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Non-steroidal anti-inflammatory drugs-aspirin interactions and with risk of cardiovascular disease in patients osteoarthritis.

Permalink

<https://escholarship.org/uc/item/7wj6d57s>

Journal

American Journal of Epidemiology, 192(9)

ISSN

0002-9262

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Publication Date

2023-04-19

DOI

10.1093/aje/kwad094

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Peer reviewed

Original Contribution

Interactions of Nonsteroidal Antiinflammatory Drugs and Aspirin and Risk of Cardiovascular Disease in Patients With Osteoarthritis

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Initially submitted August 1, 2022; accepted for publication April 13, 2023.

Nonsteroidal antiinflammatory drugs (NSAIDs) remain the mainstay of the pharmacologic management for relieving osteoarthritis pain, and low-dose aspirin is often prescribed to osteoarthritis patients who are at high risk of cardiovascular disease (CVD). We conducted cohort studies using data from The Health Improvement Network (THIN) database (2000–2019) to assess whether the relationship of initiation of naproxen or ibuprofen vs. initiation of other NSAIDs (excluding both naproxen and ibuprofen), respectively, to the risk of CVD was modified by coprescription of low-dose aspirin among the participants with osteoarthritis. Among participants without coprescription of aspirin, the risk of CVD was lower in naproxen initiators (10.3/1000 person-years) than in other NSAIDs initiators (13.2/1000 person-years; hazard ratio = 0.71, 95% confidence interval: 0.60, 0.85). Among participants with coprescription of aspirin, however, the risk of CVD was higher among naproxen initiators (36.9/1000 person-years) than that among other NSAIDs initiators (34.8/1000 person-years; hazard ratio = 1.48, 95% confidence interval: 1.12, 1.84). The association was significantly modified by coprescription of aspirin ($P < 0.001$). Similar findings were observed in the association of initiation of ibuprofen vs. other NSAIDs with the risk of CVD, which was significantly modified by coprescription of aspirin ($P < 0.001$). These findings suggest that osteoarthritis patients and clinicians should be aware of the potential CVD risk of concurrently taking naproxen or ibuprofen and low-dose aspirin.

aspirin; ibuprofen; interaction; naproxen; osteoarthritis

Abbreviations: CI, confidence interval; COX-1, cyclooxygenase-1; CVD, cardiovascular disease; HR, hazard ratio; IPW, inverse probability weights; MI, myocardial infarction; NSAID, nonsteroidal antiinflammatory drug; RD, rate difference; TXA2, thromboxane A2; THIN, The Health Improvement Network database.

Editor's note: An invited commentary on this article appears on page 1449, and the authors' response appears on page 1452.

Oral nonsteroidal antiinflammatory drugs (NSAIDs) remain the mainstay of pharmacological management for relieving osteoarthritis pain, and international guidelines strongly recommend their use for osteoarthritis (1, 2). For example, owing to its relatively favorable cardiovascular safety profile (3, 4), the proportion of initial prescriptions of naproxen for osteoarthritis increased from 3% in 2000 to 10% in 2016 in the United Kingdom (5).

In addition, for the prevention of cardiovascular disease (CVD) among older adults, the prevalence of aspirin use remained high. Data from the National Health and Nutrition Examination Survey suggested that the prevalence of aspirin use for primary prevention (i.e., among adults who were aged 50 years or older and with a 10% or greater 10-year risk of CVD but with no prior history of CVD) and secondary prevention (i.e., among adults who were aged at least 50 and with a prior history of CVD) were 37.0% and 68.1%, respectively (6). CVD is a common comorbidity in the patients with osteoarthritis (7), and low-dose aspirin is often prescribed to patients with osteoarthritis who are at high risk of CVD, while high-dose aspirin is

often prescribed for reducing pain and fever (8). Aspirin acts by irreversibly acetylating a serine residue at position 529 of platelet cyclooxygenase (COX)-1 through a binding channel of COX-1, thereby preventing the generation of platelet thromboxane A₂ (TXA₂) and TXA₂-induced platelet aggregation and vasoconstriction, leading to cardioprotective effects (9–11). In contrast, several NSAIDs are reversible inhibitors of platelet COX-1 and often cause an incomplete and intermittent inhibition of platelet TXA₂, which may be inadequate to prevent cardiovascular events (10, 12). Thus, a pharmacodynamic interaction inhibiting the platelet TXA₂ function has been suggested in patients coprescribed aspirin and certain NSAIDs through competitive binding with COX-1 (10, 12). Naproxen and ibuprofen are both nonselective NSAIDs, which have a relatively stronger ability to bind COX-1 than other NSAIDs (13); thus, previous studies have reported that ibuprofen (14–19) and naproxen (14, 20–22) could antagonize the cardioprotective effect of aspirin. However, other commonly used NSAIDs (e.g., selective COX-2 inhibitors and several nonselective NSAIDs that are relatively weak COX-1 inhibitors, such as diclofenac, meloxicam, or acetaminophen) could not affect the inhibition of platelet aggregation by aspirin (14, 15, 18, 19, 22, 23). To date, evidence on the relationship of coprescription of naproxen or ibuprofen with aspirin to the risk of CVD (i.e., myocardial infarction (MI), stroke, or heart failure) among individuals with osteoarthritis is lacking.

To address this knowledge gap, we conducted population-based cohort studies to assess the relationship of initiation of either naproxen (vs. initiation of other NSAIDs) or ibuprofen (vs. initiation of other NSAIDs) with the risk of CVD according to the status of coprescription of low-dose aspirin among participants with osteoarthritis, respectively. We further tested whether the coprescription of low-dose aspirin modified the relationships.

METHODS

Data source

We used data from The Health Improvement Network (THIN), a Cegedim database from general practitioners (GPs) in the UK that is incorporated in the IQVIA Medical Research Database. It draws approximately 19 million participants from 839 general practices and is representative of the UK population in terms of demographic characteristics and medical conditions. The database contains computerized information on sociodemographic characteristics, anthropometric characteristics, lifestyle factors, and details from visits to general practices (i.e., prescriptions, diagnoses, diagnoses and interventions from specialist referrals, hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses (24), whereas a dictionary based on the Multilex classification system (<https://www.fdbhealth.co.uk/>) is used to code drugs. This study followed the recommendations of the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) initiative for reporting observational studies in epidemiology (25).

Study design and cohort definition

We performed cohort studies to compare the risk of CVD in participants initiating naproxen with that in participants initiating other NSAIDs according to the status of coprescription of aspirin. The entry point of the current study was defined as the latest date of the following events: age 40 years; January 1, 2000; or the date of the nearest record which had a cushion time of more than 1 year with the first record in the database. We included participants aged 40 to 89 years at entry of the cohort, who carried an osteoarthritis diagnosis within January 2000 to December 2019, and had at least 1 year of continuous enrollment with a general practice prior to entering the study. The diagnosis of osteoarthritis was based on the presence of at least 1 osteoarthritis Read code. This approach has been used in previous studies (26–30) and has been preferred as opposed to case definitions based on medical visits, referrals, or prescription records in the previous validation study (31). We first identified naproxen initiators and other NSAID initiators based on the first record of naproxen and other NSAID prescription after the diagnosis of osteoarthritis, respectively. The date of initiation of naproxen or other NSAIDs was considered the index date for the corresponding participant. We excluded ibuprofen initiators in the comparator group because ibuprofen may also interact with the cardioprotective effects of aspirin (15, 17). We defined coprescription of low-dose aspirin (75–100 mg/day) with either naproxen or other NSAIDs as at least 1 prescription of low-dose aspirin from 60 days prior to the index date until the end of the follow-up (Figure 1). We excluded the participants who had been prescribed comparative NSAIDs prior to the index date, or the participants who had history of cancer or major bleeding before the index date, or who had a coprescription of high-dose aspirin (>100 mg/day) from 60 days prior to the index date until the end of the follow-up (Figure 2A). We took the same approach described above to assess the effect of the initiation of ibuprofen vs. initiation of other NSAIDs (excluding naproxen) on the risk of CVD according to whether the participants had coprescription of low-dose aspirin (Figure 2B).

Assessment of outcomes

Participants with an incident or recurrent CVD were those who had a diagnosis of MI, heart failure, or stroke during 1-year follow-up after the index date based on Read codes (32). MI, stroke, and heart failure defined by Read codes were previously validated, with the positive predictive values being 93%, 77.5%–89.3% and 83.4%, respectively (32–35).

