Original Contribution

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

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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

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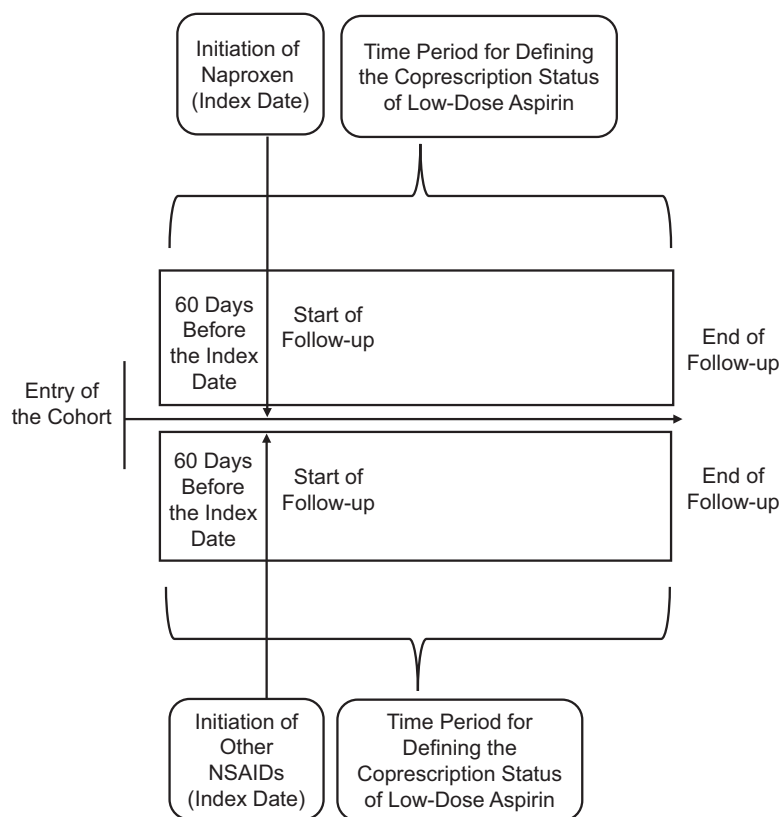
Figure 1. Design of the present study in The Health Improvement Network database, United Kingdom, 2000–2019. NSAID, nonsteroidal antiinflammatory drug.

