Title: Comparative Risks of Non-Steroidal Anti-Inflammatory Drugs on Chronic Kidney Disease

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Running title: Comparative risks of NSAIDs on CKD

Word Count of abstract: 289

Word Count of main text (excluding methods): 3,004

Number of Figures: 1

Number of Tables: 2

Abstract

Background

There have been doubts about the association between non-steroidal anti-inflammatory drugs (NSAIDs) use and worsening kidney function, and whether there is a difference between risks of individual NSAIDs is presently unclear. Therefore, this study aimed to evaluate the association between NSAID exposure and the risk of incident estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 and compare the risks between NSAID subtypes in the Chinese population.

Methods

From 2008 to 2017, a total of 1,982,488 subjects aged 18 years or above with baseline eGFR ≥ 60 ml/min/1.73 m^2 were enrolled in this retrospective cohort study. Multivariable cox proportional hazards regression adjusted for each patient's baseline characteristics was adopted to examine the association between NSAID and incident eGFR < 60 ml/min/1.73 m^2 or eGFR decline ≥ 30% with reference to baseline.

Results

After a median follow-up duration of 6.3 (interquartile range: (3.3,9.4)) years, 271,848 cases (14%) of incident eGFR < 60 ml/min/1.73 m^2 and 388,386 (21%) events of eGFR decline ≥ 30% were recorded. After adjusting for each patient's baseline characteristics, NSAID treatment was shown to be associated with a significantly higher risk of incident eGFR < 60 ml/min/1.73 m^2 (HR: 1.71 [95% CI: 1.67-1.75]) and eGFR decline ≥ 30% (HR: 1.93 [95% CI: 1.89-1.96] when compared with no NSAID, with etoricoxib exhibiting the highest risk of eGFR < 60 ml/min/1.73 m^2 (HR: 3.12 [95% CI: 2.69-3.62]) and eGFR decline ≥ 30% (HR: 3.11 [95% CI: 2.78 -3.48] and ibuprofen displaying the lowest risk of eGFR < 60 ml/min/1.73 m^2 (HR: 1.12 [95% CI: 1.02-1.23]) and eGFR decline ≥ 30% (HR: 1.32 [95% CI: 1.23 -1.41]).

Conclusion

NSAID exposure was associated with higher risks of incident eGFR < 60 ml/min/1.73 m^2 and eGFR decline ≥ 30%. Highest risk was observed in etoricoxib users, and lowest risk with ibuprofen.

Manuscript Text

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have been one of the most commonly prescribed drug in many countries including the United States (US) for the treatment of pain and inflammation.(1) Nonetheless, association between the exposure of NSAIDs and incident chronic kidney disease (CKD) has been questioned since the 1950s.(2) The risk of developing CKD in relation to chronic use of NSAIDs remains inadequately explored.

Several meta-analyses summarized the association between NSAID exposure and risk of acute kidney injury (AKI),(3, 4) but no unequivocal conclusion about NSAID use and the development of CKD has been drawn, possibly because of its insidious nature. Previous studies that investigated CKD risk were conducted in heterogenous populations and they defined NSAID use and kidney outcome differently.(5, 6) Also, patterns of NSAID use were not recorded in the majority of the case-control studies comparing CKD patients and controls.(5) More importantly, current studies have scarcely compared the different NSAID subtypes. Selective cyclooxygenase-2 (COX-2) inhibitors have been traditionally regarded as less preferable in patients with high cardiovascular risk after the withdrawal of rofecoxib from the market due to an almost doubled risk of myocardial infarction.(7) However, celecoxib, one of the selective COX-2 inhibitors, was shown to be non-inferior to naproxen and ibuprofen with respect to cardiovascular safety in the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial in 2016, (8) thus triggering doubts about real world outcomes of using COX-2 inhibitors versus non-selective NSAIDs. Whether COX-2 inhibitors, as a group, differ from traditional NSAIDs in terms of CKD risk is presently unclear, and there is no consensus on specific NSAID recommendations for CKD patients because of conflicting evidence.(9) Current evidence of CKD risk regarding chronic NSAID exposure in individuals with normal kidney function has mainly focused on the Caucasian population in the US and Europe. Since Asians might be more susceptible to kidney failure when compared to Caucasians,(10, 11) the effect of NSAID use on kidney outcome in Asian populations, especially Chinese, is of great interest.

Hence, the aim of this study was to examine the association between NSAID use and worsening kidney function. CKD risks contributed by individual NSAIDs were critically compared. In the current study, kidney risk was measured by the incidence of eGFR < 60 ml/min/1.73 m^2, eGFR decline $\geq 30\%$ and their composite, using a

population-based electronic health database in Hong Kong, which is a comprehensive dataset representative of the Southern Chinese.

