Clinical Outcomes of Aspirin Interaction with Other Non-Steroidal Anti-Inflammatory Drugs: A Systematic Review

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ABSTRACT - Purpose: Concomitant use of some non-Aspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) reduces the extent of platelet aggregation of Aspirin (acetylsalicylic acid). This is while many observational studies and clinical trials suggest that Aspirin reduces cardiovascular (CV) risk attributed to the use of NANSAIDs. Thus, the therapeutic outcome of the interaction needs to be assessed. **Methods:** We searched various databases up to October 2017 for molecular interaction studies between the drugs and long-term clinical outcomes based on randomized clinical trials and epidemiological observations that reported the effect estimates of CV risks (OR, RR or HR; 95% CI) of the interacting drugs alone or in combinations. Comparisons were made between outcomes after Aspirin alone, NANSAIDs alone and Aspirin with naproxen, ibuprofen, celecoxib, meloxicam, diclofenac or rofecoxib. **Results:** In total, 32 eligible studies (20 molecular interactions studies and 12 observational trials) were found. Conflicting *in vitro/in vivo/ex vivo* platelet aggregation data were found for ibuprofen, naproxen and celecoxib. Nevertheless, for naproxen, the interaction at the aggregation level did not amount to a loss of cardioprotective effects of Aspirin. Similarly, for ibuprofen, the results overwhelmingly suggest no negative clinical CV outcomes following the combination therapy. Meloxicam and rofecoxib neither interacted with Aspirin at the level of platelet aggregation nor altered clinical outcomes. The clinical outcomes data for celecoxib and diclofenac are in conflict. **Conclusion:** Aspirin appears to maintain its cardioprotective effect in the presence of naproxen, ibuprofen, meloxicam and rofecoxib. The limited available data suggest that the effect of interaction at the platelet aggregation level may dissipate shortly, or the reduced platelet aggregation yielded by the interaction may be sufficient for cardioprotection; i.e., no need for near complete aggregation. In addition, cardioprotective effect of Aspirin, despite reduced platelet aggregation caused by NANSAIDs, may be through its involvement in other mechanisms such as the renin-angiotensin system and/or metabolism of arachidonic acid to biologically active compounds mediated by cytochrome P450.

INTRODUCTION

Acetylsalicylic acid (Aspirin) is in clinical use since mid 19th century. In addition to being an effective analgesic, antipyretic and anti-inflammatory agent, it is used, among other indications, for its anti-platelet property to reduce all-cause mortality, cardiac death, and nonfatal myocardial infarction (MI) (1). Moreover, low-dose Aspirin, alone or in combination, is recommended for the secondary prevention of acute ischemic stroke and transient ischemic attack (2-4). In general, the anti-platelet effect of Aspirin accounted for the irreversible inhibition of platelet cyclooxygenase-1 (COX-1) enzyme. COX-1 is an enzyme that catalyzes AA to produce several prostaglandins (PG), among them thromboxane A_2 (TxA_2), a promoter of platelet aggregation (5, 6). The inhibition of the COX-1 dependent TxA_2 by Aspirin, measured by plasma thromboxane B_2 (TxB_2) is recommended to be near completion to significantly inhibit platelet function *in vivo* (7-9).

The non-Aspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) are among the most commonly used medications for a variety of indications ranging from headaches to arthritis. NANSAIDs bind and inhibit the COX enzymes which lead to inhibition of prostanoids biosynthesis including PGs, prostacyclins and thromboxanes (10). Thus, the concomitant use of some NANSAIDs appear to interact with the Aspirin's anti-platelet function, thereby, although unproven,

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may reduce its CV protection benefits (11). This, however, seems contradictory to the observations that the elevated CV risks of some NANSAIDs is lowered by addition of low dose Aspirin to the regimen (12, 13). We, therefore, hypothesized that the CV benefits of Aspirin are reduced upon concomitant administration of NANSAIDs. We tested the hypothesis through a comprehensive systematic search of available literature data to assess the CV risks of concomitant use of NANSAIDs and Aspirin with those of Aspirin alone or NANSAID. Subsequently, the clinical outcomes were compared with the results of the Aspirin-NANSAIDs interactions at the molecular level; i.e., *in vitro, in vivo* and/or *ex vivo* data. The present analysis focuses on only six commonly used NANSAIDs, i.e., ibuprofen, naproxen, diclofenac, celecoxib, rofecoxib, and meloxicam.