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.
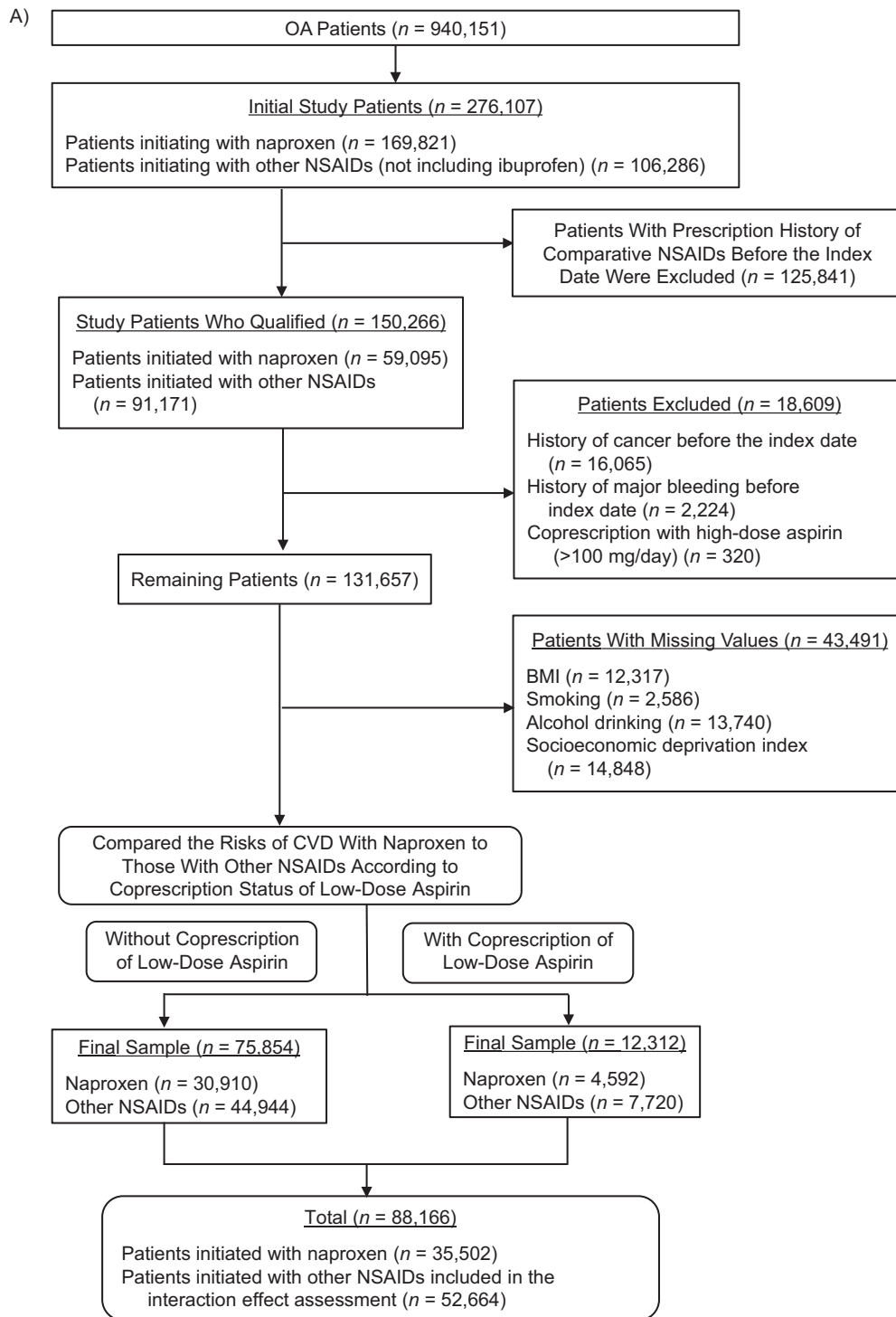
A)

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OA Patients (n = 940,151)
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Initial Study Patients (n = 276,107)

Patients initiating with naproxen (n = 169,821)
Patients initiating with other NSAIDs (not including ibuprofen) (n = 106,286)
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Patients With Prescription History of
Comparative NSAIDs Before the Index
Date Were Excluded (n = 125,841)
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Study Patients Who Qualified (n = 150,266)

Patients initiated with naproxen (n = 59,095)
Patients initiated with other NSAIDs
    (n = 91,171)
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Patients Excluded (n = 18,609)

History of cancer before the index date
    (n = 16,065)
History of major bleeding before
    index date (n = 2,224)
Coprescription with high-dose aspirin
    (>100 mg/day) (n = 320)
```

```
Remaining Patients (n = 131,657)
```

```
Patients With Missing Values (n = 43,491)

BMI (n = 12,317)
Smoking (n = 2,586)
Alcohol drinking (n = 13,740)
Socioeconomic deprivation index
    (n = 14,848)
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Compared the Risks of CVD With Naproxen to
Those With Other NSAIDs According to
Coprescription Status of Low-Dose Aspirin
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Without Coprescription
of Low-Dose Aspirin
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With Coprescription of
Low-Dose Aspirin
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Final Sample (n = 75,854)

Naproxen (n = 30,910)
Other NSAIDs (n = 44,944)
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Final Sample (n = 12,312)

Naproxen (n = 4,592)
Other NSAIDs (n = 7,720)
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Total (n = 88,166)