Methods

Study design

This was a retrospective cohort study. All individuals with eGFR ≥ 60 ml/min/1.73 m^2 between 1 January 2008 and 31 December 2017 were identified from the Hong Kong Hospital Authority's clinical database. The Hospital Authority is the statutory administrative body that manages the public healthcare sector in Hong Kong. More than 20 million attendances at 43 public hospitals, 49 specialist outpatient clinics and 73 primary care clinics under the Hospital Authority were recorded in the year 2018-2019.(12). All information, including patients' characteristics and outcome events were extracted from the electronic health database of the Hospital Authority's Clinical Management System. Clinicians and related healthcare professionals in the Hospital Authority were well-trained to record clinical information and patient demographics, including patients' diagnoses, prescriptions, laboratory tests and results, emergency department visits, hospitalizations, and specialist and general outpatient clinic visits in the Clinical Management System. Validity and coding accuracy of the database has previously been evaluated by high-quality population-based epidemiological studies.(13, 14) The baseline eGFR for each patient within the subject inclusion period was determined at the date of the first dispensing record of NSAID or the first attendance record of any clinical service under the Hospital Authority if NSAID was never prescribed in the subject inclusion period. Each patient was followed until the incidence of outcome events, death, or the last visit before 31 December 2018, whichever occurred first.

Drug exposure

Nine types of oral NSAIDs, namely celecoxib, etoricoxib, diclofenac, ibuprofen, indomethacin, mefenamic acid, naproxen, piroxicam, and sulindac, were included in this study. All frequencies of use, including scheduled and as-needed use, were included. Previous studies reported that the incidence of NSAID-associated adverse events would significantly increase after 4 consecutive weeks of treatment. (15) Hence, NSAID treatment in this study was defined as prescription of NSAIDs for a minimum of 28 days per month to avoid random effect due to short-term or one-off NSAID treatment.

NSAID exposure was considered a time-varying variable in order to take into account the dynamic change of NSAID treatment status in each patient during follow-up.

Study outcome

The primary outcomes of this study were incident eGFR < 60 ml/min/1.73 m^2, eGFR decline ≥30% when compared to baseline value, and their composite. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese (eGFR in ml/min/1.73 m^2 = 186 × [(serum creatinine in μmol/L) × 0.011]-1.154 × (age)-0.203 × (0.742 if female) × 1.233, whereas 1.233 is the adjusted coefficient for the Chinese population). The Serum creatinine (Jaffe's kinetic method) was measured with a Dimension AR system (Dade Behring, Deerfield, IL, USA) or equivalent model. One single eGFR value was used in defining primary outcome in the main analysis. The main analysis was then repeated by only including patients who had two consecutive eGFR values with at least two months in between and both satisfying the outcome criteria in one of the sensitivity analyses.

Ethical approval

Ethical approval for this study was granted by the Institutional Review Board of the Hong Kong Hospital Authority.

Baseline characteristics as confounders

Baseline characteristics consisted of age, gender, smoking status, body mass index (BMI), systolic blood pressure (BP), diastolic BP, fasting blood glucose, low-density lipoprotein (LDL) cholesterol, eGFR, comorbidities, and the use of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents and aspirin. (16) All laboratory assays were performed in laboratories accredited by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

Statistical analysis

Missing data for baseline characteristics were treated by multiple imputation with the chained equation method. Each missing value was imputed five times based on all baseline characteristics and all outcomes including incident eGFR<60 ml/min/1.73 m^2

and ≥ 30% decline, hence generating five different datasets which were applied in the same analysis. The results were then pooled according to the Rubin's rule (17).

Patients were categorized into ten groups, including one non-user group and nine NSAID-user groups, based on their NSAIDs prescription at baseline. Before conducting the analysis, fine stratification weights were applied to minimize potential confounding bias and selection bias among different treatment groups (18). This method was an extension of propensity score matching that combines propensity score stratification with weighting technique. The propensity scores were used to create fine stratums based on a fixed width of probability. This approach can avoid extreme weights when exposure prevalence is low and propensity score distribution is skewed (18). The fine stratification weights were conducted by using the 'MMWS' package in Stata with the fifty quantiles categories of propensity score for each stratum (19).

