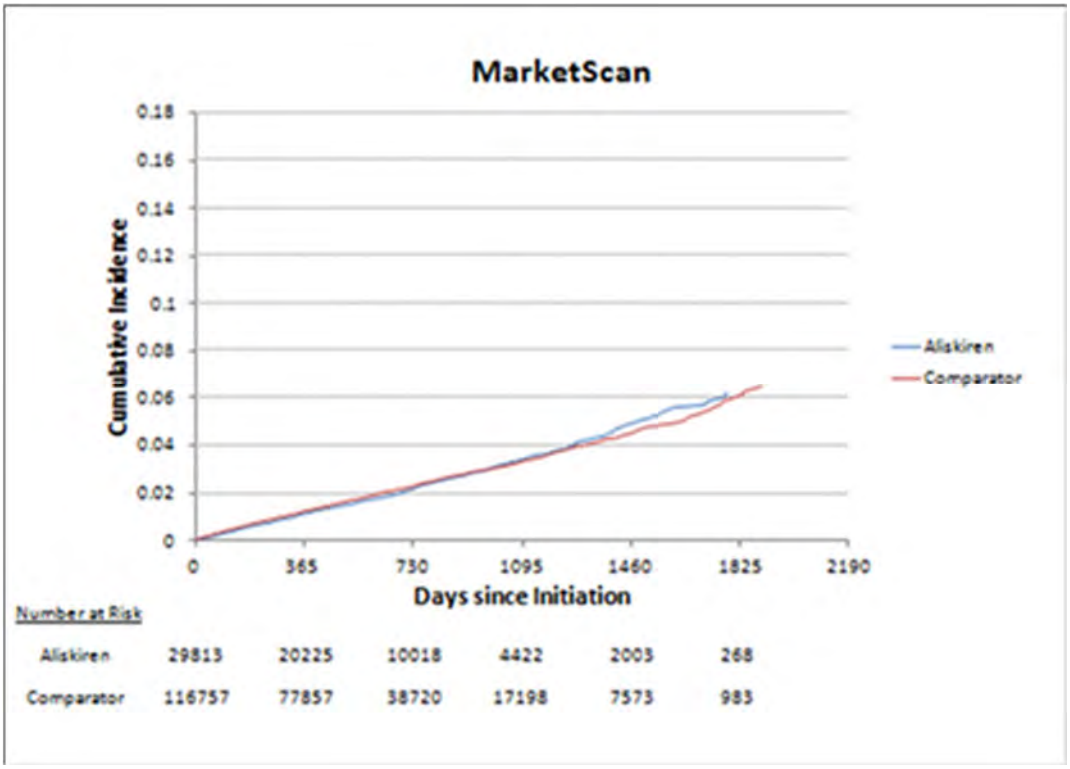
Annex 2-Figure 2-22 Cumulative incidence of stroke in Cohort 2, ITT – MarketScan



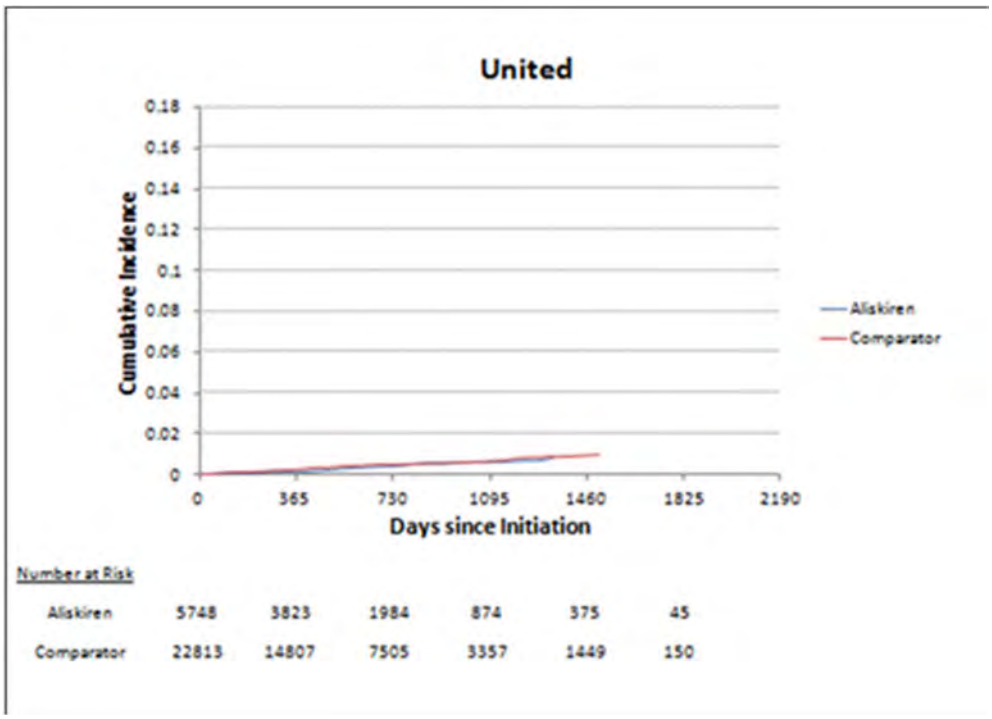
Annex 2-Figure 2-23 Cumulative incidence of ischemic stroke in Cohort 2, ITT – United



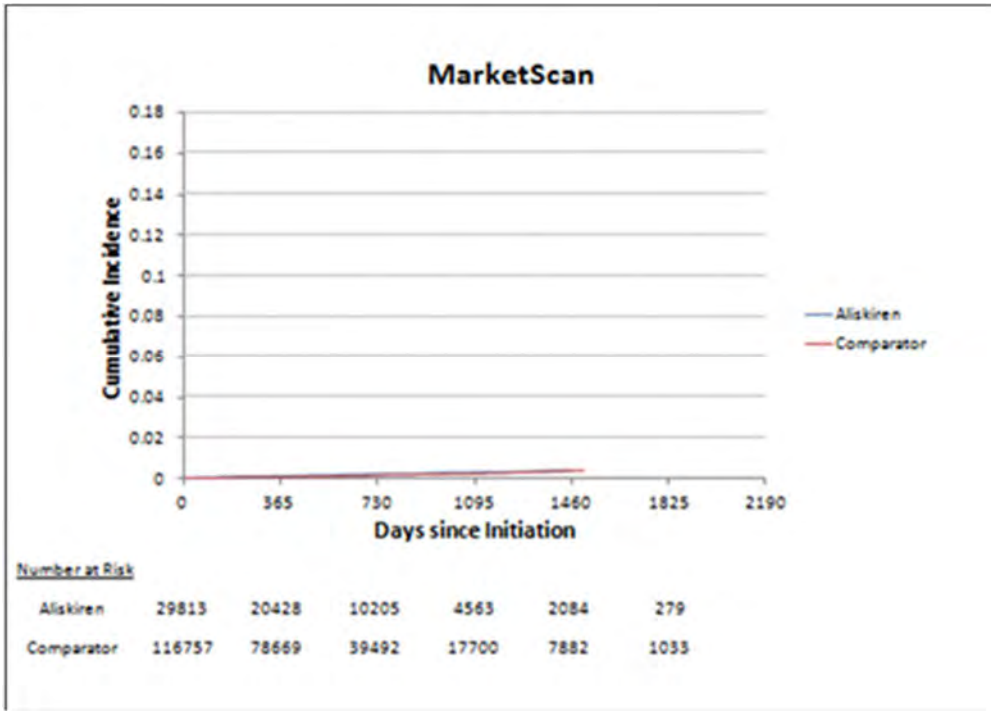
Annex 2-Figure 2-24 Cumulative incidence of ischemic stroke in Cohort 2, ITT – MarketScan



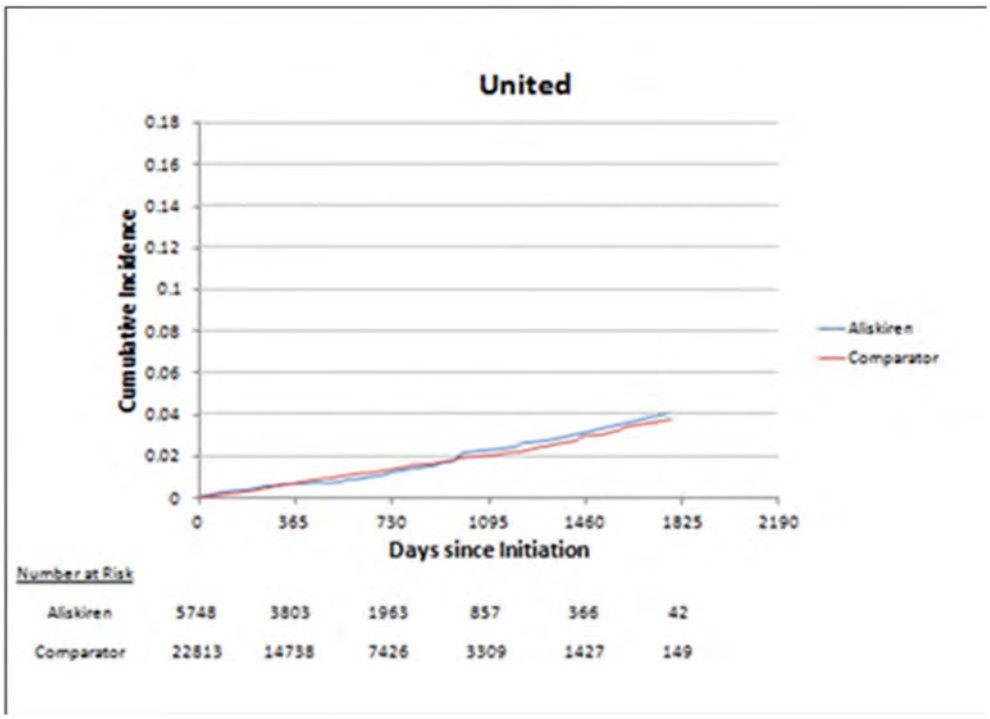
Annex 2-Figure 2-25 Cumulative incidence of hemorrhagic stroke in Cohort 2, ITT – United



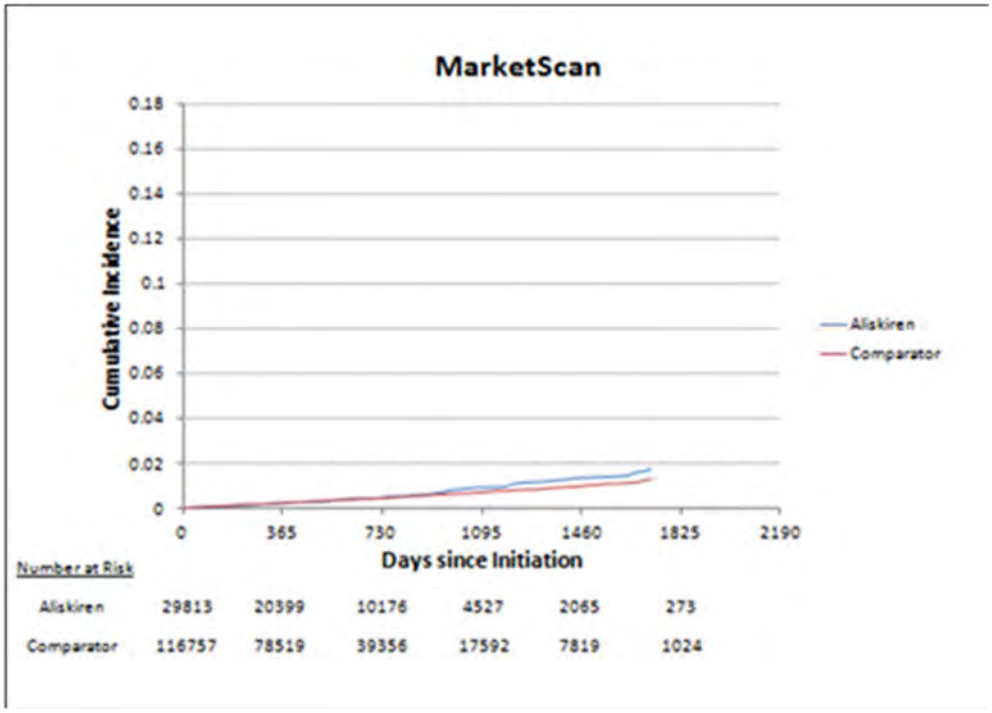
Annex 2-Figure 2-26 Cumulative incidence of hemorrhagic stroke in Cohort 2, ITT – MarketScan



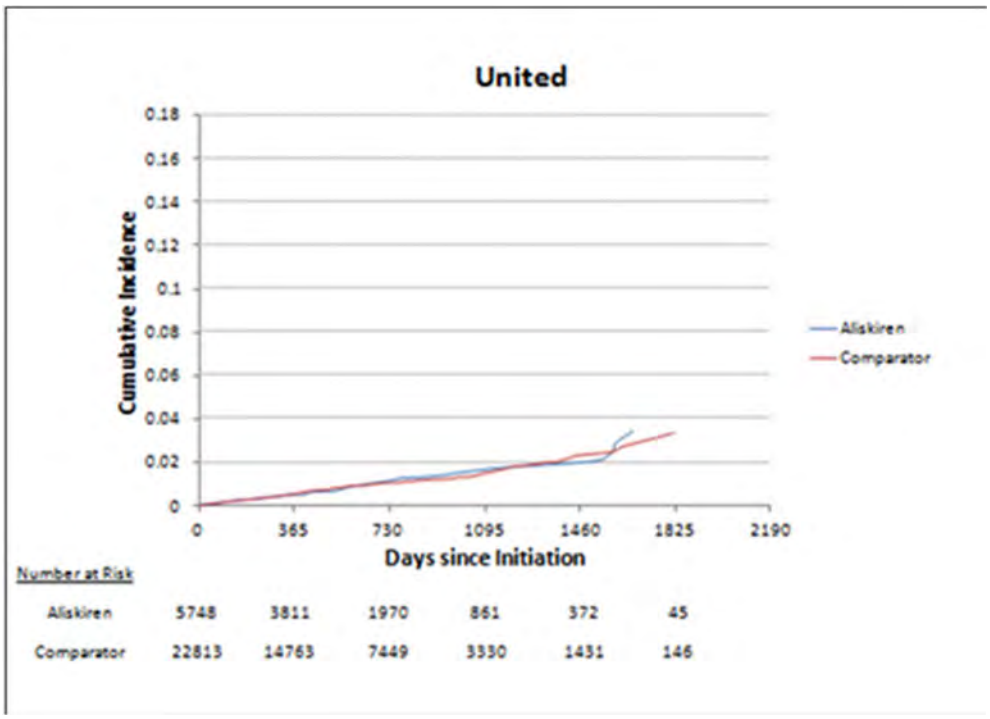
Annex 2-Figure 2-27 Cumulative incidence of transient ischemic attack in Cohort 2, ITT – United



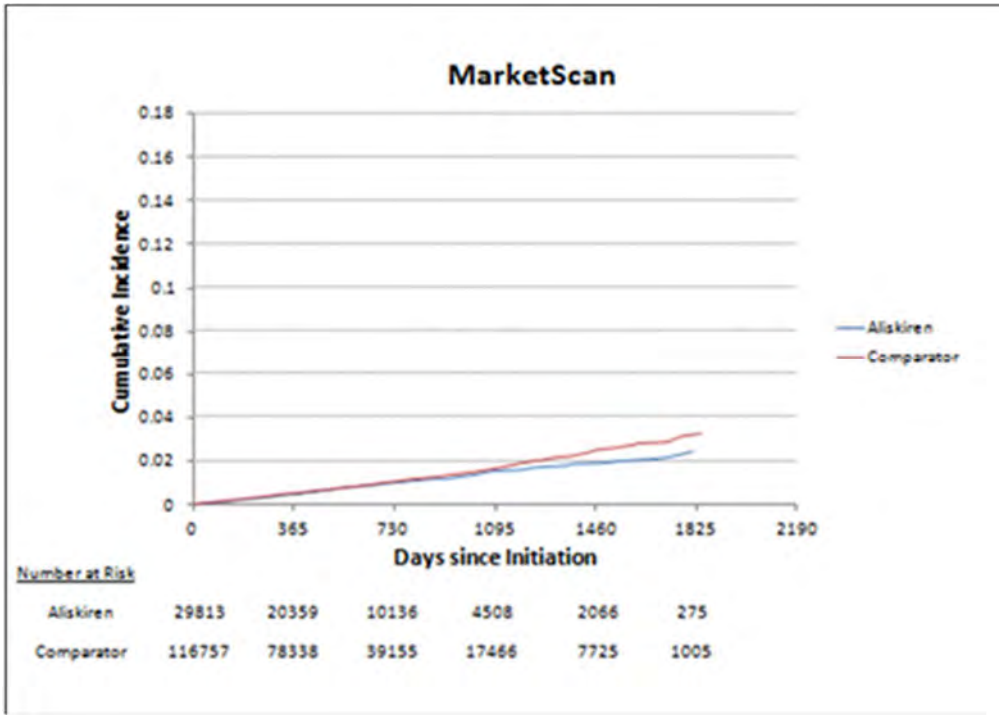
Annex 2-Figure 2-28 Cumulative incidence of transient ischemic attack in Cohort 2, ITT – MarketScan



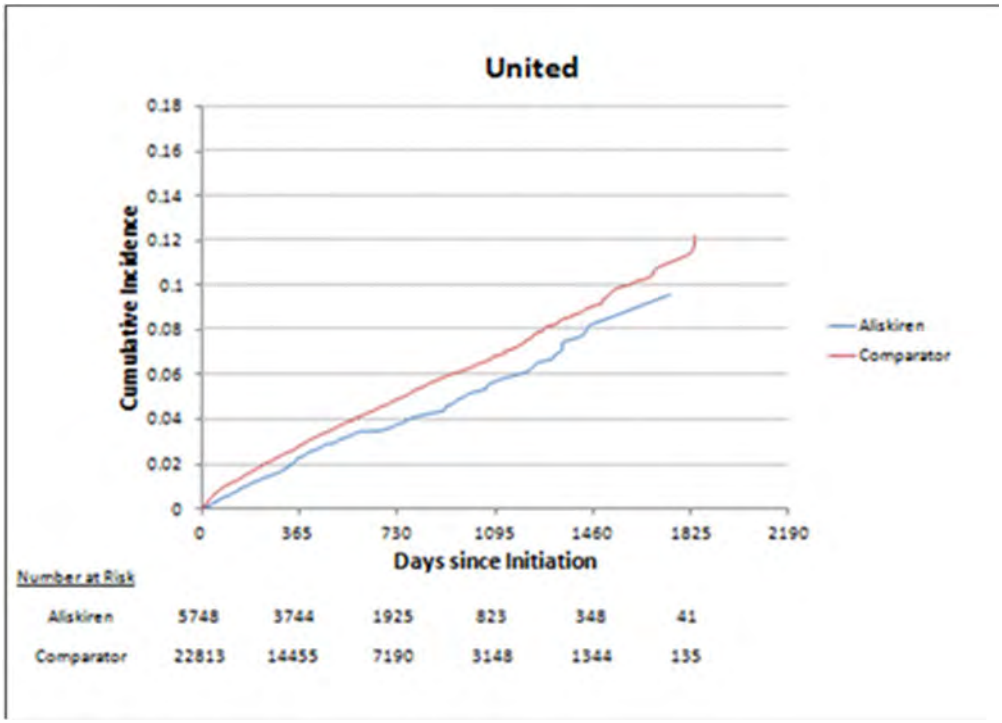
Annex 2-Figure 2-29 Cumulative incidence of myocardial infarction in Cohort 2, ITT – United



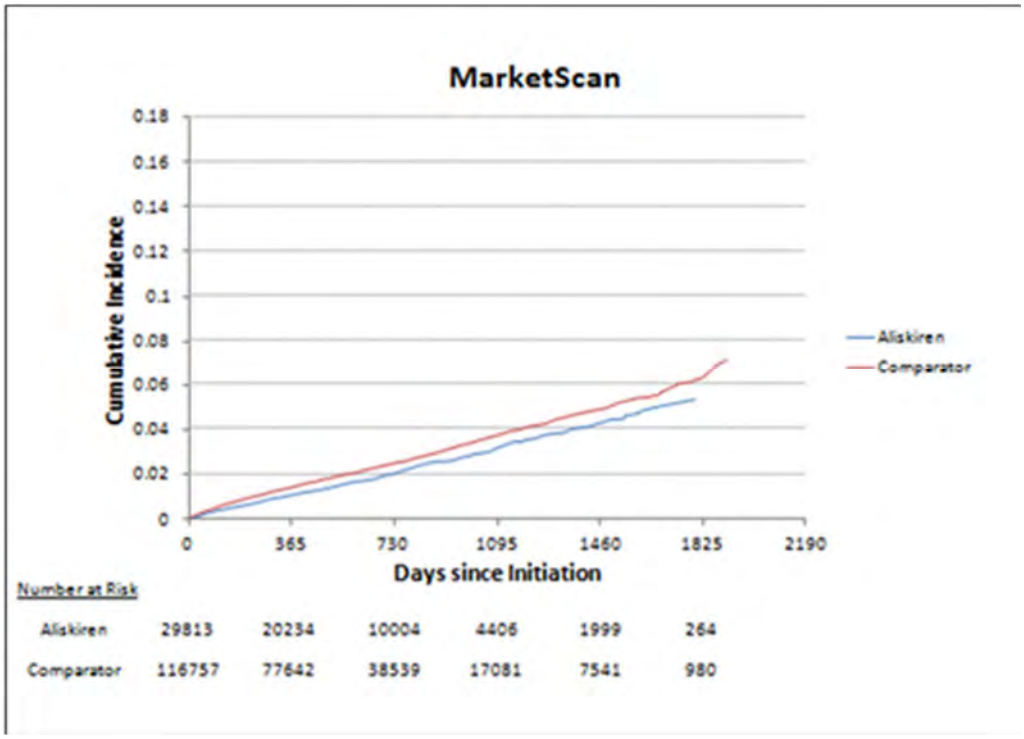
Annex 2-Figure 2-30 Cumulative incidence of myocardial infarction in Cohort 2, ITT – MarketScan



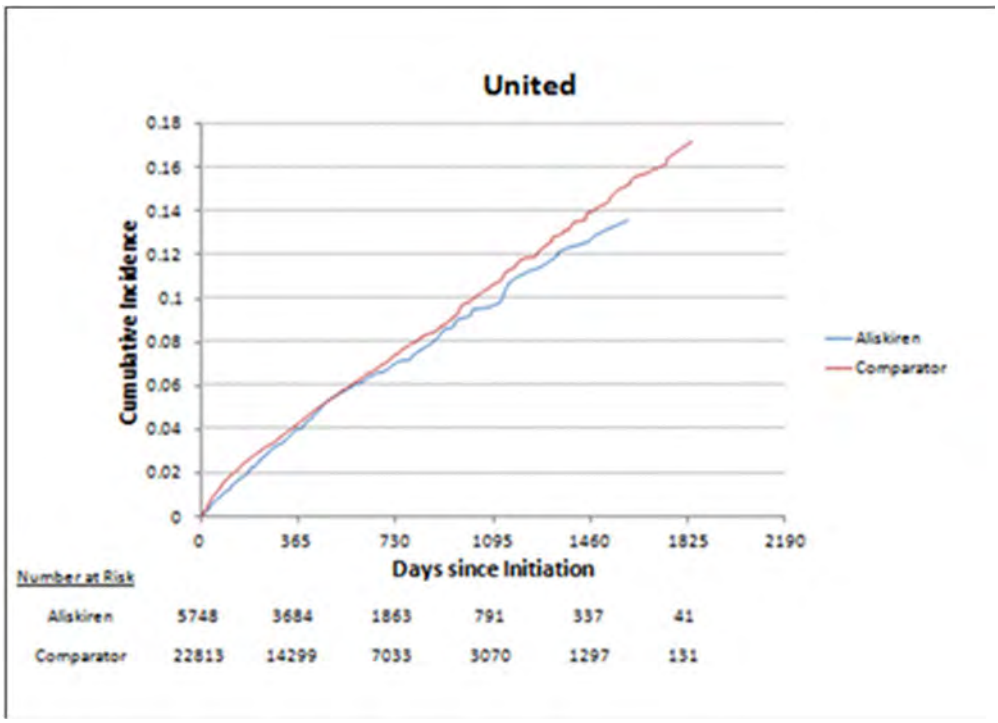
Annex 2-Figure 2-31 Cumulative incidence of heart failure in Cohort 2, ITT – United



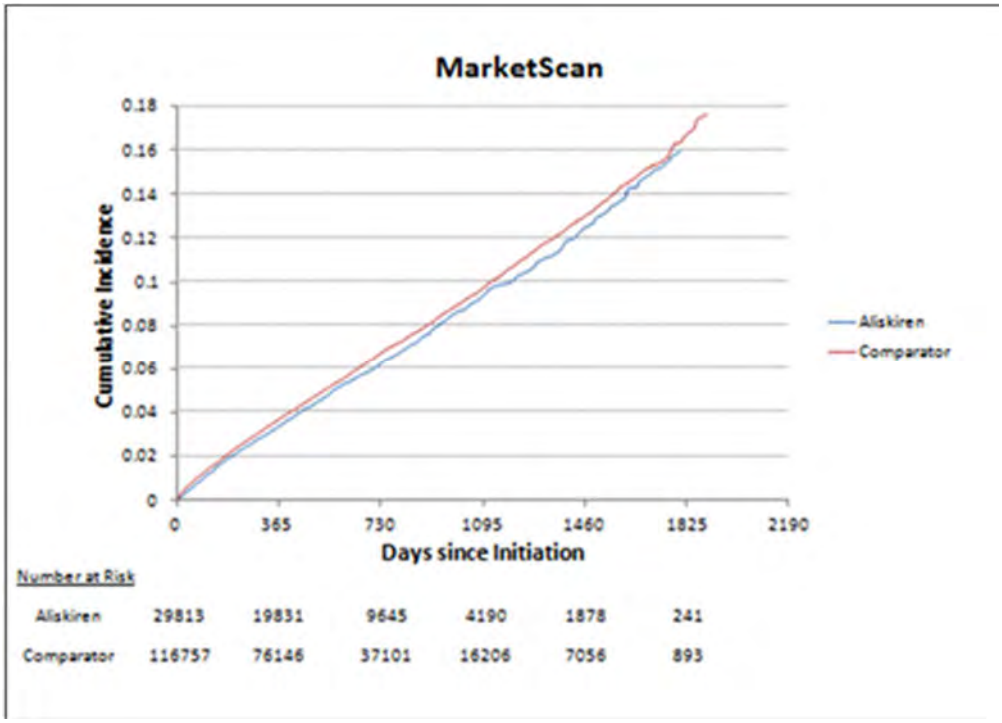
Annex 2-Figure 2-32 Cumulative incidence of heart failure in Cohort 2, ITT – MarketScan



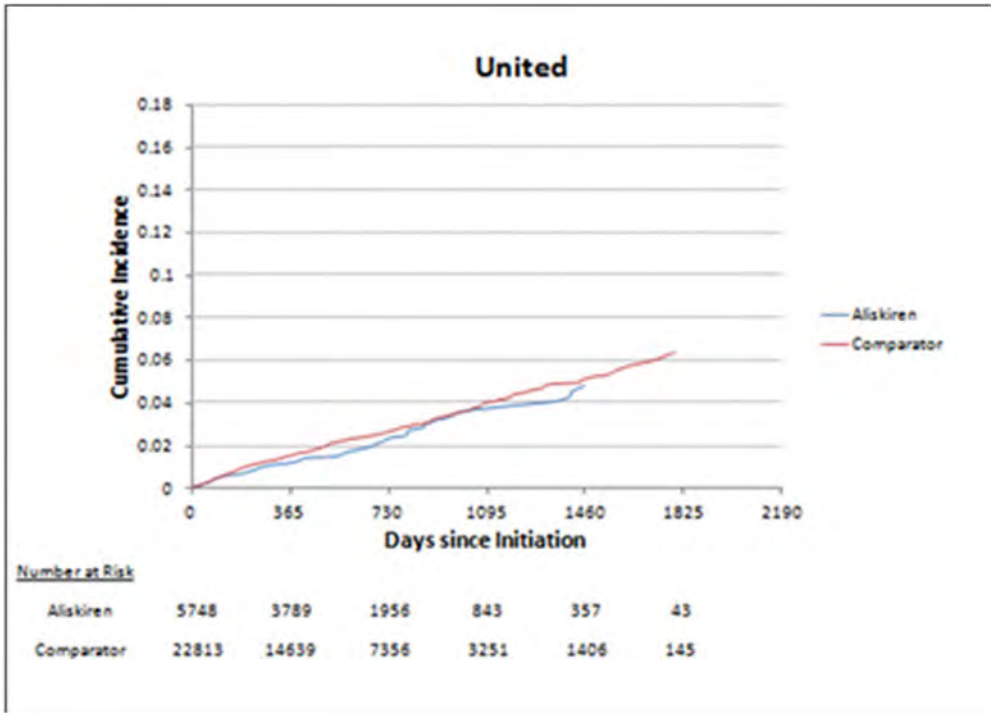
Annex 2-Figure 2-33 Cumulative incidence of acute renal failure in Cohort 2, ITT – United



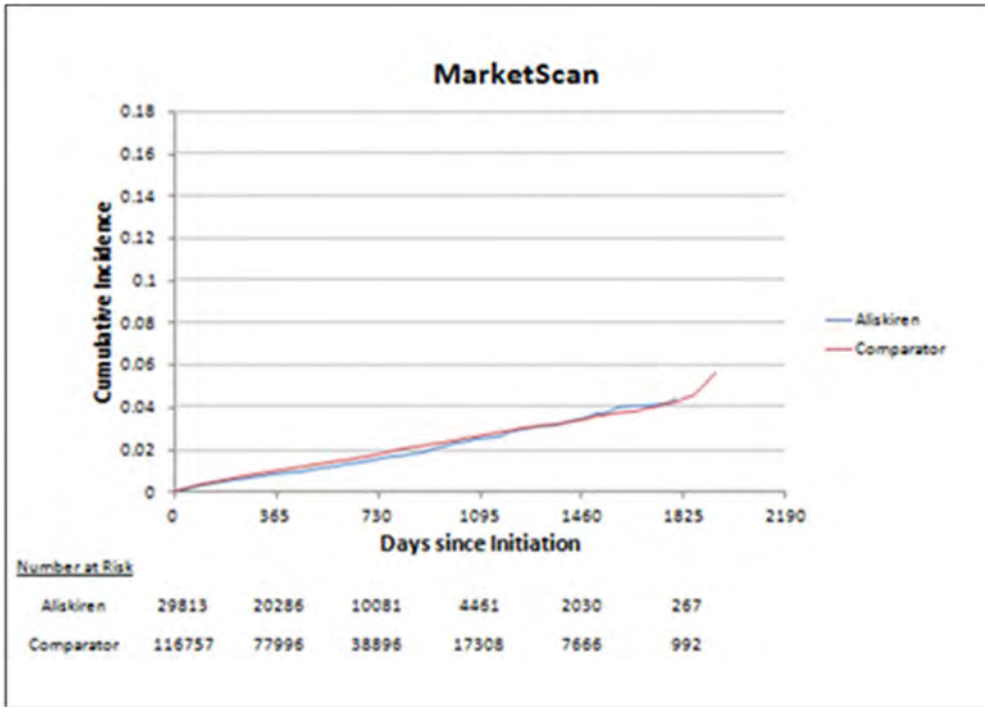
Annex 2-Figure 2-34 Cumulative incidence of acute renal failure in Cohort 2, ITT – MarketScan



