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Association of Opioids and Nonsteroidal Anti-inflammatory Drugs With Outcomes in CKD: Findings From the CRIC (Chronic Renal Insufficiency Cohort) Study

Min Zhan, PhD[1], **Rebecca M. Doerfler, PhD**[2], **Dawei Xie, PhD**[3], **Jing Chen, MD**[4], **Hsiang-Yu Chen, MS**[3], **Clarissa J Diamantidis, MD**[5], **Mahboob Rahman, MD**[6], **Ana C. Ricardo, MD**[7], **James Sondheimer, MD**[8], **Louise Strauss, BSN**[6], **Lee-Ann Wagner, MD**[2], **Matthew R Weir, MD**[2], **Jeffrey C Fink, MD**[1,2] **CRIC Study Investigators**

[1.]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore MD

[2.]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD

[3.]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA

[4.]Department of Medicine, Tulane University School of Medicine, New Orleans, LA

[5.]Department of Medicine, Duke University School of Medicine, Durham, NC

[6.]Department of Medicine, Case Western University, Cleveland, Ohio

[7.]Department of Medicine, University of Illinois at Chicago, Chicago, Illinois

[8.]Department of Medicine, Wayne State University School of Medicine, Detroit, MI

Abstract

Rationale & Objective: Safe analgesic choices are limited in chronic kidney disease (CKD). We conducted a comparative analysis of harm from opioids versus nonsteroidal anti-inflammatory drugs in CKD.

Study Design: Prospective cohort study

Corresponding author: Jeffrey C Fink MD, MS, University of Maryland School of Medicine, Baltimore, 22 S Greene St, Rm N3e03, Baltimore, MD, 21201; jfink@som.umaryland.edu.

CRIC Study Investigators: Lawrence J. Appel, MD, MPH; Harold I. Feldman, MD, MSCE; Alan S. Go, MD; Jiang He MD, PhD; John W. Kusek, PhD; James P. Lash, MD; Panduranga S. Rao, MD; Mahboob Rahman, MD; Raymond R. Townsend, MD.

Authors' Contributions: research idea and study design: MZ, JCF; data acquisition: DX, HYC; data analysis/interpretation: MZ, MR, ACR, JS, LS, L-AW, JCF; data curation: RMD, JCF; data visualization: RMD, JCF, JC; statistical analysis: MZ; supervision or mentorship: CJD, MRW. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Setting & Participants: 3939 patients with CKD in the Chronic Renal Insufficiency Cohort (CRIC) study.

Exposures: 30-day analgesic use reported at annual visits.

Outcomes: a composite outcome of 50% glomerular filtration rate (GFR) reduction and kidney failure requiring kidney replacement therapy (KRT), as well as the outcomes of kidney failure requiring KRT, hospitalization, and pre-kidney failure death.

Analytical Approach: Marginal structural models with time-updated exposures.

Results: Participants were followed for a median of 6.84 years with 391 (9.9%) and 612 (15.5%) reporting baseline opioid and NSAID (non-steroidal anti-inflammatory drug) use, respectively. Time-updated opioid use was associated with the kidney disease composite outcome, kidney failure with KRT, death (HRs of 1.4 [95% CI, 1.2-1.7], 1.4 [95% CI, 1.1-1.7], and 1.5 [95% CI, 1.2-2.0], respectively), and hospitalization (rate ratio (RR), 1.7; 95% CI, 1.6-1.9) versus opioid non-users. Similar results were found in an analysis restricted to a sub-cohort of participants reporting ever using other (non-opioid, non-NSAID) analgesics or tramadol. Time-updated non-steroidal anti-inflammatory drug use was associated with an increased risk for the kidney disease composite (HR, 1.2; 95% CI, 1.0-1.5) and hospitalization (RR, 1.1; 95% CI, 1.0-1.3); however, these associations were not significant in the sub-cohort. The association of non-steroid anti-inflammatory drug use with the kidney disease composite outcome varied by race, with a significant risk in blacks (HR, 1.3; 95% CI, 1.0-1.7). NSAID use was associated with a lower risk of kidney failure with KRT in women and individuals with GFR < 45 mL/min/1.73 m2 (HRs of 0.63 [95% CI, 0.45-0.88], 0.77 [95% CI, 0.59-0.99], respectively).

Limitations: Limited periods of recall of analgesic use and potential confounding by indication

Conclusion: Opioid use had a stronger association with adverse events than nonsteroidal anti-inflammatory drugs, with the latter's association with kidney disease outcomes limited to specific sub-groups, notably those of black race.