Descriptive statistics were used to summarize baseline characteristics. The incident rates for each outcome and their corresponding 95% confidence intervals (CIs) were calculated based on Poisson distribution. Multivariable Cox proportional hazard regression adjusted for each patient's baseline characteristics, as shown in the baseline characteristics section, was used to evaluate the association between NSAID exposure and the risk of outcome events. Considering the dynamic nature of NSAID treatment status in each patient during follow-up, NSAID exposure was treated as a time-varying covariate in the current model. To ensure robustness of the results, eight sensitivity analyses were conducted in this study. The minimum duration of NSAID treatment to be included in the analysis was reduced from 28 days to 7 days, 14 days, and 21 days in the first three sensitivity analyses respectively. After that, a complete case analysis was performed to avoid biases caused by imputation inaccuracy. In the next two sensitivity analyses, patients with follow up duration less than 1 year were excluded to minimize reverse causality, and the main analysis was repeated without using fine stratification weights. In the seventh sensitivity analysis, only patients who had two consecutive eGFR values with at least two months in between, while both satisfying the outcome criteria, were included. Lastly, an additional analysis was performed to examine patients who had both incident eGFR < 60mL/min/1.73m^2 and eGFR decline ≥ 30%.

In the subgroup analyses, differential associations between NSAID treatment and outcomes were explored. Patients were divided into subgroups by gender (female, male), age (<65, ≥65 years), the Charlson Comorbidity Index (20) (<3, ≥3), and the use of anti-hypertensive drugs (no, yes). Statistical significance of interactions between the NSAID treatment group and each subgroup was examined.

Two-tailed tests with p-value significance level of 0.05 were adopted by this study. The statistical analysis was executed in Stata version 15.1 (College Station, Texas).

Results

A total of 1,982,488 subjects were included in this study. As shown in **Supplementary Table 1**, most baseline characteristics had a percentage of data completion of above 50%, except for BMI (38%). The total number of complete cases was 577,889. After excluding unmatched individuals in fine stratification weights, 1,889,692 were included in the analysis. Weighted baseline characteristics for each NSAID treatment group are summarized in **Table 1**. The average age of participants was 55 ± 17 years old and 47% of them were male. 8% of the participants had received NSAID treatment. Among these people, diclofenac (58%) was the most frequently prescribed NSAID, followed by naproxen (19%) and ibuprofen (10%). Unweighted baseline characteristics of subjects are listed in **Supplementary Table 2**.

After a median follow-up duration of 6.3 years (interquartile range: (3.3,9.4)) (12,606,178 person years), 271,848 cases (14 %) of incident eGFR < 60 ml/min/1.73 m^2, 388,386 events (21%) of eGFR decline ≥30% and 419,506 cases (23%) of their composite among all participants were recorded. The incident rates of incident eGFR < 60 ml/min/1.73 m^2 were 22.8 (95% CI: 22.7-22.9) and 33.0 (95% CI: 32.3-33.8) cases per 1000 person-years in non-users and NSAID-users respectively. Regarding eGFR decline ≥30%, the incident rates were 33.4 (95% CI: 33.3-33.6) and 62.1 (95% CI: 61.0-63.2) cases per 1000 person-years in non-users and NSAID-users respectively. As for the composite of incident eGFR < 60 ml/min/1.73 m^2 and eGFR decline ≥30%, the incidence rates were 36.8 (95% CI: 36.6-36.9) and 68.0 (95% CI: 66.9-69.1) cases per 1000 person-years in non-users and NSAID-users respectively (**Table 2**). **Figure 1** illustrates the results of Cox proportional hazard regression for the association between

NSAID treatment and the outcomes. Our findings indicated that any NSAID treatment was associated with a significantly higher risk of incident eGFR < 60 ml/min/1.73 m^2 (HR: 1.71 [95% CI: 1.67-1.75]), eGFR decline ≥30% (HR: 1.93 [95% CI: 1.89-1.96]), and their composite (HR: 1.88 [95% CI: 1.85-1.91]).