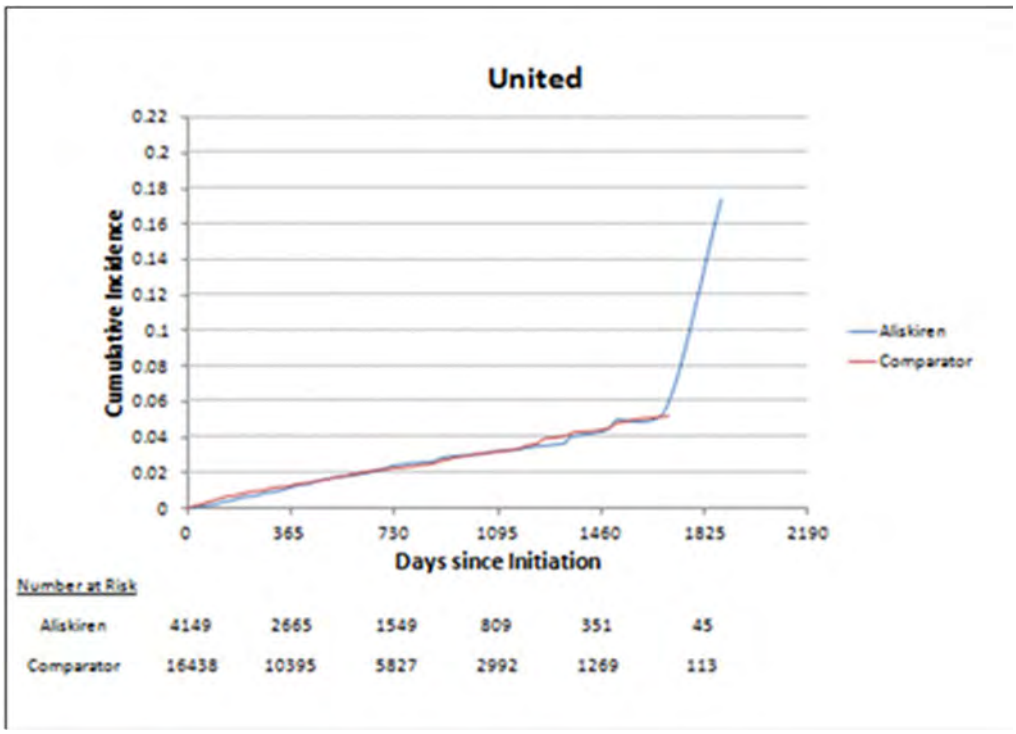
Annex 2-Figure 2-35 Cumulative incidence of end-stage renal disease in Cohort 2, ITT – United



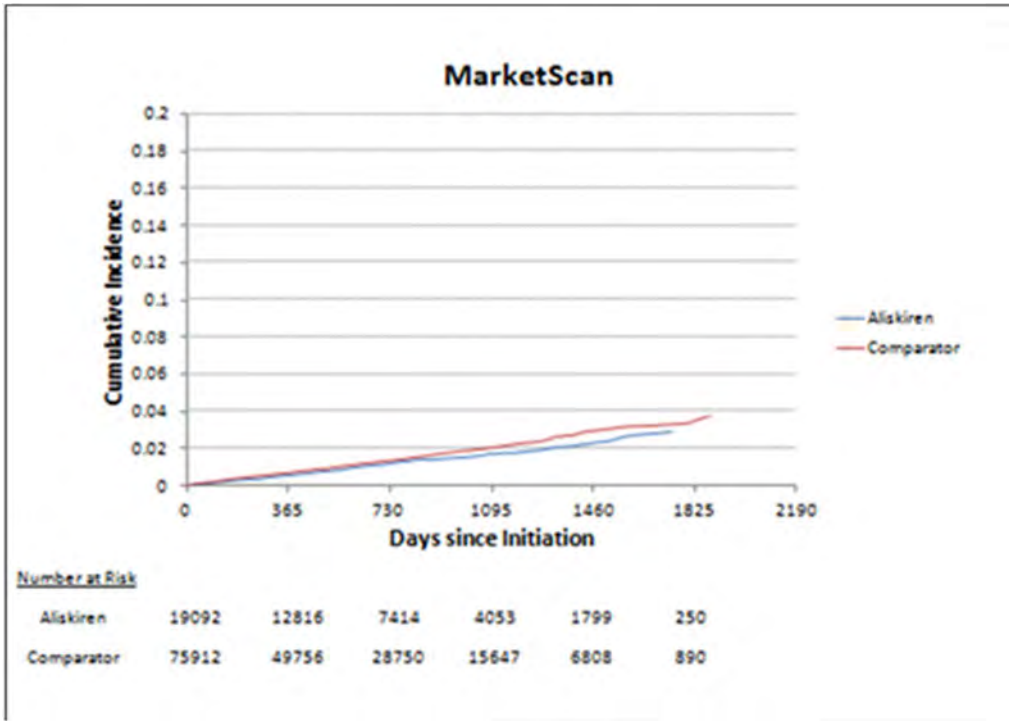
Annex 2-Figure 2-36 Cumulative incidence of end-stage renal disease in Cohort 2, ITT – MarketScan



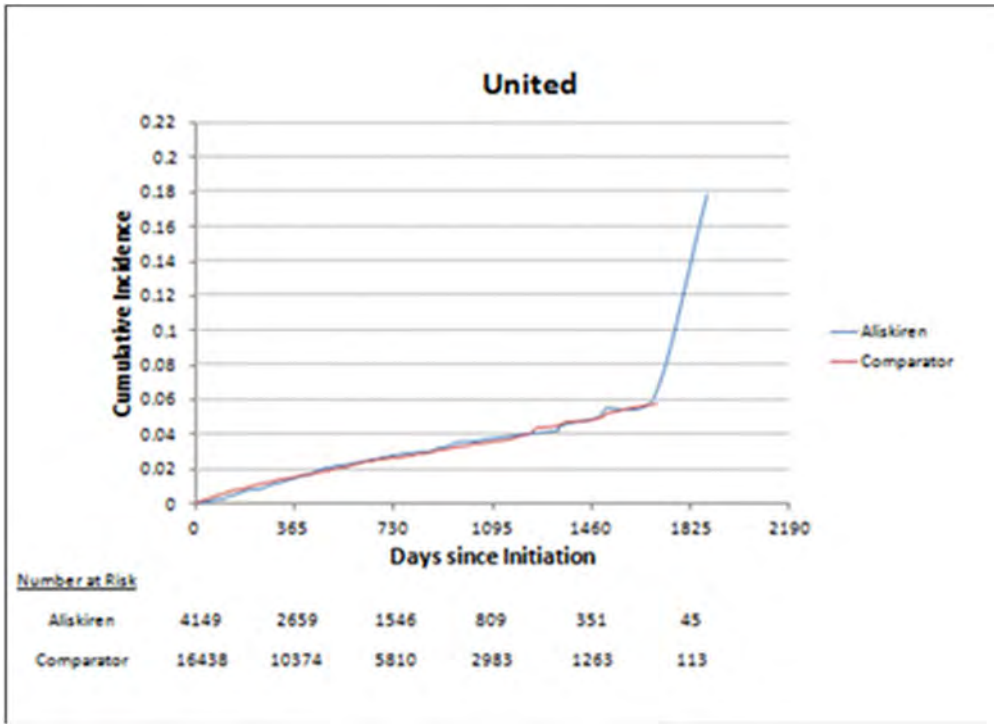
Annex 2-Figure 2-37 Cumulative incidence of cerebrovascular accidents in Cohort 3, ITT – United



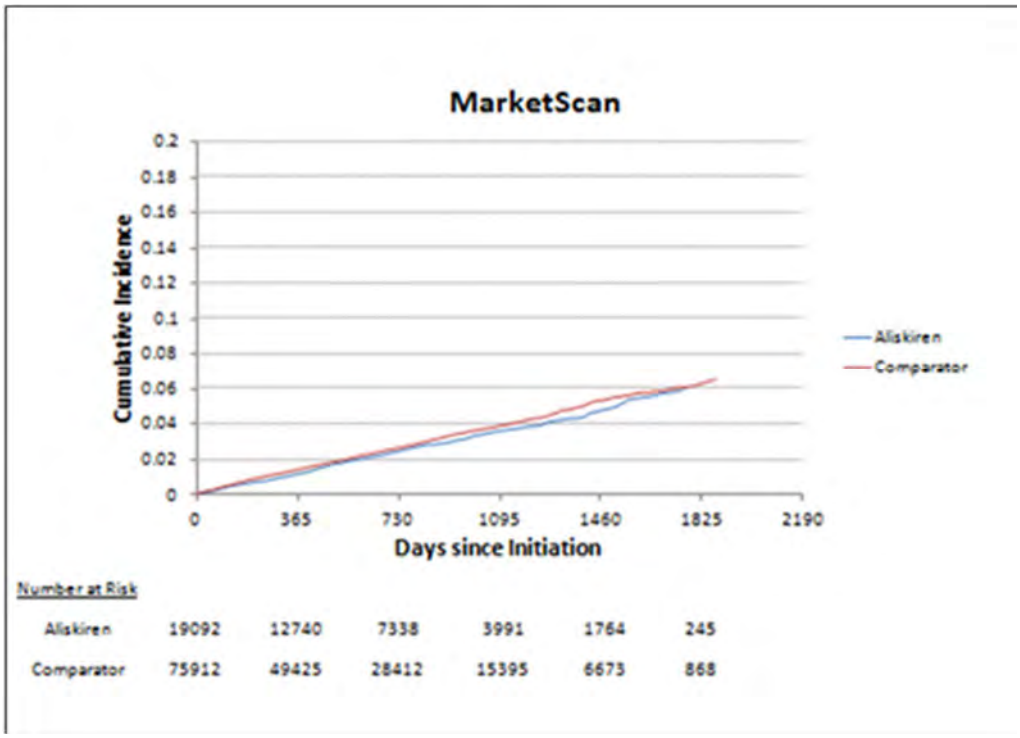
Annex 2-Figure 2-38 Cumulative incidence of cerebrovascular accidents in Cohort 3, ITT – MarketScan



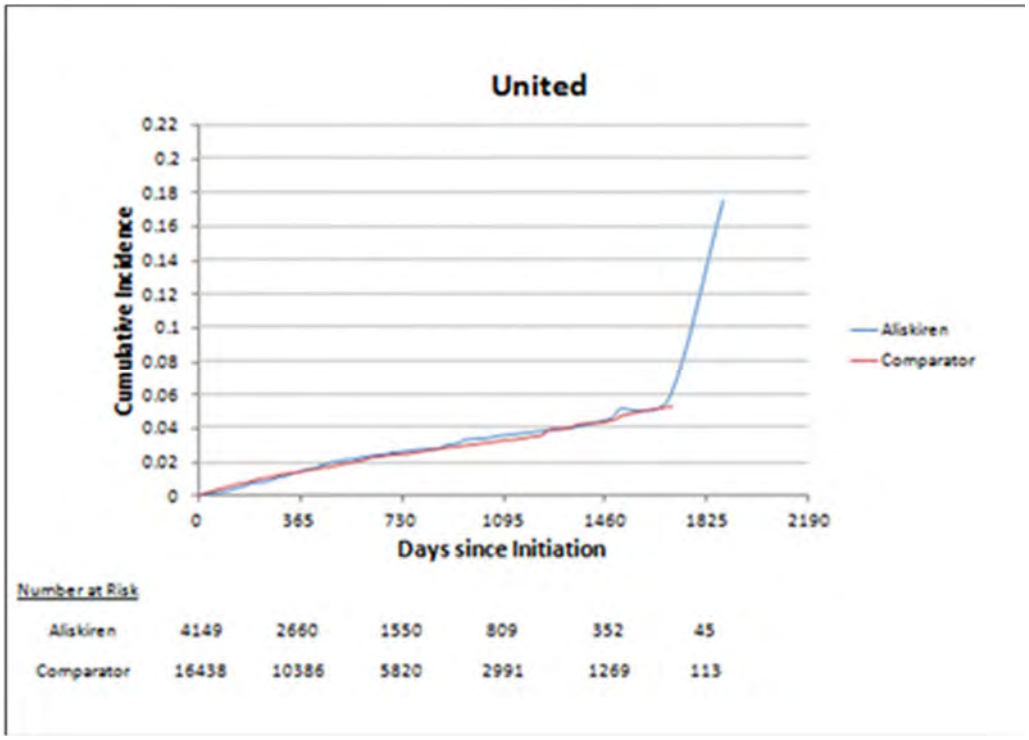
Annex 2-Figure 2-39 Cumulative incidence of stroke in Cohort 3, ITT – United



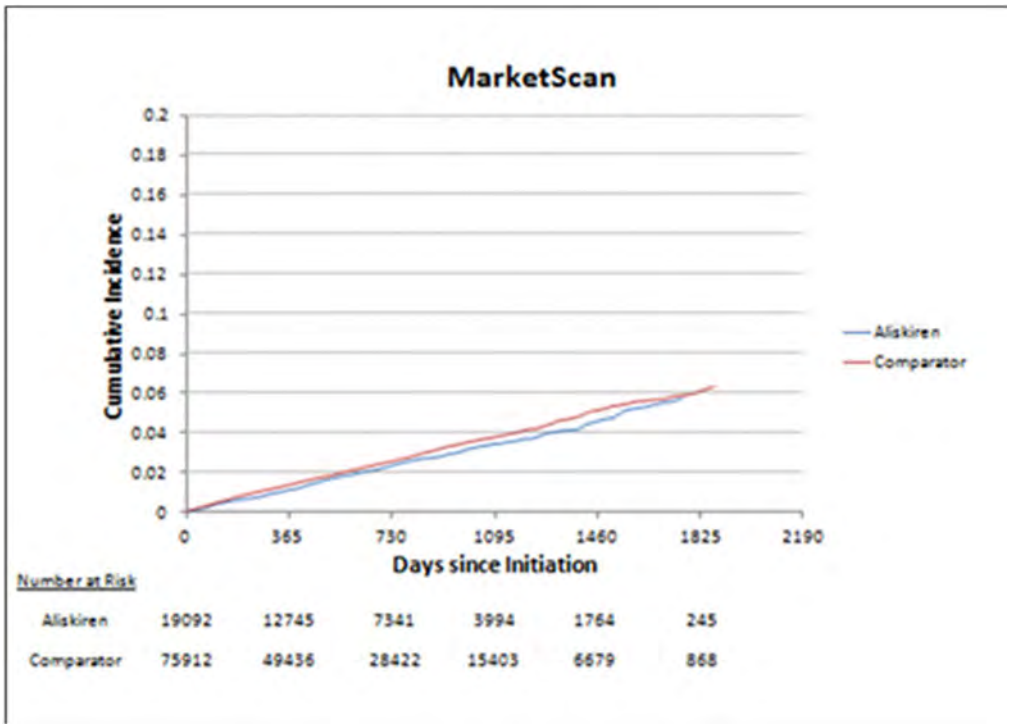
Annex 2-Figure 2-40 Cumulative incidence of stroke in Cohort 3, ITT – MarketScan



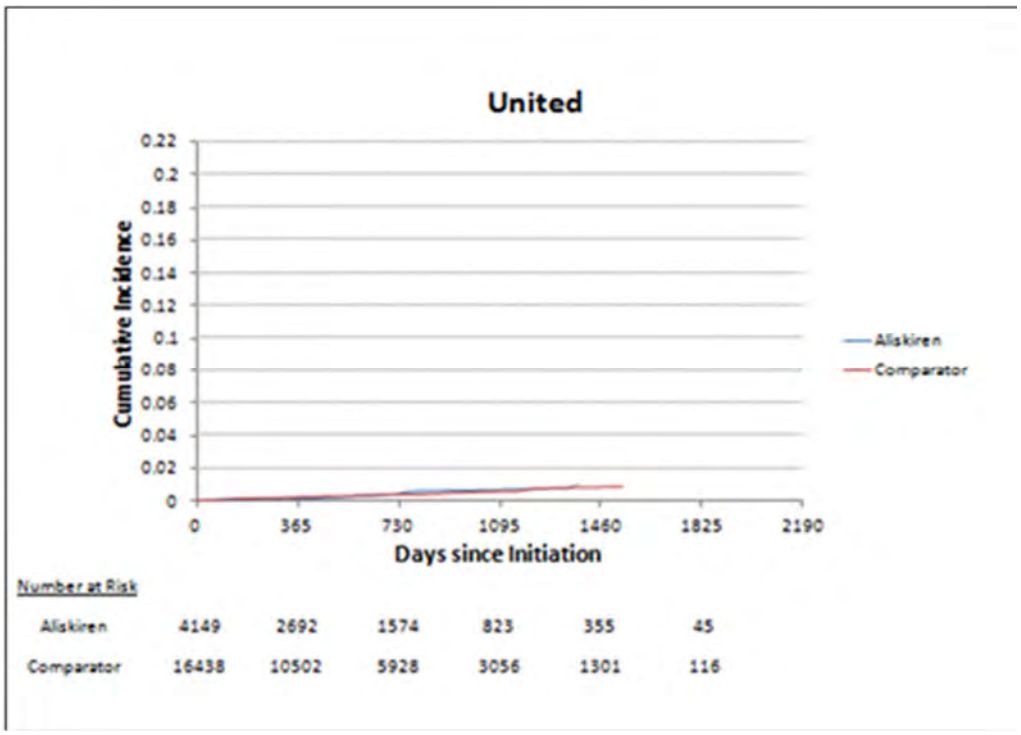
Annex 2-Figure 2-41 Cumulative incidence of ischemic stroke in Cohort 3, ITT – United



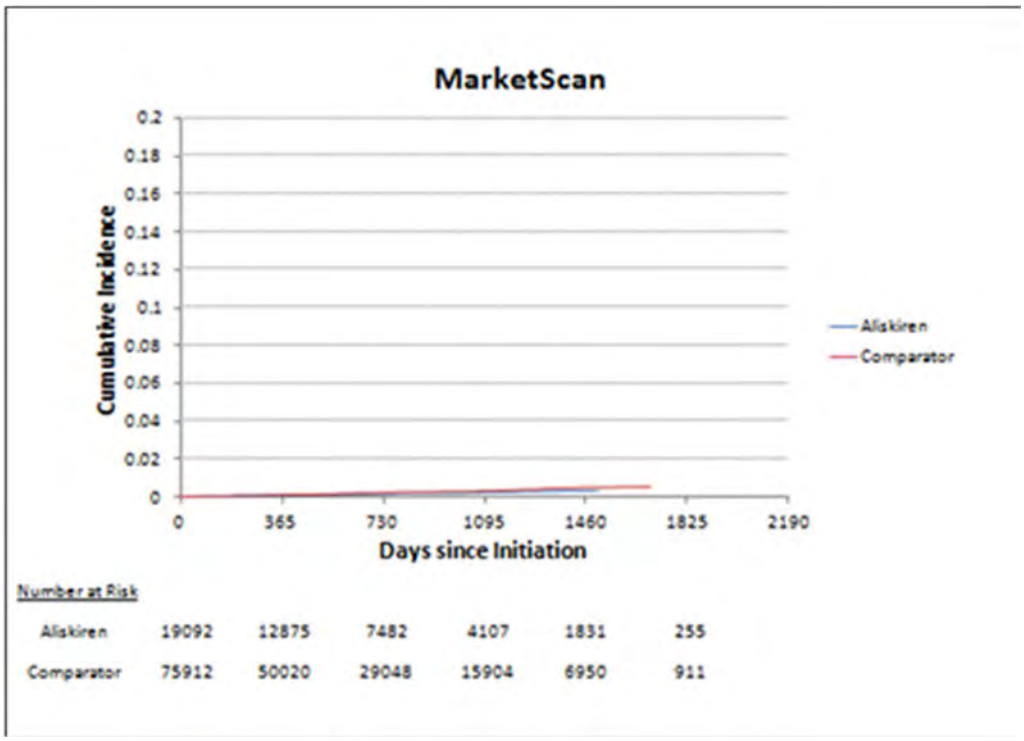
Annex 2-Figure 2-42 Cumulative incidence of ischemic stroke in Cohort 3, ITT – MarketScan



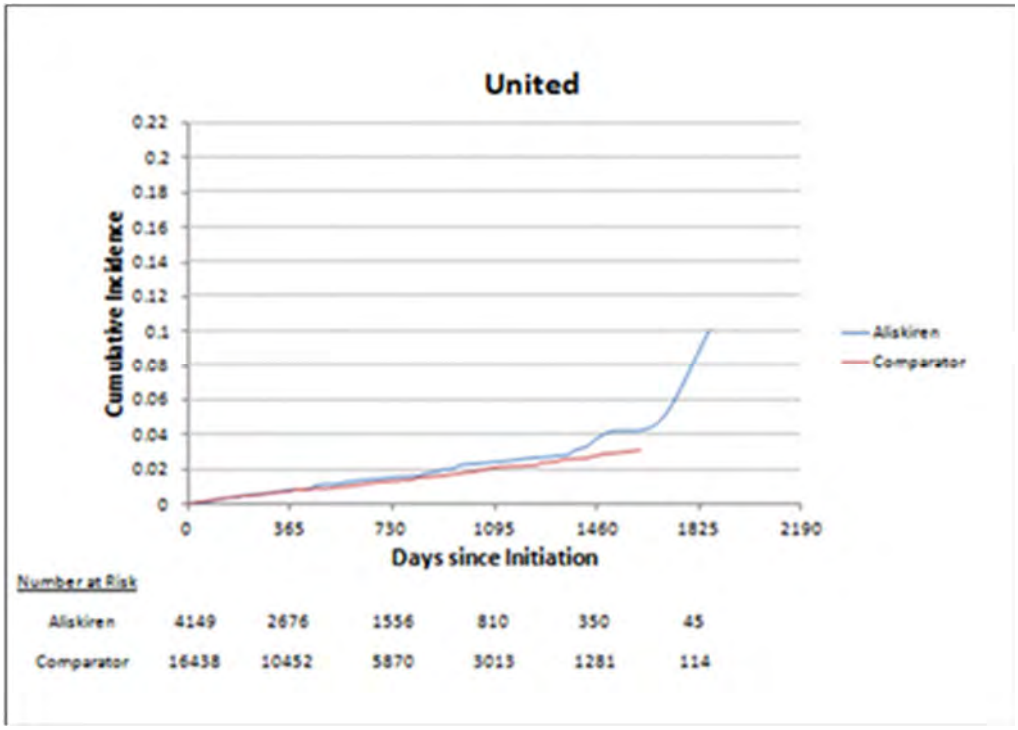
Annex 2-Figure 2-43 Cumulative incidence of hemorrhagic stroke in Cohort 3, ITT – United



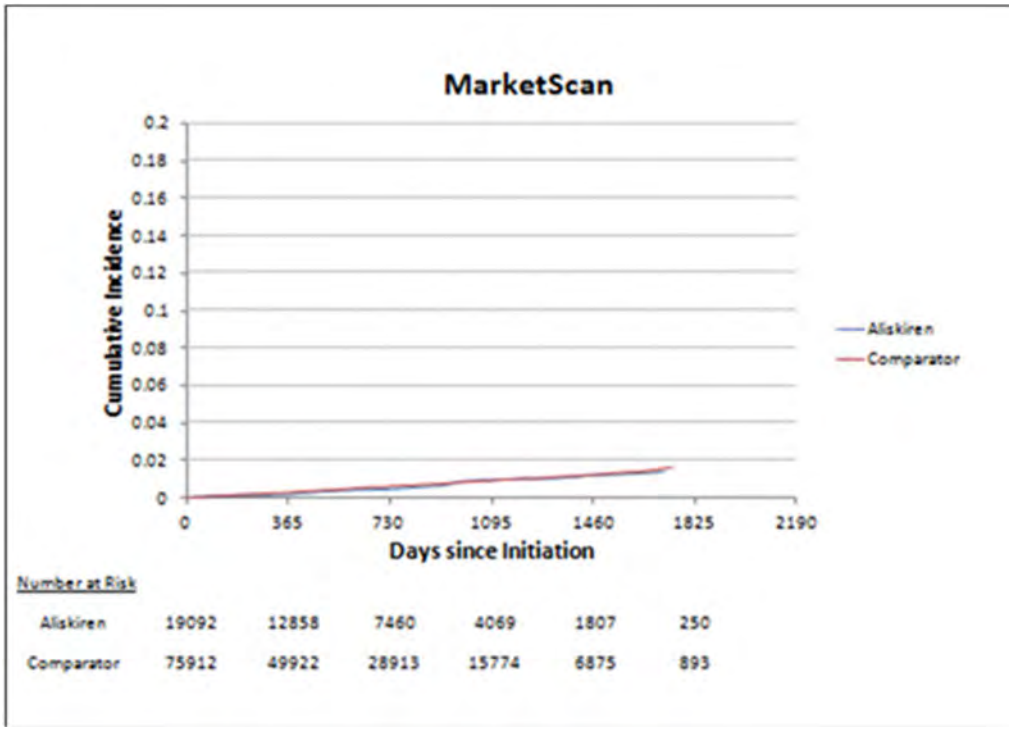
Annex 2-Figure 2-44 Cumulative incidence of hemorrhagic stroke in Cohort 3, ITT – MarketScan



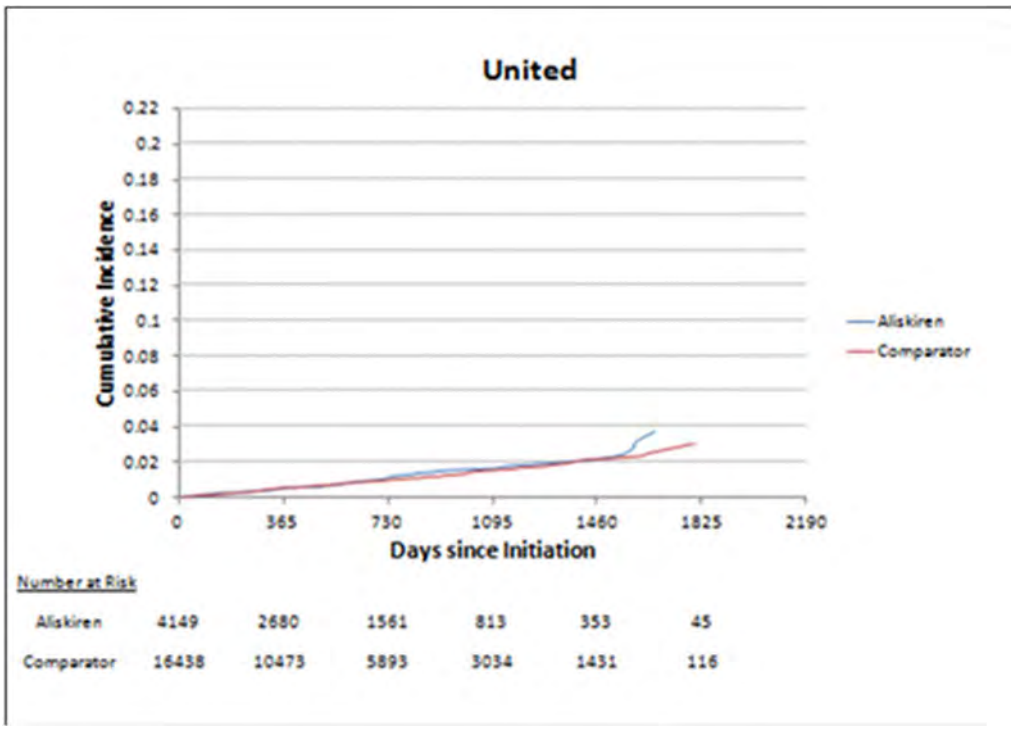
Annex 2-Figure 2-45 Cumulative incidence of transient ischemic attack in Cohort 3, ITT – United



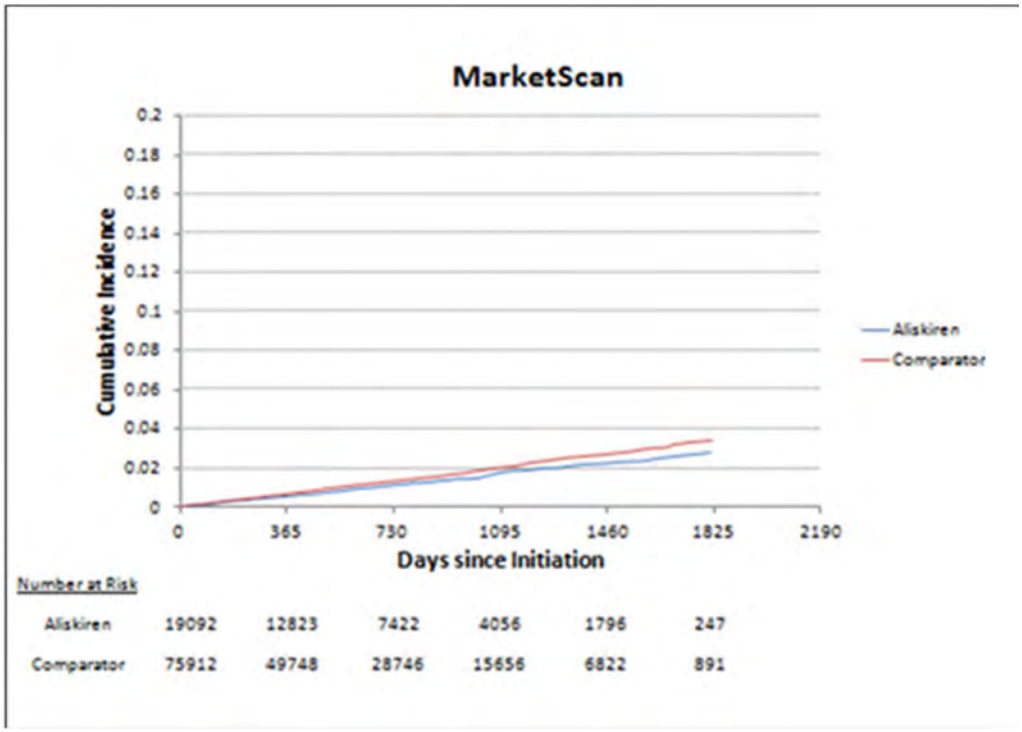
Annex 2-Figure 2-46 Cumulative incidence of transient ischemic attack in Cohort 3, ITT – MarketScan



