ORIGINAL RESEARCH

Excess Risk for Atherosclerotic Cardiovascular Outcomes Among US Adults With HIV in the Current Era

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Background—In the 2000s, adults with HIV had a higher risk for atherosclerotic cardiovascular disease (ASCVD) compared with those without HIV. There is uncertainty if this excess risk still exists in the United States given changes in antiretroviral therapies and increased statin use.

Methods and Results—We compared the risk for ASCVD events between US adults aged ≥19 years with and without HIV who had commercial or supplemental Medicare health insurance between January 1, 2011, and December 31, 2016. Beneficiaries with HIV (n=82 426) were frequency matched 1:4 on age, sex, and calendar year to those without HIV (n=329 704). Beneficiaries with and without HIV were followed up through December 31, 2016, for ASCVD events, including myocardial infarction, stroke, and lower extremity artery disease hospitalizations. Most beneficiaries were aged <55 years (79%) and men (84%). Over a median follow-up of 1.6 years (maximum, 6 years), there were 3287 ASCVD events, 2190 myocardial infarctions, 891 strokes, and 322 lower extremity artery disease events. The rate per 1000 person-years among beneficiaries with and without HIV was 5.53 and 3.49 for ASCVD, respectively, 3.58 and 2.34 for myocardial infarction, respectively, 1.49 and 0.94 for stroke, respectively, and 0.65 and 0.31 for lower extremity artery disease hospitalizations, respectively. The multivariable-adjusted hazard ratio (95% CI) for ASCVD, myocardial infarction, stroke, and lower extremity artery disease hospitalizations comparing beneficiaries with versus without HIV was 1.29 (1.18–1.40), 1.26 (1.13–1.39), 1.30 (1.11–1.52), and 1.46 (1.11–1.92), respectively.

Conclusions—Adults with HIV in the United States continue to have a higher ASCVD risk compared with their counterparts without HIV. **(*J Am Heart Assoc*. 2020;9:e013744. DOI: 10.1161/JAHA.119.013744.)**

Key Words: HIV • myocardial infarction • peripheral artery disease • stroke

HIV infection is a global epidemic, and its prevalence continues to increase.[1] At the end of 2015, >1 million people had HIV in the United States.[1] Among US adults and adolescents diagnosed with HIV, 63% received some HIV medical care, 49% received continuous HIV care, and 51% achieved viral suppression.[1] The use of antiretroviral therapies (ARTs), in societies where they are widely available, has reduced deaths from opportunistic infections.[2,3] This has resulted in an increased proportion of deaths among people with HIV being attributed to atherosclerotic cardiovascular disease (ASCVD).[1,4–7]

Studies conducted in the United States from the 1990s and early 2000s reported that people with HIV infection have a higher risk for ASCVD events, including myocardial infarction (MI) and stroke, than their counterparts without HIV.[8–11] A retrospective cohort study using data from 1996 to 2011 on HIV-positive and HIV-negative members of Kaiser Permanente Southern California and Kaiser Permanente Northern California health plans reported that an excess risk for MI may no longer exist for US adults with HIV.[12] The authors hypothesized that the similar rates of MI in people with and without HIV may have resulted from increased awareness of HIV-associated cardiovascular risk and use of statins and antihypertensive agents, in addition to decreased use of hyperlipidemia-inducing protease inhibitors (PIs).[12,13] Other studies conducted during this time period suggest that HIV may still be associated with higher ASVD risk outside the United States.[6]

The main aim of the current study was to determine whether the risk for ASCVD, including MI, stroke, and lower

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Accompanying Tables S1 through S9 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013744

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Clinical Perspective

What Is New?

- The current analysis suggests that HIV is associated with a higher risk of atherosclerotic cardiovascular disease events, including myocardial infarction, stroke, and lower extremity arterial disease, in the contemporary era, despite more extensive use of antiretroviral therapy and increased use of statins.

What Are the Clinical Implications?

- Clinicians should be aware of the higher risk of atherosclerotic cardiovascular disease in people living with HIV and provide guideline-recommended therapy to lower their risk.

extremity artery disease (LEAD) events, is higher among patients with HIV compared with their counterparts without HIV in a contemporary cohort of US adults. We examined these associations overall and within subgroups of patients taking and not taking statins. To accomplish this aim, we conducted a retrospective cohort study using data from the MarketScan database (Truven Health Analytics, IBM Watson Health, Ann Arbor, MI).

Methods

Study Population

The MarketScan database contains administrative and claims data from individuals enrolled in various employer-sponsored healthcare plans and Medicare supplemental plans. We identified beneficiaries in the MarketScan database who had HIV infection, defined by meeting either of the following criteria between January 1, 2011, and December 31, 2016: (1) ≥1 hospitalization with a discharge diagnosis code for HIV in any position or (2) ≥2 pharmacy claims for ART. Discharge diagnosis codes for HIV included an *International Classification of Diseases, Ninth Revision* (*ICD-9*), code of 042.x to 044.x or V08 or an *ICD-10* code of B20.xx to B22.xx, B24.xx, or Z21.xx. Table S1 shows the list of ART medication by drug classes used in the current study. We restricted the study population to beneficiaries meeting the definition of HIV who were aged ≥19 years; had continuous health insurance coverage, including pharmacy benefits; and lived in the United States for the 365 days before being identified as having HIV in the MarketScan database. For each beneficiary, the index date was defined as the earliest date for which they had a diagnosis of HIV or at least 2 prescription fills for ART while meeting all of the criteria described above.

Beneficiaries without HIV were frequency matched to those with HIV. Specifically, for each beneficiary in the MarketScan database without HIV, we selected a random date between January 1, 2011, and December 31, 2016, and defined this as their index date. We further restricted the population to beneficiaries aged ≥19 years who had continuous health insurance coverage, including pharmacy benefits, and lived in the United States for the 365 days before their index date. For each beneficiary in the HIV cohort, we randomly selected 4 beneficiaries without HIV from the same age group (ie, 19–44, 45–54, 55–64, and ≥65 years), sex, and calendar year of their index date. The Institutional Review Board at the University of Alabama at Birmingham approved the current analysis and waived the requirement to obtain informed consent. Data used in the current study are available from Truven Health Analytics. Other study information is available from the corresponding author.

Beneficiary Characteristics

Beneficiary characteristics analyzed included age, sex, calendar year of their index date, and geographic region of residence. We used claims in the 365 days before each beneficiary's index date from the MarketScan database to identify the presence of comorbidities, including a history of coronary heart disease, stroke, peripheral artery disease, diabetes mellitus, heart failure, chronic kidney disease, liver disease, and depression. In addition, we used claims to identify receipt of cardiologist care, a hospitalization for any reason, tobacco use, use of antihypertensive medication, statin use and intensity, use of nonstatin lipid-lowering medication, and polypharmacy. Table S2 provides definitions for each of these variables. Use of ART medication was defined by ≥2 prescription fills for a nucleoside reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitor (NNRTI), PI, fusion inhibitor, entry inhibitor, integrase strand transfer inhibitor, or pharmacokinetic enhancer within 365 days before each beneficiary's index date, inclusive.

Cardiovascular Events During Follow-Up

Beneficiaries were followed up from their index date for the composite of ASCVD, including MI, stroke, and LEAD hospitalizations.[14,15] In addition, each component of the composite outcome was analyzed separately. Definitions of ASCVD, MI, stroke, and LEAD hospitalizations are shown in Table S3. ASCVD, MI, stroke, and LEAD hospitalizations were assessed through December 31, 2016, the last date for which we had outcome data available. For each outcome, beneficiaries were followed up until the earliest occurrence of their first event, loss of health insurance coverage, or December 31, 2016. Data on mortality are not available in the MarketScan database.

Statistical Analysis

We calculated baseline characteristics, the cumulative incidence of ASCVD using the Kaplan-Meier method, and the rate of ASCVD among beneficiaries with HIV and matched controls without HIV. Cox regression models were used to calculate hazard ratios for ASCVD comparing beneficiaries with versus without HIV. In addition to an unadjusted model, 2 models with progressive adjustment for covariates were used. Model 1 included adjustment for age, sex, calendar year, geographical region of residence, and history of coronary heart disease, diabetes mellitus, stroke, peripheral artery disease, and heart failure. Model 2 included adjustment for variables in model 1 and chronic kidney disease, liver disease, cardiologist care, a prior hospitalization for any reason, depression, tobacco use, polypharmacy, antihypertensive medication use, statin use and high versus low/moderate intensity, and nonstatin lipid-lowering medication use. We also calculated the cumulative incidence, event rate, and unadjusted and adjusted hazard ratios for an MI, stroke, and LEAD hospitalization, separately, comparing beneficiaries with versus without HIV.

We used Cox regression models to calculate multivariable-adjusted hazard ratios for an ASCVD, MI, stroke, and LEAD hospitalization comparing beneficiaries with versus without HIV within subgroups defined by each of the characteristics included in the multivariable-adjusted model. These models included adjustment for all variables in model 2 described above. To test whether hazard ratios for an ASCVD, MI, stroke, and LEAD hospitalization were different across subgroups defined by beneficiary characteristics, calculations were repeated in the overall population, including interaction terms between HIV infection status and each characteristic (eg, HIV×sex). We used the likelihood ratio test to calculate the *P* value for the interaction between HIV and characteristics with >2 levels (eg, age or calendar year). All the analyses described above were repeated stratified by statin use. Analyses were conducted in SAS, version 9.4 (SAS Institute Inc, Cary, NC) using a 2-sided level of significance $\alpha<0.05$.

Results

Baseline Characteristics of Study Population

There were 82 426 beneficiaries aged ≥19 years with commercial or supplemental Medicare health insurance in the MarketScan database with HIV who met the inclusion criteria for the current analysis (Figure S1). The characteristics of beneficiaries with HIV and matched controls without HIV (n=329 704) are shown in Table 1. Most beneficiaries with HIV and their matched controls were aged <55 years and men. There was a <1% difference in the percentage with diabetes mellitus, history of coronary heart disease, history of stroke, and history of peripheral artery disease between beneficiaries with and without HIV. A history of chronic kidney disease and liver disease, cardiologist care, a prior hospitalization for any reason, depression, tobacco use, polypharmacy, and antihypertensive medication use were more common among beneficiaries with HIV than their counterparts without HIV. Overall, 18.9% and 16.3% of beneficiaries with and without HIV were taking a statin, respectively. Most beneficiaries with HIV (96.0%) had ≥2 fills for ART medication within the 365 days before their index date, inclusive. Among beneficiaries with HIV, 50.2% were taking a nucleoside reverse transcriptase inhibitor, 44.2% were taking an NNRTI, 25.1% were taking a PI, and 21.7% were taking other ART classes.

Incidence of ASCVD Events

Over a median follow-up of 1.6 years (maximum, 6.0 years), there were 3287 ASCVD events, 2190 MIs, 891 strokes, and 322 LEAD events. Compared with beneficiaries without HIV, those with HIV had a higher cumulative incidence of ASCVD, MI, stroke, and LEAD hospitalizations (Figure 1). The risk for each outcome was higher among beneficiaries with versus without HIV in unadjusted and multivariable-adjusted models (Table 2). The multivariable-adjusted hazard ratio for ASCVD comparing beneficiaries with versus without HIV was 1.29 (95% CI, 1.18–1.40). The multivariable-adjusted hazard ratios (95% CIs) for an MI, stroke, and LEAD hospitalization in beneficiaries with versus without HIV were 1.26 (1.13–1.39), 1.30 (1.11–1.52), and 1.46 (1.11–1.92), respectively.

Beneficiaries with HIV had a higher risk for an ASCVD, MI, stroke, and LEAD hospitalization versus those without HIV within most subgroups defined by beneficiary characteristics (Figure 2 and Table S4). The hazard ratio for ASCVD was higher among beneficiaries aged 19 to 44 years versus those aged ≥45 years (*P*=0.04). Hazard ratios for ASCVD and stroke hospitalizations associated with HIV infection were statistically significantly higher among beneficiaries with versus without a prior hospitalization for any reason (each *P*-interaction<0.05). Hazard ratios for LEAD hospitalization were higher in beneficiaries without diabetes mellitus or liver disease. No other statistically significant differences were present when comparing hazard ratios for an ASCVD, MI, stroke, or LEAD hospitalization among beneficiaries with versus without HIV across subgroups.

