Association Between Prior Bisphosphonate Use and COVID-19-Related Outcomes

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Introduction

- Throughout the COVID-19 pandemic, massive global efforts to repurpose existing drugs as potential therapeutic options for COVID-19 have been undertaken. Drug repurposing, whereby a drug already proven to be safe and effective in humans for another approved clinical indication is evaluated for novel clinical use, may allow for faster identification and deployment of therapeutic agents compared to traditional drug discovery pipelines.[1]
- Here, we have investigated bisphosphonates (BPs), a class of small-molecule drugs that inhibit bone resorption by osteoclasts.[2] BPs are widely prescribed as either oral or intravenous formulations to treat osteoporosis, Paget disease, and malignancy-induced hypercalcemia. Additionally, BPs are used as adjuvant therapy for breast cancer.[3]
- Aside from depleting osteoclasts, clinical and experimental studies indicate that BPs exert a plethora of immunomodulatory effects, providing a rationale for exploring BPs as potential repurposed drug candidates for COVID-19.[4]
- Observational studies have reported decreased in-hospital mortality for patients in the ICU and reduced incidence of pneumonia and pneumonia-related mortality in patients treated with amino-BPs versus controls.[5-6]

Objective

- The objective of this study was to determine whether prior use of BPs is associated with reduced incidence and/or severity of COVID-19.

Methods

Study Design

- A retrospective cohort study was performed using health insurance claims data from January 1, 2019, to June 30, 2020 (study period), in order to assess the relationship between use of BPs and three COVID-19-related outcomes: (a) testing for SARS-CoV-2 infection; (b) COVID-19 diagnosis; and (c) hospitalization with a COVID-19 diagnosis.
- Endpoints were assessed during the observation period of March 1, 2020, to June 30, 2020, following patient stratification based on the use of BPs during the pre-observation period (January 1, 2019, to February 29, 2020).

Data Source

- Data used for this study included closed medical and outpatient-pharmacy-dispensed claims between January 1, 2019, and June 30, 2020, from the Komodo Health payer-complete dataset.
- This dataset is derived from over 150 private insurers in the US and includes patients with commercial, individual, state exchange-purchased, Medicare Advantage, and Medicaid managed-care insurance coverage, and is comprised of claims data from over 140 million individuals in the US from 2015 to 2020.

Primary Analysis Cohort

- Inclusion criteria:
  – Continuous medical and prescription insurance eligibility January 1, 2019, through June 30, 2020.
- Exclusion criteria:
  – Patients with missing information for age, gender, insurance type, or state/region were excluded.
- Exposure of interest:
  – Patients were classified as BP users if they had any claim during the pre-observation period for one of the following: alendronate, alendronic acid, etidronate, ibandronate, ibandronic acid, pamidronate, risedronate, and zoledronic acid.
  – This long duration was chosen because of the extended bioavailability of BPs, which accumulate in bone where they are retained and slowly released for up to several years.[7]
- Covariates:
  – Covariates included age, gender, insurance type (commercial, dual, Medicaid, Medicare), having had any primary care physician (PCP) visit in 2019, and comorbidity burden.
  – The variable "PCP visit in 2019" was used to control for prior healthcare-use behavior and was assigned based on any physician office claim with one of the following provider types: family practice, general practice, geriatric medicine, internal medicine, and preventive medicine.
  – Comorbidity score assignment was calculated following the Charlson Comorbidity Index (CCI) methodology[8] and was based on diagnosis codes present during the pre-observation period.
  – The assigned CCI score was used as the comorbidity covariate for the primary cohort propensity score matching, but to better control for differences in comorbidity burden when assessing outcomes, all regression analyses involving the primary analysis cohort included the following in lieu of the aggregate CCI score: osteoporosis, cancer, chronic obstructive pulmonary disease (COPD), depression, dyslipidemia, hypertension, obesity, type 2 diabetes, cardiovascular disease overall, sickle cell anemia, stroke, dementia, HIV/AIDS, chronic kidney disease/end-stage renal disease (CKD/ESRD), and liver disease.
- Cohort matching:
  – For the primary analysis, BP users were propensity score matched to BP non-users using multiple variables including age, gender, insurance type, CCI, and any PCP visit in 2019.
  – To account for the differential geographic spread of COVID-19, matching was performed within each geographic region separately (Northeast, Midwest, South, West) and then combined.
  – In addition, a cohort build was also performed after restricting to patients from New York (NY) state only, since this state was the site of the largest outbreak in the initial COVID-19 surge in the US.
  – All matching algorithms used a greedy-match propensity score technique[9] with a max permitted propensity score difference of 0.015.
- Definition of endpoints:
  – COVID-19-related hospitalization was assigned based on the presence of an International Classification of Diseases, Tenth Revision (ICD-10) code on any inpatient medical service claim indicating test-confirmed 2019 Novel Coronavirus (2019-nCoV) acute respiratory disease, specifically U07.1.
  – COVID-19-related diagnosis was assigned based on any medical service claim with the ICD-10 diagnosis code U07.1.
  – SARS-CoV-2 testing was assigned using Current Procedural Terminology (CPT) codes indicating a test for active infection, specifically 87635, 87636, and 87637.

Methods, continued

Statistical Analysis

- Unadjusted analyses assessing the association between BP use and COVID-19-related outcomes were performed for the primary analysis cohort using Chi-square tests for categorical variables and calculation of the crude unadjusted odds ratio (OR) in the matched cohort groups overall, when stratified by region and in NY state alone, and when further stratified by age and gender. Chi-square tests for categorical variables and t-tests for continuous variables were also performed to assess differences in demographic and clinical characteristics of BP users compared to BP non-users both pre-match and post-match to assess the success of the propensity score match.
- Multivariate logistic regression analyses, modeled separately to determine the adjusted OR for each COVID-19-related primary and secondary outcome while adjusting for demographic and clinical characteristics, were performed on the matched primary analysis cohort with all regions combined, when stratified by region, and in NY state alone. The primary exposure of interest was BP use (yes/no) during the pre-observation period. Additional demographic/clinical characteristics also included as regression model covariates were age; gender; region (for all regions-combined analyses); insurance type; PCP visit in 2019; and the following comorbid conditions: osteoporosis, cancer, COPD, depression, dyslipidemia, hypertension, obesity, type 2 diabetes, cardiovascular disease overall, sickle cell anemia, stroke, dementia, HIV/AIDS, CKD/ESRD, and liver disease.
- All tests were two-tailed, and p-values of less than 0.05 were considered significant. All analyses were performed using SAS 9.4 (Cary, NC).

