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

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Ethical approval

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

Scientific approval

Transparency

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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.

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

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 worldwide¹. 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 countries¹⁰. 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 States¹⁶, 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 thrombosis²⁰. 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 serotonin²², and an elevated plasma serotonin is a common feature of cardiovascular disease often associated with enhanced platelet activation and thrombosis²³. To date, there is paucity of information on the risk of cardiovascular diseases with tramadol use²⁴⁻²⁷. 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 association¹⁷.

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 diagnoses²⁸, and a drug dictionary based on data from the Multilex classification system is used to code drugs²⁹. 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 studies³⁰.

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 Index³¹), 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 medication²⁶. 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 death³⁴. 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 \pm 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 death³⁴. We used the "COVSANDWICH" statement in the PROC PHREG procedure in SAS to account for the correlation in the matched pair³⁵. We tested the proportional hazards assumption by using the Kolmogorov supremum test³⁶.

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 days³⁷) 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 personyears) 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 analyses²⁶. 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 serotonin¹⁹, a key factor in the process of platelet aggregation, mediating vascular homeostasis and thrombosis²¹. A previous in vivo study demonstrated that mice selectively deficient in serotonin exhibited reduced risk of thrombosis and thromboembolism⁴². 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 surgery²⁵.

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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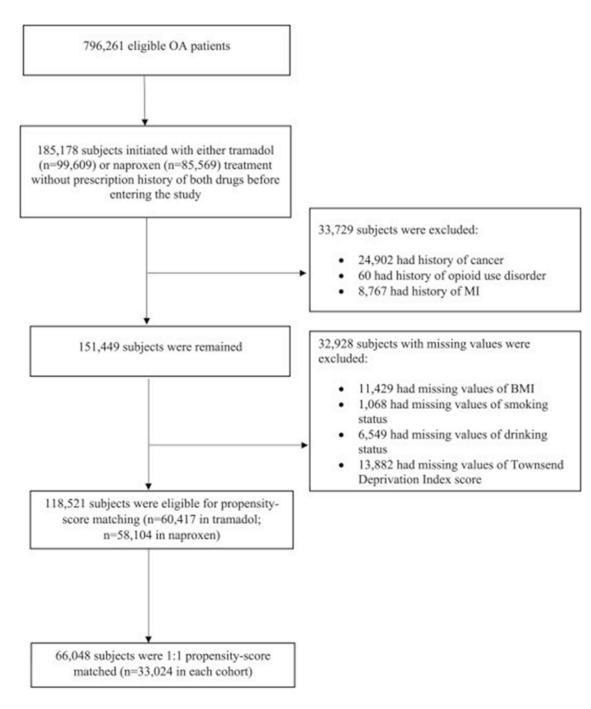


Figure 1. Selection Process of Included Subjects for the Comparison between Tramadol and Naproxen.

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

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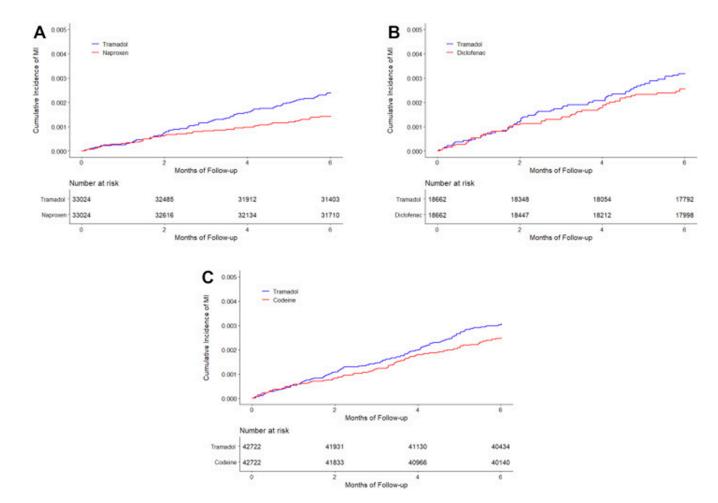


Figure 2. Time to Incident Myocardial Infarction for the Propensity-score Matched Cohorts of Patients with Osteoarthritis and Tramadol Initiation Comparing with Initiation of Naproxen (A), Diclofenac (B), or Codeine (C).

A, risk of MI for tramadol and naproxen were 2.4/1000 and 1.4/1000 over six-month followup, 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.

	T	Tramadol vs. Naproxen)Xen	Tr	Tramadol vs. Diclofenac	enac		Tramadol vs. Codeine	eine
	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									
$(SD)^{\uparrow}$	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

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Table 1.

