Diclofenac use and cardiovascular risks: series of nationwide cohort studies

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Cite this as: *BMJ* 2018;362:k3426
http://dx.doi.org/10.1136/bmj.k3426

Accepted: 19 July 2018

ABSTRACT

OBJECTIVE
To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of paracetamol, and no initiation.

DESIGN
Series of 252 nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design).

SETTING
Danish, nationwide, population based health registries (1996-2016).

PARTICIPANTS
Individuals eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases (that is, with low baseline risk). The study included 1 370 832 diclofenac initiators, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 healthcare seeking paracetamol initiators matched by propensity score, and 1 303 209 healthcare seeking non-initiators also matched by propensity score.

MAIN OUTCOME MEASURES
Cox proportional hazards regression was used to compute the intention to treat hazard ratio (as a measure of the incidence rate ratio) of major adverse cardiovascular events within 30 days of initiation.

RESULTS
The adverse event rate among diclofenac initiators increased by 50% compared with non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7), 20% compared with paracetamol or ibuprofen initiators (both 1.2, 1.1 to 1.3), and 30% compared with naproxen initiators (1.3, 1.1 to 1.5). The event rate for diclofenac initiators increased for each component of the combined endpoint (1.2 (1.1 to 1.4) for atrial fibrillation/flutter, 1.6 (1.3 to 2.0) for ischaemic stroke, 1.7 (1.4 to 2.0) for heart failure, 1.9 (1.6 to 2.2) for myocardial infarction, and 1.7 (1.4 to 2.1) for cardiac death) as well as for low doses of diclofenac, compared with non-initiators. Although the relative risk of major adverse cardiovascular events was highest in individuals with low or moderate baseline risk (that is, diabetes mellitus), the absolute risk was highest in individuals with high baseline risk (that is, previous myocardial infarction or heart failure). Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation.

CONCLUSIONS
Diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Diclofenac is the most commonly used non-steroidal anti-inflammatory drug (NSAID) in low, middle, and high income countries

Its cardiovascular risks compared with other traditional NSAIDs have never been examined in a randomised controlled trial, and current concerns about these risks make such a trial unethical to conduct

A series of Danish nationwide cohort studies, each mimicking the strict design criteria of a clinical trial (emulated trial design), included 1 370 832 initiators of diclofenac, 3 878 454 initiators of ibuprofen, 291 490 initiators of naproxen, 764 781 healthcare seeking initiators of paracetamol (matched by propensity score), and 1 303 209 healthcare seeking NSAID non-initiators (matched by propensity score)

WHAT THIS STUDY ADDS

The incidence rate ratio of major adverse cardiovascular events at 30 days among diclofenac initiators increased by 50% versus non-initiators, by 20% versus ibuprofen or paracetamol initiators, and by 30% versus naproxen initiators

The increased risk was observed for atrial fibrillation or flutter, ischaemic stroke, heart failure, myocardial infarction, and cardiac death; both sexes of all ages; and even at low doses of diclofenac.

Risk of upper gastrointestinal bleeding at 30 days with diclofenac was similar to that of naproxen, but considerably higher than for no NSAID initiation, paracetamol, and ibuprofen

Introduction

The cardiovascular risks of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) remain a major safety concern after rofecoxib's thromboembolic properties were revealed.[1] Diclofenac is a traditional non-steroidal anti-inflammatory drug (NSAID) with cyclo-oxygenase-2 (COX 2) selectivity similar to COX 2 inhibitors,[2] but its cardiovascular risks compared with those of other traditional NSAIDs have never been examined in a randomised controlled trial.[3] Current concerns about these risks, as stated by the European Society of Cardiology,[4] now make such a trial unethical to conduct.

Diclofenac is the most frequently used NSAID in low, middle, and high income countries, and is available over the counter in most countries;[5] therefore, its cardiovascular risk profile is of major clinical and public health importance. As a consequence, the European Medicines Agency has again called for a safety assessment of diclofenac.[6] In response, we conducted a series of cohort studies, each mimicking the strict design criteria of a clinical trial (a so-called emulated trial design), to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs.

Methods

Setting

The Danish national health service provides universal tax supported healthcare, guaranteeing unfettered access to general practitioners and hospitals, and part reimbursement for prescribed drug treatments, including diclofenac.[7] Individual level linkage of all Danish registries is possible by use of a unique personal identifier assigned to each Danish citizen at birth and to residents on immigration.[8]

Apart from low dose ibuprofen (200 mg) and diclofenac (from 16 July 2007 to 14 December 2008), all non-aspirin NSAIDs require a prescription in Denmark.[9] Regular users of over-the-counter NSAIDs have an incentive to obtain a prescription because prescription costs are partially reimbursed through the Danish national health service's insurance programme.[9]

Data sources

We used the Danish National Patient Registry covering all Danish hospitals to identify the study population, their comorbidities, and non-fatal endpoints.[10] Each hospital discharge or outpatient visit (since 1977 and 1995, respectively) is recorded in the registry with one primary diagnosis and potentially several secondary diagnoses classified according to the ICD-8 (international classification of diseases, 8th revision) and ICD-10 thereafter.[10] Data on general practice contacts were obtained from the Danish National Health Insurance Service Registry.[11]

We used the Danish National Prescription Registry to identify drug use.[7] Since 1995, this registry has maintained detailed records of all prescriptions dispensed from all Danish pharmacies.[7] We obtained mortality and migration data from the Danish Civil Registration System,[8] which has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[8] Cause of death data were obtained from the Danish Register of Causes of Death.[12]

