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# Risk of Opioid Overdose Associated with Concomitant Use of Methadone and Statins

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## Abstract

Methadone has a high potential for risky drug–drug interactions (DDIs) that can lead to opioid overdose, yet evidence on the magnitude of this risk remains limited. Since methadone is transported via P-glycoprotein (P-gp), the use of statins that inhibit P-gp may elevate methadone plasma concentrations, potentially leading to opioid overdose. We explored this hypothesis by examining whether concomitant use of methadone and P-gp-inhibiting statins was associated with opioid overdose. Using Medicaid claims data from 2003 to 2020, we conducted a cohort study among new concomitant users of methadone and statins. We compared overdose rates among individuals exposed to P-gp-inhibiting statins (simvastatin, atorvastatin, or lovastatin) versus those exposed to rosuvastatin (negative control), adjusting for baseline covariates. We identified 69,263 individuals newly exposed to methadone and a statin of interest; the overall incidence rate of opioid overdose was 26.0 per 1,000 person-years. Adjusted hazard ratios (HRs) for methadone + P-gp-inhibiting statins consistently showed no association, ranging from 0.76 (95% CI=0.48–1.22) for atorvastatin to 0.78 (95% CI=0.50–1.22) for simvastatin, compared with methadone + rosuvastatin. Similar results were observed in sensitivity analysis that treated all P-gp-inhibiting statins as a single exposure group, as well as analyses stratified by baseline diagnosis of opioid

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AUTHOR CONTRIBUTIONS

C.C. wrote the manuscript; C.C., T.A.M., and S.H. designed the research; C.C., T.A.M., C.M.B., S.H., W.B.B., and C.E.L. performed the research; C.M.B. and W.B.B. analyzed the data; C.M.B. and W.B.B. contributed new reagents/analytical tools.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

use disorder or overdose, the duration of baseline methadone use, and calendar year intervals. Our findings suggest that concomitant use of methadone with simvastatin, atorvastatin, or lovastatin is not associated with the risk of opioid overdose compared to concomitant use of methadone and rosuvastatin.

**Keywords**

Methadone; statin; opioids; drug interactions; opioid overdose; Medicaid; real-world evidence; pharmacoepidemiology; population health

## INTRODUCTION

Methadone is an opioid approved by the United States (US) Food and Drug Administration for managing moderate to severe pain and as part of medication-assisted therapy.[1] While effective, it carries a risk of opioid overdose.[1,2] Due to its complex metabolism, methadone has a high potential for drug-drug interactions (DDIs) with many commonly used medications.[1,2] Both the drug label and clinical guideline recommend caution when combining methadone with other medications that may interact with it, as these interactions can elevate methadone plasma levels and increase the risk of overdose.[1,2] However, evidence on the magnitude of harm from these interactions remains limited.[2]

One potential interaction involves methadone and P-glycoprotein (P-gp) modifiers.[3] Methadone is a substrate of P-gp, an active transport protein that limits drug absorption in the intestines by pumping drugs back into the intestinal lumen, thereby limiting systemic exposure.[4] Previous pharmacokinetic studies suggest that concomitant treatment with P-gp inhibitors can elevate methadone concentrations during the absorption phase following oral administration, potentially leading to unanticipated increases in methadone's sedative effects.[5–7] In a prior hypothesis-generating screening study, we observed in a sensitivity analysis that concomitant use of methadone and simvastatin (a P-gp inhibitor[8]) was associated with double the rate of opioid overdose compared to use of methadone alone.[9] The potential interaction is further supported by previous research showing that concomitant use of simvastatin with the oral anticoagulant dabigatran, another P-gp substrate, was associated with a heightened risk of bleeding.[10] Given the common use of statins among methadone users and the severe, yet potentially preventable, risk of opioid overdose, our study evaluated the risk of opioid overdose associated with concomitant use of methadone and P-gp-inhibiting statins.

## METHODS

We conducted a retrospective cohort study using claims data from individuals enrolled in state Medicaid programs between January 1, 2003, and December 31, 2020. The University of Pennsylvania's institutional review board approved the study and waived the need for informed consent (#832191).

Our cohort consisted exclusively of person-time concomitantly exposed to methadone (object drug) plus one of the following statins: simvastatin, atorvastatin, and lovastatin,

which are P-gp-inhibiting statins[8] and precipitants of interest; or rosuvastatin, the negative control precipitant.[11] Rosuvastatin was selected as the negative control precipitant because it does not inhibit P-gp[8] and is more commonly used than other non-P-gp-inhibiting statins. Since P-gp inhibitors increase the bioavailability of oral but not intravenous methadone,[5] we restricted our analysis to patients who received methadone orally, covering 96% of methadone-exposed patients in our dataset.

