Supplementary e-Appendix.

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M1: Drug exposure definitions

Treatment courses of all drugs were defined using the date-time stamps of administration in the electronic health record. Courses of long acting RAS-I and amlodipine were defined by consecutive doses where each dose was administered within 36 hours of the previous dose. We chose 36 hours based on the average duration of the medications and to allow a grace period for dosing delays which are not uncommon in the inpatient setting. The duration of each course was extended for 24 hours after the date and time of the last administered dose, based on the average duration of effect for this set of medications. Analgesic and short-acting RAS-I (captopril, quinapril, valsartan) courses were defined by consecutive doses where each dose was administered within 24 hours of the previous dose. As above, 24 hours was chosen based on the average duration and to allow a grace period. The duration of each course was extended for 12 hours after the date and time of the last administered dose, based on the average duration of effect for the analgesics of interest.

M2: Definition of pre-exposure acute kidney injury (AKI)

Pre-exposure AKI was defined by applying Kidney Disease Improving Global Outcomes (KDIGO) creatinine and dialysis criteria (1) from hospital admission up to the index date. Baseline creatinine for pre-exposure AKI was defined as the average of prior outpatient or prior hospital discharge values obtained from 365 days before to 7 days before the index hospitalization admission date. Where these data were missing, the baseline value was defined as the lowest value during the initial seven days of hospitalization, up to the index date. Pre-exposure AKI episodes were considered resolved if creatinine returned to within 25% of baseline. We excluded patients with non-resolved AKI that was within 2 weeks prior to the index date.

M3: Diagnosis code algorithms for defining comorbid illness

The table below details the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9 CM) and International Classification of Diseases, Tenth revision, Clinical Modification (ICD-10 CM) diagnosis code algorithms used to define eligibility and comorbid illness variables. Code algorithms were drawn from published validation studies where possible. In the absence of published algorithms, ICD-9 CM diagnosis code lists were manually reviewed, with corresponding ICD-10 CM codes identified via forward and backward mapping using the Centers for Medicare & Medicaid Services General Equivalence Mappings.[7] Comorbidities were considered present if coded during the index admission or a prior encounter within the two preceding years.

Table S1. Diagnosis code algorithms

Comorbidity	ICD-9 codes	ICD-10 codes
Atrial fibrillation[8]	427.31, 427.32	I48
Heart Failure[9,10]	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5– I42.9, I43.x, I50.x, P29.0
Myocardial infarction[9,10]	410.x, 412.x	I21.x, I22.x, I25.2
Hypertension[9,10,a]	401.x, 402.x–405.x	I10.x, I11.x–I13.x, I15.x, I16.x
Valvular disease[9,10]	093.2, 394.x–397.x, 424.x, 746.3–746.6, V42.2, V43.3	A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2– Z95.4

Cerebrovascular disease[9,10]	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x
Chronic pulmonary disease[9,10]	416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Diabetes mellitus[9,10]		
Non-complicated	250.0–250.3	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Complicated	250.4–250.9	E10.2–E10.8, E11.2–E11.8, E12.2– E12.8, E13.2–E13.8, E14.2–E14.8
Liver disease[9,10]	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4
Cancer[9,10]		
Non-metastatic	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Metastatic	196.x–199.x	C77.x–C80.x
Weight loss[9,10]	260.x–263.x, 783.2, 799.4	E40.x–E46.x, R63.4, R64
Fluid and electrolyte disorder[9,10]	253.6, 276.x	E22.2, E86.x, E87.x
Chronic kidney disease[9,11]	250.4x, 403.xx, 404.xx, 581.xx, 582.xx, 583.xx, 584.xx, 585.xx, 586.xx, 587.xx, 588.xx, V45.1, V56.xx, 39.95, 54.98	E10.2x, E11.2x, E13.2x, I12.x, I13.x, N02.2, N03.x, N04.3, N04.4, N04.8, N04.9, N05.2, N05.5, N05.8, N05.9, N18.x, N19.x, N25.x, N26.x, Z49.x, Z99.2x
Solid organ transplant[b,c]	V42.0, V42.1, V42.6, V42.7, 55.6, 996.81	Z94.0, Z94.2, Z94.1, Z94.3, Z94.4, T86.1, T86.2, T86.3, T86.4, Z48.21, Z48.22, Z48.23, Z48.24, Z48.280

Cardiac arrhythmias[9,10]	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0–427.4, 427.6–427.9, 785.0, 996.01, 996.04, V45.0, V53.3	I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Peripheral vascular disease[9,10]	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Pulmonary circulation disorder[9,10]	415.0, 415.1, 416.x, 417.0, 417.8, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9
Obstructive sleep apnea[b]	327.2 780.51 780.53 780.57	g47.3
HIV/AIDS[9,10]	042.x–044.x	B20.x–B22.x, B24.x

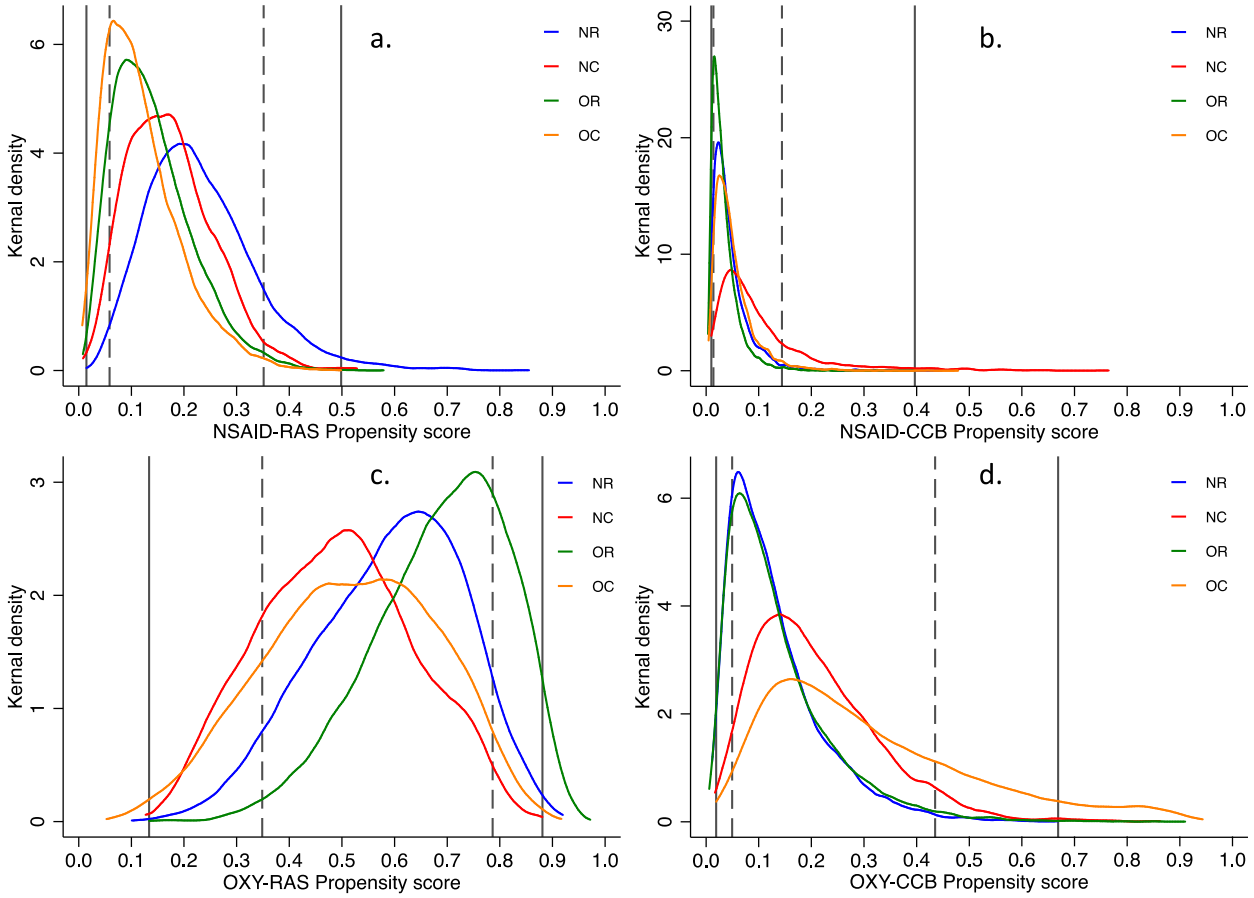
a- Modified from Quan (reference 3) to include I16; b- Code list generated via manual review of ICD-9 CM codes with corresponding ICD-10 CM identified via GEM; c- includes lung, heart, liver, and kidney transplant procedures;