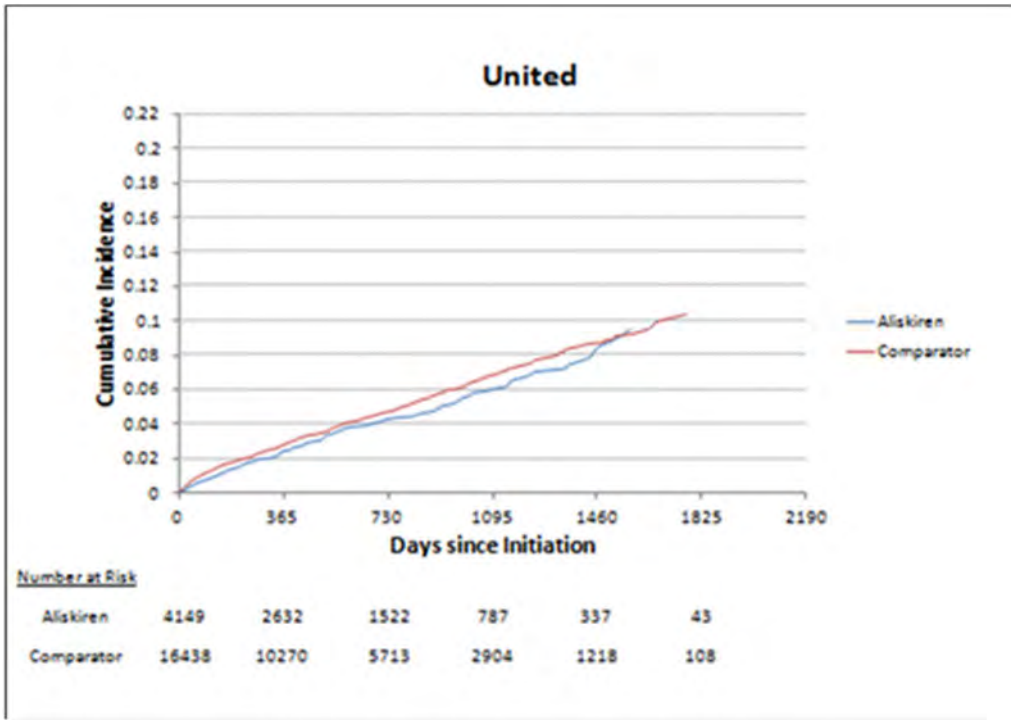
Annex 2-Figure 2-47 Cumulative incidence of myocardial infarction in Cohort 3, ITT – United



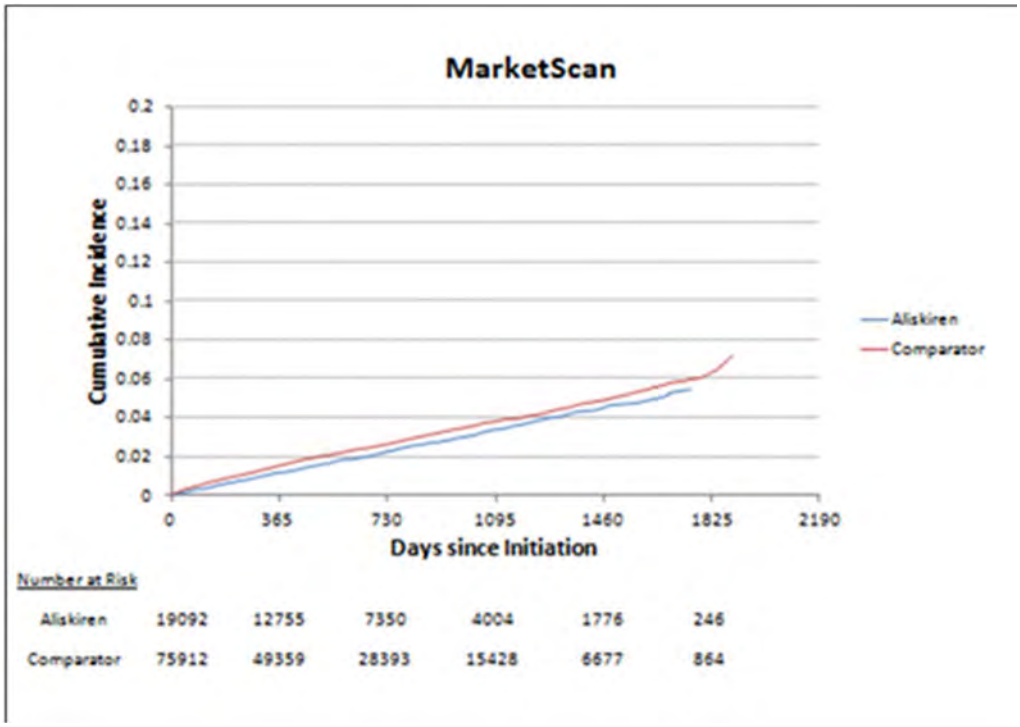
Annex 2-Figure 2-48 Cumulative incidence of myocardial infarction in Cohort 3, ITT – MarketScan



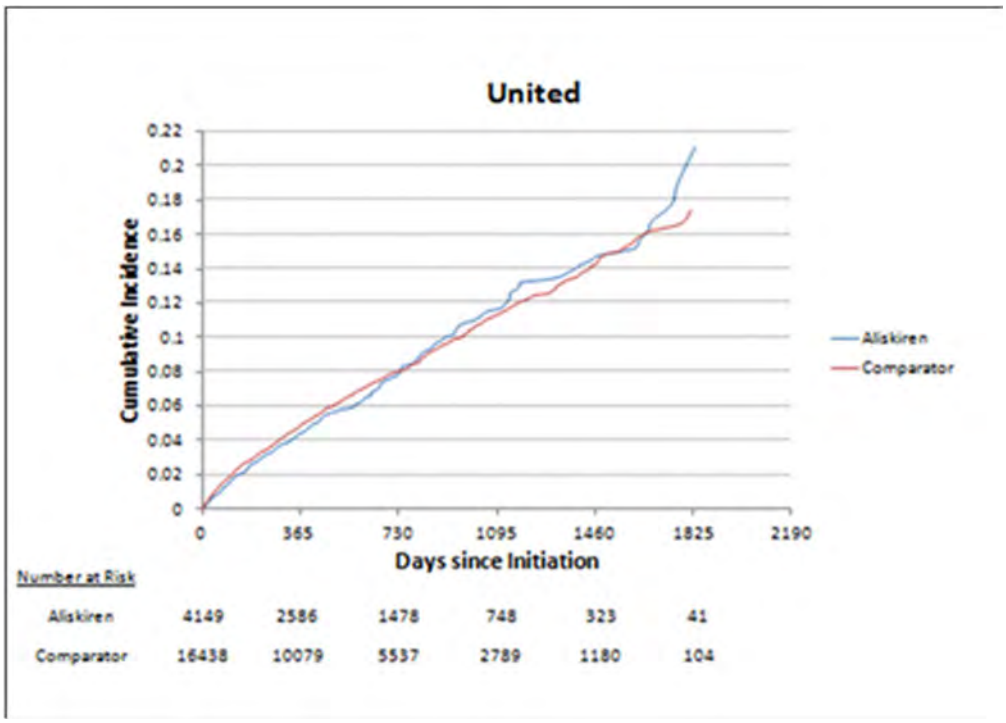
Annex 2-Figure 2-49 Cumulative incidence of heart failure in Cohort 3, ITT – United



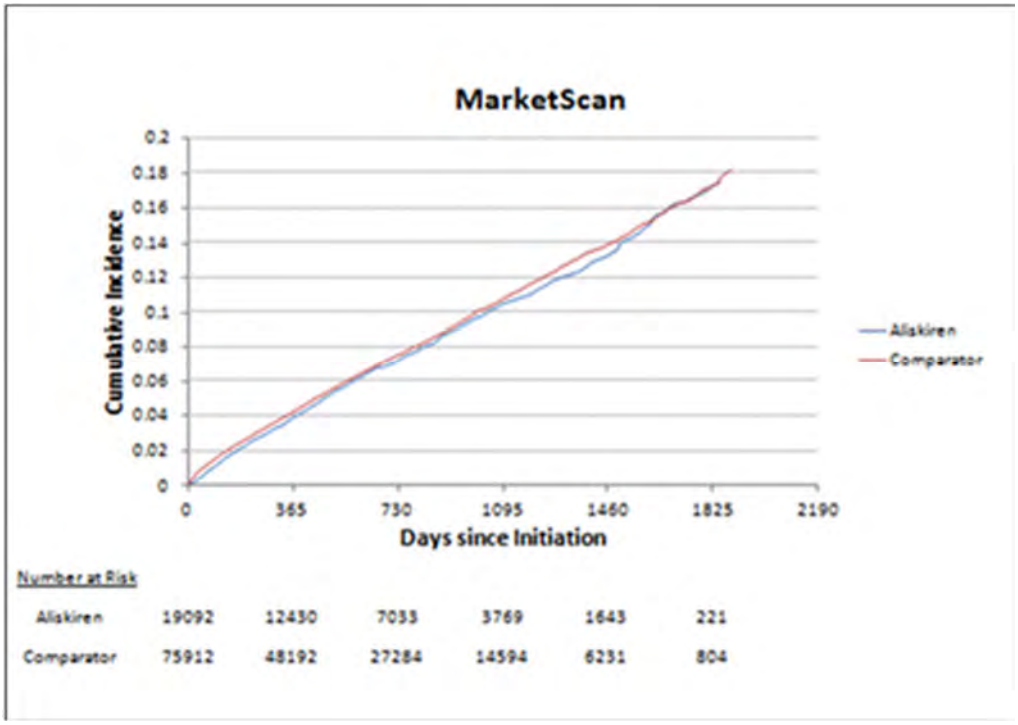
Annex 2-Figure 2-50 Cumulative incidence of heart failure in Cohort 3, ITT – MarketScan



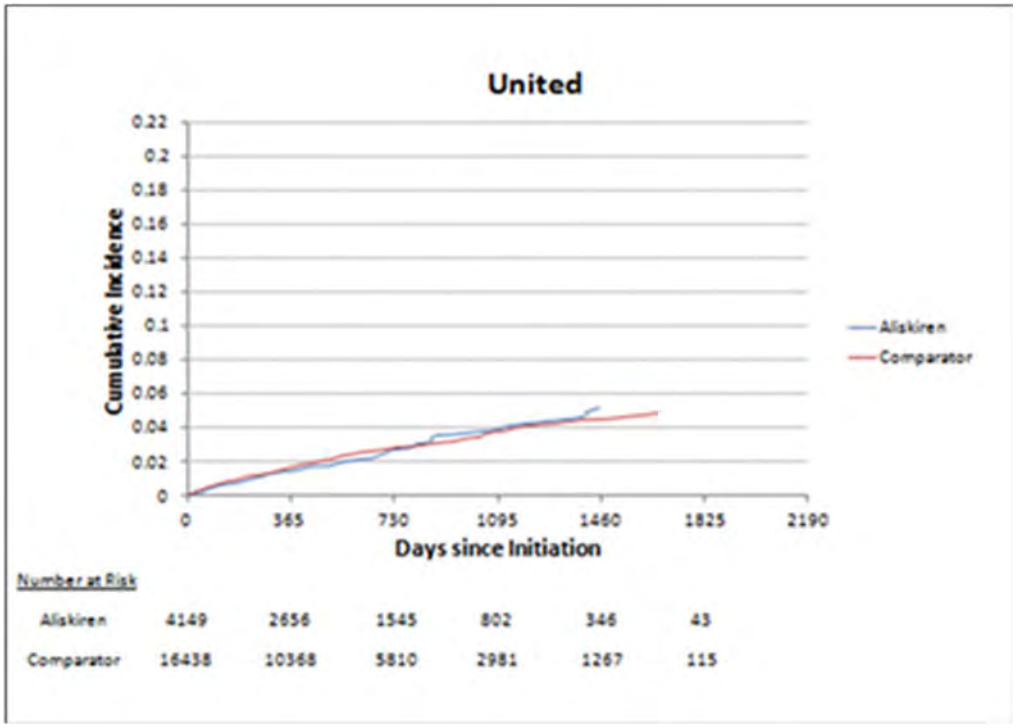
Annex 2-Figure 2-51 Cumulative incidence of acute renal failure in Cohort 3, ITT – United



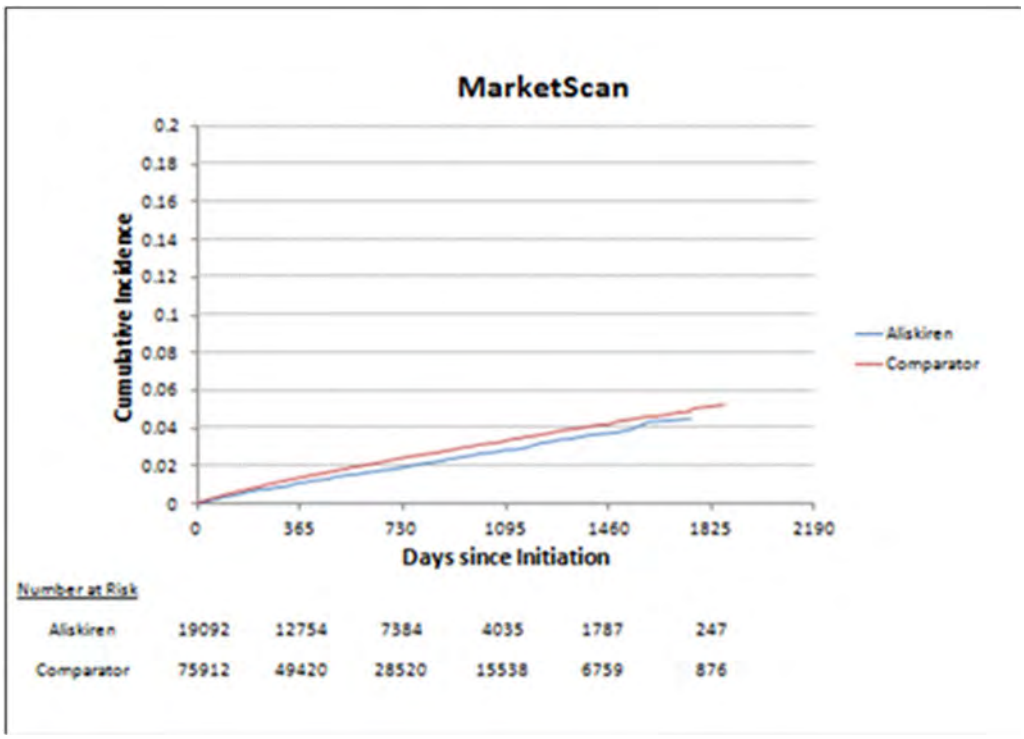
Annex 2-Figure 2-52 Cumulative incidence of acute renal failure in Cohort 3, ITT – MarketScan



Annex 2-Figure 2-53 Cumulative incidence of end-stage renal disease in Cohort 3, ITT – United

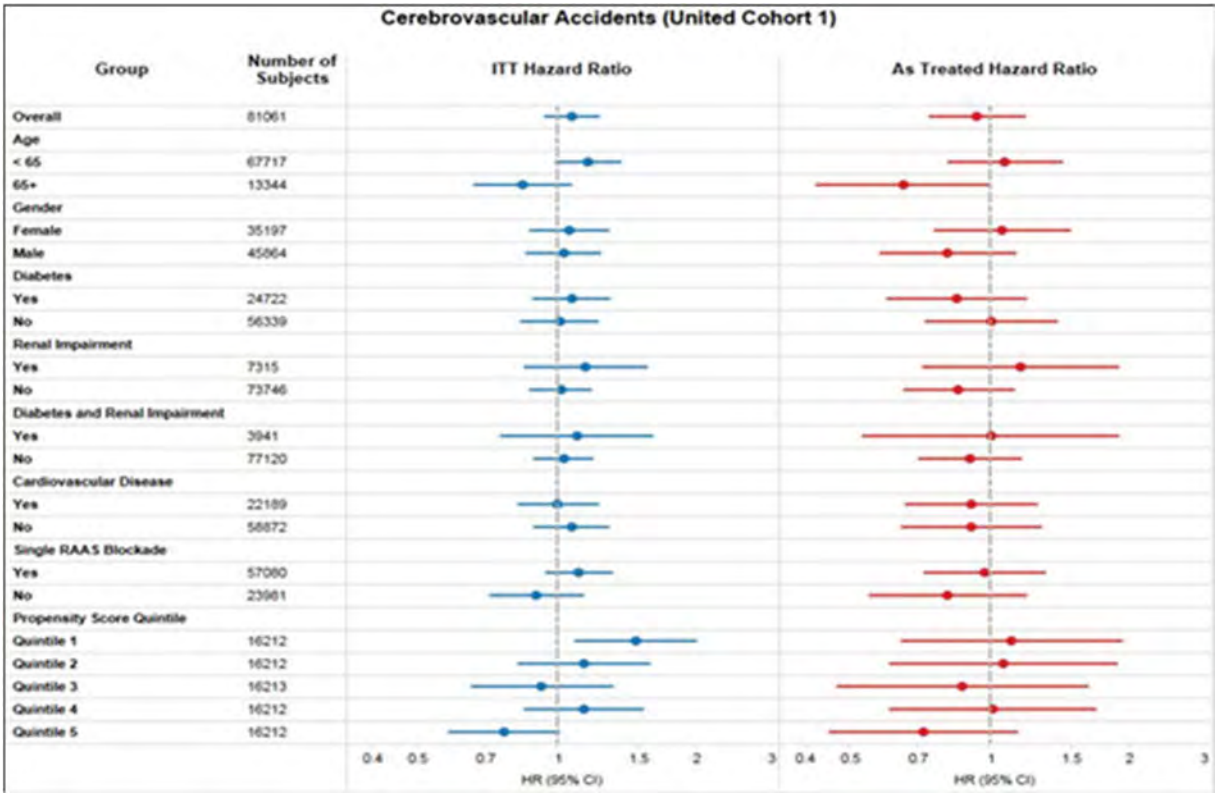


Annex 2-Figure 2-54 Cumulative incidence of end-stage renal disease in Cohort 3, ITT – MarketScan

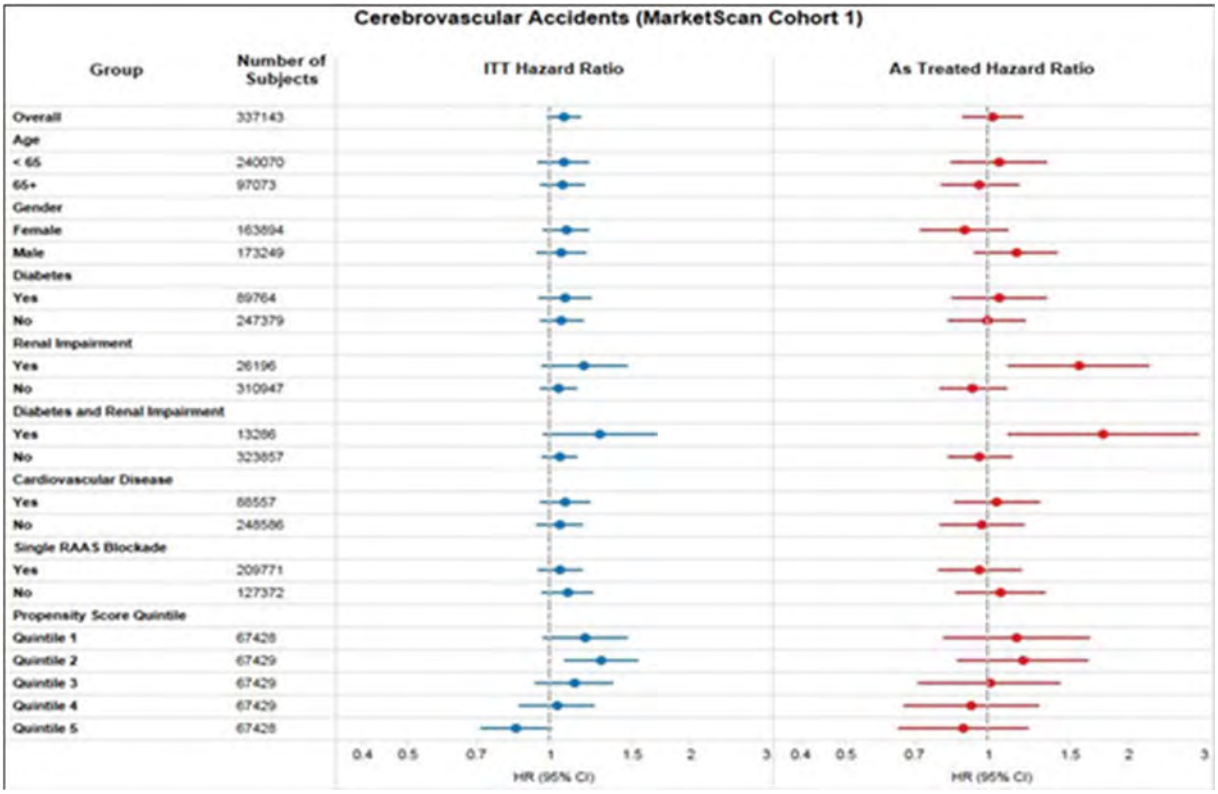


Annex 2.5.2 Forest plots

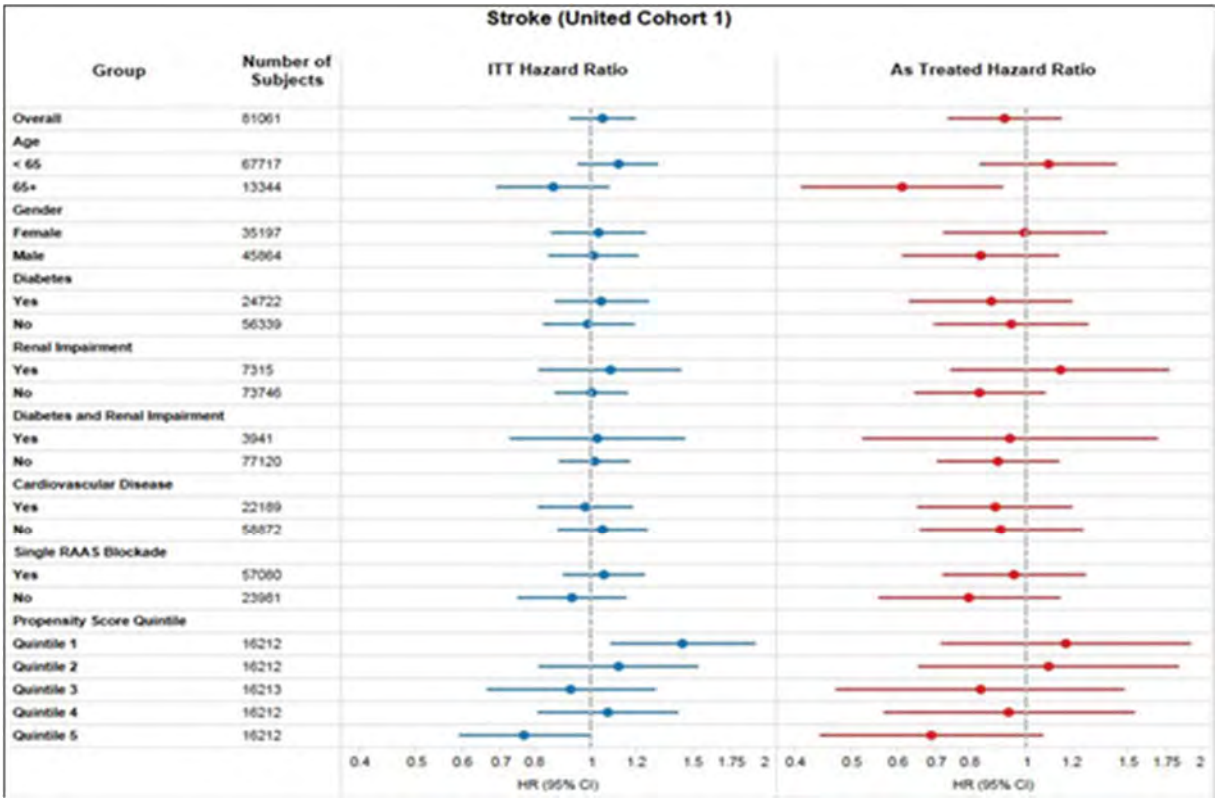
Annex 2-Figure 2-55 Forest plot for cerebrovascular accidents in Cohort 1 – United



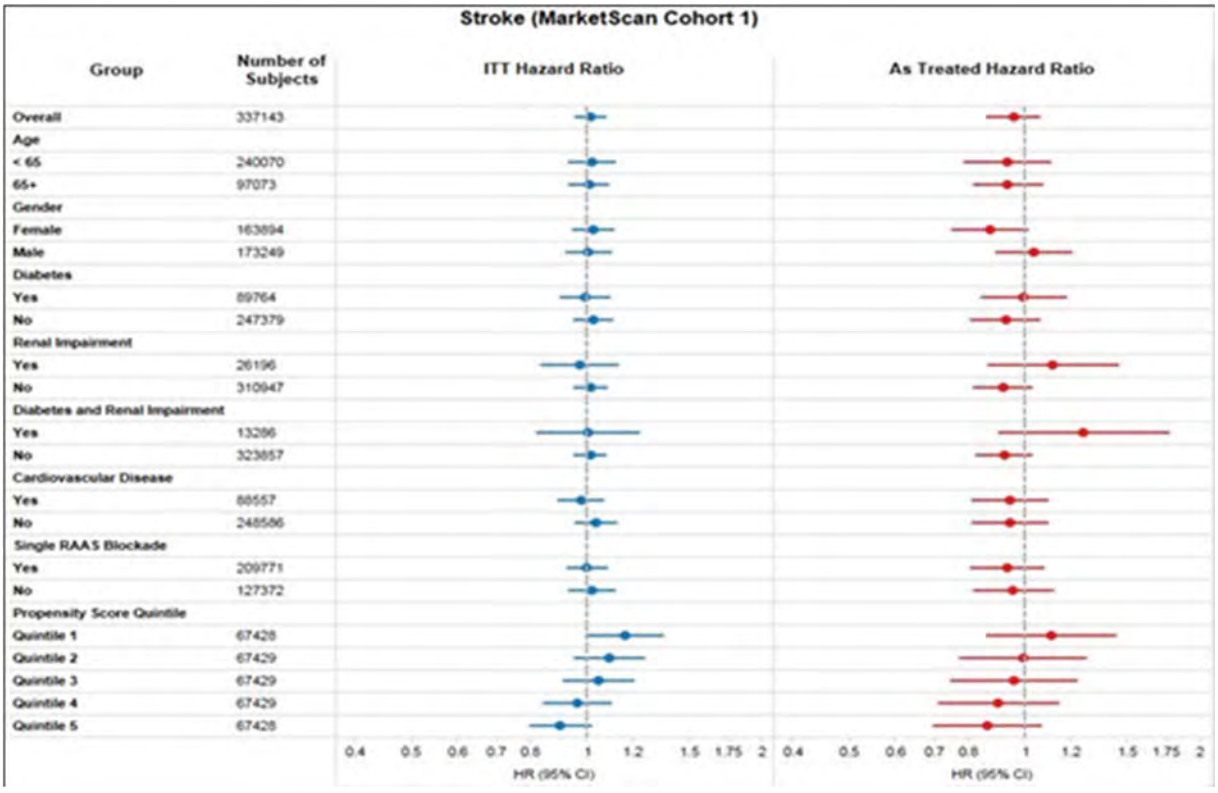
Annex 2-Figure 2-56 Forest plot for cerebrovascular accidents in Cohort 1 – MarketScan



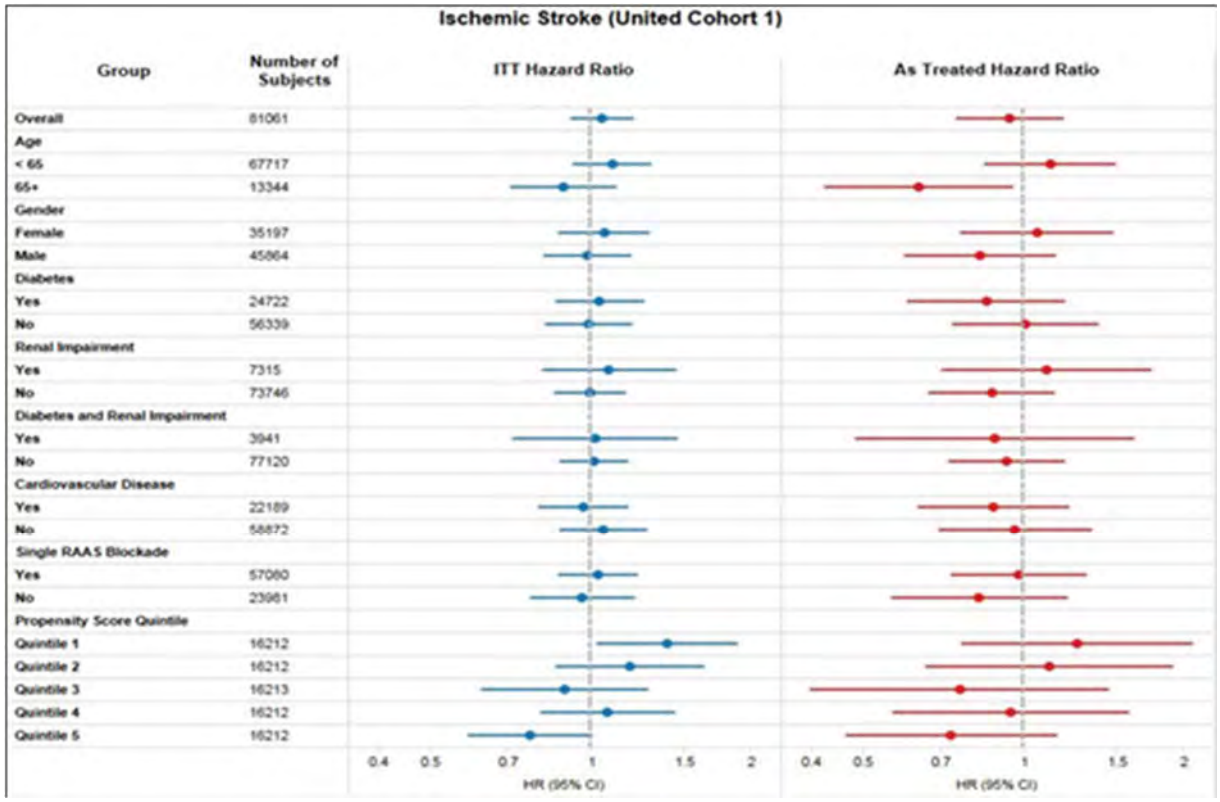
Annex 2-Figure 2-57 Forest plot for stroke in Cohort 1 – United



