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High- vs. low-dose diclofenac and cardiovascular risks: a target trial emulation

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ABSTRACT

Aims: To examine the dose-dependency of diclofenac's cardiovascular risks.

Methods and results: Using Danish health registries and the target trial emulation design, we conducted a series of 300 nationwide cohort studies during 1996–2020, each mimicking the strict design criteria of a clinical trial. Adults eligible for inclusion had no recent NSAID prescriptions, contraindications (gastrointestinal diseases, thrombocytopenia, or heart failure), or conditions with

low adherence (dementia or psychiatric disease). Diclofenac initiators were compared to healthcare-seeking non-initiators and head-to-head using an approximated high dose of ≥150 mg/day vs. low dose of <150 mg/day. Cox regression was used to compute the incidence rate ratio (IRR) of major adverse cardiovascular events (MACE) within 30 days following initiation. We adjusted for age, sex, calendar period, comorbidity, comedication, and socioeconomic position. Compared with non-initiators (n=3,789,617), diclofenac initiators (n=1,894,834) had an approximately 50% increased rate of MACE (IRR 1.53, 95% confidence interval [CI]: 1.43–1.63), reflecting IRRs of 1.54 (95% CI: 1.40–1.69) for myocardial infarction, 1.29 (1.14–1.45) for ischemic stroke, and 1.92 (1.71–2.16) for cardiac death. The risk increase was observed for most conditions with chronic pain, in particular headache (IRR 5.10, 95% CI: 1.46–17.85). The risk increase was similar for initiators of high- (IRR 1.55, 95% CI: 1.40–1.71) and low-dose diclofenac (IRR 1.52, 1.41–1.63), which was confirmed in a head-to-head analysis (IRR 1.01, 95% CI: 0.90–1.12).

Conclusions: Initiators of high- and low-dose diclofenac had comparable increased cardiovascular risks. This finding provides evidence against the assumption that low-dose diclofenac is risk-neutral.

INTRODUCTION

The cardiovascular risks of non-steroidal anti-inflammatory drugs (NSAIDs) remain a major safety concern after rofecoxib's thromboembolic properties were revealed.[1] Diclofenac has cyclo-oxygenase (COX)-2 selectivity similar to coxibs[2] and the European Medicines Agency has called for an assessment of its safety.[3] Level 1a evidence supports that the cardiovascular risks of diclofenac are comparable with those of coxibs[4] and worse than those of other traditional NSAIDs.[5] Yet, the importance of dose remains unknown.

Randomized trials have examined outcomes related only to high-dose diclofenac (150 mg/day).[4] It remains therefore unclear whether the adverse effects of diclofenac also relate to low-dose formulations. It is also unknown whether any dose-dependent risks depend on age, sex,

baseline cardiovascular risk, or indication for chronic use, such as musculoskeletal disorders, headache, or cancer.

Underscoring the public health importance, diclofenac is the most frequently utilized NSAID in low-, middle-, and high-income countries. It is available over-the-counter in low doses in most countries,[6] and also continues to be prescribed, even to cardiac patients,[7] under the unproven assumption that it is risk-neutral in low doses.[8] Randomization to different doses of diclofenac has become unethical because of its adverse cardiovascular risk profile.[5,9] Questions about dose-dependency therefore cannot be answered using randomized controlled trials (RCTs). To provide the best alternative evidence to support clinical decision making, we emulated such target trials to compare the cardiovascular risks of high- vs. low-dose diclofenac.

METHODS

Setting

The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including diclofenac.[10] Individual-level linkage of all Danish registries is possible using the unique personal identifier assigned to each Danish citizen at birth and to residents upon immigration.[11]

All NSAIDs require a prescription in Denmark, except for ibuprofen (200 mg tablets) and diclofenac during the brief period from July 16, 2007 to December 14, 2008.[12] However, regular users of diclofenac during the 2007–2008 period also had an incentive to obtain it by prescription because prescription costs were partially reimbursed through the Danish National Health Service's insurance program.[12]

Data sources

We used the Danish National Prescription Registry to identify drug use, as registered by Anatomical Therapeutic Chemical codes.[10] Since 1995, this registry has maintained detailed records of all prescriptions dispensed from all Danish pharmacies.[10] We used the Danish National Patient Registry, which covers all Danish hospitals, to identify comorbidities and non-fatal outcomes.[13] Each hospital discharge since 1977 and each outpatient clinic visit since 1995 is recorded in the registry with one primary diagnosis and potentially several secondary discharge diagnoses classified according to the *International Classification of Diseases*, *Eighth Revision* until the end of 1993 and *Tenth Revision* thereafter.[13] Data on contacts with general practitioners were obtained from the National Health Service Registry.[14] Mortality and migration data were obtained from the Danish Civil Registration System,[11] which has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[11] Cause of death data were obtained from the Danish Register of Causes of Death.[15] All registry codes are provided in eTable 1.

Study design

As previously described,[5] we used population-based registries to conduct a series of cohort studies known as target trial emulations. Here, we emulated the eligibility criteria, washout period, treatment groups, and follow-up period of a hypothetical RCT (our target trial), as it could have been designed if ethically possible (Figure 1 and eTable 2).[16,17] Study entry, on the date of prescription redemption for initiators and the matching date for non-initiators, constituted the baseline for each member of the study cohorts. *Eligible* persons at baseline were adults (≥18 years) with (1) ≥365 days of continuous prescription records; (2) no NSAID prescriptions redeemed on the date of diclofenac redemption or within 365 days before, and (3) not meeting any exclusion

criteria (Figure 2 provides flow chart).

