

# Relationship Between Diclofenac Dose and Risk of Gastrointestinal and Cardiovascular Events: Meta-Regression Based on Two Systematic Literature Reviews

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## ABSTRACT

**Background:** NSAIDs are associated with risks of gastrointestinal (GI) and cardiovascular (CV) toxicities. It has been reported that the risks of GI and CV events are dose related, resulting in guidance explicitly emphasizing the use of NSAIDs at the lowest effective dose for the shortest duration. To understand the potential benefits of using lower doses of diclofenac, a more detailed understanding of the relationship of diclofenac dose and the risks of GI and CV events is required.

**Objective:** The objective of this study was to extend previous research quantifying the NSAID dose-toxicity relationship by modeling dose as a continuous measure, allowing for an assessment of the risks of major GI and CV events for patients taking specific diclofenac doses compared with NSAID nonusers.

**Methods:** We used studies identified in 2 recently published systematic reviews of observational studies that examined the risks of major GI and CV events associated with the use of oral NSAIDs. We developed meta-regression models, considering dose as a continuous measure, to estimate the risks of major GI and CV events for different daily doses of conventional oral diclofenac relative to nonuse of NSAIDs.

**Results:** Seven of the 59 GI publications, contributing 11 dose-specific risk ratio observations, and 12 of the 51 CV studies, contributing 21 dose-specific risk ratio observations, were eligible for inclusion in the meta-regression. The models indicated positive linear relationships between diclofenac dose and the relative risks of major GI and CV events for the range of doses examined.

**Conclusions:** To our knowledge, this is the first study to quantify and aggregate the continuous relationship between the risk of GI or CV events

and the dosage of an NSAID. With the recent availability of new low doses of diclofenac, the models may be used to estimate the potential reduction in risk of adverse events at these doses. (*Clin Ther.* 2014;36:906–917) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

**Key Words:** cardiovascular safety, diclofenac, dose-related toxicity, gastrointestinal complications, meta-analysis.

## INTRODUCTION

NSAIDs are a diverse group of medications used to treat patients with acute and chronic pain as well as to reduce inflammation.<sup>1</sup> Although NSAIDs are commonly prescribed due to their proven efficacy in treating pain, they often present safety and tolerability issues, including serious concerns related to gastrointestinal (GI), cardiovascular (CV), and renal toxicity. Traditional, nonselective NSAIDs such as diclofenac have been associated with GI events and in particular upper GI bleeding/perforation (UGIB).<sup>2</sup> Efforts have been taken to mediate NSAID toxicity, including use of proton pump inhibitors for their gastroprotective effects, development of cyclooxygenase-2 (COX-2) selective inhibitors, and development of topical NSAIDs. Newer, COX-2-selective NSAIDs were developed in part for the potential to reduce the risk of GI events but have subsequently demonstrated an increased risk of CV events. In

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particular, rofecoxib, a COX-2–selective inhibitor, was removed from the market in late 2004 when a clinical study demonstrated that the drug was associated with increased rates of CV events in patients with colorectal polyps.<sup>3</sup> Subsequently, efforts focused on understanding whether the risks observed with rofecoxib were also present for other COX-2–selective inhibitors and for nonselective NSAIDs.

Large pharmacoepidemiologic studies<sup>4–6</sup> corroborated findings from NSAID clinical trials of toxicity risks. Additional studies have examined the risk of low versus high doses of NSAIDs and found increased safety risks for patients receiving high doses of NSAIDs compared with patients receiving low doses of these agents.<sup>7–11</sup> Based on pooled evidence, regulatory agencies, including the US Food and Drug Administration,<sup>12</sup> the European Medicines Agency,<sup>13</sup> and Health Canada,<sup>14</sup> have explicitly recommended the use of NSAIDs at the lowest effective dose for the shortest duration.

In the present study, we examined the dose–toxicity relationship of conventional oral diclofenac to explore the potential benefits of the novel low-dose oral diclofenac product\* recently approved by the US Food and Drug Administration as a treatment for acute pain.

Due to the low incidence of serious GI and CV adverse events, conducting a randomized clinical trial to determine the difference in serious GI and CV adverse event rates between low-dose diclofenac and conventional diclofenac would require a patient sample size in the hundreds of thousands and a trial duration of many years. In the absence of data from randomized trials, the Methods Guide for Comparative Effectiveness Studies by the Agency for Healthcare Research and Quality<sup>15</sup> recommends examining available observational data by using appropriate statistical techniques. Therefore, the data used to quantify the relationship between diclofenac dosage and major GI and CV adverse event risks were obtained from publications of observational studies included in recently published systematic literature reviews.

To our knowledge, no meta-analysis study has attempted to quantify the continuous relationship between the increased risk of major GI and CV events and the increased dosage of diclofenac. This study extends previous NSAID dose–toxicity research by modeling dose as a continuous measure, allowing for

an assessment of the risks of GI and CV events for patients taking specific conventional oral diclofenac doses compared with NSAID nonusers.