Among all the NSAID subtypes, ibuprofen was found to be associated with the lowest risks of incident eGFR < 60 ml/min/1.73 m^2 (HR: 1.12 [95% CI: 1.02-1.23]), eGFR decline ≥30% (HR: 1.31 [95% CI: 1.22-1.41]), and their composite (HR: 1.34 [95% CI: 1.25-1.43]), while etoricoxib had significantly higher risks of incident eGFR < 60 ml/min/1.73 m^2 (HR: 3.12 [95% CI: 2.69-3.62]), eGFR decline ≥30% (HR: 3.11 [95% CI: 2.78-3.48]), and their composite (HR: 3.13 [95% CI: 2.80-3.49]) in comparison to other NSAIDs. Eight sensitivity analyses were performed by including NSAID treatment of shorter duration, reducing from 28 days to (1) 7 days (**Supplementary Figures 1**); (2) 14 days (**Supplementary Figures 2**); (3) 21 days (**Supplementary Figures 3**); the inclusion of (4) patients with no missing baseline characteristics only (**Supplementary Figures 4**); (5) patients with more than 1 year of follow-up only (**Supplementary Figures 5**); and repeating the analysis (6) without fine stratification weights (**Supplementary Figures 6**); (7) by defining outcome with two consecutive eGFR values with at least two months in between, while both satisfying the criteria (**Supplementary Figures 7**); and (8) to examine patients who had both incident eGFR < 60 ml/min/1.73 m^2 and eGFR decline ≥30% (**Supplementary Figures 8**). Similar results from the sensitivity analyses further confirmed the findings of our main analysis.

As shown in Supplementary **Figure 9**, the subgroup analyses showed that NSAID treatment interacted with all subgroups (gender, age, Charlson Comorbidity Index, and use of anti-hypertensive drugs) on the risk of incident eGFR < 60 ml/min/1.73 m^2 , eGFR decline ≥30% and their composite. In general, the effect of NSAID treatment on kidney outcomes was similar between males and females, but it was attenuated in older individuals, those who took anti-hypertensive drugs and those with a higher Charlson Comorbidity Index.

Discussion

This large-scale study adds value to the presently available evidence for NSAID associated CKD risk in a Chinese population with normaleGFR. All studied NSAIDs

were found to be significantly associated with elevated risks of incident eGFR < 60 ml/min/1.73 m^2 and eGFR decline ≥30%. Ibuprofen seemed to have the lowest risk of eGFR < 60 ml/min/1.73 m^2 and the risk was substantially lower than that of etoricoxib. While NSAIDs should be reserved for situations when benefits outweigh risks, this study remains a retrospective observation and further study regarding causality is warranted.

*Association between NSAID and kidney function*Past studies in the early 2000s failed to demonstrate an association between NSAID use and CKD, with most of them being case-control studies with limited sample sizes and were based on self-reported drug use, (21-23) while the present study attempted to minimize differences in variables among large-size groups. In the current study, associations between NSAID exposure and risk of kidney outcomes were shown, which was in agreement with the majority of the more recent cohort studies. (24-27) On the other hand, our findings contradicted a prior clinical study which reported that 6-month exposure to high dose celecoxib had no impact on GFR in 44 elderly patients with prostate carcinoma,(28) and another Swiss study which demonstrated no significant difference in kidney function between NSAID users and non-users in 4101 rheumatoid arthritis (RA) patients with baseline eGFR>30mL/min.(29) The difference in our findings could be attributed to their highly disease-specific population, in which the effect of NSAIDs could be obscured by other co-morbidities. The current study included a substantially larger number of subjects without kidney function impairment who also had longer follow-up periods. Together with a greater number of outcome events recorded, all these suggested a much greater power of the current study to identify the association between NSAID use and eGFR < 60 ml/min/1.73 m^2. Moreover, the Swiss study (29) compared between the two groups by mean absolute eGFR change per year instead of percentage change or rate of incident CKD. Therefore, direct comparison between our findings may not be appropriate.

Comparison between NSAIDs

In this study, etoricoxib, which is a COX-2 selective inhibitor, was shown to be associated with the highest risk of adverse kidney outcomes, followed by other non-selective NSAIDs and celecoxib, with ibuprofen displaying the lowest risk. To a certain extent, this finding aligned with results from a systematic review which reported association between NSAID use and kidney risks for rofecoxib, celecoxib, naproxen, diclofenac and indomethacin, but not for meloxicam and ibuprofen. (30) Ibuprofen appeared to be safer among the list of NSAIDs in both studies, although they did not reveal a statistically higher risk for ibuprofen, possibly because only studies that involved meloxicam were taken into consideration which in turn restricted the scope of

their analysis, and kidney risks were only reported as secondary outcomes in most of their included studies. In contrast, two large clinical trials, namely the PRECISION trial and the Celecoxib Long-Term Arthritis Safety Study (CLASS) study, which were not included in the above systematic review revealed different findings, reported that patients taking celecoxib were less susceptible to kidney events when compared to those taking ibuprofen. (8, 31) Discrepancy between our findings could be ascribed to the difference in defining kidney events. The incidence of acute kidney failure and the persistence of elevated serum creatinine for ≥24 hours were considered in the PRECISION trial, whereas occurrence of peripheral edema, increased creatinine level and hypertension during the 6-month treatment period were regarded as kidney adverse events in the CLASS study. On the contrary, acute events were not taken into account in the current study. Whether short-term increases in creatinine and acute kidney events translate into risk of developing CKD remained unclear. Furthermore, Asians only constituted a minority in their trials. Therefore, direct comparison between the current study and previous randomized clinical trials should be interpreted with caution.