Analyses Stratified by Statin Use

Characteristics of beneficiaries with and without HIV who were taking and not taking a statin, separately, are presented in Table S5. The rates of ASCVD, MI, stroke, and LEAD hospitalizations were higher in beneficiaries with versus without HIV among both those taking and not taking statins (Table 3). Among beneficiaries taking and not taking statins,

Table 1. Characteristic of Beneficiaries With HIV and Age-, Sex-, and Calendar Year–Matched Beneficiaries Without HIV in the MarketScan Database

Characteristics	Beneficiaries Without HIV (n=329 704)	Beneficiaries With HIV (n=82 426)
Calendar year		
2011	136 516 (41.4)	34 129 (41.4)
2012	53 244 (16.1)	13 311 (16.1)
2013	36 516 (11.1)	9129 (11.1)
2014	36 832 (11.2)	9208 (11.2)
2015	32 092 (9.7)	8023 (9.7)
2016	34 504 (10.5)	8626 (10.5)
Age, y		
19–44	140 600 (42.6)	35 150 (42.6)
45–54	118 472 (35.9)	29 618 (35.9)
55–64	60 328 (18.3)	15 082 (18.3)
≥65	10 304 (3.1)	2576 (3.1)
Male sex	276 548 (83.9)	69 137 (83.9)
Geographic region of residence		
Northeast	61 519 (18.7)	15 330 (18.6)
North central	75 444 (22.9)	11 186 (13.6)
South	126 531 (38.4)	38 255 (46.4)
West	62 749 (19.0)	16 557 (20.1)
Unknown	3461 (1.0)	1098 (1.3)
Diabetes mellitus	24 719 (7.5)	6664 (8.1)
History of CHD	9704 (2.9)	2815 (3.4)
History of stroke	907 (0.3)	596 (0.7)
History of peripheral artery disease	579 (0.2)	309 (0.4)
History of heart failure	1004 (0.3)	700 (0.8)
Chronic kidney disease	4629 (1.4)	3849 (4.7)
Liver disease	1295 (0.4)	2325 (2.8)
Cardiologist care	6627 (2.0)	2807 (3.4)
Any hospitalization	12 981 (3.9)	10 128 (12.3)
Depression	39 379 (11.9)	19 669 (23.9)
Tobacco use	9418 (2.9)	5640 (6.8)
Polypharmacy	32 883 (10.0)	27 602 (33.5)
Antihypertensive medication use	77 733 (23.6)	23 740 (28.8)
Statin use		
Overall	53 842 (16.3)	15 619 (18.9)
Low-/moderate-intensity statin use	44 421 (13.5)	12 049 (14.6)
High-intensity statin use	9421 (2.8)	3570 (4.3)
Nonstatin lipid-lowering medication use	14 744 (4.5)	6558 (8.0)
ART use	…	79 095 (96.0)
NRTIs	…	41 372 (50.2)
NNRTI	…	36 465 (44.2)

Continued

Table 1. Continued

Characteristics	Beneficiaries Without HIV (n=329 704)	Beneficiaries With HIV (n=82 426)
Protease inhibitors	…	20 713 (25.1)
Other*	…	17 890 (21.7)

Data are given as number (percentage) of each group. ART indicates antiretroviral therapy; CHD, coronary heart disease; NNRTI, non-NRTI; NRTI, nucleoside reverse transcriptase inhibitor.
*Other ART includes fusion inhibitors, entry inhibitors, integrase strand transfer inhibitors, and pharmacokinetic enhancers.

HIV was associated with an increased risk for ASCVD and MI after multivariable adjustment. After multivariable adjustment, the hazard ratio for stroke associated with HIV infection was 1.30 (95% CI, 1.07–1.58) among beneficiaries not taking statins and 1.25 (95% CI, 0.95–1.64) among their counterparts taking statins. The multivariable-adjusted hazard ratio for LEAD hospitalization associated with HIV infection was 1.62 (95% CI, 1.13–2.32) among beneficiaries not taking statins and 1.27 (95% CI, 0.83–1.94) among their counterparts taking statins. There was no evidence of effect

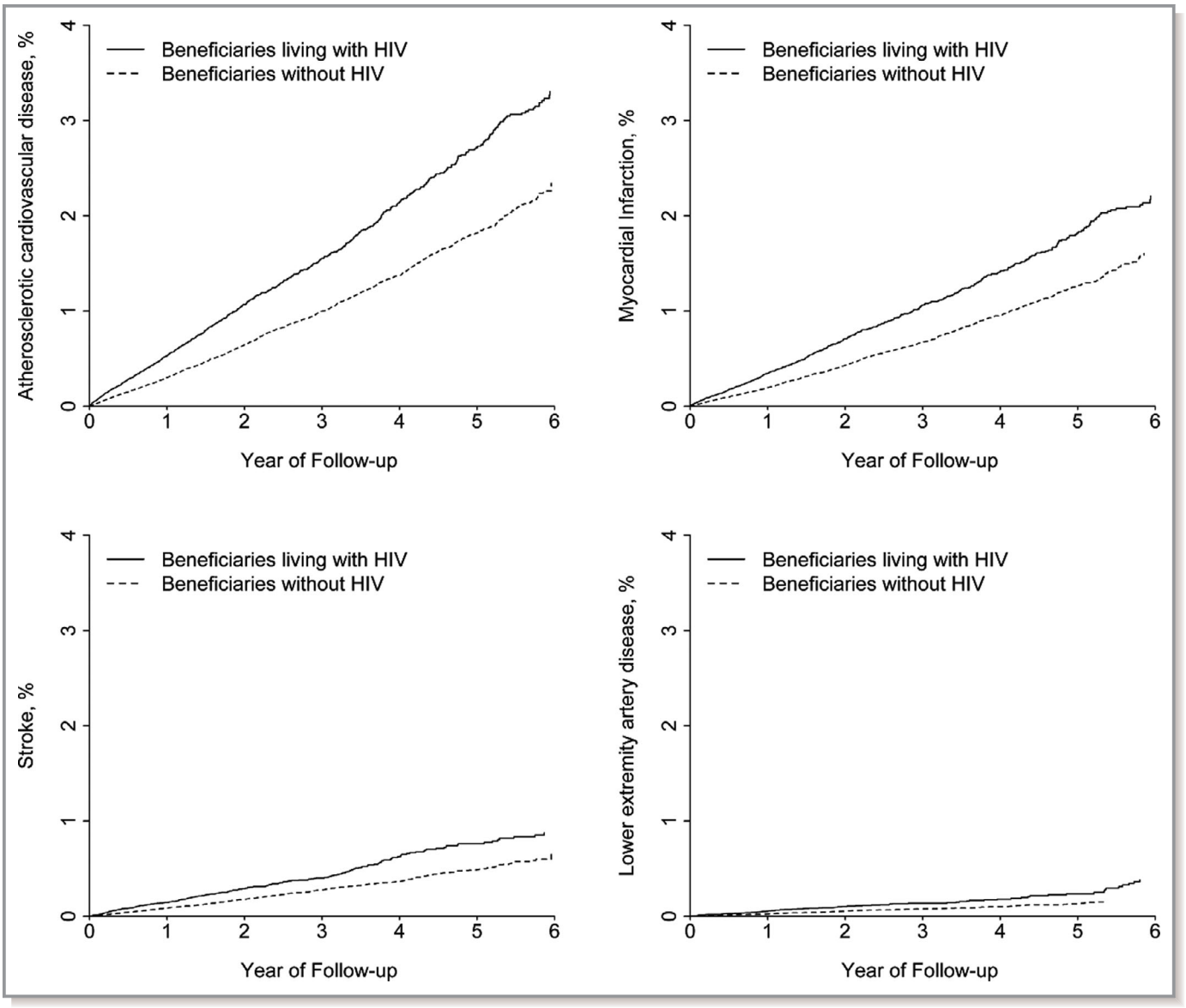

Figure 1. Cumulative incidence of atherosclerotic cardiovascular disease, myocardial infarction, stroke, and lower extremity artery disease hospitalizations among beneficiaries with HIV and age-, sex-, and calendar year–matched beneficiaries without HIV in the MarketScan database. Atherosclerotic cardiovascular disease includes myocardial infarction, stroke, and lower extremity artery disease hospitalizations.

Table 2. Rate and Hazard Ratios for ASCVD, MI, Stroke, and LEAD Hospitalizations Among Beneficiaries With HIV Versus Age-, Sex-, and Calendar Year–Matched Beneficiaries Without HIV in the MarketScan Database

Variables	Beneficiaries Without HIV (n=329 704)	Beneficiaries With HIV (n=82 426)
ASCVD		
Events	2356	931
Follow-up in person-years	675 955	168 294
Rate (95% CI), per 1000 person-years	3.49 (3.34–3.63)	5.53 (5.18–5.89)
Hazard ratio (95% CI)		
Unadjusted	1 (Reference)	1.57 (1.46–1.70)
Model 1	1 (Reference)	1.51 (1.40–1.64)
Model 2	1 (Reference)	1.29 (1.18–1.40)
MI		
Events	1586	604
Follow-up in person-years	677 211	168 780
Rate (95% CI), per 1000 person-years	2.34 (2.23–2.46)	3.58 (3.29–3.86)
Hazard ratio (95% CI)		
Unadjusted	1 (Reference)	1.53 (1.39–1.68)
Model 1	1 (Reference)	1.47 (1.34–1.62)
Model 2	1 (Reference)	1.26 (1.13–1.39)
Stroke		
Events	638	253
Follow-up in person-years	678 673	169 412
Rate (95% CI), per 1000 person-years	0.94 (0.87–1.01)	1.49 (1.31–1.68)
Hazard ratio (95% CI)		
Unadjusted	1 (Reference)	1.59 (1.37–1.84)
Model 1	1 (Reference)	1.50 (1.29–1.75)
Model 2	1 (Reference)	1.30 (1.11–1.52)
LEAD		
Events	212	110
Follow-up in person-years	679 271	169 547
Rate (95% CI), per 1000 person-years	0.31 (0.27–0.35)	0.65 (0.53–0.77)
Hazard ratio (95% CI)		
Unadjusted	1 (Reference)	1.96 (1.52–2.53)
Model 1	1 (Reference)	1.81 (1.40–2.35)
Model 2	1 (Reference)	1.46 (1.11–1.92)

ASCVD includes MI, stroke, and LEAD hospitalizations. The median (maximum) follow-up for all outcome events was 1.6 (6.0) years. Model 1 adjusts for age, sex, calendar year, geographic region of residence, history of coronary heart disease, diabetes mellitus, stroke, peripheral artery disease, and heart failure. Model 2 adjusts for variables in model 1 plus chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, statin use and statin intensity, and nonstatin lipid-lowering medication use. ASCVD indicates atherosclerotic cardiovascular disease; LEAD, lower extremity artery disease; MI, myocardial infarction.

modification between statin use and HIV status on any of the outcomes after multivariable adjustment (all *P* values for interaction>0.10). Hazard ratios for ASCVD, MI, stroke, and LEAD hospitalization associated with HIV infection across subgroups defined by beneficiary characteristics stratified by statin use are shown in Tables S6 through S9.