Keywords

chronic kidney disease (CKD); analgesics; opioids; non-steroidal anti-inflammatory drug (NSAID); end-stage renal disease (ESRD); pain management; COX-2 inhibitor; kidney function; kidney disease progression; drug safety; outcomes

Introduction:

Pain is common among patients with all stages of chronic kidney disease (CKD), but safe treatment options are not well-defined [1, 2]. Much literature describes the ill-effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the kidney[3, 4]. Nevertheless, the National Kidney Foundation endorses limited NSAID use for management of occasional pain in CKD, but advises against long-term use [5]. Other disease-specific guidelines exclude NSAIDs from chronic pain treatment algorithms [6]. However, recent studies demonstrate the renal safety of NSAIDs in some chronic diseases, adding to the controversy regarding their use in CKD[7, 8]. As a result, recommendation for NSAID avoidance have been challenged, even in Stage 3 to 5 CKD [7] .

Coincident with the concern for NSAID use in CKD is acknowledgment of the opioid epidemic and recommendations to avoid long-term opioid use. In 2013, American healthcare providers wrote ~ 250 million opioid prescriptions[9], and in 2014 almost 2 million persons either misused opioids, or suffered from an opioid use disorder (OUD)[10]. About 1 in 4 people prescribed long-term opioids for non-cancer pain struggle with an OUD[11]. More than 183,000 adults died from opioid overdose between 1999-2015[10]. Government and health agencies have established pain management guidelines intent on directing prescribers towards more judicious opioid use. Notable examples include the World Health Organization (WHO) 3-step analgesic ladder for cancer-related pain[12], and the Center for Disease Control (CDC) Guideline for Prescribing Opioids for Chronic Pain[10]. The CDC Guide for chronic pain management recommends non-pharmacologic and non-opioid therapies including acetaminophen, selected antidepressant, anticonvulsants, as well as NSAIDs before long-term opioid use[10].

Prior work from the Chronic Renal Insufficiency Cohort (CRIC) study revealed that 24% of study participants reported NSAID use at study entry or at least one follow-up visit[13]. In addition, initiation or discontinuation of NSAIDs is often associated with supplementation or replacement, respectively, with opioids [13]. Hence these analgesic classes are both likely to be used, and interchanged in CKD; however, comparative outcomes of using drugs from these analgesic classes is not known. In this analysis of the CRIC study, our objective is to evaluate the association of opioid and NSAID use with clinical outcomes in patients with CKD not requiring KRT.

Methods:

Study Design and Participants:

The CRIC study commenced in 2003 with Phase I&II enrollment completed in 2006, and continued follow-up to date with the design previously described [14] . This analysis examined 3,939 participants who gave informed consent and were enrolled at 21 to 74 years old with age-specific eGFR eligibility criteria of 20-70 ml/min/1.73 m^2, from seven U.S. centers with 13 clinical sites, and Institutional Review Board approval at each site. Briefly, CRIC participants underwent annual in-center visits providing demographic information, medical history and status update, vital signs, blood and urine samples, and other survey-based information. GFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, the prevailing clinical measure of kidney function at study commencement[15].

Medication ascertainment:

Coordinators recorded participants' prescription, over the counter (OTC) medications, supplements, and vitamins from 30 days preceding the study visit. To reduce recall bias, participants were asked to maintain a list or bring medications to visits. The drug name, frequency, total daily dosage (TDD), dosage units, and administration route were documented. Individual medications and constituents of combinations were identified using the First Databank® dictionary

Classification of analgesics:

The CRIC data file was closed in May 2014 to permit data cleaning and preparation for this analysis. The NSAID category included all oral NSAIDs and cyclooxygenase 2 (COX-2) inhibitors. Aspirin was classified as an NSAID if the TDD was greater than 325 mg, the dose frequency was more than once daily, or the drug was part of a combination analgesic (excluding aspirin & dipyridamole). Members of the opioid class included all orally administered narcotics as designated in First Databank® such as hydrocodone, codeine, oxycodone. Methadone represented less than 0.1% of opioid entries and no buprenorphine/naloxone use was reported. Opioids used as cold or cough remedy were excluded. Members of the other (non-opioid, non-NSAID) class included predominately acetaminophen. Since tramadol has overlapping but distinct pharmacological properties from narcotics [16], it was considered as a separate class unless taken in combination with an NSAID or an opioid, in which case the medication was classified in the latter's category. We defined the time-updated opioid and NSAID use at each clinical visit as whether a patient had reported NSAID or opioid at that visit or any one of the previous CRIC visits. The class of other (non-opioid, non-NSAID) analgesics included all other oral analgesics heretofore not classified. Of note, more than 90% of those entries were acetaminophen alone or in combination with another agent (e.g, diphenhydramine). No intravenous or topical analgesics were included in the analysis.