Design

We used population based registries to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical controlled trial (eTable 1).[13 14] Eligible individuals were those aged at least 18 years with at least one year of continuous prescription records before date of study entry, who did not meet the exclusion criteria (listed below), and who did not redeem NSAID prescriptions in the 12 month washout period before enrolment. Among all eligible individuals in January 1996 (the first trial month), we identified all diclofenac initiators and the following three comparator groups:

- Active NSAID comparators: we identified initiators of ibuprofen or naproxen to enable comparison with other traditional NSAIDs. Initiation was defined as filling a first prescription within the trial month. Any person who fulfilled criteria for both the diclofenac group and an active comparator group was categorised according to the first drug redeemed. If the two drugs were redeemed on the same day, the person was excluded.
- Non-user comparators: we identified non-initiators of NSAIDs from the general population, who were alive and fulfilled the eligibility criteria in January 1996. To account for healthcare seeking behaviour, further restriction was made to individuals with a general practice contact within the trial month. We calculated the propensity score for all eligible individuals initiating diclofenac at enrolment by fitting a logistic regression model including covariates on sex, age, year, comorbidity, and drug treatment use.[15] We then matched non-initiators to diclofenac initiators (1:1) by propensity score within a maximum matching range of 0.025 and without replacement.
- Active non-NSAID comparator: we matched paracetamol initiators from the general population to diclofenac initiators by propensity score. We used a similar matching approach as above, except for adding to the general practice contact criteria that comparators should also redeem a prescription for paracetamol within the trial month. As an analogue to the washout period in the active NSAID comparisons, we also required that paracetamol initiators and NSAID non-initiators had not been enrolled in trials in the previous 12 months.

In all models, enrolled individuals in the January trial were followed from baseline (that is, date of prescription redemption for NSAID/paracetamol initiators and general practice contact for non-initiators) until the first occurrence of a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up, whichever occurred first.

To increase the number of initiators and events, we subsequently applied the approach described above to every month between January 1996 and December 2016, thereby creating a series of emulated trials (n=252), each with a one month enrolment period (fig 1). Fulfilling the eligible criteria at any given baseline, participants could potentially take part in several trials. Thus, NSAID non-initiators in the January 1996 "trial" could still be included in the January 1997 "trial." By contrast, all enrolled individuals in the January 1996 "trial" were ineligible for inclusion in the subsequent 12 months.

Exclusion criteria

Exclusion criteria were based on all information recorded in the Danish National Patient Registry (within five years) and Danish National Prescription Registry (within one year). Exclusion criteria were previous cardiovascular disease (angina pectoris, myocardial infarction, coronary intervention (percutaneous coronary intervention or coronary artery bypass grafting), heart failure, stroke, peripheral vascular disease, venous thromboembolism, atrial fibrillation or flutter, or use of digoxin, nitrates, antiplatelet drugs, or anticoagulant drugs within one year), chronic kidney

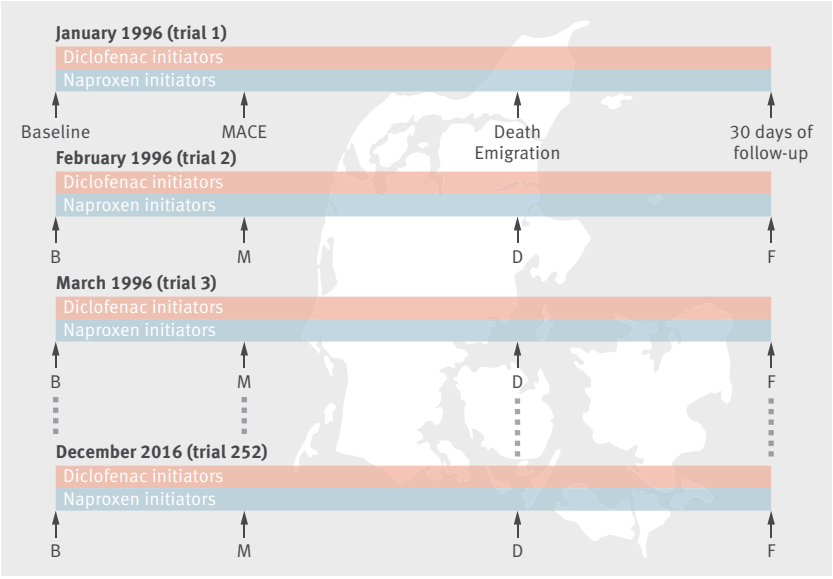

Fig 1 | Emulated trial design, to compare rates of major adverse cardiovascular events among diclofenac initiators with rates among non-initiators or initiators of active comparator drugs in Denmark. Individual level linkage of nationwide population based registries was used to emulate the eligibility criteria, washout period, treatment groups, and follow-up period of a clinical controlled trial. Eligible individuals were aged at least 18 years who had at least one year of prescription history and none of the exclusion criteria. All initiators of diclofenac and naproxen were identified during the month of January 1996. Each person was followed up to a non-fatal endpoint, death, loss to follow-up, or 30 days of follow-up. Enrolment was repeated in the months of February and March, and subsequently for every month up to December 2016. The series of 252 emulated trials were then statistically pooled into one model, generating a sample size of 1 370 832 diclofenac initiators and 291 490 naproxen initiators. A similar approach was used to identify ibuprofen initiators (n=3 878 454) and propensity score matched initiators of paracetamol (n=764 781) and NSAID non-initiators (n=1 303 209). B=baseline; MACE=major adverse cardiovascular events; D=death or emigration; F=30 days of follow-up

disease, chronic liver disease, other alcoholism related diseases, ulcer disease, malignancy, schizophrenia (or use of antipsychotic drugs), or dementia.