Discussion

In the current analysis of US adults with commercial or Medicare health insurance, those with HIV had a higher risk for ASCVD events versus their counterparts without HIV. The risks for MI, stroke, and LEAD hospitalizations were each higher in

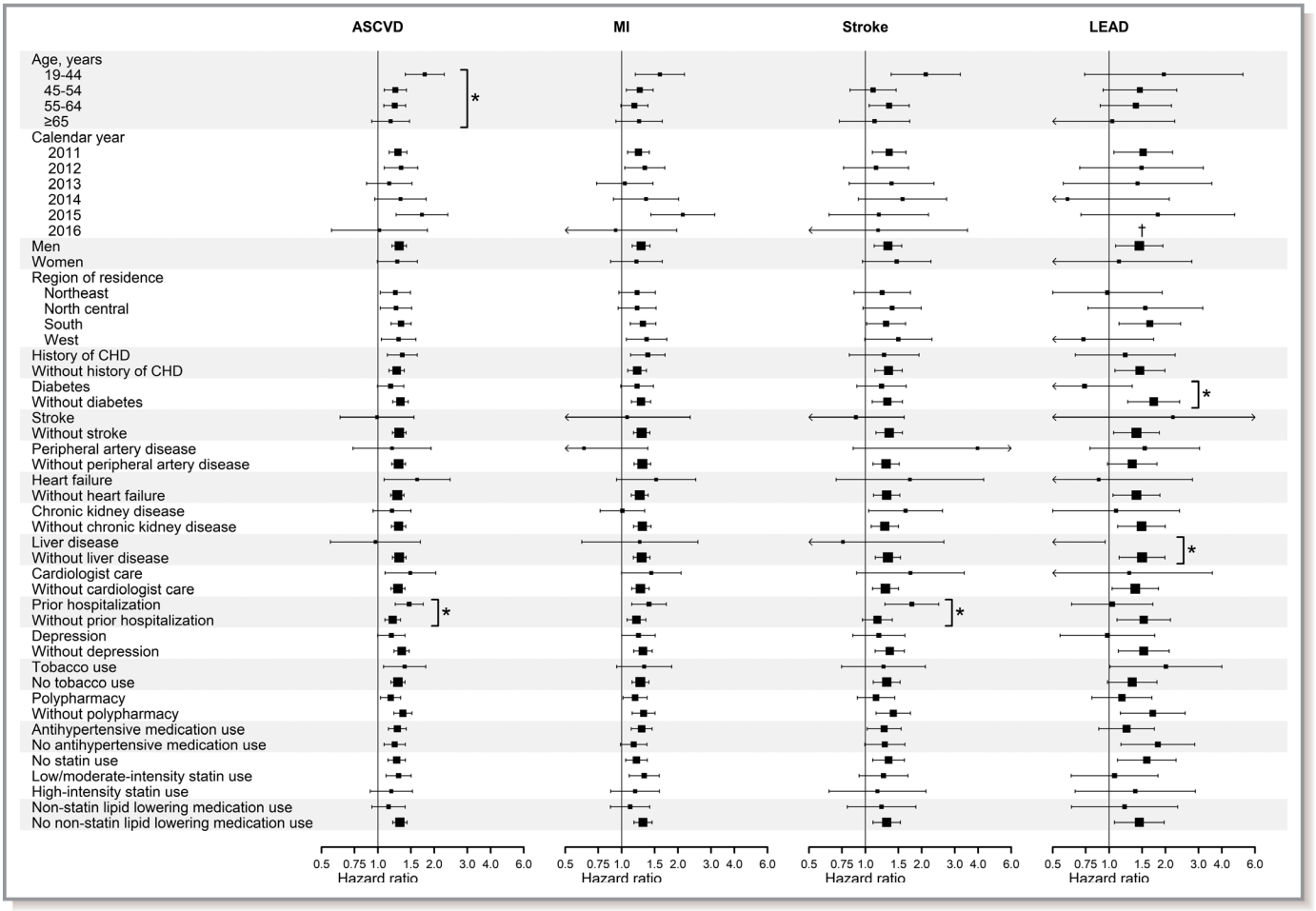

Figure 2. Hazard ratios (HRs) for atherosclerotic cardiovascular disease (ASCVD), myocardial infarction (MI), stroke, and lower extremity artery disease (LEAD) hospitalizations among beneficiaries with vs without HIV across subgroups defined by beneficiary characteristics. Squares represent mean point estimates for HRs, and horizontal bars represent 95% CIs. HRs and 95% CIs are shown in Table S4. HRs include adjustment for age, sex, calendar year, geographic region of residence, history of coronary heart disease (CHD), diabetes mellitus, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, statin use and statin intensity, and nonstatin lipid-lowering medication use. *$P<0.05$ comparing HRs for outcome events associated with HIV infection across subgroups. All other P values comparing HRs for outcome events associated with HIV infection across subgroups defined by beneficiary characteristics were ≥0.05. †Data not shown given the small number of events. Specifically, there were 6 LEAD hospitalizations during follow-up among beneficiaries in 2016.

beneficiaries with versus without HIV. The higher risk for ASCVD events associated with HIV was present within most subgroups and did not differ between people taking and not taking a statin. Results from the current analysis suggest that US adults with HIV continue to have a higher risk for ASCVD events versus those without HIV in the contemporary era, despite more extensive use of ART and increased use of statin therapy.

A meta-analysis of observational studies conducted between 1990 and 2015 found that the risk ratio associated with HIV infection was 1.79 (95% CI, 1.54–2.08) for MI and 2.56 (95% CI, 1.43–4.81) for stroke.[6] This meta-analysis included 4 studies from the United States that were all conducted before 2006. Data from a cohort study evaluating MI risk from 1996 to 2011 in Kaiser Permanente Southern California and Kaiser Permanente Northern California health plan members with and without HIV found that the multivariable-adjusted relative risk for MI associated with HIV infection declined over time, from 1.8 (95% CI, 1.3–2.6) in 1996 to 1999 to 1.0 (95% CI, 0.7–1.4) in 2010 to 2011.[12] Both Kaiser Permanente Southern California and Kaiser Permanente Northern California use a system-wide, integrated risk reduction strategy that may result in higher use of preventive interventions, lower viral loads, and higher CD4 levels versus patients receiving care elsewhere in the United States.[12,13] Therefore, these results may not be generalizable to all US adults with HIV. Results from the current analysis of a contemporary cohort of US adults with various employer-sponsored healthcare plans or Medicare supplemental health care suggest that US adults with HIV continue to have a higher risk for ASCVD, including MI, stroke, and LEAD

Table 3. Risk and Hazard Ratios for ASCVD, MI, Stroke, and LEAD Hospitalizations Among Beneficiaries With HIV Versus Age-, Sex-, and Calendar Year–Matched Beneficiaries Without HIV, Stratified by Statin Use in the MarketScan Database

Variables	Taking Statin Therapy		Not Taking Statin Therapy		*P* Value*
	Beneficiaries Without HIV (n=53 842)	Beneficiaries With HIV (n=15 619)	Beneficiaries Without HIV (n=275 862)	Beneficiaries With HIV (n=66 807)	
ASCVD					
Events	920	366	1436	565	. . .
Follow-up in person-years	118 585	35 211	557 370	133 083	. . .
Rate (95% CI), per 1000 person-years	7.76 (7.26–8.26)	10.39 (9.33–11.46)	2.58 (2.44–2.71)	4.25 (3.90–4.60)	. . .
Hazard ratio (95% CI)					
Unadjusted	1 (Reference)	1.33 (1.18–1.50)	1 (Reference)	1.63 (1.48–1.80)	0.01
Model 1	1 (Reference)	1.44 (1.27–1.63)	1 (Reference)	1.50 (1.36–1.66)	0.50
Model 2	1 (Reference)	1.28 (1.12–1.46)	1 (Reference)	1.24 (1.12–1.39)	0.90
MI					
Events	635	253	951	351	. . .
Follow-up in person-years	119 040	35 396	558 171	133 384	. . .
Rate (95% CI), per 1000 person-years	5.33 (4.92–5.75)	7.15 (6.27–8.03)	1.70 (1.60–1.81)	2.63 (2.36–2.91)	. . .
Hazard ratio (95% CI)					
Unadjusted	1 (Reference)	1.34 (1.16–1.55)	1 (Reference)	1.54 (1.37–1.74)	0.14
Model 1	1 (Reference)	1.44 (1.24–1.67)	1 (Reference)	1.42 (1.26–1.62)	>0.99
Model 2	1 (Reference)	1.29 (1.10–1.51)	1 (Reference)	1.18 (1.03–1.35)	0.47
Stroke					
Events	225	85	413	168	. . .
Follow-up in person-years	119 737	35 739	558 936	133 672	. . .
Rate (95% CI), per 1000 person-years	1.88 (1.63–2.12)	2.38 (1.87–2.88)	0.74 (0.67–0.81)	1.26 (1.07–1.45)	. . .
Hazard ratio (95% CI)					
Unadjusted	1 (Reference)	1.27 (0.99–1.63)	1 (Reference)	1.70 (1.42–2.03)	0.06
Model 1	1 (Reference)	1.40 (1.08–1.81)	1 (Reference)	1.55 (1.28–1.86)	0.38
Model 2	1 (Reference)	1.25 (0.95–1.64)	1 (Reference)	1.30 (1.07–1.58)	0.61
LEAD					
Events	102	45	110	65	. . .
Follow-up in person-years	119 898	35 749	559 373	133 798	. . .
Rate (95% CI), per 1000 person-years	0.85 (0.69–1.02)	1.26 (0.89–1.63)	0.20 (0.16–0.23)	0.49 (0.37–0.60)	. . .
Hazard ratio (95% CI)					
Unadjusted	1 (Reference)	1.36 (0.92–2.03)	1 (Reference)	2.35 (1.68–3.29)	0.04
Model 1	1 (Reference)	1.52 (1.01–2.27)	1 (Reference)	2.00 (1.42–2.80)	0.27
Model 2	1 (Reference)	1.27 (0.83–1.94)	1 (Reference)	1.62 (1.13–2.32)	0.33

ASCVD includes MI, stroke, and LEAD hospitalizations. Model 1 adjusts for age, sex, calendar year, geographic region of residence, history of coronary heart disease, diabetes mellitus, stroke, peripheral artery disease, and heart failure. Model 2 adjusts for variables in model 1 plus chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, and nonstatin lipid-lowering medication use. ASCVD indicates atherosclerotic cardiovascular disease; LEAD, lower extremity artery disease; MI, myocardial infarction.

*Comparing hazard ratios associated with HIV infection among beneficiaries taking vs not taking statin therapy.

hospitalizations. These results are consistent with a prior publication of the VACS (Veterans Aging Cohort Study) conducted from 2003 to 2014, showing that people with HIV have a higher risk for LEAD events compared with their counterparts without HIV.[16]

The current results highlight the need for implementing interventions aimed to reducing the excess risk for ASCVD among individuals with HIV in the contemporary era. According to the 2018 American Heart Association and American College of Cardiology guideline on the management of blood cholesterol, HIV should be considered as a risk-enhancing factor for ASCVD when starting a clinician-patient discussion on statin therapy initiation.[17] The importance of ASCVD prevention and treatment in people with HIV was further stressed in the 2019 American Heart Association Scientific Statement "Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV."[7] In the current analysis, adults with HIV had a higher prevalence of chronic kidney disease, tobacco use, and use of antihypertensive medication in addition to a higher risk for ASCVD events versus their counterparts without HIV. Despite their higher prevalence of cardiovascular risk factors and higher risk for ASCVD events, the proportion of adults with HIV who were taking a statin was similar to those without HIV. Although we were not able to assess all indications for statin use (eg, low-density lipoprotein cholesterol [LDL-C] $\geq$190 mg/dL), only 16.3% of beneficiaries with HIV were taking a statin, suggesting that statin therapy may be underused in this high-risk population. A higher prevalence of comorbidities, including nonalcoholic fatty liver disease/lipodystrophy, viral hepatitis, chronic kidney disease, and polypharmacy, and concerns of drug interactions with certain classes of ART (eg, PIs and cobicistat) may contribute to an underuse of statin therapy in beneficiaries with HIV.[18]

Several factors may contribute to the higher risk for ASCVD events among beneficiaries with versus without HIV. The LDL-C reduction after the initiation of a statin may be smaller among patients with HIV.[19] NNRTIs reduce blood-statin levels and diminish the LDL-C response to statins.[20] As a result, high-risk HIV patients taking a statin who are treated with NNRTIs may have higher LDL-C levels than their counterparts without HIV. In the current analysis, 44.2% of beneficiaries with HIV were taking an NNRTI. It is possible that a small LDL-C reduction with statins among people with HIV may have contributed to the higher risk for ASCVD events associated with HIV infection in the current study. Other mechanisms that may contribute to the higher risk for ASCVD events associated with HIV infection include higher concentrations of atherogenic remnant lipoproteins,[21] impaired macrophage cholesterol efflux,[22,23] and a higher prevalence of nonlipid risk factors, such as smoking,[24] visceral adiposity,[25,26] insulin resistance,[26,27] chronic kidney disease,[28] chronic inflammation and immune activation,[29,30] and coagulation disorders.[29,31] In 3 large international HIV treatment trials, higher biomarkers of inflammation (interleukin-6 and high sensitivity CRP [C-reactive protein]) and coagulation (D-dimer) were associated with a greater risk of a fatal ASCVD event and all-cause mortality.[31]

Some ARTs can increase the risk for ASCVD events. Prior studies have reported that the PIs indinavir and ritonavir-boosted lopinavir increase the risk for cardiovascular events.[9,32] Currently, the most commonly used ritonavir-boosted PIs are darunavir and atazanavir.[4,33] In the prospective D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, the use of ritonavir-boosted darunavir but not ritonavir-boosted atazanavir was associated with a higher risk of cardiovascular events.[9,32] We have previously shown that the use of PI-based ART regimens declined from 50.8% in 2007 to 25.5% in 2015 among beneficiaries with HIV in the MarketScan database.[18] It is not known whether the reduction in PI-based ART among people with HIV will be accompanied by subsequent declines in ASCVD events.

