Effect of Renin-Angiotensin System Inhibitors on the Comparative Nephrotoxicity of NSAIDs and Opioids during Hospitalization

Todd A. Miano 1,2,3 Michael G. S. Shashaty 2,4 Wei Yang 1,2,3 Jeremiah R. Brown 5,6,7 Athena Zuppa 8 and Sean Hennessy 1,2,3

Abstract

Background Nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly important alternatives to opioids for analgesia during hospitalization as health systems implement opioid-minimization initiatives. Increasing NSAID use may increase AKI rates, particularly in patients with predisposing risk factors. Inconclusive data in outpatient populations suggests that NSAID nephrotoxicity is magnified by renin-angiotensin system inhibitors (RAS-I). No studies have tested this in hospitalized patients.

Methods Retrospective, active-comparator cohort study of patients admitted to four hospitals in Philadelphia, Pennsylvania. To minimize confounding by indication, NSAIDs were compared to oxycodone, and RAS-I were compared to amlodipine. We tested synergistic NSAID+RAS-I nephrotoxicity by comparing the difference in AKI rate between NSAID versus oxycodone in patients treated with RAS-I to the difference in AKI rate between NSAID versus oxycodone in patients treated with amlodipine. In a secondary analysis, we restricted the cohort to patients with baseline diuretic treatment. AKI rates were adjusted for 71 baseline characteristics with inverse probability of treatment-weighted Poisson regression.

Results The analysis included 25,571 patients who received a median of 2.4 days of analgesia. The overall AKI rate was 23.6 per 1000 days. The rate difference (RD) for NSAID versus oxycodone in patients treated with amlodipine was 4.1 per 1000 days (95% CI, −2.8 to 11.1), and the rate difference for NSAID versus oxycodone in patients treated with RAS-I was 5.9 per 1000 days (95% CI, 1.9 to 10.1), resulting in a nonsignificant interaction estimate: 1.85 excess AKI events per 1000 days (95% CI, 6.23 to 9.92). Analysis in patients treated with diuretics produced a higher, albeit nonsignificant, interaction estimate: 9.89 excess AKI events per 1000 days (95% CI, −5.04 to 24.83).

Conclusions Synergistic nephrotoxicity was not observed with short-term NSAID+RAS-I treatment in the absence of concomitant diuretics, suggesting that RAS-I treatment may not be a reason to choose opioids in lieu of NSAIDs in this population. Synergistic nephrotoxicity cannot be ruled out in patients treated with diuretics.

Introduction Nonsteroidal anti-inflammatory drugs (NSAIDs) are essential options for analgesia in patients who are hospitalized (1–3). They have similar efficacy compared with opioids for multiple indications (1,4–6), and are recommended as first-line treatment for mild to moderate pain (1–3). Moreover, NSAID use during hospitalization is increasing as health systems across the United States implement opioid-minimization interventions (7–10), efforts encouraged by the US Surgeon General and analgesia guideline organizations (1,2,11). A recent national survey of 81 hospitals showed that 98% had implemented such measures, with the third most common intervention being the increased use of NSAIDs and other nonopioids (7).

Increasing NSAID use in patients who are hospitalized may increase AKI rates, particularly in patients with predisposing risk factors (12–14). Minimizing NSAID-AKI risk requires avoidance of nephrotoxicity risk factors, especially modifiable factors such as drug-
drug interactions. Inconclusive evidence in outpatient populations suggests that NSAID nephrotoxicity is magnified by renin-angiotensin system inhibitors (RAS-I) (13–17). NSAIDs can vasodilate the afferent glomerular arterioles (12), whereas RAS-I vasodilate the efferent arterioles (18). The combined effects are postulated to produce synergistic reductions in transglomerular pressure that compromise glomerular filtration (19). Some studies suggest that NSAID-AKI risk is doubled by RAS-I treatment (16,17), whereas others show no signal of synergistic nephrotoxicity (13,14,15).

Additional uncertainty stems from whether outpatient studies can be extrapolated to the inpatient setting, where patients have a higher baseline AKI risk, but also tend to receive much shorter durations of combined therapy. This represents a critical knowledge gap: if NSAID+RAS-I is truly nephrotoxic in this setting, the combination may contribute substantially to AKI and associated downstream effects including CKD (20); if not, withholding such therapy may unnecessarily expose patients to opioids, with corresponding risks of adverse drug events (21) and long-term opioid use and abuse syndromes (22,23). The potential effect on global kidney disease burden is substantial, given that approximately 15–20 million patients receive analgesia during hospitalization each year (21,24), and RAS-I are the most commonly used antihypertensives (25). We thus aimed to determine whether NSAID+RAS-I treatment has synergistic effects on AKI rates in patients who are hospitalized.

Materials and Methods
Overview of Study Design
We conducted a retrospective cohort study of patients who are hospitalized that compared AKI rate in patients treated with NSAID+RAS-I versus control patients who received comparator drugs lacking effects on kidney function (26). Oxycodone was the comparator for NSAIDs because it is a commonly used, non-nephrotoxic analgesic (21). Amlodipine was the active comparator for RAS-I because it has similar indications compared with RAS-I (27), and it does not vasodilate the efferent arterioles (28). We tested synergistic interaction by comparing the difference in AKI rate between NSAID versus oxycodone in patients treated with RAS-I to the difference in AKI rate between NSAID versus oxycodone in patients treated with amlodipine. We estimated interaction on the multiplicative (ratio of rate ratios) and additive (difference-in-differences) scales (29).