We included new users of combination methadone and statin therapy. Patients entered the cohort on the index date—the first date of overlapping prescription supplies of both methadone and a statin of interest. Eligible patients had no combined exposure during the 183 days before the index date (the baseline period) and met the following criteria: 1) age ≥18 years on the index date; 2) continuous Medicaid enrollment (allowing up to a 45-day gap), without Medicare eligibility during the baseline; 3) use of only one statin of interest on the index date; and 4) no hospitalization on the index date, as inpatient prescription use was unmeasurable.

The outcome of interest was opioid overdose resulting in emergency department or inpatient hospitalization, identified using validated algorithms (see Table S1).[12–15] Patients were followed from the index date until the earliest of: an outcome event, discontinuation of methadone or statin, initiation of another statin of interest, death, end of Medicaid enrollment, start of Medicare eligibility, or the study's end on December 31, 2020.

We considered a total of 64 baseline covariates known or suspected to affect opioid overdose risk. These included demographic characteristics (age, sex, race, geographic region, and calendar year interval) on the index date, and healthcare utilization indicators, comorbidities, and previous prescription use, all measured during the 183-day baseline. Additionally, we assessed total days of baseline methadone use, average daily methadone dose in morphine milligram equivalents (MME) in the 90 days before the index date, cumulative methadone dose in MME on the index date, and cumulative dose of non-methadone opioids in MME on the index date.

We created multinomial propensity score (PS) models and applied overlap weights (OW) to balance measured covariates between each P-gp inhibiting statin group and the rosuvastatin group.[16] Standardized mean differences (SDiffs) were used to assess covariate balance between each statin group and rosuvastatin, with an SDiff > 0.1 indicating imbalance. We then used weighted Cox proportional hazard models to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for opioid overdose, comparing each P-gp inhibiting statin to rosuvastatin.

We conducted three secondary analyses to examine the robustness of our findings. First, we increased study power by combining all P-gp-inhibiting statins into a single exposure group for comparison with rosuvastatin. Second, we stratified analyses by prior opioid use characteristics: 1) presence of an opioid use disorder or overdose during the baseline (yes or no); and 2) duration of baseline methadone use (0 days, 1–89 days, or ≥90 days). Finally, since the statins under study were introduced in different years and the incidence of opioid

overdose likely varied over time, we conducted a post hoc stratified analysis by repeating the primary analysis within each 3-year interval (2003–2005,…,2008–2020).

## RESULTS

We identified 30,765, 26,772, 5,967, and 5,759 concomitant users of methadone with simvastatin, atorvastatin, rosuvastatin, and lovastatin, respectively. Table 1 lists the selected characteristics of these patient groups before weighting (Table S2 details all characteristics pre-weighting). The mean (±standard deviation) age across all groups was approximately 51 (±8) years, with most patients being female (54.6% to 60.2%) and non-Hispanic White (70.3% to 76.5%). Patients using P-gp-inhibiting statins had baseline clinical characteristics generally similar to those of rosuvastatin users, with a few exceptions, including a higher prevalence of opioid use disorder or overdose and obesity among atorvastatin users, a lower prevalence of HIV among simvastatin and lovastatin users, and less baseline benzodiazepine use among atorvastatin users. After PS weighting, all baseline covariates were balanced between users of P-gp-inhibiting statins and rosuvastatin, with SDiffs≤0.1 (Table S3).

Concomitant users of methadone and simvastatin, atorvastatin, rosuvastatin, and lovastatin were followed for a median of 36 days, during which 320 overdose events were identified (Table S4). The overall unadjusted incidence rate was 26.0 per 1,000 person-years, ranging from 25.5 per 1,000 person-years for atorvastatin to 28.5 per 1,000 person-years for rosuvastatin (Table S4). Table 2 presents the associations between statin groups and risk for opioid overdose in different prespecified analyses. In the primary analysis, adjusted HRs suggested comparable opioid overdose risks across statin types relative to rosuvastatin: 0.78 (0.50–1.22) for simvastatin, 0.76 (0.48–1.22) for atorvastatin, and 0.78 (0.44–1.39) for lovastatin. Sensitivity analysis also indicated no significant differences in opioid overdose rates between P-gp-inhibiting statins and rosuvastatin. These findings remained consistent across stratified analyses by baseline opioid use disorder or overdose diagnosis, baseline methadone use duration, and calendar year intervals (Table S5).

