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MAJOR ARTICLE

Risk of Cardiovascular Events Among Patients Initiating Efavirenz-Containing Versus Efavirenz-Free Antiretroviral Regimens

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Background. Efavirenz (EFV), an antiretroviral medication used to treat human immunodeficiency virus (HIV) infection, can increase lipid levels. Because hyperlipidemia is associated with increased risk for cardiovascular (CV) events, this study compared the risk of CV events in patients initiating EFV-containing vs EFV-free antiretroviral regimens.

Methods. Antiretroviral-naive HIV-positive (HIV+) patients ages 18–64 were selected from commercial and Medicaid insurance claims databases. Patients with ≥1 claim for antiretroviral medications between January 1, 2007 and December 31, 2013 were classified into 2 cohorts: EFV-containing or EFV-free regimens. Patients were required to have 6 months of continuous enrollment before initiation, with no evidence of a CV event during this time. Patients were observed from initiation until the occurrence of a CV event, disenrollment, or study end. Cardiovascular events were identified through diagnosis or procedure codes for myocardial infarction, stroke, percutaneous coronary intervention, or coronary artery bypass graft. We calculated unadjusted incidence rates (IRs) and fit propensity-score-weighted Cox proportional hazards models.

Results. There were 22 212 patients (11 978 EFV-containing and 10 234 EFV-free) identified in the commercial database and 7400 patients identified (2943 EFV-containing and 4457 EFV-free) in the Medicaid database. Cardiovascular events were rare (commercial IR = 396 per 100 000 person-years; Medicaid IR = 973 per 100 000 person-years). In propensity-score-weighted models, hazards of CV events were significantly lower for EFV-containing regimens in the commercial database (hazard ratio [HR] = 0.68; 95% confidence interval [CI], .49–.93) No significant difference was found in the Medicaid database (HR = 0.83; 95% CI, .58–1.19).

Conclusions. This analysis found no evidence of increased risk of CV events among HIV+ patients initiating EFV-containing regimens.

Keywords. antiretroviral agents; efavirenz; human immunodeficiency virus; major adverse cardiovascular events.

In the United States, there are an estimated 1.2 million people living with human immunodeficiency virus (HIV) infection [1]. These individuals face a number of health issues including increased risk for cardiovascular (CV) disease. Several analyses have evaluated the incidence of myocardial infarction (MI) among HIV-positive (HIV+) individuals, with reported rates ranging from 3.5 per 1000 people to 11.1 per 1000 people [2]. Compared with similarly aged HIV-negative (HIV−) people, HIV+ people had MI rates that were 1.5 to 2 times greater [3]. Human immunodeficiency virus-positive infection has also been associated with increased risk for ischemic stroke [4].

Although antiretroviral (ARV) therapy—the current standard of care for the treatment of HIV infection—reduces HIV-related morbidity and mortality [5], associations between the use of certain ARVs and increased risk for CV events have been reported. Two nucleoside reverse-transcriptase inhibitors (NRTIs), abacavir and didanosine, have been linked to increases in MI, although the pathway through which these medications affect MI risk is unknown [6–8]. In addition, several analyses have found that HIV+ patients treated with protease inhibitors (PIs), specifically indinavir and lopinavir, had greater risk of experiencing a CV event, including MI and coronary artery disease [2, 8, 9]. It has been hypothesized that the increase in risk associated with these PIs is due in part to dyslipidemia resulting from PI use [10].

Efavirenz (EFV), a non-NRTI (NNRTI), has been associated with hyperlipidemia in some patients with HIV [11]. Although abnormal lipid levels are known to be associated with increased risk of MI [12], the association between EFV use and CV disease is unclear. Two large studies have found no association with EFV use and MI but did not examine other CV outcomes [7, 9], although another analysis reported an increase in the risk of incident CV events associated with NNRTI use [13].

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Therefore, the objective of this analysis was to compare incidence rates (IRs) and hazards of CV events between patients initiating EFV-containing vs EFV-free ARV regimens in 2 real-world databases. The CV events evaluated in this analysis included MI, stroke, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and a composite of any of the aforementioned CV events.

