

# Are prescribers not aware of cardiovascular contraindications for diclofenac? A claims data analysis

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**Abstract.** Scholle O, Kollhorst B, Haug U (Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany; University of Bremen, Bremen, Germany). Are prescribers not aware of cardiovascular contraindications for diclofenac? A claims data analysis. *J Intern Med* 2020; **287**: 171–179.

**Objectives.** To compare diclofenac use before and after implementation of European risk minimization measures in 2013, focusing on diclofenac initiators and prevalence of congestive heart failure (NYHA class II–IV), ischaemic heart disease, peripheral arterial disease and cerebrovascular disease (new contraindications) in these patients in Germany.

**Methods.** We included adults with health insurance coverage on 1 January 2011 (cohort 2011) or 1 January 2014 (cohort 2014) and during a 1-year pre-observation period. We defined diclofenac initiators as persons filling a prescription of systemic diclofenac in 2011 (cohort 2011) or 2014 (cohort 2014) and without such a prescription during the respective pre-observation period.

## Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are mainly used for the treatment of pain and are amongst the most widely used drugs worldwide. Their anti-inflammatory and analgesic effect is primarily caused by inhibiting the enzyme cyclooxygenase (COX), specifically its isoform COX-2. As the additional inhibition of another major isoform (COX-1) by traditional NSAIDs has been related to upper gastrointestinal complications, selective COX-2 inhibitors (coxibs) were developed and expected to be better tolerated [1]. However, there was increasing evidence on cardiovascular side effects of coxibs which, for example led to the market withdrawal of rofecoxib [2]. The

**Results.** Each cohort comprised >10 million persons. Between 2011 and 2014, the age-standardized proportion of persons initiating diclofenac decreased by 29% (from 8.2% to 5.8%) amongst female patients and by 26% (from 8.5% to 6.3%) amongst male patients; in the subgroup of persons with new contraindications, this proportion decreased by 33% (from 9.8% to 6.6%) amongst female patients and by 31% (from 10.0% to 6.7%) amongst male patients. Amongst diclofenac initiators, the proportion of those with new contraindications did not change between 2011 (12.0%) and 2014 (11.8%).

**Conclusion.** The overall decline of about 30% in diclofenac initiation between 2011 and 2014 was largely independent of the presence or absence of new contraindications. The proportion of diclofenac initiators with a new contraindication remained at a high level (more than one in ten patients), demonstrating the need for research at the prescriber level (e.g. interventional studies) and further measures to improve patient safety.

**Keywords:** cardiovascular diseases, contraindications, diclofenac, Europe, risk minimization measures.

risk of cardiovascular events is suggested to result from the impact of selective COX-2 inhibition on cardioprotective prostacyclin mechanisms [3].

Amongst traditional NSAIDs, the selectivity regarding COX-2 inhibition differs considerably and is assumed to be highest for diclofenac [4]. In contrast to ibuprofen and naproxen, diclofenac shows a window of primary inhibition of COX-2 at the end of a dosing interval that may result in a higher cardiovascular risk of diclofenac compared with other traditional NSAIDs [5]. This was confirmed by two meta-analyses of clinical trials, a systematic review of population-based controlled observational studies and a recent pharmacoepidemiological study [6–9]. Schmidt *et al.* [9] estimated that

amongst patients with previous myocardial infarction or heart failure—hence, high-risk patients—the absolute rate of major adverse cardiovascular events per 1000 diclofenac initiators per year is approximately increased by an additional 40 events (half of them fatal) compared with noninitiators.

A major regulatory consequence of the evidence about cardiovascular side effects of diclofenac was the legally binding decision of the European Commission on diclofenac-containing medicines in 2013. It confirmed the conclusion of the European Medicines Agency (EMA) that the cardiovascular risk of diclofenac is similar to that of coxibs and that the same risk minimization measures should apply [10]. Consequently, the following absolute contraindications were newly applied to systemic diclofenac throughout the European Union (EU): established congestive heart failure (NYHA class II–IV), ischaemic heart disease, peripheral arterial disease and cerebrovascular disease. Along with the amendments in the product information, it was further decided that there should be a direct healthcare professional communication about the update [11]. Consequently, a Dear Doctor Letter (called ‘Rote Hand Brief’ in German)—referring to the new cardiovascular contraindications—was sent to every practising physician and pharmacist in Germany by the marketing authorization holders in July 2013 [12].