Assessment of covariates

Covariates prior to the index date were obtained from THIN. These included sociodemographic factors (i.e., age at index date, sex, and Townsend Deprivation Index), body mass index, osteoarthritis duration (year from the osteoarthritis diagnosis to the index date), lifestyle factors (i.e., alcohol use and smoking status), comorbidities (i.e., myocardial infarction, stroke, heart failure, hypertension,

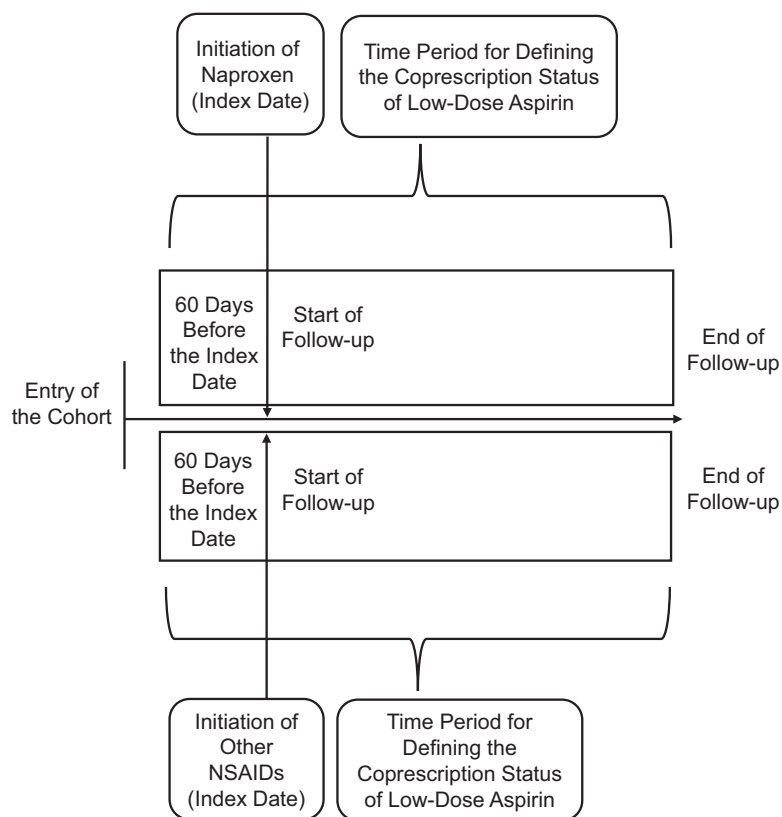


Figure 1. Design of the present study in The Health Improvement Network database, United Kingdom, 2000–2019. NSAID, nonsteroidal antiinflammatory drug.

diabetes, hyperlipidemia, liver disease, chronic kidney disease, pneumonia or infection, chronic obstructive pulmonary disease, ischemic heart disease, fracture, gastroesophageal reflux disease, gastrointestinal bleeding, gout, rheumatoid arthritis, depression, peptic ulcer disease, transient ischemic attack, atrial fibrillation, cerebrovascular accident), and medication use (i.e., opioids, antihypertensive medicines, antidiabetic medicines, proton pump inhibitors, angiotensin receptor blocker, diuretics, glucocorticoids, estrogens, anticoagulants, antiplatelets, and nitrates) prior to the index date, and health-care utilization during the 1 year before the index date.

Statistical analysis

The baseline characteristics were compared between initiators of naproxen and initiators of other oral NSAIDs using standard differences according to the coprescription status of aspirin. We compared the incident and recurrent composite CVD rate (i.e., MI, stroke, or heart failure) among initiators of naproxen with that among initiators of other oral NSAIDs according to the coprescription status of aspirin. Participants were followed from the index date to the first of the following events to occur: composite CVD, death, drug discontinuation (i.e., no prescription refill of either naproxen or other NSAIDs for the respective class of medication for

more than 60 days), a switch to or addition of comparator drug, a disenrollment from THIN, 1-year follow-up, age of 90, or the end of study period (December 2019). We used inverse probability weights (IPW) to balance the distribution of potential confounders (see Assessment of Covariates). We estimated the absolute rate difference (RD) in the risk of CVD between the 2 comparison groups. We fitted a Cox proportional hazards model to estimate the hazard ratio (HR) with a 95% confidence interval (CI) accounting for competing events (i.e., death) using the Fine-Gray subdistribution hazard model (36). We tested the proportional hazards assumption using the Kolmogorov supremum test. When the proportional hazards assumption was violated, we used R (R Foundation for Statistical Computing, Vienna, Austria) package “coxphw” to conduct a weighted Cox regression to obtain unbiased average HR estimates irrespective of proportionality of hazards (37). We examined the relationship of naproxen vs. other NSAIDs to the risk of CVD among the participants without and with coprescription of aspirin, separately. Then, we combined these 2 populations (i.e., participants without coprescription of aspirin and participants with coprescription of aspirin) into one data set, repeated the analysis, and tested whether such relationships were modified by coprescription of low-dose aspirin by adding an interaction term (i.e., naproxen (yes or no) × coprescription status of aspirin (yes or no)) in the Cox regression model.

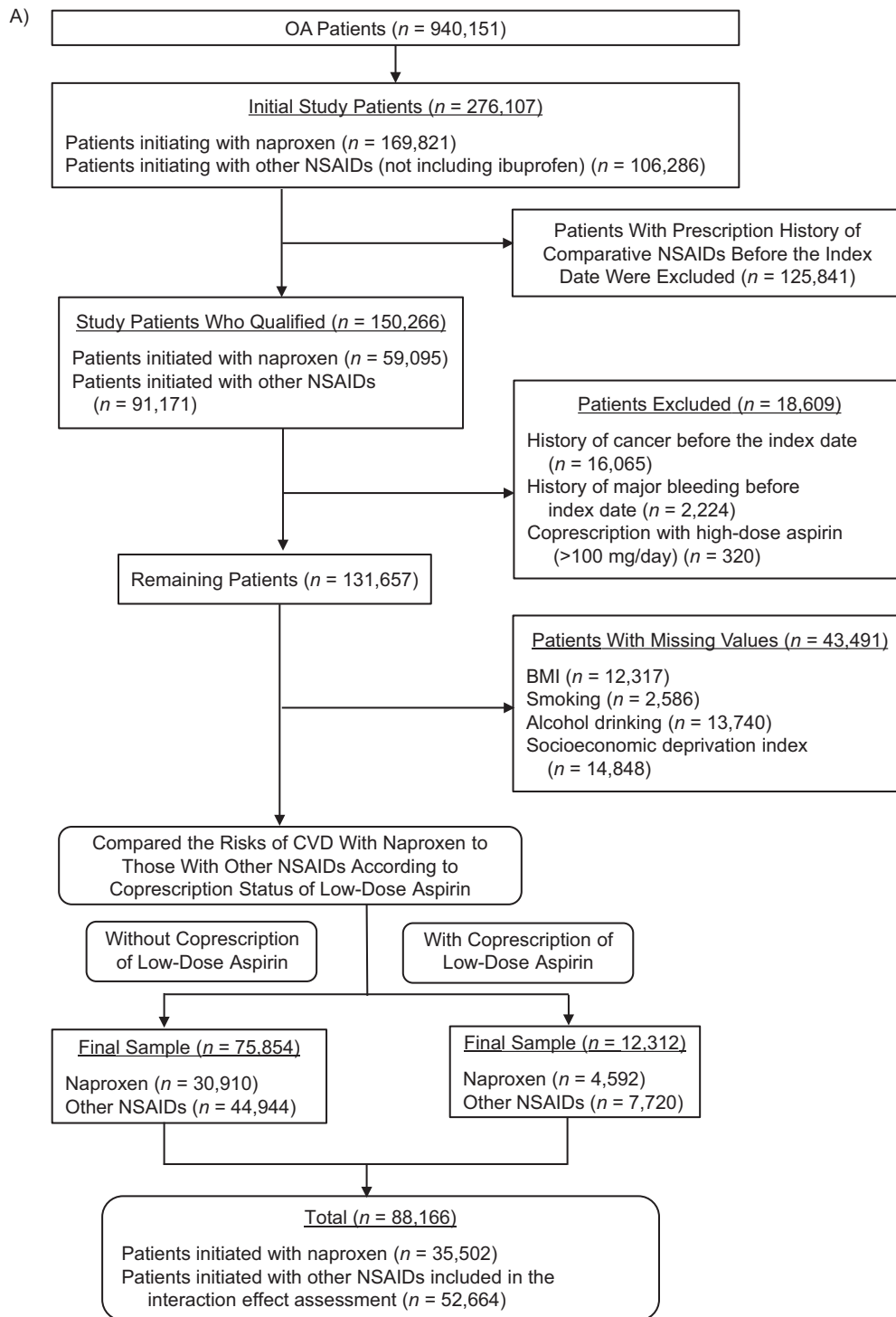


Figure 2 Continues

Using the same approach, we examined the effect of initiation of ibuprofen vs. initiation of other NSAIDs (excluding naproxen) on the risk of CVD according to the coprescription status of low-dose aspirin. We tested whether such relationships were modified by concomitant prescription of

low-dose aspirin by adding an interaction term (i.e., ibuprofen (yes or no) \times aspirin (yes or no)) in the Cox regression model.