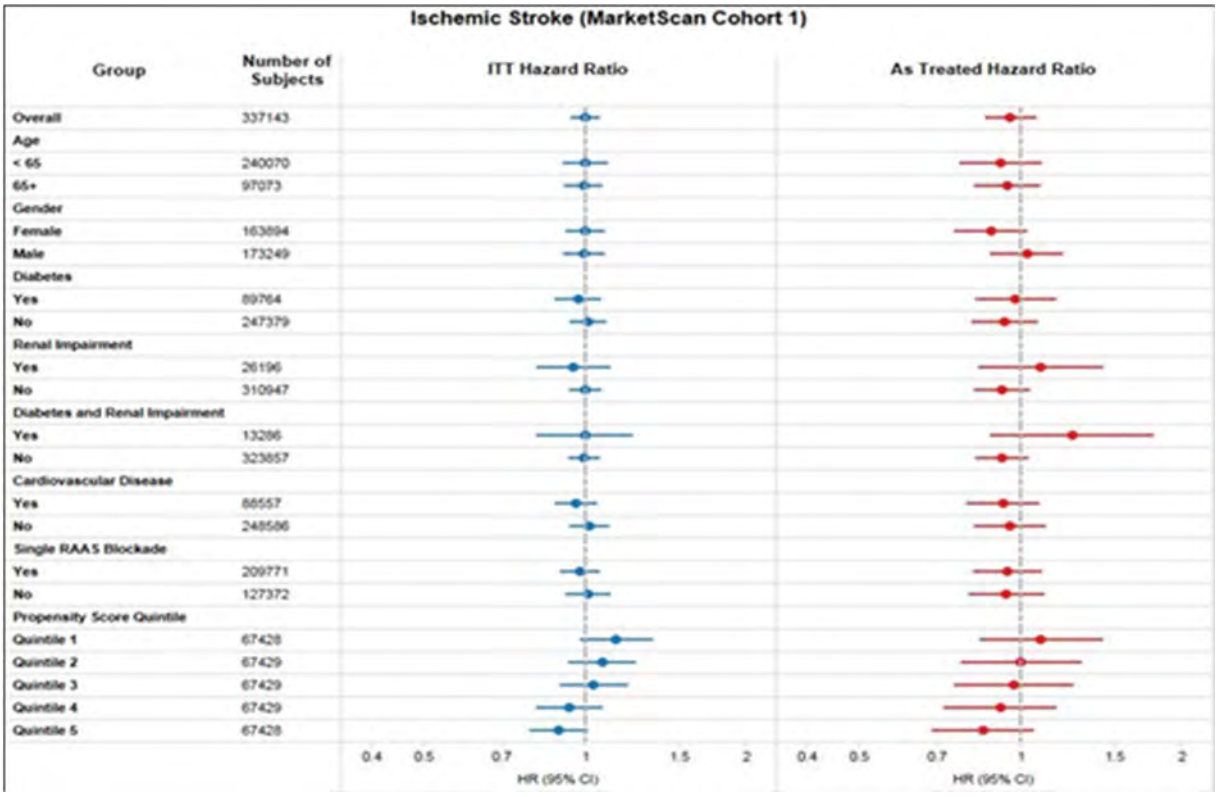
Annex 2-Figure 2-58 Forest plot for stroke in Cohort 1 – MarketScan



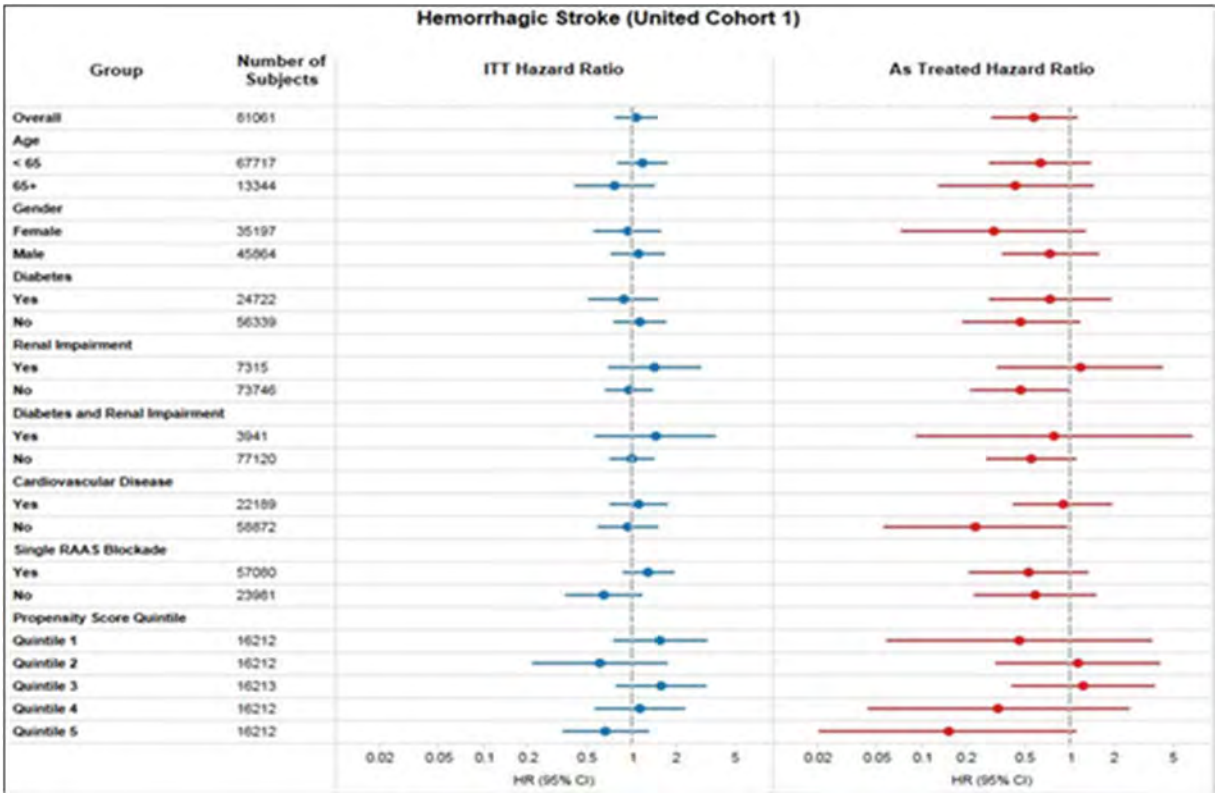
Annex 2-Figure 2-59 Forest plot for ischemic stroke in Cohort 1 – United



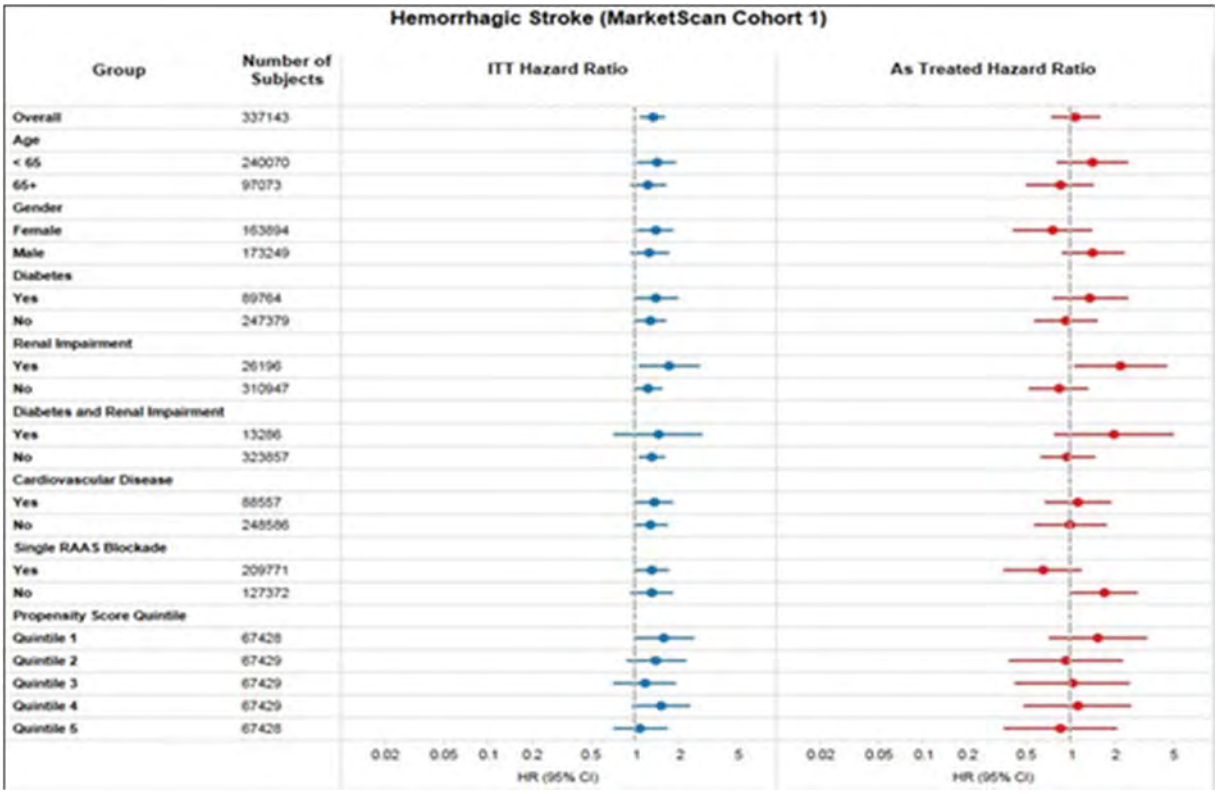
Annex 2-Figure 2-60 Forest plot for ischemic stroke in Cohort 1 – MarketScan



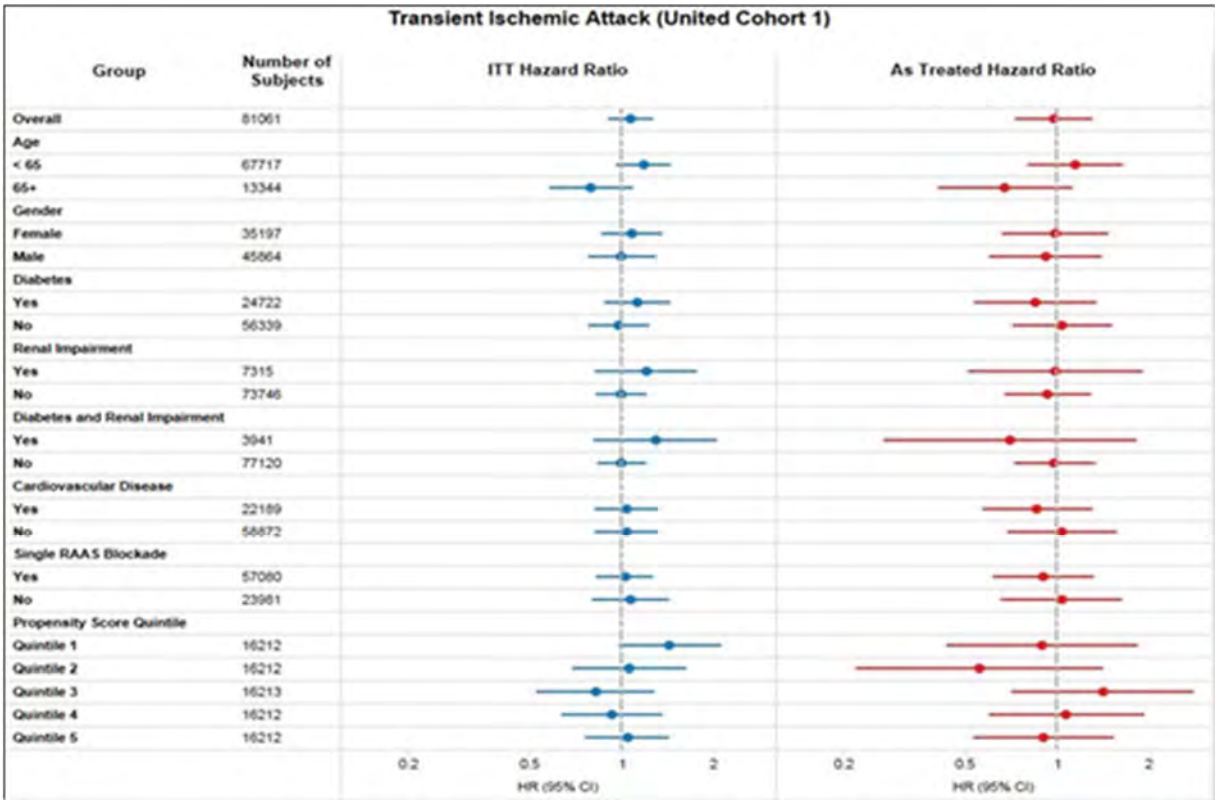
Annex 2-Figure 2-61 Forest plot for hemorrhagic stroke in Cohort 1 – United



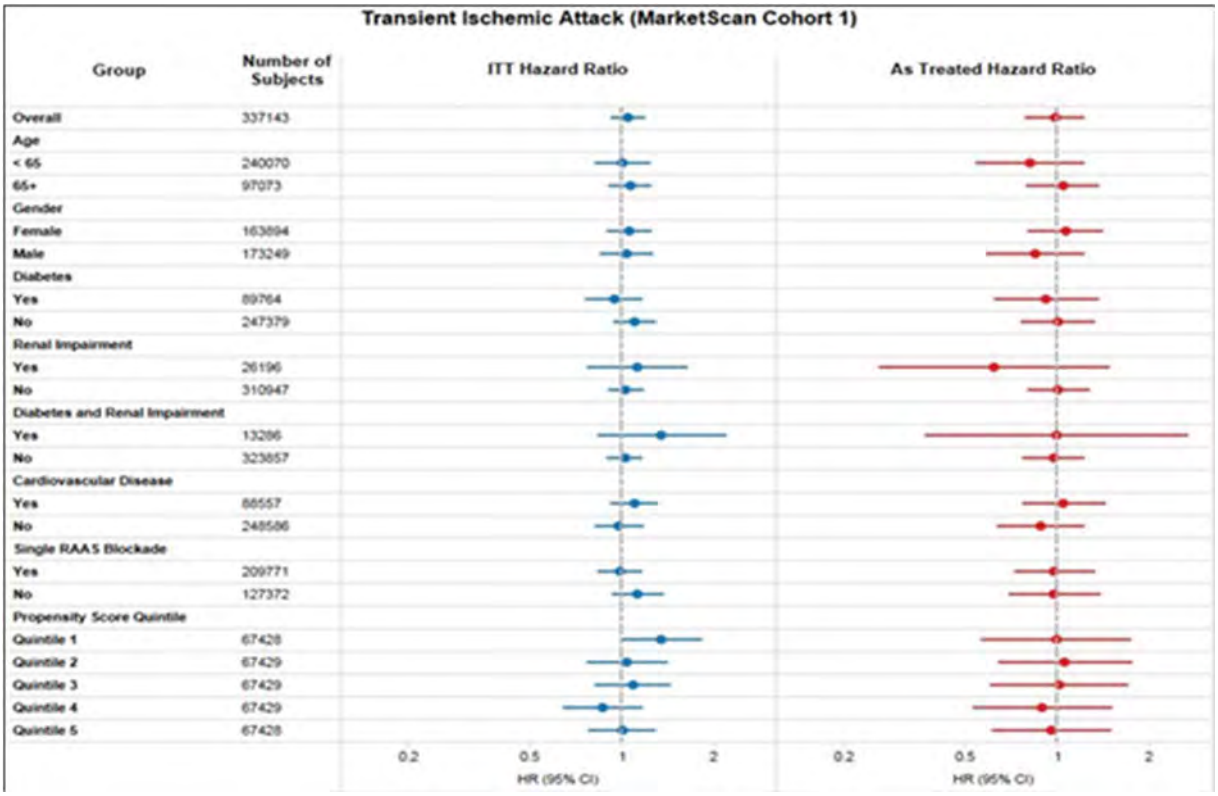
Annex 2-Figure 2-62 Forest plot for hemorrhagic stroke in Cohort 1 – MarketScan



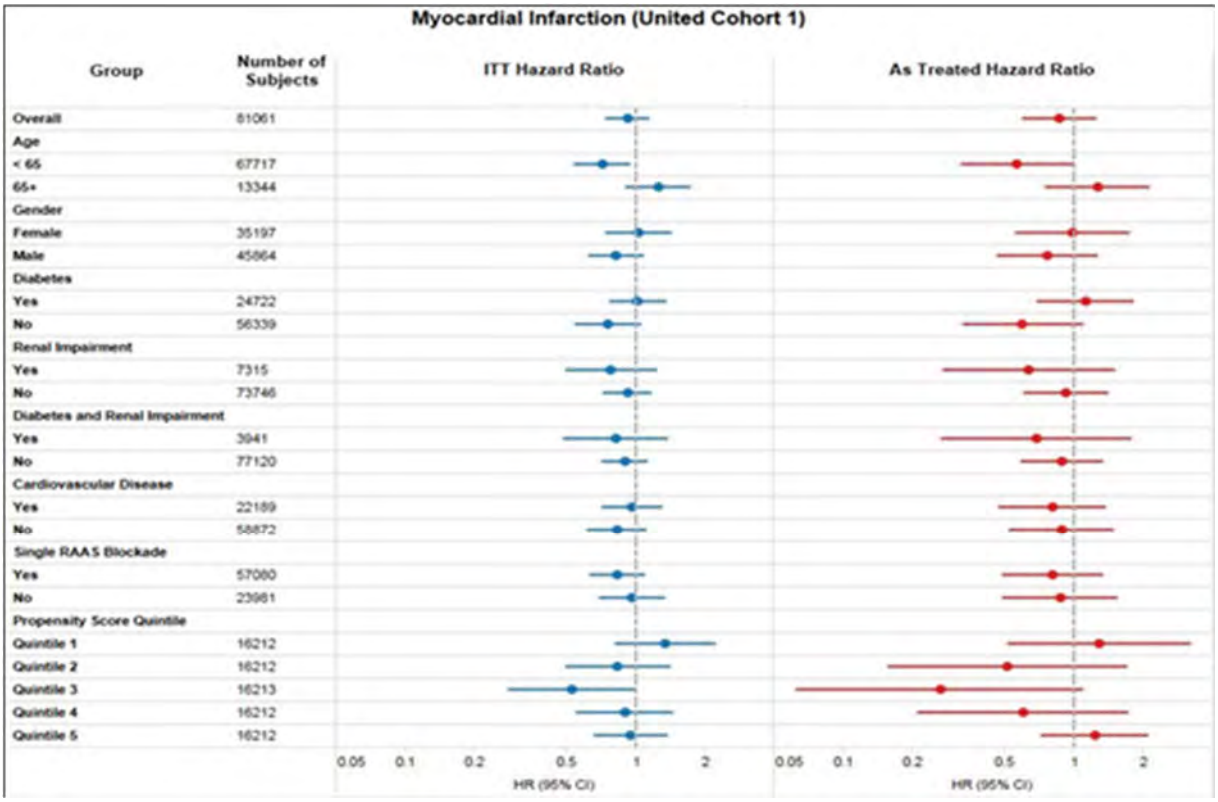
Annex 2-Figure 2-63 Forest plot for transient ischemic attack in Cohort 1 – United



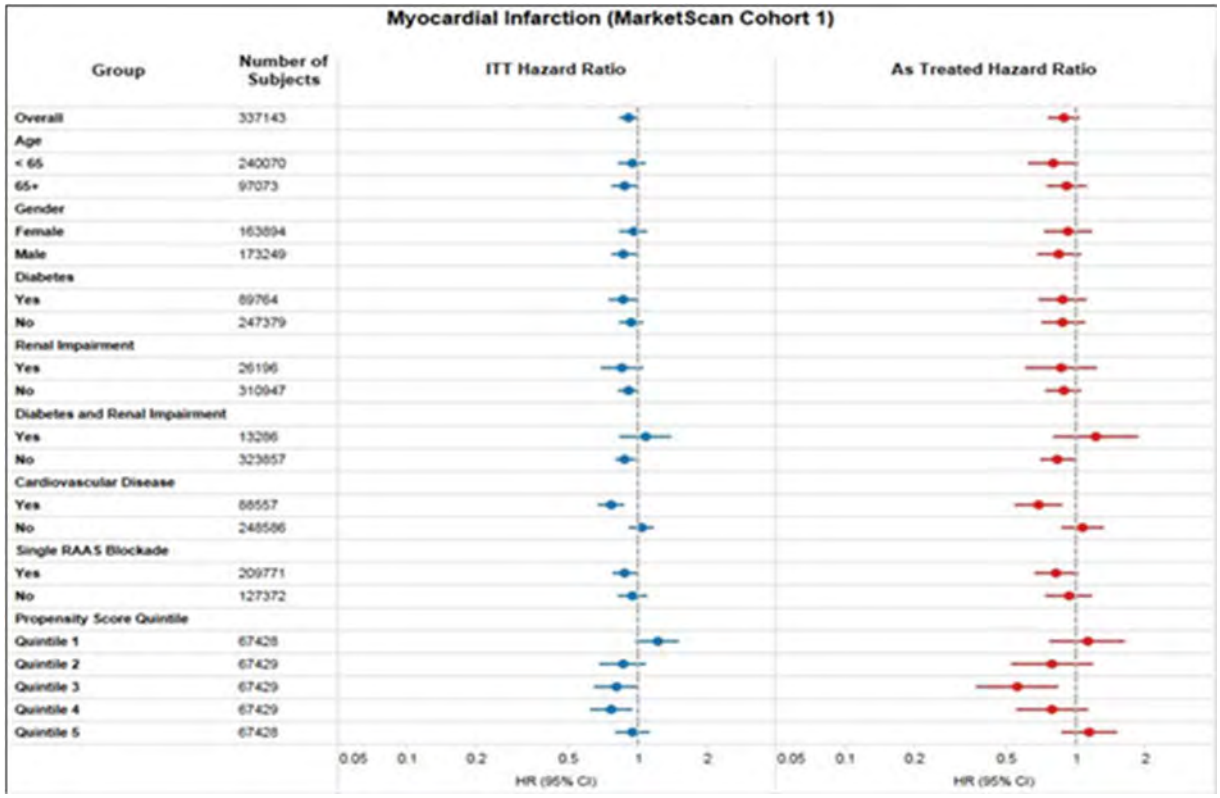
Annex 2-Figure 2-64 Forest plot for transient ischemic attack in Cohort 1 – MarketScan



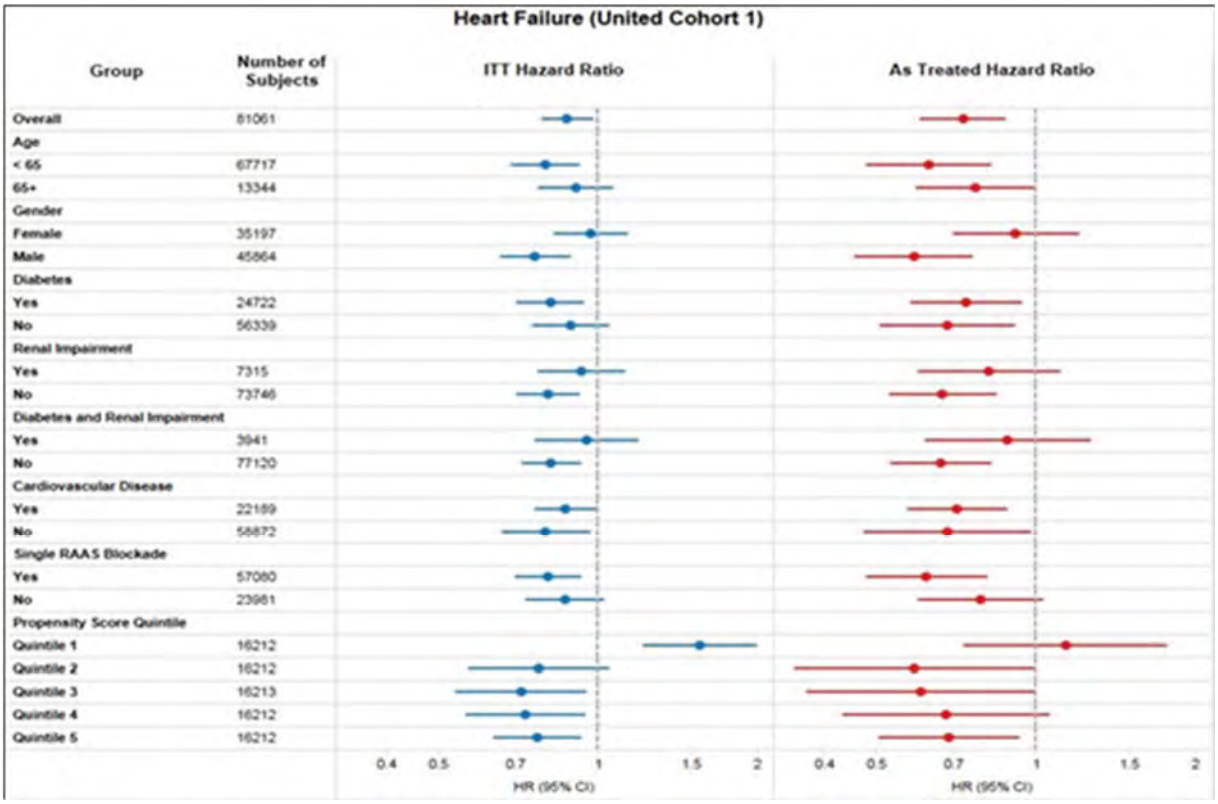
Annex 2-Figure 2-65 Forest plot for myocardial infarction in Cohort 1 – United



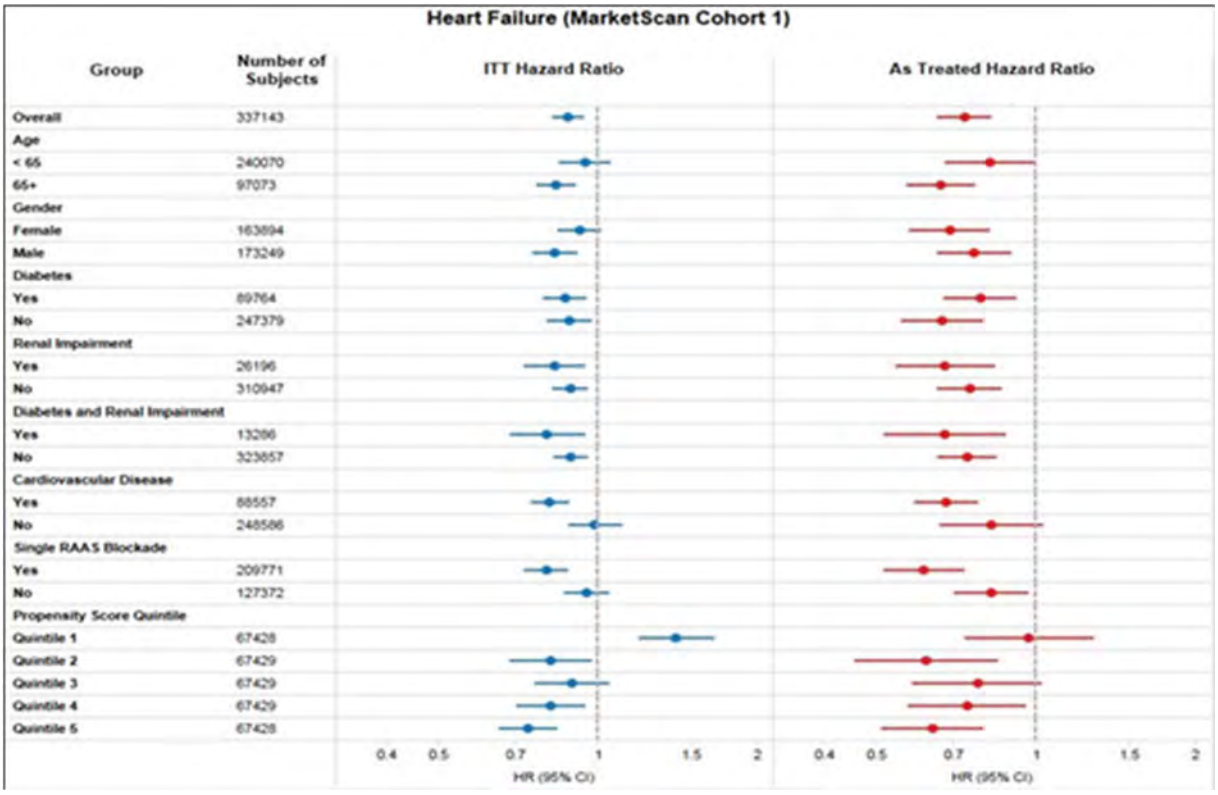
Annex 2-Figure 2-66 Forest plot for myocardial infarction in Cohort 1 – MarketScan



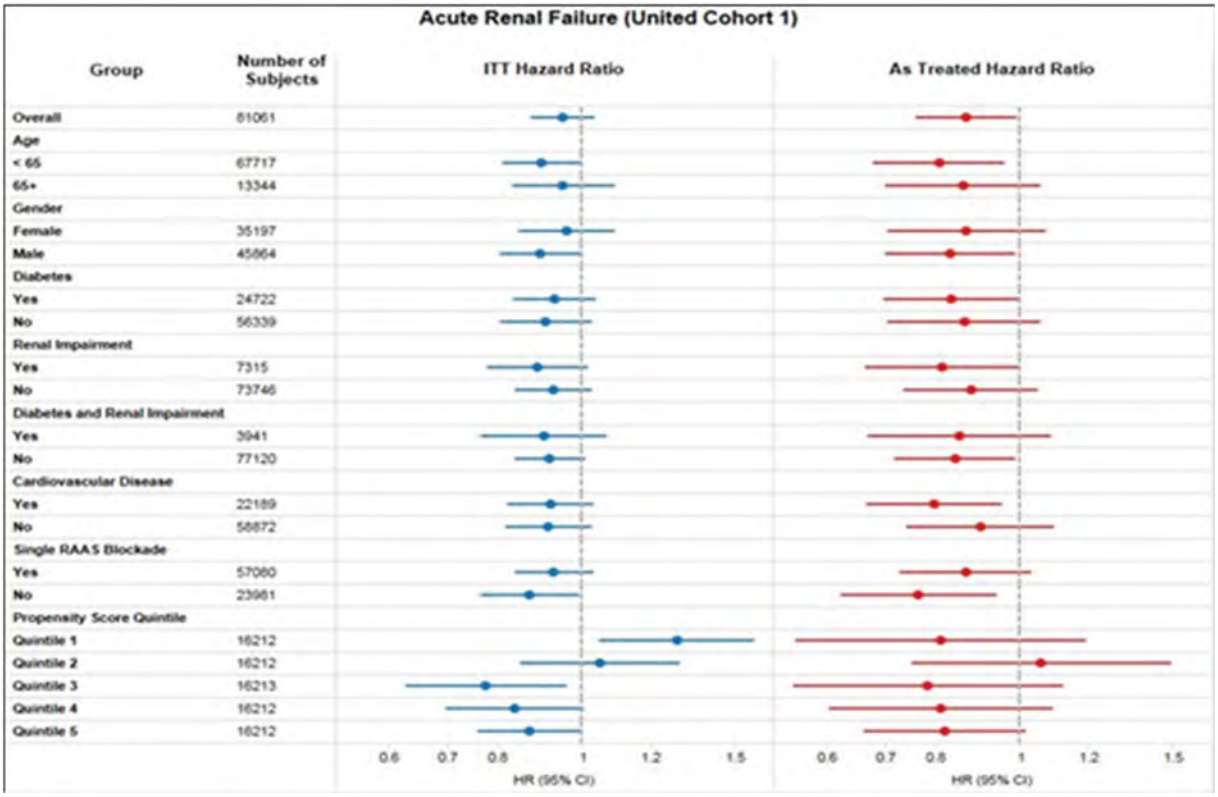
Annex 2-Figure 2-67 Forest plot for heart failure in Cohort 1 – United