Exclusion criteria were based on all information recorded in the Danish National Patient Registry within the past five years and in the Danish National Prescription Registry within the past 90 days.[8,11] Exclusion criteria were based on likelihood of low adherence (dementia, schizophrenia, or antipsychotic drug use) and labelled contraindications (ulcer disease/anti-ulcer drugs, gastrointestinal bleeding, inflammatory bowel disease, thrombocytopenia, and heart failure).[18]

Among all eligible individuals in January 1996 (the first trial month), we identified *diclofenac initiators* and *healthcare-seeking non-initiators*. Non-initiators were matched 2:1 to initiators on age and sex and had to have ≥1 contact with a general practitioner within 90 days before baseline to match the healthcare-seeking behaviour of initiators. To increase the number of initiators and events, we applied the above approach to every month between January 1996 and December 2020, thereby creating a series of 300 target trial emulations, each with a one-month enrolment period. As an analogue to the wash-out period used for diclofenac initiators, we required that non-initiators had not enrolled in any trial during the previous 365 days. In all trials, enrolled individuals were followed from baseline until the first occurrence of a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up, whichever occurred first.

Diclofenac dose

We examined the cardiovascular risk associated with diclofenac initiation by comparing (1) initiators vs. non-initiators, overall and stratified by dose; and (2) initiators of high vs. low dose (head-to-head). The cut-off between high- and low-dose diclofenac does not have a standard definition. Previous trials typically used a daily dose of 150 mg as a measure of high dose.[4] As the prescribed drug dose is not available in the prescription registry, we approximated daily dose based on pill dose. The recommended average dosing of diclofenac in Danish national guidelines is two

to three times a day.[19] Counts obtained in a feasibility study revealed that less than 1% of all diclofenac prescriptions were for either 12.5 mg or 25 mg pills, approximately 70% of prescriptions were for 50 mg pills, and close to 30% were for either 75 or 100 mg pills. Taking into consideration previous categorization of diclofenac doses in RCTs, recommended daily dosing, and prescribed pill doses, we defined high dose (≥150 mg/daily) as redemption of ≥75 mg pills and low dose (<150 mg/daily) as redemption of ≤50 mg pills.

Endpoints

The primary endpoint — Major Adverse Cardiovascular Events (MACE) — was a composite of myocardial infarction, ischemic stroke, and cardiac death. Nonfatal events were identified from the inpatient primary or secondary diagnoses recorded after baseline. Cardiac death was defined as death from any cardiac cause. Secondary endpoints included the individual MACE components.

Baseline characteristics

We characterized the study cohort by age, sex, comorbidities, comedication use, and socioeconomic position, as listed in Table 1. Comorbidity was based on a complete five-year inpatient and outpatient medical history obtained from the Danish National Patient Registry (both primary and secondary diagnoses). Comedication use was defined as a redeemed prescription for a drug other than diclofenac within 90 days before enrolment. To increase the completeness of diabetes, chronic obstructive pulmonary disease, and hypertension, we combined diagnoses with redeemed prescriptions for diabetic, respiratory, or antihypertensive drugs. We defined hypertension as a hospital diagnosis or prescription redemption of ≥2 antihypertensive drug classes within 90 days before enrolment.

Statistical analyses

Main analysis

We calculated incidence rates per 100 person-years. We estimated an observational analogue of the intention-to-treat hazard ratio as a measure of the incidence rate ratio (IRR), by fitting a Cox proportional-hazards model, using time since start of follow-up as the time scale and a time-independent covariate for treatment assignment. We pooled data from all trials into a single model and included each trial as a stratum in the regression (using values from 1 to 300). The covariable values for each person-'trial' were based on the data recorded most recently at the start of the respective 'trial'. Because individuals could participate in more than one 'trial', we used a robust variance estimator to estimate conservative 95% confidence intervals.[20] Adjustments were made for age, sex, calendar period, comorbidities, and co-medication use, as listed in Table 1.

Subgroup analyses

We stratified our analyses by age, sex, baseline cardiovascular risk, and conditions with chronic pain. In addition to analyses focusing on the primary low-risk population (defined by the eligibility criteria), further analyses were restricted to patients with diabetes mellitus (*i.e.*, moderate baseline risk) and previous myocardial infarction (*i.e.*, high baseline risk). Conditions with chronic pain were categorized as inflammatory rheumatic disease, degenerative rheumatic disease, soft tissue disorders, osteoporosis, headache, and cancer.

Sensitivity analyses

We performed the following sensitivity analyses: (1) to reduce the influence of participation in consecutive trials, we added previous trial participation as an exclusion criterion; (2) to reduce confounding from socioeconomics position, we adjusted additionally for civil status, employment, income quartile, and educational level; (3) to examine the sensitivity of outcome definitions, we restricted the endpoints to primary diagnoses and first-time events; (4) to provide further insights into the chosen dose cut-off, we compared initiators taking diclofenac at all individual tablet doses against non-initiators, as well as against each other using 50 mg as reference; and (5) as accumulating prescriptions during follow-up potentially could indicate a higher average daily dose than estimated from the prescribed pill dose, we examined the proportion of patients redeeming additional diclofenac prescriptions during the 30-day follow-up, and the influence of censoring on such prescription redemptions.

