Title: Comparative Risks of Non-Steroidal Anti-Inflammatory Drugs on Cardiovascular Diseases: A Population-based Cohort Study

Authors: Eric Yuk Fai Wan, PhD[1 2*], Esther Yee Tak Yu, MBBS[1*], Linda Chan, BMBS[1], Anna Hoi Ying Mok, MClinPharm[1], Yuan Wang, MStat[1], Esther Wai Yin Chan, PhD[2 4], Ian Chi Kei Wong, PhD[2 3 4], Cindy Lo Kuen Lam, MD[1]

1 Department of Family Medicine and Primary Care, the University of Hong Kong, Hong Kong
2 Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, the University of Hong Kong, Hong Kong
3 Research Department of Practice and Policy, School of Pharmacy, University College London
4 Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong

Address for correspondence:
Dr. Eric Yuk Fai Wan
Postal Address: Department of Family Medicine and Primary Care, the University of Hong Kong, 3/F Ap Lei Chau Clinic, 161 Main Street, Ap Lei Chau, Hong Kong.
Tel. (852) 2552 4690
Fax. (852) 2814 7475
Email: yfwan@hku.hk

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Abstract

Through examining the incidence of cardiovascular diseases (CVD) among non-steroidal anti-inflammatory drug (NSAID) users and non-users, this study aims to compare the risks contributed by different NSAIDs in a Chinese population. The retrospective cohort including 4,298,368 adults without CVD from electronic health records between 2008 and 2017 in Hong Kong was adopted. 4.5% of individuals received NSAIDs including celecoxib, etoricoxib, diclofenac, ibuprofen, indomethacin, mefenamic acid or naproxen for four consecutive weeks or more at baseline. Cox regression, including NSAID use as a time-dependent covariate and adjusted with patient's characteristics, was conducted to examine the association between NSAID exposure and incident CVD. After a median follow-up of 6.9 years (30 million person-years), a total of 258,601 cases of incident CVD was recorded. NSAID use was shown to be associated with a significantly higher risk of CVD (HR: 1.32 [95% CI: 1.28-1.37]) compared to non-NSAID use. Similar results in coronary heart disease (HR: 1.37 [95% CI: 1.31-1.43]), stroke (HR: 1.27 [95% CI: 1.21-1.33]), and heart failure (HR: 1.25 [95% CI: 1.16-1.34]) were obtained. Overall, similar CVD risk was observed across users of NSAIDs, except for etoricoxib that showed a higher risk (HR: 2.01 [95% CI: 1.63-2.48]. Considering that a higher CVD risk was consistently displayed among NSAID users, NSAIDs should be used cautiously, and the usage of etoricoxib in the Chinese population should be reviewed.

Manuscript Text

Introduction

The risks of heart attack and stroke associated with non-steroidal anti-inflammatory drugs (NSAIDs) were reiterated when the United States (US) Food and Drug Administration (FDA) strengthened the label warning of all prescription NSAIDs in 2015.[1] Nevertheless, NSAIDs have still been widely used for the treatment of pain and inflammation, and the proportion of users has been even higher among patients who have cardiovascular diseases (CVD). [2] At present, there is no evidence supporting a difference in analgesic efficacy between NSAIDs.[3,4] Therefore, gastrointestinal and cardiovascular (CV) risks have been the main concerns when physicians prescribe NSAIDs. The practice of prescribing selective cyclooxygenase (COX)-2 inhibitors, such as celecoxib and etoricoxib, and concomitant use of proton pump inhibitors (PPIs) is common in patients who are at greater risk of gastrointestinal complications, while it has been unclear whether there is an NSAID with heightened CV risks.

Various types of NSAIDs have different selectivity towards COX enzymes, in addition to differences in pharmacokinetic properties, potencies and metabolism, [5] thereby potentially displaying different cardiovascular risks. Previous studies suggested that naproxen seemed to have the best cardiovascular safety profile among NSAIDs, [6-8] whereas a recent guideline recommended to avoid the use of older COX-2 inhibitors, such as diclofenac, when a traditional NSAID has to be prescribed because of its apparently heightened cardiovascular risk.[9] However, most of these recommendations were based on studies conducted in Western populations. The superiority or inferiority of a particular NSAID in terms of cardiovascular safety has been insufficiently explored in Asian populations. It is generally recommended to avoid the use of NSAIDs in patients with established CVD[9], but to the best of our knowledge, no single drug has been recommended against use due to its adverse CV risk profile in the Asian populations.