Patients initiated with naproxen (n = 35,502)
Patients initiated with other NSAIDs included in the
    interaction effect assessment (n = 52,664)
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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) × 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
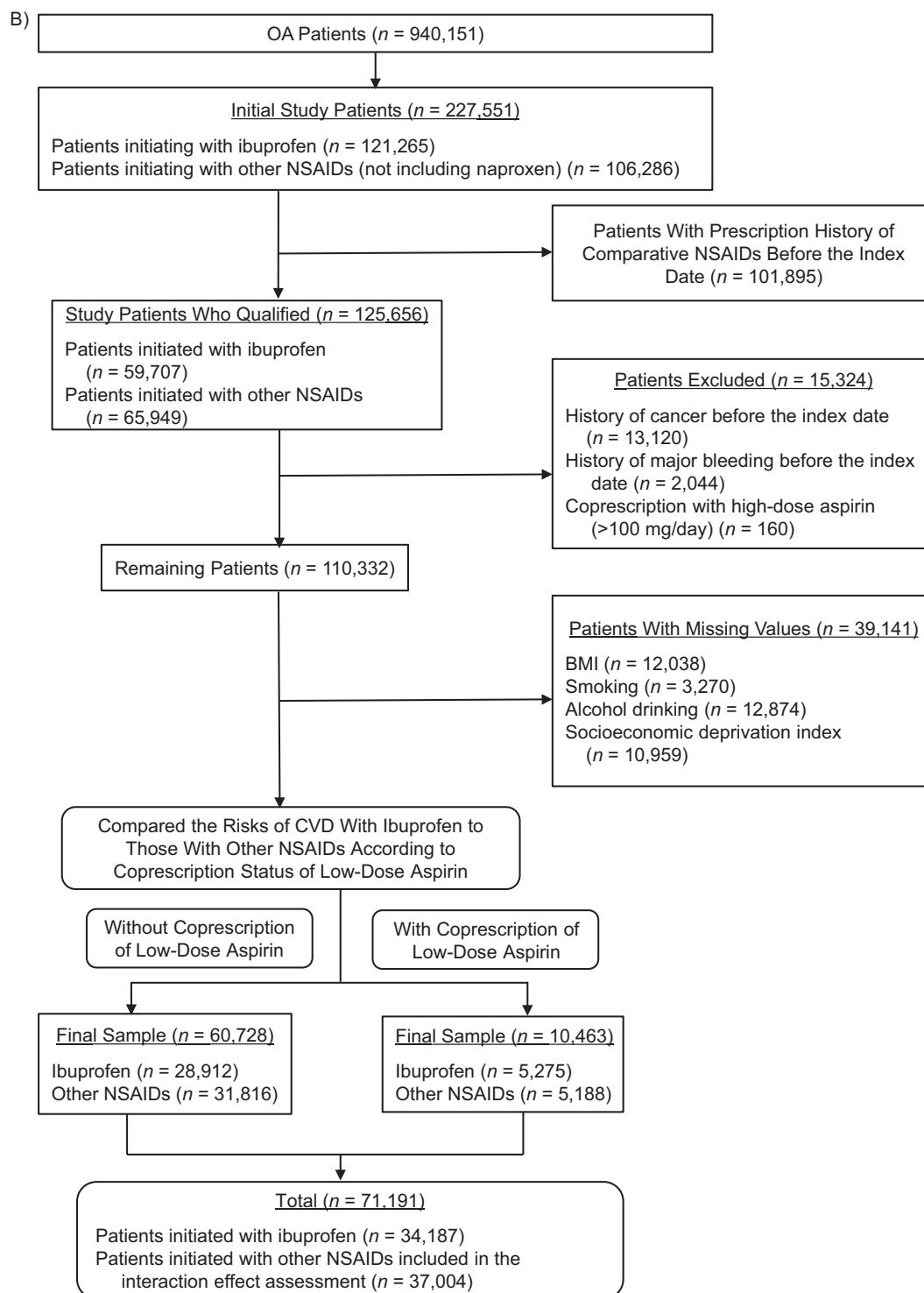
Figure 2. Selection process of included patients with osteoarthritis (OA) initiating naproxen or other nonsteroidal antiinflammatory drugs (NSAIDs) (A) and patients with OA initiating ibuprofen or other NSAIDs (B) in The Health Improvement Network database, United Kingdom, 2000–2019. BMI, body mass index; 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] (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
Demographic												
Age, years	64.8 (10.8)[c]	63.7 (11.0)[c]	0.105	64.1 (10.8)[c]	64.1 (11.0)[c]	0.006	71.6 (9.2)[c]	71.2 (9.4)[c]	0.047	71.2 (9.2)[c]	71.7 (8.9)[c]	0.057
Socioeconomic deprivation index[d]	2.6 (1.3)[c]	2.6 (1.3)[c]	0.011	2.6 (1.3)[c]	2.6 (1.3)[c]	<0.001	2.8 (1.4)[c]	2.8 (1.4)[c]	0.004	2.8 (1.3)[c]	2.9 (1.4)[c]	0.060
Female sex	60.6	58.9	0.033	59.6	59.6	0.001	50.7	51.0	0.006	50.8	51.1	0.018