However, up to now, no study has been published—neither from Germany nor from any other European country—that investigates whether the physicians’ prescribing behaviour has changed since these risk minimization measures were implemented in 2013. Based on a large German claims database, we therefore aimed to characterize diclofenac users in 2014 compared with 2011 and to assess the prevalence of new contraindications amongst these patients.

## Materials and methods

### *Data source*

This study was conducted using the German Pharmacoepidemiological Research Database (GePaRD) [13]. GePaRD contains claim data from four statutory health insurance providers in Germany and currently includes information on about 25 million persons who have been insured with one of the participating providers since 2004 or later. Per data year, there is information on approximately 17% of the German population and all geographical

regions of Germany are represented. In Germany, about 90% of the general population are covered by statutory health insurance. The healthcare system is characterized by uniform access to all levels of care and free choice of providers.

In addition to demographic data, GePaRD contains information on the dispensation of reimbursable drugs prescribed by physicians as well as on outpatient and inpatient services and diagnoses. Information on drugs includes the anatomical therapeutic chemical (ATC) code, the prescription and dispensation date, the specialty of the prescriber and the number of defined daily doses (DDDs). Diagnoses are coded according to the German modification of the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM). For inpatient diagnosis codes, the exact date is available, whilst outpatient diagnosis codes are only available on a quarterly basis. In the outpatient setting, the additional coding of diagnostic certainty is mandatory in Germany. This coding differentiates between ‘confirmed,’ ‘suspected,’ ‘status post’ and ‘excluded’ diagnoses.

### *Study design and study population*

To characterize the prescribing behaviour regarding diclofenac before and after the risk minimization measures, we focused on diclofenac initiators since prescribers evaluate the risk–benefit ratio of diclofenac use in these patients for the first time—including potential assessment of absolute contraindications. Therefore, we deemed new users of diclofenac more suitable than prevalent users to detect changes in prescribing behaviour.

We included all individuals aged 18 years or older with health insurance coverage on 1 January 2011 (cohort 2011) or 1 January 2014 (cohort 2014) as well as during a 1-year pre-observation period. The 1-year pre-observation period was required to distinguish between prevalent users and diclofenac initiators and to assess whether contraindications of diclofenac were present. Follow-up ended with end of insurance coverage due to any reason (including death). As mentioned above, we mainly required information from the pre-observation period, but required follow-up information for an additional analysis in which we assessed whether there was a second diclofenac prescription within 6 months after the first diclofenac prescription (see Data analysis).

We defined diclofenac initiators as cohort members with any dispensation of systemic diclofenac (ATC code M01AB05 or M01AB55) in 2011 (cohort 2011) or 2014 (cohort 2014) and without such a dispensation during the respective pre-observation period. We divided the remaining cohort members into the following mutually exclusive groups: nonusers of diclofenac, defined as persons without any dispensation of diclofenac (neither during the pre-observation period nor during follow-up) and prevalent users of diclofenac, defined as persons with a dispensation of diclofenac during the pre-observation period (irrespective of whether or not diclofenac was further dispensed during follow-up).

Analogously, we assessed use of any NSAIDs and categorized the cohort into mutually exclusive groups as described above for diclofenac (i.e. nonusers, initiators or prevalent users of any NSAIDs), considering all ATC codes starting with M01A instead of diclofenac-specific codes.

#### *Identification of patients with new contraindications*

To identify patients with new contraindications for diclofenac, we considered in- and outpatient diagnoses coded during the pre-observation period. For diclofenac initiators, we specifically assessed the inpatient diagnoses coded in the 365 days before the date of the first prescription of diclofenac and the outpatient diagnoses coded in the three quarters prior to or in the quarter of the first prescription. With respect to inpatient diagnoses, we considered main and secondary hospital discharge diagnoses. Outpatient diagnoses were only included if they had the status 'confirmed' and were coded in more than one of the four quarters. In a sensitivity analysis, we only considered inpatient diagnoses to identify patients with contraindications. Whilst it is clear that this approach underestimates the prevalence of contraindications, this sensitivity analysis aimed to assess whether the (potential) changes between 2011 and 2014 are similar when only codes with the highest degree of validity are considered.