## METHODS

### Data Sources

Given the wealth of information on the safety profile of NSAIDs, we were able to locate 2 recently published systematic reviews of NSAID observational studies that met our meta-regression objectives: a systematic review of GI toxicity<sup>7</sup> and a systematic review of CV toxicity.<sup>8</sup> The search strategy of Castellsague et al<sup>7</sup> was restricted to observational studies published in English between January 1, 1980, and May 31, 2011, in the PubMed database. The authors used MeSH terms and free-text terms for individual NSAIDs and COX-2–selective inhibitors and GI disease. The search strategy of McGettigan and Henry<sup>8</sup> was limited to electronic databases for published articles (case-control, case-crossover, and controlled cohort designs that reported on CV risks associated with the use of the individual drugs in population settings) between January 1, 1985, and November 30, 2010, with no language restriction. These 2 systematic reviews were used as the basis for identifying potentially relevant diclofenac studies.

### Additional Meta-Regression Inclusion and Exclusion Criteria

We applied criteria to the published studies identified in the 2 systematic reviews to assess the relationship between GI and CV events and diclofenac dose via meta-regression analyses. Specifically, from all the studies included in the 2 published systematic literature reviews, we identified studies that included oral diclofenac and evaluated GI or CV risks and then reviewed each one to determine whether the study reported dosing information. The criteria for selecting studies for inclusion in the analysis were thoroughly documented, including the development of a flow chart similar to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.<sup>16</sup>

### Drug Exposures and Outcomes

Exposure to diclofenac was based on “current use” as defined in each study. All studies defined a dose in milligrams, and none reported dose per weight (eg, milligrams per kilogram). The majority of the studies defined exposure as any diclofenac use up to 30 days

\*Trademark: Zorvolex<sup>®</sup> (Iroko Pharmaceuticals LLC, Philadelphia, Pennsylvania).

before the event date (ie, the day on which the GI or CV event occurred). Studies presented either a single result for a total daily dose (a specific dosage or dosage described by using summary statistics) or results according to dosage category.

Where studies presented information according to diclofenac dosage category (eg, the odds ratio of an UGIB with diclofenac use of <100 mg daily), the outcomes for GI and CV events were recorded by using dose categories. We then derived a specific dosage based on either the midpoint of the category or the most commonly used dosage in the category; all dose derivations were confirmed by 2 rheumatologists who are experts in the use of NSAIDs. This step facilitated meta-regression model development by associating the outcome effect with a specific dose as a continuous measure.

For studies that presented a single overall GI or CV risk ratio, dose was obtained from summary statistics (eg, median). Finally, when a specific dosage was presented, the outcome linked to that dosage was used.

Studies reported a mix of safety outcomes. A majority of the GI studies reported on UGIB (ie, complicated ulcer), with 2 studies reporting first hospitalization for an upper GI event.<sup>17,18</sup> The most commonly reported outcome in the CV studies was acute myocardial infarction (AMI), with some studies reporting other outcomes: CV disease, death, stroke, hospitalization for a CV event, or a composite measure of multiple outcomes. In their respective systematic reviews, McGettigan and Henry<sup>8</sup> allowed individual studies to contribute >1 outcome whereas Castellsague et al<sup>7</sup> did not. We followed the approach by Castellsague et al, in which each study was allowed to contribute only 1 outcome. We chose the outcome based on the most commonly reported outcome across all the studies. If a study presented >1 relevant outcome, a hierarchy was imposed by clinical relevance, as follows:

- GI event: UGIB was the most commonly reported event. If a study did not report UGIB (1 study), we used first hospitalization for an upper GI event.
- CV event: AMI was the most commonly reported event. If a study did not report AMI, we used CV disease, death, stroke, or hospitalization for a CV event, in that order.

### Statistical Analysis

A type of meta-analysis, meta-regression, was used to quantify the dose-toxicity relationship of oral

diclofenac with serious upper GI and CV events. Meta-analysis is a quantitative technique that integrates and condenses information from independent studies. Meta-regression is similar to simple regression analyses in which an outcome variable is predicted according to the values of a number of explanatory (independent) variables.

In the 2 meta-regression models for this study, the dependent variable was the risk ratio of the toxicity event (ie, upper GI event, CV event). The meta-regressions were based on a linear mixed-effects model that accounted for within-study correlation for studies that contributed >1 observation. The explanatory variable was a continuous measurement of dosage. The model was weighted by the inverse of the trial-specific dependent variable precision (ie, variance). In effect, this meant that studies with larger sample sizes had more influence in the meta-regression model. SEs of the effect estimate were derived by using the CI for the outcome effect.