Outcomes:

We examined four clinical outcomes including kidney failure requiring KRT, the composite of kidney failure with KRT and 50% reduction of eGFR from baseline, pre-kidney failure death, and number of pre-kidney failure hospitalizations between two consecutive annual visits. GFR was estimated annually[15]. Death was ascertained through report from next of kin, retrieval of death certificates or obituaries, review of hospital records, and linkage with the Social Security Mortality Master File[17]. Kidney failure with KRT was ascertained by CRIC study personnel and cross-reference to the US Renal Data System[18] . For Kidney failure with KRT and the composite kidney disease outcome, participant follow-up was censored at the time of death, withdrawal, loss to follow-up, or the end of the follow-up period, whichever occurred first. For pre-kidney failure death and number of hospitalizations, participant follow-up was censored at the time of KRT initiation, withdrawal, loss to follow-up, or the end of the follow-up period, whichever occurred first.

Covariates:

We considered several clinically relevant covariates including baseline factors: gender, race, education level, and income reported at study entry. Time-dependent covariates included age, any alcohol drinking, comorbidities (diabetes, cardiovascular disease, hypertension, asthma, non-skin cancer, hyperkalemia, and arthritis), GFR, urinary protein-creatinine ratio (UPCR), response on the Beck's depression, symptom severity, and Kidney Disease Quality of Life 36 questionnaire (KDQOL-36) burden and symptoms sub-scales, SF-12 physical composite (including a question asking how much pain impeded activities of daily living), SF-12 mental composite, nephrologist visits, and other analgesic use (non-opioid/non-NSAID analgesic, tramadol) collected at annual visits. Urinary protein and creatinine were

also measured using standard assays. Urinary Protein-creatinine ratios from 24-hour and spot urine specimens were combined to a single urinary protein-creatinine ratio (UPCR) variable.

Statistical Methods:

For descriptive analyses, X^2-tests and t-tests compared discrete characteristics and continuous variables, respectively, across groups. We examined the association between time-updated opioid and NSAID use and the study outcomes while controlling for time-dependent covariates. We applied joint marginal structural models (MSMs) as several time-dependent covariates including eGFR could both be a consequence and a predictor for analgesic use. The challenges of making causal inferences from observational data have been previously discussed and illustrated with steps of fitting joint MSMs described [19].

In brief, we used a pooled logistic regression model to predict the probability of time-updated NSAID use at each visit based on NSAID use and opioid use at the previous visit and covariates at the previous visit. Another pooled logistic regression model was applied to predict the probability of time-updated opioid use at each visit based on NSAID use at both the current and the previous visit, opioid use at the previous visit, and covariates at the previous visit. The inverse probability weights were computed and stabilized. To control for informative censoring, the inverse probability of censoring weight was also computed and stabilized. The final weight was the product of the NSAID and opioid exposure, and the censoring weight. The final weight was also truncated at 99th percentile. Finally, we fit a weighted discrete failure time model for each of the survival outcomes through generalized estimating equations (GEE) and using the final weight developed from the logistic regression models. Only baseline covariates were included in the discrete failure time models. For the hospitalizations, we fit a weighted Poisson regression model using GEE and the final weight.

We performed the analyses using the full cohort and a sub-cohort including participants who ever used another (non-opioid, non-NSAID) analgesic or tramadol at baseline or during follow-up as a surrogate for need of pain relief. We also performed stratified analyses using demographic variables, and key predictors of kidney outcomes: baseline age (<65, >=65), sex, race (Non-Black, Black), diabetes status, eGFR (<= vs > 45 ml/min/1.79 m^2), and UPCR dichotomized at the sample median.

To demonstrate our results were robust and not due to unmeasured confounding, we examined the association of opioids and NSAIDs with risk of incident diabetes as a negative control outcome among CRIC participants without diabetes at enrollment and using the joint marginal structural models as described above.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results:

The 3939 participants had a median follow-up of 6.84 years. There were a total of 24838 visits for time to kidney failure with KRT or pre-kidney failure death, and 24552 visits for

the composite outcome of kidney failure with KRT and 50% reduction in eGFR. Tables 1 & 2 show the overall baseline characteristics of CRIC participants grouped by reported baseline opioid and NSAID use. Comparing the 391 (9.9%) participants who reported baseline opioid use to the 3548 (90.1%) who did not, the former group was more likely to be female, black, have an annual income of less than or equal to $50,000, have a history of rheumatoid arthritis, cardio-vascular disease, asthma, and non-skin cancer, and were less likely to report alcohol drinking. Compared to the 3327 (84.5%) participants who did not report baseline NSAID use, the 612 (15.5%) who did were more likely to be 45-64 years old, female, non-black, a college graduate or with higher education, with an income greater than $50,000, and to report drinking alcohol. Those reporting baseline NSAID use also were more likely to have a history of asthma, higher eGFR and were less likely to have diabetes, cardiovascular disease, hypertension, previous hyperkalemia and/or prior visit with a nephrologist. Opioid users were more likely to have depressive symptoms than non-users and lower KDQOL-36 and its components domains (Table 2). However, NSAID users had higher KDQOL-36 scores compared with non-users.