RESULTS

Baseline characteristics

We included 1,894,834 diclofenac initiators, including 1,349,623 on low dose and 545,211 on high dose, and 3,789,617 healthcare-seeking non-initiators. With a wash-out period of 365 days, the majority (71%) of diclofenac initiators participated only in one trial; 19% participated in two trials; 6.2% in three trials; 2.2% in four trials; and only 1.5% in 5 or more trials. Non-initiators and diclofenac initiators were similar overall regarding age (median 51 years), sex (45% male), and prevalence of rheumatic diseases and hyperthyroidism. Except for obesity, diclofenac initiators had a lower prevalence of cardiovascular-related comorbidities (chronic kidney disease, diabetes, COPD, and hypertension) compared with non-initiators. Initiators of high-dose diclofenac were

slightly more likely to be women and have comorbidity than initiators of low-dose diclofenac (Table 1).

Initiators vs. non-initiators

We observed 3903 MACE (1755 MIs, 1170 ischemic strokes, and 1156 cardiac deaths) during 470,451 person-years of follow-up. Overall MACE rates per 100 person-years were 1.01 for diclofenac initiators and 0.74 for healthcare-seeking non-initiators (eTable 3). We found a 50% higher MACE rate among diclofenac initiators compared with non-initiators (IRR 1.53, 95% confidence interval [CI]: 1.43–1.63) (Figure 3 and eTable 3). The IRR was consistently increased for all the individual components of MACE: 1.54 (95% CI: 1.40–1.69) for MI, 1.29 (1.14–1.45) for ischemic stroke, and 1.92 (1.71–2.16) for cardiac death.

Comparing diclofenac initiators with non-initiators (Figure 4, left panel; eTables 5–6), we found that the adjusted IRR for MACE appeared higher for women (1.81, 95% CI: 1.63–2.00) than for men (1.37, 95% CI: 1.26–1.49); was independent of age; and was higher in patients with low baseline risk (1.71, 95% CI: 1.59–1.84) compared to those with moderate (1.49, 95% CI: 1.24–1.79) or high baseline risk (0.98, 95% CI: 0.83–1.16). The results were also consistent with those of the main analyses when we compared diclofenac initiators vs. non-initiators among patients with inflammatory rheumatic disease, soft tissue disease, osteoporosis, and cancer. However, the effect estimate appeared reduced among diclofenac initiators compared with non-initiators among patients with degenerative rheumatic disease (IRR 1.05, 95% CI: 0.85–1.29) and further increased among patients with headache (IRR 5.10, 95% CI: 1.46–17.85).

High vs. low dose

When comparing diclofenac initiators with non-initiators (Figure 3), the magnitude of effect on MACE did not differ between initiators of high-dose (IRR 1.55, 95% CI: 1.40–1.71) and low-dose

diclofenac (IRR 1.52, 95% CI: 1.41–1.63). Consistently, when comparing initiators of high- and low-dose diclofenac directly (Figure 5 and eTable 4), we found almost identical rates of MACE with an adjusted IRR of 1.01 (95% CI: 0.90–1.12). This result was consistent for the individual components of MACE (Figure 5) as well as all subgroup analyses (Figure 4, right panel; eTables 5–6).

Sensitivity analyses

The results were consistent with those of the main analysis: (1) when restricting to enrollment in only one trial (data not shown); (2) after adjusting for socioeconomic position (data not shown); (3) when restricting to primary diagnoses and first-time events (eTables 7–8); (4) when changing the cut-off to categorize high and low doses (eTables 9–10); and (5) when censoring on any additional diclofenac prescription redemptions during follow-up (occurred for 12% of both low-dose and high-dose initiators; adjusted IRR for MACE=1.01, 95% CI: 0.90–1.13 when comparing high-dose vs. low-dose).

DISCUSSION

We found that diclofenac initiators had an approximately 50% increased rate of MACE compared with healthcare seeking non-initiators. This result was supported by consistently increased rates for myocardial infarction, ischemic stroke, and cardiac death. The rate increase was highest in women and individuals with low baseline risk. Importantly, the increased rate of MACE was comparable in magnitude for initiators of high- and low-dose diclofenac, as categorized in our study. The head-to-head comparison of high- and low-dose initiators confirmed these results with a relative effect estimate of 1. Also, the cardiovascular risks associated with diclofenac initiation were observed also for patients with chronic pain related to inflammatory rheumatic disease, soft tissue disease,

osteoporosis, headache, and cancer. Most pronounced, patients with headache had a 5-fold increased rate of MACE after diclofenac initiation.

Previous literature

Meta-analyses of existing randomized[4] trial and observational data[21] have found consistently that diclofenac use, compared with no use, is associated with MACE and that the magnitude of risk for high-dose diclofenac (IRR 1.41, 95% CI: 1.12–1.78) is comparable to that for coxibs (IRR 1.37, 95% CI: 1.14–1.66).[4] Initiation of diclofenac has also been associated with increased cardiovascular risk compared with paracetamol and nonselective NSAIDs (ibuprofen and naproxen).[5] Despite the call for further safety assessment of diclofenac by the European Medicines Agency,[3] studies elucidating the dose-dependency of diclofenac's cardiovascular risks are lacking. Meta-analyses of RCTs have been unable to provide answers as >99% of all trials with cardiovascular outcomes have used diclofenac in high doses,[4] rendering it impossible to make inferences about or comparisons with low-dose diclofenac. In contrast, meta-analyses on the effectiveness of diclofenac dose for the treatment of pain in knee or hip osteoarthritis could not show superiority of low-dose diclofenac (70 mg/day) compared with placebo.[22] Balancing risks and benefits by combining these results with our, it seems increasingly difficult to accept associated cardiovascular side effects of low-dose diclofenac, if not even effective for pain relief.