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Transiol Nervoirs Suprova Suprova Suprova Support Condition Conditio		T	Tramadol vs. Naproxen	oxen	Tr	Tramadol vs. Diclofenac	enac	L	Tramadol vs. Codeine	eine
introblemic linek3130000404141introblemic linek939393939393gaive barf linek191700112121212gaive barf linek191700112121212gaive barf linek141323290001314gaive barf linek141414141414for linek131012121212for linek13101312121314for linek13101312141414for linek13101212121313for linek1312121214141414for linek14141414141414for linek14141414141414for linek14141414141414for linek14141414141414for linek14141414141414for linek14141414141414for linek14141414141414for linek14141414141414for linek1414 <td< th=""><th></th><th>Tramadol (n=33,024)</th><th>Naproxen (n=33,024)</th><th>Standardized differences</th><th>Tramadol (n=18,662)</th><th>Diclofenac (n=18,662)</th><th>Standardized differences</th><th>Tramadol (n=42,722)</th><th>Codeine (n=42,722)</th><th>Standardized differences</th></td<>		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
model lend diese 99 97 004 129 126 126 126 model lend diese 19 17 001 23 33 33 33 model section 13 011 21 13 001 34 35 35 model section 13 011 21 13 001 13 35 35 rest entroperation 13 13 010 21 13 14 44 rest entroperation 13 010 13 13 13 13 13 rest entroperation 13 010 13 14 14 14 13 rest entroperation 13 010 13 14 14 13 13 rest entroperation 13 010 14 14 14 14 14 rest entroperation 13 13 13 14 14 14 14 14 rest entrope	Transient ischemic attack	3.1	3.0	0.005	3.8	3.6	0.010	4.0	4.1	0.003
genter failure 19 17 001 32 29 003 35 35 main 74 73 001 21 011 21 29 003 35 35 main vacular 15 14 001 21 19 003 98 003 98 003 99 90 main vacular 15 14 001 21 17 003 18 003 93 96 main vacular 12 12 003 12 14 011 17 18 19 19 19 main vacular 12 12 003 12 12 12 13 13 main vacular 12 12 12 12 12 12 13 13 main vacular 12 12 12 12 12 12 12 13 main vacular 12 12 12 12 12	Ischemic heart disease	6.6	9.7	0.004	12.9	12.8	0.002	12.9	12.6	0.006
min 74 73 005 99 90 4001 98 96 minul vaculat 13 14 37 0011 21 13 91 96 minul vaculat 13 13 011 21 13 0011 21 14 44 minu vaculation 73 002 73 0031 53 37 0010 44 44 minu vaculation 72 73 0031 53 53 53 53 53 54 53 ethil vacuuation 147 143 013 53 53 53 53 53 ethil vacuuation 147 143 144 140 140 140 140 ethil vacuuation 147 143 144 140 140 140 ethil vacuuation 147 143 140 140 140 140 ethil vacuuation 147 143 140 140	Congestive heart failure	1.9	1.7	0.011	3.2	2.9	0.013	3.5	3.5	<0.001
model is a production of the productin the productin the production of the production of the productic	Angina	7.4	7.3	0.005	6.6	6.6	<0.001	9.8	9.6	0.007
are throughoughoughoughoughoughoughoughoughough	Peripheral vascular disease	1.5	1.4	0.011	2.1	1.9	0.012	1.8	1.9	0.004
monitor infection 12 12 002 10 68 007 80 79 infideminia 170 173 007 155 159 000 169 168 eminia 09 09 009 135 137 138 133 eminia 13 123 010 013 141 140 153 133 enversion 141 137 003 141 140 140 140 133 133 enversion 141 317 003 141 140 <td>Venous thromboembolism</td> <td>3.4</td> <td>3.5</td> <td>0.003</td> <td>3.9</td> <td>3.7</td> <td>0.010</td> <td>4.4</td> <td>4.4</td> <td>0.001</td>	Venous thromboembolism	3.4	3.5	0.003	3.9	3.7	0.010	4.4	4.4	0.001
ethiotenia[70[73007[55[59001[69[68ethiotenia09090040303031313ethia03124033127003127036138138ethia133301030123127030134133138ethia14714903042912920301147133138ethia14714903041411400304140133138ethia14337030262626007162163138ethia163163163163163164163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163163163163ethia163163163163163163<	Pneumonia or infection	7.2	7.2	0.002	7.0	6.8	0.007	8.0	7.9	0.004
emia090909000121313core verias12812700031251270005138138core verias0330100042912920001340338existion videose14714900061411400009140140existion videose54530002626000076262existion videose162162000115315500076262ety destructive1919001015315500076262ety destructive1919001015315500076262ety destructive1919001015315500076262ety destructive1919001015315500076262ety destructive1919100153156162ety destructive212000115156162ety destructive21200012221000716363ety destructive31202323232325ety destructive323330033413452625ety destructive340003232323363363ety destructive342002323232625e	Hyperlipidaemia	17.0	17.3	0.007	15.5	15.9	0.010	16.9	16.8	0.003