Endpoints

The primary endpoint—major adverse cardiovascular events—was a composite of non-fatal events[10] and cardiac death.[8] Non-fatal events were defined as first time inpatient diagnoses of atrial fibrillation or flutter, ischaemic stroke, heart failure, and myocardial infarction.[10] For atrial fibrillation or flutter, we also included first time outpatient diagnoses. Cardiac death was defined as death from any cardiac cause. Secondary endpoints included all the individual components of major adverse cardiovascular events. Finally, we stratified cardiac death according to underlying causes.

Participant characteristics

We characterised the study population by age, sex, comorbidity, and drug treatment use at baseline. We compared the distribution of baseline covariates in the propensity score matched samples using the standardised difference[16] and illustrated graphically the propensity score distribution before and after matching. Comorbidity was based on the complete five year inpatient and outpatient medical history in the Danish National Patient Registry (both primary and secondary diagnoses). Drug treatment use was defined as a redeemed prescription within 90 days before enrolment. To increase the completeness of diabetes, chronic obstructive pulmonary disease, and hypertension ascertainment, we also searched the Danish National Prescription Registry for any previous prescription redemption of diabetic, respiratory, or antihypertensive drugs. We defined hypertension as a hospital diagnosis or redemption of at least two prescriptions for antihypertensive drug classes within 90 days before enrolment.[17] All registry codes are provided in eTable 2.

Intention to treat analysis

We estimated an observational analogue of the intention to treat hazard ratio, as a measure of the incidence rate ratio, 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 one model and included each trial as a stratum in the regression (using values from 1 to 252). The covariate values for each "trial" were based on the data most recently recorded at the start of the respective trial. Because individuals could participate in more than one of these trials, we used a robust variance estimator to estimate conservative 95% confidence intervals.[18] In the active NSAID comparator models, we adjusted for the baseline covariates on sex, age, year, comorbidity, and drug treatment use. Adjustment was used rather than propensity score matching to approximate a trial setting.

Participant subgroups

In addition to our primary low risk population (defined by eligibility criteria), we repeated the sampling and analyses for patients with diabetes mellitus (that is, at moderate cardiovascular risk at baseline) and for patients with previous myocardial infarction or heart failure (that is, at high cardiovascular risk at baseline). In the high risk group, cardiovascular drug use within one year was omitted as an exclusion criterion. To facilitate the interpretation of the relative effect estimates, we also calculated adjusted incidence rate differences according to baseline cardiovascular risk. Finally, we stratified the study population by age (<65, 65-79, or ≥80 years), sex, calendar period (1996-2002, 2003-09, and 2010-16), and diclofenac dose (low dose (<100 mg) *v* high dose (100 mg) tablets).

Sensitivity analyses

We performed the following sensitivity analyses, in order to:

1. Omit the restriction among NSAID non-initiators to healthcare seekers, to examine the confounding-reducing effect of this inclusion criterion
2. Examine upper gastrointestinal bleeding as a control outcome in the model validation

3. Exclude trial sampling from July 2007 to December 2008, to quantify potential non-differential misclassification due to use of diclofenac obtained over the counter
4. Censor patients on redemption of a prescription for an NSAID other than the active comparator drug received at baseline, to examine the potential impact of crossover
5. Allow only one trial entry per person
6. Change the cutoff limit for low dose diclofenac (from <100 mg to <75 mg and <50 mg tablets), to examine the effect of dose definitions, as high dose diclofenac (150 mg/day) has accounted for almost all outcomes in previous trials[3]
7. Examine subtypes of myocardial infarction separately (ST segment elevation, non-ST segment elevation, and unspecified) to investigate differential effects on severity
8. Use a rule-out approach[19] to estimate how strongly a single unmeasured binary confounder would need to be associated with use of diclofenac and major adverse cardiovascular events to fully explain our findings.

As a worst case scenario, we assumed a confounder prevalence of 25% and use of diclofenac by 4% of the population.[9]

Patient involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

Participant characteristics

We identified 1 370 832 diclofenac initiators who met the inclusion criteria, 3 878 454 ibuprofen initiators, 291 490 naproxen initiators, 764 781 matched paracetamol initiators, and 1 303 209 matched non-initiators (67 623 initiators could not be matched, mainly due to advanced age; table 1). Men accounted for about 45% of diclofenac and ibuprofen initiators, 35% of paracetamol initiators, and 40% of naproxen initiators. The median age was 46-49 years among NSAID initiators and 56 years among paracetamol initiators. The proportion of individuals contributing to more than one trial was 31% for diclofenac (1.6% contributed to ≥5 trials), 49.6% for paracetamol (12.3%), 47% for ibuprofen (4.6%), 23% for naproxen (2.2%), and 19% for NSAID non-initiators (0.04%). Diclofenac was initiated primarily for short term treatment. Thus, 44% of patients redeemed one prescription, 19% redeemed two, and 10% redeemed three; only 9% redeemed 10 or more prescriptions. Most diclofenac initiators (75%) redeemed only one prescription within six months of initiation. The design yielded fairly equal distributions of comorbidities and drug treatment use across exposure groups (standardised differences <10%), indicating that diclofenac and ibuprofen/naproxen initiators had similar characteristics and that the propensity score matching was successful (table 1 and eFigure 1).

