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Statin Use Is Associated With Incident Diabetes Mellitus Among Patients in the HIV Outpatient Study

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Abstract

Introduction—Statin therapy is effective in the prevention of cardiovascular disease in the general population but has been shown to modestly increase the risk for incident diabetes mellitus (DM).

Methods—We analyzed incident DM in HIV Outpatient Study (HOPS) participants followed at 8 HIV clinic sites during 2002–2011, comparing rates among those who initiated statin therapy during that period with those who did not. Using Cox proportional hazards models, we examined the association between cumulative years of statin exposure and the risk of developing DM, after controlling for age, sex, race/ethnicity, antiretroviral history, prevalent hepatitis C, body mass index, and cumulative exposure to protease inhibitor therapy. We also adjusted for propensity scores to account for residual confounding by indication.

Results—Of 4692 patients analyzed, 590 (12.6%) initiated statin therapy and 355 (7.2%) developed DM. Incident DM was independently associated with statin therapy (adjusted hazard ratio, 1.14 per year of statin use), as well as older age, Hispanic/Latino ethnicity, non-Hispanic/Latino black race, antiretroviral-naive status, prevalent hepatitis C, and body mass index ≥30 kg/m^2 ($P < 0.05$ for all). The association of statin use with incident DM was similar in the model adjusted for propensity score.

Conclusions—Statin use was associated with a modestly increased risk of incident DM in an HIV-infected population, similar to existing data for the general population. HIV-infected patients should be monitored for glucose intolerance, but statins should not be withheld if clinically indicated for cardiovascular disease risk reduction.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. For the list of HIV Outpatient Study Investigators, see Appendix 1.

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Keywords

statin; diabetes; low-density lipoprotein

INTRODUCTION

The benefit of statin therapy in primary and secondary prevention of myocardial infarctions has been established in multiple large studies.[1–4] More recently, the association of statin use with increased risk for development of diabetes mellitus (DM) has been noted.[5–8] The JUPITER study found a 25% increase in incident DM with the use of rosuvastatin.[9] In a meta-analysis of 13 statin trials consisting of 91,120 subjects, Sattar et al[10] found a 9% increased risk of incident DM in patients receiving statin therapy. In addition, the association of statins with incident DM has been found to be more prominent in certain populations such as the elderly, women, and Asians.[11,12]

Cardiovascular disease (CVD) in HIV-infected population occurs more frequently when compared with HIV-uninfected controls.[13] Not only are the cohorts of HIV-infected individuals in the United States enriched in persons with traditional cardiovascular risk factors such as tobacco use and obesity but also they are steadily aging, which increases their risk of developing CVD.[14] In addition to these traditional CVD risk factors, the dyslipidemic effects of some antiretroviral agents and the chronic inflammation resulting from HIV infection may also contribute to CVD risk.[15–17] As such, increasing numbers of HIV-infected patients are being prescribed statins. We studied patients enrolled in the HIV Outpatient Study (HOPS) to determine whether the use of statin therapy was associated with an increased incidence of DM.

METHODS

The HIV Outpatient Study

The HOPS is an open prospective cohort study of HIV-infected patients in 6 US cities at 9 public, university, and private clinics that specialize in the treatment of the HIV disease. Since HOPS inception in 1993, research coordinators have been abstracting patient data, including sociodemographic characteristics, diagnoses, treatments, and laboratory values, from medical charts and entering these data into an electronic database for central processing and analysis. All HOPS clinicians have extensive experience treating HIV-infected patients. The HOPS protocol has been reviewed and approved annually by the Centers for Disease Control and Prevention (Atlanta, GA), Cerner Corporation (Kansas City, MO), and each local site's institutional review board. The study protocol conforms to the guidelines of the US Department of Health and Human Services for the protection of human subjects in research; all participants have provided written informed consent.

Study Population and Inclusion Criteria

HOPS patients already participating in the HOPS in 2002 and those who had their first HOPS visit between 2002 and 2011 were included. Patients were required to have had at least 2 clinical visits during 2002–2011 to be included in these analyses. The index date was

defined to be the latter of either January 1, 2002, or the first HOPS visit thereafter. Patients with an existing diagnosis of DM or statin exposure before index date were excluded.

