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Association of Tramadol with Risk of Myocardial Infarction Among Patients with Osteoarthritis

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Author Contributions

Drs Zhang and Lei had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lei and Zhang are joint corresponding authors. All authors have read, provided critical feedback on intellectual content and approved the final manuscript. Concept and design: Wei, Lei, Zhang. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Wei, Lei, Zhang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Wei, Lu, Zhang. Obtained funding: Wei, Dubreuil, LaRochelle, Zeng, Choi, Lei, Zhang. Administrative, technical, or material support: Wei, Zeng, Choi, Lei, Zhang. Supervision: Lei, Zhang.

Conflict of Interest Disclosures

The authors have declared that no competing interests exist.

Ethical approval

The Institutional Review Board approved this study, with waiver of informed consent.

Scientific approval

The protocol of this study was approved by the THIN Scientific Review Committee (18THIN078).

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Abstract

Objective—Tramadol has been widely used among patients with osteoarthritis (OA); however, there is paucity of information on its cardiovascular risk. We aimed to examine the association of tramadol with risk of myocardial infarction (MI) among patients with OA.

Design—Among OA patients aged 50 to 90 years without history of MI, cancer, or opioid use disorder in The Health Improvement Network database in the United Kingdom (2000-2016), three sequential propensity-score matched cohort studies were assembled, i.e., (1) patients who initiated tramadol or naproxen (negative comparator); (2) patients who initiated tramadol or diclofenac (positive comparator); and (3) patients who initiated tramadol or codeine (a commonly used weak opioid). The outcome was incident MI over six-months.

Results—Among tramadol and naproxen initiators (n=33,024 in each cohort), 77 (4.8/1000 person-years) and 46 (2.8/1000 person-years) incident MI occurred, respectively. The rate difference (RD) and hazard ratios (HR) for incident MI with tramadol initiation were 1.9 (95% confidence interval [CI] 0.6 to 2.3)/1000 person-years and 1.68 (95% CI 1.16 to 2.41) relative to naproxen initiation, respectively. Among tramadol and diclofenac initiators (n=18,662 in each cohort), 58 (6.4/1000 person-years) and 47 (5.1/1000 person-years) incident MIs occurred, respectively. The corresponding RD and HR for incident MI were 1.2 (95%CI −2.1 to 14.1)/1000 person-years and 1.24 (95%CI 0.84 to 1.82), respectively. Among tramadol and codeine initiators (n=42,722 in each cohort), 127 (6.1/1000 person-years) and 103 (5.0/1000 person-years) incident MI occurred, respectively, and the corresponding RD and HR were 1.1 (95%CI:−0.3 to 2.5)/1000 person-years and 1.23 (95%CI:0.95 to 1.60), respectively.

Conclusions—In this population-based cohort of patients with OA, the six-month risk of MI among initiators of tramadol was higher than that of naproxen, but comparable to, if not lower than, those of diclofenac or codeine.

Keywords

Osteoarthritis; Tramadol; Myocardial Infarction; Cohort

INTRODUCTION

Osteoarthritis (OA) is a leading cause of pain, disability, and socioeconomic cost worldwide[1]. To date, there is no effective treatment available that can halt OA progression, and the main goal of clinical management remains pain control with treatments such as oral non-steroidal anti-inflammatory drugs (NSAIDs)[2]. However, the safety of NSAIDs, particularly cardiovascular risk, has raised a great concern. Of the commonly used NSAIDs, diclofenac had the highest, whereas naproxen had the lowest risk of cardiovascular risk (mainly myocardial infarction [MI])[3–9].

Tramadol, a weak opioid agonist, is a commonly used pain relief medication and is currently available in more than 100 countries[10]. Owing to its perceived lower risk of serious cardiovascular adverse effects than NSAIDs[11–13], as well as a lower risk of addiction and respiratory depression compared with traditional opioids[14, 15], tramadol has been considered a reasonable option for treatment of many pain conditions, e.g., OA. The use of tramadol

among patients with OA has been increasing rapidly around the world[16, 17]. For example, the use of tramadol for management of knee OA doubled from 5% in 2003 to 10% in 2009 in the United States[16], and the prevalence of patients with OA with prescriptions for tramadol increased from 3.4% to 9.8% between 2000 and 2015 in the United Kingdom (UK)[17].

Tramadol inhibits the reuptake of serotonin[18, 19], a crucial mediator of platelet aggregation in vascular homeostasis and thrombosis[20]. Tramadol has been frequently associated with the serotonin syndrome but codeine has not [21]. In addition, tramadol has been showed to increase the free plasma concentration of serotonin[22], and an elevated plasma serotonin is a common feature of cardiovascular disease often associated with enhanced platelet activation and thrombosis[23]. To date, there is paucity of information on the risk of cardiovascular diseases with tramadol use[24–27]. Results from two randomized controlled trials (tramadol versus nonuse or placebo) were inconclusive owing to the relatively short follow-up time (ranging from 1 to 42 days) and small number of participants (ranging from 31 to 64 in each arm)[24, 25]. Of two observational studies that compared tramadol with either non-users or users of other opioids, neither found that tramadol use increased risk of cardiovascular disease[26, 27]. Nevertheless, our recent population-based cohort study of patients with OA reported a higher mortality rate from cardiovascular diseases among initiators of tramadol than initiators of several commonly used NSAIDs (e.g., naproxen and diclofenac). However, because of relatively small number of deaths from each specific cause, most studies were lack of power to detect clinically meaningful association[17].

