Brief Communications

Association between NSAID Exposure and Kidney Function Decline in Primary Care Patients

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There are limited data evaluating chronic nonsteroidal anti-inflammatory drug (NSAID) exposure and decline in kidney function in primary care practice where rates of NSAID prescribing are high (1,2). The majority of published observational studies have evaluated the association of prescription NSAID use with AKI using claims data in focused geographic areas outside of the United States (1). It is estimated that >36 million Americans use over-the-counter (OTC) NSAIDs and data suggest that many users, regardless of age, exceed the recommended dose (1,3,4). Education materials for prescription (e.g., Food and Drug Administration Medication Guide) and OTC (label) NSAIDs have also been noted to have content that is not aligned with the universal precautions for health literacy. Poor literacy around NSAID education materials has been documented among primary care patients with CKD (5). This study sought to evaluate eGFR changes associated with chronic NSAID exposure in a large, geographically vast, primary care cohort using data from the DARTNet Practice Performance Registry receiving prescription and OTC NSAIDs (6).

This project was determined to not require oversight by the University of Michigan Institutional Review Board. This determination was based on the fact that the data set analyzed had no protected health information. Eligible patients were ≥18 years old and had at least two eGFR measurements (between <90 and >29 ml/min per 1.73 m²) at least 3 months apart. Baseline was defined as the first qualifying eGFR during the study period of January 1, 2011 to December 31, 2016. Historic NSAID exposure was determined from both electronic prescriptions and string and numeric matching to capture OTC use. Use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), and diuretics was captured. Some dose information was incomplete (e.g., dose or duration) so data were categorized by total daily dose of NSAIDs as high (>200 mg) or low (<200 mg); to be conservative, unknown dose was classified as high. Duration was calculated for each medication as 1 year before 3 years after baseline for each individual patient, or 4 years total. The primary outcome was eGFR over time with repeated measures. Before analyzing the primary outcome, propensity scores (eGFR >30 and <90 ml/min per 1.73 m² at baseline) were calculated for likelihood of exposure to aspirin or other NSAIDs. Total exposure was calculated for NSAIDs as follows: total dose=(0.5×low dose duration in days)+(high dose duration in days). These values were summed across all NSAIDs to create a variable for cumulative exposure (Supplemental Table 1). The ACEi, ARB, and diuretic exposure was coded as a dichotomous variable for any exposure during the observation period, or no exposure. Records were excluded from analysis if they had missing start date information or listed exposure to more than three NSAID medications because this was presumed to be the result of inaccurate medication reconciliation, although it may have been accurate in some cases. General linear mixed models (longitudinal) with random effects for patients were used for analysis of eGFR over time. Covariates included CKD stage at baseline, age, sex, and comorbidities (diabetes, heart failure, hypertension, liver disease, obesity). Propensity score quintiles were included as a categoric variable in the analysis. Time since baseline and NSAID exposure were included as main effects, with differential change over time tested using a two-way interaction effect (time×exposure). The differential change over time with exposure to ACEi/ARB and diuretics was included in the model.

A total of 97,238 patients were included in the final analysis. Patients that had NSAID exposure were older, more likely to be male, had slightly lower eGFR at baseline, and were significantly more likely to have a diagnosis of CKD, diabetes, heart failure, hypertension, liver disease, or obesity (Table 1). There were significantly more patients with CKD stage 3 in the NSAID-exposed group and patients with CKD stage 3 had markedly higher declines in eGFR (Table 2). The mean±SD total NSAID exposure was 48.7±31.9 months. The NSAID-exposed population was significantly less likely to be treated with ACEi or ARB, but there was no difference in diuretic use between the

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groups. The eGFR in patients who were unexposed declined by a mean (SE) of $-0.174 (0.019) \text{ ml/min per 1.73 m}^2$ per year (Table 2). Among patients who were exposed to NSAIDs, eGFR declined by an additional $-0.0604 (SE 0.012) \text{ ml/min per 1.73 m}^2$ per year per unit increase in exposure (i.e., 35% greater decline in eGFR per dose unit increase). The rate of eGFR decline among patients exposed to NSAIDs who were taking ACEi/ARB or diuretics was greater than patients who were unexposed; however, a statistically significant reduction in eGFR of $-0.146 \text{ ml/min}$ per $1.73 \text{ m}^2$ ($P=0.027$) was only associated with diuretic use in patients who were exposed (Supplemental Table 2). In this study, NSAID exposure was associated with a greater decline in eGFR compared with patients who were unexposed, with greater decline associated with greater cumulative exposure. This finding is similar to a previous study that found eGFR declined by 0.08 ml/min per 1.73 m^2 over the mean 2.75 years follow-up for each 100 unit increase in dose (7).