METHODS

Study Design and Data Sources

This was a retrospective observational cohort study conducted in the Truven Health MarketScan Commercial Claims and Encounters (commercial) and Multi-State Medicaid (Medicaid) insurance claims databases. In the United States, commercial insurance is most commonly procured through an employer that may self-insure its employees or offer them insurance through a health plan. The commercial database contains insurance claims collected from a convenience sample of over 300 large self-insured employers and over 25 health plans in the United States, whereas the Medicaid database contains insurance claims collected from a convenience sample of state Medicaid programs from 15 geographically dispersed states in the United States that primarily insure low-income individuals and pregnant women [14]. The databases include the inpatient and outpatient medical claims, outpatient prescription drug claims, and enrollment information of enrollees in a variety of fee-for-service (pay for each service) and managed care health plans (delivery system aimed at reducing costs and improving quality often buy paying providers a fixed fee per patient [capitation] regardless of services provided) or Medicaid insurance. There are approximately 138 million employees and their dependents included in the commercial database and approximately 29 million enrollees included in the Medicaid database. Study variables were measured using *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes, Current Procedural Terminology (CPT) codes, Healthcare Common Procedure *Coding* System (HCPCS) codes, and National Drug Codes (NDCs), as appropriate.

All records contained within the databases are statistically deidentified and fully compliant with the conditions designated by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Regulations. Institutional Review Board approval was not sought, because the data did not contain any individually identifiable data.

Patient Selection and Study Period

Human immunodeficiency virus-positive patients initiating ARV therapy between January 1, 2007 and December 31, 2013 were included in the analysis. In particular, patients with at least 1 prescription claim with an NDC for EFV, a non-EFV NNRTI, a PI, an integrase inhibitor, a fusion inhibitor, or a CCR5 antagonist were selected. The date of first claim was designated as the index date, and the medication filled on that date was designated the index drug. Patients with EFV on the index date were classified as initiating an EFV-containing regimen, and those with no EFV on the index date were classified as initiating an EFV-free regimen. Patients were required to be age 18–64 years on the index date and to be continuously enrolled with medical and pharmacy benefits for the 6 months before the index date (preperiod), with no evidence of CV event of interest (as described below) during this time. Patients were also required to have at least 1 medical claim with a diagnosis of HIV infection (ICD-9-CM 042, V08, 795.71, 079.53) and no claims for ARV medications before the index date; these 2 criteria used all available prior data starting in 2004. Finally, patients in the Medicaid database were required to have no evidence of dual eligibility for Medicare (public health insurance for individuals who are elderly or disabled), which would potentially prevent complete capture of insurance claims for ARV or other prescriptions.

The primary analysis used an intent-to-treat design with variable length follow-up. Patients were categorized as initiating an EFV-containing regimen or EFV-free regimen based on the claim on the index date and were observed from the index date to the earliest of the following events: occurrence of a CV event, disenrollment from insurance benefits, or the end of study data. Patients were not required to be on ARV medications for any prespecified length of time, and changes to drug exposure did not result in ending follow-up in the intent-to-treat analysis. In a sensitivity analysis, an as-treated follow-up period was used to evaluate CV events in which patients were observed based on exposure to initiated ARV. The as-treated follow-up period was defined as the time period lasting from the index date to the earliest of the following events: occurrence of CV event, disenrollment from insurance benefits, end of study data, day before a gap of 30+ days without index drug "on hand" based on service dates and day supply fields on prescription claims, or a claim for EFV for patients in the EFV-free cohort. Efavirenz patients who discontinued and then continued on other ARV medications did not contribute to the EFV-free cohort, and patients who initiated a non-EFV regimen but who were treated with EFV later during follow-up did not contribute to the EFV-containing cohort.

Outcomes

The primary outcome of interest was the occurrence of a CV event during follow-up. Patients' medical claims were evaluated for 4 CV events: MI, stroke, PCI, and CABG. Myocardial infarction was defined as an inpatient medical claim with a diagnosis code for MI (ICD-9-CM 410.xx) recorded in the primary diagnosis position [15]. Stroke was similarly defined as an inpatient medical claim with a diagnosis code for stroke (ICD-9-CM 430.xx, 431.xx, 434.x1, 436.xx) recorded in the primary diagnosis

position [16]. The primary diagnosis position should represent the most serious diagnosis from the patient's hospitalization. Percutaneous coronary intervention and CABG were defined as an inpatient or outpatient medical claim with an ICD-9-CM procedure, CPT, or HCPCS code (see Supplementary Table 1) indicative of the procedures recorded in any procedure code position. In addition to capturing the occurrence of each type of CV event individually during follow-up, a composite CV-event measure including all 4 outcomes was created. For each CV event and the composite event measure, person-time was calculated as the number of days from the index date until the first occurrence of the CV event, disenrollment from insurance benefits, or end of study data (December 31, 2014). Patients who did not have a CV event were censored.