Currently, there are no data from large clinical trials to guide interventions for the prevention of ASCVD in people with HIV. Despite the lack of data, statin therapy may have antiatherothrombotic properties in HIV-infected people, beyond LDL-C lowering, because of direct effects on reducing atherogenic lipoproteins and indirect effects on mitigating proinflammatory responses.[30,34] The contribution of statin therapy to reduce ASCVD events in people with HIV is being examined in the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV).[35] Specifically, REPRIEVE is testing whether pitavastatin reduces ASCVD risk among low- to moderate-risk patients with HIV who have LDL-C $<$130 mg/dL. Pitavastatin has no major drug interactions with ART regimens and is considered a safer agent in HIV-infected patients. Results from REPRIEVE may expand current indications for statin therapy among people with HIV.

The current analysis has several strengths, including using contemporary data from a large, nationwide cohort of US adults. Patients were followed for up to 6 years. Beneficiaries with HIV were matched by age, sex, and calendar year to controls without HIV selected from the same data source. The current analysis also has potential limitations. We analyzed data from beneficiaries with and without HIV who had commercial health insurance or Medicare supplemental health insurance. Therefore, results from the current study may not be generalizable to adults with HIV without health insurance. We used claims-based algorithms to identify cardiovascular risk factors that may result in some misclassification. The algorithm used to define tobacco use has high specificity, but low sensitivity.[36] Therefore, tobacco use was likely underestimated in the current study. Frazier and colleagues estimated that the prevalence of smoking in 2014 was 33.6% among adults with HIV in the Medical Monitoring Project, a surveillance system of US adults with HIV, and 16.8% among US adults from the

general population using data from the National Health Interview Survey.[37] Data on race and ethnicity, diet, exercise, illicit drug use, and mortality are not available in MarketScan. Data on LDL-C and other lipids and estimated glomerular filtration rate are not available for most beneficiaries in the MarketScan database and, therefore, were not analyzed. In addition, we did not have access to HIV viral load, CD4 count, and inflammatory markers to explore the potential contribution of immunodeficiency and residual inflammatory risk, which may play a role in the risk for ASCVD events among individuals with HIV. We defined statin use with pharmacy fills in the 365 days before each beneficiary's index date. Some beneficiaries may have stopped or started taking a statin after their index date, which may result in misclassification.

Conclusions

In the current analysis of contemporary data, US adults with health insurance and HIV had a higher risk for ASCVD compared with their counterparts without HIV. Beneficiaries with HIV also had a higher risk for MI, stroke, and LEAD hospitalizations versus their counterparts without HIV when each of these outcomes was analyzed separately. The higher risk of ASCVD among US adults with versus without HIV was present for those taking and not taking a statin. Clinicians should assess ASCVD risk for their patients with HIV and provide guideline-recommended treatment to lower this risk.

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SUPPLEMENTAL MATERIAL

Table S1. List of antiretroviral therapy included in the current analysis by drug classes.

Drug class	Medications
Nucleoside reverse transcriptase inhibitors	Abacavir Didanosine Stavudine Zidovudine
Non-nucleoside reverse transcriptase inhibitors	Delavirdine Efavirenz Etravirine Nevirapine Rilpivirine
Protease inhibitors	Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Nelfinavir Ritonavir (excluding combinations containing paritaprevir) Saquinavir Tipranavir
Fusion inhibitors	Enfuvirtide
Entry inhibitors	Maraviroc
Integrase strand transfer inhibitors	Dolutegravir Elvitegravir Raltegravir
Pharmacokinetic enhancers	Cobicistat

Lamivudine, tenofovir and emtricitabine were not included in the list of antiretroviral drugs as these medications are also used to treat hepatitis C infection or for human immunodeficiency virus pre-exposure prophylaxis.

Table S2. Definitions for beneficiary characteristics analyzed in the current study.

Characteristic	Definition
Age	Calculated on the index date using MarketScan beneficiary summary data.
Sex	Based on MarketScan beneficiary summary data.
Calendar year	Based on the index date.
Geographic region of residence	Based on MarketScan beneficiary summary data.
History of CHD[1]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with an ICD-9 diagnosis code of 410.xx-414.xx, V45.81 or V45.82. (b) At least 1 outpatient physician evaluation and management claim with an ICD-9 diagnosis code of 410.xx-414.xx, V45.81 or V45.82. (c) At least 1 inpatient or outpatient claim with an ICD-9 procedure code of 00.66, 36.0, 36.01-36.19, 36.2 or a current procedural terminology (CPT) code of 33510-33519, 33521-33523, 33530, 33533-33536, 92980-92982, 92984, 92995, 92996, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with an ICD-10 diagnosis code of I21.09, I21.19, I21.11, I21.29, I21.4, I21.3, I25.10, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z9861. (b) At least 1 outpatient physician evaluation and management claim with an ICD-10 diagnosis code of I21.09, I21.19, I21.11, I21.29, I21.4, I21.3, I25.10, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z9861. (c) At least 1 inpatient or outpatient claim with an ICD-10 procedure code of 0210, 0211, 0212, 0213, 0270, 0271, 0272, 0273, 02C0, 02C1, 02C2, 02C3, 3E07 or a CPT code 33510-33519, 33521-33523, 33530, 33533-33536, 92980-92982, 92984, 92995, 92996, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944.

Characteristic	Definition
Stroke[2]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient ICD-9 diagnosis code (any position) of 430.xx, 431.xx, 433.x1, 434.x1 or 436.x. (b) At least 1 outpatient physician evaluation and management claim with ICD-9 diagnosis code (any position) of 430.xx, 431.xx, 433.x1, 434.x1 or 436.x. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date, inclusive: (a) At least 1 inpatient ICD-10 diagnosis (primary or secondary position) of I60.xx, I61.xx, I63.xx, I67.89. (b) At least 1 outpatient physician evaluation and management claim with ICD-10 diagnoses (any position) of I60.xx, I61.xx, I63.xx, I67.89.
History of peripheral artery disease[3]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient ICD-9 diagnosis code (any position) of 440.20-440.24, 440.31, 444.2x, 443.9, or 444.81. (b) At least 2 outpatient physician evaluation and management claims with an ICD-9 diagnosis code (any position) of 440.20-440.24, 440.31, 444.2x, 443.9, or 444.81, with the 2 claims on separate days. (c) At least 1 inpatient or outpatient claim with a CPT code 37205 or 75962. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient ICD-10 diagnosis code (any position) of I70.209, I70.219, I70.229, I70.25, I70.269, I70.499, I73.9. (b) At least 2 outpatient physician evaluation and management claims with an ICD-10 diagnosis code (any position) of I70.209, I70.219, I70.229, I70.25, I70.269, I70.499, I73.9, with the 2 claims on separate days (c) At least 1 inpatient or outpatient claim with a CPT code 37205 or 75962.

Characteristic	Definition
Diabetes[4-6]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with discharge ICD-9 diagnosis (any position) of 250.xx, 357.2, 362.0x, or 366.41. (b) At least 2 outpatient physician evaluation and management claims with ICD-9 diagnosis (any position) of 250.xx, 357.2, 362.0x, or 366.41, with the 2 claims occurring at least 7 days apart (c) At least 1 prescription drug event record for an oral antidiabetic drug fill or insulin. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with a discharge ICD-10 diagnosis (any position) of E0836, E0842, E0936, E0942, E1010, E1011, E1029, E10311, E10319, E1036, E1039, E1040, E1042, E1051, E10618, E10620, E10621, E10622, E10628, E10630, E10638, E10641, E10649, E1065, E1069, E108, E109, E1100, E1101, E1129, E11311, E11319, E11329, E11339, E11349, E11359, E1136, E1139, E1140, E1142, E1151, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1310, E1336, E1342. (b) At least 2 carrier physician evaluation and management claims with ICD-10 diagnosis (any position) of E0836, E0842, E0936, E0942, E1010, E1011, E1029, E10311, E10319, E1036, E1039, E1040, E1042, E1051, E10618, E10620, E10621, E10622, E10628, E10630, E10638, E10641, E10649, E1065, E1069, E108, E109, E1100, E1101, E1129, E11311, E11319, E11329, E11339, E11349, E11359, E1136, E1139, E1140, E1142, E1151, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1310, E1336, E1342, with the 2 claims occurring at least 7 days apart. (c) At least 1 prescription drug event record for an oral antidiabetic drug fill or insulin.
History of heart failure[7]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) ≥1 inpatient claim with ICD-9 diagnosis code (any position) of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.X (b) ≥2 outpatient physician evaluation and management claims on separate calendar days with ICD-9 diagnosis code (any position) of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) ≥1 inpatient claim with ICD-10 diagnoses (any position) of I110, I130, I132, I501, I5020, I5021, I5022, I5023, I5030, I5031, I5032, I5033, I5040, I5041, I5042, I5043, I509 (b) ≥2 outpatient physician evaluation and management claims on separate calendar days with ICD-10 diagnoses (any position) of I110, I130, I132, I501, I5020, I5021, I5022, I5023, I5030, I5031, I5032, I5033, I5040, I5041, I5042, I5043, I509.

Characteristic	Definition
History of chronic kidney disease[8]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with ICD-9 diagnosis code (any position) of 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, 794.4. (b) At least 1 outpatient physician evaluation and management claim with ICD-9 diagnosis code (any position) of 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.x1, 403.x0, 404.x2, 404.x3, 404.x0, 404.x1, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, 794.4 Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) ≥1 inpatient claim with a discharge diagnosis code of chronic kidney disease (ICD-10 CM diagnosis code of A1811, A5275, C649, C689, D3000, D4100, D4120, D593, E1021, E1029, E1121, E1129, E748, I120, I129, I130, I1310, I1311, I132, I701, I722, K767, M1030, N003, N008, N009, N013, N022, N032, N033, N035, N038, N039, N040, N043, N044, N048, N049, N052, N055, N058, N059, N08, N1330, N170, N171, N172, N178, N179, N181, N182, N183, N184, N185, N186, N189, N19, N250, N251, N2581, N2589, N259, N269,Q6102, Q6119, Q612, Q613, Q614, Q615, Q618, Q6210, Q6211, Q6212, Q6231, Q6239, R944) in any discharge diagnosis position. (b) ≥1 physician evaluation and management claim with a diagnosis code of chronic kidney disease (ICD-10 diagnosis code of A1811, A5275, C649, C689, D3000, D4100, D4120, D593, E1021, E1029, E1121, E1129, E748, I120, I129, I130, I1310, I1311, I132, I701, I722, K767, M1030, N003, N008, N009, N013, N022, N032, N033, N035, N038, N039, N040, N043, N044, N048, N049, N052, N055, N058, N059, N08, N1330, N170, N171, N172, N178, N179, N181, N182, N183, N184, N185, N186, N189, N19, N250, N251, N2581, N2589, N259, N269,Q6102, Q6119, Q612, Q613, Q614, Q615, Q618, Q6210, Q6211, Q6212, Q6231, Q6239, R944) in any position.

Characteristic	Definition
Liver disease[4, 6]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with ICD-9 diagnosis code (any position) of 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0x–456.2x, 570.xx, 571.xx, 572.2x–572.8, 573.3, 573.4, 573.8, 573.9, V42.7. (b) At least 2 outpatient physician evaluation and management claims with ICD-9 diagnosis code (any position) of 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0x–456.2x, 570.xx, 571.xx, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7. Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with ICD-10 diagnosis code (any position) of B18.x, I85.xx, I86.4, I98.2, K70.x, K71.1x, K71.3-K71.5x, K71.7, K72.xx-K74.xx, K76.0, K76.2x-K76.9x, Z94.4. (b) At least 2 outpatient physician evaluation and management claims with ICD-10 diagnosis code (any position) of B18.x, I85.xx, I86.4, I98.2, K70.x, K71.1x, K71.3-K71.5x, K71.7, K72.xx-K74.xx, K76.0, K76.2x-K76.9x, Z94.4.
Depression[7, 9]	Algorithm based on ICD-9 codes: defined by any of the following using claims within 365 days prior to or on the index date. (a) At least 1 inpatient claim with ICD-9 diagnosis code (any position) of 296.2x, 296.3x, 296.5x, 300.4x, 309.xx, 311.xx. (b) At least 1outpatient physician evaluation and management claim with ICD-9 diagnosis code (any position) of 296.2x, 296.3x, 296.5x, 300.4x, 309.xx, 311.xx. (c) At least 2 pharmacy claims for amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, levomilnacipran, maprotiline, milnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, perphenazine, phenelzine, protriptyline, selegiline, sertraline, tranylcypromine, trazodone, trimipramine or venlafaxine. Algorithm based on ICD-10 codes: defined by any of the following using claims within 365 days prior to or on the index date. (a) At least 1 inpatient claim with ICD-10 diagnosis code (any position) of F20.4, F31.3x-F31.5x, F32.x, F33.xx, F34.1, F41.2, F43.2x. (b) At least 1 outpatient physician evaluation and management claim with ICD-10 diagnosis code (any position) of F20.4, F31.3x-F31.5x, F32.x, F33.xx, F34.1, F41.2, F43.2x. (c) At least 2 pharmacy claims for amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, levomilnacipran, maprotiline, milnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, perphenazine, phenelzine, protriptyline, selegiline, sertraline, tranylcypromine, trazodone, trimipramine or venlafaxine.
Cardiologist care	Defined by ≥1 outpatient physician evaluation and management claim with provider type code 250 within 365 days prior to or on the index date.