All P values were 2-sided and $P < 0.05$ was considered significant for all tests. All statistical analyses were

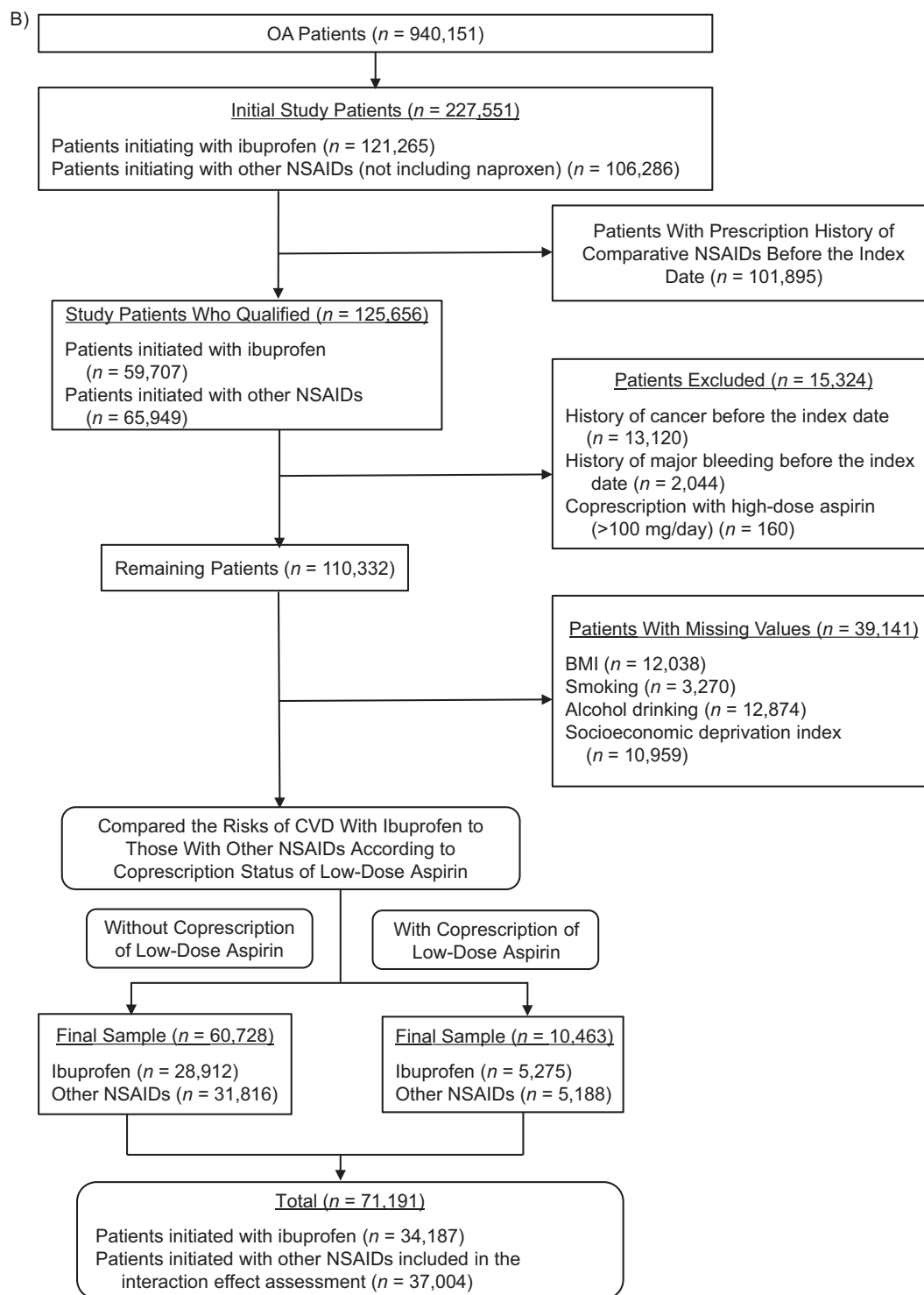


Figure 2. Selection process of included patients with osteoarthritis (OA) initiating naproxen or other nonsteroidal antiinflammatory drugs (NSAIDs) (A) and patients with OA initiating ibuprofen or other NSAIDs (B) in The Health Improvement Network database, United Kingdom, 2000–2019. BMI, body mass index; CVD, cardiovascular disease.

Table 1. Baseline Characteristics in Participants With Osteoarthritis Initiating Naproxen or Other NSAIDs According to Coprescription of Aspirin Status After Inverse Probability Weighting, Using Data From the Health Improvement Network Database, United Kingdom, 2000–2019

| Variable | No Coprescription of Aspirin | | | | Coprescription of Aspirin | | | |
|--|--|--|-------------------------------------|--|--------------------------------------|---|-------------------------------------|---|
| | Before Inverse Probability Weighting | | After Inverse Probability Weighting | | Before Inverse Probability Weighting | | After Inverse Probability Weighting | |
| | Naproxen ^a NSAIDs ^{a,b} (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Naproxen ^a (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Naproxen ^a (n = 4,592) | Other NSAIDs ^{a,b} (n = 7,720) | Naproxen ^a (n = 4,592) | Other NSAIDs ^{a,b} (n = 7,720) |
| Age, years | 64.8 (10.8) ^c | 63.7 (11.0) ^c | 64.1 (10.8) ^c | 64.1 (11.0) ^c | 71.6 (9.2) ^c | 71.2 (9.4) ^c | 71.2 (9.2) ^c | 71.7 (8.9) ^c |
| Socioeconomic deprivation index ^d | 2.6 (1.3) ^c | 2.6 (1.3) ^c | 2.6 (1.3) ^c | 2.6 (1.3) ^c | 2.8 (1.4) ^c | 2.8 (1.4) ^c | 2.8 (1.3) ^c | 2.9 (1.4) ^c |
| Female sex | 60.6 | 58.9 | 59.6 | 59.6 | 50.7 | 51.0 | 50.8 | 51.1 |
| OA duration, years | 7.3 (7.3) ^c | 6.2 (7.0) ^c | 6.7 (7.1) ^c | 6.6 (7.1) ^c | 8.5 (8.0) ^c | 7.7 (7.9) ^c | 7.9 (7.9) ^c | 8.7 (8.1) ^c |
| BMI ^e | 28.9 (5.8) ^c | 28.2 (5.5) ^c | 28.5 (5.6) ^c | 28.5 (5.7) ^c | 29.8 (5.9) ^c | 28.9 (5.5) ^c | 29.2 (5.5) ^c | 29.4 (5.3) ^c |
| Drinking | | | | | | | | |
| None | 19.9 | 19.3 | 19.6 | 19.4 | 23.7 | 23.8 | 23.4 | 21.4 |
| Past | 2.8 | 1.9 | 2.3 | 2.4 | 3.6 | 3.1 | 2.9 | 2.5 |
| Current | 77.3 | 78.8 | 78.1 | 78.2 | 72.7 | 73.1 | 73.7 | 76.1 |
| Smoking | | | | | | | | |
| None | 54.9 | 54.8 | 54.9 | 54.8 | 46.4 | 48.6 | 48.4 | 52.7 |
| Past | 30.3 | 27.1 | 28.3 | 28.2 | 39.9 | 37.3 | 37.1 | 35.1 |
| Current | 14.8 | 18.1 | 16.8 | 17.0 | 13.7 | 14.1 | 14.5 | 12.2 |
| Myocardial infarction | 3.7 | 4.4 | 3.1 | 3.0 | 7.2 | 6.1 | 6.4 | 6.3 |
| Stroke | 1.4 | 1.4 | 1.4 | 1.3 | 3.0 | 2.6 | 2.1 | 2.2 |
| Heart failure | 1.2 | 1.5 | 1.4 | 1.4 | 2.0 | 2.2 | 2.1 | 2.1 |
| Hypertension | 39.5 | 33.9 | 36.3 | 36.1 | 69.6 | 64.9 | 66.6 | 64.8 |
| Diabetes | 12.0 | 7.7 | 9.5 | 9.6 | 29.2 | 24.7 | 26.1 | 22.7 |
| Hyperlipidemia | 14.4 | 10.1 | 12.0 | 12.1 | 26.6 | 24.3 | 25.2 | 25.4 |
| Liver disease | 2.4 | 1.4 | 1.8 | 2.0 | 2.7 | 1.9 | 2.6 | 1.8 |
| Chronic kidney disease | 6.6 | 3.1 | 4.5 | 4.4 | 16.8 | 8.6 | 11.8 | 12.1 |
| Standard Difference | 0.105 | 0.011 | 0.033 | 0.001 | 0.006 | 0.006 | 0.047 | 0.057 |
| Standard Difference | 0.011 | 0.011 | 0.011 | <0.001 | 0.002 | 0.002 | 0.004 | 0.060 |
| Standard Difference | 0.118 | 0.118 | 0.118 | 0.005 | 0.149 | 0.149 | 0.149 | 0.038 |
| Standard Difference | 0.066 | 0.066 | 0.066 | 0.010 | 0.033 | 0.033 | 0.033 | 0.055 |
| Standard Difference | 0.100 | 0.100 | 0.100 | 0.006 | 0.054 | 0.054 | 0.054 | 0.095 |

