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Global Clinical Epidemiology

aliskiren

Non-interventional Study Report

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Incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data

REDACTED STUDY REPORT

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Research question and objectives	Due to the lack of real-world data on colorectal hyperplasia in association with aliskiren exposure, Novartis sought to determine the incidence of colorectal hyperplasia in hypertensive patients exposed to aliskiren. The primary objective of this study was to determine age- and sex-stratified incidence rates of colorectal hyperplasia in adult hypertensive patients exposed to aliskiren, adult hypertensive patients exposed to antihypertensive drugs other than aliskiren, and in a sample of patients without a diagnosis of hypertension and without the use of antihypertensive drugs. Additionally, age- and sex-stratified incidence rates of gastrointestinal (GI) cancer in hypertensive patients exposed to aliskiren as well as in adult hypertensive patients exposed to antihypertensive drugs other than aliskiren, and in a sample of patients without a diagnosis of hypertension and without the use of antihypertensive drugs were determined. As a secondary objective, the study assessed the relative risk of colorectal hyperplasia and of GI cancer in hypertensive patients exposed to aliskiren versus hypertensive patients exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use.
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1 Abstract

Title	Incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data 16 March 2015 [redacted]
Keywords	Hypertension, GI cancer, colorectal, aliskiren
Rationale and background	Aliskiren (Rasilez®) is the first orally active direct renin inhibitor approved for the treatment of hypertension. Aliskiren's inhibitory effect on angiotensin I generation, through renin blockade, is highly specific and long-lasting (up to 24 hours). Colorectal hyperplasia is listed as a potential risk in the aliskiren risk management plan (RMP). This is based upon findings in a rodent carcinogenicity study; however, these findings have not been confirmed in a 2-year marmoset study or in targeted clinical studies including a colonoscopy study. Information in the literature on the incidence rate of colorectal cancer or more generally colorectal hyperplasia in hypertensive patients is very limited. [redacted] the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to perform a non-interventional study to determine the incidence of colorectal hyperplasia in aliskiren-treated patients, in hypertensive patients not exposed to aliskiren but treated with other antihypertensive drugs, as well as in a non-hypertensive population (without antihypertensive treatment).
Research question and objectives	Due to the lack of published real-world data on colorectal hyperplasia in association with aliskiren exposure, Novartis sought to determine the incidence of colorectal hyperplasia in hypertensive patients exposed to aliskiren. The primary objective of this study was to determine age- and sex-stratified incidence rates of colorectal hyperplasia in adult hypertensive patients exposed to aliskiren, adult hypertensive patients exposed to antihypertensive drugs other than aliskiren, and in a sample of patients without a diagnosis of hypertension and without the use of antihypertensive drugs. Additionally, age- and sex-stratified incidence rates of gastrointestinal (GI) cancer in hypertensive patients exposed to aliskiren as well as in adult hypertensive patients exposed to antihypertensive drugs other than aliskiren, and in a sample of patients without a diagnosis of hypertension and without the use of antihypertensive drugs were determined. As a secondary objective, the study assessed the relative risk of colorectal hyperplasia and of GI cancer in hypertensive patients exposed to aliskiren versus hypertensive patients exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use.
Study design	Retrospective cohort study with secondary use of data derived from a large United States (US) health claims database (IMS PharMetrics Plus) including a large aliskiren-exposed population. The use of a US data source for this

	study was agreed with the CHMP in March 2013.
Setting	This was a retrospective cohort study with use of secondary data derived from the PharMetrics Plus database with a study period from 1 July 2006 through 30 June 2014. Using the index window from 1 July 2007 through 30 June 2013, patients (for the treatment groups) were selected into the study if they satisfied all of the four following criteria:(1) had at least 1 prescription for an antihypertensive medication (the first such prescription was defined as a patient's index date), (2) evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) in 365-day pre-index, (3) were 18+ years of age at the time of the index date, and (4) had continuous health plan enrollment for a minimum of 365 days prior to and following the index date. Individuals for the non-hypertensive population were selected into the study cohort if they satisfied all of the four following criteria : (1) no prescriptions for an antihypertensive medication between 1 July 2006 and 30 June 2014 (2) no evidence of a hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) any time between 1 July 2006 and 30 June 2014), (3) were 18+ years of age at the time of the index date (a randomly assigned date during the index window), and (4) had continuous health plan enrollment for a minimum of 365 days prior to and following the index date. Patients were excluded if they had a gap in enrollment ≥ 30 days at any time during the post-index period, no recorded gender or age, or other incomplete data in the database. In addition, for the assessment of incident colorectal hyperplasia, patients with a prior history of colorectal hyperplasia (defined as one or more diagnosis code for colorectal hyperplasia during the 365 day pre-index period or within the first 30 days following the index date) were excluded. For the assessment of incident GI cancer, those with prior history of GI cancer (defined as one or more diagnosis code for GI cancer during the 365 day pre-index period or within the first 30 days following the index date) were excluded. The follow-up period for a patient began on the index date and ended on the earliest of one of the following: (1) recorded diagnosis of colorectal hyperplasia (when investigating colorectal hyperplasia) or recorded diagnosis of GI cancer (when investigating GI cancer); (2) end of enrollment in the database; (3) end of the study period (30 June 2014) Patients were stratified into one of two mutually exclusive groups, incident and prevalent antihypertensive users, based on their experience with antihypertensive therapy. Patients with no evidence of antihypertensive prescription(s) in the 365 days prior to the index date were stratified into the incident antihypertensive treatment user group, while patients with evidence of at least 1 antihypertensive prescription in the 365 days prior to the index date was stratified into the prevalent antihypertensive user group.
Subjects and study size, including dropouts	A total of 8,109,320 patients (23,768 aliskiren users, 2,278,653 other antihypertensive users, and 5,806,899 non-hypertensive patients) were included in the colorectal hyperplasia assessment cohort. The GI cancer assessment cohort was comprised of 8,369,545 total patients (25,740 aliskiren users, 2,434,387 other antihypertensive users, and 5,909,418 non-hypertensive patients). As explained above, these cohorts only differ in that they exclude patients with history of the corresponding event during the pre-index period or within 30 days of initiating therapy (colorectal and GI cancer, respectively).
Variables and data sources	Endpoints of interest: colorectal hyperplasia and GI cancer was identified using corresponding ICD-9-CM codes from both inpatient and outpatient claims.

	Evidence of antihypertensive drug use, the primary exposure of interest, was defined as a prescription for an antihypertensive medication between 1 July 2007 and 30 June 2013. Antihypertensive therapy exposure was further categorized into monotherapy, dual combination, or triple-plus combination based on index antihypertensive drug regimen. Additional variables of interest included age, gender, geographic region, health plan type, payer type, available days of follow-up, Charlson comorbidity index score, screening procedures for colorectal cancer or GI cancer, and various comorbid conditions and drug therapies. Incidence rates (IRs) with 95% confidence intervals (CIs) were calculated per 10,000 person-years (PYs) for colorectal hyperplasia and GI cancer using three methodologies: 1) IR calculations were estimated for each of the cohorts (i.e., aliskiren users, other antihypertensive therapy users, and non-hypertensive patients) by demographic, clinical, and lifestyle factors, 2) an intention-to-treat approach was also applied such that IR calculations were based on the antihypertensive drug used within 30 days after the index date (i.e., index therapy), and 3) IRs were lastly calculated based on the regimen with the longest exposure time. The IMS PharMetrics Plus Health Plan Claims Database was used for this retrospective database analysis.
Results	Disposition: There were 2,065 incident users of aliskiren and 917,564 incident users of other antihypertensive therapies, and 21,703 prevalent aliskiren users and 1,361,089 prevalent users of other antihypertensive therapies within the colorectal hyperplasia assessment cohort. Demographics and subjects characteristics: Within the overall colorectal hyperplasia assessment cohort, aliskiren patients were approximately 3 years older on average compared to all other antihypertensive therapy patients [mean age 57.7 years (SD ±11.2) vs. 54.8 years (SD ±11.2), respectively]. The non-hypertensive patients were on average much younger, with a mean age of 39.4 years (SD ±13.4). The majority of aliskiren and other antihypertensive therapy users were between the ages of 45-64 years; whereas the majority of non-hypertensive patients were between the ages of 18-44 years. Patients age ≥65 years made up 23.6%, 16.2%, and 2.0% of the aliskiren, other antihypertensive therapy, and non-hypertensive patients; respectively. The aliskiren sample was composed of slightly more males compared to users of other antihypertensive therapies (% male: 54.5 vs. 50.7). Comorbid conditions were generally higher among aliskiren users compared to users of other antihypertensive therapies and non-hypertensive patients for the total and prevalent treatment populations, with the most prevalent conditions being diabetes mellitus and coronary heart disease or angina. Incident aliskiren and other antihypertensive therapy users were more similar with regards to demographic and clinical characteristics. Follow-up: All patients (aliskiren users, other antihypertensive therapy users, and non-hypertensive patients) were followed (post-index) for an average of 3 years. Colorectal hyperplasia incidence rates: The overall IR per 10,000 person-years (PYs) of colorectal hyperplasia by demographic, clinical, and lifestyle factors in all aliskiren users was 621.7 (95% CI: 603.8, 640.1). In general, IRs of colorectal hyperplasia were highest among males and increased with increasing age. The IR of colorectal hyperplasia for males age ≥65 years was higher than the overall IR: 909.3, 95% CI: [838.1, 986.5]). Patients with diabetes and concomitant use of statins also had a higher incidence of

	colorectal hyperplasia when compared to the overall IR for all aliskiren users (IR = 717.9, 95% CI: [685.9, 751.3] and 719.1, 95% CI: [678.9, 761.7], respectively). The overall IR of colorectal hyperplasia for incident aliskiren users was 473.9 (95% CI: [424.2, 529.4]); for prevalent aliskiren users, IR of colorectal hyperplasia was 636.5 (95% CI: [617.5, 656.0]). For all patients using antihypertensive therapy other than aliskiren, the overall IR per 10,000 PYs of colorectal hyperplasia by demographic, clinical, and lifestyle factors was 516.4 (95% CI: [514.8, 518.0]). The IRs of colorectal hyperplasia for other antihypertensive therapy users were higher in males than females and increased with increasing age. Compared to the overall IR, the incidence of colorectal hyperplasia among other antihypertensive therapy users was higher in patients with familial adenomatous polyps/hereditary nonpolyposis (IR = 1,317.6; 95% CI: [1,147.5, 1,513.0]) and concomitant statin use (IR = 616.0, 95% CI: [612.4, 619.7]); but lower in patients with obesity (IR= 493.5, 95% CI: [440.7, 454.4]). The overall IR per 10,000 PYs of colorectal hyperplasia for incident users of other antihypertensive therapy was 470.5 95% CI: [467.9, 473.1]); for prevalent users of other antihypertensive therapy the overall IR of colorectal hyperplasia was 539.7 (95% CI: [537.7, 541.7]). Among non-hypertensive patients, the overall IR per 10,000 PYs of colorectal hyperplasia by demographic, clinical, and lifestyle factors was 168.3 (95% CI: [167.7, 169.0]. The IRs of colorectal hyperplasia among non-hypertensive patients tended to increase with increasing age, but were similar between males and females. The IR of colorectal hyperplasia for non-hypertensive patients aged ≥65 years was 458.2 (95% CI: [450.4, 466.2]). Compared to the overall IR of colorectal hyperplasia for non-hypertensive patients, patients with any comorbid condition, concomitant use of statins or NSAIDs, or obesity had a higher incidence of colorectal hyperplasia. The overall IR of colorectal hyperplasia in the 30 days after the index date was 517.3 (95% CI: 515.7, 518.9) for all antihypertensive therapy patients. The IR per 10,000 PYs of colorectal hyperplasia among aliskiren monotherapy users was 633.7 (95% CI: [60.26, 666.4]). The highest rate was observed in patients prescribed alpha blocker monotherapy (IR = 766.1, 95% CI [749.5, 783.1]) and the lowest in patients that were prescribed other antihypertensive monotherapies (IR = 343.3, 95% CI [325.9, 361.7]). The overall IR of colorectal hyperplasia for all incident therapy users was 470.5 (95% CI: [467.9, 473.1]). The IR per 10,000 PYs of colorectal hyperplasia for incident aliskiren monotherapy users was 464.8 (95% CI: [408.6, 528.8). Among all incident monotherapy users, the IR of colorectal hyperplasia was highest for those prescribed alpha blockers (IR = 728.8, 95% CI: [707.9, 750.3]) and lowest for those prescribed other antihypertensive therapies (IR = 312.4, 95% CI: [289.3, 337.3]). In general, IRs were higher in males compared to females and tended to increase with age. By exposure time, for monotherapy aliskiren users, IR of colorectal hyperplasia was 514.8 (95% CI: [458.5, 578.1]). The IR of colorectal hyperplasia was highest in patients prescribed alpha blockers monotherapy (IR = 732.3, 95% CI [711.9, 753.2]) and the lowest in patients that were prescribed other antihypertensive monotherapies (IR = 286.6, 95% CI [263.6, 311.5]). For incident aliskiren monotherapy users, the IR of colorectal hyperplasia based on exposure time was 501.3 (95% CI: [418.2, 600.9]). In general, IRs were higher in males compared to females and tended to increase with age. The overall adjusted relative risk (hazard ratio [HR]) for colorectal hyperplasia for all patients (i.e., incident and prevalent patients combined) exposed to aliskiren versus all patients exposed to antihypertensive drugs

	other than aliskiren was 1.08 (95% CI: 1.05, 1.11). The overall relative risk for colorectal hyperplasia for incident aliskiren users versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use was 1.31 (95% CI: 1.17, 1.46).Incident other antihypertensive therapy users also had a significantly greater risk of colorectal hyperplasia compared to non-hypertensive patients (HR: 1.38, 95% CI: [1.37, 1.40]). Across all cohorts (i.e., aliskiren treated patients, patients treated with other antihypertensive therapies and the non-hypertensive population sample), IRs of colorectal hyperplasia were higher among patients with a pre-diagnosis screening procedure and a post-index diagnosis (range across cohorts: 142.0-477.0) compared to patients with a post-index diagnosis alone (range across cohorts: 26.3-144.7). The GI cancer assessment cohort included 2,193 incident aliskiren users, 972,369 incident users of other antihypertensive therapy, and 23,547 prevalent aliskiren users, and 1,462,018 prevalent other antihypertensive users. The overall IR per 10,000 PYs of GI cancer by demographic, clinical, and lifestyle factors in all aliskiren users was 29.0 (95% CI: [25.7, 32.8]). In general, IRs of GI cancer for all aliskiren users tended to increase with increasing age and was greatest in males age ≥65 years (IR= 48.1, 95% CI: [35.4, 65.3]). The overall IRs per 10,000 PYs of GI cancer in incident and prevalent aliskiren users were 16.8 (95% CI: [9.8, 29.0]) and 30.2 (95% CI: [26.6, 34.2]), respectively. For demographic, clinical, and lifestyle subgroups, IRs of GI cancer for aliskiren users were generally based on relatively few patients/events yielding low rates with wide confidence intervals not conducive to interpretation. For all patients using antihypertensive therapy other than aliskiren, the overall IR per 10,000 PYs of GI cancer by demographic, clinical, and lifestyle factors was 23.1 (95% CI: [22.8, 23.4]). The IR of GI cancer among all other antihypertensive therapy users was higher in males than females and increased as age increased. The highest IR of GI cancer was observed in male patients aged ≥65 years (IR= 45.3, 95% CI: [43.7, 46.9]). Compared to the overall IR, the incidence of GI cancer among other antihypertensive therapy users was higher in patients with stomach polyps (IR = 53.3, 95% CI: [46.7, 60.8]), concomitant PPI and statin use (IR = 31.1, 95% CI: [30.0, 32.2]) and 24.5, 95% CI: [23.9, 25.2], respectively), and alcohol dependence syndrome (IR =31.1, 95% CI: [26.7, 36.2]). Use of hormone replacement therapy was associated with a lower incidence of GI cancer compared to the overall IR (IR = 20.4, 95% CI: [18.8, 22.1]). The overall IR per 10,000 PYs of GI cancer for incident users of other antihypertensive therapy was 21.4 (95% CI: [20.9, 21.9]); for prevalent users of other antihypertensive therapy the overall IR of GI cancer was 24.0 (95% CI: [23.6, 24.3]). Among non-hypertensive patients, the overall IR per 10,000 PYs of GI cancer by demographic, clinical, and lifestyle factors was 7.8 (95% CI: [7.7, 7.9]). The IR of GI cancer among non-hypertensive patients was higher in females (IR = 8.3, 95% CI: [8.1, 8.5]) than males (IR = 7.2, 95% CI: [7.0, 7.4]) and increased with increasing age. Patients with any comorbid condition, concomitant use of PPIs, statins, or hormone replacement therapy, or obesity had a higher incidence of GI cancer compared to all non-hypertensive patients. The overall IR of GI cancer in the 30 days after the index date was 23.2 (95% CI: [22.9, 23.5]) for all antihypertensive therapy patients. The IR per 10,000 PYs of GI cancer among aliskiren monotherapy users was 25.8 (95%

	CI: [20.6, 32.4]), and was similar to all other monotherapy regimens. The overall IR of GI cancer for incident therapy users was 21.4 (95% CI: [20.9, 21.9]). For incident aliskiren monotherapy users, the IR per 10,000 PYs of GI cancer was 10.5 (95% CI: [4.7, 23.5]), and was similar to all other monotherapy except alpha blockers, which were associated with the highest IR of GI cancer among monotherapy users (IR = 30.3, 95% CI: [26.7, 34.4]). In general, IRs were higher in males compared to females and tended to increase with age. By exposure time, the IR of GI cancer all aliskiren monotherapy users was 15.5 (95% CI: [8.3, 28.7]), and was similar to all other monotherapy regimens. The IR of GI cancer among incident aliskiren monotherapy users was 15.0 (95% CI: [5.6 - 39.8], and was similar to all other monotherapy regimens. The wide CI resulting from the observation of few patients/events should be considered when interpreting these finding. In general, IRs were higher in males compared to females and tended to increase with age. The overall adjusted relative risk (HR) for GI cancer for all hypertensive patients (i.e., incident and prevalent samples combined) exposed to aliskiren versus all hypertensive patients exposed to antihypertensive drugs other than aliskiren was 1.03 (95% CI: 0.91, 1.16). The overall relative risk for GI cancer for incident aliskiren users versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use was 1.02 (95% CI: 0.59, 1.76). Incident other antihypertensive therapy users had a significantly greater risk of GI cancer compared to non-hypertensive patients (HR: 1.51, 95% CI: [1.46, 1.56). Across all cohorts (i.e., aliskiren treated patients, patients treated with other antihypertensive therapies and the non-hypertensive population sample), IRs of GI cancer were lower among patients with a pre-diagnosis screening procedure and a post-index diagnosis (range across cohorts: 0.9-7.6) compared to patients with a post-index diagnosis alone (range across cohorts: 6.9-21.4).
Discussion	Within the colorectal hyperplasia assessment cohort antihypertensive treatment populations, overall unadjusted IRs per 10,000 PYs based on demographic, clinical, and lifestyle factors ranged from 168.3 (95% CI: [167.7, 169.0]) in the non-antihypertensive sample to 636.5 (95% CI: [617.5, 656.0]) in prevalent users of aliskiren.Overall unadjusted IRs stratified by index therapy ranged from 470.5 (95% CI: [467.9, 473.1]) among incident users of antihypertensive therapies to 540.9 (95% CI: [538.9, 542.9]) among prevalent antihypertensive therapy users.The overall unadjusted IRs stratified by antihypertensive therapy exposure time ranged from 501.3 (95% CI: [418.2, 600.9]) in the incident antihypertensive treatment cohort to 524.6 (95% CI: [451.2, 610.0]) in the prevalent antihypertensive treatment cohort. Among the antihypertensive treatment populations, IRs of colorectal hyperplasia were consistently higher in the prevalent users compared to the incident users and all users (i.e., incident and prevalent combined).Prevalent antihypertensive therapy user groups (i.e., prevalent aliskiren users and prevalent users of antihypertensive therapies other than aliskiren) were larger, older (more patients age $\geq$ 65 years), had more comorbidities and used more co-medications compared to incident antihypertensive users.IRs of colorectal hyperplasia presented by demographic, clinical, and lifestyle factors among incident aliskiren users were similar to incident users of other antihypertensive therapies, which may be a reflection of the similar demographic and clinical make-up of the two treatment populations. The lowest IRs were observed in the non-hypertensive patient population, which

	was a younger and healthier sample compared to the treated patient groups. When compared to the overall IRs for all patients, the incident antihypertensive treatment cohort and the prevalent antihypertensive treatment cohort patients who were prescribed monotherapy alpha blockers were consistently associated with higher IRs of colorectal hyperplasia whereas patients taking monotherapy beta blockers and other monotherapies (defined as vasodilators, selective aldosterone receptors, and centrally acting alpha agonists) were consistently observed as having lower IRs of colorectal hyperplasia. Among dual combination therapy users, those prescribed a regimen that included an ACEI but not aliskiren were consistently observed as having lower IRs of colorectal hyperplasia. We believe this is the first study to report IRs of colorectal hyperplasia stratified by all classes of therapy and, as such, future research is needed to substantiate the findings from the current study. Among incident therapy users, IRs of colorectal hyperplasia for aliskiren-containing regimens were generally based on few patients and events which resulted in wide confidence intervals, precluding meaningful comparisons to the other antihypertensive therapies. The results from the Cox models support the findings from the unadjusted IR estimates by showing that after controlling for demographic and clinical factors, the risk of colorectal hyperplasia was slightly higher in aliskiren users than users of other antihypertensive therapies among the total and prevalent populations; however, the risk was similar among incident therapy users. Within the GI cancer assessment cohort, overall unadjusted IRs per 10,000 PYs stratified by demographic, clinical, and lifestyle factors ranged from 7.8 (95% CI: [7.7, 7.9]) in the non-antihypertensive sample to 30.2 (95% CI: [26.6, 34.2]) in prevalent users of aliskiren. Overall unadjusted IRs stratified by index therapy ranged from 21.4 (95% CI: [20.9, 21.9]) in among incident users of antihypertensive therapies to 24.0 (95% CI: [23.79, 24.4]) among prevalent antihypertensive therapy users. The overall unadjusted IRs stratified by antihypertensive therapy exposure time ranged from 15.0 (95% CI: [5.6, 39.8]) in the incident antihypertensive treatment cohort to 15.8 (95% CI: [7.1, 35.2]) in the prevalent antihypertensive treatment cohort. When compared to their respective overall IRs, the incident, prevalent, and all (incident and prevalent combined) antihypertensive treatment cohort users who were prescribed alpha blocker monotherapy had higher IRs of GI cancer whereas IRs among patients taking ACEI monotherapy were consistently lower. Among patients treated with triple plus combination therapy, those prescribed a regimen that included neither an ACEI nor aliskiren were consistently observed as having higher IRs of GI cancer compared to the respective overall IRs for all patients, incident antihypertensive users, and prevalent antihypertensive users. We believe this is the first study to report IRs of GI cancer stratified by all classes of therapy warranting the need for further research. Results from the relative risk assessments revealed that patients exposed to aliskiren versus hypertensive users exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use revealed that the use of aliskiren was not associated with an increased risk of GI cancer when compared to other antihypertensive therapy users, and compared non-hypertensive patients. It is possible that these comparisons were not adequately powered to detect significant differences in risks given the smaller number of aliskiren users. The difference in sample sizes between aliskiren and other antihypertensive therapy users might explain why, after controlling for demographic and clinical characteristics, the risk of GI cancer

	was similar between aliskiren users and non-hypertensive patients, but greater in other antihypertensive therapy users when compared to non-hypertensive patients.
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List of abbreviations

AB	Alpha Blocker
ACEI	Angiotensin-Converting Enzyme inhibitor
ARB	Angiotensin II Receptor Blocker
BB	Beta Blocker
CCB	Calcium Channel Blocker
CCI	Charlson Comorbidity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPT	Current Procedural Terminology
CRC	Colorectal Cancer
EMA	European Medicine Agency
FOBT	Fecal Occult Blood Test
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
GPI	Generic Product Identification
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard Ratio
IC	Ischemic Colitis
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	Interquartile Range
IR	Incidence Rate
NDC	National Drug Code
NSAID	Nonsteroidal anti-inflammatory drug
PPI	Proton Pump Inhibitor
PPO	Preferred Provider Organization
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-Year

RMP	Risk Management Plan
US	United States

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4 Milestones

Table 4-1 Study milestones

Milestone	Planned date	Actual date
Protocol approved by EMA		1 July 2014
Final study report	At study protocol approval (1-Jul-2014) + 12 months	27 May 2015

5 Rationale and background

Aliskiren (Rasilez®) is the first orally active direct renin inhibitor approved for the treatment of hypertension. Aliskiren's inhibitory effect on angiotensin I generation, through renin blockade, is highly specific and long-lasting (24 hours) (Frampton and Curran 2007).

Colorectal hyperplasia is listed as a potential risk in the aliskiren risk management plan (RMP). This is based upon findings in a rodent carcinogenicity study. However, these findings have not been confirmed in a 2-year marmoset study or in targeted clinical studies including a colonoscopy study. Therefore, the increased risk of colorectal hyperplasia observed in the rodent study may reflect high intraluminal drug concentrations in rats or could be a species-specific difference between rats and humans in response to aliskiren exposure [Rasilez/Riprazo/RasilezHCT/Rasilamlo/Rasitrio EU RMP v.11.1 from 14-Jan-2015/ Core RMP v 10.0 from 25-Nov-2013. 13-Sep-2012].

Known risk factors for colorectal cancer (CRC) include genetic susceptibility, inflammatory bowel disease (IBD) (Eaden et al 2001, Herrington et al 2012), alcohol use, obesity, and diabetes mellitus (Ahmed et al 2006, Esposito et al 2012). Epidemiologic studies examining a potential association of hypertension with the development of colorectal cancer (CRC) have reported inconsistent findings. The relationship between hypertension and the development of CRC is not clearly defined. Most published epidemiologic studies did not find an increased CRC risk in patients with hypertension compared to normotensive patients (e.g. Negri et al 1999, Lindgren et al 2005, Stürmer et al 2006, Kim et al 2007, Aleksandrova et al 2011). However, there is also some evidence from observational studies that hypertension might be associated with an increased CRC risk (Othman and Zin 2008, Stocks et al 2008, Pelucchi et al 2010), especially in hypertensive patients with type 2 diabetes mellitus and obesity (Stocks

et al 2008). Additionally, there is some evidence that the mortality of CRC may be higher in hypertensive compared to normotensive patients (Batty et al 2003, Watanabe et al 2005).

Information in the literature on the incidence rate data of colorectal cancer or more general of colorectal hyperplasia in hypertensive patients is very limited though. Bhaskaran et al (2012) assessed the overall risk of cancer and risk of major site specific cancers (breast, lung, colon, prostate) in adult hypertensive patients who were exposed to angiotensin receptor blockers (ARBs) for at least one year using data from the United Kingdom (UK) General Practice Research Database (GPRD). They estimated an incidence rate of colon cancer in 'ever users' of ARBs of 1.0 per 1,000 patient-years (95% confidence interval [CI]: 0.9-1.1). In a similar retrospective analysis of adult hypertensive patients in the GPRD (Azoulay et al 2012), the use of ARBs was associated with a modest decreased risk of colorectal cancer (adjusted risk ratio: 0.88; 95% CI: 0.81–0.96).

In the context of the Rasilez Follow-up Measures regarding the carcinogenic potential of aliskiren the Committee for Medicinal Products for Human Use (CHMP) requested from Novartis to do a non-interventional study (NIS) to estimate the incidence of colorectal hyperplasia in aliskiren-treated patients, in patients using other antihypertensive drugs and in the general population not treated with any antihypertensive drug. Based on that request, Novartis committed to do a NIS with secondary use of data derived from a large United States (US) health claims database (IMS PharMetrics Plus). Furthermore, since Novartis was asked to add gastrointestinal (GI) cancer as a pre-specified endpoint in all new aliskiren clinical trials, Novartis proposed to additionally assess GI cancer.

6 Research question and objectives

Due to the lack of real-world data on colorectal hyperplasia in association with aliskiren exposure, this study evaluated the incidence of colorectal hyperplasia in hypertensive patients exposed to aliskiren. Therefore, the overall objective of this non-interventional study was to assess the risk of colorectal hyperplasia among hypertensive patients using aliskiren, relative to those using other antihypertensive drugs, as well as a non-hypertensive cohort.

6.1 Primary objective

To determine age- and sex-stratified incidence rates of colorectal hyperplasia in the following mutually exclusive patient cohorts:

- Adult hypertensive patients exposed to aliskiren
- Adult hypertensive patients exposed to antihypertensive drugs other than aliskiren
- A sample of adult patients without a diagnosis of hypertension and without antihypertensive use

In addition, age- and sex-stratified incidence rates of GI cancer in hypertensive patients exposed to aliskiren as well as in the two additional groups (i.e. hypertensive patients exposed to antihypertensive drugs other than aliskiren, and the non-hypertensive sample) was estimated.

6.2 Secondary objective

As a secondary objective, the relative risk of colorectal hyperplasia and GI cancer was assessed in hypertensive patients exposed to aliskiren versus hypertensive patients exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use.

7 Amendments and updates to the protocol

The protocol stated that, to account for potential changes in the therapeutic regimen, incidence rates will be presented based on the antihypertensive therapy used prior to the end of follow-up. Because two other methods of calculating incidence rates were also used (based on index regimen and regimen with the longest exposure), and due to the fact that the outcomes assessed are malignant in nature and not acute events, this analysis was deemed redundant and therefore was not performed. The protocol also stated that propensity score matching will be employed to control for confounding in the relative risk estimations; however, as confounding was controlled for in the Cox proportional hazards models used to estimate the relative risks, propensity score matching was not needed. It was initially planned that relative risk estimates of GI cancer would include constructing Cox models for eight individual GI neoplasms. Upon initial evaluation of events, it was determined that the count of events for each of the neoplasms was too small to produce a valid model. Therefore, all events were combined into a single GI cancer model. Lastly, a random selection of non-hypertensive patients was planned so that the size of the non-hypertensive population would be the same as that of the hypertensive population. After applying the attrition steps and initial evaluation of the age distribution of the populations, it was determined that random selection could have a negative impact on the number of patients in the older age groups and was not warranted; thus all eligible non-hypertensive patients were used in the study.

8 Research methods

8.1 Study design

This study was a retrospective cohort study with use of secondary data derived from a large United States (US) health claims database (IMS PharMetrics Plus).

The use of a US data source for this study was agreed with the CHMP in March 2013.

8.2 Setting

This was a retrospective cohort study with use of secondary data derived from the PharMetrics Plus database with a study period from 1 July 2006 through 30 June 2014.

The index window was defined as the period from 1 July 2007 through 30 June 2013. Patients were selected into the study cohort if they met the criteria listed below.

8.3 Subjects

Selection criteria - aliskiren users

1. at least 1 prescription for aliskiren in the index window (the first such prescription was defined as a patient's index date),

2. evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) in the pre-index period (365 days prior to the index date),
3. ≥18 years of age at the time of the index date,
4. continuous health plan enrollment for a minimum of 365 days prior to and following the index date.
5. Patients were not included if they had no recorded gender or age, or other incomplete data related to the measures of interest (e.g., missing days supply for antihypertensive medications).

Selection criteria – other antihypertensive therapy users

1. at least 1 prescription for antihypertensive medication other than aliskiren within the index window (the first such prescription was defined as a patient's index date),
2. evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) in the pre-index period,
3. ≥18 years of age at the time of the index date, and
4. continuous health plan enrollment for a minimum of 365 days prior to and following the index date.
5. Patients were not included if they had no recorded gender or age, or other incomplete data related to the measures of interest (e.g., missing days supply for antihypertensive medications).

Selection criteria – non-hypertensive patients

1.no prescriptions for any antihypertensive medication between 1 July 2006 and 30 June 2014 (study window),

2.no evidence of a hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) any time within the study window,

3.≥18 years of age at the time of the index date (defined below), and

4. continuous health plan enrollment for a minimum of 365 days prior to the index date and a minimum of 365 days following the index date (see Section 9.3.1).

Additionally for all three groups:

1. patients with a prior history of colorectal hyperplasia (defined as one or more diagnosis code for colorectal hyperplasia during the pre-index period or within the first 30 days following the index date) were excluded for the assessment of incident colorectal hyperplasia.

2. patients with prior history of GI cancer (defined as one or more diagnosis code for GI cancer during the pre-index period or within the first 30 days following the index date) were excluded for the assessment of incident GI cancer.

8.3.1 Patient index date selection

Treated cohorts (exposed to/not exposed to aliskiren)

Pharmacy claims for all hypertensive patients were examined starting on 1 July 2007 and continuing through the end of the index window (30 June 2013) to identify any claims for

aliskiren (Table 16-1). Patients with at least 1 prescription for aliskiren **at any time** during the index window, regardless of evidence of any other antihypertensive medication use prior to the aliskiren claim, were considered index aliskiren patients, and the first aliskiren claim identified during the index window was considered the index date.

For all other hypertensive patients with no evidence of any aliskiren claims during the index window, the date of the first prescription for an antihypertensive medication other than aliskiren (Table 16-1, Table 16-2, Table 16-3) was considered the index date.

Non-hypertensive Patients

A random date within the index window (1 July 2007 and 30 June 2013) was chosen to represent the index date for the non-hypertensive patients. To assign an index date, each date within the index window was sequentially numbered, and a random number generator initialized by a specified seed was used to assign a number to each patient, corresponding to the index date.

Table 9-1 outlines the definitions for "study window", "index window" and "index date".

Table 8-1 Definitions: study window, index window and index date

Term	Definition, timing
Study window	1 July 2006 – 30 June 2014
Index window using 365-day pre/post periods	1 July 2007 – 30 June 2013
Index date (aliskiren)	Date of first aliskiren claim within the index window
Index date (all other antihypertensive medications)	Date of first prescription claim for antihypertensive medication (other than aliskiren) within the index window
Index date (non-hypertensive cohort)	Randomly assigned date within the index window, using a random number generator

8.3.2 Follow-up period

The follow-up period for a patient began on the index date and ended on the earliest occurrence of one of the following:

1. Recorded diagnosis of colorectal hyperplasia (when investigating colorectal hyperplasia) or recorded diagnosis of GI cancer (when investigating GI cancer);
2. End of enrollment in the database;
3. End of the study period (30 June 2014).

Non-hypertensive patients were followed for the same period as the hypertensive cohorts, beginning from the index date until the end of the study period.

8.4 Variables

8.4.1 Endpoints of interest

8.4.1.1 Colorectal hyperplasia

All patients with a diagnosis of colorectal hyperplasia during fixed follow-up were identified. Colorectal hyperplasia was defined using both inpatient and outpatient claims as evidence of any diagnosis as outlined in Table 16-6. An important limitation of claims data is the inability to distinguish colorectal polyps and colorectal cysts from neoplasms. There were no specific ICD-9-CM diagnosis codes for colorectal cysts, and colorectal polyps can be coded as benign or malignant neoplasms. To verify the accuracy of the ICD-9-CM diagnosis, we searched for screening procedures for colorectal hyperplasia (e.g., fecal occult blood test [FOBT], sigmoidoscopy, and colonoscopy [see Table 16-9 for procedure codes]) within 3 months prior to the diagnosis. Since requiring patients to have a screening procedure prior to diagnosis could result in false negatives, potentially driving down the actual incidence of colorectal hyperplasia (i.e., by missing some patients who actually have the disease recorded as indicated by the ICD-9-CM diagnosis codes, but for some reason do not have the test recorded in the database) we also report a tabulation of patients with/without a screening test versus those with/without an ICD-9-CM diagnosis as a sensitivity test to compare observed ICD-9-CM diagnoses (or lack thereof) with screening rates.

8.4.1.2 Gastrointestinal cancer

GI cancer was defined using both inpatient and outpatient claims as evidence of a recorded diagnosis of malignant neoplasms of any of the following sites: mouth, esophagus, stomach, small intestine, appendix, anus, and gastrointestinal stromal cancer. See Table 16-7 for relevant diagnosis codes. To verify the accuracy of the ICD-9-CM diagnosis, we searched for screening procedures for GI cancer (e.g., endoscopy, gastroscopy, and H. pylori testing) prior to the diagnosis. Since requiring patients to have a screening procedure prior to diagnosis could result in false negatives, potentially driving down the actual incidence of GI cancer, we also report a tabulation of patients with/without a screening test versus those with/without an ICD-9-CM diagnosis to compare observed ICD-9-CM diagnoses (or lack thereof) with screening rates.

8.4.2 Exposure of interest – antihypertensive drug use

Evidence of antihypertensive drug use, the primary exposure, was defined as a prescription for an antihypertensive medication between 1 July 2007 and 30 June 2013. Following identification, treated patients were stratified into 1 of 2 mutually exclusive cohorts based on use of antihypertensive medications, as follows:

- **Incident antihypertensive therapy users:** No evidence of any antihypertensive prescription in the 365 days prior to the index date;
- **Prevalent antihypertensive therapy users:** Evidence of at least 1 antihypertensive prescription in the 365 days prior to the index date.

To capture antihypertensive therapy exposure, patients were classified as monotherapy initiators, dual combination initiators, or triple-plus combination initiators based on their

index antihypertensive drug use. See Table 16-1, Table 16-2, and Table 16-3 for relevant drug codes.

Patients were classified according to their antihypertensive therapy use (based on the therapy(ies) identified on their prescription claims)into the following groups (classification of individual antihypertensive drugs/drug classes):

- Monotherapy regimens (Table 16-1):
  a. Aliskiren
  b. Angiotensin-converting enzyme inhibitors (ACEI) (e.g., captopril, enalapril, lisinopril)
  c. Angiotensin II receptor blockers (ARB) (e.g., valsartan, candesartan, losartan)
  d. Alpha blockers (AB) (e.g., prazosin, terazosin, phentolamine)
  e. Beta blockers (BB) (e.g., atenolol, metoprolol, carvedilol)
  f. Calcium channel blockers (CCB) (e.g., amlodipine, diltiazem, verapamil)
  g. Diuretics (including thiazides such as hydrochlorothiazide and chlorthalidone; loop diuretics such as furosemide, torasemide, and bumetanide; and potassium-sparing diuretics such as amiloride, spironolactone, and triamterene)
  h. Other antihypertensive drug monotherapies (e.g., vasodilators, selective aldosterone receptor antagonists, centrally acting alpha agonists)
- Dual combination regimens (fixed-dose (Table 16-2) and free dose combinations; note that these are mutually exclusive categories):
  a. Dual combination regimens including aliskiren (including the free dose combination of aliskiren and ACEI as a specific sub-group of interest)
  b. Dual combination regimens including an ACEI but not aliskiren
  c. Dual combination regimens including neither an ACEI nor aliskiren
- Triple-plus combination regimens (fixed-dose (Table 16-3) and free dose combinations; note that these are mutually exclusive categories):
  a. Triple-plus combination regimens including aliskiren
  b. Triple-plus combination regimens including an ACEI but not aliskiren
  c. Triple-plus combination regimens including neither an ACEI nor aliskiren

To be classified into a dual or triple-plus free-agent combination therapy cohort, patients had to have each of the drugs that qualified the patient for that cohort within the first 30 days after the index date (including the index date) **and** at least one additional prescription for each of those drugs within days supply + 30 days of the first prescription of those drugs. For example, if days supply of the first prescription is 30 days, patients must receive at least one additional prescription of the product within 60 days of that first drug.

If a patient initiated combination therapy by filling multiple agents on the latest start date (last date within the index window that a patient can fill a 30- day supply) **and** had exactly one fill of each drug in the 30-day window (i.e., there were no other fills or the maximum allowable time without drug was exceeded), the patient was considered combination therapy, defined by those drugs identified on the latest start date.

Patients were classified as monotherapy, dual combination, or triple-plus combination users, as detailed above, based on the index antihypertensive therapies identified.

Duration of treatment exposure was calculated for the treated antihypertensive cohort as the total number of days covered by the index drug(s) during the follow-up period ([last prescription date – index prescription date] + days supply of last prescription).

Please note that for non-hypertensive patients, the duration of treatment was not calculated due to their lack of treatment; thus, duration of follow-up (number of days from index date until the end of follow-up) was used for determination of incidence rates.

8.4.3 Other variables

Demographic characteristics were based on data from the index date and included the following:

- Age and age group (18-44, 45-64, ≥ 65 years)
- Gender (male, female)
- Geographic region (Northeast, Midwest, South, West)
- Health plan type (consumer-directed healthcare product, HMO, indemnity, point-of-service [POS], PPO, unknown)
- Payer type (commercial, Medicaid, Medicare Risk, self-insured, unknown)

Baseline clinical characteristics were also evaluated from the index date or during the defined pre-index period, unless otherwise noted:

- Available days of follow-up (post-index)
- Charlson Comorbidity Index (CCI) score, Dartmouth-Manitoba adaptation (pre-index); **Note:** the Dartmouth-Manitoba adaptation of the CCI is the recommended approach for longitudinal claims database analyses where DRG and ICD procedure codes are not consistently available
- Comorbid conditions (history of helicobacter pylori infection, history of stomach lymphoma, history of stomach surgery, irritable bowel syndrome, ischemic bowel disease, chronic diarrhea, chronic constipation, peripheral vascular disease, vascular insufficiency of intestine, acute coronary syndrome, coronary heart disease or angina, heart failure, stroke or transient ischemic attack, ulcerous rectocolitis, Crohn's disease, diabetes mellitus), pre- and post-index (see Table 16-8 for relevant diagnosis codes)
- Screening procedures for colorectal hyperplasia or GI cancer (for colorectal hyperplasia: fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy; for GI cancer: endoscopy, gastroscopy, H. pylori testing), pre- and post-index (see Table 16-9 for relevant procedure codes)
- Co-medication (e.g. prescription non-steroidal anti-inflammatory drugs [NSAIDs], statins, hormone replacement therapy, proton pump inhibitors [PPIs], anti-diabetic drugs) (see Table 16-4 for relevant drug codes)

8.5 Data sources and measurement

The data for this study was retrieved from the IMS PharMetrics Plus Health Plan Claims Database with a study period from 1 July 2006 through 30 June 2014. [redacted] was the

designated contract research organization (CRO) performing the analyses following their own internal standard operating procedures (SOPs).

IMS' collaboration with Health Intelligence Company, which operates as Blue Health Intelligence, allows IMS' bio-pharmaceutical clients sole access to one of the largest US health plan claims databases and adds to IMS' market leading health plan claims database. The aggregated IMS PharMetrics Plus database is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage in 2011 represent 42 million active lives. Data are available from 2006 onwards; with a typical 3-4 month lag due to claims adjudication.

PharMetrics Plus data has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area in the US are represented, with coverage of data from 96% of US hospitals, 91% of all US doctors, and representation from 85% of the Fortune 100 companies.

In addition to standard fields such as inpatient and outpatient diagnoses (ICD-9-CM) and procedures, retail and mail order prescription records, PharMetrics Plus has detailed information on pharmacy and medical benefits (copayment, deductible), inpatient stays (admission type and source, discharge status) and provider details (specialty, provider ID). All 3-digit zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography.

Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, gender, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), and start and stop dates of health-plan enrolment.

Due to the broad reach of the data, records in the PharMetrics Plus database are representative of the national, commercially insured population in terms of age and gender for individuals aged 65 and under. The data are also longitudinal, with more than 30 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are Health Insurance Portability and Accountability Act (HIPAA) compliant to protect patient privacy.

8.6 Bias

If an incorrect diagnosis was listed in the medical record, or the medical record was incomplete, then patients might have been misclassified, resulting in measurement bias. We attempted to counter this by conducting validity checks of the diagnosis by identifying corresponding screening tests prior to diagnosis. An additional source of bias may have been in the hierarchical selection of aliskiren patients over other antihypertensive therapies. While this approach was warranted to achieve comparable sample sizes between the treated cohorts given the smaller proportion of aliskiren users compared to users of all other anti-hypertensive therapies, this potentially introduces selection bias into the cohorts.

8.7 Study size

Because this was an exploratory, non-interventional study and not a hypothesis testing study, power analysis for sample size estimation was not conducted. Sample size was limited to the number of patients available in the database meeting the study inclusion criteria.

8.8 Data transformation

Not applicable

8.9 Statistical methods

All analyses employed SAS version 9.2 (SAS Institute Inc., Cary, NC) and were performed by [redacted] All data are reported for the aggregate population, as well as stratified by the incident and prevalent antihypertensive treatment cohorts.

Main summary measures

Unless otherwise specified, results for categorical measures will be provided as the frequency and percentage of total study patients observed in each category. For continuous variables, descriptive statistics (mean, standard deviation [SD], range, median, and interquartile range [IQR]) will be presented. When necessary, continuous variables will be categorized into intervals, with the distribution of patients for each interval provided. No statistical analyses will be performed, and all comparisons between cohorts will be descriptive in nature only. All analyses are on observed, not projected, data.

Statistical methods applied to the study

For the primary analyses, incidence rates (IRs) with 95% confidence intervals (CIs) were calculated per 10,000 person-years (PYs) for colorectal hyperplasia and GI cancer using three methodologies: 1) IR calculations were estimated for each of the cohorts (i.e., aliskiren users, other antihypertensive therapy users, and non-hypertensive patients) by demographic, clinical, and lifestyle factors, 2) an intention-to-treat approach was also applied such that IR calculations were based on the antihypertensive drug used within 30 days after the index date (i.e., index therapy), and 3) IRs were lastly calculated based on the regimen with the longest exposure time.

For methods 1 and 2, the incidence rates were based on person-time contributed throughout the entire follow-up period, and were calculated as total number of subjects with at least one event divided by person-years [time from index date until first occurrence of event (for those subjects with an event) and up to the end of follow-up time (for others)] x 10,000. These rates are reported by age group (18-44, 45-64, $\geq$ 65 years), gender, clinical, and lifestyle factors, as well as by index antihypertensive drug therapy. To assess the impact of lifestyle factors on the incidence of colorectal hyperplasia, ICD-9-CM diagnosis codes were applied, where available,

as proxy measures to partially assess the impact of some risk factors in severe cases (303.xx for alcohol dependence syndrome, 278.0xx for overweight and obesity).

For method 3, additional IRs that take into account patients' varying exposure to antihypertensive medications were calculated based on the person-time contributed to the regimen with the longest duration of exposure, where person-time was counted from the index date of this regimen until the time of the first event occurring after the start of this regimen. IRs with 95% CIs were calculated using the number of stratum-specific identified cases over the stratum-specific total person-time of follow-up. To identify the regimen with the longest duration of exposure, patients' exposure time to the drug regimen was defined by the total number of days a patient was on therapy for each drug. For combination therapy, therapy days were defined as the total number of days that the antihypertensive drug was on-hand for all drugs in the regimen. A treatment gap of 60 days was allowed, so as to capture those patients who may have been on combination therapy but may have experienced a gap in days supply of one or more drugs in the regimen. Thus, a patient was considered on therapy if he/she had days supply of all of the drugs in the regimen within 60 days of the end of supply of the previous fill. IRs with 95% CIs were calculated using the number of stratum-specific identified cases over the stratum-specific total person-time of follow-up. IRs are also presented by index drug, and with rates for each index drug stratified by age and gender.

For the secondary analyses, we used Cox proportional hazard models to estimate relative risks (expressed as HRs with 95% CIs) for colorectal hyperplasia for: hypertensive patients exposed to aliskiren versus hypertensive patients exposed to other antihypertensive drugs, hypertensive patients exposed to aliskiren versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use, and hypertensive patients exposed antihypertensive drugs other than aliskiren versus a sample of patients without a diagnosis of hypertension and without antihypertensive therapy. Predictor variables included baseline demographic factors and clinical factors. Patients were followed from their index date until the end of follow-up to determine if they developed colorectal hyperplasia. HRs with 95% CIs for GI cancer were also estimated using the same method.

Methods used to examine subgroups and interactions

IR calculations were performed in patients with the following medical histories: diabetes, irritable bowel syndrome, ischemic bowel disease, ulcerative colitis, ulcerous rectocolitis, Crohn's disease, familial adenomatous polyps, hereditary nonpolyposis.

Stratifications were also performed in patients with exposure to the following drug classes within 365 days prior to the index date: non-steroidal anti-inflammatory drugs (NSAIDs) and HMG-CoA reductase inhibitors (statins) within the colorectal hyperplasia assessment cohort, and HRTs, PPIs and anti-diabetic drugs within the GI cancer assessment cohort. IRs associated with these medications were reported by age group and gender.

Missing data

Not applicable (the analytical dataset contained no missing values).

Sensitivity/Validation analyses

To verify the accuracy of the ICD-9-CM diagnosis, a search was performed for screening procedures for colorectal hyperplasia (e.g., fecal occult blood test [FOBT], sigmoidoscopy, and colonoscopy) and GI cancer (e.g., endoscopy, gastroscopy, and H. pylori testing) within 3 months prior to the diagnosis. Since requiring patients to have a screening procedure prior to diagnosis could result in false negatives, potentially underestimating the actual incidence of colorectal hyperplasia/GI cancer, a tabulation of patients with/without a screening test versus those with/without an ICD-9-CM diagnosis as an additional measure was provided

Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change

The protocol states that to account for potential changes in the therapeutic regimens, incidence rates will be presented based on the antihypertensive therapy used prior to the end of follow-up. Because two other methods of calculating incidence rates were used (based on index regimen and regimen with the longest exposure) and due to the fact that the outcomes assessed are malignant in nature and not acute events, this analysis was deemed redundant and was not performed. The protocol also states that propensity score matching will be employed to control for confounding in the relative risk estimations; however, as confounding was controlled for in the Cox models used to estimate the relative risks, propensity score matching was not necessary. It was initially planned that relative risk estimates of GI cancer would include constructing Cox models for eight individual GI neoplasms. Upon initial evaluation of events, it was determined that the count of events for each of the neoplasms was too small to produce a valid model. Therefore, all events were combined into a single GI cancer model.
Lastly, a random selection of non-hypertensive patients was planned so that the size of the non-hypertensive population would be the same as that of the hypertensive population. After applying the attrition steps and initial evaluation of the age distribution of the populations, it was determined that random selection could have a negative impact on the number of patients in the older age groups and was not warranted; thus all eligible non-hypertensive patients were used in the study.

8.10 Quality control

Data contributions from the PharMetrics Plus claims database are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. All statistical codes were quality checked by a separate programmer prior to closing out the study. At the end of the project, all project related programming code, tables, and documents are archived and stored on a server where they can be retrieved when needed in the future. A password is required to log into the system where all data are stored.

9 Results

All results are presented in detail in Appendix 1.

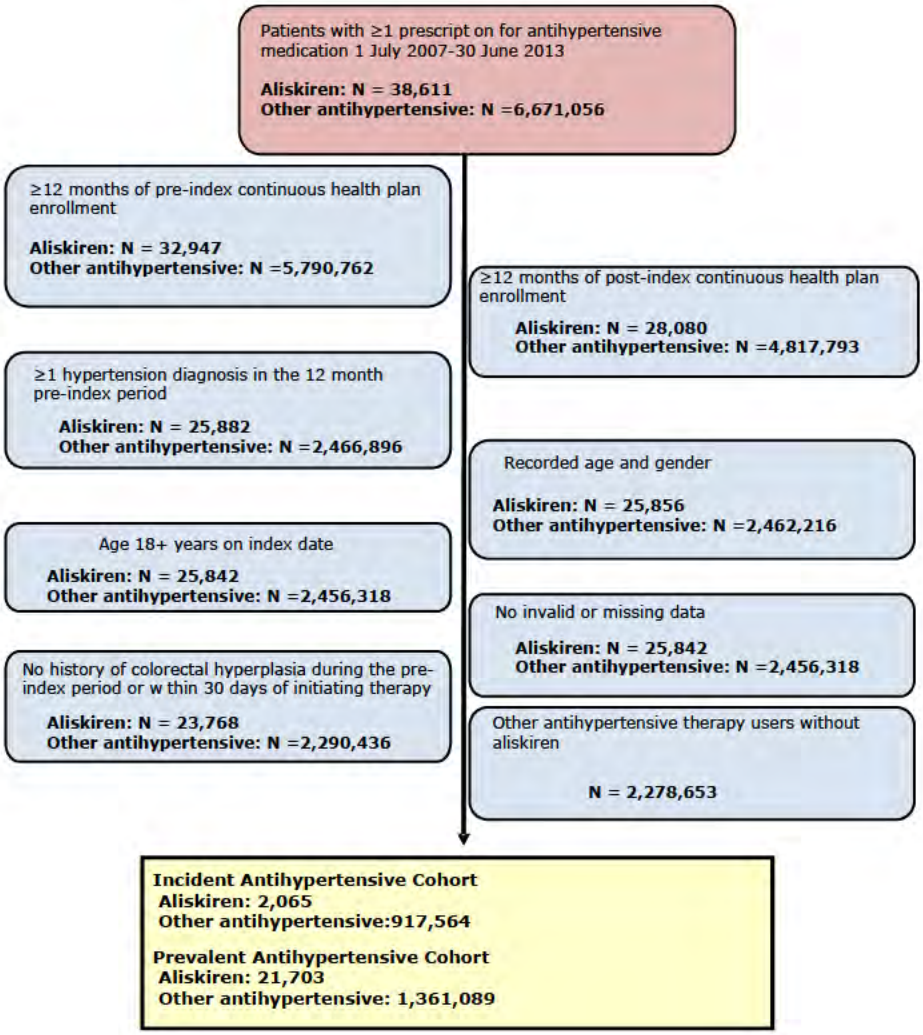
9.1 Colorectal Hyperplasia Cohort

9.1.1 Participants

Patients were selected for analysis if they had evidence of a hypertension diagnosis; had ≥ 1 prescription for an antihypertensive medication within 365 days after the hypertension diagnosis date; were ≥18 years of age; had continuous health plan enrollment for ≥365 days before and after the first qualifying aliskiren/antihypertensive drug prescription; and had no prior history of colorectal hyperplasia. Patients were further stratified into incident and prevalent antihypertensive treatment cohorts based on evidence of antihypertensive drug prescriptions in the 365 days prior to the index date.

Within the colorectal hyperplasia assessment cohort, a total of 38,611 aliskiren and 6,671,056 other antihypertensive therapy users with a diagnosis of hypertension between 1 July 2007 and 30 June 2013 were initially identified in the data extract along with 12,615,141 patients with neither a hypertension diagnosis nor a prescription for an antihypertensive medication of interest between 1 July 2006 and 30 June 2014. After applying the study inclusion and exclusion criteria, 23,768 (61.6%) aliskiren patients, 2,278,653 (34.2%) other antihypertensive patients and 5,806,899 (46.0%) non-hypertensive patients were available for analysis. There were 2,065 incident aliskiren users, 917,564 incident users of other antihypertensive therapies, 21,703 prevalent aliskiren users and 1,361,089 prevalent users of other antihypertensive therapies within the colorectal hyperplasia assessment cohort (Table 15-1; Figure 9-1).