Characteristic	Definition
Any hospitalization	Defined by ≥1 inpatient claim within 365 days prior to or on the index date.
Tobacco use[10]	Algorithm based on ICD-9 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with an ICD-9 diagnosis code of 305.1, 649.0x, 989.84, or V15.82 (b) At least 1 outpatient physician evaluation and management claim with an ICD-9 diagnosis code of 305.1, 649.0x, 989.84, or V15.82 (c) At least 1 inpatient or E/M outpatient claim with a CPT code of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F (d) At least 1 pharmacy claim for nicotine or varenicline Algorithm based on ICD-10 codes: Any of the following using claims within 365 days prior to or on the index date: (a) At least 1 inpatient claim with an ICD-10 diagnosis code of F17.200, O99.330-O99.335, T65.221A, T65.222A, T65.223A, T65.224A, T65.291A, T65.292A, T65.293A, T65.294A, Z72.0, Z87.891 (b) At least 1 outpatient physician evaluation and management claim with an ICD-10 diagnosis code of F17.200, O99.330-O99.335, T65.221A, T65.222A, T65.223A, T65.224A, T65.291A, T65.292A, T65.293A, T65.294A, Z72.0, Z87.891 (c) At least 1 inpatient or E/M outpatient claim with a CPT code of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F (d) At least 1 pharmacy claim for nicotine or varenicline
Antihypertensive medication use	Defined by ≥1 prescription fill for any thiazides, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, diuretics, beta blockers, direct renin inhibitors, alpha-1 blockers, central $alpha_1$-agonists or direct vasodilators within 365 days prior to or on the index date.
Statin use and intensity	No statin use was defined by having no prescription fill for any statin dose and type within 365 days prior to or on the index date. Use of low/moderate-intensity statin was defined by ≥1 prescription fill for a statin but no high-intensity statin fills within 365 days prior to or on the index date. Use of high-intensity statin was defined by ≥1 prescription fill for any high-intensity statin in the 365 days prior to the MI hospital discharge date, inclusive. High-intensity statin includes atorvastatin 40-80 mg, rosuvastatin 20-40 mg and simvastatin 80 mg.
Non-statin lipid-lowering medication use	Defined by ≥1 prescription fill for ezetimibe, fibrates, niacin, or bile acid sequestrants, within 365 days prior to or on the index date.
Polypharmacy	Defined by having prescription fills for ≥10 different medications (based on the generic names) within 365 days prior to or on the index date. Fills for the same generic name were counted only once. For example, 10 prescription fills for atorvastatin were count as filling 1 medication.

CHD: coronary heart disease; CPT: current procedural terminology; ICD-9: international classification of diseases, ninth revision; ICD-10: international classification of diseases, tenth revision.

Table S3. Definition for outcomes events analyzed in the current study.

Outcome	Definition
Atherosclerotic cardiovascular disease hospitalization	Includes myocardial infarction, stroke, or lower extremity artery disease hospitalizations, as defined below
Myocardial infarction hospitalization	Overnight inpatient claim with an ICD-9 discharge diagnosis code of 410.xx except 410.x2 which represents a subsequent episode of care or an ICD-10 code I21.xx in any position.
Stroke hospitalization	Inpatient claim with an ICD-9 discharge diagnosis code of 430.xx, 431.xx, 433.x1, 434.x1 or 436.xx or an ICD-10 discharge diagnosis code of I60, I61 or I63 in the primary position.
Lower extremities artery disease hospitalization	The earliest of the following events: • An overnight inpatient claim with a discharge diagnosis code for acute limb ischemia in the primary discharge diagnosis position. • An overnight inpatient claim with a procedure code for embolectomy, thrombectomy or peripheral surgical revascularization in any position. • An overnight inpatient claim with a procedure code for thrombolysis in the absence of a discharge diagnosis code for acute myocardial infarction, ischemic stroke or pulmonary embolism in any position. • An overnight inpatient claim with a procedure code for lower extremity amputation above the ankle in any position, in the absence of a discharge diagnosis code for traumatic amputation of a leg on the same hospitalization. Amputations were counted as an event only if the patient had ≥1 inpatient or outpatient claim with a diagnosis code for peripheral artery disease in any position prior to or on the date of the amputation. *List of codes:* ICD9 diagnosis codes for acute limb ischemia: 444.0, 444.01, 444.09, 444.22, 444.81. ICD10 diagnosis codes for acute limb ischemia: I74.01, I74.09, I74.3, I74.5. CPT procedure codes for embolectomy or thrombectomy: 34201, 34203. ICD9 procedure codes for peripheral surgical revascularization: 38.08, 38.16, 38.18, 38.38, 38.48, 38.68, 38.88, 39.25, 39.29. ICD10 procedure codes for peripheral surgical revascularization: 0312096, 0312097, 0312098, 0312099, 031209B, 031209C, 03120A6, 03120A7, 03120A8, 03120A9, 03120AB, 03120AC, 03120J6, 03120J7, 03120J8, 03120J9, 03120JB, 03120JC, 03120K6, 03120K7, 03120K8, 03120K9, 03120KB, 03120KC, 03120Z6, 03120Z7, 03120Z8, 03120Z9, 03120ZB, 03120ZC, 031309B, 031309C, 03130A6, 03130A7, 03130A8, 03130A9, 03130AB, 03130AC, 03130J6, 03130J7, 03130J8, 03130J9, 03130JB, 03130JC, 03130K6, 03130K7, 03130K8, 03130K9, 03130KB,

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313099.

CPT procedure codes for peripheral surgical revascularization: 35302, 35303, 35304, 35305, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35480, 35481, 35482, 35483, 35485, 35521, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35583, 35585, 35587, 35621, 35623, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35875, 35876.

ICD9 procedure codes for thrombolysis: 99.10.

ICD10 procedure codes for thrombolysis: 3E03317, 3E04317, 3E05317, 3E06317, 3E08317.

CPT procedure codes for thrombolysis: 37184, 37211, 37213.

ICD9 diagnosis codes for acute myocardial infarction: 410.x0, 410.x1.

ICD10 diagnosis codes for acute myocardial infarction: I21.x, I21.xx.

ICD9 diagnosis codes for ischemic stroke: 433.x1, 434.x1.

ICD10 diagnosis codes for ischemic stroke: I63, I63.x, I63.xx, I63.xxx.

ICD9 diagnosis code for pulmonary embolism: 415.1x.

ICD10 diagnosis codes for pulmonary embolism: T80.0XXA, T81.718A, T81.72XA, T82.817A, T82.818A, I26.90, I26.99.

ICD9 procedure codes for lower extremity amputation above the ankle: 84.13, 84.14, 84.15, 84.16, 84.17.

ICD10 procedure codes for lower extremity amputation above the ankle: 0Y6M0Z0, 0Y6N0Z0, 0Y6H0Z3, 0Y6J0Z3, 0Y670ZZ, 0Y680ZZ, 0Y6C0Z1, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6H0Z1, 0Y6H0Z2, 0Y6J0Z1, 0Y6J0Z2, 0Y620ZZ, 0Y630ZZ, 0Y640ZZ.

CPT procedure codes for lower extremity amputation above the ankle: 27590, 27591, 27592, 27598, 27880, 27881, 27882, 27888.

ICD9 diagnosis code for traumatic amputation of a leg: 897.x.

ICD10 diagnosis codes for traumatic amputation of a leg: S78.xxxA, S88.xxxA, where xxx can be any 3-digit number.

ICD9 diagnosis codes for peripheral artery disease: 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.3, 440.30, 440.31, 440.32, 440.4, 443.9.

ICD10 diagnosis codes for peripheral artery disease: I70.2, I70.20, I70.201, I70.202, I70.203, I70.208, I70.209, I70.21, I70.211, I70.212, I70.213, I70.218, I70.219, I70.22, I70.221, I70.222, I70.223, I70.228, I70.229, I70.23, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.24, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248,

I70.249, I70.25, I70.26, I70.261, I70.262, I70.263, I70.268, I70.269, I70.29, I70.291, I70.292, I70.293, I70.298, I70.299, I70.3, I70.30, I70.301, I70.302, I70.303, I70.308, I70.309, I70.31, I70.311, I70.312, I70.313, I70.318, I70.319, I70.32, I70.321, I70.322, I70.323, I70.328, I70.329, I70.33, I70.331, I70.332, I70.333, I70.334, I70.335, I70.338, I70.339, I70.34, I70.341, I70.342, I70.343, I70.344, I70.345, I70.348, I70.349, I70.35, I70.36, I70.361, I70.362, I70.363, I70.368, I70.369, I70.39, I70.391, I70.392, I70.393, I70.398, I70.399, I70.4, I70.40, I70.401, I70.402, I70.403, I70.408, I70.409, I70.41, I70.411, I70.412, I70.413, I70.418, I70.419, I70.42, I70.421, I70.422, I70.423, I70.428, I70.429, I70.43, I70.431, I70.432, I70.433, I70.434, I70.435, I70.438, I70.439, I70.44, I70.441, I70.442, I70.443, I70.444, I70.445, I70.448, I70.449, I70.45, I70.46, I70.461, I70.462, I70.463, I70.468, I70.469, I70.49, I70.491, I70.492, I70.493, I70.498, I70.499, I70.5, I70.50, I70.501, I70.502, I70.503, I70.508, I70.509, I70.51, I70.511, I70.512, I70.513, I70.518, I70.519, I70.52, I70.521, I70.522, I70.523, I70.528, I70.529, I70.53, I70.531, I70.532, I70.533, I70.534, I70.535, I70.538, I70.539, I70.54, I70.541, I70.542, I70.543, I70.544, I70.545, I70.548, I70.549, I70.55, I70.56, I70.561, I70.56, I70.562, I70.563, I70.568, I70.569, I70.59, I70.591, I70.592, I70.593, I70.598, I70.599, I70.6, I70.60, I70.601, I70.602, I70.603, I70.608, I70.609, I70.61, I70.611, I70.612, I70.613, I70.618, I70.619, I70.62, I70.621, I70.622, I70.623, I70.628, I70.629, I70.63, I70.631, I70.632, I70.633, I70.634, I70.635, I70.638, I70.639, I70.64, I70.641, I70.642, I70.643, I70.644, I70.645, I70.648, I70.649, I70.65, I70.66, I70.661, I70.662, I70.663, I70.668, I70.669, I70.69, I70.691, I70.692, I70.693, I70.698, I70.699, I70.7, I70.70, I70.701, I70.702, I70.703, I70.708, I70.709, I70.71, I70.711, I70.712, I70.713, I70.718, I70.719, I70.72, I70.721, I70.722, I70.723, I70.728, I70.729, I70.73, I70.731, I70.732, I70.733, I70.734, I70.735, I70.738, I70.739, I70.74, I70.741, I70.742, I70.743, I70.744, I70.745, I70.748, I70.749, I70.75, I70.76, I70.761, I70.762, I70.763, I70.768, I70.769, I70.79, I70.791, I70.792, I70.793, I70.798, I70.799, I70.92, I73.9.

CPT: current procedural terminology; ICD-9: international classification of diseases, ninth revision; ICD-10: international classification of diseases, tenth revision.

Table S4. Hazard ratios for atherosclerotic cardiovascular disease, myocardial infarction, stroke and lower extremity artery disease hospitalizations among beneficiaries with versus without HIV across subgroups defined by beneficiary characteristics in the MarketScan database.

