

Non-Steroidal Anti-Inflammatory Drug Use and the Risk of Acute Myocardial Infarction in the General German Population: A Nested Case–Control Study

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Abstract

Introduction Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased relative risk of acute myocardial infarction (AMI), but the label warnings refer particularly to patients with cardiovascular risk factors. The magnitude of relative AMI risk for patients with and without cardiovascular risk factors varies between studies depending on the drugs and doses studied. **Objectives** The aim of our study was to estimate population-based relative AMI risks for individual and widely used NSAIDs, for a cumulative amount of NSAID use, and for patients with and without a prior history of cardiovascular risk factors.

Methods Based on data from the German Pharmacoepidemiological Research Database (GePaRD) of about 17 million insurance members from four statutory health insurance providers, for the years 2004–2009, a nested case–control study was conducted within a cohort of 3,476,931 new NSAID users classified into current, recent, or past users. Up to 100 controls were matched to each case by age, sex, and length of follow-up using risk set

sampling. Multivariable conditional logistic regression was applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Duration of NSAID use was calculated by the cumulative amount of dispensed defined daily doses (DDDs), and stratified analyses were conducted for potential effect modifiers.

Results Overall, 17,236 AMI cases were matched to 1,714,006 controls. Elevated relative AMI risks were seen for current users of fixed combinations of diclofenac with misoprostol (OR 1.76, 95% CI 1.26–2.45), indometacin (1.69, 1.22–2.35), ibuprofen (1.54, 1.43–1.65), etoricoxib (1.52, 1.24–1.87), and diclofenac (1.43, 1.34–1.52) compared with past use. A low cumulative NSAID amount was associated with a higher relative AMI risk for ibuprofen, diclofenac, and indometacin. The relative risk associated with current use of diclofenac, fixed combinations of diclofenac with misoprostol, etoricoxib, and ibuprofen was highest in the younger age group (<60 years) and similar for patients with or without major cardiovascular risk factors.

Conclusion Relative AMI risk estimates differed among the 15 investigated individual NSAIDs. Diclofenac and ibuprofen, the most frequently used NSAIDs, were associated with a 40–50% increased relative risk of AMI, even for low cumulative NSAID amounts. The relative AMI risk in patients with and without cardiovascular risk factors was similarly elevated.

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Key Points

Relative acute myocardial infarction (AMI) risk estimates differed among the 15 investigated individual non-steroidal anti-inflammatory drugs (NSAIDs).

Diclofenac and ibuprofen, which are the most frequently used NSAIDs, were associated with a 40–50% increased relative risk of AMI, even for low cumulative NSAID amounts.

The relative AMI risk in patients with and without cardiovascular risk factors was similarly elevated.

1 Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used therapeutics in the general population [1]. They have a wide range of clinical indications, such as short- or long-term pain states and a range of musculoskeletal disorders. Gastrointestinal side effects of the traditional NSAIDs (tNSAIDs) led to the development of cyclooxygenase-2 (COX-2) selective NSAIDs. However, several clinical trials yielded an increased risk of adverse cardiovascular events for COX-2 selective NSAIDs, resulting in the withdrawal of rofecoxib in 2004 [2] and valdecoxib in 2005 [3]. During the last decade, several European [4–14] and international [15–22] observational studies as well as meta-analyses [23–29] indicated an elevated risk of acute myocardial infarction (AMI) for both tNSAIDs and COX-2 selective NSAIDs. In 2015, the US Food and Drug Administration (FDA) strengthened the label warning of all prescription NSAIDs regarding an increased risk of AMI or stroke. However, there was not enough evidence to make recommendations regarding individual NSAIDs. Additionally, NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of the risk increase, depending on the drugs and doses studied [15, 17, 26, 30].

Against this background, the aim of the present study was to investigate the risk of AMI of commonly used individual COX-2 selectives and tNSAIDs and of the cumulative amount of NSAID use among the general population and to assess the effect of potential effect modifiers such as age, sex, and cardiovascular risk factors.

2 Methods

2.1 Data Source

This study was based on data from the German Pharmacoepidemiological Research Database (GePaRD), which has been described elsewhere [31, 32]. For the present study, claims data for about 17 million insurance members from four statutory health insurance providers (SHIs) from all geographical regions of Germany were included using the years 2004–2009. Besides demographic data, the database contains inpatient and outpatient diagnoses coded according to the German Modification of the International Classification of Diseases (ICD-10 GM), inpatient and outpatient diagnostic and therapeutic procedures, and outpatient drug dispensing. Inpatient data include information on admission and discharge dates. Dispensing data are available for all outpatient dispensing reimbursed by the SHIs and contain the dispensed drugs characterized by central pharmaceutical number (PZN), the dates of prescription and dispensing, as well as information on the prescribing physician. These data are linked to a pharmaceutical reference database, adding information on the defined daily dose (DDD), the anatomical-therapeutic-chemical (ATC) code, strength, packaging size, and the generic and brand names.

In Germany, utilization of health insurance data for scientific research is regulated by the code of Social Law. All contributing SHIs and their regulatory authorities approved the use of the data for this study. Informed consent was not required by law, since the study was based on pseudonymous data, and the necessary permissions were granted.