METHODS

This systematic review with a trial registration number of PROSPERO 2018 CRD42018084556 has been carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as listed in the Supplements (14).

Search strategy

The study focus was only on ibuprofen, naproxen, diclofenac, meloxicam, celecoxib and rofecoxib. Both authors independently searched published studies indexed in MEDLINE, EMBASE, CINAHL, Web of Science, and the Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database) from inception to October 2017. The search terms were compiled from the names of individual NANSAIDs, acetylsalicylic acid, Aspirin, cyclooxygenase, COX, cardiovascular, myocardial infarction, stroke, cerebrovascular, cardioprotection, platelet, platelet aggregation, platelet aggregation inhibit, anti-platelet effect, blood platelets, and drug interaction. The detailed search strategy is provided as supplementary material. We also searched the Clinical Trials Registry platforms for ongoing studies for any additional relevant references. The bibliographies of included reports were searched for relevant additional studies. Abstracts and unpublished studies were not included.

Study selection and data extraction

Both authors examined the titles and abstracts of studies to identify studies that potentially meet the inclusion criteria. The inclusion criteria were as follows: (i) Randomized controlled trials (RCTs) or observational studies (cohort or case-control studies) that include treatment with Aspirin alone or NANSAID alone as well as concomitant use of NANSAIDs with Aspirin. The association between the treatments and risk of CV (MI), cerebrovascular events (stroke) or all-cause mortality were assessed for studies that included odds ratios (ORs), relative risks (RRs) and/or hazard ratios (HRs) with 95% confidence interval (CI). (ii) molecular interactions trials (*in vitro*, *in vivo* or *ex vivo*) in human addressing the interaction at the platelet level between NANSAIDs and Aspirin.

The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility. Disagreements were settled through discussion and consensus. Extracted information included study information (i.e. authors, location, publication date, type of study, number of participants, and study duration), patient characteristics (i.e. age, sex, previous CV events including stroke, Aspirin use, and NANSAIDs use), intervention and comparator (i.e. drugs and doses) and outcomes (i.e. events/total for all study population or subgroups).

The identified studies were excluded if: (i) they were reviews, questionnaire, thesis, letters, simulated studies, meeting summary, conference abstracts, editorial or commentary articles; (ii) had no eligible outcomes or did not report direct comparisons of individual NANSAIDs; (iii) used extra-oral route of administration (e.g., topical use for analgesia) or used other drugs with NANSAIDs or Aspirin.

Quality assessment

The methodological quality of the included observational studies (cohort and case-control studies) was appraised using scales adopted from the Newcastle-Ottawa quality scale (NOS) (15). Based on the study design (cohort or case-control study), each study was evaluated using the appropriate scoring system. Eight items in the included cohort and case-control studies were identified and assessed. Cohort and case-control studies with 6-9,

3-5, and 0-2 points were classified as high, fair or poor quality, respectively.

RESULTS

Eligible studies

Our search strategy yielded 3,563 potentially relevant articles from which 3,498 were found ineligible because they were not epidemiological studies or molecular interactions experiments. Sixty-five articles underwent full-length article review. Twenty-five of these were excluded because they did not report the outcome of interest (MI or stroke), 5 were excluded because they did not report direct comparison of individual NANSAIDs with or without use of Aspirin, and 3 were excluded because of combination other than Aspirin with NANSAIDs or use of formulation other than oral. Twelve studies (5 cohort studies and 7 case-control studies) with 80,845 events met our eligibility criteria and were included in the analysis (12, 13, 16-25). The eligible studies scored good quality based on the calculated NOS scores (cohorts, 8-9/9 and case-controls 6-8/9) (Table 9).

