Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) cause bronchospasm in susceptible patients with asthma, often termed aspirin-exacerbated respiratory disease (AERD), with the risk being greatest after acute exposure. Selective NSAIDs that preferentially inhibit COX-2 might be safer.

Objective: We sought to systematically evaluate changes in symptoms and pulmonary function after acute selective NSAID or COX-2 inhibitor exposure in patients with the AERD phenotype.

Methods: A systematic review of databases was performed to identify all blinded, placebo-controlled clinical trials evaluating acute selective NSAID or COX-2 inhibitor exposure in patients with AERD. Effect estimates for changes in respiratory function and symptoms were pooled by using fixed-effects meta-analysis, with heterogeneity investigated.

Results: No significant difference in respiratory symptoms (risk difference, −0.01; 95% CI, −0.03 to 0.01; $P = .57$), decrease in FEV_1 of 20% or greater (RD, 0.00; 95% CI, −0.02 to 0.02; $P = .77$), or nasal symptoms (RD, −0.01; 95% CI, −0.04 to 0.02; $P = .42$) occurred with COX-2 inhibitors (eg, celecoxib). Selective NSAID exposure caused respiratory symptoms in approximately 1 in 13 patients with AERD (RD, 0.08; 95% CI, 0.02 to 0.14; $P = .01$). No significant differences were found according to leukotriene antagonist exposure or whether NSAIDs were randomly allocated.

Conclusion: According to clinical trial evidence in patients with stable mild-to-moderate asthma with AERD, acute exposure to COX-2 inhibitors is safe, and selective NSAIDs exhibit a small risk. Thus COX-2 inhibitors could be used in patients with AERD or in patients with general asthma unwilling to risk nonselective NSAID exposure when oral challenge tests are unavailable. (J Allergy Clin Immunol 2014;134:40-5.)

Key words: *Asthma, aspirin-exacerbated respiratory disease, aspirin-induced asthma, aspirin-sensitive asthma, nonsteroidal anti-inflammatory agents, COX-2 inhibitors, systematic review, meta-analysis, pharmacoepidemiology*

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause bronchoconstriction in susceptible patients with asthma. This effect is due to inhibition of the enzyme COX-1, which is constitutively expressed in most tissues and is responsible for prostaglandin synthesis. Inhibition of COX-1 in susceptible patients alters the balance between proinflammatory and anti-inflammatory mediators, leading to increased levels of cysteinyl leukotrienes and associated bronchoconstriction.[1,2] Although initially described with aspirin, cross-reactivity with other commonly prescribed nonselective NSAIDs is thought to occur in the majority of patients with this phenotype, principally referred to as aspirin-exacerbated respiratory disease (AERD) and sometimes referred to as aspirin-intolerant or aspirin-sensitive asthma.[3,4] In patients with AERD, risk from NSAIDs is considered greatest after acute exposure, with reactions typically occurring within 3 hours of ingestion. Approximately 10% of adult asthmatic patients are thought to have AERD, and reactions can be severe, with case reports of serious adverse events and death as a result of NSAID exposure.[5-7] Patients with the AERD phenotype are more likely to have chronic rhinosinusitis and nasal polyps, with exposures also commonly triggering upper respiratory tract symptoms, such as rhinorrhea and nasal obstruction.[8-10]

Guidelines for the management of asthma currently recommend questioning patients about past reactions before NSAID exposure or simply highlight avoidance of NSAID therapy.[11,12] This in itself can be problematic because self-awareness of NSAID-induced symptoms in patients with asthma is not universal.[13] As such, these recommendations have important clinical implications for the use of NSAIDs, which are effective anti-inflammatory, analgesic, and antipyretic agents, to the extent that NSAIDs are often either withheld or prescribed with uncertain clinical consequences. Additionally, patients might be unwilling to accept the risk associated with first (incident) exposure or conversely might risk exposure from over-the-counter

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Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
NSAID: Nonsteroidal anti-inflammatory drug

medications without appropriate medical supervision. In patients with suspected AERD, the use of all NSAIDs is contraindicated by the US Food and Drug Administration, with no comment regarding risk from the newer and more selective agents.[14] This contraindication is mirrored in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency–approved Summary of Product Characteristics for COX-2 inhibitors, which clearly states that COX-2 inhibitors should not be taken if patients have a history of asthma after taking aspirin or any other NSAID.[15] Selective NSAIDs, such as meloxicam, and COX-2 inhibitors, such as celecoxib, act through preferential inhibition of COX-2 over COX-1, leaving the balance between proinflammatory and anti-inflammatory mediators unaltered and cysteinyl leukotriene levels unchanged.[16] Therefore selective NSAIDs, COX-2 inhibitors, or both would be expected to have a lower risk of adverse respiratory effects in patients with AERD. However, the degree of COX-2 selectivity for these NSAIDs varies between different drugs, with selective NSAIDs considered less selective than COX-2 inhibitors, especially at higher doses.[17] The aim of this meta-analysis of blinded placebo-controlled clinical trials is to evaluate respiratory symptoms and changes in respiratory function in patients with AERD after acute selective NSAID and COX-2 inhibitor exposure to help better inform their use in asthmatic patients.