## DISCUSSION

In this large cohort study, we observed no difference in opioid overdose rates between methadone recipients concomitantly treated with P-gp-inhibiting statins and those concomitantly treated with rosuvastatin. This finding was consistent across all sensitivity and stratified analyses.

In our sample, the overall incidence rate of opioid overdose was 26.0 per 1,000 person-years, which is consistent with the previously reported range of 11.3 to 41.3 per 1,000 person-years observed among methadone users in Medicaid data.[17,18]

Our main findings seem to differ from those of previous screening work, where we found that in a zero-grace period analysis, the combined use of methadone and simvastatin was associated with a 1.96-fold increase in overdose rates compared with methadone use alone, while the combined use of methadone with rosuvastatin showed no increased overdose rates.[9] This difference in results may be explained by the different comparison groups used in the two studies: the previous study compared statin use versus non-use, whereas the

current study compared different types of statins, both among methadone users. By using a negative control for the precipitant drug, the current study reduces confounding from both measured and unmeasured factors and answers a research question more relevant to clinical practice.[19] Our results suggest that, among methadone users, P-gp-inhibiting statins are unlikely to increase the risk of opioid overdose compared to rosuvastatin, a non-P-gp-inhibiting statin. Therefore, clinicians managing patients on methadone may consider these P-gp-inhibiting statins a safe option in terms of opioid overdose risk.

Despite the theoretical potential for P-gp-inhibiting statins to increase methadone's absorption and bioavailability by inhibiting its P-gp-mediated efflux, our study observed no clinical effects as a result of this interaction. This lack of clinical effects can be explained by two possibilities. First, although methadone is identified as a P-gp substrate in several studies, the impact of P-gp transport on methadone's pharmacokinetics might be minimal. Indeed, studies in healthy volunteers showed that P-gp inhibitors ritonavir and lopinavir did not affect methadone's bioavailability despite inhibiting intestinal P-gp transporter activity.[20,21] Additionally, genetic variations in P-gp did not influence methadone's peak concentration levels after oral administration,[22,23] suggesting that P-gp-mediated transport may not significantly limit methadone absorption. Second, the statin concentration used in clinical settings might be too low to significantly inhibit P-gp. In vitro studies showing statins' inhibition of P-gp often involved concentrations much higher than those achieved through standard dosing.[8,24] Furthermore, genetic variability in cytochrome P450 metabolism may cause some individuals to metabolize statins more efficiently, resulting in lower statin concentrations and reduced P-gp inhibition.[25] As a result, the statin concentrations achieved in clinical settings may not be sufficient to produce the level of P-gp inhibition needed to significantly affect methadone metabolism and lead to clinically meaningful DDIs.

The strengths of our study include its large sample size, the use of a negative control for the precipitant drug, and the application of validated outcome measures.

Our study also has several limitations. First, there is potential exposure misclassification since we measured concomitant medication use through prescription overlap without data on actual adherence. Second, as with any observational study using secondary data, we cannot rule out the potential for confounding. The most relevant residual confounding in our study might be confounding by indication, i.e., whether methadone was used for pain or opioid use disorder. To mitigate this, we adjusted for covariates including various pain conditions, alcohol use disorder, opioid use disorder or overdose, and other drug use disorders during the baseline period. Despite these adjustments, concerns remained about the possibility of unmeasured confounding factors, such as nonmedical drug use. Third, our data did not capture overdose cases that did not result in emergency department visits or inpatient hospitalization, possibly leading to an underestimation of the total number of overdose cases. However, by using an outcome algorithm with a high positive predictive value, our study likely reduces biases in estimating relative risk. Fourth, our data spanned from 2003 to 2020, a period during which underlying factors related to overdose, overdose rates, and the distribution of statin use may have changed, potentially introducing confounding or effect modification. However, we accounted for this by including calendar year interval

as a covariate and conducting stratified analyses by calendar year intervals, which yielded results consistent with our primary findings. Finally, although methadone is commonly used in medication-assisted therapy, approximately 90% of our study sample did not have a diagnosis of opioid use disorder or overdose at baseline, suggesting that their methadone use was likely for pain management. Thus, our stratified analysis of patients with a baseline diagnosis of opioid use disorder or overdose may be underpowered. Future research using a different data source may focus on this high-risk patient group.

