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DRUG SAFETY

Comparative cardiovascular safety of nonsteroidal anti-inflammatory drugs in patients with hypertension: a population-based cohort study

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Keywords cardiovascular safety, cohort study, COX-2 selective, hypertension, nonsteroidal anti-inflammatory drugs, pharmacoepidemiology

AIMS

Previous studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with higher cardiovascular risks. However, few have been active comparison studies that directly assessed the potential differential cardiovascular risk between NSAID classes or across individual NSAIDs. We compared the risk of major cardiovascular events between cyclooxygenase 2 (COX-2)-selective and nonselective NSAIDs in patients with hypertension.

METHODS

We conducted a cohort study of patients with hypertension who initiated COX-2-selective or nonselective NSAIDs in a population-based Taiwanese database. The outcomes included hospitalization for the following major cardiovascular events: ischaemic stroke, acute myocardial infarction, congestive heart failure, transient ischaemic attack, unstable angina or coronary revascularization. We followed patients for up to 4 weeks, based on the as-treated principle. We used inverse probability weighting to control for baseline and time-varying covariates, and estimated the on-treatment hazard ratios (HRs) and 95% conservative confidence interval (CIs).

RESULTS

We identified 2749 eligible COX-2-selective NSAID users and 52 880 eligible nonselective NSAID users. The HR of major cardiovascular events comparing COX-2-selective with nonselective NSAIDs after adjusting for baseline and time-varying covariates was 1.07 (95% CI 0.65, 1.74). We did not observe a differential risk when comparing celecoxib to diclofenac (HR 1.17; 95% CI 0.61, 2.25), ibuprofen (HR 1.36; 95% CI 0.58, 3.18) or naproxen (HR 0.75; 95% CI 0.23, 2.44). There was an increased risk with COX-2-selective NSAIDs, however, when comparing COX-2-selective NSAIDs with mefenamic acid (HR 2.11; 95% CI 1.09, 4.09).

CONCLUSIONS

Our results provide important information about the comparative cardiovascular safety of NSAIDs in patients with hypertension.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- A number of studies have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2(COX-2)-selective and nonselective NSAIDs, are associated with an increased risk of cardiovascular adverse outcomes.
- It is unclear if there is a differential cardiovascular risk between NSAID classes or across individual NSAIDs because there have been limited active comparison studies, especially in patients with hypertension.

WHAT THIS STUDY ADDS

- In this population-based cohort study, which included 55 629 patients with hypertension, we observed no difference in cardiovascular risk between patients who were on COX-2-selective and nonselective NSAID treatment.
- There was no apparent difference in cardiovascular risk when comparing celecoxib with diclofenac, ibuprofen or naproxen, although a significantly increased risk was observed when comparing celecoxib with mefenamic acid.
- Our results provide important information about the comparative safety of various NSAIDs in patients with hypertension in real-world settings. The findings suggest that with a low-to-moderate daily dose and a short-term treatment period, most commonly used NSAIDs, including celecoxib, diclofenac, ibuprofen and naproxen, have similar cardiovascular safety profiles.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit **cyclooxygenase** enzymes (COX, including COX-1 and COX-2) and are classified as COX-2-selective and nonselective NSAIDs based on their selectivity for COX-2 inhibition. Both types of NSAIDs are widely used for their anti-inflammatory and pain-relieving effects. The cardiovascular safety of NSAIDs, however, has been a subject of considerable debate for decades [1, 2]. The Vioxx Gastrointestinal Outcome Research (VIGOR) trial raised a concern about a higher risk of myocardial infarction (MI) associated with rofecoxib in patients with rheumatoid arthritis, leading to the voluntary withdrawal of rofecoxib from the market in 2004 [3, 4]. Since then, multiple randomized controlled trials (RCTs) and observational studies reported that other COX-2-selective and nonselective NSAIDs may also be associated with adverse cardiovascular thrombotic events [5–9].

There is still conflicting evidence about the comparative cardiovascular safety of NSAIDs. Some research has suggested that the harmful cardiovascular effect observed with rofecoxib may not be a class effect for all COX-2-selective NSAIDs, and that the cardiovascular risk may also vary across individual nonselective NSAIDs, with naproxen having a better safety profile [10, 11]. One early meta-analysis of RCTs, mainly conducted in arthritis patients, suggested that COX-2-selective NSAIDs, as a class, have a higher risk of MI than nonselective NSAIDs, with a hazard ratio (HR) of 1.46 [95% confidence interval (CI) 1.02, 2.09] [12]. However, two large-scale, non-inferior RCTs in arthritis patients [13, 14] and some active comparison observational studies in elderly patients or those hospitalized for coronary heart disease (CHD) [15–18] found no difference in cardiovascular risk when comparing individual COX-2-selective NSAIDs (celecoxib and etoricoxib) with individual nonselective NSAIDs (diclofenac, ibuprofen and naproxen). A recent observational study in Canadian and European healthcare databases also suggested that, as compared to non-use of NSAIDs, the risk of MI with celecoxib did not appear to be higher than that with diclofenac, ibuprofen and naproxen in the general population [19].