METHODS

A systematic review of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials databases was performed with a prespecified protocol and search strategy (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org) to identify all blinded, placebo-controlled clinical trials published on or before April 11, 2013, that evaluated the effects of acute oral selective NSAIDs (meloxicam, nimesulide, and nabumetone) or COX-2 inhibitor exposure (rofecoxib, celecoxib, and etoricoxib) in patients with the AERD phenotype. AERD was defined according to documented asthma and respiratory reactions to aspirin or other NSAIDs. Exposures of up to 7 days were included. Identified references were independently screened by a minimum of 2 reviewers. Full texts were obtained for articles considered of relevance and independently appraised by the reviewers, with inclusion based on consensus. Manual searches from reference lists of included studies were performed to identify additional trials. Only English-language publications and published data from trials were included in the meta-analysis. Methodological quality and risk of bias were evaluated for each trial by using the Cochrane collaboration tool for assessing risk of bias.[18] Publication bias was assessed with funnel plots to examine for asymmetry. The systematic review was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews) requirements.

Statistical analysis

Extracted data from included studies were entered into an SPSS version 18 database (SPSS, Chicago, Ill). A decrease in FEV_1 of 20% or greater and incidence of symptoms were calculated and presented as the risk difference. Selective NSAIDs or COX-2 inhibitors were evaluated in patients with AERD only. For studies that evaluated selective NSAIDs or COX-2 inhibitors in mixed populations (eg, patients classified as NSAID intolerant as a result of other types of reactions, such as cutaneous reactions or angioedema), only asthmatic patients who had experienced bronchospasm in response to aspirin or NSAIDs were included in the analysis from the mixed population. Symptoms were defined as respiratory symptoms (consisting of wheezing, dyspnea, or cough) and upper respiratory tract symptoms (consisting of rhinorrhea or nasal obstruction). Measures of FEV_1 calculated relative to original baseline FEV_1 values were appropriate. Heterogeneity among studies was assessed by using the I^2 statistic, with values of greater than 40% indicating heterogeneity. Subgroup analysis was performed to assess whether studies withheld leukotriene antagonists or were randomized. Meta-analysis was performed in Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) according to standard Cochrane methodology by using a Mantel-Haenszel summary to calculate the risk difference with a fixed-effect method of analysis.[19]

Sensitivity analyses

Sensitivity analyses were performed according to whether trials only included patients with asthma defined according to American Thoracic Society/British Thoracic Society guidelines, reversibility in FEV_1 of 15% or greater in response to β_2-agonist stimulation, or response to methacholine/histamine/NSAID provocation challenges. Sensitivity analysis was also performed according to whether trials confirmed the diagnosis of AERD through oral provocation challenge or only described withholding β_2-agonists at least 6 hours before testing.

RESULTS

Of 1604 references screened, 14 blinded, placebo-controlled clinical trials evaluating acute selective oral NSAID exposure in patients with AERD were included in the main analysis (Fig 1 and Table I[16,20-32]). For selective NSAIDs or COX-2 inhibitors, 14 studies provided data on respiratory symptoms, 12 studies provided data on a decrease in FEV_1 of 20% or greater, and 9 studies provided data on nasal symptoms. A total of 485 acute oral selective NSAID or COX-2 inhibitor exposures were evaluated in 426 adult patients with AERD (mean age, 46 years; 38% male). Celecoxib and rofecoxib were the most commonly evaluated COX-2 inhibitors, and meloxicam was the most commonly evaluated selective NSAID. Characteristics of the selective NSAIDs or COX-2 inhibitors evaluated are summarized in Table I and Table E3 in this article's Online Repository at www.jacionline.org. All studies evaluated between 1 and 4 single-dose exposures performed over consecutive days.

COX-2 inhibitors

Compared with placebo, no significant difference was found after acute oral COX-2 inhibitor exposure in regard to respiratory symptoms (risk difference, −0.01; 95% CI, −0.03 to 0.01; P = .57), decrease in FEV_1 of 20% or greater (risk difference, 0.00; 95% CI, −0.02 to 0.02; P = .77), or nasal symptoms (risk difference, −0.01; 95% CI, −0.04 to 0.02; P = .42) in patients with AERD (Figs 2-4).

Selective NSAIDs

Compared with placebo, the risk difference for selective NSAIDs causing respiratory symptoms was 0.08 (95% CI, 0.02 to 0.14; P = .01). This was a statistically significant increase, equating to a number needed to treat of 13 to cause respiratory symptoms in 1 patient with AERD. Effect sizes for a decrease in FEV_1 of 20% or greater (risk difference, 0.08; 95% CI, −0.11 to 0.27; P = .77) and nasal symptoms (risk difference, 0.07; 95% CI, −0.05 to 0.18; P = .26) were similar but not statistically significant (Figs 2-4).