We previously provided stratum-specific estimates of the cardiovascular risks of diclofenac compared with non-initiators by baseline cardiovascular risk and dose.[5] Although we already then achieved larger sample sizes than previous trials combined, our estimates were still limited by imprecision (data only until 2016) and potential confounding by indication (comparison made only with non-initiators).[5] Our current study addressed these limitations by increasing sample size (data through 2020), comparing high- and low-dose initiators directly, adjusting additionally for socioeconomic position, and examining effect modification by underlying type of chronic pain.

Over-the-counter and prescription sales of diclofenac remain common worldwide despite persistent concerns about its cardiovascular safety over decades.[7] Unproven assumptions about presumed risk-neutral doses of diclofenac likely influence the inappropriate use.[9] Nonetheless, initiatives from medical societies and medicines agencies have proven effective in reducing diclofenac use in some countries like the Scandinavian countries. Thus, in Denmark the number of persons using diclofenac has declined by more than 75% since 2008[23] as direct consequence of recommendations from the Danish Medicines Agency in 2008 and Danish Society for Cardiology in 2009 to use diclofenac with caution due to an increased risk of cardiovascular disease.[12] Following the abovementioned study from 2018,[5] the medicines agencies in both Norway and Sweden have also announced their withdrawal of over-the-counter diclofenac due to cardiovascular safety concerns.

Mechanisms

The adverse cardiovascular risks of diclofenac are well established.[4,5] Selective COX-2 inhibition in general are assumed to favour thrombosis by inhibiting generation of COX-2-derived vascular prostacyclin without affecting COX-1-mediated thromboxane A_2.[24] COX-2 inhibition is also associated with acceleration of atherogenesis,[25] blood pressure elevation,[26] risk of heart failure decompensation,[27] and arrhythmia.[28] Due to its short half-life of 1–2 hours, diclofenac is prescribed at doses high enough for effective analgesia throughout the dosing interval. The plasma concentration of diclofenac therefore greatly exceeds that necessary to inhibit COX-2 early in the dosing interval and coincidently inhibits COX-1 (attained selectivity).[29] As its plasma concentration falls, diclofenac continues to inhibit COX-2 completely, while its effect on COX-1 subsides gradually, generating a "window" of pure COX-2 inhibition that is considered important for its adverse risk profile.[30] While we can only speculate, our results indicate that these mechanisms also apply to diclofenac in low doses. Finally, the results for diclofenac initiators vs.

non-initiators stratified by baseline risk were consistent with the observation that effect estimates for cardiovascular outcomes associated with NSAID use are typically lower among those at higher baseline risk.[5,31]

Strengths and limitations

The Danish universal health care system and registry infrastructure permitted use of the target trial emulation design.[32] The sample size, with almost 2 million diclofenac initiators, is larger than the combined size of all previous meta-analyses of observational and randomized studies of NSAIDs.[4,21,33] The largest meta-analysis of randomized trials (The Coxib and traditional NSAID Trialists' Collaboration) included 45 major vascular events in 47 trials comparing different traditional NSAIDs against placebo (18,018 participants; 8,253 person-years) and only 3 major vascular events in the only trial comparing different traditional NSAIDs (733 participants; 134 person-years).[4] As these trials were not restricted to diclofenac, the event rate during diclofenac exposure was considerable lower.

Our population-based design, in the setting of a tax-supported universal health care system, largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups,[32] The Prescription Registry permitted complete identification of all diclofenac prescriptions,[10] and the influence of over-the-counter diclofenac availability in the brief period around 2007–2008 has been shown to be negligible.[23] Although we had to use prescription data as a proxy for actual diclofenac use, we based drug exposure information on redeemed prescriptions rather than issued prescriptions.[10] Required co-payments increased the likelihood of compliance. A concern is that we used pill dose as proxy for daily dose. Further refinement of dose among chronic users (*e.g.*, using the average duration of time between previous prescription redemptions and number of pills per package) was not possible because diclofenac was primarily used for short-term treatment. Thus, 75% of all initiators redeemed only one prescription

within six months of initiation (only 9% redeemed 10 or more prescriptions in total).[5] Some patients (e.g., those with inflammatory arthritis) may use a higher dose at night (e.g., 100 mg) than during the day (e.g., 50 mg at a time). For this reason, they could have been classified as initiators of high-dose diclofenac (if using 100 mg tablets at night and 50 mg tablets during the day) or of low-dose diclofenac (if using one or two 50 mg tablets at a time). Importantly, our sensitivity analyses showed that using different cut-offs for categorizing dose did not change any conclusions. Our data did not allow differentiation of very low-dose diclofenac (≈25–37.5 mg/daily) because corresponding tablet sizes (12.5 mg) were rarely prescribed in Denmark. The registry-based cardiovascular diagnoses used in the study have been shown to have high positive predictive values[34] and the mortality and migration data were accurate and complete.[11]

The new-user design, inherent in the target trial emulation design, resembled drug allocation in RCTs,[35] but lack of randomization was a limitation. Indication for use was not available in the prescription registry, but we did stratify by the most common chronic pain conditions treated with NSAIDs. Due to the generally shared indications for use, the head-to-head comparison of high- vs. low-dose diclofenac reduced confounding by indication. Still, dose could also reflect severity of underlying diseases. As well, dosing NSAIDs for non-chronic conditions often reflects personal preference among prescribing physicians rather than explicit guidelines. In addition, we note that after applying strict inclusion and exclusion criteria, the baseline characteristics were not substantially different. Hence the unadjusted and adjusted results also were not substantially different. The balance in measured covariates between initiators of high- and low-dose diclofenac also increased the likelihood of balance among unmeasured variables.