CVD has been a leading cause of death in China, accounting for more than 40% of all deaths. [10] Therefore, identifying the actual CVD risks associated with NSAID use in the Chinese population, and the NSAID with lower CVD risk is of clinical importance. By examining the incidence of CVD in a cohort of individuals without CVD, this study aimed to compare different NSAIDs with regards to their cardiovascular safety.

Methods

Ethical approval

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

Study design

This retrospective cohort study included patients without CVD history identified from the Hong Kong Hospital Authority's (HA) electronic health database, with a subject inclusion period between 1 January 2008 and 31 December 2017. The HA manages 43 public hospitals, 49 specialist outpatient clinics and 73 primary care clinics with more than 20 million attendances in the year 2018-2019 [11]. The diagnosis of CVD was defined as the incidence of coronary heart disease, stroke, or heart failure, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code and the International Classification of Primary Care-2 (ICPC-2) code. Patient demographics, including patients' diagnoses and prescriptions were entered into the electronic health database of the HA by well-trained clinicians and related healthcare professionals. All the clinical information in the current study was extracted from this database, the coding accuracy and validity of which has been approved by previous high-quality population-based epidemiological studies [12-14]. The date of the first dispensing record of a NSAID for each patient in the subject inclusion period or the first attendance record of any clinical service if a NSAID was never used in the subject inclusion period was defined as the baseline. To minimize the reverse causality, patients with less than one year of follow-up duration were excluded from this study. Each patient was followed until the incidence of the outcome events, death or the last visit record on or before 31 December 2018, whichever occurred first.

Drug exposure

This study focused on seven types of oral NSAIDs, including celecoxib, etoricoxib, diclofenac, ibuprofen, indomethacin, mefenamic acid, and naproxen. Since it has been reported that the incidence of NSAID-associated adverse events increased significantly after 4 consecutive weeks of treatment [15,16], this study adopted a cutoff value of 28 days of treatment with NSAIDs. Only treatment duration of more than 28 days per month would be regarded as NSAID exposure so as to minimize random effect attributed to short-term or one-off NSAID treatment.

Study outcome

The primary outcome of this study was any incident CVD, defined as the incidence of coronary heart disease (CHD), stroke, or heart failure. The secondary outcomes were (1) incidence of CHD, (2) incidence of stroke, and (3) incidence of heart failure. Diagnosis of CHD, stroke, and heart failure was determined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 410-414, 430-438, and 428, and International Classification of Primary Care-2 (ICPC-2) code of K74-K76, K89-K91, and K77, respectively. These codes have been shown to provide high coding accuracy in diagnosing myocardial infarction and stroke with positive predictive values of 85.4% (95% confidence interval (CI) 78.8% to 90.6%) and 91.1% (95% CI: 83.2% to 96.1%), respectively [13].

Baseline characteristics

Baseline characteristics included age, sex, smoking status, comorbidities, Charlson Comorbidity Index and the use of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents and aspirin. Previous study demonstrated reliability of the electronic health database of the HA to capture demographics and use of drugs with an almost perfect level of data completeness regarding demographics (100%) and drug prescription (99.98%) [17].