To address this knowledge gap, we conducted three population-based cohort studies among patients with OA to compare the risk of incident MI, a major cardiovascular disease and a leading cause of morbidity and mortality worldwide, among initiators of tramadol with initiators of two commonly used NSAIDs, i.e., naproxen (negative comparator)[3–8] and diclofenac (positive comparator)[4–9], respectively, as well as with initiators of codeine, one of the most commonly used weak opioids. With this design, the potential selection bias and indication bias, if it occurred, could be minimized.

METHODS

Data Source

The Health Improvement Network (THIN) is an electronic medical record database derived from the records of general practitioners (GPs) in the UK. THIN contains health information on approximately 17 million patients from 770 general practices in the UK. Health care information is recorded on site at each practice and includes socio-demographics, anthropometrics, lifestyle factors, details from GP visits, diagnoses from specialists' referrals and hospital admissions, as well as results of laboratory tests. The Read classification system is used to code specific diagnoses[28], and a drug dictionary based on data from the Multilex classification system is used to code drugs[29]. THIN is a population-based cohort representative of the UK general population since individuals in the UK are required to be registered with a GP, regardless of health status. THIN data reflect a routine medical practice environment and have been shown to be valid for use in clinical and epidemiological research studies[30].

Study Design and Cohort Definition

Eligible participants consisted of those who were aged 50 to 90 years old with history of OA based on Read codes between January 2000 and December 2016 who had not been prescribed tramadol or its active comparator (naproxen, diclofenac, or codeine) one year before entering the study cohort. Participants with history of MI, cancer, or opioid use disorder before study entry were ineligible for the current analysis (Codes lists for OA, MI, tramadol, naproxen, diclofenac and codeine were available in Supplement).

We conducted three sequential propensity-score matched cohort studies to compare the risk of incident MI among tramadol initiators with that among initiators of naproxen, diclofenac, or codeine, respectively. For example, to compare the risk of incident MI between tramadol initiators and naproxen initiators, eligible participants were required to be prescribed neither tramadol nor naproxen one year before entering the study. The date of initiation of tramadol and naproxen was considered as the index date for the corresponding participant. We divided calendar time into 17 one-year blocks from January 2000 to December 2016. Within each time block propensity-score for tramadol initiation was calculated for each participant using logistic regression. The variables included in the model were sociodemographic factors (i.e., age at index date, sex, Townsend Deprivation Index[31]), body mass index (BMI), lifestyle factors (i.e., alcohol use, smoking status), OA site, OA duration, comorbidities prior to the index date, medication use prior to the index date, and healthcare utilization during the past one year before the index date (see Table 1). Within each time block, each tramadol initiator was matched to one naproxen initiator using a greedy matching algorithm. We took the same approach to assemble another two cohort studies, i.e., initiators of tramadol vs. initiators of diclofenac, and initiators of tramadol vs. initiators of codeine.

Assessment of Outcome

The outcome was incident MI (including fatal and non-fatal MI) within the first six months after initiation of tramadol or its comparative medication[26]. MI was identified using Read codes. Previous studies have used this approach to define MI[8,32,33] and demonstrated a high confirmation rate (i.e., 95%)[32].

Statistical Analysis

The baseline characteristics of the tramadol cohort were compared with the naproxen, diclofenac, and codeine cohorts, respectively. For each subject, person-years of follow-up were calculated as the amount of time from the index date to the first of the following events: incident MI, disenrollment from a GP practice participating in THIN, death, or the end of six month follow-up period. We calculated the risk of incident MI for each cohort and plotted cumulative incidence curves while accounting for competing risk of death[34]. The absolute rate difference (RD) in MI was estimated between the tramadol cohort with each of the comparison cohorts using the following formula: RD = rate (tramadol) - rate (comparison); $SE_{RD} = \sqrt{\frac{a}{PT_a^2} + \frac{b}{PT_b^2}}$ where a and b refer to the number of events in each cohort, and PT_a and PT_b refer to the total person-time accumulated in each cohort, and 95% CI: RD ± 1.96*SE_{RD}. We applied cause-specific Cox proportional hazard models adjusting for propensity score to obtain the hazard ratio (HR) of incident MI for the tramadol cohort

related to each of its comparator cohorts accounting for competing risk of death[34]. We used the "COVSANDWICH" statement in the PROC PHREG procedure in SAS to account for the correlation in the matched pair[35]. We tested the proportional hazards assumption by using the Kolmogorov supremum test[36].

Four sensitivity analyses were performed to assess the robustness of our study findings. First, we conducted an "as-treated" analysis to account for non-adherence of medications under investigation. Specifically, we censored the follow-up at the time when participants either changed (e.g., switching from tramadol to naproxen or vice versa, when comparing tramadol with naproxen) or discontinued (i.e., no prescription refill for the respective class of medication with a period of over 60 days[37]) their initiated medication. Second, we performed an analysis among participants whose OA was diagnosed during the study period (i.e., incident OA) to minimize potential misclassification of the duration of OA. Third, since individuals with missing values (i.e., BMI, alcohol use, smoking status, and Townsend Deprivation Index) were not included in our primary analyses, we used a sequential regression method to impute missing values for these four variables based on a set of covariates as predictors. To minimize random error, we imputed five datasets, calculating effect estimates from each imputed dataset, and using PROC MIANALYZE in SAS to combine the results from the five datasets to generate average estimates and their confidence intervals (CIs)[38]. Fourth, since approximately half of the eligible participants were not included in the analysis after propensity-score matching, we also used the conventional covariate adjustment approach, i.e., classic multivariable Cox-proportional hazard model, to test the study hypothesis[39, 40].