Hypertension is a major risk factor for cardiovascular diseases [20], and the destabilization of blood pressure is a potential effect modifier of NSAID-related cardiovascular events [21, 22]. Few studies, however, have used an active comparison approach to compare the safety spectrum among different NSAIDs in this population. Previous studies have found that patient characteristics and treatment duration may differ between COX-2-selective and nonselective NSAID users [15–18]. We aimed to examine the risk of major cardiovascular events in patients with hypertension taking COX-2-selective *vs*. nonselective NSAIDs. Specifically, we used inverse probability weighting to account for potential baseline and time-dependent confounding and differential follow-up, and modelled the cardiovascular risk associated with up to 4 weeks of continuous NSAID use.

Methods

Data source and source population

A single-payer National Health Insurance programme began in Taiwan in 1995, achieving an enrolment rate of 99% by 2014. The National Health Research Institute constructed the National Health Insurance Research Database (NHIRD), which consisted of linked data from demographic and enrolment records, hospital admissions, outpatient visits and pharmacy dispensing claims from hospitals, outpatient clinics and community pharmacies. The source population for the study included all beneficiaries in the Longitudinal Health Insurance Database, which comprised a random sample of one million individuals from the NHIRD with longitudinally linked, annually updated data, with the exception of information about deaths. The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee.

Study population and study drugs

We identified patients initiating treatment with oral COX-selective or nonselective NSAIDs at outpatient visits between 1 January 2010 and 31 December 2012 using the World Health Organization's Anatomical Therapeutic Chemical

(ATC) classification system codes (see Table S1 for a list of codes). We defined NSAID initiation as the first oral NSAID dispensed during the study period, with no dispensing for oral or intravenous forms of NSAIDs in the preceding 180 days. The index date was the date of the first dispensing of a study NSAID. To ensure that sufficient data were available to capture baseline characteristics, we excluded patients with fewer than 180 days of continuous enrolment before the index date and required patients to have at least one inpatient or outpatient visits during this time window. We further restricted the cohort to patients having at least one inpatient or two outpatient diagnoses of hypertension [International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM) codes 401–405] in the 180 days before the index date [23]. We excluded patients aged under 20 years on the index date, patients with missing age or ambiguous gender information, and patients initiating both a COX-2-selective and nonselective NSAID on the index date.

Follow-up and outcomes

We defined the outcomes of interest – major cardiovascular events – as the first hospitalization for ischaemic stroke, acute MI, congestive heart failure, transient ischaemic attack, unstable angina and coronary revascularization (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty) during follow-up. We defined each outcome using validated claims-based algorithms (Table S2) with positive predictive values of 88% for ischaemic stroke [24], 80% for acute MI [25], 84% for congestive heart failure [26], 77% for transient ischaemic attack [27], 88% for unstable angina [28], 98% for coronary artery bypass grafting [29] and 95–96% for percutaneous transluminal coronary angioplasty [29]. As congestive heart failure may be indirectly related to renal effects rather than the thromboembolic effects of NSAIDs, we also conducted another analysis that excluded congestive heart failure from the outcome definition.

To minimize the possibility of exposure misclassification during the follow-up, we followed patients based on the as-treated principle. Specifically, we followed patients for up to 28 days (i.e. 4 weeks), from the index date to the earliest of the following: outcome occurrence; index NSAID treatment discontinuation; NSAID treatment change; or last date of hospital discharge, outpatient visit or community pharmacy visit. NSAID treatment discontinuation occurred when more than 14 days elapsed between the end of one dispensing and the date of the next dispensing, if any. NSAID treatment change (switch or addition) occurred when an NSAID was dispensed that was different from the index study drug (i.e. a patient with an index COX-2-selective NSAID filling a nonselective NSAID, and vice versa). As our data source did not include information on deaths, we censored patients on the last date of their hospital discharge, outpatient visit or community pharmacy visit during follow-up, to reduce potential outcome misclassification or biases associated with the inability to capture cardiovascular-related deaths (i.e. misclassifying patients who have died due to cardiovascular causes as being alive and having no cardiovascular outcomes). Disenrollment from the National Health Insurance programme was uncommon.

Covariate assessment and adjustment

We considered two groups of covariates: baseline and time-varying covariates. Baseline covariates included age on the index date, gender, calendar year of the index date, comorbidities, other medication use and resource utilization recorded within 180 days before the index date. We ascertained comorbidities based on inpatient and outpatient diagnosis files, and determined medication use based on the pharmacy dispensing claims of outpatient clinics and community pharmacies. We measured resource utilization based on the records of hospital admissions and outpatient visits.

Time-varying covariates included cardiovascular comorbidities and cardiovascular medications, updated weekly during the follow-up period. For cardiovascular comorbidities, provided that patients had one comorbidity at any time during follow-up, the status would be carried forward through the remainder of their follow-up period. For cardiovascular medications, whether patients used one medication in a week depended on the pharmacy claim records in that week. Therefore, patients might use one drug in one week and then discontinue it in the following week. Tables S3 and S4 provide more detailed information on covariates.

Statistical analysis

We applied two analytical approaches. In the first approach, we adjusted for confounding and potential selection bias arising from differential loss to follow-up using measured baseline covariates only. Specifically, we used all measured baseline covariates to estimate the inverse probability of treatment weight (IPTW) and the inverse probability of censoring weight (IPCW) [30, 31]. The IPTW was calculated as the inverse of the treatment probability, given all measured baseline covariates, and the IPCW was calculated as the inverse of the probability of remaining uncensored, given treatment status and all measured baseline covariates. To reduce the variability of the weights, we 'stabilized' them by replacing the numerator of the IPTW by the average treatment probability, and the numerator of the IPCW by the probability of remaining uncensored, given the treatment status and select baseline covariates. We fitted logistic regression models to estimate all the probabilities. Appendix S1 describes the computation steps in detail.