Table continues

Table 1. Continued

| Variable | No Coprescription of Aspirin | | | | | | Coprescription of Aspirin | | | | | |
|---------------------------------------|---------------------------------------|---|---------------------|---------------------------------------|---|---------------------|--------------------------------------|--|---------------------|--------------------------------------|--|---------------------|
| | Before Inverse Probability Weighting | | | After Inverse Probability Weighting | | | Before Inverse Probability Weighting | | | After Inverse Probability Weighting | | |
| | Naproxen ^a (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Standard Difference | Naproxen ^a (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Standard Difference | Naproxen ^a (n = 4,592) | Other NSAIDs ^{a,b} (n = 7,720) | Standard Difference | Naproxen ^a (n = 4,592) | Other NSAIDs ^{a,b} (n = 7,720) | Standard Difference |
| Pneumonia or infection | 5.3 | 5.6 | 0.015 | 5.5 | 5.5 | <0.001 | 7.0 | 6.9 | 0.003 | 6.5 | 5.8 | 0.028 |
| Chronic obstructive pulmonary disease | 4.4 | 3.5 | 0.046 | 3.8 | 3.9 | 0.004 | 8.2 | 7.0 | 0.047 | 6.9 | 6.1 | 0.030 |
| Ischemic heart disease | 5.3 | 6.8 | 0.063 | 6.2 | 6.1 | 0.002 | 42.5 | 42.0 | 0.011 | 43.2 | 48.0 | 0.097 |
| Fracture | 28.8 | 24.5 | 0.098 | 26.2 | 26.2 | 0.002 | 27.6 | 25.7 | 0.043 | 25.5 | 28.7 | 0.072 |
| Gastroesophageal reflux disease | 14.7 | 10.5 | 0.125 | 12.2 | 12.2 | 0.002 | 17.0 | 13.8 | 0.088 | 14.8 | 12.5 | 0.067 |
| Gastrointestinal bleeding | 0.2 | 0.1 | 0.008 | 0.1 | 0.2 | 0.005 | 0.2 | 0.3 | 0.026 | 0.1 | 0.2 | 0.016 |
| Gout | 6.0 | 4.6 | 0.062 | 5.2 | 5.2 | 0.001 | 9.6 | 8.1 | 0.053 | 8.0 | 7.3 | 0.027 |
| Rheumatoid arthritis | 1.4 | 1.2 | 0.018 | 1.3 | 1.3 | 0.002 | 1.6 | 1.6 | 0.004 | 1.5 | 1.5 | 0.001 |
| Depression | 15.8 | 12.6 | 0.094 | 13.9 | 13.8 | 0.002 | 13.6 | 12.1 | 0.044 | 12.3 | 11.6 | 0.023 |
| Peptic ulcer disease | 3.8 | 4.3 | 0.025 | 4.0 | 4.2 | 0.011 | 5.0 | 5.8 | 0.035 | 4.8 | 4.8 | 0.002 |
| Transient ischemic attack | 1.6 | 1.5 | 0.007 | 1.6 | 1.5 | 0.006 | 8.2 | 7.3 | 0.032 | 7.4 | 6.6 | 0.031 |
| Angina | 3.3 | 4.5 | 0.065 | 4.0 | 4.0 | 0.001 | 25.5 | 27.1 | 0.037 | 27.6 | 25.1 | 0.057 |
| Atrial fibrillation | 2.3 | 2.3 | 0.001 | 2.4 | 2.3 | 0.008 | 6.5 | 7.4 | 0.037 | 6.5 | 6.1 | 0.016 |
| Cerebrovascular accident | 1.4 | 1.4 | 0.003 | 1.4 | 1.3 | 0.010 | 7.0 | 6.6 | 0.014 | 6.9 | 5.6 | 0.055 |
| Opioids | 33.9 | 22.4 | 0.257 | 26.7 | 26.8 | 0.003 | 44.3 | 29.7 | 0.306 | 35.1 | 39.4 | 0.089 |
| ACE inhibitors | 25.0 | 18.0 | 0.170 | 20.8 | 20.7 | 0.002 | 57.5 | 48.1 | 0.189 | 49.7 | 47.6 | 0.041 |
| Beta-receptor inhibitors | 21.5 | 20.3 | 0.029 | 20.7 | 20.8 | 0.002 | 53.9 | 48.7 | 0.105 | 50.1 | 46.5 | 0.071 |

Table continues

Table 1. Continued

| Variable | No Coprescription of Aspirin | | | | Coprescription of Aspirin | | | | | | | |
|------------------------------|--------------------------------------|--|-------------------------------------|---------------------|--------------------------------------|--|-------------------------------------|---------------------|------------------------|------------------------|------------------------|-------|
| | Before Inverse Probability Weighting | | After Inverse Probability Weighting | | Before Inverse Probability Weighting | | After Inverse Probability Weighting | | | | | |
| | Naproxen ^a (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Standard Difference | Standard Difference | Naproxen ^a (n = 30,910) | Other NSAIDs ^{a,b} (n = 44,944) | Standard Difference | Standard Difference | | | | |
| Antihypertensive medicine | 49.4 | 43.7 | 0.114 | 0.003 | 46.0 | 46.1 | 0.003 | 0.118 | 86.4 | 85.4 | 88.7 | 0.070 |
| Antidiabetic medicine | 8.4 | 5.5 | 0.113 | 0.001 | 6.6 | 6.6 | 0.001 | 0.099 | 20.0 | 18.7 | 17.5 | 0.064 |
| Calcium channel blockers | 23.5 | 17.5 | 0.148 | 0.002 | 19.9 | 19.8 | 0.002 | 0.098 | 46.5 | 44.9 | 51.1 | 0.092 |
| PPIs | 59.9 | 30.2 | 0.625 | 0.003 | 42.1 | 42.3 | 0.003 | 0.587 | 53.2 | 42.7 | 57.7 | 0.091 |
| Angiotensin receptor blocker | 10.4 | 6.4 | 0.147 | 0.001 | 8.1 | 8.1 | 0.001 | 0.144 | 17.1 | 15.6 | 18.5 | 0.035 |
| Loop diuretics | 9.8 | 9.6 | 0.010 | 0.002 | 9.7 | 9.7 | 0.002 | 0.008 | 23.0 | 24.0 | 23.3 | 0.008 |
| Glucocorticoids | 17.7 | 11.8 | 0.165 | 0.001 | 14.2 | 14.2 | 0.001 | 0.161 | 18.2 | 15.7 | 18.5 | 0.009 |
| Estrogen | 22.3 | 19.5 | 0.068 | 0.002 | 20.7 | 20.6 | 0.002 | 0.095 | 13.6 | 12 | 14.0 | 0.010 |
| Insulin | 1.9 | 1.2 | 0.053 | 0.003 | 1.5 | 1.4 | 0.003 | 0.045 | 4.9 | 5.0 | 4.5 | 0.021 |
| Anticoagulant | 3.5 | 3.0 | 0.028 | 0.002 | 3.1 | 3.2 | 0.002 | 0.009 | 5.0 | 4.7 | 4.0 | 0.049 |
| Antiplatelet | 3.3 | 2.0 | 0.082 | 0.004 | 2.4 | 2.5 | 0.004 | 0.219 | 9.1 | 6.7 | 10.8 | 0.063 |
| Nitrates | 5.9 | 6.0 | 0.002 | 0.003 | 5.9 | 5.9 | 0.003 | 0.057 | 32.0 | 31.0 | 33.2 | 0.026 |
| Hospitalizations | 0.3 (0.8) ^c | 0.2 (0.7) ^c | 0.160 | 0.002 | 0.2 (0.7) ^c | 0.2 (0.7) ^c | 0.002 | 0.116 | 0.3 (0.9) ^c | 0.3 (0.9) ^c | 0.3 (0.9) ^c | 0.056 |
| General practice visits | 5.7 (5.2) ^c | 5.2 (5.3) ^c | 0.108 | 0.002 | 5.4 (5.0) ^c | 5.4 (5.4) ^c | 0.002 | 0.073 | 7.1 (6.4) ^c | 6.9 (6.6) ^c | 7.3 (6.2) ^c | 0.025 |
| Specialist referrals | 0.6 (1.0) ^c | 0.4 (0.8) ^c | 0.283 | 0.006 | 0.5 (0.9) ^c | 0.5 (0.9) ^c | 0.006 | 0.271 | 0.5 (1.0) ^c | 0.4 (0.9) ^c | 0.5 (0.9) ^c | 0.057 |