Figure 9-1 Attrition of the Colorectal Hyperplasia Cohort



9.1.2 Demographic and Clinical Characteristics

9.1.2.1 All Patients

Within the colorectal hyperplasia assessment cohort, aliskiren patients were approximately 3 years older on average compared to all other antihypertensive therapy patients [mean age 57.7 years (SD ±11.2) vs. 54.8 years (SD ±11.2), respectively]. The mean age of non-hypertensive patients was younger at 39.4 years (SD ±13.4). The majority of aliskiren and other antihypertensive therapy users were between the ages of 45-64 years; whereas the majority of non-hypertensive patients were between the ages of 18-44 years. Patients age ≥65 years made up 23.6%, 16.2%, and 2.0% of the aliskiren, other antihypertensive therapy, and non-hypertensive patients; respectively. The aliskiren sample was composed of slightly more males compared to users of other antihypertensive therapies (% male: 54.5 vs. 50.7). Among

non-hypertensive patients, there were more females than males (% female = 54.0). The majority of aliskiren users resided in the South (51.0%), whereas users of other antihypertensive therapies were weighted more in the Northeast and Midwest geographic regions. Non-hypertensive patients were almost equally dispersed between the Midwest and South regions. Nearly all patients were covered by a PPO health plan. For full demographic characteristics of all patients within the colorectal hyperplasia cohort, see Table 15-2.

The mean CCI score of all aliskiren patients within the colorectal hyperplasia cohort was higher than that of all other antihypertensive therapy users [1.5 (SD ±1.8) vs. 0.9 (SD ±1.3)].Approximately 37% of aliskiren users and 55% of users of other antihypertensive therapies had a CCI score of 0. More than 91% of non-hypertensive patients had a CCI score of 0 (mean [SD] score = 0.1 [±0.5]). Comorbidities were more prevalent among aliskiren than other antihypertensive therapy users; with the most frequently observed conditions in the pre-index period for both groups being diabetes mellitus (37.2% and 22.6%, respectively) and coronary heart disease or angina (20.7% and 12.9%, respectively). Post-index comorbidity rates were similar to those of the pre-index period. Aliskiren users also had a higher rate of comorbidities than non-hypertensive patients.

The overall rate of pre-index screening procedures was low for both aliskiren and other antihypertensive therapy users (~15%). The most frequently observed screening procedure in all aliskiren users and all users of other antihypertensive therapies was FOBT (9.5% and 9.8%, respectively) followed by colonoscopy (4.4% and 4.5%, respectively). Roughly 6% of non-hypertensive patients had a screening test of any kind. Frequencies of post-index FOBTs and sigmoidoscopy procedures were similar among all aliskiren users and all users of other antihypertensive therapies. The frequency of colonoscopy procedures doubled in the post-index period in both the aliskiren users and users of other antihypertensive therapies to 9.5% and 9.0%, respectively. The frequency of sigmoidoscopy procedures was low (<1.0%) in both groups before and after the index date.

Proportions of co-medications utilized within the pre-index period were generally higher among all aliskiren users. The most frequently observed co-medication within the pre-index period for both the aliskiren patients and users of other antihypertensive therapies was within the statin class (40.0% vs. 28.9%). Within the pre-index period, anti-diabetic drugs were observed more frequently within aliskiren users compared to users of other antihypertensive therapies (30.3% vs. 16.3%). Co-medication results from the post-index period were similar to that of the pre-index period. NSAIDs were the most commonly used medication during the pre- and post-index periods for non-hypertensive patients. The mean amount of available post-index follow-up time was slightly longer among all other antihypertensive users compared to all aliskiren users [1,253.3 (SD ±735.5) vs. 1,113.6 (SD ±613.6) days]. Mean follow-up time for non-hypertensive patients was 1021 (SD ±543.8) days. Clinical characteristics of all patients within the colorectal hyperplasia assessment cohort are presented in detail in Table 15-4.

9.1.2.2 Incident Antihypertensive Therapy Users

The mean age of incident aliskiren patients was similar to that of incident other antihypertensive therapy patients [51.8 years (SD ±11.0) vs. 52.4 years (SD ±11.6)]. A higher proportion of males was observed in incident aliskiren users compared to incident other antihypertensive therapy users (59.7% vs. 53.0%). The majority of incident patients were

covered by a commercial PPO insurance plan. For full demographic characteristics of the incident patient samples, see Table 15-3. With respect to clinical characteristics, the mean CCI score for incident users of aliskiren and incident users of other antihypertensive therapies was 0.8 (SD ±1.3) and comorbid conditions were generally similar between the two groups. The most frequently observed comorbid condition in the pre-index period in both incident aliskiren users and incident users of other antihypertensive therapies was diabetes mellitus (21.4% and 18.4%, respectively) followed by coronary heart disease or angina (8.6% and 10.0%, respectively). Post-index comorbidity rates were similar to those of the pre-index period. The most frequently observed screening procedure in the pre-index period in incident aliskiren users and incident users of other antihypertensive therapies was FOBT (9.1% and 8.4%, respectively) followed by colonoscopy (3.4% and 3.6%, respectively) and sigmoidoscopy procedures (0.05% and 0.2%, respectively). The frequency of colonoscopy procedures increased in the post-index period in both the aliskiren users and users of other antihypertensive therapies (8.2% in both groups). Proportions of co-medications utilized within the pre-index period were generally similar among incident aliskiren users and incident users of other antihypertensive therapies. The most frequently observed co-medication within the pre-index period for both the aliskiren patients and users of other antihypertensive therapies was within the NSAID class (18.1% and 19.5%, respectively).Within the post-index period, statin medications were observed most frequently among both the incident aliskiren and incident users of other antihypertensive therapies (30.0% and 32.9%, respectively). The mean amount of available post-index follow-up time was slightly longer among incident aliskiren users compared to users of other antihypertensive therapies [1,167.4 (SD ±633.3) vs. 1,049.5 (SD ±586.8) days]. Clinical characteristics of the incident samples within the colorectal hyperplasia assessment cohort are presented in detail in Table 15-5.

9.1.2.3 Prevalent Antihypertensive Therapy Users

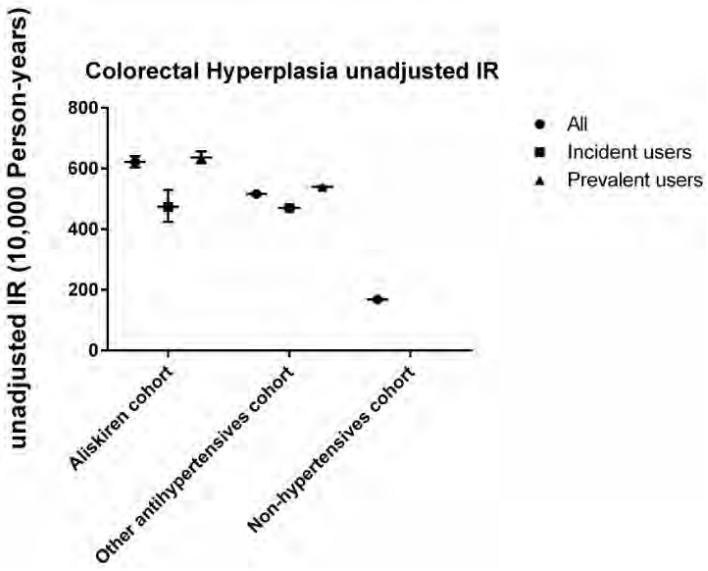
The mean age of prevalent aliskiren patients was slightly older than that of prevalent other antihypertensive therapy patients [58.3 years (SD ±11.1) vs. 56.5 years (SD ±10.6)] (Table 15-3). Among prevalent aliskiren users, the mean CCI score was 1.6 (SD ±1.8) compared to 1.0 (SD ±1.4) for prevalent users of other antihypertensive therapies (34.6% of aliskiren users vs. 52.0% of other antihypertensive therapy users had a CCI score of 0). Comorbid conditions were accordingly higher amongst prevalent aliskiren users compared to prevalent users of other antihypertensive therapies. The most frequently observed comorbid condition in the pre-index period in both aliskiren users and users of other antihypertensive therapies was diabetes mellitus (38.7% and 25.5%, respectively) followed by coronary heart disease or angina (21.8% and 14.8%, respectively). Post-index comorbidity rates were similar to those of the pre-index period. The most frequently observed screening procedure within the pre-index period in prevalent aliskiren users and prevalent users of other antihypertensive therapies was FOBT (9.5% and 10.7%, respectively) followed by colonoscopy (4.5% and 5.0%, respectively). The frequency of colonoscopy procedures increased in the post-index period in both the aliskiren users and users of other antihypertensive therapies (9.6% in both groups). Sigmoidoscopy was infrequently observed (<1.0% in both groups within pre and post-index periods). In general, prevalent aliskiren users utilized more co-medications than prevalent users of other antihypertensive therapies with the exception of hormone replacement therapy, which was more frequently observed in the prevalent users of other antihypertensive therapies (6.6% vs. 5.8%). The most frequently observed co-medication within the pre-index period for

both the aliskiren patients and users of other antihypertensive therapies was within the statin drug class (42.4% and 37.8%, respectively). Within the post-index period, statin medications were again observed most frequently among both the prevalent aliskiren and prevalent users of other antihypertensive therapies (46.6% and 40.8%, respectively). The mean amount of available post-index follow-up time was slightly longer among prevalent users of other antihypertensive therapies compared to prevalent aliskiren users [1,390.7 (SD ±791.6) vs. 1,108.5 (SD ±611.5) days]. Clinical characteristics of the prevalent samples within the colorectal hyperplasia assessment cohort are presented in detail in Table 15-5.

Of note, prevalent antihypertensive therapy users were not required to be new to index therapy during the selection process, thus patients may have had prescriptions for the index therapy during the pre-index period. An exploratory assessment of pre-index aliskiren use revealed that 900 (4.15%) prevalent aliskiren users received aliskiren during the pre-index period.

9.1.3 Incidence Rates – by Demographic, Clinical, and Lifestyle Factors

Figure 9-2 Colorectal Hyperplasia unadjusted Incident Rates



9.1.3.1 All Aliskiren Patients

Table 15-7 and Figure 9-2Colorectal Hyperplasia unadjusted Incident Ratess present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among all aliskiren patients (i.e., incident and prevalent aliskiren users combined) stratified by demographic, clinical, and lifestyle factors. The overall IR of colorectal hyperplasia per 10,000 PYs for all aliskiren patients was 621.7 (95% CI: [603.8.8, 640.1]).

IRs of colorectal hyperplasia for all aliskiren patients were highest among males and increased with increasing age. The IR for males aged ≥65 years was substantially higher than the overall IR (IR = 909.3, 95% CI: [838.1, 986.5]). When comorbidities were taken into account, patients with diabetes had an increased incidence of colorectal hyperplasia compared

to the overall aliskiren population (IR: 717.9, 95% CI: [685.9, 751.3]), For all other comorbidities, IRs of colorectal hyperplasia for aliskiren users were generally based on relatively few patients/events yielding low rates with wide confidence intervals not conducive to interpretation. When concomitant use of NSAIDs and statins were taken into account, statin use was associated with higher IRs of colorectal hyperplasia (IR = 719.1, 95% CI: [678.9, 761.7]) compared to IRs in patients that used NSAIDs and compared to the overall IR. Because only a small sample of patients had a diagnosis of alcohol dependence syndrome, IRs for this lifestyle factor yielded wide confidence intervals that should be interpreted with caution. However, when compared to the overall IR, the lifestyle factor obesity did not appear to increase the incidence of colorectal hyperplasia among all aliskiren users.

9.1.3.2 Incident Aliskiren Users

Table 15-8 and Figure 9-2Colorectal Hyperplasia unadjusted Incident Ratess present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among incident aliskiren users stratified by demographic, clinical, and lifestyle factors. The overall IR of colorectal hyperplasia per 10,000 PYs for incident aliskiren users was 473.9 (95% CI: [424.2, 529.4]). Within the gender stratum, IRs per 10,000 PYs for males was 490.6 (95% CI: [426.5, 564.3]), and for females the IR of colorectal hyperplasia was 448.4 (95% CI: [374.1, 537.5]). Sample sizes across most subgroups for incident aliskiren users were extremely small, thus IR calculations with respect to comorbidity, comedication, and lifestyle factors were based on relatively few patients/events, yielding wide confidence intervals not conducive to interpretation.

9.1.3.3 Prevalent Aliskiren Users

Table 15-8 presents unadjusted IRs per 10,000 PYs of colorectal hyperplasia among prevalent aliskiren patients stratified by demographic, clinical, and lifestyle factors. The overall IRs of colorectal hyperplasia per 10,000 PYs for prevalent aliskiren users was 636.5 (95% CI: [617.5, 656.0]). Within age and gender strata, the IR of colorectal hyperplasia was highest for males aged ≥65 years (IR: 903.5, 95% CI: [831.4, 981.9]). In general, IRs tended to increase with increasing age. When evaluated by comorbid conditions, the IR of colorectal hyperplasia for prevalent aliskiren users with diabetes was higher than the overall IR (722.6, 95% CI: [689.7, 757.0]). IRs of colorectal hyperplasia were higher in prevalent aliskiren patients with concomitant use of statins (728.0, 95% CI: [686.3, 772.2] compared to those that used NSAIDs and the overall IR. Examination of lifestyle factors revealed similar IRs of colorectal hyperplasia among prevalent aliskiren users with an obesity diagnosis (643.3, 95% CI: [588.0, 703.8]) compared to all prevalent aliskiren users. The IR of colorectal hyperplasia associated with a diagnosis of alcohol dependence syndrome was based on a small sample of patients which yielded a wide confidence interval not conducive to interpretation.

9.1.3.4 All Other Antihypertensive Therapy Users

Table 15-7 and Figure 9-2Colorectal Hyperplasia unadjusted Incident Ratess present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among all patients using antihypertensive therapies other than aliskiren, presented by demographic, clinical, and lifestyle factors. The IR of colorectal hyperplasia per 10,000 PYs for all other anti-hypertensive therapy users was 516.4 (95% CI: [514.8, 518.0]). The IR of colorectal hyperplasia for other antihypertensive therapy users was higher in males than females, and

increased with increasing age. Males aged ≥65 years had the highest incidence of colorectal hyperplasia (IR= 806.1, 95% CI: [798.3, 814.1]).

When comorbidities were taken into account familial adenomatous polyps/hereditary nonpolyposis was associated with the highest IR of colorectal hyperplasia (IR = 1,317.6; 95% CI: [1,147.5, 1,513.0]) compared to the other comorbidities and compared to the overall IR. When concomitant use of NSAIDs and statins was considered, statin use was associated with a higher incidence of colorectal hyperplasia (IR = 616.0, 95% CI: [612.4, 619.7]) compared to the overall IR and to the IR for NSAID users. When compared to the overall IR, lifestyle factors (i.e., alcohol dependence and obesity) did not appear to increase IRs of colorectal hyperplasia among other antihypertensive therapy users. In fact, patients with obesity had a lower IR than the overall other antihypertensive therapy user group (IR= 493.5, 95% CI: [440.7, 454.4]).

9.1.3.5 Incident Other Antihypertensive Therapy Users

Table 15-8 and Figure 9-2Colorectal Hyperplasia unadjusted Incident Ratess present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among incident other antihypertensive therapy users based on demographic, clinical, and lifestyle factors. The overall IR of colorectal hyperplasia per 10,000 PYs for incident users of other anti-hypertensive therapy was 470.5 95% CI: [467.9, 473.1]). Within the gender stratum, the IR per 10,000 PYs for males was 512.7 (95% CI: [509.0, 516.5]). The IR of colorectal hyperplasia for females was lower than that of males and that of the overall incident other antihypertensive therapy user group: 423.8 (95% CI: [420.2, 427.4]). With respect to comorbidity, patients with any one of the comorbidities of interest had a higher occurrence of colorectal hyperplasia compared to all incident other antihypertensive therapy users. The highest IR was observed in patients with familial adenomatous polyps/hereditary nonpolyposis (IR = 1,4786; 95% CI: [1,187.6, 1,840.8]). It is important to note that this rate was based on a few events among a small sample of patients (i.e., 80 events among 261 patients) and should be interpreted with caution. Concomitant use of statins was associated with a higher IR of colorectal hyperplasia (IR = 582.7, 95% CI: [576.1, 589.5] vs. the overall IR), whereas obesity was associated with a lower IR of colorectal hyperplasia vs. the overall IR (IR = 435.6, 95% CI: [427.4, 444.0]).

9.1.3.6 Prevalent Other Antihypertensive Therapy Users

Table 15-8 presents unadjusted IRs per 10,000 PYs of colorectal hyperplasia among prevalent other antihypertensive therapy users, stratified by demographic, clinical, and lifestyle factors. The overall IR of colorectal hyperplasia per 10,000 PYs for prevalent users of other anti-hypertensive therapies was 539.7 (95% CI: [537.7, 541.7]). Within age and gender strata, the IR of colorectal hyperplasia was highest for males ≥65 years of age (IR= 807.8, 95% CI: [798.7, 817.0]). In general, IRs tended to increase with increasing age. When evaluated by comorbid conditions, patients with any one of the comorbidities of interest with the exception of vascular insufficiency of the intestine had a higher incidence of colorectal hyperplasia compared to all prevalent other antihypertensive therapy users. The highest IR was observed in patients with familial adenomatous polyps/hereditary nonpolyposis (IR = 1,229.2; 95% CI: [1,028.6, 1,468.9]); though this is based on a small sample of patients with this condition (n=333). The IR of colorectal hyperplasia was higher in prevalent users of other

antihypertensive therapies that used statins compared to those that used NSAIDs and compared to the overall IR for all prevalent users of other antihypertensive therapies (IR=629.5 [95% CI: 625.1, 633.9]). Examination of lifestyle factors revealed a higher IR of colorectal hyperplasia among prevalent users of other antihypertensive therapies with alcohol dependence syndrome (IR=577.0, 95% CI: [547.2, 608.3]) and a lower IR of colorectal hyperplasia among those with an obesity diagnosis (IR= 529.2 [95% CI: 522.1, 536.4]) when compared to all prevalent users of other antihypertensive therapies.

9.1.3.7 Non-hypertensive Patients

Table 15-7 and Figure 9-2Colorectal Hyperplasia unadjusted Incident Ratess present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among non-hypertensive patients stratified by demographic, clinical, and lifestyle factors. The IR of colorectal hyperplasia per 10,000 PYs for non-hypertensive patients was 168.3 (95% CI: [167.7, 169.0]. IRs of colorectal hyperplasia among non-hypertensive patients tended to increase with increasing age, but were similar between males and females. The IR of colorectal hyperplasia for non-hypertensive patients aged ≥65 years was 458.2 (95% CI: [450.4, 466.2]).

When comorbidities were taken into account, patients with any one of the comorbidities of interest had a higher occurrence of colorectal hyperplasia compared to all non-hypertensive patients. This was particularly noticeable among patients aged ≥65 years. Patients with concomitant use of NSAIDs or statins had a higher occurrence of colorectal hyperplasia compared to the overall IR for all non-hypertensive patients (IR_{NSAIDS} = 249.9, 95% CI: [244.0, 255.9]; $IR_{statins}$ = 582.2, 95% CI: [572.6, 592.0]). When compared to the overall IR, obesity was associated with a higher IR of colorectal hyperplasia (IR = 216.5, 95% CI: [210.8, 222.4]).

9.1.4 Incidence Rates – by Index Therapy

9.1.4.1 All Antihypertensive Therapy Users

Table 15-6 presents antihypertensive drug use within 30 days after the patients' index date for the colorectal hyperplasia assessment cohort. Among all patients within the cohort, monotherapy was the most frequently observed treatment classification (approximately 54%). Aliskiren was the least prescribed regimen among the monotherapy (0.3%), dual-combination (0.2%) and triple-plus combination therapies (0.5%). The most frequently observed mono, dual and triple plus combination therapies were ACEI therapy (17.1%), dual combination therapy including neither an ACEI nor aliskiren (16.8%), and triple-plus combination therapy including an ACEI but not aliskiren (7.6%), respectively. The mean duration of exposure to the index therapy was 520 (SD ±592) days.

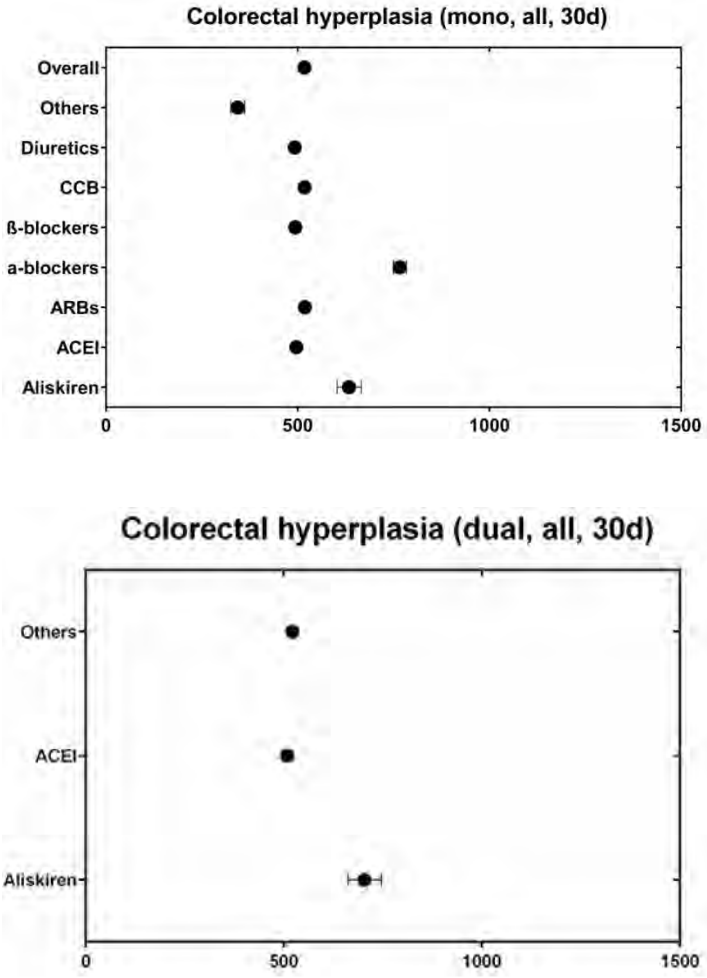
Table 15-9 and Figure 9-3 present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among all treated patients based on antihypertensive drug use within 30 days after the index date (i.e., index therapy). The overall IR for all patients was 517.3 (95% CI: [515.7, 518.9]). The IR per 10,000 PYs of colorectal hyperplasia among aliskiren monotherapy users was 633.7 (95% CI: [60.26, 666.4]). Among all monotherapy users, IR of colorectal hyperplasia was highest for those using alpha blockers (IR = 766.1, 95% CI: [749.5, 783.1]) and lowest for patients that were prescribed other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 343.3, 95% CI: [325.9, 361.7]).

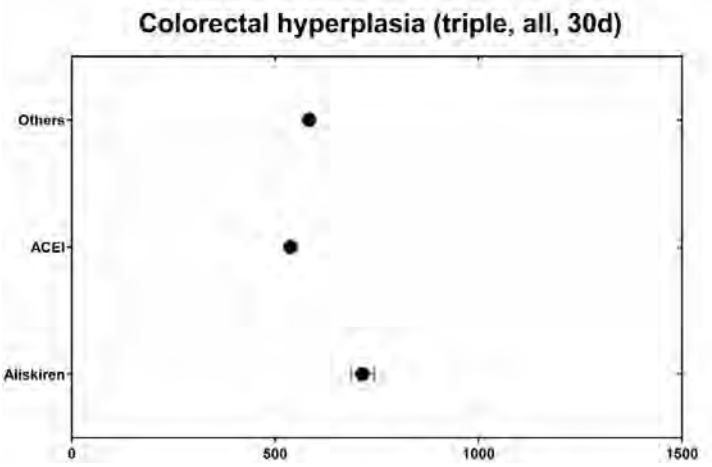
Compared to the overall IR, the IR of colorectal hyperplasia was higher for monotherapy users of aliskiren and alpha blockers, and lower for monotherapy users of ACEI's, beta blockers, diuretics, and other antihypertensive therapies.

When evaluating the incidence of colorectal hyperplasia by indexed dual-combination therapy, the highest IR was observed in patients prescribed a dual combination therapy including aliskiren (IR = 703.6, 95% CI: [662.7, 746.9]) and lowest in patients prescribed a dual-combination therapy including an ACEI but not aliskiren (IR = 508.0, 95% CI: [504.0, 511.9]) when compared to the overall IR and compared to the IR of other dual-combination regimens.

Among the triple-plus combination therapy users, IR of colorectal hyperplasia was highest among patients prescribed a triple-plus combination therapy that included aliskiren (IR = 714.5, 95% CI: [686.8, 743.3]) and lowest among triple-plus combination therapy including an ACEI but not aliskiren (IR = 538.2, 95% CI: [532.4, 544.0]). The IRs of colorectal hyperplasia associated with all triple-plus combination regimens were higher than the overall IR. In general, IRs of colorectal hyperplasia based on index therapy were higher among males and increased with age for all types of antihypertensive initiators (i.e., monotherapy, dual and triple-plus combinations).

Figure 9-3 Colorectal hyperplasia unadjusted Incident Rates mono, dual and triple combination





9.1.4.2 Incident Antihypertensive Therapy Users

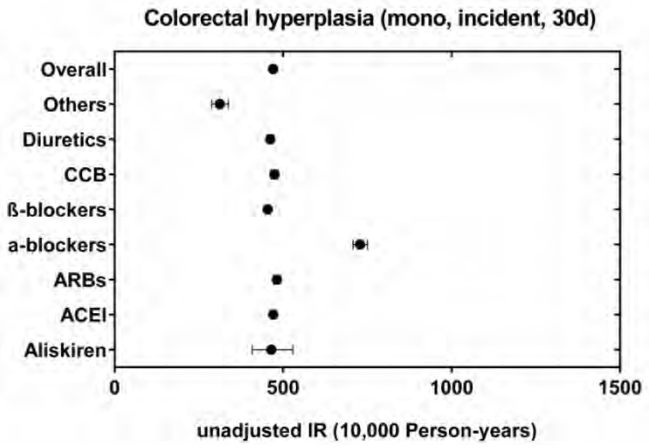
Incident antihypertensive therapy patients within the colorectal hyperplasia cohort were more likely to receive monotherapy (approximately 67.4%) compared to other therapies, and the most frequently observed monotherapy was ACEI therapy (23.2%) (Table 15-6).The most frequently observed regimens outside of the monotherapy classification were dual combination including an ACEI but not aliskiren (approximately 13.6% in each cohort) and dual-combination including neither an ACEI nor aliskiren (11.8%).Triple-plus combination therapy was only observed in 7% of patients. The mean duration of exposure to the index therapy in incident antihypertensive therapy users was 352 (SD ±431) days.

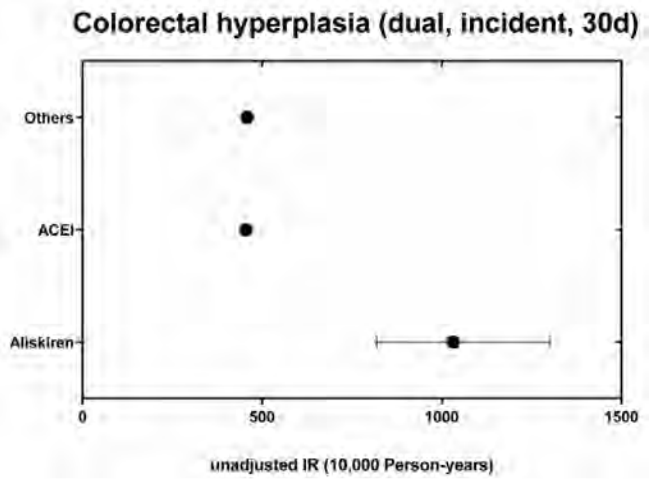
Table 15-9 and Figure 9-4 present unadjusted IRs per 10,000 PYs of colorectal hyperplasia among incident antihypertensive therapy users based on antihypertensive drug use within 30 days after the index date (index therapy). The overall IR of colorectal hyperplasia for all incident therapy users was 470.5 (95% CI: [467.9, 473.1]). The IR per 10,000 PYs of colorectal hyperplasia for incident aliskiren monotherapy users was 464.8 (95% CI: [408.6, 528.8). Among all incident monotherapy users, the IR of colorectal hyperplasia was highest for those prescribed alpha blockers (IR = 728.8, 95% CI: [707.9, 750.3]) and lowest for those prescribed other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 312.4, 95% CI: [289.3, 337.3]). Compared to the overall IR, the IR of colorectal hyperplasia was higher for monotherapy alpha blocker users and lower for monotherapy users of beta blockers and other antihypertensive therapies.

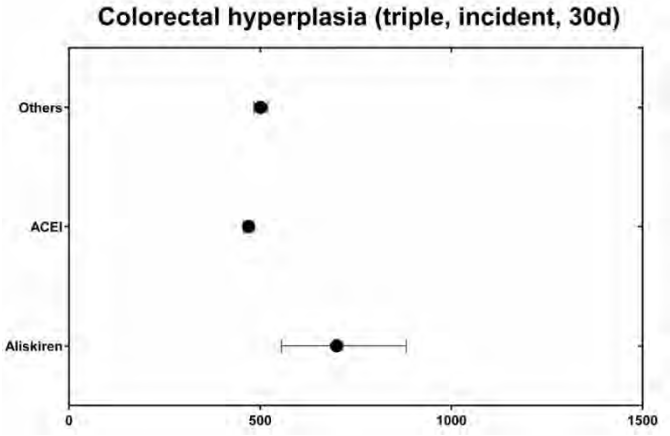
When evaluating the incidence of colorectal hyperplasia by index therapy in dual-combination therapy users, the highest IR was observed in patients prescribed a dual combination therapy including aliskiren (IR = 1,031.6, 95% CI: [818.8, 1,299.6]). Incident therapy users whose index therapy was a dual combination regimen including an ACEI but not aliskiren or dual combination regimen including neither an ACEI nor aliskiren had lower IRs of colorectal hyperplasia than all incident treated patients.

Among the triple-plus combination therapy users, the IR of colorectal hyperplasia was highest among patients prescribed a triple-plus combination therapy that included aliskiren (IR = 700.2, 95% CI: [555.8, 882.2]) and lowest among triple-plus combination therapy including an ACEI but not aliskiren (IR = 469.6, 95% CI: [457.5, 482.1]). The IR of colorectal hyperplasia for patients prescribed a triple-plus combination regimen including neither an ACEI nor aliskiren was higher than the overall IR for all incident treated patients. In general, IRs of colorectal hyperplasia based on index therapy among incident antihypertensive therapy users were higher among males and increased as age increased within all therapy classifications (i.e., monotherapy, dual-, and triple-plus combination regimens).

Figure 9-4 Colorectal hyperplasia unadjusted Incident Rates mono, dual and triple combination (incident users)







9.1.4.3 Prevalent Antihypertensive Therapy Users

Prevalent antihypertensive therapy users within the colorectal hyperplasia cohort received monotherapy more frequently (45.2%) compared to dual (37%) and triple-plus combination (17.8%) therapies (Table 15-6). The mean duration of exposure to the index therapy in prevalent patients was 633 (SD ±655) days (Table 15-6).

Table 15-9 presents unadjusted IRs per 10,000 PYs of colorectal hyperplasia among prevalent antihypertensive therapy users based on antihypertensive drug use within 30 days after the index date (index therapy). The overall IR per 10,000 PYs of colorectal hyperplasia among prevalent hypertensive therapy users was 540.9 (95% CI: [538.9, 542.9]). For prevalent aliskiren monotherapy users the IR of colorectal hyperplasia was 677.9 (95% CI: [641.9, 716.0]). Among all prevalent monotherapy users, the IR of colorectal hyperplasia was highest for those prescribed alpha blockers (IR = 820.9, 95% CI: [794.1, 848.7]). The lowest overall IR of colorectal hyperplasia among prevalent monotherapy users was observed in patients that were prescribed other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 374.9, 95% CI: [349.3, 402.5]). Compared to the overall IR for all prevalent therapy users, the IR of colorectal hyperplasia was higher for aliskiren and alpha blocker monotherapy users, and lower for monotherapy users of ACEIs, beta blockers, diuretics, and other antihypertensive therapies.

When evaluating the incidence of colorectal hyperplasia by index dual-combination therapy for prevalent antihypertensive therapy users, the highest IR was observed in patients prescribed a dual combination therapy including aliskiren (IR = 687.8, 95% CI: [646.5, 731.8]) and lowest among patients on dual combination therapy including an ACEI but not aliskiren (IR = 529.4, 95% CI: [524.6, 534.2]). Compared to the overall IR for all prevalent therapy users, IR of colorectal hyperplasia was higher for patients prescribed dual combination regimens including aliskiren and lower for those prescribed a dual combination regimen including ACEI but not aliskiren.

Within the triple-plus combination therapy users, IRs of colorectal hyperplasia were highest among patients prescribed a triple-plus combination therapy that included aliskiren (IR = 714.9, 95% CI: [686.8, 744.2]). IRs of colorectal hyperplasia were higher for all triple-plus combination regimens than the overall IR for prevalent therapy users. IRs of colorectal

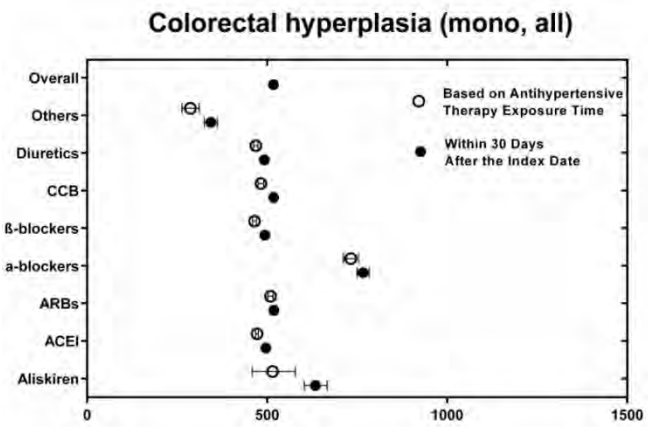
hyperplasia based on index therapy were higher among males and generally increased as age increased in each stratum and for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

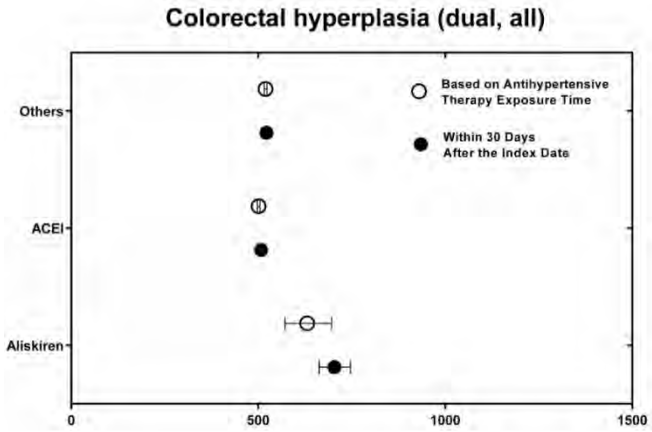
9.1.5 Incidence Rates – by Exposure Time

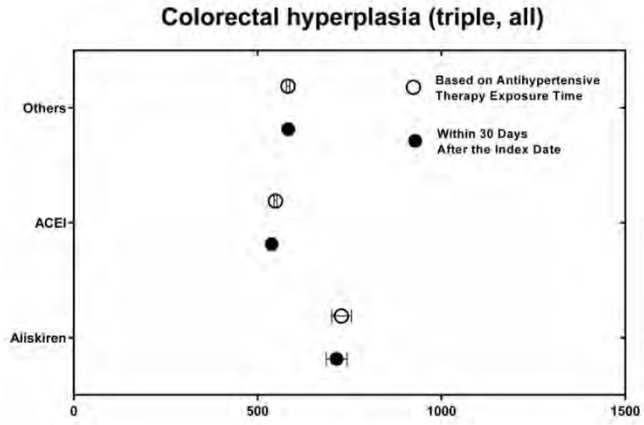
9.1.5.1 All Antihypertensive Therapy Users

Table 15-10 and Figure 9-5 present unadjusted IRs per 10,000 PYs of colorectal hyperplasia based on patients' exposure time to antihypertensive therapy. For monotherapy aliskiren users, IR of colorectal hyperplasia was 514.8 (95% CI: [458.5, 578.1]). Among all monotherapy users, the IR of colorectal hyperplasia based on exposure time was highest among those prescribed alpha blockers (IR = 732.3, 95% CI: [711.9, 753.2]) and lowest among patients that used other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 286.6, 95% CI: [263.6, 311.5]). Within the dual-combination therapy initiator group, IR of colorectal hyperplasia was greatest among patients that were prescribed regimens that included aliskiren (IR = 630.7, 95% CI: [571.4, 696.2]) and lowest among patients prescribed regimens that included an ACEI but not aliskiren (IR = 501.0, 95% CI: [497.2, 504.9]). Within the triple-plus combination therapy initiator group, the IR of colorectal hyperplasia was highest among patients prescribed a regimen that included aliskiren (IR = 727.8, 95% CI: [701.7, 754.9]) and lowest among patients prescribed a triple-plus combination regimen with an ACEI but not aliskiren (IR = 548.5, 95% CI: [544.7, 552.3]). IRs of colorectal hyperplasia based on patients' exposure time to antihypertensive therapy were higher among males and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

Figure 9-5 Colorectal hyperplasia unadjusted Incident Rates based on therapy exposure time and after the index date





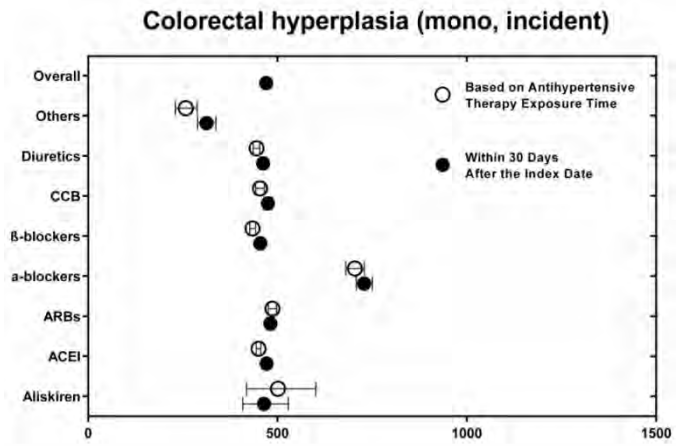


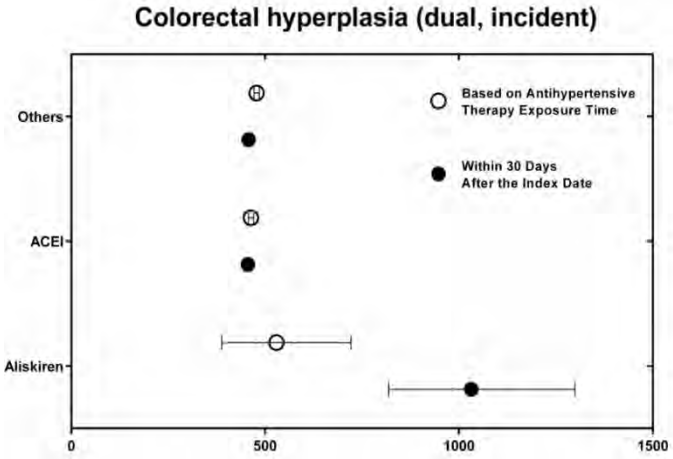
9.1.5.2 Incident Antihypertensive Therapy Users

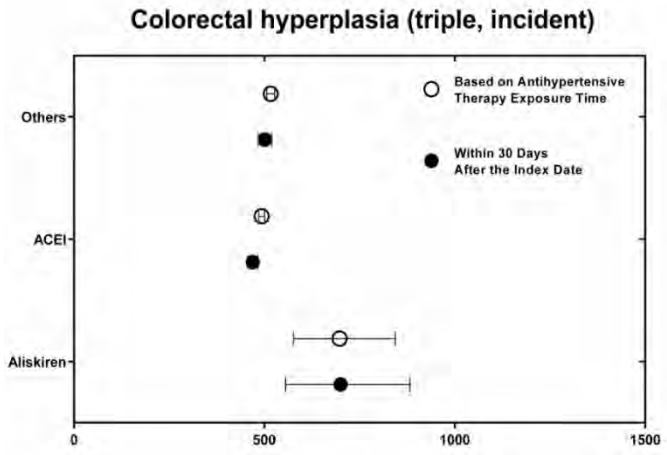
Table 15-10 and Figure 9-6 present unadjusted IRs per 10,000 PYs of colorectal hyperplasia based on incident therapy users' exposure time to antihypertensive therapy. For incident aliskiren monotherapy users, the IR of colorectal hyperplasia based on exposure time was 501.3 (95% CI: [418.2, 600.9]). Among all incident monotherapy users, IR of colorectal hyperplasia was highest among those that used alpha blockers (IR = 704.6, 95% CI: [680.6, 729.5]) and lowest among incident patients that used other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 257.8, 95% CI: [230.6, 288.3]). Within the dual combination therapy initiator group, IRs of colorectal hyperplasia were similar among incident therapy users that were prescribed regimens that included aliskiren (IR = 529.0, 95% CI: [388.0, 721.1]), regimens that included an ACEI but not aliskiren (IR = 463.2, 95% CI: [456.9, 469.7]), and regimens that included neither an ACEI nor aliskiren (IR=477.8, 95% CI: [471.0, 484.7]). Within the triple-plus combination therapy initiator group, IR of colorectal hyperplasia were highest among incident patients prescribed a regimen that included aliskiren (IR = 697.4, 95% CI: [576.5, 843.6]) and lowest among incident patients prescribed a triple-plus combination with an ACEI but not aliskiren (IR = 492.7, 95% CI: [485.2, 500.2]). With the exception of combination regimens including aliskiren, IRs of colorectal hyperplasia based on incident patients exposure time to

antihypertensive therapy were generally higher among males and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

Figure 9-6 Colorectal hyperplasia unadjusted Incident Rates based on therapy exposure time and after the index date (incident users)







9.1.5.3 Prevalent Antihypertensive Therapy Users

Table 15-10 presents unadjusted IRs per 10,000 PYs of colorectal hyperplasia based on prevalent antihypertensive therapy users' exposure time to antihypertensive therapy. For prevalent aliskiren monotherapy users, the IR of colorectal hyperplasia based on exposure time was 524.6 (95% CI: [451.2, 610.0]), Among all prevalent monotherapy users, IR of colorectal hyperplasia was highest among patients that were prescribed alpha blockers (IR = 792.4, 95% CI: [755.0, 831.6]) and lowest among prevalent patients that were prescribed other antihypertensive therapies (i.e., vasodilators, selective aldosterone receptors, and centrally acting alpha agonists; IR = 333.8, 95% CI: [294.3 378.5]). Within the dual combination therapy initiator group, IR of colorectal hyperplasia was greatest among prevalent patients that were prescribed regimens that included aliskiren (IR = 644.8, 95% CI: [581.0, 715.5]) and lowest among prevalent patients prescribed regimens that included an ACEI but not aliskiren (IR = 519.7 95% CI: [514.9, 524.5]). Within the triple-plus combination therapy initiator group, IR of colorectal hyperplasia was highest among prevalent patients prescribed a regimen that included aliskiren (IR = 729.0, 95% CI: [702.3, 756.7]) and lowest among prevalent patients taking a triple-plus combination regimen that included neither an ACEI nor aliskiren (IR = 598.9, 95% CI: [593.5, 604.4]). IRs of colorectal hyperplasia based on prevalent patients' exposure time to antihypertensive therapy were higher among males compared to females and, with few exceptions, increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

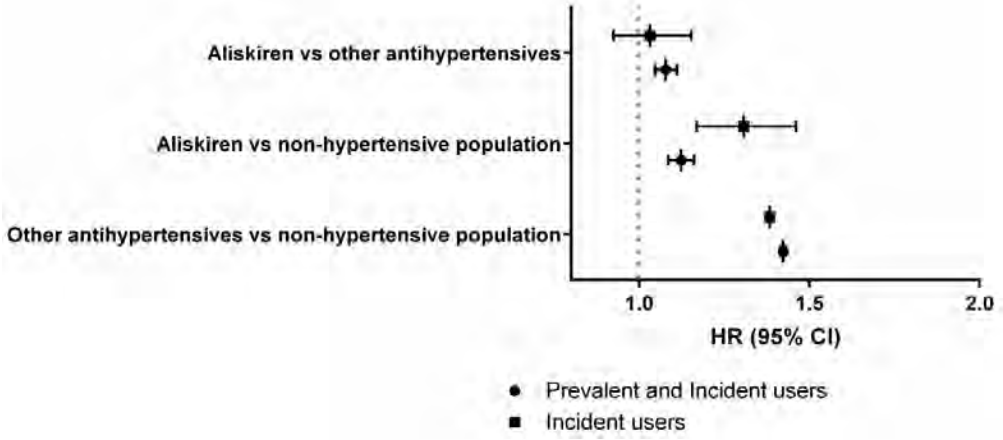
9.1.6 Relative Risk of Colorectal Hyperplasia

Table 15-11, Table 15-12, and Figure 9-7 present the relative risks (presented as HRs) of colorectal hyperplasia for all aliskiren users compared to all users of other antihypertensive therapies (Table 15-11) and incident and prevalent aliskiren users vs. incident and prevalent users of other antihypertensive therapies (Table 15-12). The overall relative risk of colorectal hyperplasia for all patients exposed to aliskiren versus all patients exposed to antihypertensive drugs other than aliskiren was 1.08 (95% CI: 1.05, 1.11). The overall relative risk of colorectal hyperplasia among incident antihypertensive therapy patients exposed to aliskiren versus incident patients exposed to antihypertensive drugs other than aliskiren was 1.03 (95% CI: 0.92, 1.15). The overall relative risk of colorectal hyperplasia among prevalent antihypertensive therapy patients exposed to aliskiren versus prevalent patients exposed to antihypertensive drugs other than aliskiren was 1.08 (95% CI: 1.04, 1.11). Factors that significantly increased the risk of colorectal hyperplasia included age, male gender, CCI score, history of H. pylori infection, irritable bowel syndrome, chronic constipation, Crohn's disease, screening by FOBT or sigmoidoscopy, and concomitant use of NSAIDs, statins, HRTs, or PPIs. Factors that significantly decreased the risk of colorectal hyperplasia included geographic region, payer type, history of stomach lymphoma, PVD, heart failure, stroke or TIA, screening by colonoscopy, and concomitant use of anti-diabetic drugs.

Compared to non-hypertensive patients, the risk of colorectal hyperplasia was statistically higher among incident aliskiren users (HR: 1.31, 95% CI: [1.17, 1.46]; Table 15-13).Factors associated with increased risk of colorectal hyperplasia include age, male gender, CCI score, history of H. pylori infection, irritable bowel syndrome, chronic diarrhea and constipation,

PVD, coronary heart disease or angina, ulcerous rectocolitis, Crohn's disease, screening by FOBT or sigmoidoscopy, and concomitant use of NSAIDs, statins, HRT, or PPI. Likewise, Incident other antihypertensive therapy users also had a higher risk of colorectal hyperplasia compared to non-hypertensive patients (HR: 1.38, 95% CI: [1.37, 1.40]; Table 15-31).

Figure 9-7 Colorectal hyperplasia adjusted Hazard Ratios



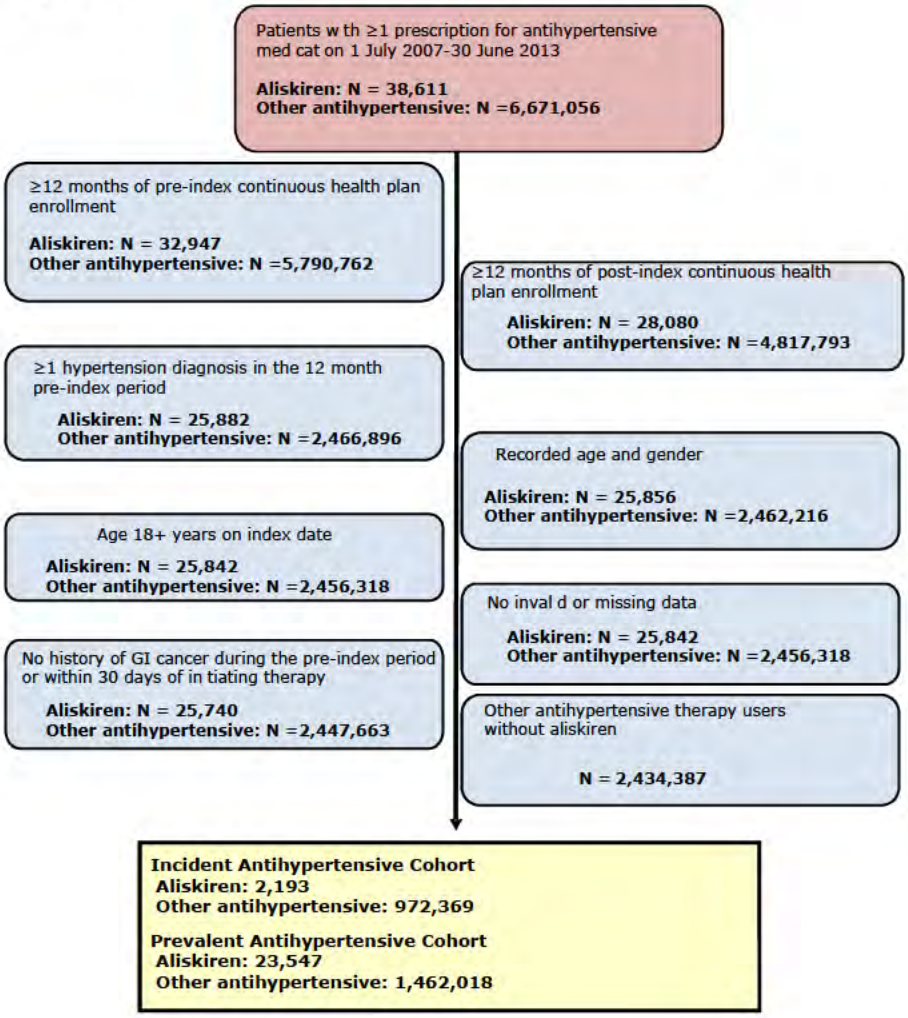
9.2 GI Cancer Cohort

9.2.1 Participants

Patients were selected for analysis into the GI cancer assessment cohort if they had evidence of a hypertension diagnosis; had ≥ 1 prescription for an antihypertensive medication within 365 days after the hypertension diagnosis date; were ≥18 years of age; had continuous health plan enrollment for ≥365 days before and after the first qualifying aliskiren/antihypertensive drug prescription; and had no prior history of GI cancer. Eligible patients were stratified into incident and prevalent antihypertensive treatment cohorts based on evidence of antihypertensive drug prescriptions in the 365 days prior to the index date.

Within the GI cancer assessment cohort, a total of 38,611 aliskiren and 6,671,056 other antihypertensive users with a diagnosis of hypertension between 1 July 2007 and 30 June 2013 and ≥1 prescription for aliskiren were initially identified in the data extract along with 12,615,141 patients with neither a hypertension diagnosis nor a prescription for an antihypertensive medication of interest between 1 July 2006 and 30 June 2014. After applying the study inclusion and exclusion criteria, 25,740 (66.7%) aliskiren patients, 2,434,387 (36.5%) other antihypertensive patients and 5,909,418 (46.8%) non-hypertensive patients were available for analysis. There were 2,193 incident aliskiren users, 972,369 incident users of other antihypertensive therapies, 23,547 prevalent aliskiren users and 1,462,018 prevalent users of other antihypertensive therapies within the GI cancer assessment cohort (Table 15-16; Figure 9-8).

Figure 9-8 Attrition of the GI Cancer Cohort



9.2.2 Demographic and Clinical Characteristics

9.2.2.1 All Patients

Within the GI cancer assessment cohort, all aliskiren patients were approximately 3 years older than all users of other antihypertensive therapies [mean age: 58.0 years (SD ±11.1) vs. 55.2 years (SD ±11.1)]. The mean age of non-hypertensive patients was younger at 39.6 (SD ±13.5) years. The majority of aliskiren and other antihypertensive therapy users were between the ages of 45-64 years; whereas the majority of non-hypertensive patients were between the ages of 18-44 years. Patients age ≥65 years comprised 24.4%, 16.7%, and 2.1% of the aliskiren, other antihypertensive therapy, and non-hypertensive patients; respectively. A

similar gender distribution as that observed with the colorectal hyperplasia assessment cohort was observed with the GI cancer assessment cohort, with the proportion of males being slightly higher among all aliskiren users compared to other antihypertensive therapy users (% male: 54.7 vs. 51.2, respectively), and females being more frequently represented (54%) among non-hypertensive patients. The majority of all patients among the GI cancer assessment cohorts were covered by a commercial PPO insurance plan (Table 15-17).

The mean CCI score of all aliskiren patients within the GI cancer assessment cohort was higher compared to that of all other antihypertensive therapy users [1.6 (SD ±1.8) vs. 0.9 (SD ±1.4)]. Accordingly, comorbid conditions were generally higher among all aliskiren users compared to users of other antihypertensive therapies as well as non-hypertensive patients. Approximately 36% of aliskiren users and 54% of users of other antihypertensive therapies had a CCI score of 0. Most non-hypertensive patients (91.1%) had a CCI score of 0, and comorbidities were present in ≤1% of patients. The most frequently observed comorbid conditions in the pre-index period in both aliskiren users and users of other antihypertensive therapies were diabetes mellitus (37.7% and 22.8%, respectively) and coronary heart disease or angina (21.2% and 13.2%, respectively). Post-index comorbidity rates were similar to those of the pre-index period. The most frequently observed screening procedure in the pre-index period in all aliskiren users and users of other antihypertensive therapies was endoscopy including gastroscopy (5.8% and 4.2%, respectively). Similarly, endoscopy including gastroscopy was the most frequently observed screening procedure in the post-index period for aliskiren (6.3%) and other antihypertensive therapy users (4.5%). As observed in the colorectal hyperplasia assessment cohort, the proportions of co-medications utilized among the GI cancer assessment cohort were greater among all aliskiren users compared to all users of other antihypertensive therapies (in both pre-index and post-index periods) and the most frequently observed co-medication in both the pre-index and post-index periods for both the aliskiren patients and users of other antihypertensive therapies was within the statin class.NSAIDs were the most commonly used medication during the pre- and post-index periods for non-hypertensive patients. The mean amount of available post-index follow-up time was slightly longer among all other antihypertensive users compared to all aliskiren users in the GI cancer assessment cohort [1,230.5 (SD ±739.1) vs. 1,092.3 (SD ±618.8) days].Mean follow-up time for non-hypertensive patients was 1016 (SD ±544.9) days. Clinical characteristics of the GI cancer assessment cohort are presented in detail in Table 15-19.

9.2.2.2 Incident Antihypertensive Therapy Users

For incident therapy users within the GI cancer assessment cohort, incident aliskiren users and incident users of other antihypertensive therapies were of similar age [mean age: 52.2 years (SD ±11.0) vs. 52.7 years (SD ±11.6)]. There was, however, a higher proportion of males observed among incident aliskiren users compared to other antihypertensive therapy users (60.0% vs. 53.4%).The majority of incident patients among the GI cancer assessment cohorts were covered by a commercial PPO insurance plan (Table 15-18).