Statistical analysis

Patients were categorized into eight groups, based on their NSAID prescription at baseline. Baseline characteristics were reported using descriptive statistics. Selection bias among different treatment groups was adjusted using fine stratification weights [18]. This method combines propensity score stratification with weighting technique to serve as an extension of propensity score method. Based on a fixed width of probability, the fine stratums were created using propensity scores. This approach can avoid extreme weights due to low exposure prevalence and skewed propensity score distribution [18]. Using the 'MMWS' package in Stata, the fine stratification weights were conducted with fifty quantiles categories of propensity score for each stratum [19]. Following Poisson distribution, the incident rates and their corresponding 95% confidence intervals (CIs) were calculated for each outcome. Multivariable Cox proportional hazard model was used to evaluate the association between NSAID exposure and the

risk of outcome events regression. NSAID exposure was considered as a time-varying covariate to capture the dynamic status of each patient's NSAID treatment during follow-up. The model was adjusted for all the baseline characteristics. In this study, five sensitivity analyses were performed. The first three sensitivity analyses were conducted by including patients who had been treated with NSAIDs consecutively for 7 days, 14 days and 21 days respectively. Afterwards, patients with follow up duration less than 3 years were excluded to avoid the problem of reverse causality. In the last sensitivity analysis, the analysis was conducted without using fine stratification weights.

The subgroup analyses explored the statistical significance of interactions between NSAID treatment and the following baseline characteristic groups, including sex (female, male), age (<50, ≥50 years), the use of anti-hypertensive drugs (no, yes), the use of Aspirin (no, yes), and the Charlson Comorbidity Index [20,21] (<3, ≥3).

This study applied two-tailed tests with p-value significance level of 0.05. The statistical analysis was conducted using Stata version 15.1 (College Station, Texas).

Results

A total of 4,298,368 patients were included in this study. **Table 1** summarizes weighted baseline characteristics for each NSAID treatment group. The participants had an average age of 47.6 ± 17.0 years at baseline and 44.8% of them were male. 4.54% of the participants received NSAID treatment at baseline. Diclofenac (59.2%) was the most frequently prescribed NSAID, followed by naproxen (17.2%) and ibuprofen (9.93%). Baseline characteristics without fine stratification weighting are reported in **Supplementary Table 1**.

A total of 258,601 cases of incident CVD, including 115,221 CHD cases, 127,988 stroke events, and 61,466 cases of incident heart failure were recorded after a median follow-up of 6.9 years (30,009,885 person-years). As shown in **Table 2**, the incidence rates of CVD were 8.83 (95% CI: 8.79-8.86) and 11.06 (95% CI: 10.71-11.42) cases per 1000 person-years respectively in non-users and NSAID-users. As for CHD, the incidence rates were 3.87 (95% CI: 3.85-3.89) and 5.01 (95% CI: 4.78-5.25) cases per 1000 person-years respectively in non-users and NSAID-users. In terms of stroke, the

incidence rates were 4.31 (95% CI: 4.29-4.34) and 5.07 (95% CI: 4.83-5.32) cases per 1000 person-years respectively in non-users and NSAID-users. With regard to heart failure, the incidence rates were 2.06 (95% CI: 2.04-2.08) and 2.09 (95% CI: 1.95-2.24) cases per 1000 person-years respectively in non-users and NSAID-users. The results of Cox proportional hazard regression for the association between NSAID treatment and the outcomes are illustrated in **Figure 1**, indicating that any NSAID treatment was associated with a significantly higher risk of CVD (HR: 1.32 [95% CI: 1.28-1.37]), CHD (HR: 1.37 [95% CI: 1.31-1.43]), stroke (HR: 1.27 [95% CI: 1.21-1.33]), and heart failure (HR: 1.25 [95% CI: 1.16-1.34]). Among all the studied NSAIDs, mefenamic acid was found to be associated with the lowest risks of any CVD events (HR: 1.25 [95% CI: 1.01-1.55]) and stroke (HR: 0.95 [95% CI: 0.66-1.37]), while ibuprofen was associated with the lowest risks of CHD (HR: 1.12 [95% CI: 0.93-1.34]) and heart failure (HR: 1.09 [95% CI: 0.84-1.42]). On the other hand, etoricoxib was associated with the highest risks of all outcome events, including any CVD events (HR: 2.01 [95% CI: 1.63-2.48]), CHD (HR: 1.49 [95% CI: 1.04-2.13]), stroke (HR: 2.24 [95% CI: 1.69-2.97]), and heart failure (HR: 2.31 [95% CI: 1.51-3.54]). Five sensitivity analyses using different periods for NSAID treatments, 3-year restriction on follow up duration and analysis without weighting, as shown in **Supplementary Figure 1,** produced similar findings, hence confirming findings from our main analysis. **Supplementary Figure 2** reports the results of subgroup analyses, suggesting that the effect of NSAID treatment was different in people with different age (<50, ≥50 years) and Charlson Comorbidity Index (<3, ≥3). The effect of NSAID on CV outcomes was less prominent in patients who were older and had a higher Charlson's Comorbidity Index.