In this analysis, we included patients from 8 clinics in 6 US cities: the Infectious Disease Research Institute in Tampa, FL; the Dupont Circle Physicians Group in Washington, DC; the Denver Infectious Disease Consultants of Rose Medical Center and National Jewish Health in Denver, CO; Northwestern Memorial HIV Center and the HIV Clinic at the University of Illinois at Chicago Hospital in Chicago, IL; Stony Brook Hospital Division of Infectious Disease in East Setauket, NY; and the HIV clinic at Temple University Hospital In Philadelphia, PA. We used the HOPS database with patient information updated through December 31, 2011.

Definitions of Outcome Variable

The outcome of interest was the onset of DM. Patients could be classified as diabetic through diagnosis of DM in the HOPS database or based on documented laboratory values or treatments. A positive laboratory test, indicative of DM, consisted of either (1) at least 1 fasting glucose laboratory measurement greater than 125 mg/dL or greater than or equal to 7 mmol/L or (2) at least 1 glucose 2-hour test result greater than 200 mg/dL or greater than or equal to 11 mmol/L. A patient was also classified as diabetic if he/she underwent treatment with insulin or other antidiabetic medications for at least 30 continuous days. Patients with a diagnosis of lipodystrophy, who later had fasting blood sugar #125 mg/dL while taking rosiglitazone or pioglitazone to treat lipodystrophy, were not classified as diabetic.

Definitions of Predictor Variables

Exposure to statins constituted taking any of the following medications during the study period for any length of time: atorvastatin, fluvastatin sodium, pravastatin sodium, lovastatin, simvastatin, cerivastatin sodium, rosuvastatin calcium, ezetimibe/simvastatin, niacin/lovastatin, or amlodipine/atorvastatin. For this analysis, cumulative statin exposure was documented as a time-varying covariate to account for patients who discontinued and subsequently restarted statin therapy.

We assessed treatment with statins by medical chart abstraction. As an additional data quality assurance measure, sites were systematically queried regarding specific patients' statin history if available data suggested that the patient was likely to have been prescribed statins but no such exposure was noted. Specifically, we queried patients who had no record in the HOPS database of taking statins but who had a low-density lipoprotein cholesterol test with a result >130 mg/dL that subsequently declined by at least 30 mg/dL at the next screening.

We categorized patients as having prevalent hepatitis C at the index date if they had either a documented diagnosis of hepatitis C in the HOPS database or if they had a hepatitis C viral load, genotype, or antibody laboratory result indicative of hepatitis C recorded on or before the index date for the study.[18]

Analysis Methods

We studied the time from the index date to diagnosis of DM. Patients were censored at the earliest of death, loss to follow-up, or December 31, 2011, if DM had not occurred by that time. We calculated incidence of DM per 100 person-years of observation. We multiply imputed missing data for race/ethnicity, antiretroviral exposure at the index date, and body mass index (BMI).[19] We performed univariate and multivariable Cox proportional hazard analyses to assess the association between cumulative statin use and the risk of developing DM in the absence of other precluding events (i. e., death) while adjusting for age, sex, race/ethnicity, exposure to antiretroviral therapy, prevalent hepatitis C, BMI, and cumulative use of protease inhibitors (PIs). Both cumulative statin use and use of PIs were modeled as time-varying covariates, such that, for example, persons who were initially not prescribed PIs and later prescribed PIs contributed observation time to both exposure groups. Furthermore, because we assessed cumulative statin use, a hypothetical patient who was prescribed statins for 2 years and then not prescribed statins for the remaining 9 months of HOPS observation would have been assigned a 2-year statin exposure value during his/her final 9 months of observation. We investigated the frequency of clinical hyperglycemia diagnosis, defined as a fasting blood glucose level between 101 and 125 mg/dL, in this cohort as a potential confounding factor, but its prevalence was low (0.1%), so this factor was disregarded in the analyses. We derived an adjusted hazard ratio of time to development of DM based on cumulative statin exposure in years.