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis; PPI, proton pump inhibitor.

^a Values are shown as %.

^b Other NSAIDs included the following drugs: diclofenac, meloxicam, paracetamol, piroxicam, celecoxib, etoricoxib, rofecoxib, valdecoxib, lumiracoxib, tenoxicam, aceclofenac, acemetacin, azapropazone, benzydamine, dextetoprofen, diflunisal, etodolac, fenbufen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, sulindac, and tiaprofenic acid.

^c Values are expressed as mean (standard deviation).

^d The socioeconomic deprivation index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

^e Weight (kg)/height (m)².

^f Frequency during the past 1 year.

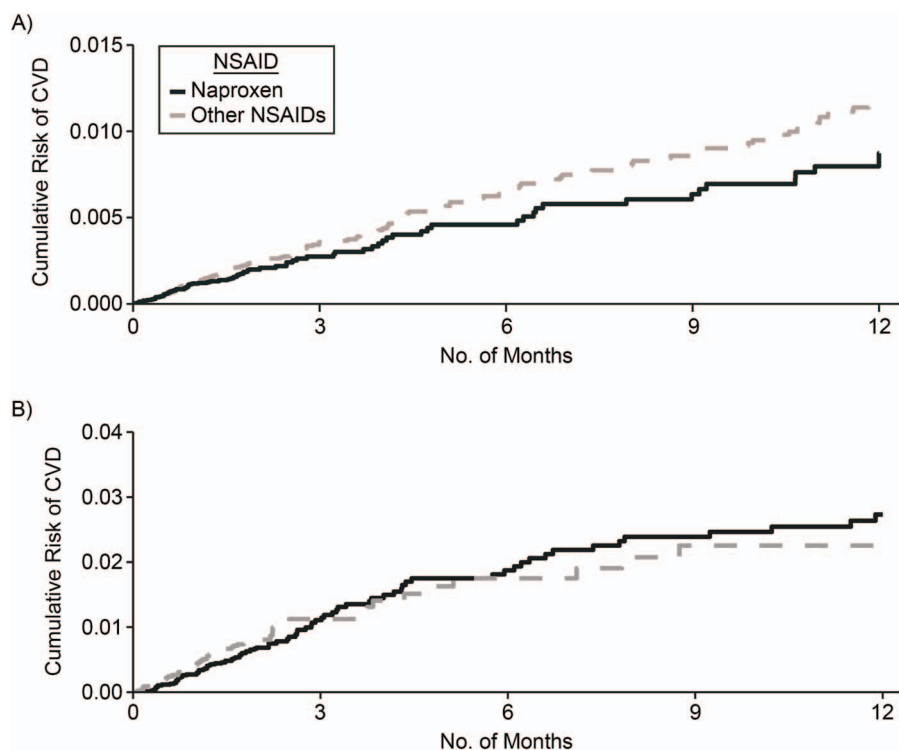


Figure 3. Cumulative risk of cardiovascular disease (CVD) between naproxen initiators and other nonsteroidal antiinflammatory drugs (NSAIDs) initiators among patients without coprescription of aspirin (A) and patients with coprescription of aspirin (B) in The Health Improvement Network database, United Kingdom, 2000–2019.

performed with SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and R Studio, version 1.1.456 (Posit, Boston, Massachusetts).

Ethical approval

This study was approved by the THIN Scientific Review Committee (18THIN078_A2). THIN is a registered trademark of Cegecim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses deidentified data provided by patients as part of their routine primary care.

RESULTS

Among the 940,151 participants with osteoarthritis who were 40 to 89 years from January 2000 to December 2019 and had at least 1 year of continuous enrollment with a general practice prior to entering the study, we identified 169,821 participants initiating naproxen (18.06%), 121,265 participants initiating ibuprofen (12.90%), and 106,286 participants initiating other NSAIDs (11.31%) (Figure 2). After excluding participants with comparative NSAIDs prescription history before entering the study, with cancer or major bleeding history or coprescription with high-dose aspirin,

and with missing information on body mass index, smoking, alcohol drinking, and socioeconomic deprivation index, a total of 88,166 participants (35,502 naproxen initiators vs. 52,664 other NSAIDs initiators) were included in the analysis for the association between naproxen and risk of CVD (Figure 2A). Among the participants without coprescription of low-dose aspirin (30,910 naproxen initiators vs. 44,944 other NSAIDs initiators), the mean age was 64 years and 59% were women (Table 1). Among the participants with coprescription of low-dose aspirin (4,592 naproxen initiators vs. 7,720 other NSAIDs initiators), the mean age was 71 years and 51% were women, and the proportion of follow-up time that the participants were exposed to low-dose aspirin for naproxen initiators and other NSAIDs initiators was 80% and 73%, respectively. After IPW, the characteristics between the 2 comparison groups were well balanced with all standardized differences < 0.1 (Table 1).

As shown in Figure 3A, among the participants without coprescription of aspirin, the risk of CVD was lower in naproxen initiators (10.3 per 1,000 person-years) than in other NSAIDs initiators (13.2 per 1,000 person-years). The RD of CVD for naproxen initiators compared with initiators of other NSAIDs was -2.8 (95% CI: $-5.6, -0.1$) per 1,000 person-years and the HR was 0.71 (95% CI: 0.60, 0.85) (Table 2). In contrast, among the participants with coprescription of aspirin, the risk of CVD was higher in naproxen initiators (36.9 per 1,000 person-years) than that in

Table 2. Association Between Naproxen and Risk of Cardiovascular Disease Comparing With Other NSAIDs in Participants With Osteoarthritis, Using Data From the Health Improvement Network Database, United Kingdom, 2000–2019

| Aspirin Coprescription | No. of Participants | No. of Events | Mean Follow-up, years | Per 1,000 Person-Years | | | Crude | | | Weighted ^a | | | Incident CVD, Weighted | | | | |
|------------------------|---------------------|---------------|-----------------------|------------------------|------|------------|-------|------------|------|-----------------------|------|------------|------------------------|--------|--|--|--|
| | | | | Incidence Rate | RD | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI | | | |
| No | | | | | | | | | | | | | | | | | |
| Naproxen | 30,910 | 91 | 0.29 | 10.3 | -2.8 | -5.6, -0.1 | 0.77 | 0.60, 0.99 | 0.71 | 0.60, 0.85 | 0.80 | 0.66, 0.97 | | | | | |
| Other NSAIDs | 44,944 | 191 | 0.32 | 13.2 | 0 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | | | | | |
| Yes | | | | | | | | | | | | | | | | | |
| Naproxen | 4,592 | 50 | 0.30 | 36.9 | 2.1 | 0.7, 3.5 | 1.11 | 1.00, 1.42 | 1.61 | 1.25, 2.07 | 1.46 | 1.05, 2.06 | | | | | |
| Other NSAIDs | 7,720 | 92 | 0.34 | 34.8 | 0 | Referent | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent | | | | | |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR hazard ratio; NSAID, nonsteroidal antiinflammatory drug; RD, rate difference.