cose veits 12 0.03 12.7 0.03 13.8 13.8 creiculary disease 30.3 30.1 0.04 29.1 29.2 0.001 34.0 33.8 resiculary disease 30.3 30.1 0.004 29.1 29.2 0.001 34.0 33.8 resion 14.7 14.9 0.006 14.1 14.0 0.001 14.0 14.0 14.0 14.0 nit dy disease 5.4 5.3 0.002 4.7 4.3 0.007 6.2 6.2 differilation 1 3.7 0.020 4.7 4.3 0.019 7.0 6.2 differilation 1.1 1.1 0.12 0.01 1.5 0.01 6.2 6.2 ety discrete 0.5 0.020 0.23 0.2 1.5 0.5 6.2 6.2 discrete 1.3 0.020 0.23 0.2 0.01 6.2 6.2 6.2 6.3	Dementia	6.0	0.9	0.004	0.8	0.8	0.001	1.2	1.3	0.006
r circulatory disease30330.10.00429.129.20.00134.033.8resion14.714.90.00614.114.00.00414.014.014.0nic obstructive 3.4 3.3 0.005 4.1 14.00.00414.014.014.0nic obstructive 3.4 3.3 0.002 4.7 4.3 0.004 14.0 14.014.0nic obstructive 3.4 3.3 0.002 4.7 4.3 0.004 5.2 5.2 nic obstructive 3.1 0.002 4.7 4.3 0.007 6.2 6.2 nic obstructive 1.9 1.9 0.001 1.5 0.007 16.2 6.2 nic obstructive 1.9 0.001 1.5 0.007 16.2 6.2 6.2 nic obstructive 2.1 0.001 1.5 0.007 16.2 16.2 nic obstructive 2.1 0.001 0.02 2.2 2.1 0.007 16.2 16.2 nic obstructive 2.1 2.0 0.001 1.5 1.7 0.007 16.2 2.5 nic obstructive 3.1 0.002 2.2 2.1 0.007 16.2 2.5 nic obstructive 3.1 3.3 3.3 3.3 3.3 3.3 3.3 3.3 nic obstructive 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 nic obstructive 3	Varicose veins	12.8	12.7	0.003	12.5	12.7	0.005	13.8	13.8	0.001
escion[4.7][4.9][0.06][4.1][4.0][4.0][4.0][4.0]and obstractive55556000666and obstractive555000766and obstractive666007666and obstractive66007066and obstractive161615001766and obstractive191900111166and obstractive191900111111and obstractive212000111111and obstractive212000011111and obstractive212000011111and obstractive2120000001111and obstractive212000000000011and obstractive212021212100000000and obstractive31313131313131313131 <td>Other circulatory disease</td> <td>30.3</td> <td>30.1</td> <td>0.004</td> <td>29.1</td> <td>29.2</td> <td>0.001</td> <td>34.0</td> <td>33.8</td> <td>0.003</td>	Other circulatory disease	30.3	30.1	0.004	29.1	29.2	0.001	34.0	33.8	0.003
mic obstructive5.45.30.0026.26.00.0076.26.2at this liation4.13.70.0204.74.30.097.06.9at this liation16.216.20.00115.315.50.00716.216.2ety16.216.20.00115.315.50.00716.216.216.2this liation1.91.90.010.50.010.50.0716.216.2this liation1.91.91.90.0011.51.50.0716.216.2this obstructor sleep1.91.90.0011.50.0010.50.0716.216.2this obstructive2.12.00.0022.22.10.0052.52.52.5unatoid arthritis2.12.00.0022.22.10.0052.52.5unatoid arthritis2.12.00.0022.52.52.52.5unatoid arthritis2.10.0033.413.450.0053.673.63trindo static3.23.30.0033.413.450.0053.673.66trindo static3.23.233.033.233.230.0053.673.66trindo static3.33.413.450.0053.673.66trindo static3.33.413.450.0053.673.66trindo static3.4 <td>Depression</td> <td>14.7</td> <td>14.9</td> <td>0.006</td> <td>14.1</td> <td>14.0</td> <td>0.004</td> <td>14.0</td> <td>14.0</td> <td>0.001</td>	Depression	14.7	14.9	0.006	14.1	14.0	0.004	14.0	14.0	0.001
If the3.70.0204.74.30.0197.06.9ety16.216.216.20.00115.30.01716.216.2ue0.50.50.00115.30.01716.216.2ue0.50.0115.30.010.50.5the1.91.91.90.011.50.010.50.5plotoder sleep1.91.91.90.011.51.50.010.50.5matoid arthrits2.12.00.0022.22.10.0071.81.8matoid arthrits2.12.00.0022.22.10.0052.52.5matoid arthrits2.12.00.0023.22.10.0053.63.63attoid arthrits3.10.0033.13.10.0063.13.10.0053.63attoid arthrits3.23.33.040.023.53.633.63attoid arthrits3.10.0033.413.453.643.63attoid arthrits3.23.33.040.0023.633.63attoid arthrits3.10.0033.233.040.0033.633.63attoid arthrits3.13.13.233.040.0033.633.63attoid arthrits3.13.13.233.040.0033.633.63attoid arthritor3.33.33.23	Chronic obstructive pulmonary disease	5.4	5.3	0.002	6.2	6.0	0.007	6.2	6.2	0.003