Covariates

Several demographic and clinical variables were measured to describe the patient cohorts and adjust the statistical analyses. Demographic characteristics were measured on the index date and included age, sex, region (available only in commercial data), and race (available only in Medicaid data). Clinical characteristics were based on diagnosis and procedure codes on medical claims and NDC codes on prescription claims during the 6-month preperiod. Variables included factors related to CV events, such as $CHADS_2$ score, hypertension, dyslipidemia, and circulatory disease. $CHADS_2$ is a classification scheme based on congestive heart failure, hypertension, age, diabetes, and history of stroke or transient ischemic attack, which is used to predict stroke risk [17, 18]. The initiated ARV regimen was defined as all ARV medications filled on the index and within 13 days after the index. The full list of covariates is presented in Table 1 and Table 2. Use of other ARV medications during follow-up was captured.

Statistical Analysis

The commercial and Medicaid patient populations were analyzed separately. For both patient populations, data presentations are stratified by cohort and the variable distributions were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Unadjusted IRs for each CV event and the composite CV event were calculated as the number of patients with the event divided by sum of person-time. To account for differences in baseline characteristics between the 2 cohorts, propensity score weights were generated with a logistic regression model that included the characteristics in Tables 1 and 2 as predictors and a binary indicator for EFV-containing regimen as the dependent variable. To assess the balance achieved by the propensity score weights, weighted *t* tests and weighted χ^2 tests were used to compare the distributions of variables included in the propensity score between the EFV-containing cohorts and the EFV-free cohorts. All tests were not significant, and therefore the weighting obtained balance between the cohorts. Propensity-score-weighted Cox proportional hazards models were then fit to compare the hazards of CV event between the cohorts. Because of the potential association with the use of other ARV medications (such as abacavir, didanosine, lopinavir, and indinavir) and CV events [8, 19], it was planned a priori to test for effect measure modification of the relationship between EFV and CV events with use of abacavir (as part of the index regimen or during follow-up) using the Breslow-Day test. In the commercial population, the test was significant for effect measure modification; therefore, additional models were fit separately for commercially insured patients with versus without evidence of abacavir use. The small number of patients using didanosine precluded the test for effect modification. Because lopinavir and indinavir are anchor agents and, therefore, comparators of EFV, effect modification is not theoretically possible.

Table 1. Characteristics of Commercially Insured Antiretroviral-Naive HIV+ Patients Initiating Efavirenz-Containing vs Efavirenz-Free Regimens

	EFV-Containing Regimen N = 11 978		EFV-Free Regimen N = 10 234		
Characteristic	N	%	N	%	*P* Value
Age in Years (mean, SD)	40.2	10.5	40.7	10.4	<.001
Male	10 300	86.0%	8129	79.4%	<.001
Region[a]					<.001
Northeast	1795	15.0%	1791	17.5%	
North Central	1922	16.0%	1264	12.4%	
South	6 229	52.0%	5174	50.6%	
West	1875	15.7%	1865	18.2%	
Unknown	157	1.3%	140	1.4%	
Capitation[b]	2342	19.6%	1960	19.2%	.451
$CHADS_2$ Score[c]					.666
0	9923	82.8%	8500	83.1%	
1	1671	14.0%	1384	13.5%	
2	316	2.6%	286	2.8%	
3–6	68	0.6%	64	0.6%	
Diabetes Mellitus[d]	575	4.8%	501	4.9%	.742
Hypertension[d]	1976	16.5%	1650	16.1%	.452
Dyslipidemia[d]	1420	11.9%	1359	13.3%	.001
Renal Disease	331	2.8%	416	4.1%	<.001
Tobacco Use Disorder	617	5.2%	479	4.7%	.107
COPD	175	1.5%	141	1.4%	.602
Anemia	1052	8.8%	844	8.2%	.154
Hepatitis C	240	2.0%	246	2.4%	.042
Alcohol Abuse Disorder	90	0.8%	71	0.7%	.614
Drug Abuse Disorder	752	6.3%	635	6.2%	.822
Autoimmune/Inflammatory Disorders	440	3.7%	377	3.7%	.967
Circulatory Disease	2729	22.8%	2245	21.9%	.131
Oral Contraceptives	69	0.6%	102	1.0%	<.001

Abbreviations: COPD, chronic obstructive pulmonary disorder; EFV, efavirenz; HIV+, human immunodeficiency virus-positive; SD, standard deviation.

[a] Commercial population only.

[b] Presence of claim with capitated payment arrangement.

[c] $CHADS_2$ is based on the presence of diagnoses of congestive heart failure, hypertension, diabetes, and stroke or transient ischemic attack and age ≥75 [16, 17].

[d] Both diagnoses and medication use were evaluated.