All P values were 2-sided and $P < 0.05$ was considered significant for all tests. All statistical analyses were conducted using SAS V9.4.

RESULTS

In total, 796,261 OA patients met our inclusion criteria for the comparison between tramadol and naproxen. Of them 99,609 initiated a tramadol and 85,569 initiated a naproxen, without prescription history of either drug before entering the study. We excluded 33,729 subjects who had history of MI, cancer, or opioid use disorder, and 32,928 subjects who had missing information on BMI, smoking status, alcohol drinking, or Townsend Deprivation Index Score. Of the remaining (n=118,521), 33,024 initiators of tramadol were successfully propensity-score matched to the same number of initiators of naproxen (Figure 1). Similarly, the selection process for the comparison between tramadol and diclofenac or tramadol and codeine are shown in the Supplement.

The baseline characteristics of each propensity-score matched cohort are shown in Table 1. The mean age of participants ranged from 68.3 to 70.1 years, and slightly more than 60% were women. Overall, the characteristics in the propensity-score matched cohorts were well-balanced, with all standardized differences < 0.1.[41]

The risk of incident MI was higher in the tramadol cohort than that in the naproxen cohort (Figure 2A). As shown in Table 2, during the six months follow-up period 77 (4.8 per 1000

person-years) incident MI occurred in the tramadol cohort and 46 (2.8 per 1000 person-years) in the naproxen cohort. The RD for incident MI in the tramadol cohort was 1.9 (95% CI: 0.6 to 3.3) per 1000 person-years, compared with the naproxen cohort. The corresponding HR was 1.68 (95% CI: 1.16 to 2.41). The proportional hazard assumption was not violated (P = 0.25). Sensitivity analyses including the "as-treated" approach, restricting to participants with incident OA, missing data imputation, and the conventional covariate adjustment approach did not change the results materially (Table 2).

The risk of incident MI in the tramadol cohort (6.4 per 1000 person-years) was comparable to, if not lower than that in the diclofenac cohort (5.1 per 1000 person-years) (Figure 2B, Table 3). The RD of incident MI for the tramadol cohort was 1.2 (95% CI: −1.0 to 3.4) per 1000 person-years compared with the diclofenac cohort, and the corresponding HR was 1.24 (95% CI: 0.84 to 1.82). Sensitivity analyses (i.e., "as-treated" approach, restricting to participants with incident OA, missing data imputation, and the conventional covariate adjustment approach) did not change the results materially (Table 3).

Similarly, the risk of incident MI in the tramadol cohort (6.1 per 1000 person-years) was comparable to, if not lower than that in the codeine cohort (5.0 per 1000 person-years) (Figure 2C, Table 4). The RD of incident MI for tramadol was 1.1 (95% CI: −0.3 to 2.5) per 1000 person-years, compared with codeine cohort. The corresponding HR was 1.23 (95% CI: 0.95 to 1.60). The results of sensitivity analyses remained consistent (Table 4).

DISCUSSION

Using data collected from THIN, the six-month risk of incident MI among initiators of tramadol was higher than that of naproxen initiators, but comparable to initiators of diclofenac and codeine, two analgesics that have been associated with an increased risk of cardiovascular adverse effects in the previous studies[4–9, 26]. Our findings were independent of the major confounders and remained consistent in various sensitivity analyses, suggesting that the observed associations were robust.

Comparison with Previous Studies

One large propensity-score matched cohort study using the US Medicare database reported that the incidence rates of composite cardiovascular events (including MI, stroke, heart failure, revascularization, and out-of-hospital cardiac death) over the 180 days follow-up period was slightly lower among tramadol initiators (11 per 100 person-years) than that among codeine initiators (17 per 100 person-years)[26]. The study, however, did not examine the relation of tramadol prescription to individual cardiovascular event (e.g., MI), and some potential confounders (e.g., BMI, smoking, and drinking) were not controlled for in the analyses[26]. Another case-control study conducted among patients with osteoarthritis in Spain did not show a statistically significant association between tramadol use and the risk of acute coronary events (i.e., acute MI or unstable angina) when nonuse served as the referent exposure (odds ratio [OR] = 1.10, 95% CI: 0.93 to 1.29)[27]. However, in the same study the association of naproxen use vs. nonuse with acute coronary events (OR = 1.25, 95% CI: 1.04 to 1.48) was stronger than that of diclofenac use vs. nonuse with acute

coronary events (OR = 1.16, 95% CI: 1.06 to 1.27)[27]; this finding contradicts most previous studies[3–9].