Twenty molecular interactions studies addressing the interactions between NANSAIDs and Aspirin were included. The detailed flow chart of search methodology and selection process is shown in Figure 1. Table 1 compares the outcomes of both platelet effects and clinical outcomes. Data on the selected NANSAIDs are provided in Tables 2-7. The detailed characteristics of molecular interactions experiments studies are described in Table 8. The clinical data on the interactions between Aspirin and different type of NANSAIDs are summarized in Table 9.

Platelet aggregation

The 20 eligible molecular interaction studies with the information on the interactions indicated that, in general, the anti-platelet effect of Aspirin is reduced in the presence of ibuprofen, naproxen or celecoxib (Tables 1 and 8). However, meloxicam, rofecoxib and diclofenac do not interfere with the anti-platelet effect of Aspirin.

Cardiovascular outcomes

The 12 studies (12, 13, 16-23) listed in Tables 1 and 9 reported CV risks of Aspirin alone as well as in combination with various NANSAIDs. The results suggest that the addition of naproxen to an Aspirin regimen does not result in a loss of beneficial effects of the latter (Tables 1 and 3). Similarly, the reported ibuprofen-Aspirin interaction at the level of platelets does not seem to diminish the cardioprotective effect of Aspirin (Table 1). However, 2 of the 10 eligible studies have reported diminished clinical benefit of Aspirin caused by ibuprofen (17, 24). Indeed, one of the 2 studies (17) has made the same observation for celecoxib and diclofenac (Table 1). As depicted in Table 2, there are only two studies (24, 25) that found changes in all-cause mortality for Aspirin plus ibuprofen compared with Aspirin alone users. One of these studies (25) found that addition of ibuprofen did not increase the risk of all-cause mortality (HR, 0.84; CI 0.70-1.01) but the other one (24) did (HR, 1.93; CI 1.30-2.87). The latter also found an increased risk of CV mortality for the combination (HR, 1.73; CI 1.05-2.84).

Table 1. Summary of *in vitro*, *in vivo*, *ex vivo* and clinical data on the interactions between Aspirin and different type of NANSAIDs

	Anti-platelet effect of Aspirin diminished				Beneficial effect of Aspirin in reducing CV risks diminished	
NANSAIDs	*in vitro*		*in vivo/ex vivo*		Clinical data	
Ibuprofen		Yes [26-28]	No [29]	Yes [30-36]	No [12, 18-23, 25]	Yes [17, 24]
Naproxen	No [26]	Yes [37]	No [38]	Yes [34-37, 39]	No [12, 16-19, 23]	
Diclofenac	No [26, 27]		No [30, 31, 38]		No [19, 23]	Yes [12, 17]
Celecoxib		Yes [27]	No [32, 34, 35, 40]	Yes [41]	No [12, 13]	Yes [17]
Rofecoxib	NA		No [30, 42]		No [12, 13, 17]	
Meloxicam	No [26]		No [43]		No [12, 16]	

NA, not available

Table 2. Reports of concomitant ibuprofen/Aspirin use regarding CV/all-cause mortality risks.

Beneficial effect of Aspirin in reducing CV risks NOT diminished		Beneficial effect of Aspirin in reducing CV risks diminished	
Reference	**Conclusions (RR/OR/HR (95% CI))**	**Reference**	**Conclusions (RR/OR/HR (95% CI))**
(12)	RR for MI: Aspirin+ibuprofen, 1.22 (0.83-1.78); Aspirin alone, 1.04 (0.96-1.12); ibuprofen alone, 1.02 (0.80-1.32).	**(17)**	HR for MI: Aspirin+ibuprofen, 1.50 (1.33-1.70); Aspirin alone 0.98 (0.94-1.03).
(18)	RR for MI: Aspirin+ibuprofen, 1.28 (1.16-1.40); ibuprofen alone, 1.12 (1.06-1.19).	**(24)**	HR for all-cause mortality: Aspirin+ibuprofen, 1.93 (1.30-2.87) *vs* Aspirin alone; HR for CV mortality: 1.73 (1.05-2.84) *vs* Aspirin alone.
(19)	HR for MI: Aspirin+ibuprofen, ever exposed, 1.01 (0.58-1.76), ≥ 30 days: 1.13 (0.54-2.39), ≥ 60 days: 1.83 (0.76-4.42) *vs* nonexposed subjects.		
(20)	OR for MI: Aspirin+ibuprofen, 0.74 (0.57-0.97); Aspirin alone, 0.87 (0.75-1.00).		
(21)	RR for MI: Aspirin+ibuprofen, 0.61 (0.50-0.73) *vs* Aspirin alone users.		
(22)	OR for MI: Aspirin+ibuprofen, 1.01 (0.47-2.20) *vs* Aspirin alone; Aspirin+ibuprofen, > 4 times/week, 2.03 (0.60-6.84); Aspirin+ibuprofen, < 4 times/week, 0.60 (0.21-1.66).		
(23)	OR for MI: Aspirin+ibuprofen, 1.08 (0.74-1.58) *vs* Aspirin alone users.		
(25)	HR for death: Aspirin+ibuprofen, 0.84 (0.70-1.01) *vs* Aspirin alone users.		