The mean CCI score for patients within the GI cancer assessment cohort was 0.8 (SD ±1.3) for incident aliskiren users and incident users of other antihypertensive therapies. Likewise, a similar distribution of comorbid conditions was observed between the two groups. The most frequently observed comorbid condition in the pre-index period in both aliskiren users and users of other antihypertensive therapies was diabetes mellitus (21.3% and 18.6%,

respectively) followed by coronary heart disease or angina (8.9% and 10.2%, respectively). Post-index comorbidity rates were similar to that of the pre-index period. The most frequently observed screening procedure within the pre-index period in incident aliskiren users and incident users of other antihypertensive therapies was endoscopy including gastroscopy (3.6% and 3.9%, respectively). Screening procedures were observed with similar frequency during the post-index period. Proportions of co-medications utilized within the pre-index period were generally similar among incident aliskiren users and incident users of other antihypertensive therapies. The most frequently observed co-medication within the pre-index period for both the incident aliskiren users and incident users of other antihypertensive therapies was within the NSAID class (18.2% and 19.5%, respectively). The use of co-medications generally increased during the post-index period in both groups with the exception of hormone replacement therapy which remained stable. Statin medications were observed most frequently among both the incident aliskiren and incident users of other antihypertensive therapies (30.8% and 33.4%, respectively) during the post-index period. The mean amount of available post-index follow-up time was slightly longer among incident aliskiren users compared to users of other antihypertensive therapies [1,148.2 (SD ±638.3) vs. 1,032.2 (SD ±591.7 days]. Clinical characteristics of the incident samples within the GI cancer assessment cohort are presented in detail in Table 15-20.

9.2.2.3 Prevalent Antihypertensive Therapy Users

Among prevalent therapy users within the GI cancer assessment cohort, prevalent aliskiren users were about 2 years older than prevalent users of other antihypertensive therapies [mean age: 58.6 years (SD ±11.0) vs. 56.8 years (SD ±10.5)], and there was a slightly higher proportion of males observed in aliskiren users compared to other antihypertensive therapy users (54.2% vs. 49.7%).The majority of prevalent therapy users were covered by a commercial PPO insurance plan (Table 15-18).

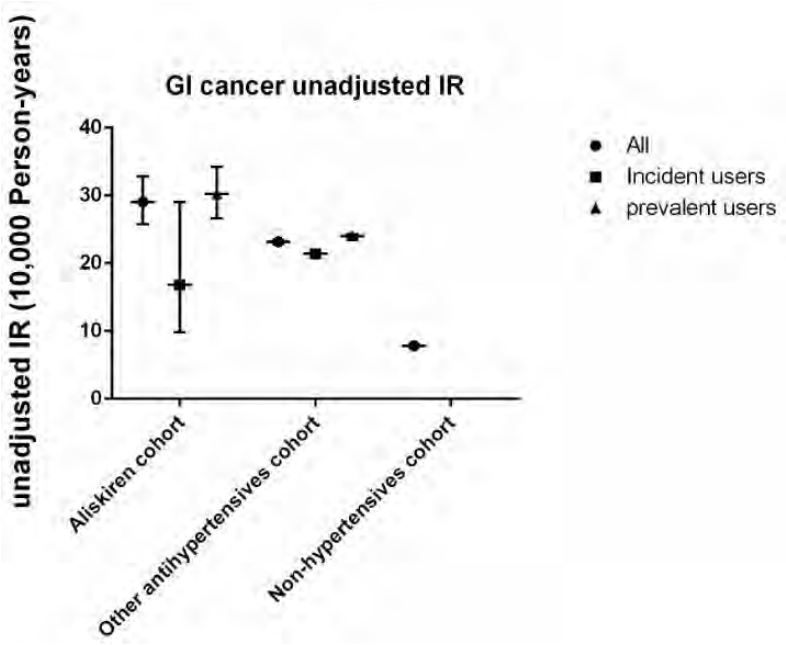
The mean CCI score among patients within the GI cancer assessment cohort was 1.6 (SD ±1.8) for prevalent users of aliskiren and 1.0 (SD ±1.4) for prevalent users of other antihypertensive therapies (33.7% of aliskiren users vs. 51.4% of other antihypertensive therapy users had a CCI score of 0). Accordingly, proportions of the most frequently observed comorbid conditions were slightly higher among prevalent aliskiren users compared to prevalent users of other antihypertensive therapies. The most frequently observed comorbid condition within the pre-index period in both aliskiren users and users of other antihypertensive therapies was diabetes mellitus (39.2% and 25.7%, respectively) followed by coronary heart disease or angina (22.4% and 15.1%, respectively). Post-index comorbidity rates were similar to those of the pre-index period. The most frequent screening procedure observed in the pre-index period was endoscopy including gastroscopy in prevalent aliskiren users (6.0%) and prevalent users of other antihypertensive therapies (4.4%). Endoscopy including gastroscopy was also the most frequently used screening procedure during the post-index period. Proportions of co-medications utilized within the pre-index period were slightly higher among prevalent aliskiren users compared to prevalent users of other antihypertensive therapies with the exception of hormone replacement therapy which was observed with slightly greater frequency in the prevalent users of other antihypertensive therapies compared to prevalent aliskiren users (6.5% vs. 5.9%). The proportion of anti-diabetic drug utilization was much greater among prevalent aliskiren users compared to users of other antihypertensive therapies (32.6% vs. 20.6%). The most frequently observed co-medication within the pre-

index period for both the prevalent aliskiren users and prevalent users of other antihypertensive therapies was within the statin drug class (43.0% and 38.3%, respectively).Within the post-index period, statin medications were again observed most frequently among both the prevalent aliskiren and prevalent users of other antihypertensive therapies (47.2% and 41.2%, respectively). Within both groups, the proportions of patients taking co-medications remained relatively stable during the post-index period. The mean amount of available post-index follow-up time was longer among prevalent users of other antihypertensive therapies compared to prevalent aliskiren [1,362.3 (SD ±795.7) vs. 1,087.1 (SD ±616.7 days]. Clinical characteristics of the prevalent samples within the GI cancer assessment cohort are presented in detail in Table 15-20.

Of note, prevalent antihypertensive therapy users were not required to be new to index therapy during the selection process, thus patients may have had prescriptions for the index therapy during the pre-index period. An exploratory assessment of pre-index aliskiren use revealed that 990 (4.20%) prevalent aliskiren users received aliskiren during the pre-index period.

9.2.3 Incidence Rates – by Demographic, Clinical, and Lifestyle Factors

Figure 9-9 GI cancer unadjusted Incident Rates



9.2.3.1 All Aliskiren Users

Table 15-22 and Figure 9-9 present unadjusted IRs per 10,000 PYs of GI cancer among all aliskiren users by demographic, clinical, and lifestyle factors. The overall IR of GI cancer per 10,000 PYs for aliskiren users was 29.0 (95% CI: [25.7, 32.8]). IRs increased with increasing age. The IR of GI cancer was greatest in males ≥65 years of age (IR= 48.1, 95% CI: [35.4, 65.3]).

For the comorbid conditions and lifestyle factors assessment, IRs of GI cancer for aliskiren users were generally based on relatively few patients/events yielding low rates with wide confidence intervals. Exceptions included the comorbid condition diabetes (IR=37.0, 95% CI: [30.9, 44.2]) and the lifestyle factor obesity (IR = 27.0, 95% CI: [18.4, 39.6]). Concomitant use of PPIs or statins was not a factor in the occurrence of GI cancer (IRs of GI cancer for those who used PPIs or statins were similar to the overall IR for all aliskiren users).

9.2.3.2 Incident Aliskiren Users

Table 15-23 and Figure 9-8 present unadjusted IRs per 10,000 PYs of GI cancer among incident aliskiren users based on demographic, clinical, and lifestyle factors. The overall IR of GI cancer was 16.8 (95% CI: [9.8, 29.0]) for incident aliskiren users. Overall, IRs of GI cancer for incident aliskiren users were based on few patients and events (in total, 13 events were observed in 2,193 incident aliskiren users) yielding low rates with wide confidence intervals. Thus, caution is advised when interpreting sub-group IRs based on demographic, clinical, and lifestyle factors.

9.2.3.3 Prevalent Aliskiren Users

Table 15-23 presents unadjusted IRs per 10,000 PYs of GI cancer among prevalent aliskiren users stratified by demographic, clinical, and lifestyle factors. The overall IR of GI cancer per 10,000 PYs for prevalent aliskiren users was 30.2 (95% CI: [26.6, 34.2]). The IR of GI cancer among prevalent aliskiren users was highest amongst males aged ≥65 years (IR = 47.4, 95% CI: [34.7, 64.9]). When examined by comorbid conditions, only diabetes had ample patient counts to produce interpretable IRs (IR = 37.5, 95% CI: [31.3, 45.0]). When evaluated by co-medication strata, IRs for PPI and statin users were similar to the overall IR for prevalent aliskiren users. The IR of GI cancer for patients with a diagnosis of obesity was also similar to the overall IR for prevalent aliskiren users.

9.2.3.4 All Other Antihypertensive Therapy Users

Table 15-22 and Figure 9-9 present unadjusted IRs per 10,000 PYs of GI cancer among all users of antihypertensive therapies other than aliskiren, stratified by demographic, clinical, and lifestyle factors. The overall IR of GI cancer per 10,000 PYs for other antihypertensive therapy users was 23.1 (95% CI: [22.8, 23.4]). The IR of GI cancer among all other antihypertensive therapy users was higher in males than females and increased as age increased. The highest IR of GI cancer was observed in male patients aged ≥65 years (IR= 45.3, 95% CI: [43.7, 46.9]).

When IRs were evaluated by comorbid conditions, each of the comorbid conditions of interest was associated with an IR of GI cancer higher than the overall IR. Stomach polyps were associated with the highest IR of GI cancer among all comorbidities (IR = 53.3, 95% CI: [46.7, 60.8]). When concomitant medications were taken into account, PPI and statin use was associated with increased incidence of GI cancer (IR = 31.1, 95% CI: [30.0, 32.2]) and 24.5, 95% CI: [23.9, 25.2], respectively) whereas the use of hormone replacement therapy was associated with a lower incidence of GI cancer (IR = 20.4, 95% CI: [18.8, 22.1]) compared to the overall IR for all other antihypertensive therapy users. Alcohol dependence was also associated with a higher IR of GI cancer when compared to the overall IR (IR =31.1, 95% CI: [26.7, 36.2]).

9.2.3.5 Incident Other Antihypertensive Therapy Users

Table 15-23 and Figure 9-9 present unadjusted IRs per 10,000 PYs of GI cancer among incident other antihypertensive therapy users stratified by demographic, clinical, and lifestyle factors. The overall IR of GI cancer for incident other antihypertensive therapy users was 21.4 (95% CI: [20.9, 21.9]). IRs were generally higher for patients ≥65 years of age, and were highest in males aged ≥ 65 years (IR = 45.1, 95% CI: [42.0, 48.5]).

When IRs were evaluated by comorbid conditions, each of the comorbid conditions of interest was associated with an IR of GI cancer higher than the overall IR. Stomach polyps were associated with the highest IR of GI cancer among all comorbidities (IR = 57.8, 95% CI: [45.7, 73.0]). When concomitant medications were taken into account, the use of PPIs was associated with an increased incidence of GI cancer (IR = 29.9, 95% CI: [27.9, 32.0]) compared to the overall IR for all incident other antihypertensive therapy users. Alcohol dependence was also associated with a higher IR of GI cancer when compared to the overall IR (IR =31.2, 95% CI: [24.8, 39.4]).

9.2.3.6 Prevalent Other Antihypertensive Therapy Users

Table 15-23 presents unadjusted IRs per 10,000 PYs of GI cancer among prevalent other antihypertensive therapy users stratified by demographic, clinical, and lifestyle factors. The overall IR of GI cancer per 10,000 PYs for prevalent users of other anti-hypertensive therapies was 24.0 (95% CI: [23.6, 24.3]). When looking at age and gender overall, IRs of GI cancer increased as age increased and were higher in males than females. The IR of GI cancer was highest in males ≥65 years of age (IR = 45.3, 95% CI: [43.5, 47.3]).

When examined by comorbid conditions, each of the comorbid conditions of interest was associated with an IR of GI cancer higher than the overall IR. Stomach polyps were associated with the highest IR of GI cancer among all comorbidities (IR = 51.4, 95% CI: [43.8, 60.4]). With regards to co-medications, IRs of GI cancer were higher in prevalent other antihypertensive therapy users with concomitant use of PPIs (IR = 31.5, 95% CI: [30.3, 32.8]) and statins (IR = 25.3, 65% CI: [24.5, 26.1]), but lower in those with concomitant use of hormone replacement therapy (IR = 20.2, 95% CI: [18.5, 22.1]) compared to the overall IR. Alcohol dependence syndrome was associated with an increased incidence of GI cancer compared to the overall IR for all prevalent other antihypertensive therapy users (IR = 31.0, 95% CI: [25.2, 38.0]).

9.2.3.7 Non-hypertensive Patients

Table 15-22 and Figure 9-9 present unadjusted IRs per 10,000 PYs of GI cancer among non-hypertensive patients stratified by demographic, clinical, and lifestyle factors. The overall IR of GI cancer per 10,000 PYs for non-hypertensive patients was 7.8 (95% CI: [7.7, 7.9]). In non-hypertensive patients, the IR of GI cancer was higher in females (IR = 8.3, 95% CI: [8.1, 8.5]) than males (IR = 7.2, 95% CI: [7.0, 7.4]) and increased with increasing age.

With respect to comorbid conditions, each of the comorbid conditions of interest was associated with an IR of GI cancer higher than the overall IR for non-hypertensive patients. Stomach polyps were associated with the highest IR of GI cancer among all comorbidities (IR = 29.0, 95% CI: [22.7, 37.0]). When medications were taken into account, use of PPIs (IR = 17.3, 95% CI: [15.8, 18.9], statins (IR = 15.1, 95% CI: [13.7, 16.6]), and hormone

replacement therapies (IR= 13.8, 95% CI: [12.1, 15.8]) were associated with an increased incidence of GI cancer compared to the overall IR for non-hypertensive patients. When compared to the overall IR, obesity was associated with a higher IR of GI cancer for non-hypertensive patients (IR = 9.4, 95% CI: [8.3, 10.6]). Incidence Rates – by Index Therapy

9.2.3.8 All Antihypertensive Therapy Users

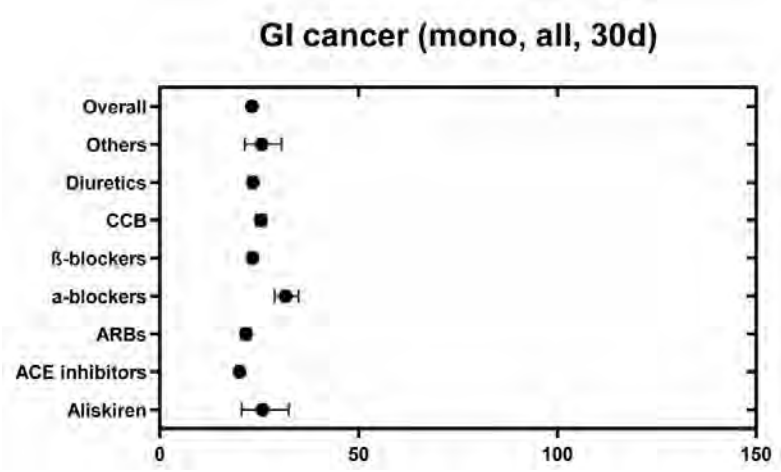
Like the colorectal hyperplasia cohort, monotherapy was the most frequently observed treatment classification among all patients in the GI cancer cohort (54%) (Table 15-21). Overall, ~1% of patients were prescribed a regimen which included aliskiren. Aliskiren patients made up 0.3% of monotherapy, 0.2% of dual-combination, and 0.5% of triple-plus combination regimens. The most frequently observed mono-, dual- and triple- plus combination therapies were ACEI therapy (17%), dual combination therapy including neither an ACEI nor aliskiren (16.8%), and triple-plus combination therapy including an ACEI but not aliskiren (7.6%), respectively. The mean duration of exposure to the index therapy was 522 (SD ± 592) days.

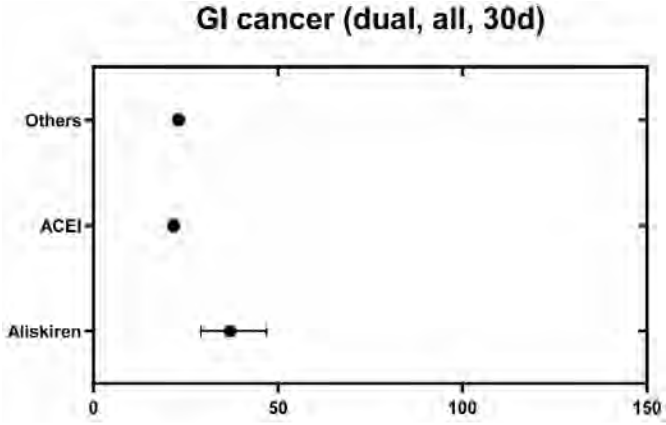
Table 15-24 and Figure 9-10 present unadjusted IRs per 10,000 PYs of GI cancer among all treated patients based on antihypertensive drug use within 30 days after the index date (i.e., index therapy). The overall IR of GI cancer for all treated patients was 23.2 (95% CI: [22.9, 23.5]). The IR per 10,000 PYs of GI cancer among aliskiren monotherapy users was 25.8 (95% CI: [20.6, 32.4]), and was similar to all other monotherapy regimens. Compared to the overall IR, the IR of GI cancer among monotherapy users was lower for those prescribed ACEIs and higher among alpha blocker and calcium channel blocker users.

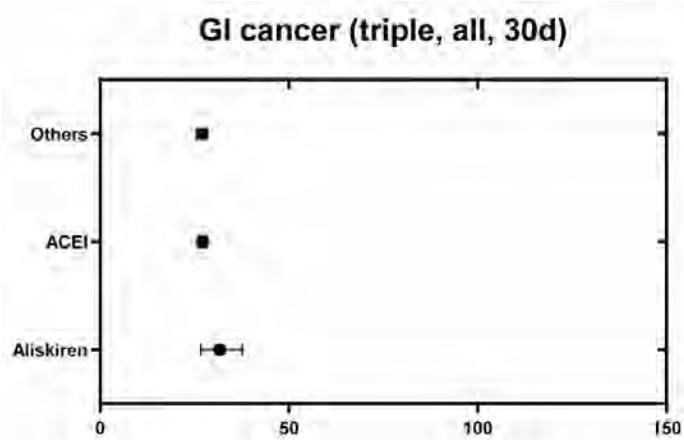
When evaluating the incidence of GI cancer by index therapy in dual-combination therapy users, the highest IR was observed in patients prescribed a dual combination therapy including aliskiren (IR = 37.0, 95% CI: [29.1, 46.9]). Compared to the overall IR, the incidence of GI cancer was higher among patients prescribe dual combination regimens that include aliskiren and lower for dual combination regimens that include an ACEI but not aliskiren.

IRs of GI cancer were similar among triple-plus combination therapy users (IR for triple-plus combination regimen including aliskiren = 31.7, 95% CI: [26.7, 37.6]). Each triple-plus combination regimen was associated with an IR of GI cancer greater than the overall IR for all treated patients. In general, IRs of GI cancer stratified by index therapy were higher among males and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

Figure 9-10 GI cancer unadjusted Incident Rates mono, dual and triple combination







9.2.3.9 Incident Antihypertensive Therapy Users

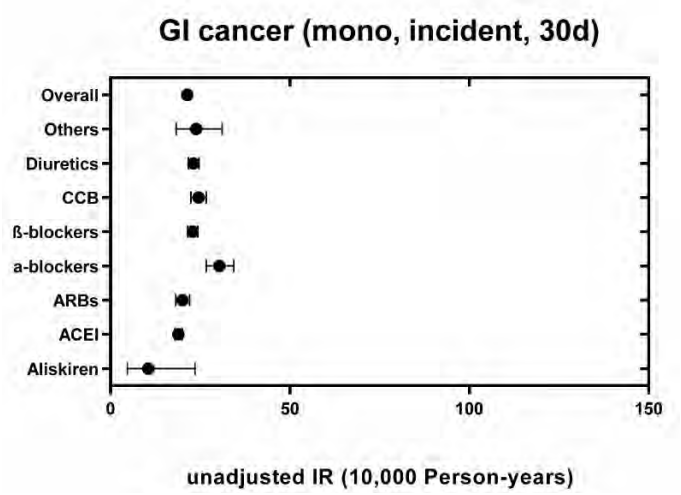
Incident GI cancer assessment cohorts were more likely to receive monotherapy compared to other therapies (approximately 67.5%) and the most frequently observed monotherapy was ACEI (23.2%). Overall, <1% of incident therapy users used an aliskiren-containing regimen. The most frequently observed regimens outside of the monotherapy classification were dual combination including an ACEI but not aliskiren (13.6%) and dual-combination including neither an ACEI nor aliskiren (11.8%). Triple-plus combination therapy was only observed in 7% of patients. The mean duration of exposure to the index therapy was 353(SD ±431) days.

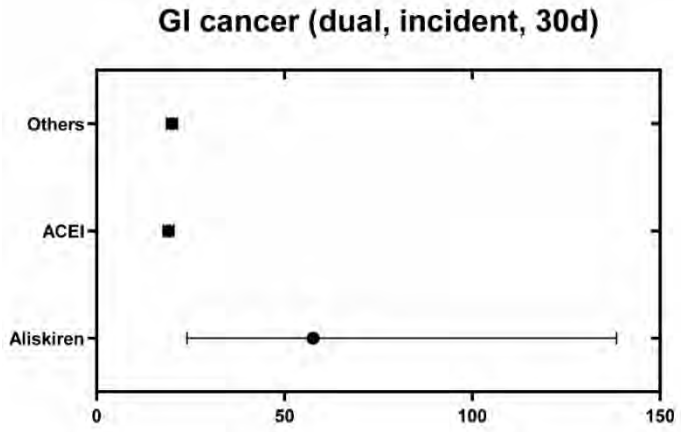
Table 15-24, Figure 9-10 and Figure 9-11 present unadjusted IRs per 10,000 PYs of GI cancer among incident antihypertensive therapy users based on antihypertensive drug use within 30 days after the index date (index therapy). The overall IR of GI cancer for incident therapy users was 21.4 (95% CI: [20.9, 21.9]). For incident aliskiren monotherapy users, the IR per 10,000 PYs of GI cancer was 10.5 (95% CI: [4.7, 23.5]), and was similar to all other monotherapies except alpha blockers, which were associated with the highest IR of GI cancer among monotherapy users (IR = 30.3, 95% CI: [26.7, 34.4]). Monotherapy ACEI users had a lower incidence of GI cancer compared to the overall IR for all incident therapy users, whereas patients who used alpha blockers or calcium channel blockers had a higher incidence of GI cancer.

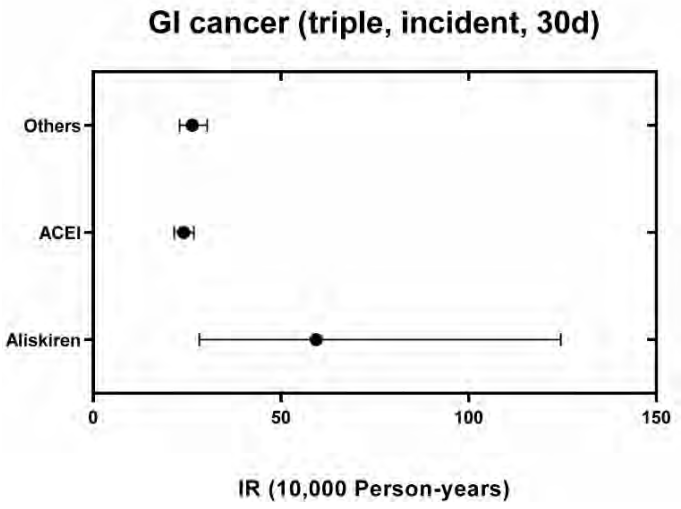
When evaluating the incidence of GI cancer by antihypertensive drug use within 30 days after index in dual-combination therapy users, the highest IRs were observed in patients taking a dual combination therapy including aliskiren (IR = 57.6, 95% CI: [24.0,138.4]); however, this was based on a few events among a small sample of patients (i.e., 5 events among 253 patients). Compared to the overall IR for all incident therapy users, patients prescribed a dual combination regimen that included an ACEI but not aliskiren had a lower incidence of GI cancer.

Within the triple-plus combination therapy users, IR of GI cancer was highest among patients taking a triple-plus combination therapy that included aliskiren (IR = 59.4, 95% CI: [28.3, 124.6]) and lowest among triple-plus combination therapy including an ACEI but not aliskiren (IR = 24.1, 95% CI: [21.6, 26.8]). The IR of GI cancer was higher in patients prescribed a triple-plus combination regimen that included neither an ACEI nor aliskiren compared to the overall IR for all incident therapy users. Within each treatment classification (mono-, dual-, and triple-plus regimens), IRs of GI cancer for aliskiren-containing regimens were based on a few patients and events yielding wide confidence intervals, which should be taken into consideration when interpreting these results.

Figure 9-11 GI cancer unadjusted Incident Rates mono, dual and triple combination (incident users)







9.2.3.10 Prevalent Antihypertensive Therapy Users

Prevalent patients within the GI cancer cohort received monotherapy more frequently (45.2%) compared to dual (37%) and triple-plus combination (17.8%) therapies. The mean duration of exposure to the index therapy in prevalent patients was 632 (SD ± 654) days. Table 15-24 presents unadjusted IRs per 10,000 PYs of GI cancer among prevalent patients based on antihypertensive drug use within 30 days after the index date (index therapy). The overall IR of GI cancer for prevalent therapy users was 24.0 (95% CI: [23.7, 24.4]). For prevalent aliskiren monotherapy users, the IR per 10,000 PYs of GI cancer was 29.6 (95% CI: [23.3, 37.5]), and was similar to IR of GI cancer for all other monotherapy regimens except ACEI's which were associated with a lower IR of GI cancer (IR = 20.8, 95% CI: [19.9, 21.8]). Compared to the overall IR of GI cancer for all prevalent treated patients, monotherapy users of ACEIs had a lower incidence of GI cancer while the incidence of GI cancer was higher in patients prescribed alpha blockers.

When evaluating the incidence of GI cancer by index therapy in dual-combination therapy users among prevalent therapy users, the highest IR of GI cancer (compared to all dual-combination therapy users and the overall prevalent therapy population) was observed in patients prescribed a dual combination therapy including aliskiren (IR = 35.9, 95% CI: [28.1, 46.0]). IRs were similar among prevalent patients taking dual combinations including an ACEI but not aliskiren and those including neither an ACEI nor aliskiren.

Within the triple-plus combination therapy users, IRs of GI cancer were similar among the three groups examined (i.e., triple-plus combination including aliskiren, triple-plus combination including an ACEI but not aliskiren and triple-plus combination including neither an ACEI nor aliskiren). These groups all had a higher incidence of GI cancer compared to the overall prevalent therapy user population. IRs of GI cancer based on index therapy were generally higher among males and generally increased as age increased in each stratum and for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations); however, some IRs within these strata were frequently based on relatively few patients/events yielding low rates with wide confidence intervals. As such, these data should be interpreted with caution.

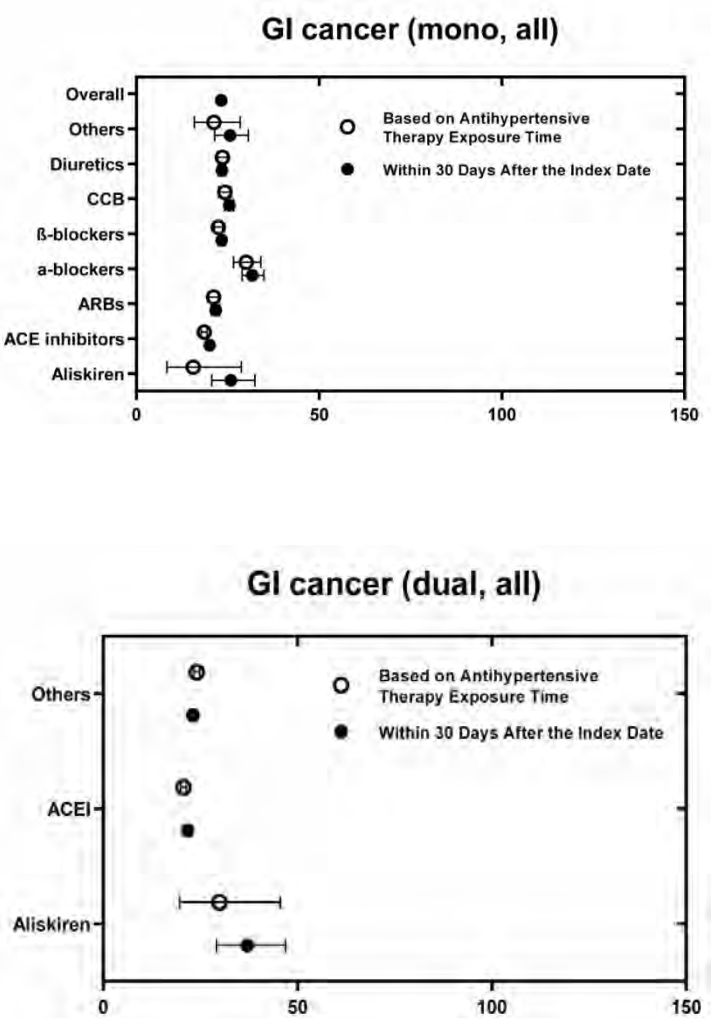
9.2.4 Incidence Rates – by Exposure Time

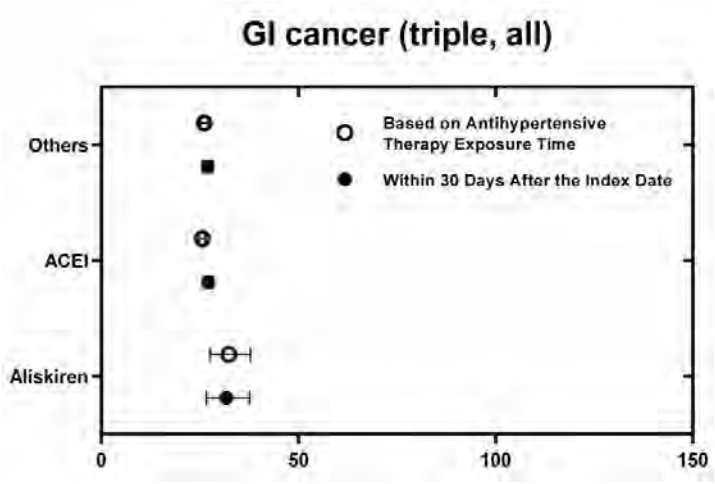
9.2.4.1 All Antihypertensive Therapy Users

Table 15-25 and Figure 9-12 present unadjusted IRs per 10,000 PYs of GI cancer based on all patients' (i.e., incident and prevalent patients combined) exposure time to antihypertensive therapy. The IR of GI cancer for all aliskiren monotherapy users was 15.5 (95% CI: [8.3, 28.7]), and was similar to all other monotherapy regimens. The observation of a few events among a small sample of aliskiren monotherapy users (there were 10 events among 2007 patients), and the resulting wide confidence intervals should be taken into consideration when interpreting this finding. Within the dual-combination therapy initiator group, the IR of GI cancer among patients that were prescribed regimens that included aliskiren (29.9, 95% CI: [19.7, 45.5]) was similar to the other dual-combination regimen; however, the wide confidence interval for the aliskiren-containing regimen should be considered. Within the triple-plus combination therapy initiator group, the IR of GI cancer was highest among patients prescribed a regimen that included aliskiren (IR = 32.3, 95% CI: [27.6, 37.8]) and

lowest among patients prescribed a triple-plus combination regimen with an ACEI but not aliskiren (IR = 25.6, 95% CI: [24.8, 26.3]). In general, IRs of GI cancer based on patients' exposure time to antihypertensive therapy were higher among males and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations); however, these IRs were frequently based on relatively few patients/events yielding low rates with wide confidence intervals. As such, these data should be interpreted with caution.

Figure 9-12 GI cancer unadjusted Incident Rates based on therapy exposure time and after the index date

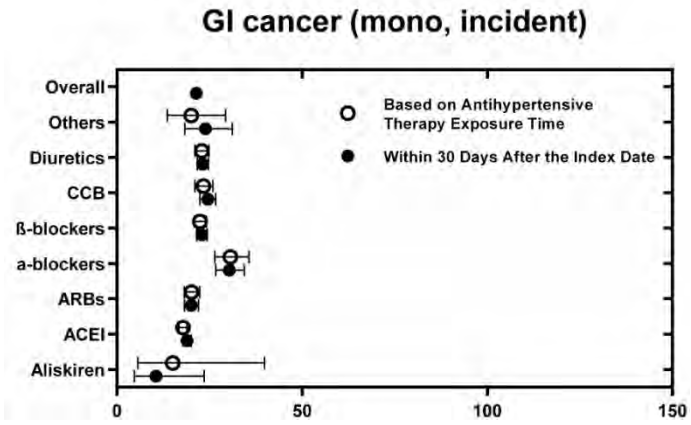


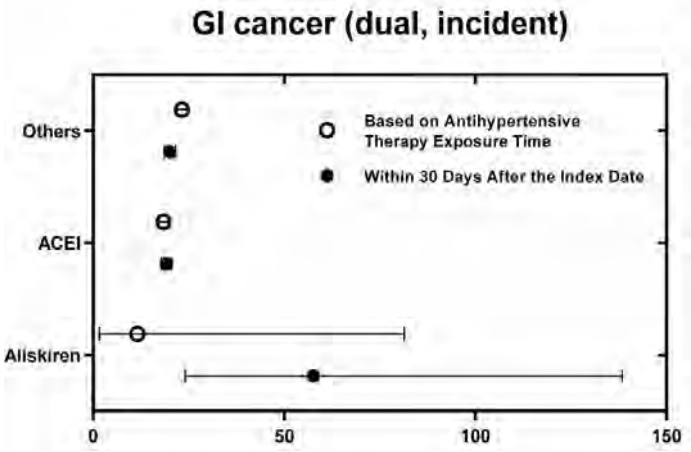


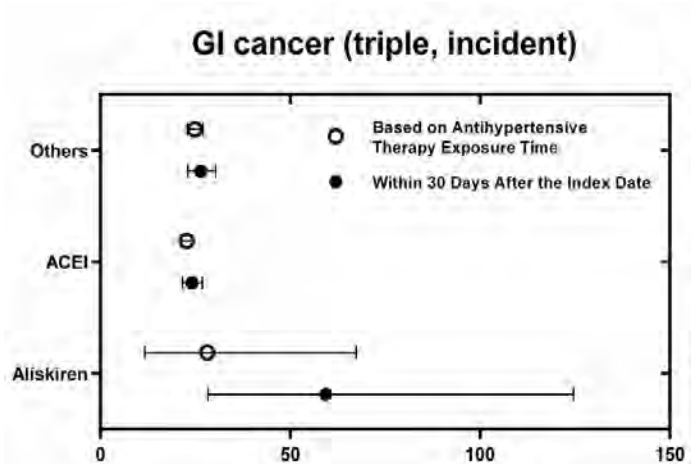
9.2.4.2 Incident Therapy Users

Table 15-25 and Figure 9-13 present unadjusted IRs per 10,000 PYs of GI cancer based on incident patients' exposure time to antihypertensive therapy. The IR of GI cancer among incident aliskiren monotherapy users was 15.0 (95% CI: [5.6 - 39.8], and was similar to all other monotherapy regimens. This should be interpreted in the context of the wide confidence interval that resulted from few patients/events (there were 4 events among 820 patients). Within the dual combination therapy initiator group, only 1 event was observed in patients prescribed a dual combination regimen that included aliskiren (IR = 11.5, 95% CI: [1.6, 81.4]). IRs of GI cancer among the other incident dual-combination regimens were 23.2 (95% CI: [21.9, 24.7]) for regimens that included neither an ACEI nor aliskiren (IR = and 18.4 (95% CI: [17.2, 19.6]) for dual combinations including an ACEI but not aliskiren. Likewise, within the triple-plus combination therapy initiator group, the IR of GI cancer for combinations including aliskiren was based on a few patients/events (IR = 28.1, 95% CI: [11.7, 67.4]), and any comparisons with the other triple-plus combination regimens should be interpreted with this in mind. In general, IRs for incident patients' exposure time to antihypertensive therapy were higher among males and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations).

Figure 9-13 GI cancer unadjusted Incident Rates based on therapy exposure time and after the index date (incident use)







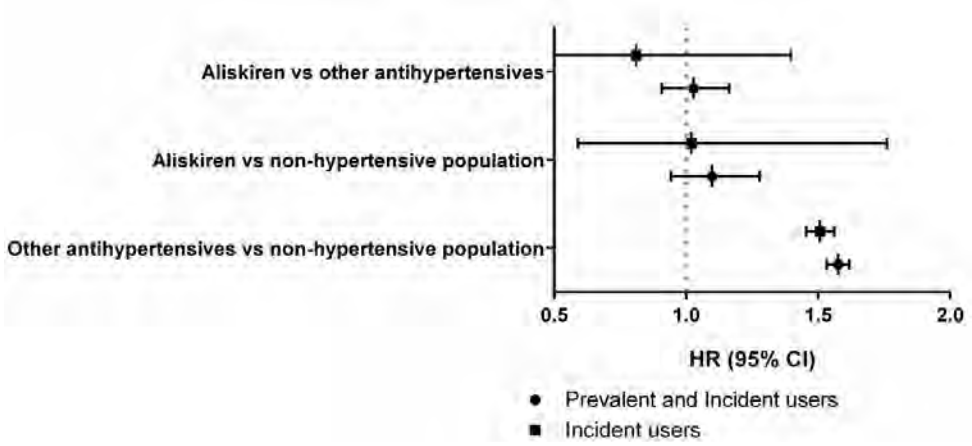
9.2.4.3 Prevalent Antihypertensive Therapy Users

Table 15-25 presents unadjusted IRs per 10,000 PYs of GI cancer based on prevalent patients' exposure time to antihypertensive therapy. The IR of GI cancer among prevalent users of aliskiren monotherapy was 15.8 (95% CI: [7.1, 35.2]). This estimate was based on 6 events among 1,187 patients, yielding a wide confidence interval which overlapped with the confidence intervals for the IR estimates for all other monotherapy regimens. Within the dual combination therapy initiator group, IRs of GI cancer were similar across all regimens: regimens that included aliskiren: IR = 32.4 (95% CI: [21.1, 49.7]), regimens that included an ACEI but not aliskiren: IR = 21.7 (95% CI: [20.8, 22.6]), and regimens that included neither an ACEI nor aliskiren: IR = 24.3 (95% CI: [23.4, 25.2]). Within the triple-plus combination therapy initiator group, the IR of GI cancer was highest among prevalent patients prescribed a regimen that included aliskiren (IR = 32.5, 95% CI: [27.7, 38.1]). Overall, IRs of GI cancer based on prevalent patients' exposure time to antihypertensive therapy were higher among males compared to females and increased with age for all types of antihypertensive users (i.e., monotherapy, dual and triple-plus combinations). However, as with other IRs of GI cancer, these IRs were frequently based on relatively few patients/events yielding low rates with wide confidence intervals. As such, these data should be interpreted with caution.

9.2.5 Relative Risk of GI Cancer

Table 15-26, Table 15-27, and Figure 9-14 present the relative risks (presented as hazard ratio [HR]) of GI cancer for all aliskiren users compared to all users of other antihypertensive therapies (Table 15-26) and incident and prevalent aliskiren users vs. incident and prevalent users of other antihypertensive therapies (Table 15-27). The overall relative risk of GI cancer for all patients exposed to aliskiren versus all patients exposed to antihypertensive drugs other than aliskiren was 1.03 (95% CI: 0.91, 1.16). The overall relative risk of GI cancer among incident antihypertensive therapy patients exposed to aliskiren versus incident patients exposed to antihypertensive drugs other than aliskiren was 0.81 (95% CI: 0.47, 1.40). The overall relative risk of GI cancer among prevalent antihypertensive therapy patients exposed to aliskiren versus prevalent patients exposed to antihypertensive drugs other than aliskiren was 1.05 (95% CI: 0.93, 1.20). Compared to non-hypertensive patients, the risk of GI cancer was similar among incident aliskiren users (HR: 1.02, 95% CI: [0.59, 1.76]; Table 15-28). Conversely, incident other antihypertensive therapy users had a significantly greater risk of GI cancer compared to non-hypertensive patients (HR: 1.51, 95% CI: [1.46, 1.56]; Table 15-32).

Figure 9-14 GI cancer adjusted Hazard Ratios



9.3 Other analyses

Table 15-14 presents incidence rates (Per 10,000 Person-years) of colorectal hyperplasia in patients with a pre-diagnosis screening procedure and a post-index diagnosis vs. with a post-index diagnosis alone. Within each cohort (i.e., aliskiren treated, other antihypertensive therapy treated, and non-hypertensive patients), IRs of colorectal hyperplasia were substantially higher in patients who had a screening test prior to diagnosis (IR range across cohorts: 142.0 – 477.0) compared to those with only an ICD-9-CM diagnosis of colorectal hyperplasia (IR range across cohorts: 26.3 – 144.7). In the GI cancer assessment cohort, IRs of GI cancer were lower among patients with a pre-diagnosis screening procedure and a post-index GI cancer diagnosis (range across cohorts: 0.9-7.6) compared to patients with a post-index diagnosis alone (range across cohorts: 6.9 - 21.4; Table 15-29).

Table 15-15 and Table 15-30 display the cross-tabulations of having a screening test performed prior to diagnosis versus having a colorectal hyperplasia (Table 15-15) or GI cancer (Table 15-30) post-index diagnosis alone. In most cases, there was a significant relationship between having a screening test performed prior to diagnosis and diagnosis status (yes/no). The majority of patients without an observed event also did not have a recorded screening procedure, and ≤25% of patients with an event had a screening procedure recorded.

9.4 Adverse events and adverse reactions

Adverse events were not assessed in this study. Due to the nature of the study design (i.e., retrospective cohort study of aggregated health care records), it was not feasible to make a causality assessment of adverse events and adverse reactions at the individual case level.

10 Discussion

10.1 Key results

The primary objective of this study was to determine age- and sex-stratified incidence rates of colorectal hyperplasia in three mutually exclusive patient cohorts (i.e., adult hypertensive

patients exposed to aliskiren, adult hypertensive patients exposed to antihypertensive drugs other than aliskiren, and a sample of patients without a diagnosis of hypertension and without antihypertensive use). In addition, age- and sex-stratified incidence rates of GI cancer in hypertensive patients exposed to aliskiren as well as in the two additional groups (i.e. hypertensive patients exposed to antihypertensive drugs other than aliskiren and the non-hypertensive sample) were estimated.

10.1.1 Colorectal Hyperplasia

Overall unadjusted IRs stratified by demographic, clinical, and lifestyle factors ranged from 168.3 (95% CI: [167.7, 169.0]) in the non-antihypertensive sample to 636.5 (95% CI: [617.5, 656.0]) in prevalent users of aliskiren. Overall unadjusted IRs stratified by index therapy ranged from 470.5 (95% CI: [467.9, 473.1]) among incident users of antihypertensive therapies to 540.9 (95% CI: [538.9, 542.9]) among prevalent antihypertensive therapy users. The overall unadjusted IRs stratified by antihypertensive therapy exposure time ranged from 501.3 (95% CI: [418.2, 600.9]) in the incident antihypertensive treatment cohort to 524.6 (95% CI: [451.2, 610.0]) in the prevalent antihypertensive treatment cohort.

There were several trends worth noting among the three cohorts (i.e., aliskiren users, users of other antihypertensive therapies and the non-hypertensive sample). In particular, IRs increased with increasing age in all three groups. As age is a known risk factor for colorectal cancer, this finding is not unexpected. Compared to females, higher IRs of colorectal hyperplasia were observed in males in both of the treated groups (i.e. aliskiren and other antihypertensive therapy users); however, there were no gender differences in IR of colorectal hyperplasia among non-hypertensive patients, as suggested by the overlapping CIs. The observation of higher IRs of colorectal hyperplasia in men compared to women coincides with what has been published by The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), which reported age-adjusted IRs of colorectal cancer as 48.9 cases per 100,000 in men vs. 37.1 cases per 100,000 in women (SEER Cancer Statistics Factsheets) but additional literature is sparse.As such, further research is warranted to substantiate the gender differences observed in the current study. Compared to the overall IRs within each group, IRs associated with diabetes, ulcerative colitis/rectocolitis and familial adenomatous polyps/hereditary nonpolyposis were higher within the aliskiren users, users of other antihypertensive therapies and within the non-hypertensive sample. These findings are consistent with the existing literature as all three conditions represent putative risk factors for the development of colorectal cancer (Haggar & Boushey 2009, Levi et al. 2002).

When unadjusted IRs were stratified by index therapy, several trends were observed. When compared to the overall IRs, the incident antihypertensive therapy users and the prevalent antihypertensive therapy users who were prescribed monotherapy alpha blockers were consistently observed to have higher IRs of colorectal hyperplasia whereas patients taking monotherapy beta blockers and other monotherapies (defined as vasodilators, selective aldosterone receptors, and centrally acting alpha agonists) were consistently observed as having lower IRs of colorectal hyperplasia. Among dual combination therapy users, those prescribed a regimen that included an ACEI but not aliskiren were consistently observed as having lower IRs of colorectal hyperplasia. Other researchers have reported decreased rates of cancer in conjunction with the use of beta blockers (e.g., Coope & Warrender 1986) though others still have reported conflicting results (e.g., Jansen et al 2012).To our knowledge, this is

the first study to report IRs of colorectal hyperplasia stratified by all antihypertensive drug classes; additional research to add to the existing evidence base is needed.

A secondary objective of the study was to assess the relative risk of colorectal hyperplasia in hypertensive patients exposed to aliskiren versus hypertensive patients exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use. The results from the Cox models revealed an increased risk of colorectal hyperplasia in other antihypertensive therapy users compared to the non-hypertensive sample, an increased risk of colorectal hyperplasia in patients using aliskiren compared to the non-hypertensive sample and a slight increase in the risk of colorectal hyperplasia in aliskiren users compared to users of antihypertensives other than aliskiren. As seen in the unadjusted results, factors significantly affecting the relative risk of colorectal hyperplasia included older age, male gender and the presence of diabetes, ulcerative colitis/rectocolitis, and familial adenomatous polyps/hereditary nonpolyposis. Relative risk models were adjusted for a number of demographic and clinical characteristics including age, gender, CCI score, and a priori variables of interest such as comorbidities (e.g., Crohn's Disease), screening procedures (e.g., FOBT) and co-medications (e.g., proton pump inhibitors) but it was not possible to control for every potential confounder. The non-hypertensive sample was generally younger with an age structure different than that of the antihypertensive therapy patients. For example, 62.5% of the non-hypertensive sample was between the ages of 18 and 44 compared to 17.0% and 11.5% in the other antihypertensive users and users of aliskiren, respectively. The non-hypertensive therapy sample also had fewer comorbid conditions with 91.3% of the sample falling within the CCI score of 0 category compared to 54.8% and 36.8% in the other antihypertensive users and users of aliskiren, respectively. Furthermore, comedications of interest were observed with less frequency in the non-antihypertensive sample compared to the antihypertensive patient samples. These differences may have contributed to the observed findings. Differences in age, comorbidities and comedications were greater between aliskiren users and users of other antihypertensive therapies and even greater still between the aliskiren patients and the non-antihypertensive therapy sample. Age, CCI score and comedications of interest were adjusted for in the regression models but it is important to bear these differences in mind when interpreting the findings as other underlying/unmeasured variables (including hypertension itself) related to these differences may increase the risk of colorectal hyperplasia.

The findings of increased relative risks of colorectal hyperplasia in patients exposed to antihypertensive therapies (i.e., the sample of aliskiren users and the sample of patients treated with antihypertensive therapies other than aliskiren) compared to patients within the non-hypertensive sample may be due to the fact that the non-hypertensive group was free from antihypertensive exposure, free from hypertension itself, relatively younger and healthier (i.e., with fewer comorbidities), or due to some combination of overt and underlying factors. The slight increase in the risk of colorectal hyperplasia in aliskiren users compared to users of antihypertensives other than aliskiren may have been due to the higher rate of comorbidities observed in aliskiren users, which have been shown to be a factor in the development of colorectal cancer (Singh S et al. 2014). Additionally, there were several comorbid conditions found in the present study that have been implicated in an increased incidence of colorectal cancer in other studies. These included ulcerative colitis/rectocolitis, Crohn's disease, and familial adenomatous polyps/hereditary nonpolyposis (e.g.,Haggar & Boushey 2009). Other

explanations of the observed difference in the relative risk of colorectal hyperplasia between aliskiren users and users of other antihypertensive therapies may be related to differences in age and other clinical factors. That is, aliskiren users were older, in poorer overall health (i.e., aliskiren users had more comorbid conditions compared to users of other antihypertensive therapies) and used more concomitant medications. The extent to which these factors affect the relative risk of colorectal hyperplasia should be the focus of subsequent research.

Within the aliskiren users and the users of antihypertensive therapies other than aliskiren a trend was noted where the highest IRs were observed among the prevalent users and the lowest IRs were seen within the incident user groups. This finding may be explained at least in part by the fact that the incident users, by definition, had no exposure to antihypertensive therapies during the 365 days before the index date potentially lowering the IRs of and relative risks for colorectal hyperplasia. Additionally, in general, incident patients were younger and healthier (i.e., with fewer comorbid conditions) compared to prevalent patients which may have contributed to the observed results.

To validate the use of ICD-9-CM diagnoses as a measure of colorectal hyperplasia, we checked patients' records for the occurrence of a screening procedure prior to diagnosis. Our evaluation revealed that only a small proportion of patients had a record of having a screening procedure, which suggests that including only patients with a screening procedure and ICD-9-CM diagnosis may lead to false assumptions by excluding patients with colorectal hyperplasia that did not have a screening test. As such, we are confident that relying on ICD-9-CM diagnosis alone to estimate incidence rates of colorectal hyperplasia was an acceptable approach.

10.1.2 GI Cancer

Within the GI cancer assessment cohort, overall unadjusted IRs per 10,000 PYs stratified by demographic, clinical, and lifestyle factors ranged from 7.8 (95% CI: [7.7, 7.9]) in the non-antihypertensive sample to 30.2 (95% CI: [26.6, 34.2]) in prevalent users of aliskiren. Overall unadjusted IRs stratified by index therapy ranged from 21.4 (95% CI: [20.9, 21.9]) among incident users of antihypertensive therapies to 24.0 (95% CI: [23.7, 24.4]) among prevalent antihypertensive therapy users. The overall unadjusted IRs stratified by antihypertensive therapy exposure time ranged from 15.0 (95% CI: [5.6, 39.8]) in the incident antihypertensive treatment cohort to 15.8 (95% CI: [7.1, 35.2]) in the prevalent antihypertensive treatment cohort.

Among the three cohorts (i.e., aliskiren users, users of other antihypertensive therapies and the non-hypertensive sample) an overall trend was observed where IRs increased with increasing age in all patients (i.e., incident and prevalent patients combined).As increased age is also a risk factor for GI cancer, this finding is not unexpected. Aside from this age-related finding, results were generally similar among the three cohorts though it should be noted that many IRs were based on relatively few patients/events yielding low rates with wide confidence intervals not conducive to interpretation.

When IRs were provided by index therapy, two trends were observed. When compared to the overall IRs for all patients, the incident antihypertensive treatment users and the prevalent antihypertensive treatment users who were prescribed alpha blocker monotherapy had consistently higher IRs of GI cancer whereas IRs among patients taking ACEI monotherapy

were consistently lower. Among patients treated with triple plus combination therapy, those prescribed a regimen that included neither an ACEI nor aliskiren were consistently observed as having higher IRs of GI cancer compared to the respective overall IRs for all patients, incident antihypertensive users, and prevalent antihypertensive users. As was the case with the corresponding colorectal hyperplasia assessment results, we believe this is the first study to report IRs of GI cancer stratified by all antihypertensive drug classes warranting the need for further research.

Results related to the secondary objective (i.e., relative risk of GI cancer in hypertensive patients exposed to aliskiren versus hypertensive patients exposed to antihypertensive drugs other than aliskiren and versus a sample of patients without a diagnosis of hypertension and without antihypertensive drug use) revealed that the use of aliskiren was not associated with an increased risk of GI cancer when compared to other antihypertensive therapy users, and compared the non-hypertensive sample. Given the small number of aliskiren users, it is possible that these comparisons were not adequately powered to detect significant effects if they indeed existed. The difference in sample sizes between aliskiren and other antihypertensive therapy users might explain why, after controlling for demographic and clinical characteristics, the risk of GI cancer was similar between aliskiren users and non-hypertensive patients, but greater in other antihypertensive therapy users when compared to non-hypertensive patients.

As was the case with the colorectal hyperplasia assessment cohort, we validated the use of ICD-9-CM diagnoses as a measure of GI cancer by assessing patients' records for the occurrence of a screening procedure prior to diagnosis. The evaluation revealed that only a small proportion of patients had a record of having a screening procedure, which suggests that including only patients with a screening procedure and an ICD-9-CM diagnosis may lead to false assumptions by excluding patients with actual disease but no screening test. We are therefore confident that relying on ICD-9-CM diagnosis alone to estimate incidence rates is an acceptable approach.

10.2 Limitations

A general limitation of non-interventional studies is that patients are not randomly assigned to treatment, and receipt of treatment and treatment type may be determined by disease severity. As a health plan claims database, the data used for this study was collected primarily for billing and reimbursement purposes, not for research. Additionally, the PharMetrics Plus claims dataset does not include information from patients that do not participate in commercial plans (e.g., uninsured patients and those covered only by Medicare (Part D)). As such, patients ≥65 years are under-represented in the database and in this study (only 2% of non-hypertensive patients were ≥65 years) which may have led to an under-reporting of the incidence of colorectal hyperplasia and GI cancer, as these conditions primarily occur in individuals over the age of 65 years. Furthermore, the PharMetrics Plus database does not provide information on systemic factors that could affect care, including plan limits on medication use. Due to the large and diverse nature of the plans in the database, however, these factors should have a minimal impact on the study results.

Comparison of the treated hypertensive population to the non-hypertensive population was limited by our inability to randomly select a non-hypertensive population of similar demographic and clinical make-up as the treated hypertensive population. The resultant non-

hypertensive population was younger and healthier, thus they had fewer risk factors for colorectal hyperplasia and GI cancer.

The relationship between pharmacy submission of claims and patients' receipt and consumption of the medication is assumed and not directly measured. However, prior work suggests that medication exposure measures can be accurately derived from pharmacy claims (Grymonpre et al 2006). This study also assumes that all information needed for case classification is present and not differential across the cohorts of interest.

The aliskiren exposed population is markedly smaller compared to all other antihypertensive drug classes. What's more, the large number of strata in some of the main analyses coupled with the low incidence of events of interest (particularly GI cancer) and the limited population size, resulted in relatively few cases identified and IR estimates with wide 95% CIs that must be interpreted with caution.

Duration of disease and duration of treatment prior to the index date (for prevalent antihypertensive therapy users) was not assessed in this study. It is possible that the higher IR of colorectal hyperplasia and GI cancer among prevalent therapy users may be confounded by a longer disease course and treatment period.

10.3 Interpretation

As aliskiren is likely to be used as second or third-line therapy, it is plausible that exposure to multiple classes of antihypertensive therapies may increase one's risk of developing colorectal hyperplasia, an interpretation that is supported by the fact that the relative risk for colorectal hyperplasia was similar between incident aliskiren and incident users of antihypertensive therapies other than aliskiren. Consideration should also be given to the fact that the prevalent cohorts were older with more comorbidities, and this was particularly evident among aliskiren users. Specifically, the aliskiren users had greater prevalence of coronary heart disease/angina, stroke/TIA, peripheral vascular disease and diabetes, and comedications (e.g., statins, anti-diabetic drugs) which may have implications on the risks of developing colorectal hyperplasia. Considering also that incident users of antihypertensive therapy (i.e., incident aliskiren and other antihypertensive therapy users) were similar with respect to baseline characteristics and had similar rates of colorectal hyperplasia, it can be inferred that the development of colorectal hyperplasia might be more influenced by increased prevalence of comorbid disease than by the class of antihypertensive therapy.