Table 3 displays the crude rates of outcomes in the year following observed visits classified by opioid and NSAID use alone, in combination, or use of neither class of analgesic. The crude incidence of death was highest in the opioid only group and opioid and NSAID group, with crude rates (per 100 person-years) of 3.5 (95% CI, 2.84.3) and 3.5 (95% CI, 2.2-5.5), respectively. The crude incidence of kidney failure with KRT in the opioid and other (non-opioid, non-NSAID group) were 4.2 (95% CI, 3.4-5.2) and 4.3 (95% CI, 4.0-4.6) per 100 person-years, respectively, appearing to be higher than the crude rates in NSAID-only group (1.9 (95% CI, 1.4-2.5) per 100 person-years) and opioid and NSAID group (2.5 [95% CI, 0.1-1.5] per 100 person-years). A similar pattern was observed for the composite kidney disease outcome, with crude rates in the opioid and other analgesic groups of 5.9 (95% CI, 5.3-6.3) and 5.9 (95% CI, 5.5-6.3) per 100 person-years, respectively. For hospitalizations, the opioid-only group had the highest crude rate of hospitalizations while the NSAID-only group had the lowest crude rate (108.6 [95% CI, 99.1-118.9] vs58.0 [95% CI, 51.5-65.3] per 100 person-years).

Table 4 shows the association of time-updated opioid and NSAID exposure with outcomes in the full cohort with the risk estimates expressed as a hazard ratio (HR) for the kidney disease outcomes and as rate ratios (RR) for hospitalization. Time-updated opioid use was associated with increased adjusted risk of all four outcomes relative to never using opioids during CRIC participation, with HRs of 1.4 (95% CI, 1.2-1.7), 1.4 (95% CI, 1.1-1.7), 1.5 (95% CI, 1.2-2.0), and RR of 1.7 (95% CI, 1.6-1.9), for the kidney disease composite, kidney failure with KRT, death, and hospitalization, respectively. Time-updated NSAID use was associated with a modestly increased hazard of the kidney disease composite and risk of hospitalizations relative to never using NSAID with an HR of 1.2 (95% CI, 1.0-1.5) and a RR of 1.1 (95% CI, 1.0-1.3). However, there was no significant association between time-updated NSAID use and kidney failure with KRT or death.

Table 4 demonstrates the associations of time-updated opioid and NSAID exposure with outcomes in the sub-cohort comprising those participants ever exposed to other analgesics (non-opioid, non-NSAID) or tramadol during the study. The strength of association between

opioid use and the outcomes were comparable to the full cohort. The association between NSAID use and hospitalization, kidney failure with KRT, the kidney disease composite, and death was no longer significant.

The forest plots (Figure 1, Table S1) display the varying HRs for the association of each analgesic group and the outcomes within sub-groups designated by age, gender, race, diabetes, GFR, and UPCR at baseline. The association between time-updated NSAID use and the composite kidney disease outcome was stronger in blacks versus non-blacks (HRs of 1.31 [95% CI, 1.01-1.69] and 0.83 [95% CI, 0.64-1.09], respectively, p=0.02 for effect modification). The association of time-updated NSAID use and kidney failure with KRT also varied across gender and baseline eGFR with a higher HR for males versus females (HRs of 1.21 [95% CI, 0.91-1.61] and 0.63 [95% CI, 0.45-0.88], respectively, p=0.004 for effect modification) and a significantly lower risk of kidney failure with KRT in the lower versus higher eGFR sub-groups (HRs of 0.77 [95% CI, 0.56-1.0] and 1.38 [95% CI, 0.89-2.14], respectively, for eGFR <= and >45 mL/min/1.73 m2; p=0.02 for effect modification). The association of pre-kidney failure hospitalization with opioid use (Figure S1a, Table S1) was higher in the lower versus higher baseline UPCR sub-groups (RRs of 1.90 [95% CI, 1.66-2.17] and 1.54 [95% CI, 1.36-1.74], respectively, for UPCRs below and above the median; p=0.02 for effect modification). Varying association between NSAID use and pre-kidney failure hospitalization had no significant effect modification (Figure S1b, Table S1).

Sensitivity analyses examined 1442 CRIC participants without diabetes at enrollment. In this subgroup, neither opioid nor NSAID use were associated with incident diabetes (HRs of 1.27 [95% CI, 0.87-1.84] and 1.03 [95% CI, 0.73-1.45], respectively).