The meta-regression model was as follows:

For study  $i$  and dose  $j$ , the dependent variable (ie, risk ratio)  $y_{ij}$  can be written as

$$y_{ij} = 1 + \alpha x_{ij} + \gamma_i + \varepsilon_{ij},$$

where

$y_{ij}$  is the dependent variable (ie, risk ratio) from study  $i$  and dosage  $j$

- $\alpha$  is the fixed effect associated with the change in the dependent variable for 1-unit increase of dosage
- $x_{ij}$  is the dosage from study  $i$  and dosage  $j$
- study-specific random intercept  $\gamma_i$  follows normal distribution with mean zero and unknown common variance  $\sigma^2$
- $\varepsilon_{ij}$  is the error term following a normal distribution with mean zero and known variance  $s_{ij}^2$  from study  $i$  and dosage  $j$
- the error terms ( $\varepsilon_{ij}$ ) from each study are independent and the correlation between different doses (if applicable) within a study is assumed to be 0.5
- the error term ( $\varepsilon_{ij}$ ) and study-specific random intercept ( $\gamma_i$ ) are independent

We assumed that the odds ratio, incidence rate ratio, and hazard ratio reported in studies all were equivalent to the risk ratio on the basis of the low incidence assumption.<sup>19</sup> Incidence rates, where provided, were converted to an incidence rate ratio based on the incidence of GI events for the NSAID nonuser population.<sup>20</sup> This derivation was not necessary for the

CV end point because all of the studies provided an outcome measure in terms of a ratio to NSAID nonusers. We assumed that the risk ratio was 1 when the dose was zero. This was accomplished by scaling the risk ratios (subtracting 1 from the risk ratios) and setting the intercept to zero. It was then necessary to add 1 to any estimated results from the meta-regression to derive the estimated risk ratios. From the model, we tested the null hypothesis that  $\alpha = 0$  versus  $\alpha \neq 0$  and if the test was significant (2-sided) at the 0.05 level, then we concluded that there was a relationship between diclofenac dose and GI/CV events.

## RESULTS

### Literature Search and Characteristics of Included Studies

#### GI Studies

Of the 59 GI publications selected by Castellsague et al<sup>7</sup> in their qualitative synthesis, 30 included diclofenac. Of these, 7 studies presented daily dose data for oral diclofenac and were appropriate for inclusion (Figure 1). Of these 7 studies, 5 were case-control studies and 2 were cohort studies. For the case-control studies, the number of case subjects ranged from 175 to 2813, and the number of control subjects ranged from 347 to 20,002. Cases typically were defined as adult patients with a first-

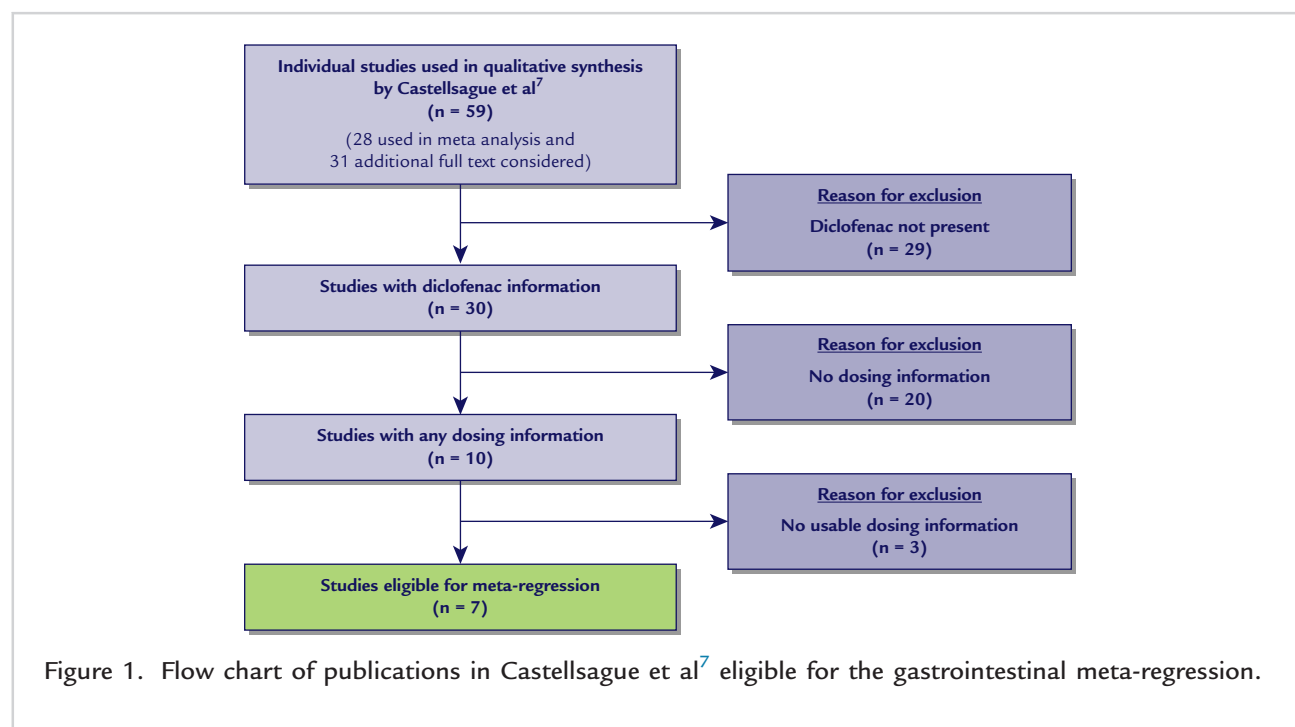
time diagnosis in a hospital of an UGIB during the reference period. Across all case-control studies, 169 GI events among patients using diclofenac were identified.