11 Generalizability

The generalizability of the study results is limited by the use of claims data from a commercially insured US population. Findings presented here may not apply to the uninsured or those insured by noncommercial programs (e.g., Medicare, Medicaid). The database is, however, generally representative of the US population (as compared to figures reported by the US Census Bureau) with respect to age with the exception of the population that is 65 years old or older which is underrepresented (6% of the PharMetrics Plus population compared to 13% of the census reported population).

Among the antihypertensive treatment populations IRs of colorectal hyperplasia were consistently higher in the prevalent users compared to the incident users and all users (i.e., incident and prevalent combined).Prevalent antihypertensive therapy user groups (i.e., prevalent aliskiren users and prevalent users of antihypertensive therapies other than aliskiren) were larger, older, had more patients age ≥ 65 years, had more comorbidities and used more co-medications compared to incident antihypertensive users, perhaps explaining the observed differences. IRs of colorectal hyperplasia presented by demographic, clinical, and lifestyle factors among incident aliskiren users were similar to incident users of other antihypertensive therapies, which may be a reflection of the similar demographic and clinical make-up of the two treatment populations. The lowest IRs were observed in the non-hypertensive patient population, which was a younger and healthier sample compared to the treated patient groups. The adjusted results were in line with the findings from the unadjusted IR estimates, after controlling for demographic and clinical factors, the risk of colorectal hyperplasia was higher in aliskiren users than users of other antihypertensive therapies among the total (HR 1.08; 95% CI 1.05-1.11) and prevalent populations (HR 1.08; 95% CI 1.04-1.11); however, the risk was similar among incident therapy users (HR 1.03; 95% CI 0.92-1.53).

The GI cancer assessment cohort was relatively small with many strata yielding results not conducive to interpretation. Adjusted results revealed that the use of aliskiren was not associated with an increased risk of GI cancer when compared to other antihypertensive therapy users (HR 1.03; 95% CI 0.91-1.16), and compared non-hypertensive patients (HR 1.09; 95% CI 0.94-1.28). It is possible that these comparisons were not adequately powered to detect significant differences in risks given the smaller number of aliskiren users (2,193 persons were incident users of aliskiren, and 23,547 people were prevalent users of aliskiren). The difference in sample sizes between aliskiren and other antihypertensive therapy users might explain why, after controlling for demographic and clinical characteristics, the risk of GI cancer was similar between aliskiren users and non-hypertensive patients, but greater in other antihypertensive therapy users when compared to non-hypertensive patients.

12 Conclusion

Among the antihypertensive treatment populations IRs of colorectal hyperplasia were consistently higher in the prevalent users compared to the incident users and all users (i.e., incident and prevalent combined).Prevalent antihypertensive therapy user groups (i.e., prevalent aliskiren users and prevalent users of antihypertensive therapies other than aliskiren) were larger, older, had more patients age ≥ 65 years, had more comorbidities and used more co-medications compared to incident antihypertensive users, perhaps explaining the observed differences. IRs of colorectal hyperplasia presented by demographic, clinical, and lifestyle factors among incident aliskiren users were similar to incident users of other antihypertensive therapies, which may be a reflection of the similar demographic and clinical make-up of the two treatment populations. The lowest IRs were observed in the non-hypertensive patient population, which was a younger and healthier sample compared to the treated patient groups.The adjusted results were in line with the findings from the unadjusted IR estimates, after controlling for demographic and clinical factors, the risk of colorectal hyperplasia was higher in aliskiren users than users of other antihypertensive therapies among the total (HR 1.08; 95% CI 1.05-1.11) and prevalent populations (HR 1.08; 95% CI 1.04-1.11); however, the risk was similar among incident therapy users (HR 1.03; 95% CI 0.92-1.53).

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13 References

[Ahmed RL, Schmitz KH, Anderson KE, et al (2006)] The metabolic syndrome and risk of incident colorectal cancer. Cancer; 107(1):28-36.

[Aleksandrova K, Boeing H, Jenab M, et al (2011)] Metabolic syndrome and risks of colon and rectal cancer: the European prospective investigation into cancer and nutrition study. Cancer Prev Res (Phila); 4:1873-83.

[Azoulay L, Assimes TL, Yin H, et al (2012)] Long-term use of angiotensin receptor blockers and the risk of cancer. PLoS One; 7(12):e50893 (Internet) Available from: <http://www.plosone.org/article/fetchObject.action;jsessionid=DC6E5A21ED81AA0181DD226F292E475C?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0050893&representation=PDF> (Accessed 19 June 2013).

[Batty GD, Shipley MJ, Marmot MG, et al (2003)] Blood pressure and site specific cancer mortality: evidence from the original Whitehall study. Br J Cancer; 89:1243-7.

[Bhaskaran K, Douglas I, Evans S, et al (2012)] Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. BMJ; 344:e2697 (Internet) Available from: <http://www.bmj.com/highwire/filestream/580988/field_highwire_article_pdf/0/bmj.e2697.full.pdf> (Accessed 19 June 2013)

[Coope, J., & Warrender, T. S. (1986)] Randomised trial of treatment of hypertension in elderly patients in primary care. BMJ, 293(6555), 1145-1151.

[Eaden JA, Abrams KR, Mayberry JF (2001)] The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut; 48(4):526-35.

[Esposito K, Chiodini P, Colao A, et al (2012)] Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care; 35(11):2402-11.

[Frampton JE and Curran MP (2007)] Aliskiren: a review of its use in the management of hypertension. Drugs; 67(12):1767-92.

[Grymonpre R, Cheang M, Fraser M, et al (2006)] Validity of a prescription claims database to estimate medication adherence in older persons. Medical Care; 44(5):471-7.

[Helicobacter and Cancer Collaborative Group (2001)] Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut, *49*(3), 347-353.

[Herrinton LJ, Liu L, Levin TR, et al (2012)] Incidence and mortality of colorectal adenocarcinoma in persons with inflammatory bowel disease from 1998 to 2010. Gastroenterology; 143(2):382-89.

[ISPE (2008)] Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf; 17:200-8.

[HaggarFA, & Boushey RP (2009)] Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clinics in colon and rectal surgery, 22(4), 191.

[Jansen L, Below J, Chang-Claude J, et al (2012)] Beta blocker use and colorectal cancer risk. Cancer, 118(16), 3911-3919.

[Kim JH, Lim YJ, Kim YH, et al (2007)] Is metabolic syndrome a risk factor for colorectal adenoma? Cancer Epidemiol Biomarkers Prev; 16(8):1543-6.

[Levi F, Pasche C, Lucchini F, et al (2002)] Diabetes mellitus, family history, and colorectal cancer. Journal of epidemiology and community health, 56(6), 479-480.

[Lindgren AM, Nissinen AM, Tuomilehto JO, et al (2005)] Cancer pattern among hypertensive patients in North Karelia, Finland. J Hum Hypertens; 19:373-9.

[Negri E, Bosetti C, La Vecchia C, et al (1999)] Allergy and other selected diseases and risk of colorectal cancer. Eur J Cancer; 35(13):1838-41.

[Othman NH and Zin AAM (2008)] Association of colorectal carcinoma with metabolic diseases; experience with 138 cases from Kelantan, Malaysia. Asian Pac J Cancer Prev; 9:747-51.

[Pelucchi C, Negri E, Talamini R, et al (2010)] Metabolic syndrome is associated with colorectal cancer in men. Eur J Cancer; 46(10):1866-72.

[SEER Cancer Statistics Factsheets: Colon and Rectum] Cancer National Cancer Institute. Bethesda, MD, (Internet) Available from: http://seer.cancer.gov/statfacts/html/colorect.html (Accessed 13 May 2015).

[Singh S, Singh PP, Murad MH, et al (2014)] Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol; 109(9):1375-89.

[Stocks T, Lukanova A, Johansson M, et al (2008)] Components of the metabolic syndrome and colorectal cancer risk; a prospective study. Int J Obes (Lond); 32:304-14.

[Stürmer T, Buring JE, Lee IM, et al (2006)] Metabolic abnormalities and risk for colorectal cancer in the Physicians' Health Study. Cancer Epidemiol Biomarkers Prev; 15(12):2391-7.

[Vandenbroucke JP, von Elm E, Altman DG, et al (2007)] Strengthening the reporting of observational studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology; 18(6):805-35.

[Watanabe Y, Ozasa K, Ito Y, et al (2005)] Medical history of circulatory diseases and colorectal cancer death in the JACC study. J Epidemiol; 15(Suppl II):S168-72.

14 Other information

N/A

15 Appendix 1 – Results Tables

Table 15-1 Attrition of Study Sample – Colorectal Hyperplasia Cohort

	Aliskiren Patients Excluded		Aliskiren Patients Remaining		Other Antihypertensive Therapy Patients Excluded		Other Antihypertensive Therapy Patients Remaining		Non-hypertensive Population Excluded		Non-hypertensive Population Remaining	
	N	%	N	%	N	%	N	%	N	%	N	%
Total patients with NEITHER a prescription for an antihypertensive medication NOR a diagnosis of hypertension (ICD-9-CM codes 401.xx - 405.xx) between 1st July 2006 and 30th June 2014 (study window)	NA		NA		NA		NA				12,615,141	
Total patients with ≥1 prescription for an antihypertensive medication between 1 July 2007 and 30 June 2013 (index window).			38,611				6,671,056		NA		NA	
Attrition Reason:												
Patient has less than 12 months of pre-index continuous health plan enrollment (not including index date)	5,664	14.7	32,947	85.3	880,294	13.2	5,790,762	86.8%	1,931,835	15.3%	10,683,306	84.7%
Patient has less than 12 months of post-index continuous health plan enrollment(including index date)	4,867	12.6	28,080	72.7	972,969	14.6	4,817,793	72.2%	1,738,323	13.8%	8,944,983	70.9%
Patient does not have evidence of at least 1 hypertension	2,198	5.7	25,882	67.0	2,350,897	35.2	2,466,896	37.0%	NA		NA	

	Aliskiren Patients Excluded		Aliskiren Patients Remaining		Other Antihypertensive Therapy Patients Excluded		Other Antihypertensive Therapy Patients Remaining		Non-hypertensive Population Excluded		Non-hypertensive Population Remaining	
diagnosis (ICD-9-CM codes 401.xx - 405.xx) in the 12-month pre-index period												
Patient has no recorded age or gender	26	0.1%	25,856	67.0%	4,680	0.1%	2,462,216	36.9	836	0.0	8,944,147	70.9
Patient is less than 18 years of age on index date	14	0.0	25,842	66.9	5,898	0.1	2,456,318	36.8	3,028,183	24.0	5,915,964	46.9
Patient has invalid or missing data	0	0.0	25,842	66.9	0	0.0	2,456,318	36.8	0	0.0	5,915,964	46.9
Patient has a prior history of colorectal hyperplasia in the 12 months prior to the index date or within 30 days of initiating therapy (for non-hypertensive population within 30 days since index date)	2,074	5.4	23,768	61.6	165,882	2.5	2,290,436	34.3	109,065	0.9	5,806,899	46.0
“Other antihypertensive therapy” patients who also had prescriptions for aliskiren during the index window					11,783	0.2	2,278,653	34.2				
Patients Available for Analysis:												
Incident Antihypertensive Treatment Cohort			2,065	8.7			917,564	40.2	NA			
Prevalent Antihypertensive Treatment Cohort			21,703	91.3			1,361,089	59.8	NA			
Non-hypertensive Population Cohort	NA				NA						5,806,899	

Table 15-2 Demographic Characteristics – All Patients – Colorectal Hyperplasia Cohort

Characteristic	All Aliskiren Patients (N= 23,768)		All Other Antihypertensive Therapy Patients (N= 2,278,653)		All Non-hypertensive Patients (N= 5,806,899)	
Age: (years)						
Mean	57.7		54.8		39.4	
SD	11.2		11.2		13.4	
Range	18	83	18	83	18	83
Median	58		55		39	
Interquartile range (1st Q, 3rd Q)	50	64	48	62	28	50
Age Group: (n, %)						
18 - 44 years	2,741	11.5%	386,660	17.0%	3,630,378	62.5%
45-64 years	15,410	64.8%	1,522,644	66.8%	2,061,837	35.5%
65+ years	5,617	23.6%	369,349	16.2%	114,684	2.0%
Gender: (n, %)						
Female (overall)	10,820	45.5%	1,122,526	49.3%	3,133,731	54.0%
18 - 44 years	953	8.8%	171,698	15.3%	1,888,775	60.3%
45-64 years	6,670	61.6%	751,575	67.0%	1,176,124	37.5%
65+ years	3,197	29.5%	199,253	17.8%	68,832	2.2%
Male (overall)	12,948	54.5%	1,156,127	50.7%	2,673,168	46.0%
18 - 44 years	1,788	13.8%	214,962	18.6%	1,741,603	65.2%
45-64 years	8,740	67.5%	771,069	66.7%	885,713	33.1%
65+ years	2,420	18.7%	170,096	14.7%	45,852	1.7%
Geographic Region: (n, %)						
Northeast	4,086	17.2%	543,966	23.9%	1,214,238	20.9%
Midwest	5,487	23.1%	666,267	29.2%	2,072,022	35.7%
South	12,114	51.0%	806,093	35.4%	1,930,623	33.2%
West	2,081	8.8%	262,327	11.5%	590,016	10.2%
Health Plan Type: (n, %)						
Consumer-directed	36	0.2%	5,061	0.2%	42,108	0.7%
HMO	1,473	6.2%	322,838	14.2%	635,164	10.9%
Indemnity	1,325	5.6%	148,319	6.5%	189,427	3.3%
POS	1,055	4.4%	153,976	6.8%	364,143	6.3%
PPO	19,750	83.1%	1,631,146	71.6%	4,543,402	78.2%
Unknown	129	0.5%	17,313	0.8%	32,655	0.6%
Payer Type: (n, %)						
Commercial	13,793	58.0%	1,480,041	65.0%	3,936,375	67.8%
Self-insured group	9,292	39.1%	672,512	29.5%	1,790,488	30.8%

Characteristic	All Aliskiren Patients (N= 23,768)		All Other Antihypertensive Therapy Patients (N= 2,278,653)		All Non-hypertensive Patients (N= 5,806,899)	
Medicaid	41	0.2%	14,258	0.6%	35,785	0.6%
Medicare Risk	574	2.4%	104,600	4.6%	18,631	0.3%
Unknown	68	0.3%	7,242	0.3%	25,620	0.4%

Table 15-3 Demographic Characteristics – Incident and Prevalent Antihypertensive Users – Colorectal Hyperplasia Cohort

Characteristic	Incident Aliskiren Treatment Cohort (N= 2,065)		Incident Other Antihypertensive Treatment Cohort (N= 917,564)		Prevalent Aliskiren Treatment Cohort (N= 21,703)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,361,089)	
Age: (years)								
Mean	51.8		52.4		58.3		56.5	
SD	11.0		11.6		11.1		10.6	
Range	18	81	18	83	18	83	18	81
Median	52		53		58		57	
Interquartile range (1st Q, 3rd Q)	45	59	45	60	51	64	50	63
Age Group: (n, %)								
18 - 44 years	506	24.5%	217,350	23.7%	2,235	10.3%	169,310	12.4%
45-64 years	1,348	65.3%	595,184	64.9%	14,062	64.8%	927,460	68.1%
65+ years	211	10.2%	105,030	11.4%	5,406	24.9%	264,319	19.4%
Gender: (n, %)								
Female (overall)	832	40.3%	431,075	47.0%	9,988	46.0%	691,451	50.8%
18 - 44 years	150	18.0%	95,594	22.2%	803	8.0%	76,104	11.0%
45-64 years	559	67.2%	281,436	65.3%	6,111	61.2%	470,139	68.0%
65+ years	123	14.8%	54,045	12.5%	3,074	30.8%	145,208	21.0%
Male (overall)	1,233	59.7%	486,489	53.0%	11,715	54.0%	669,638	49.2%
18 - 44 years	356	28.9%	121,756	25.0%	1,432	12.2%	93,206	13.9%
45-64 years	789	64.0%	313,748	64.5%	7,951	67.9%	457,321	68.3%
65+ years	88	7.1%	50,985	10.5%	2,332	19.9%	119,111	17.8%
Geographic Region: (n, %)								
Northeast	371	18.0%	199,374	21.7%	3,715	17.1%	344,592	25.3%
Midwest	462	22.4%	253,019	27.6%	5,025	23.2%	413,248	30.4%

South	1,097	53.1%	376,161	41.0%	11,017	50.8%	429,932	31.6%
West	135	6.5%	89,010	9.7%	1,946	9.0%	173,317	12.7%
Health Plan Type: (n, %)								
Consumer-directed	3	0.1%	4,164	0.5%	33	0.2%	897	0.1%
HMO	117	5.7%	94,271	10.3%	1,356	6.2%	228,567	16.8%
Indemnity	87	4.2%	37,563	4.1%	1,238	5.7%	110,756	8.1%
POS	111	5.4%	44,352	4.8%	944	4.3%	109,624	8.1%
PPO	1,733	83.9%	728,442	79.4%	18,017	83.0%	902,704	66.3%
Unknown	14	0.7%	8,772	1.0%	115	0.5%	8,541	0.6%
Payer Type: (n, %)								
Commercial	1,191	57.7%	561,528	61.2%	12,602	58.1%	918,513	67.5%
Self-insured group	819	39.7%	317,686	34.6%	8,473	39.0%	354,826	26.1%
Medicaid	17	0.8%	9,365	1.0%	24	0.1%	4,893	0.4%
Medicare Risk	30	1.5%	23,289	2.5%	544	2.5%	81,311	6.0%
Unknown	8	0.4%	5,696	0.6%	60	0.3%	1,546	0.1%

Table 15-4 Clinical Characteristics – All Patients – Colorectal Hyperplasia Cohort

Characteristic	All Aliskiren Patients (N= 23,768)		All Other Antihypertensive Therapy Patients (N= 2,278,653)		All Non-hypertensive Patients (N=5,806,899)	
Pre-index						
Charlson Comorbidity Index (CCI) Score: (n, %)						
0	8,735	36.8%	1,249,610	54.8%	5,302,711	91.3%
1-2	9,682	40.7%	803,060	35.2%	469,381	8.1%
3-4	3,647	15.3%	165,735	7.3%	20,566	0.4%
5+	1,704	7.2%	60,248	2.6%	14,241	0.2%
Mean	1.5		0.9		0.1	
SD	1.8		1.3		0.5	
Range	0	15	0	19	0	15
Median	1		0		0	
Interquartile range (1st Q, 3rd Q)	0	2	0	1	0	0
Comorbid Conditions of Interest in the Pre-index Period: (n, %)						
History of H. pylori infection	72	0.3%	5,894	0.3%	6,454	0.1%
History of stomach lymphoma	1	0.0%	428	0.0%	238	0.0%
History of stomach surgery	34	0.1%	4,370	0.2%	2,368	0.0%
Irritable bowel syndrome	353	1.5%	29,254	1.3%	43,376	0.7%
Chronic diarrhea	45	0.2%	3,315	0.1%	3,701	0.1%

Chronic constipation	632	2.7%	46,633	2.0%	58,085	1.0%
Peripheral vascular disease	2,598	10.9%	110,854	4.9%	31,567	0.5%
Vascular insufficiency of intestine (including ischemic bowel disease)	42	0.2%	2,635	0.1%	1,036	0.0%
Acute coronary syndrome	614	2.6%	46,065	2.0%	1,973	0.0%
Coronary heart disease or angina	4,913	20.7%	293,934	12.9%	19,846	0.3%
Heart failure	1,851	7.8%	81,645	3.6%	2,400	0.0%
Stroke or transient ischemic attack	2,438	10.3%	125,949	5.5%	24,221	0.4%
Ulcerous rectocolitis	84	0.4%	7,913	0.3%	13,749	0.2%
Crohn's disease	74	0.3%	7,113	0.3%	13,154	0.2%
Diabetes mellitus	8,844	37.2%	516,078	22.6%	71,273	1.2%
Screening Procedures in the Pre-index Period: (n, %)						
Fecal Occult Blood Test	2,247	9.5%	222,306	9.8%	218,897	3.8%
Sigmoidoscopy	66	0.3%	5,996	0.3%	6,209	0.1%
Colonoscopy	1,038	4.4%	101,642	4.5%	101,918	1.8%

Co-medications: (n, %)

Characteristic	**All Aliskiren Patients (N= 23,768)**		**All Other Antihypertensive Therapy Patients (N= 2,278,653)**		**All Non-hypertensive Patients (N=5,806,899)**	
Prescription NSAIDs (including aspirin)	6,227	26.2%	510,410	22.4%	680,314	11.7%
Statins	9,508	40.0%	657,545	28.9%	211,704	3.6%
Hormone replacement therapy	1,332	5.6%	119,693	5.3%	114,162	2.0%
Proton Pump Inhibitor	5,658	23.8%	377,470	16.6%	259,219	4.5%
Anti-diabetic drugs	7,209	30.3%	370,336	16.3%	56,603	1.0%
Post-index						
Available Days of Follow-up (Post-index):						
Mean	1113.6		1253.3		1021.0	
SD	613.6		735.5		543.8	
Range	31	2556	31	2557	31	2557
Median	999		1078		885	
Interquartile range	621	1531	638	1843	579	1357
Comorbid Conditions of Interest in the Post-index Period: (n, %)						
History of H. pylori infection	95	0.4%	7,352	0.3%	7,494	0.1%
History of stomach lymphoma	7	0.0%	504	0.0%	252	0.0%
History of stomach surgery	89	0.4%	7,065	0.3%	2,502	0.0%
Irritable bowel syndrome	364	1.5%	29,670	1.3%	46,096	0.8%
Chronic diarrhea	62	0.3%	4,320	0.2%	4,065	0.1%

Chronic constipation	742	3.1%	56,058	2.5%	65,208	1.1%
Peripheral vascular disease	2,701	11.4%	124,201	5.5%	34,737	0.6%
Vascular insufficiency of intestine (including ischemic bowel disease)	57	0.2%	3,218	0.1%	1,276	0.0%
Acute coronary syndrome	532	2.2%	35,608	1.6%	2,000	0.0%
Coronary heart disease or angina	5,008	21.1%	303,414	13.3%	20,608	0.4%
Heart failure	2,008	8.4%	87,758	3.9%	2,674	0.0%
Stroke or transient ischemic attack	2,469	10.4%	130,547	5.7%	26,436	0.5%
Ulcerous rectocolitis	102	0.4%	9,138	0.4%	15,376	0.3%
Crohn's disease	99	0.4%	7,921	0.3%	14,384	0.2%
Diabetes mellitus	9,040	38.0%	542,428	23.8%	78,068	1.3%
Screening Procedures in the Post-index Period: (n, %)						
Fecal Occult Blood Test	2,111	8.9%	202,972	8.9%	222,454	3.8%
Sigmoidoscopy	89	0.4%	7,216	0.3%	7,299	0.1%
Colonoscopy	2,262	9.5%	205,967	9.0%	184,294	3.2%
Co-medications: (n, %)						
Prescription NSAIDs (including aspirin)	6,129	25.8%	551,495	24.2%	707,240	12.2%
Statins	10,726	45.1%	857,214	37.6%	236,630	4.1%
Hormone replacement therapy	1,253	5.3%	116,292	5.1%	115,100	2.0%
Proton Pump Inhibitor	6,087	25.6%	455,204	20.0%	279,097	4.8%

Characteristic	**All Aliskiren Patients (N= 23,768)**		**All Other Antihypertensive Therapy Patients (N= 2,278,653)**		**All Non-hypertensive Patients (N=5,806,899)**	
Anti-diabetic drugs	7,800	32.8%	443,290	19.5%	62,413	1.1%

Table 15-5 Clinical Characteristics – Incident and Prevalent Antihypertensive Users – Colorectal Hyperplasia Cohort

Characteristic	Incident Aliskiren Treatment Cohort (N= 2,065)		Incident Other Antihypertensive Treatment Cohort (N= 917,564)		Prevalent Aliskiren Treatment Cohort (N= 21,703)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,361,089)	
Pre-index								
Charlson Comorbidity Index (CCI) Score: (n, %)								
0	1,215	58.8%	541,264	59.0%	7,520	34.6%	708,346	52.0%
1-2	662	32.1%	302,000	32.9%	9,020	41.6%	501,060	36.8%
3-4	135	6.5%	54,597	6.0%	3,512	16.2%	111,138	8.2%
5+	53	2.6%	19,703	2.1%	1,651	7.6%	40,545	3.0%
Mean	0.8		0.8		1.6		1.0	
SD	1.3		1.3		1.8		1.4	
Range	0	10	0	16	0	15	0	19
Median	0		0		1		0	
Interquartile range (1st Q, 3rd Q)	0	1	0	1	0	2	0	1
Comorbid Conditions of Interest in the Pre-index Period: (n, %)								
History of H. pylori infection	3	0.1%	2,783	0.3%	69	0.3%	3,111	0.2%
History of stomach lymphoma	0	0.0%	163	0.0%	1	0.0%	265	0.0%
History of stomach surgery	3	0.1%	1,776	0.2%	31	0.1%	2,594	0.2%
Irritable bowel syndrome	27	1.3%	10,590	1.2%	326	1.5%	18,664	1.4%
Chronic diarrhea	1	0.0%	1,138	0.1%	44	0.2%	2,177	0.2%
Chronic constipation	48	2.3%	18,674	2.0%	584	2.7%	27,959	2.1%
Peripheral vascular disease	89	4.3%	36,458	4.0%	2,509	11.6%	74,396	5.5%

Characteristic	Incident Aliskiren Treatment Cohort (N= 2,065)		Incident Other Antihypertensive Treatment Cohort (N= 917,564)		Prevalent Aliskiren Treatment Cohort (N= 21,703)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,361,089)	
Vascular insufficiency of intestine (including ischemic bowel disease)	0	0.0%	977	0.1%	42	0.2%	1,658	0.1%
Acute coronary syndrome	15	0.7%	19,455	2.1%	599	2.8%	26,610	2.0%
Coronary heart disease or angina	178	8.6%	91,896	10.0%	4,735	21.8%	202,038	14.8%
Heart failure	46	2.2%	24,595	2.7%	1,805	8.3%	57,050	4.2%
Stroke or transient ischemic attack	106	5.1%	49,043	5.3%	2,332	10.7%	76,906	5.7%
Ulcerous rectocolitis	2	0.1%	2,990	0.3%	82	0.4%	4,923	0.4%
Crohn's disease	2	0.1%	2,918	0.3%	72	0.3%	4,195	0.3%
Diabetes mellitus	441	21.4%	168,937	18.4%	8,403	38.7%	347,141	25.5%
Screening Procedures in the Pre-index Period: (n, %)								
Fecal Occult Blood Test	187	9.1%	77,008	8.4%	2,060	9.5%	145,298	10.7%
Sigmoidoscopy	1	0.0%	1,822	0.2%	65	0.3%	4,174	0.3%
Colonoscopy	71	3.4%	33,165	3.6%	967	4.5%	68,477	5.0%
Co-medications: (n, %)								
Prescription NSAIDs (including aspirin)	373	18.1%	178,708	19.5%	5,854	27.0%	331,702	24.4%
Statins	298	14.4%	142,557	15.5%	9,210	42.4%	514,988	37.8%
Hormone replacement therapy	69	3.3%	30,440	3.3%	1,263	5.8%	89,253	6.6%
Proton Pump Inhibitor	233	11.3%	101,533	11.1%	5,425	25.0%	275,937	20.3%
Anti-diabetic drugs	233	11.3%	90,613	9.9%	6,976	32.1%	279,723	20.6%
Post-index								
Available Days of Follow-up (Post-index):								
Mean	1167.4		1049.5		1108.5		1390.7	
SD	633.3		586.8		611.5		791.6	

Range	31	2556	31	2557	31	2556	31	2557
Characteristic	Incident Aliskiren Treatment Cohort (N= 2,065)		Incident Other Antihypertensive Treatment Cohort (N= 917,564)		Prevalent Aliskiren Treatment Cohort (N= 21,703)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,361,089)	
Median	1047		911		994		1229	
Interquartile range	645	1638	572	1442	618	1521	731	2273
Comorbid Conditions of Interest in the Post-index Period: (n, %)								
History of H. pylori infection	3	0.1%	3,644	0.4%	92	0.4%	3,708	0.3%
History of stomach lymphoma	0	0.0%	173	0.0%	7	0.0%	331	0.0%
History of stomach surgery	8	0.4%	3,226	0.4%	81	0.4%	3,839	0.3%
Irritable bowel syndrome	17	0.8%	11,275	1.2%	347	1.6%	18,395	1.4%
Chronic diarrhea	2	0.1%	1,583	0.2%	60	0.3%	2,737	0.2%
Chronic constipation	47	2.3%	23,619	2.6%	695	3.2%	32,439	2.4%
Peripheral vascular disease	99	4.8%	45,584	5.0%	2,602	12.0%	78,617	5.8%
Vascular insufficiency of intestine (including ischemic bowel disease)	2	0.1%	1,227	0.1%	55	0.3%	1,991	0.1%
Acute coronary syndrome	20	1.0%	15,287	1.7%	512	2.4%	20,321	1.5%
Coronary heart disease or angina	209	10.1%	103,192	11.2%	4,799	22.1%	200,222	14.7%
Heart failure	59	2.9%	29,693	3.2%	1,949	9.0%	58,065	4.3%
Stroke or transient ischemic attack	118	5.7%	52,444	5.7%	2,351	10.8%	78,103	5.7%
Ulcerous rectocolitis	3	0.1%	3,567	0.4%	99	0.5%	5,571	0.4%
Crohn's disease	3	0.1%	3,271	0.4%	96	0.4%	4,650	0.3%
Diabetes mellitus	466	22.6%	183,133	20.0%	8,574	39.5%	359,295	26.4%
Screening Procedures in the Post-index Period: (n, %)								
Fecal Occult Blood Test	157	7.6%	70,897	7.7%	1,954	9.0%	132,075	9.7%
Sigmoidoscopy	4	0.2%	2,600	0.3%	85	0.4%	4,616	0.3%

Colonoscopy	170	8.2%	75,186	8.2%	2,092	9.6%	130,781	9.6%
Co-medications: (n, %)								
Prescription NSAIDs (including aspirin)	485	23.5%	222,945	24.3%	5,644	26.0%	328,550	24.1%
Characteristic	Incident Aliskiren Treatment Cohort (N= 2,065)		Incident Other Antihypertensive Treatment Cohort (N= 917,564)		Prevalent Aliskiren Treatment Cohort (N= 21,703)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,361,089)	
Statins	620	30.0%	302,218	32.9%	10,106	46.6%	554,996	40.8%
Hormone replacement therapy	80	3.9%	35,491	3.9%	1,173	5.4%	80,801	5.9%
Proton Pump Inhibitor	341	16.5%	162,882	17.8%	5,746	26.5%	292,322	21.5%
Anti-diabetic drugs	360	17.4%	144,474	15.7%	7,440	34.3%	298,816	22.0%

Table 15-6 Antihypertensive Drug Use within 30 days since Index – Colorectal Hyperplasia Cohort

Measure	**All Hypertensive Patients (N= 2,302,421)**		**Incident Antihypertensive Treatment Cohort (N= 919,629)**		**Prevalent Antihypertensive Treatment Cohort (N= 1,382,792)**	
Monotherapy Initiators: (n, %)						
Aliskiren	7,740	0.3%	1,506	0.2%	6,234	0.5%
Angiotensin-converting enzyme inhibitors	393,278	17.1%	213,015	23.2%	180,263	13.0%
Angiotensin II receptor blockers	151,843	6.6%	62,809	6.8%	89,034	6.4%
Alpha blockers	36,386	1.6%	23,721	2.6%	12,665	0.9%
Beta blockers	282,792	12.3%	130,586	14.2%	152,206	11.0%
Calcium channel blockers	137,584	6.0%	63,375	6.9%	74,209	5.4%
Diuretics	222,236	9.7%	117,118	12.7%	105,118	7.6%
Others (vasodilators, selective aldosterone receptor antagonists, centrally acting alpha agonists)	12,401	0.5%	7,267	0.8%	5,134	0.4%
Dual-combination Therapy Initiators: (n, %)						

Dual combination including aliskiren	5,140	0.2%	254	0.0%	4,886	0.4%
Dual combination including an ACEI but not aliskiren	355,263	15.4%	125,526	13.6%	229,737	16.6%
Dual combination including neither an ACEI nor aliskiren	386,074	16.8%	108,724	11.8%	277,350	20.1%
Triple-plus Combination Therapy Initiators: (n, %)						
Triple-plus combination therapy including aliskiren	11,559	0.5%	376	0.0%	11,183	0.8%
Triple-plus combination therapy including an ACEI but not aliskiren	174,301	7.6%	42,590	4.6%	131,711	9.5%
Triple-plus combination therapy including neither an ACEI nor aliskiren	125,824	5.5%	22,762	2.5%	103,062	7.5%
Duration of exposure of index therapy (days)						
Mean	520.4		351.7		632.6	
SD	592.3		430.7		655.1	
Range	0	2740	0	2740	0	2720
Median	305		165		429	

Measure	**All Hypertensive Patients (N= 2,302,421)**		**Incident Antihypertensive Treatment Cohort (N= 919,629)**		**Prevalent Antihypertensive Treatment Cohort (N= 1,382,792)**	
Interquartile range (1st Q, 3rd Q)	86	746	46	506	113	916

Table 15-7 Incidence Rates (per 10,000 person-years) of Colorectal Hyperplasia – All Patients

	All Aliskiren Patients		**All Other Antihypertensive Patients**								**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Overall:	23,768	4,508	621.7	603.8	640.1	2,278,653	404,015	516.4	514.8	518.0	5,806,899	273,445	168.3	167.7	169.0
By Age Group:															

18 - 44	2,741	138	140.6	119.0	166.1	386,660	17,874	123.3	121.5	125.1	3,630,378	40,357	39.2	38.8	39.5
45 – 64	15,410	3,249	681.6	658.5	705.4	1,522,644	312,644	595.4	593.4	597.5	2,061,837	220,220	389.2	387.5	390.8
65+	5,617	1,121	745.9	703.5	790.9	369,349	73,497	654.1	649.4	658.9	114,684	12,868	458.2	450.4	466.2
By Gender:															
Male (overall)	12,948	2,658	673.5	648.3	699.6	1,156,127	224,151	574.1	571.8	576.5	2,673,168	126,224	168.9	168.0	169.9
18 - 44	1,788	95	148.1	121.1	181.1	214,962	9,707	120.8	118.4	123.2	1,741,603	18,672	37.7	37.2	38.3
45 – 64	8,740	1,985	743.6	711.6	777.0	771,069	174,273	669.7	666.6	672.9	885,713	101,610	421.0	418.5	423.6
65+	2,420	578	909.3	838.1	986.5	170,096	40,171	806.1	798.3	814.1	45,852	5,942	545.2	531.5	559.3
Female (overall)	10,820	1,850	559.8	534.9	585.9	1,122,526	179,864	458.8	456.7	460.9	3,133,731	147,221	167.8	167.0	168.7
18 - 44	953	43	126.4	93.8	170.5	171,698	8,167	126.3	123.6	129.1	1,888,775	21,685	40.5	40.0	41.0
45 - 64	6,670	1,264	602.6	570.3	636.8	751,575	138,371	522.5	519.7	525.2	1,176,124	118,610	365.5	363.4	367.6
65+	3,197	543	626.2	575.7	681.1	199,253	33,326	533.0	527.3	538.7	68,832	6,926	403.0	393.7	412.6
By Comorbidity:															
Diabetes (overall)	8,844	1,852	717.9	685.9	751.3	516,078	99,962	572.7	569.1	576.2	71,273	5,580	301.8	294.0	309.8
Male gender (overall)	5,030	1,136	778.0	734.1	824.6	273,895	57,293	629.9	624.7	635.1	32,629	2,772	332.4	320.2	345.0
18 – 44	373	27	209.9	144.0	306.1	29,861	1,422	125.7	119.4	132.4	13,222	188	52.4	45.4	60.4

45 – 64	3,455	814	797.3	744.3	854.0	187,628	42,709	675.8	669.4	682.3	17,520	2,294	529.6	508.3	551.7
65+	1,202	295	950.1	847.6	1,064.9	56,406	13,162	800.0	786.5	813.8	1,887	290	692.9	617.6	777.4
Female gender (overall)	3,814	716	639.5	594.3	688.0	242,183	42,669	510.4	505.6	515.3	38,644	2,808	276.6	266.6	287.1
	All Aliskiren Patients		**All Other Antihypertensive Patients**								**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
18 – 44	226	13	165.0	95.8	284.2	25,118	1,441	151.2	143.6	159.2	17,590	328	67.6	60.7	75.4
45 – 64	2,336	470	661.7	604.5	724.3	164,508	32,131	556.6	550.5	562.7	19,119	2,248	462.5	443.7	482.0
65+	1,252	233	704.8	619.8	801.3	52,557	9,097	556.7	545.4	568.3	1,935	232	528.4	464.6	600.9
Irritable bowel syndrome (overall)	353	80	754.1	605.7	938.9	29,254	6,051	607.7	592.5	623.2	43,376	3,408	289.1	279.5	298.9
Male gender (overall)	106	26	802.9	546.7	1,179.2	7,790	1,794	688.9	657.8	721.5	9,844	778	291.7	271.9	312.9
18 - 44	19	2	254.2	63.6	1,016.5	1,672	167	272.3	234.0	316.9	6,466	262	146.4	129.7	165.2
45 - 64	68	20	1,018.4	657.0	1,578.5	4,989	1,307	783.9	742.5	827.5	3,177	471	563.7	515.0	616.9
65+	19	4	820.3	307.9	2,185.7	1,129	320	989.5	886.8	1,104.1	201	45	1,069.2	798.3	1,432.0
Female gender (overall)	247	54	732.7	561.1	956.6	21,464	4,257	578.9	561.8	596.5	33,532	2,630	288.3	277.5	299.5
18 - 44	22	0	0.0	0.0	0.0	3,267	300	250.2	223.4	280.1	19,383	688	128.1	118.8	138.0

45 – 64	152	39	856.0	625.4	1,171.5	14,488	3,239	641.3	619.5	663.7	13,311	1,818	510.6	487.7	534.6
65+	73	15	757.6	456.8	1,256.7	3,709	718	650.7	604.8	700.1	838	124	657.3	551.2	783.8
Vascular insufficiency of intestine (including ischemic bowel disease) (overall)	42	8	623.8	311.9	1,247.3	2,635	470	552.8	505.0	605.1	1,036	92	339.3	276.6	416.2
Male gender (overall)	9	2	844.5	211.2	3,376.7	1,021	206	661.4	577.0	758.2	344	30	328.4	229.6	469.7
18 - 44						97	10	309.6	166.6	575.4	176	9	193.9	100.9	372.7
45 - 64	5	1	572.3	80.6	4,062.7	623	124	634.0	531.7	756.1	154	18	426.5	268.7	676.9
65+	4	1	1,610.8	226.9	11,435.0	301	72	861.5	683.8	1,085.3	14	3	1,097.5	354.0	3,403.0
Female gender (overall)	33	6	573.8	257.8	1,277.2	1,614	264	490.1	434.4	552.9	692	62	344.8	268.8	442.3
18 - 44	1	0	0.0	0.0	0.0	115	10	225.5	121.3	419.1	277	11	143.9	79.7	259.8
45 – 64	16	3	539.5	174.0	1,672.6	920	172	545.2	469.5	633.1	366	39	414.6	302.9	567.5

	All Aliskiren Patients		**All Other Antihypertensive Patients**								**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+	16	3	707.2	228.1	2,192.8	579	82	458.4	369.2	569.2	49	12	1,292	733.7	2,274.

															9
Ulcerative colitis/rectocolitis (overall)	84	24	1,122.9	752.6	1,675.3	7,913	2,059	820.5	785.8	856.7	13,749	2,159	610.7	585.5	637.1
Male gender (overall)	34	12	1,387.6	788.0	2,443.4	3,851	1,132	947.1	893.5	1,003.9	5,966	1,043	685.0	644.7	727.9
18 – 44	2	0	0.0	0.0	0.0	567	119	615.1	513.9	736.1	3,597	509	543.5	498.3	592.8
45 – 64	23	11	1,867.7	1,034.3	3,372.5	2,569	804	1,001.3	934.4	1,073.0	2,247	500	891.1	816.3	972.7
65+	9	1	536.7	75.6	3,810.0	715	209	1,051.3	918.0	1,203.9	122	34	1,358.7	970.8	1,901.5
Female gender (overall)	50	12	943.0	535.5	1,660.4	4,062	927	705.3	661.3	752.2	7,783	1,116	554.6	523.0	588.1
18 – 44	6	1	608.8	85.8	4,322.2	497	83	499.2	402.6	619.1	4,221	465	416.0	379.8	455.5
45 - 64	29	7	930.2	443.5	1,951.2	2,707	661	740.8	686.4	799.5	3,382	621	726.7	671.7	786.2
65+	15	4	1,124.2	421.9	2,995.3	858	183	715.6	619.1	827.1	180	30	750.5	524.7	1,073.3
Crohn's disease (overall)	74	13	591.0	343.2	1,017.8	7,113	1,692	742.0	707.5	778.3	13,154	1,710	501.1	477.9	525.4
Male gender (overall)	37	7	642.3	306.2	1,347.4	3,228	813	792.9	740.3	849.4	5,759	791	532.4	496.5	570.8
18 – 44	2	0	0.0	0.0	0.0	539	82	443.0	356.7	550.0	3,863	430	426.8	388.3	469.1
45 – 64	30	7	825.2	393.4	1,730.8	2,202	596	840.0	775.2	910.2	1,820	341	737.6	663.3	820.2
65+	5	0	0.0	0.0	0.0	487	135	1,033.	873.1	1,223.4	76	20	1,260.4	813.2	1,953.

								5							7
Female gender (overall)	37	6	540.6	242.9	1,203.3	3,885	879	700.4	655.6	748.3	7,395	919	477.0	447.1	508.9
18 - 44	4	0	0.0	0.0	0.0	654	122	578.1	484.1	690.3	4,411	452	390.8	356.4	428.6
45 – 64	22	3	430.8	138.9	1,335.6	2,597	642	748.5	692.8	808.7	2,841	448	606.8	553.2	665.7
65+	11	3	1,114.3	359.4	3,454.9	634	115	617.9	514.7	741.8	143	19	598.0	381.4	937.5

	All Aliskiren Patients					**All Other Antihypertensive Patients**					**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Familial adenomatous polyps/Hereditary nonpolyposis (overall)	13	6	1,930.2	867.2	4,296.4	594	201	1,317.6	1,147.5	1,513.0	476	140	1,391.2	1,178.9	1,641.9
Male gender (overall)	7	4	2,754.7	1,033.9	7,339.7	236	96	1,536.8	1,258.2	1,877.1	118	35	1,293.2	928.5	1,801.1
18 - 44						8	3	1,195.5	385.6	3,706.9	35	11	1,375.7	761.9	2,484.1
45 - 64	1	0	0.0	0.0	0.0	159	63	1,407.0	1,099.1	1,801.0	74	20	1,164.7	751.4	1,805.4
65+	6	4	3,198.3	1,200.4	8,521.4	69	30	1,976.1	1,381.6	2,826.2	9	4	2,108.3	791.3	5,617.4

Female gender (overall)	6	2	1,207.4	302.0	4,827.8	358	105	1,165.7	962.7	1,411.4	358	105	1,427.3	1,178.8	1,728.2
18 – 44						15	4	841.5	315.8	2,242.0	72	12	738.5	419.4	1,300.3
45 - 64	3	2	2,884.2	721.3	11,532.4	262	77	1,170.6	936.3	1,463.6	260	86	1,614.4	1,306.8	1,994.3
65+	3	0	0.0	0.0	0.0	81	24	1,227.8	823.0	1,831.9	26	7	1,731.1	825.3	3,631.3
By Co-Medication:															
NSAIDs (overall)	1,758	306	561.6	502.1	628.2	166,765	29,585	517.9	512.0	523.8	100,221	6,682	249.9	244.0	255.9
Male gender (overall)	840	148	565.3	481.2	664.1	73,462	14,512	588.3	578.8	597.9	36,239	2,545	264.2	254.2	274.7
18 - 44	73	4	161.6	60.6	430.5	11,824	569	134.8	124.2	146.4	19,826	306	56.0	50.1	62.6
45 - 64	606	113	588.0	489.0	707.0	51,319	11,435	659.0	647.0	671.2	15,661	2,107	526.2	504.2	549.2
65+	161	31	690.6	485.7	982.0	10,319	2,508	810.0	778.9	842.4	752	132	807.6	681.0	957.9
Female gender (overall)	918	158	558.2	477.6	652.4	93,303	15,073	464.4	457.1	471.9	63,982	4,137	241.8	234.5	249.3
18 - 44	63	7	329.8	157.2	691.8	13,024	658	140.8	130.4	152.0	33,374	569	62.3	57.4	67.6
45 – 64	612	109	559.7	463.9	675.3	64,812	11,743	514.1	504.9	523.5	29,031	3,380	445.1	430.3	460.4
65+	243	42	626.1	462.7	847.1	15,467	2,672	540.8	520.7	561.7	1,577	188	497.3	431.1	573.7

Statins (overall)	5,512	1,160	719.1	678.9	761.7	515,330	106,659	616.0	612.4	619.7	93,214	13,887	582.2	572.6	592.0
Male gender (overall)	3,242	756	794.6	739.9	853.3	299,555	66,505	667.3	662.2	672.4	49,134	7,618	603.6	590.2	617.3
	All Aliskiren Patients		**All Other Antihypertensive Patients**							**All Non-hypertensive Patients**					
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	**Patients**	**Events**		**IR**	**95% CI**	
18 - 44	287	20	192.2	124.0	297.9	30,739	1,638	139.5	132.9	146.4	11,074	375	118.6	107.2	131.2
45 – 64	2,247	560	838.7	772.1	911.2	213,187	51,071	714.3	708.1	720.5	35,387	6,653	749.1	731.4	767.4
65+	708	176	979.2	844.7	1,135.1	55,629	13,796	840.2	826.3	854.3	2,673	590	1,020.4	941.3	1,106.2
Female gender (overall)	2,270	404	610.6	553.9	673.2	215,775	40,154	546.5	541.2	551.9	44,080	6,269	558.2	544.6	572.2
18 – 44	94	7	230.8	110.0	484.0	12,324	739	156.4	145.5	168.0	5,122	139	94.9	80.4	112.1
45 – 64	1,318	251	629.6	556.4	712.6	149,066	29,935	582.3	575.7	588.9	34,981	5,510	622.5	606.3	639.2
65+	858	146	627.6	533.6	738.1	54,385	9,480	547.0	536.1	558.1	3,977	620	677.8	626.5	733.3
By Lifestyle factors:															
Alcohol dependence syndrome,	87	17	663.0	412.2	1,066.5	14,545	2,315	529.3	508.2	551.3	13,374	604	176.4	162.8	191.0

defined by ICD-9-CM 303.x (overall)															
Male gender (overall)	77	14	606.4	359.2	1,024.0	10,639	1,781	560.0	534.6	586.6	8,471	346	159.0	143.1	176.6
18 - 44	13	0	0.0	0.0	0.0	2,485	98	123.7	101.5	150.8	6,064	74	47.1	37.5	59.1
45 – 64	56	14	820.3	485.9	1,385.1	7,303	1,471	685.5	651.4	721.5	2,351	267	451.2	400.2	508.7
65+	8	0	0.0	0.0	0.0	851	212	873.9	763.8	999.8	56	5	395.7	164.7	950.8
Female gender (overall)	10	3	1,174.0	378.6	3,640.1	3,906	534	447.4	411.0	487.0	4,903	258	206.7	182.9	233.5
18 – 44	1	0	0.0	0.0	0.0	837	37	139.2	100.8	192.1	3,094	51	63.6	48.3	83.6
45 – 64	9	3	1,243.8	401.1	3,856.3	2,757	448	537.3	489.8	589.5	1,755	195	448.3	389.6	515.9
65+						312	49	522.0	394.5	690.6	54	12	1,098.9	624.1	1,934.9
Obesity, defined by ICD-9-CM 278.0x(overall)	2,630	495	628.7	575.7	686.6	191,302	31,674	493.5	488.1	499.0	98,295	5,394	216.5	210.8	222.4
Male gender (overall)	1,381	281	681.3	606.1	765.8	84,465	15,289	554.5	545.8	563.4	29,070	1,828	254.0	242.7	266.0
18 – 44	225	8	99.9	50.0	199.8	22,052	995	129.6	121.8	137.9	17,878	246	53.7	47.4	60.9
	All Aliskiren Patients		**All Other Antihypertensive Patients**							**All Non-hypertensive Patients**					

	Patients	Events	IR	95% CI	Patients	Events	IR	95% CI		Patients		Events	IR	95% CI	
45 – 64	996	225	767.6	673.5	874.7	55,646	12,523	696.5	684.4	708.8	10,844	1,522	598.2	568.9	629.0
65+	160	48	1,223.0	921.6	1,622.8	6,767	1,771	925.4	883.3	969.5	348	60	833.8	647.4	1,073.9
Female gender (overall)	1,249	214	570.8	499.2	652.6	106,837	16,385	447.5	440.7	454.4	69,225	3,566	201.3	194.8	208.0
18 – 44	188	8	123.8	61.9	247.6	26,962	1,318	136.9	129.7	144.5	45,141	750	63.4	59.0	68.1
45 – 64	880	172	651.4	561.0	756.4	71,371	13,406	549.6	540.3	558.9	23,412	2,723	474.4	456.9	492.6
65+	181	34	734.5	524.8	1,027.9	8,504	1,661	640.3	610.3	671.9	672	93	663.6	541.5	813.1

Table 15-8 Incidence Rates (per 10,000 person-years) of Colorectal Hyperplasia – Incident and Prevalent Cohorts

	Incident Aliskiren Treatment Cohort					Incident Other Antihypertensive Treatment Cohort					Prevalent Aliskiren Treatment Cohort					Prevalent Other Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Overall:	2,065	313	473.9	424.2	529.4	917,564	124,134	470.5	467.9	473.1	21,703	4,195	636.5	617.5	656.0	1,361,089	279,881	539.7	537.7	541.7
By Age Group:																				
18 – 44	506	21	115.2	75.1	176.6	217,350	7,342	108.1	105.7	110.6	2,235	117	146.4	122.1	175.5	169,310	10,532	136.6	134.0	139.2
45 - 64	1,348	248	584.0	515.7	661.4	595,18	98,818	584.5	580.8	588.1	14,062	3,001	691.1	666.8	716.3	927,460	213,82	600.6	598.1	603.2

						4											6			
65+	211	44	82 2.9	61 2.4	1,1 05. 8	105 ,03 0	17, 974	66 8.9	65 9.2	67 8.7	5,4 06	1,0 77	74 3.1	70 0.0	788 .8	264, 319	55, 523	64 9.5	64 4.1	65 4.9
By Gender:																				
Male (overall)	1,2 33	19 6	49 0.6	42 6.5	564 .3	486 ,48 9	71, 044	51 2.7	50 9.0	51 6.5	11, 715	2,4 62	69 4.1	66 7.2	722 .0	669, 638	153 ,10 7	60 7.9	60 4.9	61 1.0
18 – 44	356	16	12 3.3	75. 6	201 .3	121 ,75 6	3,9 64	10 4.6	10 1.4	10 7.9	1,4 32	79	15 4.4	12 3.8	192 .4	93,2 06	5,7 43	13 5.3	13 1.8	13 8.8
45 - 64	789	15 7	63 2.1	54 0.5	739 .1	313 ,74 8	56, 819	64 6.8	64 1.5	65 2.1	7,9 51	1,8 28	75 5.0	72 1.2	790 .4	457, 321	117 ,45 4	68 1.4	67 7.5	68 5.3
65+	88	23	1,0 73. 9	71 3.7	1,6 16. 1	50, 985	10, 261	80 1.3	78 5.9	81 6.9	2,3 32	55 5	90 3.5	83 1.4	981 .9	119, 111	29, 910	80 7.8	79 8.7	81 7.0
Female (overall)	832	11 7	44 8.4	37 4.1	537 .5	431 ,07 5	53, 090	42 3.8	42 0.2	42 7.4	9,9 88	1,7 33	56 9.4	54 3.2	596 .8	691, 451	126 ,77 4	47 5.3	47 2.7	47 7.9
18 - 44	150	5	95. 0	39. 6	228 .4	95, 594	3,3 78	11 2.6	10 8.9	11 6.5	803	38	13 2.2	96. 2	181 .6	76,1 04	4,7 89	13 8.1	13 4.3	14 2.1
45 - 64	559	91	51 6.3	42 0.4	634 .1	281 ,43 6	41, 999	51 7.1	51 2.2	52 2.1	6,1 11	1,1 73	61 0.6	57 6.6	646 .5	470, 139	96, 372	52 4.9	52 1.6	52 8.2
65+	123	21	65 5.2	42 7.2	1,0 04. 8	54, 045	7,7 13	54 8.3	53 6.2	56 0.7	3,0 74	52 2	62 5.1	57 3.7	681 .1	145, 208	25, 613	52 8.5	52 2.1	53 5.0
By Comorbidity:																				
Diabetes (overall)	441	81	62 8.9	50 5.8	781 .9	168 ,93 7	24, 950	52 8.0	52 1.5	53 4.6	8,4 03	1,7 71	72 2.6	68 9.7	757 .0	347, 141	75, 012	58 9.2	58 5.0	59 3.5
Male gender (overall)	260	52	65 8.5	50 1.8	864 .2	93, 548	14, 845	57 3.3	56 4.2	58 2.6	4,7 70	1,0 84	78 4.9	73 9.5	833 .0	180, 347	42, 448	65 2.4	64 6.2	65 8.6

18 - 44	49	1	54.1	7.6	384.0	14,841	510	11 1.3	10 2.1	12 1.4	324	26	23 6.1	16 0.7	346.7	15,020	912	13 5.5	12 7.0	14 4.6
45 - 64	183	43	778.1	577.1	1,049.2	63,996	11,472	65 0.6	63 8.8	66 2.6	3,272	771	79 8.4	74 4.0	856.8	123,632	31,237	68 5.6	67 8.0	69 3.2
65+	28	8	1,532.2	76 6.2	3,063.7	14,711	2,863	77 7.7	74 9.8	80 6.8	1,174	287	94 0.1	83 7.4	1,055.4	41,695	10,299	80 6.5	79 1.0	82 2.2