To further explore the impact of potential unmeasured confounders on the associations between opioids and NSAIDs and outcomes, we computed E-values for potential unmeasured confounders for each risk estimate and the corresponding confidence interval (see Table S2) [20, 21]. E-values ranged from 2.2 to 2.8 for the risk estimates determined for the associations between opioids and all outcomes, and between 1.4 and 2.6 for the corresponding lower confidence intervals. The E-values were in the higher portion of that range for the sub-cohort risk estimates, but closer to the null for the weaker associations reported for NSAIDs and outcomes.

We also explored potential confounding of other drug groups that may be used as analgesics including anxiolytics and antiepileptics (Table 1); however only antiepileptics were associated with the outcome of death. Hence, we repeated the analysis including antiepileptics with the time-dependent covariates input to the marginal structural models for death. The results were essentially unchanged from those reported in Table 4.

Discussion:

In this cohort of adults with CKD, we demonstrated that reported opioid use within 30 days of ascertainment and treated as a time-updated exposure was associated with a substantial risk of adverse kidney disease outcomes, death, and hospitalization. This was in contrast

with the unexpected and modest relationship of NSAID use with adverse outcomes. The association between NSAID use and adverse kidney disease events was most prominent in blacks, with a potentially beneficial association with outcomes observed in sub-groups including women and those with a lower eGFR.

Physicians have long reported associations between various analgesics and kidney disease. “Analgesic nephropathy” is characterized by papillary necrosis, chronic interstitial nephritis, and progressive decreases in GFR[22]. Phenacetin was implicated as the principal causative agent, followed by aspirin and NSAIDs. Addition of caffeine to analgesic formulations may also exacerbate kidney injury[22, 23]. Reports of analgesic nephropathy led to the worldwide ban of phenacetin and several combination analgesics [24, 25]. However, epidemiologic studies examining analgesics and kidney failure have revealed mixed findings[23, 26]. The Physician Health Study showed no risk of decreased GFR among moderate users of aspirin, acetaminophen, or NSAIDs [2728]. Several case-control studies found substantial consumption of acetaminophen, aspirin, and NSAIDs were associated with an increased risk of kidney failure [29, 30]. A study of adults with CKD and comparable controls found acetaminophen, but not aspirin, to be associated with incident disease[31]. Another study of advanced CKD not requiring KRT revealed cumulative acetaminophen and aspirin exposure was associated with a risk for CKD [32]. However, another study of patients with rheumatoid arthritis using COX-2 inhibitors showed no harmful effects from these analgesics except in advanced CKD [8]. NSAID use in a large cohort of active, healthy US soldiers demonstrated a dose-dependent increased but modest risk of both AKI and CKD.[33]

Studies, including this group’s, reveal a higher frequency (9-36%) of NSAID use in CKD than one might expect given recommendations against their use [34–37]. Approximately 20% of dialysis patients are found to have used NSAIDs consistently during years preceding KRT initiation[38]. In our report of NSAID use in the CRIC study, a quarter of study participants reported NSAID use at baseline or at least one annual visit, with a substantial proportion of users reporting treatment over the study [13]. Relatively few reports describe opioid use in non-KRT-requiring CKD, with most data coming from KRT patients [39]. One study revealed almost a third of non-KRT-requiring CKD patients were prescribed an opioid with the likelihood increasing with declining GFR[40]. This is in contradistinction to NSAID prescriptions, which diminished with declining GFR[40]. Besides the well-documented hazards of opioid use in the general population including mortality [41, 42], and lack of a beneficial treatment effect versus non-opioid analgesics [43], their risks are compounded in CKD where dosing of many opioids is affected by decreased clearance. Accumulation of both parent drugs’ metabolites[44, 45], and enhanced adverse effects with use of these drugs in CKD make the adverse outcomes described here highly plausible[46, 47].

Interpretation of the findings warrant consideration of the limitations inherent to its design. With observational analyses, one cannot overlook confounding by indication whereby use, or non-use, of one or the other analgesic is driven by factors which may be associated with the outcome of interest rather than the primary exposure, in this case, analgesic choice. To minimize confounding by indication we employed causal inference models with inverse probability weighting by expected analgesic use in the examination of the association of analgesics with outcomes. More extensive characterization of the time-updated exposure

including variations in dosage and drug discontinuation was limited by the modest sample size. Additionally, the CRIC study was limited by its lack of a detailed pain assessment including measures of severity and type of pain. However, we used a wide array available measures of severity of illness and function embedded in the KDQOL −36 and SF-12, which include a gauge of pain's impedance of work and ability to perform activities of daily living.

