Risk of Cardiovascular, Gastrointestinal, and Renal Adverse Events Associated With Diclofenac Immediate- and Extended-Release Drug Products: An Observational Study Using US Claims Data

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INTRODUCTION

- Nonsteroidal anti-inflammatory drug (NSAID) products are produced in a variety of dosing strengths, ranging from 25 to 500 mg, and multiple release formulations, including immediate-release, extended-release, and delayed-release formulations, with each having different pharmacokinetic properties, and thus, exerting differing pharmacodynamic response at various physiologic sites.
- In addition to the total daily dose used, NSAID release formulation might predispose to increase the risk of specific adverse events.
- Safety studies in many countries have shown that gastrointestinal (GI) and cardiovascular (CV) risks associated with use of NSAIDs are dependent on the dose and the formulation.[1-5]
- However, very little data exist from United States (US)-based observational studies on dose- and formulation-related risk of adverse events associated with NSAIDs, particularly for diclofenac products.
- In this study, we examined the risk of adverse GI, CV, and renal events associated with diclofenac dose and release formulation using a population-level US claims database.

METHODS

Data Source

- Data for this retrospective observational study were extracted from the MarketScan© Commercial Claims and Encounters (CCAE) and the Medicare Supplemental (MDCR) databases.
- The CCAE and MDCR databases provide longitudinal data on medical and pharmacy service utilization for individuals covered by more than 100 employer-sponsored private health insurance plans in the US.
- Medical claims include, but are not limited to, diagnoses, procedures, and other health care service utilization, including prescription drug records, along with respective dates, and detailed information on hospitalizations, including admission and discharge dates.

Patient Selection

- Patients with a new diclofenac prescription, during the study period (January 1, 2009, to December 30, 2012) were selected for initial study inclusion.
- Patients were required to have no NSAID prescriptions 2 weeks before and after the first diclofenac prescription (i.e., study index date).
- Additionally, patients were required to be ≥18 years of age at index date and have at least 12 months of continuous health plan enrollment prior to the index date (i.e., preindex date period).
- Patients with incomplete drug benefit coverage during the study period, invalid demographic or enrollment data, or invalid diclofenac prescription drug records were excluded.

Study Measures

Exposure

- Total daily dose was defined at the prescription level as a product of quantity supplied and the strength (in mgs) divided by the number of days' supply, and was grouped in to one of the following four dose categories:
  - ≤ 75 mg
  - > 75-100 mg
  - > 100-150 mg
  - > 150 mg
- The release form of the drug was defined based on the strength and salt form of diclofenac product:
  - Immediate release: Diclofenac potassium, any strength
  - Delayed/extended release: Diclofenac sodium, any strength
- Periods of diclofenac exposure and nonexposure were defined using days' supply of the prescription refills; to account for the residual effect of diclofenac and potential noncompliance, an additional 30 days was included in the exposure period after the days' supply ran out.
- Patients could contribute multiple exposure periods (i.e., periods of diclofenac exposure and nonexposure [referred to as *no current use*]).
- All exposure periods, for a given patient, represented a combination of dose and formulation characteristics (e.g., dose > 150 mg in immediate-release formulation), which were compared against periods of no current use to assess the risk of adverse outcomes related to diclofenac dose and formulation, using a multivariable regression method described in the Cohort Creation and Data Analysis section below.
- Any switches in the release form or dose titration during the follow-up resulted in initiation of a new diclofenac exposure period.

Outcomes

- Specific clinical events of interest in this analysis include the following:
  - CV events: myocardial infarction (MI), stroke, congestive heart failure (CHF)
  - GI events: upper GI bleed or perforation (UGIB), lower GI bleed (LGIB)
  - Renal failure
- Baseline history of events was assessed during the 12-month preindex date period.
- Historical events and study outcomes of interest during follow-up were assessed through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes in the inpatient and outpatient medical claims.

Cohort Creation and Data Analysis

- Based on the event history during the 12-month preindex date period, several exclusion criteria were applied to select a relatively healthy patient population at risk of the events of interest and without recent history of these outcomes (Table 1).
- Separate analytic cohorts were constructed for each of the study outcomes.

Table 1. Outcome-Specific Exclusion and Censoring Criteria Used in the Analytic Cohort Creation and Study Follow-up

Model Outcome	Exclusion Criteria (patients with a recorded history of any of the following events)	Censoring Criteria[a] (at occurrence of earliest of the following events during follow-up)
MI	MI, CHF, stroke	CHF, stroke
CHF	MI, CHF, stroke	MI, stroke,
Stroke	MI, CHF, stroke	MI, CHF
UGIB	UGIB, LGIB, uncomplicated ulcer	LGIB, uncomplicated ulcer, initiation of Arthrotec, PPI, or H2 blocker
LGIB	LGIB, UGIB	UGIB, uncomplicated ulcer, or initiation of Arthrotec, PPI, or H2 blocker
Renal failure	Renal failure	

PPI = proton pump inhibitor.