	Incident Aliskiren Treatment Cohort					**Incident Other Antihypertensive Treatment Cohort**					**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	181	29	582.1	404.5	837.6	75,389	10,105	47 3.1	46 4.0	48 2.5	3,633	687	64 2.1	59 5.9	692.0	166,794	32,564	52 3.2	51 7.5	52 8.9
18 - 44	18	1	183.6	25.9	1,303.4	12,523	507	12 8.7	11 8.0	14 0.4	208	12	16 3.7	92.9	288.2	12,595	934	16 7.1	15 6.7	17 8.2
45 - 64	124	21	615.7	401.4	944.3	50,905	7,838	54 6.1	53 4.2	55 8.4	2,212	449	66 4.0	60 5.3	728.3	113,603	24,293	56 0.0	55 3.0	56 7.1
65+	39	7	681.7	325.0	1,430.0	11,961	1,760	57 3.9	54 7.7	60 1.4	1,213	226	70 5.5	61 9.3	803.8	40,596	7,337	55 2.8	54 0.3	56 5.6
Irritable bowel syndrome (overall)	27	6	771.6	346.6	1,717.5	10,590	1,787	59 1.0	56 4.2	61 9.0	326	74	75 2.7	59 9.4	945.3	18,664	4,264	61 4.9	59 6.8	63 3.7
Male gender (overall)	11	4	1,269.7	476.5	3,382.9	2,979	550	65 9.0	60 6.2	71 6.5	95	22	75 2.6	49 5.6	1,143.0	4,811	1,244	70 3.0	66 5.0	74 3.2
18 - 44	3	0	0.0	0.0	0.0	897	81	29 5.3	23 7.5	36 7.1	16	2	31 0.0	77.5	1,239.4	775	86	25 3.6	20 5.3	31 3.3
45 - 64	7	4	2,699	780	7,070	1,737	376	78	70	86	61	16	88	54	1,424	3,231	931	78	73	83

			59.4	8.1	85.7	55		0.6	5.5	3.6			2.3	0.5	40.2	4		5.2	6.4	7.3
65+	1	0	0.0	0.0	0.0	327	93	1,183.8	966.1	1,450.6	18	4	861.2	323.2	2,294.5	802	227	927.1	814.1	1,056.0
Female gender (overall)	16	2	432.4	108.1	1,728.8	7,611	1,237	565.0	534.4	597.4	231	52	752.8	573.6	987.9	13,853	3,020	584.8	564.3	606.0
18 - 44	4	0	0.0	0.0	0.0	1,645	131	260.9	219.8	309.6	18	0	0.0	0.0	0.0	1,622	169	242.5	208.5	281.9
45 - 64	10	2	709.4	177.4	2,836.6	4,962	937	653.6	613.0	696.8	142	37	865.6	627.2	1,194.7	9,526	2,302	636.4	610.9	662.9
65+	2	0	0.0	0.0	0.0	1,004	169	666.8	573.5	775.3	71	15	775.6	467.6	1,286.6	2,705	549	645.9	594.0	702.2
Vascular insufficiency of intestine (including ischemic bowel disease) (overall)						977	152	582.2	496.7	682.6	42	8	623.8	311.9	1,247.3	1,658	318	539.8	483.6	602.5
Male gender (overall)						437	71	630.6	499.7	795.8	9	2	844.5	211.2	3,376.7	584	135	678.9	573.5	803.6
18 - 44						63	6	333.7	149.9	742.8						34	4	279.3	104.8	744.1
45 - 64						271	48	685.3	516.4	909.3	5	1	572.3	80.6	4,062.7	352	76	605.4	483.5	758.1
65+						103	17	692.1	430.2	1,113.3	4	1	1,610.8	226.9	11,435.0	198	55	932.0	715.5	1,213.9

	Incident Aliskiren Treatment Cohort					Incident Other Antihypertensive Treatment Cohort					Prevalent Aliskiren Treatment Cohort					Prevalent Other Antihypertensive Treatment Cohort				

	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Female gender (overall)						540	81	545.5	438.8	678.3	33	6	573.8	257.8	1,277.2	1,074	183	468.9	405.7	542.1
18 - 44						62	4	192.7	72.3	513.4	1	0	0.0	0.0	0.0	53	6	254.4	114.3	566.2
45 - 64						307	56	666.1	512.6	865.5	16	3	539.5	174.0	1,672.6	613	116	501.3	417.9	601.3
65+						171	21	481.2	313.8	738.0	16	3	707.2	228.1	2,192.8	408	61	451.0	350.9	579.7
Ulcerative colitis/rectocolitis (overall)	2	1	1,780.5	25 0.8	12,639.8	2,990	663	843.9	782.0	910.6	82	23	1,105.1	734.4	1,663.0	4,923	1,396	809.8	768.4	853.4
Male gender (overall)						1,511	380	968.6	875.9	1,071.0	34	12	1,387.6	788.0	2,443.4	2,340	752	936.6	872.0	1,006.0
18 - 44						306	55	657.8	505.0	856.7	2	0	0.0	0.0	0.0	261	64	582.5	456.0	744.3
45 - 64						995	273	1,046.4	929.3	1,178.2	23	11	1,867.7	1,034.3	3,372.5	1,574	531	979.6	897.7	1,066.6
65+						210	52	1,087.6	828.8	1,427.3	9	1	536.7	75.6	3,810.0	505	157	1,039.8	889.2	1,215.8
Female gender (overall)	2	1	1,780.5	25 0.8	12,639.8	1,479	283	719.5	640.4	808.4	48	11	904.3	500.8	1,632.9	2,583	644	699.3	647.3	755.4
18 - 44			0.0	0.0	0.0	266	33	453.9	322.7	638.5	6	1	608.8	85.8	4,322.2	231	50	534.4	405.1	705.2

45 - 64	2	1	1,780.5	250.8	12,639.8	962	209	815.1	711.8	933.4	27	6	861.6	387.1	1,917.9	1,745	452	710.8	648.2	779.5
65+			0.0	0.0	0.0	251	41	638.6	470.2	867.3	15	4	1,124.2	421.9	2,995.3	607	142	741.4	628.9	873.9
Crohn's disease (overall)	2	0	0.0	0.0	0.0	2,918	557	693.1	637.8	753.1	72	13	624.0	362.3	1,074.6	4,195	1,135	768.7	725.3	814.8
Male gender (overall)						1,349	281	757.2	673.7	851.1	37	7	642.3	306.2	1,347.4	1,879	532	813.2	747.0	885.3
18 - 44						330	52	553.4	421.7	726.3	2	0	0.0	0.0	0.0	209	30	329.1	230.1	470.7
45 - 64						877	200	830.4	722.9	953.8	30	7	825.2	393.4	1,730.8	1,325	396	844.9	765.7	932.4
65+						142	29	799.2	555.3	1,150.0	5	0	0.0	0.0	0.0	345	106	1,123.7	928.9	1,359.3

	Incident Aliskiren Treatment Cohort					Incident Other Antihypertensive Treatment Cohort					Prevalent Aliskiren Treatment Cohort					Prevalent Other Antihypertensive Treatment Cohort				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	2	0	0.0	0.0	0.0	1,569	276	638.0	567.0	717.9	35	6	603.8	271.3	1,344.0	2,316	603	733.3	677.0	794.2
18 - 44						397	59	526.5	407.9	679.5	4	0	0.0	0.0	0.0	257	63	636.5	497.2	814.8
45 - 64	2	0	0.0	0.0	0.0	976	181	665.4	575.2	769.8	20	3	517.1	166.8	1,603.2	1,621	461	787.0	718.4	862.3

65+						196	36	741.9	535.1	1,028.5	11	3	1,114.3	359.4	3,454.9	438	79	574.1	460.5	715.8
Familial adenomatous polyps/ Hereditary nonpolyposis (overall)	3	3	5,745.0	1,852.9	17,812.8	261	80	1,478.6	1,187.6	1,840.8	10	3	1,160.0	374.1	3,596.5	333	121	1,229.2	1,028.6	1,468.9
Male gender (overall)	1	1	5,944.6	837.4	42,201.3	96	35	1,633.8	1,173.0	2,275.4	6	3	2,336.7	753.7	7,245.2	140	61	1,486.2	1,156.3	1,910.1
18 - 44						4	1	1,055.5	148.7	7,493.2						4	2	1,280.5	320.2	5,119.9
45 - 64			0.0	0.0	0.0	61	23	1,792.5	1,191.2	2,697.4	1	0	0.0	0.0	0.0	98	40	1,252.1	918.5	1,707.0
65+	1	1	5,944.6	837.4	42,201.3	31	11	1,439.0	796.9	2,598.3	5	3	2,771.5	893.9	8,593.1	38	19	2,520.8	1,607.9	3,952.0
Female gender (overall)	2	2	5,650.2	1,413.1	22,591.8	165	45	1,376.9	1,028.0	1,844.1	4	0	0.0	0.0	0.0	193	60	1,045.4	811.7	1,346.4
18 - 44						10	4	2,153.7	808.3	5,738.4						5	0	0.0	0.0	0.0
45 - 64	2	2	5,650.2	1,413.1	22,591.8	120	34	1,426.3	1,019.1	1,996.1	1	0	0.0	0.0	0.0	142	43	1,025.3	760.4	1,382.5
65+						35	7	1,001.9	477.6	2,101.6	3	0	0.0	0.0	0.0	46	17	1,353.5	841.4	2,177.3
By Co-Medication:																				
NSAIDs (overall)	145	20	450.1	290.4	697.6	66,860	8,752	460.2	450.6	469.9	1,613	286	571.5	508.9	641.7	99,905	20,833	546.7	539.3	554.2

Male gender (overall)	62	11	58 3.5	32 3.1	1,053.6	31,530	4,583	51 5.5	50 0.8	53 0.7	778	137	56 3.9	47 6.9	666.6	41,932	9,929	62 9.3	61 7.0	64 1.8
18 - 44	15	2	50 2.1	12 5.6	2,007.7	7,602	275	11 8.9	10 5.6	13 3.8	58	2	96.3	24.1	385.0	4,222	294	15 4.2	13 7.5	17 2.8
45 - 64	41	9	66 2.0	34 4.4	1,272.2	21,188	3,762	63 9.9	61 9.8	66 0.7	565	104	58 2.4	48 0.5	705.8	30,131	7,673	66 8.8	65 4.0	68 3.9
65+	6	0	0.0	0.0	0.0	2,740	546	78 2.3	71 9.3	85 0.7	155	31	71 0.7	49 9.8	1,010.6	7,579	1,962	81 8.1	78 2.7	85 5.1

	Incident Aliskiren Treatment Cohort					**Incident Other Antihypertensive Treatment Cohort**					**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	83	9	35 1.8	18 3.0	676.1	35,330	4,169	41 1.6	39 9.3	42 4.2	835	149	57 8.7	49 2.8	679.5	57,973	10,904	48 8.4	47 9.3	49 7.6
18 - 44	15	1	18 8.2	26.5	1,336.3	8,217	304	12 2.0	10 9.0	13 6.5	48	6	37 7.0	16 9.4	839.2	4,807	354	16 2.2	14 6.2	18 0.0
45 - 64	60	7	39 7.6	18 9.6	834.1	23,479	3,333	49 9.0	48 2.4	51 6.3	552	102	57 5.8	47 4.2	699.1	41,333	8,410	52 0.3	50 9.3	53 1.6
65+	8	1	37 4.7	52.8	2,660.1	3,634	532	55 4.8	50 9.6	60 4.0	235	41	63 6.5	46 8.6	864.4	11,833	2,140	53 7.5	51 5.2	56 0.7
Statins (overall)	317	56	58 0.1	44 6.4	753.8	180,038	28,993	58 2.7	57 6.1	58 9.5	5,195	1,104	72 8.0	68 6.3	772.2	335,292	77,666	62 9.5	62 5.1	63 3.9
Male gender (overall)	206	36	54 9.9	39 6.6	762.3	110,086	18,567	61 1.5	60 2.7	62 0.3	3,036	720	81 2.6	75 5.4	874.2	189,469	47,938	69 1.7	68 5.6	69 8.0

18 - 44	42	2	11 6.9	29. 2	467 .3	15, 838	585	11 9.2	10 9.9	12 9.3	245	18	20 7.0	13 0.4	328 .6	14,9 01	1,0 53	15 4.0	14 5.0	16 3.6
45 - 64	148	29	64 9.8	45 1.5	935 .0	79, 603	14, 897	68 2.2	67 1.3	69 3.2	2,0 99	53 1	85 2.3	78 2.8	927 .9	133, 584	36, 174	72 8.4	72 0.9	73 5.9
65+ years	16	5	1,3 42. 5	55 8.8	3,2 25. 4	14, 645	3,0 85	85 2.2	82 2.6	88 2.8	692	17 1	97 1.5	83 6.3	1,1 28. 6	40,9 84	10, 711	83 6.8	82 1.1	85 2.8
Female gender (overall)	111	20	64 3.8	41 5.3	997 .9	69, 952	10, 426	53 7.7	52 7.5	54 8.1	2,1 59	38 4	60 9.0	55 1.0	673 .1	145, 823	29, 728	54 9.7	54 3.5	55 6.0
18 - 44	10	1	40 8.2	57. 5	2,8 97. 7	6,0 76	273	14 5.8	12 9.5	16 4.2	84	6	21 5.2	96. 7	478 .9	6,24 8	466	16 3.3	14 9.1	17 8.8
45 - 64	75	15	67 7.9	40 8.7	1,1 24. 4	50, 793	8,2 56	58 4.7	57 2.2	59 7.4	1,2 43	23 6	62 6.8	55 1.7	712 .1	98,2 73	21, 679	58 1.3	57 3.6	58 9.1
65+	26	4	61 6.5	23 1.4	1,6 42. 5	13, 083	1,8 97	55 8.5	53 3.9	58 4.2	832	14 2	62 7.9	53 2.7	740 .2	41,3 02	7,5 83	54 4.2	53 2.0	55 6.5
By Lifestyle factors:																				
Alcohol dependence syndrome, defined by ICD-9-CM 303.x (overall)	11	3	83 6.6	26 9.8	2,5 93. 9	7,6 39	945	47 2.7	44 3.5	50 3.8	76	14	63 4.8	37 6.0	1,0 71. 8	6,90 6	1,3 70	57 7.0	54 7.2	60 8.3
Male gender (overall)	10	3	87 6.9	28 2.8	2,7 18. 9	5,6 70	729	49 4.8	46 0.2	53 2.1	67	11	55 9.4	30 9.8	1,0 10. 1	4,96 9	1,0 52	61 6.2	58 0.1	65 4.6
18 - 44	3	0	0.0	0.0	0.0	1,5 79	43	99. 8	74. 0	13 4.6	10	0	0.0	0.0	0.0	906	55	15 2.2	11 6.9	19 8.2
45 - 64	7	3	1,2 16. 3	39 2.3	3,7 71. 1	3,7 73	621	64 2.7	59 4.1	69 5.3	49	11	75 3.5	41 7.3	1,3 60. 5	3,53 0	850	72 0.6	67 3.7	77 0.7
65+			0.0	0.0	0.0	318	65	85 1.4	66 7.7	1,0 85. 7	8	0	0.0	0.0	0.0	533	147	88 4.2	75 2.2	1,0 39. 3

	Incident Aliskiren Treatment Cohort					Incident Other Antihypertensive Treatment Cohort					Prevalent Aliskiren Treatment Cohort					Prevalent Other Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Female gender (overall)	1	0	0.0	0.0	0.0	1,969	216	410.6	359.3	469.1	9	3	1,255.0	404.8	3,891.3	1,937	318	476.5	426.9	531.9
18 - 44						523	13	87.1	50.6	150.1	1	0	0.0	0.0	0.0	314	24	205.7	137.9	306.9
45 - 64	1	0	0.0	0.0	0.0	1,361	192	537.0	466.2	618.6	8	3	1,335.0	430.6	4,139.4	1,396	256	537.6	475.6	607.6
65+						85	11	567.1	314.0	1,024.0						227	38	510.2	371.3	701.2
Obesity, defined by ICD-9-CM 278.0x(overall)	147	19	400.5	255.4	627.8	88,395	10,671	435.6	427.4	444.0	2,483	476	643.3	588.0	703.8	102,907	21,003	529.2	522.1	536.4
Male gender (overall)	69	9	387.1	201.4	744.0	41,087	5,431	484.9	472.2	498.0	1,312	272	698.9	620.6	787.1	43,378	9,858	602.2	590.4	614.2
18 - 44	24	2	199.7	49.9	798.5	13,807	478	118.5	108.3	129.6	201	6	85.7	38.5	190.7	8,245	517	141.9	130.2	154.7
45 - 64	40	7	576.3	274.7	1,208.9	25,082	4,451	668.6	649.3	688.5	956	218	775.8	679.4	886.0	30,564	8,072	712.9	697.5	728.6
65+	5	0	0.0	0.0	0.0	2,198	502	986.1	903.5	1,076.2	155	48	1,257.8	947.9	1,669.1	4,569	1,269	903.4	855.1	954.5
Female gender (overall)	78	10	413.3	222.4	768.2	47,308	5,240	394.1	383.5	404.9	1,171	204	581.6	507.0	667.2	59,529	11,145	478.0	469.2	486.9
18 - 44	17	0	0.0	0.0	0.0	16,183	588	121.8	112.3	132.0	171	8	137.7	68.9	275.4	10,779	730	152.1	141.5	163.6
45 - 64	55	8	49	24	989	28,	4,2	54	52	55	825	16	66	56	771	42,6	9,1	55	54	56

			5.0	7.5	.8	760	84	2.3	6.3	8.8		4	1.6	7.7	.0	11	22	3.0	1.8	4.5
65+	6	2	1,322.2	330.7	5,286.8	2,365	368	645.8	583.1	715.3	175	32	714.6	505.4	1,010.5	6,139	1,293	638.8	604.9	674.6

Table 15-9 Incidence Rates (per 10,000 person-years) of Colorectal Hyperplasia for Antihypertensive Drug Use within 30 Days after Index

	All Patients					Incident Antihypertensive Treatment Cohort					Prevalent Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Overall:	2,302,421	408,523	517.3	515.7	518.9	919,629	124,447	470.5	467.9	473.1	1,382,792	284,076	540.9	538.9	542.9
Monotherapy Initiators:															
Aliskiren (overall)	7,740	1,517	633.7	602.6	666.4	1,506	231	464.8	408.6	528.8	6,234	1,286	677.9	641.9	716.0
Male gender (overall)	4,146	865	671.6	628.3	717.9	908	148	486.0	413.7	571.0	3,238	717	729.1	677.6	784.5
18 - 44 years	770	46	163.2	122.2	217.9	287	16	149.7	91.7	244.4	483	30	171.4	119.9	245.2
45 - 64 years	2,748	669	798.3	740.0	861.2	568	118	641.4	535.5	768.2	2,180	551	842.5	775.0	915.8
65+ years	628	150	892.6	760.6	1,047.5	53	14	1,023.9	606.4	1,728.8	575	136	880.9	744.6	1,042.2
Female gender (overall)	3,594	652	589.5	546.0	636.5	598	83	431.4	347.9	534.9	2,996	569	622.8	573.7	676.2
18 - 44 years	417	20	132.9	85.7	206.0	116	4	97.9	36.7	260.8	301	16	145.9	89.4	238.2
45 - 64 years	2,291	453	627.9	572.7	688.5	398	64	491.6	384.8	628.1	1,893	389	657.9	595.7	726.6
65+ years	886	179	764.9	660.7	885.6	84	15	702.0	423.2	1,164.5	802	164	771.2	661.8	898.7

Angiotensin-converting enzyme inhibitors (overall)	393,278	64,489	496.4	492.5	500.2	213,015	28,485	471.2	465.8	476.7	180,263	36,004	518.3	512.9	523.6
Male gender (overall)	235,110	41,038	530.8	525.7	536.0	129,150	18,092	494.6	487.4	501.8	105,960	22,946	563.4	556.1	570.7
18 - 44 years	56,516	2,247	111.2	106.7	115.9	37,052	1,156	101.3	95.6	107.3	19,464	1,091	124.1	117.0	131.7
45 - 64 years	156,213	33,559	661.4	654.4	668.5	82,695	14,998	656.8	646.4	667.4	73,518	18,561	665.2	655.7	674.8
65+ years	22,381	5,232	821.1	799.2	843.7	9,403	1,938	829.4	793.3	867.2	12,978	3,294	816.3	788.9	844.7
Female gender (overall)	158,168	23,451	445.7	440.0	451.5	83,865	10,393	435.4	427.1	443.8	74,303	13,058	454.3	446.6	462.2
18 - 44 years	26,041	1,087	116.8	110.0	123.9	16,773	545	105.3	96.9	114.6	9,268	542	131.0	120.5	142.5
45 - 64 years	110,136	18,880	514.8	507.5	522.2	57,688	8,459	519.4	508.4	530.6	52,448	10,421	511.1	501.3	521.0
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	21,991	3,484	525.7	508.5	543.5	9,404	1,389	575.9	546.4	607.0	12,587	2,095	497.0	476.2	518.7
Angiotensin II receptor blockers (overall)	151,843	27,723	518.6	512.5	524.7	62,809	8,987	481.4	471.6	491.5	89,034	18,736	538.5	530.8	546.3
Male gender (overall)	82,482	16,023	551.5	543.0	560.1	35,477	5,258	496.4	483.2	510.0	47,005	10,765	583.1	572.2	594.2
18 - 44 years	19,330	949	125.1	117.3	133.3	10,206	363	108.5	97.9	120.3	9,124	586	138.1	127.3	149.7
45 - 64 years	55,505	13,100	679.5	667.9	691.2	22,595	4,308	654.7	635.5	674.6	32,910	8,792	692.3	678.0	706.9
65+ years	7,647	1,974	903.0	864.0	943.7	2,676	587	878.7	810.4	952.8	4,971	1,387	913.6	866.8	963.0

Female gender (overall)	69,361	11,700	479.4	470.8	488.2	27,332	3,729	461.8	447.2	476.9	42,029	7,971	488.1	477.5	498.9
18 - 44 years	9,558	514	137.0	125.6	149.3	4,905	200	123.2	107.3	141.5	4,653	314	147.5	132.0	164.7
45 - 64 years	49,595	9,375	534.5	523.8	545.4	19,231	3,020	536.5	517.7	555.9	30,364	6,355	533.5	520.6	546.8
65+ years	10,208	1,811	581.9	555.7	609.4	3,196	509	619.3	567.7	675.5	7,012	1,302	568.6	538.5	600.3
Alpha blockers (overall)	36,386	8,033	766.1	749.5	783.1	23,721	4,548	728.8	707.9	750.3	12,665	3,485	820.9	794.1	848.7
Male gender (overall)	33,306	7,572	787.9	770.4	805.9	21,341	4,216	749.6	727.3	772.6	11,965	3,356	842.0	814.0	871.0
18 - 44 years	2,608	145	179.9	152.9	211.7	2,327	118	173.8	145.1	208.2	281	27	212.3	145.6	309.5
45 - 64 years	21,071	5,111	832.0	809.5	855.1	14,104	3,034	813.6	785.2	843.1	6,967	2,077	860.4	824.2	898.2
65+ years	9,627	2,316	870.4	835.7	906.6	4,910	1,064	874.9	823.9	929.1	4,717	1,252	866.7	820.0	916.0
Female gender (overall)	3,080	461	526.6	480.6	576.9	2,380	332	538.9	483.9	600.1	700	129	497.4	418.6	591.1
18 - 44 years	777	39	179.5	131.2	245.7	711	34	179.4	128.2	251.1	66	5	180.0	74.9	432.6
45 - 64 years	1,837	338	642.7	577.8	715.1	1,425	249	680.1	600.7	770.1	412	89	557.1	452.6	685.8
65+ years	466	84	634.8	512.6	786.2	244	49	809.8	612.0	1,071.4	222	35	487.4	349.9	678.8
Beta blockers (overall)	282,792	47,328	493.5	489.1	498.0	130,586	17,048	454.4	447.6	461.3	152,206	30,280	518.6	512.8	524.5
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	

Male gender (overall)	135,849	25,344	561.2	554.3	568.2	64,636	9,334	508.5	498.3	519.0	71,213	16,010	597.3	588.1	606.6
18 - 44 years	27,378	1,247	125.2	118.5	132.4	16,401	563	112.4	103.4	122.0	10,977	684	138.3	128.3	149.1
45 - 64 years	89,366	19,606	659.8	650.6	669.1	41,187	7,355	635.7	621.3	650.4	48,179	12,251	675.1	663.2	687.2
65+ years	19,105	4,491	818.6	795.0	842.9	7,048	1,416	798.4	757.9	841.1	12,057	3,075	828.2	799.5	858.0
Female gender (overall)	146,943	21,984	433.2	427.5	439.0	65,950	7,714	402.6	393.7	411.6	80,993	14,270	451.8	444.5	459.3
18 - 44 years	29,617	1,369	126.4	119.9	133.3	17,602	594	109.8	101.3	119.0	12,015	775	143.0	133.3	153.4
45 - 64 years	94,077	16,870	515.4	507.7	523.2	40,462	6,043	516.5	503.7	529.7	53,615	10,827	514.8	505.2	524.5
65+ years	23,249	3,745	521.5	505.1	538.5	7,886	1,077	524.8	494.4	557.1	15,363	2,668	520.2	500.9	540.3
Calcium channel blockers (overall)	137,584	23,941	517.7	511.2	524.3	63,375	8,550	474.7	464.8	484.9	74,209	15,391	545.1	536.5	553.8
Male gender (overall)	66,717	12,589	570.2	560.4	580.3	32,989	4,770	511.5	497.2	526.2	33,728	7,819	613.2	599.8	626.9
18 - 44 years	13,474	573	117.7	108.5	127.8	8,571	280	106.7	94.9	120.0	4,903	293	130.6	116.5	146.4
45 - 64 years	43,417	9,765	678.6	665.3	692.2	20,748	3,805	658.6	638.0	679.8	22,669	5,960	692.0	674.7	709.8
65+ years	9,826	2,251	798.3	766.0	832.0	3,670	685	741.1	687.7	798.8	6,156	1,566	826.2	786.3	868.1
Female gender (overall)	70,867	11,352	469.7	461.1	478.4	30,386	3,780	435.3	421.6	449.3	40,481	7,572	489.0	478.1	500.1
18 - 44 years	11,452	504	119.8	109.8	130.7	7,002	248	115.2	101.7	130.5	4,450	256	124.5	110.2	140.8
45 - 64 years	44,292	8,327	542.9	531.4	554.7	18,530	2,842	538.2	518.8	558.4	25,762	5,485	545.4	531.1	560.0

65+ years	15,123	2,521	545.2	524.3	566.9	4,854	690	551.1	511.5	593.8	10,269	1,831	543.0	518.7	568.5
Diuretics (overall)	222,236	36,503	492.1	487.1	497.2	117,118	15,778	462.0	454.8	469.3	105,118	20,725	517.8	510.8	524.9
Male gender (overall)	68,523	12,481	572.1	562.1	582.2	39,664	5,938	526.0	512.8	539.6	28,859	6,543	621.4	606.6	636.7
18 - 44 years	14,935	615	116.8	107.9	126.4	10,722	338	100.4	90.3	111.7	4,213	277	145.8	129.6	164.0
45 - 64 years	42,293	9,486	706.6	692.5	720.9	23,923	4,626	691.0	671.3	711.2	18,370	4,860	722.1	702.1	742.7
65+ years	11,295	2,380	761.1	731.2	792.3	5,019	974	793.1	744.8	844.5	6,276	1,406	740.5	702.8	780.2

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	153,713	24,022	458.8	453.0	464.6	77,454	9,840	430.4	422.0	439.0	76,259	14,182	480.8	472.9	488.8
18 - 44 years	30,291	1,450	130.6	124.0	137.5	19,626	775	124.2	115.8	133.3	10,665	675	138.7	128.6	149.6
45 - 64 years	100,790	18,690	544.3	536.5	552.1	49,001	7,749	541.3	529.4	553.5	51,789	10,941	546.4	536.3	556.7
65+ years	22,632	3,882	561.2	543.8	579.1	8,827	1,316	570.0	540.0	601.6	13,805	2,566	556.8	535.7	578.8
Others (overall)	12,401	1,417	343.3	325.9	361.7	7,267	651	312.4	289.3	337.3	5,134	766	374.9	349.3	402.5
Male gender (overall)	4,284	558	416.2	383.0	452.2	2,750	268	346.8	307.7	390.9	1,534	290	510.6	455.0	572.8
18 - 44 years	1,398	33	73.6	52.3	103.6	1,093	23	72.7	48.3	109.4	305	10	75.9	40.8	141.1
45 - 64 years	2,378	403	536.7	486.8	591.7	1,421	199	503.3	438.0	578.4	957	204	573.8	500.2	658.2

65+ years	508	122	861.0	721.0	1,028.1	236	46	754.5	565.1	1,007.3	272	76	941.4	751.9	1,178.7
Female gender (overall)	8,117	859	308.3	288.3	329.6	4,517	383	292.1	264.2	322.8	3,600	476	322.7	295.0	353.0
18 - 44 years	3,384	110	88.6	73.5	106.8	2,000	47	77.5	58.2	103.2	1,384	63	99.1	77.4	126.9
45 - 64 years	3,929	635	487.5	451.1	527.0	2,199	290	462.1	411.9	518.5	1,730	345	511.2	460.0	568.1
65+ years	804	114	471.2	392.2	566.1	318	46	592.7	444.0	791.3	486	68	413.8	326.2	524.8
Dual-combination Therapy Initiators:															
Dual combination including aliskiren (overall)	5,140	1,074	703.6	662.7	746.9	254	72	1,031.6	818.8	1,299.6	4,886	1,002	687.8	646.5	731.8
Male gender (overall)	2,589	585	768.6	708.8	833.5	146	37	883.5	640.1	1,219.4	2,443	548	761.9	700.7	828.4
18 - 44 years	308	14	131.3	77.7	221.6	34	1	85.1	12.0	604.4	274	13	137.0	79.5	235.9
45 - 64 years	1,742	420	804.2	730.9	884.9	95	29	1,110.3	771.6	1,597.8	1,647	391	788.1	713.7	870.2
65+ years	539	151	1,142.0	973.6	1,339.5	17	7	1,743.7	831.3	3,657.5	522	144	1,123.2	953.9	1,322.4
Female gender (overall)	2,551	489	638.9	584.7	698.1	108	35	1,253.6	900.1	1,746.0	2,443	454	615.6	561.5	674.9
18 - 44 years	215	12	154.0	87.5	271.2	20	1	151.2	21.3	1,073.4	195	11	154.3	85.4	278.5
45 - 64 years	1,596	356	738.1	665.3	818.9	76	32	1,781.6	1,259.9	2,519.4	1,520	324	697.7	625.7	778.0
65+ years	740	121	589.8	493.5	704.8	12	2	598.1	149.6	2,391.3	728	119	589.7	492.7	705.7

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				

	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Dual combination including an ACEI but not aliskiren (overall)	355,263	62,841	508.0	504.0	511.9	125,526	16,312	455.4	448.5	462.4	229,737	46,529	529.4	524.6	534.2
Male gender (overall)	197,355	37,897	556.8	551.2	562.4	71,459	9,930	490.1	480.6	499.9	125,896	27,967	585.1	578.3	592.0
18 - 44 years	34,066	1,569	120.3	114.5	126.4	16,782	512	99.0	90.8	108.0	17,284	1,057	134.3	126.4	142.6
45 - 64 years	136,861	30,162	640.2	633.0	647.5	48,192	8,167	607.6	594.6	621.0	88,669	21,995	653.2	644.7	661.9
65+ years	26,428	6,166	779.9	760.7	799.6	6,485	1,251	759.2	718.2	802.4	19,943	4,915	785.4	763.7	807.6
Female gender (overall)	157,908	24,944	448.2	442.7	453.8	54,067	6,382	410.2	400.2	420.3	103,841	18,562	463.0	456.4	469.7
18 - 44 years	21,357	986	120.7	113.4	128.5	10,814	371	110.3	99.6	122.1	10,543	615	128.0	118.3	138.5
45 - 64 years	109,428	19,539	502.4	495.4	509.5	36,912	5,171	490.5	477.4	504.1	72,516	14,368	506.8	498.6	515.1
65+ years	27,123	4,419	514.3	499.3	529.7	6,341	840	507.5	474.3	543.0	20,782	3,579	515.9	499.2	533.1
Dual combination including neither an ACEI nor aliskiren (overall)	386,074	72,533	521.8	518.0	525.6	108,724	14,866	457.7	450.4	465.1	277,350	57,667	541.4	537.0	545.8
Male gender (overall)	171,251	35,554	588.5	582.4	594.7	52,593	7,835	502.2	491.2	513.5	118,658	27,719	618.6	611.3	625.9
18 - 44 years	27,948	1,470	130.1	123.6	136.9	12,122	421	105.2	95.6	115.7	15,826	1,049	143.7	135.3	152.7
45 - 64 years	115,039	27,262	670.8	662.8	678.8	34,510	6,237	619.0	603.8	634.5	80,529	21,025	687.8	678.6	697.2
65+ years	28,264	6,822	805.8	786.9	825.1	5,961	1,177	773.8	730.8	819.3	22,303	5,645	812.8	791.8	834.3
Female gender (overall)	214,823	36,979	470.5	465.7	475.3	56,131	7,031	416.5	406.9	426.4	158,692	29,948	485.3	479.8	490.8
18 - 44 years	27,61	1,48	132.	125	139.	11,41	410	109.	99.4	120.	16,20	1,07	143.	135	152.

	4	8	3	.8	2	4		5		6	0	8	7	.4	6
45 - 64 years	146,869	28,450	523.6	517.6	529.8	37,223	5,544	498.3	485.4	511.6	109,646	22,906	530.2	523.3	537.1
65+ years	40,340	7,041	541.0	528.5	553.8	7,494	1,077	535.8	504.7	568.8	32,846	5,964	541.9	528.3	555.9
Triple-plus Combination Therapy Initiators:															
Triple-plus combination including aliskiren (overall)	11,559	2,459	714.5	686.8	743.3	376	72	700.2	555.8	882.2	11,183	2,387	714.9	686.8	744.2
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Male gender (overall)	6,600	1,517	774.3	736.3	814.2	215	39	673.2	491.9	921.4	6,385	1,478	777.4	738.7	818.0
18 - 44 years	734	44	170.4	126.8	229.0	37	0				697	44	178.3	132.7	239.6
45 - 64 years	4,554	1,147	845.1	797.6	895.5	154	32	760.2	537.6	1,075.0	4,400	1,115	847.9	799.5	899.1
65+ years	1,312	326	948.1	850.6	1,056.8	24	7	1,596.6	761.1	3,349.0	1,288	319	939.8	842.1	1,048.8
Female gender (overall)	4,959	942	635.5	596.1	677.4	161	33	735.1	522.6	1,034.1	4,798	909	632.3	592.5	674.8
18 - 44 years	330	15	131.5	79.3	218.2	14	0				316	15	137.7	83.0	228.4
45 - 64 years	2,985	619	665.4	615.0	719.9	115	24	746.2	500.2	1,113.4	2,870	595	662.5	611.3	717.9
65+ years	1,644	308	703.1	628.8	786.2	32	9	1,183.1	615.6	2,273.9	1,612	299	694.6	620.2	778.0
Triple-plus combination including an ACEI but not aliskiren (overall)	174,301	32,755	538.2	532.4	544.0	42,590	5,640	469.6	457.5	482.1	131,711	27,115	555.0	548.4	561.6
Male gender (overall)	99,428	20,613	600.9	592.8	609.2	24,515	3,526	513.8	497.1	531.0	74,913	17,087	622.7	613.4	632.1
18 - 44 years	11,12	520	118.	108	129.	4,418	128	94.3	79.3	112.	6,703	392	129.	117	142.

	1		4	.7	1					1			2	.1	7
45 - 64 years	67,507	15,294	649.4	639.2	659.8	16,498	2,717	593.3	571.4	616.0	51,009	12,577	663.0	651.5	674.7
65+ years	20,800	4,799	754.4	733.4	776.1	3,599	681	736.1	682.8	793.5	17,201	4,118	757.5	734.8	781.0
Female gender (overall)	74,873	12,142	457.1	449.0	465.3	18,075	2,114	410.8	393.6	428.7	56,798	10,028	468.2	459.2	477.5
18 - 44 years	6,716	343	131.7	118.5	146.5	3,004	100	106.8	87.8	129.9	3,712	243	145.8	128.5	165.3
45 - 64 years	48,847	8,848	500.2	489.9	510.7	11,890	1,637	482.9	460.0	506.8	36,957	7,211	504.3	492.8	516.1
65+ years	19,310	2,951	470.6	453.9	487.9	3,181	377	459.8	415.7	508.7	16,129	2,574	472.2	454.3	490.8
Triple-plus combination including neither an ACEI nor aliskiren (overall)	125,824	25,910	583.4	576.3	590.5	22,762	3,207	501.3	484.3	519.0	103,062	22,703	597.2	589.5	605.0
Male gender (overall)	61,435	14,173	668.4	657.5	679.5	11,879	1,849	561.0	536.0	587.2	49,556	12,324	688.2	676.1	700.4
18 - 44 years	6,164	330	133.1	119.5	148.3	2,060	61	97.6	76.0	125.5	4,104	269	145.1	128.7	163.5
45 - 64 years	41,115	10,274	712.1	698.4	726.0	7,847	1,351	623.2	590.9	657.4	33,268	8,923	727.8	712.8	743.0
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	14,156	3,569	830.7	803.9	858.4	1,972	437	868.5	790.7	953.8	12,184	3,132	825.7	797.3	855.2
Female gender (overall)	64,389	11,737	505.7	496.6	514.9	10,883	1,358	437.8	415.2	461.8	53,506	10,379	516.1	506.3	526.2
18 - 44 years	4,882	273	138.4	122.9	155.8	1,743	54	98.1	75.1	128.1	3,139	219	154.0	134.9	175.8
45 - 64 years	41,57	8,25	534.	523	546.	6,845	966	494.	464.	526.	34,72	7,28	540.	528	553.

	3	5	9	.5	6			3	1	4	8	9	8	.6	4
65+ years	17,934	3,209	552.8	534.0	572.2	2,295	338	566.5	509.2	630.2	15,639	2,871	551.2	531.4	571.7

Table 15-10 Incidence Rates (per 10,000 person-years) of Colorectal Hyperplasia based on Antihypertensive Therapy Exposure Time

	All Patients					Incident Antihypertensive Treatment Cohort					Prevalent Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Monotherapy Initiators:															
Aliskiren (overall)	1,895	286	514.8	458.5	578.1	782	117	501.3	418.2	600.9	1,113	169	524.6	451.2	610.0
Male gender (overall)	1,042	173	560.1	482.5	650.1	468	74	511.3	407.1	642.1	574	99	603.1	495.3	734.4
18 - 44 years	283	15	156.2	94.2	259.2	152	8	154.6	77.3	309.1	131	7	158.2	75.4	331.8
45 - 64 years	673	140	731.0	619.4	862.7	285	57	666.9	514.4	864.6	388	83	782.6	631.2	970.5
65+ years	86	18	842.7	530.9	1,337.5	31	9	1,197.9	623.3	2,302.3	55	9	650.0	338.2	1,249.2
Female gender (overall)	853	113	458.2	381.0	550.9	314	43	485.1	359.8	654.1	539	70	443.1	350.5	560.0
18 - 44 years	139	4	88.7	33.3	236.3	60	3	159.2	51.3	493.6	79	1	38.1	5.4	270.4
45 - 64 years	577	92	552.4	450.3	677.7	208	36	610.4	440.3	846.1	369	56	520.7	400.7	676.6
65+ years	137	17	485.8	302.0	781.5	46	4	370.1	138.9	986.0	91	13	537.5	312.1	925.8
Angiotensin-converting enzyme inhibitors	289,7	43,9	471.	467	476.	162,8	20,3	450.	443.	456.	126,8	23,6	492.	485	498.

(overall)	14	71	7	.3	1	73	46	1	9	3	41	25	0	.8	3
Male gender (overall)	175,963	28,097	497.5	491.7	503.3	100,632	13,049	467.3	459.4	475.4	75,331	15,048	526.9	518.6	535.4
18 - 44 years	46,651	1,665	101.9	97.2	107.0	30,762	863	92.8	86.8	99.2	15,889	802	114.0	106.3	122.1
45 - 64 years	115,351	23,396	643.2	635.0	651.5	63,283	10,901	639.3	627.4	651.4	52,068	12,495	646.6	635.3	658.0
65+ years	13,961	3,036	805.1	777.0	834.3	6,587	1,285	815.1	771.7	860.9	7,374	1,751	797.9	761.4	836.2
Female gender (overall)	113,751	15,874	432.0	425.3	438.8	62,241	7,297	422.2	412.6	432.0	51,510	8,577	440.8	431.5	450.2
18 - 44 years	20,109	807	115.0	107.4	123.3	13,108	414	104.3	94.7	114.8	7,001	393	129.1	116.9	142.5
45 - 64 years	79,704	12,969	504.1	495.5	512.9	42,656	6,011	513.0	500.2	526.2	37,048	6,958	496.6	485.1	508.5
65+ years	13,938	2,098	524.2	502.2	547.1	6,477	872	545.9	510.8	583.4	7,461	1,226	509.7	482.0	539.1
Angiotensin II receptor blockers (overall)	112,416	19,199	509.3	502.2	516.6	53,045	7,419	486.5	475.5	497.7	59,371	11,780	524.8	515.4	534.4
Male gender (overall)	61,541	11,024	534.5	524.6	544.6	29,821	4,237	492.8	478.1	507.8	31,720	6,787	564.4	551.1	578.0
18 - 44 years	15,509	722	125.8	116.9	135.3	8,784	301	109.1	97.5	122.2	6,725	421	141.2	128.4	155.4

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
45 - 64 years	41,283	9,123	670.3	656.7	684.2	19,005	3,485	651.7	630.4	673.7	22,278	5,638	682.4	664.8	700.4
65+ years	4,749	1,179	925.2	873.9	979.6	2,032	451	915.4	834.7	1,003.9	2,717	728	931.4	866.2	1,001.6

Female gender (overall)	50,875	8,175	478.8	468.6	489.3	23,224	3,182	478.3	462.0	495.2	27,651	4,993	479.2	466.1	492.7
18 - 44 years	7,318	373	137.9	124.6	152.7	4,123	166	126.4	108.5	147.1	3,195	207	148.9	129.9	170.6
45 - 64 years	37,052	6,661	532.8	520.1	545.7	16,530	2,583	549.3	528.5	570.9	20,522	4,078	522.9	507.1	539.2
65+ years	6,505	1,141	611.4	576.9	647.9	2,571	433	680.9	619.7	748.1	3,934	708	575.5	534.6	619.5
Alpha blockers (overall)	23,925	4,837	732.3	711.9	753.2	17,671	3,188	704.6	680.6	729.5	6,254	1,649	792.4	755.0	831.6
Male gender (overall)	21,998	4,567	749.0	727.6	771.0	16,044	2,975	721.2	695.7	747.6	5,954	1,592	807.2	768.5	847.8
18 - 44 years	1,978	91	154.3	125.6	189.5	1,797	75	147.4	117.5	184.8	181	16	198.0	121.3	323.1
45 - 64 years	14,452	3,230	796.2	769.2	824.1	10,693	2,172	786.8	754.4	820.6	3,759	1,058	816.2	768.5	866.9
65+ years	5,568	1,246	858.8	812.4	907.9	3,554	728	850.9	791.3	915.0	2,014	518	870.3	798.5	948.5
Female gender (overall)	1,927	270	531.4	471.7	598.7	1,627	213	533.5	466.5	610.2	300	57	523.7	404.0	679.0
18 - 44 years	531	25	174.2	117.7	257.7	496	25	197.4	133.4	292.1	35	0	0.0	0.0	0.0
45 - 64 years	1,171	202	658.1	573.3	755.4	976	155	652.0	557.0	763.1	195	47	679.0	510.2	903.7
65+ years	225	43	746.9	553.9	1,007.0	155	33	947.3	673.5	1,332.5	70	10	439.8	236.6	817.3
Beta blockers (overall)	190,906	28,855	465.2	459.8	470.6	98,709	11,956	434.2	426.5	442.1	92,197	16,899	489.9	482.5	497.3
Male gender (overall)	90,527	15,149	524.5	516.2	532.9	47,998	6,404	484.1	472.4	496.1	42,529	8,745	558.6	547.0	570.5
18 - 44 years	21,020	866	118.3	110.6	126.4	13,281	433	109.6	99.7	120.4	7,739	433	128.4	116.9	141.1

45 - 64 years	58,932	11,995	641.4	630.0	653.0	29,998	5,084	624.4	607.5	641.9	28,934	6,911	654.4	639.2	670.0
65+ years	10,575	2,288	800.8	768.7	834.3	4,719	887	781.4	731.7	834.6	5,856	1,401	813.6	772.1	857.3
Female gender (overall)	100,379	13,706	413.5	406.6	420.4	50,711	5,552	388.1	378.0	398.4	49,668	8,154	432.7	423.4	442.2
18 - 44 years	22,837	927	116.1	108.9	123.8	14,478	444	102.4	93.3	112.3	8,359	483	132.4	121.1	144.8
45 - 64 years	64,226	10,771	505.9	496.5	515.6	30,675	4,378	510.2	495.3	525.5	33,551	6,393	503.1	490.9	515.6
65+ years	13,316	2,008	518.2	496.0	541.4	5,558	730	526.3	489.5	565.9	7,758	1,278	513.7	486.3	542.6

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Calcium channel blockers (overall)	87,732	13,619	482.8	474.7	490.9	46,298	5,832	453.8	442.3	465.6	41,434	7,787	507.0	495.9	518.4
Male gender (overall)	42,216	7,059	527.5	515.3	539.9	23,689	3,158	483.9	467.3	501.0	18,527	3,901	569.0	551.4	587.2
18 - 44 years	9,731	362	107.7	97.1	119.3	6,542	197	100.9	87.8	116.0	3,189	165	117.0	100.4	136.3
45 - 64 years	27,245	5,620	653.8	636.9	671.1	14,729	2,533	635.1	610.8	660.3	12,516	3,087	670.0	646.8	694.1
65+ years	5,240	1,077	756.5	712.6	803.0	2,418	428	730.5	664.5	803.1	2,822	649	774.6	717.2	836.5
Female gender (overall)	45,516	6,560	442.4	431.8	453.2	22,609	2,674	422.7	407.0	439.0	22,907	3,886	457.1	442.9	471.7
18 - 44 years	8,051	299	107.3	95.8	120.1	5,374	170	105.8	91.1	123.0	2,677	129	109.2	91.9	129.8
45 - 64 years	28,59	4,89	517.	502	531.	13,71	2,03	528.	506.	552.	14,87	2,86	509.	490	528.

	3	7	0	.7	6	7	0	6	1	1	6	7	0	.7	0
65+ years	8,872	1,364	531.2	503.7	560.1	3,518	474	539.2	492.8	590.0	5,354	890	527.0	493.5	562.8
Diuretics (overall)	141,024	20,903	468.5	462.2	474.9	80,560	9,930	444.6	435.9	453.4	60,464	10,973	492.4	483.3	501.7
Male gender (overall)	38,982	6,260	539.8	526.6	553.3	24,991	3,377	505.0	488.3	522.3	13,991	2,883	587.1	566.1	609.0
18 - 44 years	9,188	325	108.2	97.0	120.6	6,855	191	94.9	82.3	109.3	2,333	134	135.2	114.1	160.1
45 - 64 years	23,877	4,817	683.0	663.9	702.5	14,875	2,615	668.3	643.1	694.4	9,002	2,202	701.3	672.6	731.2
65+ years	5,917	1,118	726.0	684.7	769.8	3,261	571	750.2	691.1	814.3	2,656	547	702.4	645.9	763.7
Female gender (overall)	102,042	14,643	443.4	436.3	450.7	55,569	6,553	418.8	408.7	429.0	46,473	8,090	465.6	455.6	475.9
18 - 44 years	21,443	907	122.0	114.3	130.2	14,349	504	116.1	106.4	126.7	7,094	403	130.1	118.0	143.5
45 - 64 years	67,039	11,583	533.9	524.3	543.7	34,933	5,179	531.6	517.3	546.3	32,106	6,404	535.8	522.8	549.1
65+ years	13,560	2,153	553.3	530.4	577.2	6,287	870	555.3	519.6	593.5	7,273	1,283	552.0	522.6	583.0
Others (overall)	6,401	551	286.6	263.6	311.5	4,454	308	257.8	230.6	288.3	1,947	243	333.8	294.3	378.5
Male gender (overall)	2,088	200	342.1	297.8	393.0	1,572	116	286.8	239.1	344.0	516	84	466.4	376.6	577.6
18 - 44 years	889	18	69.7	43.9	110.6	721	12	62.6	35.6	110.2	168	6	90.2	40.5	200.8
45 - 64 years	1,009	150	539.3	459.6	632.9	724	84	460.0	371.4	569.6	285	66	691.1	543.0	879.7
65+ years	190	32	663.2	469.0	937.8	127	20	663.1	427.8	1,027.7	63	12	663.5	376.8	1,168.3

Female gender (overall)	4,313	351	262.3	236.3	291.2	2,882	192	243.0	210.9	279.9	1,431	159	290.2	248.4	339.0
18 - 44 years	2,023	39	59.3	43.3	81.2	1,389	22	56.2	37.0	85.3	634	17	63.9	39.7	102.8
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
45 - 64 years	1,986	272	452.7	401.9	509.8	1,314	149	416.3	354.5	488.8	672	123	506.3	424.3	604.2
65+ years	304	40	502.0	368.2	684.4	179	21	516.5	336.8	792.2	125	19	486.9	310.6	763.3
Dual-combination Therapy Initiators:															
Dual combination including aliskiren (overall)	2,216	394	630.7	571.4	696.2	256	40	529.0	388.0	721.1	1,960	354	644.8	581.0	715.5
Male gender (overall)	1,116	217	695.1	608.5	794.0	154	23	492.0	326.9	740.3	962	194	730.9	634.9	841.3
18 - 44 years	198	9	148.5	77.2	285.3	40	2	148.7	37.2	594.4	158	7	148.4	70.7	311.3
45 - 64 years	745	159	755.3	646.6	882.3	100	14	459.0	271.8	775.0	645	145	805.5	684.5	947.9
65+ years	173	49	1,193.5	902.1	1,579.2	14	7	2,502.7	1,193.1	5,249.7	159	42	1,097.8	811.3	1,485.5
Female gender (overall)	1,100	177	566.4	488.9	656.4	102	17	588.9	366.1	947.4	998	160	564.2	483.2	658.7
18 - 44 years	129	3	68.3	22.0	211.7	20	1	170.1	24.0	1,207.3	109	2	52.5	13.1	210.1
45 - 64 years	744	130	608.4	512.3	722.5	73	14	684.6	405.4	1,155.9	671	116	600.3	500.4	720.1
65+ years	227	44	802.3	597.1	1,078.1	9	2	789.1	197.4	3,155.2	218	42	802.9	593.4	1,086.5
Dual combination including an ACEI but not	375,2	64,9	501.	497	504.	148,6	19,9	463.	456.	469.	226,5	45,0	519.	514	524.

aliskiren (overall)	21	35	0	.2	9	26	07	2	9	7	95	28	7	.9	5
Male gender (overall)	208,023	38,962	548.4	542.9	553.8	84,737	12,160	499.7	490.9	508.7	123,286	26,802	573.7	566.9	580.6
18 - 44 years	38,575	1,759	119.4	114.0	125.1	20,445	666	103.3	95.8	111.5	18,130	1,093	131.9	124.3	140.0
45 - 64 years	143,782	31,251	639.6	632.5	646.7	56,715	9,963	623.4	611.3	635.8	87,067	21,288	647.4	638.8	656.2
65+ years	25,666	5,952	798.0	778.0	818.5	7,577	1,531	802.2	763.0	843.4	18,089	4,421	796.5	773.4	820.4
Female gender (overall)	167,198	25,973	443.5	438.2	449.0	63,889	7,747	415.6	406.5	425.0	103,309	18,226	456.5	450.0	463.2
18 - 44 years	24,774	1,159	122.3	115.5	129.6	13,216	488	116.4	106.5	127.2	11,558	671	127.0	117.8	137.0
45 - 64 years	116,203	20,593	502.4	495.5	509.3	43,402	6,216	494.7	482.6	507.2	72,801	14,377	505.7	497.5	514.1
65+ years	26,221	4,221	521.5	506.0	537.5	7,271	1,043	554.3	521.7	589.0	18,950	3,178	511.6	494.1	529.7
Dual combination including neither an ACEI nor aliskiren (overall)	391,140	71,395	519.5	515.8	523.4	131,038	18,603	477.8	471.0	484.7	260,102	52,792	536.1	531.5	540.7
Male gender (overall)	168,969	34,112	587.9	581.7	594.1	61,717	9,614	530.3	519.8	541.0	107,252	24,498	614.0	606.4	621.8
18 - 44 years	28,991	1,450	127.8	121.4	134.5	14,075	509	110.9	101.7	121.0	14,916	941	139.2	130.6	148.4
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
45 - 64 years	113,631	26,413	676.8	668.7	685.0	40,313	7,618	653.1	638.6	667.9	73,318	18,795	686.9	677.2	696.8
65+ years	26,347	6,249	816.4	796.4	836.9	7,329	1,487	792.3	753.0	833.6	19,018	4,762	824.2	801.2	848.0

Female gender (overall)	222,171	37,283	469.6	464.9	474.4	69,321	8,989	432.0	423.2	441.1	152,850	28,294	483.0	477.4	488.6
18 - 44 years	31,800	1,640	130.4	124.2	136.8	14,957	565	115.8	106.7	125.8	16,843	1,075	139.6	131.5	148.2
45 - 64 years	151,303	28,984	531.0	524.9	537.1	45,322	7,085	524.5	512.5	536.9	105,981	21,899	533.1	526.1	540.2
65+ years	39,068	6,659	544.6	531.7	557.9	9,042	1,339	552.9	524.1	583.4	30,026	5,320	542.6	528.2	557.4
Triple-plus Combination Therapy Initiators:															
Triple-plus combination including aliskiren (overall)	13,953	2,871	727.8	701.7	754.9	585	106	697.4	576.5	843.6	13,368	2,765	729.0	702.3	756.7
Male gender (overall)	7,803	1,732	782.4	746.4	820.1	334	60	674.3	523.6	868.5	7,469	1,672	786.9	750.1	825.6
18 - 44 years	774	43	165.7	122.9	223.4	66	1	52.8	7.4	374.8	708	42	174.6	129.0	236.3
45 - 64 years	5,323	1,286	845.0	800.1	892.5	225	49	810.0	612.2	1,071.8	5,098	1,237	846.5	800.6	895.0
65+ years	1,706	403	932.0	845.3	1,027.6	43	10	1,047.2	563.5	1,946.3	1,663	393	929.4	841.9	1,026.0
Female gender (overall)	6,150	1,139	658.0	620.9	697.3	251	46	729.9	546.7	974.4	5,899	1,093	655.3	617.5	695.3
18 - 44 years	363	19	167.4	106.8	262.5	26	2	299.9	75.0	1,199.0	337	17	159.2	99.0	256.0
45 - 64 years	3,630	735	694.6	646.2	746.7	169	34	772.3	551.8	1,080.8	3,461	701	691.2	641.9	744.3
65+ years	2,157	385	688.2	622.8	760.5	56	10	811.1	436.4	1,507.5	2,101	375	685.4	619.4	758.4
Triple-plus combination including an ACEI but not aliskiren (overall)	399,575	79,959	548.5	544.7	552.3	111,206	16,585	492.7	485.2	500.2	288,369	63,374	565.2	560.8	569.6
Male gender (overall)	222,254	49,145	617.0	611.6	622.5	63,520	10,368	546.0	535.6	556.6	158,734	38,777	639.2	632.9	645.6
18 - 44 years	27,996	1,557	134.2	127.7	141.1	12,550	457	108.9	99.4	119.4	15,446	1,100	148.6	140.1	157.6

45 - 64 years	149,543	36,664	678.1	671.2	685.0	42,375	8,130	651.1	637.1	665.4	107,168	28,534	686.2	678.3	694.2
65+ years	44,715	10,924	781.2	766.7	796.0	8,595	1,781	772.2	737.2	808.9	36,120	9,143	783.0	767.1	799.2
Female gender (overall)	177,321	30,814	466.0	460.8	471.2	47,686	6,217	423.6	413.2	434.3	129,635	24,597	478.0	472.1	484.0
18 - 44 years	19,319	1,139	140.0	132.1	148.3	8,615	345	117.0	105.3	130.0	10,704	794	153.1	142.8	164.1
45 - 64 years	115,217	22,489	515.4	508.7	522.2	31,489	4,828	501.8	487.8	516.1	83,728	17,661	519.2	511.6	527.0
65+ years	42,785	7,186	500.5	489.0	512.2	7,582	1,044	496.4	467.1	527.4	35,203	6,142	501.2	488.8	513.8

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Triple-plus combination including neither an ACEI nor aliskiren (overall)	266,303	56,748	582.4	577.6	587.2	63,526	10,110	516.7	506.7	526.8	202,777	46,638	598.9	593.5	604.4
Male gender (overall)	126,553	30,112	667.0	659.5	674.6	32,045	5,625	577.8	562.9	593.1	94,508	24,487	691.6	683.0	700.3
18 - 44 years	14,967	920	146.2	137.0	156.0	6,042	265	129.0	114.3	145.5	8,925	655	154.5	143.1	166.8
45 - 64 years	83,963	22,014	725.6	716.1	735.2	21,217	4,271	667.0	647.3	687.3	62,746	17,743	741.2	730.4	752.2
65+ years	27,623	7,178	843.5	824.2	863.2	4,786	1,089	851.9	802.8	904.1	22,837	6,089	842.0	821.1	863.4
Female gender (overall)	139,750	26,636	509.3	503.3	515.5	31,481	4,485	456.1	443.0	469.7	108,269	22,151	521.7	514.8	528.6
18 - 44 years	13,815	869	147.9	138.4	158.1	5,533	234	122.7	107.9	139.5	8,282	635	160.0	148.1	173.0
45 - 64 years	90,80	19,2	555.	547	563.	20,53	3,39	530.	512.	548.	70,26	15,8	560.	552	569.