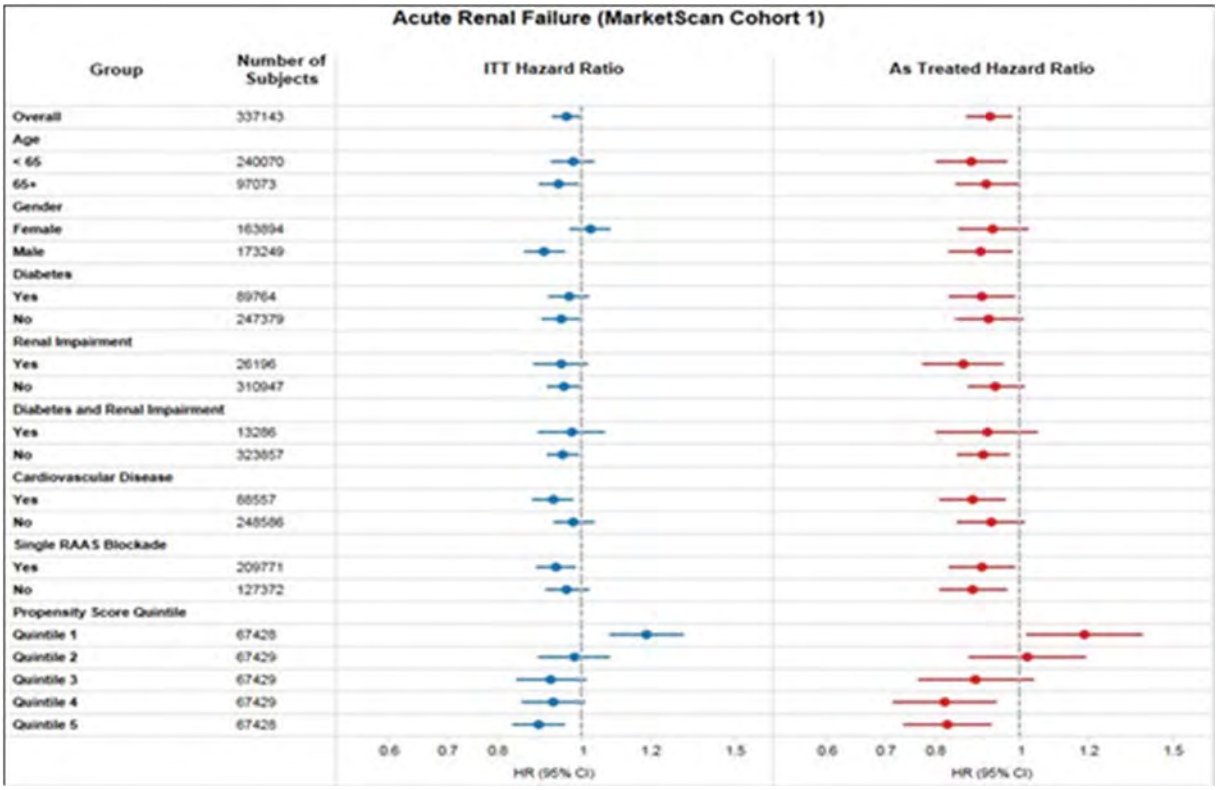
Annex 2-Figure 2-68 Forest plot for heart failure in Cohort 1 – MarketScan



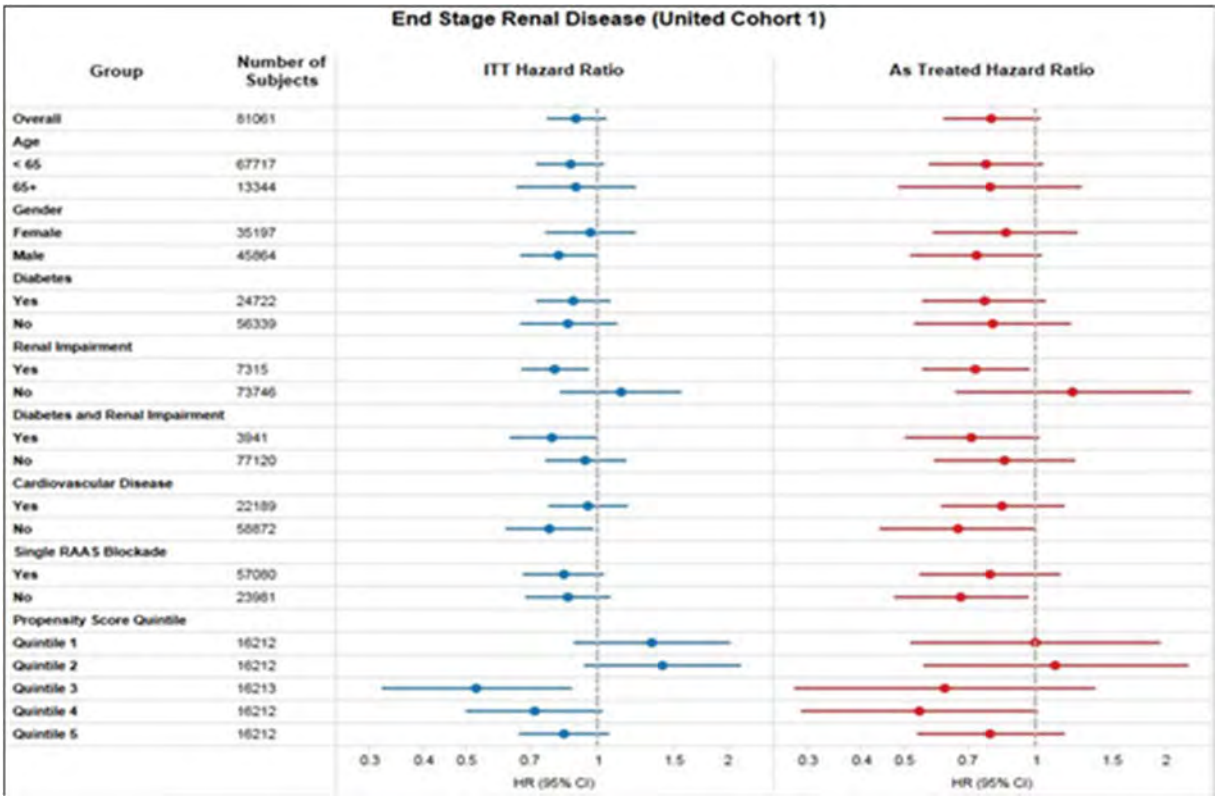
Annex 2-Figure 2-69 Forest plot for acute renal failure in Cohort 1 – United



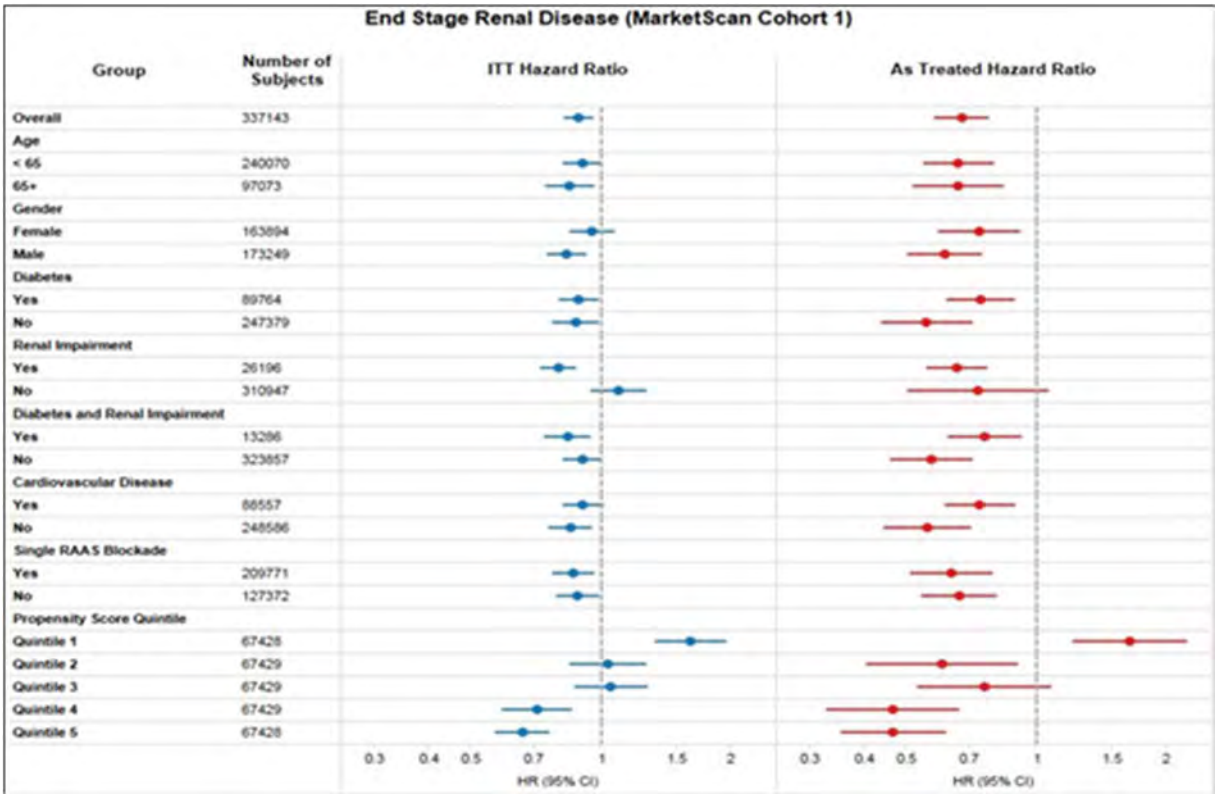
Annex 2-Figure 2-70 Forest plot for acute renal failure in Cohort 1 – MarketScan



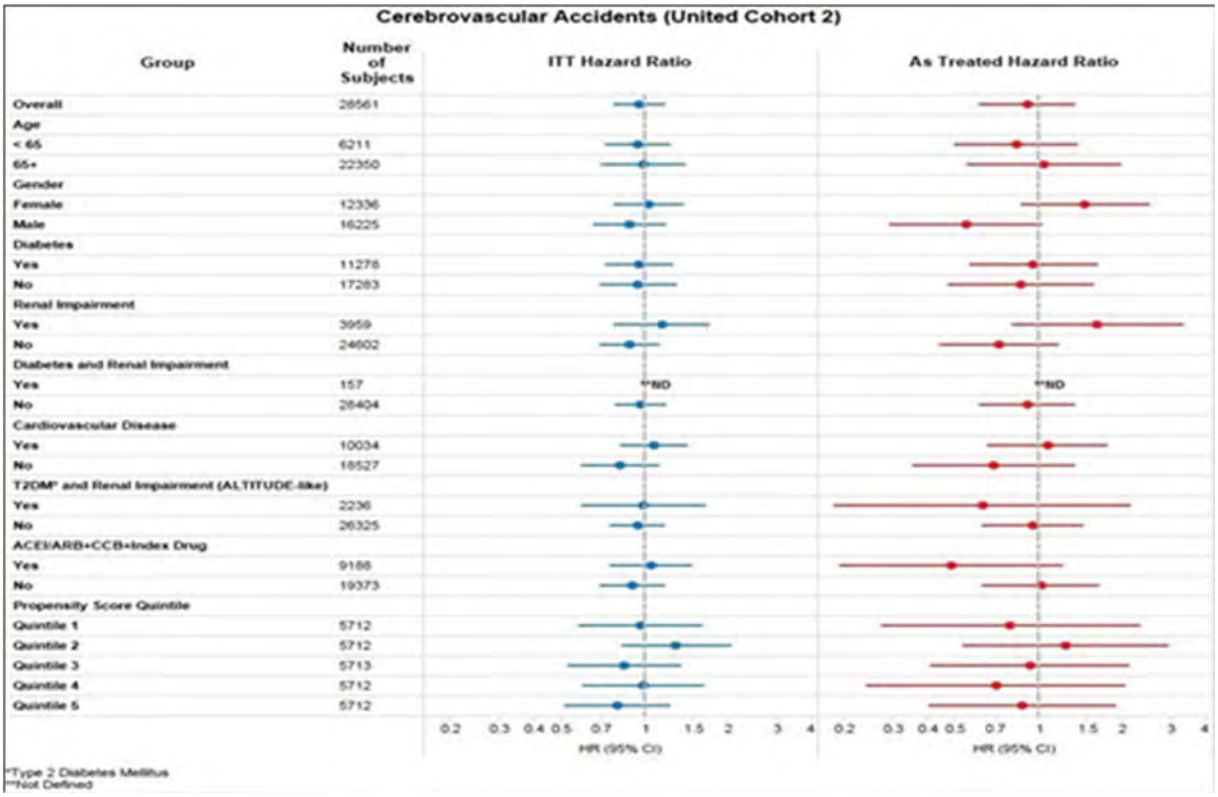
Annex 2-Figure 2-71 Forest plot for end-stage renal disease in Cohort 1 – United



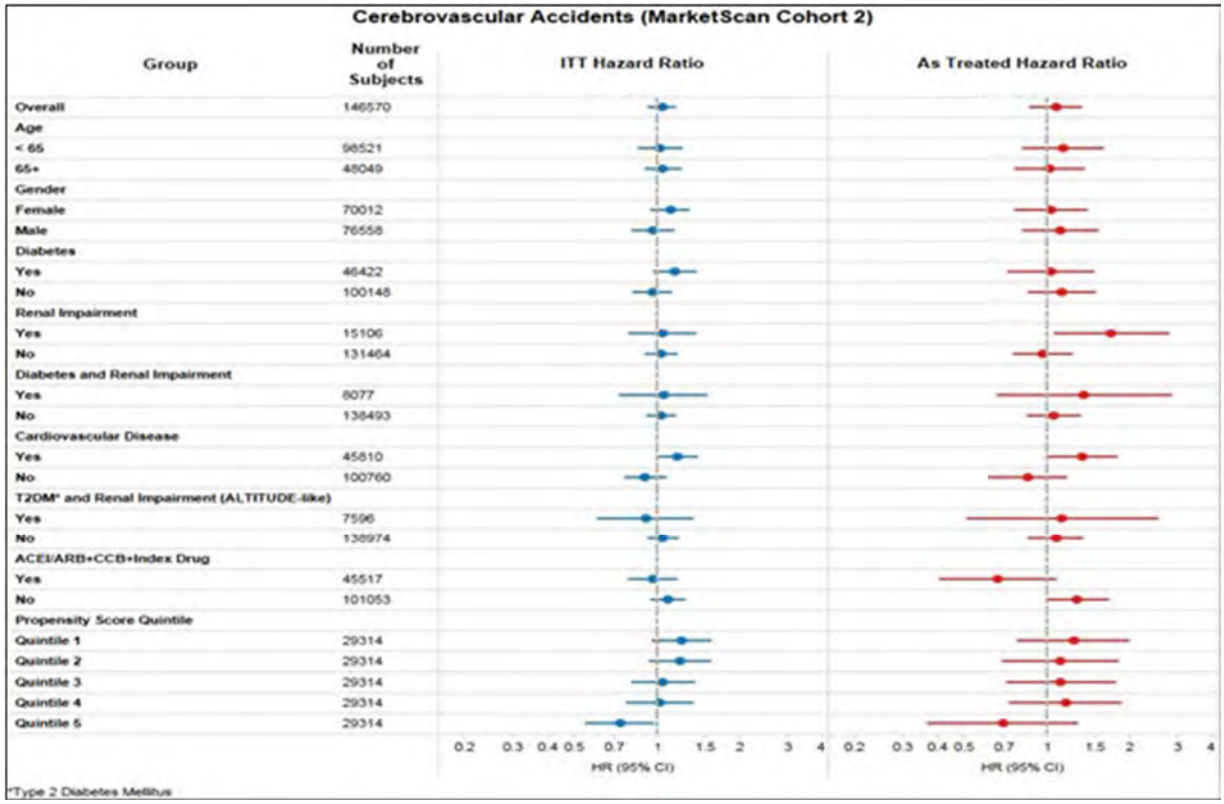
Annex 2-Figure 2-72 Forest plot for end-stage renal disease in Cohort 1 – MarketScan



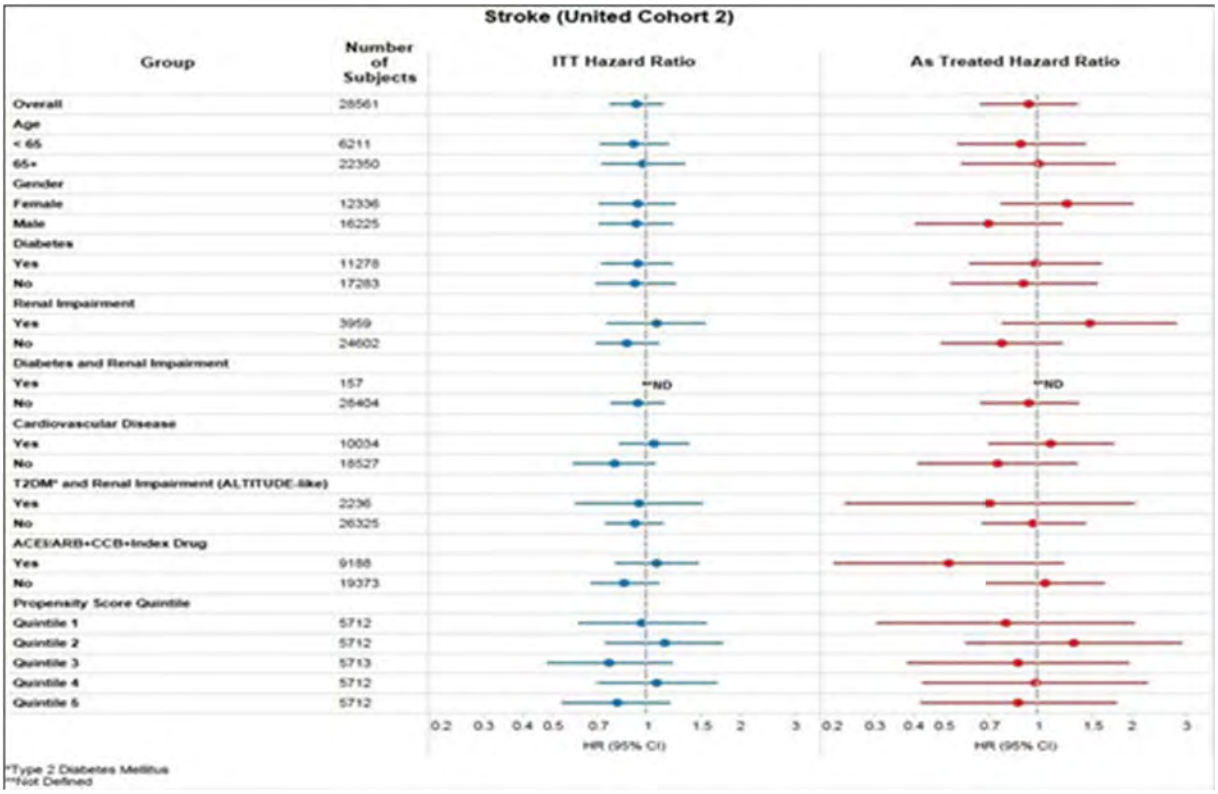
Annex 2-Figure 2-73 Forest plot for cerebrovascular accidents in Cohort 2 – United



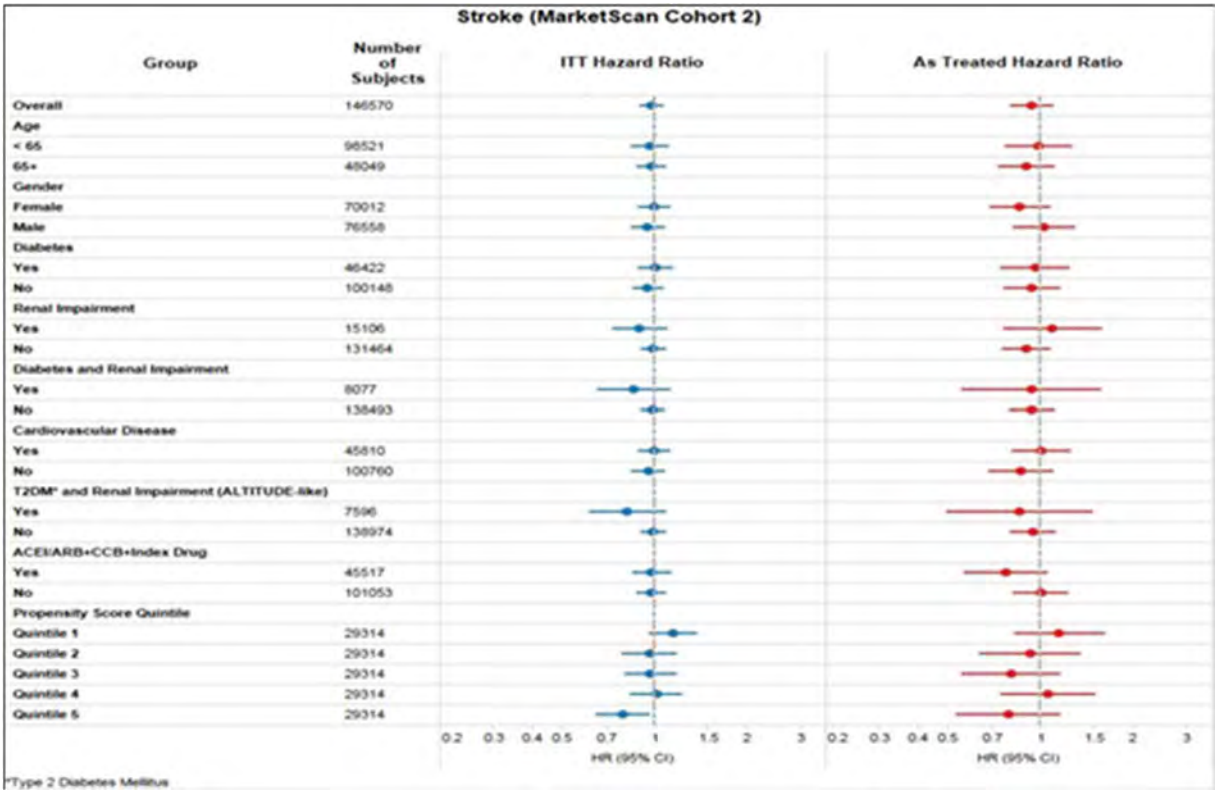
Annex 2-Figure 2-74 Forest plot for cerebrovascular accidents in Cohort 2 – MarketScan



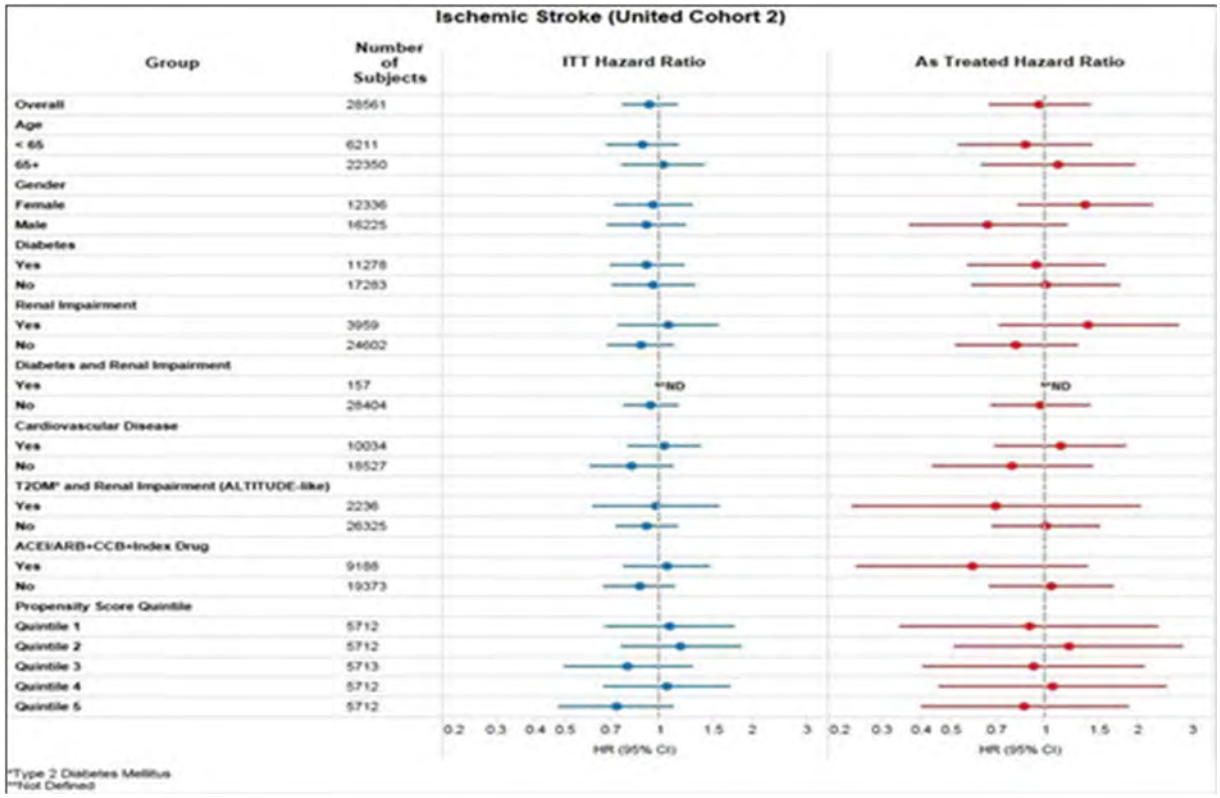
Annex 2-Figure 2-75 Forest plot for stroke in Cohort 2 – United



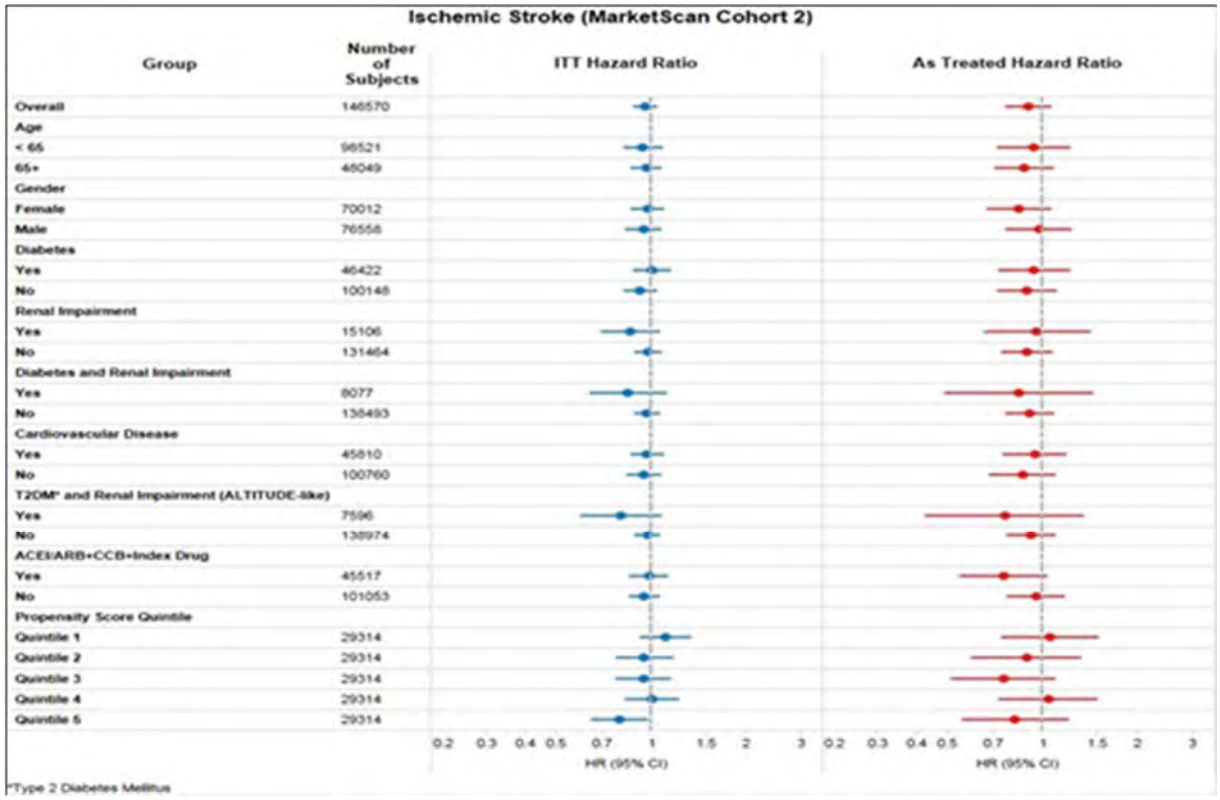
Annex 2-Figure 2-76 Forest plot for stroke in Cohort 2 – MarketScan