Source Population
The study population was drawn from patients admitted to one of four hospitals within the University of Pennsylvania Health System (UPHS) from January 1, 2004 to June 30, 2017. Inclusion criteria were age ≥18 years and at least 24 hours of concomitant treatment with a drug pair of interest. Exclusion criteria were the presence of relative contraindications to NSAIDs (baseline platelet count <100×10^11 cells/L; ESKD, RRT, or nonresolved AKI within 2 weeks before cohort entry; or baseline creatinine >2 mg/dl), relative contraindications to RAS-I treatment (pregnancy), lack of a baseline or at least one follow-up creatinine, and a history of solid organ transplant. In patients with multiple eligible episodes, only the first was included.

Drug-Drug Interaction Cohort (Cohort A)
We identified patients who received ≥24 hours of either a RAS-I or amlodipine. Eligible RAS-I were angiotensin-converting enzyme inhibitors (lisinopril, enalapril, ramipril, benazepril, quinapril, and captopril) and angiotensin II receptor blockers (losartan, irbesartan, and valsartan). Within this cohort, we identified patients who received ≥24 hours of NSAIDs or oxycodone treatment. Eligible NSAIDs were ibuprofen, ketorolac, indomethacin, naproxen, and nabumetone. Follow-up began with the first dose of concomitant exposure (i.e., the index date) and continued until a lapse in concomitant treatment >48 hours, occurrence of AKI, hospital discharge, death, or at 14 days after the index date. The specific NSAIDs and RAS-I studied were selected based on UPHS formulary availability. Detailed exposure definitions can be found in the Supplemental Methods.

Outcomes
The primary outcome was AKI at 14 days of follow-up, defined using Kidney Disease Improving Global Outcomes (KDIGO) creatinine and dialysis criteria (30). Baseline creatinine was defined as the last value before the index date. We staged AKI over 7 days after AKI onset. Secondary outcomes included KDIGO-defined AKI severity stage and AKI duration, defined as the number of days required for creatinine to return to within 25% of baseline (31). AKI duration was categorized as short (≤2 days), medium (3–6 days), and long (≥7 days) (31). Patients who required RRT were considered long duration regardless of creatinine resolution.

Data Collection
Data were obtained from Penn Data Store (PDS), Penn Medicine’s electronic health record (EHR) data warehouse. PDS includes medication administration records, laboratory values, demographics, location of care records, and diagnosis codes. PDS data on EHR procedure orders were used to define RRT episodes.

Potential confounders were selected a priori based on clinical knowledge and prior literature, with an emphasis on those associated with AKI or severity of illness (Table 1). Comorbidities were ascertained from diagnosis codes (see Supplemental Table 1). Pre-exposure AKI was defined by applying KDIGO criteria from hospital admission up to the index date (see Supplemental Methods for details). Baseline medication and laboratory variables were assessed during the 72 hours before the index date. For each laboratory measure, the value most proximate to cohort entry was collected. Baseline eGFR was calculated using the CKD Epidemiology Collaboration equation (32).

Data Analysis
Descriptive Statistics. We examined baseline covariate balance with standardized mean differences (SMD) (33). We examined balance across all possible contrasts between the four groups, because estimation of a causal synergistic interaction requires balanced covariates across all possible
Table 1. Baseline characteristics in cohort B (the primary analysis cohort) after inverse probability of treatment weighting