#### *Data analysis*

In a first step, we characterized each cohort with respect to the distribution of age and sex, proportion of cohort members with at least 1-year follow-up, number of deaths, number of nonusers, prevalent users and initiators of diclofenac as well

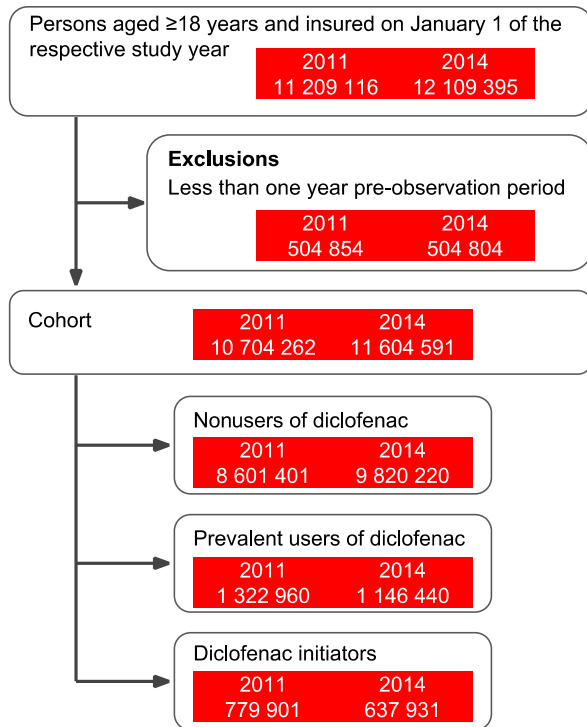
as the number of persons with any new contraindication for diclofenac. In a second step, we calculated the incidence proportion regarding diclofenac use for each cohort, with the number of diclofenac initiators in the nominator and the overall number of cohort members minus the number of prevalent users in the denominator. The group of prevalent users was not considered in the denominator as they could not become diclofenac initiators (i.e. they were not 'at risk' of initiating diclofenac). To compare the proportion of diclofenac initiators between the two cohorts, we calculated age-standardized proportions and corresponding 95% confidence intervals (CI) stratified by sex using the German population on 31 December 2011 as reference. Furthermore, we calculated the age-standardized proportion of diclofenac initiators with any new contraindication by restricting the denominator to cohort members with any new contraindication (again excluding prevalent users).

To compare trends regarding initiation of diclofenac versus any NSAID, we also calculated the age-standardized incidence proportion regarding any NSAID use by sex as described above.

We characterized diclofenac initiators in 2011 and 2014 with respect to sex, age, specialty of the prescribing physician, use of other NSAID in the year before diclofenac initiation, number of DDDs on the first prescription, potential indications and contraindications of diclofenac, and whether a second diclofenac prescription was prescribed within 6 months after the first diclofenac prescription amongst those who could be followed over this period.

#### **Results**

Each study cohort comprised more than ten million persons, and there were more than 600 000 diclofenac initiators in each study year (Fig. 1). There were slightly more women in both cohorts, and the mean age was between 49 and 52 years (Table 1). In 2011 and 2014, 96% and 97% of the cohort could be followed until the end of the year, respectively; 1% of each cohort had died by the end of the respective year. The prevalence of new contraindications was highest in prevalent users (17%–18% in men and 13% in women), followed by initiators (14% in men and 10% in women) and lowest amongst nonusers of diclofenac (11–12% in men and 8–9% in women).



**Fig. 1** Flow chart illustrating the selection process regarding cohort 2011 and cohort 2014 and the size of the subgroups in each cohort (nonusers of diclofenac, prevalent users of diclofenac, diclofenac initiators).

Table 2 shows the incidence proportions regarding diclofenac use and any NSAID use in both cohorts. Overall, the proportion of persons who were newly prescribed diclofenac decreased by 29% (from 8.2% to 5.8%) amongst female patients and by 26% (from 8.5% to 6.3%) amongst male patients between 2011 and 2014. Amongst persons with at least one of the new contraindications, the percentage change in the incidence proportion between 2011 and 2014 was higher compared with the total cohorts, but the difference was less than five percentage points. The proportion of persons who were newly prescribed any NSAID remained nearly the same in 2011 and 2014 (19% in women and 18% in men).

Table 3 shows the characteristics of persons initiating diclofenac in 2014 vs. 2011. In both years, the mean age was 53–54 years and there were slightly more women than men. Also, the specialties of the physicians prescribing diclofenac (>60% general practitioners and >20% orthopaedists) and the

distributions of (potential) indications were similar in both years. The proportion of persons who were prescribed other NSAIDs in the year before diclofenac initiation increased from 23.0% to 27.5% (+20%), and the number of DDDs on the first prescription slightly increased from 21.0 to 22.4 between 2011 and 2014. Amongst diclofenac initiators who could be followed for at least 6 months after the first prescription (97.6% in 2011 and 98.4% in 2014), the proportion of those with a second diclofenac prescription during this period was 21.6% and 19.6% in 2011 and 2014, respectively (data not shown).

