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Nonsteroidal Anti-inflammatory Drugs and Risk of Incident Heart Failure: A Systematic Review and Meta-analysis of Observational Studies

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ABSTRACT

Background: The association between the development of heart failure (HF) and use of nonsteroidal anti-inflammatory drugs (NSAIDs) is not well established.

Hypothesis: Use of NSAIDs may increase the risk of incident HF.

Methods: We conducted a systematic review and meta-analysis of observational studies that reported odds ratio, relative risk, hazard ratio, or standardized incidence ratio comparing risk of incident HF in NSAID users vs nonusers. Pooled risk ratios (RR) and 95% confidence intervals (CI) for all NSAIDs and both subclasses (conventional NSAIDs and highly selective cyclooxygenase-2 inhibitors [COXIBs]) were calculated using a random-effect, generic inverse variance method.

Results: Seven studies with 7 543 805 participants were identified and included in our data analysis. Use of NSAIDs was associated with a significantly higher risk of developing HF, with a pooled RR of 1.17 (95% CI: 1.01-1.36). Subgroup analysis showed a significantly elevated risk among users of conventional NSAIDs (RR: 1.35, 95% CI: 1.15-1.57) but not users of COXIBs (RR: 1.03, 95% CI: 0.92-1.16).

Conclusions: A significantly elevated risk of incident HF was observed among users of NSAIDs.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications with analgesic and anti-inflammatory properties. They are one of the most commonly used medications in the United States,[1] despite their notorious adverse effects.[2,3] Inhibition of the cyclooxygenase (COX) enzyme, which has 2 isoforms, COX-1 and COX-2, is the fundamental pharmacological property of NSAIDs. COX-1 is constitutively expressed under a normal physiologic condition, whereas COX-2 is generally expressed under an inflammatory state. Conventional NSAIDs have been used in clinical practice as analgesic and anti-inflammatory agents for decades. However, their utility is limited by the adverse effects associated with inhibition of the COX-1 enzyme, particularly gastrointestinal (GI) ulcers and bleeding. The highly selective COX-2 inhibitors (COXIBs) are a newer subgroup of NSAIDs that have been marketed as safer alternatives to

conventional NSAIDs after several randomized controlled trials demonstrated a superior GI safety profile.[4,5] Nonetheless, over the past decade, attention has turned to the cardiovascular adverse effects of NSAIDs after rofecoxib, a COXIB, was withdrawn from the market after a randomized controlled trial demonstrated an increased incidence of myocardial infarction (MI) among the users.[6] A subsequent meta-analysis of observational studies confirmed this increased risk. In fact, a similar MI risk was also observed in some conventional NSAIDs, such as diclofenac and indomethacin.[7]

Use of NSAIDs also may be associated with an increased risk of heart failure (HF) as a result of salt and fluid retention secondary to the reduction of prostaglandin synthesis. In fact, use of these medications has been associated with the occurrence of HF in several reported cases.[8−10] However, epidemiologic studies attempting to characterize this association yielded inconclusive results.[11−16] Therefore, we conducted a systematic review and meta-analysis of epidemiologic studies that compared the incidence of HF in NSAID users vs nonusers to further investigate this possible adverse effect.

Methods

Search Strategy

Two investigators (P.U. and N.S.) independently searched published studies indexed in the MEDLINE and Embase databases from inception to April 2015. The search terms were compiled from terms for HF and NSAIDs, including names of individual drugs in conjunction with the terms for observational studies that were suggested by Furlan et al[17] (for details, see Supporting Information, Search Strategy, in the online version of this article). A manual search of references of selected retrieved articles was also performed.

Inclusion Criteria

Studies were included into the data analysis if they met the following criteria: (1) studies had to be observational (case-control or cohort studies); (2) the authors provided relative risk (RR), odds ratio (OR), hazard ratio (HR), or standardized incidence ratio with 95% confidence intervals (CI) of incident HF for conventional NSAIDs and/or COXIBs; and (3) NSAID nonusers were used as a reference group for cohort studies, and participants without HF were used as control for studies with a case-control design.