M4: Propensity score trimming

To avoid violations of the positivity assumption (4), the primary analysis cohort was restricted to the subset of patients with overlapping multinomial propensity scores (hereafter termed Cohort B, the primary analysis cohort). This restriction was accomplished by trimming the propensity score distribution of each treatment category (x_1-x_4) as follows: 1) identify the minimum propensity score for treatment x_i for persons who actually received treatment x_i; this defines the lower bound of eligible propensity scores for treatment x_i ; 2) identify the maximum propensity score for treatment x_i for persons who received a treatment other than x_i ; 3) set the upper bound of eligible propensity scores for treatment x_i as the lowest value obtained from step 2; and 4) define Cohort B as the subset of patients who have a propensity score for each of the treatment categories that falls between the upper and lower bounds defined in steps 1-3. The multinomial propensity score distributions and the restriction bounds are shown in Figure S1.

In a secondary analysis, all models were repeated after trimming the tails of the overlapping multinomial propensity score distributions using the multinomial extensions to Sturmer's trimming rule as described by Yoshida (4,5). The rationale is to remove patients who were treated contrary to prediction, as these patients may be the most likely to have unmeasured factors that are related to both treatment and outcome (4). This trimming involves removing patients with propensity scores that are in the upper and lower tails of the overlapping multinomial propensity score distributions. For our analysis, we trimmed 1% from the upper and lower tails of the overlapping propensity score distribution for each treatment category (x_1-x_4) as follows: 1) identify the 1st percentile of the propensity score for treatment x_i for persons who actually received treatment x_i; this defines the lower bound for trimming propensity scores for treatment x_i ; 2) identify the 99th percentile of the propensity score for treatment x_i for persons who received a treatment other than x_i ; 3) set the upper trimming bound of the propensity score for treatment x_i as the lowest value obtained from step 2; and 4) define Cohort C (the trimmed cohort) as the subset of patients who have a propensity score for each of the treatment categories that falls between the upper and lower bounds defined in steps 1-3. The bounds for the trimmed cohort are shown in Figure S1.

Figure S1. Overlap of the multinomial propensity score distributions.



Each panel shows the distributions for one of the four estimated propensity scores across each of the exposure categories of interest. Indicator lines depict regions of the propensity scores that were included in the primary analysis (Cohort B, the area between the solid lines) and the sensitivity analysis that restricted to the subset of patients with propensity scores between the 1st and 99th percentiles of each propensity score distribution (Cohort C, the area between the dashed lines). a.- Distribution of the NSAID-RAS propensity score across exposure categories. b.- Distribution of the NSAID-CCB propensity score across exposure categories. c.- Distribution of the Oxycodone-RAS propensity score across exposure categories. d.-Distribution of the Oxycodone-CCB propensity score across exposure categories. NR- NSAID-RAS group; NC-NSAID-CCB group; OR- Oxycodone-RAS group; OC-Oxycodone-CCB group

M5: Methods for multivariable regression outcome modeling

The set of potential confounders for each model was the same set used in the primary analysis based on inverse probability of treatment weighting (Table 1). No variable selection procedure was applied in any of the models. The rationale for not applying variable selection is based on the following: 1) the events per variable ratio in the fully adjusted models was well above minimum thresholds for valid estimation and inference [2138 events and 78 covariate terms in the primary analysis (27 events per variable); 1187 events in the trimmed analysis (15 events per variable)]; and 2) variable selection procedures do not result in superior control of confounding and may in fact introduce bias (2).

All models included the assessment of collinearity among candidate variables. This was done by using Pearson and Spearman correlation coefficients and with cross-classification of categorical variables before multivariable modeling commenced, and with the variance inflation factor to assess collinearity in the fitted multivariable models. Linearity of the relationships between continuous

variables and acute kidney injury rate was examined visually with locally weighted regression (LOWESS) smoother plots. If evidence of non-linearity was observed, the variable was included in outcome models as a restricted cubic spline function, with four knots chosen according to Harrell's recommended percentiles (3).

Poisson regression models were checked for overdispersion by running a negative binomial regression model and evaluating the likelihood ratio test of the over-dispersion parameter (alpha). If overdispersion was detected, analysis proceeded with the negative binomial model. For multinomial logistic regression models, the independence of Irrelevant Alternatives (IIA) assumption (i.e. adding or deleting alternative outcome categories does not affect the odds among the remaining outcomes) was checked with the mlogtest command in Stata.

M6: Quantitative bias analysis

Background

Using the approach of VanderWeele (6), we estimated the effect of an unmeasured confounding variable on our interaction estimates by assuming a range of potential associations between the unmeasured confounder with both exposure and outcome. This approach requires the following assumptions: 1) That the interaction estimate is unconfounded given a hypothetical unmeasured confounder U and a set of measured covariates C; 2) That the unmeasured confounder is binary (i.e., coded as 1 = present and 0 = absent); and 3) that the unmeasured confounder does not interact with at least one of the exposures of interest. With these assumptions, the effect of the unmeasured confounder on interaction estimates on the difference scale can be estimated from the following parameters:

1. Associations of the unmeasured confounder with analgesic exposure (NSAID vs. Oxycodone) across strata of antihypertensive treatment (RAS-I vs. Amlodipine).
    a. Delta$_1$ (δ_1) = Association of U with NSAID vs. Oxycodone in the RAS-I cohort
    b. Delta$_0$ (δ_0) = Association of U with NSAID vs. Oxycodone in the Amlodipine cohort

2. Effect of the unmeasured confounder on AKI rate (on the rate difference scale [RD]) across strata of antihypertensive treatment
    a. Gamma$_1$ (γ_1) = RD for effect of U on AKI rate in both NSAID and Oxycodone subgroups in the RAS-I cohort
    b. Gamma$_0$ (γ_0) = RD for effect of U on AKI rate in both NSAID and Oxycodone subgroups in the Amlodipine cohort

With these parameters, bias of the additive interaction (β_{add}) due to the unmeasured confounder can be estimated by:

$$\beta_{add} = \delta_1 \gamma_1 - \delta_0 \gamma_0 \quad (1)$$

This equation shows that bias from unmeasured confounding is a function of 1) the difference-in-difference of the confounder prevalence across analgesia groups; and 2) the strength of the effect of the confounder on the outcome in each of the antihypertensive groups.