RR, Risk Ratio; OR, Odds Ratio; HR, Hazard Ratio; CV, Cardiovascular; MI, Myocardial Infarction. Ratios for Aspirin are listed when the assessment is made *vs* nonusers; for others, the ratio is 1 as Aspirin is used as the reference.

Table 3. Reports of concomitant naproxen/Aspirin use regarding CV risks.

Beneficial effect of Aspirin in reducing CV risks NOT diminished	
Reference	**(RR/OR/HR (95% CI))**
(12)	RR for MI: Aspirin+naproxen, 1.26 (0.60-2.62); Aspirin alone, 1.04 (0.96-1.12); naproxen alone, 1.00 (0.68-1.47).
(16)	OR for MI: Aspirin+naproxen, 1.04 (0.65, 1.67); naproxen alone, 1.21 (0.93-1.56).
(17)	HR for CV: Aspirin+naproxen, 0.94 (0.52-1.70); Aspirin alone 0.98 (0.94-1.03).
(18)	RR for MI: Aspirin+naproxen, 1.28 (1.07-1.53); naproxen alone, 1.11 (1.01-1.23).
(19)	HR for MI: Aspirin+naproxen, ever exposed, 1.04 (0.58-1.76), ≥ 30 days, 1.13 (0.54-2.39), ≥ 60 days, 1.83 (0.76-4.42) *vs* nonexposed subjects.
(23)	OR for MI: Aspirin+naproxen, 0.96 (0.49-1.86) *vs* Aspirin alone users.

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction. Ratios for Aspirin are listed when the assessment is made *vs* nonusers; for others, the ratio is 1 as Aspirin is used as the reference.

A trend towards an increase in the rate of recurrent MI has been reported in one cohort study when subjects exposed to Aspirin and ibuprofen (HR, 1.50; CI 1.33-1.70) compared with Aspirin alone users (HR, 0.98; CI 0.94-1.03) (17). A retrospective cohort study has also concluded that patients with history of CV diseases had increased risk of mortality when exposed to Aspirin plus ibuprofen compared with users of Aspirin alone (24).

DISCUSSION

This is, to the best of our knowledge, the first systematic review that compares published Aspirin-NANSAIDs interaction at the platelet level with its long-term clinical outcomes. We have used broad inclusion criteria in many databases to capture molecular interactions experiments, RCTs and observational studies for a range of NANSAIDs and Aspirin users. However, no RCTs data were found.

We found that a NANSAID-Aspirin interaction at the platelet level does not necessarily amount to a loss of beneficial effects of Aspirin. Indeed, for naproxen, studies have consistently reported no negative clinical outcomes after addition of the drug to the Aspirin regimens (Table 3). Similarly, studies overwhelmingly suggest that Aspirin maintains it beneficial effects after addition of ibuprofen to the regimen. (Table 2).

As expected, the cardioprotective effect of Aspirin is not diminished by meloxicam and rofecoxib, two NANSAIDs that do not interact with Aspirin at the platelet level (Table 1). Interestingly, diclofenac for which its lack of effect on the anti-platelet action of Aspirin has been repeatedly reported appears to diminish the clinical benefit of the latter as reported by 2 of eligible 4 studies (Table 1).