Possible Explanations

Biological mechanisms linking tramadol use to the risk of MI are not well understood. One proposed explanation is that tramadol inhibits the reuptake of serotonin[19], a key factor in the process of platelet aggregation, mediating vascular homeostasis and thrombosis[21]. A previous in vivo study demonstrated that mice selectively deficient in serotonin exhibited reduced risk of thrombosis and thromboembolism[42]. Others have postulated that tramadol use may enhance coagulation of plasma proteins and suppress thrombocyte de-aggregation process[43–46]. Furthermore, tramadol use may induce oxidative stress which has a critical role in the process of atherosclerotic diseases[47–51]. Finally, tramadol use may decrease the expression of inducible nitric oxide synthases and worsen myocardial injury in patients undergoing cardiac surgery[25].

Strengths and Limitations

Several characteristics of our study are noteworthy. We adopted a new-user design to include only initiators of tramadol, naproxen, diclofenac, and codeine. This method minimizes potential selection bias (i.e., immortal bias) introduced if prevalent medication users were included. In addition, the results from various sensitivity analyses were consistent, suggesting robustness of observed associations. Nevertheless, the present findings should be interpreted with caution. First, the hazard ratio generated from imputed data analysis (HR=1.57) was smaller than that from complete data analysis (HR=1.68); however, the difference in these effect estimates is small ([1.68-1.57)]/1.68=6.5%). Nevertheless, as in any observational study we can’t rule out the residual confounding, despite our use of propensity-score matching and several sensitivity analyses. Future studies are needed to verify our findings. Second, physician-ordered prescriptions may not reflect the actual medication use by patients. For instance, patients may not fill prescriptions, may not take the medication once filled, or may not use the medication according to physician’s instruction. As a result, misclassification of the medication use could occur and bias the study findings. However, such bias, if occurred, is likely to be non-differential and would bias the observed associations towards the null.

Clinical Implications

Our findings may have clinical implications. Although our study found tramadol use was associated with an increased risk of MI when compared with naproxen, the effect was relatively modest (RD=1.9/1000 person-years). This study suggests that tramadol may be not as safe as some clinicians have perceived with respect to cardiovascular adverse effects. Considering tramadol prescriptions have been increased rapidly worldwide, especially among patients with OA[16, 17, 52–54] and MI is a leading cause of morbidity and mortality around the world, precautions should be taken when prescribing tramadol to the patients with OA.

CONCLUSION

In this population-based cohort of patients with OA, the six-month risk of MI among initiators of tramadol was higher than that of naproxen, but comparable to, if not lower than risk with diclofenac and codeine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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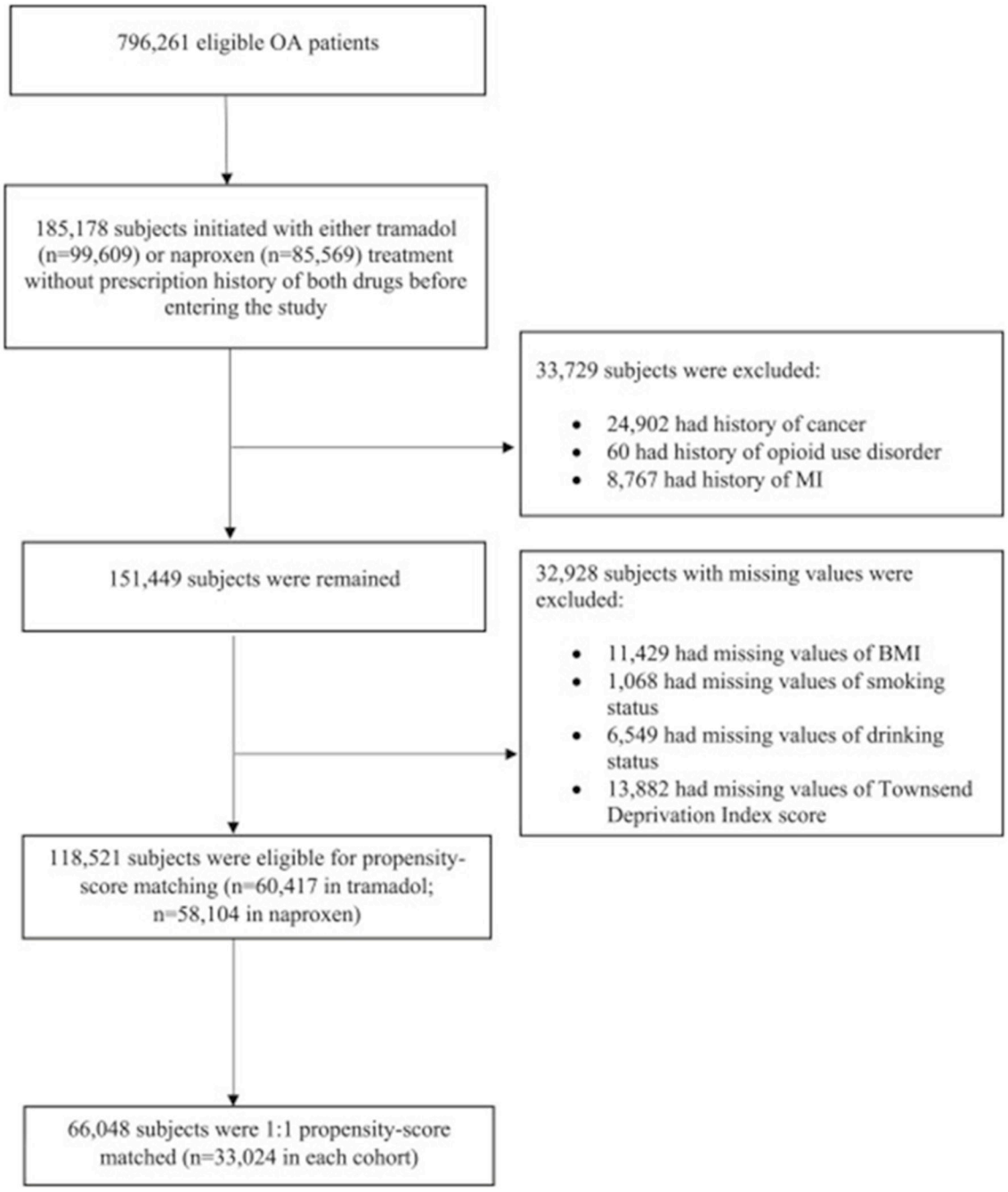