Further, if (γ_1) = (γ_0) = (γ) (i.e. U does not interact with RAS-I vs Amlodipine), then equation 1 simplifies to

$$\beta_{add} = (\delta_1 - \delta_0)\gamma \quad (2)$$

Here, with the effect of the confounder constant across all treatment groups, confounding is a function solely of the difference-in-difference of confounder prevalence. A key result of both 1 and 2 is that

confounding is not driven by covariate imbalance per se, but rather *differential imbalance* of covariates across analgesia and antihypertensive groups.

Once β_{add} has been calculated, a corrected interaction term and confidence limits can be obtained by subtracting β_{add} from each parameter (point estimate, upper, and lower confidence limit). Negative β_{add} terms indicate that the estimated interaction parameter is underestimating the true interaction, while positive β_{add} terms indicate that the estimated interaction parameter is overestimating the true interaction.

Bias analysis methods and results

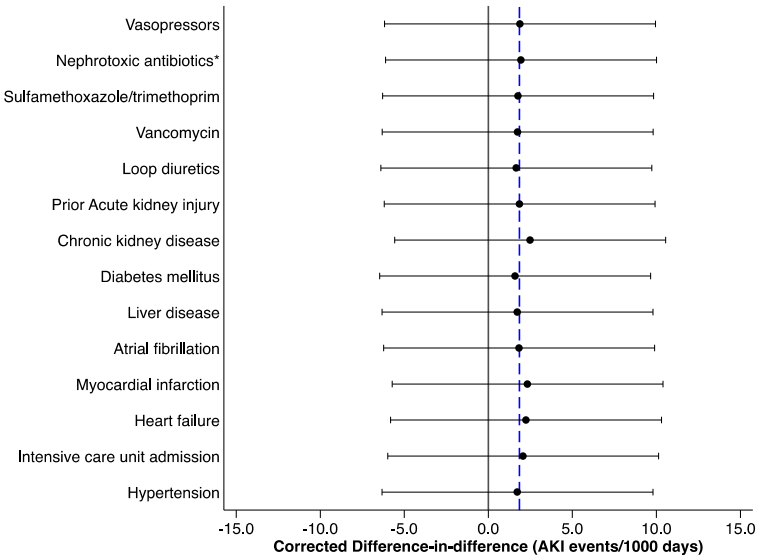
We used two general approaches to select parameters for the bias analysis (γ and δ). First, we specified bias parameters for equation 1 using the observed values from a select set of ***measured*** confounders. We then used these parameters to estimate bias ***assuming that each variable was unmeasured***. The rationale for this was to determine a realistic set of parameters based on known confounders. We selected variables with the largest unadjusted effects on AKI rate. Second, we used equation 2 to examine bias under a broader range of scenarios to determine what magnitude of unmeasured confounding would be needed to change the conclusions of the primary analysis.

Table S2. Bias analysis parameters for a set of measured covariates ***hypothetically assumed to be unmeasured***

	RAS cohort				Amlodipine cohort				
Covariate	**NSAID**	**Oxy**	δ_1	γ_1	**NSAID**	**Oxy**	δ_0	γ_0	β_{add}
Vasopressors	0.036	0.041	-0.005	5.56	0.041	0.041	0.000	19.75	-0.03
Nephrotoxic antibiotics*	0.030	0.033	-0.003	16.90	0.035	0.034	0.001	35.80	-0.09
Sulfamethoxazole / trimethoprim	0.025	0.029	-0.004	20.70	0.018	0.028	-0.010	17.00	0.09
Vancomycin	0.215	0.222	-0.007	2.46	0.201	0.212	-0.011	11.81	0.11
Loop diuretics	0.260	0.253	0.007	18.27	0.234	0.238	-0.004	16.49	0.19
Prior Acute kidney injury	0.096	0.098	-0.002	8.01	0.091	0.092	-0.001	12.49	0.00
Chronic kidney disease	0.103	0.114	-0.011	25.77	0.129	0.110	0.019	18.38	-0.63
Diabetes mellitus	0.353	0.400	-0.047	7.31	0.2235	0.277	-0.053	11.38	0.26
Liver disease	0.051	0.048	0.003	11.30	0.051	0.060	-0.009	10.22	0.13
Atrial fibrillation	0.155	0.213	-0.058	9.82	0.092	0.127	-0.035	16.99	0.03
Myocardial infarction	0.142	0.187	-0.045	12.24	0.094	0.099	-0.005	14.92	-0.48
Heart failure	0.243	0.326	-0.083	16.80	0.103	0.147	-0.044	22.90	-0.39
Intensive care unit admission	0.119	0.167	-0.048	7.34	0.170	0.181	-0.010	13.38	-0.21
Hypertension	0.884	0.879	0.005	-2.56	0.902	0.925	-0.023	6.04	0.13

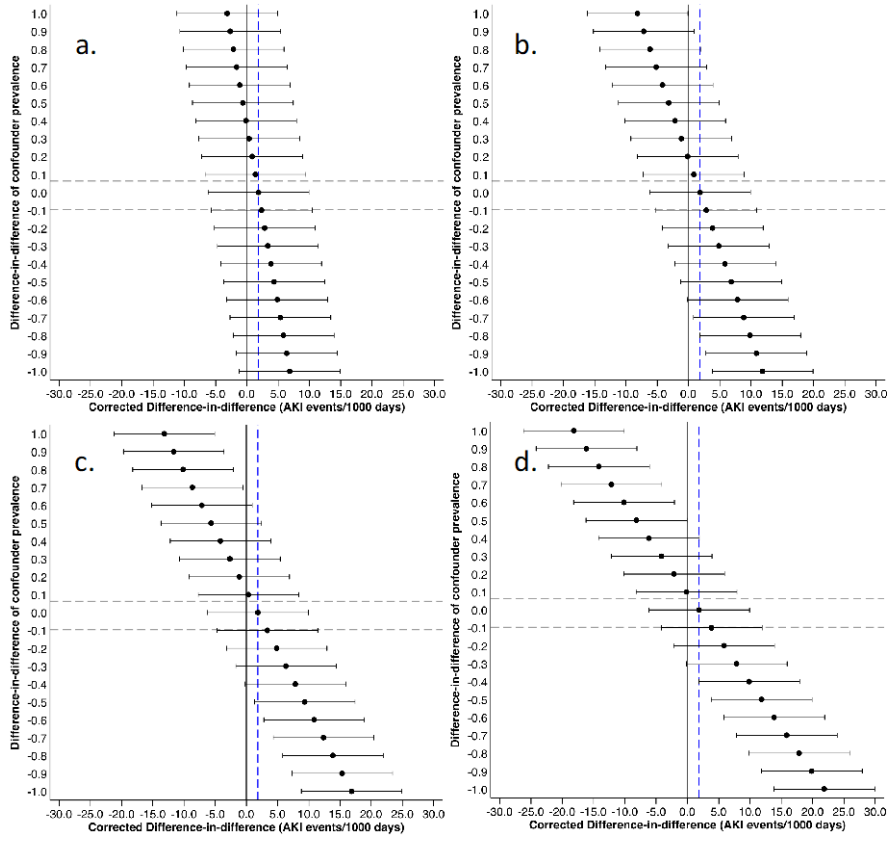
For each covariate, the prevalence differences were obtained from those reported in Table S2, and the associations with AKI rate were obtained from unadjusted analysis of the rate difference in each strata of antihypertensive treatment.