2.2 Study Design

A case-control study nested in a cohort of new NSAID users (ATC code M01, more detailed ATC codes available in Online Resource 1, see electronic supplementary material [ESM]) was conducted. Cohort members had to be continuously insured for at least 12 months before the first NSAID dispensing and had to be at least 18 years of age. In order to avoid bias by the inclusion of prevalent NSAID users, patients with an NSAID prescription within these 12 months were excluded [33]. Furthermore, patients with a diagnosis of malignant cancer (ICD-10-GM code D23.-) within these 12 months were excluded (except non-melanoma skin cancer). Cohort entry was defined as the patient's first dispensing of an NSAID between January 01, 2005 and December 31, 2009. All patients were followed from their first NSAID dispensing in the study period until either interruption of insurance status for more than 3 days,

end of insurance including death, diagnosis of malignant cancer, or the end of the study period/longest available follow-up in the database, whichever came first.

2.3 Definition of Cases and Controls

The outcome was a first hospitalization with a main discharge diagnosis of AMI (ICD-10 codes I12.-) or subsequent MI (ICD-10 codes I22.-) after cohort entry. The hospital admission day was defined as the index date of the case. Recurrent events were not examined.

From the cohort of new NSAID users, we randomly selected up to 100 controls for each case, matched by age at index date, sex, and SHI using risk set sampling. An index date was assigned to each control that resulted in the same duration of follow-up as the corresponding case, that is, cases and controls were also matched by length of follow-up. Cohort members who were hospitalized for any reason at the index date of the case were excluded from the set of potential controls, since they were not at risk of being hospitalized because of an AMI event. Patients might have served as controls for more than one case and were eligible to be selected as controls until they became a case [34].

2.4 Exposure Assessment

Classification of exposure to NSAIDs was based on the period (in days) between the index date and the end of supply of the most recent dispensing before the index date. Use status at the index date was categorized as follows: (1) current: if the supply overlapped the index date or ended within the 14-day period before the index date, (2) recent: if the supply ended between 15 and 183 days before the index date, or (3) past: if the supply ended 184 or more days before the index date. Past users of any NSAIDs were used as reference. If user numbers of individual NSAIDs were too small for analysis, they were grouped into the category of 'all other NSAIDs'. The cumulative amount of NSAID use was calculated as the sum of dispensed DDDs between cohort entry and the last dispensing before the index date. The cumulative amount was categorized into low (0–90 DDDs), medium (91–180 DDDs), and high use (≥ 181 DDDs).

2.5 Risk Factor and Confounder Assessment

Potential confounders were assessed in the 12 months preceding cohort entry. The following potentially confounding co-morbidities (obtained from inpatient as well as outpatient diagnoses) were considered in our analysis: myocardial infarction, chronic ischemic heart disease, heart

failure, stroke, hypertension, atrial fibrillation and flutter, peripheral arterial disease, other cardiovascular disease (cardiac arrhythmia/conduction disorder and arrest, cardiomyopathy, valvular disorder and endocarditis, myocarditis and pericarditis, arterial embolism and thrombosis), hyperlipidemia, osteoarthritis, rheumatoid arthritis, diabetes mellitus, chronic liver disease, kidney failure, alcohol abuse, obesity. The following drugs were assessed in the 12 months before the index date: angiotensin-converting-enzyme (ACE) inhibitors + angiotensin (AT) II antagonists, calcium channel blockers, β -blocking agents, diuretics, other antihypertensive drugs. The following confounding drugs were assessed in the 90 days before index date: aspirin, glucocorticoids, anticoagulants, statins, nitrates, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy. The exact definition of co-morbidities and co-medication in terms of ICD-10 GM codes and ATC codes is available as Online Resource in S2–S5 Tables (see ESM).

2.6 Statistical Analyses

Conditional logistic regression was conducted to obtain confounder-adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for current as well as recent use of individual NSAIDs, using past use of any NSAID as reference. If patients were simultaneously exposed to more than one NSAID, they were combined into the category 'multiple NSAID use', which was included as an additional dichotomous variable in the multivariable model.

A priori-specified confounders (Online Resource 2–5, see ESM) were always included in the model. Each potential confounder with a prevalence of 5% in controls was added to the multivariable model if the Wald test was significant (p value < 0.05). Confounder selection was then done by a backward selection approach ($p < 0.05$). To evaluate potential effect modification, analyses were stratified by sex, age (< 60 years/ ≥ 60 years), use of aspirin, platelet aggregation inhibitors, anticoagulants, ACE inhibitors + AT II, calcium channel blockers, β -blockers, nitrates, postmenopausal hormone therapy, glucocorticoids, other anti-hypertensive drugs, hypertension, other cardiovascular disease (cardiac arrhythmia/conduction disorder and arrest), atrial fibrillation and flutter, myocardial infarction, heart failure, peripheral arterial disease, stroke, diabetes mellitus, prior chronic ischemic heart disease, and hyperlipidemia (Online Resource 6 and 7, see ESM).

Confounder inclusion and selection were done in the same way as described above.

All statistical analyses were done using SAS 9.3 (SAS Institute Inc., Cary, NY, USA).