Chronic kidney effects of NSAIDs have rarely been compared critically. Some studies may have inappropriately assumed a difference between COX-2 selective inhibitors and other NSAIDs, hence reporting hazard ratios for each group while individual agents in the same group displayed highly divergent effect sizes. (32, 33) In this study, etoricoxib was shown to be associated with the highest CKD risk. To the best of our knowledge, there were only three studies which clearly indicated etoricoxib in their analyses, (25, 26, 34) but the risk of CKD for etoricoxib alone was not reported, thus making direct comparison impossible. Since there is insufficient evidence for head-to-head comparison between the NSAIDs, further investigations are important to enhance our knowledge of the comparative risks between the NSAIDs.

Possible Mechanisms

Unlike the COX-1 enzyme, COX-2 was initially believed to be an ‘induced’ isoform and did not take part in constitutive functions. However, previous clinical studies illustrated that COX-2 inhibitors produced similar hemodynamic effects in the kidney when compared to non-selective NSAIDs,(35, 36) hence confirming the role of constitutive COX-2 in kidney homeostasis and the renin-angiotensin system (RAS).(37) By inhibiting both COX-1 and COX-2 enzymes in the kidneys, NSAIDs suppress the formation of protective prostaglandins, leading to reduced kidney perfusion and sodium retention,(38) which may affect kidney function in the long run.

Why NSAIDs seem heterogenous in increasing CKD risks remained controversial.

Difference in COX selectivity has been one of the proposed mechanisms.(37) Regarding relative COX-2 versus COX-1 selectivity, etoricoxib and celecoxib came first, followed by diclofenac and sulindac. Naproxen and indomethacin were more COX-1 selective, whereas piroxicam and ibuprofen were comparatively more non-selective.(39) Interestingly, our study results somewhat mimicked this trend, with non-selective NSAIDs exhibiting the lowest risk when compared to the more COX-1 or -2 selective NSAIDs. An in vivo experiment in mice demonstrated opposite effects of COX-1 and -2 on kidney homeostasis, with COX-2 inhibition reducing kidney medullary blood flow and urine flow.(40) Previous studies have also added that COX-1 inhibition may potentially attenuate the adverse impact of COX-2 inhibition in the kidney,(41) therefore justifying why non-selective NSAIDs may do lesser harm to the kidney when compared to COX-2 inhibitors. This study revealed that etoricoxib, which was the most COX-2 selective among the studied drugs, had a significantly higher risk, but the risk associated with celecoxib use was comparable to other NSAIDs except for ibuprofen. The class effect of COX-2 inhibitors was not conspicuous in this study, which echoes the findings of a meta-analysis of randomized trials. (42)

However, some authors hypothesized that kidney outcomes of NSAIDs were not dependent on COX-2 selectivity.(43) Instead, physiochemical properties that determines drug distribution in the kidney relative to plasma concentration play a more important role, rendering celecoxib more nephrotoxic than meloxicam, despite both of them being COX-2 selective. (43, 44) Nonetheless, this study was unable to validate this hypothesis because meloxicam was not included. Instead of being two distinct drug moieties, COX-2 selective inhibitors and other NSAIDs have different positions along the continuous scale of COX selectivity, in addition to their different potencies and pharmacokinetics properties.(42) Some investigators also suspected that differences in half-lives (34) and polymorphic expression of enzymes metabolizing NSAIDs (45) were possible causes. All of these could have contributed to the observed differences, although the exact mechanism is yet to be fully elucidated and experimental data on various NSAIDs are still lacking.

Subgroup analyses

The effect of NSAID was subject to age, use of anti-hypertensive drugs and comorbidities. In this study, the adverse impact of NSAID was more prominent in younger (<65 years old) and relatively healthier patients who had Charlson comorbidity index less than 3 when compared to the older and more ill counterparts. The impact of NSAID use in older patients could be masked by their frailty and other concurrent diseases. Therefore, this possibly explains why the effect of NSAID exposure was

apparently smaller in those patients. Furthermore, this study illustrated a difference in the risk of kidney function decline between those who were on anti-hypertensive drugs versus those who were not. NSAIDs raise BP via inhibiting synthesis of PGE_2 and PGI_2, which in turn disrupt vascular tone regulation and reduce natriuresis.(46) Previous studies proposed that patients treated with anti-hypertensives were more prone to the BP-increasing effect of NSAIDs in contrast to normotensive individuals because NSAIDs could potentially reverse the effect of anti-hypertensives in addition to their intrinsic effect of elevating BP.(47, 48) Anti-hypertensive drugs acting on RAS were shown to be most affected since NSAIDs inhibit prostaglandin synthesis, which in turn interfere with the effect of bradykinin and angiotensin II.(48, 49) Although hypertension is a known risk factor for both CKD and kidney failure,(50) whether higher CKD risk was solely contributed by the drug-drug interaction between NSAIDs and anti-hypertensives is presently unknown.