Despite these limitations, our study is the first to examine the clinical consequences of the potential pharmacokinetic interaction between methadone and P-gp-inhibiting statins. Our findings suggest that concomitant use of methadone with simvastatin, atorvastatin, or lovastatin is not associated with the risk of opioid overdose compared to concomitant use of methadone and rosuvastatin. The difference between hypothesized DDIs and actual clinical outcomes underscores the importance of research like ours in exploring and verifying the real-world effects of such interactions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Conflict of Interest

Dr. Leonard recently received honoraria from the American College of Clinical Pharmacy Foundation, the Scientific and Data Coordinating Center for the NIDDK-funded Chronic Renal Insufficiency Cohort Study, and the Consortium for Medical Marijuana Clinical Outcomes Research. Dr. Leonard is a Special Government Employee of the United States (US) Food and Drug Administration and recently consulted for their Reagan-Udall Foundation. Dr. Leonard consults for Novo Nordisk and TriNetX. Dr. Leonard's spouse is an employee of Merck; neither Dr. Leonard nor his spouse owns stock in the company. Dr. Hennessy has consulted for, the Medullary Thyroid Cancer Consortium (Novo Nordisk Inc, AstraZeneca Pharmaceuticals LP, and Eli Lilly Company), Urovant Sciences, i2o Therapeutics, Bailea, Balance Therapeutics, and Lykos Therapeutics. Dr. Bilker is a paid consultant for Genentech for unrelated medications. All other authors declared no competing interests for this work.

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## STUDY HIGHLIGHTS

**What is the current knowledge on the topic?**

Methadone has a high potential for risky drug–drug interactions (DDIs) that can lead to opioid overdose, yet evidence on the magnitude of this risk remains limited. Theoretically, the potential pharmacokinetic interaction between methadone, a substrate of P-glycoprotein (P-gp), and statins that inhibit P-gp can increase the risk of opioid overdose.

**What question did this study address?**

Among methadone users, is concomitant use of P-gp-inhibiting statins (simvastatin, atorvastatin, and lovastatin) versus concomitant use of rosuvastatin, a negative control, associated with risk of opioid overdose?

**What does this study add to our knowledge?**

We found that concomitant use of methadone with P-gp-inhibiting statins (simvastatin, atorvastatin, or lovastatin) was not associated with the risk of opioid overdose when compared to concomitant use of methadone and rosuvastatin.

**How might this change clinical pharmacology or translational science?**

Clinicians managing patients on methadone may consider P-gp-inhibiting statins (simvastatin, atorvastatin, or lovastatin) a safe option in terms of opioid overdose risk.The difference between hypothesized DDIs and actual clinical outcomes highlights the critical role of studies like ours in assessing and verifying the real-world effects of such interactions.

**Table 1.**

Selected characteristics of concomitant users of methadone and statin, pre-weighting