Figure S2. Corrected interaction estimates and confidence intervals for a set of measured covariates *hypothetically assumed to be unmeasured*



The figure shows corrected interaction estimates and confidence intervals for a set of measured covariates that were *hypothetically assumed to be unmeasured*. The vertical blue dashed line represents the interaction estimate from the primary analysis (1.85 excess AKI events / 1000 days). Corrected confidence intervals that do not include the reference line at zero represents scenarios where the conclusions of the primary analysis would be changed by control of the hypothetical unmeasured confounder.

Figure S3. Bias as a function of the difference-in-difference of the prevalence of an unmeasured confounder and the unmeasured confounder's association with outcome.



Each panel shows a series of interaction estimates (bars represent corrected confidence intervals) on the rate difference scale after correcting for potential bias from an unmeasured confounder. The y-axis of each panel represents a range of values for the differential imbalance of confounder of the NSAID vs. Oxycodone comparison across strata of antihypertensive treatment (RAS-I vs. amlodipine). For example, a value of 1 represents a scenario where an unmeasured confounder is perfectly balanced in one strata (i.e., equal prevalence in NSAID and oxycodone groups), but perfectly imbalanced in the other strata (i.e., prevalence of 0% NSAID group and 100% in oxycodone group) – an extreme degree of imbalance. The horizontal grey dashed lines denote the range of differential imbalance values observed for the set of measured covariates in Table S2. The vertical blue dashed line represents the interaction estimate from the primary analysis (1.85 excess AKI events / 1000 days). Corrected confidence intervals that do not include the reference line at zero represents scenarios where the conclusions of the primary analysis would be changed by control of the hypothetical unmeasured confounder. The four panels show estimates assuming increasing strength of effect on AKI for the unmeasured confounder on the rate difference scale. **a-** unmeasured confounder increases AKI rate by 5 / 1000 days; **b-** unmeasured confounder increases AKI rate by 10 / 1000 days; **c-** unmeasured confounder increases AKI rate by 15 / 1000 days; **d-** unmeasured confounder increases AKI rate by 20 / 1000 days;

Table S3. Drug dosing

Drug class	Count (%)	Median dose (mg) per day (IQR)
NSAIDS		
Ibuprofen	2,285 (43.2)	800 (600, 1200)
Indomethacin	192 (3.6)	75 (50, 100)
Ketorolac	2,255 (42.6)	30 (30, 60)
Nabumetone	69 (1.3)	1000 (750, 1500)
Naproxen	495 (9.4)	750 (500, 1000)
RAS-I		
ACE inhibitors		
Benazepril	519 (2.4)	20 (10, 20)
Captopril	248 (1.2)	25 (12.5, 50)
Enalapril	3,010 (13.9)	10 (5, 15)
Lisinopril	9,806 (45.4)	10 (5, 20)
Quinapril	410 (1.9)	20 (10, 30)
Ramipril	1,256 (5.8)	5 (5, 10)
ARB		
Irbesartan	363 (1.7)	150 (150, 300)
Losartan	3,073 (14.2)	50 (50, 100)
Valsartan	2,924 (13.5)	160 (80, 160)
Amlodipine	n.a.	5 (5, 10)
Oxycodone	n.a.	20 (10, 30)

Table S4. Baseline characteristics in the unweighted population (Cohort A)

	RAS cohort			Amlodipine cohort		
	NSAID (n=4250)	**Oxycodone (n=17610)**	**smd**	**NSAID (n=1181)**	**Oxycodone (n=4700)**	**smd**
Demographics						
Treatment duration, days, median	2.0	2.4	0.268	2.0	2.5	0.277
Age, years, mean	60.2	63.6	0.262	60.1	64.3	0.319
Female sex, %	52.8	45.1	0.154	53.5	49.6	0.078
Race, %						
White	52.6	55.7	0.062	50.7	46.8	0.078
Black	38	34.1	0.082	41.8	43.7	0.038
Other / Unk	9.4	10.2	0.028	7.5	9.5	0.069
BMI, mean	31.4	31.2	0.023	30.5	30.4	0.006
Year, mean	2010	2010	0.074	2011	2011	0.089
Hospital admission characteristics						
Center, %						
CCH	1.2	0.7	0.062	1.2	0.6	0.073
HUP	50.4	47.1	0.066	45.7	42.7	0.060
PAH	19.9	24.2	0.102	26.2	24.2	0.048
PMC	28.5	27.9	0.012	26.8	32.5	0.125
Surgical Admission, %	54.8	62.5	0.157	59.2	68.1	0.184
Location of initial presentation, %						
ED	36.7	27.9	0.197	35.9	27.3	0.191
ICU	6	8.7	0.100	6.6	5.9	0.026
OR	24.5	25.3	0.018	28.9	27.5	0.032
Floor	28	31.2	0.070	23.2	26.4	0.069
Other	4.8	7	0.078	5.4	13	0.277
LOS prior to index, days, mean	3	3.1	0.003	3.3	2.6	0.155
ICU care at index date, %	12	16.8	0.129	17	18.1	0.029
Peri-operative recency, %						
Not in peri-operative period	77.8	74.4	0.076	68.6	70.1	0.034
POD zero	1.9	1.6	0.026	2.6	2.8	0.010
POD one	10.8	11.8	0.028	17.5	16	0.044
POD two	5.9	9	0.110	6.5	8	0.054
POD three	3.6	3.2	0.019	4.7	3.1	0.094
Mechanical ventilation, %	2.5	3.3	0.042	5	6.3	0.069
Comorbidities, %						
Heart failure	24.3	32.6	0.187	10.3	14.7	0.098
Myocardial infarction	14.2	18.7	0.124	9.4	9.9	0.013
Hypertension	88.4	87.9	0.016	90.2	92.5	0.073
Cardiac arrhythmias	19.2	23.2	0.100	14.8	16.7	0.047
Atrial fibrillation	15.5	21.3	0.149	9.2	12.7	0.090