Strengths and limitations

This study had several strengths. First, this was the first large scale cohort study which compared the risk of CKD of different NSAIDs among the Chinese population. Second, NSAID exposure was captured by the clinical database instead of self-reporting, hence minimizing recall bias. Advanced statistical methods were adopted to evaluate NSAID exposure as a time-varying variable.

Several limitations were present in this study. First, this retrospective cohort study did not provide information about causality despite displaying an association between NSAID use and kidney outcomes. Second, our database from the Hospital Authority did not cover all NSAIDs available in Hong Kong due to formulary restrictions. Third, over-the-counter (OTC) NSAID use was not captured in the current study and patients' drug adherence was not taken into account, which could vary among NSAID users. Fourth, although hazard ratios have been adjusted by patients' history of peptic ulcer disease, the pattern of physician prescribing COX-2 selective inhibitors to patients who were at greater risk of gastrointestinal complications might still be a potential confounder. Moreover, inpatient and outpatient eGFR values were not distinguished in this study. An additional sensitivity analysis that defines primary outcome as having two consecutive eGFR values below 60 ml/min/1.73 m^2 with at least two months in between was performed to reduce the likelihood of misclassifying AKI patients as CKD patients. Furthermore, multiple NSAID use during the same period was recorded in a small number of patients. The drug that was prescribed for a shorter duration in the overlapping period was omitted. Lastly, information on drug dosing and indication (i.e. which type of pain) was not available in the current study.

Conclusion

There was an association between NSAID exposure and elevated risks of incident eGFR < 60 mL/min/1.73m^2 and eGFR decline ≥ 30%. Further study is warranted to confirm the heightened risk observed in etoricoxib users. Ibuprofen appeared to be a safer choice when NSAID use is deemed necessary.

Author Contributions

E.Y.F.W., and C.L.K.L. contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis and interpretation of the results, and wrote the manuscript. A.H.Y.M. contributed to interpretation of the results and wrote the manuscript. Y.W. contributed to the statistical analysis and interpretation of the results and wrote the manuscript. All authors contributed to the interpretation of the results, reviewed and edited the manuscript. E.Y.F.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors wish to acknowledge Hong Kong Hospital Authority for the contributions of data extraction.

Conflict of interest

I.C.K.W. received funding from Pfizer, Bayer and Novartis to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. E.W.Y.C. received research grants from Bayer, Bristol-Myers Squibb, Janssen, a Division of Johnson and Johnson, Pfizer, and Takeda to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. Other authors declare that they have no competing interests.

Sources of Funding

This study is funded by the Start-up Fund from the University of Hong Kong. No funding organization had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript.

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Table 1. Baseline characteristics of of 1,982,488 subjects aged 18 years or above with baseline eGFR ≥ 60ml/min/1.73m^2 in different drug groups after weighting

	No NSAID (n=1,734,701)	NSAID (n=154,991)	Celecoxib (n=1,274)	Etoricoxib (n=1,030)	Diclofenac (n=90,829)	Ibuprofen (n=15,169)	Indomethacin (n=5,199)	Mefenamic acid (n=10,697)	Naproxen (n=28,966)	Piroxicam (n=1,308)	Sulindac (n=519)
Male	811,803 (47%)	76,236 (49%)	657 (52%)	487 (47%)	44,983 (50%)	7,486 (49%)	2,299 (44%)	5,157 (48%)	14,221 (49%)	719 (55%)	230 (44%)
Age, years	55 (17)	55 (16)	55 (16)	56 (16)	55 (15)	55 (16)	55 (16)	54 (17)	55 (16)	55 (14)	56 (15)
Current smoker	51,890 (3%)	4,813 (3%)	29 (2%)	26 (3%)	2,858 (3%)	452 (3%)	160 (3%)	333 (3%)	899 (3%)	36 (3%)	19 (4%)
Systolic BP, mmHg	132 (20)	131 (20)	130 (20)	133 (21)	131 (20)	131 (20)	132 (20)	131 (20)	131 (20)	131 (20)	131 (20)
Diastolic BP, mmHg	76 (12)	76 (12)	76 (12)	77 (13)	76 (12)	76 (12)	76 (12)	76 (12)	76 (12)	76 (12)	76 (12)
Fasting glucose, mg/dL	102 (26)	103 (27)	101 (25)	103 (29)	103 (27)	103 (28)	103 (28)	103 (29)	103 (27)	104 (28)	103 (36)