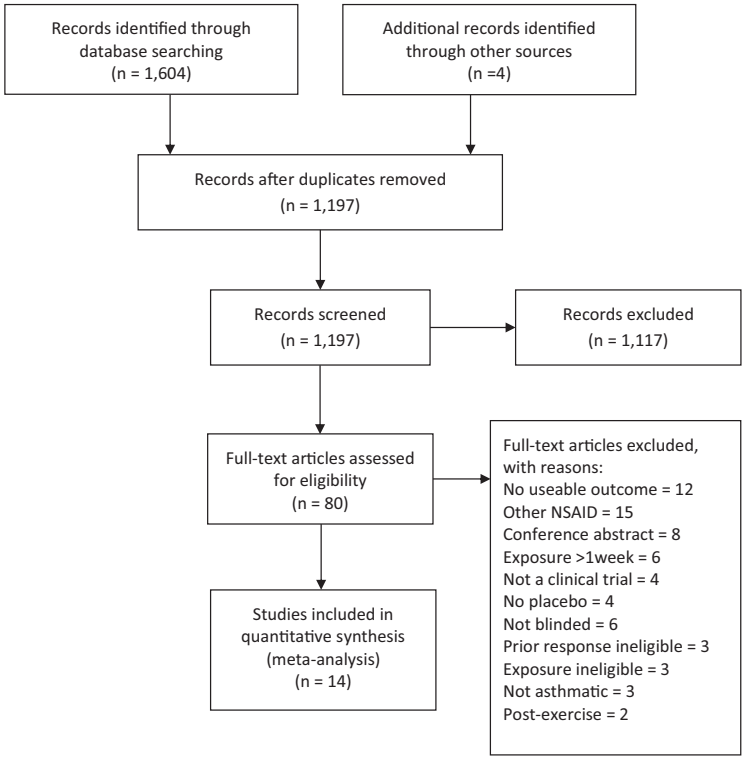

FIG 1. PRISMA flow diagram for study selection.

TABLE I. Characteristics of included studies

Study	Design	Patients*	Asthma†	SABA‡	LKT§	Selective NSAID or COX-2 inhibitor
Bavbek et al,[20] 2004	NR	31	+	−	−	Meloxicam, nimesulide, rofecoxib‖
Bavbek et al,[21] 2007	NR	13	+	+	−	Meloxicam
El Miedany et al,[22] 2006	NR	77	+	+	−	Etoricoxib‖
Gyllfors et al,[16] 2003	R	33	−	+	+	Celecoxib‖
Martin-Garcia et al,[23] 2002	NR	40	−	−	+	Rofecoxib‖
Martin-Garcia et al,[24] 2003	NR	33	−	−	+	Celecoxib‖
Micheletto et al,[25] 2006	NR	19	+	+	−	Rofecoxib‖
Prieto et al,[26] 2007	NR	29	−	−	+	Nabumetone, meloxicam
Stevenson and Simon,[27] 2001	R	32	−	−	−	Rofecoxib‖
Szczeklik et al,[28] 2001	NR	12	+	+	−	Rofecoxib‖
Valero et al,[29] 2002	NR	43	−	−	−	Rofecoxib‖
Woessner et al,[30] 2002	NR	25	+	−	−	Celecoxib‖
Woessner et al,[31] 2004	NR	22	+	−	−	Rofecoxib‖
Yoshida et al,[32] 2000	R	17	+	−	+	Celecoxib‖

+, Yes; −, no; *NR*, nonrandomized; *R*, randomized.
*Only patients with AERD selected from included studies.
†Whether studies defined asthma per the Methods section.
‡Whether studies withheld short-acting β_2-agonists *(SABA)* for at least 6 hours.
§Whether studies withheld leukotriene antagonists *(LKT)*.
‖COX-2 inhibitors (remaining unmarked drugs are classed as selective NSAIDs).

Subgroup analysis

Leukotriene antagonists. Compared with placebo, there was no significant difference in respiratory symptoms, nasal symptoms, or a decrease in FEV_1 of 20% or greater according to whether studies withheld leukotriene antagonists before acute exposure (see Figs E1-E3 in this article's Online Repository at www.jacionline.org).

Random allocation. Compared with placebo, there was no significant difference in respiratory symptoms, nasal symptoms, or decrease in FEV_1 of 20% or greater according to whether NSAID exposure or placebo was randomly allocated (see Figs E4-E6 in this article's Online Repository at www.jacionline.org).

Sensitivity analyses and risk of bias

Compared with placebo, there was no significant difference in respiratory symptoms, nasal symptoms, or decrease in FEV_1 of 20% or greater according to whether studies confirmed the diagnosis of AERD through oral provocation challenge, withheld β_2-agonists for at least 6 hours, or defined asthma as described

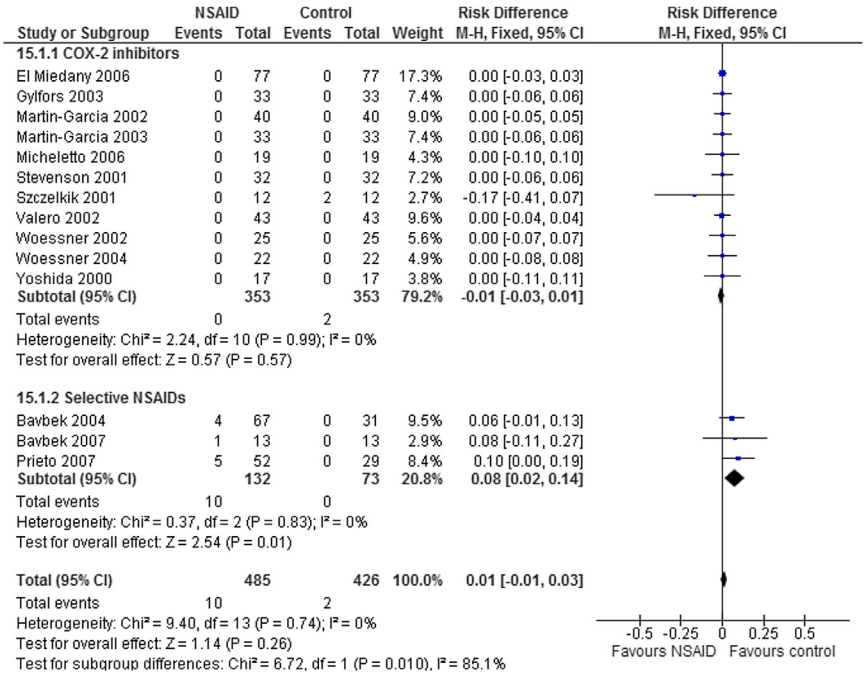

FIG 2. Respiratory symptoms after acute selective NSAID or COX-2 inhibitor exposure in patients with AERD. *M-H,* Mantel-Haenszel.