ety 162 162 001 153 155 007 162 162 ue 0.5 0.5 0.5 0.7 0.61 0.5 0.5 0.5 pdioder or sleep 1.9 1.9 0.001 0.5 0.07 1.8 1.8 pdioder or sleep 1.9 1.9 0.004 1.5 1.5 0.007 1.8 1.8 matoid arthrifs 2.1 2.0 0.002 2.2 2.1 0.007 2.5 2.5 matoid arthrifs 2.1 2.0 0.002 2.2 2.1 0.007 2.5 2.5 matoid arthrifs 2.1 2.0 0.002 2.2 2.1 0.007 2.5 2.5 matoid arthrifs 3.1 2.0 0.002 3.2 3.1 0.002 2.5 2.5 2.5 matoid arthrifs 3.2 3.31 0.002 3.03 3.1 0.002 2.5 2.5 2.5 resploids 3.2 3.31 0.002 3.03 3.1 3.04 0.02 3.5 3.63 resploids 3.4 3.2 3.32 3.23 3	Atrial fibrillation	4.1	3.7	0.020	4.7	4.3	0.019	7.0	6.9	0.002
ue 0.5 0.5 0.01 0.5 0.01 0.5 <th< td=""><td>Anxiety</td><td>16.2</td><td>16.2</td><td>0.001</td><td>15.3</td><td>15.5</td><td>0.007</td><td>16.2</td><td>16.2</td><td><0.001</td></th<>	Anxiety	16.2	16.2	0.001	15.3	15.5	0.007	16.2	16.2	<0.001
p disorder or sleep1.91.90.0041.51.50.0071.81.8 $\operatorname{matorid}$ arthritis2.12.00.0022.22.10.0062.52.5 $\operatorname{matorid}$ arthritis2.12.00.0022.32.52.52.5 $\operatorname{matorid}$ ston85.085.10.00370.371.70.03186.486.2 r NSAIDs#85.085.10.00370.371.70.03186.486.2 r NSAIDs#32.833.10.00334.134.50.00335.336.3 r NSAIDs#32.933.30.00334.134.50.00335.336.3 r NSAIDs#32.933.10.00334.134.50.00336.336.3 r NSAIDs#32.933.10.00334.134.50.00336.736.3 ri nihibitors32.433.00.01332.232.30.00235.736.7 ri nihibitors32.437.30.00132.232.30.00235.736.7 ri ni channel blockers32.432.932.332.332.336.336.736.7 ri ni channel blockers32.437.320.937.30.00235.736.736.6 ri ni channel blockers33.437.832.332.337.336.736.7 ri ni channel blockers33.437.837.33	Seizure	0.5	0.5	0.001	0.5	0.4	0.001	0.5	0.5	0.006
matrix 2.1 2.0 0.002 2.2 2.1 0.006 2.5 2.5 tion(\checkmark) \mathbf{i}	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
NSAIDs#85.085.10.00370.371.70.03186.486.2opioids#32.833.10.00630.330.40.00215.615.7in33.233.30.00334.134.50.00215.615.7inbibitors34.034.132.232.336.736.336.3inbibitors34.00.01332.232.30.00236.736.7un channel blockers32.433.00.01332.232.30.00235.935.6un channel blockers33.43.00.01332.232.30.00235.935.6un channel blockers33.43.40.01332.933.20.00235.935.9tereptor13.513.40.00131.832.30.01135.935.9tereptor inhibitor33.40.01035.635.90.01135.935.9s41.041.50.01035.635.90.01639.939.9	Medication (%)									
opioids# 3.2 3.3 0.006 30.3 30.4 0.002 15.6 15.7 in 33.2 33.3 0.003 34.1 34.5 0.008 36.3 36.3 inhibitors 34.0 34.1 0.001 32.2 34.5 0.008 36.3 36.3 inhibitors 34.0 34.1 0.001 32.2 32.3 0.002 36.7 36.6 inhibitors 32.4 33.0 0.013 32.2 32.3 0.002 35.9 35.9 inhibitor 13.5 13.4 0.001 32.2 12.3 0.002 13.6 13.6 itemplotor 13.5 13.4 0.002 12.3 12.3 0.011 35.9 35.9 itemplotor 33.4 0.010 31.8 32.3 0.011 35.9 35.9 35.9 itemplotor 34.9 0.010 35.6 35.9 0.006 39.9 39.9	Other NSAIDs#	85.0	85.1	0.003	70.3	71.7	0.031	86.4	86.2	0.006
in 33.2 33.3 0.003 34.1 34.5 0.008 36.3 36.3 inhibitors 34.0 34.1 0.001 32.2 32.3 0.002 36.7 36.6 um channel blockers 32.4 33.0 0.013 32.2 32.3 0.002 35.9 35.6 um channel blockers 32.4 33.0 0.013 32.2 32.3 0.005 35.9 35.6 tensin receptor 13.5 13.4 0.002 12.3 (-0.01) 13.6 13.6 teceptor inhibitor 33.4 <0.001 31.8 32.3 0.011 35.9 35.9 s 41.0 41.5 0.010 35.6 35.9 0.011 35.9 35.9	Other opioids#	32.8	33.1	0.006	30.3	30.4	0.002	15.6	15.7	0.001
inhibitors 34.0 34.1 0.001 32.2 32.3 0.002 36.7 36.6 um channel blockers 32.4 33.0 0.013 32.9 33.2 0.005 35.9 35.6 tensin receptor 13.5 13.4 0.002 12.3 12.3 <0.001	Aspirin	33.2	33.3	0.003	34.1	34.5	0.008	36.3	36.3	<0.001
um channel blockers 32.4 33.0 0.013 32.9 33.2 0.005 35.9 35.6 stensin receptor 13.5 13.4 0.002 12.3 12.3 <0.001	ACE inhibitors	34.0	34.1	0.001	32.2	32.3	0.002	36.7	36.6	0.002
tensin receptor 13.5 13.4 0.002 12.3 12.3 <0.01 13.6 13.6 receptor inhibitor 33.4 3.001 31.8 32.3 0.011 35.9 35.9 s 41.0 41.5 0.010 35.6 35.9 0.006 39.9 39.8	Calcium channel blockers	32.4	33.0	0.013	32.9	33.2	0.005	35.9	35.6	0.006
ceptor inhibitor 33.4 33.4 <0.001 31.8 32.3 0.011 35.9 35.9 41.0 41.5 0.010 35.6 35.9 0.006 39.9 39.8	Angiotensin receptor blocker	13.5	13.4	0.002	12.3	12.3	<0.001	13.6	13.6	<0.001
41.0 41.5 0.010 35.6 35.9 0.006 39.9 39.8	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