Sensitivity Analysis

- Multiple sensitivity analyses were performed to assess the reliability of the primary analysis results and/or to address potential unmeasured confounding.
  1) The first sensitivity analysis addressed potential confounding by indication by restricting the control group to an active comparator cohort of patients who had used non-BP anti-resorptive bone medications during the pre-observation period. Users of non-BP anti-resorptive bone medications, the smaller patient population, were then 1:1 matched to BP users, providing a sample where all patients had used bone health medications during the pre-observation period ("*Bone-Rx*" cohort). Cohort matching and regression modeling were performed following the same methodology employed for the primary analysis.
  2) The second sensitivity analysis further addressed potential baseline differences between users of BPs and users of non-BP anti-resorptive bone medications in terms of indication for treatment and risk of SARS-CoV-2 exposure. To homogenize indication for treatment, we restricted the "*Bone-Rx*" cohort to females aged older than 50 years with an osteoporosis diagnosis (ICD-10: M80.x, M81.x, M82.x), which is the main (but not the only) indication for use of anti-resorptive bone medications. In order to homogenize risk of COVID-19 exposure, we additionally (a) restricted both groups to residents of New York, Illinois, Florida, and California (four states with a high incidence of COVID-19 cases during the observation period, with each representing a geographic region),[10] and (b) matched within each state by insurance-type strata to control for differences in socioeconomic characteristics. Non-BP anti-resorptive bone medication users were then matched to BP users by age, PCP visit in 2019, and the following select comorbid conditions that included those thought to impact COVID-19 severity: cancer, COPD, depression, dyslipidemia, heart failure, hypertension, obesity, and type 2 diabetes.[11] In addition to assessing COVID-19-related outcomes, the matched cohorts that resulted from this analysis, older female patients from New York, Illinois, Florida, or California with a diagnosis of osteoporosis who were users of BP or non-BP anti-resorptive medications ("*Osteo-Dx-Rx*" cohort), were used for the third sensitivity analysis (see below).
  3) The third sensitivity analysis assessed the relationship between BP use and exploratory positive control outcomes (anticipated to be impacted by the immunomodulatory pharmacological mechanism of BPs) occurring in 2019. For this analysis, the primary, "*Bone-Rx*," and "*Osteo-Dx-Rx*" cohorts were restricted to BP users who had any BP claim during the first half of 2019 and their previously assigned BP non-user matched pair to assess the relationship between BP use and medical services for other respiratory infectious diseases (acute bronchitis, pneumonia).
  4) The fourth sensitivity analysis addressed potential bias due to the healthy adherer effect. First, we tested whether effects observed with exposure to BPs were similarly observed with exposure to other preventive drugs, namely statins, antihypertensives, antidiabetics, and antidepressants. Second, we assessed whether the association between BP use and COVID-19-related outcomes was maintained among the matched user/non-user populations of these other preventive drugs.

Results

- A total of 8,239,790 patients met the inclusion criterion of continuous medical and prescription insurance eligibility over the full study period, of which 333,107 were excluded due to missing demographic information, resulting in a total eligible sample of 7,906,603 patients.
- Of this full population, 452,051 (5.7%) and 7,454,552 (94.3%) patients were classified as BP users and BP non-users, respectively.
- Within BP users, more than 99% were prescribed an amino-BP, with oral alendronic acid (75.4%), zoledronic acid infusion (11.5%), and oral ibandronic acid (8.4%) as the most prevalent formulations.

COVID-19-Related Outcomes: Primary Analysis Cohort

- Prior to propensity score matching, there were significant differences between BP users and non-users across all demographic and clinical characteristics.
- Compared to BP non-users, BP users were older (age >60: 82.7% versus 27.7%; $p<0.001$), predominantly female (91.0% versus 57.2%; $p<0.001$), with a higher comorbidity burden (mean CCI 0.95 versus 0.60; $p<0.001$), with a larger proportion of patients residing in the Western US (21.1% versus 15.4%; $p<0.001$), covered by Medicare (43.3% versus 13.7%; $p<0.001$), and having visited a PCP in 2019 (63.8% versus 44.7%; $p<0.001$).
- Propensity score matching yielded 450,366 BP users and 450,366 BP non-users with no significant differences across demographic and clinical characteristics used in matching (**Table 1**).
- Over 98% of all BP user/non-user matches for the primary analysis cohort were completed with differences in matched propensity scores <0.000001 (overall mean difference of 0.000004, max difference of 0.0147).
- Among the full matched cohort, BP users had significantly lower rates and unadjusted (crude) odds of testing (1.2% versus 5.1%; OR=0.22; 95%CI: 0.21-0.22; $p<0.001$), diagnosis (0.7% versus 2.9%; OR=0.22; 95%CI: 0.21-0.23; $p<0.001$), and hospitalization (0.2% versus 0.7%; OR=0.24; 95%CI: 0.22-0.26; $p<0.001$) as compared to BP non-users (**Figure 1**).
- Multivariate regression analyses yielded similar results for all outcomes while additionally controlling for patient demographic and comorbidity characteristics. In the full matched cohort, BP users had lower adjusted odds of testing (OR=0.22; 95%CI: 0.21-0.23; $p<0.001$), diagnosis (OR=0.23; 95%CI: 0.22-0.24; $p<0.001$), and hospitalization (OR=0.26; 95%CI: 0.24-0.29; $p<0.001$).
- These findings were robust when comparing BP users with BP non-users when stratified by geographic region or NY state alone.

Results, continued

COVID-19-Related Outcomes: Bone-Rx Cohort

- Compared to non-BP users of anti-resorptive medications, BP users had decreased odds of testing (OR=0.31; 95%CI: 0.28-0.33; $p<0.001$), diagnosis (OR=0.35; 95%CI: 0.31-0.38; $p<0.001$), and hospitalization (OR=0.45; 95%CI: 0.36-0.56; $p<0.001$) (**Figure 2a**).
- These findings were robust when assessed separately across every geographic region as well as NY state for all outcomes except hospitalizations when restricted to the Western US ($p=0.08$).

COVID-19-Related Outcomes: Osteo-Dx-Rx Cohort

- In agreement with other results, the decrease in odds of COVID-19-related outcomes in BP users remained robust for testing (OR=0.28; 95%CI: 0.23-0.35; $p<0.001$), diagnosis (OR=0.40; 95%CI: 0.32-0.49; $p<0.001$), and hospitalization (OR=0.45; 95%CI: 0.26-0.75; $p=0.003$) (**Figure 2b**).