| Characteristics                        | RAS Cohort NSAI, n=4034<sup>a</sup> (6249<sup>b</sup>) | Oxycodone, n=16,110<sup>c</sup> (7127<sup>d</sup>) | SMD | Amlodipine Cohort NSAI, n=1181<sup>a</sup> (5782<sup>b</sup>) | Oxycodone, n=4700<sup>c</sup> (6413<sup>d</sup>) | SMD |
|----------------------------------------|-------------------------------------------------------|-------------------------------------------------|-----|--------------------------------------------------------|-------------------------------------------------|-----|
| **Demographics**                       |                                                       |                                                 |     |                                                        |                                                 |     |
| Age, years, mean                       | 62.8                                                  | 63.1                                            | 0.020 | 63.8                                                   | 63.6                                            | 0.012 |
| Female sex, %                          | 49                                                    | 48                                              | 0.016 | 50                                                     | 49                                              | 0.023 |
| Race, %                                |                                                       |                                                 |     |                                                        |                                                 |     |
| White                                  | 54                                                    | 54                                              | 0.009 | 53                                                     | 52                                              | 0.019 |
| Black                                  | 37                                                    | 37                                              | 0.005 | 39                                                     | 3                                               | 0.003 |
| Other/unknown                          | 9                                                     | 10                                              | 0.007 | 8                                                       | 9                                               | 0.039 |
| BMI in kg/m², mean                     | 31.1                                                  | 31.1                                            | 0.003 | 30.7                                                   | 30.9                                            | 0.016 |
| Year, mean                             | 2011                                                  | 2011                                            | 0.018 | 2011                                                   | 2011                                            | 0.001 |
| **Hospital admission characteristics** |                                                       |                                                 |     |                                                        |                                                 |     |
| Center, %                              |                                                       |                                                 |     |                                                        |                                                 |     |
| CCH                                    | 0.8                                                   | 0.8                                             | 0.000 | 0.8                                                    | 0.6                                             | 0.025 |
| HUP                                    | 46                                                    | 47                                              | 0.015 | 46                                                     | 47                                              | 0.020 |
| PAH                                    | 25                                                    | 25                                              | 0.003 | 25                                                     | 27                                              | 0.049 |
| PMC                                    | 29                                                    | 28                                              | 0.020 | 29                                                     | 26                                              | 0.065 |
| Surgical admission, %                  | 61                                                    | 62                                              | 0.015 | 62                                                     | 61                                              | 0.016 |
| Location of initial presentation, %    |                                                       |                                                 |     |                                                        |                                                 |     |
| ED                                     | 31                                                    | 30                                              | 0.018 | 32                                                     | 30                                              | 0.048 |
| ICU                                    | 8                                                     | 7                                               | 0.028 | 7                                                      | 7                                               | 0.005 |
| OR                                     | 27                                                    | 27                                              | 0.001 | 28                                                     | 28                                              | 0.006 |
| Floor                                  | 28                                                    | 29                                              | 0.008 | 28                                                     | 29                                              | 0.023 |
| Other                                  | 6                                                     | 7                                               | 0.052 | 6                                                      | 6                                               | 0.034 |
| LOS before index in days, mean         | 2.9                                                   | 2.9                                             | 0.005 | 2.8                                                    | 2.9                                             | 0.021 |
| ICU care at index date, %              | 16                                                    | 16                                              | 0.013 | 16                                                     | 16                                              | 0.002 |
| Perioperative recency, %               | 74                                                    | 73                                              | 0.022 | 71                                                     | 72                                              | 0.008 |
| Not in perioperative period            |                                                       |                                                 |     |                                                        |                                                 |     |
| POD zero                               | 2                                                     | 2                                               | 0.014 | 2                                                      | 2                                               | 0.012 |
| POD one                                | 13                                                    | 13                                              | 0.015 | 15                                                     | 14                                              | 0.026 |
| POD two                                | 8                                                     | 9                                               | 0.028 | 8                                                      | 10                                              | 0.053 |
| POD three                              | 4                                                     | 3                                               | 0.006 | 4                                                      | 4                                               | 0.032 |
| Mechanical ventilation, %              | 3                                                     | 4                                               | 0.039 | 4                                                      | 3                                               | 0.034 |
| Comorbidities, %                       |                                                       |                                                 |     |                                                        |                                                 |     |
| Heart failure                          | 24                                                    | 23                                              | 0.011 | 22                                                     | 21                                              | 0.013 |
| Myocardial infarction                  | 14                                                    | 14                                              | 0.002 | 13                                                     | 13                                              | 0.015 |
| Hypertension                           | 90                                                    | 90                                              | 0.003 | 92                                                     | 91                                              | 0.042 |
| Cardiac arrhythmias                    | 20                                                    | 19                                              | 0.010 | 17                                                     | 17                                              | 0.009 |
| Atrial fibrillation                    | 16                                                    | 16                                              | 0.001 | 15                                                     | 14                                              | 0.028 |
| Valvular disease                       | 16                                                    | 15                                              | 0.008 | 15                                                     | 15                                              | 0.013 |
| Stroke                                 | 10                                                    | 10                                              | 0.005 | 9                                                      | 11                                              | 0.068 |
| Peripheral vascular disease            | 14                                                    | 15                                              | 0.025 | 14                                                     | 16                                              | 0.061 |
| Pulmonary circulation disorder         | 9                                                     | 9                                               | 0.008 | 9                                                      | 7                                               | 0.044 |
| Chronic pulmonary disease              | 28                                                    | 27                                              | 0.028 | 29                                                     | 27                                              | 0.044 |
| Liver disease                          | 5                                                     | 5                                               | 0.001 | 4                                                      | 5                                               | 0.045 |
| Diabetes mellitus                      |                                                       |                                                 |     |                                                        |                                                 |     |
| None                                   | 65                                                    | 65                                              | 0.003 | 67                                                     | 67                                              | 0.001 |
| Noncomplicated                         | 28                                                    | 28                                              | 0.009 | 26                                                     | 26                                              | 0.013 |
| Complicated                            | 8                                                     | 8                                               | 0.021 | 7                                                      | 8                                               | 0.021 |
| CKD                                    | 10                                                    | 11                                              | 0.038 | 13                                                     | 11                                              | 0.058 |
| Weight loss                            | 6                                                     | 6                                               | 0.002 | 7                                                      | 7                                               | 0.005 |
| Fluid and electrolyte disorder         | 26                                                    | 26                                              | 0.009 | 28                                                     | 27                                              | 0.040 |
| Cancer                                 |                                                       |                                                 |     |                                                        |                                                 |     |
| None                                   | 82                                                    | 82                                              | 0.011 | 81                                                     | 81                                              | 0.013 |
| Nonmetastatic                          | 12                                                    | 12                                              | 0.003 | 13                                                     | 13                                              | 0.016 |
| Metastatic                             | 6                                                     | 6                                               | 0.015 | 6                                                      | 6                                               | 0.002 |
| Obstructive sleep apnea                | 15                                                    | 14                                              | 0.025 | 12                                                     | 14                                              | 0.075 |
| HIV/AIDS                               | 1                                                     | 1                                               | 0.013 | 1                                                      | 1                                               | 0.013 |
contrasts (34). Absolute SMD values $\geq 0.1$ were considered meaningful imbalance (35).

Inverse Probability of Treatment Weighting Analysis. We adjusted for covariates listed in Table 1 using inverse probability of treatment weighting (IPTW) analysis (36,37). Weights were formulated to estimate an average treatment effect (36), and were calculated from multinomial propensity scores estimated in the full cohort (cohort A). Multinomial propensity scores extend standard propensity score methods to multiple treatment groups. The key difference is that there are multiple propensity scores estimated (one for each treatment group). Multinomial propensity scores were estimated using generalized boosted models (36). Generalized boosted models are machine-learning classifiers that select the propensity score model that minimizes covariate imbalance across all treatment groups (36). Covariates with absolute SMD $>0.1$ after IPTW were included in the outcome models (38).