Despite the limited number of eligible studies, meloxicam (12, 16) (Table 4) and rofecoxib (12, 13, 17) (Table 5) do not appear to diminish the cardioprotective effect of Aspirin. This is not unexpected since these drugs do not interact with the anti-platelet properties of Aspirin (Table 1).

The data for celecoxib are not as conclusive as those available for naproxen and even ibuprofen since we found only 3 eligible studies. Two studies that suggest no loss of the beneficial effect of Aspirin (12, 13) contradict the other one (17). The reason for the conflicting results is unclear but it may be of relevance to mention that the latter study (17) stands out as the one that has also observed diminishing clinical benefit of Aspirin for ibuprofen, diclofenac as well. Nevertheless, in light of the conflicting data and the limited eligible studies, one cannot draw an unequivocal conclusion as to the clinical outcome of celecoxib-Aspirin interaction. Similarly, one cannot draw a definite conclusion regarding diclofenac as we found only 4 eligible studies, two in each side of the controversy. This is interesting since diclofenac does not interact with Aspirin at the platelet level (Table 1), thus, the loss of cardioprotective effect caused by the drug-drug interaction is unexpected.

Table 4. Reports of concomitant meloxicam/Aspirin use regarding CV risks.

Reference	Beneficial effect of Aspirin in reducing CV risks NOT diminished (RR/OR/HR (95% CI))
(12)	RR for MI: Aspirin+meloxicam, 0.78 (0.41-1.51); Aspirin alone, 1.03 (0.95-1.12); meloxicam alone, 1.61 (1.09-2.40).
(16)	OR for MI: Aspirin+meloxicam, 0.70 (0.39, 1.25); meloxicam alone, 1.41 (1.03-1.92).

RR, risk ratio; OR, odds ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 5. Reports of concomitant rofecoxib/Aspirin use regarding CV risks.

Reference	Beneficial effect of Aspirin in reducing CV risks NOT diminished (RR/OR/HR (95% CI))
(12)	RR for MI: Aspirin+rofecoxib, RR 1.51 (0.92-2.47); Aspirin alone, 1.04 (0.96-1.12); rofecoxib alone, 1.47 (1.06-2.05).
(13)	RR for MI: no history of MI, Aspirin+rofecoxib, 1.12 (0.88-1.42); rofecoxib alone, 1.30 (1.08-1.57); previous MI, Aspirin+rofecoxib, 1.50 (1.07-2.09); rofecoxib alone, 1.75 (1.23-2.50).
(17)	HR for CV: Aspirin+rofecoxib, 1.10 (0.61-1.98); Aspirin alone 0.98 (0.94-1.03).

RR, risk ratio; OR, odds ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 6. Reports of concomitant celecoxib/Aspirin use regarding CV risks.

Beneficial effect of Aspirin in reducing CV risks NOT diminished		Beneficial effect of Aspirin in reducing CV risks diminished	
Reference	**(RR/OR/HR (95% CI))**	**Reference**	**(RR/OR/HR (95% CI))**
(12)	RR for MI: Aspirin+celecoxib, 1.13 (0.63-2.03); Aspirin alone, 1.04 (0.96-1.12); celecoxib alone, 1.44 (1.04-2.01).	**(17)**	HR for CV: Aspirin+celecoxib, 1.78 (1.30-2.44); Aspirin alone, 0.98 (0.94-1.03).
(13)	RR for MI: no history of MI, Aspirin+celecoxib, 0.88 (0.70-1.11); celecoxib alone, 1.11 (0.94-1.32); previous MI, 1.27 (0.94-1.71); celecoxib alone, 1.59 (1.17-2.18).		

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction

Table 7. Reports of concomitant diclofenac/Aspirin use regarding CV risks.