Conclusions and implications

Our data indicate that initiation of diclofenac is associated with a cardiovascular health risk, both at high and low doses. These findings applied to most patients with chronic pain, in particular headache. Despite potential side effects, treatment of pain and inflammation with NSAIDs may be

worthwhile for some patients for improving quality of life. Considering its cardiovascular risk profile and poor analgetic effect in low doses, however, there seems little justification to initiate treatment with diclofenac before safer alternatives such as physiotherapy, paracetamol, or nonselective NSAIDs. Our findings provide evidence to support regulatory actions against over-the-counter sales of diclofenac and to guide clinical decision making by countermanding the persisting assumptions about a cardiovascular risk-neutral dose of diclofenac.

Data permission

The study was approved by the Danish Data Protection Agency (record number FSEID-00002467).

Contributorship statement

MS and LAN conceived the study idea. MS, LAP, and LAN designed the study. MS drafted the protocol. LAP collected the data and carried out the analyses. MS organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MS and LAP are the guarantors.

Disclosure

The authors report no conflicts of interest affecting this work.

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Transparency declaration

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.

Ethics committee approval: No ethical committee approval was needed.

Data sharing: Not allowed.

Patient involvement statement: No patient involvement.

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Table 1. Baseline characteristics of diclofenac initiators and non-initiators (1996–2020)

	Diclofenac initiators			Non-initiators†
	Overall	Low dose*	High dose*	
	n (%)	n (%)	n (%)	n (%)
Total	1,894,834 (100)	1,349,623 (100)	545,211 (100)	3,789,617 (100)
Sex, female	1,007,277 (53.2)	712,146 (52.8)	295,131 (54.1)	2,014,529 (53.2)
Age (median, IQR)	48 (35.3–60.1)	48 (35.3–60.1)	48 (35.3–60.1)	48 (35.3–60.1)
18–49 years	1,050,000 (55.4)	771,804 (57.2)	278,196 (51.0)	2,099,769 (55.4)
50–69 years	621,668 (32.8)	424,372 (31.4)	197,296 (36.2)	1,243,643 (32.8)
70 years or more	223,166 (11.8)	153,447 (11.4)	69,719 (12.8)	446,205 (11.8)
Calendar year				
1996–2000	548,112 (28.9)	407,794 (30.2)	140,318 (25.7)	1,096,208 (28.9)
2001–2005	579,678 (30.6)	427,355 (31.7)	152,323 (27.9)	1,159,348 (30.6)
2006–2010	462,497 (24.4)	328,678 (24.4)	133,819 (24.5)	924,975 (24.4)
2011–2015	195,035 (10.3)	123,748 (9.2)	71,287 (13.1)	390,064 (10.3)
2016–2020	109,512 (5.8)	62,048 (4.6)	47,464 (8.7)	219,022 (5.8)
Conditions with chronic pain				
Inflammatory rheumatic disease‡	32,666 (1.7)	21,387 (1.6)	11,279 (2.1)	56,316 (1.5)
Degenerative rheumatic disease§	212,929 (11.2)	144,459 (10.7)	68,470 (12.6)	331,807 (8.8)
Soft tissue disorders‖	126,701 (6.7)	87,035 (6.4)	39,666 (7.3)	203,524 (5.4)
Osteoporosis	12,427 (0.7)	8,155 (0.6)	4,272 (0.8)	30,306 (0.8)
Headache	15,943 (0.8)	10,380 (0.8)	5,563 (1.0)	22,522 (0.6)
Cancer	60,889 (3.2)	41,863 (3.1)	19,026 (3.5)	122,641 (3.2)
Other comorbidities				
Myocardial infarction	10,616 (0.6)	7,467 (0.6)	3,149 (0.6)	34,316 (0.9)
Ischemic stroke	7,029 (0.4)	4,705 (0.3)	2,324 (0.4)	26,356 (0.7)
Venous thromboembolism	9,528 (0.5)	6,388 (0.5)	3,140 (0.6)	26,539 (0.7)
Chronic kidney disease	3,917 (0.2)	2,757 (0.2)	1,160 (0.2)	11,352 (0.3)
Diabetes mellitus	62,052 (3.3)	41,840 (3.1)	20,212 (3.7)	186,312 (4.9)
COPD	97,839 (5.2)	68,855 (5.1)	28,984 (5.3)	265,316 (7.0)
Hypertension	160,619 (8.5)	108,401 (8.0)	52,218 (9.6)	440,956 (11.6)
Obesity	33,326 (1.8)	21,238 (1.6)	12,088 (2.2)	59,568 (1.6)
Hyperthyroidism	10,807 (0.6)	7,419 (0.5)	3,388 (0.6)	28,750 (0.8)
Medication use¶				
ACE inhibitors	63,613 (3.4)	43,255 (3.2)	20,358 (3.7)	196,755 (5.2)
ARBs	37,433 (2.0)	25,055 (1.9)	12,378 (2.3)	98,902 (2.6)
Beta-blockers	84,726 (4.5)	58,182 (4.3)	26,544 (4.9)	247,618 (6.5)
Calcium channel blockers	81,794 (4.3)	55,797 (4.1)	25,997 (4.8)	236,512 (6.2)
Diuretics	127,125 (6.7)	87,960 (6.5)	39,165 (7.2)	331,235 (8.7)
Statins	88,869 (4.7)	59,548 (4.4)	29,321 (5.4)	251,160 (6.6)
SSRIs	57,195 (3.0)	39,543 (2.9)	17,652 (3.2)	177,987 (4.7)
Systemic glucocorticoids	44,044 (2.3)	30,937 (2.3)	13,107 (2.4)	81,672 (2.2)
Socioeconomic position				
Civil status				