Valvular disease	14.9	19.5	0.121	9	11.8	0.076
Cerebrovascular disease	9.9	10.7	0.029	8.2	10.9	0.087
Peripheral vascular disease	10.8	18	0.196	8.9	17	0.219
Pulmonary circulation disorder	8.6	11.5	0.095	5	6.6	0.054
Chronic pulmonary disease	28.8	29.7	0.021	29.2	25.4	0.084
Liver disease	5.1	4.8	0.012	5.1	6	0.044
Diabetes mellitus						
None	64.7	60	0.098	77.6	72.3	0.111
Non-complicated	28.3	30.5	0.050	18	20.6	0.059
Complicated	7.1	9.5	0.087	4.4	7.1	0.094
Chronic kidney disease	6.5	13.5	0.210	7.1	17	0.298
Weight loss	6.4	6.4	0.001	7.9	8	0.005
Fluid and electrolyte disorder	25.1	26.7	0.036	27.6	29.3	0.039
Cancer						
None	83.8	83.6	0.006	79.5	76.2	0.087
Non-metastatic	11.3	11.3	0.002	13.3	15.9	0.080
Metastatic	4.9	5.2	0.013	7.2	7.9	0.031
Obstructive sleep apnea	15.4	15.5	0.005	11.9	13.2	0.037
HIV/AIDS	1.6	1.4	0.016	1.5	1.3	0.019
Kidney function						
GFR, ml/min/1.73 m2, mean	78.8	72.1	0.294	82.3	72.6	0.422
Prior acute kidney injury, %	8.8	11	0.070	10.3	9.7	0.019
Laboratory values, mean						
WBC, x 108 cells/L	9.7	9.8	0.019	10.3	10.2	0.028
Hemoglobin, g/dL	11.4	11.1	0.177	11.2	10.9	0.147
Platelets, x 1011 cells/L	242.5	234.8	0.077	246.3	235.2	0.111
Chloride, mEq/L	103.7	103.5	0.045	104	104.1	0.030
Potassium, mEq/L	4.1	4.1	0.086	4	4.1	0.096
Medications, %						
Selective beta1-blockers	38.7	42.3	0.074	37.6	38.1	0.010
Combined alpha + beta blockers	11.3	16.1	0.135	7.6	11.1	0.101
Loop diuretics	25.7	32.1	0.143	19.1	17.3	0.039
Thiazide diuretics	19	16.5	0.067	10.7	9.3	0.038
Hydralazine	7.1	9.7	0.090	9.2	10.3	0.037
Other antihypertensives[a]	8	9.5	0.053	7.1	7.7	0.021
Acid suppressants						
None	40.4	39.3	0.022	40.4	40.7	0.007
H2RA	22.3	24.6	0.053	24.5	24	0.012
PPI	37.4	36.1	0.026	35.1	35.3	0.004

Broad spectrum antibiotics[b]	11.9	12	0.004	12.6	13.3	0.022
Narrow spectrum antibiotics[c]	33.9	40.1	0.126	42.2	46.7	0.093
Vancomycin	17.4	22.4	0.120	20.6	29.4	0.212
Sulfamethoxazole / Trimethoprim	2.2	3	0.046	2	3	0.058
Other nephrotoxic antibiotics[d]	3	3.2	0.015	4.9	3.6	0.071
Other nephrotoxins[e]	1.5	2	0.035	1.9	3.4	0.108
Vasopressors	2.9	4.4	0.070	6.5	4.6	0.094

a- propranolol, clonidine, doxazosin, terazosin; b- carbapenems, cefepime, piperacillin-tazobactam, fluoroquinolones, aztreonam; c- first and second generation cephalosporins, macrolides, amoxicillin, penicillin, tetracycline, nitrofurantoin, ampicillin-sulbactam; d- aminoglycosides (amikacin, gentamicin, tobramycin), colistin; e- carboplatin, cisplatin, ifosfamide, cyclosporine, tacrolimus, methotrexate, amphotericin, acyclovir. IQR- interquartile range; smd-absolute standardized mean difference; SD- standard deviation; BMI- body mass index; CCH- Chester County Hospital; HUP- Hospital of the University of Pennsylvania; PMC- Presbyterian Medical Center; PAH- Pennsylvania Hospital; ED- emergency department; ICU- intensive care unit; OR- operating room; LOS- length of stay; POD-postoperative day; AIDS- acquired immunodeficiency syndrome; HIV- human immunodeficiency virus; GFR- glomerular filtration rate; WBC- white blood cells; H2RA-histamine-2 receptor antagonist; PPI- proton pump inhibitor

Table S5 Unadjusted acute kidney injury rates and interaction analysis on the difference scale in Cohort A

	Oxycodone rate[a]	**NSAID rate[a]**	**NSAID RD[a] within antihypertensive strata (95% CI)**
Amlodipine	22.4	22.5	0.10 (-5.13, 5.33)
RAS	26.0	25.5	-0.52 (-3.48, 2.44)
RAS RD[a] within analgesic strata (95% CI)	3.62 (1.04, 6.19)	3.00 (-2.43, 8.43)	Difference-in-difference: -0.62 (-6.64, 5.39)

a. Acute kidney injury events / thousand person days; RR- rate ratio; RD- rate difference; CI- confidence interval; BP- blood pressure group (RAS vs. amlodipine)

Table S6 Unadjusted acute kidney injury rates and interaction analysis on the ratio scale in Cohort A

	Oxycodone rate[a]	**NSAID rate[a]**	**NSAID RR within antihypertensive strata (95% CI)**
Amlodipine	22.4	22.5	1.00 (0.79, 1.27)
RAS	26.0	25.5	0.98 (0.87, 1.10)
RAS RR within analgesic strata (95% CI)	1.16 (1.03, 1.29)	1.13 0.89, 1.43)	Ratio of rate ratios: 0.97 (0.75, 1.27)

a. Acute kidney injury events / thousand person days; RR- rate ratio; RD- rate difference; CI- confidence interval; BP- blood pressure group (RAS vs. amlodipine)

Table S7. Interaction analyses of acute kidney injury rate per 1000 days on the difference scale

Primary analysis- Unadjusted			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	22.4	22.5	0.10 (-5.13, 5.33)
RAS-I	26.0	25.5	-0.52 (-3.48, 2.44)
IRD	3.62 (1.05, 6.19)	3.00 (-2.43, 8.43)	**-0.62 (-6.64, 5.39)**
Primary analysis- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	19.9	24.0	4.13 (-2.83, 11.09)
RAS-I	23.1	29.1	5.97 (1.88, 10.07)
IRD	3.22 (0.29, 6.14)	5.06 (-2.46, 12.60)	**1.85 (-6.23, 9.92)**
Primary analysis- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	15.8	21.0	5.21 (-1.96, 12.38)
RAS-I	20.6	25.6	4.94 (0.97, 8,90)
IRD	4.79 (1.68, 7.92)	4.52 (-3.05, 12.11)	**-0.27 (-8.46, 7.92)**
Primary analysis- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	22.1	27.2	5.65 (-0.66, 11.96)
RAS-I	24.3	30.0	5.67 (2.20, 9.14)
IRD	2.29 (-0.35, 4.93)	2.31 (-4.38, 9.00)	**0.02 (-7.09, 7.14)**
Duration of at least three days- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	19.2	18.6	-0.59 (-10.24, 9.05)
RAS-I	20.5	22.7	2.21 (-2.79, 7.20)
IRD	1.28 (-2.49, 5.06)	4.09 (-5.88, 14.05)	**2.80 (-7.88, 13.48)**
Duration of at least three days- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	16.1	18.3	2.18 (-7.89, 12.24)
RAS-I	18.2	21.3	3.01 (-1.99, 8.03)
IRD	2.14 (-1.42, 5.69)	2.97 (-7.38, 13.32)	**0.83 (-10.17, 11.84)**
Duration at least three days- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	22.1	21.3	-0.80 (-9.49, 7.88)
RAS-I	21.7	25.9	4.19 (-0.77, 9.14)
IRD	-0.33 (-3.91, 3.25)	4.66 (-4.67 13.99)	**4.99 (-4.91, 14.89)**
Concomitant diuretics- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	26.4	28.1	1.76 (-11.45, 14.98)
RAS-I	32.1	43.8	11.66 (4.96, 18.35)