Beneficial effect of Aspirin in reducing CV risks NOT diminished		Beneficial effect of Aspirin in reducing CV risks diminished	
Reference	**(RR/OR/HR (95% CI))**	**Reference**	**(RR/OR/HR (95% CI))**
(19)	HR for MI: Aspirin+diclofenac: ever exposed, 0.99 (0.58-1.76), ≥ 30 days: 0.80 (0.54-1.20), ≥ 60 days, 1.00 (0.61-1.65) *vs* nonexposed subjects.	**(12)**	RR for CV: Aspirin+diclofenac, 1.41 (1.03-1.93); Aspirin alone, 1.03 (0.96-1.12); diclofenac alone, 1.79 (1.52-2.12).
(23)	OR for MI: Aspirin+diclofenac, 1.16 (0.82-1.65) *vs* Aspirin alone users.	**(17)**	HR for MI: Aspirin+diclofenac, 1.74 (1.44-2.08); Aspirin alone, 0.98 (0.94-1.03).

RR, risk ratio; OR, odds ratio; HR, hazard ratio; CV, Cardiovascular; MI, Myocardial Infarction

The observation that not all NANSAIDs interact with Aspirin at the clinical level despite the fact that with the exception of meloxicam, rofecoxib and diclofenac, they interact with Aspirin at the platelet level (Table 1) highlights the heterogeneity of NANSAIDs (10) that is often ignored. For, example, Arfè *et al.* (44) who studied the risk of heart failures causes by NANSAIDs in 4 European countries noticed that only approximately one-half of the drugs used were significantly cardiotoxic. Nevertheless, they calculated the current use of any NANSAIDs, toxic or not, and concluded that the use of any NANSAID was associated with 19% increased heart failure risk.

The heterogeneity of NANSAIDs is confirmed in a crossover study (30) in which patients received 81 mg of immediate-release Aspirin followed 2 h later by ibuprofen, rofecoxib, or diclofenac for 6 days. This was followed by a washout period of 14 days, after which the same 2 medications were administered in reverse order for another 6 days. The inhibition of COX-1 was assessed by measuring serum TxB_2 level, platelet aggregation induced in platelet-rich plasma and COX-2 activity by the measuring the formation of lipopolysaccharide-stimulated PGE2 in whole blood. They noticed no significant interaction between Aspirin and rofecoxib or diclofenac. However, ibuprofen significantly interacted with Aspirin given before or after the NANSAID. The Aspirin-ibuprofen interaction has been confirmed by others (26-28, 31-36).

Although we have not made a comparison between molecular interactions studies and clinical trials for all NSAIDs, it is timely to reemphasize that their interaction with Aspirin is heterogeneous in nature. For example, naproxen, celecoxib, piroxicam, indomethacin, mefenamic acid, tiaprofenic acid, nimesulide, oxaprozin, flufenamic acid and dipyrone do interact, while loxoprofen, diclofenac, rofecoxib, etoricoxib, lumiracoxib, etodolac, ketorolac, meloxicam, acetaminophen, flurbiprofen, sulindac, and sodium salicylate do not (Table 8).

It has been suggested that the Aspirin-NANSAIDs interaction is due to a competition to bind to the Arginine-120 residue of the COX-1 channel which may prevent the acetylation of the

serine-529 residue by Aspirin (37, 45). Nevertheless, the interference of NANSAIDs with the anti-platelet effect of Aspirin seems to have no long-term consequences as the CV protection of Aspirin remains unaffected by concomitant use of, at least, naproxen and ibuprofen. We put forward three plausible explanations for the disconnect between the results of the short-term platelet experiments and those of observational studies. (i) The interaction at the platelet level may be short-lived so that the effect dissipates shortly after its occurrence. (ii) There is no need for near complete inhibition of TxB2 inhibition to benefit from the cardioprotective properties of Aspirin so that despite a reduction in the extent of anti-platelet effect, the beneficial effect persists, or (iii) the CV effect of Aspirin may not be exclusively due to the drug's anti-platelet properties.