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Translot Narrows Sundartike Translot Narrows Sundartike Translot Narrows Sundartike Sundartike Narrows Sundartike Narrows Naro		I	Tramadol vs. Naproxen	oxen	Tr	Tramadol vs. Diclofenac	enac	T	Tramadol vs. Codeine	eine
Loop dimetics 16.1 10.01 20.0 19.6 0.012 20.8 Thiazide dimetics 36.8 37.1 0.005 38.9 39.4 0.010 39.9 Patassium-sparing 6.8 6.9 6.001 9.4 0.010 39.9 Patassium-sparing 6.8 6.9 -0.001 9.4 0.010 39.9 Patassium-sparing 6.8 6.9 -0.001 9.4 0.010 39.9 Reaccorticoids 2.26 0.012 0.07 12.9 0.001 24.2 Antidabetic medicine 10.4 10.4 0.001 33.8 0.002 35.3 Antidabetic medicine 9.1 9.3 0.011 33.5 0.002 35.7 Antiepileptic medicine 9.1 9.3 0.001 35.3 0.002 5.7 Stritt 5.6 0.011 33.5 33.8 0.002 5.7 Antiepileptic medicine 9.1		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
Thizide diturctis 36.8 37.1 0.005 38.9 39.4 0.010 39.9 Potassium-sparing 6.8 6.9 <0.001 9.4 9.3 0.001 9.0 Potassium-sparing 6.8 6.9 <0.001 9.1 2.2 0.001 9.0 Potassium-sparing 6.8 6.9 <0.001 9.1 2.2 0.001 9.3 Rencorricoids 2.2.6 2.2.7 0.001 9.3 11.1 0.007 12.9 0.001 24.2 Anticogulants 5.4 5.2 0.011 33.5 3.3 0.002 3.3 Anticogulants 5.4 5.2 0.011 33.5 3.3 0.002 2.1 Anticogulants 5.4 5.2 0.011 33.5 3.3 3.3 3.3 Strip 2.40 0.01 2.3 3.3 3.3 3.3 3.3 3.3 3.3 Strip 5.3 5.3 0.01 5.3 <	Loop diuretics	16.2	16.1	0.001	20.0	19.6	0.012	20.8	20.9	0.003
Parassium-sparing duretics 6 6.001 9.4 9.3 0.001 9.0 duretics 6.8 6.9 -0.001 9.4 9.3 0.001 24.2 Glucocorticoids 2.2.6 2.2.7 0.003 21.1 21.2 0.001 24.2 Nitrates 11.3 11.1 0.007 12.9 0.002 13.5 Anticongulunts 5.4 5.2 0.011 33.5 3.3 0.005 10.7 Anticongulunts 5.4 5.2 0.011 33.5 3.3 0.005 35.5 NRI 6.5 0.01 20.7 20.6 0.001 35.5 SRI 24.0 24.0 0.01 20.7 20.6 0.002 35.7 SRI 24.0 24.0 24.0 0.003 20.1 20.2 25.6 NRI 6.5 6.6 0.001 20.7 20.6 0.002 23.7 SRI 23.1 5.3 30.05	Thiazide diuretics	36.8	37.1	0.005	38.9	39.4	0.010	39.9	40.0	0.002
Glucocorticoids 2.2.6 2.7.7 0.003 21.1 21.2 0.001 24.2 Nitrates 11.3 11.1 0.007 12.9 12.9 0.002 13.5 Antidabetic medicine 10.4 10.4 0.001 9.8 10.0 0.005 13.5 Antioagulants 5.4 5.2 0.012 5.9 5.4 0.02 13.5 Antioagulants 5.4 5.2 0.012 5.9 5.4 0.02 2.5 Strin 24.0 0.01 33.5 33.8 0.005 2.5 Strin 6.5 6.6 0.011 33.5 5.3 0.002 35.5 Strin 5.7.0 5.8 0.001 2.4 5.2 5.3 5.3 5.5 Antiopleptic medicine 9.1 9.3 0.001 5.2 5.5 5.3 5.3 5.7 Strin 5.7.0 5.6 0.001 5.2 5.3 5.3 5.5 5.5	Potassium-sparing diuretics	6.8	6.9	<0.001	9.4	9.3	0.001	9.0	8.9	0.002