3 Results

3.1 Baseline Characteristics

During the study period, 3,476,931 new NSAID users were identified with a median follow-up time of 886 days (Q1: 424 days, Q3: 1368 days). The median age at cohort entry was 48.0 years (Q1: 37 years, Q3: 61 years), and 44% of the cohort was male.

Of those new NSAID users, 17,236 cases had an AMI and 1,714,006 matched controls were randomly selected from the cohort risk set. Table 1 shows the baseline characteristics of cases and controls and also the respective unadjusted and adjusted ORs. In the case–control sample, the median age at index date was 68 years (Q1: 57 years, Q3: 77 years), and 66% were male.

3.2 Relative Risks Associated with Individual NSAID Use

Current use of fixed combinations of diclofenac with misoprostol (OR 1.76, 95% CI 1.26–2.45, Table 2) and of indometacin (1.69, 1.22–2.35) showed the highest relative AMI risks followed by the most frequently used NSAIDs in Germany, ibuprofen (1.54, 1.43–1.65), diclofenac (1.43, 1.34–1.52), and the COX-2 selective NSAID etoricoxib (1.52, 1.24–1.87). There was an increased relative AMI risk among current users of dexketoprofen (1.31, 0.80–2.16), naproxen (1.28, 0.86–1.90), piroxicam (1.21, 0.85–1.70), aceclofenac (1.21, 0.54–2.71), and dexibuprofen (1.19, 0.56–2.53), but the confidence intervals were wide and included the null value. No association was seen for the tNSAIDs meloxicam and acemetacin or for the COX-2 selective NSAIDs celecoxib and lumiracoxib. However, the number of current users was low for celecoxib and lumiracoxib and both confidence intervals include the null value.

3.3 Relative Risk Associated with Cumulative Amount of Individual NSAID Use

Low cumulative amount of NSAID use (0–90 DDDs) of indometacin (1.68, 1.12–2.51), fixed combinations of diclofenac with misoprostol (1.62, 1.04–2.52), diclofenac (1.33, 1.16–1.53), and ibuprofen (1.37, 1.19–1.58) was associated with an elevated relative risk of AMI (Table 3). This indicates that already short-term use of these NSAIDs was associated with an increased relative risk of AMI. Except for acemetacin (0.89, 0.48–1.62), celecoxib (0.86, 0.49–1.50), and phenylbutanzone (0.76, 0.18–3.27), relative risk estimates of other NSAIDs were elevated, but numbers of users were low and CIs wide, showing no statistically significant association.

High cumulative amount of NSAID use (≥ 181 DDDs) of etoricoxib (1.64, 1.05–2.55) and ibuprofen (1.26, 1.01–1.57) was associated with an increased relative risk of AMI. For indometacin (1.46, 0.54–3.98), fixed combinations of diclofenac with misoprostol (1.26, 0.54–2.93), and acemetacin (1.06, 0.36–3.06), elevated relative risks were observed, but again the confidence intervals were wide and included the null value (Table 3).

3.4 Subgroup Analyses of Cardiovascular Risk Factors

Relative AMI risk estimates were similar in males and females for current use of diclofenac, fixed combinations of diclofenac with misoprostol, etoricoxib, and ibuprofen, whereas current use of indometacin seems to be associated with a higher relative AMI risk in males than in females (Fig. 1).

The relative AMI risk seems to be higher in patients <60 years of age for current use of the respective NSAIDs with the exception of indometacin (Fig. 2).

Patients with or without prior use of aspirin, anticoagulants, or platelet aggregation inhibitors seemed to be at similar enhanced relative risk when using the examined individual NSAIDs (Fig. 3a).

Prior use of ACE inhibitors, AT II antagonists, calcium channel blockers, β -blockers, other antihypertensive drugs, or a history of hypertension appears to lower the relative risk of AMI associated with current use of NSAIDs, with the exception of indometacin. However, most CIs overlapped (Fig. 3b).

Patients with prior history of chronic ischemic heart disease or other cardiovascular disease, with atrial fibrillation, myocardial infarction or heart failure, or prior history of peripheral arterial diseases or stroke, had a similar relative risk associated with current use of the respective NSAIDs as patients without such conditions (Fig. 3c–e).

4 Discussion

This study, based on a new user NSAID cohort of more than 3 million persons, examined the relative risk of AMI associated with the use of 15 individual NSAIDs. The highest relative AMI risk was found for current use of fixed combinations of diclofenac with misoprostol, followed by indometacin, ibuprofen, etoricoxib, and diclofenac.