Propensity Score Trimming. The primary IPTW analysis was restricted to the subset of patients with comparable propensity scores (cohort B) (39). This restriction was accomplished by trimming the areas of nonoverlap in the propensity score distribution for each treatment category. Trimming methods are described in the Supplemental Methods, and the multinomial propensity score distributions and restriction bounds for cohort B are shown in Supplemental Figure 1.

In a sensitivity analysis, all models were repeated after restricting to the subset of patients with propensity scores between the first and 99th percentiles of the overlapping multinomial propensity score distributions (cohort C; see Supplemental Figure 1 for restriction bounds). The rationale

| Table 1. (Continued) |
|---------------------|
| Characteristics     | RAS Cohort | Amlodipine Cohort |
|                     | NSAID, n=4034* (6249b) | Oxycodone, n=16,110* (7127b) | SMD |
|                     | NSAID, n=1181* (5782b) | Oxycodone, n=4700* (6413b) | SMD |
| Kidney function     |            |                    |     |
| GFR, ml/min per     | 74.9       | 74.5               | 0.021 |
| 1.73 m$^2$, mean    | 10         | 10                 | 0.008 |
| Prior AKI, %        | 10         | 10                 | 0.008 |
| Laboratory values, mean |
| WBC, $\times 10^9$ cells/L | 9.9 | 9.9 | 0.014 |
| Hemoglobin, g/dL    | 11.2       | 11.1               | 0.037 |
| Platelets, $\times 10^{11}$ cells/L | 235.8 | 236.7 | 0.010 |
| Chloride, mEq/L     | 103.8      | 103.7              | 0.004 |
| Potassium, mEq/L    | 4.1        | 4.1                | 0.001 |
| Medications, %      |            |                    |     |
| Selective $\beta$-blockers | 41   | 42                 | 0.013 |
| Combined $\alpha$- and $\beta$-blockers | 12   | 12                 | 0.007 |
| Loop diuretics      | 26         | 25                 | 0.016 |
| Thiazide diuretics  | 16         | 16                 | 0.010 |
| Hydralazine         | 8          | 9                  | 0.037 |
| Other antihypertensives$^c$ | 7   | 8                  | 0.029 |
| Acid suppressants   |            |                    |     |
| None                | 39         | 40                 | 0.006 |
| H2RA                | 25         | 25                 | 0.004 |
| PPI                 | 36         | 35                 | 0.009 |
| Broad spectrum antibiotics$^d$ | 12   | 12                 | 0.008 |
| Narrow spectrum antibiotics$^e$ | 40   | 41                 | 0.026 |
| Vancomycin          | 22         | 22                 | 0.018 |
| Sulfamethoxazole/trimethoprim | 3   | 3                  | 0.026 |
| Other nephrotoxic antibiotics$^f$ | 3   | 3                  | 0.017 |
| Other nephrotoxins$^g$ | 2   | 2                  | 0.032 |
| Vasopressors        | 4          | 4                  | 0.025 |

RAS, renin-angiotensin system inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SMD, absolute standardized mean difference; BMI, body mass index; CCH, Chester County Hospital; HUP, Hospital of the University of Pennsylvania; PAH, Pennsylvania Hospital; PMC, Presbyterian Medical Center; ED, emergency department; ICU, intensive care unit; OR, operating room; LOS, length of stay; POD, postoperative day; WBC, white blood cells; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

$^a$Actual sample size.

$^b$Effective sample size after inverse probability of treatment weighting.

$^c$Propranolol, clonidine, doxazosin, terazosin.

$^d$Carbapenems, cefepime, piperacillin-tazobactam, fluoroquinolones, aztreonam.

$^e$First- and second-generation cephalosporins, macrolides, amoxicillin, penicillin, tetracycline, nitrofurantoin, ampicillin-sulbactam.

$^f$Aminoglycosides (amikacin, gentamicin, tobramycin), colistin.

$^g$Carboplatin, cisplatin, ifosfamide, cyclosporine, tacrolimus, methotrexate, amphotericin, acyclovir.

RAS, renin-angiotensin system inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SMD, absolute standardized mean difference; BMI, body mass index; CCH, Chester County Hospital; HUP, Hospital of the University of Pennsylvania; PAH, Pennsylvania Hospital; PMC, Presbyterian Medical Center; ED, emergency department; ICU, intensive care unit; OR, operating room; LOS, length of stay; POD, postoperative day; WBC, white blood cells; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

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$^g$Carboplatin, cisplatin, ifosfamide, cyclosporine, tacrolimus, methotrexate, amphotericin, acyclovir.
is to remove patients who were treated contrary to prediction, because these patients may be the most likely to have unmeasured confounders (39, 40).

**Outcome Models.** AKI rate was estimated with IPTW Poisson regression using robust variance estimation. Interaction on the ratio scale was estimated from regression model interaction terms between NSAID and RAS-I (29). Interaction on the difference scale was determined by contrasting the predicted marginal AKI rates of each exposure group (41). AKI duration and KDIGO severity stage were modeled with IPTW multinomial logistic regression.

**Sensitivity and Subgroup Analyses.** Prespecified subgroup analyses included restricting to patients who received combined exposure for ≥3 days (to examine duration response) and an analysis stratified by exposure to diuretics at baseline, because some studies suggest that synergistic NSAID–RAS-I nephrotoxicity may be limited to patients treated with diuretics (15). We also performed two additional post hoc subgroup analyses suggested during peer review: stratified analysis based on age of 65 years, and presence of diabetes mellitus II at baseline. In addition, all analyses were repeated using unweighted multivariable-adjusted Poisson regression in cohort A, because IPTW may have less power compared with multivariable regression (36, 37). Multivariable modeling procedures are detailed in the Supplemental Methods. Lastly, we performed quantitative bias analysis, in which we estimated the effect of a hypothetical unmeasured confounder on our interaction estimates (see Supplemental Methods, Supplemental Table 2, and Supplemental Figures 2 and 3 for detailed methods).