Because patients who are prescribed statins for CVD risk reduction are likely to be at higher-than-average risk of developing DM due to common underlying traditional CVD and DM risk factors, secondary multivariable Cox proportional hazards analyses included a propensity score for statin use to account for likely confounding by indication.[20,21] The propensity for statin exposure was derived based on a logistic regression model adjusting for age, sex, race/ethnicity, antiretroviral therapy, and BMI. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of 8107 HOPS participants, 5359 had at least 2 clinical visits during 2002–2011. Of these, 327 were excluded for having been diagnosed with DM and 340 for having been exposed to statins before study onset (i.e., the index date), resulting in a total of 4692 patients eligible for this analysis. Patients were followed for a median of 4.6 years (interquartile range: 1.8–9.0) after the index date, during which time 590 (12.6%) were prescribed statin therapy for a median duration of 2.4 years (interquartile range: 1.1–4.9) and 355 (7.6%) were diagnosed with incident DM. The incidence of DM was 1.5 per 100 person-years.

The most commonly prescribed types of statins were atorvastatin (n = 327), pravastatin (n = 165), and rosuvastatin (n = 92). Fifty-six patients were prescribed more than 1 statin sequentially during the course of the study. There was no statistically significant difference between atorvastatin, pravastatin, or rosuvastatin and incident DM (χ^2 P = 0.07, 0.14, 0.10, respectively).

At baseline, compared with nonusers, persons who subsequently were prescribed statin therapy (statin users) were more likely to be older (median age 44 vs. 40 years), to be of non-Hispanic/Latino white race/ethnicity (58.8% vs. 48.9%), to be antiretroviral-experienced (74.9% vs. 65.5%), to have had an AIDS-defining condition (48.6% vs. 43.4%), to not have prevalent hepatitis C (90.8% vs. 84.9%), to have had a BMI >25 kg/m^2 (50.8% vs. 43.2%), to have had a higher median CD4$^+$ T-cell count (430 vs. 394 cells/mm^3), and have had a lower median $\log_{10}$ HIV viral load (2.4 vs. 3.3 $\log_{10}$ copies/mL), all P values < 0.05 for the above baseline characteristics (Table 1). There were no statistically significant differences between statin users and nonusers in the distribution by sex, HIV risk category, and type of insurance.

In the multivariable Cox proportional hazards regression model (Table 2), incident DM was associated with the use of statins [hazard ratio: 1.14 per year of statin exposure, 95% confidence interval (CI): 1.02 to 1.28, $P = 0.020$], older age, Hispanic/Latino vs. non-Hispanic/Latino white race ethnicity, non-Hispanic/Latino black vs. non-Hispanic/Latino white race ethnicity, ARV-naive vs. ARV-experienced, prevalent hepatitis C, and BMI ≥30 kg/m^2 (compared with BMI <25 kg/m^2). No associations were found with sex or cumulative use of PIs. The propensity score–adjusted analysis yielded similar findings for the association between statin use and incident DM, except that non-Hispanic/Latino black race/ethnicity and ARV-naive status were no longer statistically associated with incident DM in this analysis (Table 2).

DISCUSSION

In our large and sociodemographically diverse cohort of aging HIV-infected patients, we found that each year of statin use was associated with 14% increase in the rate of incident DM. The rates of DM were also increased among older patients, Hispanic/Latino patients, those coinfected with hepatitis C at baseline, and those who were obese, the recognized epidemiologic risk factors for DM.[22] By contrast, we did not detect an association between antiretroviral use history, including use of PIs, and incident DM, although such association has been suggested by some prior studies and of concern because of adverse effects on lipids of some PI agents.[23–25]

The aging of HIV-infected individuals in the United States is the result of improved survival afforded by the use of increasingly less complex, better tolerated, and more effective combination antiretroviral therapies. In addition to aging of HIV-infected patients, prolonged exposure to chronic inflammation resulting from HIV infection, exposure to some antiretroviral medications that adversely affect lipids, and some behavioral risk factors (e.g., prevalent tobacco use) appear to contribute to increased rates of comorbidities among these patients, as compared with the general population.[13] CVD is one such comorbidity, and current guidelines recommend obtaining fasting lipid panels before and during treatment with ART.[23,26] Consequently, increasing numbers of HIV-infected patients are prescribed statins for primary prevention of CVD. Statin therapy has been shown to reduce incident myocardial infarctions in at-risk populations with or without previous cardiovascular events.[1–4] Because CVD risk is higher in the HIV-infected population,[13] strict attention to appropriate statin therapy is warranted.