^a The proportional hazards assumption was violated among the coprescription of aspirin group, and the weighted average HR was 1.48 (95% CI: 1.12, 1.84).

other NSAIDs initiators (34.8 per 1,000 person-years), with the RD being 2.1 (95% CI: 0.7, 3.5) per 1,000 person-years and the HR being 1.61 (95% CI: 1.25, 2.07), respectively (Figure 3B and Table 2). The proportional hazards assumption was violated, and the weighted average HR of CVD for initiation of naproxen vs. initiation of other NSAIDs was 1.48 (95% CI: 1.12, 1.84) among the participants who were coprescribed aspirin. Results from the sensitivity analysis among the participants without a history of CVD were consistent with the primary analysis (Table 2).

Combining the participants with and without coprescription of aspirin and adding an interaction term (i.e., naproxen (yes or no) × coprescription status of aspirin (yes or no)) into the Cox regression model, we found that the association between naproxen and risk of CVD compared with other NSAIDs was significantly modified by coprescription of aspirin (P for interaction < 0.001).

After excluding participants with comparative NSAIDs prescription history before entering the study, with cancer or major bleeding history or coprescription with high-dose aspirin, and with missing information of body mass index, smoking, alcohol drinking, and socioeconomic deprivation index, a total of 71,191 participants (34,187 ibuprofen initiators vs. 37,004 other NSAIDs initiators) were included in the analysis for the association between ibuprofen and risk of CVD (Figure 2B). Among the participants without coprescription of low-dose aspirin (28,912 ibuprofen initiators vs. 31,816 other NSAIDs initiators), the mean age was 65 years and 60% were women. Among the participants with coprescription of low-dose aspirin (5,275 ibuprofen initiators vs. 5,188 other NSAIDs initiators), the mean age was 72 years and 52% were women, the proportion of follow-up time that the participants were exposed to low-dose aspirin in ibuprofen initiators and other NSAIDs initiators was 81% and 71%, respectively. After IPW, the characteristics between the 2 comparison groups were well balanced with all standardized differences < 0.1 (Table 3).

As shown in Figure 4, the risk of CVD was lower in ibuprofen initiators (10.7 per 1,000 person-years) than that in other NSAIDs initiators (11.2 per 1,000 person-years) among the participants without coprescription of aspirin, but higher risk of CVD was observed in ibuprofen initiators (44.5 per 1,000 person-years) compared with that in other NSAIDs initiators (32.9 per 1,000 person-years) among the participants who were coprescribed aspirin. The corresponding RD and HR were -0.5 (95% CI: -0.8, -0.2) per 1,000 person-years and 0.77 (95% CI: 0.63, 0.95) among the participants without coprescription of aspirin, and 11.6 (95% CI: 2.2, 21.0) per 1,000 person-years and 1.35 (95% CI: 1.07, 1.70) among the participants with coprescription of aspirin, respectively (Table 4). The association of initiation of ibuprofen vs. initiation of other NSAIDs with the risk of CVD was significantly modified by coprescription of aspirin (P for interaction < 0.001).

DISCUSSION

Our study found that the association between naproxen or ibuprofen and the risk of CVD was significantly modified by the coprescription of low-dose aspirin among participants

Table 3. Baseline Characteristics in Participants With Osteoarthritis Initiating Ibuprofen or Other NSAIDs According to Coprescription of Aspirin Status After Inverse Probability Weighting, Using Data From the Health Improvement Network Database, United Kingdom, 2000–2019

| Variable | No Coprescription of Aspirin | | | | Coprescription of Aspirin | | | |
|--|--------------------------------------|-------------------------------------|---------------------|--|--------------------------------------|-------------------------------------|---------------------|---|
| | Before Inverse Probability Weighting | After Inverse Probability Weighting | Standard Difference | Other NSAIDs ^{a,b} (n = 31,816) | Before Inverse Probability Weighting | After Inverse Probability Weighting | Standard Difference | Other NSAIDs ^{a,b} (n = 5,188) |
| Age, years | 66.6 (10.8) ^c | 64.6 (11.0) ^c | 0.350 | 64.7 (11.2) ^c | 72.4 (9.4) ^c | 71.7 (9.5) ^c | 0.165 | 71.6 (9.4) ^c |
| Socioeconomic deprivation index ^d | 2.7 (1.3) ^c | 2.6 (1.3) ^c | 0.060 | 2.6 (1.3) ^c | 2.8 (1.4) ^c | 2.8 (1.4) ^c | 0.007 | 2.8 (1.3) ^c |
| Female sex | 62.7 | 60.1 | 0.105 | 60.0 | 54.7 | 52.1 | 0.102 | 51.7 |
| OA duration, years | 6.8 (7.5) ^c | 6.5 (7.3) ^c | 0.071 | 6.5 (7.3) ^c | 7.9 (8.2) ^c | 8.0 (8.3) ^c | 0.001 | 7.8 (8.0) ^c |
| BMI ^e | 28.2 (5.6) ^c | 28.3 (5.6) ^c | 0.024 | 28.2 (5.6) ^c | 28.7 (5.5) ^c | 28.9 (5.6) ^c | 0.062 | 28.8 (5.5) ^c |
| Drinking | | | 0.074 | | | | 0.019 | |
| None | 21.5 | 20.3 | | 20.4 | 24.8 | 24.3 | | 24.5 |
| Past | 2.5 | 2.3 | | 2.3 | 3.2 | 3.2 | | 3.1 |
| Current | 76.0 | 77.4 | | 77.3 | 72.0 | 72.5 | | 72.4 |
| Smoking | | | 0.059 | | | | 0.046 | |
| None | 55.5 | 54.9 | | 54.9 | 50.2 | 49.4 | | 49.2 |
| Past | 28.6 | 28.0 | | 28.0 | 36.6 | 37.4 | | 37.4 |
| Current | 15.9 | 17.1 | | 17.1 | 13.2 | 13.2 | | 13.4 |
| Myocardial infarction | 4.2 | 4.3 | 0.005 | 4.2 | 4.2 | 4.5 | 0.021 | 4.6 |
| Stroke | 2.5 | 2.3 | 0.019 | 2.4 | 2.1 | 2.8 | 0.024 | 2.8 |
| Heart failure | 2.5 | 2.5 | <0.001 | 2.5 | 2.7 | 2.7 | 0.005 | 2.6 |
| Hypertension | 39.0 | 33.0 | 0.125 | 36.0 | 65.6 | 65.2 | 0.014 | 65.4 |
| Diabetes | 10.2 | 8.0 | 0.077 | 9.1 | 25.0 | 24.7 | 0.005 | 24.5 |
| Hyperlipidemia | 11.9 | 10.1 | 0.057 | 11.1 | 24.4 | 24.1 | <0.001 | 24.0 |
| Liver disease | 1.9 | 1.4 | 0.042 | 1.7 | 1.9 | 1.8 | 0.015 | 2.0 |
| Chronic kidney disease | 5.0 | 3.2 | 0.092 | 4.1 | 11.3 | 9.9 | 0.075 | 9.7 |