Discussion

This study demonstrated significant associations between NSAID exposure and the risks of developing CVD in a Chinese population without prior CV events. Etoricoxib users displayed the highest composite risk, while naproxen and celecoxib were not shown to be superior to any other NSAIDs.

Our findings echoed results from previous studies which reported that NSAID use was associated with increased risks of stroke and myocardial infarction [22-29], as well as heart failure [30-32]. In contrast, a 2018 Canadian cohort study which covered over 2 million primary care visits by 814,049 old adults reported that the rate of acute CV outcomes observed up to 37 days after each visit were equivalent between NSAID-users and non-

users, suggesting short-term use may be potentially safe.[33] As they defined exposure as dispensing of prescription NSAID within 7 days after a visit, they aimed to address short-term CV events caused by a relatively temporary NSAID exposure in the primary care setting, thus demonstrating opposite results from the current study. Yet, there is still overwhelming evidence suggesting short-term NSAID treatment increase CVD risks, proposing there is no safe-treatment window. [9,34]

Unlike previous studies, we did not observe lower CVD risk with naproxen [6-8,35] or celecoxib [23,29,31], which are the two preferred options when NSAID use is unavoidable as recommended by current guidelines.[36] There have been doubts about the superiority of naproxen shown in earlier studies which were heavily biased by the worse outcomes for rofecoxib, which has been withdrawn from the market. [29] Later studies have also failed to demonstrate a significant difference in CVD risk between naproxen and other NSAIDs despite claiming that naproxen seems to have the lowest risk. [6,8]

Studies which were in favor of the superiority of celecoxib adopted a different study design when compared to the current investigation, focusing on a disease-specific population which carried a higher baseline CVD risk. [23,29] Examining a more transient exposure and short-term outcomes, they suggested that the risk of celecoxib was lower than other non-selective NSAIDs. [23,29] Conversely, the present study demonstrated similar stroke risks between celecoxib and other non-selective NSAIDs by including only patients who had taken NSAIDs for 4 consecutive weeks and following patients for a median duration of 6.9 years, hence explaining the difference between our results. In the Korean cohort study, since only patients who were first diagnosed with MI were included, most of them were on anti-platelet or anticoagulation therapy.[29] It has been postulated that the antiplatelet activity of aspirin can be attenuated by some NSAIDs,[37,38] but not celecoxib.[38-40] This could possibly explain why they achieved different results in a population of post-MI patients who were taking anti-platelet drugs, whereas only 2.0% of the NSAID users in the current study were taking aspirin.[29] Whilst evidence from observational studies remains inconclusive, prior randomized controlled trials also did not reveal a difference in CV outcomes between celecoxib, naproxen and ibuprofen, [41,42] which is consistent with our findings. In the subgroup analysis, the adverse impact of NSAIDs on CVD risks was less notable in relatively older patients (≥50 years old) and those with a Charlson's comorbidity index of 3 or above, since their concurrent illnesses and frailty might be more important contributors to CVD risks, hence seemingly masking the effect of NSAID usage.

In the current study, all studied NSAIDs displayed similar risks, except that etoricoxib

was associated with a substantial increase in stroke risk and HF risk. Etoricoxib has been shown to be highly correlated to the risk of ischemic stroke when compared to other NSAIDs. [43] In addition, our finding is accordant with a prior Taiwanese study which suggested ketorolac and etoricoxib were associated with the highest risk of incident heart failure,[32] and a nested case-control study conducted in Western population which revealed that ketorolac, etoricoxib and indomethacin were associated with higher risks of hospital admission for heart failure among the list of NSAIDs.[31] On the other hand, etoricoxib was found to have a similar rate of thrombotic CV events in comparison to diclofenac in a head-to-head randomized trial for the treatment of osteoarthritis or rheumatoid arthritis[44], while only less than 4% of participants were Asians. There appears to be some differences in terms of CVD risk between NSAIDs, but current evidence is highly diverse because studies were performed in heterogenous populations, using different methodologies and study outcomes.