Diclofenac and ibuprofen belong to the most frequently used NSAIDs in Europe [35], indicating a considerable public health impact. We found a 43% increased relative risk for diclofenac use, which is in the lower range of estimates reported by other nested case–control studies

Table 1 Characteristics of the study sample and odds ratios for the effects of potential confounders on acute myocardial infarction

| Patient characteristics | Cases; (<i>N</i> = 17,236) | Controls (<i>N</i> = 1,714,006) | Sex- and age-adjusted OR ^a (95% CI) | Adjusted OR ^b (95% CI) |
|---|--------------------------------|-------------------------------------|---|--------------------------------------|
| Sex | | | | |
| Female | 5869 (34.05) | 583,590 (34.05) | | |
| Male | 11,367 (65.95) | 1,130,416 (65.95) | | |
| Age in years, mean (SD) | 67.29 (13.10) | 67.17 (13.02) | | |
| Follow-up days, mean (SD) | 610.58 (440.83) | 608.96 (439.68) | | |
| Prior comorbidities^c | | | | |
| Alcohol abuse | 369 (2.14) | 26,355 (1.54) | NA | NA |
| Obesity | 2462 (14.28) | 188,707 (11.01) | 1.36 (1.30–1.42) | |
| Hypertension | 10,877 (63.11) | 894,116 (52.17) | 1.70 (1.64–1.76) | 1.25 (1.20–1.31) |
| Chronic liver disease | 2025 (11.75) | 186,016 (10.85) | 1.10 (1.05–1.15) | 0.91 (0.87–0.95) |
| Kidney failure | 1449 (8.41) | 78,260 (4.57) | NA | NA |
| Heart failure | 2722 (15.79) | 176,070 (10.27) | 1.74 (1.66–1.82) | 1.13 (1.08–1.19) |
| Osteoarthritis | 3395 (19.70) | 341,634 (19.93) | 0.98 (0.95–1.02) | NA |
| Rheumatoid arthritis | 549 (3.19) | 46,470 (2.71) | NA | NA |
| Diabetes mellitus | 4702 (27.28) | 299,397 (17.47) | 1.83 (1.77–1.90) | 1.43 (1.38–1.48) |
| Myocardial infarction | 2353 (13.65) | 82,574 (4.82) | 3.29 (3.14–3.45) | 1.84 (1.74–1.94) |
| Chronic ischemic heart disease | 5543 (32.16) | 327,376 (19.10) | 2.20 (2.13–2.28) | 1.27 (1.21–1.32) |
| Stroke | 1456 (8.45) | 92,396 (5.39) | 1.65 (1.56–1.74) | 1.23 (1.16–1.30) |
| Atrial fibrillation and flutter | 1163 (6.75) | 93,778 (5.47) | 1.26 (1.18–1.33) | 0.92 (0.86–0.98) |
| Peripheral arterial diseases | 1701 (9.87) | 100,183 (5.84) | 1.79 (1.70–1.89) | 1.28 (1.21–1.35) |
| Other cardiovascular disease | 3793 (22.01) | 308,011 (17.97) | 1.31 (1.26–1.36) | NA |
| Hyperlipidemia | 7381 (42.82) | 595,571 (34.75) | 1.44 (1.39–1.48) | 1.13 (1.09–1.16) |
| Prior drug use^c | | | | |
| ACE inhibitors + AT II antagonists | 5348 (31.03) | 399,981 (23.34) | 1.52 (1.47–1.57) | 1.00 (0.96–1.04) |
| Calcium channel blockers | 3405 (19.76) | 235,445 (13.74) | 1.59 (1.53–1.65) | 1.18 (1.13–1.23) |
| β-blocking agents | 6063 (35.18) | 435,334 (25.40) | 1.64 (1.59–1.70) | 1.05 (1.01–1.09) |
| Diuretics | 3662 (21.25) | 253,844 (14.81) | 1.63 (1.56–1.69) | 1.07 (1.02–1.12) |
| Other antihypertensive drugs | 3821 (22.17) | 304,791 (17.78) | 1.33 (1.29–1.38) | 1.03 (0.99–1.08) |
| Current use of drugs^d | | | | |
| Aspirin | 1583 (9.18) | 77,194 (4.50) | 2.19 (2.07–2.31) | 0.84 (0.76–0.92) |
| Anticoagulants | 759 (4.40) | 63,886 (3.73) | NA | NA |
| Glucocorticoids | 827 (4.80) | 54,911 (3.20) | 1.53 (1.42–1.64) | 1.43 (1.33–1.53) |
| Platelet aggregation inhibitors | 2203 (12.78) | 102,613 (5.99) | 2.38 (2.27–2.49) | 1.58 (1.45–1.73) |
| Oral contraceptives | 3 (0.02) | 186 (0.01) | 1.63 (0.52–5.09) | 1.52 (0.48–4.76) |
| Postmenopausal hormone therapy | 291 (1.69) | 39,511 (2.31) | 0.72 (0.64–0.81) | 0.74 (0.66–0.83) |
| Statins | 2912 (16.89) | 201,278 (11.74) | 1.56 (1.49–1.62) | 0.90 (0.86–0.95) |
| Nitrates | 1928 (11.19) | 57,453 (3.35) | 3.90 (3.71–4.10) | 2.43 (2.30–2.56) |
| Aspirin ^e | 86 (0.50) | 3796 (0.22) | 2.24 (1.81–2.78) | 1.45 (1.17–1.80) |

Values are numbers (percentages) unless stated otherwise

ACE angiotensin-converting enzyme, AT angiotensin, NA not available

^a Obtained from univariate conditional logistic regression model

^b Adjusted for the following covariates: obesity, hypertension, chronic liver diseases, heart failure, diabetes mellitus, myocardial infarction, chronic ischemic heart disease, stroke, atrial fibrillation and flutter, peripheral arterial diseases, other cardiovascular diseases, hyperlipidemia, ACE inhibitors + AT II antagonists, calcium channel blockers, β-blocking agents, diuretics, other antihypertensive drugs, aspirin (90 days prior to index date), glucocorticoids, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy, statins, nitrates, aspirin (30 days prior to index date)