Event rates

Within 30 days, major adverse cardiovascular events occurred among 1465 (0.10%) diclofenac initiators, 2912 (0.07%) ibuprofen initiators, 205 (0.07%) naproxen initiators, 967 (0.13%) paracetamol initiators, and 898 (0.07%) NSAID non-initiators (eTables 3-4). Corresponding rates of these events per 100 person years were 1.29 (95% confidence interval 1.23 to 1.36) for diclofenac initiators, 0.91 (0.88 to 0.94) for ibuprofen initiators, 0.85 (0.74 to 0.98) for naproxen initiators, 1.53 (1.44 to 1.63) for paracetamol initiators, and 0.83 (0.78 to 0.89) for NSAID non-initiators (eTables 3-4).

Diclofenac *v* non-use

Diclofenac initiators had a 50% increased rate of major adverse cardiovascular events compared with NSAID non-initiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7). Supporting use of a combined endpoint, event rates consistently increased for all individual outcomes: 1.2-fold for atrial fibrillation or flutter, 1.6-fold for ischaemic stroke, 1.7-fold for heart failure, 1.9-fold for myocardial infarction, and 1.7-fold for cardiac death (fig 2 and eTable 5). Cardiac death was driven by death from heart failure (incidence rate ratio 2.3, 1.3 to 4.2), cardiac arrhythmia (1.9, 1.1 to 3.3), and myocardial infarction (1.7, 1.2 to 2.4).

Diclofenac *v* paracetamol

Compared with paracetamol initiators, diclofenac initiators had a 20% increased rate of major adverse cardiovascular events (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3), reflecting a 1.2-fold increased rate of ischaemic stroke and heart failure and a 1.4-fold increased rate of atrial fibrillation or flutter and myocardial infarction (fig 2 and eTable 5). Although overall there was no association with cardiac death (incidence rate ratio 1.0, 0.8 to 1.2), stratification on underlying causes of death revealed a substantial elevated risk of fatal myocardial infarction (1.8, 1.2 to 2.6).

Diclofenac *v* ibuprofen or naproxen

Diclofenac initiators had a 20% increased rate of major adverse cardiovascular events compared with ibuprofen initiators (incidence rate ratio 1.2, 95% confidence interval 1.1 to 1.3) and a 30% increased rate compared with naproxen initiators (1.3, 1.1 to 1.5; fig 2 and eTable 5). With ibuprofen as reference, the incidence rate ratio increased 1.1-fold for atrial fibrillation or flutter and heart failure, 1.2-fold for myocardial infarction, 1.3-fold for ischaemic stroke, and 1.5-fold for cardiac death. Cardiac death was driven by death due to heart failure (incidence rate ratio 1.9, 1.2 to 3.0), cardiac arrhythmias (1.7, 1.1 to 2.7), and myocardial infarction (1.4, 1.1 to 1.8).

Table 1 | Baseline characteristics of NSAID initiators, paracetamol initiators, and NSAID non-initiators in Denmark (1996-2016)