Other Respiratory Infection Outcomes: BP Users versus BP Non-Users

- Regression modeling found that among all cohort variations modeled, BP users had a decreased odds of any medical service related to acute bronchitis (point estimates of ORs ranged from 0.23 to 0.28) and pneumonia (point estimates of ORs ranged from 0.32 to 0.36) (**Figure 3**).

Other Preventive Medication Use Sensitivity Analysis

- In comparison to BPs, the impact of other preventive drug classes on COVID-19-related outcomes was much weaker overall (**Figure 4b-4e**) and varied between geographic regions in terms of magnitude or direction.
- Furthermore, when assessing the impact of BP use within matched user/non-user preventive drug cohorts (e.g., BP users compared to BP non-users among the matched statin user and statin non-user populations), we found BP use to be consistently associated with lower odds of testing (point estimates of ORs ranged from 0.21 to 0.27), diagnosis (point estimates of ORs ranged from 0.22 to 0.30), and hospitalization (point estimates of ORs ranged from 0.25 to 0.33) across all stratified preventive user/non-user cohorts.

Table 1. Primary Analysis Cohort (All Regions), Patient Characteristics Pre-/Post-Match

	All Observations Unmatched							All Observations Matched						
	All		BP Non-Users		BP Users		p-value	All		BP Non-Users		BP Users		p-value
	N	%	N	%	N	%		N	%	N	%	N	%	
All Patients	**7,906,603**	**100.0%**	**7,454,552**	**94.3%**	**452,051**	**5.7%**		**900,732**	**100.0%**	**450,366**	**50.0%**	**450,366**	**50.0%**	
Demographics														
Age														
≤20	1,840,050	23.3%	1,838,922	24.7%	1,128	0.2%	<0.001	2,253	0.3%	1,125	0.2%	1,128	0.3%	1.00
21-40	1,446,999	18.3%	1,443,908	19.4%	3,091	0.7%		6,195	0.7%	3,104	0.7%	3,091	0.7%	
41-50	925,309	11.7%	916,758	12.3%	8,551	1.9%		17,096	1.9%	8,545	1.9%	8,551	1.9%	
51-60	1,250,190	15.8%	1,184,469	15.9%	65,721	14.5%		131,445	14.6%	65,724	14.6%	65,721	14.6%	
61-70	1,181,261	14.9%	1,024,383	13.7%	156,878	34.7%		313,822	34.8%	156,944	34.8%	156,878	34.8%	
71-80	783,775	9.9%	642,050	8.6%	141,725	31.4%		280,803	31.2%	140,366	31.2%	140,437	31.2%	
≥81	479,019	6.1%	404,062	5.4%	74,957	16.6%		149,118	16.6%	74,558	16.6%	74,560	16.6%	
Gender														
Female	4,670,960	59.1%	4,263,524	57.2%	407,436	90.1%	<0.001	811,497	90.1%	405,746	90.1%	405,751	90.1%	0.99
Male	3,235,643	40.9%	3,191,028	42.8%	44,615	9.9%		89,235	9.9%	44,620	9.9%	44,615	9.9%	
Region														
Midwest	1,467,802	18.6%	1,391,835	18.7%	75,967	16.8%	<0.001	151,802	16.9%	75,901	16.9%	75,901	16.9%	1.00
Northeast	2,152,560	27.2%	2,032,832	27.3%	119,728	26.5%		238,988	26.5%	119,494	26.5%	119,494	26.5%	
South	3,042,604	38.5%	2,881,718	38.7%	160,886	35.6%		319,408	35.5%	159,704	35.5%	159,704	35.5%	
West	1,243,637	15.7%	1,148,167	15.4%	95,470	21.1%		190,534	21.2%	95,267	21.2%	95,267	21.2%	
Insurance														
Commercial	3,938,603	49.8%	3,791,545	50.9%	147,058	32.5%	<0.001	294,070	32.6%	147,012	32.6%	147,058	32.7%	1.00
Dual	156,497	2.0%	125,090	1.7%	31,407	6.9%		59,936	6.7%	29,980	6.7%	29,956	6.7%	
Medicaid	2,594,500	32.8%	2,517,020	33.8%	77,480	17.1%		154,519	17.2%	77,272	17.2%	77,247	17.2%	
Medicare	1,217,003	15.4%	1,020,897	13.7%	196,106	43.4%		392,207	43.5%	196,102	43.5%	196,105	43.5%	
PCP Visit 2019														
No	4,283,697	54.2%	4,119,831	55.3%	163,866	36.2%	<0.001	327,383	36.3%	163,659	36.3%	163,724	36.4%	0.89
Yes	3,622,906	45.8%	3,334,721	44.7%	288,185	63.8%		573,349	63.7%	286,707	63.7%	286,642	63.6%	
Clinical Characteristics														
	mean	SD	mean	SD	mean	SD	p-value	mean	SD	mean	SD	mean	SD	p-value
CCI	0.62	1.38	0.60	1.35	0.95	1.76	<0.001	0.95	1.76	0.95	1.76	0.95	1.76	0.70

BP: bisphosphonate; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; CKD/ESRD: chronic kidney disease/end-stage renal disease; CVD: cardiovascular disease (overall); PCP: primary care physician; SD: standard deviation

Figure 1. Primary Analysis Cohort – Impact of BP Use on COVID-19-Related Outcomes