Because of the nature of a cohort study, sample sizes in these studies are typically larger than for case-control studies. Of the 2 cohort studies, Perez-Gutthann et al<sup>21</sup> included 22,146 diclofenac users and Rahme et al<sup>18</sup> included 778,759 diclofenac users, for a total of 800,905 exposed individuals. The study period for the cohort studies ranged from 2 to 8 years. The number of GI events among diclofenac users was not reported for these 2 cohort studies.

Of the 7 studies, 3 defined exposure as any diclofenac use up to 7 days before the event date, 1 study defined exposure as any diclofenac use up to 30 days before the event date, 1 study defined exposure as up to 90 days before the event date, and the remaining 2 studies required that the prescription period include the event date. Most studies required information from endoscopy or other diagnostic tests to confirm UGIB.

#### CV Studies

Of the 51 CV publications used in the McGettigan and Henry<sup>8</sup> meta-analysis, 27 articles included diclofenac. Of these, 11 reported dosing information



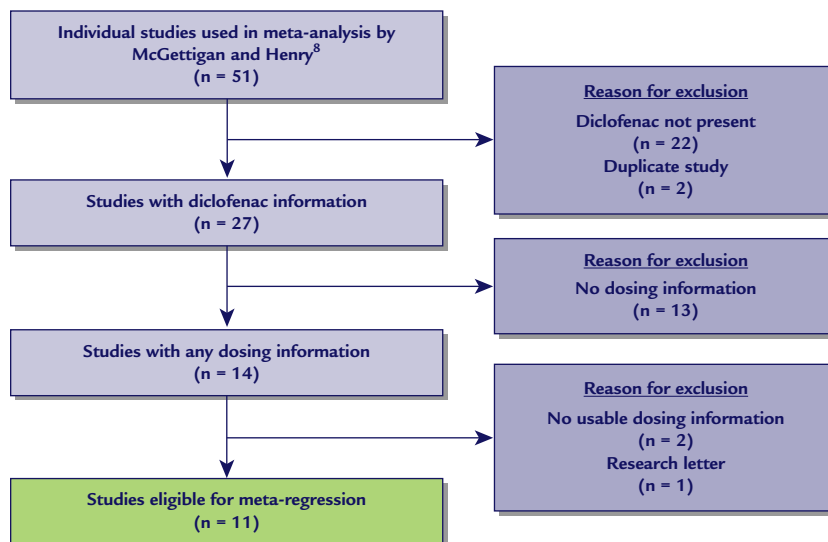


Figure 2. Flow chart of publications in McGettigan and Henry<sup>8</sup> eligible for the cardiovascular meta-regression.

for oral diclofenac and were eligible for the meta-regression analysis (Figure 2). Of the 11 CV studies, 6 were case-control studies and 5 were cohort studies. For the case-control studies, the sample size for the cases ranged from ~3000 to 800,000, whereas the sample size for controls ranged from 14,000 to 400,000. Cases typically were defined as adult patients with a first diagnosis of AMI, stroke, or other CV event during the reference period. Across all case-

control studies, the total number of CV events for cases using diclofenac was 2472. Sample sizes of the eligible cohort studies ranged from ~48,000 to 1 million patients. Some cohort studies identified the subset of patients who used diclofenac; subsets ranged from 804 patients to 172,362 patients, for a total of 189,211 exposed individuals. In the cohort studies, the study period averaged 8 years, and patient medical records from 1995 to 2005 were reviewed. The

Table I. Studies used in the gastrointestinal (GI) meta-regression model.

Observation No.	Author, Year	GI Event	Diclofenac Daily Dose (mg)	Risk Ratio (95% CI)
1	Castellsague et al, 2009 <sup>17</sup>	Upper GI hospitalization	75	2.30 (0.8-6.7)
2			100	2.00 (0.8-4.6)
3	Gutthann et al, 1997 <sup>22</sup>	Complicated ulcer	75	2.90 (1.4-5.7)
4			150	3.30 (1.6-7.0)
5	Laporte et al, 2004 <sup>23</sup>	Upper GI bleeding	50	1.80 (1.0-3.1)
6			100	4.20 (1.3-7.6)
7			150	18.20 (6.8-48.7)
8	Perez-Gutthann et al, 1999 <sup>21</sup>	Upper GI bleeding	75	2.40 (0.5-4.6)
9	Rahme et al, 2007 <sup>18</sup>	Hospitalization for upper GI bleeding	150	3.78 (2.9-3.9)
10	Sakamoto et al, 2006 <sup>24</sup>	Upper GI bleeding	75	10.90 (2.5-48.4)
11	Savage et al, 1993 <sup>25</sup>	Complicated ulcer	150	3.30 (1.6-6.9)

number of events for diclofenac users was reported less frequently for cohort studies than for case-control studies. For those studies that did provide event information, the total number of CV events for diclofenac users was  $\sim 300$ . In general, diclofenac exposure was defined as any current diclofenac use up to 30 days before the event date (ie, the day on which the CV event occurred), although this varied from 7 days to 90 days before the event date.