	0	57	1	.3	0	1	2	0	5	2	9	65	8	.1	6
65+ years	35,135	6,510	555.1	541.7	568.7	5,417	859	563.2	526.7	602.1	29,718	5,651	553.8	539.6	568.5

Table 15-11 Relative Risk of Colorectal Hyperplasia – Aliskiren vs. Other Antihypertensive Therapy – All Patients

	All Patients						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Overall:	0.076	0.015	25.25	<.0001	1.078	1.047	1.111
Age Group: (ref: 18-44 years)							
45-64 vs. 18-44 years	1.547	0.008	40145.97	<.0001	4.700	4.629	4.771
65+ years vs. 18-44 years	1.642	0.009	35109.69	<.0001	5.163	5.075	5.252
Gender (ref: females)							
Males	0.281	0.003	7068.68	<.0001	1.325	1.316	1.333
Geographic region (ref: Northeast)							
Midwest	-0.046	0.004	111.06	<.0001	0.955	0.947	0.963
South	-0.036	0.004	72.18	<.0001	0.964	0.956	0.972
West	0.005	0.006	0.55	0.458	1.005	0.992	1.017
Health Plan Type (ref: HMO)							
Indemnity	-0.151	0.008	382.10	<.0001	0.860	0.847	0.873
POS	-0.068	0.008	80.78	<.0001	0.934	0.921	0.948
PPO	-0.110	0.005	533.05	<.0001	0.896	0.887	0.904
Other/unknown	0.153	0.015	104.77	<.0001	1.166	1.132	1.201
Payer Type (ref: commercial)							
self-insured	0.003	0.004	0.83	0.363	1.003	0.996	1.010
other	-0.178	0.008	477.90	<.0001	0.837	0.824	0.850
CCI score	0.052	0.001	1237.92	<.0001	1.054	1.051	1.057
Pre-index comorbidity							
History of H. pylori infection	0.097	0.030	10.22	0.001	1.102	1.038	1.170
History of stomach lymphoma	0.202	0.099	4.15	0.042	1.224	1.008	1.486
History of stomach surgery	-0.139	0.039	12.48	0.000	0.870	0.806	0.940
Irritable bowel syndrome	0.232	0.013	314.97	<.0001	1.261	1.229	1.293
Chronic diarrhea	0.154	0.041	13.86	0.000	1.167	1.076	1.265
Chronic constipation	0.122	0.011	121.06	<.0001	1.130	1.106	1.155
Peripheral vascular disease	-0.036	0.007	23.37	<.0001	0.965	0.951	0.979
Vascular insufficiency of intestine	0.089	0.046	3.70	0.054	1.093	0.998	1.196
Acute coronary syndrome	-0.065	0.011	33.93	<.0001	0.937	0.917	0.958
Coronary heart disease or angina	0.005	0.005	1.18	0.278	1.005	0.996	1.015
Heart failure	-0.217	0.009	554.47	<.0001	0.805	0.791	0.820
Stroke or transient ischemic attack	-0.068	0.007	89.33	<.0001	0.935	0.922	0.948

	All Patients						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Ulcerous rectocolitis	0.585	0.023	670.26	<.0001	1.795	1.717	1.876
Crohn's disease	0.401	0.025	262.03	<.0001	1.493	1.422	1.567
Diabetes mellitus	-0.001	0.006	0.02	0.881	0.999	0.987	1.011
Screening Procedures							
Fecal Occult Blood Test	0.211	0.005	1940.11	<.0001	1.235	1.223	1.247
Sigmoidoscopy	0.066	0.028	5.50	0.019	1.068	1.011	1.128
Colonoscopy	-1.017	0.011	9106.90	<.0001	0.362	0.354	0.369
Co-medications:							
Prescription NSAIDs (including aspirin)	0.036	0.004	91.91	<.0001	1.036	1.029	1.044
Statins	0.139	0.003	1635.79	<.0001	1.149	1.141	1.157
Hormone replacement therapy	0.084	0.007	144.70	<.0001	1.088	1.073	1.103
Proton Pump Inhibitor	0.253	0.004	4118.14	<.0001	1.287	1.277	1.297
Anti-diabetic drugs	-0.074	0.007	130.07	<.0001	0.929	0.917	0.940

Table 15-12 Relative Risk of Colorectal Hyperplasia – Aliskiren vs. Other Antihypertensive Therapy – Incident and Prevalent Cohorts

	Incident Antihypertensive Treatment Cohort							Prevalent Antihypertensive Treatment Cohort						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Overall:	0.032	0.057	0.31	0.576	1.032	0.924	1.153	0.073	0.016	21.58	<.0001	1.075	1.043	1.109
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	1.660	0.012	18576.64	<.0001	5.259	5.135	5.386	1.457	0.010	21223.52	<.0001	4.292	4.209	4.377
65+ years vs. 18-44 years	1.774	0.015	14818.60	<.0001	5.893	5.727	6.064	1.546	0.011	19390.58	<.0001	4.694	4.593	4.797
Gender (ref: females)														
Males	0.249	0.006	1725.38	<.0001	1.282	1.267	1.297	0.296	0.004	5376.69	<.0001	1.344	1.333	1.355
Geographic region (ref: Northeast)														
Midwest	-0.060	0.008	55.13	<.0001	0.942	0.927	0.957	-0.037	0.005	51.88	<.0001	0.963	0.954	0.973
South	-0.083	0.008	114.45	<.0001	0.920	0.906	0.934	-0.012	0.005	5.59	0.018	0.988	0.978	0.998
West	-0.030	0.012	6.74	0.010	0.970	0.948	0.993	0.017	0.007	5.53	0.019	1.017	1.003	1.032
Health Plan Type (ref: HMO)														
Indemnity	-0.133	0.016	67.09	<.0001	0.875	0.848	0.904	-0.160	0.009	331.84	<.0001	0.852	0.837	0.867
POS	-0.058	0.016	13.43	0.000	0.943	0.915	0.973	-0.072	0.009	70.59	<.0001	0.930	0.915	0.946
PPO	-0.098	0.010	104.84	<.0001	0.907	0.890	0.924	-0.117	0.006	443.40	<.0001	0.890	0.880	0.899

Other/unknown	0.155	0.023	47.06	<.0001	1.168	1.117	1.220	0.120	0.021	32.81	<.0001	1.128	1.082	1.175
Payer Type (ref: commercial)														
self-insured	0.019	0.006	9.34	0.002	1.019	1.007	1.032	-0.001	0.004	0.09	0.768	0.999	0.990	1.007
other	-0.085	0.016	27.64	<.0001	0.919	0.890	0.948	-0.206	0.010	466.30	<.0001	0.814	0.799	0.829
CCI score	0.053	0.003	381.88	<.0001	1.055	1.049	1.060	0.052	0.002	846.40	<.0001	1.053	1.049	1.057
Pre-index comorbidity														
	Incident Antihypertensive Treatment Cohort							**Prevalent Antihypertensive Treatment Cohort**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
History of H. pylori infection	0.146	0.050	8.70	0.003	1.157	1.050	1.275	0.072	0.039	3.48	0.062	1.074	0.996	1.159
History of stomach lymphoma	0.265	0.169	2.46	0.117	1.304	0.936	1.817	0.171	0.122	1.96	0.162	1.187	0.934	1.508
History of stomach surgery	-0.078	0.071	1.21	0.272	0.925	0.804	1.063	-0.162	0.047	11.84	0.001	0.850	0.775	0.933
Irritable bowel syndrome	0.288	0.024	142.07	<.0001	1.333	1.272	1.398	0.208	0.016	179.79	<.0001	1.231	1.194	1.269
Chronic diarrhea	0.107	0.082	1.67	0.196	1.112	0.947	1.307	0.171	0.048	12.66	0.000	1.186	1.080	1.303
Chronic constipation	0.133	0.020	44.31	<.0001	1.142	1.098	1.187	0.118	0.013	76.68	<.0001	1.125	1.095	1.155
Peripheral vascular disease	-0.007	0.014	0.23	0.629	0.993	0.966	1.021	-0.046	0.009	28.25	<.0001	0.955	0.939	0.971
Vascular insufficiency of intestine	0.164	0.082	4.01	0.045	1.178	1.004	1.382	0.056	0.056	1.01	0.314	1.058	0.948	1.180
Acute coronary syndrome	-0.119	0.020	35.61	<.0001	0.888	0.854	0.923	-0.039	0.014	8.15	0.004	0.962	0.937	0.988
Coronary heart disease or angina	0.030	0.010	9.90	0.002	1.03	1.01	1.05	-0.001	0.006	0.05	0.827	0.99	0.98	1.01

					1	2	1					9	8	0
Heart failure	-0.240	0.019	159.51	<.0001	0.787	0.758	0.817	-0.208	0.011	386.30	<.0001	0.813	0.796	0.830
Stroke or transient ischemic attack	-0.091	0.013	49.35	<.0001	0.913	0.890	0.937	-0.057	0.009	43.66	<.0001	0.945	0.929	0.961
Ulcerous rectocolitis	0.677	0.040	283.91	<.0001	1.968	1.819	2.129	0.545	0.027	398.10	<.0001	1.725	1.635	1.820
Crohn's disease	0.424	0.043	94.86	<.0001	1.527	1.403	1.663	0.389	0.030	166.91	<.0001	1.475	1.391	1.565
Diabetes mellitus	-0.019	0.010	3.78	0.052	0.981	0.962	1.000	0.013	0.008	2.96	0.086	1.013	0.998	1.029
Screening Procedures														
Fecal Occult Blood Test	0.230	0.009	657.75	<.0001	1.258	1.236	1.281	0.202	0.006	1269.45	<.0001	1.224	1.210	1.238
Sigmoidoscopy	0.036	0.058	0.39	0.531	1.037	0.925	1.162	0.075	0.032	5.57	0.018	1.078	1.013	1.148
Colonoscopy	-1.164	0.023	2659.19	<.0001	0.312	0.299	0.326	-0.971	0.012	6446.11	<.0001	0.379	0.370	0.388
Co-medications:														
Prescription NSAIDs (including aspirin)	0.039	0.007	29.56	<.0001	1.040	1.025	1.055	0.033	0.004	57.10	<.0001	1.033	1.025	1.042
Statins	0.196	0.007	726.85	<.0001	1.216	1.199	1.234	0.120	0.004	901.75	<.0001	1.127	1.119	1.136
Hormone replacement therapy	0.111	0.015	55.65	<.0001	1.118	1.086	1.151	0.077	0.008	92.32	<.0001	1.080	1.063	1.097

	Incident Antihypertensive Treatment Cohort							**Prevalent Antihypertensive Treatment Cohort**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Proton Pump Inhibitor	0.262	0.008	992.65	<.0001	1.300	1.279	1.321	0.247	0.005	3014.98	<.0001	1.280	1.269	1.291
Anti-diabetic drugs	-0.074	0.012	36.77	<.0001	0.928	0.906	0.951	-0.083	0.008	109.79	<.0001	0.920	0.906	0.934

Table 15-13 Relative Risk of Colorectal Hyperplasia – Aliskiren vs. Non-hypertensive Patients

	Aliskiren (all patients)vs. Non-hypertensive Population							Aliskiren (incident patients only)vs. Non-hypertensive Population						
	Coefficient	Standard Error	Chi-square	p-value	HR	95% CI		Coefficient	Standard Error	Chi-square	p-value	HR	95% CI	
Overall:	0.116	0.017	44.76	<.0001	1.123	1.086	1.162	0.268	0.057	22.23	<.0001	1.307	1.169	1.461
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	2.225	0.005	164059.27	<.0001	9.249	9.150	9.349	2.222	0.006	162913.21	<.0001	9.227	9.128	9.327
65+ years vs. 18-44 years	2.317	0.010	50055.28	<.0001	10.142	9.939	10.350	2.324	0.011	48382.40	<.0001	10.212	10.003	10.426
Gender (ref: females)														
Males	0.168	0.004	1831.36	<.0001	1.183	1.174	1.193	0.167	0.004	1765.97	<.0001	1.181	1.172	1.191
Geographic region (ref: Northeast)														
Midwest	-0.084	0.005	262.66	<.0001	0.920	0.911	0.929	-0.084	0.005	260.68	<.0001	0.920	0.910	0.929
South	-0.120	0.005	484.09	<.0001	0.887	0.878	0.897	-0.122	0.005	492.49	<.0001	0.885	0.876	0.895
West	-0.031	0.008	17.36	<.0001	0.969	0.955	0.984	-0.031	0.008	16.72	<.0001	0.970	0.955	0.984
Health Plan Type (ref: HMO)														
Indeminity	-0.230	0.011	411.38	<.0001	0.794	0.777	0.812	-0.229	0.011	401.72	<.0001	0.795	0.777	0.813
POS	-0.083	0.010	75.51	<.0001	0.921	0.904	0.938	-0.080	0.010	69.62	<.0001	0.923	0.906	0.941
PPO	-0.133	0.006	464.54	<.0001	0.875	0.864	0.886	-0.134	0.006	460.57	<.0001	0.875	0.864	0.886

Other/unknown	-0.004	0.018	0.06	0.805	0.996	0.962	1.031	-0.004	0.018	0.04	0.840	0.996	0.962	1.032
Payer Type (ref: commercial)														
self-insured	0.004	0.004	1.05	0.307	1.004	0.996	1.013	0.004	0.004	0.98	0.322	1.004	0.996	1.013
other	-0.024	0.017	2.08	0.149	0.976	0.945	1.009	-0.027	0.017	2.44	0.118	0.974	0.942	1.007
CCI score	0.120	0.003	2213.06	<.0001	1.128	1.122	1.134	0.125	0.003	2315.01	<.0001	1.134	1.128	1.139
Pre-index comorbidity														
History of H. pylori infection	0.161	0.047	11.82	0.001	1.175	1.072	1.288	0.175	0.047	13.67	0.000	1.192	1.086	1.308
History of stomach lymphoma	0.148	0.169	0.76	0.383	1.159	0.832	1.615	0.130	0.169	0.59	0.443	1.139	0.817	1.586
History of stomach surgery	-0.115	0.089	1.68	0.195	0.891	0.749	1.061	-0.160	0.092	3.01	0.083	0.852	0.711	1.021
Irritable bowel syndrome	0.369	0.017	452.31	<.0001	1.446	1.398	1.496	0.369	0.018	442.50	<.0001	1.446	1.397	1.497
Chronic diarrhea	0.177	0.067	6.98	0.008	1.194	1.047	1.361	0.190	0.068	7.87	0.005	1.209	1.059	1.381
Chronic constipation	0.303	0.016	340.28	<.0001	1.354	1.311	1.398	0.307	0.017	338.61	<.0001	1.359	1.315	1.404
Peripheral vascular disease	0.038	0.018	4.55	0.033	1.039	1.003	1.076	0.085	0.019	19.80	<.0001	1.089	1.049	1.130

	Aliskiren (all patients)vs. Non-hypertensive Population							**Aliskiren (incident patients only)vs. Non-hypertensive Population**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Vascular insufficiency of intestine	0.098	0.100	0.96	0.327	1.103	0.906	1.343	0.154	0.105	2.16	0.142	1.166	0.950	1.432
Acute coronary syndrome	-0.016	0.053	0.09	0.769	0.984	0.887	1.093	-0.003	0.068	0.00	0.967	0.997	0.873	1.139
Coronary heart disease or	0.088	0.019	22.51	<.000	1.092	1.05	1.133	0.157	0.021	57.46	<.000	1.170	1.123	1.219

angina				1		3					1			
Heart failure	-0.258	0.044	34.91	<.0001	0.772	0.709	0.842	-0.194	0.070	7.70	0.006	0.823	0.718	0.944
Stroke or transient ischemic attack	-0.037	0.020	3.54	0.060	0.963	0.927	1.002	0.006	0.021	0.08	0.778	1.006	0.965	1.049
Ulcerous rectocolitis	1.195	0.023	2732.37	<.0001	3.302	3.157	3.453	1.201	0.023	2738.06	<.0001	3.323	3.177	3.476
Crohn's disease	0.926	0.025	1342.81	<.0001	2.525	2.403	2.653	0.937	0.025	1365.59	<.0001	2.553	2.429	2.683
Diabetes mellitus	0.000	0.017	0.00	0.977	1.000	0.968	1.034	0.003	0.017	0.02	0.880	1.003	0.969	1.037
Screening Procedures														
Fecal Occult Blood Test	0.368	0.007	3177.04	<.0001	1.445	1.427	1.464	0.369	0.007	3128.38	<.0001	1.446	1.428	1.465
Sigmoidoscopy	0.175	0.041	17.91	<.0001	1.191	1.099	1.292	0.194	0.042	21.47	<.0001	1.214	1.118	1.317
Colonoscopy	-1.231	0.017	5201.73	<.0001	0.292	0.282	0.302	-1.234	0.017	5116.86	<.0001	0.291	0.281	0.301
Co-medications:														
Prescription NSAIDs (including aspirin)	0.157	0.006	818.91	<.0001	1.171	1.158	1.183	0.157	0.006	792.85	<.0001	1.170	1.157	1.183
Statins	0.484	0.006	5960.30	<.0001	1.623	1.603	1.643	0.498	0.006	6138.78	<.0001	1.645	1.625	1.666
Hormone replacement therapy	0.223	0.009	597.69	<.0001	1.250	1.227	1.272	0.226	0.009	604.21	<.0001	1.254	1.231	1.276
Proton Pump Inhibitor	0.411	0.007	3703.36	<.0001	1.509	1.489	1.529	0.416	0.007	3662.17	<.0001	1.516	1.496	1.536
Anti-diabetic drugs	-0.142	0.020	49.17	<.0001	0.868	0.834	0.903	-0.145	0.022	42.94	<.0001	0.865	0.828	0.903

Table 15-14 Sensitivity Analysis – Incidence Rate (per 10,000 person-years) of Colorectal Hyperplasia with and without Pre-diagnosis Screening test

	Patients with pre-diagnosis screening procedure AND post-index diagnosis					Patients with post-index diagnosis ALONE				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Aliskiren Treated Patients	23,768	3,459	477.0	461.4	493.2	23,768	1,049	144.7	136.2	153.7
Other Antihypertensive Therapy Treated Patients	2,278,653	327,535	418.6	417.2	420.0	2,278,653	76,480	97.7	97.1	98.4
Non-hypertensive Population	5,806,899	230,716	142.0	141.5	142.6	5,806,899	42,729	26.3	26.1	26.6

Table 15-15 Cross-tabulation of the Use of Screening Tests Pre-diagnosis vs. ICD-9-CM diagnosis of Colorectal Hyperplasia

		Aliskiren Treated Patients			Other Antihypertensive Therapy Treated Patients			Non-hypertensive Population		
		Status of post-index diagnosis for colorectal hyperplasia			Status of post-index diagnosis for colorectal hyperplasia			Status of post-index diagnosis for colorectal hyperplasia		
Status of screening test procedures for colorectal hyperplasia*		YES	NO	p value	YES	NO	p value	YES	NO	p value
If with FOBT	YES	365	1,549	0.9043	35,005	152,920	<.0001	22,055	192,189	<.0001
	NO	4,143	17,711		369,010	172,1718		251,390	5,341,265	
If with sigmoidoscopy	YES	35	44	<.0001	3,098	4,273	<.0001	2,061	5,391	<.0001
	NO	4,473	19,216		400,917	1,870,365		271,384	5,528,063	

Status of screening test procedures for colorectal hyperplasia*		Aliskiren Treated Patients			Other Antihypertensive Therapy Treated Patients			Non-hypertensive Population		
		Status of post-index diagnosis for colorectal hyperplasia			Status of post-index diagnosis for colorectal hyperplasia			Status of post-index diagnosis for colorectal hyperplasia		
		Yes	No	p value	Yes	No	p value	Yes	No	p value
If with colonoscopy	Yes	3,359	930	<.0001	318,551	92,169	<.0001	225,595	101,107	<.0001
	No	1,149	18,330		85,464	1,782,469		47,850	5,432,347	
If with at least one of the 3 procedures above	Yes	3,459	2,352	<.0001	327,535	233,635	<.0001	230,716	283,629	<.0001
	No	1,049	16,908		76,480	1,641,003		42,729	5,249,825	

§ Chi-square test was applied for statistical difference

*screening procedures only include those occurring within the 3 months prior to event for those with event, and 12 month post-index for those without event.

Table 15-16 Attrition of Study Sample – GI Cancer Cohort

	Aliskiren Patients Excluded		Aliskiren Patients Remaining		Other Antihypertensive Therapy Patients Excluded		Other Antihypertensive Therapy Patients Remaining		Non-hypertensive Population Excluded		Non-hypertensive Population Remaining	
	N	%	N	%	N	%	N	%	N	%	N	%

Total patients with NEITHER a prescription for an antihypertensive medication NOR a diagnosis of hypertension (ICD-9-CM codes 401.xx - 405.xx) between 1st July 2006 and 30th June 2014 (study window)	NA		NA		NA		NA				12,615,141	
Total patients with ≥1 prescription for an antihypertensive medication between 1 July 2007 and 30 June 2013 (index window).			38,611				6,671,056		NA		NA	
Attrition Reason:												
Patient has less than 12 months of pre-index continuous health plan enrollment (not including index date)	5,664	14.7	32,947	85.3	880,294	13.2	5,790,762	86.8	1,931,835	15.3	10,683,306	84.7
Patient has less than 12 months of post-index continuous health plan enrollment(including index date)	4,867	12.6	28,080	72.7	972,969	14.6	4,817,793	72.2	1,738,323	13.8	8,944,983	70.9
Patient does not have evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx - 405.xx) in the 12-month pre-index period	2,198	5.7	25,882	67.0	2,350,897	35.2	2,466,896	37.0	NA		NA	
Patient has no recorded age or gender	26	0.1	25,856	67.0	4,680	0.1	2,462,216	36.9	836	0.0	8,944,147	70.9
Patient is less than 18 years of age on index date	14	0.0	25,842	66.9	5,898	0.1	2,456,318	36.8	3,028,183	24.0	5,915,964	46.9
Patient has invalid or missing data	0	0.0	25,842	66.9	0	0.0	2,456,318	36.8	0	0.0	5,915,964	46.9
Patient has a prior history of GI cancer in the 12 months prior to the index date or within 30 days of initiating therapy (for non-hypertensive population within 30 days since index date)	102	0.3	25,740	66.7	8,655	0.1	2,447,663	36.7	6,546	0.1	5,909,418	46.8
	Aliskiren Patients Excluded		Aliskiren Patients Remaining		Other Antihypertensive Therapy Patients Excluded		Other Antihypertensive Therapy Patients Remaining		Non-hypertensive Population Excluded		Non-hypertensive Population Remaining	
	N	%	N	%	N	%	N	%	N	%	N	%
"Other antihypertensive therapy" patients who also had prescriptions for aliskiren during the index window					13,276	0.2	2,434,387	36.5				

Patients Available for Analysis:								
Incident Antihypertensive Treatment Cohort		2,193	8.5		972,369	39.7	NA	
Prevalent Antihypertensive Treatment Cohort		23,547	91.5		1,462,018	59.7	NA	
Non-hypertensive Population Cohort	NA		NA					5,909,418

Table 15-17 Demographic Characteristics – All Patients – GI Cancer Cohort

Characteristic	All Aliskiren Patients (N= 25,740)		All Other Antihypertensive Therapy Patients (N= 2,434,387)		All Non-hypertensive Patients (N= 5,909,418)	
Age: (years)						
Mean	58.0		55.2		39.6	
SD	11.1		11.1		13.5	
Range	18	83	18	83	18	83
Median	58		56		40	
Interquartile range (1st Q, 3rd Q)	51	64	48	62	28	50
Age Group: (n, %)						
18 - 44 years	2,781	10.8%	391,375	16.1%	3,643,058	61.6%
45 - 64 years	16,681	64.8%	1,635,832	67.2%	2,144,257	36.3%
65+ years	6,278	24.4%	407,180	16.7%	122,103	2.1%
Gender: (n, %)						
Female (overall)	11,654	45.3%	1,189,560	48.9%	3,188,479	54.0%
18 - 44 years	963	8.3%	173,765	14.6%	1,895,567	59.5%
45-64 years	7,184	61.6%	799,810	67.2%	1,220,119	38.3%

65+ years	3,507	30.1%	215,985	18.2%	72,793	2.3%
Male (overall)	14,086	54.7%	1,244,827	51.1%	2,720,939	46.0%
18 - 44 years	1,818	12.9%	217,610	17.5%	1,747,491	64.2%
45-64 years	9,497	67.4%	836,022	67.2%	924,138	34.0%
65+ years	2,771	19.7%	191,195	15.4%	49,310	1.8%
Geographic Region: (n, %)						
Northeast	4,451	17.3%	584,924	24.0%	1,239,807	21.0%
Midwest	5,932	23.0%	711,352	29.2%	2,106,504	35.6%
South	13,077	50.8%	856,238	35.2%	1,961,722	33.2%
West	2,280	8.9%	281,873	11.6%	601,385	10.2%
Health Plan Type: (n, %)						
Consumer-directed	36	0.1%	5,341	0.2%	42,814	0.7%
HMO	1,610	6.3%	347,037	14.3%	647,950	11.0%
Indemnity	1,438	5.6%	160,218	6.6%	193,317	3.3%
POS	1,145	4.4%	165,099	6.8%	370,710	6.3%
PPO	21,373	83.0%	1,737,749	71.4%	4,621,103	78.2%
Unknown	138	0.5%	18,943	0.8%	33,524	0.6%
Payer Type: (n, %)						
Commercial	14,903	57.9%	1,580,986	64.9%	4,005,937	67.8%
Self-insured group	10,097	39.2%	716,349	29.4%	1,821,165	30.8%
Medicaid	44	0.2%	14,824	0.6%	36,011	0.6%
Medicare Risk	623	2.4%	114,331	4.7%	20,011	0.3%

Characteristic	**All Aliskiren Patients (N= 25,740)**		**All Other Antihypertensive Therapy Patients (N= 2,434,387)**		**All Non-hypertensive Patients (N= 5,909,418)**	

Unknown	73	0.3%	7,897	0.3%	26,294	0.4%

Table 15-18 Demographic Characteristics – Incident and Prevalent Antihypertensive Users – GI Cancer Cohort

Characteristic	Incident Aliskiren Treatment Cohort (N= 2,193)		Incident Other Antihypertensive Treatment Cohort (N= 972,369)		Prevalent Aliskiren Treatment Cohort (N= 23,547)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,472,781)	
Age: (years)								
Mean	52.2		52.7		58.6		56.8	
SD	11.0		11.6		11.0		10.5	
Range	18	81	18	83	18	83	18	81
Median	52		53		59		57	
Interquartile range (1st Q, 3rd Q)	45	60	45	60	52	65	50	63
Age Group: (n, %)								
18 - 44 years	512	23.3%	219,760	22.6%	2,269	9.6%	172,752	11.7%
45-64 years	1,444	65.8%	636,946	65.5%	15,237	64.7%	1,006,401	68.3%
65+ years	237	10.8%	115,663	11.9%	6,041	25.7%	293,628	19.9%
Gender: (n, %)								
Female (overall)	878	40.0%	453,584	46.6%	10,776	45.8%	740,833	50.3%
18 - 44 years	151	17.2%	96,631	21.3%	812	7.5%	77,535	10.5%
45-64 years	598	68.1%	298,436	65.8%	6,586	61.1%	504,668	68.1%
65+ years	129	14.7%	58,517	12.9%	3,378	31.3%	158,630	21.4%
Male (overall)	1,315	60.0%	518,785	53.4%	12,771	54.2%	731,948	49.7%
18 - 44 years	361	27.5%	123,129	23.7%	1,457	11.4%	95,217	13.0%
45-64 years	846	64.3%	338,510	65.3%	8,651	67.7%	501,733	68.5%
65+ years	108	8.2%	57,146	11.0%	2,663	20.9%	134,998	18.4%
Geographic Region: (n, %)								

Northeast	405	18.5%	212,667	21.9%	4,046	17.2%	374,756	25.4%
Characteristic	**Incident Aliskiren Treatment Cohort (N= 2,193)**		**Incident Other Antihypertensive Treatment Cohort (N= 972,369)**		**Prevalent Aliskiren Treatment Cohort (N= 23,547)**		**Prevalent Other Antihypertensive Treatment Cohort (N= 1,472,781)**	
Midwest	488	22.3%	267,902	27.6%	5,444	23.1%	445,785	30.3%
South	1,157	52.8%	396,842	40.8%	11,920	50.6%	464,677	31.6%
West	143	6.5%	94,958	9.8%	2,137	9.1%	187,563	12.7%
Health Plan Type: (n, %)								
Consumer-directed	3	0.1%	4,397	0.5%	33	0.1%	946	0.1%
HMO	124	5.7%	100,264	10.3%	1,486	6.3%	247,712	16.8%
Indemnity	98	4.5%	40,334	4.1%	1,340	5.7%	120,611	8.2%
POS	121	5.5%	47,040	4.8%	1,024	4.3%	118,708	8.1%
PPO	1,832	83.5%	770,750	79.3%	19,541	83.0%	975,399	66.2%
Unknown	15	0.7%	9,584	1.0%	123	0.5%	9,405	0.6%
Payer Type: (n, %)								
Commercial	1,264	57.6%	594,381	61.1%	13,639	57.9%	993,422	67.5%
Self-insured group	869	39.6%	336,505	34.6%	9,228	39.2%	383,449	26.0%
Medicaid	19	0.9%	9,738	1.0%	25	0.1%	5,095	0.3%
Medicare Risk	32	1.5%	25,526	2.6%	591	2.5%	89,116	6.1%
Unknown	9	0.4%	6,219	0.6%	64	0.3%	1,699	0.1%

Table 15-19 Clinical Characteristics – All Patients – GI Cancer Cohort

	All Aliskiren Patients	**All Other Antihypertensive Therapy Patients**	**All Non-hypertensive Patients**

Characteristic	(N= 25,740)		(N= 2,434,387)		(N= 5,909,418)	
Pre-index						
Charlson Comorbidity Index (CCI) Score: (n, %)						
0	9,212	35.8%	1,319,375	54.2%	5,381,654	91.1%
1-2	10,510	40.8%	863,584	35.5%	490,265	8.3%
3-4	4,059	15.8%	183,376	7.5%	22,481	0.4%
5+	1,959	7.6%	68,052	2.8%	15,018	0.3%
Mean	1.6		0.9		0.1	
SD	1.8		1.4		0.5	
Range	0	15	0	19	0	15
Median	1		0		0	
Interquartile range (1st Q, 3rd Q)	0	2	0	1	0	0
Comorbid Conditions of Interest in the Pre-index Period: (n, %)						
History of H. pylori infection	102	0.4%	7,616	0.3%	7,337	0.1%
History of stomach lymphoma	1	0.0%	455	0.0%	250	0.0%
History of stomach surgery	37	0.1%	4,517	0.2%	2,354	0.0%
Irritable bowel syndrome	434	1.7%	35,084	1.4%	47,656	0.8%
Chronic diarrhea	69	0.3%	4,764	0.2%	4,515	0.1%
Chronic constipation	798	3.1%	57,799	2.4%	65,013	1.1%
Peripheral vascular disease	2,861	11.1%	121,233	5.0%	33,110	0.6%
Vascular insufficiency of intestine (including ischemic bowel disease)	49	0.2%	3,364	0.1%	1,284	0.0%

Characteristic	All Aliskiren Patients (N= 25,740)	All Other Antihypertensive Therapy Patients (N= 2,434,387)	All Non-hypertensive Patients (N= 5,909,418)

Acute coronary syndrome	684	2.7%	49,587	2.0%	2,093	0.0%
Coronary heart disease or angina	5,464	21.2%	320,635	13.2%	21,210	0.4%
Heart failure	2,054	8.0%	88,000	3.6%	2,512	0.0%
Stroke or transient ischemic attack	2,680	10.4%	136,692	5.6%	25,458	0.4%
Ulcerous rectocolitis	123	0.5%	10,399	0.4%	16,191	0.3%
Crohn's disease	98	0.4%	8,669	0.4%	14,737	0.2%
Diabetes mellitus	9,703	37.7%	555,649	22.8%	74,235	1.3%
Screening Procedures in the Pre-index Period: (n, %)						
Endoscopy including gastroscopy	1,486	5.8%	102,718	4.2%	78,970	1.3%
H. pylori	372	1.4%	30,667	1.3%	46,464	0.8%
Co-medications: (n, %)						
Prescription NSAIDs (including aspirin)	6,732	26.2%	545,418	22.4%	696,047	11.8%
Statins	10,459	40.6%	714,712	29.4%	226,212	3.8%
Hormone replacement therapy	1,456	5.7%	128,297	5.3%	119,774	2.0%
Proton Pump Inhibitor	6,375	24.8%	417,667	17.2%	274,241	4.6%
Anti-diabetic drugs	7,915	30.7%	398,023	16.4%	58,222	1.0%
Post-index						
Available Days of Follow-up (Post-index):						
Mean	1092.3		1230.5		1016.5	
SD	618.8		739.1		544.9	
Range	1	2556	1	2557	1	2557
Median	980		1049		882	
Interquartile range	602	1511	619	1805	576	1352
Comorbid Conditions of Interest in the Post-index Period: (n, %)						
	All Aliskiren Patients		**All Other Antihypertensive Therapy Patients**		**All Non-hypertensive Patients**	

Characteristic	(N= 25,740)		(N= 2,434,387)		(N= 5,909,418)	
History of H. pylori infection	110	0.4%	8,173	0.3%	7,857	0.1%
History of stomach lymphoma	8	0.0%	565	0.0%	266	0.0%
History of stomach surgery	95	0.4%	7,435	0.3%	2,549	0.0%
Irritable bowel syndrome	405	1.6%	33,279	1.4%	48,603	0.8%
Chronic diarrhea	68	0.3%	4,826	0.2%	4,287	0.1%
Chronic constipation	831	3.2%	61,351	2.5%	67,841	1.1%
Peripheral vascular disease	2,997	11.6%	135,316	5.6%	36,230	0.6%
Vascular insufficiency of intestine (including ischemic bowel disease)	65	0.3%	3,661	0.2%	1,373	0.0%
Acute coronary syndrome	585	2.3%	38,560	1.6%	2,096	0.0%
Coronary heart disease or angina	5,576	21.7%	330,344	13.6%	21,777	0.4%
Heart failure	2,234	8.7%	94,622	3.9%	2,778	0.0%
Stroke or transient ischemic attack	2,725	10.6%	141,694	5.8%	27,644	0.5%
Ulcerous rectocolitis	133	0.5%	10,666	0.4%	16,961	0.3%
Crohn's disease	120	0.5%	9,012	0.4%	15,549	0.3%
Diabetes mellitus	9,924	38.6%	583,935	24.0%	81,036	1.4%
Screening Procedures in the Post-index Period: (n, %)						
Endoscopy including gastroscopy	1,618	6.3%	108,796	4.5%	83,155	1.4%
H. pylori	364	1.4%	28,478	1.2%	46,673	0.8%
Co-medications: (n, %)						
Prescription NSAIDs (including aspirin)	6,613	25.7%	588,910	24.2%	723,471	12.2%
Statins	11,799	45.8%	927,271	38.1%	252,087	4.3%
Hormone replacement therapy	1,365	5.3%	124,424	5.1%	120,480	2.0%
Proton Pump Inhibitor	6,812	26.5%	499,136	20.5%	292,749	5.0%
Anti-diabetic drugs	8,544	33.2%	475,456	19.5%	64,225	1.1%

Table 15-20 Clinical Characteristics – Incident and Prevalent Antihypertensive Users – GI Cancer Cohort

Characteristic	Incident Aliskiren Treatment Cohort (N= 2,193)		Incident Other Antihypertensive Treatment Cohort (N= 972,369)		Prevalent Aliskiren Treatment Cohort (N= 23,547)		Prevalent Other Antihypertensive Treatment Cohort (N= 1,462,018)	
Pre-index								
Charlson Comorbidity Index (CCI) Score: (n, %)								
0	1,275	58.1%	567,690	58.4%	7,937	33.7%	751,685	51.4%
1-2	710	32.4%	322,548	33.2%	9,800	41.6%	541,036	37.0%
3-4	148	6.7%	59,983	6.2%	3,911	16.6%	123,393	8.4%
5+	60	2.7%	22,148	2.3%	1,899	8.1%	45,904	3.1%
Mean	0.8		0.8		1.6		1.0	
SD	1.3		1.3		1.8		1.4	
Range	0	10	0	16	0	15	0	19
Median	0		0		1		0	
Interquartile range	0	1	0	1	0	2	0	1
Comorbid Conditions of Interest in the Pre-index Period: (n, %)								
History of H. pylori infection	5	0.2%	3,532	0.4%	97	0.4%	4,084	0.3%
History of stomach lymphoma	0	0.0%	177	0.0%	1	0.0%	278	0.0%
History of stomach surgery	1	0.0%	1,835	0.2%	36	0.2%	2,682	0.2%
Irritable bowel syndrome	31	1.4%	12,498	1.3%	403	1.7%	22,586	1.5%
Chronic diarrhea	1	0.0%	1,623	0.2%	68	0.3%	3,141	0.2%
Chronic constipation	57	2.6%	22,649	2.3%	741	3.1%	35,150	2.4%
Peripheral vascular disease	103	4.7%	39,706	4.1%	2,758	11.7%	81,527	5.6%

Vascular insufficiency of intestine (including ischemic bowel disease)	0	0.0%	1,240	0.1%	49	0.2%	2,124	0.1%
Acute coronary syndrome	17	0.8%	20,722	2.1%	667	2.8%	28,865	2.0%
Coronary heart disease or angina	196	8.9%	99,263	10.2%	5,268	22.4%	221,372	15.1%
Characteristic	**Incident Aliskiren Treatment Cohort (N= 2,193)**		**Incident Other Antihypertensive Treatment Cohort (N= 972,369)**		**Prevalent Aliskiren Treatment Cohort (N= 23,547)**		**Prevalent Other Antihypertensive Treatment Cohort (N= 1,462,018)**	
Heart failure	48	2.2%	26,187	2.7%	2,006	8.5%	61,813	4.2%
Stroke or transient ischemic attack	113	5.2%	52,611	5.4%	2,567	10.9%	84,081	5.8%
Ulcerous rectocolitis	3	0.1%	3,869	0.4%	120	0.5%	6,530	0.4%
Crohn's disease	5	0.2%	3,534	0.4%	93	0.4%	5,135	0.4%
Diabetes mellitus	468	21.3%	180,553	18.6%	9,235	39.2%	375,096	25.7%
Screening Procedures in the Pre-index Period: (n, %)								
Endoscopy including gastroscopy	78	3.6%	38,167	3.9%	1,408	6.0%	64,551	4.4%
H. pylori	35	1.6%	14,109	1.5%	337	1.4%	16,558	1.1%
Co-medications: (n, %)								
Prescription NSAIDs (including aspirin)	400	18.2%	189,476	19.5%	6,332	26.9%	355,942	24.3%
Statins	324	14.8%	154,933	15.9%	10,135	43.0%	559,779	38.3%
Hormone replacement therapy	74	3.4%	32,614	3.4%	1,382	5.9%	95,683	6.5%
Proton Pump Inhibitor	249	11.4%	112,236	11.5%	6,126	26.0%	305,431	20.9%
Anti-diabetic drugs	246	11.2%	96,783	10.0%	7,669	32.6%	301,240	20.6%
Post-index								
Available Days of Follow-up (Post-index):								
Mean	1148.2		1032.2		1087.1		1362.3	
SD	638.3		591.7		616.7		795.7	
Range	1	2556	1	2557	1	2556	1	2557

Median	1033		899		976		1196	
Interquartile range (1st Q, 3rd Q)	634	1616	559	1426	599	1504	704	2189
Comorbid Conditions of Interest in the Post-index Period: (n, %)								
History of H. pylori infection	4	0.2%	4,032	0.4%	106	0.5%	4,141	0.3%
Characteristic	**Incident Aliskiren Treatment Cohort (N= 2,193)**		**Incident Other Antihypertensive Treatment Cohort (N= 972,369)**		**Prevalent Aliskiren Treatment Cohort (N= 23,547)**		**Prevalent Other Antihypertensive Treatment Cohort (N= 1,462,018)**	
History of stomach lymphoma	0	0.0%	191	0.0%	8	0.0%	374	0.0%
History of stomach surgery	7	0.3%	3,345	0.3%	88	0.4%	4,090	0.3%
Irritable bowel syndrome	19	0.9%	12,554	1.3%	386	1.6%	20,725	1.4%
Chronic diarrhea	2	0.1%	1,752	0.2%	66	0.3%	3,074	0.2%
Chronic constipation	55	2.5%	25,760	2.6%	776	3.3%	35,591	2.4%
Peripheral vascular disease	109	5.0%	49,305	5.1%	2,888	12.3%	86,011	5.9%
Vascular insufficiency of intestine (including ischemic bowel disease)	2	0.1%	1,414	0.1%	63	0.3%	2,247	0.2%
Acute coronary syndrome	22	1.0%	16,380	1.7%	563	2.4%	22,180	1.5%
Coronary heart disease or angina	235	10.7%	111,200	11.4%	5,341	22.7%	219,144	15.0%
Heart failure	62	2.8%	31,745	3.3%	2,172	9.2%	62,877	4.3%
Stroke or transient ischemic attack	129	5.9%	56,251	5.8%	2,596	11.0%	85,443	5.8%
Ulcerous rectocolitis	5	0.2%	4,130	0.4%	128	0.5%	6,536	0.4%
Crohn's disease	3	0.1%	3,739	0.4%	117	0.5%	5,273	0.4%
Diabetes mellitus	498	22.7%	195,486	20.1%	9,426	40.0%	388,449	26.6%
Screening Procedures in the Post-index Period: (n, %)								
Endoscopy including gastroscopy	103	4.7%	44,570	4.6%	1,515	6.4%	64,226	4.4%
H. pylori	27	1.2%	13,172	1.4%	337	1.4%	15,306	1.0%
Co-medications: (n, %)								

Prescription NSAIDs (including aspirin)	513	23.4%	236,172	24.3%	6,100	25.9%	352,738	24.1%
Statins	676	30.8%	324,449	33.4%	11,123	47.2%	602,822	41.2%
Hormone replacement therapy	85	3.9%	37,893	3.9%	1,280	5.4%	86,531	5.9%
Proton Pump Inhibitor	362	16.5%	177,282	18.2%	6,450	27.4%	321,854	22.0%
Anti-diabetic drugs	381	17.4%	153,534	15.8%	8,163	34.7%	321,922	22.0%

Table 15-21 Antihypertensive Drug Use within 30 days since Index – GI Cancer Cohort

Measure	All Hypertensive Patients (N= 2,460,127)		Incident Antihypertensive Treatment Cohort (N= 974,562)		Prevalent Antihypertensive Treatment Cohort (N= 1,485,565)	
Monotherapy Initiators: (n, %)						
Aliskiren	8,190	0.3%	1,573	0.2%	6,617	0.4%
Angiotensin-converting enzyme inhibitors	419,086	17.0%	226,022	23.2%	193,064	13.0%
Angiotensin II receptor blockers	162,371	6.6%	66,813	6.9%	95,558	6.4%
Alpha blockers	40,465	1.6%	26,257	2.7%	14,208	1.0%
Beta blockers	301,403	12.3%	138,309	14.2%	163,094	11.0%
Calcium channel blockers	147,217	6.0%	67,132	6.9%	80,085	5.4%
Diuretics	236,997	9.6%	124,255	12.7%	112,742	7.6%
Others (vasodilators, selective aldosterone receptor antagonists, centrally acting alpha agonists)	13,000	0.5%	7,595	0.8%	5,405	0.4%
Dual-combination Therapy Initiators: (n, %)						
Dual combination including aliskiren	5,458	0.2%	253	0.0%	5,205	0.4%
Dual combination including an ACEI but not aliskiren	378,521	15.4%	132,186	13.6%	246,335	16.6%
Dual combination including neither an ACEI nor aliskiren	413,025	16.8%	114,945	11.8%	298,080	20.1%
Triple-plus Combination Therapy Initiators: (n, %)						
Triple-plus combination therapy including aliskiren	12,244	0.5%	376	0.0%	11,868	0.8%

Triple-plus combination therapy including an ACEI but not aliskiren	186,468	7.6%	44,782	4.6%	141,686	9.5%
Triple-plus combination therapy including neither an ACEI nor aliskiren	135,682	5.5%	24,064	2.5%	111,618	7.5%
Duration of exposure of index therapy (days)						
Mean	521.5		352.9		632.1	
SD	592.4		431.2		654.4	
Range	0	2740	0	2740	0	2723
Median	307		167		429	
Measure	**All Hypertensive Patients (N= 2,460,127)**		**Incident Antihypertensive Treatment Cohort (N= 974,562)**		**Prevalent Antihypertensive Treatment Cohort (N= 1,485,565)**	
Interquartile range (1st Q, 3rd Q)	86	749	47	508	112	916

Table 15-22 Incidence Rates (per 10,000 person-years) of GI Cancer – All Patients

	All Aliskiren Patients					All Other Antihypertensive Therapy Patients					All Non-hypertensive Patients				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Overall:	25,740	256	29.0	25.7	32.8	2,434,387	21,735	23.1	22.8	23.4	5,909,418	13,247	7.8	7.7	7.9
By Age Group:															
18 - 44 years	2,781	9	8.7	4.5	16.8	391,375	1,582	10.5	10.0	11.0	3,643,058	4,927	4.7	4.6	4.9
45 - 64 years	16,681	167	28.4	24.4	33.0	1,635,832	14,693	22.7	22.4	23.1	2,144,257	7,679	12.3	12.0	12.5
65+ years	6,278	80	41.8	33.6	52.1	407,180	5,460	38.4	37.4	39.4	122,103	641	20.1	18.6	21.7
By Gender:															
Male (overall)	14,086	153	31.3	26.7	36.7	1,244,827	11,650	24.3	23.9	24.8	2,720,939	5,639	7.2	7.0	7.4
18 - 44 years	1,818	5	7.4	3.1	17.8	217,610	771	9.2	8.6	9.9	1,747,491	2,020	4.0	3.9	4.2

45 - 64 years	9,497	107	31.9	26.4	38.5	836,022	7,877	23.9	23.4	24.5	924,138	3,314	12.3	11.9	12.7
65+ years	2,771	41	48.1	35.4	65.3	191,195	3,002	45.3	43.7	46.9	49,310	305	24.1	21.5	27.0
Female (overall)	11,654	103	26.1	21.5	31.7	1,189,560	10,085	21.9	21.5	22.3	3,188,479	7,608	8.3	8.1	8.5
18 - 44 years	963	4	11.3	4.2	30.1	173,765	811	12.1	11.3	12.9	1,895,567	2,907	5.4	5.2	5.6
45 - 64 years	7,184	60	23.7	18.4	30.6	799,810	6,816	21.5	21.0	22.0	1,220,119	4,365	12.2	11.9	12.6
65+ years	3,507	39	36.8	26.9	50.4	215,985	2,458	32.4	31.1	33.7	72,793	336	17.5	15.7	19.5
By Comorbidity:															
Diabetes (overall)	9,703	119	37.0	30.9	44.2	555,649	5,806	27.2	26.5	27.9	74,235	264	13.1	11.6	14.8
Male gender (overall)	5,539	75	40.5	32.3	50.8	296,913	3,280	28.9	27.9	29.9	34,185	118	12.8	10.7	15.4
18 - 44 years	385	2	14.4	3.6	57.4	30,255	134	11.4	9.6	13.5	13,312	24	6.6	4.4	9.8
45 - 64 years	3,770	53	41.0	31.3	53.7	203,436	2,117	26.5	25.4	27.6	18,782	83	16.5	13.3	20.4
65+ years	1,384	20	47.6	30.7	73.7	63,222	1,029	47.3	44.5	50.2	2,091	11	21.6	11.9	39.0
Female gender (overall)	4,164	44	32.2	24.0	43.3	258,736	2,526	25.2	24.2	26.2	40,050	146	13.3	11.3	15.7
18 - 44 years	229	0				25,483	150	15.0	12.8	17.6	17,725	44	8.9	6.6	12.0
45 - 64 years	2,550	25	28.6	19.3	42.3	176,017	1,692	24.1	23.0	25.3	20,253	94	17.0	13.9	20.8
	All Aliskiren Patients					**All Other Antihypertensive Therapy Patients**					**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	

65+ years	1,385	19	46.4	29.6	72.7	57,236	684	34.2	31.8	36.9	2,072	8	15.8	7.9	31.6
H. pylori infection (overall)	102	2	61.9	15.5	247.5	7,616	94	33.3	27.2	40.7	7,337	28	14.1	9.7	20.4
Male gender (overall)	46	1	77.1	10.9	547.2	3,239	39	32.8	24.0	44.9	2,655	9	12.4	6.5	23.9
18 - 44 years	3	0				492	3	17.0	5.5	52.8	1,483	0			
45 - 64 years	34	0				2,141	28	35.2	24.3	50.9	1,107	8	26.3	13.1	52.6
65+ years	9	1	410.9	57.9	2,917.0	606	8	37.0	18.5	73.9	65	1	58.6	8.3	415.9
Female gender (overall)	56	1	51.7	7.3	367.1	4,377	55	33.6	25.8	43.8	4,682	19	15.0	9.6	23.5
18 - 44 years	2	0				680	5	19.9	8.3	47.8	2,450	5	7.6	3.2	18.2
45 - 64 years	37	1	69.8	9.8	495.3	3,029	42	36.2	26.7	48.9	2,115	13	22.5	13.0	38.7
65+ years	17	0				668	8	35.8	17.9	71.6	117	1	34.9	4.9	247.5
Chronic stomach inflammation (overall)	852	15	52.2	31.5	86.5	60,415	853	37.3	34.8	39.8	51,342	229	15.9	14.0	18.1
Male gender (overall)	377	8	62.4	31.2	124.7	25,398	398	41.7	37.8	46.0	18,367	94	18.1	14.8	22.2
18 - 44 years	28	0				3,715	20	14.3	9.2	22.1	10,605	27	9.0	6.1	13.1
45 - 64 years	255	5	55.2	23.0	132.6	16,569	262	40.9	36.2	46.2	7,313	58	28.1	21.7	36.3
65+ years	94	3	117.8	38.0	365.3	5,114	116	67.0	55.9	80.4	449	9	84.6	44.0	162.6
Female gender (overall)	475	7	44.0	21.0	92.2	35,017	455	34.1	31.1	37.3	32,975	135	14.6	12.4	17.3

18 - 44 years	37	0				4,493	35	20.4	14.6	28.4	17,499	49	10.0	7.6	13.3
45 - 64 years	282	5	49.6	20.7	119.3	23,742	315	33.7	30.2	37.7	14,499	78	19.0	15.2	23.7
65+ years	156	2	43.3	10.8	173.1	6,782	105	45.5	37.6	55.1	977	8	33.6	16.8	67.2
Stomach polyps (overall)	185	2	30.9	7.7	123.6	10,891	219	53.3	46.7	60.8	7,898	64	29.0	22.7	37.0
Male gender (overall)	76	1	38.2	5.4	271.4	4,082	99	65.2	53.6	79.5	2,525	21	29.6	19.3	45.4
	All Aliskiren Patients					**All Other Antihypertensive Therapy Patients**					**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
18 - 44 years	4	0				391	9	61.0	31.7	117.1	942	7	26.3	12.5	55.1
45 - 64 years	47	0				2,727	68	64.9	51.2	82.3	1,490	11	26.2	14.5	47.3
65+ years	25	1	139.1	19.6	987.3	964	22	68.4	45.0	103.9	93	3	131.4	42.4	407.4
Female gender (overall)	109	1	25.9	3.7	184.1	6,809	120	46.3	38.7	55.4	5,373	43	28.7	21.3	38.7
18 - 44 years	5	0				574	6	28.9	13.0	64.4	1,694	12	24.9	14.2	43.9
45 - 64 years	68	1	39.8	5.6	282.8	4,792	83	43.9	35.4	54.4	3,428	29	30.4	21.1	43.7
65+ years	36	0				1,443	31	63.0	44.3	89.6	251	2	31.8	8.0	127.3
By Co-Medication:															
Proton pump inhibitors (overall)	3,360	41	35.5	26.2	48.3	268,207	3,261	31.1	30.0	32.2	98,109	484	17.3	15.8	18.9
Male gender	1,601	27	48.8	33.4	71.1	128,517	1,690	33.5	31.9	35.1	42,282	226	18.5	16.3	21.