Notably, analgesic use exposure ascertainment in CRIC was restricted to selfreport, limited to the 30 days preceding an annual visit, and did not necessarily reflect actual use over more distant time intervals. Previous studies have examined the fidelity of self-report of NSAID and acetaminophen use when compared to urine drug screening [48]. While the study did evaluate the use of NSAID and opioids versus non-users of these drugs, and the sub-group who were ever treated with any analgesics including the broader range of pain modulators such as acetaminophen, it did not assess the independent effect of the latter since this group served as the analysis reference group. Also, one cannot rule out the possibility analgesic choice may have been different during the years of this cohort before the opioid epidemic was more broadly recognized; however, we expect the reported associations would only be minimally influenced by secular trends in usage.

Of note, this is the first study we are aware of examining the comparative harm of NSAID vs opioid use in CKD. Both classes of agents have recognized risk profiles that are likely amplified in CKD, justifying close consideration of their risk versus benefit. Perhaps most importantly, the equipoise may be avoided with consideration of non-pharmacologic analgesic interventions that often show promising effectiveness in pain syndromes [49, 50]. In conclusion, our study findings suggest opioid use is associated with greater harm in CKD than NSAIDs, with a substantial increase in risk for death and poor kidney outcomes. The adverse effects of NSAIDs appears to be less consistent across sub-groups with evidence for patient strata where NSAID use is at least neutral and possibly beneficial. Further studies needed to confirm such variable findings. While a prospective trial comparing analgesics in CKD patients with comparable degrees of pain and indications for analgesics is desirable, such a study is unlikely. Future guidance for strategies for patients with non-KRT-requiring CKD, therefore, will be based on comparative harm studies such as this and further studies are needed to verify the reported findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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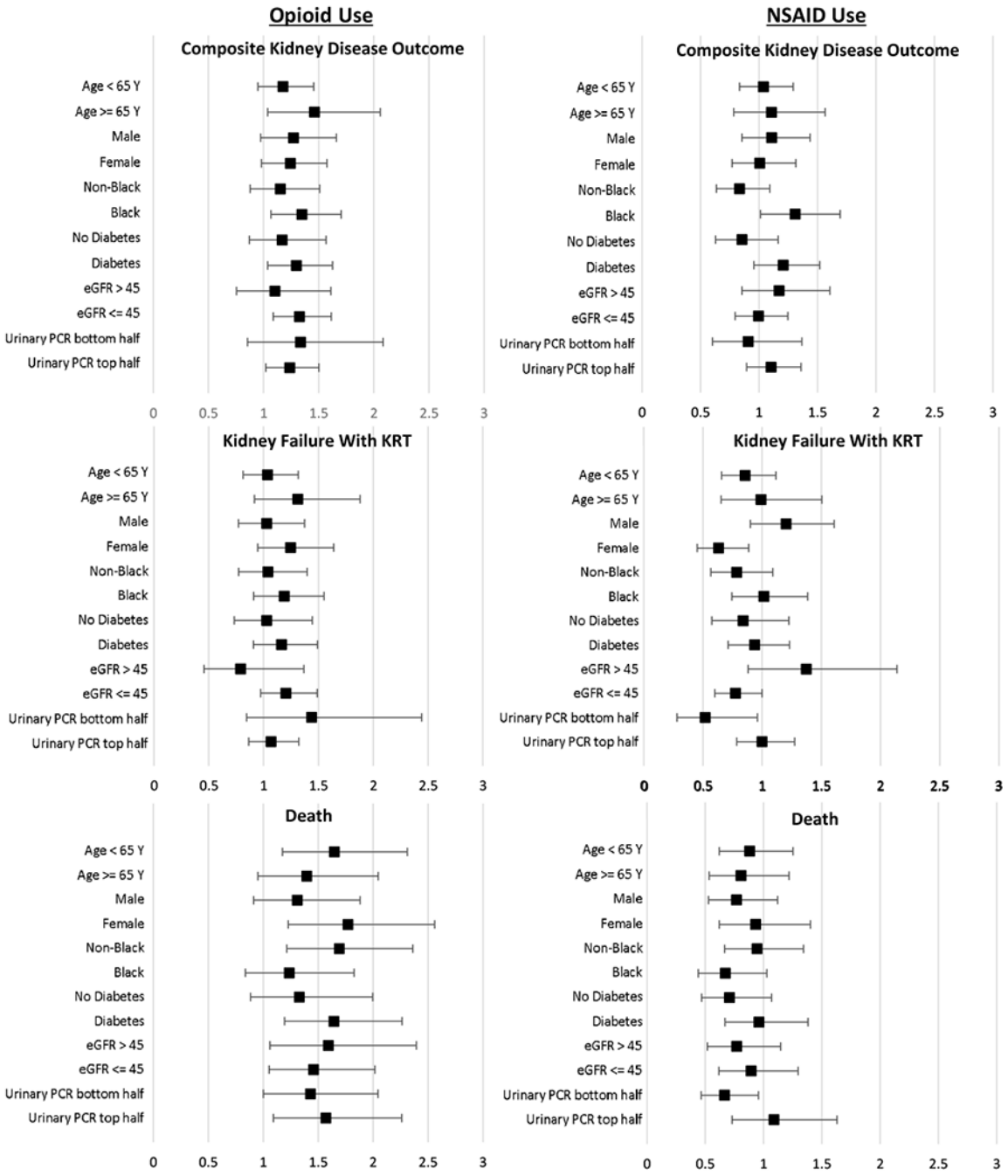