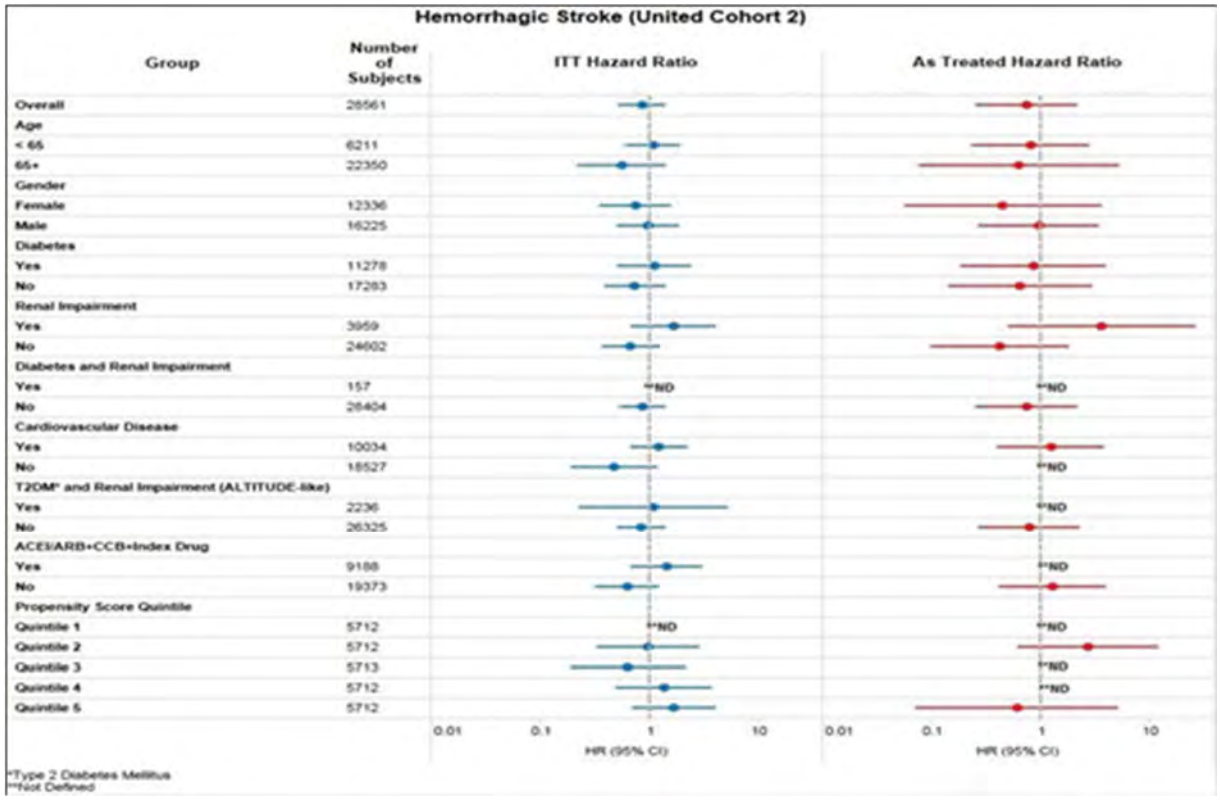
Annex 2-Figure 2-77 Forest plot for ischemic stroke in Cohort 2 – United



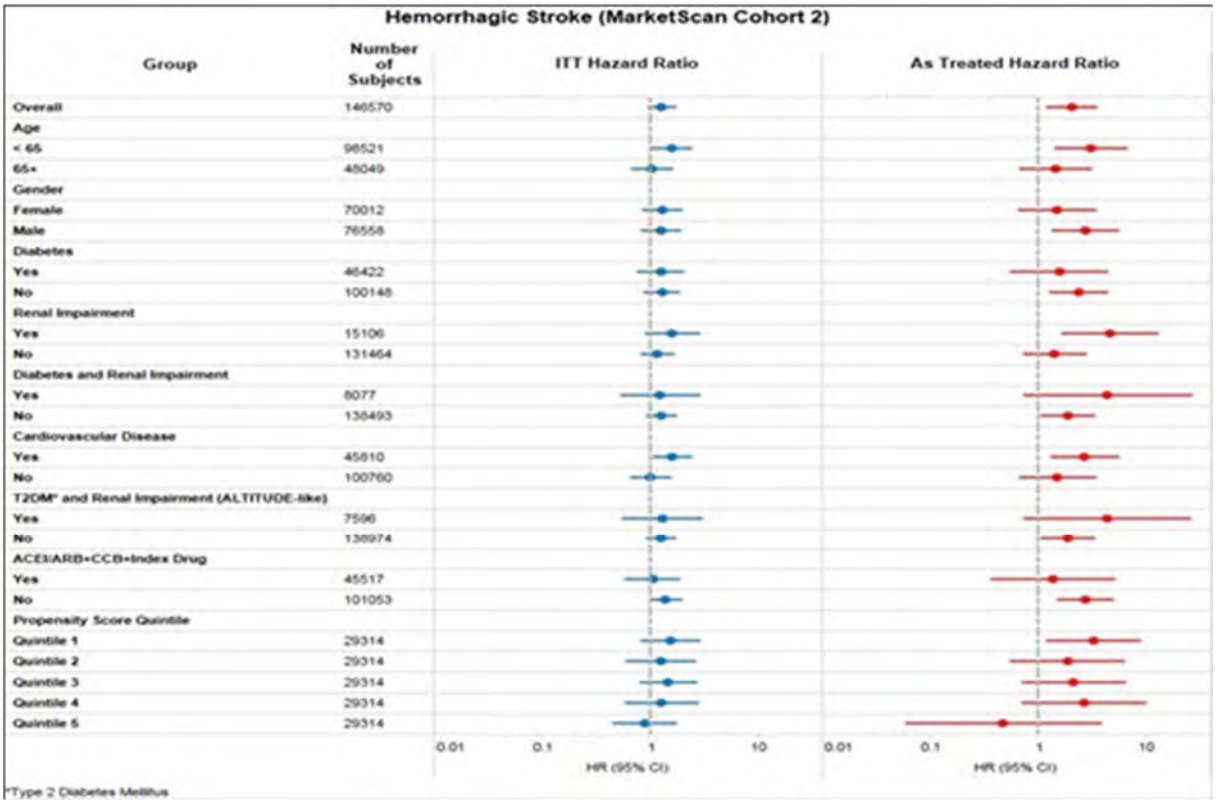
Annex 2-Figure 2-78 Forest plot for ischemic stroke in Cohort 2 – MarketScan



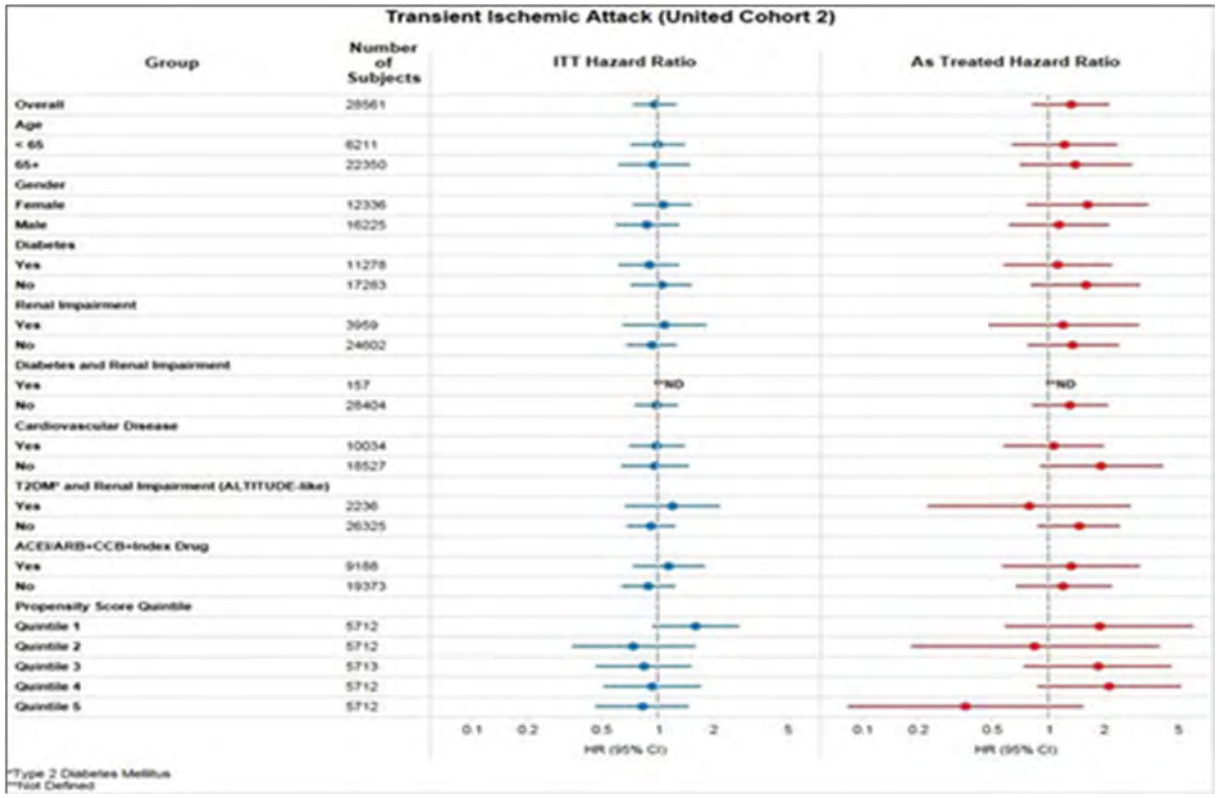
Annex 2-Figure 2-79 Forest plot for hemorrhagic stroke for Cohort 2 – United



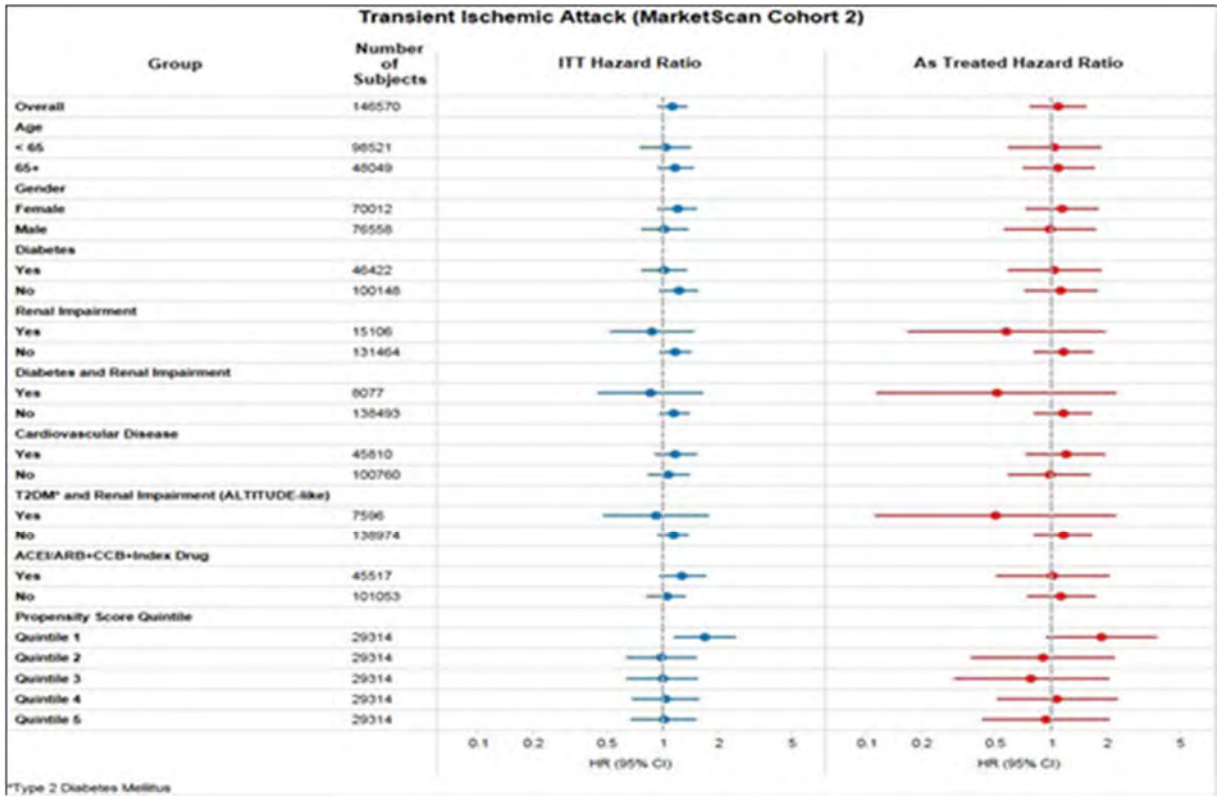
Annex 2-Figure 2-80 Forest plot for hemorrhagic stroke for Cohort 2 – MarketScan



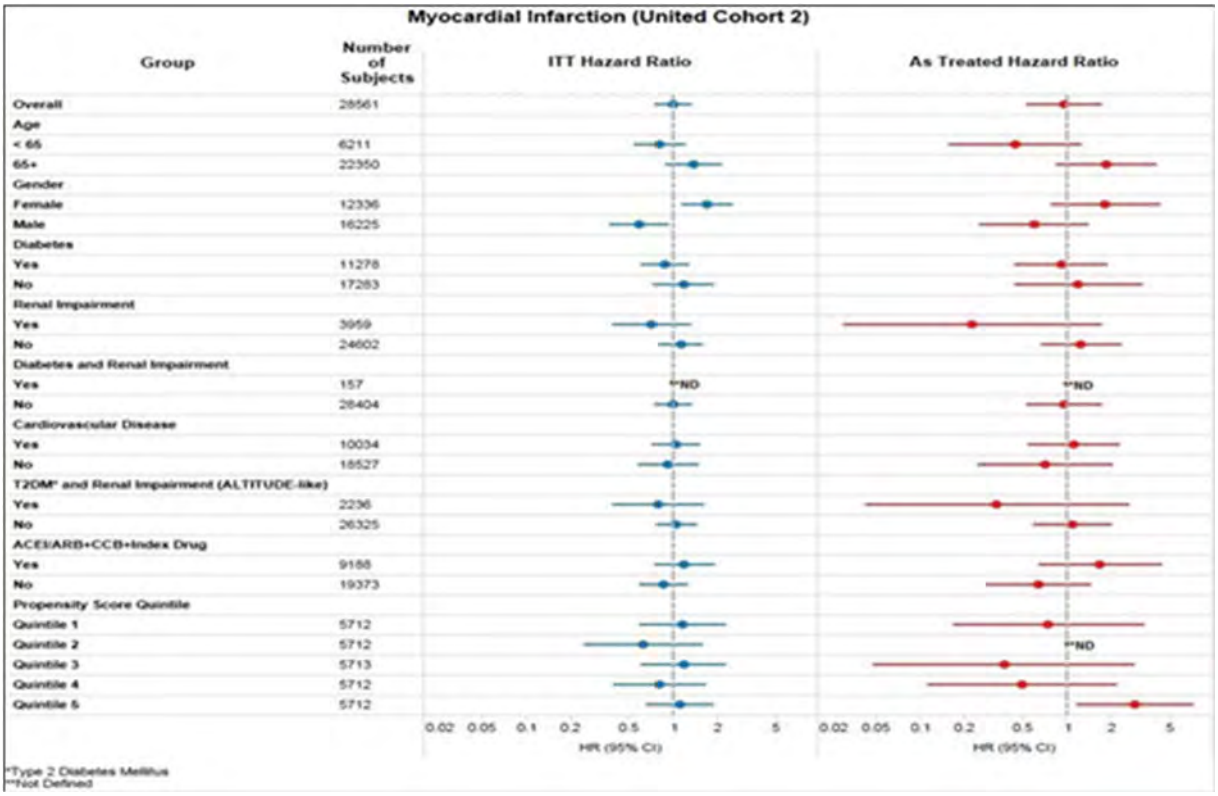
Annex 2-Figure 2-81 Forest plot for transient ischemic attack in Cohort 2 – United



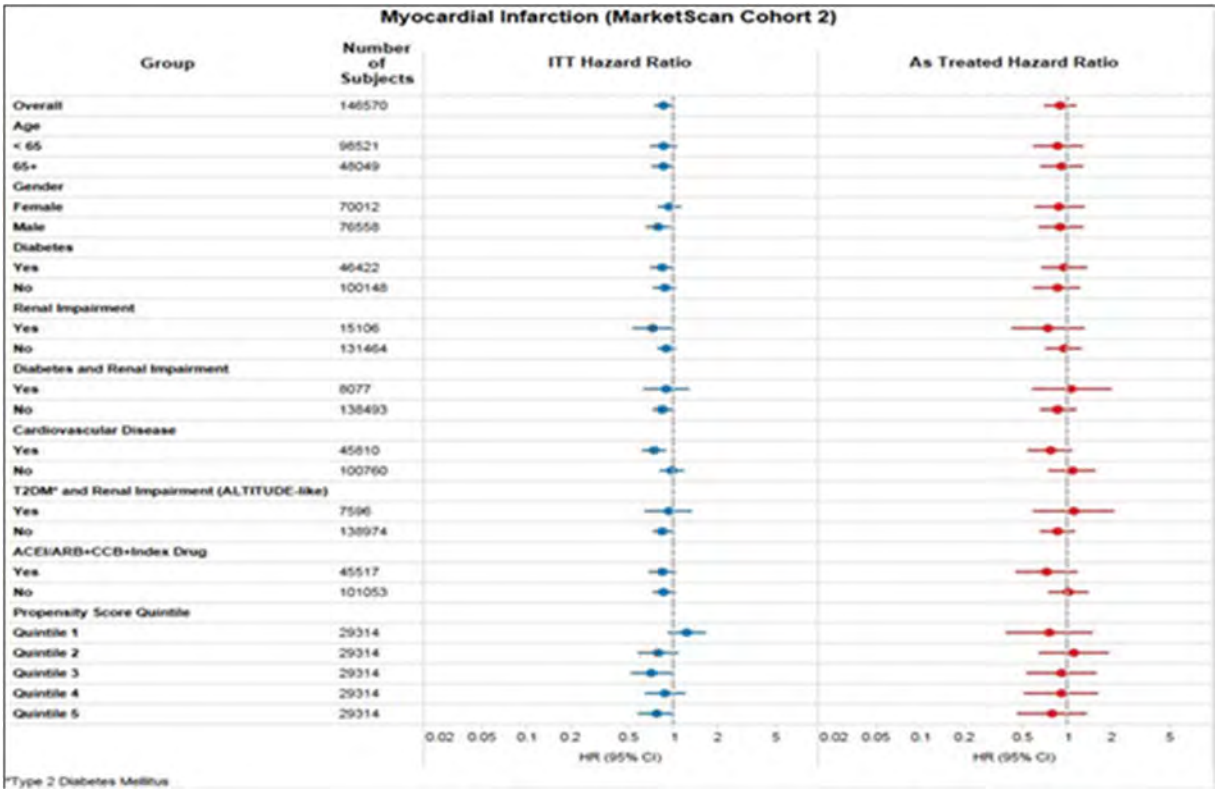
Annex 2-Figure 2-82 Forest plot for transient ischemic attack in Cohort 2 – MarketScan



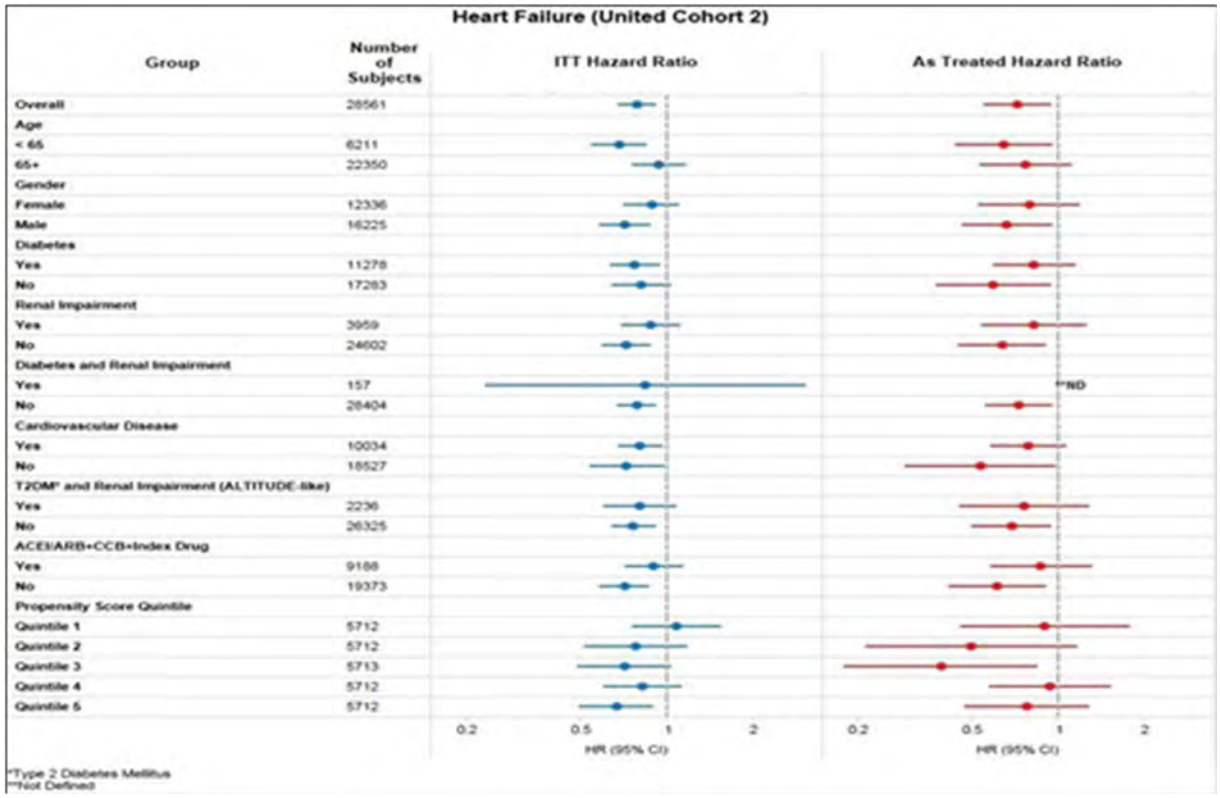
Annex 2-Figure 2-83 Forest plot for myocardial infarction in Cohort 2 – United



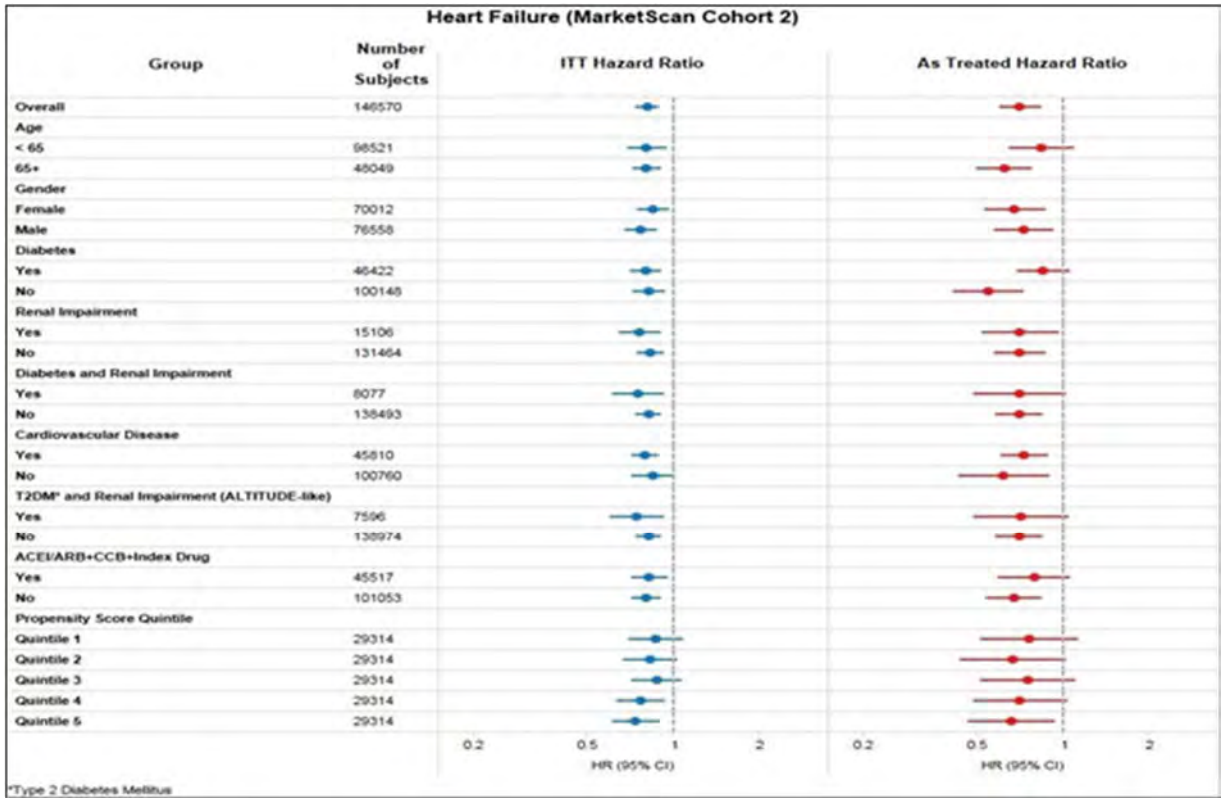
Annex 2-Figure 2-84 Forest plot for myocardial infarction in Cohort 2 – MarketScan



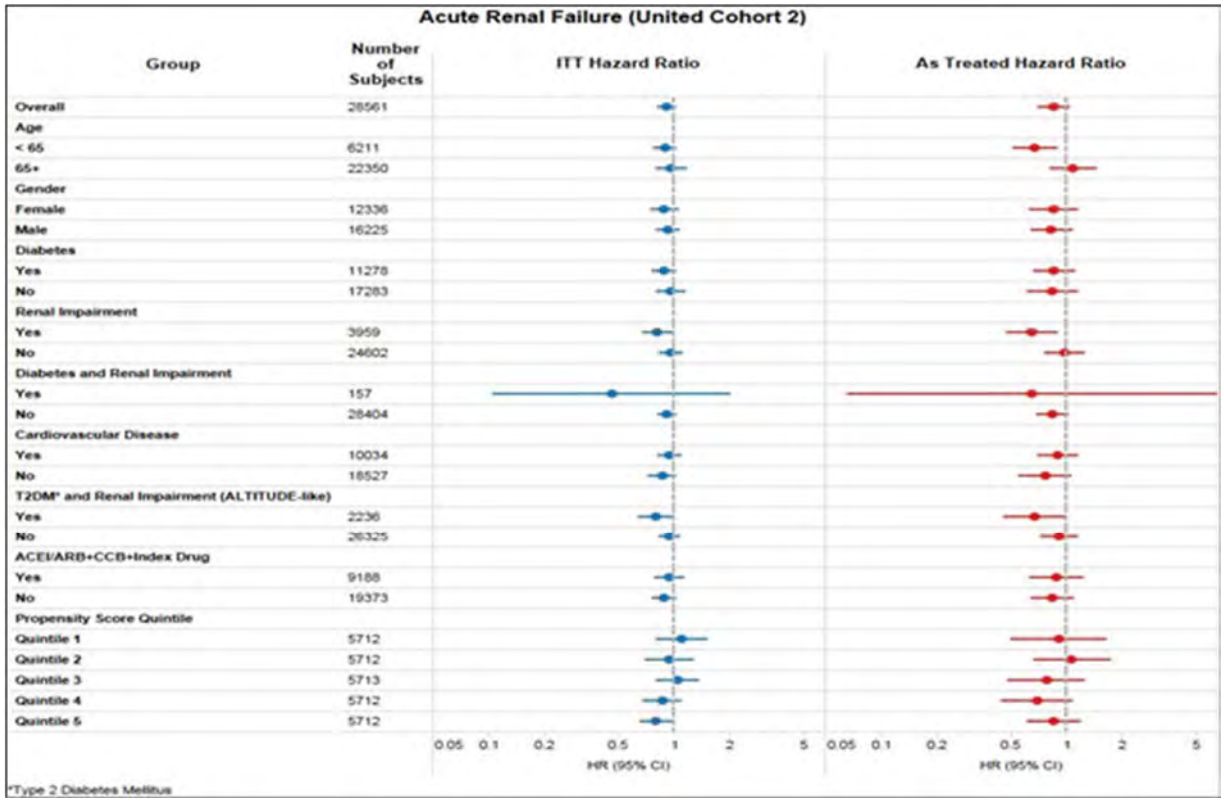
Annex 2-Figure 2-85 Forest plot for heart failure in Cohort 2 – United



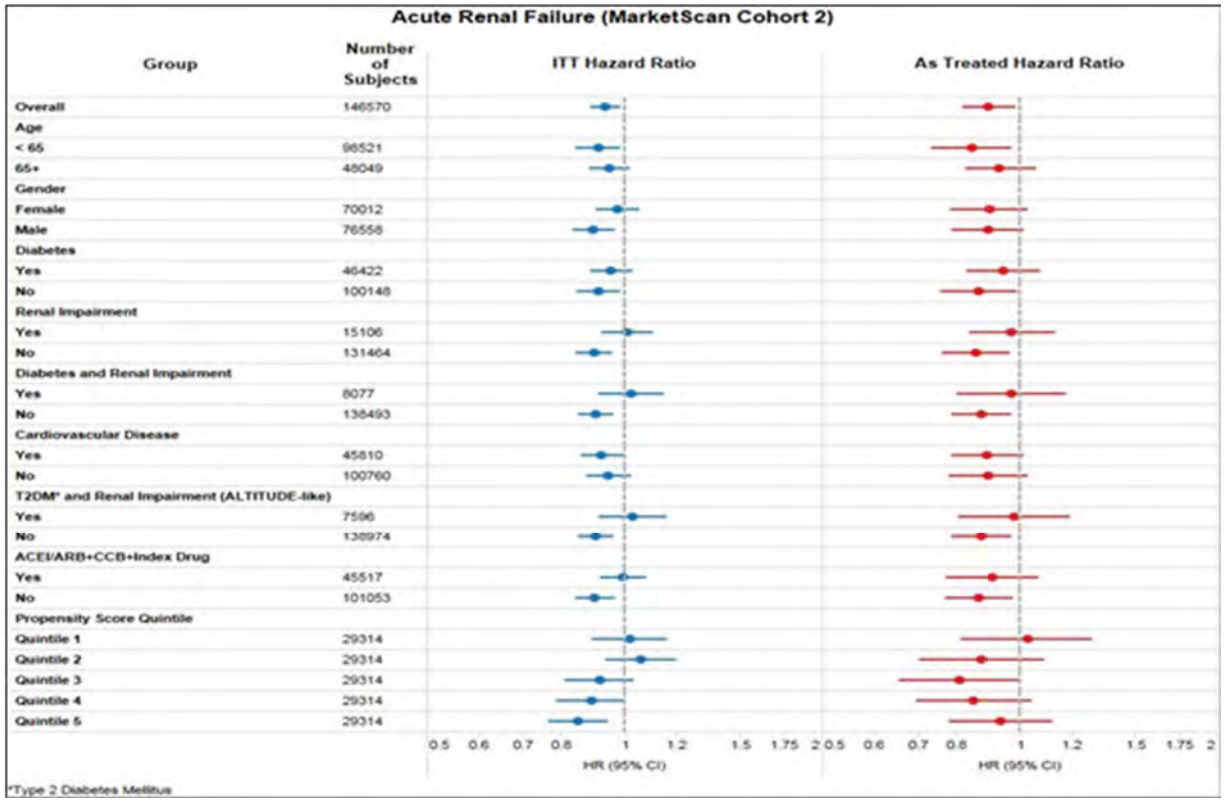
Annex 2-Figure 2-86 Forest plot for heart failure in Cohort 2 – MarketScan