	Active NSAID comparison					Active non-NSAID comparison			Non-user comparison		
	Diclofenac initiators (No (%))	Ibuprofen initiators		Naproxen Initiators		Diclofenac initiators (No (%))	Paracetamol initiators*		Diclofenac initiators (No (%))	NSAID non-initiators*	
Total		No (%)	SD (%)†	No (%)	SD (%)†		No (%)	SD (%)†		No (%)	SD (%)†
No (%)	1 370 832 (100)	3 878 454 (100)	—	291 490 (100)	—	764 781 (100)	764 781 (100)	—	1 303 209 (100)	1 303 209 (100)	—
Sex											
Male	620 687 (45.3)	1 794 969 (46.3)	−2.0	118 378 (40.6)	9.4	283 531 (37.1)	279 948 (36.6)	1.0	593 396 (45.5)	598 222 (45.9)	−0.7
Age											
Median (IQR)	48 (37.1-59.2)	48 (36.5-58.6)	—	46 (33.9-57.5)	—	56 (45.4-65.6)	56 (45.0-65.5)	—	49 (37.1-59.2)	49 (37.0-59.6)	—
18-49 years	748 873 (54.6)	2 171 622 (56.0)	−2.7	175 777 (60.3)	−11.5	281 997 (36.9)	281 997 (36.9)	−3.1	713 017 (54.7)	711 147 (54.6)	0.3
50-69 years	484 815 (35.4)	1 366 910 (35.2)	0.3	89 280 (30.6)	10.1	348 728 (45.6)	348 728 (45.6)	4.3	460 664 (35.3)	450 367 (34.6)	1.7
≥70 years	137 144 (10.0)	339 922 (8.8)	4.3	26 433 (9.1)	3.2	134 056 (17.5)	134 056 (17.5)	−1.8	129 528 (9.9)	141 695 (10.9)	−3.1
Calendar year											
1996-2000	433 181 (31.6)	730 107 (18.8)	29.7	116 749 (40.1)	−17.7	185 323 (24.2)	185 323 (24.2)	0.0	414 328 (31.8)	414 328 (31.8)	0.0
2001-05	435 908 (31.8)	858 260 (22.1)	21.9	62 814 (21.5)	23.3	217 096 (28.4)	217 096 (28.4)	0.0	412 369 (31.6)	412 369 (31.6)	0.0
2006-10	341 030 (24.9)	967 276 (24.9)	−0.1	46 329 (15.9)	22.4	217 334 (28.4)	217 334 (28.4)	0.0	322 405 (24.7)	322 405 (24.7)	0.0
2011-16	160 713 (11.7)	1 322 811 (34.1)	−55.3	65 598 (22.5)	−28.9	145 028 (19.0)	145 028 (19.0)	0.0	154 107 (11.8)	154 107 (11.8)	0.0
Comorbidities											
Diabetes	32 491 (2.4)	101 116 (2.6)	−1.5	6950 (2.4)	−0.1	28 137 (3.7)	28 137 (3.7)	−0.4	30 408 (2.3)	29 773 (2.3)	0.3
COPD	70 718 (5.2)	199 052 (5.1)	0.1	14 662 (5.0)	0.6	57 414 (7.5)	57 414 (7.5)	−0.4	66 088 (5.1)	64 279 (4.9)	0.6
Hypertension	86 466 (6.3)	268 827 (6.9)	−2.5	17 568 (6.0)	1.2	75 555 (9.9)	75 555 (9.9)	−0.1	80 941 (6.2)	79 631 (6.1)	0.4
Obesity	20 349 (1.5)	77 502 (2.0)	−3.9	4598 (1.6)	−0.8	16 565 (2.2)	16 565 (2.2)	−0.1	18 981 (1.5)	17 010 (1.3)	1.3
Hyperthyroidism	7347 (0.5)	20 583 (0.5)	0.1	1399 (0.5)	0.8	5786 (0.8)	5786 (0.8)	−0.1	6852 (0.5)	6592 (0.5)	0.3
Osteoporosis	8724 (0.6)	31 122 (0.8)	−2.0	1702 (0.6)	0.7	8587 (1.1)	8587 (1.1)	−0.7	8144 (0.6)	8420 (0.6)	−0.3
Rheumatoid arthritis	5993 (0.4)	20 249 (0.5)	−1.2	1396 (0.5)	−0.6	6242 (0.8)	6242 (0.8)	−0.9	5656 (0.4)	6048 (0.5)	−0.4
Osteoarthritis	8131 (0.6)	25 864 (0.7)	−0.9	1734 (0.6)	−0.0	7756 (1.0)	7756 (1.0)	−0.3	7622 (0.6)	7155 (0.5)	0.5
Systemic connective tissue disease	6857 (0.5)	19 826 (0.5)	−0.2	1538 (0.5)	−0.4	6794 (0.9)	6794 (0.9)	−1.0	6431 (0.5)	6259 (0.5)	0.2
Drug treatment use‡											
ACE inhibitors	34 837 (2.5)	110 253 (2.8)	−1.9	7412 (2.5)	−0.0	30 114 (3.9)	30 114 (3.9)	−0.0	32 675 (2.5)	32 760 (2.5)	0.0
ARBs	21 247 (1.5)	65 558 (1.7)	−1.1	4122 (1.4)	1.1	18 312 (2.4)	18 312 (2.4)	−0.3	19 872 (1.5)	19 031 (1.5)	0.5
β blockers	42 819 (3.1)	108 779 (2.8)	1.9	9026 (3.1)	0.2	36 369 (4.8)	36 369 (4.8)	−0.3	40 114 (3.1)	39 197 (3.0)	0.4
Calcium channel blockers	42 165 (3.1)	132 894 (3.4)	−2.0	9045 (3.1)	−0.2	37 134 (4.9)	37 134 (4.9)	0.1	39 486 (3.0)	39 470 (3.0)	0.0
Diuretics	78 849 (5.8)	200 278 (5.2)	2.6	15 408 (5.3)	2.0	70 794 (9.3)	70 794 (9.3)	0.5	73 614 (5.6)	73 970 (5.7)	−0.1
Statins	37 775 (2.8)	148 030 (3.8)	−6.0	8057 (2.8)	−0.1	33 701 (4.4)	33 701 (4.4)	0.0	35 265 (2.7)	33 943 (2.6)	0.6
SSRIs	39 459 (2.9)	117 429 (3.0)	−0.9	7809 (2.7)	1.2	34 870 (4.6)	34 870 (4.6)	−0.6	36 537 (2.8)	37 442 (2.9)	−0.4
Anti-ulcer drugs	78 697 (5.7)	215 882 (5.6)	0.8	14 543 (5.0)	3.3	70 411 (9.2)	70 411 (9.2)	−1.0	73 038 (5.6)	68 299 (5.2)	1.6
Systemic glucocorticoids	33 736 (2.5)	74 017 (1.9)	3.8	5556 (1.9)	3.8	24 268 (3.2)	24 268 (3.2)	−0.5	31 349 (2.4)	29 629 (2.3)	0.9

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; IQR=interquartile range; NSAID=non-steroidal anti-inflammatory drug; SD=standardised difference; SSRI=selective serotonin reuptake inhibitor.
*Matched to diclofenac initiators by propensity score.
†Standardised difference compared with diclofenac initiators. Ibuprofen/naproxen initiators were compared with all 1 370 832 diclofenac initiators, whereas the propensity score matched cohorts were compared only with the diclofenac initiators to whom they were matched to (that is, 764 781 and 1 303 209 diclofenac initiators for paracetamol and NSAID non-initiators, respectively).
‡Filled prescription within 90 days.