OA duration, years	7.3 (7.3)[c]	6.2 (7.0)[c]	0.144	6.7 (7.1)[c]	6.6 (7.1)[c]	0.002	8.5 (8.0)[c]	7.7 (7.9)[c]	0.102	7.9 (7.9)[c]	8.7 (8.1)[c]	0.096
BMI[e]	28.9 (5.8)[c]	28.2 (5.5)[c]	0.118	28.5 (5.6)[c]	28.5 (5.7)[c]	0.005	29.8 (5.9)[c]	28.9 (5.5)[c]	0.149	29.2 (5.5)[c]	29.4 (5.3)[c]	0.038
Lifestyle												
Drinking			0.066			0.010			0.033			0.055
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			0.100			0.006			0.054			0.095
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	
Comorbidity												
Myocardial infarction	3.7	4.4	0.045	3.1	3.0	0.005	7.2	6.1	0.031	6.4	6.3	0.004
Stroke	1.4	1.4	0.003	1.4	1.3	0.010	3.0	2.6	0.014	2.1	2.2	0.007
Heart failure	1.2	1.5	0.028	1.4	1.4	0.001	2.0	2.2	0.011	2.1	2.1	0.003
Hypertension	39.5	33.9	0.117	36.3	36.1	0.004	69.6	64.9	0.102	66.6	64.8	0.038
Diabetes	12.0	7.7	0.144	9.5	9.6	0.003	29.2	24.7	0.103	26.1	22.7	0.079
Hyperlipidemia	14.4	10.1	0.131	12.0	12.1	0.005	26.6	24.3	0.052	25.2	25.4	0.005
Liver disease	2.4	1.4	0.072	1.8	2.0	0.014	2.7	1.9	0.051	2.6	1.8	0.052
Chronic kidney disease	6.6	3.1	0.163	4.5	4.4	0.003	16.8	8.6	0.248	11.8	12.1	0.010