(overall)														1
18 - 44 years	144	1	17.7	2.5	125.3	18,220	104	14.5	11.9	17.5	20,157	53	9.0	6.9	11.8
45 - 64 years	1,067	16	42.5	26.0	69.3	87,157	1,134	32.3	30.5	34.2	20,861	156	26.0	22.2	30.4
65+ years	390	10	83.1	44.7	154.5	23,140	452	55.0	50.1	60.3	1,264	17	53.2	33.0	85.5
Female gender (overall)	1,759	14	23.3	13.8	39.4	139,690	1,571	28.9	27.5	30.4	55,827	258	16.4	14.5	18.5
18 - 44 years	92	1	30.1	4.2	213.8	13,313	75	14.4	11.5	18.1	21,050	71	12.0	9.5	15.1
45 - 64 years	1,043	7	19.0	9.0	39.8	95,942	1,067	27.9	26.2	29.6	32,251	171	18.6	16.0	21.6
65+ years	624	6	30.4	13.7	67.7	30,435	429	39.4	35.8	43.3	2,526	16	24.5	15.0	40.0
Statins (overall)	6,042	67	33.3	26.2	42.3	556,971	5,280	24.5	23.9	25.2	99,856	423	15.1	13.7	16.6
Male gender (overall)	3,562	37	30.7	22.2	42.3	325,683	3,158	25.0	24.2	25.9	52,859	214	14.3	12.5	16.4
18 - 44 years	293	1	9.0	1.3	64.0	31,172	114	9.3	7.7	11.1	11,203	29	8.9	6.2	12.8
45 - 64 years	2,444	29	34.3	23.8	49.3	231,966	2,128	23.2	22.2	24.2	38,614	166	15.2	13.1	17.7
65+ years	825	7	28.1	13.4	58.8	62,545	916	41.4	38.8	44.2	3,042	19	24.9	15.9	39.0
	All Aliskiren Patients					**All Other Antihypertensive Therapy Patients**					**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	2,480	30	37.3	26.1	53.3	231,288	2,122	23.8	22.8	24.9	46,997	209	16.0	14.0	18.3
18 - 44 years	94	1	31.5	4.4	223.4	12,504	75	15.2	12.1	19.0	5,185	16	10.6	6.5	17.

														4
45 - 64 years	1,440	13	26.6	15.4	45.8	159,724	1,346	21.4	20.3	22.6	37,452	177	16.9	14.6	19.6
65+ years	946	16	56.3	34.5	91.9	59,060	701	33.1	30.7	35.7	4,360	16	14.5	8.9	23.7
Hormone replacement therapy (overall)	699	5	20.1	8.4	48.2	73,703	613	20.4	18.8	22.1	52,764	218	13.8	12.1	15.8
Male gender (overall)	2	0				194	3	45.7	14.7	141.7	72	0			
18 - 44 years						21	0				21	0			
45 - 64 years	2	0				145	3	59.6	19.2	184.8	49	0			
65+ years						28	0				2	0			
Female gender (overall)	697	5	20.1	8.4	48.4	73,509	610	20.3	18.8	22.0	52,692	218	13.9	12.1	15.8
18 - 44 years	14	0				3,355	21	15.0	9.8	23.0	6,430	20	10.3	6.7	16.0
45 - 64 years	546	3	15.3	4.9	47.5	60,697	488	19.4	17.8	21.2	44,502	191	14.3	12.4	16.5
65+ years	137	2	42.8	10.7	170.9	9,457	101	29.1	23.9	35.3	1,760	7	15.5	7.4	32.5
By Lifestyle factors:															
Alcohol dependence syndrome, defined by ICD-9-CM 303.x (overall)	95	1	31.4	4.4	223.1	15,620	163	31.1	26.7	36.2	13,668	32	8.9	6.3	12.6
Male gender	82	1	36.2	5.1	256.8	11,474	115	29.8	24.8	35.8	8,655	17	7.5	4.6	12.

(overall)														0
18 - 44 years	13	0				2,526	4	4.8	1.8	12.8	6,092	10	6.3	3.4	11.7
45 - 64 years	59	1	47.7	6.7	338.3	7,985	92	33.9	27.7	41.6	2,494	7	10.4	5.0	21.8
65+ years	10	0				963	19	59.4	37.9	93.1	69	0			
Female gender (overall)	13	0				4,146	48	34.7	26.1	46.0	5,013	15	11.4	6.9	18.9
18 - 44 years	1	0				851	3	10.9	3.5	33.7	3,107	4	4.9	1.8	13.1
	All Aliskiren Patients					**All Other Antihypertensive Therapy Patients**					**All Non-hypertensive Patients**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
45 - 64 years	9	0				2,958	41	41.3	30.4	56.1	1,848	10	20.3	10.9	37.7
65+ years	3	0				337	4	34.8	13.1	92.9	58	1	76.1	10.7	540.1
Obesity, defined by ICD-9-CM 278.0x(overall)	2,878	26	27.0	18.4	39.6	204,763	1,777	23.1	22.1	24.2	101,651	250	9.4	8.3	10.6
Male gender (overall)	1,530	17	33.1	20.6	53.3	91,228	830	24.6	23.0	26.3	30,471	77	9.8	7.9	12.3
18 - 44 years	229	0				22,397	94	11.7	9.6	14.4	18,088	27	5.8	4.0	8.4
45 - 64 years	1,112	13	34.7	20.2	59.8	61,077	628	27.2	25.2	29.5	11,967	45	14.7	11.0	19.7
65+ years	189	4	70.8	26.6	188.6	7,754	108	40.6	33.6	49.0	416	5	52.7	21.9	126.6
Female gender (overall)	1,348	9	20.0	10.4	38.4	113,535	947	22.0	20.6	23.4	71,180	173	9.2	7.9	10.7

18 - 44 years	190	0				27,417	142	14.1	12.0	16.6	45,461	92	7.6	6.2	9.4
45 - 64 years	953	8	24.7	12.4	49.4	76,742	682	22.9	21.3	24.7	24,975	79	12.0	9.6	15.0
65+ years	205	1	17.1	2.4	121.3	9,376	123	37.6	31.5	44.9	744	2	11.8	3.0	47.2

Table 15-23 Incidence Rates (per 10,000 person-years) of GI Cancer – Incident and Prevalent Cohorts

	Incident Aliskiren Treatment Cohort					Incident Other Antihypertensive Treatment Cohort					Prevalent Aliskiren Treatment Cohort					Prevalent Other Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Overall:	2,193	13	16.8	9.8	29.0	972,369	6,515	21.4	20.9	21.9	23,547	243	30.2	26.6	34.2	1,462,018	15,220	24.0	23.6	24.3
By Age Group:																				
18 - 44 years	512	1	5.3	0.7	37.6	219,760	698	10.0	9.3	10.7	2,269	8	9.5	4.8	19.0	171,615	884	10.9	10.2	11.7
45 - 64 years	1,444	9	17.5	9.1	33.7	636,946	4,531	22.5	21.9	23.2	15,237	158	29.4	25.2	34.4	998,886	10,162	22.8	22.4	23.3
65+ years	237	3	43.1	13.9	133.7	115,663	1,286	38.8	36.7	41.0	6,041	77	41.8	33.4	52.2	291,517	4,174	38.3	37.1	39.5
By Gender:																				
Male (overall)	1,315	6	12.7	5.7	28.3	518,785	3,578	22.1	21.4	22.8	12,771	147	33.3	28.3	39.1	726,042	8,072	25.5	24.9	26.0
8 - 44 years	361	1	7.4	1.0	52.6	123,129	356	9.1	8.2	10.1	1,457	4	7.4	2.8	19.7	94,481	415	9.3	8.5	10.3
45 - 64 years	846	3	9.8	3.2	30.4	338,510	2,481	23.3	22.4	24.2	8,651	104	34.1	28.1	41.3	497,512	5,396	24.3	23.6	24.9

65+ years	108	2	64.2	16.1	256.9	57,146	741	45.1	42.0	48.5	2,663	39	47.4	34.7	64.9	134,049	2,261	45.3	43.5	47.3
Female (overall)	878	7	23.3	11.1	48.9	453,584	2,937	20.7	19.9	21.4	10,776	96	26.4	21.6	32.2	735,976	7,148	22.4	21.9	23.0
18 - 44 years	151	0				96,631	342	11.1	9.9	12.3	812	4	13.3	5.0	35.4	77,134	469	12.9	11.8	14.1
45 - 64 years	598	6	28.8	12.9	64.1	298,436	2,050	21.7	20.8	22.6	6,586	54	23.3	17.8	30.4	501,374	4,766	21.4	20.8	22.0
65+ years	129	1	26.0	3.7	184.8	58,517	545	32.6	30.0	35.5	3,378	38	37.2	27.1	51.1	157,468	1,913	32.3	30.9	33.8
By Comorbidity:																				
Diabetes (overall)	468	4	25.9	9.7	68.9	180,553	1,367	24.7	23.4	26.0	9,235	115	37.5	31.3	45.0	375,096	4,439	28.0	27.2	28.9
Male gender (overall)	276	1	10.3	1.5	73.3	100,519	797	25.9	24.2	27.8	5,263	74	42.1	33.6	52.9	196,394	2,483	30.0	28.9	31.2
18 - 44 years	50	0				15,018	49	10.4	7.8	13.7	335	2	16.6	4.2	66.4	15,237	85	12.1	9.8	14.9
45 - 64 years	195	1	14.2	2.0	100.8	68,994	530	24.8	22.8	27.1	3,575	52	42.5	32.4	55.8	134,442	1,587	27.1	25.8	28.4
65+ years	31	0				16,507	218	46.3	40.5	52.9	1,353	20	48.4	31.3	75.1	46,715	811	47.5	44.4	50.9
Female gender (overall)	192	3	51.9	16.7	161.0	80,034	570	23.1	21.3	25.1	3,972	41	31.3	23.1	42.5	178,702	1,956	25.9	24.7	27.0

18 - 44 years	18	0				12,675	59	14.5	11.2	18.7	211	0				12,808	91	15.4	12.5	18.9
	Incident Aliskiren Treatment Cohort					**Incident Other Antihypertensive Treatment Cohort**					**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				
	Patients	**Event**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
45 - 64 years	134	3	74.1	23.9	229.6	54,327	394	23.3	21.1	25.8	2,416	22	26.4	17.4	40.1	121,690	1,298	24.3	23.0	25.7
65+ years	40	0				13,032	117	31.8	26.6	38.2	1,345	19	47.8	30.5	74.9	44,204	567	34.8	32.0	37.8
H. pylori infection (overall)	5	1	688.2	96.9	4,885.3	3,532	35	32.3	23.2	44.9	97	1	32.4	4.6	230.0	4,084	59	33.9	26.3	43.8
Male gender (overall)	4	0				1,569	13	27.1	15.8	46.8	42	1	83.6	11.8	593.7	1,670	26	36.6	24.9	53.8
18 - 44 years						320	3	31.0	10.0	96.0	3	0				172	0			
45 - 64 years	4	0				1,037	8	25.0	12.5	50.0	30	0				1,104	20	42.0	27.1	65.1
65+ years						212	2	32.1	8.0	128.4	9	1	410.9	57.9	2,917.0	394	6	38.9	17.5	86.7
Female gender (overall)	1	1	2,287.0	322.2	16,235.3	1,963	22	36.3	23.9	55.1	55	0				2,414	33	32.0	22.8	45.1
18 - 44 years						419	3	23.1	7.4	71.6	2	0				261	2	16.5	4.1	65.9

45 - 64 years	1	1	2,287.0	322.2	16,235.3	1,327	17	40.9	25.4	65.7	36	0				1,702	25	33.5	22.7	49.6
65+ years						217	2	33.3	8.3	133.0	17	0				451	6	36.8	16.5	81.8
Chronic stomach inflammation (overall)	48	0				23,739	284	38.9	34.6	43.7	804	15	54.8	33.1	90.9	36,676	569	36.5	33.6	39.6
Male gender (overall)	25	0				10,463	140	43.7	37.0	51.6	352	8	66.1	33.1	132.3	14,935	258	40.7	36.0	46.0
18 - 44 years	4	0				2,083	8	12.3	6.2	24.6	24	0				1,632	12	15.9	9.0	28.0
45 - 64 years	16	0				6,793	97	46.2	37.8	56.3	239	5	58.4	24.3	140.2	9,776	165	38.4	32.9	44.7
65+ years	5	0				1,587	35	77.6	55.7	108.1	89	3	122.5	39.5	379.9	3,527	81	63.3	50.9	78.7
Female gender (overall)	23	0				13,276	144	35.1	29.8	41.4	452	7	45.8	21.9	96.2	21,741	311	33.6	30.0	37.5
18 - 44 years	1	0				2,481	19	24.4	15.5	38.2	36	0				2,012	16	17.1	10.5	27.9
45 - 64 years	19	0				8,905	108	38.8	32.2	46.9	263	5	52.7	21.9	126.5	14,837	207	31.6	27.6	36.2
65+ years	3	0				1,890	17	31.7	19.7	51.0	153	2	43.9	11.0	175.4	4,892	88	49.7	40.3	61.2

Stomach polyps (overall)	13	0			4,014	70	57.8	45.7	73.0	172	2	33.2	8.3	132.9	6,877	149	51.4	43.8	60.4
	Incident Aliskiren Treatment Cohort				**Incident Other Antihypertensive Treatment Cohort**					**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**	**Patients**	**Events**		**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Male gender (overall)	4	0			1,532	30	65.4	45.7	93.5	72	1	39.6	5.6	280.9	2,550	69	65.2	51.5	82.5
18 - 44 years					204	4	66.6	25.0	177.5	4	0				187	5	57.1	23.8	137.1
45 - 64 years	4	0			1,014	22	71.3	46.9	108.2	43	0				1,713	46	62.2	46.6	83.1
65+ years					314	4	44.3	16.6	118.2	25	1	139.1	19.6	987.3	650	18	77.8	49.0	123.5
Female gender (overall)	9	0			2,482	40	53.1	39.0	72.4	100	1	28.7	4.0	203.4	4,327	80	43.5	34.9	54.2
18 - 44 years					314	3	32.2	10.4	100.0	5	0				260	3	26.2	8.5	81.3
45 - 64 years	9	0			1,767	32	58.4	41.3	82.5	59	1	46.6	6.6	331.1	3,025	51	38.0	28.8	49.9
65+ years					401	5	44.8	18.6	107.6	36	0				1,042	26	68.3	46.5	100.3
By Co-Medication:																			

Proton pump inhibitors (overall)	181	1	15.6	2.2	110.5	89,012	824	29.9	27.9	32.0	3,179	40	36.7	26.9	50.1	179,195	2,437	31.5	30.3	32.8
Male gender (overall)	90	0				44,750	441	31.6	28.8	34.7	1,511	27	51.8	35.6	75.6	83,767	1,249	34.2	32.3	36.1
18 - 44 years	13	0				9,079	47	16.4	12.3	21.8	131	1	19.4	2.7	137.9	9,141	57	13.2	10.2	17.1
45 - 64 years	64	0				29,800	302	32.3	28.8	36.1	1,003	16	45.4	27.8	74.1	57,357	832	32.3	30.2	34.6
65+ years	13	0				5,871	92	53.7	43.7	65.8	377	10	85.7	46.1	159.3	17,269	360	55.3	49.9	61.4
Female gender (overall)	91	1	32.1	4.5	227.7	44,262	383	28.2	25.5	31.1	1,668	13	22.9	13.3	39.4	95,428	1,188	29.1	27.5	30.8
18 - 44 years	8	0				6,524	23	11.3	7.5	17.0	84	1	33.1	4.7	235.2	6,789	52	16.4	12.5	21.5
45 - 64 years	68	1	43.2	6.1	307.0	30,315	274	29.1	25.8	32.7	975	6	17.3	7.8	38.6	65,627	793	27.5	25.6	29.5
65+ years	15	0				7,423	86	40.2	32.5	49.6	609	6	31.2	14.0	69.5	23,012	343	39.2	35.3	43.6
Statins (overall)	347	3	26.0	8.4	80.6	192,915	1,333	22.5	21.4	23.8	5,695	64	33.8	26.4	43.1	364,056	3,947	25.3	24.5	26.1
Male gender (overall)	226	1	12.9	1.8	91.3	118,440	809	22.2	20.7	23.8	3,336	36	31.9	23.0	44.2	207,243	2,349	26.2	25.1	27.3
18 - 44 years	44	0				16,02	45	8.9	6.6	11.9	249	1	10.8	1.5	76.	15,14	69	9.	7.	12.

					5								5	7		6	6	1	
45 - 64 years	159	0			86,000	565	21.2	19.5	23.0	2,285	29	36.6	25.4	52.7	145,966	1,563	24.0	22.8	25.2
	Incident Aliskiren Treatment Cohort					**Incident Other Antihypertensive Treatment Cohort**				**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	23	1	178.1	25.1	1,264.3	16,415	199	42.3	36.8	48.6	802	6	24.6	11.1	54.8	46,130	717	41.2	38.3	44.3
Female gender (overall)	121	2	53.2	13.3	212.7	74,475	524	23.1	21.2	25.2	2,359	28	36.5	25.2	52.9	156,813	1,598	24.1	22.9	25.3
18 - 44 years	10	0				6,145	29	15.0	10.4	21.6	84	1	34.3	4.8	243.2	6,359	46	15.3	11.4	20.4
45 - 64 years	84	1	36.7	5.2	260.5	54,191	354	21.2	19.1	23.5	1,356	12	26.0	14.8	45.8	105,533	992	21.5	20.2	22.9
65+ years	27	1	129.0	18.2	915.5	14,139	141	35.0	29.7	41.3	919	15	54.3	32.7	90.0	44,921	560	32.7	30.1	35.5
Hormone replacement therapy (overall)	44	0				19,986	137	20.9	17.7	24.7	655	5	21.4	8.9	51.3	53,717	476	20.2	18.5	22.1
Male gender (overall)	1	0				90	0				1	0				104	3	72.4	23.4	224.6
18 - 44 years						14	0									7	0			
45 - 64 years	1	0				67	0				1	0				78	3	94.	30.	293.4

															6	5	
65+ years			9	0								19	0				
Female gender (overall)	43	0	19,896	137	21.0	17.8	24.8	654	5	21.4	8.9	51.4	53,613	473	20.2	18.4	22.1
18 - 44 years	5	0	1,399	10	20.9	11.3	38.9	9	0				1,956	11	11.9	6.6	21.5
45 - 64 years	35	0	16,551	111	20.3	16.9	24.5	511	3	16.3	5.3	50.6	44,146	377	19.2	17.3	21.2
65+ years	3	0	1,946	16	27.6	16.9	45.1	134	2	43.5	10.9	174.1	7,511	85	29.4	23.7	36.3
By Lifestyle factors:																	
Alcohol dependence syndrome, defined by ICD-9-CM 303.x (overall)	12	0	8,120	72	31.2	24.8	39.4	83	1	36.4	5.1	258.4	7,500	91	31.0	25.2	38.0
Male gender (overall)	11	0	6,040	52	30.4	23.2	39.9	71	1	42.6	6.0	302.5	5,434	63	29.3	22.9	37.5
18 - 44 years	3	0	1,606	3	6.7	2.2	20.8	10	0				920	1	2.6	0.4	18.6
45 - 64 years	8	0	4,071	44	37.8	28.1	50.8	51	1	56.3	7.9	399.7	3,914	48	31.0	23.4	41.2
65+ years			363	5	50.7	21.1	121.7	10	0				600	14	63.2	37.4	106.7
	Incident Aliskiren Treatment Cohort		**Incident Other Antihypertensive Treatment Cohort**					**Prevalent Aliskiren Treatment Cohort**					**Prevalent Other Antihypertensive Treatment Cohort**				

	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Female gender (overall)	1	0				2,080	20	33.7	21.7	52.2	12	0				2,066	28	35.5	24.5	51.4
18 - 44 years						534	1	6.5	0.9	45.9	1	0				317	2	16.4	4.1	65.7
45 - 64 years	1	0				1,453	18	43.3	27.3	68.7	8	0				1,505	23	39.9	26.5	60.0
65+ years						93	1	42.2	5.9	299.4	3	0				244	3	32.9	10.6	102.1
Obesity, defined by ICD-9-CM 278.0x(overall)	155	2	37.9	9.5	151.6	93,796	610	21.8	20.1	23.6	2,723	24	26.3	17.6	39.3	110,967	1,167	23.9	22.6	25.3
Male gender (overall)	73	1	39.2	5.5	278.3	43,931	297	22.8	20.4	25.6	1,457	16	32.8	20.1	53.5	47,297	533	25.7	23.7	28.0
18 - 44 years	25	0				14,006	53	12.7	9.7	16.6	204	0				8,391	41	10.7	7.9	14.5
45 - 64 years	42	0				27,380	210	25.7	22.5	29.5	1,070	13	36.1	20.9	62.1	33,697	418	28.1	25.5	30.9
65+ years	6	1	740.8	104.4	5,259.1	2,545	34	49.4	35.3	69.1	183	3	54.4	17.5	168.6	5,209	74	37.5	29.9	47.1
Female gender (overall)	82	1	36.7	5.2	260.8	49,865	313	20.9	18.7	23.3	1,266	8	18.9	9.4	37.8	63,670	634	22.6	20.9	24.4
18 - 44 years	17	0				16,41	72	14.4	11.4	18.1	173	0				11,00	70	1	1	17.

						7									0		3.8	0.9	4
45 - 64 years	58	1	54.0	7.6	383.5	30,825	215	23.1	20.2	26.4	895	7	22.9	10.9	48.1	45,917	467	22.9	20.9	25.0
65+ years	7	0				2,623	26	37.2	25.4	54.7	198	1	17.8	2.5	126.0	6,753	97	37.8	30.9	46.1

Table 15-24 Incidence Rates (per 10,000 person-years) of GI Cancer for Antihypertensive Drug Use within 30 Days after Index

	All Patients					Incident Antihypertensive Treatment Cohort					Prevalent Antihypertensive Treatment Cohort				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Overall:	2,460,127	21,991	23.2	22.9	23.5	974,562	6,528	21.4	20.9	21.9	1,485,565	15,463	24.0	23.7	24.4
Monotherapy Initiators:															
Aliskiren (overall)	8,190	74	25.8	20.6	32.4	1,573	6	10.5	4.7	23.5	6,617	68	29.6	23.3	37.5
Male gender (overall)	4,406	47	30.1	22.6	40.0	951	3	8.5	2.8	26.5	3,455	44	36.3	27.1	48.8
18 - 44 years	778	1	3.4	0.5	23.9	291	0				487	1	5.4	0.8	38.4
45-64 years	2,931	30	28.6	20.0	40.9	596	2	9.1	2.3	36.2	2,335	28	33.8	23.4	49.0
65+ years	697	16	73.9	45.2	120.6	64	1	53.5	7.5	380.1	633	15	75.8	45.7	125.7
Female gender (overall)	3,784	27	20.7	14.2	30.2	622	3	13.8	4.5	42.8	3,162	24	22.1	14.8	32.9

18 - 44 years	418	2	12.9	3.2	51.6	116	0				302	2	17.6	4.4	70.4
45-64 years	2,417	16	18.6	11.4	30.3	419	2	13.3	3.3	53.2	1,998	14	19.7	11.7	33.2
65+ years	949	9	31.3	16.3	60.1	87	1	38.7	5.4	274.5	862	8	30.5	15.3	61.0
Angiotensin-converting enzyme inhibitors (overall)	419,086	3,084	20.0	19.3	20.7	226,022	1,322	18.9	17.9	20.0	193,064	1,762	20.8	19.9	21.8
Male gender (overall)	251,620	1,868	20.1	19.2	21.0	137,512	794	18.6	17.4	20.0	114,108	1,074	21.3	20.1	22.6
18 - 44 years	57,155	198	9.5	8.2	10.9	37,449	101	8.6	7.1	10.5	19,706	97	10.6	8.7	12.9
45-64 years	169,254	1,330	20.9	19.8	22.0	89,421	571	20.5	18.9	22.3	79,833	759	21.2	19.7	22.7
65+ years	25,211	340	40.2	36.2	44.8	10,642	122	40.2	33.7	48.0	14,569	218	40.3	35.3	46.0
Female gender (overall)	167,466	1,216	19.8	18.7	21.0	88,510	528	19.4	17.8	21.1	78,956	688	20.2	18.7	21.7

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
18 - 44 years	26,347	110	11.4	9.4	13.7	16,962	55	10.3	7.9	13.4	9,385	55	12.7	9.8	16.5
45-64 years	117,247	858	19.6	18.4	21.0	61,327	370	19.5	17.6	21.6	55,920	488	19.8	18.1	21.6
65+ years	23,872	248	31.1	27.4	35.2	10,221	103	35.8	29.5	43.4	13,651	145	28.4	24.1	33.4
Angiotensin II receptor	162,371	1,394	21.7	20.5	22.8	66,813	434	20.0	18.2	22.0	95,558	960	22.5	21.1	24.0

blockers (overall)														
Male gender (overall)	88,578	756	21.3	19.9	22.9	37,844	234	18.9	16.6	21.5	50,734	522	22.6	20.8	24.7
18 - 44 years	19,583	69	8.7	6.9	11.0	10,317	25	7.2	4.9	10.7	9,266	44	9.8	7.3	13.2
45-64 years	60,302	558	22.7	20.9	24.7	24,490	170	21.1	18.2	24.5	35,812	388	23.5	21.3	26.0
65+ years	8,693	129	43.3	36.4	51.4	3,037	39	44.3	32.4	60.6	5,656	90	42.9	34.9	52.7
Female gender (overall)	73,793	638	22.1	20.4	23.8	28,969	200	21.5	18.7	24.6	44,824	438	22.3	20.3	24.5
18 - 44 years	9,685	49	12.5	9.4	16.5	4,957	18	10.7	6.7	17.0	4,728	31	13.8	9.7	19.6
45-64 years	52,961	470	22.2	20.3	24.3	20,515	159	24.0	20.5	28.0	32,446	311	21.4	19.1	23.9
65+ years	11,147	119	31.1	26.0	37.2	3,497	23	23.0	15.3	34.5	7,650	96	34.0	27.8	41.5
Alpha blockers (overall)	40,465	431	31.7	28.9	34.9	26,257	237	30.3	26.7	34.4	14,208	194	33.7	29.3	38.8
Male gender (overall)	37,171	414	33.0	29.9	36.3	23,720	224	31.5	27.6	35.9	13,451	190	34.9	30.3	40.2
18 - 44 years	2,667	11	12.9	7.1	23.3	2,379	10	14.0	7.5	26.0	288	1	7.2	1.0	51.3
45-64 years	23,488	237	29.3	25.8	33.2	15,723	148	30.9	26.3	36.3	7,765	89	26.9	21.9	33.1
65+ years	11,016	166	46.0	39.5	53.5	5,618	66	41.0	32.2	52.2	5,398	100	50.0	41.1	60.8
Female	3,294	17	16.6	10.3	26.8	2,537	13	18.3	10.6	31.5	757	4	12.8	4.8	34.2

gender (overall)														
18 - 44 years	796	1	4.4	0.6	31.1	729	1	5.0	0.7	35.5	67	0			
45-64 years	1,992	15	23.7	14.3	39.4	1,541	11	25.3	14.0	45.7	451	4	20.3	7.6	54.0
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	506	1	6.2	0.9	44.2	267	1	13.2	1.9	94.0	239	0			
Beta blockers (overall)	301,403	2,659	23.3	22.4	24.2	138,309	988	22.9	21.5	24.4	163,094	1,671	23.5	22.4	24.7
Male gender (overall)	146,131	1,403	25.5	24.2	26.8	68,978	525	24.4	22.4	26.6	77,153	878	26.1	24.5	27.9
18 - 44 years	27,777	113	10.9	9.1	13.1	16,623	57	11.0	8.5	14.3	11,154	56	10.8	8.3	14.0
45-64 years	96,880	936	25.0	23.5	26.7	44,431	352	25.1	22.6	27.9	52,449	584	25.0	23.0	27.1
65+ years	21,474	354	48.6	43.8	53.9	7,924	116	50.8	42.4	61.0	13,550	238	47.6	41.9	54.0
Female gender (overall)	155,272	1,256	21.3	20.1	22.5	69,331	463	21.4	19.5	23.4	85,941	793	21.2	19.8	22.7
18 - 44 years	30,027	145	12.9	10.9	15.1	17,831	62	11.1	8.7	14.2	12,196	83	14.6	11.7	18.1
45-64 years	99,988	818	20.9	19.6	22.4	42,881	308	22.7	20.3	25.3	57,107	510	20.0	18.4	21.8
65+ years	25,257	293	33.7	30.1	37.8	8,619	93	37.9	31.0	46.5	16,638	200	32.0	27.9	36.8

Calcium channel blockers (overall)	147,217	1,409	25.4	24.1	26.7	67,132	508	24.5	22.4	26.7	80,085	901	25.9	24.3	27.7
Male gender (overall)	71,926	726	26.9	25.0	28.9	35,163	284	26.1	23.2	29.3	36,763	442	27.4	25.0	30.1
18 - 44 years	13,661	45	8.9	6.6	11.9	8,686	28	10.3	7.1	14.9	4,975	17	7.2	4.5	11.6
45-64 years	47,169	501	27.5	25.2	30.1	22,374	211	30.2	26.4	34.5	24,795	290	25.9	23.1	29.1
65+ years	11,096	180	48.1	41.5	55.6	4,103	45	38.3	28.6	51.3	6,993	135	52.6	44.4	62.2
Female gender (overall)	75,291	683	23.9	22.2	25.8	31,969	224	22.7	19.9	25.9	43,322	459	24.6	22.4	26.9
18 - 44 years	11,570	65	14.9	11.7	19.0	7,066	30	13.5	9.5	19.4	4,504	35	16.4	11.8	22.8
45-64 years	47,316	423	22.8	20.7	25.1	19,675	142	23.0	19.5	27.1	27,641	281	22.7	20.2	25.5
65+ years	16,405	195	34.7	30.2	40.0	5,228	52	35.2	26.9	46.3	11,177	143	34.5	29.3	40.7
Diuretics (overall)	236,997	2,059	23.4	22.4	24.4	124,255	910	23.1	21.7	24.7	112,742	1,149	23.6	22.3	25.0

	All Patients					**Incident Antihypertensive Treatment Cohort**				**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	**Patients**		**Events**	**IR**	**95% CI**	
Male gender (overall)	74,143	692	26.0	24.1	28.0	42,581	341	25.6	23.1	28.5	31,562	351	26.3	23.7	29.2
18 - 44 years	15,096	56	10.3	7.9	13.3	10,834	38	11.0	8.0	15.1	4,262	18	9.0	5.7	14.3

45-64 years	46,316	429	25.1	22.8	27.6	26,062	211	25.6	22.3	29.3	20,254	218	24.6	21.6	28.1
65+ years	12,731	207	50.4	44.0	57.8	5,685	92	57.9	47.2	71.1	7,046	115	45.7	38.0	54.8
Female gender (overall)	162,854	1,367	22.3	21.1	23.5	81,674	569	21.8	20.1	23.7	81,180	798	22.6	21.1	24.2
18 - 44 years	30,666	151	13.1	11.1	15.3	19,826	79	12.3	9.8	15.3	10,840	72	14.1	11.2	17.7
45-64 years	107,535	942	22.8	21.4	24.3	52,234	384	22.8	20.6	25.2	55,301	558	22.8	21.0	24.8
65+ years	24,653	274	32.4	28.8	36.5	9,614	106	38.3	31.7	46.4	15,039	168	29.5	25.4	34.3
Others (overall)	13,000	119	25.6	21.4	30.6	7,595	55	23.9	18.3	31.1	5,405	64	27.3	21.3	34.8
Male gender (overall)	4,547	40	25.7	18.9	35.1	2,884	19	22.2	14.2	34.8	1,663	21	30.1	19.6	46.2
18 - 44 years	1,412	1	2.2	0.3	15.5	1,104	1	3.1	0.4	22.0	308	0			
45-64 years	2,574	29	31.8	22.1	45.8	1,527	13	28.2	16.4	48.5	1,047	16	35.6	21.8	58.1
65+ years	561	10	53.9	29.0	100.2	253	5	69.4	28.9	166.7	308	5	44.1	18.4	106.0
Female gender (overall)	8,453	79	25.5	20.5	31.8	4,711	36	24.9	18.0	34.5	3,742	43	26.1	19.3	35.1
18 - 44 years	3,412	22	17.3	11.4	26.2	2,023	10	16.1	8.6	29.9	1,389	12	18.4	10.5	32.4
45-64 years	4,167	44	28.7	21.3	38.5	2,340	20	27.5	17.7	42.6	1,827	24	29.8	20.0	44.4
65+ years	874	13	45.0	26.2	77.6	348	6	62.8	28.2	139.8	526	7	36.3	17.3	76.1

Dual-combination Therapy Initiators:															
Dual combination including aliskiren (overall)	5,458	68	37.0	29.1	46.9	253	5	57.6	24.0	138.4	5,205	63	35.9	28.1	46.0
Male gender (overall)	2,771	35	37.4	26.8	52.0	149	3	57.5	18.5	178.3	2,622	32	36.2	25.6	51.1
18 - 44 years	313	3	27.0	8.7	83.6	35	2	168.5	42.1	673.9	278	1	10.1	1.4	71.4
45-64 years	1,836	26	40.6	27.7	59.7	94	1	29.4	4.1	209.0	1,742	25	41.3	27.9	61.1
65+ years	622	6	32.2	14.5	71.8	20	0				602	6	33.4	15.0	74.3

	All Patients					**Incident Antihypertensive Treatment Cohort**				**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	**Patients**		**Events**	**IR**	**95% CI**	
Female gender (overall)	2,687	33	36.5	26.0	51.4	104	2	57.8	14.5	231.1	2,583	31	35.7	25.1	50.8
18 - 44 years	216	2	24.6	6.1	98.3	20	0				196	2	26.9	6.7	107.4
45-64 years	1,671	21	36.4	23.7	55.8	70	2	86.1	21.5	344.3	1,601	19	34.3	21.9	53.7
65+ years	800	10	41.0	22.0	76.1	14	0				786	10	41.7	22.5	77.6
Dual combination	378,521	3,216	21.7	21.0	22.5	132,186	781	19.1	17.8	20.5	246,335	2,435	22.7	21.8	23.6

including an ACEI but not aliskiren (overall)															
Male gender (overall)	211,668	1,859	22.4	21.4	23.4	75,624	461	19.7	18.0	21.6	136,044	1,398	23.5	22.3	24.7
18 - 44 years	34,453	106	7.8	6.5	9.5	16,935	42	7.9	5.8	10.7	17,518	64	7.8	6.1	9.9
45-64 years	147,764	1,331	22.6	21.4	23.8	51,571	341	21.3	19.1	23.7	96,193	990	23.0	21.6	24.5
65+ years	29,451	422	40.5	36.8	44.6	7,118	78	38.0	30.5	47.5	22,333	344	41.1	37.0	45.7
Female gender (overall)	166,853	1,357	20.8	19.8	22.0	56,562	320	18.3	16.4	20.4	110,291	1,037	21.8	20.5	23.2
18 - 44 years	21,592	80	9.4	7.6	11.7	10,921	35	10.1	7.2	14.1	10,671	45	9.0	6.7	12.0
45-64 years	116,008	955	20.6	19.4	22.0	38,868	240	19.8	17.5	22.5	77,140	715	20.9	19.5	22.5
65+ years	29,253	322	31.1	27.9	34.7	6,773	45	23.4	17.4	31.3	22,480	277	32.9	29.2	37.0
Dual combination including neither an ACEI nor aliskiren (overall)	413,025	3,864	23.0	22.3	23.7	114,945	748	20.0	18.6	21.5	298,080	3,116	23.9	23.0	24.7
Male gender (overall)	184,981	1,814	24.2	23.1	25.3	55,979	376	20.6	18.6	22.8	129,002	1,438	25.4	24.1	26.7
18 - 44 years	28,285	97	8.2	6.7	10.0	12,262	26	6.3	4.3	9.2	16,023	71	9.3	7.3	11.7
45-64 years	124,897	1,216	23.5	22.2	24.8	37,075	269	22.1	19.6	24.9	87,822	947	23.9	22.	25.5

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65+ years	31,799	501	44.2	40.5	48.3	6,642	81	41.7	33.6	51.9	25,157	420	44.7	40.6	49.2
Female gender (overall)	228,044	2,050	22.0	21.1	23.0	58,966	372	19.5	17.6	21.5	169,078	1,678	22.7	21.6	23.8
18 - 44 years	27,936	130	11.1	9.3	13.2	11,526	30	7.8	5.4	11.1	16,410	100	12.7	10.5	15.5
45-64 years	156,364	1,418	21.6	20.5	22.8	39,366	271	21.0	18.6	23.7	116,998	1,147	21.8	20.6	23.1
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	43,744	502	31.7	29.0	34.6	8,074	71	30.0	23.8	37.9	35,670	431	32.0	29.1	35.2
Triple-plus Combination Therapy Initiators:															
Triple-plus combination including aliskiren (overall)	12,244	132	31.7	26.7	37.6	376	7	59.4	28.3	124.6	11,868	125	30.9	25.9	36.8
Male gender (overall)	7,003	80	33.2	26.6	41.3	222	3	43.3	14.0	134.2	6,781	77	32.9	26.3	41.1
18 - 44 years	743	2	7.3	1.8	29.3	37	0				706	2	7.7	1.9	30.6
45-64 years	4,796	58	34.4	26.6	44.5	161	2	38.7	9.7	154.6	4,635	56	34.2	26.3	44.5
65+ years	1,464	20	44.2	28.5	68.4	24	1	163.2	23.0	1,158.3	1,440	19	42.5	27.1	66.7

Female gender (overall)	5,241	52	29.7	22.6	38.9	154	4	82.5	31.0	219.7	5,087	48	28.2	21.2	37.4
18 - 44 years	334	1	8.4	1.2	59.5	16	1	184.3	26.0	1,308.3	318	0			
45-64 years	3,140	29	26.3	18.3	37.8	109	2	57.3	14.3	229.3	3,031	27	25.3	17.3	36.9
65+ years	1,767	22	41.5	27.3	63.0	29	1	122.0	17.2	865.9	1,738	21	40.2	26.2	61.7
Triple-plus combination including an ACEI but not aliskiren (overall)	186,468	1,999	27.1	25.9	28.3	44,782	331	24.1	21.6	26.8	141,686	1,668	27.7	26.4	29.1
Male gender (overall)	107,140	1,281	30.1	28.5	31.8	25,880	210	26.4	23.1	30.3	81,260	1,071	30.9	29.1	32.9
18 - 44 years	11,250	48	10.5	7.9	14.0	4,459	19	13.6	8.7	21.4	6,791	29	9.1	6.4	13.2
45-64 years	72,694	803	27.1	25.3	29.0	17,489	129	23.9	20.1	28.4	55,205	674	27.8	25.8	30.0
65+ years	23,196	430	51.5	46.9	56.6	3,932	62	54.2	42.3	69.6	19,264	368	51.1	46.1	56.6
Female gender (overall)	79,328	718	22.9	21.3	24.7	18,902	121	20.9	17.5	25.0	60,426	597	23.4	21.6	25.3
18 - 44 years	6,790	32	11.8	8.4	16.7	3,033	14	14.6	8.6	24.6	3,757	18	10.3	6.5	16.3
45-64 years	51,813	452	21.4	19.5	23.5	12,468	89	23.0	18.7	28.3	39,345	363	21.1	19.0	23.3
65+ years	20,725	234	31.2	27.5	35.5	3,401	18	18.8	11.8	29.8	17,324	216	33.1	28.9	37.8

	All Patients					Incident Antihypertensive Treatment Cohort				Prevalent Antihypertensive Treatment Cohort					
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	Patients		Events	IR	95% CI	
Triple-plus combination including neither an ACEI nor aliskiren (overall)	135,682	1,483	27.0	25.6	28.4	24,064	196	26.4	23.0	30.4	111,618	1,287	27.0	25.6	28.6
Male gender (overall)	66,828	788	29.2	27.2	31.3	12,613	107	27.7	22.9	33.4	54,215	681	29.4	27.3	31.7
18 - 44 years	6,255	26	10.0	6.8	14.7	2,079	8	12.4	6.2	24.9	4,176	18	9.2	5.8	14.7
45-64 years	44,618	500	26.9	24.7	29.4	8,342	64	24.9	19.5	31.8	36,276	436	27.3	24.8	29.9
65+ years	15,955	262	44.8	39.7	50.6	2,192	35	53.3	38.3	74.3	13,763	227	43.8	38.4	49.8
Female gender (overall)	68,854	695	24.8	23.0	26.7	11,451	89	25.1	20.4	30.9	57,403	606	24.8	22.9	26.8
18 - 44 years	4,939	25	12.1	8.2	17.9	1,756	7	12.4	5.9	25.9	3,183	18	12.0	7.6	19.1
45-64 years	44,375	415	22.1	20.0	24.3	7,221	56	24.7	19.0	32.1	37,154	359	21.7	19.6	24.1
65+ years	19,540	255	35.7	31.6	40.4	2,474	26	36.4	24.8	53.5	17,066	229	35.6	31.3	40.5

Table 15-25 Incidence Rates (per 10,000 person-years) of GI Cancer based on Antihypertensive Therapy Exposure Time

	All Patients					Incident Antihypertensive Treatment Cohort					Prevalent Antihypertensive Treatment Cohort				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Monotherapy Initiators:															
Aliskiren	2,007	10	15.5	8.3	28.7	820	4	15.0	5.6	39.8	1,187	6	15.8	7.1	35.2
Male gender (overall)	1,103	7	19.2	9.1	40.3	495	3	17.9	5.8	55.4	608	4	20.3	7.6	54.1
18 - 44 years	290	0				156	0				134	0			
45-64 years	718	5	21.2	8.8	50.8	303	3	29.2	9.4	90.5	415	2	15.0	3.7	59.9
65+ years	95	2	76.7	19.2	306.6	36	0				59	2	124.2	31.1	496.8
Female gender (overall)	904	3	10.6	3.4	32.9	325	1	10.0	1.4	71.2	579	2	10.9	2.7	43.8
18 - 44 years	139	0				60	0				79	0			
45-64 years	616	2	10.2	2.6	40.9	215	0				401	2	15.7	3.9	62.8
65+ years	149	1	24.3	3.4	172.5	50	1	80.1	11.3	568.7	99	0			
Angiotensin-converting enzyme inhibitors	307,993	2,028	18.5	17.7	19.3	172,404	920	17.8	16.7	18.9	135,589	1,108	19.2	18.1	20.3
Male gender (overall)	187,639	1,230	18.4	17.4	19.4	106,759	569	17.7	16.3	19.2	80,880	661	19.0	17.6	20.5
18 - 44 years	47,152	149	8.8	7.5	10.4	31,072	80	8.4	6.7	10.4	16,080	69	9.4	7.4	11.9
45-64 years	124,754	893	19.7	18.5	21.1	68,268	416	20.2	18.3	22.2	56,486	477	19.4	17.7	21.2
65+ years	15,73	188	38.	33.	43.9	7,419	73	36.1	28.	45.4	8,314	115	39.4	32.	47.3

	3		0	0					7					8	
Female gender (overall)	120,354	798	18.7	17.5	20.1	65,645	351	17.9	16.1	19.8	54,709	447	19.4	17.7	21.3
18 - 44 years	20,340	81	11.1	9.0	13.8	13,259	41	10.0	7.4	13.6	7,081	40	12.6	9.2	17.1
45-64 years	84,862	570	18.7	17.2	20.3	45,350	241	17.7	15.6	20.0	39,512	329	19.5	17.5	21.7
65+ years	15,152	147	30.5	26.0	35.9	7,036	69	36.5	28.8	46.2	8,116	78	26.7	21.4	33.3
Angiotensin II receptor blockers	120,159	949	21.1	19.8	22.4	56,456	355	20.1	18.1	22.3	63,703	594	21.7	20.0	23.5
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Male gender (overall)	66,031	517	20.7	19.0	22.6	31,835	190	18.9	16.4	21.8	34,196	327	22.0	19.7	24.5
18 - 44 years	15,711	55	9.2	7.0	11.9	8,872	24	8.4	5.6	12.6	6,839	31	9.8	6.9	14.0
45-64 years	44,864	389	22.6	20.5	25.0	20,633	136	20.8	17.6	24.6	24,231	253	23.8	21.0	26.9
65+ years	5,456	73	41.9	33.3	52.7	2,330	30	45.9	32.1	65.7	3,126	43	39.5	29.3	53.3
Female gender (overall)	54,128	432	21.5	19.5	23.6	24,621	165	21.5	18.5	25.1	29,507	267	21.4	19.0	24.2
18 - 44 years	7,417	29	10.3	7.1	14.8	4,173	17	12.5	7.8	20.1	3,244	12	8.2	4.7	14.4
45-64 years	39,595	338	22.5	20.2	25.1	17,618	129	23.4	19.7	27.8	21,977	209	22.0	19.2	25.2
65+ years	7,116	65	28.4	22.2	36.2	2,830	19	24.2	15.5	38.0	4,286	46	30.5	22.9	40.7

Alpha blockers	26,593	252	30.0	26.5	34.0	19,595	172	30.6	26.4	35.6	6,998	80	28.8	23.1	35.9
Male gender (overall)	24,519	240	30.8	27.1	34.9	17,850	162	31.4	26.9	36.7	6,669	78	29.5	23.7	36.9
18 - 44 years	2,030	8	12.8	6.4	25.6	1,845	7	13.0	6.2	27.3	185	1	11.7	1.6	82.8
45-64 years	16,092	147	28.1	23.9	33.0	11,925	108	30.9	25.6	37.3	4,167	39	22.5	16.5	30.8
65+ years	6,397	85	43.7	35.4	54.1	4,080	47	42.0	31.5	55.9	2,317	38	46.1	33.6	63.4
Female gender (overall)	2,074	12	20.1	11.4	35.4	1,745	10	21.7	11.7	40.2	329	2	14.7	3.7	58.9
18 - 44 years	544	1	6.6	0.9	47.1	508	1	7.5	1.1	53.2	36	0			
45-64 years	1,279	10	26.7	14.4	49.6	1,064	8	28.2	14.1	56.4	215	2	22.0	5.5	87.8
65+ years	251	1	13.8	1.9	98.3	173	1	22.4	3.2	158.9	78	0			
Beta blockers	202,938	1,630	22.4	21.3	23.5	104,434	704	22.4	20.8	24.1	98,504	926	22.4	21.0	23.9
Male gender (overall)	97,036	836	24.2	22.6	25.9	51,121	365	23.8	21.5	26.4	45,915	471	24.4	22.3	26.8
18 - 44 years	21,311	70	9.2	7.3	11.6	13,461	42	10.3	7.6	13.9	7,850	28	7.9	5.5	11.5
45-64 years	63,868	584	25.1	23.2	27.2	32,367	249	25.4	22.4	28.8	31,501	335	24.9	22.4	27.7
65+ years	11,857	182	48.9	42.3	56.6	5,293	74	51.4	41.0	64.6	6,564	108	47.3	39.2	57.1
Female gender (overall)	105,902	794	20.8	19.4	22.3	53,313	339	21.1	19.0	23.5	52,589	455	20.6	18.8	22.6
18 - 44 years	23,151	105	12.7	10.5	15.3	14,670	50	11.2	8.5	14.8	8,481	55	14.4	11.1	18.8

45-64 years	68,278	522	20.7	19.0	22.5	32,567	219	22.0	19.3	25.1	35,711	303	19.8	17.7	22.2
	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
65+ years	14,473	167	36.1	31.0	42.0	6,076	70	42.5	33.6	53.7	8,397	97	32.5	26.6	39.7
Calcium channel blockers	93,539	804	24.2	22.5	25.9	49,005	343	23.3	21.0	25.9	44,534	461	24.8	22.7	27.2
Male gender (overall)	45,336	421	26.2	23.8	28.9	25,233	189	25.0	21.7	28.9	20,103	232	27.3	24.0	31.0
18 - 44 years	9,855	37	10.6	7.7	14.6	6,621	26	12.9	8.8	19.0	3,234	11	7.4	4.1	13.4
45-64 years	29,520	301	28.2	25.1	31.5	15,881	136	28.4	24.0	33.5	13,639	165	28.0	24.0	32.6
65+ years	5,961	83	44.3	35.7	54.9	2,731	27	36.2	24.9	52.8	3,230	56	49.6	38.2	64.4
Female gender (overall)	48,203	383	22.2	20.1	24.6	23,772	154	21.5	18.4	25.2	24,431	229	22.7	20.0	25.9
18 - 44 years	8,118	34	11.8	8.5	16.6	5,412	16	9.7	5.9	15.8	2,706	18	14.7	9.3	23.4
45-64 years	30,450	247	21.9	19.3	24.8	14,544	100	22.3	18.4	27.2	15,906	147	21.6	18.4	25.4
65+ years	9,635	102	33.0	27.2	40.1	3,816	38	36.6	26.6	50.3	5,819	64	31.2	24.4	39.9
Diuretics	150,200	1,232	23.5	22.2	24.9	85,465	585	22.9	21.1	24.8	64,735	647	24.2	22.4	26.1
Male gender (overall)	42,155	364	26.1	23.5	28.9	26,872	196	25.1	21.8	28.8	15,283	168	27.3	23.5	31.8
18 - 44 years	9,293	37	11.	8.6	16.4	6,930	28	13.5	9.4	19.6	2,363	9	8.7	4.5	16.6

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45-64 years	26,170	235	26.5	23.3	30.1	16,243	114	23.8	19.8	28.6	9,927	121	29.6	24.8	35.4
65+ years	6,692	92	46.3	37.8	56.8	3,699	54	56.0	42.9	73.1	2,993	38	37.2	27.1	51.1
Female gender (overall)	108,045	868	22.6	21.1	24.2	58,593	389	21.9	19.8	24.2	49,452	479	23.2	21.2	25.4
18 - 44 years	21,708	101	13.1	10.8	15.9	14,506	50	11.2	8.5	14.7	7,202	51	15.7	12.0	20.7
45-64 years	71,538	602	23.2	21.4	25.1	37,236	264	23.1	20.5	26.1	34,302	338	23.2	20.9	25.9
65+ years	14,799	165	34.9	29.9	40.6	6,851	75	40.0	31.9	50.2	7,948	90	31.5	25.6	38.7
Others	6,680	45	21.2	15.8	28.4	4,643	26	20.0	13.6	29.3	2,037	19	23.1	14.8	36.3
Male gender (overall)	2,208	7	10.5	5.0	22.1	1,650	5	11.2	4.7	26.9	558	2	9.2	2.3	36.7
18 - 44 years	901	1	3.8	0.5	26.8	731	1	5.1	0.7	36.1	170	0			
45-64 years	1,099	4	11.7	4.4	31.3	779	2	9.4	2.3	37.5	320	2	15.7	3.9	62.6
65+ years	208	2	34.0	8.5	136.1	140	2	54.7	13.7	218.7	68	0			

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Female gender (overall)	4,472	38	26.1	19.0	35.8	2,993	21	24.6	16.0	37.7	1,479	17	28.2	17.5	45.3
18 - 44 years	2,041	6	8.9	4.0	19.9	1,404	3	7.5	2.4	23.3	637	3	11.1	3.6	34.3
45-64 years	2,107	24	34.6	23.2	51.6	1,400	15	36.8	22.2	61.0	707	9	31.4	16.4	60.4

65+ years	324	8	85.7	42.8	171.3	189	3	62.8	20.3	194.7	135	5	109.7	45.6	263.5
Dual-combination Therapy Initiators:															
Dual combination including aliskiren	2,335	22	29.9	19.7	45.5	266	1	11.5	1.6	81.4	2,069	21	32.4	21.1	49.7
Male gender (overall)	1,181	10	26.7	14.4	49.6	157	0				1,024	10	31.1	16.7	57.8
18 - 44 years	198	1	16.1	2.3	114.0	40	0				158	1	20.7	2.9	146.7
45-64 years	781	7	27.8	13.2	58.3	99	0				682	7	32.0	15.3	67.2
65+ years	202	2	33.2	8.3	132.7	18	0				184	2	36.5	9.1	146.1
Female gender (overall)	1,154	12	33.3	18.9	58.6	109	1	29.0	4.1	206.1	1,045	11	33.8	18.7	61.0
18 - 44 years	130	2	44.9	11.2	179.5	21	1	160.9	22.7	1,142.5	109	1	26.1	3.7	185.1
45-64 years	780	6	24.0	10.8	53.4	79	0				701	6	26.7	12.0	59.5
65+ years	244	4	60.9	22.9	162.4	9	0				235	4	63.6	23.9	169.5
Dual combination including an ACEI but not aliskiren	399,824	3,186	20.6	19.9	21.3	157,106	908	18.4	17.2	19.6	242,718	2,278	21.7	20.8	22.6
Male gender (overall)	223,185	1,842	21.4	20.4	22.4	90,114	536	18.9	17.4	20.6	133,071	1,306	22.6	21.4	23.8
18 - 44 years	39,033	112	7.3	6.1	8.8	20,646	49	7.4	5.6	9.8	18,387	63	7.3	5.7	9.3
45-64 years	155,507	1,342	22.0	20.8	23.2	61,050	395	20.5	18.6	22.6	94,457	947	22.6	21.2	24.1
65+ years	28,645	388	39.6	35.8	43.7	8,418	92	37.8	30.8	46.3	20,227	296	40.1	35.8	45.0
Female gender (overall)	176,6	1,344	19.	18.	20.8	66,99	372	17.7	16.	19.6	109,64	972	20.6	19.	21.9

	39		7	7		2			0		7			3	
18 - 44 years	25,049	99	10.1	8.3	12.3	13,352	45	10.4	7.8	13.9	11,697	54	9.8	7.5	12.8
45-64 years	123,245	956	19.6	18.4	20.9	45,827	284	19.6	17.4	22.0	77,418	672	19.6	18.2	21.2
65+ years	28,345	289	29.7	26.4	33.3	7,813	43	19.3	14.3	26.1	20,532	246	32.7	28.9	37.1

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
Dual combination including neither an ACEI nor aliskiren	418,304	3,974	24.0	23.3	24.8	138,944	1,048	23.2	21.9	24.7	279,360	2,926	24.3	23.4	25.2
Male gender (overall)	182,590	1,830	25.5	24.4	26.7	65,982	515	24.1	22.1	26.2	116,608	1,315	26.1	24.8	27.6
18 - 44 years	29,363	126	10.7	9.0	12.7	14,245	44	9.3	6.9	12.5	15,118	82	11.6	9.3	14.4
45-64 years	123,584	1,212	24.4	23.1	25.8	43,523	364	25.6	23.1	28.3	80,061	848	23.9	22.4	25.6
65+ years	29,643	492	48.2	44.1	52.6	8,214	107	44.1	36.5	53.4	21,429	385	49.4	44.7	54.6
Female gender (overall)	235,714	2,144	22.9	21.9	23.9	72,962	533	22.5	20.6	24.5	162,752	1,611	23.0	21.9	24.2
18 - 44 years	32,191	170	13.0	11.2	15.1	15,112	57	11.3	8.7	14.7	17,079	113	14.0	11.6	16.8
45-64 years	161,202	1,486	22.6	21.5	23.8	48,097	378	23.9	21.6	26.4	113,105	1,108	22.2	20.9	23.5
65+ years	42,321	488	32.8	30.0	35.9	9,753	98	34.2	28.0	41.6	32,568	390	32.5	29.4	35.9
Triple-plus Combination Therapy Initiators:															
Triple-plus combination including aliskiren	14,852	155	32.3	27.6	37.8	603	5	28.1	11.7	67.4	14,249	150	32.5	27.7	38.1

Male gender (overall)	8,335	97	35.5	29.1	43.3	350	3	27.9	9.0	86.6	7,985	94	35.8	29.3	43.8
18 - 44 years	784	3	11.0	3.5	34.1	67	1	50.9	7.2	361.2	717	2	7.9	2.0	31.6
45-64 years	5,634	68	35.9	28.3	45.6	237	1	13.2	1.9	93.6	5,397	67	36.9	29.0	46.9
65+ years	1,917	26	45.9	31.3	67.5	46	1	84.1	11.9	597.4	1,871	25	45.1	30.5	66.8
Female gender (overall)	6,517	58	28.1	21.7	36.4	253	2	28.3	7.1	113.0	6,264	56	28.1	21.6	36.5
18 - 44 years	365	0				26	0				339	0			
45-64 years	3,825	36	28.4	20.5	39.3	168	1	20.3	2.9	144.2	3,657	35	28.7	20.6	40.0
65+ years	2,327	22	32.6	21.5	49.5	59	1	69.8	9.8	495.3	2,268	21	31.8	20.7	48.8
Triple-plus combination including an ACEI but not aliskiren	427,924	4,550	25.6	24.8	26.3	117,392	886	22.7	21.3	24.3	310,532	3,664	26.4	25.5	27.2
Male gender (overall)	239,866	2,755	27.7	26.7	28.7	67,385	549	24.6	22.6	26.7	172,481	2,206	28.6	27.4	29.8