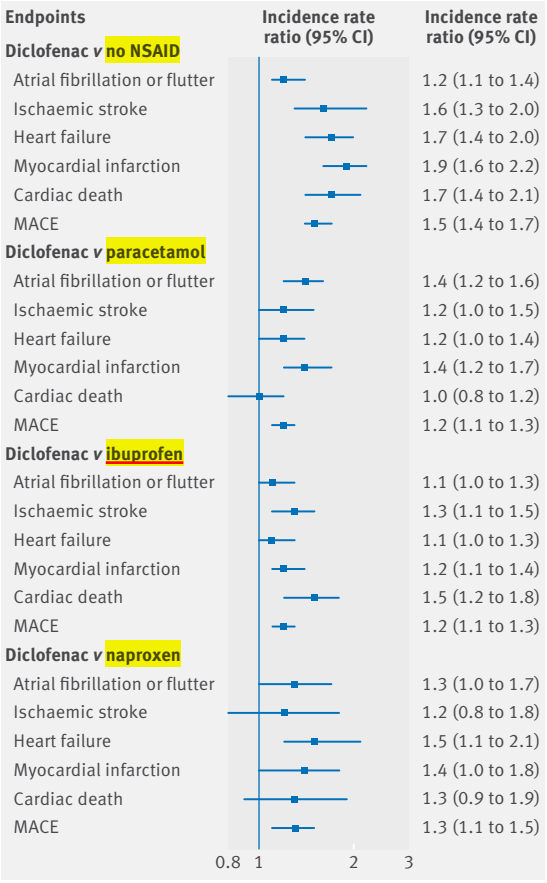

Fig 2 | Cardiovascular risks at 30 days associated with diclofenac initiation compared with no NSAID initiation and initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug; MACE=major adverse cardiovascular event

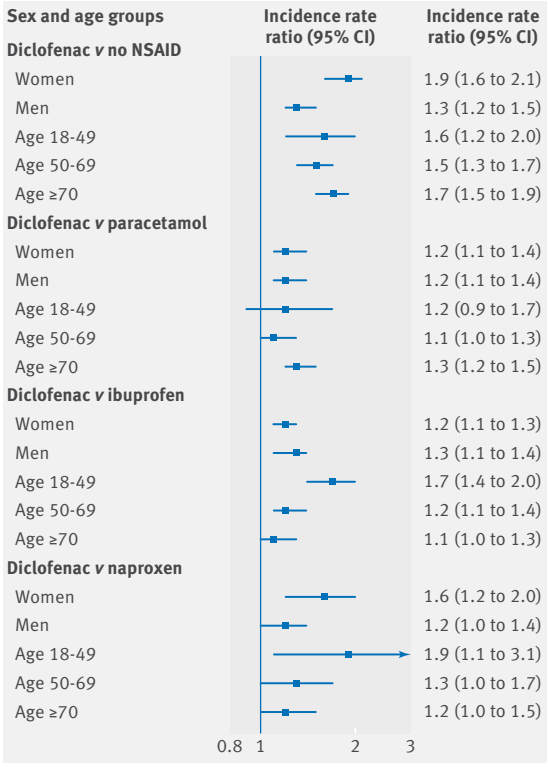

Fig 3 | Risk of major adverse cardiovascular events after diclofenac initiation according to sex and age. NSAID=non-steroidal anti-inflammatory drug

Compared with naproxen initiators, the incidence rate ratio increased 1.2-fold for ischaemic stroke, 1.3-fold for atrial fibrillation or flutter and cardiac death, 1.4-fold for myocardial infarction, and 1.5-fold for heart failure. Consistently, cardiac death was driven by death due to heart failure (incidence rate ratio 1.7, 0.6 to 5.0) and myocardial infarction (1.5, 0.8 to 2.9).

Patient subgroups

The risk of major adverse cardiovascular events remained elevated in sex and age groups (fig 3 and eTables 6-7), and across calendar periods (data not shown). While sex did not modify substantially the effect of diclofenac compared with paracetamol and ibuprofen initiation, diclofenac initiation conferred a higher risk in women than men when compared with NSAID non-initiation (incidence rate ratio 1.9 *v* 1.3) and naproxen initiation (1.6 *v* 1.2).

Stratifying on baseline cardiovascular risk (fig 4 and eTables 8-9), the point estimates for patients with moderate baseline cardiovascular risk were close to those in the overall analyses. For patients with high baseline risk, the incidence rate ratio remained marginally elevated compared with NSAID non-initiation (1.1, 1.0 to 1.3), but levelled out for the active comparator groups. By contrast, the additional absolute number of major adverse cardiovascular events per 1000 diclofenac initiators per year (adjusted incidence rate difference) increased with baseline risk (eTable 10). Thus, among patients at low baseline risk, diclofenac initiators had one additional event versus ibuprofen initiators, one additional event versus naproxen initiators, three additional events versus paracetamol initiators, and four additional events versus NSAID non-initiators. Among patients at moderate baseline risk, corresponding figures were seven, seven, eight, and 14 additional events, respectively; for those at high baseline risk, corresponding numbers were 16, 10, one, and 39 additional events, respectively.

Stratification on dose (fig 5 and eFigure 2) revealed that the increased risk related both to low and high dose diclofenac. There was a non-significant tendency towards increased effect estimates for high doses (fig 5).