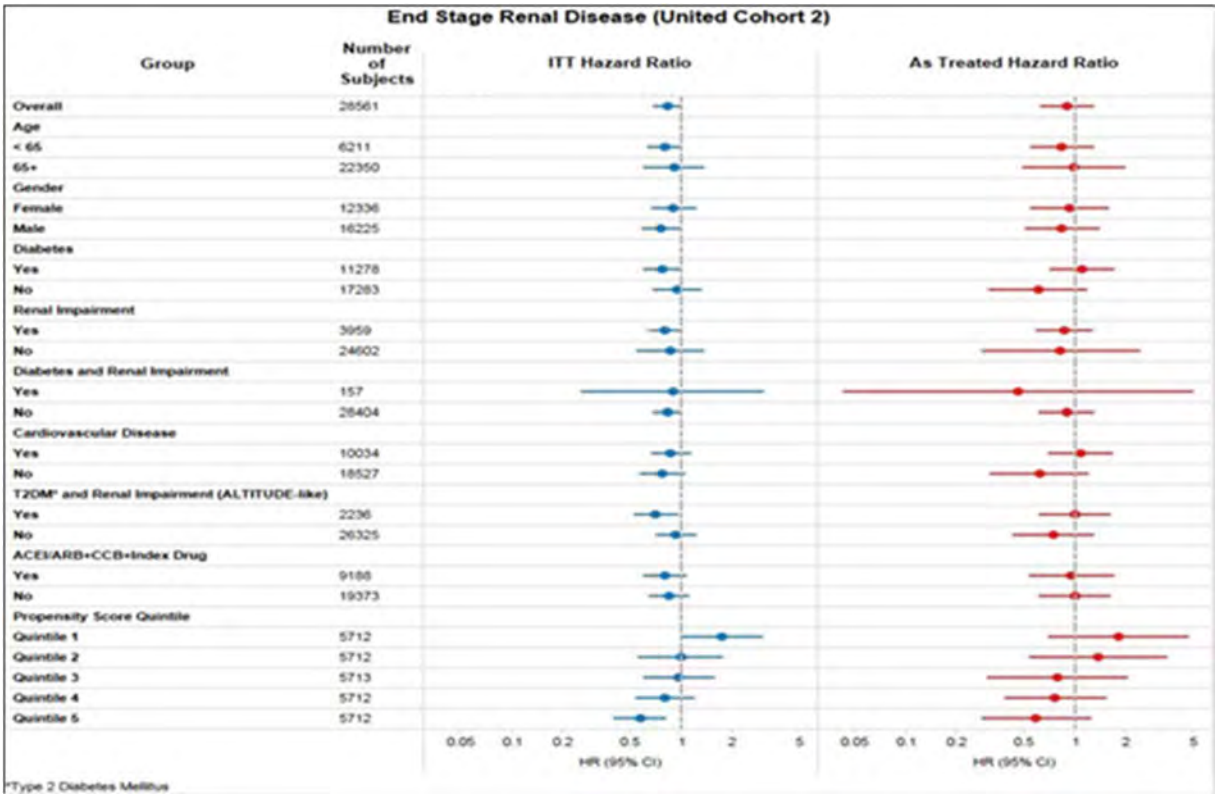
Annex 2-Figure 2-87 Forest plot for acute renal failure in Cohort 2 – United



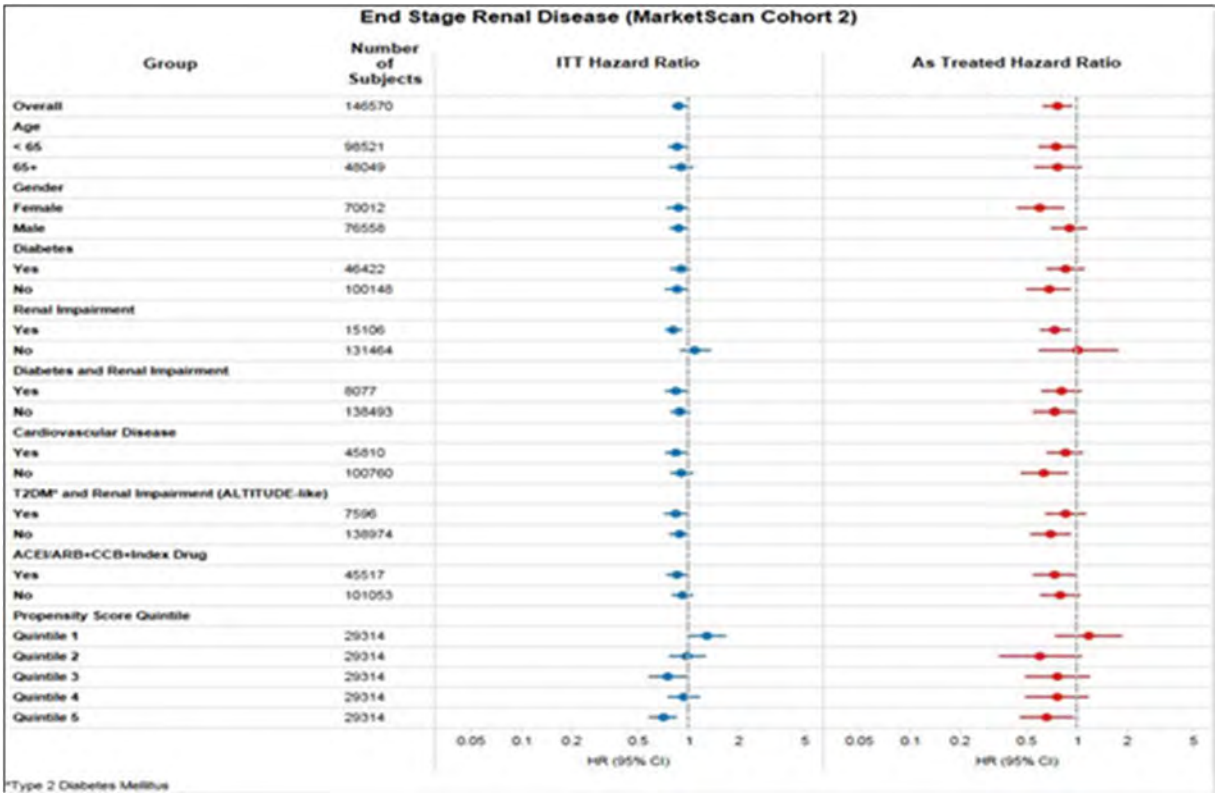
Annex 2-Figure 2-88 Forest plot for acute renal failure in Cohort 2 – MarketScan



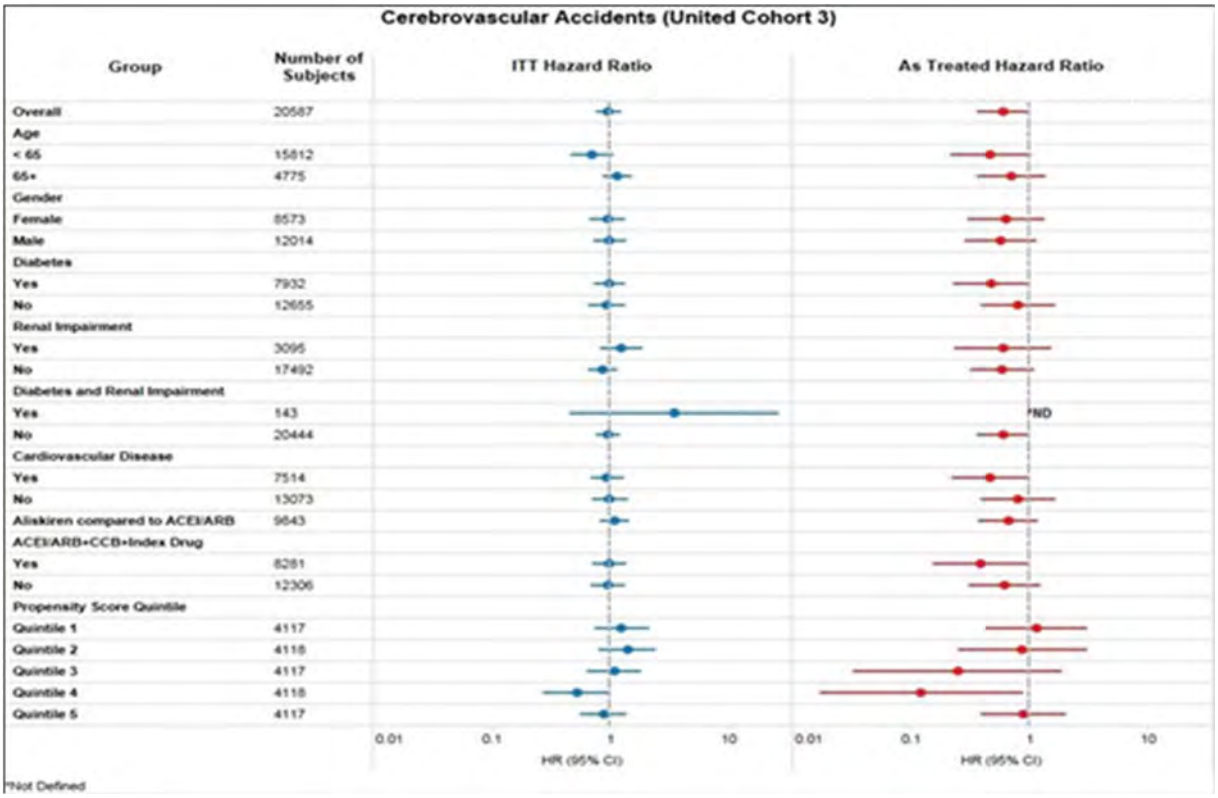
Annex 2-Figure 2-89 Forest plot for end-stage renal disease in Cohort 2 – United



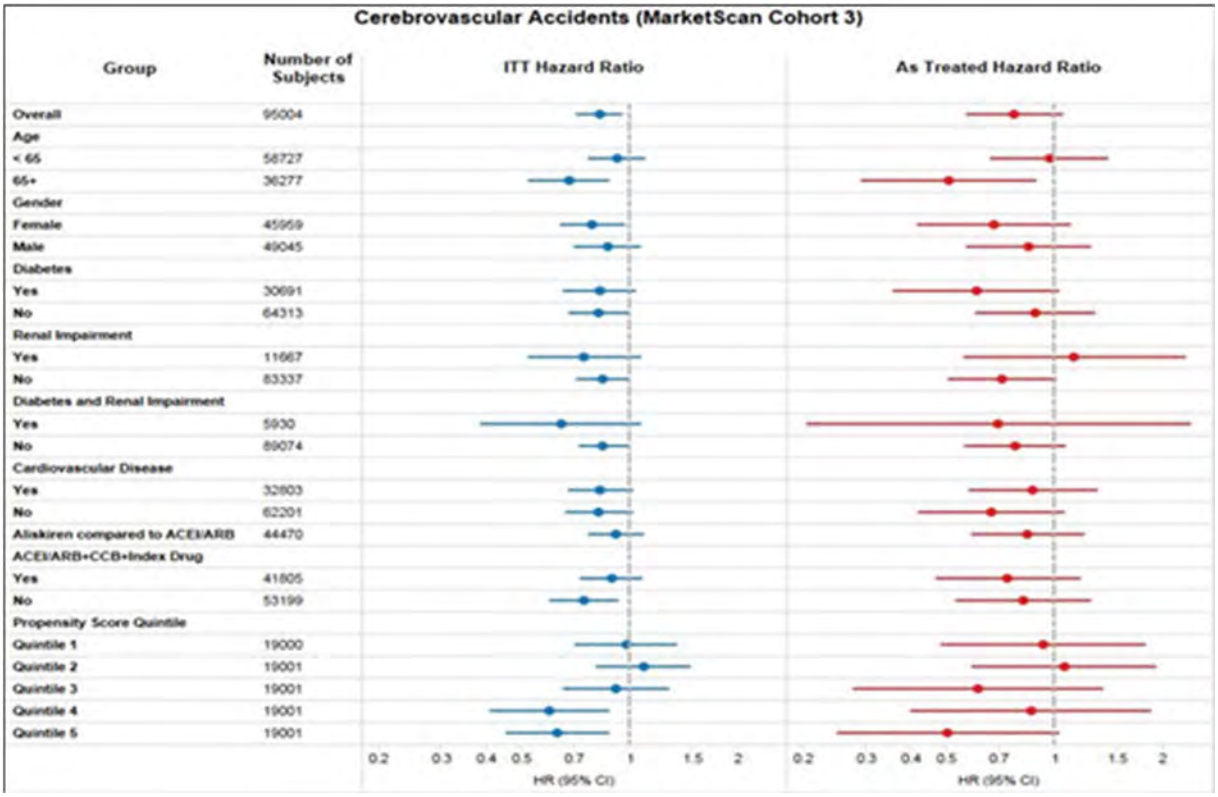
Annex 2-Figure 2-90 Forest plot for end-stage renal disease in Cohort 2 – MarketScan



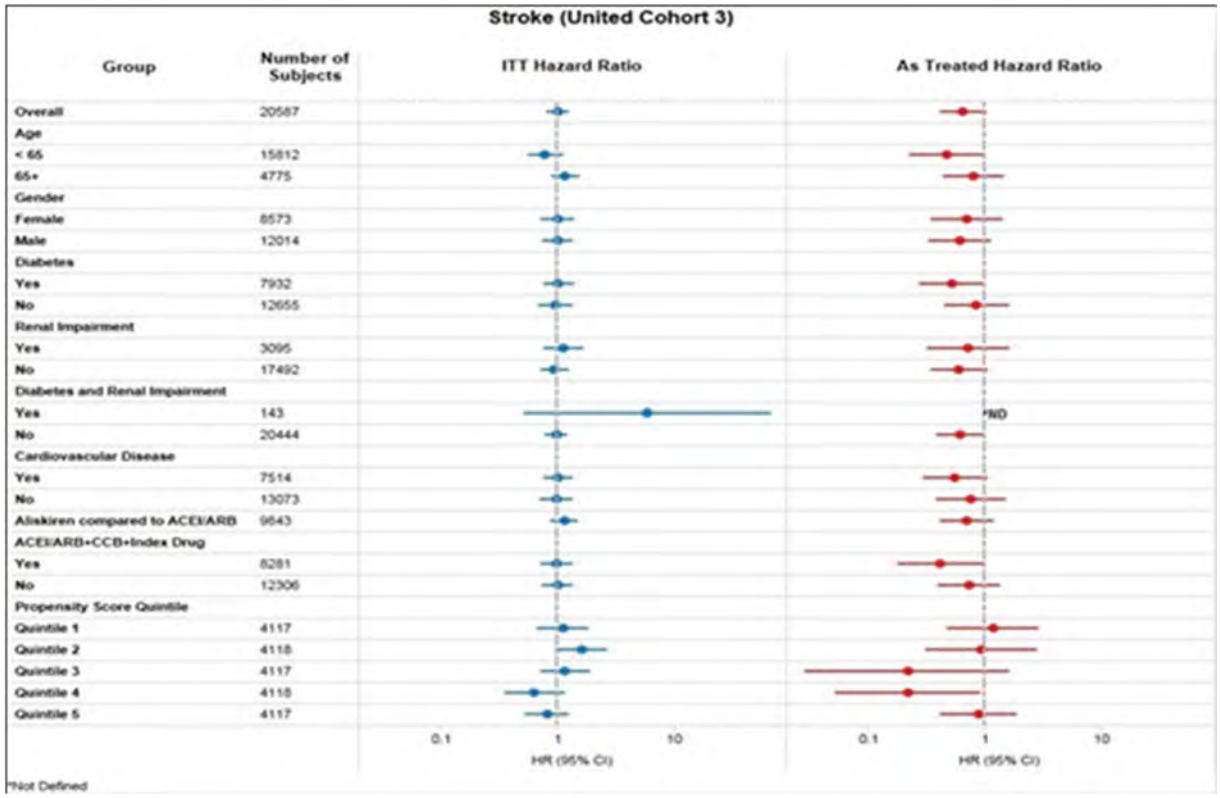
Annex 2-Figure 2-91 Forest plot for cerebrovascular accidents in Cohort 3 – United



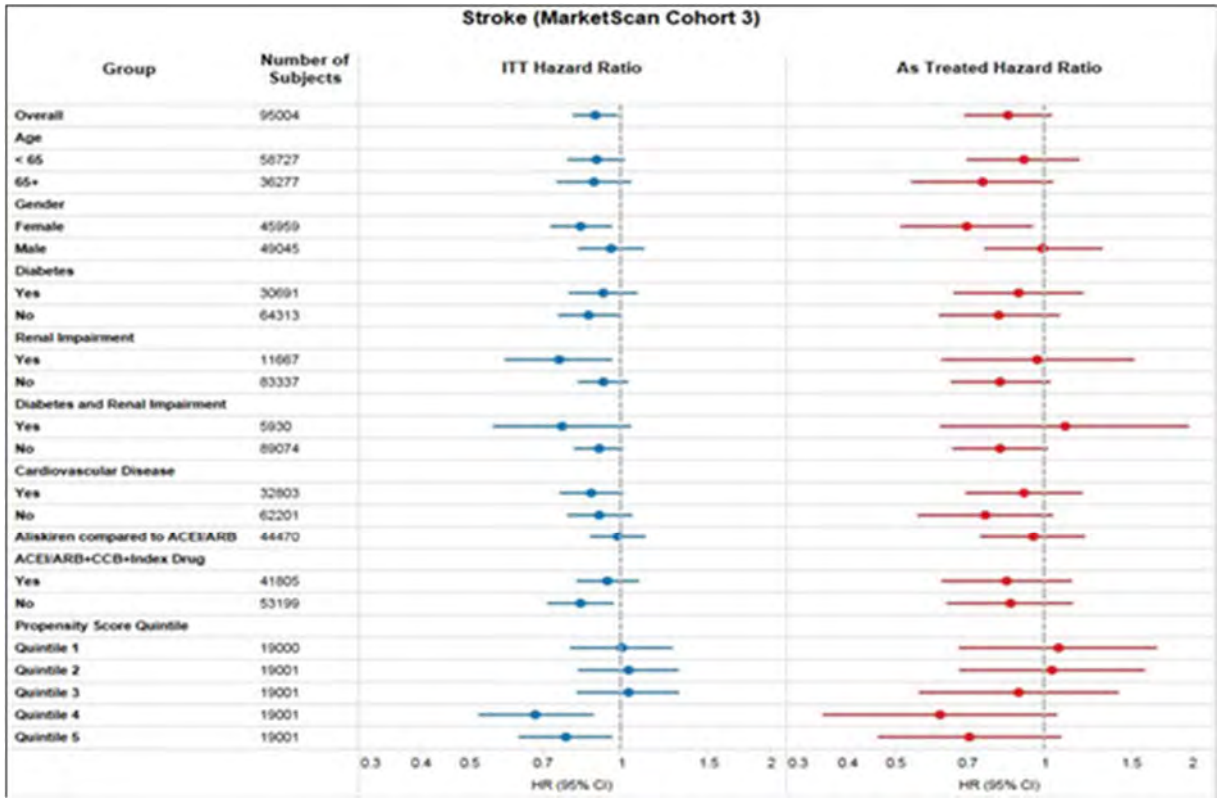
Annex 2-Figure 2-92 Forest plot for cerebrovascular accidents in Cohort 3 – MarketScan



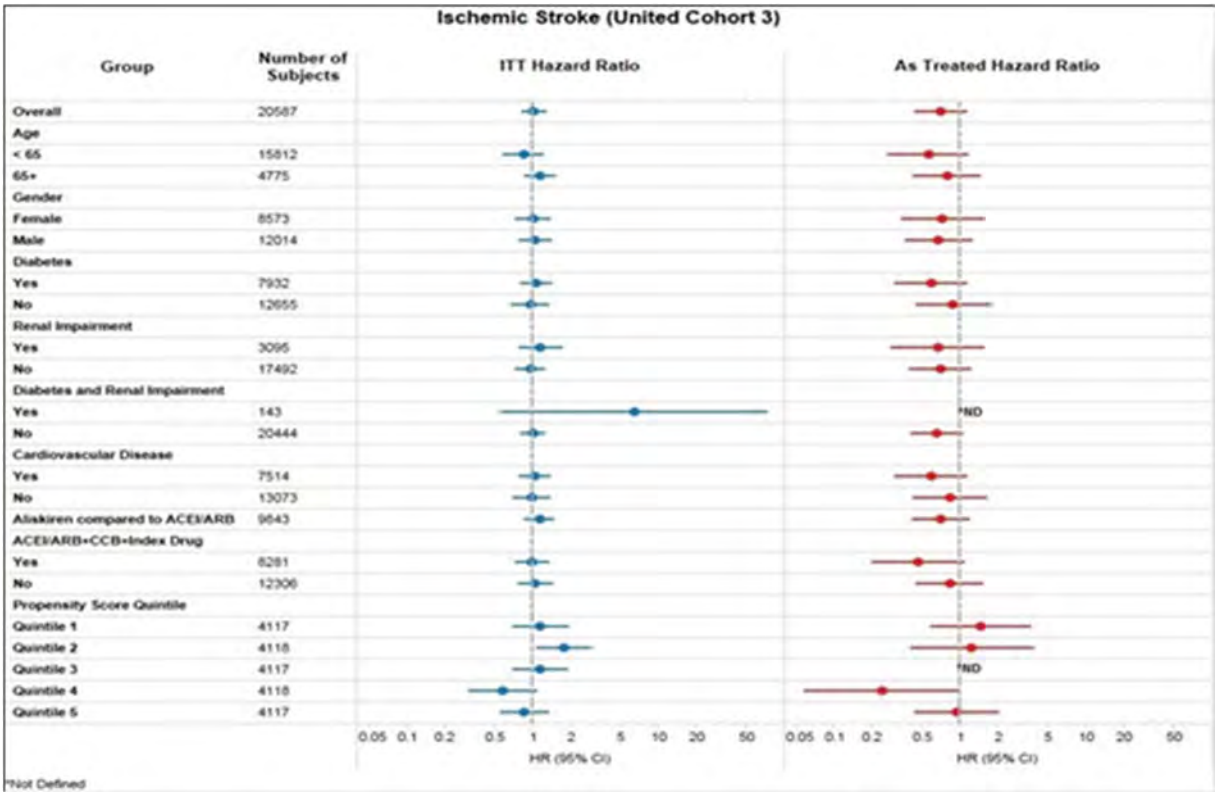
Annex 2-Figure 2-93 Forest plot for stroke in Cohort 3 – United



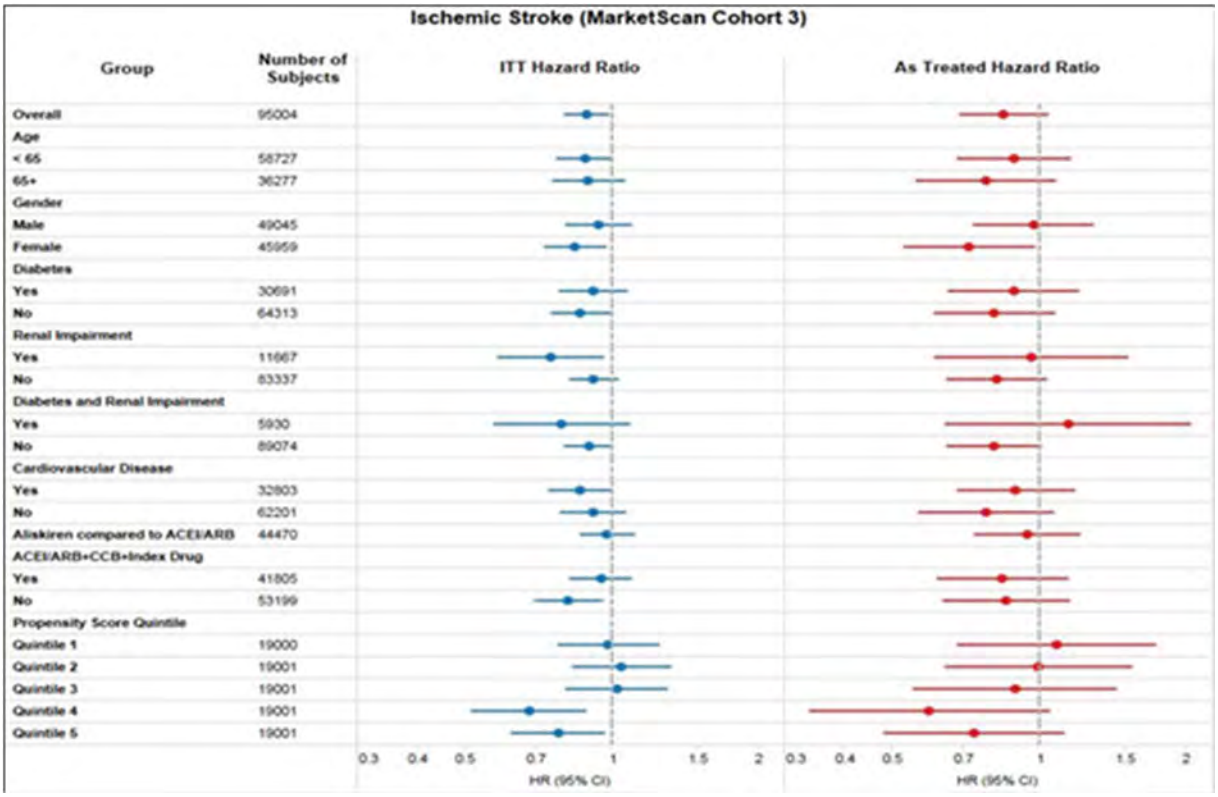
Annex 2-Figure 2-94 Forest plot for stroke in Cohort 3 – MarketScan



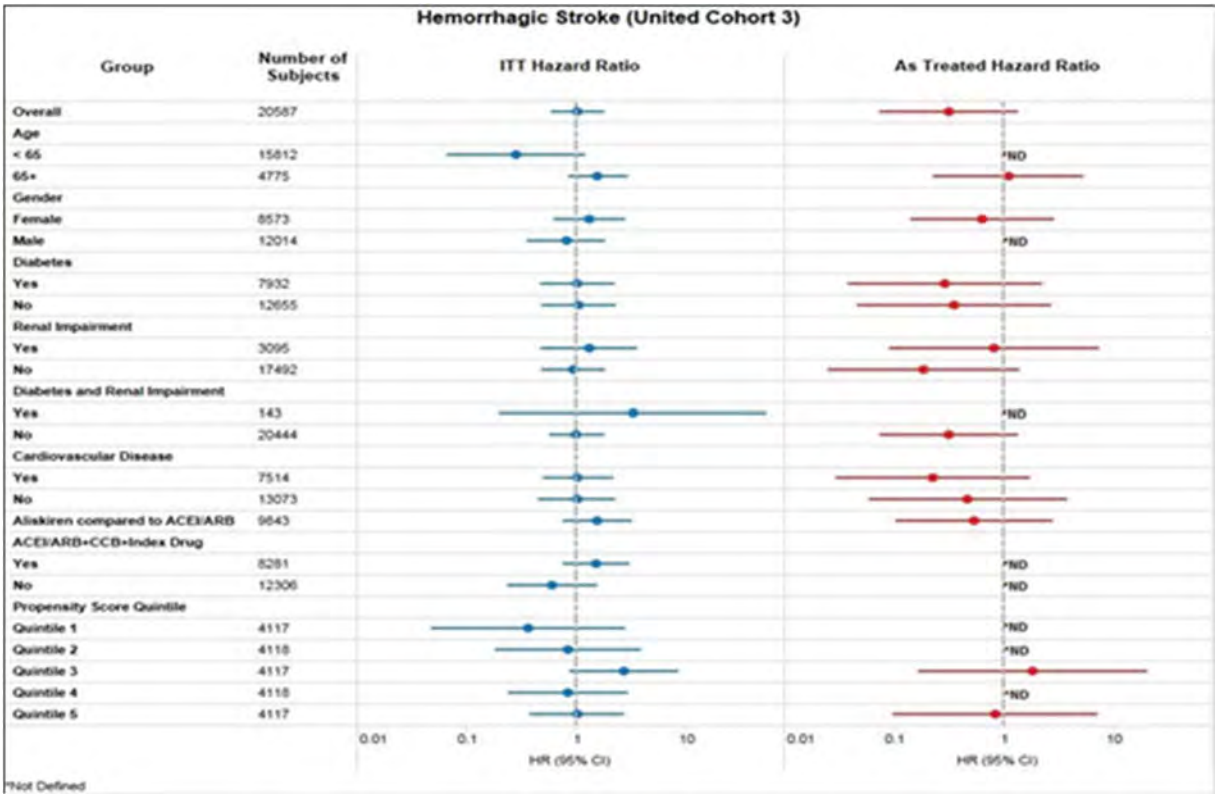
Annex 2-Figure 2-95 Forest plot for ischemic stroke in Cohort 3 – United