DM has been found to be more frequent among HIV-infected patients than matched controls in some but not all studies.[27,28] Our analysis did not include an HIV-uninfected comparison group, but studies to date point to the association between HIV infection and/or its treatments and higher rates of DM. Tien et al[28] found that HIV infection was associated with doubling in incidence of DM in women participating in the Women's Interagency HIV Study (WIHS); older age, higher BMI, and family history of DM, but not Hispanic/Latino or black ethnicity, were other leading factors. Previously, Brown et al[29] found that the rate of DM in HIV-infected Multicenter AIDS Cohort Study (MACS) participants with combination antiretroviral therapy (cART) exposure was 4 times as high as that of HIV-seronegative MACS participants, whereas HIV-infected participants who were not prescribed cART had DM rates similar to those of HIV-negative controls, which appeared in part explained by the increased risk for DM with the use of ritonavir-containing cART in this study. By contrast, Butt et al[30] found that after adjustment for known risk factors, HIV-infected veterans had a lower risk of diabetes (odds ratio: 0.84, 95% CI: 0.72 to 0.97), whereas hepatitis C virus coinfection and exposure to nucleoside and non-nucleoside reverse transcriptase inhibitors were associated with higher risk for DM. Hepatitis C has been associated with incident diabetes in other studies, as well.[31,32]

In prior analyses of data from 2 CDC-funded HIV cohorts (2003–2006), we found that among HIV-infected women prescribed cART, over 10% in total and over 20% of Hispanics/Latinos had prevalent DM. Traditional risk factors such as older age, Hispanic/Latino race/ethnicity, obesity, hepatitis C virus infection, and to a lesser extent, cumulative PI use were associated with DM in these HIV-infected women. PI use may reflect the effects of both cART-associated "return to health" and PI-associated metabolic toxicities. In analyses standardized for demographics, HIV-infected women were more likely to have hyperglycemia and less likely to be obese than counterparts as captured in the National Health and Nutrition Examination Survey.[27]

The finding in our HIV-infected cohort of a 14% increase (95% CI: 2 to 28) in the rate of incident DM per year of statin use is on par with the estimates from the general population. Sattar et al[10] conducted a large meta-analysis of statin use and incident DM and found that the odds of incident DM over a mean period of 4 years were 9% higher in patients prescribed statins compared with those not prescribed statins (odds ratio: 1.09, 95% CI: 1.02 to 1.17), which was also the finding from another meta-analysis by Mills et al[7] including some of the same studies (odds ratio: 1.09, 95% CI: 1.02 to 1.16). We also found associations of incident DM with the previously documented risk factors in the general population: older age, Hispanic/Latino race/ethnicity, prevalent hepatitis C coinfection, and higher BMI.[33] Culver et al[11] found a negative association with increasing BMI in HIV-uninfected postmenopausal women. Other studies have demonstrated a higher risk of incident DM in specific populations such as the elderly, postmenopausal women, and Asians.[11,12] Incident DM has also been associated with higher statin dose, the degree of lowering of low-density lipoprotein cholesterol levels, and use of specific statins.[6,12] We found that the risk of incident DM in our study was comparable or possibly slightly higher than the risk seen in studies in the general population, suggesting that HIV-infected individuals treated with statins are at modestly increased risk for incident DM. The

biological mechanisms underlying the relationship between statin use and incident diabetes observed in this and other cohorts are not yet well understood.

There are several limitations to our observational study. We analyzed data abstracted from medical charts that were obtained in the course of routine HIV care. Not all patients had regular glucose measurements, which might result in underdiagnosis of DM. However, the frequency of glucose monitoring was not statistically higher for patients when they were being prescribed statins vs. not (data not shown), so the association between statin use and increased rate of DM is unlikely to result from surveillance bias. We cannot rule out that residual bias persisted because patients placed on statins may have been at higher risk for CVD and possibly at higher risk for DM, but we attempted to account for potential confounding by indication through a propensity score adjustment. The relatively small size of our study population and incident DM outcomes was another limitation. The relatively small size of our study population and incident DM outcomes (n=355) was another limitation. DM prevalence in the HOPS was previously estimated at 19.3% for women and 12.2% for men with at least 6 months of antiretroviral medication exposure.[33] Because of sample size constraints, we did not have sufficient statistical power to examine different statins and statin doses and their relative associations with incident DM, including a potential dose–response relationship.