It has been postulated that COX-2 selectivity of NSAIDs that leads to unopposed thromboxane-A2 (TXA_2) facilitates thrombosis,[45] which in turn leads to heightened CVD risks. Etoricoxib, which has the highest COX-2 to COX-1 selectivity ratio [9] among the studied NSAIDs, was shown to be associated with the highest CVD risks. However, a class effect of COX-2 inhibitors was not observed.[5] Celecoxib, which is also a selective COX-2 inhibitor, was not as worse as etoricoxib as reported by the current study, and was even superior to other NSAIDs as described in previous studies.[23,29,31] A meta-analysis also concluded that etoricoxib may carry higher CVD risks when compared to celecoxib.[46] Although it has been suggested that COX inhibition exacerbates water retention which subsequently precipitates heart failure, whether COX-2 selectivity of etoricoxib contributes to its enhanced HF risk remains unknown. [32] Several other mechanisms have been proposed to explain the difference in CVD risks among NSAIDs, including difference in pharmacokinetics properties and potencies,[5] dose and timing of NSAID exposure,[26] and polymorphic expression of enzymes metabolizing NSAIDs. [47] In addition, whether patients are concurrently taking aspirin also matters, because NSAIDs may interfere with the antiplatelet activity of aspirin and perform differently in various patient populations. [48] Therefore, studies conducted in different populations should be interpreted cautiously.

Strengths and limitations

This study presented several strengths. First of all, this study utilized an electronic clinical database to capture NSAID usage, thus minimizing recall bias. Only subjects who were put on NSAID treatment for more than 4 consecutive weeks were considered NSAID-users, and drug exposure was treated as a time-varying variable to take into

account changes in treatment status. The imbalance in the baseline risk between NSAID users and non-NSAID user was negligible.

Several limitations have to be addressed. Firstly, this study did not consider the dose-response relationship of NSAIDs. Secondly, drug compliance and over the counter (OTC) NSAID use were not considered. However, it has been suggested that the information of patient-reported OTC NSAID use does not significantly alter the risk estimates for the association between NSAID use and the risk of acute myocardial infarction when compared to using pharmacy data alone,[49] hence confirming the validity of the current study. Thirdly, residual confounding should not be neglected, and the nature of this retrospective cohort study imposed limitations on explaining the causal relationship between NSAIDs and CVD risks. Lastly, there might be under-detection of cases when the diagnosis code was missing for an outcome event.

Conclusion

Our results demonstrated elevated CVD risks in Chinese patients who had taken NSAIDs for four or more consecutive weeks, and therefore, NSAIDs should be used with caution. Among the list of NSAIDs studied, etoricoxib was particularly shown to be associated with a higher CVD risk. In the absence of evidence supporting of its superior efficacy, the usage of etoricoxib as a first-line treatment in the Chinese population should be reviewed.

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.

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Data Sharing

Data will not be made available to others because the data custodians have not given permission.

Conflict of interest

E.Y.F.W has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, and the Hong Kong Research Grant Council, outside the submitted work. C.L.K.L. has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, the Hong Kong Research Grant Council, the Hong Kong College of Family Physicians, and Kerry Group Kuok Foundation, outside the submitted work. E.Y.T.Y has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, outside the submitted work. L.C. has received research grants from the University of Hong Kong, and also received speaker fees from the University of Hong Kong-Shenzhen Hospital, outside the submitted work. E.W.Y.C. has received research grants from the Hong Kong Research Grant Council, Narcotics Division of the Security Bureau of the Government of the Hong Kong SAR, Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, National Health and Medical Research Council in Australia , Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, and Takeda, outside the submitted work. I.C.K.W. has received research funding from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grant Council, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also received speaker fees from Janssen and Medice, outside the submitted work. Other authors declare that they have no competing interests.

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