Married	1,177,076 (62.1)	822,119 (60.9)	354,957 (65.1)	2,295,133 (60.6)
Divorced	201,969 (10.7)	141,466 (10.5)	60,503 (11.1)	401,290 (10.6)
Single	508,667 (26.8)	380,906 (28.2)	127,761 (23.4)	1,084,468 (28.6)
Unknown	7,122 (0.4)	5,132 (0.4)	1,990 (0.4)	8,726 (0.2)
Employment				
Employed	1,245,373 (65.7)	895,530 (66.4)	349,843 (64.2)	2,411,738 (63.6)
Unemployed	151,399 (8.0)	109,815 (8.1)	41,584 (7.6)	309,718 (8.2)
Early retirement	204,365 (10.8)	143,539 (10.6)	60,826 (11.2)	468,565 (12.4)
Pension	291,310 (15.4)	199,153 (14.8)	92,157 (16.9)	598,342 (15.8)
Unknown	2,387 (0.1)	1,586 (0.1)	801 (0.1)	1,254 (0.0)
Income quartiles				
1 (low)	455,904 (24.1)	326,308 (24.2)	129,596 (23.8)	982,645 (25.9)
2	480,744 (25.4)	344,518 (25.5)	136,226 (25.0)	933,002 (24.6)
3	488,496 (25.8)	349,698 (25.9)	138,798 (25.5)	917,667 (24.2)
4 (high)	469,318 (24.8)	328,838 (24.4)	140,480 (25.8)	955,948 (25.2)
Unknown	372 (0.0)	261 (0.0)	111 (0.0)	355 (0.0)
Educational level				
Short	614,014 (32.4)	443,928 (32.9)	170,086 (31.2)	1,162,536 (30.7)
Medium	798,513 (42.1)	569,553 (42.2)	228,960 (42.0)	1,563,113 (41.2)
Long	382,835 (20.2)	265,202 (19.7)	117,633 (21.6)	881,343 (23.3)
Unknown	99,472 (5.2)	70,940 (5.3)	28,532 (5.2)	182,625 (4.8)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, Interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SCTD, systemic connective tissue disease; SSRI, selective serotonin reuptake inhibitor

*Doses were defined as high (>50 mg pills) and low (≤50 mg pills).

†Healthcare-seeking non-initiators of any NSAIDs.

‡ Defined as reactive arthritis, inflammatory polyarthritis, inflammatory spondylopathies, or systemic connective tissue disease.

§ Defined as osteoarthritis, other joint disorders (including arthralgia), spondylosis and other spondylopathies, intervertebral disc disorders, or dorsalgia.

|| Defined as disorders of synovium and tendons, fibromyalgia, or other soft tissue disorders.

¶ Redeemed prescription within 90 days.