Both in 2011 and 2014, the proportion of diclofenac initiators with any of the new contraindications hardly changed. New contraindications were diagnosed in 12.0% and 11.8% of diclofenac initiators in 2011 and 2014, respectively. In the sensitivity analysis considering new contraindications only if they were coded in the inpatient setting in the year before cohort entry, the proportions of diclofenac initiators with new contraindications also hardly changed between 2011 (2.9%) and 2014 (2.7%). Amongst diclofenac initiators with any of the new contraindications, the distribution of the specialty of the prescribing physician was the same in both years and equal to all diclofenac initiators as described above.

## Discussion

The present study assessed the impact of the risk minimization measures on diclofenac that were taken in 2013 by European and national—in our case German—authorities. The two major findings are that (i) in routine clinical practice, fewer persons were newly prescribed diclofenac in the year following the risk minimization measures than 2 years before the measures; however, (ii) the proportion of diclofenac initiators with serious cardiovascular contraindications remained on the same considerably high level. More than one in ten persons were prescribed diclofenac despite the presence of new contraindications.

To the best of our knowledge, no other study has been published so far that investigated the impact of the European risk minimization measures regarding new contraindications for diclofenac implemented in 2013. Our analysis, which allowed assessment of specific trends in relevant subgroups, revealed an overall decline in diclofenac use in Germany which, however, was not

**Table 1.** Description of cohort 2011 and cohort 2014, stratified by sex

	2011		2014	
	Men	Women	Men	Women
<b>Entire cohort</b>				
Overall (n)	4 781 831	5 922 431	5 264 481	6 340 110
Age in years (mean, SD)	49.3 (17.56)	51.0 (17.90)	50.3 (17.57)	52.1 (17.90)
Follow-up throughout the study year (n, %)	4 579 798 (95.8)	5 673 796 (95.8)	5 117 815 (97.2)	6 170 156 (97.3)
Number of deaths in the study year (n, %) <sup>a</sup>	48 361 (1.0)	55 180 (0.9)	56 799 (1.1)	61 707 (1.0)
<b>Nonusers of diclofenac</b>				
Overall (n)	3 843 439	4 757 962	4 442 433	5 377 787
New contraindication (n, %) <sup>a,b</sup>	427 023 (11.1)	364 449 (7.7)	552 941 (12.4)	463 611 (8.6)
<b>Prevalent users of diclofenac</b>				
Overall (n)	581 847	741 113	521 646	624 794
New contraindication (n, %) <sup>a,b</sup>	99 665 (17.1)	93 965 (12.7)	91 434 (17.5)	81 550 (13.1)
<b>Diclofenac initiators</b>				
Overall (n)	356 545	423 356	300 402	337 529
New contraindication (n, %) <sup>a,b</sup>	50 903 (14.3)	42 416 (10.0)	41 650 (13.9)	33 537 (9.9)

<sup>a</sup>Percentages are based on the number of persons in the respective subgroup.

<sup>b</sup>Including congestive heart failure (NYHA class II–IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see Methods section).

specific to persons with any of the new contraindications. Interestingly, a decline in diclofenac use starting many years before the risk minimization measures were implemented has been reported for some European countries [14, 15], which may indicate that the overall decline after 2013 is an ongoing trend not caused by these measures.

Overall, our results suggest that prescribers of diclofenac are not aware of cardiovascular contraindications in Germany, a fact we find alarming—even more so in view of the most recent summary and judgment of the evidence regarding cardiovascular safety of nonaspirin NSAIDs published in 2016 by the working group for Cardiovascular Pharmacotherapy of the European Society of

**Table 2.** Age-standardized incidence proportions of diclofenac/any NSAID initiators in cohort 2014 compared to cohort 2011

	Incidence proportions, % (95% CI) <sup>a</sup>		Change
	2011	2014	
<b>Diclofenac</b>			
Women (all)	8.19 (8.17, 8.22)	5.80 (5.78, 5.82)	–29.1%
Women with new contraindication <sup>b</sup>	9.82 (9.51, 10.13)	6.57 (6.33, 6.82)	–33.1%
Men (all)	8.49 (8.47, 8.52)	6.27 (6.24, 6.29)	–26.2%
Men with new contraindication <sup>b</sup>	10.04 (9.68, 10.40)	6.98 (6.69, 7.27)	–30.5%
<b>Any NSAIDs</b>			
Women	18.94 (18.90, 18.98)	18.76 (18.72, 18.80)	–0.9%
Men	17.63 (17.59, 17.67)	17.93 (17.88, 17.97)	1.7%

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

<sup>a</sup>Age-standardized using the German population on 31 December 2011 as reference.