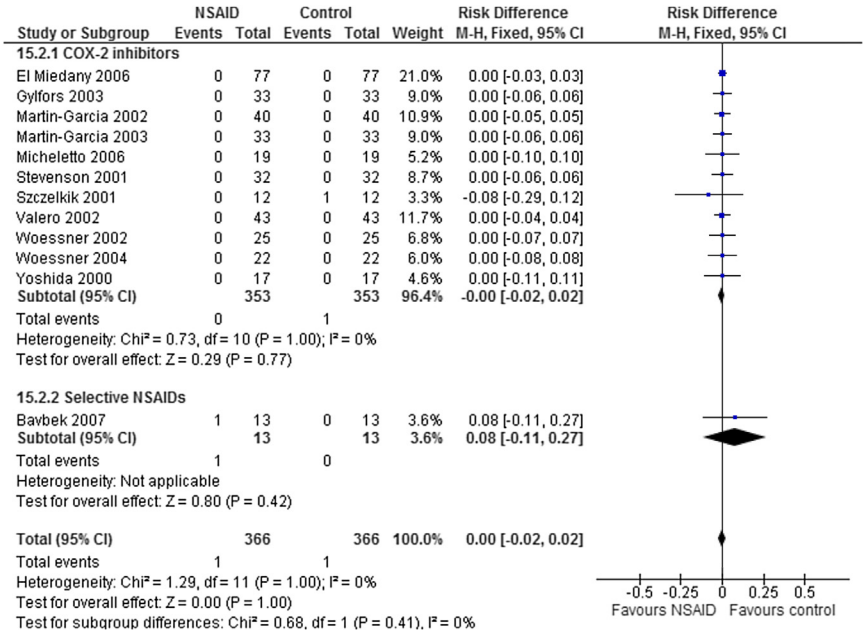

FIG 3. Decrease in FEV_1 of 20% or greater after acute selective NSAID or COX-2 exposure in patients with AERD. *M-H,* Mantel-Haenszel.

in the Methods section. No significant heterogeneity was found by using the I^2 statistic. For the methodological qualities assessed, risk of bias was either low or unclear when studies did not provide explicit details from which to make an informed judgment (see Fig E7 in this article's Online Repository at www.jacionline.org). No funnel plot asymmetry was found to suggest publication bias.

DISCUSSION

This study found no significant differences in adverse respiratory effects after acute exposure to COX-2 inhibitors and a small but statistically significant risk with selective NSAIDs in patients with AERD. Reactions to selective NSAIDs occurred in approximately 1 in 13 patients with AERD. Assuming a prevalence of AERD of 10%, this would equate to selective NSAIDs causing

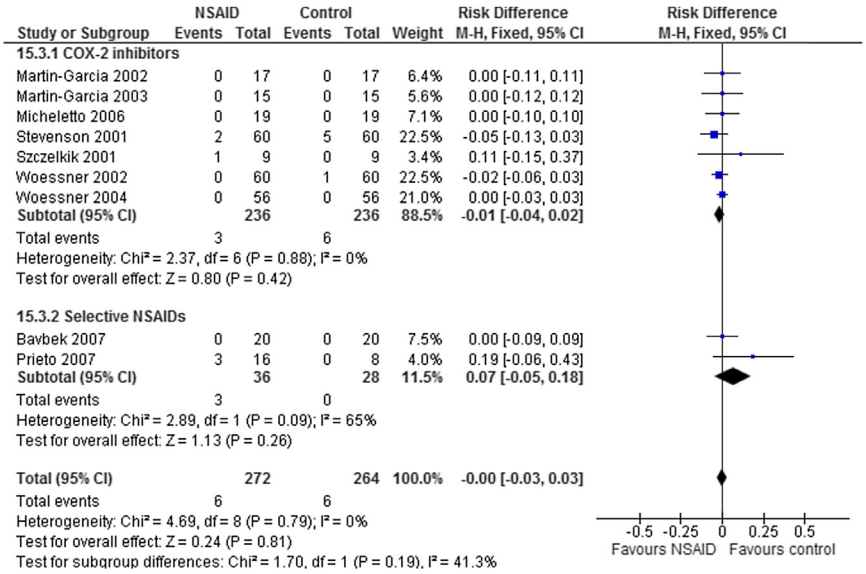

FIG 4. Nasal symptoms after acute selective NSAID or COX-2 exposure in patients with AERD. *M-H,* Mantel-Haenszel.

symptoms in approximately 0.8% of the general asthmatic population.

The selective NSAIDs evaluated are at least 10-fold more selective for COX-2 than COX-1, whereas COX-2 inhibitors are generally considered to be more than 100 times more selective for COX-2 in human subjects.[33] In patients with AERD, cysteinyl leukotriene levels increase during NSAID-induced reactions, which might theoretically be attenuated by leukotriene antagonists. As such, failure to discontinue such medications at the time of oral challenge testing could potentially mask or underestimate the true risk from exposure. Although several studies in our analysis continued leukotriene antagonist exposure during challenge testing, no evidence was found to suggest that the lack of adverse respiratory effects in patients with AERD challenged with selective NSAIDs or COX-2 inhibitors was influenced by this.