Sensitivity analyses

In sensitivity analyses, restriction to healthcare seeking behaviour among NSAID non-initiators was shown to infer important confounder control, because omission of this criterion increased the incidence rate ratio for major adverse cardiovascular events considerably (2.0, 95% confidence interval 1.8 to 2.2). Diclofenac initiation increased upper gastrointestinal bleeding risk at 30 days by approximately 2.5-fold compared with ibuprofen (incidence rate ratio 2.5,

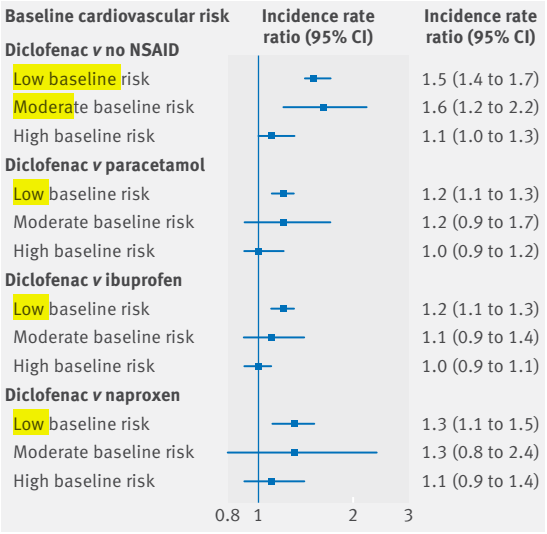

Fig 4 | Risk of major adverse cardiovascular events after diclofenac initiation according to baseline cardiovascular risk. NSAID=non-steroidal anti-inflammatory drug

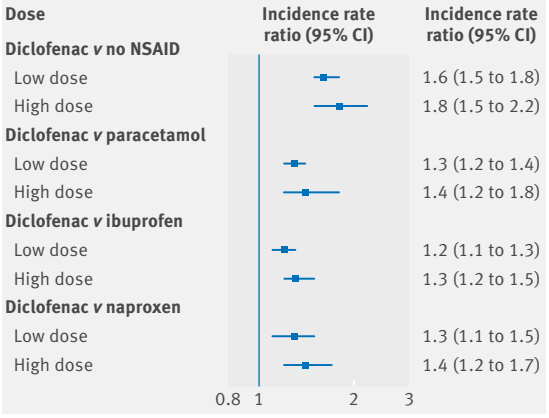

Fig 5 | Risk of major adverse cardiovascular events comparing initiation of low and high dose diclofenac with no NSAID initiation or initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug

2.1 to 3.1) or paracetamol (2.4, 2.0 to 2.9), 4.5-fold compared with no initiation (4.4, 3.5 to 5.5), and to a similar extent as naproxen (0.9, 0.7 to 1.1; eTables 11-13). The results were not influenced by potential over-the-counter use of diclofenac in part of 2007-08 (data not shown), potential crossover between exposure groups (eTable 14), restriction to only one trial entry per person (eTable 15), changes to the low dose cutoff limit (data not shown), and myocardial infarction subtype (data not shown). Finally, an unmeasured confounder that was twice as frequent among diclofenac initiators versus among non-initiators would still need to increase the risk of major adverse cardiovascular events by a factor of nine or more to fully explain the results, if no increased risk actually existed (eFigure 3).

Discussion

In our study, we found that diclofenac initiators were at increased risk of major adverse cardiovascular events—both compared with no NSAID initiation, initiation of paracetamol as an analgesic alternative to NSAIDs, as well as initiation of other traditional NSAIDs. Risk estimates compared with no initiation, paracetamol initiation, and ibuprofen or naproxen initiation increased for almost all individual components of major adverse cardiovascular events (that is, atrial fibrillation or flutter, ischaemic stroke, heart failure, acute myocardial infarction, and cardiac death). The risk increase applied to men and women of all ages. Although the absolute risks were highest in individuals with high baseline cardiovascular risk, the relative risks were highest in those with the lowest baseline risk. While NSAID use previously was considered risk-neutral in short treatment periods and low doses,[20] the risks were apparent even within 30 days and also for low doses of diclofenac. Finally, the upper gastrointestinal bleeding risk of diclofenac was comparable to that for naproxen, but considerably higher than for paracetamol use, ibuprofen use, and no use.

Strengths and limitations

The Danish registry infrastructure made the emulated trial design possible. To our knowledge, the sample size of more than 6.3 million initiators of diclofenac, paracetamol, ibuprofen, or naproxen is larger than all previous meta-analyses of observational and randomised studies taken together.[3 21-23] The largest meta-analysis of randomised trials (Coxib and traditional NSAID Trialists' Collaboration) included only 70 major vascular events in 158 trials comparing traditional NSAIDs with placebo (38 081 participants; 16 217 person years) and 24 major vascular events in 335 trials comparing different traditional NSAIDs (68 507; 22 418).[3] By comparison, our study included over 4500 adverse events among NSAID initiators, close to 1000 adverse events among paracetamol initiators, and a similar number among non-initiators. The tendency we observed for reduced relative risk estimates as baseline risk increased and in comparisons with active comparator drugs is consistent with the principle that effect estimates are highest among individuals at lowest baseline risk.