Study eligibility was independently determined by the 2 aforementioned investigators. Quality of the included studies was also independently appraised by the 2 investigators using the Newcastle-Ottawa quality-assessment scale, which evaluates each study in 3 main areas: (1) the selection of the study groups, (2) the comparability of the groups, and (3) the ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively.[18] The third investigator (C.T.) oversaw this literature-review process and resolved any disagreements.

Data Extraction

A standardized data-collection form was used to extract the following information: title of the article, first author's last name, country of origin, year when the study was conducted, year of publication, study design, study size, study population, names of evaluated NSAIDs, definition and diagnosis of HF, average duration of follow-up (for cohort studies), potential confounders that were adjusted, and adjusted pooled-effect estimates with 95% CI. To ensure the accuracy of the data extraction, this process was independently performed by all investigators. Any discrepancy was resolved by referring back to the original study.

Statistical Analysis

Data analysis was performed using Review Manager (RevMan) software, version 5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). Adjusted point estimates were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird, which assigned weight of each study based on its standard error.[19] We performed overall analysis and subgroup analysis for conventional NSAIDs and COXIBs. We reported the pooled-effect estimate of HF risk using the combination of the data from case-control and cohort studies to increase the power of our estimates. The OR of case-control study was used as

an estimate of the RR to pool this data with the RR or HR of cohort study. The use of OR as an estimate for RR was considered acceptable in this study, as the outcome of interest was relatively uncommon. We used a random-effect model rather than a fixed-effect model, given the high likelihood of between-study variance due to the different study design, population, and outcome measurement. If the study provided data on risk of NSAIDs overall, that risk would be used to calculate the pooled-effect estimate. If the study provided only risk of individual NSAIDs, the risk would be pooled together first, using the same random-effect, generic inverse variance method. The pooled risk would be used as effect estimate for that study to combine with data from other studies.

The statistical heterogeneity of this study was assessed by the Cochran Q test. This test is complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0% to 25% indicates insignificant heterogeneity; 26% to 50% indicates low heterogeneity; 51% to 75% indicates moderate heterogeneity; and 76% to 100% indicates high heterogeneity.[20]

Publication bias was assessed by visualization of funnel plot and the Egger regression test. Comprehensive Meta-analysis version 2.0 (Biostat, Englewood, NJ) was used to perform the regression analysis.

Results

Our search strategy yielded 8314 potentially relevant studies (3695 studies from MEDLINE and 4619 studies from Embase), including 3594 duplicates. Based on title and abstract review, 4646 studies were excluded that clearly did not meet our inclusion criteria (1504 basic science studies, 1132 non−case-control/cohort observational studies, 1012 interventional studies, 512 review articles, 334 editorials/correspondences, and 152 miscellaneous), leaving 74 studies for full-length article review. Fifty-four studies were excluded because they were interventional studies, and another 11 studies were excluded as they were descriptive studies without a control group. Two studies reported the risk of first hospitalization for HF among NSAID users, but they included patients with prior history of HF; therefore, these studies were excluded, as their outcomes were not incident HF.[21,22] Seven studies (4 case-control studies[11,13,15,23] and 3 cohort studies[12,14,16]) with 7 543 805 participants met our eligibility criteria and were included for data analyses. The detailed characteristics and Newcastle-Ottawa quality-assessment scale of the case-control and cohort studies are described in tables 1 and 2, respectively.

The overall risk of incident HF among NSAID users was 1.17 (95% CI: 1.01-1.36). Elevated risk was consistently observed in most studies, although without reaching statistical significance. Our meta-analysis, taking advantage of combining all existing data, was able to prove a statistical significance. The I^2 of this study was 53%, which indicated a moderately significant statistical heterogeneity. Subgroup analysis according to study design revealed an increased risk in both subgroups, although without reaching statistical significance. Figure 1 demonstrates a forest plot of all NSAIDs.