	ASCVD		Myocardial infarction		Stroke		LEAD	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Age, years								
19-44	1.78 (1.40, 2.26)		1.60 (1.18, 2.16)		2.10 (1.37, 3.21)		1.96 (0.74, 5.18)	
45-54	1.24 (1.08, 1.42)	0.04	1.25 (1.06, 1.47)	0.36	1.10 (0.83, 1.46)	0.08	1.46 (0.93, 2.30)	0.80
55-64	1.23 (1.07, 1.40)		1.17 (0.99, 1.38)		1.34 (1.05, 1.72)		1.39 (0.90, 2.16)	
≥65	1.17 (0.93, 1.48)		1.24 (0.94, 1.66)		1.12 (0.73, 1.73)		1.04 (0.48, 2.23)	
Calendar year								
2011	1.28 (1.15, 1.43)		1.23 (1.08, 1.41)		1.34 (1.09, 1.65)		1.52 (1.06, 2.18)	
2012	1.33 (1.08, 1.63)		1.33 (1.04, 1.70)		1.14 (0.76, 1.69)		1.49 (0.70, 3.19)	
2013	1.15 (0.87, 1.52)	0.44	1.04 (0.74, 1.48)	0.10	1.38 (0.82, 2.32)	0.94	1.42 (0.57, 3.53)	†
2014	1.32 (0.96, 1.81)		1.35 (0.91, 2.03)		1.58 (0.92, 2.72)		0.60 (0.17, 2.07)	
2015	1.72 (1.25, 2.36)		2.12 (1.43, 3.14)		1.18 (0.64, 2.17)		1.82 (0.71, 4.70)	
2016	1.02 (0.57, 1.85)		0.93 (0.44, 1.97)		1.17 (0.39, 3.51)		†	
Men	1.30 (1.19, 1.42)	0.89	1.27 (1.14, 1.42)	0.74	1.32 (1.11, 1.56)	0.62	1.45 (1.08, 1.93)	0.58
Women	1.27 (0.99, 1.62)		1.20 (0.87, 1.64)		1.47 (0.97, 2.25)		1.13 (0.46, 2.75)	
Region of residence								
Northeast	1.24 (1.03, 1.49)		1.21 (0.97, 1.52)		1.23 (0.87, 1.74)		0.98 (0.50, 1.92)	
North central	1.25 (1.03, 1.51)	0.97	1.21 (0.96, 1.53)	0.81	1.39 (0.97, 1.98)	0.82	1.56 (0.77, 3.16)	0.39
South	1.33 (1.18, 1.51)		1.30 (1.11, 1.52)		1.29 (1.01, 1.63)		1.65 (1.13, 2.41)	
West	1.29 (1.04, 1.59)		1.36 (1.06, 1.74)		1.50 (0.99, 2.26)		0.73 (0.31, 1.74)	
History of CHD	1.35 (1.13, 1.63)	0.56	1.38 (1.12, 1.71)	0.33	1.26 (0.82, 1.93)	0.81	1.22 (0.66, 2.25)	0.57
Without history of CHD	1.26 (1.15, 1.39)		1.21 (1.08, 1.36)		1.33 (1.12, 1.57)		1.46 (1.07, 1.98)	
Diabetes	1.17 (1.00, 1.38)	0.26	1.21 (0.99, 1.48)	0.69	1.22 (0.90, 1.65)	0.70	0.74 (0.41, 1.32)	0.01
Without diabetes	1.32 (1.20, 1.45)		1.27 (1.13, 1.43)		1.31 (1.09, 1.58)		1.73 (1.26, 2.38)	
Stroke	0.99 (0.63, 1.56)	0.27	1.07 (0.49, 2.31)	0.62	0.89 (0.49, 1.61)	0.20	2.19 (0.47, 10.15)	0.53
Without stroke	1.30 (1.20, 1.42)		1.28 (1.16, 1.42)		1.34 (1.14, 1.58)		1.40 (1.06, 1.86)	
Peripheral artery disease	1.19 (0.74, 1.93)	0.71	0.63 (0.29, 1.39)	0.08	3.97 (0.86, 18.27)	0.19	1.55 (0.79, 3.04)	0.71
Without peripheral artery disease	1.29 (1.19, 1.41)		1.29 (1.16, 1.42)		1.29 (1.10, 1.52)		1.33 (0.98, 1.80)	
Heart failure	1.62 (1.08, 2.43)	0.25	1.53 (0.94, 2.49)	0.44	1.73 (0.70, 4.29)	0.53	0.88 (0.28, 2.81)	0.44
Without heart failure	1.27 (1.17, 1.38)		1.25 (1.13, 1.39)		1.30 (1.10, 1.52)		1.40 (1.05, 1.87)	
Chronic kidney disease	1.19 (0.94, 1.50)	0.50	1.01 (0.77, 1.33)	0.11	1.64 (1.04, 2.58)	0.33	1.09 (0.50, 2.37)	0.48
Without chronic kidney disease	1.29 (1.18, 1.41)		1.29 (1.16, 1.44)		1.27 (1.08, 1.51)		1.49 (1.11, 1.99)	
Liver disease	0.97 (0.56, 1.69)	0.27	1.25 (0.61, 2.54)	0.93	0.76 (0.22, 2.62)	0.40	0.18 (0.03, 0.98)	0.01
Without liver disease	1.30 (1.20, 1.42)		1.28 (1.15, 1.41)		1.32 (1.13, 1.54)		1.50 (1.13, 1.98)	
Cardiologist care	1.49 (1.09, 2.03)	0.36	1.44 (1.00, 2.08)	0.47	1.74 (0.90, 3.37)	0.39	1.28 (0.46, 3.56)	0.90
Without cardiologist care	1.28 (1.17, 1.39)		1.26 (1.13, 1.40)		1.28 (1.09, 1.50)		1.38 (1.04, 1.84)	

Prior hospitalization	1.47 (1.24, 1.75)	0.04	1.40 (1.13, 1.73)	0.24	1.77 (1.27, 2.46)	0.02	1.04 (0.63, 1.71)	0.23
Without prior hospitalization	1.20 (1.09, 1.32)		1.20 (1.07, 1.35)		1.16 (0.97, 1.40)		1.53 (1.10, 2.12)	
Depression	1.18 (1.00, 1.40)	0.18	1.23 (1.00, 1.51)	0.63	1.18 (0.86, 1.63)	0.42	0.98 (0.55, 1.76)	0.18
Without depression	1.34 (1.22, 1.47)		1.30 (1.16, 1.46)		1.35 (1.13, 1.62)		1.53 (1.12, 2.09)	
Tobacco use	1.39 (1.07, 1.80)	0.57	1.32 (0.94, 1.85)	0.83	1.25 (0.75, 2.10)	0.92	2.01 (1.01, 4.00)	0.29
No tobacco use	1.28 (1.17, 1.39)		1.26 (1.14, 1.40)		1.30 (1.10, 1.53)		1.33 (0.98, 1.80)	
Polypharmacy	1.17 (1.03, 1.32)	0.06	1.18 (1.02, 1.37)	0.25	1.14 (0.91, 1.44)	0.21	1.17 (0.81, 1.69)	0.18
Without polypharmacy	1.36 (1.22, 1.52)		1.31 (1.14, 1.51)		1.41 (1.14, 1.74)		1.71 (1.15, 2.55)	
Antihypertensive medication use	1.27 (1.14, 1.42)	0.63	1.28 (1.13, 1.46)	0.34	1.26 (1.02, 1.55)	0.99	1.24 (0.88, 1.74)	0.18
No antihypertensive medication use	1.23 (1.08, 1.40)		1.16 (0.99, 1.37)		1.27 (0.99, 1.62)		1.82 (1.16, 2.87)	
No statin use	1.26 (1.13, 1.40)		1.20 (1.05, 1.37)		1.33 (1.09, 1.61)		1.59 (1.11, 2.28)	
Low/moderate-intensity statin use	1.29 (1.11, 1.51)	0.84	1.32 (1.10, 1.59)	0.66	1.25 (0.92, 1.68)	0.88	1.07 (0.63, 1.83)	0.48
High-intensity statin use	1.18 (0.91, 1.53)		1.18 (0.88, 1.60)		1.16 (0.64, 2.11)		1.38 (0.66, 2.89)	
Non-statin lipid lowering medication use	1.14 (0.93, 1.40)	0.23	1.11 (0.87, 1.41)	0.24	1.22 (0.80, 1.86)	0.76	1.21 (0.63, 2.32)	0.60
No non-statin lipid lowering medication use	1.31 (1.20, 1.43)		1.30 (1.16, 1.45)		1.30 (1.10, 1.54)		1.45 (1.07, 1.97)	

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio; LEAD: lower extremity artery disease.

HRs include adjustment for age, sex, calendar year, geographic region of residence, history of CHD, diabetes, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, statin use and statin intensity, and non-statin lipid-lowering medication use.

* Comparing HR for outcome events associated with HIV infection across subgroups defined by beneficiary characteristics.
† Data not shown given the small number of events. Specifically, there were 6 LEAD hospitalizations during follow-up among beneficiaries in 2016.

Table S5. Characteristics of beneficiaries with HIV and age, sex and calendar year-matched beneficiaries without HIV stratified by statin use in the MarketScan database.

	Taking statins		Not taking statins	
	Beneficiaries without HIV (n=53,842)	**Beneficiaries with HIV** (n=15,619)	**Beneficiaries without HIV** (n=275,862)	**Beneficiaries with HIV** (n=66,807)
Age, years, n (%)				
19-44	5,223 (9.7%)	2,190 (14.0%)	135,377 (49.1%)	32,960 (49.3%)
45-54	22,741 (42.2%)	6,742 (43.2%)	95,731 (34.7%)	22,876 (34.2%)
55-64	20,732 (38.5%)	5,454 (34.9%)	39,596 (14.4%)	9,628 (14.4%)
≥65	5,146 (9.6%)	1,233 (7.9%)	5,158 (1.9%)	1,343 (2.0%)
Calendar year, n (%)				
2011	24,412 (45.3%)	7,558 (48.4%)	112,104 (40.6%)	26,571 (39.8%)
2012	8,423 (15.6%)	2,366 (15.1%)	44,821 (16.2%)	10,945 (16.4%)
2013	5,467 (10.2%)	1,509 (9.7%)	31,049 (11.3%)	7,620 (11.4%)
2014	5,521 (10.3%)	1,442 (9.2%)	31,311 (11.4%)	7,766 (11.6%)
2015	4,706 (8.7%)	1,303 (8.3%)	27,386 (9.9%)	6,720 (10.1%)
2016	5,313 (9.9%)	1,441 (9.2%)	29,191 (10.6%)	7,185 (10.8%)
Male sex, n (%)	47,810 (88.8%)	13,650 (87.4%)	228,738 (82.9%)	55,487 (83.1%)
Geographic region of residence, n (%)				
Northeast	10,114 (18.8%)	3,027 (19.4%)	51,405 (18.6%)	12,303 (18.4%)
North central	12,756 (23.7%)	1,990 (12.7%)	62,688 (22.7%)	9,196 (13.8%)
South	21,658 (40.2%)	6,700 (42.9%)	10,4873 (38.0%)	31,555 (47.2%)
West	8,746 (16.2%)	3,671 (23.5%)	54,003 (19.6%)	12,886 (19.3%)
Unknown	568 (1.1%)	231 (1.5%)	2,893 (1.0%)	867 (1.3%)
History of CHD, n (%)	7,370 (13.7%)	1,905 (12.2%)	2,334 (0.8%)	910 (1.4%)
Diabetes, n (%)	14,571 (27.1%)	3,253 (20.8%)	10,148 (3.7%)	3,411 (5.1%)
History of stroke, %	547 (1.0%)	265 (1.7%)	360 (0.1%)	331 (0.5%)
History of peripheral artery disease, n (%)	353 (0.7%)	153 (1.0%)	226 (0.1%)	156 (0.2%)
History of heart failure, n (%)	585 (1.1%)	273 (1.7%)	419 (0.2%)	427 (0.6%)
Chronic kidney disease, n (%)	2,245 (4.2%)	1,218 (7.8%)	2,384 (0.9%)	2,631 (3.9%)
Liver disease, n (%)	267 (0.5%)	340 (2.2%)	1,028 (0.4%)	1,985 (3.0%)
Cardiologist care, n (%)	2,728 (5.1%)	1,229 (7.9%)	3,899 (1.4%)	1,578 (2.4%)
Any hospitalization, n (%)	4,054 (7.5%)	1,884 (12.1%)	8,927 (3.2%)	8,244 (12.3%)
Depression, n (%)	10,635 (19.8%)	4,949 (31.7%)	28,744 (10.4%)	14,720 (22.0%)
Tobacco use, n (%)	2,577 (4.8%)	1,038 (6.6%)	6,841 (2.5%)	4,602 (6.9%)
Polypharmacy, n (%)	15,515 (28.8%)	8,611 (55.1%)	17,368 (6.3%)	18,991 (28.4%)
Antihypertensive medication use, n (%)	35,045 (65.1%)	8,762 (56.1%)	42,688 (15.5%)	14,978 (22.4%)
Statin use, n (%)				
No statin use	-	-	275,862 (100%)	66,807 (100%)
Low/moderate-intensity statin use	44,421 (82.5%)	12,049 (77.1%)	-	-
High-intensity statin use	9,421 (17.5%)	3,570 (22.9%)	-	-
Non-statin lipid-lowering medication use, n (%)	9,266 (17.2%)	3,599 (23.0%)	5,478 (2.0%)	2,959 (4.4%)
ART use, n (%)	-	15,243 (97.6%)	-	63,852 (95.6%)
NRTIs	-	6,672 (42.7%)	-	34,700 (51.9%)
NNRTI	-	6,768 (43.3%)	-	29,697 (44.5%)
Protease inhibitors	-	4,228 (27.1%)	-	16,485 (24.7%)
Other	-	3,043 (19.5%)	-	14,847 (22.2%)

ART: antiretroviral therapy; CHD: coronary heart disease; HIV: human immunodeficiency virus; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors.
Other ART includes fusion inhibitors, entry inhibitors, integrase strand transfer inhibitors, and pharmacokinetic enhancers.