In summary, consistent with prior meta-analyses, the association between statin use and incident DM for HIV-infected patients was similar in magnitude to that found in the general population. The benefits of statin therapy outweigh the risk of incident DM in the primary prevention of CVD in non–HIV-infected adults,[9,34] and statin use should be indicated by the guidelines for CVD prevention[23,26,35] until further studies suggest otherwise. Likewise, patients should be monitored for glucose intolerance consistent with the guidelines recommended for the general population when receiving statin therapy and treated per standard of care if glucose intolerance arises.

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APPENDIX 1. HIV Outpatient Study Investigators

The HIV Outpatient Study (HOPS) Investigators include the following persons and sites: John T. Brooks, Kate Buchacz, Marcus D. Durham, Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, GA; Harlen Hays, Kathleen C. Wood, Darlene Hankerson, Rachel Hart, Thilakavathy Subramanian, Carl Armon, Bonnie Dean, Dana Franklin, Cerner Corporation, Vienna, VA; Frank J. Palella, Joan S. Chmiel, Saira Jahangir, Conor Daniel Flaherty, Jerian Denise Dixon-Evans, Feinberg School of Medicine, Northwestern University, Chicago, IL; Kenneth A. Lichtenstein, Cheryl Stewart, National Jewish Health, Denver, CO; John Hammer, Kenneth S. Greenberg, Barbara Widick, Rosa Franklin, Rose Medical Center, Denver, CO; Bienvenido G. Yangco, Kalliope Chagaris, Infectious Disease Research Institute, Tampa, FL; Doug Ward, Troy Thomas, Matt Starr, Dupont Circle Physicians Group, Washington, DC; Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, Jane Esteves, State University of New York (SUNY), Stony Brook, NY; Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, Princess Graham, Temple University School of Medicine, Philadelphia, PA; Richard M. Novak, Andrea Wendrow,

Renata Smith, University of Illinois at Chicago, Chicago, IL; Benjamin Young, Barbara Widick, Mia Scott, APEX Family Medicine, Denver, CO.

TABLE 1

Demographic Characteristics of Patients Without Prevalent Diabetes Who Did and Did Not Initiate Statin Therapy, the HOPS, 2002–2011 (N = 4692)

Characteristic	Not Prescribed Statins N= 4102 (87.4%)	Prescribed Statins N= 590 (12.6%)	*P*
Age at index date, n (%), yrs*			<0.001
<35	1218 (29.7)	60 (10.2)	
35–49	2244 (54.7)	370 (62.7)	
≥50	640 (15.6)	160 (27.1)	
Age at index date, median (IQR)	40 (34–46)	44 (40–50)	<0.001
Sex, n (%)			0.077
Female	918 (22.4)	113 (19.2)	
Male	3184 (77.6)	477 (80.8)	
Race/ethnicity, n (%)			<0.001
Non-Hispanic/Latino white	2006 (48.9)	347 (58.8)	
Non-Hispanic/Latino black	1451 (35.4)	150 (25.4)	
Hispanic/Latino	483 (11.8)	68 (11.5)	
Other/unknown	162 (3.9)	25 (4.2)	
Antiretroviral history at index date, n (%)			<0.001
Experienced	2688 (65.5)	442 (74.9)	
Naive	1096 (26.7)	109 (18.5)	
Unknown	318 (7.8)	39 (6.6)	
HIV transmission risk, n (%)			0.056
Heterosexual	1099 (26.8)	154 (26.1)	
Injection drug use	388 (9.5)	45 (7.6)	
Men who have sex with men	2308 (56.3)	360 (61)	
Other/unknown	307 (7.5)	31 (5.3)	
Insurance, n (%)			0.080
Private	2195 (53.5)	338 (57.3)	
Public	1537 (37.5)	213 (36.1)	
Other/unknown	370 (9.0)	39 (6.6)	
AIDS at index date, n (%)			0.016
No	2322 (56.6)	303 (51.4)	
Yes	1780 (43.4)	287 (48.6)	
Prevalent hepatitis C at index date, n (%)			<0.001
No	3483 (84.9)	536 (90.8)	
Yes	619 (15.1)	54 (9.2)	
BMI at index date, n (%), kg/m^2			0.003
<25	2022 (49.3)	255 (43.2)	
25–29	1208 (29.4)	193 (32.7)	
≥30	567 (13.8)	107 (18.1)	
Unknown	305 (7.4)	35 (5.9)	