Figure 1. Selection Process of Included Subjects for the Comparison between Tramadol and Naproxen.

OA, osteoarthritis; MI, myocardial infarction; BMI, body mass index.

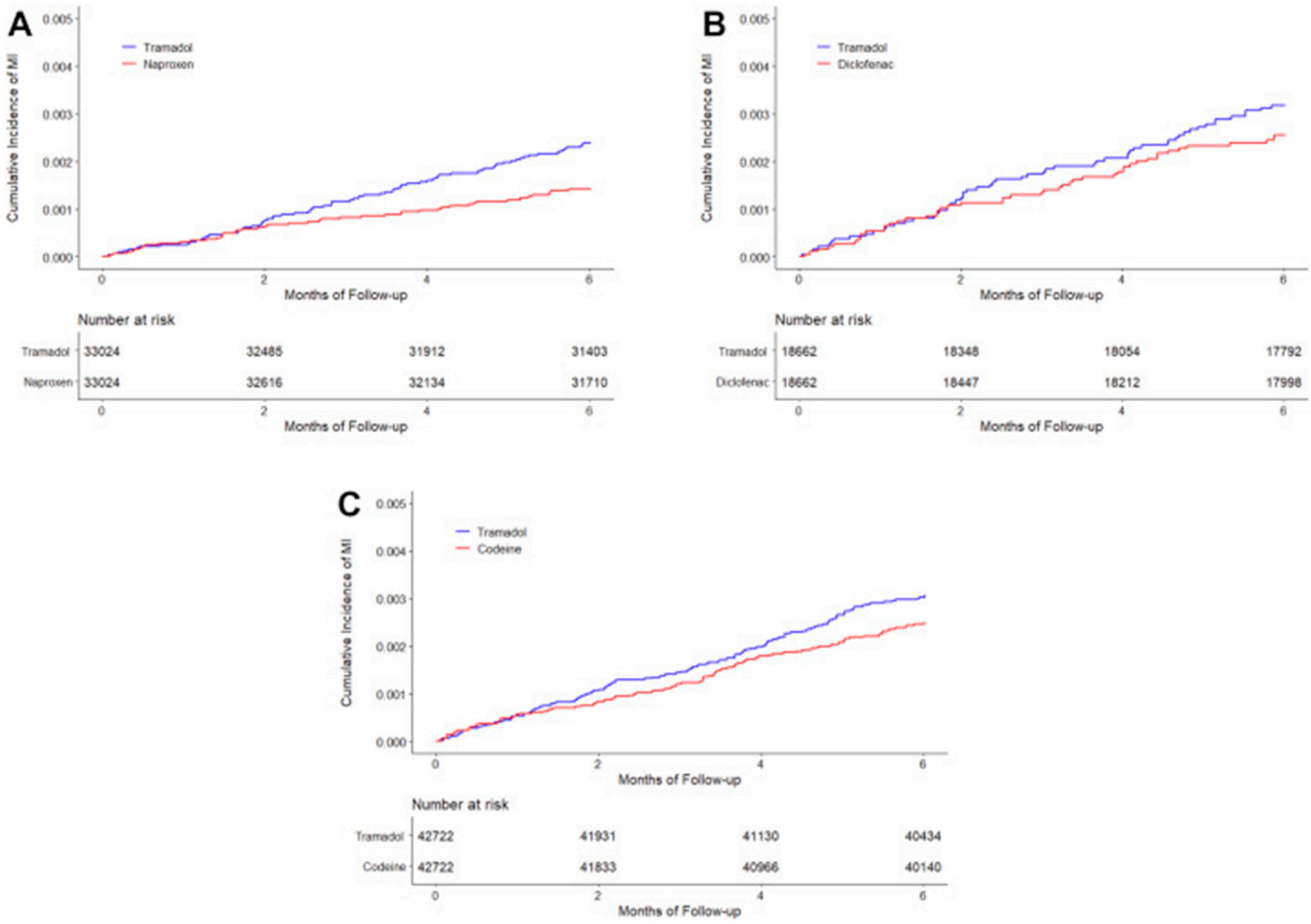

Figure 2. Time to Incident Myocardial Infarction for the Propensity-score Matched Cohorts of Patients with Osteoarthritis and Tramadol Initiation Comparing with Initiation of Naproxen (A), Diclofenac (B), or Codeine (C).