## Meta-Regression

### GI Model

Table I<sup>17,18,21–25</sup> provides a summary of the 11 doses and corresponding risk ratios from the 7 GI studies. The results of the GI model indicated a positive linear relationship between oral diclofenac dose and the risk of a GI event; that is, as the diclofenac dose increased, the risk of a GI event increased. The fixed-effect model parameter for diclofenac dose was 0.01776 (95% CI, 0.01361–0.02191), with an associated *P* value of  $<0.001$ , indicating a linear relationship between diclofenac dose and GI risk ratio. The following equation converted diclofenac daily dosage (in milligrams) to an estimated risk ratio that represented risk per milligram of diclofenac dose: estimated GI risk ratio =  $(0.01776 \times \text{daily dose}) + 1$ .

Table II provides the model-derived, estimated risk ratios for a serious GI event for a range of daily diclofenac doses (as found in conventional oral diclofenac and low-dose oral diclofenac), compared with no exposure (ie, NSAID nonuse). Figure 3 depicts the meta-regression line, with the individual risk ratios plotted.

Additional models (eg, categorical dose, polynomial transformations) and visual plots suggested that the model with a linear effect for dose was appropriate for describing the relationship between diclofenac dose and the risk ratio of a GI event. We assessed the model fit and assumptions. We visually examined model residuals for normality, and the plots showed an approximate normal distribution of the residuals.

We examined outliers to see whether any observation contributed considerable influence on the regression line. We discovered a potential outlier in the study reported by Sakamoto et al,<sup>24</sup> a study conducted in Japan with a small number of events (10 among case subjects and 3 among control subjects), which reported a risk ratio of 10.9. We performed a sensitivity analysis by excluding this study, and the results were compared with those from the main model (data not shown). The sensitivity model results were similar to those from the main model, indicating that the effect of the study by Sakamoto et al was minimal, in

Table II. Estimated risk of a serious gastrointestinal (GI) event relative to nonuse of NSAIDs according to dose of conventional and low-dose diclofenac.\*

Daily Dose	Estimated GI Risk Ratio (SE; 95% CI)
Conventional diclofenac	
50 (eg, 25 mg BID)	1.89 (0.092; 1.68–2.10)
100 (eg, 50 mg BID)	2.78 (0.184; 2.36–3.19)
150 (eg, 50 mg TID)	3.66 (0.275; 3.04–4.29)
Low-dose diclofenac*	
36 (18 mg BID)	1.67 (0.070; 1.52–1.83) <sup>†</sup>
54 (18 mg TID)	2.03 (0.106; 1.79–2.27)
70 (35 mg BID)	2.33 (0.138; 2.02–2.64)
105 (35 mg TID)	3.00 (0.207; 2.54–3.48)

\*Trademark: Zorvolex® (Iroko Pharmaceuticals LLC, Philadelphia, Pennsylvania). The difference in molecular weight between conventional and low-dose diclofenac was taken into account when dose was calculated. Specifically daily doses of 105 mg, 70 mg, 54 mg and 36 mg of low-dose diclofenac were converted to 113 mc, 75 mg, 58 mg and 38 mg of conventional diclofenac, respectively.

<sup>†</sup>The GI meta-regression model was based on a range of daily doses as low as 50 mg; the GI risk ratio estimated for a daily dose of diclofenac of 36 mg (adjusted to 38 mg) reflects an application of the risk equation beyond the values included in the model<sup>37,38</sup>.

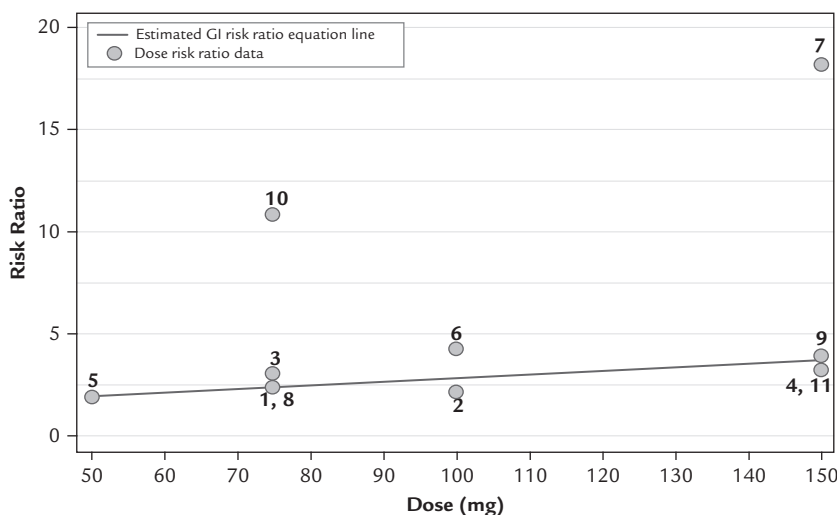


Figure 3. Relationship between diclofenac daily dose and the estimated risk ratio of a serious gastrointestinal event. Numbers correspond to the observations in Table I.

part because of its large variance and resulting low weight. Our final sensitivity analysis excluded the 2 studies that used a calculated incidence rate ratio in the meta-regression analysis.<sup>18,21</sup> The results were comparable to those of the main model but with a slightly lower fixed-effect model parameter for diclofenac dose (data not shown).