Nitrates 11.3 11.1 0.007 12.9 12.9 0.002 13.5 Antidiabetic medicine 10.4 10.4 0.012 5.9 5.4 0.025 10.7 Anticoagulants 5.4 5.2 0.012 5.9 5.4 0.025 18.8 Benzodiazepines 3.6.1 3.6.6 0.011 33.5 33.8 0.007 35.5 SNR 2.4.0 2.4.0 0.001 2.9.7 20.6 0.007 35.5 SNR 2.4.0 2.4.0 0.001 2.9.7 20.6 0.007 35.5 SNR 2.4.0 0.001 2.9.7 20.6 0.002 5.7 SNR 5.5 6.6 0.001 2.9.7 20.6 0.002 5.7 Nitionie 5.7 0.005 5.4 0.002 5.7 2.6 Place 5.7 0.003 5.1 5.0 5.0.1 0.002 5.7 Healtherer 2.1 0.4 (0.8)<	Glucocorticoids	22.6	22.7	0.003	21.1	21.2	0.001	24.2	24.0	0.003
Antidiabetic medicine 104 104 104 104 104 001 98 100 0005 101 Anticoagulants 5.4 5.2 0.012 5.9 5.4 0.025 8.8 Benzodiazepines 36.1 36.6 0.011 33.5 33.8 0.007 35.5 StR1 24.0 24.0 0.011 23.5 33.8 0.007 35.5 StR1 24.0 24.0 0.001 20.7 20.6 0.002 35.7 StR1 24.0 0.7 20.5 6.5 0.004 5.2 20.1 35.5 Antieplieptic medicine 9.1 9.3 0.005 5.1 20.5 5.3 20.0 20.5 5.7 Antieplieptic medicine 9.1 2.3 0.005 5.3 2.4.7 0.005 5.3 Hath 57.0 56.8 0.005 24.8 2.4.7 0.002 25.6 Heath 53.1 0.30.8 0.0	Nitrates	11.3	11.1	0.007	12.9	12.9	0.002	13.5	13.5	0.001
Anticoagulants 5.4 5.2 0.012 5.9 5.4 0.025 8.8 Benzodiazepines 36.1 36.6 0.011 33.5 33.8 0.007 35.5 SSR1 24.0 24.0 0.011 33.5 33.8 0.007 35.5 SNR1 6.5 6.6 0.001 20.7 20.6 0.007 35.5 SNR1 6.5 6.6 0.004 5.2 5.3 0.002 5.7 SNR1 6.5 6.0 0.004 5.2 5.3 0.002 5.7 Anticplicptic medicine 9.1 9.3 0.003 5.1 0.005 5.7 5.6 0.002 5.7	Antidiabetic medicine	10.4	10.4	<0.001	9.8	10.0	0.005	10.7	10.6	0.002
Benzodiazepines 36.1 36.6 0.011 33.5 33.8 0.007 35.5 SNR1 24.0 24.0 0.001 20.7 20.6 0.002 22.1 SNR1 6.5 6.6 0.001 20.7 20.6 0.002 22.1 NR1 6.5 6.6 0.004 5.2 5.3 0.005 5.3 Anticplicptic medicine 9.1 9.3 0.003 6.9 6.9 <0.001	Anticoagulants	5.4	5.2	0.012	5.9	5.4	0.025	8.8	8.7	0.004
SSR1 24.0 24.0 0.001 20.7 20.6 0.002 22.1 SNR1 6.5 6.6 0.004 5.2 5.3 0.005 5.7 Antiepileptic medicine 9.1 9.3 0.005 6.9 6.9 6.001 8.5 PPIs 57.0 56.8 0.003 50.1 50.3 0.002 53.7 H2 blockers 23.1 23.3 0.005 24.8 24.7 0.002 53.7 H2 blockers 23.1 23.3 0.005 24.8 24.7 0.002 53.7 H2 blockers 23.1 23.3 0.005 24.8 24.7 0.002 53.6 Healthcare utilization, $0.4(0.9)$ 0.005 23.6 0.002 25.6 Healthcare utilizations ⁴ $0.4(0.9)$ 0.005 24.8 24.7 0.002 25.6 Healthcare utilizations ⁴ $0.4(0.9)$ $0.4(0.9)$ $0.3(0.9)$ $0.$	Benzodiazepines	36.1	36.6	0.011	33.5	33.8	0.007	35.5	35.3	0.004
SNR1 6.5 6.6 0.004 5.2 5.3 0.005 5.7 Antieplieptic medicine 9.1 9.3 0.005 6.9 6.9 6.001 8.5 PPIs 57.0 56.8 0.003 50.1 50.3 0.002 53.7 H2 blockers 23.1 23.3 0.003 50.1 50.3 0.002 53.6 H2 blockers 23.1 23.3 0.003 50.1 50.3 0.002 53.6 H2 blockers 23.1 23.3 0.003 24.7 0.002 53.6 Healthcare utilization, $0.4 (0.8)$ $0.4 (0.9)$ 0.024 $0.3 (0.8)$ $0.3 (0.9)$ $0.5 (1.0)$ Hospitalizations, [‡] $6.9 (5.6)$ $6.9 (5.8)$ 0.006 $7.0 (6.0)$ $7.0 (6.2)$ $0.7 (1.0)$ General practice visits, [‡] $6.9 (5.6)$ $0.9 (0.2)$ 0.002 $0.5 (0.9)$ $0.7 (0.0)$ Specialist referrals, [‡] $0.7 (1.1)$ $0.7 (0.2)$	SSRI	24.0	24.0	0.001	20.7	20.6	0.002	22.1	22.1	0.002