Figure 1.

Forest plots of adjusted hazard ratios of the composite kidney disease outcome, kidney failure with KRT, death, comparing time-updated opioid use in the past versus none, and time-updated NSAID use versus none, stratified by key demographic and case-mix subgroups and adjusted for all other covariates in primary analysis.

Table 1:

Baseline Characteristics of CRIC participants overall and by opioid and NSAID use

	Opioid use at baseline					NSAID use at baseline				
	No (n=3548)		Yes (n=391)		P	No (n=3327)		Yes (n=612)		P
Age (years)					0.3					0.003
21-<45	494 (13.9%)		44 (11.3%)			462 (13.9%)		76 (12.4%)		
45-<65	2025	(57.1)	236	(60.4)		1872	(56.3)	389	(63.6)	
65+	1029	(29.0)	111	(28.4)		993	(29.8)	147	(24.0)	
Male sex	2004	(56.5)	157	(40.2)	<0.001	1908	(57.3)	253	(41.3)	<0.001
Black race	1472	(41.5)	186	(47.6)	0.02	1432	(43.0)	226	(36.9)	0.005
Diabetes	1720	(48.5)	188	(48.1)	0.9	1668	(50.1)	240	(39.2)	<0.001
Hypertension	3062	(86.3)	329	(84.1)	0.2	2892	(86.9)	499	(81.5)	<0.001
Any cardiovascular disease	1159	(32.7)	157	(40.2)	0.003	1156	(34.7)	160	(26.1)	<0.001
Rheumatoid Arthritis[a]	411	(12.2)	81	(22.3)	<0.001	404	(12.8)	88	(15.1)	0.1
Asthma[b]	419	(12.0)	79	(20.5)	<0.001	401	(12.3)	97	(16.1)	0.01
Cancer (excluding non-melanoma skin cancer	168	(4.7)	28	(7.2)	0.04	167	(5.0)	29	(4.7)	0.8
Drinking alcohol	743	(20.9)	50	(12.8)	<0.001	649	(19.5)	144	(23.5)	0.02
Prior visit with nephrologist	2328	(65.6)	273	(69.8)	0.1	2295	(69.0)	306	(50.0)	<0.001
Education[c]					0.06					<0.001
Less than high school	752	(21.2)	76	(19.4)		739	(22.2)	89	(14.6)	
High school graduate	660	(18.6)	81	(20.7)		631	(19.0)	110	(18.0)	
Some college	1015	(28.6)	131	(33.5)		955	(28.7)	191	(31.3)	
College graduate or higher	1120	(31.6)	103	(26.3)		1002	(30.1)	221	(36.2)	
Income					0.006					0.001
$20,000 or under	1102	(31.1)	138	(35.3)		1082	(32.5)	158	(25.8)	
$20,001 - $50,000	847	(23.9)	111	(28.4)		809	(24.3)	149	(24.3)	
$50,001 - $100,000	673	(19.0)	61	(15.6)		603	(18.1)	131	(21.4)	
More than $100,000	369	(10.4)	23	(5.9)		311	(9.3)	81	(13.2)	
Don’t wish to answer	557	(15.7)	58	(14.8)		522	(15.7)	93	(15.2)	
Non-opioid/non-NSAID analgesic use	560	(15.8)	114	(29.2)	<0.001	532	(16.0)	142	(23.2)	<0.001
Tramadol use	72	(2.0)	18	(4.6)	0.001	73	(2.2)	17	(2.8)	0.4
Anxiolytic use[d]	107	(3.0)	38	(9.7)	<0.001	109	(3.3)	36	(5.9)	0.002
Anti-epileptic use[e]	289	(8.2)	95	(24.3)	<0.001	315	(9.5)	69	(11.3)	0.2

N=3939. Values given to count (percent).