We then multiplied the stabilized IPTW and the stabilized IPCW, to obtain an overall weight for each patient. This allowed us to create a weighted population in which the receipt of NSAID treatment and loss to follow-up were independent of the measured baseline covariates. We truncated the overall weight at the first and 99th percentile cut-points, to minimize further the influence of extreme weights. With a person-week data structure, we used the generalized estimating equations and the robust variance estimators to fit a weighted pooled logistic regression model, which approximated a weighted Cox model, and estimated HRs and conservative 95% CIs of major cardiovascular events. As we followed patients based on the as-treated principle, the HRs would represent the on-treatment effect

while patients remained on their index COX-2-selective NSAID treatment *vs*. patients who remained on their index nonselective NSAID treatment during the follow-up.

In the second approach, we repeated the same steps as above, except that now we estimated the stabilized IPTW and stabilized IPCW using both baseline and time-varying covariates updated weekly, and fitted pooled logistic regression models to estimate all the probabilities [32–35]. The denominator of the stabilized IPTW was the treatment probability, given the treatment history, all measured baseline covariates and all measured time-varying covariates; the denominator of the stabilized IPCW was the probability of remaining uncensored, given the treatment history, all measured baseline covariates and all measured time-varying covariates. The numerator of the stabilized IPTW was the treatment probability, given the treatment history and select baseline covariates; the numerator of the stabilized IPCW was the probability of remaining uncensored, given the treatment history and select baseline covariates. Appendix S2 provides detailed computation steps.

Subgroup and sensitivity analyses

To examine if the HR would be different across individual nonselective NSAIDs, we conducted additional analyses to compare COX-2-selective NSAIDs (celecoxib and etoricoxib) separately with diclofenac, ibuprofen, naproxen and mefenamic acid, which are expected to be commonly used in clinical settings.

We also conducted several sensitivity analyses, to examine the robustness of our results. First, use of low-dose aspirin is a potential marker for patients' underlying cardiovascular risk. Therefore, we additionally included the interaction term of NSAID use and low-dose aspirin in the outcome model, to examine if there was any effect modification by patients' underlying cardiovascular risk. Secondly, we performed a 'first exposure carried forward' (or 'intention-to-treat') analysis by following patients regardless of NSAID treatment discontinuation or change and censoring them only at the first outcome occurrence, the last date of accessing medical resources or 28 days from the index date.

Thirdly, besides using inverse probability weighting to adjust for both baseline and time-varying covariates, we estimated propensity scores (PSs) – the probabilities of initiating COX-2-selective NSAIDs – using all measured baseline covariates and conducted PS matching to minimize confounding effects by baseline covariates. We also performed inverse probability weighting after PS matching, to account for time-varying covariates. Finally, we used high-dimensional PSs (hd-PSs) to identify and include an additional 50 empirically identified variables in the PS model [36, 37].

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [38], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [39].

Results

Baseline characteristics

We identified a total of 55 629 eligible patients (Figure 1). Among patients initiating COX-2-selective NSAIDs (N = 2749), celecoxib (65%) was prescribed more commonly than etoricoxib (35%). Among patients initiating nonselective NSAIDs (N = 52 880), diclofenac (34%), mefenamic acid (22%) and ibuprofen (15%) were most commonly prescribed; only 3% of patients initiated naproxen. The mean [standard deviation (SD)] age of the cohort was 64 (13) years and 51% were male. Compared with patients initiating nonselective NSAIDs, patients initiating COX-2-selective NSAIDs were more likely to be older and female, and appeared to have more comorbidities, more medication use and higher resource utilization (Table 1).

After applying the stabilized IPTW derived from baseline covariates, the balance in baseline covariates between COX-2-selective and nonselective NSAID groups improved, with most of the covariates showing an absolute standardized difference of less than 0.1, although there were still slight differences between treatment groups (Table 1). Tables S5–S8 show differences in baseline covariates when comparing COX-2-selective NSAIDs to individual nonselective NSAIDs. Table S9 presents the distributions of stabilized IPTW and IPCW weights.