Table 2. Characteristics of Medicaid-Insured Antiretroviral-Naive HIV+ Patients Initiating Efavirenz-Containing vs Efavirenz-Free Regimens

Characteristic	EFV-Containing Regimen N = 2943		EFV-Free Regimen N = 4457		*P* Value
	N	%	N	%	
Age in Years (mean, SD)	42.3	11.0	40.6	11.1	<.001
Male	1644	55.9%	2112	47.4%	<.001
Race[a]					
White	468	15.9%	735	16.5%	.809
Black	2059	70.0%	3119	70.0%	
Hispanic	35	1.2%	60	1.3%	
Other	30	1.0%	45	1.0%	
Unknown/Missing	351	11.9%	498	11.2%	
Capitation[b]	1226	41.7%	1685	37.8%	<.001
$CHADS_2$ Score[c]					.004
0	1895	64.4%	3051	68.5%	
1	722	24.5%	958	21.5%	
2	246	8.4%	332	7.4%	
3–6	80	2.7%	116	2.6%	
Diabetes Mellitus[d]	303	10.3%	419	9.4%	.204
Hypertension[d]	982	33.4%	1270	28.5%	<.001
Dyslipidemia[d]	325	11.0%	434	9.7%	.070
Renal Disease	263	8.9%	443	9.9%	.151
Tobacco Use Disorder	650	22.1%	1028	23.1%	.325
COPD	235	8.0%	257	5.8%	<.001
Anemia	575	19.5%	850	19.1%	.618
Hepatitis C	302	10.3%	488	10.9%	.349
Alcohol Abuse Disorder	122	4.2%	225	5.1%	.072
Drug Abuse Disorder	850	28.9%	1404	31.5%	.017
Autoimmune/Inflammatory Disorders	163	5.5%	217	4.9%	.201
Circulatory Disease	1181	40.1%	1668	37.4%	.019
Oral Contraceptives	18	0.6%	38	0.9%	.242

Abbreviations: COPD, chronic obstructive pulmonary disorder; EFV, efavirenz; HIV+, human immunodeficiency virus-positive; SD, standard deviation.

[a] Medicaid population only.

[b] Presence of claim with capitated payment arrangement.

[c] $CHADS_2$ is based on the presence of diagnoses of congestive heart failure, hypertension, diabetes, and stroke or transient ischemic attack and age ≥75 [16, 17].

[d] Both diagnoses and medication use were evaluated.

RESULTS

Patient Population

There were 98 675 commercially insured patients and 31 806 Medicaid-insured patients with an ARV prescription initially identified in the 2 study databases. After applying the patient selection criteria, the final populations comprised 22 212 commercially insured patients and 7400 Medicaid-insured patients. In the commercial population, 11 978 patients (53.9%) initiated an EFV-containing regimen. In the Medicaid population, 2943 patients (39.8%) initiated an EFV-containing regimen. Full information on the attrition of the patient populations associated with each study selection criterion is presented in Supplementary Table 2. Patients in the EFV-free cohort initiated a variety of ARV medications. Among the commercial population, 23.6% initiated atazanavir, 18.6% initiated raltegravir, 15.5% initiated darunavir, 10.8% initiated rilpivirine, and 8.8% initiated elvitegravir. Among the Medicaid population, 33.8% initiated atazanavir, 13.3% initiated raltegravir, 12.0% initiated darunavir, 6.5% initiated rilpivirine, and 4.2% initiated elvitegravir. Regarding backbone medication use in the EFV-containing cohorts, almost all patients initiated tenofovir/emtricitabine (94.4% in the commercial population and 92.7% in the Medicaid population). In the EFV-free cohort in the commercial population, 75.1% of patients initiated tenofovir, 71.5% initiated emtricitabine, and 18.1% initiated lamivudine. In the EFV-free cohort in the Medicaid population, 71.8% of patients initiated tenofovir, 68.0% initiated emtricitabine, and 20.8% initiated lamivudine.