Figure 1. Study design

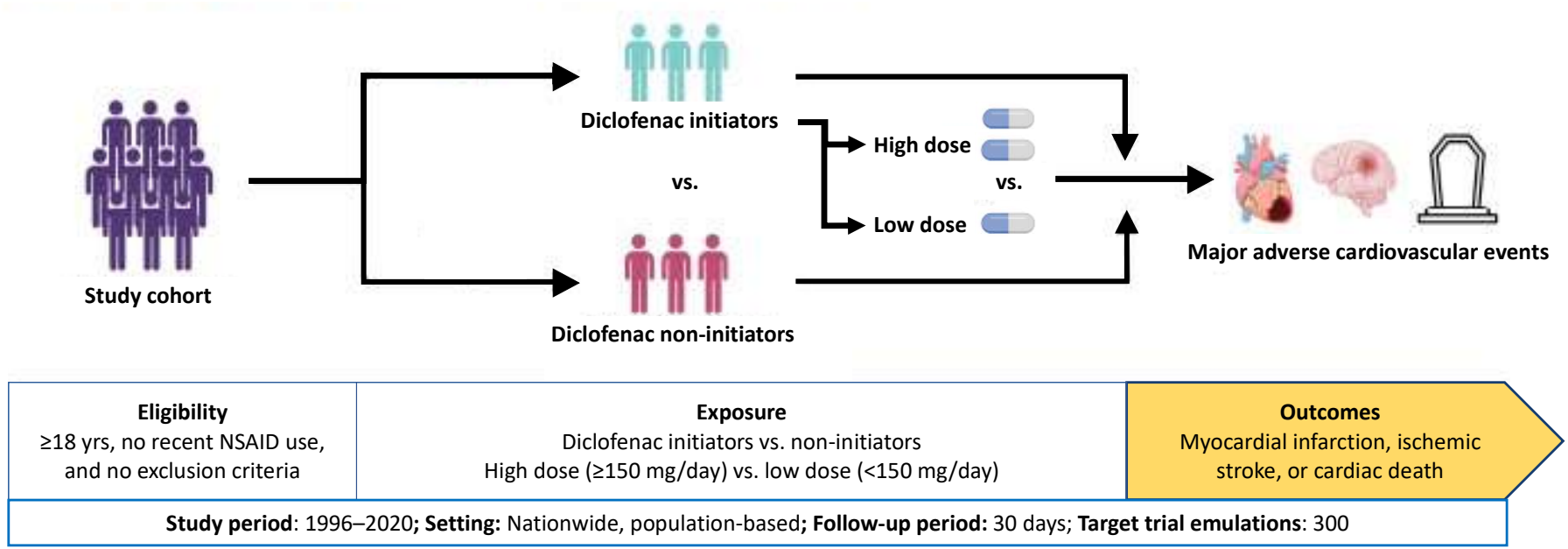

Figure 2. Flow chart of study cohort

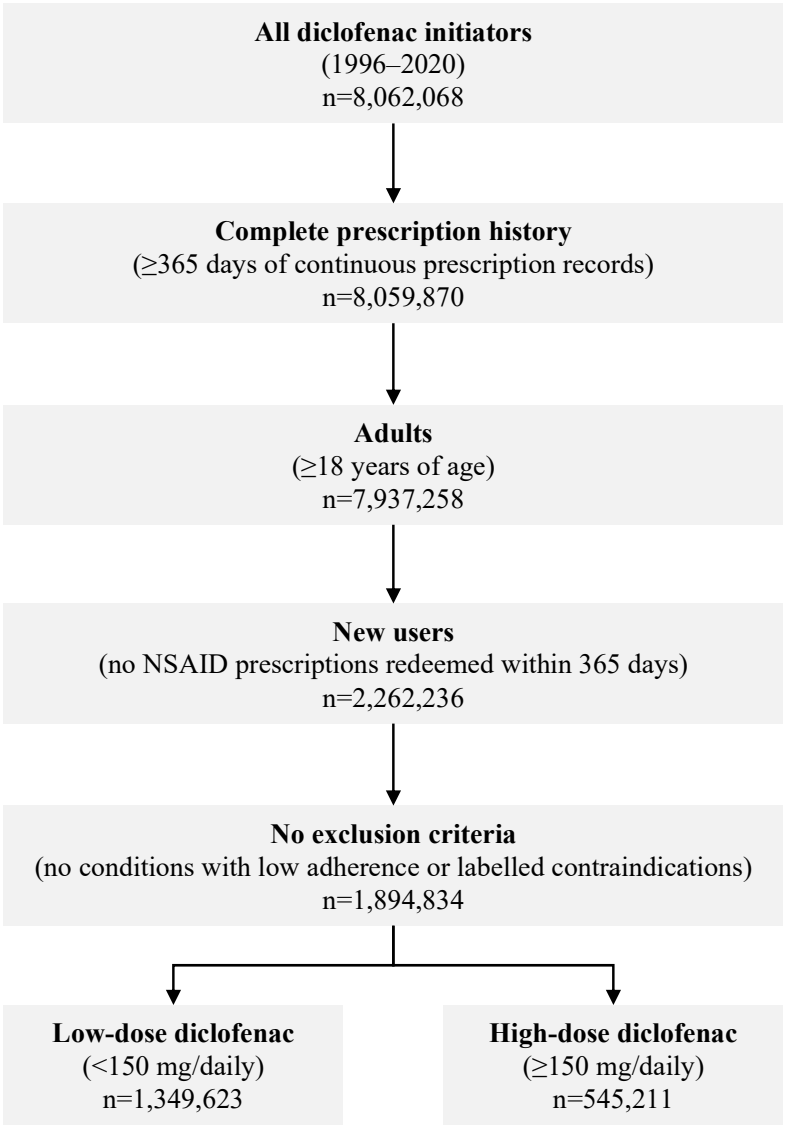

Figure 3. 30-day major adverse cardiovascular event rates among diclofenac initiators vs. non-initiators according to dose.