Strengths and limitations

To our knowledge, this is the largest evaluation of clinical trial evidence on the safety of selective NSAIDs and COX-2 inhibitors in patients with AERD. We included only blinded, placebo-controlled studies to minimize bias. Although not all studies randomly allocated NSAID exposure as part of their test procedures, subgroup analysis between randomized and nonrandomized studies showed the same results. The included studies predominantly evaluated selective NSAIDs or COX-2 inhibitors in patients with AERD with stable, mild-to-moderate persistent asthma. As such, results from this meta-analysis might not be applicable to patients with unstable asthma or those who have experienced severe life-threatening reactions requiring intubation after aspirin or NSAID exposure.[34] This analysis was careful to include only asthmatic patients with documented aspirin or NSAID respiratory intolerance, and results might not be applicable to patients with NSAID-induced anaphylaxis, angioedema, or cutaneous reactions. Although anaphylactic reactions to COX-2 inhibitors have been reported, these events are rare and possibly distinct to isolated respiratory or nasal reactions commonly encountered by patients with AERD.[35-37] Up to 90% of patients with AERD demonstrate nasal responses to aspirin or nonselective NSAIDs, which do not appear to occur with COX-2 inhibitors. Although not considered as clinically important as potentially life-threatening respiratory reactions, nasal reactions in patients with asthma significantly affect quality of life.[10,38] The effect of atopy remains uncertain because of the lack of individual patient data. Moderate doses of selective NSAIDs or COX-2 inhibitors were administered during oral challenge testing, and we cannot exclude the possibility of reactions occurring after acute high-dose exposure. As such, safe initiation of COX-2 inhibitors in patients with AERD should initially involve a low dose with gradual dose titration.

Clinical implications

Challenge tests are the only way of confirming the AERD phenotype but are not widely recommended or used in routine clinical practice.[11,12] In light of this fact, recommendations in clinical asthma guidelines regarding the safe use of NSAIDs in patients with an unknown AERD phenotype are inadequate. It is clear that recommendations from some of the included clinical trials have not been widely adopted into clinical practice, possibly as a result of regulatory agency–approved product information leaflets continuing to contraindicate all NSAIDs in patients with AERD with no comment regarding the use of or risk from COX-2 inhibitors.[14,15] The findings from this study indicate that COX-2 inhibitors are safe, at least when initiated at low doses in patients with stable mild-to-moderate asthma. In patients with uncontrolled asthma, it would be prudent to optimize asthma controller therapy with inhaled corticosteroids to reduce the risk of adverse events in this population.[34] It is also likely that patients in real life could be prescribed montelukast or zileuton, should uncertainties remain.[39]

Ultimately, the use of any drug depends on its risk and benefit. COX-2 inhibitors are associated with increased cardiovascular risk, and an overall risk assessment should be made to avoid unintended consequences.[40] As such, the lowest effective dose

should be used for the shortest period of time, with scheduled medical review. Nevertheless, the use of COX-2 inhibitors appears to provide a safe and effective means to anti-inflammatory and analgesic treatment in asthmatic patients with true AERD or those asthmatic patients unwilling to accept the potential risk from nonselective NSAID exposure when oral challenge tests are unavailable.

Clinical implications: COX-2 inhibitors are safe in patients with AERD and could be used as an alternative NSAID in patients with AERD or general asthma who are unwilling to accept the risk from incident NSAID exposure.

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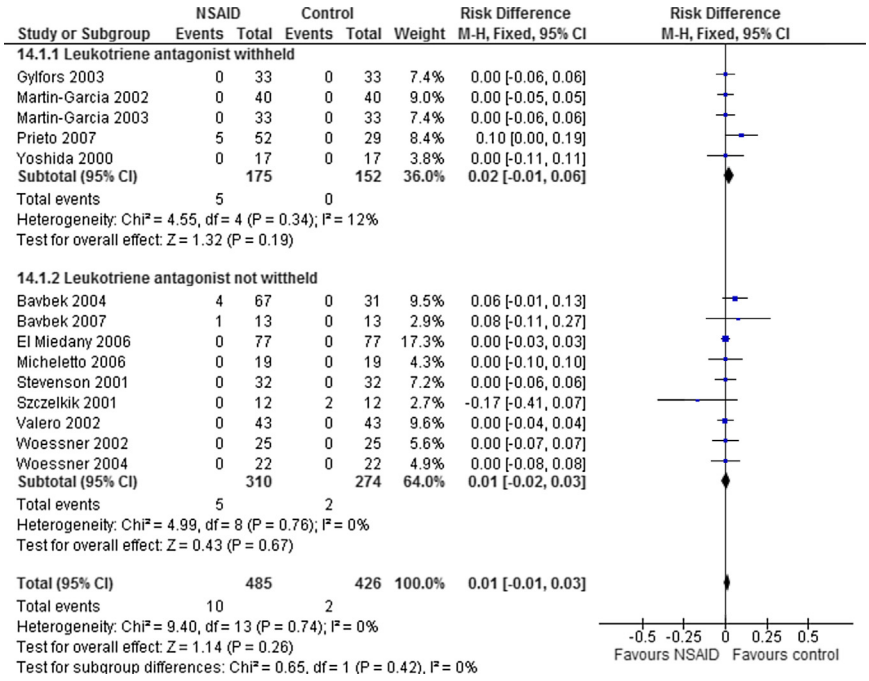

FIG E1. Respiratory symptoms after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to leukotriene antagonist exposure status. *M-H,* Mantel-Haenszel.