Patient characteristics are presented in Tables 1 and 2. Mean age ranged from 40–42 years old across the cohorts. The EFV-containing cohort had a significantly larger proportion of males. In the Medicaid population, a significantly smaller proportion of patients in the EFV-containing cohort had a $CHADS_2$ score of 0, compared with the EFV-free cohort, indicating greater overall stroke risk in the EFV-containing cohort. There was no significant difference in $CHADS_2$ score by cohort in the commercial population. Overall, the EFV-containing and EFV-free cohorts were similar on many clinical characteristics related to CV disease with a few exceptions. Among commercially insured patients, the EFV-containing cohort had significantly smaller proportions of patients with dyslipidemia, renal disease, hepatitis C, and at least 1 prescription for an oral contraceptive. Among the Medicaid-insured patients, the EFV-containing cohort had significantly larger proportions of patients with hypertension, chronic obstructive pulmonary disease, and circulatory disease, but a significantly smaller proportion of patients with a diagnosis of drug abuse disorder. During the follow-up period, 28.8% of the EFV-free cohort had a claim for abacavir, didanosine, indinavir, or lopinavir, which have also been associated with CV events compared with 6.9% of the EFV-containing cohort in the commercial population. In the Medicaid population, 34.1% of the EFV-free cohort had a claim for 1 of the aforementioned drugs compared with 9.9% in the EFV-containing cohort.

Cardiovascular Events During Intent-to-Treat Follow-up Period

Using an intent-to-treat follow-up period, patients in the EFV-containing cohort were observed for an average of 23.2 months compared with 19.3 months in the EFV-free cohort in the commercial population. In the Medicaid population, the EFV-containing cohort was observed for an average of 23.4 months compared with 19.6 months in the EFV-free cohort. Cardiovascular events were rare during follow-up for both patient populations. Unadjusted IRs are presented in Figure 1 and Figure 2. In the commercially insured population, 79 patients in the EFV-containing cohort had a CV event (IR = 343.3 per 100 000 person-years [PYs]; 95% confidence interval [CI], 271.8–427.9)

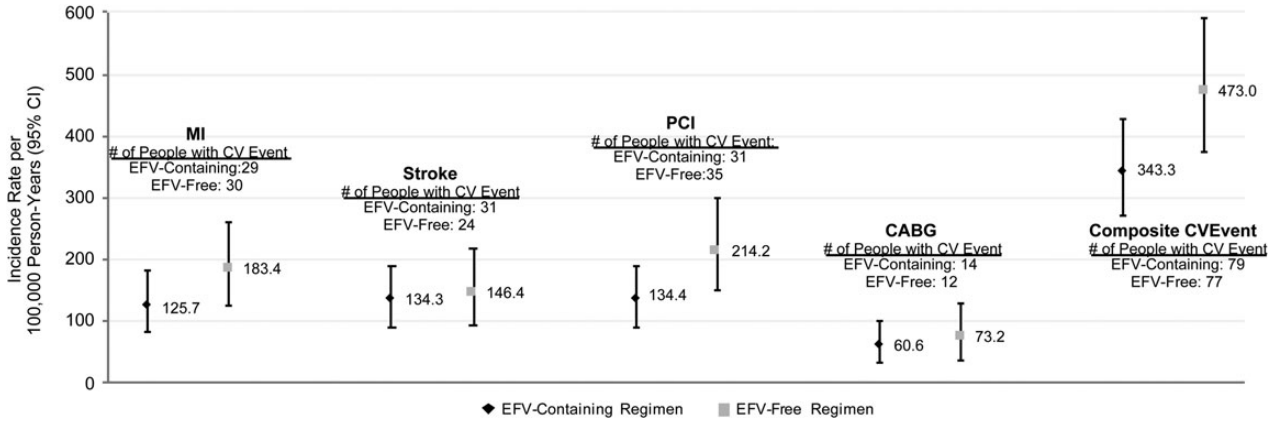

Figure 1. Unadjusted incidence rates for cardiovascular events among commercially insured antiretroviral-naive human immunodeficiency virus-positive patients initiating efavirenz (EFV)-containing versus EFV-free regimens: intent-to-treat follow-up period. Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

and 77 patients in the EFV-free cohort had a CV event (IR = 473.0 per 100 000 PYs; 95% CI, 373.3–591.2). The IRs for the composite CV event were higher in the Medicaid-insured population where 54 patients in the EFV-containing cohort had a CV event (IR = 954.9 per 100 000 PYs; 95% CI, 717.3–1245.9) and 71 patients in the EFV-free cohort had a CV event (IR = 987.6 per 100 000 PYs; 95% CI, 771.3–1245.7). In both populations, the rates of CV events were highest among the oldest group of patients who were aged 55–65 (commercial, EFV-containing cohort IR = 900.7 per 100 000 PYs and EFV-free cohort IR = 1668.3 per 100 000 PYs; Medicaid, EFV-containing cohort IR = 1738.6 per 100 000 PYs and EFV-free cohort IR = 2359.5 per 100 000 PYs).