Table 1. Characteristics of Case-Control Studies in the Meta-analysis

	Page et al[11]	García-Rodríguez et al[13]	Huerta et al[15]	Mangoni et al[23]
Country	Australia (New South Wales)	United Kingdom	United Kingdom	Australia
Year of publication	2000	2003	2006	2010
Study design	Case control	Case control	Case control	Case control
Cases	Patients who were admitted at the study hospitals with the primary diagnosis of HF from 1993 to 1995 were consecutively recruited. The study included patients both with and without prior diagnosis of heart diseases but also provided separate analysis for each category.	All patients age 40–84 y first diagnosed with HF between January 1, 1996, and December 31, 1996. Cases were identified from the United Kingdom General Practice Research Database, which covered approximately 3 million residents across the United Kingdom. Cases were verified by reviewing medical records.	All patients age 60–84 y first hospitalized with HF between January 1, 1997, and December 31, 2000. Cases were identified from the United Kingdom General Practice Research Database, which covered approximately 3 million residents across the United Kingdom. Cases were verified by reviewing medical records. The study included patients both with and without prior diagnosis of HF but also provided separate analysis for each category.	All patients age ≥65 y hospitalized with HF between January 1, 2002, and June 30, 2006. Cases were identified from the DVA database. DVA provided care with minimal copay to all Australian war veterans, spouses, and dependents. Cases with prior diagnosis of HF were excluded.
Controls	Sex- and age-matched patients admitted at the same hospital. Controls must have no history of HF and must not have clinical or radiologic evidence of HF.	Sex- and age-matched subjects without HF randomly selected from the same database	Sex- and age-matched subjects without HF randomly selected from the same database	Sex-, age-, and state of residence–matched subjects without HF randomly selected from the same database
NSAIDs assessed in the study	Diclofenac, ibuprofen, ketoprofen, tiaprofenic acid, mefenamic acid, indomethacin, sulindac, diflunisal, naproxen, piroxicam, tenoxicam	Aceclofenac, acemetacin, diclofenac, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, tiaprofenic acid, apazone, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam	Aceclofenac, acemetacin, azapropazone, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, tiaprofenic acid, apazone, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam	Diclofenac, naproxen, ibuprofen, meloxicam, diflunisal, piroxicam, indomethacin, ketoprofen, mefenamic acid, tiaprofenic acid, celecoxib, lumiracoxib, rofecoxib
Definition of NSAID exposure	Use of any NSAID within 1 week prior to admission	Supply of the most recent prescription listed within 30 days prior to the index date	Supply of the most recent prescription listed within 30 days prior to the index date	Supply of the most recent prescription listed within 30 days prior to the index date
Verification of NSAID exposure	Structured interview within 1 week of admission	Prescription information from the database	Prescription information from the database	Prescription information from the database
Cases, n	76	471	428	18 903
Controls, n	478	2807	2420	376 633
Female sex, %, cases/ controls	45.8/46.8	48.0/48.0	48.0/48.0	34.7/34.7

Table 1. Continued

	Page et al[11]	García-Rodríguez et al[13]	Huerta et al[15]	Mangoni et al[23]
Average age, y, cases/ controls	76.6/75.1	NA	NA	65.3/65.3
Confounders adjusted for	History of renal disease, respiratory disease, and PAD; use of β-blockers, calcium channel antagonists, antidiabetic drugs, oral steroids	Age, sex, BMI, smoking, alcohol; use of steroids, acetaminophen, anticoagulants; DM, COPD, CAD, asthma, renal failure, valvular diseases, rhythm disorders, HTN	Age, sex, calendar year, BMI, smoking, alcohol; use of steroids, acetaminophen, anticoagulants; DM, CAD, COPD, asthma, valvular diseases, rhythm disorders, renal failure, HTN, hospitalizations in previous year	Age; public or private hospital admissions (for DM, obesity, dementia, HTN, CAD, respiratory disease, liver disease, RA, or renal disease) at any time prior to the index date; use of salicylic acid and derivatives or medications for obesity, DM, CAD, dementia, and COPD within 4 months prior to index date
Newcastle-Ottawa scale	Selection, 3 stars; comparability, 1 star; exposure, 3 stars	Selection, 4 stars; comparability, 1 star; exposure, 3 stars	Selection, 4 stars; comparability, 1 star; exposure, 3 stars	Selection, 3 stars; comparability, 1 star; exposure, 3 stars

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DVA, Department of Veterans' Affairs; HF, heart failure; HTN, hypertension; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs; PAD, peripheral arterial disease; RA, rheumatoid arthritis.