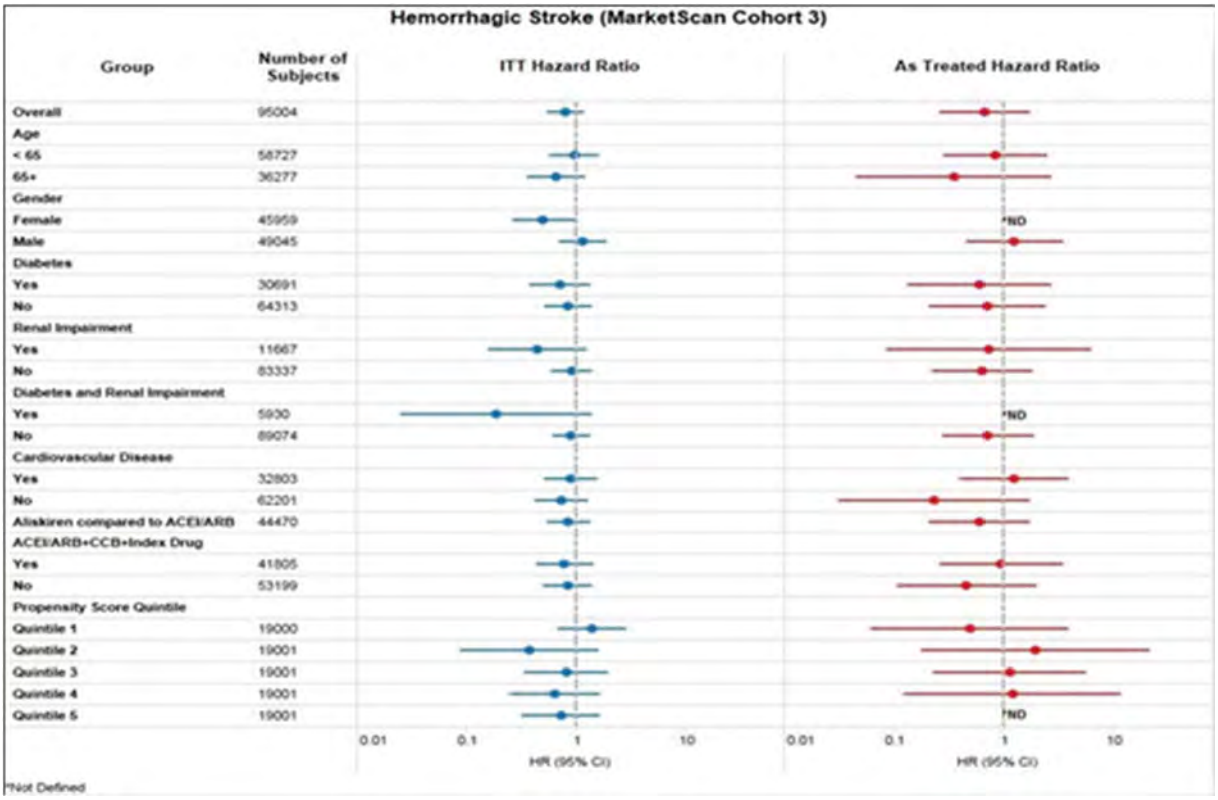
Annex 2-Figure 2-96 Forest plot for ischemic stroke in Cohort 3 – MarketScan



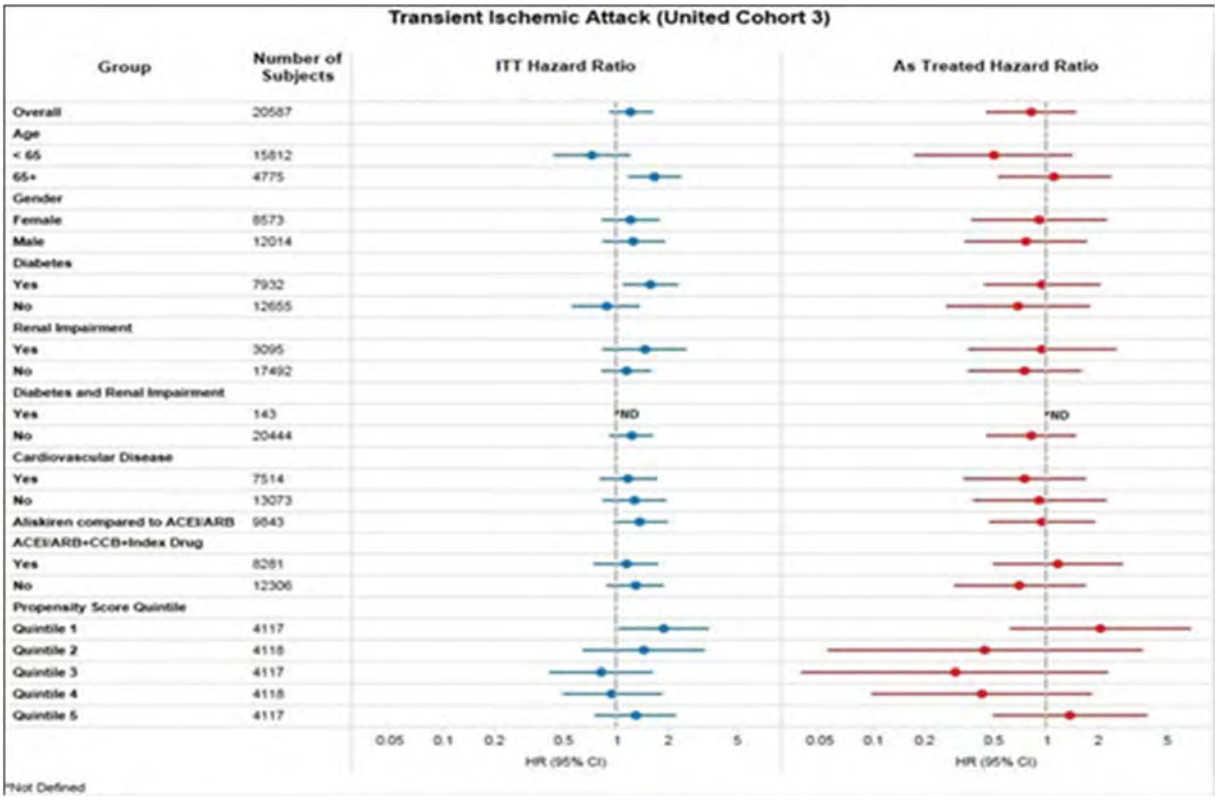
Annex 2-Figure 2-97 Forest plot for hemorrhagic stroke in Cohort 3 – United



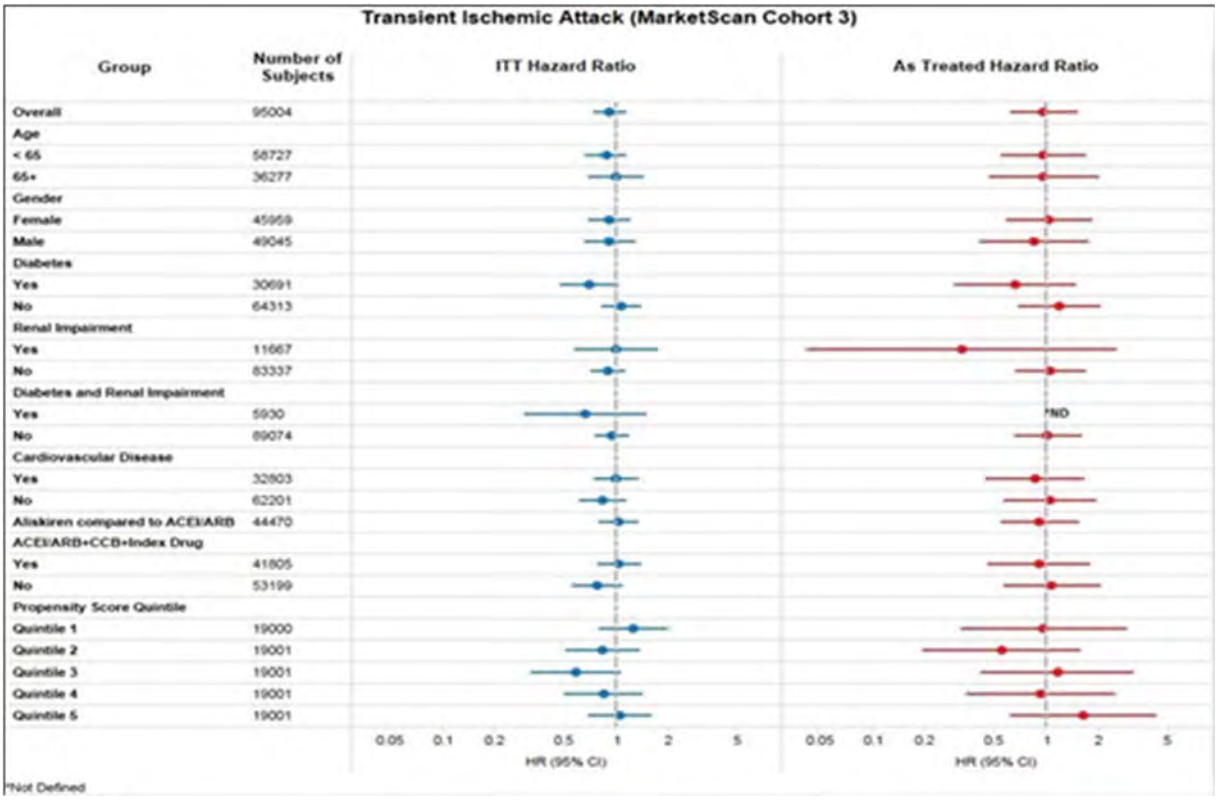
Annex 2-Figure 2-98 Forest plot for hemorrhagic stroke in Cohort 3 – MarketScan



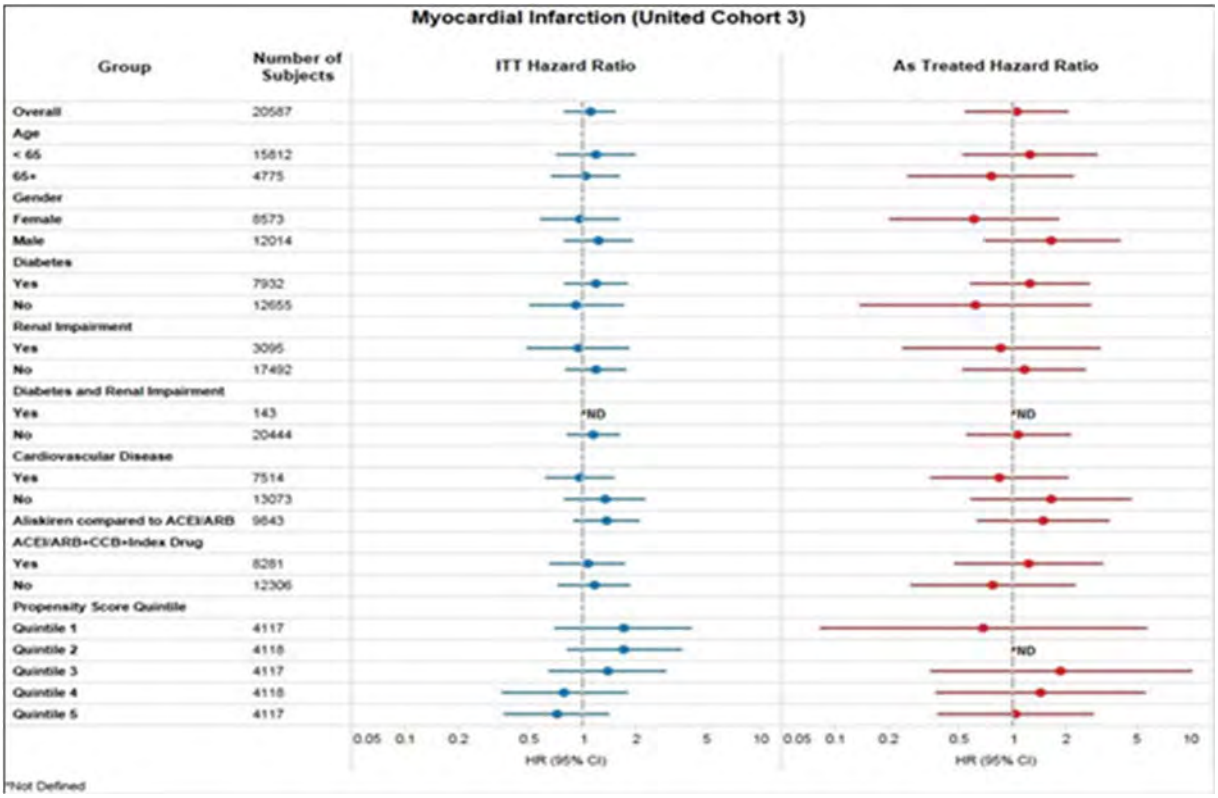
Annex 2-Figure 2-99 Forest plot for transient ischemic attack in Cohort 3 – United



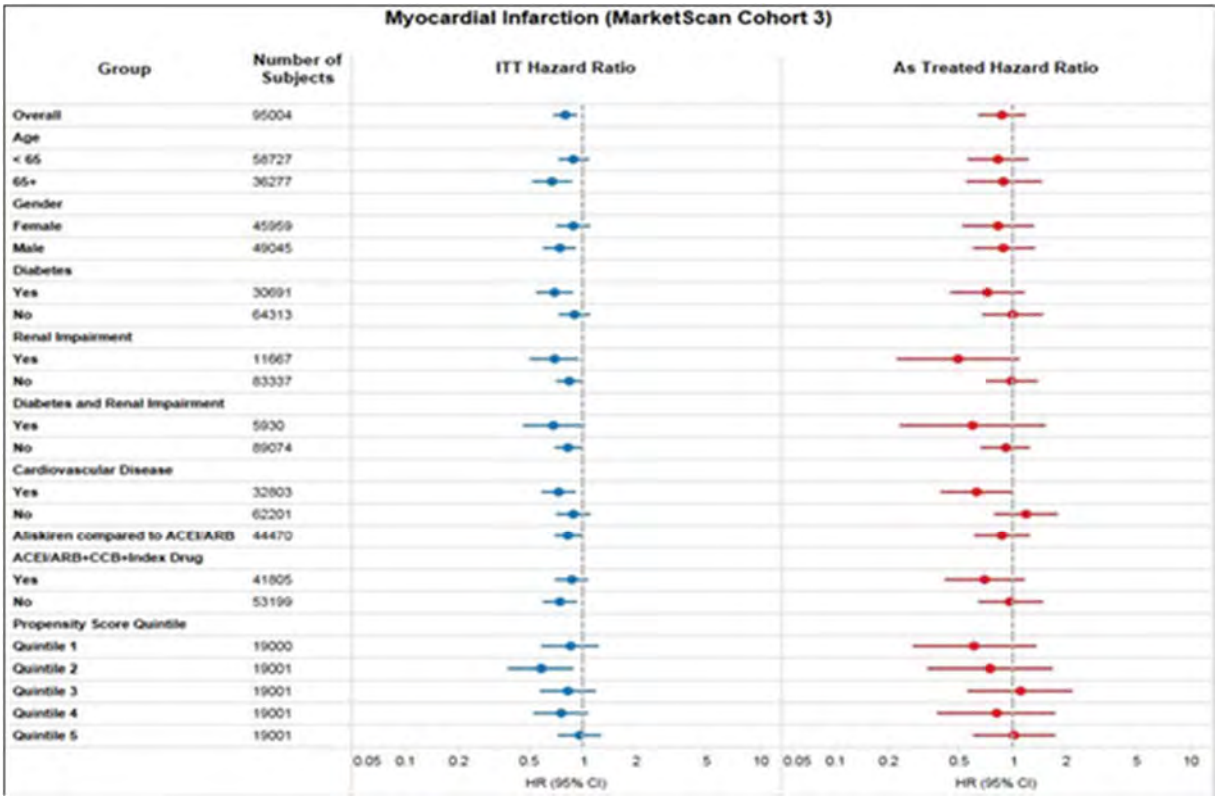
Annex 2-Fig. 2-100 Forest plot for transient ischemic attack in Cohort 3 – MarketScan



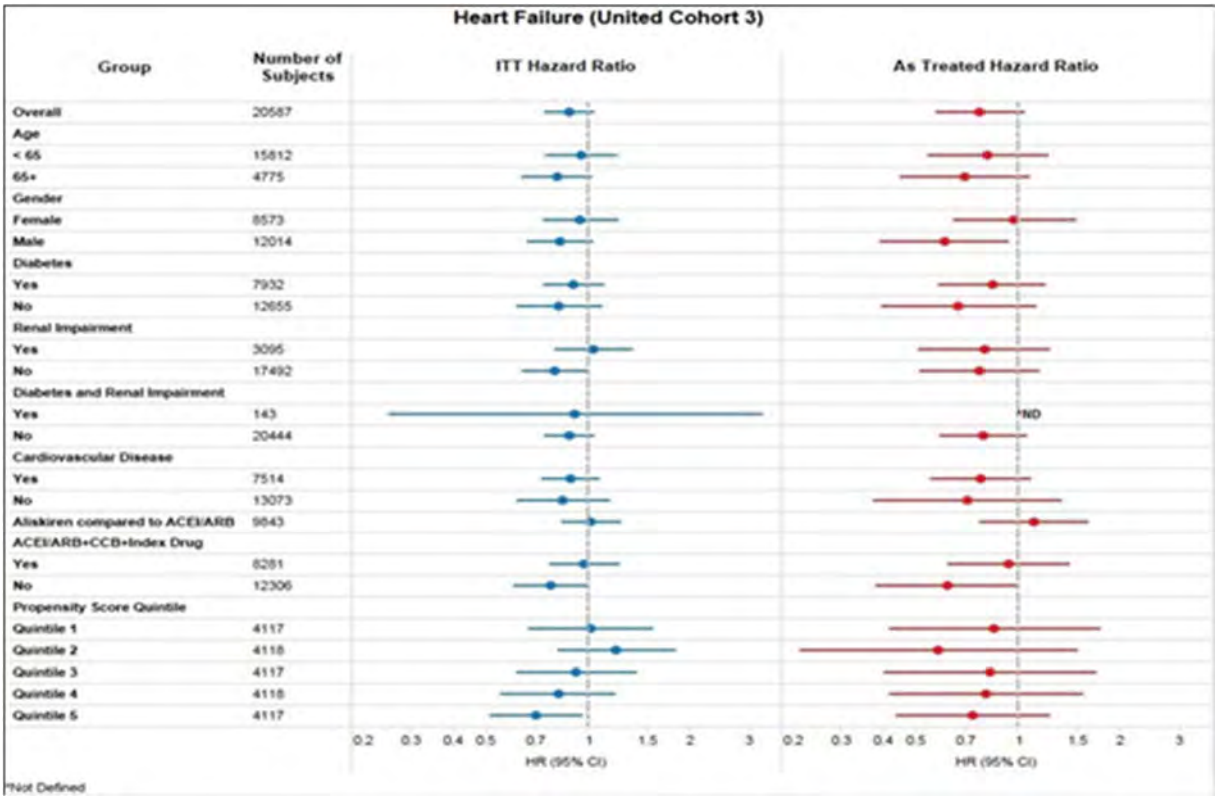
Annex 2-Fig. 2-101 Forest plot for myocardial infarction in Cohort 3 – United



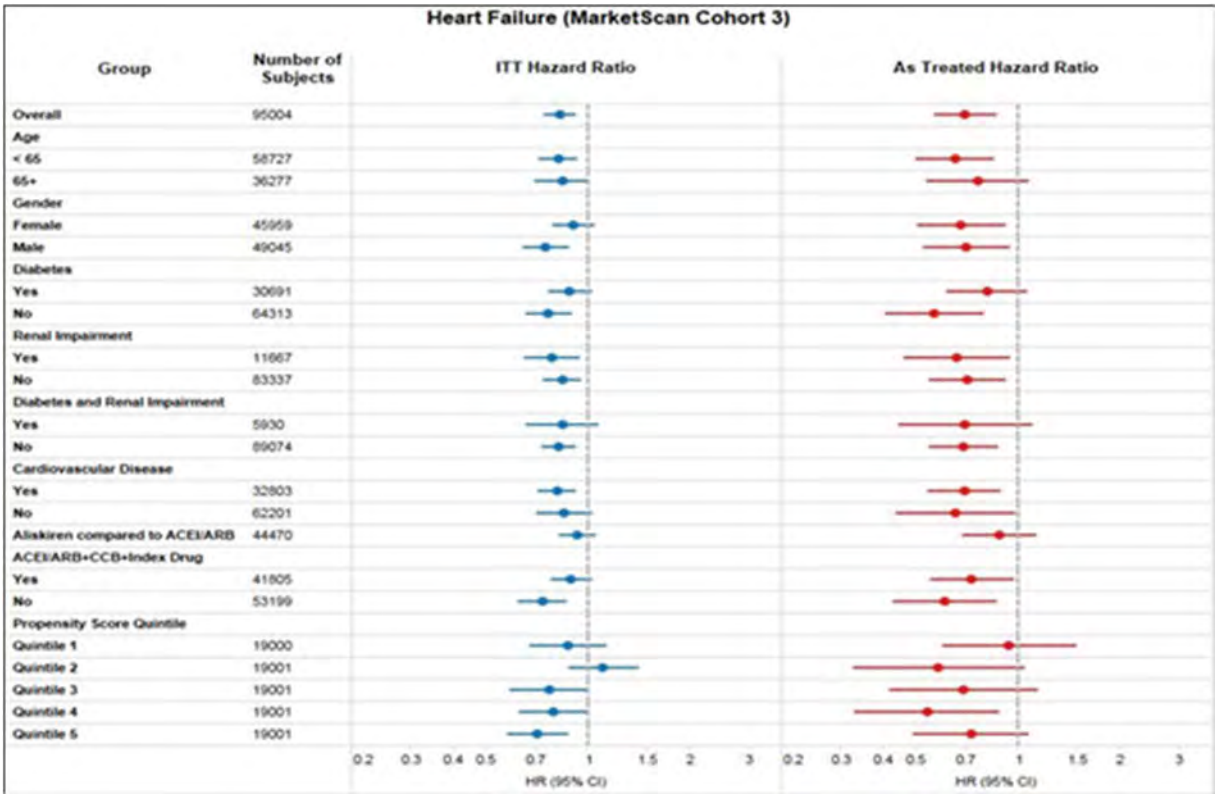
Annex 2-Fig. 2-102 Forest plot for myocardial infarction in Cohort 3 – MarketScan



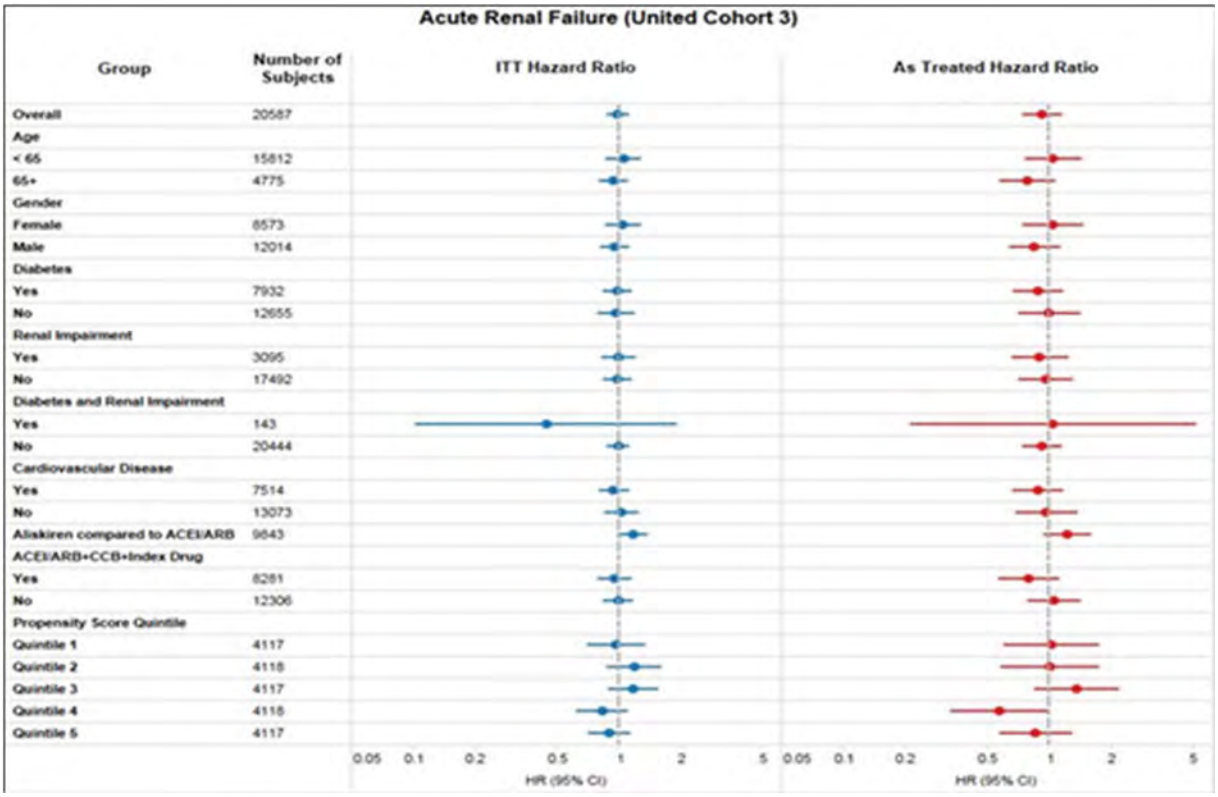
Annex 2-Fig. 2-103 Forest plot for heart failure in Cohort 3 – United



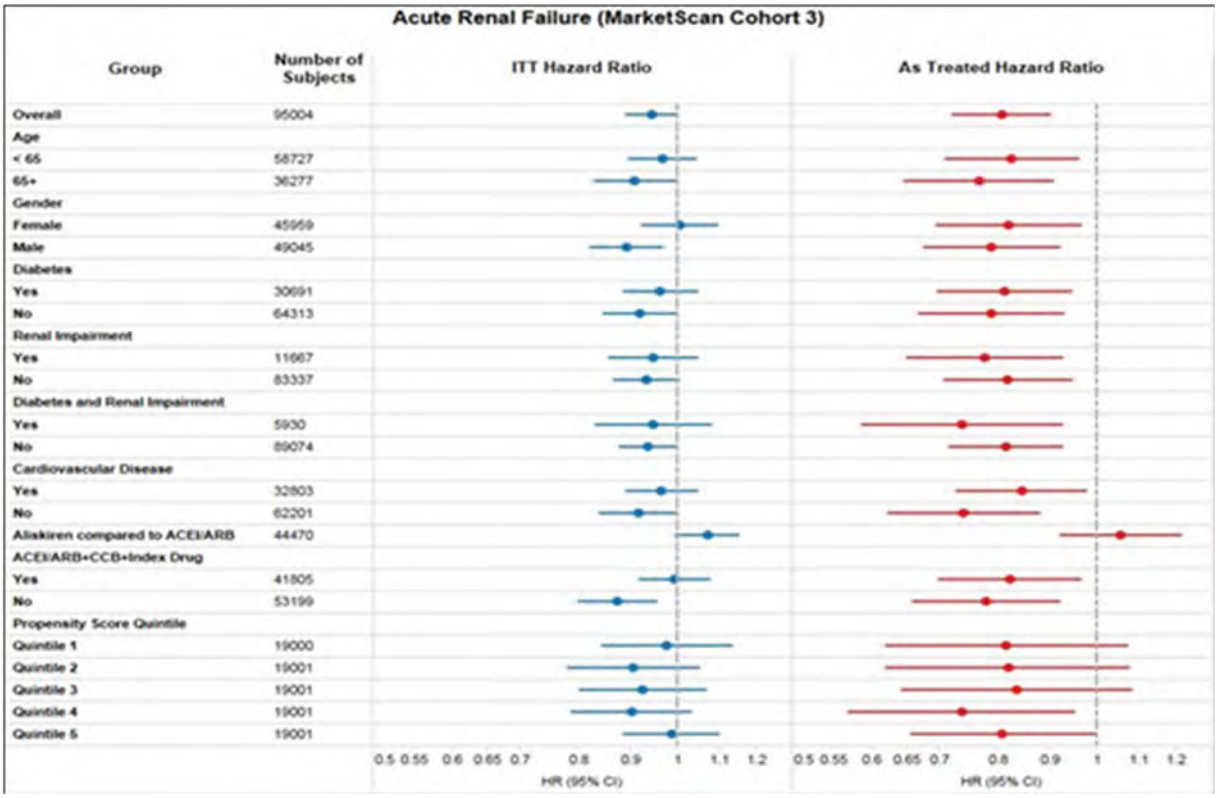
Annex 2-Fig. 2-104 Forest plot for heart failure in Cohort 3 – MarketScan



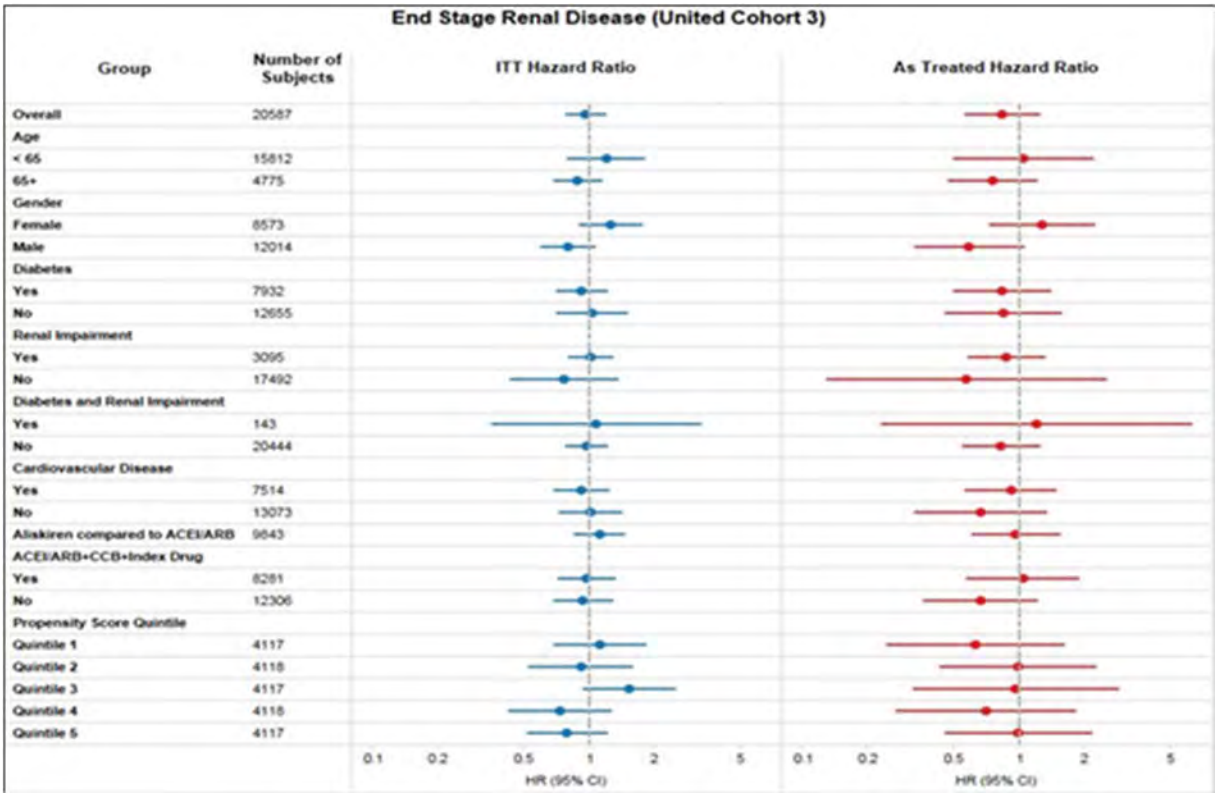
Annex 2-Fig. 2-105 Forest plot for acute renal failure in Cohort 3 – United



Annex 2-Fig. 2-106 Forest plot for acute renal failure in Cohort 3 – MarketScan



Annex 2-Fig. 2-107 Forest plot for end-stage renal disease in Cohort 3 – United



Annex 2-Fig. 2-108 Forest plot for end-stage renal disease in Cohort 3 – MarketScan