In propensity-score-weighted models (Table 3), patients in the EFV-containing cohort in the commercially insured sample had significantly lower hazards of a CV event overall (hazard ratio [HR] = 0.68; 95% CI, .49–.93) and of a PCI (HR = 0.56; 95% CI, .35–.92). There were no significant differences in hazards for CV events in the Medicaid population. As noted above, the analyses of the commercial population were also stratified by abacavir use. Among patients with abacavir use (n = 2029), there were no significant differences in hazards of CV events. Among those without abacavir use (n = 20 183), the EFV-containing cohort had significantly lower hazards of CV events (HR = 0.61; 95% CI, .43–.86) and of PCI (HR = 0.50; 95% CI, .29–.85). Unweighted models are presented in Supplementary Table 3.

Sensitivity Analyses

Using an as-treated follow-up period, patients in the EFV-containing cohort were observed for an average of 14.4 months compared with10.2 months in the EFV-free cohort in the commercial population. In the Medicaid population, the

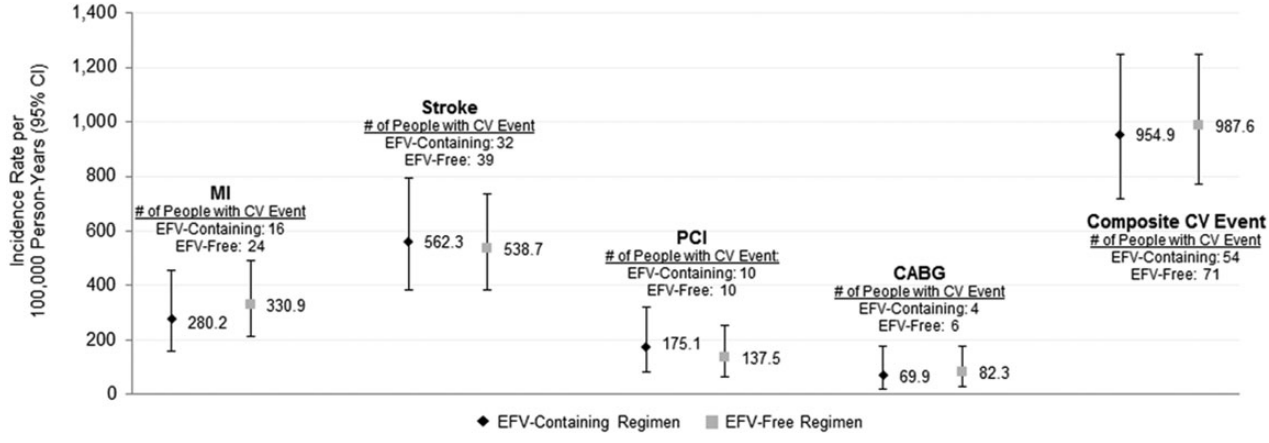

Figure 2. Unadjusted incidence rates for cardiovascular (CV) events among Medicaid-insured antiretroviral-naive human immunodeficiency virus-positive patients initiating efavirenz (EFV)-containing versus EFV-free regimens: intent-to-treat follow-up period. Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3. Propensity-Score-Weighted Hazard Ratios For CV Events Over an Intent-To-Treat Follow-up Period Among Commercially Insured and Medicaid-Insured Antiretroviral-Naive HIV+ Patients Initiating Efavirenz-Containing vs Efavirenz-Free Regimens

	Hazard Ratio (95% CI) for CV Event Comparing EFV-Containing Regimens With EFV-Free Regimens			
	Commercial			
CV Event	All Patients (N = 22 212)	Patients With Abacavir Use (N = 2029)	Patients Without Abacavir Use (N = 20 183)	Medicaid (N = 7400)
MI	0.60 (0.36–1.01)	1.58 (0.42–5.90)	0.52 (0.30–0.91)	0.69 (0.36–1.31)
Stroke	0.93 (0.54–1.60)	0.72 (0.14–3.75)	0.90 (0.50–1.61)	0.94 (0.58–1.52)
PCI	0.56 (0.35–0.92)[a]	1.16 (0.32–4.15)	0.50 (0.29–0.85)[a]	0.94 (0.39–2.27)
CABG	0.73 (0.33–1.57)	3.49 (0.58–20.94)	0.54 (0.23–1.27)	0.60 (0.17–2.11)
Composite CV Event	0.68 (0.49–0.93)[a]	1.33 (0.59–2.99)	0.61 (0.43–0.86)[a]	0.83 (0.58–1.19)

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; EFV, efavirenz; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Statistically significant.