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
Medication												
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	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
Antihypertensive medicine	49.4	43.7	0.114	46.0	46.1	0.003	89.3	85.4	0.118	86.4	88.7	0.070
Antidiabetic medicine	8.4	5.5	0.113	6.6	6.6	0.001	22.7	18.7	0.099	20.0	17.5	0.064
Calcium channel blockers	23.5	17.5	0.148	19.9	19.8	0.002	49.8	44.9	0.098	46.5	51.1	0.092
PPIs	59.9	30.2	0.625	42.1	42.3	0.003	70.6	42.7	0.587	53.2	57.7	0.091
Angiotensin receptor blocker	10.4	6.4	0.147	8.1	8.1	0.001	21.2	15.6	0.144	17.1	18.5	0.035
Loop diuretics	9.8	9.6	0.010	9.7	9.7	0.002	24.3	24.0	0.008	23.0	23.3	0.008
Glucocorticoids	17.7	11.8	0.165	14.2	14.2	0.001	22.0	15.7	0.161	18.2	18.5	0.009
Estrogen	22.3	19.5	0.068	20.7	20.6	0.002	15.2	12	0.095	13.6	14.0	0.010
Insulin	1.9	1.2	0.053	1.5	1.4	0.003	6.0	5.0	0.045	4.9	4.5	0.021
Anticoagulant	3.5	3.0	0.028	3.1	3.2	0.002	4.9	4.7	0.009	5.0	4.0	0.049
Antiplatelet	3.3	2.0	0.082	2.4	2.5	0.004	13.2	6.7	0.219	9.1	10.8	0.063
Nitrates	5.9	6.0	0.002	5.9	5.9	0.003	33.6	31.0	0.057	32.0	33.2	0.026
Health-Care Utilization[f]												
Hospitalizations	0.3 (0.8)[c]	0.2 (0.7)[c]	0.160	0.2 (0.7)[c]	0.2 (0.7)[c]	0.002	0.4 (1.0)[c]	0.3 (0.9)[c]	0.116	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	5.4 (5.0)[c]	5.4 (5.4)[c]	0.002	7.4 (6.5)[c]	6.9 (6.6)[c]	0.073	7.1 (6.4)[c]	7.3 (6.2)[c]	0.025
Specialist referrals	0.6 (1.0)[c]	0.4 (0.8)[c]	0.283	0.5 (0.9)[c]	0.5 (0.9)[c]	0.006	0.7 (1.2)[c]	0.4 (0.9)[c]	0.271	0.5 (1.0)[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, dexketoprofen, diflunisal, etodolac, fenbufen, flurbiprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, sulindac, and tiaprofenic acid.
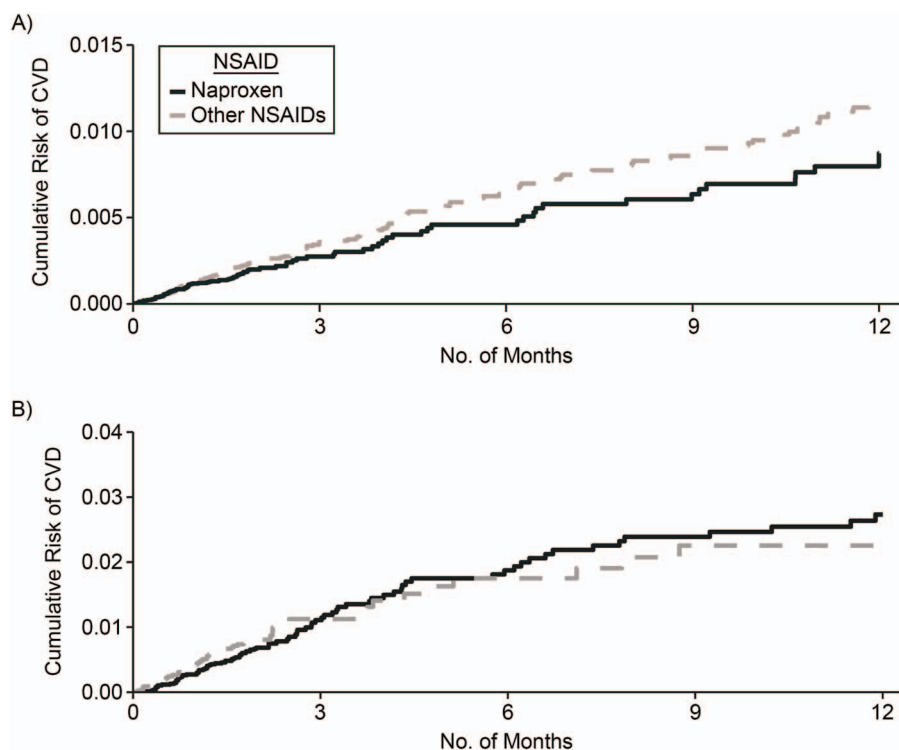[c] Values are expressed as mean (standard deviation).
[d] The socioeconomic deprivation index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).
[e] Weight (kg)/height (m)[2].
[f] Frequency during the past 1 year.