IRD	5.73 (-0.05, 11.51)	15.62 (1.62, 29.62)	**9.89 (-5.04, 24.83)**
Concomitant diuretics- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	23.1	26.5	3.37 (-10.25, 16.98)
RAS-I	28.9	41.1	12.23 (5.41, 19.04)
IRD	5.79 (0.12, 11.46)	14.64 (0.49, 28.79)	**8.86 (-6.29, 24.01)**
Concomitant diuretics- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	30.3	31.7	1.31 (-10.75, 13.36)
RAS-I	32.6	44.6	11.92 (5.45, 18.39)
IRD	2.30 (-3.27, 7.87)	12.9 (0.44, 25.40)	**10.62 (-2.91, 24.14)**
Without concomitant diuretics- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	**IRD**
Amlodipine	17.3	20.1	2.72 (-4.73, 10.18)
RAS-I	18.4	17.1	-1.24 (-4.96, 2.48)
IRD	1.01 (-2.29, 4.32)	-2.96 (-10.58, 4.67)	**-3.97 (-12.28, 4.34)**
Without concomitant diuretics- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	15.5	20.1	4.65 (-2.84, 12.14)
RAS-I	17.6	16.9	-0.65 (-4.51, 3.21)
IRD	2.13 (-1.16, 5.41)	-3.17 (-10.90, 4.56)	**-5.29 (-13.69, 3.10)**
Without concomitant diuretics- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	16.9	23.8	6.78 (-0.06, 13.63)
RAS-I	18.6	19.1	0.41 (-3.29, 4.12)
IRD	1.67 (-1.11, 4.45)	-4.70 (-11.97, 2.56)	**-6.37 (-14.05,1.31)**
Age at least 65 years- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	23.3	24.1	0.76 (-9.68, 11.19)
RAS-I	25.0	28.6	3.6 (-2.09, 9.33)
IRD	1.71 (-3.01, 6.42)	4.57 (-6.43, 15.57)	**2.86 (-9.11, 14.84)**
Age at least 65 years- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	18.9	19.6	0.69 (-10.10, 11.48)
RAS-I	22.2	23.3	1.11 (-4.82, 7.05)
IRD	3.24 (-1.72, 8.21)	3.67 (-7.59, 14.94)	**0.43 (-11.89, 12.74)**
Age at least 65 years- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	25.1	31.8	6.75 (-4.02, 17.53)

RAS-I	27.5	35.3	7.84 (1.89, 13.79)
IRD	2.42 (-1.54, 6.39)	3.52 (-8.11, 15.15)	**1.09 (-11.09, 13.27)**
Age less than 65 years- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	16.9	20.6	3.61 (-4.78, 11.99)
RAS-I	19.5	24.3	4.77 (0.29, 9.24)
IRD	2.57 (-1.76, 6.89)	3.73 (-4.74, 12.19)	**1.16 (-8.3, 10.67)**
Age less than 65 years- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	9.7	20.9	11.17 (2.17, 20.18)
RAS-I	15.9	20.4	4.41 (-0.31, 9.13)
IRD	6.29 (2.49, 10.09)	-0.46 (-9.89, 8.96)	**-6.76 (-16.93, 3.40)**
Age less than 65 years- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	19.8	24.9	5.16 (-2.61, 12.95)
RAS-I	21.7	26.1	4.33 (0.16, 8.49)
IRD	1.90 (-1.76, 5.57)	1.07 (-7.00, 9.14)	**-0.84 (-9.56, 7.88)**
With Diabetes mellitus II- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	21.9	19.4	-2.49 (-13.89, 8.89)
RAS-I	24.9	29.4	4.39 (-1.68, 10.47)
IRD	3.06 (-2.45, 8.57)	9.95 (-1.79, 21.69)	**6.89 (-6.11, 19.89)**
With Diabetes mellitus II- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	16.9	27.9	11.00 (-5.28, 27.28)
RAS-I	22.5	28.8	6.30 (-1.24, 13.85)
IRD	5.68 (-0.90, 12.25)	0.98 (-15.72, 17.67)	**-4.69 (-22.64, 13.24)**
With Diabetes mellitus II- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	29.4	28.9	-0.48 (-13.61, 12.64)
RAS-I	29.9	36.3	6.39 (-0.05, 12.82)
IRD	0.56 (-4.83, 5.96)	7.43 (-6.14, 21.01)	**6.87 (-7.61, 21.35)**
Without Diabetes mellitus II- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	16.7	24.5	7.7 (-1.15, 16.62)
RAS-I	19.2	24.7	5.49 (1.24, 9.75)
IRD	2.45 (-0.79, 5.69)	0.21 (-9.16, 9.59)	**-2.24 (-12.09, 7.61)**
Without Diabetes mellitus II- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRD

Amlodipine	14.4	21.4	7.07 (-0.66, 14.81)
RAS-I	17.1	21.9	4.81 (0.08, 9.54)
IRD	2.73 (-0.83, 6.28)	0.46 (-7.89, 8.82)	**-2.26 (-11.36, 6.84)**
Without Diabetes mellitus II- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRD
Amlodipine	18.2	26.0	7.82 (0.96, 14.69)
RAS-I	21.2	26.8	5.63 (1.52, 9.74)
IRD	3.00 (0.09, 5.91)	0.81 (-6.63, 8.25)	**-2.19 (-10.08, 5.69)**

a- rate per 1000 person-days; IRD- Incidence rate difference

Table S8. Interaction analyses of acute kidney injury rate per 1000 days on the ratio scale

Primary analysis- Unadjusted			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	22.4	22.5	1.00 (0.79, 1.27)
RAS-I	26.0	25.5	0.98 (0.87, 1.10)
IRR	1.16 (1.03, 1.29)	1.13 (0.89, 1.43)	**0.97 (0.75, 1.27)**
Primary analysis- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	19.9	24.0	1.21 (0.89, 1.63)
RAS-I	23.1	29.1	1.26 (1.09, 1.45)
IRR	1.16 (1.00, 1.34)	1.21 (0.89, 1.63)	**1.04 (0.74, 1.45)**
Primary analysis- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	15.8	21.0	1.33 (0.93, 1.91)
RAS-I	20.6	25.6	1.24 (1.05, 1.45)
IRR	1.30 (1.08, 1.57)	1.22 (0.86, 1.72)	**0.93 (0.63, 1.38)**
Primary analysis- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	22.1	27.2	1.26 (0.99, 1.59)
RAS-I	24.3	30.0	1.23 (1.09, 1.39)
IRR	1.10 (0.98, 1.24)	1.08 (0.85, 1.37)	**0.98 (0.76, 1.28)**
Duration of at least three days- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	19.2	18.6	0.97 (0.58, 1.63)
RAS-I	20.5	22.7	1.11 (0.89, 1.38)
IRR	1.07 (0.88, 1.29)	1.22 (0.73, 2.05)	**1.14 (0.66, 1.99)**
Duration of at least three days- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	16.1	18.3	1.14 (0.65, 1.99)
RAS-I	18.2	21.3	1.17 (0.92, 1.48)
IRR	1.13 (0.91, 1.41)	1.16 (0.67, 2.02)	**1.03 (0.57, 1.86)**
Duration at least three days- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	22.1	21.3	0.96 (0.64, 1.45)
RAS-I	21.7	25.9	1.19 (0.98, 1.45)
IRR	0.99 (0.84, 1.16)	1.22 (0.80, 1.86)	**1.24 (0.79, 1.93)**
Concomitant diuretics- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	26.4	28.1	1.07 (0.66, 1.71)
RAS-I	32.1	43.8	1.36 (1.16, 1.59)