	Incidence of Outcome Events by Exposure to Bisphosphonates: Number of Events / Non-User Patients (%)	Number of Events / User Patients (%)	Odds of Event: Crude OR (95%CI)	Adjusted OR (95%CI)
(i) All Regions Combined				
SARS-CoV-2 Test	22,948 / 450,366 (5.1)	5,189 / 450,366 (1.2)	0.22 (0.21-0.22)	0.22 (0.21-0.23)
COVID-19 Diagnosis	13,265 / 450,366 (2.9)	3,024 / 450,366 (0.7)	0.22 (0.21-0.23)	0.23 (0.22-0.24)
COVID-19 Hospitalization	2,995 / 450,366 (0.7)	715 / 450,366 (0.2)	0.24 (0.22-0.26)	0.26 (0.24-0.29)
(ii) Region = Northeast				
SARS-CoV-2 Test	7,147 / 119,494 (6.0)	1,684 / 119,494 (1.4)	0.22 (0.21-0.24)	0.23 (0.21-0.24)
COVID-19 Diagnosis	6,242 / 119,494 (5.2)	1,578 / 119,494 (1.3)	0.24 (0.23-0.26)	0.25 (0.23-0.26)
COVID-19 Hospitalization	1,191 / 119,494 (1.0)	314 / 119,494 (0.3)	0.26 (0.23-0.30)	0.29 (0.26-0.33)
(iii) Region = Midwest				
SARS-CoV-2 Test	3,583 / 75,901 (4.7)	868 / 75,901 (1.1)	0.23 (0.22-0.25)	0.24 (0.22-0.26)
COVID-19 Diagnosis	1,716 / 75,901 (2.3)	383 / 75,901 (0.5)	0.22 (0.20-0.25)	0.24 (0.22-0.27)
COVID-19 Hospitalization	515 / 75,901 (0.7)	121 / 75,901 (0.2)	0.23 (0.19-0.29)	0.26 (0.21-0.32)
(iv) Region = South				
SARS-CoV-2 Test	6,865 / 159,704 (4.3)	1,553 / 159,704 (1.0)	0.22 (0.21-0.23)	0.22 (0.21-0.23)
COVID-19 Diagnosis	2,911 / 159,704 (1.8)	624 / 159,704 (0.4)	0.21 (0.19-0.23)	0.22 (0.20-0.24)
COVID-19 Hospitalization	682 / 159,704 (0.4)	167 / 159,704 (0.1)	0.24 (0.21-0.29)	0.26 (0.23-0.30)
(v) Region = West				
SARS-CoV-2 Test	5,353 / 95,267 (5.6)	1,084 / 95,267 (1.1)	0.19 (0.18-0.21)	0.20 (0.18-0.21)
COVID-19 Diagnosis	2,396 / 95,267 (2.5)	439 / 95,267 (0.5)	0.18 (0.16-0.20)	0.19 (0.17-0.21)
COVID-19 Hospitalization	607 / 95,267 (0.6)	113 / 95,267 (0.1)	0.19 (0.15-0.23)	0.20 (0.16-0.25)
(vi) Region = New York State				
SARS-CoV-2 Test	2,826 / 49,862 (5.7)	772 / 49,862 (1.5)	0.26 (0.24-0.28)	0.26 (0.24-0.28)
COVID-19 Diagnosis	2,796 / 49,862 (5.6)	811 / 49,862 (1.6)	0.27 (0.26-0.30)	0.28 (0.26-0.31)
COVID-19 Hospitalization	486 / 49,862 (1.0)	136 / 49,862 (0.3)	0.28 (0.23-0.34)	0.33 (0.27-0.40)

Adjusted OR Forest Plot

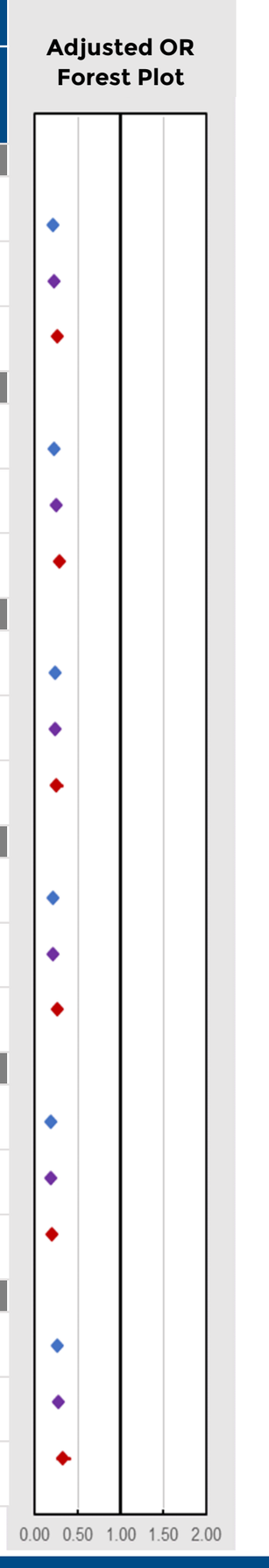


Figure 2a. COVID-19-Related Outcomes in "*Bone-Rx*" Cohort

	Incidence of Outcome Events by Exposure to Bisphosphonates: Number of Events / Non-User Patients (%)	Number of Events / User Patients (%)	Odds of Event: Crude OR (95%CI)	Adjusted OR (95%CI)
All Regions Combined				
SARS-CoV-2 Test	2,438 / 50,498 (4.8)	760 / 50,498 (1.5)	0.30 (0.28-0.33)	0.31 (0.28-0.33)
COVID-19 Diagnosis	1,307 / 50,498 (2.6)	461 / 50,498 (0.9)	0.35 (0.31-0.39)	0.35 (0.31-0.38)
COVID-19 Hospitalization	276 / 50,498 (0.5)	123 / 50,498 (0.2)	0.44 (0.36-0.55)	0.45 (0.36-0.56)

Adjusted OR Forest Plot

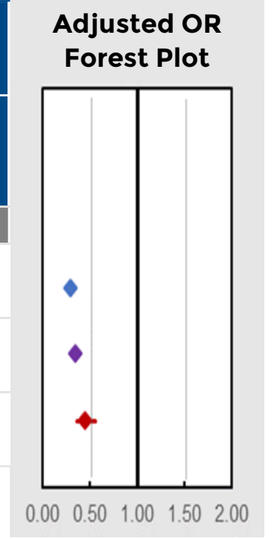


Figure 2b. COVID-19-Related Outcomes in "*Osteo-Dx-Rx*" Cohort

	Incidence of Outcome Events by Exposure to Bisphosphonates: Number of Events / Non-User Patients (%)	Number of Events / User Patients (%)	Odds of Event: Crude OR (95%CI)	Adjusted OR (95%CI)
All Regions Combined				
SARS-CoV-2 Test	395 / 7,949 (5.0)	115 / 7,949 (1.4)	0.28 (0.23-0.35)	0.28 (0.23-0.35)
COVID-19 Diagnosis	300 / 7,949 (3.8)	121 / 7,949 (1.5)	0.40 (0.32-0.49)	0.40 (0.32-0.49)
COVID-19 Hospitalization	47 / 7,949 (0.6)	21 / 7,949 (0.3)	0.45 (0.27-0.75)	0.45 (0.26-0.75)