EFV-containing cohort was observed for an average of 9.7 months compared with 7.8 months in the EFV-free cohort. Unadjusted IRs for the sensitivity analyses measured over the as-treated follow-up period are presented in Supplementary Figure 1A and 1B. Because the as-treated follow-up period was shorter than the intent-to-treat follow-up period, the number of patients with a CV event was smaller. Incidence rates for the composite CV event were 286.2 per 100 000 PYs (95% CI, 205.4–388.3) for the EFV-containing cohort and 414.3 per 100 000 PYs (95% CI, 290.0–573.6) for the EFV-free cohort in the commercial population and 1 016.9 per 100 000 PYs (95% CI, 651.6–1513.1) for the EFV-containing cohort and 870.1 per 100 000 PYs (95% CI, 563.1–1284.4) for the EFV-free cohort in the Medicaid population. Results from unweighted and propensity-score-weighted Cox proportional hazards models are presented in Supplementary Tables 4 and 5. There were no significant differences in hazards of CV event comparing the EFV-containing cohort and the EFV-free cohort in the commercial (HR = 0.66; 95% CI, .42–1.04) or Medicaid (HR = 0.98; 95% CI, .56–1.72) databases. This was also true for each individual CV event. When limiting to commercially insured patients with no abacavir use, the EFV-containing cohort had significantly lower hazards of a CV event (HR = 0.58; 95% CI, .35–.95).

DISCUSSION

In this real-world, claims-based analysis of ARV-naive patients with HIV, there was no evidence of increased risk of MI, stroke, PCI, or CABG with EFV. Cardiovascular events were rare in both databases, and results were consistent in patients with commercial insurance and those with Medicaid and when using either an intent-to-treat or an as-treated follow-up period. This study adds to the body of literature regarding ARV use and CV disease, which indicates that some ARV medications may be linked to increased risk of CV events.

Human immunodeficiency virus-positive individuals may be at increased risk for CV events, such as MI and stroke, compared with HIV− individuals, due to both HIV infection itself and the use of ARV therapy. A study by Freiberg et al [3] conducted in the Veterans Aging Cohort Study Virtual Cohort reported that the mean number of acute MI events was consistently higher for HIV+ veterans compared with HIV− veterans across different age groups. In addition, after adjusting for standard Framingham risk factors and other patients characteristics, HIV+ veterans had a 48% higher risk of incident MI (HR = 1.48; 95% CI, 1.27–1.72) [3]. The finding was of similar magnitude and significance when HIV+ patients with controlled HIV (viral load <500 copies/mL) were compared with HIV− veterans [3]. Sico et al [4] used data from the same cohort to evaluate risk of ischemic stroke in HIV+ veterans. They found that HIV+ veterans had 17% greater risk of stroke compared with their HIV− controls [4]. A South Carolina Medicaid claims-based analysis by Tripathi et al [13] attempted to differentiate the risk of CV events (defined as incident MI, stroke, PCI, and angina pectoris) attributable to HIV infection versus ARV use by comparing HIV+ enrollees treated with ARVs and treatment-naive HIV+ enrollees to HIV− enrollees. The researchers found significantly increased risk for a CV event when comparing treated HIV+ patients with HIV− patients (HR = 1.15; 95% CI, 1.04–1.27) [13]. The researchers also found increased risk among treatment-naive HIV+ patients vs HIV− patients, although this result was not statistically significant (HR = 1.18; 95% CI, .98–1.41) [13]. Finally, an analysis of veterans by Desai et al [20] found that EFV exposure was associated with increased odds of CV events (odds ratio = 1.40; 95% CI, 1.19–1.66) using marginal structural models. However, when using Cox proportional hazards models, as was done in the analysis presented here, no association was found [20].

The results from the analysis presented in this manuscript are consistent with the findings from 2 other cohort studies. Lang et al [9] conducted a nested case-control study in a French hospital cohort between 2000 and 2006 to evaluate associations between ARV use and MI. They identified 289 MI cases that were matched

to 884 controls [9]. Of the cases, 109 were exposed to EFV for a median time of 1.42 years, and of the controls, 295 were exposed for a median time of 1.69 years [9]. In a series of models that controlled for traditional risk factors and NRTI use, no significant association between EFV use and MI was found (odds ratios = 1.01) [9]. An analysis by Worm et al [7] conducted as part of the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) study reported similar results. There were 33 308 patients observed for approximately 6 years each; of these, 580 patients had an MI [7]. Almost all patients had been exposed to ARV medications, and there was no significant association between exposure to EFV and higher rates of MI (relative rate = 1.02) [7]. The previously mentioned analysis by Tripathi et al [13] of South Carolina Medicaid did report increased risk for CV events associated with additional months of treatment with NNRTIs but did not specify which NNRTIs were used by patients.