#### CV Model

Table III<sup>26–36</sup> provides a summary of the 21 doses and corresponding risk ratios from the 11 CV studies. The results of the CV model indicated a positive linear relationship for oral diclofenac dose and the risk of a CV event. The fixed-effect model parameter for dose was 0.002585 (95% CI, 0.001655–0.003514) with a *P* value <0.001, indicating a linear relationship between diclofenac dose and CV risk ratio. The following equation converted the diclofenac daily dose in milligrams to an estimated risk ratio that represented risk per milligram of diclofenac dose: estimated CV risk ratio = (0.002585 × daily dose) + 1.

Table IV provides the model-derived estimated risk ratios for a CV event for a range of daily doses (as found in conventional oral diclofenac and low-dose diclofenac) compared with no exposure (ie, NSAID nonuse). Figure 4 depicts the meta-regression line, with the individual risk ratios plotted. The CV parameter estimate was lower compared with the GI estimate,

therefore providing a lower model-derived estimated risk ratio for a CV event. Similar to the GI model, we assessed the linearity of the dose variable by examining additional models (eg, categorical dose, polynomial transformations) and visual plots. Linearity was not as clear as in the GI model, particularly for 2 doses with limited data (ie, 125 and 225 mg), for which the relationship seemed to shift from the general linear form. However, when reviewing all the evidence together, we deemed the linear dose model to be adequate for describing the relationship between diclofenac dose and the risk ratio of a CV event. Because the main model analyzed a composite CV event end point, it was of interest to construct a separate model that analyzed only the studies that reported the risk ratio for AMI. Of the 11 CV studies, 7 studies reported the risk ratio for AMI. The results of this AMI model were comparable to those of the main CV model, with a fixed-dose parameter of 0.002942 and a corresponding SE of 0.000438. We reviewed the model fit and assumptions for both the main CV and AMI models. We visually examined model residuals for normality, and the plots did not show any evident deviation from the normality assumption. In addition, we examined the data for outliers. We discovered a potential outlier in the study reported by Gislason et al<sup>32</sup>: the dose of 125 mg was associated with a risk ratio of 9.1. The authors did not provide the sample size associated with the specific

Table III. Studies used in the cardiovascular meta-regression model.

Observation No.	Author, Year	Cardiovascular Event	Diclofenac Daily Dose (mg)	Risk Ratio (95% CI)
1	Andersohn et al, 2006 <sup>26</sup>	Acute myocardial infarction	75	1.31 (1.06–1.62)
2			150	1.35 (1.13–1.61)
3	Bak et al, 2003 <sup>27</sup>	Stroke	100	1.10 (0.7–1.7)
4	Fischer et al, 2005 <sup>28</sup>	Acute myocardial infarction	75	1.22 (0.96–1.56)
5			100	1.25 (0.85–1.83)
6	Fosbøl et al, 2010 <sup>29</sup>	Coronary death or nonfatal myocardial infarction	75	0.96 (0.59–1.57)
7			100	2.01 (1.56–2.59)
8	García Rodríguez et al, 2008 <sup>30</sup>	Acute myocardial infarction	75	1.51 (1.20–1.89)
9			150	1.80 (1.49–2.18)
10	Gislason et al, 2006 <sup>31</sup>	Acute myocardial infarction	75	1.66 (1.04–2.63)
11			100	1.69 (0.96–2.98)
12	Gislason et al, 2009 <sup>32</sup>	Acute myocardial infarction	75	1.18 (0.81–1.72)
13			125	9.10 (3.45–23.98)
14	Ray et al, 2009 <sup>33</sup>	Cardiovascular disease or death	100	1.43 (1.14–1.78)
15			150	1.34 (1.09–1.65)
16	Roumie et al, 2009 <sup>34</sup>	Composite cardiovascular event	125	1.01 (0.76–1.34)
17	van Staa et al, 2008 <sup>35</sup>	Acute myocardial infarction	100	1.30 (1.20–1.40)
18			150	1.50 (1.38–1.62)
19			225	1.35 (0.97–1.88)
20			300	2.28 (1.23–4.24)
21	Varas-Lorenzo et al, 2009 <sup>36</sup>	Acute myocardial infarction	100	1.02 (0.75–1.38)

result; however, because of the high associated variance, we speculated that the result was based on a small sample size. Because the study contributed 2 observations to the analysis and the lower dose result was in line with the other results, it was not reasonable to exclude the higher-dose observation but reasonable to include the lower-dose observation. Therefore, we did not exclude any data from this study.