Adjusted OR Forest Plot

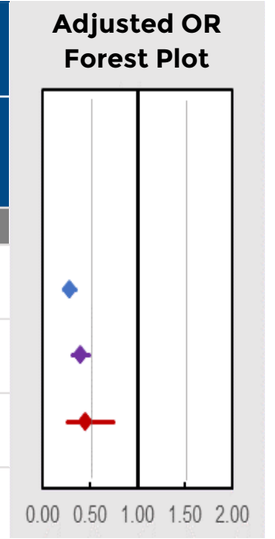


Figure 3. Other Respiratory Infection Outcomes in BP Users versus BP Non-Users

	Incidence of Outcome Events by Exposure to Bisphosphonates: Number of Events / Non-User Patients (%)	Number of Events / User Patients (%)	Odds of Event: Crude OR (95%CI)	Adjusted OR (95%CI)
Any Medical Service for Acute Bronchitis (Q3/Q4, 2019)				
Primary Cohort	19,613 / 326,638 (6.0)	4,525 / 326,638 (1.4)	0.22 (0.21-0.23)	0.23 (0.22-0.23)
Bone-Rx-Cohort	2,015 / 36,282 (5.6)	639 / 36,282 (1.8)	0.30 (0.28-0.33)	0.31 (0.29-0.34)
Osteo-Dx-Rx Cohort	361 / 5,591 (6.5)	103 / 5,591 (1.8)	0.27 (0.22-0.34)	0.28 (0.24-0.32)
Any Medical Service for Pneumonia (Q3/Q4, 2019)				
Primary Cohort	16,160 / 326,638 (5.0)	4,942 / 326,638 (1.5)	0.30 (0.29-0.30)	0.32 (0.31-0.34)
Bone-Rx-Cohort	2,522 / 36,282 (7.0)	996 / 36,282 (2.7)	0.38 (0.35-0.41)	0.40 (0.37-0.43)
Osteo-Dx-Rx Cohort	288 / 5,591 (5.2)	101 / 5,591 (1.8)	0.34 (0.27-0.43)	0.36 (0.33-0.39)