Table S6. Hazard ratios for an atherosclerotic cardiovascular disease hospitalization among beneficiaries with versus without HIV across subgroups defined by beneficiary characteristics stratified by statin use.

	Taking a statin		Not taking a statin	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Age, years				
19-44	1.36 (0.79, 2.33)		1.80 (1.38, 2.36)	
45-54	1.43 (1.13, 1.80)	0.76	1.14 (0.97, 1.35)	0.03
55-64	1.20 (0.99, 1.47)		1.23 (1.03, 1.48)	
≥65	1.26 (0.91, 1.74)		1.06 (0.75, 1.50)	
Calendar year				
2011	1.29 (1.09, 1.53)		1.23 (1.07, 1.42)	
2012	1.24 (0.89, 1.72)		1.30 (1.00, 1.69)	
2013	1.38 (0.87, 2.19)	>0.99	0.92 (0.64, 1.33)	0.08
2014	1.17 (0.70, 1.97)		1.36 (0.90, 2.04)	
2015	1.24 (0.65, 2.35)		1.93 (1.33, 2.80)	
2016	1.29 (0.49, 3.36)		0.74 (0.33, 1.63)	
Men	1.28 (1.12, 1.48)	0.82	1.27 (1.13, 1.42)	0.99
Women	1.22 (0.82, 1.82)		1.26 (0.92, 1.73)	
Region of residence				
Northeast	1.33 (1.00, 1.77)		1.12 (0.88, 1.42)	
North central	1.28 (0.94, 1.74)	0.57	1.21 (0.94, 1.55)	0.61
South	1.19 (0.97, 1.47)		1.40 (1.19, 1.64)	
West	1.43 (1.03, 1.97)		1.17 (0.88, 1.55)	
History of CHD	1.29 (1.04, 1.61)	0.96	1.55 (1.09, 2.21)	0.24
Without history of CHD	1.28 (1.08, 1.50)		1.22 (1.09, 1.37)	
Diabetes	1.11 (0.89, 1.38)	0.14	1.24 (0.96, 1.60)	0.99
Without diabetes	1.38 (1.17, 1.63)		1.24 (1.10, 1.39)	
Stroke	0.67 (0.35, 1.30)	0.06	1.41 (0.71, 2.79)	0.66
Without stroke	1.32 (1.15, 1.50)		1.25 (1.12, 1.39)	
Peripheral artery disease	0.75 (0.36, 1.55)	0.13	2.15 (1.03, 4.49)	0.11
Without peripheral artery disease	1.31 (1.14, 1.49)		1.23 (1.11, 1.38)	
Heart failure	2.43 (1.40, 4.20)	0.02	1.18 (0.64, 2.17)	0.87
Without heart failure	1.24 (1.08, 1.42)		1.25 (1.12, 1.39)	
Chronic kidney disease	1.28 (0.93, 1.77)	0.97	1.07 (0.77, 1.49)	0.32
Without chronic kidney disease	1.28 (1.11, 1.48)		1.26 (1.12, 1.41)	
Liver disease	4.07 (1.24, 13.32)	0.07	0.52 (0.26, 1.02)	0.01
Without liver disease	1.25 (1.10, 1.43)		1.28 (1.15, 1.43)	
Cardiologist care	1.53 (1.04, 2.24)	0.31	1.52 (0.90, 2.59)	0.49
Without cardiologist care	1.24 (1.08, 1.43)		1.25 (1.12, 1.40)	
Prior hospitalization	1.58 (1.23, 2.04)	0.05	1.37 (1.09, 1.73)	0.25
Without prior hospitalization	1.18 (1.01, 1.38)		1.18 (1.04, 1.33)	
Depression	1.30 (1.02, 1.65)	0.89	1.04 (0.82, 1.32)	0.07
Without depression	1.27 (1.09, 1.49)		1.32 (1.17, 1.49)	
Tobacco use	1.33 (0.88, 2.01)	0.85	1.40 (0.99, 1.98)	0.45
No tobacco use	1.26 (1.10, 1.45)		1.23 (1.10, 1.38)	
Polypharmacy	1.17 (1.00, 1.38)	0.05	1.14 (0.95, 1.37)	0.33
Without polypharmacy	1.55 (1.24, 1.93)		1.27 (1.11, 1.45)	
Antihypertensive medication use	1.27 (1.10, 1.47)	0.97	1.25 (1.07, 1.47)	0.65
No antihypertensive medication use	1.28 (0.95, 1.72)		1.20 (1.03, 1.38)	
Non-statin lipid lowering medication use	1.04 (0.81, 1.34)	0.08	1.40 (0.97, 2.01)	0.59
No non-statin lipid lowering medication use	1.37 (1.18, 1.60)		1.24 (1.11, 1.38)	

CHD: coronary heart disease; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio.

Hazard ratios include adjustment for age, sex, calendar year, geographic region of residence, history of CHD, diabetes, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, and non-statin lipid-lowering medication use.

* Comparing HR for atherosclerotic cardiovascular disease hospitalizations associated with HIV infection across subgroups defined by beneficiary characteristics.

Table S7. Hazard ratios for a myocardial infarction hospitalization among beneficiaries with versus without HIV across subgroups defined by beneficiary characteristics stratified by statin use.

	Taking a statin		Not taking a statin	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Age, years				
19-44	1.14 (0.60, 2.18)		1.66 (1.18, 2.35)	
45-54	1.50 (1.15, 1.96)	0.57	1.10 (0.90, 1.35)	0.19
55-64	1.17 (0.92, 1.50)		1.14 (0.90, 1.44)	
≥65	1.34 (0.90, 1.98)		1.08 (0.71, 1.66)	
Calendar year				
2011	1.28 (1.05, 1.56)		1.16 (0.97, 1.39)	
2012	1.21 (0.81, 1.80)		1.32 (0.96, 1.81)	
2013	1.48 (0.86, 2.53)	0.92	0.71 (0.44, 1.14)	0.01
2014	1.14 (0.58, 2.24)		1.41 (0.84, 2.36)	
2015	1.84 (0.86, 3.93)		2.14 (1.34, 3.42)	
2016	1.93 (0.62, 5.99)		0.47 (0.15, 1.47)	
Men	1.32 (1.12, 1.56)	0.41	1.19 (1.04, 1.37)	0.67
Women	1.05 (0.65, 1.70)		1.30 (0.85, 1.98)	
Geographic region of residence				
Northeast	1.38 (0.98, 1.94)		1.01 (0.74, 1.37)	
North central	1.46 (1.02, 2.07)	0.75	1.04 (0.75, 1.42)	0.46
South	1.15 (0.89, 1.48)		1.37 (1.13, 1.67)	
West	1.52 (1.05, 2.20)		1.21 (0.86, 1.70)	
History of CHD	1.32 (1.03, 1.69)	0.93	1.60 (1.06, 2.41)	0.15
Without history of CHD	1.28 (1.05, 1.57)		1.15 (1.00, 1.32)	
Diabetes	1.16 (0.89, 1.50)	0.32	1.25 (0.91, 1.72)	0.74
Without diabetes	1.39 (1.14, 1.69)		1.16 (1.01, 1.35)	
Stroke	0.68 (0.22, 2.15)	0.25	1.36 (0.39, 4.78)	0.91
Without stroke	1.32 (1.13, 1.55)		1.20 (1.05, 1.37)	
Peripheral artery disease	0.40 (0.11, 1.49)	0.07	0.93 (0.29, 2.98)	0.62
Without peripheral artery disease	1.33 (1.14, 1.56)		1.20 (1.05, 1.37)	
Heart failure	2.35 (1.19, 4.65)	0.10	1.12 (0.55, 2.30)	0.93
Without heart failure	1.27 (1.08, 1.49)		1.18 (1.03, 1.35)	
Chronic kidney disease	1.17 (0.79, 1.72)	0.58	0.85 (0.57, 1.27)	0.09
Without chronic kidney disease	1.32 (1.11, 1.57)		1.21 (1.05, 1.40)	
Liver disease	5.63 (0.97, 32.61)	0.14	0.67 (0.29, 1.57)	0.17
Without liver disease	1.28 (1.09, 1.50)		1.21 (1.06, 1.39)	
Cardiologist care	1.60 (1.02, 2.50)	0.31	1.26 (0.67, 2.39)	0.88
Without cardiologist care	1.26 (1.06, 1.49)		1.20 (1.05, 1.38)	
Prior hospitalization	1.68 (1.23, 2.29)	0.08	1.17 (0.88, 1.56)	>0.99
Without prior hospitalization	1.20 (1.00, 1.44)		1.16 (1.00, 1.35)	
Depression	1.44 (1.08, 1.93)	0.41	1.01 (0.76, 1.36)	0.17
Without depression	1.26 (1.04, 1.52)		1.26 (1.09, 1.46)	
Tobacco use	1.54 (0.91, 2.62)	0.51	1.11 (0.71, 1.73)	0.76
No tobacco use	1.28 (1.08, 1.51)		1.19 (1.04, 1.37)	
Polypharmacy	1.20 (0.99, 1.46)	0.10	1.12 (0.89, 1.41)	0.64
Without polypharmacy	1.56 (1.20, 2.02)		1.18 (1.00, 1.40)	
Antihypertensive medication use	1.33 (1.12, 1.58)	0.46	1.20 (0.98, 1.46)	0.70
No antihypertensive medication use	1.16 (0.80, 1.67)		1.13 (0.95, 1.36)	
Non-statin lipid lowering medication use	1.04 (0.77, 1.40)	0.09	1.27 (0.81, 1.98)	0.77
No non-statin lipid lowering medication use	1.42 (1.18, 1.70)		1.18 (1.02, 1.35)	

CHD: coronary heart disease; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio.

Hazard ratios include adjustment for age, sex, calendar year, geographic region of residence, history of CHD, diabetes, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, and non-statin lipid-lowering medication use.

* Comparing HR for myocardial infarction hospitalizations associated with HIV infection across subgroups defined by beneficiary characteristics.

Table S8. Hazard ratios for a stroke hospitalization among beneficiaries with versus without HIV across subgroups defined by beneficiary characteristics stratified by statin use.