We performed a final sensitivity analysis that excluded studies which assessed CV events associated with rehospitalization. Three studies examined patients after their initial CV event to estimate the risk of a repeat hospitalization for a CV event associated with diclofenac use.<sup>31–33</sup> The sensitivity analysis results were comparable to those of the main CV model results, suggesting that the studies which assessed CV events associated with rehospitalization did not significantly influence the relationship between diclofenac dose and risk of a CV event (data not shown).

## DISCUSSION

### Summary of Results and Interpretation

We examined the relationship between oral diclofenac dosage and toxicity of GI and CV events by using observational studies identified in 2 previous systematic reviews.<sup>7,8</sup> Although previous meta-analysis studies have reported that higher doses of NSAIDs are associated with an increased risk of these events, the comparison was made by using nonspecific categories of high and low NSAID doses. We extended this research by modeling dose as a continuous measure, allowing an assessment of the risk of safety events for patients taking specific diclofenac doses compared with NSAID nonusers. Although the fixed-effect model parameter for CV events was smaller than the GI events, the results from both models indicated positive linear relationships between diclofenac dose and the risks for a GI or CV event. The models may be used to explore the potential benefits of low-dose oral diclofenac. For example, substitution of



Table IV. Estimated risk of a cardiovascular event relative to nonuse of NSAIDs according to dose of conventional and low-dose diclofenac.\*

Daily Dose	Estimated Risk Ratio (SE; 95% CI)
Conventional diclofenac	
50 (eg, 25 mg BID)	1.13 (0.022; 1.08–1.18) <sup>†</sup>
100 (eg, 50 mg BID)	1.26 (0.044; 1.17–1.35)
150 (eg, 50 mg TID)	1.39 (0.067; 1.25–1.53)
Low-dose diclofenac*	
36 (18 mg BID)	1.10 (0.017; 1.06–1.13) <sup>†</sup>
54 (18 mg TID)	1.15 (0.026; 1.10–1.20) <sup>†</sup>
70 (35 mg BID)	1.19 (0.033; 1.12–1.26)
105 (35 mg TID)	1.29 (0.050; 1.19–1.40)

\*Trademark: Zorvolex® (Iroko Pharmaceuticals LLC, Philadelphia, Pennsylvania). The difference in molecular weight between conventional and low-dose diclofenac was taken into account when dose was calculated. Specifically daily doses of 105 mg, 70 mg, 54 mg and 36 mg of low-dose diclofenac were converted to 113 mc, 75 mg, 58 mg and 38 mg of conventional diclofenac, respectively.

<sup>†</sup>The cardiovascular meta-regression model was based on a range of daily doses as low as 75 mg; the cardiovascular risk ratios estimated for daily doses of conventional oral diclofenac of 50 mg and of low-dose diclofenac of 54 mg (adjusted to 58 mg) and 36 mg (adjusted to 38 mg) reflect applications of the risk equation beyond the values included in the model.

105 mg daily of low-dose oral diclofenac for the 150-mg daily dose of conventional oral diclofenac was estimated to reduce the risk of serious GI events by 18% and of serious CV events by 7%. To our knowledge, this is the first meta-regression estimating the relationship between daily dose as a continuous measure and risk of GI and CV events, and it provides further support for guidelines that explicitly recommend the use of NSAIDs at the lowest effective dosage for the shortest duration.

### Advantages and Limitations

The use of observational studies in our meta-regressions is a strength compared with designs that included only randomized controlled trials (RCTs). In general, RCTs are focused on primary efficacy results and

have insufficient power to detect group differences in rare adverse events.<sup>39</sup> Observational studies have the potential to approximate more closely the real-world effect of the intervention and can comprise a much larger number of patients, including minority or vulnerable populations, than would be practical for an RCT and are always necessary to adequately assess harm.<sup>40</sup> The Agency for Healthcare Research and Quality also recommends conducting comparative effectiveness analyses by using data from observational trials.<sup>15</sup> Our analyses included data on >2500 diclofenac users experiencing CV events and >300 diclofenac users experiencing GI events.

Our analyses, which attempted to use every study included in the 2 systematic reviews that provided information on diclofenac dosage, modeled dose as a continuous measure. This was accomplished by associating specific doses with risk effects based on the information presented in each individual article from these systematic reviews. Two rheumatologists who are expert in the use of NSAIDs reviewed all dosages and confirmed the daily dose category used in the meta-regression. Because our models examined all information provided in each study, it was necessary to use sophisticated modeling techniques to account for the fact that, if studies reported >1 result (ie, risk ratios reported for multiple dose categories), these results from the same study are correlated. We modeled the adjusted estimates, when available, of the risk ratios from each study (as is appropriate for meta-analyses of observational studies).