Antiepileptic medicine 9.1 9.3 0.005 6.9 6.9 6.0 8.5 PPIs 57.0 56.8 0.003 50.1 50.3 0.002 53.7 H2 blockers 23.1 23.3 0.003 50.1 50.3 0.002 53.7 H2 blockers 23.1 23.3 0.005 24.8 24.7 0.002 53.6 Halthcare utilizations ⁴ $0.4 (0.8)$ $0.4 (0.9)$ 0.002 $0.3 (0.8)$ $0.3 (0.9)$ 0.030 $0.5 (1.0)$ Hospitalizations ⁴ $0.4 (0.8)$ $0.4 (0.9)$ 0.024 $0.3 (0.8)$ $0.3 (0.9)$ $0.5 (1.0)$ General practice visits ⁴ $6.9 (5.6)$ $6.9 (5.8)$ 0.006 $7.0 (6.0)$ $7.0 (6.2)$ $0.7 (1.0)$ Specialist referrals ⁴ $0.7 (1.1)$ $0.7 (1.1)$ $0.7 (1.0)$ $7.0 (6.0)$ 0.003 $0.7 (1.0)$ Propensity score (SD) $0.5 (0.2)$ $0.5 (0.2)$ $0.6 (0.2)$ $0.6 (0.2)$ $0.6 (0.2)$ $0.7 (0.2)$ $0.7 (0.$	SNRI	6.5	6.6	0.004	5.2	5.3	0.005	5.7	5.7	<0.001
PPIs57.056.80.00350.150.30.00253.7H2 blockers23.123.30.00524.824.70.00225.6Healthcare utilization, mean (SD)123.30.00524.824.70.00225.6Hospitalizationst0.4 (0.9)0.24 (0.9)0.0240.3 (0.8)0.3 (0.9)0.05 (1.0)Hospitalizationst0.4 (0.9)0.0240.3 (0.8)0.3 (0.9)0.0300.5 (1.0)General practice visitst6.9 (5.6)6.9 (5.8)0.0067.0 (6.0)7.0 (6.2)0.0057.7 (6.8)Specialist referralst0.7 (1.1)0.7 (1.1)0.0050.5 (0.9)0.5 (0.9)0.0030.7 (1.0)Propensity score (SD)0.5 (0.2)0.5 (0.2)0.0020.4 (0.2)0.0020.6 (0.1)	Antiepileptic medicine	9.1	9.3	0.005	6.9	6.9	<0.001	8.5	8.5	<0.001
H2 blockers23.123.30.00524.824.70.00225.6Healthcare utilization, mean (SD)Hospitalizations*0.4 (0.9)0.00240.3 (0.8)0.3 (0.9)0.00300.5 (1.0)Hospitalizations*0.4 (0.9)0.4 (0.9)0.00240.3 (0.8)0.3 (0.9)0.00300.5 (1.0)Hospitalizations*0.4 (1.1)0.7 (1.1)0.0067.0 (6.0)7.0 (6.0)0.0057.7 (6.8)Specialist referrals*0.7 (1.1)0.7 (1.1)0.0050.5 (0.9)0.5 (0.9)0.0030.7 (1.0)Propensity score (SD)0.5 (0.2)0.5 (0.2)0.0020.4 (0.2)0.4 (0.2)0.0020.6 (0.1)A constructive DM1 body mass index a number vasaes SD standard deviation NSAD and stani inflammatory dure ACH and construction of the constru	PPIs	57.0	56.8	0.003	50.1	50.3	0.002	53.7	53.4	0.005
Healthcare utilization, mean (SD) $0.4 (0.8)$ $0.4 (0.9)$ 0.024 $0.3 (0.8)$ $0.3 (0.9)$ 0.030 $0.5 (1.0)$ Hospitalizations [‡] $0.4 (0.8)$ $0.4 (0.9)$ 0.024 $0.3 (0.8)$ $0.3 (0.9)$ 0.030 $0.5 (1.0)$ General practice visits [‡] $6.9 (5.6)$ $6.9 (5.8)$ 0.006 $7.0 (6.0)$ $7.0 (6.2)$ 0.005 $7.7 (6.8)$ Specialist referrals [‡] $0.7 (1.1)$ $0.7 (1.1)$ 0.006 $7.0 (6.0)$ $7.0 (6.2)$ 0.003 $0.7 (1.0)$ Propensity score (SD) $0.5 (0.2)$ $0.5 (0.2)$ 0.002 $0.4 (0.2)$ $0.4 (0.2)$ 0.002 $0.6 (0.1)$	H2 blockers	23.1	23.3	0.005	24.8	24.7	0.002	25.6	25.5	0.003