<sup>b</sup>Including congestive heart failure (NYHA class II–IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see Methods section).

**Table 3.** Characteristics of diclofenac initiators and proportion of contraindications amongst diclofenac initiators in 2014 compared to 2011

Characteristic	2011 (n = 779 901)	2014 (n = 637 931) <sup>a</sup>
Female sex (n, %)	423 356 (54.3)	337 529 (52.9)
Age in years (mean, SD)	53.2 (16.54)	53.6 (16.34)
Specialty of the prescribing physician (n, %)		
General practitioner	480 934 (61.7)	389 303 (61.0)
Orthopaedist	168 921 (21.7)	139 883 (21.9)
Surgeon	50 437 (6.5)	43 168 (6.8)
Other	71 701 (9.2)	57 982 (9.1)
Unknown/multiple different	7908 (1.0)	7595 (1.2)
Use of other NSAID in the year before diclofenac initiation (n, %)	179 539 (23.0)	175 119 (27.5)
Initially prescribed DDDs (mean, SD)	21.0 (15.51)	22.4 (16.26)
(Potential) indications of diclofenac (n, %) <sup>b</sup>		
Inflammatory polyarthropathies (M05–M14)	75 082 (9.6)	66 755 (10.5)
Arthrosis (M15–M19)	216 822 (27.8)	186 786 (29.3)
Spondylopathies (M45–M49)	149 866 (19.2)	132 501 (20.8)
Other soft tissue disorders, not elsewhere classified (M79)	82 522 (10.6)	76 369 (12.0)
Pain in back, joint, or limb (M54, M25.5, M79.6)	468 795 (60.1)	391 540 (61.4)
Pain, not elsewhere classified (R52)	51 429 (6.6)	53 148 (8.3)
Injury of unspecified body region (T14)	66 408 (8.5)	55 021 (8.6)
Any of above	607 452 (77.9)	505 171 (79.2)
New contraindications (n, %) <sup>b</sup>		
Congestive heart failure (NYHA class II–IV) (I50.03–05, I50.12–14)	7521 (1.0)	6692 (1.0)
Ischaemic heart disease (I20–I25)	61 885 (7.9)	47 572 (7.5)
Peripheral arterial disease (I73.9)	11 427 (1.5)	8644 (1.4)
Cerebrovascular disease (I60–I69, G45, G46)	35 662 (4.6)	31 266 (4.9)
Any new contraindication <sup>c</sup>	93 319 (12.0)	75 187 (11.8)

DDD, defined daily doses; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

<sup>a</sup>N = 68 525 (10.7%) were also included in 2011.

<sup>b</sup>One person could have more than one potential diagnosis or contraindication. For potential indications—deviating from contraindications (see Methods section)—an outpatient diagnosis in one of the four quarters was sufficient.

<sup>c</sup>Only based on inpatient diagnoses, N = 22 873 (2.9%) and N = 17 194 (2.7%) had any new contraindication in 2011 and 2014, respectively.

Cardiology [4]. This working group recommends against prescribing diclofenac due to missing evidence about its therapeutic superiority and in view of its associated cardiovascular risk [4]. This exceeds the EMA assessment report published 3 years earlier (in 2013), which concluded that the risk–benefit balance for systemic diclofenac ‘remains favourable subject to the agreed [...] additional risk minimisation measures, in the form of a DHPC letter’ [11]. Also, a recently published study by Schmidt and colleagues confirmed the cardiovascular health risks of diclofenac compared

with no use of NSAIDs, paracetamol use and use of other traditional NSAIDs and did not suggest a lower risk of upper gastrointestinal bleeding for diclofenac compared with other NSAIDs [9]. Importantly, the cardiovascular risks were even seen within 30 days from initiation and also for low doses. In other words, the cardiovascular risks are not restricted to persons with chronic use of diclofenac and are thus also relevant to those persons receiving only one prescription of diclofenac, that is to the vast majority of diclofenac initiators in our study (80% in 2014).