A, risk of MI for tramadol and naproxen were 2.4/1000 and 1.4/1000 over six-month follow-up, respectively, with corresponding risk difference of 1.0/1000 (95%CI: 0.3/1000 to 1.6/1000) over six months; B, risk of MI for tramadol and diclofenac were 3.1/1000 and 2.5/1000 over six-month follow-up, respectively, with corresponding risk difference of 0.6/1000 (95%CI: −0.2/1000 to 1.4/1000) over six months; C, risk of MI for tramadol and codeine were 3.0/1000 and 2.5/1000 over six-month follow-up , respectively, with corresponding risk difference of 0.6/1000 (95%CI: −0.2/1000 to 1.4/1000) over six months.

Table 1.

Basic Characteristics of Propensity-score Matched Patients with Osteoarthritis

	Tramadol vs. Naproxen			Tramadol vs. Diclofenac			Tramadol vs. Codeine		
	Tramadol (n=33,024)	**Naproxen (n=33,024)**	**Standardized differences**	**Tramadol (n=18,662)**	**Diclofenac (n=18,662)**	**Standardized differences**	**Tramadol (n=42,722)**	**Codeine (n=42,722)**	**Standardized differences**
Demographics									
Age, mean (SD), y	68.3 (9.6)	68.4 (9.4)	0.010	69.5 (9.7)	69.7 (9.5)	0.023	70.1 (9.6)	70.1 (9.7)	0.002
Socioeconomic deprivation index, mean (SD)[†]	2.7 (1.4)	2.7 (1.4)	0.007	2.8 (1.4)	2.9 (1.4)	0.008	2.7 (1.4)	2.7 (1.3)	0.001
Female (%)	61.8	62.4	0.013	64.5	65.5	0.021	64.0	64.2	0.004
BMI, mean (SD), kg/m^2	29.0 (5.8)	29.0 (5.7)	0.005	28.6 (5.7)	28.7 (5.6)	0.005	28.6 (5.6)	28.6 (5.5)	<0.001
OA site (%)									
Knee OA	25.0	25.0	0.001	22.1	22.3	0.005	25.8	25.6	0.005
Hip OA	12.9	12.9	0.001	12.5	12.7	0.006	13.4	13.3	0.004
Hand OA	5.3	5.0	0.015	4.3	4.1	0.011	5.4	5.4	0.001
OA duration, mean (SD), y	7.8 (7.3)	7.9 (7.3)	0.002	7.6 (7.4)	7.6 (7.6)	0.001	8.3 (7.6)	8.3 (7.4)	0.002
Lifestyle factors									
Alcohol (%)			0.006			0.005			0.007
None	20.3	20.5		23.2	23.4		21.6	21.4	
Past	2.7	2.8		2.5	2.5		2.9	2.9	
Current	76.9	76.7		74.2	74.1		75.4	75.7	
Smoking (%)			0.007			0.009			0.004
None	53.1	52.8		53.5	53.3		54.7	54.5	
Past	32.6	32.8		31.3	31.2		32.7	32.9	
Current	14.2	14.4		15.1	15.5		12.6	12.5	
Comorbidity (%)									
Peptic ulcer	6.3	6.1	0.008	8.7	8.5	0.009	7.4	7.5	0.002
Chronic kidney disease	10.3	10.2	0.002	7.2	7.0	0.008	10.9	10.7	0.005
Stroke	3.3	3.2	0.006	3.7	3.8	0.003	4.3	4.5	0.008
Diabetes	14.5	14.5	0.001	13.4	13.7	0.010	14.9	14.9	0.002
Hypertension	50.0	50.3	0.006	50.9	51.7	0.017	52.9	52.8	0.002
Liver disease	2.4	2.4	<0.001	2.4	2.4	0.004	2.6	2.6	0.001