| Characteristic | Rosuvastatin | Atorvastatin | | Lovastatin | | Simvastatin | |
|---|---|---|---|---|---|---|---|
| | % | % | SDiff[a] | % | SDiff[a] | % | SDiff[a] |
| Users, N | 5,967 | 26,772 | | 5,759 | | 30,765 | |
| ***Demographics*** | | | | | | | |
| Age on index date, mean (SD) | 51.1 (8.3) | 51.6 (8.3) | 0.05 | 51.0 (8.4) | 0.01 | 51.0 (8.5) | 0.02 |
| Female | 59.7 | 54.6 | 0.10 | 60.2 | 0.01 | 57.6 | 0.04 |
| Race | | | | | | | |
| White, non-Hispanic | 76.5 | 70.3 | 0.16* | 73.7 | 0.05 | 71.6 | 0.15* |
| Black, non-Hispanic | 10.2 | 14.9 | | 11.3 | | 14.7 | |
| Other or Unknown | 13.4 | 14.8 | | 15.0 | | 13.7 | |
| US census region of residence | | | | | | | |
| Midwest | 16.5 | 22.9 | 0.31* | 18.7 | 0.63* | 23.4 | 0.18* |
| Northeast | 17.2 | 19.5 | | 7.2 | | 14.8 | |
| South | 39.0 | 25.2 | | 21.2 | | 32.8 | |
| West | 27.3 | 32.4 | | 52.9 | | 28.9 | |
| ***Health system use during the 183-day baseline period*** | | | | | | | |
| Any inpatient admission | 24.4 | 29.6 | 0.12* | 21.7 | 0.06 | 29.2 | 0.11* |
| Number of prescriptions for unique active ingredients, mean (SD) | 13.9 (6.7) | 12.9 (6.2) | 0.16* | 12.7 (6.4) | 0.18* | 13.0 (6.7) | 0.13* |
| ***Comorbidities in the 183-day baseline period*** | | | | | | | |
| Opioid use disorder or overdose | 8.0 | 12.8 | 0.16* | 7.9 | 0.01 | 10.1 | 0.07 |
| Alcohol use disorder | 2.7 | 4.0 | 0.07 | 3.0 | 0.02 | 3.7 | 0.05 |
| Other drug abuse (not including OUD) | 9.0 | 9.2 | 0.01 | 7.9 | 0.04 | 10.0 | 0.03 |
| Tobacco use | 13.8 | 16.6 | 0.08 | 11.7 | 0.06 | 15.2 | 0.04 |
| HIV | 2.8 | 2.7 | 0.01 | 0.2 | 0.21* | 0.7 | 0.16* |
| Obesity | 1.4 | 3.9 | 0.15* | 1.2 | 0.02 | 1.4 | 0.00 |
| Obstructive sleep apnea | 9.2 | 8.8 | 0.02 | 8.6 | 0.02 | 8.1 | 0.04 |
| Back pain | 60.8 | 61.9 | 0.02 | 60.9 | 0.00 | 62.5 | 0.03 |
| Neck pain | 23.0 | 22.1 | 0.02 | 21.7 | 0.03 | 22.8 | 0.00 |

| Characteristic | Rosuvastatin | Atorvastatin | | Lovastatin | | Simvastatin | |
|---|---|---|---|---|---|---|---|
| | % | % | SDiff[a] | % | SDiff[a] | % | SDiff[a] |
| Anxiety | 18.6 | 21.0 | 0.06 | 17.4 | 0.03 | 19.5 | 0.02 |
| Bipolar disorder | 7.9 | 7.9 | 0.00 | 8.7 | 0.03 | 8.8 | 0.03 |
| Depression | 16.1 | 19.1 | 0.08 | 15.6 | 0.01 | 16.7 | 0.02 |
| Epilepsy | 2.0 | 1.6 | 0.03 | 1.8 | 0.01 | 2.3 | 0.02 |
| Schizophrenia | 2.8 | 4.2 | 0.08 | 3.9 | 0.06 | 4.2 | 0.08 |
| Other mental disorders[b] | 5.2 | 6.1 | 0.04 | 5.4 | 0.01 | 5.6 | 0.01 |
| ***Concomitant medications in the 183 days prior to (and including) the index date*** | | | | | | | |
| SSRI antidepressants | 36.3 | 33.2 | 0.06 | 37.2 | 0.02 | 35.4 | 0.02 |
| SNRI antidepressants | 20.5 | 18.3 | 0.06 | 16.6 | 0.10 | 17.8 | 0.07 |
| TCA antidepressants | 16.7 | 16.8 | 0.00 | 19.4 | 0.07 | 17.1 | 0.01 |
| Other antidepressants | 24.3 | 24.0 | 0.01 | 27.5 | 0.07 | 24.3 | 0.00 |
| Anticonvulsants | 16.3 | 16.0 | 0.01 | 15.4 | 0.02 | 16.2 | 0.00 |
| Antipsychotics | 19.3 | 18.2 | 0.03 | 17.8 | 0.04 | 18.7 | 0.02 |
| Benzodiazepines | 51.8 | 45.1 | 0.13* | 48.4 | 0.07 | 51.0 | 0.01 |
| Gabapentinoids | 38.9 | 41.0 | 0.04 | 36.4 | 0.05 | 39.4 | 0.01 |
| Skeletal muscle relaxants | 42.5 | 39.5 | 0.06 | 43.4 | 0.02 | 41.6 | 0.02 |
| Other sedatives or hypnotics | 39.0 | 34.6 | 0.09 | 34.6 | 0.09 | 35.9 | 0.06 |
| P-gp inhibitors[c] | 4.3 | 3.7 | 0.03 | 4.1 | 0.01 | 3.8 | 0.03 |
| ***Opioid-related covariates*** | | | | | | | |
| Total days of methadone use during baseline, mean (SD) | 72.8 (78.8) | 70.2 (78.2) | 0.03 | 68.4 (77.0) | 0.06 | 65.9 (76.3) | 0.09 |
| Average daily methadone MME in 90 days prior to index date | | | | | | | |
| 0 | 43.3 | 45.1 | 0.10 | 44.2 | 0.07 | 45.5 | 0.09 |
| <50 | 16.1 | 16.4 | | 17.5 | | 17.0 | |
| 50 to <100 | 10.0 | 11.5 | | 11.0 | | 10.4 | |
| 100 to 150 | 9.9 | 9.5 | | 9.1 | | 9.1 | |
| ≥150 | 20.7 | 17.5 | | 18.2 | | 18.0 | |
| Cumulative methadone MME on index date | | | | | | | |
| <50 | 23.9 | 26.6 | 0.10 | 25.2 | 0.04 | 24.7 | 0.04 |
| 50 to <100 | 30.2 | 31.3 | | 30.8 | | 31.0 | |
| 100 to 150 | 12.6 | 12.7 | | 12.2 | | 12.9 | |