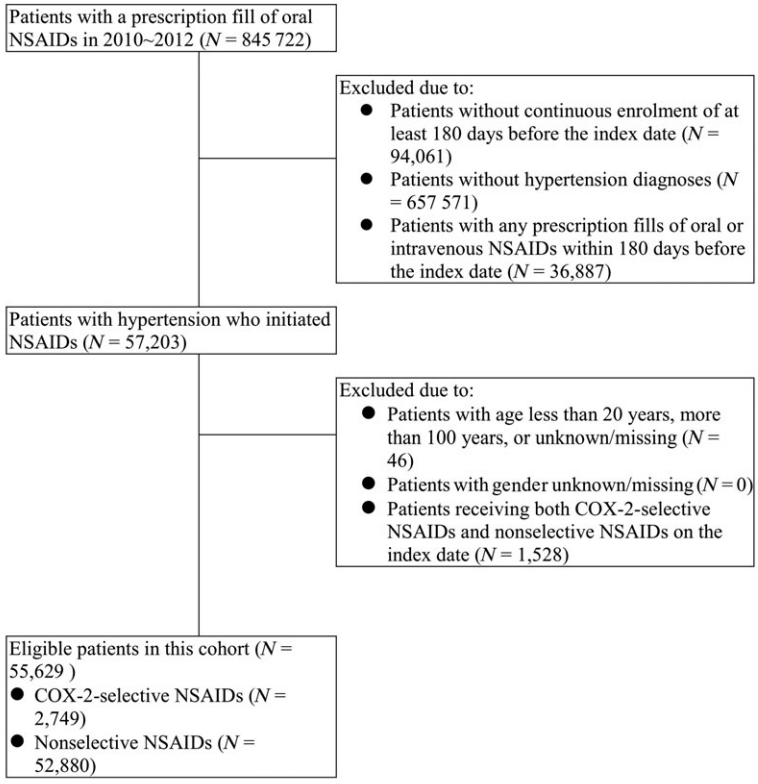
Follow-up and outcomes

The mean follow-up duration was 24 days for COX-2-selective NSAIDs and 18 days for nonselective NSAIDs. The crude incidence rate was 122 per 1000 person-years (based on 22 outcome events) in the COX-2-selective NSAID group and 76 per 1000 person-years (based on 193 events) in the nonselective NSAID group (Table 2). There were 7919 patients (14% of the study cohort) who remained uncensored 4 weeks after the cohort entry. COX-2-selective NSAID initiators were more likely to be uncensored than nonselective NSAID initiators (proportion of remaining uncensored: 50% *vs*. 12%). The mean daily dose used for individual NSAIDs was: 210 mg for celecoxib, 60 mg for etoricoxib, 107 mg for diclofenac, 1084 mg for ibuprofen, 694 mg for naproxen and 1248 mg for mefenamic acid.

Risk of major cardiovascular events comparing COX-2-selective vs. nonselective NSAIDs

The crude HR of major cardiovascular events comparing COX-2-selective *vs*. nonselective NSAIDs in the primary on-treatment analysis was 1.99 (95% CI, 1.28, 3.09) (Table 3). The adjusted HR was 1.09 (95% CI 0.64, 1.86) in the analysis that adjusted only for baseline covariates. After adjusting for both baseline and time-varying covariates, the adjusted HR was 1.07 (95% CI 0.65, 1.74). There were 137 events (13 for COX-2-selective NSAIDs and 124 for nonselective NSAIDs) when we excluded congestive heart failure from the outcome definition. The adjusted HR did not change materially (1.07; 95% CI 0.56, 2.04).

Comparing COX-2-selective NSAIDs *vs*. individual nonselective NSAIDs yielded adjusted HRs of: 0.91 (95% CI 0.51, 1.63) *vs*. diclofenac; 1.22 (95% CI 0.58, 2.57) *vs*. ibuprofen;



COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs

Figure 1

Flow chart of the study cohort assembly. COX, cyclooxygenase; NSAIDs, non-steroidal anti-inflammatory drugs

0.67 (95% CI 0.24, 1.91) *vs*. naproxen; and 1.63 (95% CI 0.91, 2.93) *vs*. mefenamic acid (Table 3). We observed no differential risks of major cardiovascular events when comparing celecoxib with diclofenac (adjusted HR 1.17; 95% CI 0.61, 2.25), ibuprofen (adjusted HR 1.36; 95% CI 0.58, 3.18) or naproxen (adjusted HR 0.75; 95% CI 0.23, 2.44). Nevertheless, there was a significantly increased risk when comparing celecoxib with mefenamic acid (adjusted HR 2.11; 95% CI 1.09, 4.09). We could not compare etoricoxib with individual nonselective NSAIDs separately because of limited outcome events for etoricoxib. Use of low-dose aspirin did not significantly modify the adjusted HRs of celecoxib *vs*. diclofenac (*P*-value for interaction: 0.17), celecoxib *vs*. ibuprofen ($P = 0.27$), celecoxib *vs*. naproxen ($P = 0.20$) or celecoxib *vs*. mefenamic acid ($P = 0.13$).

Table S10 shows the findings for each comparison using the 'first exposure carried forward' approach; these were similar to the results using the as-treated approach. When we applied PS matching to control for baseline covariates, we observed numerically elevated HRs comparing celecoxib *vs*. diclofenac (1.44; 95% CI 0.68, 3.04), ibuprofen (1.43; 95% CI 0.57, 3.50) and mefenamic acid (2.12; 95% CI 0.88, 3.08). The HR comparing celecoxib *vs*. naproxen was 0.74 (95% CI 0.21, 2.65). After applying inverse probability weighting to handle time-varying covariates further in the PS-matched analysis, the adjusted HRs of celecoxib *vs*. diclofenac (1.20; 95% CI 0.51, 2.80) and celecoxib *vs*. ibuprofen (1.05; 95% CI 0.37, 2.98) attenuated toward the null, while celecoxib still showed a different, but not significantly so, risk profile *vs*. mefenamic acid (adjusted HR 1.83; 95% CI 0.70, 4.81). The HR comparing celecoxib *vs*. naproxen did not change materially (0.74; 95% CI 0.21, 2.68) (Table S11). In general, the results based on baseline PS matching followed by inverse probability weighting did not differ substantially compared with those from the main analysis of using inverse probability weighting for both baseline and time-varying covariates, although the risk estimates tended to be more imprecise. The analysis with hd-PS matching followed by inverse probability weighting yielded similar results, although risk estimates for some comparisons could not be calculated because we were unable to match enough patients initiating nonselective NSAIDs to each patient initiating COX-2-selective NSAIDs in the matching step (Table S12).