	All Patients					**Incident Antihypertensive Treatment Cohort**					**Prevalent Antihypertensive Treatment Cohort**				
	Patients	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**		**Patients**	**Events**	**IR**	**95% CI**	
18 - 44 years	28,344	125	10.3	8.7	12.3	12,695	44	10.2	7.6	13.6	15,649	81	10.4	8.4	12.9
45-64 years	161,507	1,753	25.5	24.3	26.7	45,216	365	24.2	21.8	26.8	116,291	1,388	25.8	24.5	27.2
65+ years	50,015	877	47.1	44.1	50.4	9,474	140	48.0	40.7	56.7	40,541	737	47.0	43.7	50.5
Female gender (overall)	188,058	1,795	22.9	21.9	24.0	50,007	337	20.2	18.2	22.5	138,051	1,458	23.6	22.4	24.9

18 - 44 years	19,555	103	12.1	10.0	14.7	8,689	33	10.8	7.7	15.3	10,866	70	12.8	10.1	16.2
45-64 years	122,386	1,134	21.6	20.4	22.9	33,180	236	21.2	18.7	24.1	89,206	898	21.7	20.3	23.2
65+ years	46,117	558	32.2	29.6	34.9	8,138	68	27.6	21.7	35.0	37,979	490	32.9	30.1	36.0
Triple-plus combination including neither an ACEI nor aliskiren	286,779	3,154	26.1	25.2	27.1	67,429	571	24.9	22.9	27.0	219,350	2,583	26.4	25.4	27.5
Male gender (overall)	137,729	1,647	28.6	27.2	30.0	34,297	302	25.9	23.1	29.0	103,432	1,345	29.2	27.7	30.8
18 - 44 years	15,163	52	7.9	6.0	10.3	6,109	11	5.1	2.8	9.3	9,054	41	9.2	6.7	12.4
45-64 years	91,421	1,044	26.5	24.9	28.1	22,832	195	24.9	21.6	28.6	68,589	849	26.9	25.1	28.7
65+ years	31,145	551	47.5	43.7	51.6	5,356	96	57.2	46.8	69.8	25,789	455	45.8	41.8	50.2
Female gender (overall)	149,050	1,507	23.9	22.7	25.2	33,132	269	23.8	21.2	26.9	115,918	1,238	23.9	22.6	25.3
18 - 44 years	13,980	84	13.6	11.0	16.9	5,590	28	14.2	9.8	20.5	8,390	56	13.4	10.3	17.4
45-64 years	96,831	943	22.2	20.9	23.7	21,689	181	24.2	20.9	28.0	75,142	762	21.8	20.3	23.4
65+ years	38,239	480	33.2	30.4	36.3	5,853	60	32.8	25.4	42.2	32,386	420	33.3	30.2	36.6

Table 15-26 Relative Risk of GI Cancer – Aliskiren vs. Other Antihypertensive Therapy – All Patients

	All Patients						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Overall:	0.027	0.063	0.19	0.664	1.028	0.908	1.163
Age Group: (ref: 18-44 years)							
45-64 vs. 18-44 years	0.702	0.027	692.50	<.0001	2.017	1.914	2.125
65+ years vs. 18-44 years	1.037	0.031	1138.95	<.0001	2.820	2.655	2.994
Gender (ref: females)							
Males	0.132	0.014	85.80	<.0001	1.141	1.110	1.173
Geographic region (ref: Northeast)							
Midwest	-0.192	0.019	105.34	<.0001	0.826	0.796	0.856
South	-0.110	0.018	36.60	<.0001	0.896	0.864	0.928
West	-0.067	0.026	6.53	0.011	0.935	0.888	0.984
Health Plan Type (ref: HMO)							
Indeminity	0.001	0.031	0.00	0.982	1.001	0.941	1.064
POS	-0.045	0.033	1.82	0.178	0.956	0.895	1.021
PPO	0.011	0.021	0.26	0.612	1.011	0.970	1.053
Other/unknown	0.029	0.065	0.20	0.652	1.030	0.906	1.171
Payer Type (ref: commercial)							
self-insured	-0.036	0.016	5.15	0.023	0.965	0.936	0.995
other	0.035	0.030	1.35	0.245	1.036	0.976	1.098
CCI score	0.279	0.004	4525.35	<.0001	1.322	1.311	1.332
Pre-index comorbidity							
History of H. pylori infection	-0.082	0.105	0.62	0.432	0.921	0.750	1.131
History of stomach lymphoma	1.060	0.190	31.24	<.0001	2.886	1.990	4.185

History of stomach surgery	0.292	0.114	6.63	0.010	1.340	1.072	1.674
Irritable bowel syndrome	0.025	0.053	0.23	0.630	1.026	0.925	1.137
Chronic diarrhea	0.027	0.128	0.05	0.831	1.028	0.800	1.320
Chronic constipation	0.067	0.039	2.99	0.084	1.069	0.991	1.153
Peripheral vascular disease	-0.191	0.028	47.55	<.0001	0.826	0.782	0.872
Vascular insufficiency of intestine	-0.138	0.147	0.88	0.348	0.871	0.653	1.162
Acute coronary syndrome	-0.102	0.045	5.22	0.022	0.903	0.827	0.986
Coronary heart disease or angina	0.010	0.020	0.26	0.613	1.010	0.971	1.051
Heart failure	-0.349	0.033	114.26	<.0001	0.705	0.661	0.752
Stroke or transient ischemic attack	-0.268	0.027	98.77	<.0001	0.765	0.726	0.807
Ulcerous rectocolitis	-0.043	0.095	0.20	0.653	0.958	0.796	1.154

	All Patients						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Crohn's disease	0.209	0.095	4.82	0.028	1.232	1.023	1.484
Diabetes mellitus	-0.256	0.025	105.21	<.0001	0.774	0.737	0.813
Screening Procedures							
Endoscopy including gastroscopy	0.322	0.027	138.60	<.0001	1.380	1.308	1.456
H. pylori testing	-0.059	0.060	0.96	0.328	0.943	0.838	1.061
Co-medications:							
Prescription NSAIDs (including aspirin)	0.053	0.016	11.00	0.001	1.054	1.022	1.088
Statins	-0.024	0.015	2.54	0.111	0.976	0.948	1.006
Hormone replacement therapy	-0.024	0.032	0.55	0.458	0.977	0.918	1.039
Proton Pump Inhibitor	0.152	0.017	78.70	<.0001	1.164	1.125	1.203
Anti-diabetic drugs	-0.049	0.027	3.18	0.074	0.953	0.903	1.005

Table 15-27 Relative Risk of GI Cancer – Aliskiren vs. Other Antihypertensive Therapy – Incident and Prevalent Cohorts

	Incident Antihypertensive Treatment Cohort							Prevalent Antihypertensive Treatment Cohort						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Overall:	-0.210	0.278	0.57	0.449	0.810	0.470	1.397	0.051	0.065	0.61	0.435	1.052	0.926	1.195
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	0.722	0.041	308.53	<.0001	2.059	1.899	2.231	0.676	0.035	368.87	<.0001	1.967	1.835	2.107
65+ years vs. 18-44 years	1.032	0.051	411.03	<.0001	2.808	2.541	3.102	1.023	0.039	673.30	<.0001	2.781	2.574	3.004
Gender (ref: females)														
Males	0.103	0.026	15.75	<.0001	1.108	1.053	1.166	0.145	0.017	71.85	<.0001	1.156	1.118	1.195
Geographic region (ref: Northeast)														
Midwest	-0.102	0.035	8.40	0.004	0.903	0.842	0.967	-0.226	0.022	104.48	<.0001	0.798	0.764	0.833
South	-0.097	0.034	8.33	0.004	0.907	0.849	0.969	-0.111	0.022	26.02	<.0001	0.895	0.858	0.934
West	-0.032	0.049	0.41	0.522	0.969	0.879	1.067	-0.084	0.031	7.24	0.007	0.920	0.865	0.977
Health Plan Type (ref: HMO)														
Indeminity	-0.002	0.067	0.00	0.971	0.998	0.874	1.138	0.005	0.036	0.02	0.881	1.005	0.937	1.078
POS	-0.004	0.072	0.00	0.954	0.996	0.865	1.146	-0.059	0.038	2.44	0.118	0.942	0.875	1.015
PPO	0.030	0.043	0.48	0.490	1.030	0.947	1.120	0.003	0.024	0.02	0.890	1.003	0.957	1.052
Other/unknown	0.127	0.098	1.67	0.197	1.13	0.93	1.37	-0.018	0.092	0.04	0.849	0.98	0.82	1.17

					5	6	6					3	1	7
Payer Type (ref: commercial)														
self-insured	-0.034	0.027	1.50	0.221	0.967	0.917	1.020	-0.039	0.019	4.02	0.045	0.962	0.926	0.999
other	0.007	0.061	0.01	0.914	1.007	0.893	1.135	0.047	0.035	1.84	0.175	1.049	0.979	1.123
CCI score	0.327	0.007	2323.45	<.0001	1.387	1.369	1.406	0.254	0.005	2375.29	<.0001	1.289	1.276	1.302
Pre-index comorbidity														
	Incident Antihypertensive Treatment Cohort							**Prevalent Antihypertensive Treatment Cohort**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
History of H. pylori infection	-0.141	0.172	0.67	0.412	0.868	0.620	1.217	-0.063	0.132	0.23	0.633	0.939	0.724	1.217
History of stomach lymphoma	1.386	0.269	26.62	<.0001	3.997	2.361	6.767	0.825	0.268	9.47	0.002	2.282	1.349	3.858
History of stomach surgery	0.104	0.211	0.24	0.623	1.109	0.734	1.676	0.374	0.135	7.71	0.006	1.454	1.116	1.894
Irritable bowel syndrome	-0.176	0.108	2.67	0.102	0.839	0.679	1.036	0.093	0.060	2.39	0.122	1.097	0.975	1.235
Chronic diarrhea	-0.015	0.252	0.00	0.953	0.985	0.602	1.614	0.051	0.148	0.12	0.733	1.052	0.786	1.407
Chronic constipation	0.098	0.068	2.09	0.148	1.103	0.966	1.259	0.043	0.047	0.85	0.358	1.044	0.952	1.145
Peripheral vascular disease	-0.198	0.053	13.82	0.000	0.820	0.739	0.911	-0.181	0.032	30.99	<.0001	0.835	0.783	0.890
Vascular insufficiency of intestine	0.276	0.216	1.64	0.201	1.318	0.863	2.014	-0.389	0.201	3.74	0.053	0.678	0.457	1.005
Acute coronary syndrome	-0.095	0.082	1.34	0.247	0.909	0.774	1.068	-0.093	0.053	3.02	0.082	0.912	0.821	1.012
Coronary heart disease or angina	-0.054	0.040	1.79	0.180	0.94	0.87	1.02	0.034	0.023	2.15	0.143	1.03	0.98	1.08

					8	6	5					4	9	2
Heart failure	-0.459	0.068	45.92	<.0001	0.632	0.553	0.722	-0.295	0.037	62.03	<.0001	0.745	0.692	0.801
Stroke or transient ischemic attack	-0.365	0.049	54.99	<.0001	0.694	0.630	0.764	-0.223	0.032	47.96	<.0001	0.800	0.751	0.852
Ulcerous rectocolitis	0.046	0.171	0.07	0.789	1.047	0.749	1.463	-0.079	0.114	0.48	0.486	0.924	0.739	1.155
Crohn's disease	-0.163	0.197	0.68	0.408	0.850	0.578	1.249	0.347	0.109	10.21	0.001	1.415	1.144	1.750
Diabetes mellitus	-0.400	0.042	91.29	<.0001	0.670	0.618	0.728	-0.176	0.031	31.83	<.0001	0.839	0.789	0.891
Screening Procedures														
Endoscopy including gastroscopy	0.478	0.048	99.31	<.0001	1.612	1.468	1.771	0.249	0.033	55.87	<.0001	1.283	1.202	1.370
H. pylori testing	-0.048	0.101	0.22	0.637	0.953	0.781	1.163	-0.068	0.075	0.84	0.360	0.934	0.807	1.081
Co-medications:														
Prescription NSAIDs (including aspirin)	0.063	0.031	4.02	0.045	1.065	1.001	1.132	0.047	0.019	6.28	0.012	1.048	1.010	1.087
Statins	-0.017	0.033	0.27	0.604	0.983	0.920	1.049	-0.030	0.017	3.12	0.077	0.970	0.938	1.003
Hormone replacement therapy	0.118	0.065	3.27	0.071	1.126	0.990	1.279	-0.063	0.036	3.02	0.082	0.939	0.874	1.008
Proton Pump Inhibitor	0.150	0.036	17.39	<.0001	1.162	1.083	1.248	0.158	0.020	65.62	<.0001	1.171	1.127	1.217

	Incident Antihypertensive Treatment Cohort							**Prevalent Antihypertensive Treatment Cohort**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Anti-diabetic drugs	0.027	0.052	0.26	0.610	1.027	0.927	1.137	-0.088	0.033	7.12	0.008	0.916	0.859	0.977

Table 15-28 Relative Risk of GI Cancer – Aliskiren vs. Nonhypertensive Patients

	Aliskiren (all patients) vs. Non-hypertensive Population							Aliskiren (incident patients only) vs. Non-hypertensive Population						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Overall:	0.094	0.078	1.45	0.229	1.098	0.943	1.279	0.019	0.279	0.00	0.944	1.020	0.590	1.761
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	0.851	0.019	2072.93	<.0001	2.341	2.257	2.429	0.842	0.019	2013.74	<.0001	2.322	2.238	2.409
65+ years vs. 18-44 years	1.141	0.043	693.41	<.0001	3.131	2.876	3.409	1.149	0.045	664.64	<.0001	3.155	2.891	3.443
Gender (ref: females)														
Males	-0.047	0.018	7.07	0.008	0.954	0.921	0.988	-0.053	0.018	8.57	0.003	0.949	0.916	0.983
Geographic region (ref: Northeast)														
Midwest	-0.283	0.024	141.04	<.0001	0.753	0.719	0.790	-0.281	0.024	136.40	<.0001	0.755	0.721	0.792
South	-0.090	0.024	14.31	0.000	0.914	0.872	0.958	-0.083	0.024	12.08	0.001	0.920	0.878	0.964
West	0.030	0.033	0.87	0.351	1.031	0.967	1.099	0.036	0.033	1.22	0.269	1.037	0.972	1.106
Health Plan Type (ref: HMO)														
Indeminity	-0.042	0.053	0.61	0.435	0.959	0.864	1.065	-0.046	0.054	0.71	0.399	0.955	0.860	1.062
POS	-0.130	0.048	7.42	0.007	0.878	0.799	0.964	-0.129	0.048	7.21	0.007	0.879	0.800	0.966
PPO	0.077	0.030	6.83	0.009	1.080	1.020	1.145	0.077	0.030	6.69	0.010	1.080	1.019	1.145

Other/unknown	0.098	0.080	1.50	0.220	1.103	0.943	1.291	0.102	0.081	1.59	0.208	1.107	0.945	1.296
Payer Type (ref: commercial)														
self-insured	-0.050	0.019	6.86	0.009	0.951	0.916	0.987	-0.048	0.019	6.13	0.013	0.953	0.917	0.990
other	0.125	0.069	3.27	0.071	1.134	0.990	1.298	0.115	0.071	2.64	0.104	1.121	0.977	1.288
CCI score	0.415	0.006	4273.04	<.0001	1.514	1.495	1.533	0.423	0.006	4384.51	<.0001	1.526	1.507	1.545
Pre-index comorbidity														
History of H. pylori infection	-0.207	0.188	1.21	0.272	0.813	0.562	1.176	-0.198	0.191	1.08	0.300	0.820	0.564	1.193
History of stomach lymphoma	1.093	0.334	10.69	0.001	2.985	1.550	5.748	1.041	0.334	9.70	0.002	2.833	1.471	5.455
History of stomach surgery	0.835	0.210	15.79	<.0001	2.305	1.527	3.479	0.741	0.220	11.35	0.001	2.098	1.363	3.230
Irritable bowel syndrome	0.117	0.077	2.29	0.130	1.124	0.966	1.307	0.121	0.078	2.38	0.123	1.128	0.968	1.315
Chronic diarrhea	-0.156	0.251	0.39	0.534	0.855	0.522	1.400	-0.091	0.252	0.13	0.719	0.913	0.558	1.495

	Aliskiren (all patients) vs. Non-hypertensive Population							**Aliskiren (incident patients only) vs. Non-hypertensive Population**						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Chronic constipation	0.199	0.063	9.84	0.002	1.220	1.077	1.381	0.232	0.064	13.13	0.000	1.261	1.112	1.429
Peripheral vascular disease	-0.079	0.076	1.08	0.298	0.924	0.796	1.072	0.017	0.081	0.05	0.832	1.017	0.868	1.192
Vascular insufficiency of intestine	0.489	0.280	3.05	0.081	1.631	0.942	2.824	0.637	0.280	5.19	0.023	1.891	1.093	3.270
Acute coronary syndrome	0.115	0.212	0.29	0.587	1.122	0.740	1.701	0.164	0.292	0.31	0.575	1.178	0.664	2.089

Coronary heart disease or angina	-0.180	0.090	3.95	0.047	0.836	0.700	0.997	-0.160	0.108	2.19	0.139	0.852	0.689	1.053
Heart failure	-0.424	0.152	7.83	0.005	0.654	0.486	0.881	0.014	0.207	0.00	0.947	1.014	0.676	1.522
Stroke or transient ischemic attack	-0.285	0.081	12.31	0.001	0.752	0.641	0.882	-0.204	0.087	5.50	0.019	0.815	0.687	0.967
Ulcerous rectocolitis	0.093	0.131	0.50	0.478	1.097	0.849	1.418	0.085	0.134	0.40	0.527	1.088	0.838	1.414
Crohn's disease	0.620	0.114	29.58	<.0001	1.859	1.487	2.325	0.602	0.116	26.98	<.0001	1.825	1.454	2.290
Diabetes mellitus	-0.363	0.075	23.31	<.0001	0.696	0.601	0.806	-0.376	0.079	22.73	<.0001	0.687	0.588	0.801
Screening Procedures														
Endoscopy including gastroscopy	0.392	0.051	58.72	<.0001	1.479	1.338	1.635	0.413	0.052	62.88	<.0001	1.512	1.365	1.674
H. pylori testing	0.139	0.082	2.92	0.088	1.149	0.980	1.349	0.130	0.083	2.46	0.117	1.138	0.968	1.339
Co-medications:														
Prescription NSAIDs (including aspirin)	0.136	0.025	30.33	<.0001	1.146	1.092	1.203	0.133	0.025	27.98	<.0001	1.142	1.087	1.200
Statins	0.090	0.035	6.55	0.011	1.094	1.021	1.172	0.093	0.036	6.55	0.011	1.097	1.022	1.178
Hormone replacement therapy	0.064	0.047	1.81	0.179	1.066	0.971	1.170	0.070	0.048	2.16	0.142	1.073	0.977	1.179
Proton Pump Inhibitor	0.264	0.033	64.26	<.0001	1.303	1.221	1.390	0.269	0.034	63.74	<.0001	1.309	1.225	1.398
Anti-diabetic drugs	0.032	0.087	0.13	0.715	1.032	0.870	1.225	0.087	0.095	0.85	0.357	1.091	0.906	1.314

Table 15-29 Sensitivity Analysis – Incidence Rate (per 10,000 person-years) of GI Cancer with and without Pre-diagnosis Screening test

	Patients with pre-diagnosis screening procedure AND post-index diagnosis					Patients with post-index diagnosis ALONE				
	Patients	Events	IR	95% CI		Patients	Events	IR	95% CI	
Aliskiren Treated Patients	25,740	67	7.6	6.0	9.6	25,740	189	21.4	18.6	24.7
Other Antihypertensive Therapy Treated Patients	2,434,387	4,523	4.8	4.7	5.0	2,434,387	17,212	18.3	18.0	18.6
Non-hypertensive Population	5,909,418	1,458	0.9	0.8	0.9	5,909,418	11,789	6.9	6.8	7.1

Table 15-30 Cross-tabulation of the Use of Screening Tests Pre-diagnosis vs. ICD-9-CM diagnosis of GI Cancer

Status of screening test procedures for GI cancer*		Aliskiren Treated Patients			Other Antihypertensive Therapy Treated Patients			Non-hypertensive Population		
		Status of post-index diagnosis for GI Cancer			Status of post-index diagnosis for GI Cancer			Status of post-index diagnosis for GI Cancer		
		Yes	No	p value	Yes	No	p value	Yes	No	p value
If with endoscopy including gastroscopy	**Yes**	65	1,560	<.0001	4,416	105,830	<.0001	1,396	82,132	<.0001
	No	191	23,924		17,319	2,306,822		11,851	5,814,039	
If with H. pylori testing	**Yes**	4	358	0.7857	303	28,102	0.0017	157	46,485	<.0001
	No	252	25,126		21,432	2,384,550		13,090	5,849,686	
If with at least one of the 2 procedures above	**Yes**	67	1,808	<.0001	4,523	125,833	<.0001	1,458	119,497	<.0001
	NO	189	23,676		17,212	2,286,819		11,789	5,776,674	

Chi-square test was applied for statistical difference

screening procedures only include those occurring within the 3 months prior to event for those with event, and 12 month post-index for those without event.

Table 15-31 Supplemental Table– Relative Risk of Colorectal Hyperplasia – Other Antihypertensive Therapy Users vs. Non-hypertensive Patients

	other antihypertensive therapy (all patients)vs. Non-hypertensive Population							other antihypertensive therapy (incident patients only)vs. Non-hypertensive Population						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
Overall:	0.352	0.003	14373.79	<.0001	1.423	1.414	1.431	0.325	0.004	6863.87	<.0001	1.384	1.373	1.395
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	2.078	0.005	210388.74	<.0001	7.991	7.920	8.062	2.169	0.005	185915.18	<.0001	8.746	8.661	8.833
65+ years vs. 18-44 years	2.158	0.006	127909.23	<.0001	8.657	8.555	8.760	2.264	0.008	80976.02	<.0001	9.625	9.477	9.777
Gender (ref: females)														
Males	0.235	0.003	8443.65	<.0001	1.265	1.258	1.271	0.192	0.003	3377.50	<.0001	1.211	1.203	1.219
Geographic region (ref: Northeast)														
Midwest	-0.063	0.003	355.03	<.0001	0.939	0.933	0.945	-0.077	0.004	311.00	<.0001	0.926	0.918	0.934
South	-0.067	0.003	389.51	<.0001	0.935	0.929	0.942	-0.107	0.004	573.09	<.0001	0.898	0.891	0.906
West	-0.010	0.005	4.09	0.043	0.990	0.981	1.000	-0.031	0.006	23.82	<.0001	0.970	0.958	0.982

Health Plan Type (ref: HMO)														
Indeminity	-0.172	0.006	723.69	<.0001	0.842	0.831	0.852	-0.202	0.009	466.66	<.0001	0.817	0.802	0.832
POS	-0.068	0.006	132.66	<.0001	0.934	0.923	0.945	-0.074	0.008	82.33	<.0001	0.928	0.914	0.943
PPO	-0.117	0.004	948.20	<.0001	0.890	0.883	0.896	-0.125	0.005	577.35	<.0001	0.882	0.873	0.891
Other/unknown	0.103	0.011	83.45	<.0001	1.109	1.085	1.134	0.050	0.014	12.89	0.000	1.051	1.023	1.080
Payer Type (ref: commercial)														
self-insured	0.003	0.003	1.42	0.234	1.003	0.998	1.009	0.009	0.004	7.15	0.008	1.010	1.003	1.017
other	-0.163	0.007	499.51	<.0001	0.850	0.837	0.862	-0.058	0.012	25.19	<.0001	0.943	0.922	0.965
CCI score	0.069	0.001	2828.22	<.0001	1.072	1.069	1.075	0.088	0.002	2171.42	<.0001	1.092	1.088	1.096
Pre-index comorbidity														
History of H. pylori infection	0.133	0.026	26.97	<.0001	1.143	1.087	1.202	0.156	0.034	20.70	<.0001	1.169	1.093	1.250
History of stomach lymphoma	0.196	0.086	5.25	0.022	1.216	1.029	1.438	0.195	0.120	2.65	0.104	1.215	0.961	1.536

	other antihypertensive therapy (all patients)vs. Non-hypertensive Population							**other antihypertensive therapy (incident patients only)vs. Non-hypertensive Population**						
	Coefficient	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-square**	**p-value**	**HR**	**95% CI**	
History of stomach surgery	-0.148	0.036	16.64	<.0001	0.862	0.803	0.926	-0.116	0.056	4.22	0.040	0.891	0.798	0.995
Irritable bowel syndrome	0.283	0.011	726.70	<.0001	1.328	1.301	1.355	0.342	0.014	581.81	<.0001	1.408	1.370	1.448
Chronic diarrhea	0.148	0.035	17.31	<.0001	1.159	1.081	1.2	0.120	0.052	5.29	0.022	1.12	1.01	1.250

							42					8	8	
Chronic constipation	0.178	0.009	365.88	<.0001	1.195	1.173	1.217	0.229	0.013	319.84	<.0001	1.257	1.226	1.289
Peripheral vascular disease	-0.044	0.007	40.85	<.0001	0.957	0.944	0.970	-0.010	0.011	0.70	0.404	0.991	0.969	1.013
Vascular insufficiency of intestine	0.049	0.042	1.34	0.247	1.050	0.967	1.141	0.085	0.064	1.74	0.187	1.089	0.960	1.235
Acute coronary syndrome	-0.078	0.011	49.00	<.0001	0.925	0.905	0.946	-0.134	0.019	49.59	<.0001	0.874	0.842	0.908
Coronary heart disease or angina	-0.013	0.005	7.34	0.007	0.987	0.978	0.996	0.018	0.009	4.44	0.035	1.019	1.001	1.036
Heart failure	-0.259	0.009	797.51	<.0001	0.772	0.758	0.786	-0.300	0.018	272.47	<.0001	0.741	0.715	0.768
Stroke or transient ischemic attack	-0.086	0.007	159.04	<.0001	0.917	0.905	0.930	-0.113	0.011	104.31	<.0001	0.894	0.874	0.913
Ulcerous rectocolitis	0.853	0.016	2817.89	<.0001	2.346	2.273	2.421	1.048	0.020	2776.13	<.0001	2.852	2.743	2.965
Crohn's disease	0.642	0.018	1318.03	<.0001	1.900	1.835	1.967	0.785	0.022	1286.66	<.0001	2.192	2.100	2.288
Diabetes mellitus	-0.014	0.006	6.12	0.013	0.986	0.975	0.997	-0.033	0.009	14.85	0.000	0.967	0.951	0.984
Screening Procedures														
Fecal Occult Blood Test	0.273	0.004	4931.79	<.0001	1.314	1.304	1.324	0.328	0.005	3811.85	<.0001	1.388	1.374	1.403
Sigmoidoscopy	0.093	0.023	15.93	<.0001	1.098	1.048	1.149	0.126	0.034	13.74	0.000	1.134	1.061	1.212
Colonoscopy	-1.079	0.009	14077.28	<.0001	0.340	0.334	0.346	-1.202	0.014	7684.19	<.0001	0.301	0.293	0.309
Co-medications:														
Prescription NSAIDs (including aspirin)	0.077	0.003	603.29	<.0001	1.080	1.073	1.086	0.117	0.004	697.33	<.0001	1.124	1.114	1.134
Statins	0.213	0.003	4746.88	<.0001	1.237	1.229	1.244	0.362	0.005	5641.29	<.0001	1.437	1.423	1.450
Hormone replacement therapy	0.130	0.006	538.41	<.0001	1.139	1.126	1.151	0.196	0.008	628.32	<.0001	1.217	1.198	1.236

Proton Pump Inhibitor	0.288	0.003	6960.75	<.0001	1.334	1.325	1.343	0.351	0.005	4328.33	<.0001	1.420	1.405	1.435
Anti-diabetic drugs	-0.102	0.006	265.46	<.0001	0.903	0.892	0.914	-0.123	0.011	132.13	<.0001	0.884	0.865	0.903

Table 15-32 Supplemental Table– Relative Risk of GI Cancer – Other Antihypertensive Therapy Users vs. Non-hypertensive Patients

	other antihypertensive therapy (all patients) vs. Non-hypertensive Population							other antihypertensive therapy(incident patients only) vs. Non-hypertensive Population						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
Overall:	0.455	0.014	1113.51	<.0001	1.576	1.534	1.619	0.410	0.018	520.16	<.0001	1.507	1.455	1.561
Age Group: (ref: 18-44 years)														
45-64 vs. 18-44 years	0.838	0.015	2999.59	<.0001	2.311	2.243	2.381	0.849	0.017	2502.57	<.0001	2.336	2.260	2.415
65+ years vs. 18-44 years	1.156	0.022	2820.14	<.0001	3.178	3.045	3.317	1.143	0.031	1403.79	<.0001	3.138	2.955	3.331
Gender (ref: females)														
Males	0.058	0.011	27.58	<.0001	1.060	1.037	1.084	-0.002	0.015	0.03	0.873	0.998	0.969	1.027
Geographic region (ref: Northeast)														
Midwest	-0.233	0.015	250.84	<.0001	0.792	0.769	0.815	-0.232	0.020	136.25	<.0001	0.793	0.763	0.825
South	-0.096	0.015	43.52	<.0001	0.909	0.883	0.935	-0.089	0.020	20.75	<.0001	0.915	0.880	0.950

West	-0.031	0.021	2.20	0.138	0.970	0.931	1.010	0.010	0.027	0.14	0.713	1.010	0.957	1.066
Health Plan Type (ref: HMO)														
Indeminity	-0.015	0.027	0.32	0.569	0.985	0.934	1.038	-0.038	0.042	0.82	0.364	0.963	0.886	1.045
POS	-0.087	0.027	9.95	0.002	0.917	0.869	0.968	-0.106	0.040	7.01	0.008	0.900	0.832	0.973
PPO	0.028	0.017	2.61	0.106	1.028	0.994	1.063	0.055	0.024	5.04	0.025	1.056	1.007	1.108
Other/unknown	0.059	0.050	1.36	0.243	1.060	0.961	1.170	0.112	0.062	3.28	0.070	1.119	0.991	1.263
Payer Type (ref: commercial)														
self-insured	-0.042	0.012	11.70	0.001	0.959	0.936	0.982	-0.044	0.016	7.79	0.005	0.957	0.927	0.987
other	0.041	0.027	2.28	0.131	1.042	0.988	1.100	0.033	0.046	0.52	0.471	1.034	0.945	1.131
CCI score	0.313	0.004	7784.72	<.0001	1.367	1.358	1.377	0.372	0.005	6226.25	<.0001	1.450	1.437	1.464
Pre-index comorbidity														
History of H. pylori infection	-0.123	0.093	1.74	0.187	0.885	0.737	1.062	-0.217	0.130	2.79	0.095	0.805	0.624	1.038
History of stomach lymphoma	1.049	0.164	40.75	<.0001	2.856	2.069	3.942	1.243	0.209	35.24	<.0001	3.466	2.299	5.225

	other antihypertensive therapy (all patients) vs. Non-hypertensive Population							**other antihypertensive therapy(incident patients only) vs. Non-hypertensive Population**						
	Coefficient	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**		**Coefficient**	**Standard Error**	**Chi-Square**	**p-value**	**HR**	**95% CI**	
History of stomach surgery	0.333	0.102	10.65	0.001	1.395	1.142	1.703	0.341	0.152	5.02	0.025	1.406	1.044	1.895
Irritable bowel syndrome	0.061	0.044	1.95	0.163	1.06	0.97	1.158	0.015	0.063	0.06	0.808	1.01	0.89	1.150

					3	6						6	7	
Chronic diarrhea	-0.001	0.114	0.00	0.995	0.999	0.799	1.249	-0.068	0.178	0.15	0.703	0.934	0.659	1.325
Chronic constipation	0.109	0.033	10.70	0.001	1.115	1.045	1.190	0.150	0.047	10.34	0.001	1.162	1.060	1.274
Peripheral vascular disease	-0.214	0.026	65.38	<.0001	0.807	0.766	0.850	-0.191	0.045	18.27	<.0001	0.826	0.757	0.902
Vascular insufficiency of intestine	-0.061	0.130	0.22	0.640	0.941	0.729	1.214	0.308	0.171	3.24	0.072	1.361	0.973	1.904
Acute coronary syndrome	-0.113	0.045	6.39	0.012	0.894	0.819	0.975	-0.083	0.079	1.11	0.293	0.920	0.788	1.074
Coronary heart disease or angina	-0.015	0.020	0.60	0.439	0.985	0.948	1.024	-0.100	0.037	7.11	0.008	0.905	0.841	0.974
Heart failure	-0.420	0.032	167.68	<.0001	0.657	0.616	0.700	-0.528	0.064	67.57	<.0001	0.590	0.520	0.669
Stroke or transient ischemic attack	-0.310	0.026	143.41	<.0001	0.733	0.697	0.771	-0.394	0.043	84.16	<.0001	0.674	0.620	0.734
Ulcerous rectocolitis	-0.008	0.078	0.01	0.919	0.992	0.852	1.156	0.061	0.106	0.33	0.567	1.062	0.864	1.307
Crohn's disease	0.358	0.074	23.37	<.0001	1.430	1.237	1.653	0.358	0.100	12.80	0.000	1.430	1.176	1.739
Diabetes mellitus	-0.301	0.024	158.03	<.0001	0.740	0.706	0.775	-0.436	0.037	138.49	<.0001	0.647	0.601	0.695
Screening Procedures														
Endoscopy including gastroscopy	0.332	0.024	185.13	<.0001	1.394	1.329	1.462	0.432	0.035	149.28	<.0001	1.540	1.437	1.651
H. pylori testing	0.026	0.049	0.30	0.587	1.027	0.933	1.130	0.081	0.064	1.61	0.205	1.084	0.957	1.229
Co-medications:														
Prescription NSAIDs (including aspirin)	0.082	0.014	36.05	<.0001	1.085	1.056	1.114	0.111	0.020	32.22	<.0001	1.118	1.076	1.162
Statins	0.000	0.014	0.00	0.975	1.000	0.973	1.028	0.038	0.025	2.43	0.119	1.039	0.990	1.091
Hormone replacement therapy	-0.009	0.027	0.13	0.721	0.991	0.940	1.043	0.083	0.039	4.61	0.032	1.087	1.007	1.172

Proton Pump Inhibitor	0.172	0.015	125.01	<.0001	1.188	1.153	1.224	0.219	0.025	78.51	<.0001	1.244	1.186	1.306
Anti-diabetic drugs	-0.056	0.026	4.46	0.035	0.946	0.898	0.996	0.024	0.046	0.27	0.601	1.024	0.936	1.121

16 Appendix 2 – Codes

Table 16-1 Single Agent Antihypertensive Drugs

Drug class	Generic names	GPI codes/HCPC codes
Direct renin inhibitor	Aliskiren	3617*
Angiotensin-converting enzyme inhibitors (ACEI)	captopril, enalapril, lisinopril, benazepril, fosinopril, perindopril, quinapril, ramipril, trandolapril, moexipril	3610*, 369985*, 36991*
Angiotensin II receptor blockers (ARB)	valsartan, candesartan, losartan, eprosartan, irbesartan, olmesartan, telmisartan, azilsartan	3615*, 36994*
Alpha blockers (AB)	prazosin, terazosin, doxazosin, alfuzosin, tamsulosin, silodosin	362020*, (excluding 36202010*, 36202020*), 568520*, 568599022*
Beta blockers (BB)	atenolol, metoprolol, carvedilol, acebutolol, bisoprolol, nadolol, nebivolol, propranolol, pindolol, betaxolol, timolol, penbutolol	33*, 3699*
Calcium channel blockers (CCB)	amlodipine, diltiazem, verapamil, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, clevidipine	34*, 409925* / C9248
Diuretics	thiazides (hydrochlorothiazide, chlorthiazide, chlorthalidone, indapamide, methylclothiazide, metolazone);	2699100220*, 369910023*, 3699500260*, 3699700260*, 369980022*, 3720*, 3750*, 3760*, 379900* /
	loop diuretics (furosemide, torasemide, bumetanide, ethacrynic acid); or	S0171, J1940, J3265, J1205
	potassium-sparing diuretics (amiloride, spironolactone, triamterene)	
Vasodilators	hydralazine, diazoxide, minoxidil	3640*
Selective aldosterone receptor antagonists	eplerenone	36250030*
Centrally acting alpha agonists	clonidine, guanabenz, guanfacine, methyldopa, alseroxylon, deserpidine, rauwolfia (serpentina), reserpine, guanadrel, guanethidine, rescinnamine	362010*, 362030*, 36202010*, 36202020*

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Table 16-2 Dual Fixed Combination Antihypertensive Drugs

Drug classes	GPI codes
AB + Diuretic	369955027*
ACEI + CCB	369915*

Drug classes	GPI codes
ACEI + Diuretic	369918*
ARB + CCB	369930*
ARB + Diuretic	369940*
BB + Diuretic	369920*
Centrally acting alpha agonist + Diuretic	369910*, 369950*, 369955023* (excluding 369910022*, 36991003*)
Centrally acting alpha agonist + Vasodilator	369910022*
Direct renin inhibitor + ARB	369965*
Direct renin inhibitor + CCB	369967*
Direct renin inhibitor + Diuretic	369960*
Vasodilator + Diuretic	369990*

AB = Alpha Blocker; ACEI = Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin II Receptor Blocker; BB = Beta Blocker; CCB = Calcium Channel Blocker.

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Table 16-3 Triple-plus Fixed Combination Antihypertensive Drugs

Drug classes	GPI codes
ARB + CCB + Diuretic	369945*
Centrally acting alpha agonist + Vasodilator + Thiazide diuretic	36991003*

ARB = Angiotensin II Receptor Blocker; CCB = Calcium Channel Blocker.

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Table 16-4 Concomitant Medications

Drug class	Generic names	GPI codes
antidiabetics oral	acarbose	27500010000310
		27500010000320
		27500010000340
	acetohexamide	27200010000305
		27200010000310
	alogliptin benzoate	27550010100310
		27550010100320
		27550010100330
	alogliptin-metformin hcl	27992502100320
		27992502100330
	alogliptin-pioglitazone	27994002100320
		27994002100325
		27994002100330
		27994002100340

	27994002100345
	27994002100350
bromocriptine mesylate (diabetes)	27574020100320
canagliflozin	27700020000320
	27700020000330
canagliflozin-metformin hcl	27996002200320
	27996002200330
	27996002200340
	27996002200350
chlorpropamide	27200020000305
	27200020000310
dapagliflozin propanediol	27700040200310
	27700040200320
empagliflozin	27700050000310
	27700050000320
glimepiride	27200027000310
	27200027000320
	27200027000340
glipizide	27200030000305
	27200030000310
	27200030000410
	27200030000420
	27200030007505
	27200030007510
	27200030007520
glipizide-metformin hcl	27997002350320
	27997002350325
	27997002350340
glyburide	27200040000305
	27200040000310
	27200040000315
glyburide micronized	27200040100310
	27200040100320
	27200040100330

	27200040100340
glyburide-metformin	27997002400310 27997002400320 27997002400330
linagliptin	27550050000320
linagliptin-metformin hcl	27992502400320 27992502400330 27992502400340
metformin hcl	27250050000320 27250050000340 27250050000350 27250050002020 27250050007520 27250050007530 27250050007560 27250050007570 27250050007580 27250050007590
metformin hcl-dietary management product	27999002506320
miglitol	27500050000310 27500050000320 27500050000340
nateglinide	27280040000320 27280040000330
pioglitazone hcl	27607050100320 27607050100330 27607050100340
pioglitazone hcl-glimepiride	27997802400320 27997802400340
pioglitazone hcl-metformin hcl	27998002400320 27998002400340 27998002407515 27998002407530
repaglinide	27280060000310

	27280060000320
	27280060000330
repaglinide-metformin hcl	27995002700320
	27995002700330
rosiglitazone maleate	27607060100320
	27607060100330
	27607060100340
rosiglitazone maleate-glimepiride	27997802600310
	27997802600320
	27997802600340
	27997802600355
	27997802600360
rosiglitazone maleate-metformin hcl	27998002600320
	27998002600330
	27998002600335
	27998002600350
	27998002600355
saxagliptin hcl	27550065100320
	27550065100330
saxagliptin-metformin hcl	27992502607520
	27992502607530
	27992502607540
sitagliptin phosphate	27550070100320
	27550070100330
	27550070100340
sitagliptin-metformin hcl	27992502700320
	27992502700340
	27992502707520
	27992502707530
	27992502707540
sitagliptin-simvastatin	27993002700303
	27993002700305
	27993002700307
	27993002700310
	27993002700320
	27993002700340

	tolazamide	27200050000305 27200050000310 27200050000315
	tolbutamide	27200060000305 27200060000310
antidiabetics other	albiglutide	2717001000D120 2717001000D130
	exenatide	27170020001920 2717002000D120 2717002000D220 2717002000D240
	liraglutide	2717005000D220
	pramlintide acetate	27150050102020 2715005010D220 2715005010D240
insulins	insulin aspart	27104002002020 2710400200D220 2710400200E220
	insulin aspart protamine & aspart (human)	27104070001820 2710407000D320
	insulin detemir	27104006002020 2710400600D220
	insulin glargine	27104003002020 2710400300D220 2710400300E220
	insulin glulisine	27104004002022 2710400400D220 2710400400E220
	insulin isophane & reg (human)	27104090001810 27104090001820 2710409000D320
	insulin isophane (human)	27104020001805 2710402000D320

	insulin lispro (human)	27104005002020 2710400500D220 2710400500E220
	insulin lispro protamine & lispro (human)	27104080001820 27104080001840 2710408000D320 2710408000D340
	insulin reg (human) buffered	27104015002005
	insulin regular (human)	27104010002005 27104010002015 27104010002920 27104010002930 27104010002960
	insulin zinc (human)	27104030001805
	insulin zinc extended (human)	27104050001805

Table 16-5 HCPCS Codes

HCPCS Codes	Procedure Description
A4230	infus set ext insulin pump nonndle cannula type
A4231	infusion set external insulin pump needle type
A4232	syringe w/ndle external insulin pump sterile 3cc
A4253	bld glu test/reagt strips home bld glu mon-50
A4255	platforms home blood glucose monitor 50 per box
A4258	spring-powered device for lancet each
A4259	lancets per box of 100
A9274	external amb insulin del system disposable ea
E0784	external ambulatory infusion pump insulin
G9147	op iv insulin tx measure: rq; &/uun; &/glu; &/k+
J1815	injection insulin per 5 units
J1817	insulin administration through dme per 50 units
J1820	injection insulin up to 100 units
K0548	injection insulin lispro up to 50 units
S5550	insulin rapid onset; 5 units
S5551	insulin most rapid onset; 5 units
S5552	insulin intermediate acting; 5 units
S5553	insulin long acting; 5 units
S5560	insulin delivery device reusable pen; 1.5 ml sz
S5561	insulin delivery device reusable pen; 3 ml size
S5565	insulin cartridge insulin devc not pump; 150 u
S5566	insulin cartridge insulin devc not pump; 300 u

S5570	insulin deliv device disposable pen; 1.5 ml size
S5571	insulin deliv device disposable pen; 3 ml size
S8490	insulin syringes
S9145	insulin pump initiation instruction use of pump
S9353	home infusion therapy cont insulin; per diem
Generic names	GPI codes/HCPC codes
NSAIDs	6610*, J1885
Statins	3940*
Hormone replacement therapy	24* (excluding 24000025*), J1410, J1435, J0900, J0970, J1000, J1056, J1060, J1380, J1390
Proton pump inhibitors (PPIs)	4927*

Table 16-6 Diagnosis Codes for Colorectal Hyperplasia

ICD-9-CM code	Description	Type
153	Malignant neoplasm of colon	Malignant neoplasm
153.0	Malignant neoplasm of hepatic flexure	Malignant Neoplasm
153.1	Malignant neoplasm of transverse colon	Malignant neoplasm
153.2	Malignant neoplasm of descending colon. Left colon	Malignant neoplasm
153.3	Malignant neoplasm of sigmoid colon. Sigmoid (flexure)	Malignant neoplasm
153.4	Malignant neoplasm of cecum. Ileocecal valve	Malignant neoplasm
153.6	Malignant neoplasm of ascending colon. Right colon	Malignant neoplasm
153.7	Malignant neoplasm of splenic flexure	Malignant neoplasm
153.8	Malignant neoplasm of other specified sites of large intestine. Malignant neoplasm of contiguous or overlapping sites of colon whose point of origin cannot be determined	Malignant neoplasm
153.9	Malignant neoplasm of colon, unspecified. Large intestine NOS	Malignant neoplasm
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus	Malignant neoplasm
154.0	Malignant neoplasm of rectosigmoid junction. Colon with rectum; Rectosigmoid (colon)	Malignant neoplasm
154.1	Malignant neoplasm of rectum. Rectal ampulla	Malignant neoplasm
154.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus. Anorectum; Cloacogenic zone; Malignant neoplasm of contiguous or overlapping sites of rectum, rectosigmoid junction, and anus whose point of origin cannot be determined	Malignant neoplasm
230.3	Carcinoma in situ of colon	Malignant neoplasm
230.4	Carcinoma in situ of rectum	Malignant neoplasm
211.3	Benign neoplasm of colon. Appendix; Cecum; Ileocecal valve; Large intestine NOS	Benign neoplasm
211.4	Benign neoplasm of rectum and anal canal. Anal canal or sphincter; Anus NOS; Rectosigmoid junction	Benign neoplasm

ICD-9-CM code	Description	Type
V12.72	Personal history of colonic polyps	Personal history of colonic polyps
569.0	Anal and rectal polyp. Anal and rectal polyp NOS	Anal and rectal polyps

Note: We are unable to clearly distinguish between colorectal polyps, cysts and neoplasms within the data. Colorectal polyps can be benign or malignant neoplasms as indicated in the far right column of the above table. There are no specific ICD-9-CM diagnosis codes for colorectal cysts; if they are benign they would be assigned to the benign neoplasm codes. There is a separate code for rectal polyps (569.0)

Table 16-7 Diagnosis Codes for GI Cancer

ICD-9-CM code	Description	Type
144	Malignant neoplasm of floor of mouth	Malignant neoplasm of mouth
144.0	Malignant neoplasm of anterior portion of floor of mouth	Malignant neoplasm of mouth
144.1	Malignant neoplasm of lateral portion of floor of mouth	Malignant neoplasm of mouth
144.8	Malignant neoplasm of other sites of floor of mouth	Malignant neoplasm of mouth
144.9	Malignant neoplasm of floor of mouth, part unspecified	Malignant neoplasm of mouth
145	Malignant neoplasm of other and unspecified parts of mouth	Malignant neoplasm of mouth
145.0	Malignant neoplasm of cheek mucosa	Malignant neoplasm of mouth
145.1	Malignant neoplasm of vestibule of mouth	Malignant neoplasm of mouth
145.2	Malignant neoplasm of hard palate	Malignant neoplasm of mouth
145.3	Malignant neoplasm of soft palate	Malignant neoplasm of mouth
145.4	Malignant neoplasm of uvula	Malignant neoplasm of mouth
145.5	Malignant neoplasm of palate, unspecified	Malignant neoplasm of mouth
145.6	Malignant neoplasm of retromolar area	Malignant neoplasm of mouth
145.8	Malignant neoplasm of other specified parts of mouth	Malignant neoplasm of mouth
145.9	Malignant neoplasm of mouth, unspecified	Malignant neoplasm of mouth
150	Malignant neoplasm of esophagus	Malignant neoplasm of esophagus
150.0	Malignant neoplasm of cervical esophagus	Malignant neoplasm of esophagus
150.1	Malignant neoplasm of thoracic esophagus	Malignant neoplasm of esophagus
150.2	Malignant neoplasm of abdominal esophagus	Malignant neoplasm of esophagus
150.3	Malignant neoplasm of upper third of esophagus	Malignant neoplasm of esophagus
150.4	Malignant neoplasm of middle third of esophagus	Malignant neoplasm of esophagus
150.5	Malignant neoplasm of lower third of esophagus	Malignant neoplasm of esophagus
150.8	Malignant neoplasm of other specified part of esophagus	Malignant neoplasm of esophagus

ICD-9-CM code	Description	Type
150.9	Malignant neoplasm of esophagus, unspecified	Malignant neoplasm of esophagus
151	Malignant neoplasm of stomach	Malignant neoplasm of stomach
151.0	Malignant neoplasm of cardia	Malignant neoplasm of stomach
151.1	Malignant neoplasm of pylorus	Malignant neoplasm of stomach
151.2	Malignant neoplasm of pyloric antrum	Malignant neoplasm of stomach
151.3	Malignant neoplasm of fundus of stomach	Malignant neoplasm of stomach
151.4	Malignant neoplasm of body of stomach	Malignant neoplasm of stomach
151.5	Malignant neoplasm of lesser curvature of stomach, unspecified	Malignant neoplasm of stomach
151.6	Malignant neoplasm of greater curvature of stomach, unspecified	Malignant neoplasm of stomach
151.8	Malignant neoplasm of other specified sites of stomach	Malignant neoplasm of stomach
151.9	Malignant neoplasm of stomach, unspecified	Malignant neoplasm of stomach
152	Malignant neoplasm of small intestine, including duodenum	Malignant neoplasm of small intestine
152.0	Malignant neoplasm of duodenum	Malignant neoplasm of small intestine
152.1	Malignant neoplasm of jejunum	Malignant neoplasm of small intestine
152.2	Malignant neoplasm of ileum	Malignant neoplasm of small intestine
152.3	Malignant neoplasm of Meckel's diverticulum	Malignant neoplasm of small intestine
152.8	Malignant neoplasm of other specified sites of small intestine	Malignant neoplasm of small intestine
152.9	Malignant neoplasm of small intestine, unspecified	Malignant neoplasm of small intestine
153.5	Malignant neoplasm of appendix vermiformis	Malignant neoplasm of appendix
154.2	Malignant neoplasm of anal canal. Anal sphincter	Malignant neoplasm of anus
154.3	Malignant neoplasm of anus, unspecified	Malignant neoplasm of anus
230.0	Carcinoma in situ of lip, oral cavity, and pharynx. Gingiva; Hypopharynx	Malignant neoplasm of mouth
230.1	Carcinoma in situ of esophagus	Malignant neoplasm of esophagus
230.2	Carcinoma in situ of stomach	Malignant neoplasm of stomach
230.5	Carcinoma in situ of anal canal	Malignant neoplasm of anus
230.6	Carcinoma in situ of anus, unspecified	Malignant neoplasm of anus
230.7	Carcinoma in situ of other and unspecified parts of intestine	Malignant neoplasm of small intestine
159.0	Malignant neoplasm of intestinal tract, part unspecified. Intestine NOS	Gastrointestinal stromal tumor (GIST)*
159.8	Malignant neoplasm of other sites of digestive system and intra-abdominal organs. Malignant neoplasm of digestive organs and peritoneum whose point	GIST*

ICD-9-CM code	Description	Type
159.9	Malignant neoplasm of ill-defined sites within the digestive organs and peritoneum. Alimentary canal or tract NOS; Gastrointestinal tract NOS	GIST*
238.1	Neoplasm of uncertain behavior of connective and other soft tissue. Peripheral, sympathetic, and parasympathetic nerves and ganglia; Stromal tumors	GIST*
171.5	Malignant neoplasm of connective and other soft tissue of abdomen	GIST*
V10.00	Personal history of malignant neoplasm of unspecified site in gastrointestinal tract	Personal history codes
V10.01	Personal history of malignant neoplasm of tongue	Personal history codes
V10.02	Personal history of malignant neoplasm of other and unspecified parts of oral cavity	Personal history codes
V10.03	Personal history of malignant neoplasm of esophagus	Personal history codes
V10.04	Personal history of malignant neoplasm of stomach	Personal history codes

* **Note:** There are no specific ICD-9-CM diagnosis codes for GIST. Some possible codes for GIST are listed

Table 16-8 Comorbid Conditions

Condition	ICD-9-CM diagnosis codes
Helicobacter pylori infection	041.86
Stomach lymphoma	202.83
Stomach surgery	43500-43999, S2085, S2082
Irritable bowel syndrome	564.1
Peripheral vascular disease	440, 440.0–440.2, 440.20–440.24, 440.29, 440.3, 440.30–440.32, 440.8, 440.9, 443, 443.0–443.2, 443.21–443.24, 443.29, 443.8, 443.81, 443.89, 443.9, 445.0, 445.01, 445.02, 445.81, 445.89, 447.8, 447.9, 459.30–459.33, 459.39, 459.8, 459.81
Vascular insufficiency of intestine (including ischemic bowel disease)	557.x
Chronic constipation	564.0x
Chronic diarrhea	564.5
Acute coronary syndrome	411.1, 411.8, 411.81, 411.89
Coronary heart disease and angina (Including acute coronary syndrome)	410–410.92, 411–411.89, 412, 413–413.9, 414–414.9
Heart failure	428.xx, 402.x1, 404.x1, 404.x3
Stroke or transient ischemic attack	325, 430–432, 432.0, 432.1, 432.9, 433, 433.0, 433.00, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 433.90, 433.91, 434, 434.0, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 435,

Condition	ICD-9-CM diagnosis codes
	435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.0, 437.1, 437.3–437.9, 438, 438.0, 438.1, 438.10–438.12, 438.19, 438.2, 438.20–438.22, 438.3, 438.30–438.32, 438.4, 438.40, 438.41, 438.42, 438.5, 438.50–438.53, 438.6–438.8, 438.81–438.85, 438.89, 438.9, 852.01, 852.02, 852.03, 852.04, 852.05, 852.06, 852.1, 852.10
Ulcerative colitis/Ulcerous rectocolitis	556.xx
Crohn's disease	555.xx
Diabetes mellitus	250.xx
Familial adenomatous polyps	153.xx, 154.xx, 197.5, 211.3x, 211.4x
Hereditary nonpolyposis	153.xx, 154.xx, 197.5, 211.3x, 211.4x
Chronic stomach inflammation	535.1x, 535.5x
Stomach polyps	211.1x

Table 16-9 Screening Procedures

Procedure	Procedure codes
Endoscopy including gastroscopy	0057T, S2215, 0133T, 0008T, 42.21-42.23, 44.11-44.13, 45.16, 43200-43206, 43215-43217, 43219-43220,43226-43228, 43231, 43232, 43234-43252,43255-43259, 44360, 44361, 44363-44366, 44370, 44372, 44373, 44376-44380, 44382, 44383, 991110, 91111
H. Pylori testing	83009, 83013, 83014, 87338, 87339, 86677
FOBT	82270-82274, G0107, G0394, G0328
Sigmoidoscopy	45.24, 45300, 45303, 45305, 45307-45309, 45315, 45317, 45320, 45321, 45327, 45330-45335, 45337-45342, 45345, 48.21, 48.22, 48.23, G0104, G0106
Colonoscopy	0066T, 0067T, 0529F, 3018F, 74261-74263, 44388-44394, 44397, 45.23, 45355, 45378-45387, 45391, G0105, G0120, G0121