^c Assessed during the 12 months before cohort entry

^d Assessed during the 90 days before index date

^e Assessed during the 30 days before index date

Table 2 Crude and adjusted relative risk of acute myocardial infarction associated with current use of NSAIDs compared with past use

| | Cases (<i>N</i> = 17,236) | Controls (<i>N</i> = 1,714,006) | Sex- and age-adjusted OR ^a (95% CI) | Adjusted OR ^b (95% CI) |
|------------------------------|-------------------------------|-------------------------------------|--|-----------------------------------|
| Past use of any NSAID (ref.) | 14,035 (81.43) | 1,409,397 (82.22) | 1.0 | 1.0 |
| Current use of | | | | |
| Diclofenac | 1440 (8.35) | 114,424 (6.68) | 1.50 (1.41–1.60) | 1.43 (1.34–1.52) |
| Ibuprofen | 986 (5.72) | 70,308 (4.10) | 1.67 (1.55–1.80) | 1.54 (1.43–1.65) |
| Etoricoxib | 97 (0.56) | 6407 (0.37) | 1.63 (1.33–2.00) | 1.52 (1.24–1.87) |
| Meloxicam | 31 (0.18) | 2779 (0.16) | 1.23 (0.86–1.75) | 1.09 (0.76–1.56) |
| Diclofenac, combinations | 36 (0.21) | 2173 (0.13) | 1.90 (1.36–2.64) | 1.76 (1.26–2.45) |
| Naproxen | 25 (0.15) | 1935 (0.11) | 1.40 (0.94–2.07) | 1.28 (0.86–1.90) |
| Piroxicam | 33 (0.19) | 2818 (0.16) | 1.33 (0.94–1.88) | 1.21 (0.85–1.70) |
| Indometacin | 37 (0.21) | 2171 (0.13) | 1.91 (1.37–2.65) | 1.69 (1.22–2.35) |
| Acemetacin | 18 (0.10) | 1757 (0.10) | 1.13 (0.71–1.80) | 1.06 (0.66–1.69) |
| Celecoxib | 24 (0.14) | 2678 (0.16) | 0.97 (0.65–1.45) | 0.89 (0.59–1.33) |
| Dexketoprofen | 16 (0.09) | 1268 (0.07) | 1.52 (0.92–2.49) | 1.31 (0.80–2.16) |
| Phenylbutazone | 2 (0.01) | 264 (0.02) | 0.84 (0.21–3.39) | 0.72 (0.18–2.19) |
| Aceclofenac | 6 (0.03) | 518 (0.03) | 1.35 (0.60–3.01) | 1.21 (0.54–2.71) |
| Dexibuprofen | 7 (0.04) | 595 (0.03) | 1.34 (0.63–2.82) | 1.19 (0.56–2.53) |
| Lumiracoxib | 2 (0.01) | 239 (0.01) | 0.88 (0.22–3.54) | 0.84 (0.21–3.39) |

Values are numbers (percentages) unless stated otherwise

ACE angiotensin-converting enzyme, AT angiotensin, NSAID non-steroidal anti-inflammatory drug

^a Obtained from univariate conditional logistic regression model

^b Adjusted for the following covariates: obesity, hypertension, chronic liver diseases, heart failure, diabetes mellitus, myocardial infarction, chronic ischemic heart disease, stroke, atrial fibrillation and flutter, peripheral arterial diseases, other cardiovascular diseases, hyperlipidemia, ACE inhibitors + AT II antagonists, calcium channel blockers, β -blocking agents, diuretics, other antihypertensive drugs, aspirin (90 days prior to index date), glucocorticoids, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy, statins, nitrates, aspirin (30 days prior to index date), recent use of any NSAID, current use of other NSAIDs, current use of multiple NSAIDs

[7, 8, 11, 12] and one meta-analysis [27] ranging from 1.37 to 1.67. Except in two studies [12, 18], never users were chosen as the reference group, which might have led to higher effect estimates compared with our study. Current use of fixed combinations of diclofenac with misoprostol was associated with a >70% elevated AMI risk. As no other study gave estimates for this fixed combination of diclofenac, we assume they pooled these therapeutics with diclofenac alone in the analyses, which might also explain lower risk estimates for diclofenac alone in our study. However, the fixed combination is probably given to a highly selected population with a high risk of gastrointestinal complications as it is more expensive and the co-pay is higher. If this selected population is also at a higher risk for AMI (e.g., due to higher age, co-morbidity), the observed effect would at least partly be caused by confounding by indication.

For ibuprofen, estimates reported in the literature are more inconsistent. A number of previously published nested case-control studies found relative risk estimates similar to ours, ranging from 1.24 (1.11–1.39) to 1.59 (0.88–2.89) [11, 19] compared with non-users, or 1.56

(1.19–2.05) [12] compared with remote users, whereas other studies found almost no effect [7–9].