A systematic review and meta-analysis by Bavinger et al [8] published in 2013 identified 27 studies that included 125 analyses of ARV medications and CV events. The researchers categorized analyses into 2 types: those evaluating the association between cumulative ARV use over a period of years and CV events, and those evaluating the association between recent ARV use within 6 months and CV events [8]. There were 8 analyses that could be combined in a meta-analysis [8]. Results were conflicting regarding cumulative abacavir use; however, recent use was found to be associated with increased risk of MI [8]. Bavinger et al [8] commented that there is still uncertainty as to whether there is truly an association between ARV medications and CV disease because there are few randomized controlled trials powered to conduct these comparisons, and observational studies may be biased by confounding by indication. They called for prospective studies designed specifically to answer this important research question [8].

Two open-label, randomized studies have evaluated the use of abacavir in combination with EFV [21, 22]. The first compared ARV-naive adults initiating abacavir/lamivudine plus EFV versus those initiating tenofovir/emtricitabine plus EFV [21]. The second analysis included patients with high cholesterol who were on abacavir/lamivudine plus EFV for at least 6 months [22]. Patients were randomized to switch immediately to EFV/tenofovir/emtricitabine or to continue on their current regimen and switch to EFV/tenofovir/emtricitabine after 12 weeks [22]. In both analyses, use of abacavir/lamivudine was associated with worse lipid levels [21, 22]. The analysis presented here found that use of abacavir modified the association between EFV and CV events in commercial patients, meaning the risk for CV events for patients on EFV differs depending on the use of abacavir. This indicates that there may be an interaction between EFV and abacavir use. However, the test for effect measure modification was only found to be significant in the commercial population. More research is needed to evaluate this relationship.

This analysis has limitations that should be noted. First, because the study was based in claims data that are collected for billing purposes rather than research, there may be misclassification of study outcomes and covariates. Misclassification is likely to be nondifferential. For both MI and stroke, previously published validated algorithms were used [16]. In these analyses, the sensitivity and specificity of MI were 94% and 99%, respectively [15], whereas the positive predictive value of stroke was 80% [16]. In addition, it is unlikely that administrative coding errors would be present on adjudicated insurance claims related to serious and expensive CV procedures such as PCI and CABG. However, stroke or MI events that resulted in death without hospitalization or those occurring after patients have been censored due to end of continuous enrollment or end of data would not be captured. Second, claims for ARV medications indicate that patients filled a prescription for the medication. Based on claims data, it cannot be known whether patients took the medication as directed. Therefore, exposure may be misclassified as well, particularly in the as-treated sensitivity analysis. Again, this is likely nondifferential by cohort. Bias due to informative censoring may have occurred in the as-treated analysis if patients were switched from one ARV to another due to risk for CV events. Third, certain clinical and lifestyle factors such as blood pressure, lipid levels, CD4, viral load, diet, exercise, smoking, and family history of CV disease are not available in claims data, and therefore uncontrolled confounding may have bias our study results if there were differences between the study cohorts. Fourth, the analysis compared patients treated with EFV with patients treated with other ARV medications. In both cohorts, patients may have been on other ARV medications or other non-ARV medications that affect CV risk during the follow-up period. Although baseline use of medications to treat hypertension and dyslipidemia were accounted for in the propensity score model, if there were systematic differences in medications used between the 2 cohorts, the effect estimates may be biased. Finally, these findings may not be generalizable to patients who become insured at the time of ART initiation, patients who are insured through Medicare, or patients who are uninsured.

This analysis also has several strengths. The sample sizes for the cohorts were large, and many patients were observed for more than 1 year. In addition, the data used were more recent than other published analyses. Therefore, more recently approved ARV medications and formulations were included here. Furthermore, a diverse patient population was analyzed because the study was conducted in a commercial database that includes both fee-for-service and managed care patients as well as in a Medicaid database.

CONCLUSIONS

This real-world claims-based analysis of HIV+ patients insured through commercial plans or through Medicaid revealed no evidence for an increase in risk for CV events associated with initiation of EFV in intent-to-treat and as-treated analyses but

possibly a lower risk relative to some regimens In addition, the association between EFV and CV events may be differ by the presence of abacavir, but further research is needed.

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Potential conflicts of interest. LR reports employment at Bristol-Myers Squibb and ownership of Bristol-Myers Squibb stocks. AMF and SSJ report employment at Truven Health Analytics which received funding from Bristol-Myers Squibb to conduct this analysis. ETN reports employment at Bristol-Myers Squibb. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Supplementary Data

Supplementary material is available online at Open Forum Infectious Diseases online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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