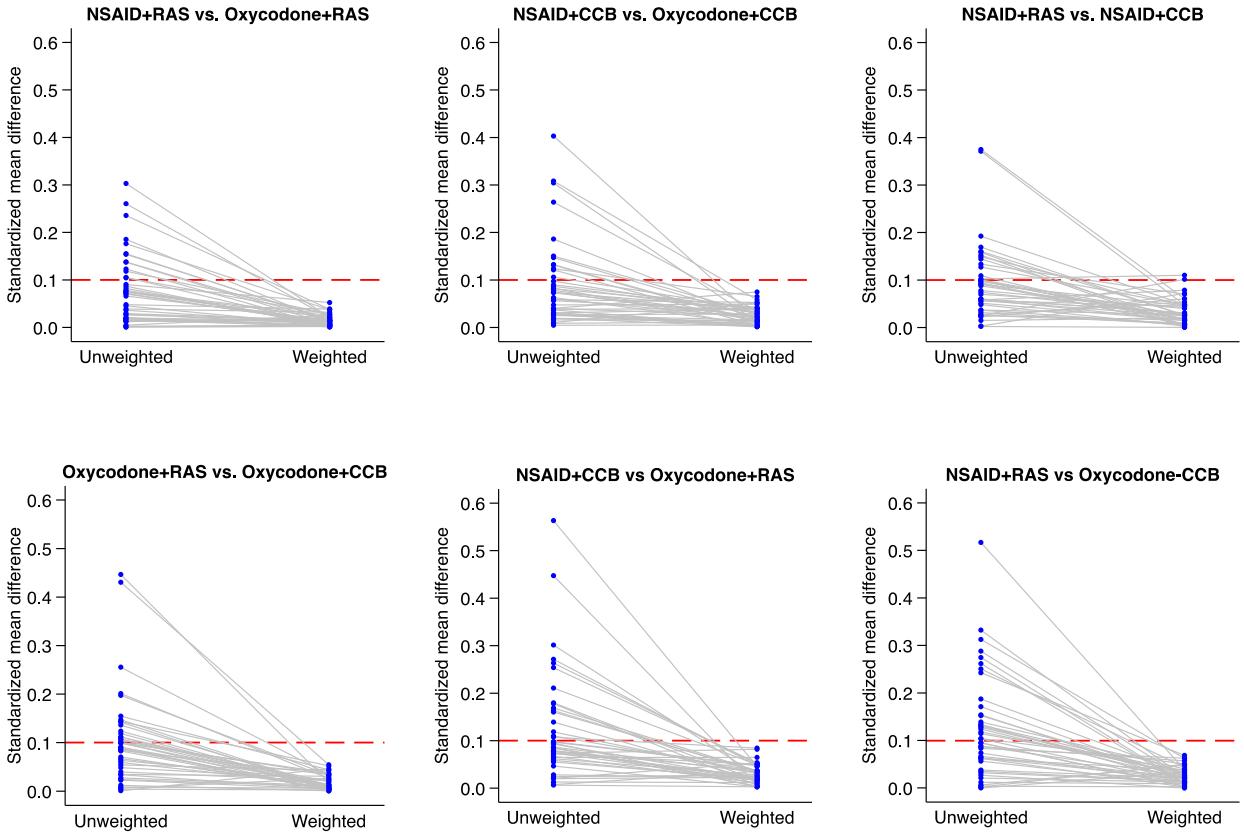
IRR	1.22 (0.98, 1.51)	1.56 (0.98, 2.48)	**1.28 (0.77, 2.12)**
Concomitant diuretics- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	23.1	26.5	1.15 (0.68, 1.94)
RAS-I	28.9	41.1	1.42 (1.19, 1.69)
IRR	1.25 (0.99, 1.59)	1.55 (0.94, 2.57)	**1.24 (0.72, 2.16)**
Concomitant diuretics- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	30.3	31.7	1.04 (0.71, 1.53)
RAS-I	32.6	44.6	1.37 (1.17, 1.59)
IRR	1.08 (0.89, 1.29)	1.41 (0.97, 2.04)	**1.31 (0.87, 1.97)**
Without concomitant diuretics- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	17.3	20.1	1.16 (0.79, 1.69)
RAS-I	18.4	17.1	0.93 (0.75, 1.16)
IRR	1.06 (0.87, 1.28)	0.85 (0.58, 1.26)	**0.81 (0.52, 1.25)**
Without concomitant diuretics- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	15.5	20.1	1.30 (0.88, 1.92)
RAS-I	17.6	16.9	0.96 (0.77, 1.21)
IRR	1.14 (0.93, 1.39)	0.84 (0.57, 1.26)	**0.74 (0.47, 1.16)**
Without concomitant diuretics- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	16.9	23.8	1.39 (1.03, 1.89)
RAS-I	18.6	19.1	1.02 (0.84, 1.24)
IRR	1.09 (0.94, 1.29)	0.80 (0.58, 1.11)	**0.73 (0.51, 1.04)**
Age at least 65 years- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	23.3	24.1	1.03 (0.67, 1.59)
RAS-I	25.0	28.6	1.15 (0.93, 1.40)
IRR	1.07 (0.88, 1.31)	1.19 (0.76, 1.85)	**1.11 (0.68, 1.79)**
Age at least 65 years- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	18.9	19.6	1.04 (0.59, 1.80)
RAS-I	22.2	23.3	1.05 (0.81, 1.36)
IRR	1.17 (0.91, 1.51)	1.19 (0.68, 2.07)	**1.01 (0.55, 1.87)**
Age at least 65 years- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	25.1	31.8	1.27 (0.89, 1.79)

RAS-I	27.5	35.3	1.29 (1.08, 1.53)
IRR	1.09 (0.94, 1.28)	1.11 (0.77, 1.59)	**1.01 (0.69, 1.49)**
Age less than 65 years- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	16.9	20.6	1.21 (0.79, 1.86)
RAS-I	19.5	24.3	1.24 (1.03 1.51)
IRR	1.15 (0.89, 1.49)	1.18 (0.79, 1.76)	**1.03 (0.64, 1.64)**
Age less than 65 years- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	9.7	20.9	2.15 (1.28, 3.63)
RAS-I	15.9	20.4	1.27 (0.99, 1.63)
IRR	1.65 (1.16, 2.36)	0.98 (0.62, 1.54)	**0.59 (0.33, 1.05)**
Age less than 65 years- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	19.8	24.9	1.26 (0.91, 1.75)
RAS-I	21.7	26.1	1.19 (1.02, 1.41)
IRR	1.09 (0.91, 1.31)	1.04 (0.76, 1.44)	**0.95 (0.66, 1.36)**
With Diabetes mellitus II- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	21.9	19.4	0.89 (0.49, 1.57)
RAS-I	24.9	29.4	1.18 (0.95, 1.45)
IRR	1.14 (0.89, 1.46)	1.51 (0.86, 2.65)	**1.32 (0.72, 2.45)**
With Diabetes mellitus II- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	16.9	27.9	1.65 (0.86, 3.16)
RAS-I	22.5	28.8	1.28 (0.97, 1.68)
IRR	1.34 (0.92, 1.94)	1.04 (0.57, 1.88)	**0.77 (0.38, 1.56)**
With Diabetes mellitus II- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	29.4	28.9	0.98 (0.62, 1.55)
RAS-I	29.9	36.3	1.21 (1.01, 1.46)
IRR	1.02 (0.85, 1.22)	1.26 (0.79, 1.98)	**1.23 (0.76, 2.00)**
Without Diabetes mellitus II- IPTW in Cohort B			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	16.7	24.5	1.46 (0.99, 2.15)
RAS-I	19.2	24.7	1.29 (1.07, 1.54)
IRR	1.15 (0.95, 1.38)	1.01 (0.69, 1.48)	**0.88 (0.58, 1.34)**
Without Diabetes mellitus II- IPTW in trimmed cohort (Cohort C)			
	Oxycodone rate[a]	NSAID rate[a]	IRR