Varying estimates between tNSAIDs could be explained by different COX-1/COX-2 selectivity [7], even though the underlying pathophysiology mechanism of an associated cardiovascular risk is still speculative [25]. While selective NSAIDs only block COX-2 enzymes, non-selective NSAIDs inhibit both COX-1 and COX-2 enzymes and subsequently inhibit, competitively and irreversibly, the synthesis of prostacyclin and thromboxane. The inhibition of COX-2-dependent prostacyclin leads to a reduction of inflammation and pain but might also increase the risk of coronary thrombosis [36]. Individual NSAIDs have a different mechanism to inhibit COX enzyme function. Some NSAIDs, like ibuprofen, meloxicam, celecoxib, and etoricoxib, seemed to be less COX-2 selective than rofecoxib, diclofenac, indometacin, or piroxicam [37, 38], which would lead to higher relative risk estimates for the latter NSAIDs. Interestingly, we estimated somewhat higher relative risks for ibuprofen and etoricoxib than for diclofenac. Furthermore, a previously reported cardioprotective effect of naproxen [5, 10, 19] could not be confirmed by

Table 3 Adjusted relative risk of acute myocardial infarction associated with cumulative amount of current NSAID use^a

| Drug currently used | Low NSAID use (0–90 days) | | High NSAID use (>180 days) | |
|--------------------------|---------------------------|-----------------------------------|----------------------------|-----------------------------------|
| | Cases/controls (n) | Adjusted OR ^b (95% CI) | Cases/controls (n) | Adjusted OR ^b (95% CI) |
| Diclofenac | 137/83,698 | 1.33 (1.16–1.53) | 229/16,623 | 1.04 (0.86–1.25) |
| Ibuprofen | 738/54,972 | 1.37 (1.19–1.58) | 140/8521 | 1.26 (1.01–1.57) |
| Etoricoxib | 59/4047 | 1.19 (0.87–1.64) | 28/1374 | 1.64 (1.05–2.55) |
| Meloxicam | 19/1885 | 1.04 (0.64–1.69) | 6/509 | 0.78 (0.33–1.87) |
| Diclofenac, combinations | 25/1527 | 1.62 (1.04–2.52) | 7/384 | 1.26 (0.54–2.93) |
| Naproxen | 17/1242 | 1.28 (0.76–2.16) | 5/407 | 0.73 (0.28–1.90) |
| Piroxicam | 25/2094 | 1.25 (0.81–1.93) | 3/388 | 0.60 (0.18–1.98) |
| Indometacin | 30/1737 | 1.68 (1.12–2.51) | 5/233 | 1.46 (0.54–3.98) |
| Acemetacin | 12/1188 | 0.89 (0.48–1.62) | 4/374 | 1.06 (0.36–3.06) |
| Celecoxib | 14/1550 | 0.86 (0.49–1.50) | 6/690 | 0.82 (0.34–1.97) |
| Dexketoprofen | 16/1188 | 1.48 (0.87–2.51) | 0/38 | NA |
| Phenylbutanzone | 2/249 | 0.76 (0.18–3.27) | 0/6 | NA |
| Aceclofenac | 5/410 | 1.17 (0.46–2.99) | 1/51 | 0.75 (0.07–8.38) |
| Dexibuprofen | 5/463 | 1.08 (0.43–2.71) | 1/73 | 0.41 (0.04–3.81) |
| Lumiracoxibe | 1/171 | 0.96 (0.13–7.31) | 0/18 | NA |

Values are numbers unless stated otherwise

Reference is medium NSAID use (91–180 days)

ACE angiotensin-converting enzyme, AT angiotensin, DDDs defined daily doses NA not available, NSAID non-steroidal anti-inflammatory drug

^a Estimated by the cumulative DDDs

^b Adjusted for the following covariates: obesity, hypertension, chronic liver diseases, heart failure, diabetes mellitus, myocardial infarction, chronic ischemic heart disease, stroke, atrial fibrillation and flutter, peripheral arterial diseases, other cardiovascular diseases, hyperlipidemia, ACE inhibitors + AT II antagonists, calcium channel blockers, β -blocking agents, diuretics, other antihypertensive drugs, aspirin (90 days prior to index date), glucocorticoids, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy, statins, nitrates, aspirin (30 days prior to index date), recent use of any NSAID, current use of other NSAIDs, current use of multiple NSAIDs

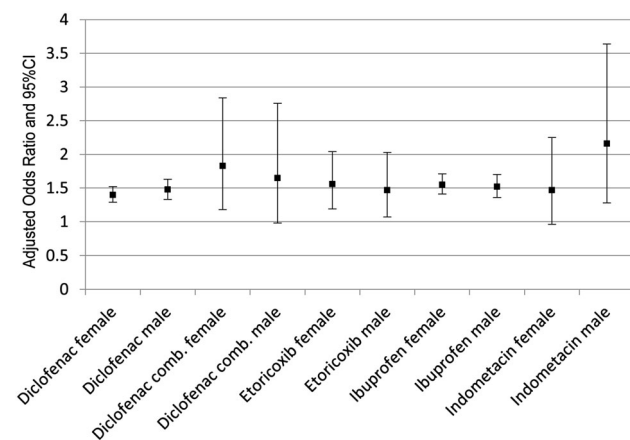


Fig. 1 Adjusted relative risk of acute myocardial infarction associated with current use of NSAIDs compared with past use stratified by sex. NSAIDs non-steroidal anti-inflammatory drugs

our study, which is in line with other publications [6, 7, 11, 18, 21].