**Results**

The selection of patients into the study is depicted in Figure 1. Our initial query identified 114,491 episodes of concomitant exposure to a drug pair of interest, of which 61,360 courses (in 43,201 patients) had a duration ≥24 hours. From this population, 27,741 patients were included in cohort A (the propensity score estimation cohort). After multinomial propensity score estimation, an additional 2,170 patients were excluded due to noncomparable propensity scores, leaving 25,571 patients in cohort B (the primary analysis cohort).

**Patient Characteristics before Weighting in Cohort A**

The median duration of combined analgesic and antihypertensive treatment was approximately 2 days in all study

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**Figure 1.** Exclusions applied to obtain the primary and sensitivity analysis cohorts. CCB, calcium channel blocker (amlodipine); NSAID, nonsteroidal anti-inflammatory drug; Oxy, oxycodone; RAS, renin-angiotensin system inhibitors.
groups, reflecting the short-term, acute pain indications that are common in the inpatient setting (Supplemental Tables 3 and 4). The daily doses of NSAID and oxycodone courses were generally low to moderate (Supplemental Table 3). In patients treated with RAS-I, patients treated with NSAIDs versus oxycodone tended to be younger, female patients admitted through the emergency department (Supplemental Table 4). They were less likely to have heart failure, atrial fibrillation, and other cardiovascular diseases. As expected, patients treated with NSAIDs had higher baseline eGFR compared with those treated with oxycodone.

In patients treated with NSAIDs, those treated with RAS-I were less likely to be in the intensive care unit or in the perioperative period at baseline (Supplemental Table 4), more often had heart failure, myocardial infarction, other cardiovascular disease, and diabetes mellitus type II. Patients treated with RAS-I also had lower baseline eGFR and were more likely to be exposed to concomitant diuretic therapy.

Patient Characteristics after Weighting in Cohort B (Primary Analysis Cohort)

The weighted population characteristics are shown in Table 1, and a summary of SMDs for all possible contrasts among the four treatment groups before and after weighting is shown in Supplemental Figure 4. IPTW successfully balanced covariates across all possible group contrasts. Obstructive sleep apnea and CKD variables had SMD values >0.1 and were thus included in the weighted outcome models.

Analysis of AKI Rate

There were 2138 AKI events observed during 90,571 person-days of follow-up. No interaction between NSAID+RAS-I was evident in the unadjusted analysis in cohort A, either on the difference (Supplemental Table 5) or the ratio (Supplemental Table 6) scales. Results of the weighted outcome analysis in cohort B are shown in Table 2 (difference scale) and Table 3 (ratio scale), which shows the effect of NSAID versus oxycodone on AKI rate to be similar in patients treated with RAS-I and those treated with amlodipine: difference in difference 1.85 (95% CI, −6.23 to 9.92) excess AKI events per 1000 days. Repeating the analysis without an interaction term between NSAID+RAS-I showed significant, independent associations between NSAID treatment, RAS-I treatment, and increased AKI rates (Table 4).

| Antihypertensive Strata | Oxycodone Ratea | NSAID Ratea | NSAID RD within Antihypertensive Strata (95% CI)b |
|-------------------------|----------------|-------------|-----------------------------------------------|
| Amlodipine              | 19.9           | 24.0        | 4.13 (−2.83 to 11.09)                          |
| RAS                     | 23.1           | 29.1        | 5.97 (1.88 to 10.07)                           |
| RAS RD within analgesic strata (95% CI)b | 3.22 (0.29 to 6.14) | 5.06 (−2.46 to 12.60) | Difference in difference: 1.85 (−6.23 to 9.92) |

The difference-in-difference estimate suggests that the effect of NSAIDs on AKI rate does not differ across antihypertensive groups. NSAID, nonsteroidal anti-inflammatory drug; RD, rate difference; RAS, renin-angiotensin system inhibitor.

AKI Severity Stage and Duration

The majority of AKI events were stage 1 (1707/2138; 80%), with stage 2 and stage 3 events representing 14% and 6% of events, respectively. RRT was uncommon (21 events; 0.1%). There was no statistically significant evidence for synergistic effects of NSAID+RAS-I treatment on AKI severity or duration (Supplemental Figures 5 and 6).

Subgroup and Sensitivity Analyses

Figure 2 summarizes interaction estimates from the prespecified subgroup and sensitivity analyses, with the corresponding interaction tables reported in Supplemental Tables 7 and 8. Interaction estimates were more consistent with synergistic NSAID+RAS-I effects in patients treated for ≥3 days and in patients receiving diuretics at baseline. However, the confidence intervals around these estimates included the null value. Repeating all primary and subgroup analyses in cohort B (the trimmed cohort) produced similar results, as did repeating all analyses using multivariable Poisson regression (Figure 2, Supplemental Tables 7 and 8). Post hoc subgroup analysis by age and diabetes did not show strong evidence of altered NSAID–RAS-I effects (Supplemental Tables 7 and 8). Quantitative bias analysis (Supplemental Figures 2 and 3, Supplemental Table 2) showed that our primary interaction estimate is robust to unmeasured confounding under a wide range of plausible scenarios. Unmeasured confounding could change the primary conclusions only under extreme circumstances: an unmeasured confounder would need to have a very strong effect on AKI (e.g., increases AKI rate by 15–20 events/1000 days) and would need to show a degree of imbalance several fold more extreme than that observed for any of the measured covariates. Taken together, the results suggest that unmeasured confounding is unlikely to change our conclusions.