Adjusted OR Forest Plot

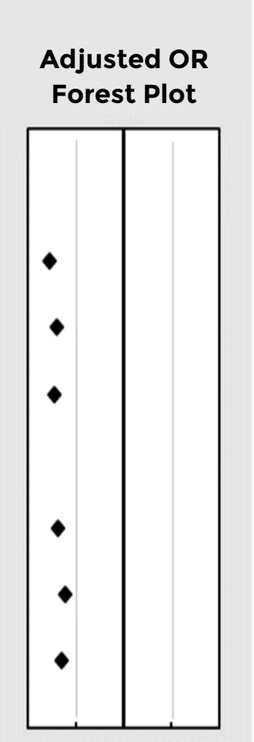


Figure 4a. Other Preventive Medications Sensitivity Analysis – Cohort Build

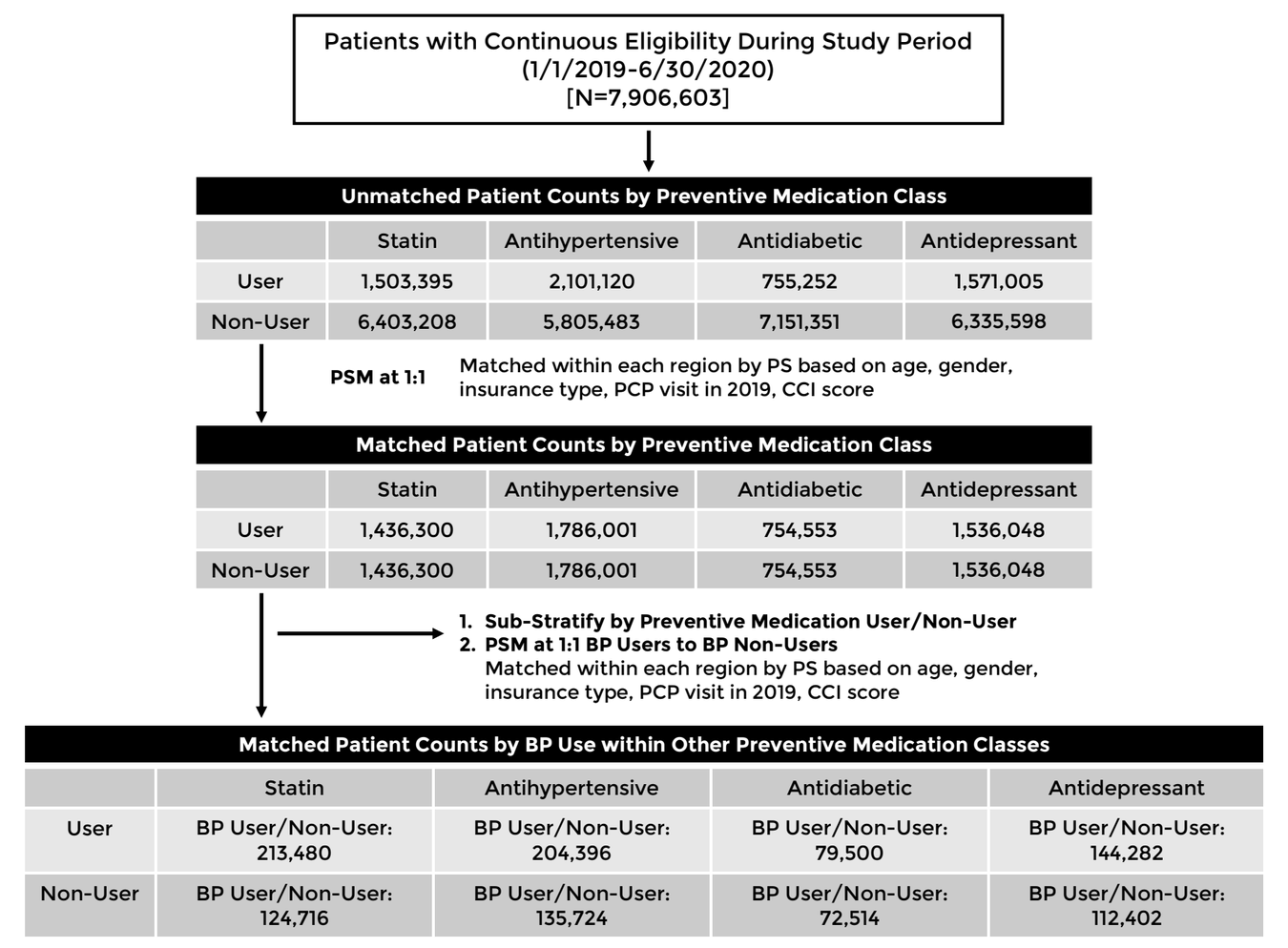


Figure 4b. Other Preventive Medications Sensitivity Analysis – Statins

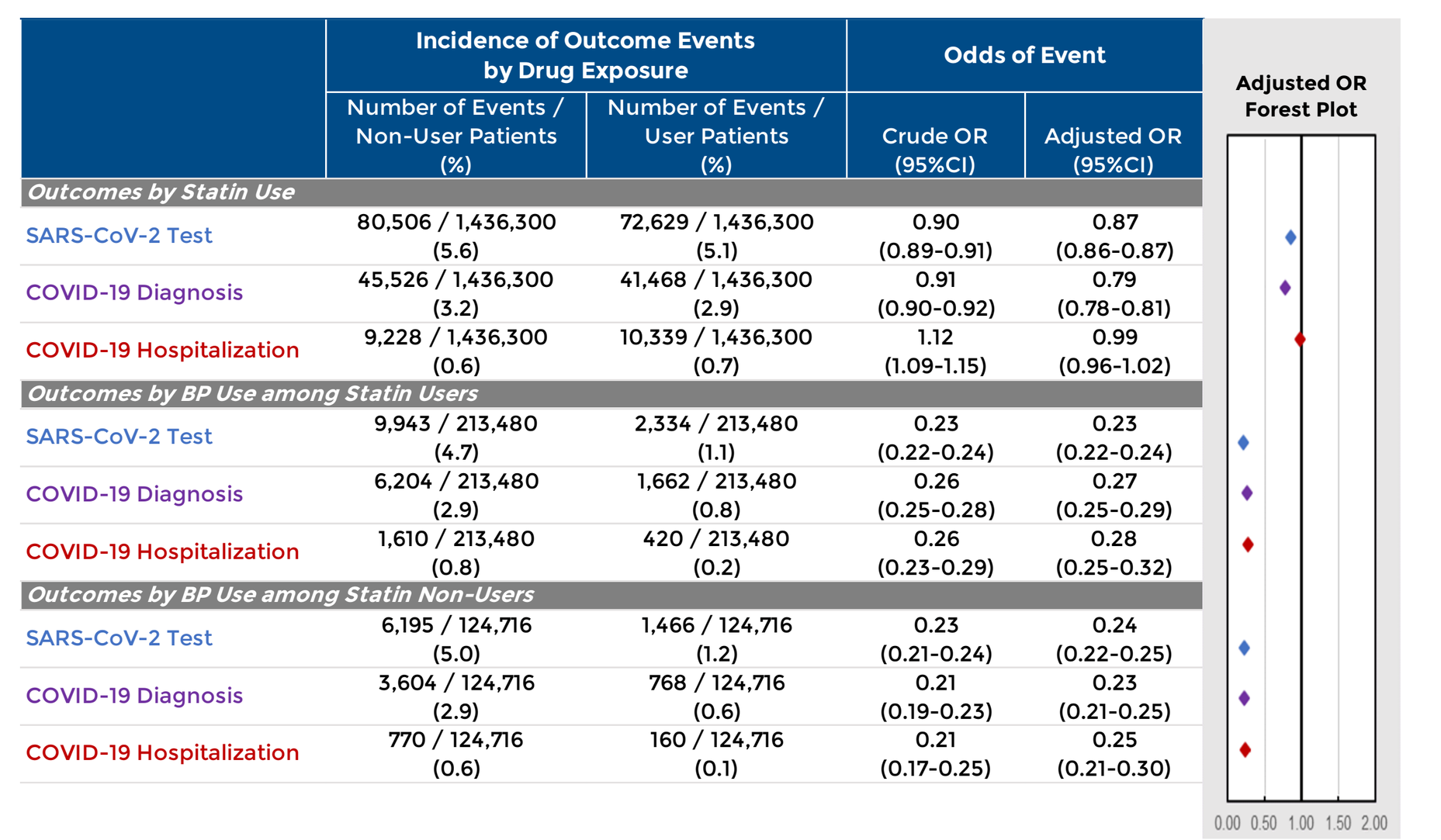