a) 197 missing

b) 312 missing for opioid use and 69 missing for NSAID use

c) 76 missing for opioid use and 1 missing for NSAID use

[d] 353 missing for opioid use and 28 missing for NSAID use

[e] 296 missing for opioid use and 28 missing for NSAID use

Table 2:

Baseline characteristics by opioid and NSAID use

	All participants		Opioid Use				NSAID Use			
			No		Yes		No		Yes	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
eGFR (ml/min/1.73 m^2)	3939	43 ± 13	3548	43 ± 14	391	43 ± 14	3327	42 ± 13	612	48 ± 13
UPCR mcg/mg	3772	1 ± 2	3397	1 ± 2.4	375	0.7 ± 2	3185	1 ± 2	587	0.6 ± 2
Beck's Score	3889	8 ± 8	3506	8 ± 8	383	11 ± 9	3288	8 ± 8	601	8 ± 8
Symptom Severity Score	3919	151 ±177	3531	144 ±173	388	220 ±199	3307	150 ±176	612	159 ±184
KDQOL Burden of Kidney Disease	3913	82 ± 24	3527	83 ± 23	386	78 ± 26	3306	81 ± 24	607	87 ± 22
KDQOL Symptoms	3921	83 ± 15	3534	84 ± 14	387	77 ± 17	3312	84 ± 15	609	83 ± 14
SF-12 Physical Composite	3847	41 ± 12	3464	42 ± 11	383	33 ± 10	3245	41 ± 12	602	41 ± 12
SF-12 Mental Composite	3847	50 ± 11	3464	51 ± 10	383	47 ± 11	3245	50 ± 11	602	50 ± 11

N=3939

Table 3.

Crude rate of events (per 100 person-years) following annual visits classified by reported Opioid and NSAID use *

	Pre-kidney failure Death			Kidney Failure with KRT			Composite kidney disease outcome			Pre-kidney failure Hospitalization		
Analgesic use	**events**	**total visits**	**Rate per 100 visits (95 % CI)**	**events**	**total visits**	**Rate per 100 visits (95 % CI)**	**events**	**total visits**	**Rate per 100 visits (95 % CI)**	**events**	**total visits**	**Rate per 100 visits (95 % CI)**
Opioid (no NSAID)	85	2420	3.5 (2.8, 4.3)	84	1998	4.2 (3.4, 5.2)	114	1942	5.9 (5.3, 6.3)	2169	1998	108.6 (99.1, 118.9)
NSAID (no opioid)	38	2780	1.4 (1.0, 1.9)	46	2465	1.9 (1.4, 2.5)	60	2454	2.4 (1.9, 3.2)	1429	2465	58.0 (51.5, 65.3)
Other (non-opioid, non-NSAID)	402	19097	2.1 (1.9, 2.3)	683	15960	4.3 (4.0, 4.6)	930	15744	5.9 (5.5, 6.3)	9786	15960	61.3 (58.6, 64.2)
Opioid & NSAID	19	541	3.5 (2.2, 5.5)	12	476	2.5 (1.4, 4.4)	11	473	2.3 (1.2, 4.2)	426	476	89.5 (75.2, 106.6)

* Total number of visits used for pre-kidney failure death is 24838. Total number of visits for kidney failure with KRT, and pre-kidney failure hospitalization is 20899. Total number of visits for the composite kidney disease outcome is 20613.

Table 4:

Associations of time-updated cumulative NSAID and opioid exposure with outcomes, adjusting for time-dependent covariates in the full cohort and a sub-cohort comprised of participants who ever used other analgesics or tramadol during CRIC study

Outcome	Full cohort		Sub-cohort	
	HR* (95% CI)	P value	HR* (95% CI)	P value
Composite kidney disease outcome**				
Opioid use	1.4 (1.2, 1.7)	<0.001	1.6 (1.3, 2.0)	<0.001
NSAID use	1.2 (1.0, 1.5)	0.04	1.1 (0.9, 1.4)	0.2
Kidney failure with KRT				
Opioid use	1.4 (1.1, 1.7)	0.005	1.5 (1.2, 2.0)	<0.001
NSAID use	1.1 (0.8, 1.3)	0.6	1.0 (0.7, 1.3)	0.9
Pre-kidney failure death				
Opioid use	1.5 (1.2, 2.0)	0.002	1.6 (1.1, 2.2)	0.009
NSAID use	0.9 (0.7, 1.1)	0.3	1.2 (0.8, 1.7)	0.5
Hospitalization				
Opioid use	1.7 (1.6, 1.9)	<0.001	1.7 (1.5, 1.9)	<0.001
NSAID use	1.1 (1.0, 1.3)	0.01	1.1 (0.9, 1.3)	0.08

Other analgesics are non-opioid, non-NSAID.