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 Cegedim 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
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 | | | 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
Demographic												
Age, years	66.6 (10.8)[c]	62.8 (10.9)[c]	0.350	64.6 (11.0)[c]	64.7 (11.2)[c]	0.002	72.4 (9.4)[c]	70.9 (9.5)[c]	0.165	71.7 (9.5)[c]	71.6 (9.4)[c]	0.006
Socioeconomic deprivation index[d]	2.7 (1.3)[c]	2.6 (1.3)[c]	0.060	2.6 (1.3)[c]	2.6 (1.3)[c]	0.003	2.8 (1.4)[c]	2.8 (1.3)[c]	0.007	2.8 (1.4)[c]	2.8 (1.3)[c]	0.003
Female sex	62.7	57.6	0.105	60.1	60.0	0.002	54.7	49.6	0.102	52.1	51.7	0.007
OA duration, years	6.8 (7.5)[c]	6.3 (7.1)[c]	0.071	6.5 (7.3)[c]	6.5 (7.3)[c]	0.001	7.9 (8.2)[c]	7.9 (8.2)[c]	0.001	8.0 (8.3)[c]	7.8 (8.0)[c]	0.014
BMI[e]	28.2 (5.6)[c]	28.3 (5.6)[c]	0.024	28.3 (5.6)[c]	28.2 (5.6)[c]	0.005	28.7 (5.5)[c]	29.0 (5.6)[c]	0.062	28.9 (5.6)[c]	28.8 (5.5)[c]	0.004
Lifestyle												
Drinking			0.074			0.002			0.019			0.005
None	21.5	19.0		20.3	20.4		24.8	24.2		24.3	24.5	
Past	2.5	2.0		2.3	2.3		3.2	3.1		3.2	3.1	
Current	76.0	79.0		77.4	77.3		72.0	72.7		72.5	72.4	
Smoking			0.059			0.001			0.046			0.004
None	55.5	54.4		54.9	54.9		50.2	47.9		49.4	49.2	
Past	28.6	27.5		28.0	28.0		36.6	38.1		37.4	37.4	
Current	15.9	18.1		17.1	17.1		13.2	14.0		13.2	13.4	
Comorbidity												
Myocardial infarction	4.2	4.3	0.005	4.3	4.2	0.003	4.2	5.0	0.021	4.5	4.6	0.003
Stroke	2.5	2.3	0.019	2.4	2.4	0.003	2.1	1.5	0.024	2.8	2.8	0.001
Heart failure	2.5	2.5	<0.001	2.5	2.5	0.001	2.7	2.8	0.005	2.7	2.6	0.003
Hypertension	39.0	33.0	0.125	36.1	36.0	0.001	65.6	64.9	0.014	65.2	65.4	0.005
Diabetes	10.2	8.0	0.077	9.1	9.1	<0.001	25.0	24.7	0.005	24.7	24.5	0.006
Hyperlipidemia	11.9	10.1	0.057	11.1	11.1	0.002	24.4	24.4	<0.001	24.1	24.0	0.003
Liver disease	1.9	1.4	0.042	1.7	1.7	<0.001	1.9	2.1	0.015	1.8	2.0	0.014
Chronic kidney disease	5.0	3.2	0.092	4.1	4.1	<0.001	11.3	9.1	0.075	9.9	9.7	0.007