Characteristic	Not Prescribed Statins N= 4102 (87.4%)	Prescribed Statins N= 590 (12.6%)	*P*
CD4 cell count (cells/mm^3) at index date, n (%)†			0.071
<50	280 (6.8)	29 (4.9)	
50–199	499 (12.2)	66 (11.2)	
200–349	703 (17.1)	100 (16.9)	
350–499	697 (17.0)	105 (17.8)	
≥500	1240 (30.2)	215 (36.4)	
Unknown	683 (16.7)	75 (12.7)	
CD4 cell count, median (IQR)	394 (216–593)	430 (260–658)	<0.001
Viral load (copies/mL) at index date, n (%)†			<0.001
0–1000	1584 (38.6)	295 (50.0)	
999–99,999	1318 (32.1)	153 (25.9)	
≥100,000	498 (12.1)	47 (8.0)	
Unknown	702 (17.1)	95 (16.1)	
Log_{10} viral load, median (IQR)	3.3 (1.7–4.6)	2.4 (1.4–4.3)	<0.001

*Index date is the date of the first HOPS visit in 2002 or thereafter.

†Closest laboratory measurement up to 6 months before and 1 week after index date.

IQR, interquartile range.

TABLE 2

Risk Factors for Incident DM Among Participants With No Prior Statin Exposure, the HOPS, 2002–2011 (N = 4692)

	Univariate Analysis		Multivariable Analysis		Multivariable Analysis with Propensity Score Adjustment	
Variable	**Hazard Ratio**	***P***	**Hazard Ratio**	***P***	**Hazard Ratio**	***P***
Statin exposure (per 1 yr)*	1.19 (1.07–1.32)	0.002	1.14 (1.02–1.28)	0.020	1.14 (1.02–1.27)	0.019
Age (per 10 yrs)	1.52 (1.37–1.69)	<0.001	1.59 (1.42–1.77)	<0.001	1.94 (1.32–2.86)	<0.001
Sex						
Female	1.51 (1.20–1.90)	<0.001	1.13 (0.89–1.45)	0.320	1.14 (0.89–1.45)	0.320
Male	Referent		Referent		Referent	
Race/ethnicity						
Hispanic/Latino	2.21 (1.64–2.98)	<0.001	1.96 (1.44–2.66)	<0.001	1.86 (1.35–2.57)	<0.001
Non-Hispanic/Latino black	1.69 (1.33–2.14)	<0.001	1.39 (1.08–1.79)	0.012	1.17 (0.79–1.75)	0.435
Non-Hispanic/Latino white	Referent		Referent		Referent	
Antiretroviral history						
Naive	1.16 (0.92–1.47)	0.206	1.34 (1.05–1.70)	0.019	1.23 (0.93–1.64)	0.153
Experienced	Referent		Referent		Referent	
Prevalent hepatitis C	1.96 (1.53–2.51)	<0.001	1.60 (1.24–2.06)	0.003	1.55 (1.20–2.01)	<0.001
BMI, kg/m^2						
<25	Referent		Referent		Referent	
25–29	1.19 (0.91–1.55)	0.198	1.18 (0.90–1.54)	0.229	1.26 (0.94–1.70)	0.122
≥30	3.19 (2.57–4.12)	<0.001	2.95 (2.26–3.84)	<0.001	3.58 (2.30–5.59)	<0.001
PI use (per 1 yr)*	1.59 (0.85–2.96)	0.144	1.74 (0.93–3.25)	0.085	1.73 (0.92–3.24)	0.087
Propensity score†					0.051 (0.00–11.43)	0.282

*Cumulative use during study period.

†See Methods for description.