Discussion

In the present longitudinal, population-based cohort study, we examined the cardiovascular safety of NSAIDs in patients with hypertension by using inverse probability weighting to account for baseline and time-varying covariates alike. There was no strong evidence to suggest a higher cardiovascular risk

Table 1

Baseline characteristics by NSAID group: COX-2-selective NSAIDs *vs.* nonselective NSAIDs

	Total study cohort (*N* = 55 629)			Weighted cohort[a]		
	COX-2 selective NSAIDs (*N* = 2749)	Nonselective NSAIDs (*N* = 52 880)	Standardized difference	COX-2-selective NSAIDs (*N* = 2749)	Nonselective NSAIDs (*N* = 52 880)	Standardized difference
Age at initiation, years, mean (SD)	74.1 (9.7)	63.0 (12.9)	0.97	70.1 (8.3)	63.6 (13.0)	0.60
Male, %	39.8	51.3	−0.23	45.2	50.7	−0.11
Initiation year, %						
2010	61.3	64.6	−0.07	62.9	64.4	−0.03
2011	25.0	24.5	0.01	24.7	24.6	0.00
2012	13.7	10.9	0.09	12.4	11.0	0.04
Comorbidities, %						
Ischaemic heart disease[b]	22.1	16.3	0.15	19.2	16.6	0.07
Myocardial infarction[b]	1.4	0.8	0.06	1.1	0.8	0.03
Cardiac dysrhythmia[b]	9.5	6.0	0.13	8.0	6.1	0.07
Congestive heart failure[b]	7.8	5.2	0.10	7.2	5.3	0.08
Cerebrovascular disease[b]	19.1	10.2	0.25	15.7	10.7	0.15
Ischaemic stroke[b]	10.1	5.3	0.18	8.5	5.6	0.11
Haemorrhagic stroke[b]	1.9	1.0	0.07	1.5	1.2	0.04
Peripheral vascular disease[b]	2.0	1.0	0.08	1.5	1.2	0.04
Disorders of lipid metabolism[b]	32.2	33.1	−0.02	33.3	33.2	0.01
Diabetes mellitus[b]	31.6	29.6	0.04	32.6	29.7	0.06
Thyroid disease	8.1	4.9	0.13	6.6	5.0	0.07
COPD	5.0	3.5	0.07	4.3	3.6	0.04
Asthma	7.6	8.0	−0.01	8.4	7.9	0.02
Chronic liver disease	21.9	16.3	0.14	21.0	16.6	0.11
Gastritis or peptic ulcer disease	7.1	3.4	0.17	6.0	3.6	0.11
Chronic kidney disease	50.6	11.2	0.94	22.3	13.2	0.24
Rheumatoid arthritis/ osteoarthritis	12.2	2.4	0.39	6.0	2.9	0.15
Osteoporosis	7.5	8.1	−0.02	8.0	8.0	−0.00
Gout	7.5	4.4	0.13	6.8	4.6	0.10
Any cancer	4.8	1.8	0.17	3.3	2.0	0.08
Dementia	22.1	16.3	0.15	19.2	16.6	0.07

(*continues*)

Table 1

(Continued)

	Total study cohort (*N* = 55 629)			Weighted cohort[a]		
	COX-2 selective NSAIDs (*N* = 2749)	Nonselective NSAIDs (*N* = 52 880)	Standardized difference	COX-2-selective NSAIDs (*N* = 2749)	Nonselective NSAIDs (*N* = 52 880)	Standardized difference
Medication use, %						
ACEIs/ARBs[c]	61.9	56.9	0.10	61.3	57.2	0.08
***β*-Blockers**[c]	41.0	42.0	−0.02	39.8	42.0	−0.04
Calcium channel blockers[c]	65.0	62.8	0.05	63.7	62.9	0.02
Diuretics[c]	26.2	20.3	0.14	23.7	20.6	0.07
Other antihypertensive agents[c]	10.4	8.8	0.06	9.7	8.8	0.03
Nitrates[c]	15.3	8.5	0.21	11.3	8.8	0.08
Antiarrhythmic agents[c]	3.9	1.9	0.12	3.3	2.0	0.08
Digoxin[c]	2.8	1.3	0.10	2.1	1.4	0.05
Aspirin[c]	35.7	27.8	0.17	33.8	28.2	0.12
Clopidogrel[c]	6.0	2.6	0.17	4.4	2.7	0.09
Warfarin[c]	1.9	1.0	0.07	1.7	1.0	0.06
Statins/fibrates[c]	28.5	27.6	0.02	29.3	27.6	0.04
Insulin[c]	5.3	3.4	0.09	4.6	3.5	0.06
Oral antidiabetic agents[c]	28.3	27.0	0.03	29.1	27.1	0.05
Histamine-2 antagonists/ PPIs	19.6	18.2	0.04	20.3	18.3	0.05
Antiepileptic agents	9.5	5.0	0.17	7.7	5.3	0.10
Antidepressants	10.5	6.1	0.16	7.8	6.3	0.06
Anxiolytic agents	37.0	29.1	0.17	34.7	29.5	0.11
Hypnotic agents	18.3	13.0	0.15	16.6	13.3	0.09
Antipsychotic agents	7.6	6.0	0.06	7.1	6.1	0.04
Oestrogen	1.2	1.4	−0.02	1.1	1.4	−0.02
Uric acid-lowering agents	10.4	10.4	−0.00	11.1	10.4	0.02
Resource utilization, mean (SD)						
No. of hospitalizations	1.8 (2.7)	1.2 (2.3)	0.25	1.6 (2.3)	1.2 (2.4)	0.19
No. of outpatient visits	17.5 (11.1)	14.2 (9.1)	0.33	16.4 (8.8)	14.3 (9.2)	0.23