These data indicate a dose-dependent decline in eGFR and underscores the need to conservatively dose or avoid NSAIDs in patients who are at high risk to prevent a more rapid decline in eGFR. Patients exposed to prescription and OTC NSAIDs in our cohort had a higher burden of risk factors for kidney injury as well as other side effects of this drug class (8). A subanalysis of the Chronic Renal Insufficiency Cohort found that 24% of participants reported use of NSAIDs, suggesting that despite evidence for risk, clinicians still prescribe NSAIDs (9). Knowledge about NSAIDs and kidney risks in the general population is poor, especially with regard to OTC products (5). OTCs have perceived safety based on widespread availability and direct-to-consumer advertising (10). Providing NSAID education to people at risk for and with CKD should be part of the Advancing American Kidney Health Initiative’s awareness campaign (11). Clinicians should also be educated, because they will face continued challenges in balancing the risk of NSAIDs with alternative therapies, including opioid analgesics, in high-risk populations (12).

### Author Contributions

J. Carroll, L. Dickinson, C. Fox, W. Pace, A. Pai, and J. Vassalotti wrote the original draft and reviewed and edited the manuscript.

### Table 1. Demographic characteristics of participants in the NSAID-unexposed and -exposed cohort

| Variable             | Unexposed (N=52,986) | Exposed (N=44,252) | Total (N=97,238) | P Value |
|----------------------|----------------------|--------------------|------------------|---------|
| Gender, % male (n)   | 45 (22,961)          | 47 (21,291)        | 46 (44,252)      | <0.001  |
| Age (in yr), mean (SD) | 62.77 (12.09)       | 65.63 (11.01)      | 64.12 (11.68)    | <0.001  |
| Baseline eGFR (in ml/min per 1.73 m^2), mean (SD) | 72.43 (13.15) | 71.47 (13.67) | 71.98 (13.41) | <0.001  |
| Stage 3 CKD, % (n)   | 17 (8990)            | 20 (9300)          | 19 (18,290)      | <0.001  |
| Any CKD diagnosis, % (n) | 5 (2547)            | 6 (2572)           | 5 (5119)         | <0.001  |
| Diabetes, % (n)      | 4 (2268)             | 5 (2299)           | 5 (4567)         | <0.001  |
| Heart failure, % (n) | 0.64 (330)           | 0.83 (378)         | 0.73 (708)       | 0.0006  |
| Hypertension, % (n)  | 38 (19,803)          | 45 (20,567)        | 42 (40,370)      | <0.001  |
| Liver disease, % (n) | 2 (926)              | 2 (949)            | 2 (1875)         | 0.001   |
| Obesity, % (n)       | 5 (2407)             | 6 (2521)           | 5 (4928)         | <0.001  |
| ACEi/ARB use, % (n)  | 12 (6057)            | 10 (4470)          | 11 (10,527)      | <0.001  |
| Diuretic use, % (n)  | 7 (3606)             | 7 (3156)           | 7 (6762)         | 0.61    |

NSAID, nonsteroidal anti-inflammatory drug; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