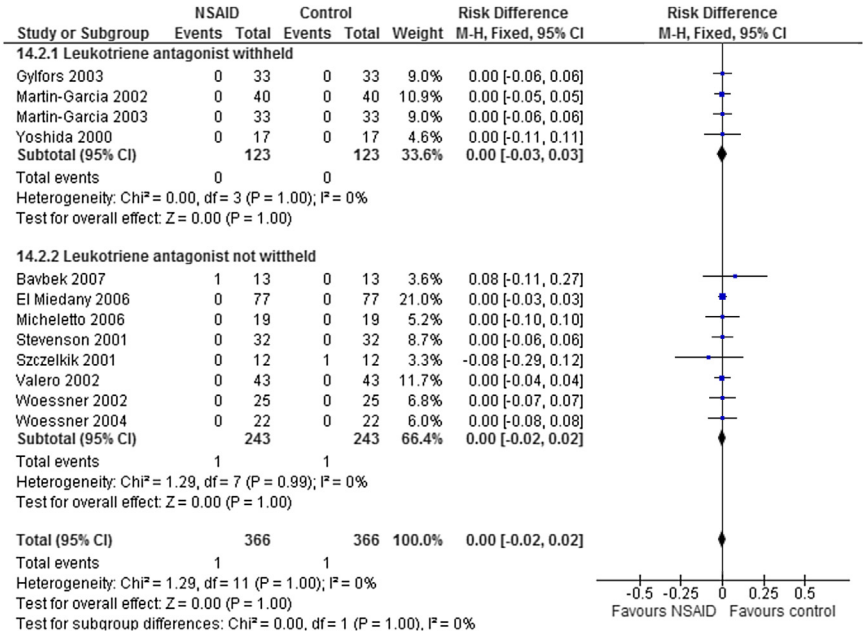

FIG E2. Decreases in FEV_1 of 20% or greater after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to leukotriene antagonist exposure status. *M-H,* Mantel-Haenszel.

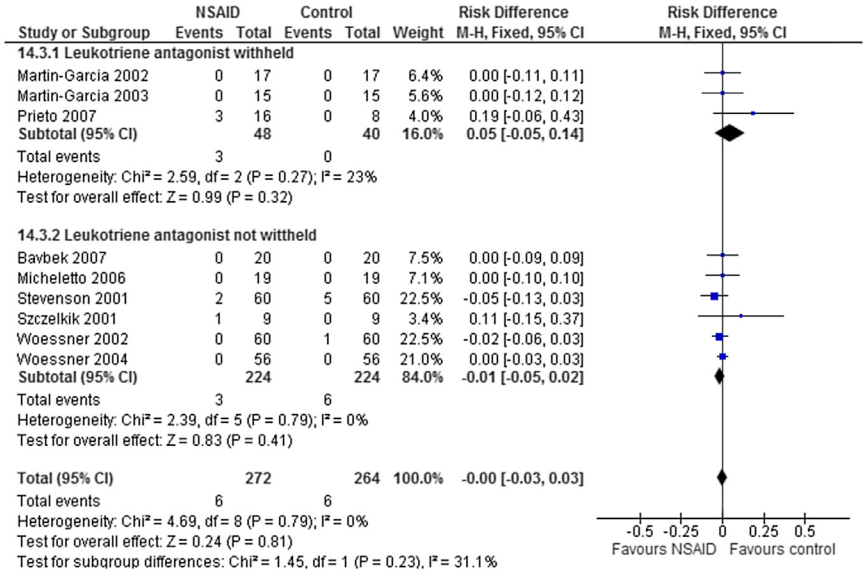

FIG E3. Nasal symptoms after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to leukotriene antagonist exposure status. *M-H,* Mantel-Haenszel.

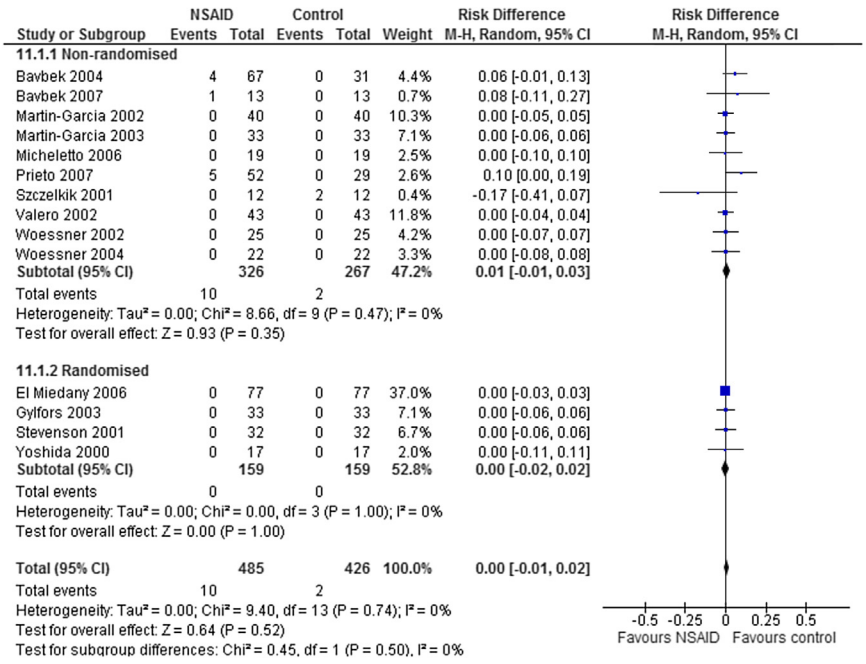

FIG E4. Respiratory symptoms after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to random allocation. *M-H,* Mantel-Haenszel.