Five studies[11−15] reported risk of incident HF in users of conventional NSAIDs compared with nonusers. Elevated risk was, again, consistently observed in all studies, even though it was not statistically significant in most studies. The pooled RR was 1.35, and it was statistically significant (95% CI: 1.15-1.57). The I^2 of this analysis was 0%, which indicated a nonsignificant statistical heterogeneity. Figure 2 demonstrates a forest plot of these 5 studies.

On the other hand, risk of incident HF among COXIB users was reported in only 2 studies.[14,16] The pooled RR was modestly elevated, at 1.03, without reaching statistical significance (95% CI: 0.92-1.16). The statistical heterogeneity was insignificant, with an I^2 of 0%. Figure 3 demonstrates a forest plot of the COXIB studies.

Sensitivity Analysis

We conducted a jackknife sensitivity analysis by excluding 1 study at a time from the pooled analysis. The pooled RRs for all NSAIDs from this sensitivity analysis ranged from 1.06 to 1.24.

Evaluation for Publication Bias

For a funnel plot evaluating publication bias for all NSAID studies, see Supporting Information, Figure, in the online version of this article. Visual inspection of this funnel plot does not reveal any obvious asymmetry, and, therefore, does not provide suggestive evidence for publication bias. Furthermore, there is no evidence of publication bias detected by the Egger regression test ($P = 0.57$).

Discussion

To the best of our knowledge, this is the first meta-analysis of observational studies that summarizes the risk of incident HF among users of NSAIDs. We were able to assess the risk for NSAIDs as a single group, as well as performing subgroup analysis for both conventional NSAIDs and COXIBs.

An increased risk of incident HF among NSAID users has been consistently observed in several epidemiological studies.[11−16] However, because this outcome of interest was relatively uncommon, most of these studies failed to show a statistical significance. Our meta-analysis, by combining all available data, was able to demonstrate a statistically significant elevated risk of incident HF among NSAID users, with 17% excess risk. Subgroup analysis showed a significantly elevated risk among users of conventional NSAIDs and a modestly increased risk among users of COXIBs, without a statistical significance. The statistical heterogeneity was moderate in the overall analysis but was insignificant in each subgroup analysis, suggesting that the difference between subgroups was responsible for this heterogeneity.

There are a few possible pathophysiologic explanations for this increased risk. The most widely accepted one is related to elevated blood pressure and fluid retention. Endothelium-derived prostaglandins, such as prostaglandin I_2 (PGI_2), have a vasodilatory effect on the peripheral vasculature. Thus, inhibition of the COX enzyme could directly lead to vasoconstriction and hypertension.[24,25]