### Table 2. eGFR change over 12 months among patients who were NSAID exposed and unexposed

| Variable             | Unexposed (N=52,986) | Exposed (N=44,252) | Total (N=97,238) | P Value |
|----------------------|----------------------|--------------------|------------------|---------|
| Intercept            | 92.48 (0.18)         | —                  | —                | —       |
| Age                  | $-0.2403 (0.0035)$   | —                  | —                | <0.001  |
| Gender               |                      |                    |                  | —       |
| Female (male is referent) | $-0.0102 (0.0580)$  | 0.08               | —                |         |
| Diabetes             | $-0.1563 (0.1382)$   | 0.26               | —                |         |
| Heart failure        | 0.2419 (0.3351)      | 0.47               | —                |         |
| HTN                  | 0.1648 (0.0658)      | 0.01               | —                |         |
| Liver disease        | 0.1880 (0.2070)      | 0.36               | —                |         |
| Obesity              | 0.1591 (0.1323)      | 0.23               | —                |         |
| CKD stage 3          | $-22.7033 (0.0755)$  | <0.001             | —                |         |
| NSAID dose           | 0.1633 (0.0239)      | <0.001             | —                |         |
| eGFR change per 12 mo in nonexposed (slope) | $-0.1743 (0.0186)$  | <0.001             | —                |         |
| Difference in eGFR slope per unit change for NSAID exposed patients | $-0.0604 (0.0108)$  | <0.001             | —                |         |

NSAID, nonsteroidal anti-inflammatory drug; HTN, hypertension.
J. Carroll, A. Pai, and G. Pulver were responsible for project administration; C. Fox, W. Pace, A. Pai, and J. Vassalotti conceptualized the study; L. Dickinson was responsible for methodology; L. Dickinson, W. Pace, and G. Pulver were responsible for formal analysis; A. Pai was responsible for validation; and W. Pace was responsible for data curation.

Disclosures
L. Dickinson reports other from National Research Network, American Academy of Family Physicians during the conduct of the study; and grants from National Institute of Diabetes and Digestive and Kidney Diseases outside the submitted work. J. Vassalotti reports other from Janssen and other from Renalytix AI, outside the submitted work. All remaining authors have nothing to disclose.

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Supplemental Material
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Supplemental Table 1. Categorical exposure variables based on years of exposure to NSAIDs.

Supplemental Table 2. eGFR change over 12 months among NSAID unexposed and exposed patients taking ACEi/ARB or diuretics.

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### Supplemental TOC

Table 1S. Categorical exposure variables based on years of exposure to NSAIDs

Table 2S. eGFR change over 12 months among NSAID unexposed and exposed patients taking ACEi/ARB or diuretics

| Categorical exposure variable | N     | Total exposure Min, Max (months) | Average number of NSAIDs Mean (sd) | Average total exposure Mean (sd) |
|-------------------------------|-------|---------------------------------|------------------------------------|---------------------------------|
| 0                             | 52,024| 0                               | 0                                 | 0                               |
| 1                             | 15,021| >0 to 24                        | 1.06 (.26)                        | 19.0 (7.7)                      |
| 2                             | 18,355| >24 to 48                       | 1.19 (.43)                        | 44.9 (6.2)                      |
| 3                             | 1,175 | >48 to 60                       | 2.29 (.48)                        | 53.8 (3.7)                      |
| 4                             | 11,124| >60                             | 2.51 (.70)                        | 94.4 (26.9)                     |
Table 2S. eGFR change over 12 months among NSAID unexposed and exposed patients taking ACEi/ARB or diuretics

| Variable | Adjusted models | p-value |
|----------|-----------------|---------|
| eGFR over time | N=97,232 | | |
| Variable | Coefficient (SE) | |
| Intercept (by propensity score quintile) | 92.35 (.18) | ---- |
| Age | -.2450 (.0036) | <.0001 |
| Gender | Female -.0723 (.0581) | .2136 |
| | Male (ref) | |
| Diabetes | -.1591 (.1382) | .2495 |
| Heart Failure | .1915 (.3351) | .5676 |
| HTN | .0561 (.0680) | .4094 |
| Liver disease | .1642 (.2070) | .4278 |
| Obesity | .1297 (.1324) | .3274 |
| ACEi/ARB | .4358 (.1695) | .0101 |
| Diuretic | -.6263 (.1478) | <.0001 |
| CKD Stage 3 | -22.6818 (.0756) | <.0001 |
| NSAID dose (at baseline) | .1551 (.0240) | <.0001 |
| eGFR change per 12 months in non-exposed (slope) | -.1332 (.0198) | <.0001 |
| Difference in eGFR slope for NSAID exposed patients taking concomitantACEi/ARB | -.1379 (.0774) | .0750 |
| Difference in eGFR slope for NSAID exposed patients taking concomitant diuretics | -.1464 (.0663) | .0272 |
| **Difference** in eGFR slope per dose unit increase for all NSAID exposed patients | **.0639 (.0108)** | **<.0001** |