Hospitalizations ⁴ $0.4 (0.8)$ $0.4 (0.9)$ 0.024 $0.3 (0.8)$ $0.3 (0.9)$ 0.030 $0.5 (1.0)$ General practice visits ⁴ $6.9 (5.6)$ $6.9 (5.8)$ 0.006 $7.0 (6.0)$ $7.0 (6.2)$ 0.005 $7.7 (6.8)$ Specialist referrals ⁴ $0.7 (1.1)$ $0.7 (1.1)$ $0.7 (1.1)$ 0.005 $0.5 (0.9)$ $0.5 (0.9)$ 0.003 $0.7 (1.0)$ Propensity score (SD) $0.5 (0.2)$ $0.5 (0.2)$ 0.002 $0.4 (0.2)$ 0.002 $0.6 (0.1)$	Healthcare utilization, mean (SD)									
General practice visits \ddagger 6.9 (5.6) 6.9 (5.8) 0.006 7.0 (6.0) 7.0 (6.2) 0.005 7.7 (6.8) Specialist referrals \ddagger 0.7 (1.1) 0.7 (1.1) 0.005 0.5 (0.9) 0.5 (0.9) 0.6 (0.0) 0.003 0.7 (1.0) Propensity score (SD) 0.5 (0.2) 0.602 0.4 (0.2) 0.4 (0.2) 0.002 0.6 (0.1)	$\operatorname{Hospitalizations}^{\mathcal{I}}$	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
Specialist referrals [‡] $0.7 (1.1)$ $0.7 (1.1)$ 0.005 $0.5 (0.9)$ $0.5 (0.9)$ 0.003 $0.7 (1.0)$ Propensity score (SD) $0.5 (0.2)$ 0.002 $0.4 (0.2)$ 0.002 $0.6 (0.1)$ OA conservativities BMI body mass index: number: V vases: SD standard deviation: NSAID non-standard daviation Mark Andre ACF and conscience of the optimized provided and infinite provided and infinite of the optimized provided provided and infinite of the optimized provided provided provided and infinite of the optimized provided prov	General practice visits \ddagger	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
Propensity score (SD) 0.5 (0.2) 0.5 (0.2) 0.002 0.4 (0.2) 0.4 (0.2) 0.6 (0.1) OA conservativities BMI holds mass index: a number: y years: SD strandard deviation: NSAID non-strandal anti-inflammatory dura: ACF anti-density conservativities and service and serv	Specialist referrals \sharp	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
AA ootsooseheidio RMI kodu maaa indaer n numbar v vaare SD standard daviation. NSAID non-stanvidal anti-inflammatoru dmar ACF anviotancin convartii	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)	0.00
Or, oscoaturius, DWI, Goty mass mucs, it, numoet, y, years, DV, standar ueviation, NOV-Storouat ant-initiating or ug. ACE, anglotensin convention reuptake inhibitor; SNRI, Serotonin-norepinephrine reuptake inhibitor; PPIs, proton pump inhibitors; H2 blockers, histamine-2 blockers.	OA, osteoarthritis; BMI, body m reuptake inhibitor; SNRI, Seroto	ass index; n, numł nin-norepinephrin	oer; y, years; SD, st e reuptake inhibito	andard deviation; NS r; PPIs, proton pump	AID, non-steroida inhibitors; H2 bloo	ll anti-inflammator ckers, histamine-2	y drug; ACE, angiote blockers.	nsin converting en	zyme; SSRI, Selec	ctive serotonin

Osteoarthritis Cartilage. Author manuscript; available in PMC 2021 February 01.

 $\dot{\tau}$ 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.

fFrequency 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.