Table 2. Characteristics of Cohort Studies in the Meta-analysis

	Feenstra et al[12]	Mamdani et al[14]	Bäck et al[16]
Country	The Netherlands	Canada	Sweden
Study design	Prospective cohort	Retrospective cohort	Retrospective cohort
Year	2002	2004	2012
Cases	All residents of Ommoord, a suburb city of Rotterdam, age ≥55 y, were invited to participate in this study. 78% of eligible residents agreed to participate. The first cross-sectional study started in June 1990. Participants with prevalent HF at study entrance were excluded from the analyses. Cross-sectional survey was conducted periodically by home interviews and participant visits to the research center.	All residents of Ontario, Canada, age ≥66 y and who were prescribed NSAIDs from April 17, 2000, to March 31, 2001, with a supply that lasted ≥30 days. Cases were identified from an administrative health care database that covered 1.3 million individuals ≥65 y. The study included patients with and without prior diagnosis of HF but provided separate analysis for each category.	All Swedish residents age ≥18 y. Medical information was retrieved from Swedish patient register, prescribed drug register, and cause of death register. Follow-up started on July 1, 2005, and ended on December 31, 2008. Residents with history of MI, stroke, HF, and AF prior to the start date were excluded.
NSAIDs assessed in the study	Nonselective NSAIDs	Celecoxib, rofecoxib, and nonselective NSAIDs	Celecoxib, etoricoxib
Definition of NSAID exposure	Period of exposure was defined as duration of prescription plus a carryover period of 7 days	≥2 prescriptions for NSAIDs from April 17, 2000, to March 31, 2001, with a supply that lasted ≥30 days	Period of exposure was defined as duration of prescription plus a carryover period of 30 days
Verification of NSAID exposure	Verified with the pharmacy database of the study, which comprehensively covered all prescriptions dispensed to participants	Verified with pharmacy records that were linked to the administrative health care database	Verified with the Swedish national prescribed drug register
Control	NSAID use was analyzed as a time-dependent variable (ie, duration of nonexposure to NSAIDs served as control)	Residents age ≥66 y with no history of NSAID exposure, randomly selected from the same database	NSAID use was analyzed as a time-dependent variable (ie, duration of nonexposure to NSAIDs served as control)
Diagnosis of HF	HF was of special interest in the study. The continuous follow-up of all participants was aimed at identifying all events of interest, including HF. It was part of the routine follow-up procedure that all available data on the events of interest, such as hospital discharge note and outpatient visit note, were analyzed. Two research physicians independently evaluated and verified the HF diagnosis.	The primary outcome was admission with primary diagnosis of HF, which was identified from the Canadian Institute for Health Information discharge abstract database.	Diagnostic code from the database. No further verification was performed.
Follow-up	Until a diagnosis of incident HF, death, emigration out of system, or December 31, 1998	Until occurrence of study endpoint, death, or March 31, 2001	Until occurrence of study endpoint, death, or December 31, 2008
Cases, n	7277	44 258 (32 834 COXIBs and 11 424 nonselective NSAIDs)	6 991 645
Controls, n	7277	98 409	6 991 645

Table 2. Continued

	Feenstra et al[12]	Mamdani et al[14]	Bäck et al[16]
Average age, y, cases/controls	70.0/70.0	75.4/76.3	50.0/50.0
Female sex, %, cases/controls	62.0/62.0	55.0/68.0	50.8/50.8
Average follow-up, y, cases/controls	6.0/6.0	0.5/0.5	NA/NA
Confounders adjusted for	Age, sex; sCr ≥1.1 mg/dL; HTN, history of MI, AF; concomitant cardiovascular and pulmonary medication	Age, sex; medications used; hospitalization; socioeconomic status	Age, sex; medications used; socioeconomic status; educational level; RA
Newcastle-Ottawa scale	Selection, 4 stars; comparability, 2 stars; outcome, 3 stars	Selection, 4 stars; comparability, 1 star; outcome, 3 stars	Selection, 4 stars; comparability, 2 stars; outcome, 3 stars

Abbreviations: AF, atrial fibrillation; COXIB, highly selective cyclooxygenase-2 inhibitor; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; sCr, serum creatinine.

Moreover, renal prostaglandins, particularly prostaglandin E_2 (PGE_2) and PGI_2, play a major role in maintaining renal blood flow and glomerular filtration rate, especially in a volume-depleted state. They also have an inhibitory effect on the sodium reabsorption in the loop of Henle and cortical collecting tubule, and on the water reabsorption in the collecting tubules, driven by the antidiuretic hormone.[26−28] These prostaglandins are locally derived from the COX-2 enzyme in the renal cortex and juxtaglomerular cells. Thus, inhibition of the COX-2 enzyme by either conventional NSAIDs or COXIBs could lead to blood-volume expansion, resulting in clinically evident HF, particularly in those who have an underlying ventricular dysfunction.

In fact, the vasoconstrictive and volume-expansion effects of NSAIDs are even more pronounced in patients with established HF, as the included studies have also demonstrated that use of NSAIDs was associated with a higher incidence of HF exacerbation, with RRs ranging from 8.6 to 26.3.[11,12,15]

Based on this pathogenesis, theoretically, increased risk of incident HF should be seen with use of both conventional NSAIDs and COXIBs. Our meta-analysis, however, could not demonstrate a statistically significant increased risk among COXIB users. This nonsignificant result could be secondary to a smaller sample size, as only 2 studies reported the risk of incident HF among COXIB users. More studies are required to clarify this risk.