[a] In all models patients were censored if they reached end of follow-up (December 31, 2012), started a nonindex NSAID, or disenrolled from the health plan.

Note: When modeling each outcome, patients with a recorded history of the event or a related event prior to diclofenac initiation were excluded from the model. Additionally, follow-up for each of the outcomes was censored when a related event was observed.

- All patients contributed to the study follow-up until earliest of the censoring events, as listed in Table 1, for each respective outcome.
- Multivariable time-to-event analyses were conducted to assess the risk of adverse events using repeated-measures Cox proportional hazards models, with time-dependent variables for total daily dose and release formulation.
- All multivariable models controlled for relevant demographic and clinical risk factors measured during the 12-month preindex period; hazard ratios and 95% CIs were estimated.
- Analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

- A total of 851,549 diclofenac users (57% female; median age 50 years) met the initial study inclusion criteria.
- Table 2 provides a description of baseline demographic and clinical characteristics of the overall sample.
- At diclofenac initiation, median total daily dose was 150 mg (range: 1-400 mg), and most (88%) prescriptions were extended/delayed release (with 93% delayed-release and 7% extended-release formulation).
- Multivariable Cox proportional hazards analyses showed that when taking extended/delayed-release diclofenac at a total daily dose of >150 mg, the risk of UGIB was nearly 3.5 times greater (hazard ratio [HR]: 3.48, 95% confidence interval [CI]: 2.25-5.37) compared with no current use.
- The immediate-release diclofenac formulation, at the same dose category (>150 mg), was associated with nearly 2.5 times greater risk of UGIB (HR: 2.59, 95% CI: 1.55-4.33) compared with no current use.
- HRs with 95% confidence intervals (CIs) for the risk of study outcome associated with dose categories and release formulations are presented in the Table 3.
- The forest plot of HR and 95% CI, in Figure 1, graphically displays the magnitude of association between diclofenac total daily dose >150 mg and the risk of study outcomes as compared with no current diclofenac use, according to the release formulation.

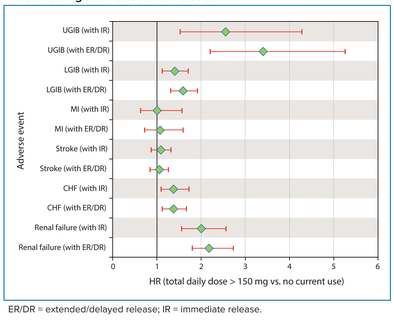
Table 2. Baseline Demographic and Clinical Characteristics of Diclofenac Patients (Prior to Application of an Outcome-Specific Exclusion Criteria)

Characteristics	All Diclofenac Patients (N = 851,549)	
Age at index (years)		
Mean (SD)	49.16 (13.91)	
Median	50.00	
(Min, Max)	(18.00, 105.00)	
Sex (n, %)		
Male	366,002	42.98%
Female	485,547	57.02%
Geographic region (n, %)		
Northeast	105,738	12.42%
Midwest	198,916	23.36%
South	405,439	47.61%
West	124,885	14.67%
Unknown	16,571	1.95%
Charlson Comorbidity Index score assessed over the 12 months prior to index[a]		
Mean (SD)	0.95 (1.39)	
Median	0.00	
(Min, Max)	(0.00, 21.00)	
Distribution (n, %)		
0	430,675	50.58%
1	221,576	26.02%
2	108,177	12.70%
3+	91,121	10.70%
Events of interest assessed over the 12 months prior to index (n, %)		
MI	1,980	0.23%
Stroke	13,358	1.57%
CHF	10,744	1.26%
Hypertension	246,483	28.95%
UGIB	1,061	0.12%
LGIB	12,340	1.45%
Uncomplicated ulcer	3,245	0.38%
Dyspepsia	7,268	0.85%
Renal failure	3,034	0.36%
Outpatient prescriptions of interest assessed over the 12 months prior to index (n, %)		
Nonindex NSAIDS	205,138	24.09%
Proton pump inhibitor	138,079	16.22%
H2 receptor antagonist	18,651	2.19%
Misoprostol	17,768	2.09%
Sucralfate	5,790	0.68%
Bisphosphonates	24,929	2.93%
Warfarin	9,607	1.13%
Anticoagulants	14,072	1.65%
Corticosteroids	247,476	29.06%
Clopidogrel	13,383	1.57%
Antiplatelet agents	18,166	2.13%
Other CV drugs[b]	260,731	30.62%

[a] Individual components of the Charlson Comorbidity Index and other comorbidities (e.g., hyperlipidemia) also were assessed.

[b] Includes angiotensin-converting enzyme/angiotensin receptor blockers, aldosterone inhibitors, beta blockers, and other antihypertensives.