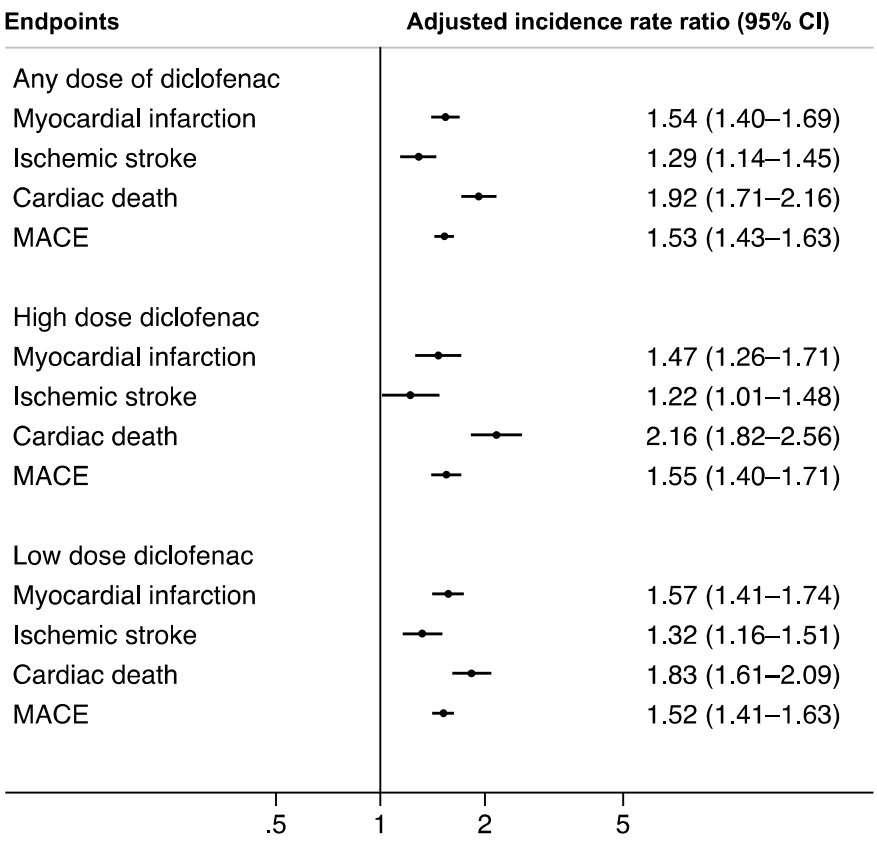

Figure 4. Major adverse cardiovascular event rates among diclofenac initiators vs. non-initiators and initiators of high-dose vs. low-dose diclofenac, by sex, age, baseline cardiovascular risk, and conditions with chronic pain.

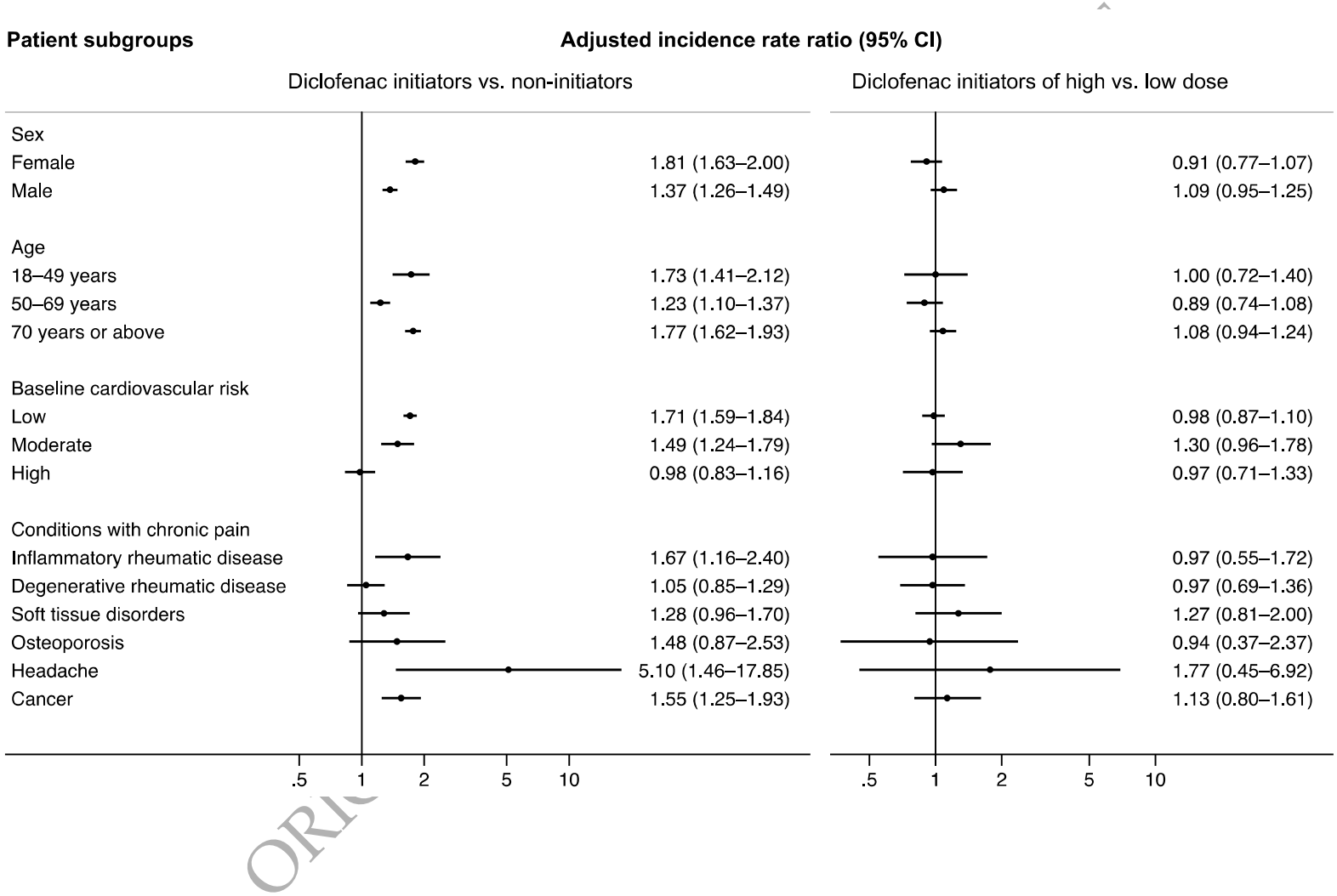

Figure 5. 30-day major adverse cardiovascular event rates among initiators of high-dose vs. low-dose diclofenac.