For all, except one eligible study, the CV risk was assessed after > 30 days exposure to the combination while typically, the effect of NANSAIDs on the anti-platelet activity of Aspirin is studied after short exposure times. Thus, the data on the therapeutic outcome of the short-term exposure to Aspirin-NANSAIDs are limited. However, the results published by Kimmel *et al.* (22) based on a case-control study that assessed the risk only one week before the date of onset of MI are useful in this context. They have reported that addition of NANSAIDs to Aspirin regiment does not increase the CV risk within one week post combination therapy. To this, one may add the fact that, to the best of our knowledge, there is no published report suggestive of a quick negative clinical CV outcome in individual patients who took NANSAIDs therapy while on Aspirin. Furthermore, data from a small size clinical trial, suggest that the effect of naproxen and diclofenac on the Aspirin-induced inhibition of platelet aggregation is short-lived (38). In a randomized placebo-controlled trial, Galliard-Grigioni *et al.* treated healthy subjects with 100 mg aspirin daily in combination with either three doses of either 1 g acetaminophen, 50 mg diclofenac, 250 mg naproxen or placebo, and assessed the platelet function. Initially, naproxen enhanced, and diclofenac reduced the anti-aggregatory action of Aspirin while acetaminophen had no effect. After 4 days of treatment, however, the platelet aggregation was equally inhibited by all Aspirin-NANSAID combinations.

In practice, a near complete inhibition of TxB2, thereby platelet aggregation is aimed to obtain cardioprotective effects of Aspirin (27). This is while the anti-platelet action of Aspirin is shown to be dose-dependent (46), i.e., low doses of the drug may not completely inhibit TxB2. Nevertheless, Aspirin has been shown to be cardioprotective after low doses (Table 9). This may suggest that to benefit from the CV properties of Aspirin, a complete inhibition of TxB2 is not needed. Thus, a reduced platelet aggregation activity of Aspirin resulted from combination therapies with NANSAIDs, unless proven through appropriately designed clinical trials, may have no significant clinical consequences.

In addition to its anti-platelet effect, Aspirin may reduce CV risks through other mechanisms. Both inflammation and some NANSAIDs appear to increase CV risks (10). Through animal studies, it has been shown that inflammatory conditions impair the balance of vasodilator/vasoconstrictor components of renin-angiotensin system (RAS) within the heart (47). The RAS is a major regulator of human physiology and has a key role in the CV homeostasis. Interestingly, NANSAIDs appear to be void of significant effects on RAS, instead, they are able to restore the imbalances that are resulted by inflammation (47). Alternatively, an altered protective/toxic balance of the cardioactive CYP450-mediated metabolites of arachidonic acid has been reported to be involved in the cardiotoxic effects of NANSAIDs (48). Whether Aspirin influences the RAS or the CYP450-mediated metabolites of arachidonic acid, remains unknown. Nevertheless, the possibility of CV protection by Aspirin through mechanisms other than its platelet effect is plausible.

The current analysis has limitations some of which are inherent to the nature of included studies. First, we have found that the published clinical evidence was sparse and has substantial limitations. To highlight this point, we were unable to assess the heterogeneity since some studies reported RR/OR while other did HR. Second, the primary outcomes of some studies that we included in our review were not CV (MI or stroke) risks as they reported the latter as secondary outcomes. Last, we were unable to perform meta-analysis as the same reference (Aspirin alone, NANSAID alone or nonusers) or outcome (OR, RR or HR) had not been used across the eligible studies.

CONCLUSION

Low-dose Aspirin is widely used to prevent MI and other CV diseases. However, there is evidence that concurrent use of some, but not all NANSAIDs, may

inhibit the anti-platelet effect of Aspirin. Naproxen, meloxicam and rofecoxib do not appear to influence the cardioprotective effect of Aspirin. Similarly, a large body of evidence supports that ibuprofen co-administration with Aspirin does not antagonize the anti-platelet effect of Aspirin. Altogether, it appears that the NANSAID-Aspirin interaction at the level of platelets does not necessarily amount to a loss of beneficial effects of Aspirin. The limited available data suggest that the effect of the drug-drug interactions on the platelet aggregation may dissipate shortly. In addition, it is plausible that the reduced platelet aggregation resulted by the interaction may be sufficient for cardioprotection; i.e., no need for near complete aggregation. In addition, the cardioprotective effect of Aspirin despite reduced platelet aggregation caused by NANSAIDs may be through its involvement in other mechanisms such as the RAS and/or metabolism of arachidonic acid to biologically active compounds mediated by CYP450.