There are several limitations to our work. Foremost, we did not conduct an independent systematic review of the literature and instead relied on 2 existing, recently published systematic literature reviews that met the goals of our study. Castellsague et al<sup>7</sup> reviewed literature published in English and included in the PubMed database from 1980 through 2011. McGettigan and Henry<sup>8</sup> reviewed literature without language restrictions from 1985 through 2010 in the following databases: Medline, EMBASE, PubMed, Cochrane Library, Google Scholar, epidemiologic research Web sites, abstracts of scientific meetings, and bibliographies of relevant studies. Although these were recent searches, there is a possibility that newer literature has been published that could influence results. To assess this limitation, we performed a limited literature search by using PubMed to identify any new literature published from 2010 through January 2012; no new articles were found that met our eligibility criteria. The majority of the databases used in these search criteria do not include information on unpublished

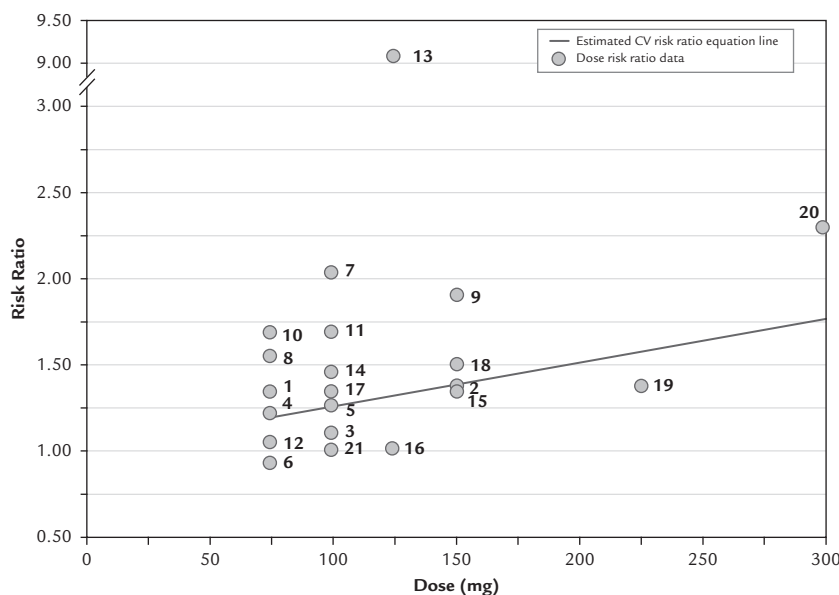


Figure 4. Relationship between diclofenac daily dose and the estimated risk ratio of a cardiovascular event. Numbers correspond to the observations in Table III.

studies, nor did we conduct a separate review of unpublished literature to minimize publication bias. We also excluded other adverse events including renal dysfunction, hypertension, exacerbation of congestive heart failure, less serious upper GI events (eg, uncomplicated ulcer, dyspepsia), and lower GI events.

With any meta-analysis, heterogeneity across individual studies included in the meta-analysis is a potential limitation. Although the populations across individual studies generally were similar, some did examine distinct patient populations (eg, patients rehospitalized after first AMI, patients aged  $\geq 50$  years). For most studies, diclofenac exposure and outcomes were based on available and typically limited information collected in large databases. A variety of GI and CV outcomes were presented, and we imposed a hierarchy of outcomes for use in the analysis. We assumed that it was appropriate to combine different outcomes in a single analysis (eg, AMI and stroke) based on the fact that these outcomes were similar in nature with similar risk profiles; this method was confirmed by our rheumatology experts and was the method used by McGettigan and Henry<sup>8</sup> in their meta-analysis. Lastly, we assumed a linear relationship between diclofenac dose and GI or CV events and examined this linearity assumption by using the various techniques described earlier. However, we were limited

by the relatively small number of studies supplying observations to the model.

## CONCLUSIONS

Our analysis found a continuous linear dose relationship between specific diclofenac doses and the risk of a serious GI or CV event and provides further support for guidelines that recommend the use of NSAIDs at the lowest effective dose for the shortest duration. Compared with the risk of these events for comparable patients who are not taking NSAIDs, the risk of serious GI and CV events is expected to increase as diclofenac dosage increases. Using this relationship, the risk of serious GI and CV adverse event occurring at any daily dose of diclofenac can be estimated. This is particularly helpful because a new low-dose diclofenac drug product recently has become available in the United States. Although our findings are consistent with other published studies that found high doses of NSAIDs to be associated with increased risk of GI and CV events, more data are needed to definitively quantify the relationship between diclofenac and GI and CV events.

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made substantial contributions to the following: (1) the conception and design of the study, acquisition of data, and analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

### CONFLICTS OF INTEREST

This study was conducted by RTI Health Solutions through funding provided by Iroko Pharmaceuticals. Ms. Odom, Ms. Mladi, Mr. Sherif, Ms. Miles, Dr. Wang, and Dr. Ronquest are employees of RTI Health Solutions. Dr. Saag is an employee of the University of Alabama at Birmingham and served as clinical consultant through funding provided by Iroko Pharmaceuticals. The study's sponsor approved the study design; the collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

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