This study could neither examine the relative risk of rofecoxib nor find enhanced relative risk estimates for the association between the use of celecoxib or

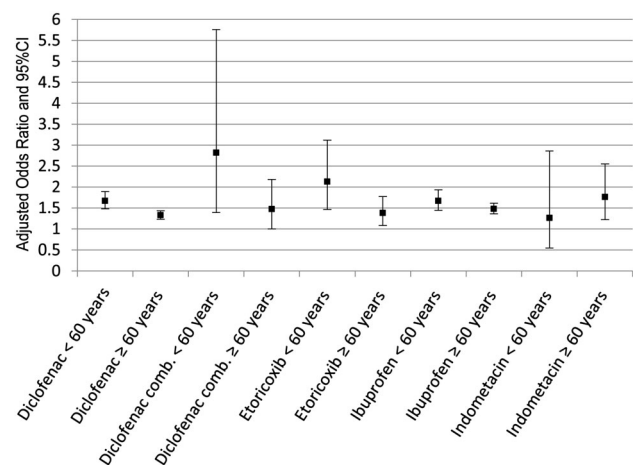


Fig. 2 Adjusted relative risk of acute myocardial infarction associated with current use of NSAIDs compared with past use stratified by age. NSAIDs non-steroidal anti-inflammatory drugs

lumiracoxib and AMI, but this does not mean that the use of celecoxib and lumiracoxib is not associated with a higher relative risk of AMI as numbers of current users were too low to get significant results. Both confidence