	Taking a statin		Not taking a statin	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Age, years				
19-44	1.67 (0.58, 4.82)		2.14 (1.34, 3.41)	
45-54	1.28 (0.75, 2.20)	0.93	1.04 (0.74, 1.45)	0.09
55-64	1.28 (0.87, 1.89)		1.39 (1.00, 1.92)	
≥65	1.10 (0.59, 2.04)		1.12 (0.61, 2.06)	
Calendar year				
2011	1.20 (0.84, 1.73)		1.38 (1.07, 1.78)	
2012	1.29 (0.69, 2.38)		1.00 (0.58, 1.73)	
2013	1.70 (0.65, 4.42)	†	1.28 (0.68, 2.42)	0.84
2014	1.28 (0.51, 3.22)		1.72 (0.86, 3.45)	
2015	0.59 (0.15, 2.37)		1.50 (0.75, 2.99)	
2016	†		0.92 (0.23, 3.73)	
Men	1.19 (0.89, 1.59)	0.27	1.37 (1.11, 1.69)	0.83
Women	1.87 (0.92, 3.82)		1.26 (0.74, 2.15)	
Geographic region of residence				
Northeast	1.20 (0.66, 2.17)		1.21 (0.78, 1.87)	
North central	0.82 (0.40, 1.69)	0.75	1.72 (1.13, 2.61)	0.53
South	1.46 (0.98, 2.18)		1.16 (0.86, 1.58)	
West	1.25 (0.60, 2.60)		1.61 (0.98, 2.66)	
History of CHD	1.17 (0.71, 1.95)	0.81	1.53 (0.66, 3.52)	0.83
Without history of CHD	1.29 (0.94, 1.77)		1.32 (1.08, 1.61)	
Diabetes	1.08 (0.72, 1.63)	0.48	1.39 (0.88, 2.18)	0.78
Without diabetes	1.32 (0.92, 1.90)		1.30 (1.04, 1.61)	
Stroke	0.62 (0.24, 1.60)	0.13	1.26 (0.52, 3.04)	>0.99
Without stroke	1.34 (1.01, 1.77)		1.32 (1.08, 1.61)	
Peripheral artery disease	†	†	†	†
Without peripheral artery disease	1.23 (0.93, 1.61)		1.31 (1.07, 1.59)	
Heart failure	1.55 (0.47, 5.17)	0.58	2.72 (0.51, 14.45)	0.36
Without heart failure	1.21 (0.91, 1.59)		1.32 (1.08, 1.60)	
Chronic kidney disease	1.42 (0.74, 2.72)	0.70	1.84 (0.95, 3.59)	0.35
Without chronic kidney disease	1.22 (0.91, 1.64)		1.29 (1.05, 1.58)	
Liver disease	†	†	†	†
Without liver disease	1.20 (0.91, 1.57)		1.36 (1.12, 1.65)	
Cardiologist care	1.52 (0.68, 3.42)	0.60	3.05 (0.88, 10.55)	0.20
Without cardiologist care	1.21 (0.91, 1.61)		1.30 (1.06, 1.58)	
Prior hospitalization	1.40 (0.87, 2.27)	0.49	2.09 (1.30, 3.33)	0.02
Without prior hospitalization	1.16 (0.84, 1.61)		1.14 (0.91, 1.43)	
Depression	0.94 (0.58, 1.52)	0.17	1.39 (0.89, 2.16)	0.86
Without depression	1.39 (1.01, 1.92)		1.31 (1.05, 1.63)	
Tobacco use	0.97 (0.41, 2.29)	0.56	1.64 (0.83, 3.25)	0.46
No tobacco use	1.25 (0.94, 1.67)		1.29 (1.05, 1.58)	
Polypharmacy	1.16 (0.84, 1.60)	0.47	1.10 (0.79, 1.54)	0.26
Without polypharmacy	1.47 (0.92, 2.33)		1.40 (1.10, 1.78)	
Antihypertensive medication use	1.14 (0.84, 1.54)	0.28	1.38 (1.04, 1.84)	0.49
No antihypertensive medication use	1.65 (0.92, 2.95)		1.20 (0.92, 1.58)	
Non-statin lipid lowering medication use	0.99 (0.58, 1.70)	0.41	1.80 (0.88, 3.68)	0.43
No non-statin lipid lowering medication use	1.32 (0.97, 1.79)		1.29 (1.06, 1.59)	

CHD: coronary heart disease; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio.

Hazard ratios include adjustment for age, sex, calendar year, geographic region of residence, history of CHD, diabetes, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, and non-statin lipid-lowering medication use.

* Comparing HR for stroke hospitalizations associated with HIV infection across subgroups defined by beneficiary characteristics.
† Data not shown given the small number of events. Specifically, among beneficiaries taking a statin, there were 6 stroke events in those in 2016, 9 stroke events in those with a history of peripheral artery disease, and 4 stroke events in those with a history of liver disease. Among beneficiaries not taking a statin, there were 3 stroke events in those with a history of peripheral artery disease and 9 stroke events in those with a history of liver disease.

Table S9. Hazard ratios for a lower extremity artery disease hospitalization among beneficiaries with versus without HIV across subgroups defined by beneficiary characteristics stratified by statin use.

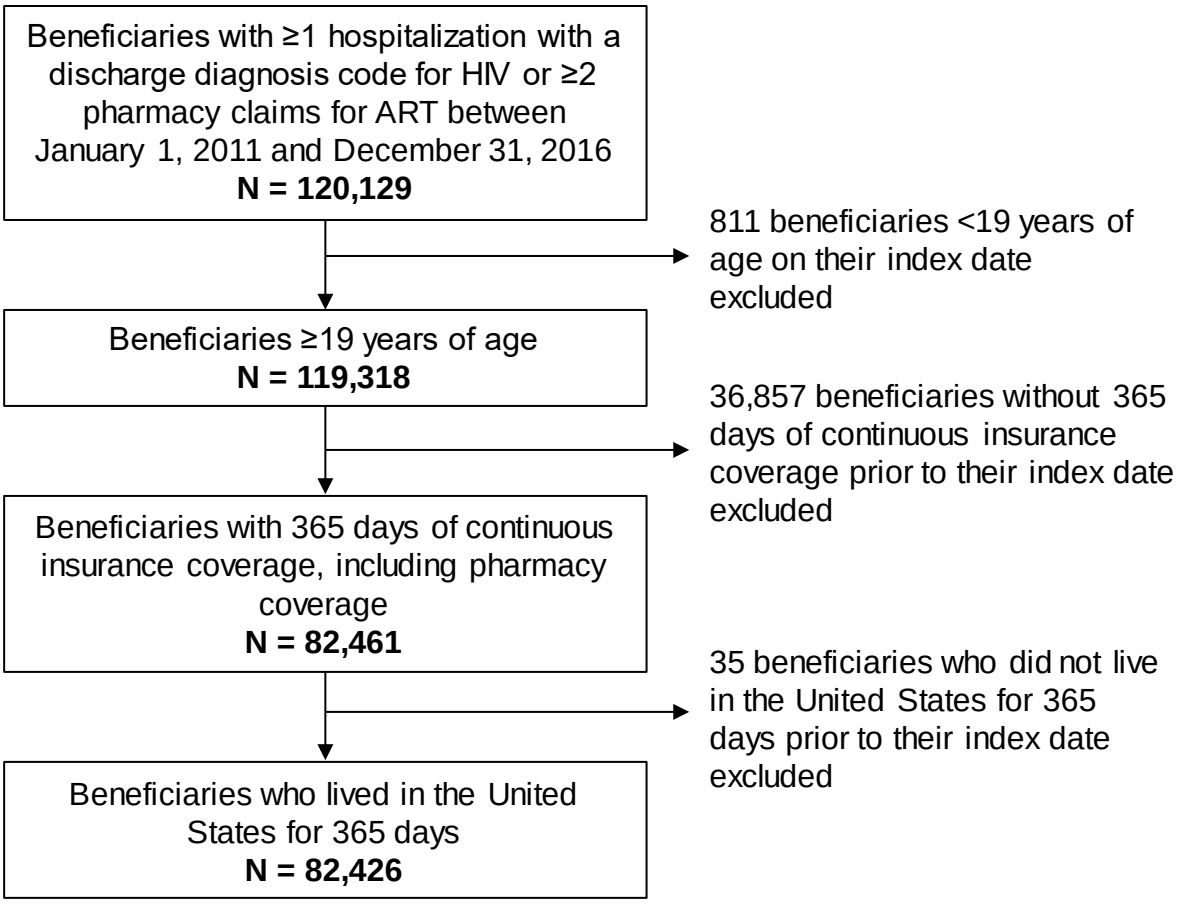
	Taking a statin		Not taking a statin	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Age, years				
19-44	1.16 (0.11, 11.82)		2.11 (0.72, 6.19)	
45-54	0.64 (0.24, 1.71)	0.31	1.95 (1.16, 3.30)	0.56
55-64	1.66 (0.94, 2.94)		1.11 (0.56, 2.20)	
≥65	0.91 (0.31, 2.64)		1.23 (0.39, 3.90)	
Calendar year				
2011	1.55 (0.90, 2.68)		1.47 (0.91, 2.39)	
2012	0.82 (0.20, 3.42)		2.70 (1.08, 6.77)	
2013	1.10 (0.28, 4.29)	†	1.43 (0.37, 5.58)	†
2014	0.71 (0.12, 4.37)		0.27 (0.03, 2.82)	
2015	†		1.78 (0.57, 5.56)	
2016	†		†	
Men	1.28 (0.83, 1.97)	0.35	1.60 (1.09, 2.37)	0.79
Women	0.43 (0.05, 3.90)		1.41 (0.51, 3.93)	
Region of residence				
Northeast	0.41 (0.13, 1.33)		1.70 (0.71, 4.06)	
North central	1.42 (0.50, 4.01)	0.41	1.91 (0.69, 5.29)	0.10
South	1.19 (0.62, 2.26)		2.04 (1.26, 3.28)	
West	2.25 (0.64, 7.95)		0.20 (0.04, 0.99)	
History of CHD	1.49 (0.72, 3.06)	0.52	0.87 (0.27, 2.77)	0.32
Without history of CHD	1.08 (0.63, 1.83)		1.65 (1.12, 2.43)	
Diabetes	0.73 (0.33, 1.63)	0.12	0.77 (0.33, 1.81)	0.09
Without diabetes	1.56 (0.93, 2.62)		1.76 (1.17, 2.65)	
Stroke	†	†	†	†
Without stroke	1.22 (0.78, 1.91)		1.53 (1.06, 2.21)	
Peripheral artery disease	1.08 (0.39, 2.95)	0.92	2.96 (0.96, 9.10)	0.17
Without peripheral artery disease	1.21 (0.75, 1.95)		1.38 (0.93, 2.05)	
Heart failure	1.62 (0.36, 7.20)	0.73	0.12 (0.00, 3.85)	0.13
Without heart failure	1.14 (0.72, 1.78)		1.62 (1.11, 2.34)	
Chronic kidney disease	1.18 (0.41, 3.36)	0.90	1.19 (0.33, 4.33)	0.63
Without chronic kidney disease	1.27 (0.79, 2.04)		1.66 (1.14, 2.42)	
Liver disease	†	†	†	†
Without liver disease	1.24 (0.81, 1.90)		1.73 (1.20, 2.49)	
Cardiologist care	1.41 (0.40, 4.97)	0.66	0.97 (0.13, 7.41)	0.62
Without cardiologist care	1.11 (0.70, 1.75)		1.57 (1.08, 2.28)	
Prior hospitalization	0.93 (0.42, 2.03)	0.43	1.22 (0.62, 2.38)	0.56
Without prior hospitalization	1.33 (0.80, 2.22)		1.66 (1.07, 2.56)	
Depression	1.38 (0.63, 3.00)	0.67	0.61 (0.25, 1.46)	0.03
Without depression	1.10 (0.66, 1.85)		1.85 (1.24, 2.75)	
Tobacco use	1.40 (0.49, 4.01)	0.80	2.43 (0.89, 6.61)	0.31
No tobacco use	1.18 (0.73, 1.89)		1.45 (0.97, 2.17)	
Polypharmacy	1.00 (0.60, 1.64)	0.20	1.50 (0.84, 2.67)	0.86
Without polypharmacy	1.80 (0.85, 3.80)		1.64 (1.02, 2.64)	
Antihypertensive medication use	1.15 (0.72, 1.83)	0.47	1.40 (0.85, 2.31)	0.44
No antihypertensive medication use	1.72 (0.64, 4.63)		1.87 (1.12, 3.13)	
Non-statin lipid lowering medication use	1.04 (0.47, 2.30)	0.74	2.88 (0.86, 9.69)	0.40
No non-statin lipid lowering medication use	1.24 (0.75, 2.06)		1.55 (1.05, 2.27)	

CHD: coronary heart disease; CI: confidence interval; HIV: human immunodeficiency virus; HR: hazard ratio.

Hazard ratios include adjustment for age, sex, calendar year, geographic region of residence, history of CHD, diabetes, stroke, peripheral artery disease, heart failure, chronic kidney disease, liver disease, cardiologist care, any hospitalization, depression, tobacco use, polypharmacy, antihypertensive medication use, and non-statin lipid-lowering medication use.

* Comparing HR for lower extremity artery disease hospitalizations associated with HIV infection across subgroups defined by beneficiary characteristics.
† Data not shown given the small number of lower extremity artery disease hospitalizations (n<10) in each cell.

Figure S1. Flow-chart of beneficiaries with HIV in the MarketScan database included in and excluded from the current analysis.



ART: antiretroviral therapy; HIV: human immunodeficiency virus.
Persons without HIV were matched 4:1 on age, sex and calendar year with persons with HIV in the MarketScan database.

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