	Tramadol vs. Naproxen			Tramadol vs. Diclofenac			Tramadol vs. Codeine		
	Tramadol (n=33,024)	**Naproxen (n=33,024)**	**Standardized differences**	**Tramadol (n=18,662)**	**Diclofenac (n=18,662)**	**Standardized differences**	**Tramadol (n=42,722)**	**Codeine (n=42,722)**	**Standardized differences**
Transient ischemic attack	3.1	3.0	0.005	3.8	3.6	0.010	4.0	4.1	0.003
Ischemic heart disease	9.9	9.7	0.004	12.9	12.8	0.002	12.9	12.6	0.006
Congestive heart failure	1.9	1.7	0.011	3.2	2.9	0.013	3.5	3.5	<0.001
Angina	7.4	7.3	0.005	9.9	9.9	<0.001	9.8	9.6	0.007
Peripheral vascular disease	1.5	1.4	0.011	2.1	1.9	0.012	1.8	1.9	0.004
Venous thromboembolism	3.4	3.5	0.003	3.9	3.7	0.010	4.4	4.4	0.001
Pneumonia or infection	7.2	7.2	0.002	7.0	6.8	0.007	8.0	7.9	0.004
Hyperlipidaemia	17.0	17.3	0.007	15.5	15.9	0.010	16.9	16.8	0.003
Dementia	0.9	0.9	0.004	0.8	0.8	0.001	1.2	1.3	0.006
Varicose veins	12.8	12.7	0.003	12.5	12.7	0.005	13.8	13.8	0.001
Other circulatory disease	30.3	30.1	0.004	29.1	29.2	0.001	34.0	33.8	0.003
Depression	14.7	14.9	0.006	14.1	14.0	0.004	14.0	14.0	0.001
Chronic obstructive pulmonary disease	5.4	5.3	0.002	6.2	6.0	0.007	6.2	6.2	0.003
Atrial fibrillation	4.1	3.7	0.020	4.7	4.3	0.019	7.0	6.9	0.002
Anxiety	16.2	16.2	0.001	15.3	15.5	0.007	16.2	16.2	<0.001
Seizure	0.5	0.5	0.001	0.5	0.4	0.001	0.5	0.5	0.006
Sleep disorder or sleep apnea	1.9	1.9	0.004	1.5	1.5	0.007	1.8	1.8	0.001
Rheumatoid arthritis	2.1	2.0	0.002	2.2	2.1	0.006	2.5	2.5	<0.001
Medication (%)									
Other NSAIDs[#]	85.0	85.1	0.003	70.3	71.7	0.031	86.4	86.2	0.006
Other opioids[#]	32.8	33.1	0.006	30.3	30.4	0.002	15.6	15.7	0.001
Aspirin	33.2	33.3	0.003	34.1	34.5	0.008	36.3	36.3	<0.001
ACE inhibitors	34.0	34.1	0.001	32.2	32.3	0.002	36.7	36.6	0.002
Calcium channel blockers	32.4	33.0	0.013	32.9	33.2	0.005	35.9	35.6	0.006
Angiotensin receptor blocker	13.5	13.4	0.002	12.3	12.3	<0.001	13.6	13.6	<0.001
Beta receptor inhibitor	33.4	33.4	<0.001	31.8	32.3	0.011	35.9	35.9	0.001
Statins	41.0	41.5	0.010	35.6	35.9	0.006	39.9	39.8	0.002

	Tramadol vs. Naproxen			Tramadol vs. Diclofenac			Tramadol vs. Codeine		
	Tramadol (n=33,024)	**Naproxen (n=33,024)**	**Standardized differences**	**Tramadol (n=18,662)**	**Diclofenac (n=18,662)**	**Standardized differences**	**Tramadol (n=42,722)**	**Codeine (n=42,722)**	**Standardized differences**
Loop diuretics	16.2	16.1	0.001	20.0	19.6	0.012	20.8	20.9	0.003
Thiazide diuretics	36.8	37.1	0.005	38.9	39.4	0.010	39.9	40.0	0.002
Potassium-sparing diuretics	6.8	6.9	<0.001	9.4	9.3	0.001	9.0	8.9	0.002
Glucocorticoids	22.6	22.7	0.003	21.1	21.2	0.001	24.2	24.0	0.003
Nitrates	11.3	11.1	0.007	12.9	12.9	0.002	13.5	13.5	0.001
Antidiabetic medicine	10.4	10.4	<0.001	9.8	10.0	0.005	10.7	10.6	0.002
Anticoagulants	5.4	5.2	0.012	5.9	5.4	0.025	8.8	8.7	0.004
Benzodiazepines	36.1	36.6	0.011	33.5	33.8	0.007	35.5	35.3	0.004
SSRI	24.0	24.0	0.001	20.7	20.6	0.002	22.1	22.1	0.002
SNRI	6.5	6.6	0.004	5.2	5.3	0.005	5.7	5.7	<0.001
Antiepileptic medicine	9.1	9.3	0.005	6.9	6.9	<0.001	8.5	8.5	<0.001
PPIs	57.0	56.8	0.003	50.1	50.3	0.002	53.7	53.4	0.005
H2 blockers	23.1	23.3	0.005	24.8	24.7	0.002	25.6	25.5	0.003
Healthcare utilization, mean (SD)									
Hospitalizations‡	0.4 (0.8)	0.4 (0.9)	0.024	0.3 (0.8)	0.3 (0.9)	0.030	0.5 (1.0)	0.5 (1.1)	0.002
General practice visits‡	6.9 (5.6)	6.9 (5.8)	0.006	7.0 (6.0)	7.0 (6.2)	0.005	7.7 (6.8)	7.7 (6.5)	0.006
Specialist referrals‡	0.7 (1.1)	0.7 (1.1)	0.005	0.5 (0.9)	0.5 (0.9)	0.003	0.7 (1.0)	0.7 (1.1)	0.003
Propensity score (SD)	0.5 (0.2)	0.5 (0.2)	0.002	0.4 (0.2)	0.4 (0.2)	0.002	0.6 (0.1)	0.6 (0.1)	0.009

OA, osteoarthritis; BMI, body mass index; n, number; y, years; SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin-norepinephrine reuptake inhibitor; PPIs, proton pump inhibitors; H2 blockers, histamine-2 blockers.

†The Socio-Economic Deprivation Index (i.e., Townsend Deprivation Index) was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

#Other NSAIDs or opioids means other NSAIDs or opioids use prior to the index date.

‡Frequency during the past one year.

Table 2.