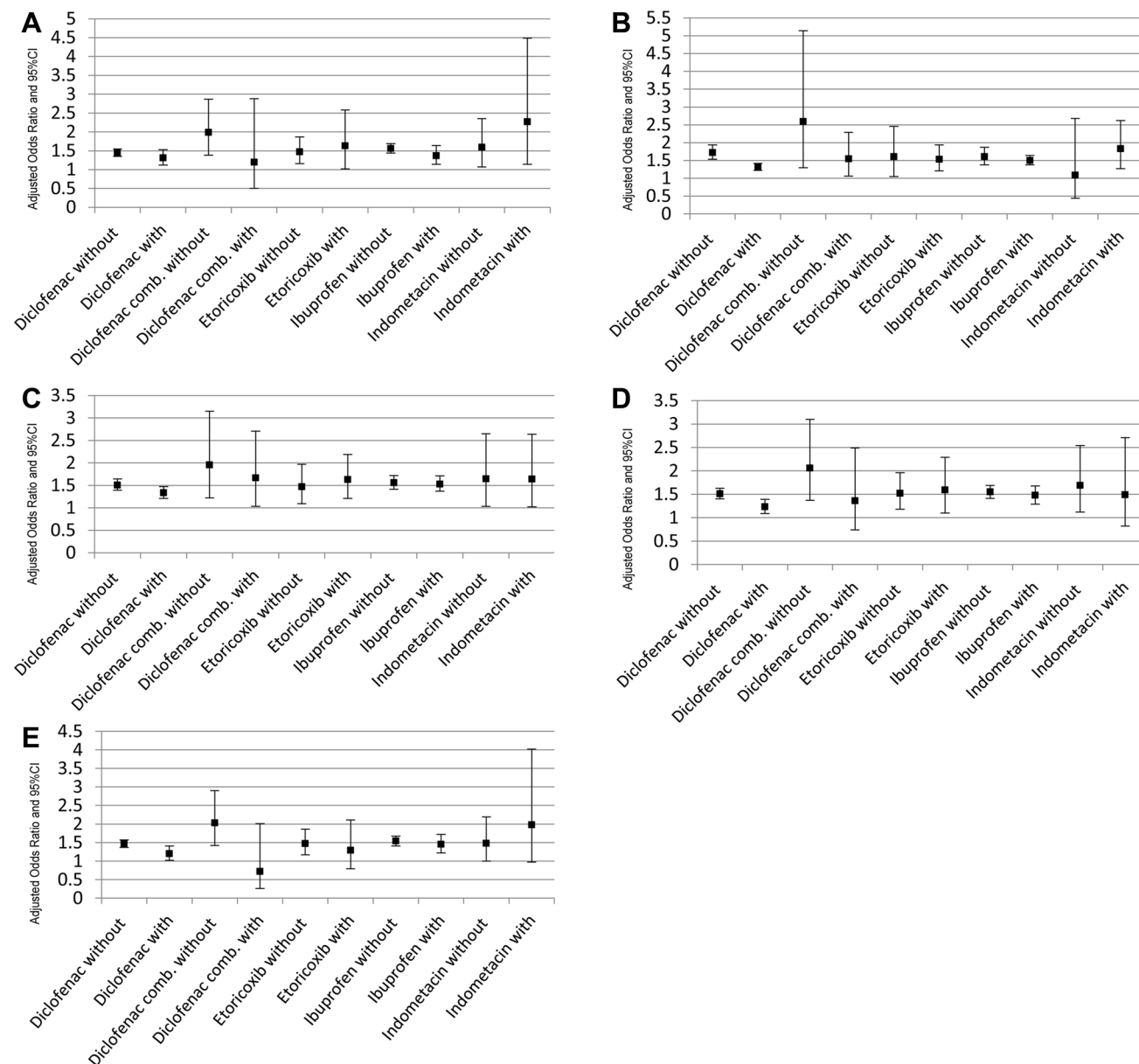


Fig. 3 Adjusted relative risk of acute myocardial infarction associated with current use of NSAIDs compared with past use and stratified by subgroups of cardiovascular risk factors: **a** with and without prior use of aspirin, anticoagulants, or platelet aggregation inhibitors; **b** with and without prior use of ACE inhibitors, AT II antagonists, calcium channel blockers, β -blockers, other antihypertensive drugs or

diagnosis of hypertension; **c** with prior history of chronic ischemic heart disease or other cardiovascular disease; **d** with and without prior atrial fibrillation, myocardial infarction or heart failure; **e** with and without prior history of peripheral arterial diseases or stroke. *NSAIDs* non-steroidal anti-inflammatory drugs

intervals included the null value of one and extend beyond 1.3. Furthermore, for etoricoxib, with many more users and thus a higher power, we found—as expected—a 52% increased relative AMI risk for current use. Compared with the much higher numbers of non-selective NSAID users, the low numbers of COX-2 selective users are mainly due to the withdrawal of rofecoxib in 2004 and the controversially discussed risk of other COX-2 selective inhibitors from then on.

The FDA strengthened the label warnings for an increased risk of AMI or stroke in patients with or without heart disease or risk factors for heart disease, and the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) recommended the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors. This means that patients with serious underlying heart or circulatory conditions should not use diclofenac, or only after careful consideration.

Results of our study suggest careful NSAID prescription in patients with or without prior cardiovascular risk factors as the relative risk of AMI seemed to be similarly enhanced in these patients for most examined individual NSAIDs. This is in line with a number of previous studies which found similar risks of adverse cardiovascular events associated with NSAID use in individuals with and without prior cardiovascular risk factors [15, 17, 26, 30]. We found that the relative risk for individual NSAID use varies by age with higher relative AMI risks observed in younger people (<60 years of age).

Common guidelines propose to keep the duration of NSAID use as short as possible [39]. Still, little is known about the AMI risk of each individual NSAID in terms of treatment duration, and the limited number of studies considering this aspect showed inconsistent results [4, 6, 7, 10, 19, 20]. Our study supports the notion of an early onset of AMI. This is in line with several other studies which reported high relative risks shortly after treatment onset for diclofenac, ibuprofen, and rofecoxib [4, 6, 19, 20], as well as for celecoxib and etoricoxib [6, 20]. Other studies found no consistent trend [7] or even higher effects with longer duration for all NSAIDs, except for naproxen, where a more protective effect with increasing duration was seen [10]. This effect was also seen in our study.

Limitations of our study are mainly due to the nature of the underlying administrative data. Due to German data protection regulations, it was not possible to validate AMI cases against patient charts.

The analysis is based on dispensing data and we have no information on whether the patient took the drug as recommended or whether the drug was taken at all. However, administrative claims data are often considered as the gold standard to assess drug exposure information. They are free of recall bias and prescriptions have to be filled in the pharmacy and are submitted complete and detailed in electronic form so that information on dispensing date, product, and dispensed strength is precise [40]. NSAID exposure could have been misclassified for patients who self-paid for prescriptions or bought certain NSAIDs over the counter (OTC). Additionally, patients might have been wrongly coded as current users while already being a recent user or wrongly coded as a recent user while still using the drug. Both would result in non-differential misclassification of exposure which usually leads to results biased towards the null, that is, an underestimation of the actual association between NSAID use and AMI risk.

Information on lifestyle including socio-economic status, smoking, alcohol use, BMI, or physical activity were either not available or only to a very limited degree, which might have led to residual confounding.

Even with the large sample size of our study, some NSAIDs had very low case numbers which limited the performance of some stratified analyses. Furthermore, we could not assess the dose of the respective NSAIDs as this information is not available in the database, and neither did we have information on the prescribed daily dose. Instead, we estimated the cumulative amount of individual NSAID use by the cumulative amount of DDDs.

The main strength of this study is the broad, unselected, representative population and the size of its source population with 17 million insurance members, allowing the investigation of risk profiles of individual NSAIDs in a general population.

5 Conclusion

Relative AMI risk estimates differed among the 15 investigated individual NSAIDs. Diclofenac and ibuprofen, the most frequently used NSAIDs, were associated with a 40–50% increased relative risk of AMI, even for low cumulative NSAID amounts. The AMI risk in patients with and without cardiovascular risk factors was similarly elevated.

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Compliance with ethical standards

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Conflict of interest As employees of the Leibniz Institute for Prevention Research and Epidemiology—BIPS, KT, BK, and TS have performed research studies sponsored by pharmaceutical companies (Bayer-Schering, Celgene, GSK, Mundipharma, Novartis, Purdue, Sanofi-Aventis, Sanofi-Pasteur, Stada, and Takeda) unrelated to this study.

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