Figure 4c. Other Preventive Medications Sensitivity Analysis – Antihypertensives

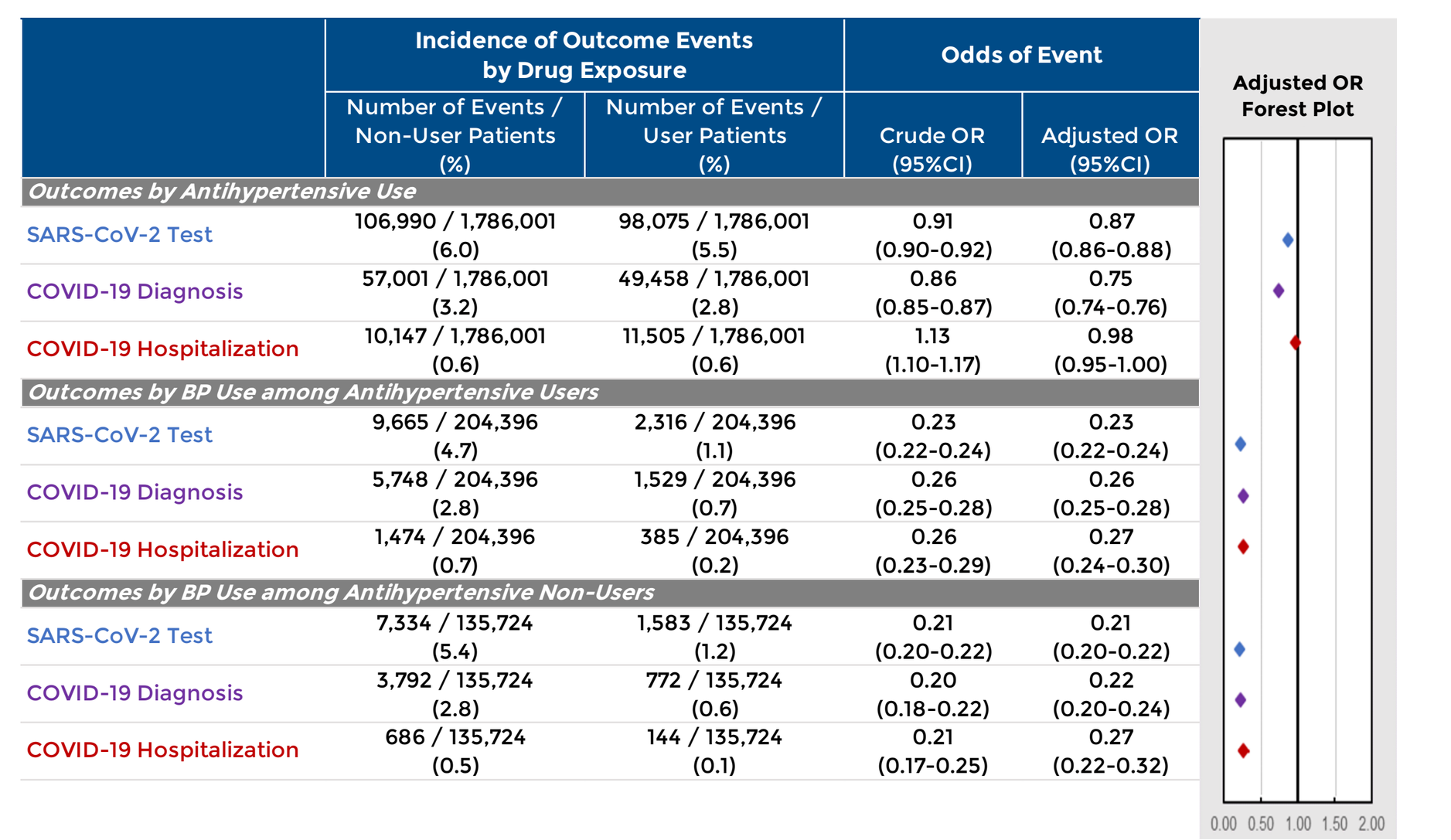


Figure 4d. Other Preventive Medications Sensitivity Analysis – Oral Antidiabetics

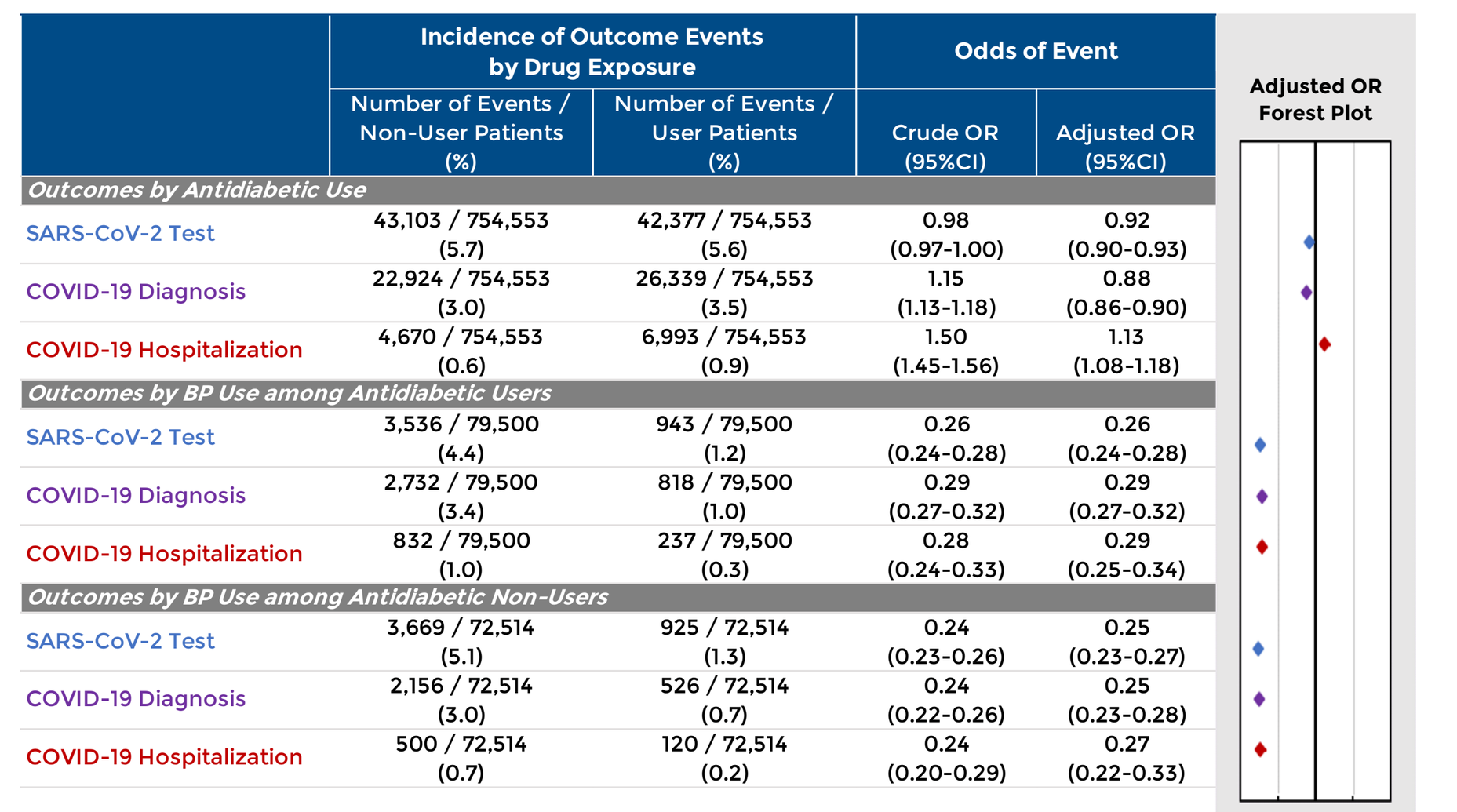
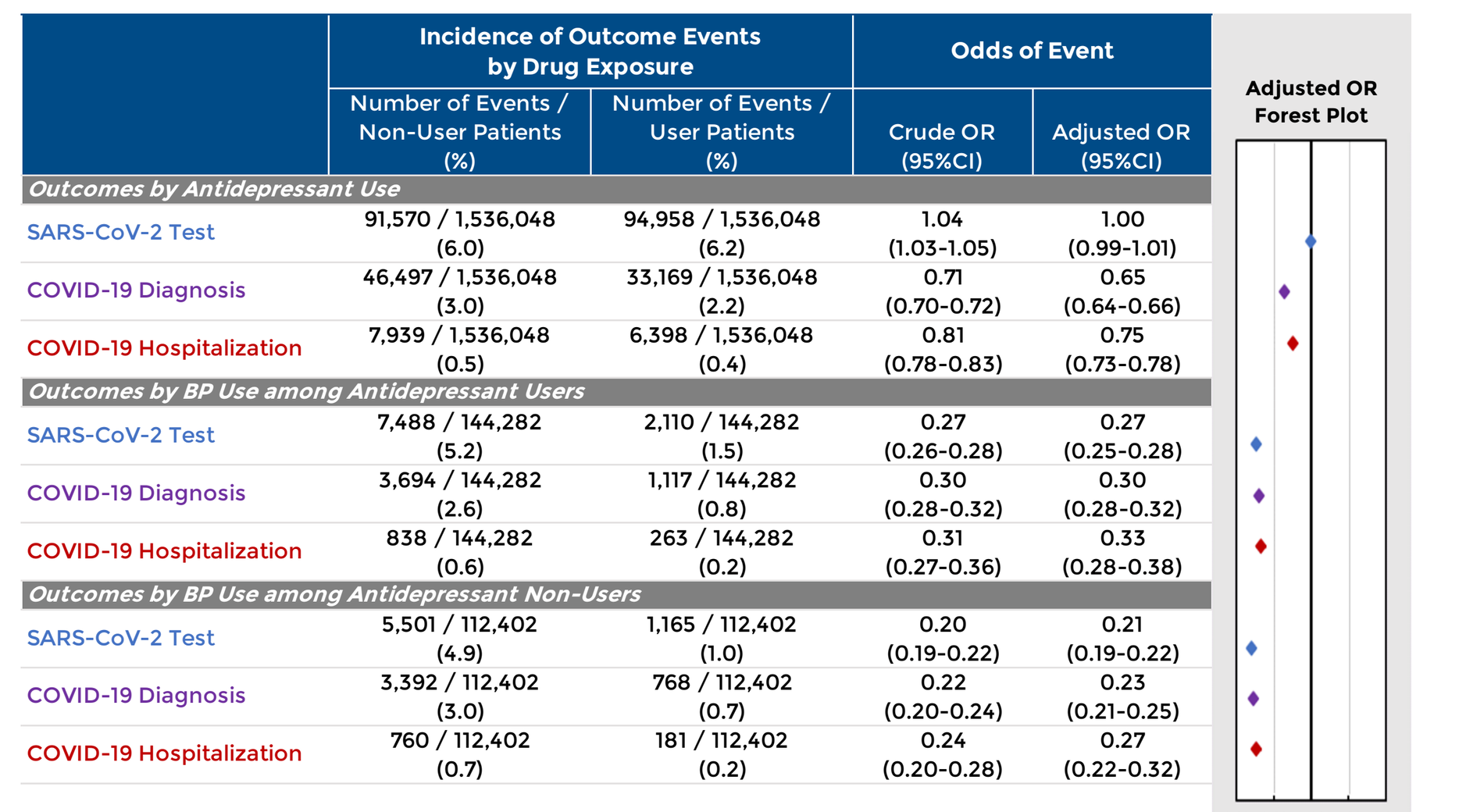