Discussion

We conducted a large-scale analysis of the NSAID+RAS-I interaction using a rigorous study design and analysis procedures to control confounding. To our knowledge, this is the first study to examine this question in patients who are hospitalized. We found that, despite a clear association of short-term NSAID use with AKI, NSAID nephrotoxicity was not meaningfully increased by concomitant RAS-I treatment. We could not, however, rule out the possibility of synergistic nephrotoxicity with NSAID+RAS-I among patients also taking diuretics.
Intervals around the interaction parameter. The upper
confidence bound of our interaction estimate to represent an acceptable risk compared with opioid analgesia.

Although there is a dearth of prior evidence in patients who are hospitalized, prior outpatient studies have examined the NSAID+RAS-I interaction with conflicting results (13–17). Dreischulte et al. (16) conducted a case-control study that compared NSAIDs versus no NSAIDs in a cohort of patients treated with RAS-I, showing a 60% increase in the odds of AKI associated with NSAID treatment. The lack of an active-comparator cohort in this study, such as patients exposed to a non-RAS antihypertensive, makes it impossible to determine whether these results reflect a true drug-drug interaction (i.e., synergistic toxicity between NSAID and RAS-I) or simply the known nephrotoxic effects of NSAIDs independent of RAS-I treatment (29). In a second case-control study, Lapi et al. (15) also compared NSAIDs versus no NSAIDs in a RAS-I-treated cohort, finding no evidence of higher AKI risk with combined NSAID+RAS-I treatment. Notably, this analysis found that NSAIDs conferred a higher AKI risk only in patients treated with both RAS-I and diuretics.

Our analyses differs from these prior outpatient studies in that we specifically tested for synergistic effects by comparing the difference in AKI rate between NSAID versus oxycodone in patients treated with RAS-I to the difference in AKI rate between NSAID versus oxycodone in patients treated with amlodipine (29). The use of active comparators for both the NSAID and RAS-I groups serves to minimize confounding by indication (26). Moreover, our approach to testing interaction directly addresses the relevant clinical question: is NSAID toxicity altered by RAS-I treatment? The presence of a synergistic interaction between two treatments implies that there are persons for whom AKI would occur if both treatments were present but not if only one or the other were present (29,43). Our results suggest that, at least for short-term (2–3 days) treatment in the absence of diuretics, RAS-I treatment does not alter AKI risk during NSAID analgesia. Thus, in patients who would otherwise be deemed candidates for NSAID therapy, RAS-I treatment may not be a reason to choose opioids over NSAIDs.

In secondary analyses, we observed stronger interaction signals in the subset of patients treated with NSAID+RAS-I for ≥3 days, and in patients who were receiving baseline diuretics. A higher risk with longer treatment duration is consistent with prior evidence describing duration-dependent nephrotoxicity with ketorolac (44). Synergistic nephrotoxicity with diuretics is consistent with the results from Lapi et al. (15), and other case reports and case series in outpatient populations (45). This three-way interaction is postulated to result from diuretic-mediated decreases of inflow to the glomerulus, combined with disrupted renal blood flow autoregulation induced by NSAID+RAS-I treatment (15). In our analysis, the upper bound of the interaction estimate in the diuretic cohort was 24.8 excess AKI events per 1000 days, an increase that many would judge as clinically meaningful.

### Table 4. Main effects estimates of NSAID and RAS exposure

| Exposure | IRR (95% CI) | IRD (95% CI)* |
|----------|-------------|---------------|
| **NSAID** |             |               |
| Weighted analysis in cohort B | 1.24 (1.06 to 1.44) | 5.09 (1.13 to 9.05) |
| Weighted analysis in cohort C | 1.28 (1.07 to 1.53) | 5.07 (1.03 to 9.11) |
| Multivariable regression in cohort A | 1.23 (1.11 to 1.37) | 5.59 (2.51 to 8.66) |
| **RAS inhibitors** |             |               |
| Weighted analysis in cohort B | 1.18 (1.00 to 1.39) | 4.06 (0.34 to 7.78) |
| Weighted analysis in cohort C | 1.25 (1.02 to 1.54) | 4.71 (0.81 to 8.61) |
| Multivariable regression in cohort A | 1.09 (0.96 to 1.22) | 2.27 (–0.23 to 4.77) |

NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system; IRR, incident rate ratio; IRD, incidence rate difference. *AKI events/1000 person days.
Given the uncertainty of the confidence intervals around this estimate, larger studies of individuals exposed to diuretics are warranted. However, given the similar findings in prior outpatient studies, it may be reasonable to avoid the NSAID+RAS-I combination in patients treated with diuretics.

Our study has limitations. First, the observational design is susceptible to residual confounding. We minimized confounding with the active-comparator study design (26), and by collecting and controlling for all available potential confounders in IPTW analyses. In addition, we conducted quantitative bias analysis which suggested that our results are robust to unmeasured confounding under a wide range of plausible scenarios. Second, although the use of active comparators may help to reduce confounding, this approach may limit generalizability. Strictly speaking, our results suggest that combined NSAID+RAS-I treatment may not synergistically worsen AKI risk in comparison with our control drugs (oxycodone and amlodipine). It may be the case that our inability to detect a meaningful interaction was driven by similar synergistic effects across the studied groups, rather than the absence of synergistic NSAID+RAS-I toxicity. Although possible, this seems unlikely given the proposed effects of amlodipine on renal vascular tone (28) and lack of known oxycodone nephrotoxicity (21). Third, although our primary analysis did not detect a meaningful NSAID+RAS-I interaction, this might not hold in other populations with higher AKI risk. Fourth, we were unable to examine the effect of NSAID daily dose due to the multiple different NSAIDs and RAS-I included, limiting the numbers of patients that received any specific drug and dose combination. Fifth, our findings may not apply to longer NSAID+RAS-I treatment durations. Notably, such long durations were relatively uncommon in our cohort: only 20% of the 114,491 episodes of concomitant therapy were of ≥3 days. Lastly, there may be numerous other factors that alter the effect of the NSAID–RAS-I interaction (e.g., severity of illness factors such as admission to the intensive care unit and comorbid illnesses such as heart failure). Sample size limited our ability to identify such factors because the examination of three-way interactions require severalfold greater sample sizes compared with two-way interactions.