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
Medication												
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	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
Antihypertensive medicine	48.1	41.5	0.133	44.9	44.9	<0.001	86.6	85.1	0.042	85.8	85.8	0.001
Antidiabetic medicine	7.1	5.5	0.065	6.4	6.3	0.001	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	<0.001	46.0	43.6	0.048	44.8	44.9	0.004
PPIs	40.5	31.3	0.191	35.8	35.8	0.001	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	0.004	16.7	15.9	0.023	16.0	15.8	0.006
Loop diuretics	10.3	8.6	0.059	9.5	9.5	0.002	24.5	23.1	0.034	23.5	23.4	0.003
Glucocorticoids	13.9	10.8	0.093	12.4	12.3	0.002	15.7	14.6	0.032	15.0	15.3	0.008
Estrogen	18.5	17.4	0.029	17.9	18.0	0.001	11.2	10.2	0.032	10.7	10.7	0.001
Insulin	1.6	1.2	0.034	1.4	1.4	<0.001	5.2	5.1	0.007	5.0	4.9	0.006
Anticoagulant	3.1	3.0	0.011	3.1	3.1	0.002	4.4	4.3	0.005	4.2	4.3	0.004
Antiplatelet	2.6	2.1	0.038	2.4	2.3	0.003	8.8	7.2	0.059	7.9	7.6	0.012
Nitrates	6.2	5.3	0.038	5.8	5.8	0.001	31.2	29.2	0.043	30.2	30.1	0.002
Health-Care Utilization[f]												
Hospitalizations	0.3 (0.8)[c]	0.2 (0.7)[c]	0.098	0.2 (0.7)[c]	0.2 (0.7)[c]	0.002	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]	<0.001	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]	<0.001	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.
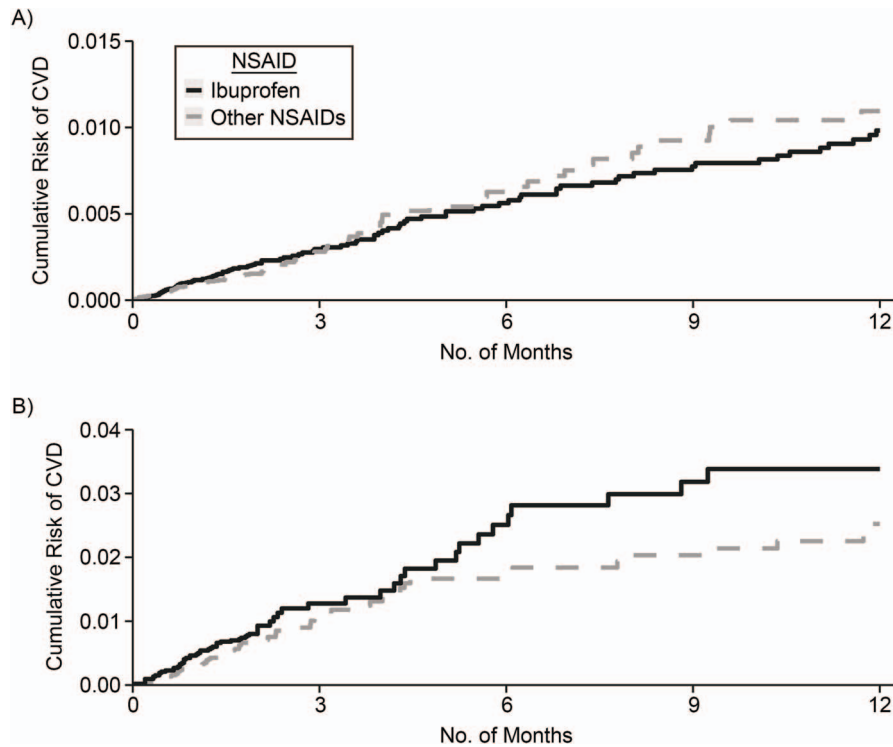
[a] Values are shown as %.