Amlodipine	14.4	21.4	1.49 (1.00, 2.21)
RAS-I	17.1	21.9	1.28 (1.02, 1.61)
IRR	1.19 (0.94, 1.51)	1.02 (0.69, 1.51)	**0.86 (0.54, 1.35)**
Without Diabetes mellitus II- multivariable regression in full cohort (Cohort A)			
	Oxycodone rate[a]	NSAID rate[a]	IRR
Amlodipine	18.2	26.0	1.43 (1.08, 1.89)
RAS-I	21.2	26.8	1.27 (1.08, 1.48)
IRR	1.17 (099, 1.36)	1.03 (0.78, 1.37)	**0.89 (0.64, 1.22)**

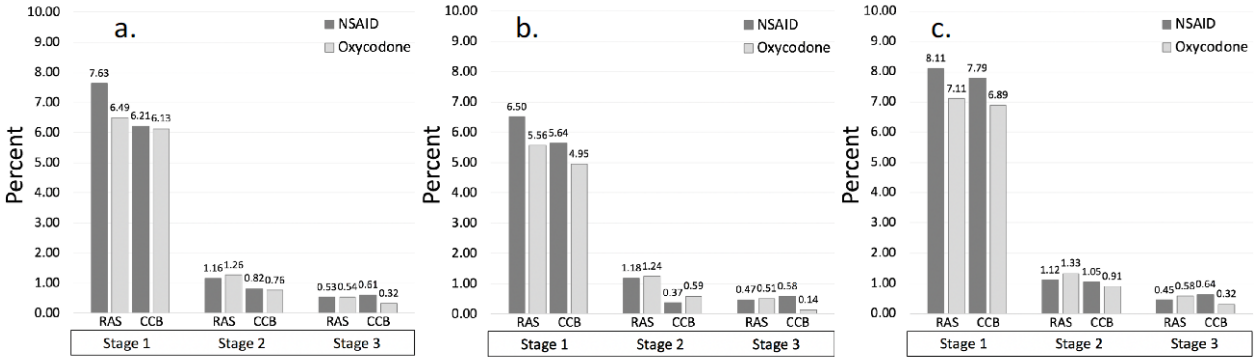
a- rate per 1000 person-days; IRR- incidence rate ratio

Figure S4. Absolute standardized mean differences



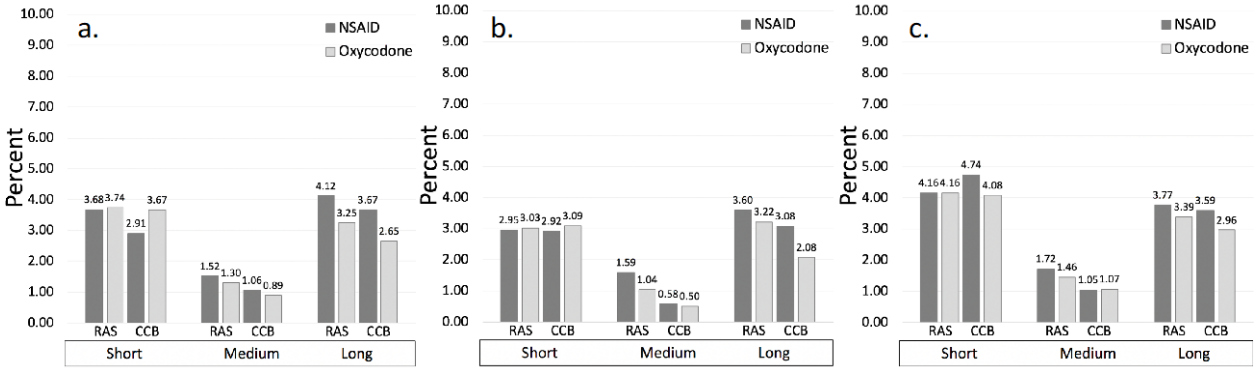
In each panel, blue dots represent the absolute standardized mean differences (SMD) for a separate covariate before and after inverse probability of treatment weighting (IPTW). The reference line (red dash) is set at a SMD value of 0.10, the threshold for imbalance.

Figure S5. Predicted Acute kidney injury stage stratified by treatment group



Each panel of the figure depicts the predicted distribution of acute kidney injury severity stage across strata of analgesia and antihypertensive exposure groups. a- estimates derived from inverse probability of treatment weighted multinomial logistic regression in Cohort B (p=0.6342 for interaction between analgesia and antihypertensive groups); b- estimates derived from inverse probability of treatment weighted multinomial logistic regression in Cohort C (p=0.2944 for interaction between analgesia and antihypertensive groups); c- estimates derived multivariable adjusted multinomial logistic regression model (p=0.3244 for interaction between analgesia and antihypertensive groups). RAS- renin-angiotensin system inhibitors; CCB- calcium channel blocker (amlodipine)

Figure S6. Predicted Acute kidney injury duration stratified by treatment group



Each panel of the figure depicts the predicted distribution of acute kidney injury duration across strata of analgesia and antihypertensive exposure groups. a- estimates derived from inverse probability of treatment weighted multinomial logistic regression in Cohort B (p=0.8135 for interaction between analgesia and antihypertensive groups); b- estimates derived from inverse probability of treatment weighted multinomial logistic regression in Cohort C (p=0.7989 for interaction between analgesia and antihypertensive groups); c- estimates derived from multivariable adjusted multinomial logistic regression model (p=0.8013 for interaction between analgesia and antihypertensive groups). RAS- renin-angiotensin system inhibitors; CCB- calcium channel blocker (amlodipine)

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1-138
2. Steyerberg EW, Eijkemans MJ, Habbema JD. Stepwise selection in small data sets: a simulation study of bias in logistic regression analysis. J Clin Epidemiol. 1999 Oct;52(10):935-42.
3. Harrell Jr FE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001
4. Stürmer T, Rothman KJ, Avorn J, et al.Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution—a simulation study. Am J Epidemiol. 2010;172(7):843–854.
5. Yoshida K, Solomon DH, Haneuse S, et al. Multinomial Extension of Propensity Score Trimming Methods: A Simulation Study. *Am J Epidemiol*. 2019;188(3):609–616
6. Vanderweele TJ, Mukherjee B, Chen J. Sensitivity analysis for interactions under unmeasured confounding. *Stat Med*. 2012;31(22):2552–2564.
7. 2018 ICD-10 CM and general equivalence mappings. Available at: https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs. Accessed 10/27/18
8. Jensen PN, Johnson K, Floyd J, et al. A systematic review of validated methods for identifying atrial fibrillation using administrative data. Pharmacoepidemiol Drug Saf. 2012; Suppl 1:141-7
9. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11): 1130-1139.
10. Simard M, Sirois C, Candas B. Validation of the Combined Comorbidity Index of Charlson and Elixhauser to Predict 30-Day Mortality Across ICD-9 and ICD-10. Med Care. 2018;56:441-447.
11. Grams ME, Rebholz CM, McMahon B, et al. Identification of incident CKD stage 3 in research studies. Am J Kidney Dis. 2014;64:214-21.