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| Characteristic | Rosuvastatin | Atorvastatin | | Lovastatin | | Simvastatin | |
|---|---|---|---|---|---|---|---|
| | % | % | SDiff[a] | % | SDiff[a] | % | SDiff[a] |
| ≥150 | 33.3 | 29.4 | | 31.8 | | 31.4 | |

SD, standard deviation; SDiff, standardized difference; ED, emergency department; SD, standard deviation; OUD, opioid use disorder; HIV, human immunodeficiency virus; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; TCA, tricyclic antidepressants; P-gp, P-Glycoprotein; MME, morphine milligram equivalents.

[a] SDiff is calculated by comparing the statin group versus the rosuvastatin group.

[b] Other mental disorders include post-traumatic stress disorder (PTSD), attention-deficit or hyperactivity disorder (ADHD), personality disorder, and autism.

[c] P-gp inhibitors included ketoconazole, quinidine, verapamil.

[*] SDiff>0.10, indicating imbalanced covariate distribution vs. rosuvastatin.

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**Table 2.**

Adjusted hazard ratios for opioid overdose comparing P-gp-inhibiting statins versus rosuvastatin among methadone users

| Statin Group (versus rosuvastatin) | Adjusted Hazard Ratio (95% CI) |
|---|---|
| **Primary analysis** | |
| Atorvastatin | 0.76 (0.48–1.22) |
| Lovastatin | 0.78 (0.44–1.39) |
| Simvastatin | 0.78 (0.50–1.22) |
| **Sensitivity analysis by grouping all P-gp inhibiting statins as one exposure group** | |
| P-gp inhibiting statins | 0.90 (0.61–1.34) |
| **Stratified analysis by diagnosis of opioid use disorder or overdose at baseline** | |
| Having diagnosis of opioid use disorder or overdose at baseline (N=7,480) | |
| Atorvastatin (n=3,435) | 1.03 (0.31–3.42) |
| Lovastatin (n=455) | 1.29 (0.31–5.46) |
| Simvastatin (n=3,110) | 1.31 (0.40–4.25) |
| Not having diagnosis of opioid use disorder or overdose at baseline (N=61,783) | |
| Atorvastatin (n=23,337) | 0.72 (0.43–1.20) |
| Lovastatin (n=5,304) | 0.83 (0.45–1.55) |
| Simvastatin (n=27,655) | 0.72 (0.44–1.18) |
| **Stratified analysis by duration of methadone use at baseline** | |
| 0 day of methadone use at baseline (N=30,153) | |
| Atorvastatin (n=11,679) | 0.68 (0.37–1.23) |
| Lovastatin (n=2,457) | 0.82 (0.47–1.43) |
| Simvastatin (n=13,521) | 0.61 (0.28–1.35) |
| 1–89 days of methadone use at baseline (N=12,726) | |
| Atorvastatin (n=4,597) | 0.97 (0.32–2.97) |
| Lovastatin (n=1,102) | 0.99 (0.26–3.73) |
| Simvastatin (n=5,984) | 0.36 (0.12–1.13) |
| ≥90 days of methadone use at baseline (N=26,384) | |
| Atorvastatin (n=10,496) | 1.03 (0.39–2.70) |
| Lovastatin (n=2,200) | 1.80 (0.58–5.61) |
| Simvastatin (n=11,260) | 1.40 (0.55–3.53) |

CI, confidence interval.