Table continues

Table 3. Continued

| Variable | No Coprescription of Aspirin | | | | | | Coprescription of Aspirin | | | | | |
|---------------------------------------|--|---|---------------------|--|---|---------------------|---------------------------------------|--|---------------------|---------------------------------------|--|---------------------|
| | Before Inverse Probability Weighting | | | After Inverse Probability Weighting | | | Before Inverse Probability Weighting | | | After Inverse Probability Weighting | | |
| | Ibuprofen ^a (n = 28,912) | Other NSAIDs ^{a,b} (n = 31,816) | Standard Difference | Ibuprofen ^a (n = 28,912) | Other NSAIDs ^{a,b} (n = 31,816) | Standard Difference | Ibuprofen ^a (n = 5,275) | Other NSAIDs ^{a,b} (n = 5,188) | Standard Difference | Ibuprofen ^a (n = 5,275) | Other NSAIDs ^{a,b} (n = 5,188) | Standard Difference |
| Pneumonia or infection | 4.8 | 4.8 | 0.001 | 4.8 | 4.8 | <0.001 | 6.7 | 6.1 | 0.028 | 6.4 | 6.2 | 0.005 |
| Chronic obstructive pulmonary disease | 4.5 | 3.4 | 0.058 | 3.9 | 3.9 | <0.001 | 6.6 | 7.0 | 0.016 | 6.6 | 6.6 | 0.002 |
| Ischemic heart disease | 7.0 | 6.7 | 0.012 | 6.9 | 6.8 | 0.003 | 41.9 | 42.5 | 0.012 | 42.1 | 42.1 | 0.001 |
| Fracture | 25.7 | 24.9 | 0.018 | 25.3 | 25.3 | <0.001 | 27.1 | 25.6 | 0.033 | 26.2 | 25.6 | 0.014 |
| Gastroesophageal reflux disease | 12.2 | 10.4 | 0.057 | 11.3 | 11.3 | 0.001 | 14.0 | 14.2 | 0.005 | 14.0 | 13.9 | 0.004 |
| Gastrointestinal bleeding | 0.2 | 0.1 | 0.015 | 0.2 | 0.2 | 0.002 | 0.2 | 0.2 | 0.003 | 0.2 | 0.2 | 0.010 |
| Gout | 3.5 | 5.2 | 0.083 | 4.4 | 4.4 | <0.001 | 5.7 | 8.7 | 0.118 | 7.0 | 7.1 | 0.002 |
| Rheumatoid arthritis | 1.2 | 1.4 | 0.018 | 1.3 | 1.3 | 0.002 | 1.3 | 2.0 | 0.057 | 1.5 | 1.7 | 0.013 |
| Depression | 13.8 | 12.7 | 0.033 | 13.3 | 13.2 | 0.004 | 13.7 | 12.1 | 0.048 | 12.6 | 12.5 | 0.003 |
| Peptic ulcer disease | 4.5 | 4.7 | 0.012 | 4.7 | 4.7 | 0.001 | 5.7 | 6.3 | 0.024 | 6.0 | 6.1 | 0.006 |
| Transient ischemic attack | 1.7 | 1.5 | 0.021 | 1.6 | 1.6 | 0.001 | 8.0 | 7.8 | 0.006 | 7.9 | 7.7 | 0.004 |
| Angina | 4.5 | 4.3 | 0.012 | 4.5 | 4.5 | 0.001 | 26.9 | 26.2 | 0.016 | 26.5 | 26.4 | 0.001 |
| Atrial fibrillation | 2.4 | 2.4 | <0.001 | 2.4 | 2.4 | 0.001 | 7.2 | 7.4 | 0.006 | 7.3 | 7.2 | 0.001 |
| Cerebrovascular accident | 1.5 | 1.3 | 0.019 | 1.4 | 1.4 | 0.003 | 7.1 | 6.5 | 0.024 | 6.8 | 6.8 | 0.001 |
| Opioids | 26.1 | 21.0 | 0.121 | 23.6 | 23.5 | 0.002 | 33.6 | 28.0 | 0.121 | 30.5 | 29.7 | 0.017 |
| ACE inhibitors | 21.6 | 17.7 | 0.098 | 19.7 | 19.7 | 0.001 | 48.2 | 47.3 | 0.017 | 47.4 | 47.1 | 0.005 |
| Beta receptor inhibitors | 21.1 | 18.5 | 0.064 | 19.9 | 19.8 | 0.001 | 48.5 | 46.8 | 0.034 | 47.8 | 47.5 | 0.006 |

Table continues

Table 3. Continued

| Variable | No Coprescription of Aspirin | | | | Coprescription of Aspirin | | | | | | |
|------------------------------|--------------------------------------|--|-------------------------------------|------------------------|--------------------------------------|---|-------------------------------------|---------------------|------------------------|------------------------|-------|
| | Before Inverse Probability Weighting | | After Inverse Probability Weighting | | Before Inverse Probability Weighting | | After Inverse Probability Weighting | | | | |
| | Ibuprofen ^a (n = 28,912) | Other NSAIDs ^{a,b} (n = 31,816) | Standard Difference | Standard Difference | Ibuprofen ^a (n = 5,275) | Other NSAIDs ^{a,b} (n = 5,186) | Standard Difference | Standard Difference | | | |
| Antihypertensive medicine | 48.1 | 41.5 | 0.133 | 44.9 | 44.9 | 86.6 | 85.1 | 0.042 | 85.8 | 85.8 | 0.001 |
| Antidiabetic medicine | 7.1 | 5.5 | 0.065 | 6.4 | 6.3 | 19.4 | 18.5 | 0.023 | 18.7 | 18.4 | 0.007 |
| Calcium channel blockers | 21.5 | 16.7 | 0.123 | 19.1 | 19.1 | 46.0 | 43.6 | 0.048 | 44.8 | 44.9 | 0.004 |
| PPIs | 40.5 | 31.3 | 0.191 | 35.8 | 35.8 | 51.5 | 44.2 | 0.146 | 47.5 | 46.9 | 0.014 |
| Angiotensin receptor blocker | 8.6 | 6.7 | 0.071 | 7.6 | 7.7 | 16.7 | 15.9 | 0.023 | 16.0 | 15.8 | 0.006 |
| Loop diuretics | 10.3 | 8.6 | 0.059 | 9.5 | 9.5 | 24.5 | 23.1 | 0.034 | 23.5 | 23.4 | 0.003 |
| Glucocorticoids | 13.9 | 10.8 | 0.093 | 12.4 | 12.3 | 15.7 | 14.6 | 0.032 | 15.0 | 15.3 | 0.008 |
| Estrogen | 18.5 | 17.4 | 0.029 | 17.9 | 18.0 | 11.2 | 10.2 | 0.032 | 10.7 | 10.7 | 0.001 |
| Insulin | 1.6 | 1.2 | 0.034 | 1.4 | 1.4 | 5.2 | 5.1 | 0.007 | 5.0 | 4.9 | 0.006 |
| Anticoagulant | 3.1 | 3.0 | 0.011 | 3.1 | 3.1 | 4.4 | 4.3 | 0.005 | 4.2 | 4.3 | 0.004 |
| Antiplatelet | 2.6 | 2.1 | 0.038 | 2.4 | 2.3 | 8.8 | 7.2 | 0.059 | 7.9 | 7.6 | 0.012 |
| Nitrates | 6.2 | 5.3 | 0.038 | 5.8 | 5.8 | 31.2 | 29.2 | 0.043 | 30.2 | 30.1 | 0.002 |
| Hospitalizations | 0.3 (0.8) ^c | 0.2 (0.7) ^c | 0.098 | 0.2 (0.7) ^c | 0.2 (0.7) ^c | 0.4 (1.1) ^c | 0.3 (1.0) ^c | 0.051 | 0.3 (1.0) ^c | 0.3 (1.0) ^c | 0.003 |
| General practice visits | 5.6 (5.4) ^c | 4.9 (5.3) ^c | 0.136 | 5.3 (5.1) ^c | 5.3 (5.7) ^c | 7.1 (6.6) ^c | 6.6 (6.3) ^c | 0.078 | 6.9 (6.3) ^c | 6.9 (6.7) ^c | 0.004 |
| Specialist referrals | 0.5 (0.9) ^c | 0.4 (0.8) ^c | 0.121 | 0.4 (0.9) ^c | 0.4 (0.9) ^c | 0.5 (0.9) ^c | 0.4 (0.9) ^c | 0.093 | 0.5 (0.9) ^c | 0.5 (0.9) ^c | 0.006 |

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis; PPI, proton pump inhibitor.

^a Values are shown as %.

^b Other NSAIDs included the following drugs: diclofenac, meloxicam, paracetamol, piroxicam, celecoxib, etoricoxib, rofecoxib, valdecoxib, lumiracoxib, tenoxicam, aceclofenac, acemetacin, azapropazone, benzydamine, dextketoprofen, diflunisal, etodolac, fenbufen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, sulindac, and tiaprofenic acid.

^c Values are expressed as mean (standard deviation).

^d The socioeconomic deprivation index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

^e Weight (kg)/height (m)².

^f Frequency during the past 1 year.