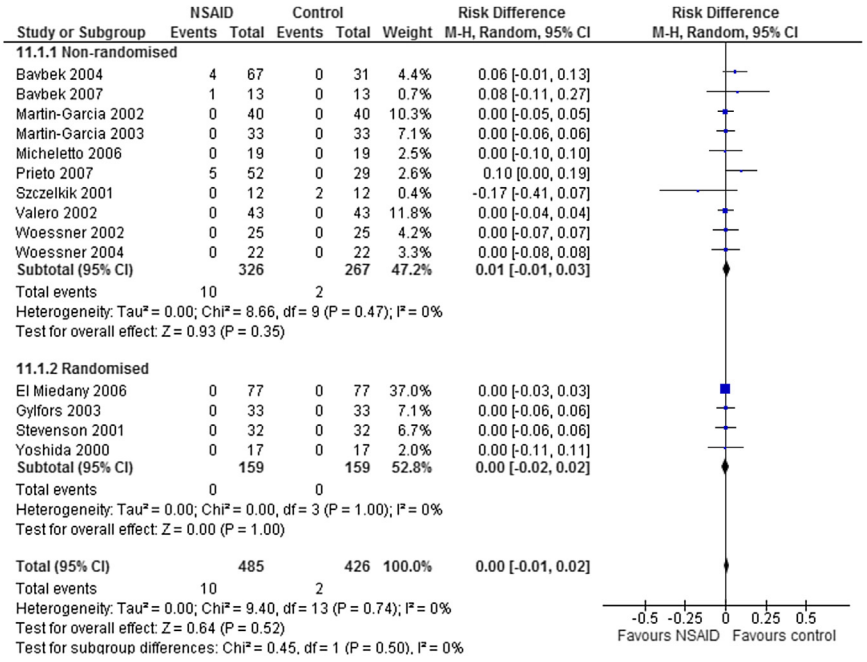

FIG E5. Decreases in FEV_1 of 20% or greater after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to random allocation. *M-H,* Mantel-Haenszel.

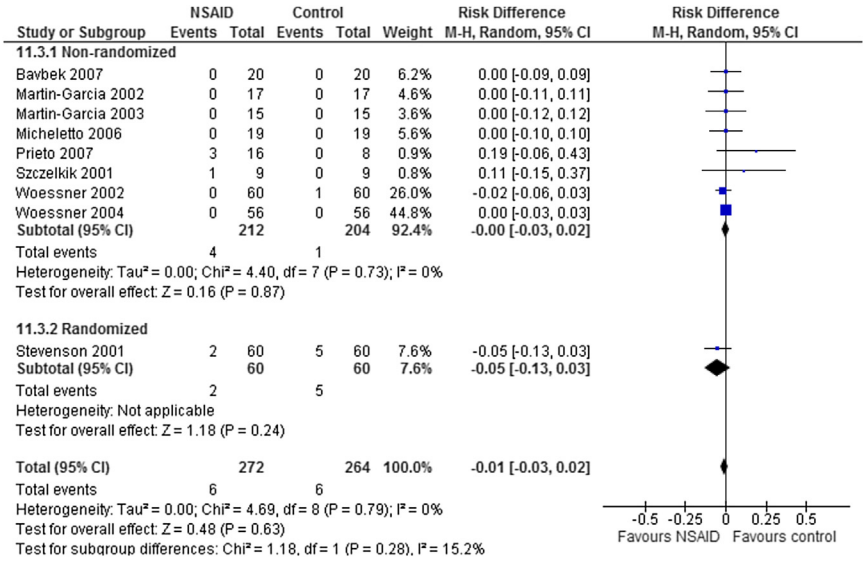

FIG E6. Nasal symptoms after acute selective NSAIDs or COX-2 inhibitors in patients with AERD according to random allocation. *M-H,* Mantel-Haenszel.

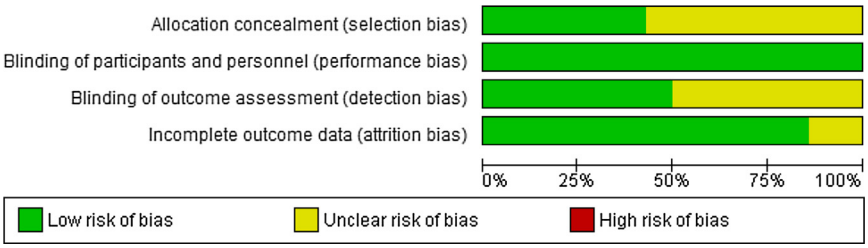

FIG E7. Risk of bias table for included studies.