The population based design in the setting of a tax supported, universal healthcare system largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups. The study had no missing data on exposure, confounders, or events. The prescription registry permitted identification of diclofenac use and is virtually complete.[7 9] Our new user design resembled drug allocation in randomised controlled trials.[24] Although we had to use prescription data as a proxy for actual NSAID use, we did not base drug exposure information on written prescriptions, but on actual dispensing at pharmacies.[7] Required copayments increased the likelihood of compliance,[25] although non-compliance in taking the prescribed tablet dose could

have masked a dose-response effect. Over-the-counter use of low dose ibuprofen accounted for 30-35% of total ibuprofen sales and 15-25% of total NSAID sales during the study period.[7] As shown, misclassification of diclofenac use did not affect the results substantially. Non-differential misclassification by over-the-counter ibuprofen use would bias the effect estimates towards unity, if it occurred, and cannot explain the results. The cardiovascular registry diagnoses used in the study have been validated[26] and the mortality and migration data were accurate and complete.[8]

Although the models of healthcare seeking non-initiators and paracetamol initiators varied by design compared with the active NSAID comparators (propensity score matching *v* adjustment), both were based on and controlled for the same measured covariates. The fairly equal distribution of measured covariates among the NSAID groups increased the likelihood that unmeasured variables were also equally distributed. Moreover, confounding by indication was not a concern in the active drug comparisons owing to the shared indications for use of traditional NSAIDs. Still, the emulated trial design lacked baseline randomisation, and therefore, unmeasured confounding cannot be excluded.

Mechanisms

Owing 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).[27] As 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.[28] Neither ibuprofen nor naproxen show such a window, because their inhibition of COX-1 exceeds that of COX-2 throughout the dosing interval.[27] Selective COX-2 inhibition favours thrombosis by inhibiting generation of COX-2 derived vascular prostacyclin while not affecting COX-1 mediated thromboxane A_2.[29]

Other factors contributing to the cardiovascular toxicity of COX-2 inhibitors include acceleration of atherogenesis,[30] elevation or destabilisation of blood pressure,[31] and risk of heart failure decompensation.[32 33] COX-2 derived prostacyclin also acts as an endogenous anti-arrhythmic agent through inhibition of epicardial sympathetic nerve activity.[34-36] COX-2 inhibition could therefore render patients more susceptible to arrhythmias such as atrial fibrillation.[27] The inhibition of COX-2 up regulation might be particularly harmful during myocardial ischaemia, because thromboxane and prostacyclin are released from the acutely ischaemic myocardium and their balance is related to arrhythmia risk[37] and infarct size.[38]

Previous literature

This large study directly compares the risks of diclofenac initiation with those of paracetamol, ibuprofen, and naproxen for various cardiovascular outcomes. Comparing diclofenac initiation with no NSAID initiation, the consistency between our results and those of previous meta-analyses of both trial and observational data provides strong evidence to guide clinical decision making. The Coxib and traditional NSAID Trialists' Collaboration meta-analysis found a 40% increased risk of vascular events associated with diclofenac use versus placebo or no use (incidence rate ratio 1.41, 95% confidence interval 1.12 to 1.78), driven by an increased rate of myocardial infarction (1.70, 1.19 to 2.41).[3] Also in line with our results, the meta-analysis showed that diclofenac users had an increased risk of heart failure (1.85, 1.17 to 2.94) and vascular death (1.65, 0.95 to 2.85).[3]

The discrepancy between our estimated 60% increased risk and the meta-analysis' estimate for any stroke (1.18, 0.79 to 1.78) could be explained by our focus on ischaemic stroke.[3] The incidence rate ratio for atrial fibrillation or flutter found in our study was lower than previously reported (1.73, 1.53-1.97),[39] in part owing to our ability to control for healthcare seeking behaviour. Finally, the meta-analysis estimated the excess absolute rate of major adverse cardiovascular events per 1000 diclofenac initiators per year as three events among low risk individuals (of which one was fatal) and seven to eight events among high risk individuals (of which two were fatal).[3] Compared with non-initiators, we found a similar excess rate among low risk individuals (about four major adverse cardiovascular events, including one fatal cardiac event), but an even greater rate in high risk individuals (about 40 events, of which about half were fatal).

Conclusions and implications

Our study provides an overview of the spectrum and magnitude of cardiovascular risks related to initiation of diclofenac. We also showed that diclofenac initiators had an upper gastrointestinal bleeding risk similar to that of naproxen initiators and more than twice the risk of ibuprofen initiators. Treatment of pain and inflammation with NSAIDs may be worthwhile for some patients to improve quality of life despite potential side effects. Considering its cardiovascular and gastrointestinal risks, however, there is little justification to initiate diclofenac treatment before other traditional NSAIDs.[40]

It is time to acknowledge the potential health risk of diclofenac and to reduce its use. Diclofenac should not be available over the counter, and when prescribed, should be accompanied by an appropriate front package warning about its potential risks. Moreover, the choice to use diclofenac as the reference group to provide evidence of safety of selective COX-2 inhibitors represents a potential flaw in safety trials.[41-43] Future trials should instead use low dose ibuprofen (≤1200 mg/day) or naproxen (≤500 mg/day) as comparators.[4] In conclusion, our data support that initiation of diclofenac poses a cardiovascular health risk, both compared with no use, paracetamol use, and use of other traditional NSAIDs.

Contributors: MS and LP conceived the study idea and designed the study. LP collected the data and carried out the analyses. MS organised 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 LP are the guarantors.

Funding: The study was supported by the Department of Clinical Epidemiology's Research Foundation at Aarhus Universityand the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation, Novo Nordisk Foundation, and Danish Research Council (grants 11-108354 and 11-115818). The funding sources had no role in the design, conduct, analysis, or reporting of the study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Department of Clinical Epidemiology's Research Foundation at Aarhus University and PROCRIN for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data permission: The study was approved by the Danish Data Protection Agency (record No FSEID-00002467).

Data sharing: Not permitted.

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Web appendix: Supplemental data