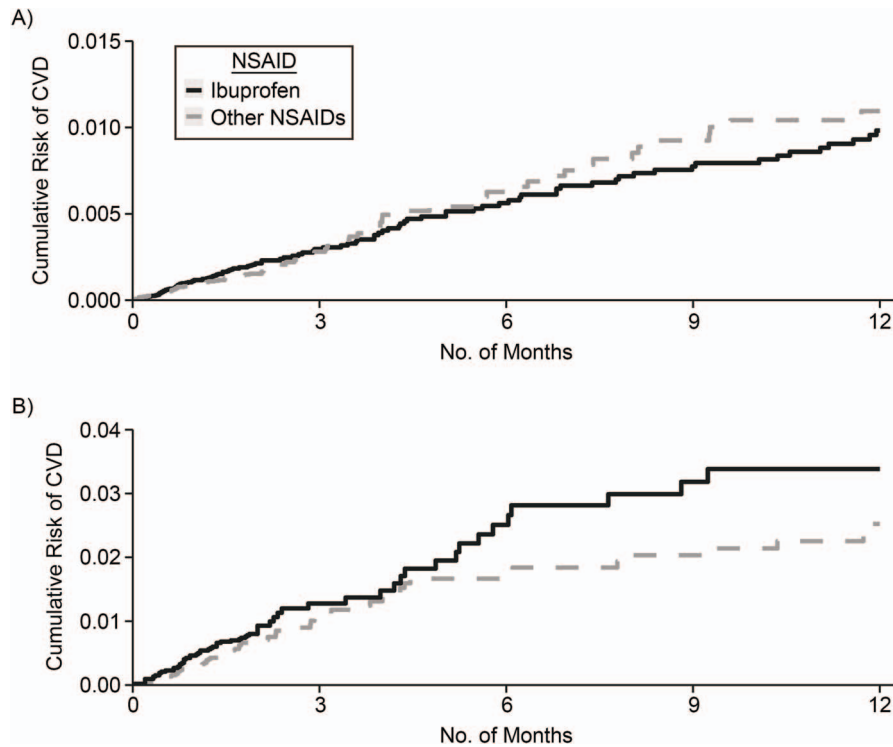


Figure 4. Cumulative risk of cardiovascular disease (CVD) between ibuprofen initiators and other nonsteroidal antiinflammatory drugs (NSAIDs) initiators among patients without coprescription of aspirin (A) and patients with coprescription of aspirin (B) in The Health Improvement Network database, United Kingdom, 2000–2019.

with osteoarthritis. The risk of CVD was lower in naproxen or ibuprofen initiators than that in other NSAIDs initiators among those without coprescription of low-dose aspirin, but higher in naproxen or ibuprofen initiators than that in other NSAIDs initiators among those with coprescription of low-dose aspirin.

Aspirin inhibits the synthesis of TXA₂, which is the major product of arachidonic acid in platelets, serving as potent platelet agonists and vasoconstrictors, by irreversibly acetylating a serine residue at position 529 of platelet COX-1 (9–11). The inhibition of COX-1-dependent TXA₂ in platelets by low-dose aspirin is irreversible and completable (38, 39). In contrast, several NSAIDs are reversible inhibitors of platelet COX-1 and often cause an incomplete and intermittent inhibition of platelet TXA₂, which may be inadequate to prevent cardiovascular events (10, 12). The drug-drug interaction between aspirin and certain NSAIDs, which have longer half-lives than aspirin, occurred through competitive binding at the active docking site of COX-1 (10, 12, 15). Moreover, not all NSAIDs can interfere with the antiplatelet effect of aspirin due to their pharmacodynamics and impedance of the access of aspirin to the serine residue at position 529 of COX-1 among NSAIDs (3, 15, 23). Previous studies have reported that ibuprofen (14–18) and naproxen (14, 20–22) could antagonize the cardioprotective effect of aspirin, while other commonly used NSAIDs (e.g., selective COX-2 inhibitors, diclofenac, meloxicam,

or acetaminophen) did not affect the inhibition of platelet aggregation by aspirin (14, 15, 18, 19, 22, 23). Consistent with previous studies, we found that naproxen and ibuprofen were associated with a higher risk of CVD than other NSAIDs (except naproxen or ibuprofen) among the participants with coprescription of low-dose aspirin.

Using a real-world, population-based electronic database and a study design emulating a randomized controlled trial by IPW, we found that the risk of CVD among naproxen or ibuprofen initiators was higher than that among other NSAIDs initiators among osteoarthritis patients who had coprescriptions of low-dose aspirin. These findings are pertinent to the management of patients with osteoarthritis who are at high risk of CVD. Second, we adopted a new-user design to include only initiators of naproxen or ibuprofen and other NSAIDs. This method would minimize potential selection bias (i.e., immortal bias) if prevalent medication users were included. Third, our finding that the effect of ibuprofen on the risk of CVD was significantly modified by coprescription of aspirin is consistent with those of previous studies, supporting the credibility of our study hypothesis.

The limitations of our study should be acknowledged. First, as in any observational study we cannot rule out residual confounding, despite our use of the IPW method. Second, physician-ordered prescriptions may not reflect the actual medication use by patients; thus, misclassification of

Table 4. Association Between Ibuprofen and Risk of Cardiovascular Disease Comparing With Other NSAIDs in Participants With Osteoarthritis in The Health Improvement Network Database, United Kingdom, 2000–2019

| Aspirin Coprescription | No. of Participants | No. of Events | Mean Follow-Up, Years | Per 1,000 Person-Years | | | Crude | | | Weighted ^a | | |
|------------------------|---------------------|---------------|-----------------------|------------------------|------|------------|-------|------------|------|-----------------------|----------|----------|
| | | | | Incidence Rate | RD | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| No | | | | | | | | | | | | |
| Ibuprofen | 28,912 | 81 | 0.26 | 10.7 | -0.5 | -0.8, -0.2 | 0.84 | 0.71, 0.99 | 0.77 | 0.63, 0.95 | Referent | Referent |
| Other NSAIDs | 31,816 | 117 | 0.33 | 11.2 | 0 | Referent | 1.00 | Referent | 1.00 | Referent | Referent | Referent |
| Yes | | | | | | | | | | | | |
| Ibuprofen | 5,275 | 63 | 0.27 | 44.5 | 11.6 | 2.2, 21.0 | 1.26 | 1.01, 1.80 | 1.35 | 1.07, 1.70 | Referent | Referent |
| Other NSAIDs | 5,188 | 60 | 0.35 | 32.9 | 0 | Referent | 1.00 | Referent | 1.00 | Referent | Referent | Referent |

Abbreviations: CI, confidence interval; HR hazard ratio; NSAID, nonsteroidal antiinflammatory drug; OA, osteoarthritis; RD, rate difference.

^a The proportional hazard assumption was violated among the no coprescription of aspirin group, and the weighted average HR was 0.80 (95% CI: 0.66, 0.98).

the medication use could occur and bias the study findings. Such bias, if it occurs, is likely to be random and would bias the observed association toward the null. Third, administrative data are often lacking information on over-the-counter medications use. As a result, the exposure assessment is susceptible to misclassification bias. To address this potential bias, we performed a sensitivity analysis among participants aged 60 years or older. Because the National Health Service England provides free health care for most services, including medications, ordered by general practices for individuals aged 60 years or older, it is unlikely that most patients who are 60 years or older would purchase NSAIDs or low-dose aspirin over the counter without a prescription. The results from this sensitivity analysis showed that the relationship of naproxen initiation to the risk of CVD did not change materially when compared with other NSAIDs. Among the participants without coprescription of aspirin, naproxen was associated with a lower risk of CVD than other NSAIDs (HR = 0.84, 95% CI: 0.70, 0.96); among the participants with coprescription of aspirin, naproxen was associated with an increased risk of CVD compared with other NSAIDs (HR = 1.42, 95% CI: 1.10, 1.82), and the association of naproxen vs. other NSAIDs with the risk of CVD was significantly modified by coprescription of aspirin (P for interaction < 0.001).

In conclusion, the association of naproxen and ibuprofen with the risk of CVD was significantly modified by coprescription of low-dose aspirin among participants with osteoarthritis. Considering that coprescription of these medications in individuals with osteoarthritis is common, patients and clinicians should be aware of the potential risk of CVD when concurrently taking low-dose aspirin and naproxen or ibuprofen. Other NSAIDs or alternative treatment strategies for pain relief that do not undermine the cardioprotective effect of aspirin should be used when patients are taking low-dose aspirin.

ACKNOWLEDGMENTS

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General Hospital, Harvard Medical School, Boston, Massachusetts, United States (Yuqing Zhang).

This work was funded by the National Natural Science Foundation of China (grants 81930071, U21A20352, and 82072502), the Science and Technology Program of Hunan Province (grant 2019RS2010), the Project Program of National Clinical Research Center for Geriatric Disorders (grants 2020LNJJ03, 2021LNJJ06), and the Natural Science Foundation of Hunan Province (grant 2022JJ20100).

Data from this study are available for purchase from The Health Improvement Network (THIN) (info@the-health-improvement-network.co.uk).

The views expressed in this article are those of the authors and do not reflect those of funding bodies.

Conflict of interest: none declared.

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