BMI, kg/m^2	24.5 (4.0)	24.7 (4.0)	24.4 (4.4)	24.6 (4.4)	24.7 (4.0)	24.7 (4.0)	24.8 (4.0)	24.7 (4.2)	24.7 (4.0)	25.2 (3.9)	24.4 (4.1)
LDL cholesterol, mg/dL	117 (35)	117 (35)	116 (36)	115 (34)	117 (34)	117 (35)	117 (35)	116 (36)	117 (35)	118 (35)	118 (37)
eGFR, ml/min/1.73m^2	113 (28)	114 (27)	116 (27)	115 (26)	114 (27)	114 (28)	115 (30)	114 (27)	114 (27)	114 (27)	115 (29)
Charlson comorbidity index	2.4 (1.9)	2.4 (1.8)	2.4 (1.8)	2.5 (1.9)	2.4 (1.8)	2.5 (1.8)	2.5 (1.9)	2.4 (1.9)	2.4 (1.8)	2.5 (1.7)	2.6 (1.8)
Coronary heart disease	80,730 (5%)	7,351 (5%)	62 (5%)	59 (6%)	4,261 (5%)	704 (5%)	227 (4%)	564 (5%)	1,366 (5%)	76 (6%)	31 (6%)
Heart failure	24,404 (1%)	2,162 (1%)	16 (1%)	13 (1%)	1,314 (1%)	198 (1%)	69 (1%)	128 (1%)	394 (1%)	23 (2%)	9 (2%)
Diabetes mellitus	205,218 (12%)	19,186 (12%)	134 (11%)	123 (12%)	11,077 (12%)	1,856 (12%)	659 (13%)	1,475 (14%)	3,605 (12%)	190 (15%)	64 (12%)
Atrial fibrillation	31,443 (2%)	2,847 (2%)	22 (2%)	13 (1%)	1,744 (2%)	267 (2%)	94 (2%)	137 (1%)	534 (2%)	26 (2%)	11 (2%)
Peripheral vascular disease	3,928 (0.2%)	549 (0.4%)	1 (0.1%)	5 (0.5%)	316 (0.3%)	46 (0.3%)	21 (0.4%)	55 (0.5%)	93 (0.3%)	10 (0.8%)	1 (0.2%)
Stroke	85,152 (5%)	8,133 (5%)	54 (4%)	64 (6%)	4,809 (5%)	763 (5%)	275 (5%)	539 (5%)	1,522 (5%)	84 (6%)	23 (4%)

Amputation	1,725 (0.1%)	176 (0.1%)	3 (0.3%)	4 (0.4%)	92 (0.1%)	19 (0.1%)	4 (0.1%)	15 (0.1%)	36 (0.1%)	3 (0.2%)	0 (0%)
Dementia	14,142 (0.8%)	587 (0.4%)	5 (0.4%)	6 (0.6%)	287 (0.3%)	82 (0.5%)	15 (0.3%)	68 (0.6%)	120 (0.4%)	2 (0.2%)	0 (0%)
Lung disease	55,372 (3%)	4,989 (3%)	37 (3%)	33 (3%)	2,931 (3%)	488 (3%)	155 (3%)	337 (3%)	936 (3%)	55 (4%)	18 (3%)
Connective tissue disease	4,131 (0.2%)	516 (0.3%)	3 (0.2%)	3 (0.3%)	272 (0.3%)	50 (0.3%)	9 (0.2%)	31 (0.3%)	139 (0.5%)	6 (0.4%)	2 (0.4%)
Peptic ulcer	38,341 (2%)	3,516 (2%)	37 (3%)	22 (2%)	2,049 (2%)	329 (2%)	123 (2%)	253 (2%)	649 (2%)	45 (3%)	10 (2%)
Liver disease	41,312 (2%)	3,640 (2%)	23 (2%)	37 (4%)	2,158 (2%)	351 (2%)	116 (2%)	251 (2%)	664 (2%)	25 (2%)	15 (3%)
Hemiplegia	7,510 (0.4%)	742 (0.5%)	2 (0.1%)	2 (0.2%)	444 (0.5%)	73 (0.5%)	31 (0.6%)	38 (0.4%)	151 (0.5%)	0 (0%)	2 (0.4%)
Leukemia	2,244 (0.1%)	112 (0.1%)	2 (0.1%)	0 (0%)	43 (0%)	26 (0.2%)	6 (0.1%)	15 (0.1%)	20 (0.1%)	0 (0%)	0 (0%)
Malignant lymphoma	2,706 (0.2%)	175 (0.1%)	1 (0.1%)	1 (0.1%)	87 (0.1%)	27 (0.2%)	6 (0.1%)	18 (0.2%)	33 (0.1%)	1 (0.1%)	0 (0%)