Association between Tramadol Initiation and Risk of Incident Myocardial Infarction within Six-month Follow-up Comparing with Initiation of Naproxen among Patients with Osteoarthritis

	Tramadol	Naproxen
Primary analysis		
Participants (n)	33,024	33,024
Incident myocardial infarction (n)	77	46
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years) *	4.8	2.8
RD (1000 person-years, 95% CI)	1.9 (0.6, 3.3)	0.0 (reference)
HR (95% CI)	1.68 (1.16, 2.41)	1.00 (reference)
"As-treated" approach **		
Participants (n)	33,024	33,024
Incident myocardial infarction (n)	40	23
Mean follow-up (year)	0.25	0.24
Rate (1000 person-years)	4.9	2.9
RD (1000 person-years, 95% CI)	2.0 (0.1, 3.9)	0.0 (reference)
HR (95% CI)	1.66 (1.00, 2.76)	1.00 (reference)
Incident OA patients		
Participants (n)	20,159	20,159
Incident myocardial infarction (n)	35	20
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years)	3.6	2.0
RD (1000 person-years, 95% CI)	1.5 (0.1, 3.0)	0.0 (reference)
HR (95% CI)	1.75 (1.01, 3.03)	1.00 (reference)
Missing data imputation		
HR (95% CI)	1.57 (1.13, 2.17)	1.00 (reference)
Conventional covariate adjustment approach		
HR (95% CI)	1.59 (1.19, 2.12)	1.00 (reference)

RD, rate difference; HR, hazard ratio; n, number; 95% CI, 95% confidence interval; OA, osteoarthritis.

* Number (rate) of competing event (i.e., death) in tramadol and naproxen cohort was 457 (28.3/1000 person-years) and 207 (12.8/1000 person-years), respectively.

** 82% and 85% participants discontinued or switched their initiated treatment in tramadol and naproxen cohort, respectively.

Table 3.

Association between Tramadol Initiation and Risk of Incident Myocardial Infarction within Six-month Follow-up Comparing with Initiation of Diclofenac among Patients with Osteoarthritis

	Tramadol	Diclofenac
Primary analysis		
Participants (n)	18,662	18,662
Incident myocardial infarction (n)	58	47
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years) *	6.4	5.1
RD (1000 person-years, 95% CI)	1.2 (−1.0, 3.4)	0.0 (reference)
HR (95% CI)	1.24 (0.84, 1.82)	1.00 (reference)
"As-treated" approach **		
Participants (n)	18,662	18,662
Incident myocardial infarction (n)	39	27
Mean follow-up (year)	0.25	0.23
Rate (1000 person-years)	8.4	6.2
RD (1000 person-years, 95% CI)	2.3 (−1.3, 5.8)	0.0 (reference)
HR (95% CI)	1.32 (0.81, 2.15)	1.00 (reference)
Incident OA patients		
Participants (n)	9,902	9,902
Incident myocardial infarction (n)	26	20
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years)	5.4	4.1
RD (1000 person-years, 95% CI)	1.3 (−1.5, 4.0)	0.0 (reference)
HR (95% CI)	1.30 (0.73, 2.33)	1.00 (reference)
Missing data imputation		
HR (95% CI)	1.04 (0.73, 1.48)	1.00 (reference)
Conventional covariate adjustment approach		
HR (95% CI)	1.23 (0.88, 1.73)	1.00 (reference)

RD, rate difference; HR, hazard ratio; n, number; 95% CI, 95% confidence interval; OA, osteoarthritis.

* Number (rate) of competing event (i.e., death) in tramadol and diclofenac cohort was 370 (40.6/1000 person-years) and 205 (22.3/1000 person-years), respectively.

** 81% and 86% participants discontinued or switched their initiated treatment in tramadol and diclofenac cohort, respectively.

Table 4.

Association between Tramadol Initiation and Risk of Incident Myocardial Infarction within Six-month Follow-up Comparing with Initiation of Codeine among Patients with Osteoarthritis

	Tramadol	Codeine
Primary analysis		
Participants (n)	42,722	42,722
Incident myocardial infarction (n)	127	103
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years) *	6.1	5.0
RD (1000 person-years, 95% CI)	1.1 (−0.3, 2.5)	0.0 (reference)
HR (95% CI)	1.23 (0.95, 1.60)	1.00 (reference)
"As-treated" approach **		
Participants (n)	42,722	42,722
Incident myocardial infarction (n)	66	47
Mean follow-up (year)	0.25	0.21
Rate (1000 person-years)	6.2	5.1
RD (1000 person-years, 95% CI)	1.1 (−1.0, 3.2)	0.0 (reference)
HR (95% CI)	1.21 (0.83, 1.76)	1.00 (reference)
Incident OA patients		
Participants (n)	25,104	25,104
Incident myocardial infarction (n)	60	59
Mean follow-up (year)	0.49	0.49
Rate (1000 person-years)	4.9	4.8
RD (1000 person-years, 95% CI)	0.1 (−1.7, 1.8)	0.0 (reference)
HR (95% CI)	1.01 (0.71, 1.45)	1.00 (reference)
Missing data imputation		
HR (95% CI)	1.13 (0.88, 1.46)	1.00 (reference)
Conventional covariate adjustment approach		
HR (95% CI)	1.16 (0.92, 1.47)	1.00 (reference)

RD, rate difference; HR, hazard ratio; n, number; 95% CI, 95% confidence interval; OA, osteoarthritis.

* Number (rate) of competing event (i.e., death) in tramadol and codeine cohort was 791 (38.0/1000 person-years) and 822 (39.6 /1000 person-years), respectively.

** 82% and 89% participants discontinued or switched their initiated treatment in tramadol and codeine cohort, respectively.