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD, standard deviation

[a]Weighted by the inverse probability of treatment weight derived by baseline covariates

[b]Cardiovascular comorbidities included ischaemic heart disease, myocardial infarction, cardiac dysrhythmia, congestive heart failure, cerebrovascular disease, ischaemic stroke, haemorrhagic stroke, peripheral vascular disease, disorders of lipid metabolism, and diabetes mellitus

[c]Cardiovascular medications included ACEIs/ARBs, β-blockers, calcium channel blockers, diuretics, other antihypertensive agents, nitrates, antiarrhythmic agents, digoxin, aspirin, clopidogrel, warfarin, statins/fibrates, insulin and oral antidiabetic agents

Table 2

Follow-up and incidence rates of major cardiovascular events, by NSAID group

	COX-2-selective NSAIDs	Nonselective NSAIDs	Celecoxib	Diclofenac	Ibuprofen	Naproxen	Mefenamic acid
Total No. of patients	2749	52 880	1779	17 882	7927	1497	11 830
Total follow-up person-days	65 782	932 905	42 521	318 051	130 405	26 280	195 681
Mean follow-up days (SD)	23.93 (6.30)	17.64 (5.84)	23.90 (6.35)	17.79 (5.64)	16.45 (5.15)	17.56 (6.24)	16.54 (4.72)
No. of patients with events	22	193	17	73	24	7	30
Crude incidence rate per 1000 person-years (95% CI)	122.15 (80.43–185.52)	75.56 (65.62–87.01)	146.03 (90.78–234.90)	83.83 (66.65–105.45)	67.22 (45.06–100.29)	97.29 (46.38–204.08)	56.00 (39.15–80.09)

CI, confidence interval; COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation

Table 3

Hazard ratios of major cardiovascular events in patients who were on COX-2-selective NSAID treatment *vs.* patients who were on nonselective NSAID treatment during the follow-up

Comparison	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) Weighted by stabilized IPTW and IPCW estimated from baseline covariates	Adjusted hazard ratio (95% CI) Weighted by stabilized IPTW and IPCW estimated from baseline and time-varying covariates
COX-2-selective NSAIDs *vs.*			
nonselective NSAIDs	1.99 (1.28, 3.09)	1.09 (0.64, 1.86)	1.07 (0.65, 1.74)
Diclofenac	1.80 (1.12, 2.88)	0.89 (0.51, 1.57)	0.91 (0.51, 1.63)
Ibuprofen	2.29 (1.29, 4.05)	0.82 (0.37, 1.81)	1.22 (0.58, 2.57)
Naproxen	1.49 (0.64, 3.44)	0.49 (0.19, 1.30)	0.67 (0.24, 1.91)
Mefenamic acid	2.77 (1.61, 4.77)	1.65 (0.86, 3.17)	1.63 (0.91, 2.93)
Celecoxib *vs.*			
Diclofenac	2.16 (1.28, 3.65)	1.20 (0.65, 2.22)	1.17 (0.61, 2.25)
Ibuprofen	2.77 (1.49, 5.13)	1.06 (0.45, 2.46)	1.36 (0.58, 3.18)
Naproxen	1.80 (0.76, 4.31)	0.50 (0.19, 1.35)	0.75 (0.23, 2.44)
Mefenamic acid	3.35 (1.85, 6.04)	2.17 (1.04, 4.54)	2.11 (1.09, 4.09)

CI, confidence interval; COX, cyclooxygenase; IPCW, inverse probability of censoring weight; IPTW, inverse probability of treatment weight; NSAID, non-steroidal anti-inflammatory drug

with COX-2-selective NSAIDs (celecoxib and etoricoxib) or celecoxib alone compared with diclofenac, ibuprofen and naproxen. However, we observed an elevated risk when comparing celecoxib with mefenamic acid.

Biological plausibility of NSAID-associated cardiovascular thrombotic effects

The mechanisms of NSAID-associated cardiovascular thrombotic effects have not been comprehensively elucidated. It has been hypothesized that COX-2-selective NSAIDs inhibit the synthesis of **prostacyclin (PGI_2)** but not **thromboxane A_2**, which leads to an imbalance between these two eicosanoids and an increase in platelet aggregation, vasoconstriction and cardiovascular-related adverse events [1, 2]. The extent of COX-2 inhibition can be quantified based on the ratio of the concentrations required to produce a 50% inhibition in the activity of the isozymes (i.e. COX-1/COX-2 IC_{50} value), with a higher value indicating greater COX-2 selectivity. COX-2 selectivity for rofecoxib (255) is higher than for etoricoxib (162), celecoxib (32), diclofenac (24), ibuprofen (0.6) and naproxen (0.5) [40, 41].