Cancer	95,455 (6%)	8,791 (6%)	80 (6%)	53 (5%)	5,004 (6%)	830 (5%)	300 (6%)	864 (8%)	1,545 (5%)	79 (6%)	33 (6%)
Use of anti-diabetic drugs	207,087 (12%)	19,217 (12%)	136 (11%)	125 (12%)	11,090 (12%)	1,858 (12%)	639 (12%)	1,536 (14%)	3,596 (12%)	178 (14%)	55 (11%)
Use of lipid-lowering agents	184,958 (11%)	16,640 (11%)	121 (9%)	104 (10%)	9,441 (10%)	1,634 (11%)	555 (11%)	1,491 (14%)	3,076 (11%)	157 (12%)	55 (11%)
Use of anti-hypertensive drugs	625,677 (36%)	56,366 (36%)	427 (33%)	396 (38%)	32,717 (36%)	5,455 (36%)	1,838 (35%)	4,421 (41%)	10,409 (36%)	508 (39%)	186 (36%)
Use of aspirin	178,623 (10%)	16,147 (10%)	127 (10%)	143 (14%)	9,378 (10%)	1,617 (11%)	526 (10%)	1,220 (11%)	2,933 (10%)	148 (11%)	55 (11%)

All parameters are expressed in either number (percentage) or mean (SD)

NSAID = non-steroidal anti-inflammatory drug; BP = blood pressure; BMI = body mass index; LDL cholesterol = low-density lipoprotein-cholesterol; eGFR = estimated glomerular filtration rate.

Table 2. Incidence of eGFR < 60mL/min/1.73m^2 and eGFR decline ≥ 30% according to NSAID use

		eGFR < 60 ml/min/1.73 m^2		eGFR decline ≥ 30%		Composite‡	
	Subject	Event	Incidence rate†	Event	Incidence rate†	Event	Incidence rate†
No NSAIDs	1,734,701	263,112	22.8 (22.7,22.9)	373,051	33.4 (33.3,33.6)	402,932	36.8 (36.6,36.9)
Any NSAIDs	154,991	8,736	33.0 (32.3,33.8)	15,335	62.1 (61.0,63.2)	16,574	68.0 (66.9,69.1)
Celecoxib	1,274	213	32.2 (27.1,38.5)	375	63.8 (56.4,72.4)	392	67.8 (60.2,76.7)
Etoricoxib	1,030	183	45.0 (38.7,52.6)	322	88.8 (79.0,100.0)	335	93.5 (83.6,104.8)
Diclofenac	90,829	5,925	34.1 (33.2,35.0)	10,487	64.7 (63.4,66.0)	11,267	70.4 (69.0,71.8)
Ibuprofen	15,169	465	24.8 (22.5,27.5)	817	45.9 (42.6,49.5)	930	52.9 (49.4,56.7)
Indomethacin	5,199	320	33.5 (30.0,37.6)	505	56.5 (51.5,62.2)	577	65.8 (60.3,71.9)
Mefenamic acid	10,697	144	16.7 (11.8,24.4)	284	34.0 (27.4,42.6)	306	37.0 (30.1,46.1)
Naproxen	28,966	1,361	34.5 (32.6,36.5)	2,343	63.5 (60.8,66.3)	2,541	69.7 (66.9,72.7)
Piroxicam	1,308	78	33.4 (25.3,45.1)	124	56.7 (44.7,72.8)	138	63.9 (50.6,81.9)
Sulindac	519	47	35.8 (27.3,47.9)	78	63.7 (50.1,82.2)	90	76.4 (61.1,96.7)

NSAID = non-steroidal anti-inflammatory drug.

† Incidence rate (cases/1000 person-years) with 95% CI based on Poisson distribution.

‡ Composite is defined by either incident eGFR < 60ml/min/1.73m^2 or eGFR decline ≥ 30%.