Another possible explanation is related to the fact that use of some NSAIDs (such as rofecoxib and diclofenac) is linked to an increased risk of MI,[7] which is a major risk factor for HF.

Study Limitations

Even though the primary studies included in this meta-analysis are of high quality, there are some limitations, and, thus, our results should be interpreted with caution.

First, most of the included studies were conducted using coding-based medical registry, raising a concern of coding inaccuracy and incompleteness. Most of the included studies also relied on prescription information from their database, which did not guarantee consumption of the medications and would not capture over-the-counter NSAID use. The only exception is the study by Page et al,[11] which used structured interviews to identify NSAID exposure. However, this method had its own problem, as cases (participants with the event of interest) tended to recall exposure better than controls (recall bias).[29] Second, most of the included studies were conducted in older populations. In fact, the mean ages of participants in 3 cohort studies were 70.0, 75.4, and 50.0 years. Therefore, our results are not generalizable to the general population, especially to younger patients with lower baseline cardiovascular risk. Third, most of the primary studies included in this meta-analysis identified incident cases of HF from an admission database. Therefore, cases of milder HF that did not require hospitalization would not be identified. We also did not have data on the subtypes of HF. Fourth, the definition of NSAID exposure was not entirely consistent between studies, with time of exposure ranging from 7 to 30 days prior to the index
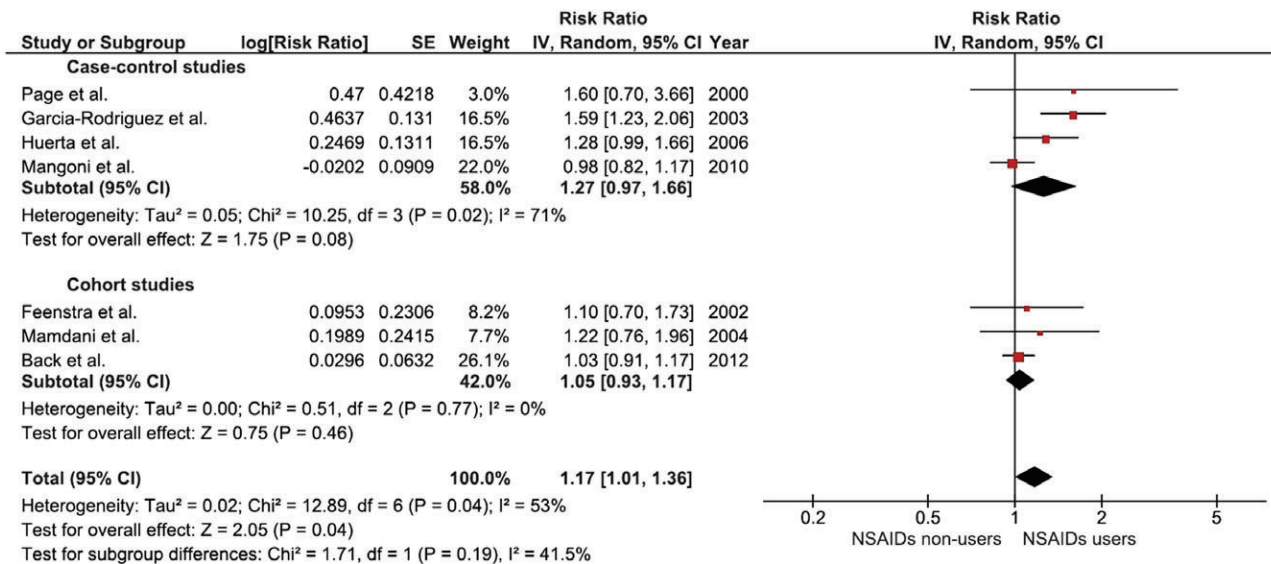
Figure 1 — Forest plot of all NSAIDs

Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Year
Case-control studies					
Page et al.	0.47	0.4218	3.0%	1.60 [0.70, 3.66]	2000
Garcia-Rodriguez et al.	0.4637	0.131	16.5%	1.59 [1.23, 2.06]	2003
Huerta et al.	0.2469	0.1311	16.5%	1.28 [0.99, 1.66]	2006
Mangoni et al.	-0.0202	0.0909	22.0%	0.98 [0.82, 1.17]	2010
Subtotal (95% CI)			58.0%	1.27 [0.97, 1.66]	

Heterogeneity: Tau² = 0.05; Chi² = 10.25, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 1.75 (P = 0.08)

Cohort studies					
Feenstra et al.	0.0953	0.2306	8.2%	1.10 [0.70, 1.73]	2002
Mamdani et al.	0.1989	0.2415	7.7%	1.22 [0.76, 1.96]	2004
Back et al.	0.0296	0.0632	26.1%	1.03 [0.91, 1.17]	2012
Subtotal (95% CI)			42.0%	1.05 [0.93, 1.17]	

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.75 (P = 0.46)

Total (95% CI)			100.0%	1.17 [1.01, 1.36]	

Heterogeneity: Tau² = 0.02; Chi² = 12.89, df = 6 (P = 0.04); I² = 53%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Chi² = 1.71, df = 1 (P = 0.19), I² = 41.5%

NSAIDs non-users — NSAIDs users

Figure 1. Forest plot of all NSAIDs. Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; NSAID, nonsteroidal anti-inflammatory drug; SE, standard error.
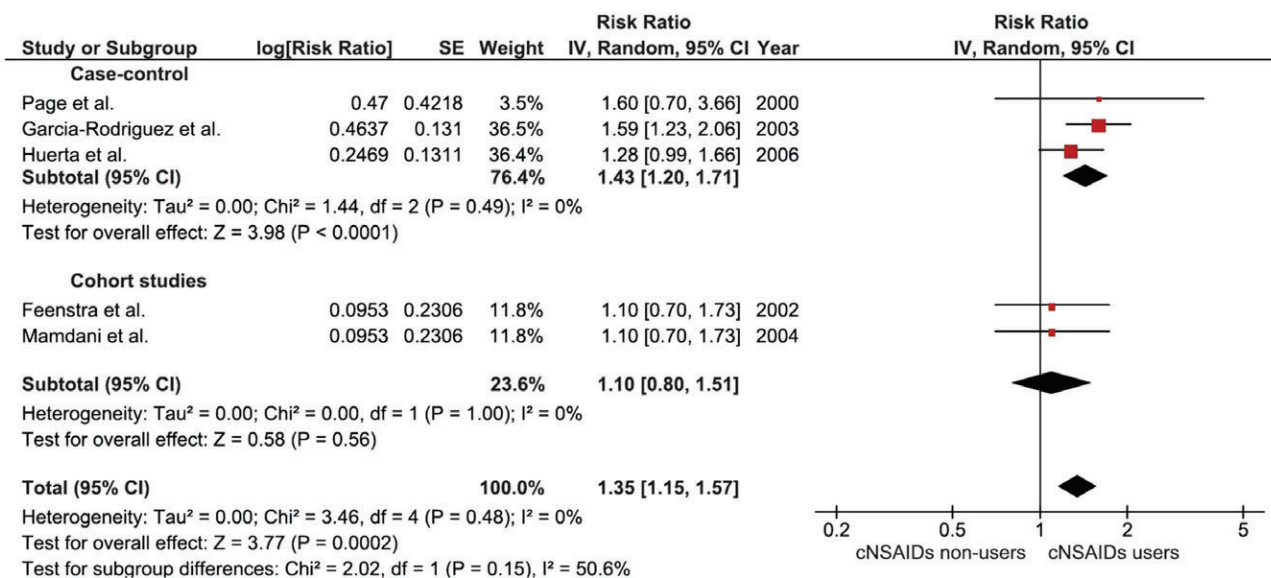