Figure 1. Risk of Adverse Events Associated With Diclofenac Total Daily Dose > 150 mg and Release Formulation



ER/DR = extended/delayed release; IR = immediate release.

LIMITATIONS AND FUTURE RESEARCH

- The analysis was based on retrospective administrative claims data collected for reimbursement purposes, and includes diagnosis and procedure codes, which, if recorded incorrectly, may cause misclassification of events and disease conditions.
- We did not have access to patients' medical charts or complete information on their medical history, and hence, the history of events was determined using claims data for a 12-month period prior to diclofenac initiation.
- Prescription drug information used to calculate total daily dose only represents medications prescribed and filled, and not necessarily taken; to account for possible noncompliance, an additional 30 days after end of the prescription was included in the diclofenac exposure period.
- The data are not entirely representative of the US population since they primarily reflects care provided to younger commercially insured patients; patients aged 65 years and older are underrepresented.
- The risks estimated in our study are possibly underestimated given that the study cohort was restricted to relatively healthier patients and an outcome-specific censoring approach was used. Future studies will be needed to estimate the risk among patients with prior history of the outcomes and without censoring events related with the exposure or the outcome being evaluated.
- In addition, the extended-release and delayed-release formulations of the drug were combined into a single group for the purpose of this analysis, with the majority of the group (93%) represented by delayed-release formulation. However, given the difference in pharmacokinetic properties between the two, it is important to examine in the future whether extended-release formulation (available only in 100 mg strength) has a differential risk profile compared with the delayed-release formulation (available in 25, 50, and 75 mg strengths).

CONCLUSIONS

- In an analysis of US health care claims, increased risks of certain outcomes were associated with increased doses of diclofenac compared with no current use and with extended/delayed-release formulation compared with the immediate-release formulation among new users of diclofenac with no prior history of the event; risks were particularly greater for UGIB and renal failure.
- The risks of CV events were observed to be similar between diclofenac extended/delayed-release formulation and the immediate-release formulation.
- While the findings of this study suggest an association between diclofenac daily dose, release formulation, and the risk of outcomes, additional studies may further elucidate causal inferences.

DISCLOSURE

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Table 3. Diclofenac Dose and Release Formulation Associated Risk of CV, GI, and Renal Failure Events: Results From Multivariable Cox Proportional Hazards Models

Adverse Event		Total Sample	Release Formulation	Hazard Ratio[a] (95% CI)			
				Total Daily Dose ≤ 75 mg	Total Daily Dose > 75-100 mg	Total Daily Dose > 100-150 mg	Total Daily Dose > 150 mg
GI	UGIB	835,424	Immediate	1.260 (0.806-1.970)	1.889 (1.354-2.634)	1.636 (1.163-2.303)	2.555 (1.530-4.268)
			Extended/Delayed	1.681 (1.185-2.385)	2.519 (2.063-3.076)	2.183 (1.882-2.531)	3.409 (2.208-5.263)
	LGIB	838,252	Immediate	1.178 (0.997-1.391)	1.141 (1.005-1.297)	1.118 (0.983-1.271)	1.386 (1.122-1.712)
			Extended/Delayed	1.354 (1.185-1.548)	1.313 (1.204-1.431)	1.285 (1.212-1.363)	1.594 (1.320-1.925)
CV	MI	827,389	Immediate	0.809 (0.589-1.111)	1.148 (0.897-1.469)	1.019 (0.790-1.313)	1.006 (0.645-1.569)
			Extended/Delayed	0.861 (0.682-1.086)	1.221 (1.058-1.409)	1.084 (0.983-1.195)	1.070 (0.724-1.582)
	Stroke	827,389	Immediate	1.062 (0.923-1.222)	1.149 (1.024-1.290)	1.004 (0.891-1.131)	1.070 (0.866-1.323)
			Extended/Delayed	1.040 (0.942-1.149)	1.126 (1.051-1.207)	0.984 (0.936-1.033)	1.049 (0.868-1.267)
	CHF	827,389	Immediate	1.080 (0.913-1.277)	1.114 (0.968-1.282)	1.060 (0.918-1.223)	1.369 (1.086-1.726)
			Extended/Delayed	1.079 (0.960-1.212)	1.113 (1.024-1.210)	1.059 (1.000-1.121)	1.368 (1.121-1.670)
Renal	Renal failure	848,515	Immediate	1.109 (0.913-1.348)	1.245 (1.057-1.465)	1.274 (1.080-1.503)	2.005 (1.569-2.563)
			Extended/Delayed	1.205 (1.053-1.380)	1.353 (1.231-1.487)	1.384 (1.299-1.475)	2.179 (1.780-2.668)

[a] Hazard risk ratio estimates represent the hazard risk rate of the study outcome during current use of diclofenac at a particular total daily dose (e.g., >150 mg) relative to the hazard risk rate of the outcome during no current use of diclofenac.