TABLE E1. PICOS approach (participants, interventions, comparators, outcomes, and study design) used for the systematic review

Population	Included	Patients with AERD
	Excluded	Patients without AERD, patients with COPD, and healthy patients
Intervention	Included	Oral selective NSAID exposure
	Excluded	Oral aspirin or nonselective NSAIDs
Comparator	Included	Placebo
Outcomes	Included	Symptoms
		Decrease in FEV_1 ≥20%
	Excluded	Other measures of airway resistance
Studies	Included	Controlled clinical trials in human subjects
		Single- or double-blind

COPD, Chronic obstructive pulmonary disease.

TABLE E2. Example MEDLINE search strategy

1	asthma*.af.	49	aspirin-like.ti,ab,sh.
2	(bronchial adj3 hyperreactivity*).af.	50	(aspirin adj2 like).ti,ab,sh.
3	(bronchial adj3 hyper-reactivity*).af.	51	33 and (49 or 50)
4	(bronchial adj3 hyperrespons*).af.	52	nsaid*.ti,ab,sh.
5	(bronchial adj3 hyper-respons*).af.	53	34 or 35 or 39 or 40 or 41 or 42 or 46 or 47 or 48 or 51 or 52
6	(airway adj3 hyperreactivity*).af.	54	inhibitor*.ti,ab,sh.
7	(airway adj3 hyper-reactivity*).af.	55	antagonist*.ti,ab,sh.
8	(airway adj3 hyperrespons*).af.	56	cyclooxygenase*.ti,ab,sh.
9	(airway adj3 hyper-respons*).af.	57	cyclo-oxygenase*.ti,ab,sh.
10	(reversible adj3 obstruction).af.	58	(cyclo adj2 oxygenase*).ti,ab,sh.
11	'respiratory sounds'.af.	59	cox*.ti,ab,sh.
12	wheez*.af.	60	(prostaglandin adj2 synth*).ti,ab,sh.
13	or/1-12	61	(prostaglandin-endoperoxide adj2 synth*).ti,ab,sh.
14	random*.af.	62	54 and (56 or 57 or 58 or 59 or 60 or 61)
15	factorial*.af.	63	55 and (56 or 57 or 58 or 59 or 60 or 61)
16	crossover*.af.	64	Aspirin.ti,ab,sh.
17	cross-over*.af.	65	Aceclofenac.ti,ab,sh.
18	placebo*.af.	66	acemetacin.ti,ab,sh.
19	(singl* adj blind*).af.	67	Azoproprazone.ti,ab,sh.
20	(doubl* adj blind*).af.	68	Celecoxib.ti,ab,sh.
21	single-blind*.af.	69	Dexibuprofen.ti,ab,sh.
22	double-blind*.af.	70	Dexketoprofen.ti,ab,sh.
23	assign$.af.	71	Diclofenac.ti,ab,sh.
24	allocat$.af.	72	Etodolac.ti,ab,sh.
25	volunteer$.af.	73	Etoricoxib.ti,ab,sh.
26	randomized controlled trial.pt.	74	Fenbufen.ti,ab,sh.
27	controlled clinical trial.pt.	75	Fenoprofen.ti,ab,sh.
28	or/14-27	76	Fluribuprofen.ti,ab,sh.
29	analgesi*.ti,ab,sh.	77	Ibuprofen.ti,ab,sh.
30	anti-inflammator*.ti,ab,sh.	78	Indomethacin.ti,ab,sh.
31	antiinflammator*.ti,ab,sh.	79	Ketorolac.ti,ab,sh.
32	(anti adj2 inflammator*).ti,ab,sh.	80	Ketoprofen.ti,ab,sh.
33	agent.ti,ab,sh.	81	Mefenamic acid.ti,ab,sh.
34	29 and (30 or 31 or 32)	82	Meloxicam.ti,ab,sh.
35	33 and (30 or 31 or 32)	83	Nabumetone.ti,ab,sh.
36	non-steroidal*.ti,ab,sh.	84	Naproxen.ti,ab,sh.
37	nonsteroidal*.ti,ab,sh.	85	Parecoxib.ti,ab,sh.
38	(non adj2 steroidal*).ti,ab,sh.	86	Piroxicam.ti,ab,sh.
39	36 and (30 or 31 or 32)	87	Rofecoxib.ti,ab,sh.
40	37 and (30 or 31 or 32)	88	Sulindac.ti,ab,sh.
41	38 and (30 or 31 or 32)	89	Tenoxicam.ti,ab,sh.
42	33 and (36 or 37 or 38)	90	Tolfenamic acid.ti,ab,sh.
43	antirheumatic.ti,ab,sh.	91	Tiaprofenic acid.ti,ab,sh.
44	anti-rheumatic.ti,ab,sh.	92	Phenylbutazone.ti,ab,sh.
45	(anti adj2 rheumatic).ti,ab,sh.	93	or/64-92
46	43 and (36 or 37 or 38)	94	53 or 62 or 63 or 93
47	44 and (36 or 37 or 38)	95	13 and 28 and 94
48	45 and (36 or 37 or 38)		

This search strategy was used for a larger synthesis of NSAID exposure in asthmatic patients. Only selective NSAIDs were used for this review.

TABLE E3. Dose ranges for the selective NSAID and COX-2 inhibitors evaluated in patients with AERD

Selective NSAIDs	Dose (mg)	COX-2 inhibitors	Dose (mg)
Meloxicam	7.5-15	Rofecoxib	25-50
Nimesulide	100	Celecoxib	200-400
Nabumetone	1000-2000	Etoricoxib	60-120