Synergistic nephrotoxicity was not observed with short-term NSAIDs+RAS-I treatment in the absence of concomitant diuretics, suggesting that RAS-I treatment may not be a reason to choose opioids in lieu of NSAIDs in this population. Synergistic nephrotoxicity cannot be ruled out in patients treated with diuretics.

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Author Contributions

J. Brown, S. Hennessy, M. Shashaty, W. Yang, and A. Zuppa provided supervision; S. Hennessy was responsible for resources; S. Hennessy and T. Miano conceptualized the study; T. Miano wrote the original draft and was responsible for data curation, project administration, and visualization; M. Shashaty, T. Miano, and W. Yang were responsible for formal analysis; all authors were responsible for methodology and reviewed and edited the manuscript; and all authors agree to be accountable for all aspects of the work.

Figure 2. Interaction estimates from the primary analysis, sensitivity analyses, and prespecified subgroups. (A) Interaction measures on the ratio scale (ratio of rate ratios [RRR]). Each point represents an RRR estimate, with 95% CI represented by the capped bars. Values above one favor excess AKI with NSAID+RAS-I. (B) Interaction measures on the difference scale (difference in differences [DID]). Each point represents a DID estimate, with 95% CI represented by the capped bars. Values above zero favor excess AKI with NSAID+RAS-I. IPTW, inverse probability of treatment weighting; MV, multivariable.
Disclosures

J. Brown has received consulting fees from Bracco Scientific. S. Hennessy has received consulting fees from the following companies: Braeburn Pharmaceuticals Inc, Esteve Pharmaceuticals LLC, Greenwich Biosciences Inc, Hoffman La Roche, Indivior Inc, Inspiron Delivery Sciences LLC, Janssen Research & Development LLC, Laboratoire HRA PHARMA, Lexicon Pharmaceuticals Inc, Lilly USA LLC, Mallincrodt Pharmaceuticals, Medulary Thyroid Cancer Consortium (AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Novo Nordisk Inc, GlaxoSmithKline LLC), Merck Research Laboratories, Nektar Therapeutics Inc, Novo Nordisk, Pacira Pharmaceuticals Inc, PTC Therapeutics Inc, Purdue Pharma LP, Sage Therapeutics, Sanofi US Services Inc, Shire Human Genetic Therapies Inc, and Transdermal Immediate Release Fentanyl REMS (BioDelivery Sciences International Inc, Insys Therapeutics Inc, Mylan Inc, Par Pharmaceutical Inc, Santryl Therapeutics Inc, SpecGX LLC [a wholly owned subsidiary of Mallinckrodt Inc], Teva Pharmaceuticals USA Inc, West Therapeutic Development LLC). In addition, S. Hennessy leads the Center for Pharmacoepidemiology Research and Training, which has received support for pharmacoepidemiology training programs from Pfizer Inc. A. Zuppa has served on an advisory committee for Pfizer. All remaining authors have nothing to disclose.

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Supplemental Material

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Supplemental Methods.

Supplemental Table 1. Diagnosis code algorithms.

Supplemental Figure 1. Overlap of the multinomial propensity score distributions.

Supplemental Table 2. Bias analysis parameters for a set of measured covariates hypothetically assumed to be unmeasured.

Supplemental Figure 2. Corrected interaction estimates and confidence intervals for a set of measured covariates hypothetically assumed to be unmeasured.

Supplemental Figure 3. Bias as a function of the difference-in-difference of the prevalence of an unmeasured confounder and the unmeasured confounder’s association with outcome.

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Supplemental Figure 4. Absolute standardized mean differences.

Supplemental Figure 5. Predicted acute kidney injury stage stratified by treatment group.

Supplemental Figure 6. Predicted acute kidney injury stage stratified by treatment group.

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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 fibrillation⁸ | 427.31, 427.32   | I48               |
| Heart Failure⁹,¹⁰  | 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 infarction⁹,¹⁰ | 410.x, 412.x   | I21.x, I22.x, I25.2 |
| Hypertension⁹,¹⁰,ª | 401.x, 402.x–405.x | I10.x, I11.x–I13.x, I15.x, I16.x |
| Valvular disease⁹,¹⁰ | 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 |
| Condition                           | Code       | ICD-10 Codes                     |
|------------------------------------|------------|---------------------------------|
| 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\(^6,6\)      | 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 |
| Condition                              | ICD-9 Codes                                                                 | ICD-10 Codes                                                                 |
|----------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Cardiac arrhythmias                    | 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            | 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         | 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                | 327.2 780.51 780.53 780.57                                                  | g47.3                                                                        |
| HIV/AIDS                               | 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 (x1-x4) 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 (x1-x4) 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. \( \delta_1 \) = Association of U with NSAID vs. Oxycodone in the RAS-I cohort
   b. \( \delta_0 \) = 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. \( \gamma_1 \) = RD for effect of U on AKI rate in both NSAID and Oxycodone subgroups in the RAS-I cohort
   b. \( \gamma_0 \) = 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 \( \beta_{\text{add}} \) due to the unmeasured confounder can be estimated by:

\[
\beta_{\text{add}} = \delta_1 \gamma_1 - \delta_0 \gamma_0
\]