Comparison with other studies

It remains to be determined whether COX-2-selective NSAIDs have a different cardiovascular safety profile than nonselective NSAIDs. COX-2-selective NSAIDs as a class, including rofecoxib,

lumiracoxib, valdecoxib, celecoxib and etoricoxib, have been linked to a higher risk of MI than nonselective NSAIDs in a meta-analysis of RCTs that included primarily arthritis patients [12]. However, two RCTs of arthritis patients found no significant differences in thrombotic cardiovascular events across individual NSAIDs [13, 14]. In the 18-month Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme [13], the HR for thrombotic cardiovascular events was 0.95 (95% CI 0.81, 1.11) for etoricoxib (60–90 mg daily) *vs.* diclofenac (150 mg daily). In the 30-month Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial [14], the HR for thrombotic cardiovascular events was 0.82 (95% CI 0.69, 0.97) for celecoxib (around 200 mg daily) *vs.* ibuprofen (around 2000 mg daily) and 0.95 (95% CI 0.80, 1.13) for celecoxib (around 200 mg daily) *vs.* naproxen (around 850 mg daily). Similarly, cohort studies conducted in elderly patients or in patients hospitalized for serious CHD detected no difference in the risk of MI, stroke or recurrent serious CHD comparing celecoxib with diclofenac [15], ibuprofen [15, 16] or naproxen [17, 18].

Our findings of no significant difference in cardiovascular risk between COX-2-selective NSAIDs (celecoxib and etoricoxib) or celecoxib alone and several individual nonselective NSAIDs (ibuprofen, diclofenac and naproxen) in patients with hypertension are in line with previous noninferior RCTs [13, 14] and active comparison observational studies [15–18]. However, we observed that celecoxib had an apparent higher cardiovascular risk compared with mefenamic acid. There have been a number of studies evaluating the cardiovascular risk associated with mefenamic acid compared with no NSAID treatment, but the results have been mixed [42–44]. The mean daily dose of mefenamic acid used in our study was lower than the normal daily dose (1248 mg *vs.* 1500 mg). Mefenamic acid is commonly used for dysmenorrhoea and dental pain, rather than arthritis in clinical settings, and patients may tend to take the drug irregularly. Mefenamic acid might thus be less likely to interfere with the COX system and present a lower cardiovascular risk than celecoxib. However, this was the only statistically significant result out of the many subgroup analyses. Therefore, the possibility that this was a chance finding could not be ruled out. Further studies are required to examine the underlying mechanisms and replicate our findings.

The dosage and treatment duration of NSAIDs might play a role in cardiovascular risk [6, 19, 45]. Patients included in the MEDAL programme and in the PRECISION trial received moderate-to-high daily doses of NSAIDs with a longer treatment duration [13, 14]. The mean daily dose was lower and the treatment duration shorter in our study compared with the MEDAL program and the PRECISION trial, but the use pattern reflected actual use in real-world clinical settings. These differences may partially explain our neutral findings across these individual NSAIDs. The pattern of low-dose, short-term use of NSAIDs was also observed in three German, UK and French adult cohorts [46–48].

Strengths and weaknesses of the study

As hypertension is a prevalent condition and a major risk factor for cardiovascular diseases [20], our results provide important information about the comparative safety of alternative NSAID use, and suggest that most commonly used NSAIDs, including naproxen, have similar cardiovascular safety profiles in this vulnerable population. Our results also suggest that the relationship between NSAIDs and cardiovascular risk is complex, and that it might be more appropriate to describe NSAID-associated cardiovascular safety by individual drug rather than as a whole drug class.

Consistent with previous observational studies [15–18], our study found that patients receiving COX-2-selective NSAIDs were sicker and tended to have a longer treatment duration than those receiving nonselective NSAIDs. Unlike previous studies, which usually considered baseline confounding only, our study simultaneously accounted for baseline and time-varying confounding and potential selection bias due to informative censoring using inverse probability weighting. The method accounts for time-varying confounders more appropriately compared with conventional regression approaches [32–35]. The results were also qualitatively similar when we applied conventional PS or hd-PS matching to adjust for baseline covariates, and inverse probability weighting to account further for time-varying covariates.

There were several limitations to our study. First, pharmacy claims data provide accurate information about the prescriptions that are filled but do not necessarily reflect whether and when patients take the drugs. However, most NSAIDs (>90% of approved products) are available via a prescription and are reimbursed by the National Health Insurance programme in Taiwan. This allowed us to ascertain exposure status more comprehensively than other database studies, which often have incomplete capture of NSAIDs due to considerable over-the-counter use. Secondly, the number of outcome events was limited for individual NSAIDs in our study, and several analyses might have been underpowered. For example, there were only seven outcome events for naproxen, so the adjusted HRs comparing COX-2-selective NSAIDs *vs.* naproxen (0.67; 95% CI 0.24, 1.91) or celecoxib *vs.* naproxen (0.75; 95% CI 0.23, 2.44) were unstable, with wide confidence intervals. However, reassuringly, our findings were in line with previous active comparison RCTs and observational studies [13–18]. Furthermore, we only had five outcome events for etoricoxib and were unable to compare this agent with individual nonselective NSAIDs. Similarly, we were also not able to examine individual components of the composite cardiovascular outcome. Further research, using the whole Taiwanese population, using an active comparison study design, is likely to provide more precise findings.