Given the high clinical and public health relevance of our findings, this topic requires urgent attention, both, on the national level and international level. In Germany, observational and interventional studies are needed focusing on the clinical knowledge amongst prescribing physicians regarding new contraindications of diclofenac and on ways to improve treatment decisions. This includes qualitative and quantitative studies to understand barriers to using computerized clinical decision support systems [16] and the potential of integrating pharmacists into the surveillance of medication decisions. The planned implementation of an electronic health card in Germany bringing together information on a patient's morbidity and drugs prescribed by (various) physicians could be exploited in this regard and may facilitate the cooperation between physicians and pharmacists.

Knowledge on NSAIDs with a more favourable risk profile such as ibuprofen or naproxen need to be increased [4]. More than 70% of diclofenac initiators with absolute cardiovascular contraindications in our study were not prescribed other NSAIDs before diclofenac prescription. This indicates that alternative and safer treatment options require more attention. As a consequence of our study, it will also be important to investigate temporal trends in the occurrence of adverse cardiovascular drug reactions following NSAID use given that evaluation of safety outcomes is another element of monitoring risk minimization measures [17].

On the international level, it will be important to conduct similar studies in other settings in order to assess whether there is also a lack of effectiveness of the risk minimization measures for diclofenac in countries other than Germany. The two available studies from other European countries [18, 19] reporting on NSAID use amongst persons with cardiovascular contraindications only used data before 2013 [18, 19]; did not report drug-specific results [18]; and focused on geographical differences rather than trends [19]. The impact of risk minimization measures may depend on how the new contraindications were communicated to healthcare professionals and on the structure of the healthcare system [20]. For example, the gatekeeper role of general practitioners in the UK could be favourable regarding adequate consideration of contraindications as they have—in contrast to specialists—a comprehensive patient record [21]. On the other hand, our results did not indicate that

general practitioners are more aware of contraindications than specialists in Germany.

#### *Strengths and limitations*

A major strength of our study is that it provides real-world evidence as we used a large claims database that includes information on about 17% of the general population in Germany and from all types of prescribers (i.e. not limited to certain specialties). Given that each physician in Germany is likely to have patients insured at one of the health insurance providers included in our database, we expect that our database includes the vast majority of prescribers and is representative of routine clinical care in Germany. The focus on diclofenac initiators allowed us to specifically characterize the prescription behaviour before and after the risk minimization measures. Similar to other claims data, our database does not include information on drugs dispensed over-the-counter (OTC). However, as we aimed to characterize the prescribing behaviour of physicians regarding diclofenac, we do not consider this a limitation of our study. The validity of diagnosis codes in claims data may generally be considered suboptimal, but this is typically less of an issue for 'hard' diagnoses such as ischaemic heart disease, peripheral arterial disease and cerebrovascular disease. In addition, we used an algorithm that avoids overestimating the presence of contraindications. Restricting the analysis to inpatient diagnoses—for which studies showed high validity [22]—confirmed the main results as there was also no substantial decline in the proportion of diclofenac initiators with new contraindications. As expected, the proportions of patients with contraindications were lower in the sensitivity analysis given that not all persons with contraindications may have been hospitalized and the hospitalizations that occurred may have occurred more than 1 year before diclofenac initiation. The prevalence of NYHA classes II–IV may have been underestimated given the common use of unspecific codes for NYHA, that is codes that do not allow distinguishing between NYHA classes I–IV. We did not consider these unspecific NYHA codes to provide a conservative estimate of the proportion of diclofenac initiators with contraindications.

As we used a pre–post comparison to investigate whether the measures taken in 2013 were effective, our study was restricted to data until the end of 2014 which appears a reasonable time frame. We do not expect substantial changes after 2014 but further analyses with more recent data will be

informative to check for potential delayed effects. We did not perform tests of statistical significance to compare both cohorts as the large number of individuals in our study may result in statistically significant differences, which, however, may not be clinically relevant.

### Conclusion

Our study suggests that prescribers of diclofenac are not aware of cardiovascular contraindications in Germany. New contraindications of diclofenac were present in more than one in ten patients who were newly prescribed diclofenac exposing them to a risk of cardiovascular side effects hardly justifiable in view of safer treatment alternatives. In Germany, interventional studies at the prescriber level are urgently needed to improve patient safety and it is important to determine the extent of the problem on the international level.

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### Conflict of interest statement

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; the authors are working at the Leibniz Institute for Prevention Research and Epidemiology—BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are postauthorization safety studies (PASS) requested by health authorities. The studies and the resulting publications are not influenced by the pharmaceutical industry.

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