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 \( \gamma_1 = \gamma_0 = \gamma \) (i.e. U does not interact with RAS-I vs Amlodipine), then equation 1 simplifies to

\[
\beta_{\text{add}} = (\delta_1 - \delta_0)\gamma
\]

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

| Covariate                    | RAS cohort | Amlodipine cohort |
|------------------------------|------------|-------------------|
|                              | NSAID      | Oxy   | $\delta_1$ | $\gamma_1$ | NSAID   | Oxy   | $\delta_0$ | $\gamma_0$ | $\beta_{add}$ |
| Vasopressors                 | 0.041      | -0.005 | 5.56       |           | 0.041   | 0.000  | 19.75      | -0.03      |
| Nephrotoxic antibiotics*     | 0.030      | -0.003 | 16.90      |           | 0.035   | 0.001  | 35.80      | -0.09      |
| Sulfamethoxazole / trimethoprim | 0.025    | -0.004 | 20.70      |           | 0.018   | 0.028  | -0.010     | 17.00      | 0.09      |
| Vancomycin                   | 0.215      | -0.007 | 2.46       |           | 0.201   | 0.212  | -0.011     | 11.81      | 0.11      |
| Loop diuretics               | 0.260      | 0.007  | 18.27      |           | 0.234   | 0.238  | -0.004     | 16.49      | 0.19      |
| Prior Acute kidney injury    | 0.096      | -0.002 | 3.01       |           | 0.091   | 0.092  | -0.001     | 12.49      | 0.00      |
| Chronic kidney disease       | 0.103      | -0.011 | 25.77      |           | 0.129   | 0.110  | 0.019      | 18.38      | -0.63     |
| Diabetes mellitus            | 0.353      | 0.040  | 7.31       |           | 0.2235  | 0.277  | -0.053     | 11.38      | 0.26      |
| Liver disease                | 0.051      | 0.003  | 11.30      |           | 0.051   | 0.060  | -0.009     | 10.22      | 0.13      |
| Atrial fibrillation          | 0.155      | -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      | Oxycodone             | smd               | NSAID                  | Oxycodone             | smd               |
|                        | (n=4250)   | (n=17610)             |                   | (n=1181)               | (n=4700)              |                   |
| 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 |
| Condition                        | Value 1 | Value 2 | p-value | Value 3 | Value 4 | p-value |
|---------------------------------|---------|---------|---------|---------|---------|---------|
| 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 antihypertensivesa         | 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   |
| Drug Category                          | Median 1 | Median 2 | IQR 1  | IQR 2  | SD 1   | SD 2   |
|---------------------------------------|----------|----------|--------|--------|--------|--------|
| 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<sup>a</sup> | NSAID rate<sup>a</sup> | NSAID RD<sup>a</sup> 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<sup>a</sup> 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) |

<sup>a</sup> 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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)          |

<sup>a</sup> 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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<sup>a</sup> | NSAID rate<sup>a</sup> | 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 | Oxycodone rate | NSAID rate | IRD |
|-----|----------------|------------|-----|
| Concomitant diuretics- IPTW in trimmed cohort (Cohort C) |
| 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) |
| 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 |
| 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) |
| 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) |
| 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 |
| 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) |
| 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) |
| Amlodipine | 25.1 | 31.8 | 6.75 (-4.02, 17.53) |
|                          | Oxycodone rate | NSAID rate | IRD       |
|--------------------------|----------------|------------|-----------|
| **Age less than 65 years - IPTW in Cohort B** |                |            |           |
| 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)** |                |            |           |
| 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)** |                |            |           |
| 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** |                |            |           |
| 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)** |                |            |           |
| 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)** |                |            |           |
| 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** |                |            |           |
| 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           |                |            |           |
| NSAID rate               |                |            |           |
| IRD                      |                |            |           |
### Amlodipine

| Drug     | Rate  | Confidence Interval |
|----------|-------|---------------------|
| Amlodipine      | 14.4  | 7.07 (-0.66, 14.81) |
| RAS-I          | 17.1  | 4.81 (0.08, 9.54)   |
| IRD           | 2.73 (-0.83, 6.28) | 0.46 (-7.89, 8.82) |

**Without Diabetes mellitus II**

#### Multivariable regression in full cohort (Cohort A)

| Drug     | 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 (-11.08, 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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 | NSAID rate | 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                  | Oxycodone rate | NSAID rate | IRR       |
|---------------------|----------------|------------|-----------|
| **Concomitant diuretics- IPTW in trimmed cohort (Cohort C)** |                |            |           |
| 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)** | | | |
| 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** |                |            |           |
| 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)** | | | |
| 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)** | | | |
| 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** |                |            |           |
| 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)** | | | |
| 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)** | | | |
| Amlodipine          | 25.1           | 31.8       | 1.27 (0.89, 1.79) |
|               | Oxycodone rate | NSAID rate | IRR         |
|---------------|----------------|------------|-------------|
| 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** |               |            |             |
| 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)** |   |            |             |
| 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)** |   |            |             |
| 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** |               |            |             |
| 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)** |   |            |             |
| 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)** |   |            |             |
| 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** |               |            |             |
| 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)** |   |            |             |
| 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- multivariable regression in full cohort (Cohort A)

|                | Oxycodone rate<sup>a</sup> | NSAID rate<sup>a</sup> | 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 (0.99, 1.36)           | 1.03 (0.78, 1.37)       | 0.89 (0.64, 1.22) |

<sup>a</sup>- 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 from 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)
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