Figure 4e. Other Preventive Medications Sensitivity Analysis – Antidepressants



Limitations

- The first limitation of our study is the assumption that BP users and non-users had a similar risk of SARS-CoV-2 infection during the observation period. However, our dataset does not allow us to restrict patient observations to those with known exposure to SARS-CoV-2.
- A second limitation is the restricted information available to assess and match BP users to BP non-users by sociodemographic risk factors, such as socioeconomic status and racial/ethnic minority status, that are associated with COVID-19 incidence and mortality.
- A third limitation is that the healthy adherer effect could have potentially contributed to the association of BP use with a lower incidence of exploratory outcomes.
- A fourth limitation is potential censoring of patients who died during the observation period, resulting in truncated insurance eligibility and exclusion based on the continuous insurance eligibility requirement. However, modeling the impact of censoring by using death rates observed in BP users and non-users in the first six months of 2020 and attributing all deaths as COVID-19 related did not significantly alter the decreased odds of COVID-19 diagnosis in BP users.
- Additional limitations could also arise from comorbidities and misclassification bias due to the diagnostic and procedure codes used to identify study outcomes.

Conclusions

- This study examined the association between recent exposure to BPs and subsequent COVID-19-related outcomes during the initial outbreak of the COVID-19 pandemic in the US.
- Our findings demonstrate that amino-BP users experienced a three- to five-fold reduced incidence of SARS-CoV-2 testing, COVID-19 diagnosis, and COVID-19-related hospitalization during this period.
- This dramatic difference in outcomes was consistently observed when comparing BP users to BP non-users in a propensity score-matched general population, when comparing to users of other anti-resorptive bone medications, when further restricting the latter cohort to female osteoporosis patients that were matched by comorbidities within state of residence and by insurance type and when comparing BP users to BP non-users stratified by use of other preventive medications.
- Our findings are consistent with previous observational studies, prior to the advent of COVID-19, that had reported associations between BP use and reduced incidence of pneumonia and pneumonia-related mortality.[6, 13-14] Accordingly, we observed in our population that BP use was associated with decreased odds of medical services for acute bronchitis and pneumonia during the second half of 2019. Taken together, these findings suggest that BPs may play a protective role in respiratory tract infections from a variety of causes, including SARS-CoV-2.
- Other recent retrospective studies have explored, to some extent, associations of anti-resorptive medication use and COVID-19-related outcomes, albeit in much smaller patient populations than were analyzed here. One study found no differences in the COVID-19-related risk of hospitalization, ICU admission, and mortality among 1,997 female patients diagnosed with COVID-19 who received anti-osteoporosis medication as compared to propensity score-matched COVID-19 patients who were not receiving such drugs.[15] This study did not examine the incidence of COVID-19 among BP users, but it raises the possibility that the subset of BP users who do develop sufficient pathology to be diagnosed with COVID-19 may have a similar clinical course as BP non-users.
- Another retrospective cohort study in Italy examining the association of oral amino-BP use and incidence of COVID-19-related hospitalization and mortality found no difference between BP users and BP non-users or users of non-BP anti-resorptive medications.[16] However, the overall incidence of COVID-19 hospitalization in the primary cohort (151/126,370 patients, or 0.12%) of this study was markedly lower than in the present analysis (3,710/900,732 patients, or 0.41%).
- A third study examined the influence of various anti-osteoporosis drugs, including BPs, on the cumulative incidence of COVID-19 in 2,102 patients with non-inflammatory rheumatic conditions that were compared to population estimates in the same geographic region.[17] In this analysis, users of non-BP anti-resorptive medications and zoledronate, but not users of oral BPs, had a lower incidence and relative risk of COVID-19 diagnosis and hospitalization.
- The large size of our dataset allowed for a range of fully powered, stratified analyses to be performed to explore the robustness of our findings and to address unmeasured confounding factors and other sources of potential bias that can occur in retrospective studies using insurance claims data.
- Additional well-controlled prospective clinical studies will be needed to rigorously assess whether the observed reduction in COVID-19-related outcomes is directly caused by BPs and remains true in patient populations not commonly prescribed BPs.

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