Figure 2 — Forest plot of conventional NSAIDs

Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Year
Case-control					
Page et al.	0.47	0.4218	3.5%	1.60 [0.70, 3.66]	2000
Garcia-Rodriguez et al.	0.4637	0.131	36.5%	1.59 [1.23, 2.06]	2003
Huerta et al.	0.2469	0.1311	36.4%	1.28 [0.99, 1.66]	2006
Subtotal (95% CI)			76.4%	1.43 [1.20, 1.71]	

Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.98 (P < 0.0001)

Cohort studies					
Feenstra et al.	0.0953	0.2306	11.8%	1.10 [0.70, 1.73]	2002
Mamdani et al.	0.0953	0.2306	11.8%	1.10 [0.70, 1.73]	2004
Subtotal (95% CI)			23.6%	1.10 [0.80, 1.51]	

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

Total (95% CI)			100.0%	1.35 [1.15, 1.57]	

Heterogeneity: Tau² = 0.00; Chi² = 3.46, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)
Test for subgroup differences: Chi² = 2.02, df = 1 (P = 0.15), I² = 50.6%

cNSAIDs non-users — cNSAIDs users

Figure 2. Forest plot of conventional NSAIDs. Abbreviations: CI, confidence interval; cNSAIDs, conventional nonsteroidal anti-inflammatory drugs; df, degrees of freedom; IV, inverse variance; SE, standard error.
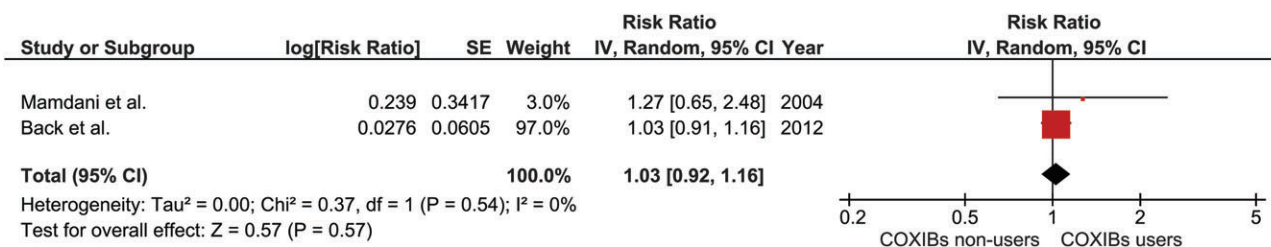

Figure 3 — Forest plot of COXIBs

Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Year
Mamdani et al.	0.239	0.3417	3.0%	1.27 [0.65, 2.48]	2004
Back et al.	0.0276	0.0605	97.0%	1.03 [0.91, 1.16]	2012
Total (95% CI)			100.0%	1.03 [0.92, 1.16]	

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)

COXIBs non-users — COXIBs users

Figure 3. Forest plot of COXIBs. Abbreviations: CI, confidence interval; COXIB, highly selective cyclooxygenase-2 inhibitor; df, degrees of freedom; IV, inverse variance; SE, standard error.

date. It would also raise the question of how much HF could be attributed to NSAID use for the short period of time. Fifth, we did not search for unpublished data; therefore, publication bias might have been present. It should be noted that evaluation for publication bias was relatively unreliable in this study, as the number of included studies was small. Last, this is a meta-analysis of observational studies, which, by study design, are at risk for several types of bias.[30] For example, participants who took NSAIDs might undergo more medical examination and laboratory surveillance, resulting in detection bias. Physicians might also preferentially avoid prescribing NSAIDs to patients with increased baseline risk for cardiac dysfunction, leading to selection bias of healthier participants to the exposed group.

Conclusion

A statistically significant elevated risk of incident HF was observed among NSAID users in this meta-analysis. Subgroup analysis showed a significantly elevated risk among users of conventional NSAIDs. Although we could not demonstrate a statistically significant elevated risk among COXIB users, we acknowledge that this could be related to the smaller sample size. Physicians must weigh the potential risks of HF and other adverse events related to NSAIDs, such as renal failure, MI, and GI bleeding, against their clinical benefit when prescribing these medications.

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