[b] Other NSAIDs included the following drugs: diclofenac, meloxicam, paracetamol, piroxicam, celecoxib, etoricoxib, rofecoxib, valdecoxib, lumiracoxib, tenoxicam, aceclofenac, acemetacin, azapropazone, benzydamine, dexketoprofen, 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
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
Other NSAIDs	31,816	117	0.33	11.2	0	Referent	1.00	Referent	1.00	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
Other NSAIDs	5,188	60	0.35	32.9	0	Referent	1.00	Referent	1.00	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

REFERENCES

1. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol*. 2020;72(2):220–233.
2. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. *J Am Acad Orthop Surg*. 2022;30(9):e721–e729.
3. Angiolillo DJ, Weisman SM. Clinical pharmacology and cardiovascular safety of naproxen. *Am J Cardiovasc Drugs*. 2017;17(2):97–107.
4. Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA*. 2019;321(10):969–982.
5. Zeng C, Zhang W, Doherty M, et al. Initial analgesic prescriptions for osteoarthritis in the United Kingdom, 2000–2016. *Rheumatology (Oxford)*. 2021;60(1):147–159.
6. Rhee TG, Kumar M, Ross JS. Age-related trajectories of cardiovascular risk and use of aspirin and statin among U.S. adults aged 50 or older, 2011–2018. *J Am Geriatr Soc*. 2021; 69(5):1272–1282.
7. Swain S, Sarmanova A, Coupland C, et al. Comorbidities in osteoarthritis: a systematic review and meta-analysis of observational studies. *Arthritis Care Res (Hoboken)*. 2020; 72(7):991–1000.
8. Patrono C. Fifty years with aspirin and platelets. *Br J Pharmacol*. 2022.
9. Loll PJ, Picot D, Garavito RM. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase. *Nat Struct Biol*. 1995;2(8): 637–643.
10. Russo NW, Petrucci G, Rocca B. Aspirin, stroke and drug-drug interactions. *Vascul Pharmacol*. 2016;87:14–22.
11. Patrono C, Baigent C. Role of aspirin in primary prevention of cardiovascular disease. *Nat Rev Cardiol*. 2019;16(11): 675–686.
12. Gurbel P, Tantry U, Weisman S. A narrative review of the cardiovascular risks associated with concomitant aspirin and NSAID use. *J Thromb Thrombolysis*. 2019;47(1):16–30.
13. Meek IL, Van de Laar MA, H EV. Non-steroidal anti-inflammatory drugs: an overview of cardiovascular risks. *Pharmaceuticals (Basel)*. 2010;3(7):2146–2162.
14. Meek IL, Vonkeman HE, Kasemier J, et al. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. *Eur J Clin Pharmacol*. 2013;69(3):365–371.
15. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med*. 2001;345(25):1809–1817.
16. Gengo FM, Rubin L, Robson M, et al. Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. *J Clin Pharmacol*. 2008;48(1):117–122.
17. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet*. 2003;361(9357): 573–574.
18. Schuijt MP, Huntjens-Fleuren HW, de Metz M. The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. *Br J Pharmacol*. 2009;157(6):931–934.
19. Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. *Clin Pharmacol Ther*. 2006;80(3):264–274.
20. Anzellotti P, Capone ML, Jeyam A, et al. Low-dose naproxen interferes with the antiplatelet effects of aspirin in healthy subjects: recommendations to minimize the functional consequences. *Arthritis Rheum*. 2011;63(3):850–859.
21. Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol*. 2005;45(8): 1295–1301.
22. Li X, Fries S, Li R, et al. Differential impairment of aspirin-dependent platelet cyclooxygenase acetylation by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci U S A*. 2014;111(47):16830–16835.
23. Gladding PA, Webster MW, Farrell HB, et al. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. *Am J Cardiol*. 2008;101(7):1060–1063.
24. Chisholm J. The Read clinical classification. *BMJ*. 1990; 300(6732):1092.
25. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457.
26. Zeng C, Bennell K, Yang Z, et al. Risk of venous thromboembolism in knee, hip and hand osteoarthritis: a general population-based cohort study. *Ann Rheum Dis*. 2020;79(12):1616–1624.
27. Lu N, Misra D, Neogi T, et al. Total joint arthroplasty and the risk of myocardial infarction: a general population, propensity score-matched cohort study. *Arthritis Rheumatol*. 2015;67(10):2771–2779.
28. Neogi T, Li S, Peloquin C, et al. Effect of bisphosphonates on knee replacement surgery. *Ann Rheum Dis*. 2018;77(1): 92–97.
29. Wei J, Neogi T, Terkeltaub R, et al. Thiazide diuretics and risk of knee replacement surgery among patients with knee osteoarthritis: a general population-based cohort study. *Osteoarthr Cartil*. 2019;27(10):1454–1461.
30. Wei J, Wood MJ, Dubreuil M, et al. Association of tramadol with risk of myocardial infarction among patients with osteoarthritis. *Osteoarthr Cartil*. 2020;28(2):137–145.
31. Lix L, Yogendran M, Burchill C, et al. *Defining and Validating Chronic Diseases: an Administrative Data Approach*. Winnipeg, Manitoba: Manitoba Centre for Health Policy; 2006. http://www.umanitoba.ca/centres/mchp/reports.htm. Accessed November 9, 2020.

32. Fardet L, Petersen I, Nazareth I. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. *BMJ*. 2012;345:e4928.

33. Ruigómez A, Martín-Merino E, Rodríguez LA. Validation of ischemic cerebrovascular diagnoses in The Health Improvement Network (THIN). *Pharmacoepidemiol Drug Saf*. 2010;19(6):579–585.

34. Gaist D, Wallander MA, Gonzalez-Perez A, et al. Incidence of hemorrhagic stroke in the general population: validation of data from The Health Improvement Network. *Pharmacoepidemiol Drug Saf*. 2013;22(2):176–182.

35. Maru S, Koch GG, Stender M, et al. Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K.

primary care setting. *Diabetes Care*. 2005;28(1):20–26.

36. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601–609.

37. Dunkler D, Ploner M, Schemper M. Weighted Cox regression using the R package coxphw. *J Stat Softw*. 2018;84(1):1–26.

38. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest*. 1982;69(6):1366–1372.

39. Patrono C, Ciabattoni G, Patrignani P, et al. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation*. 1985;72(6):1177–1184.