Thirdly, our data source did not include information on deaths, which prevented us from evaluating the association between use of NSAIDs and overall or cardiovascular death. Finally, the prescribing habits or preferences of health professionals, different NSAID indications, different safety warnings, and contraindications might have led to an imbalance in covariates between patients receiving different NSAIDs. In the current study, we observed that patients who initiated COX-2-selective NSAIDs were older and had more comorbidities. We applied different analytical approaches, including inverse probability weighting, to account for potential baseline and time-varying confounders. The balance in baseline covariates between treatment groups improved after inverse probability weighting. However, patients

receiving COX-2-selective NSAIDs still tended to be slightly sicker than those receiving nonselective NSAIDs, which might have biased the results further away from the null. In addition, although we considered a large number of covariates in the analysis, we could not rule out the possibility of unmeasured confounding, such as education level, smoking status or body mass index.

Conclusion

In conclusion, the present population-based cohort study found that, under low-to-moderate daily dose and a short-term treatment period, there was no apparent difference in cardiovascular risk comparing celecoxib with diclofenac, ibuprofen and naproxen in patients with hypertension. A potential increased cardiovascular risk with celecoxib when compared with mefenamic acid warrants further investigation.

Competing Interests

There are no competing interests to declare.

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Contributors

Y.-H.D., C.-H.C. and S.T. were responsible for the study concept and design; L.-C.W. carried out data analysis; all authors contributed to the interpretation of the data; Y.-H.D. drafted the manuscript; C.-H.C., J.-S.H. and S.T. carried out critical revision of the manuscript for important intellectual content; C.-H.C. was responsible for acquisition of the funding and data; C.-H.C. was the principal investigator. All of the authors have read, contributed to and approved the final manuscript, and agreed to transfer the copyright ownership in the event of acceptance. Y.-H.D. and C.-H.C. are the grantors.

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Supporting Information

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http://onlinelibrary.wiley.com/doi/10.1111/bcp.13537/suppinfo

Table S1 Anatomical Therapeutic Chemical (ATC) classification system codes used to identify initiators of cyclooxygenase 2 (COX-2)-selective and nonselective NSAIDs

Table S2 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis or procedure codes, or Taiwan health insurance service claims codes used to identify outcomes of interest

Table S3 International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes used to identify baseline and time-varying comorbidities

Table S4 Anatomical Therapeutic Chemical (ATC) classification system codes used to identify baseline and time-varying medication use

Table S5 Baseline characteristics by nonsteroidal anti-inflammatory drug (NSAID) group after weighting: cyclooxygenase 2 (COX-2)-selective NSAIDs *vs*. diclofenac

Table S6 Baseline characteristics by nonsteroidal anti-inflammatory drug (NSAID) group after weighting: cyclooxygenase 2 (COX-2)-selective NSAIDs *vs*. ibuprofen

Table S7 Baseline characteristics by nonsteroidal anti-inflammatory drug (NSAID) group after weighting: cyclooxygenase 2 (COX-2)-selective NSAIDs *vs*. naproxen

Table S8 Baseline characteristics by nonsteroidal anti-inflammatory drug (NSAID) group after weighting: cyclooxygenase 2 (COX-2)-selective NSAIDs *vs*. mefenamic acid

Table S9 Distribution of the stabilized inverse probability of treatment weight (IPTW) and the stabilized inverse probability of censoring weight (IPCW) estimated from baseline covariates when comparing cyclooxygenase 2 (COX-2)-selective nonsteroidal anti-inflammatory drugs (NSAIDs) with nonselective NSAIDs

Table S10 Hazard ratios of major cardiovascular events in patients who initiated cyclooxygenase 2 (COX-2)-selective nonsteroidal anti-inflammatory drug (NSAID) treatment *vs*. patients who initiated nonselective NSAID treatment, using the 'first exposure carried forward' or 'intention-to-treat' approach

Table S11 Hazard ratios of major cardiovascular events in patients who were on cyclooxygenase 2 (COX-2)-selective nonsteroidal anti-inflammatory drug (NSAID) treatment *vs*. patients who were on nonselective NSAID treatment during the follow-up, using the propensity score matching approach followed by inverse probability weighting

Table S12 Hazard ratios of major cardiovascular events in patients who were on cyclooxygenase 2 (COX-2)-selective nonsteroidal anti-inflammatory drug (NSAID) treatment *vs*. patients who were on nonselective NSAID treatment during the follow-up, using the high-dimensional propensity score matching approach, followed by inverse probability weighting

Appendix S1 Estimation of the stabilized inverse probability of treatment weight (IPTW) and the stabilized inverse probability of censoring weight (IPCW) based on baseline covariates only

Appendix S2 Estimation of the stabilized inverse probability of treatment weights (IPTW) and the stabilized inverse probability of censoring weight (IPCW) based on previous treatment histories, baseline covariates and time-varying covariates simultaneously