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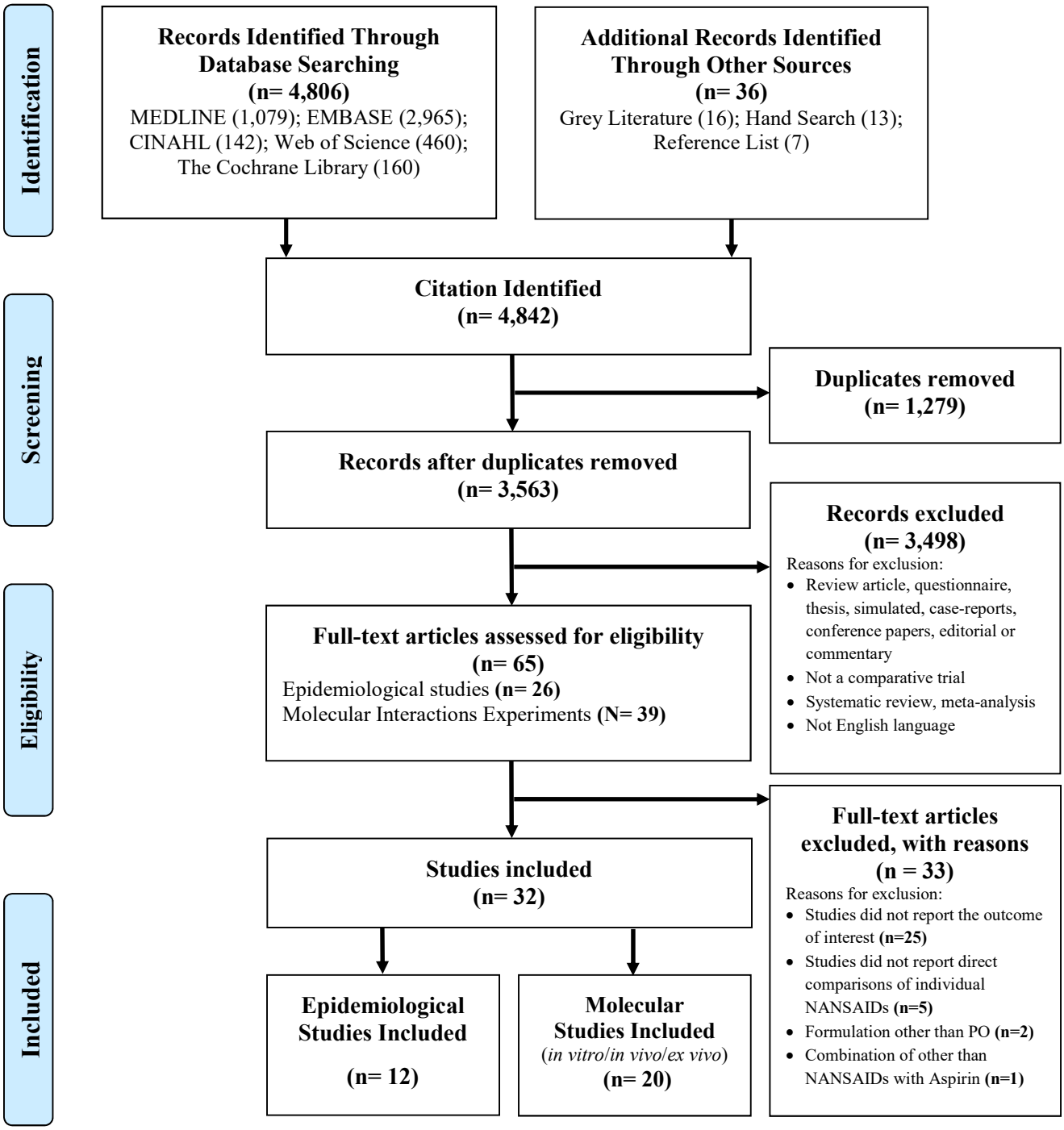

Figure 1. PRISMA (14) flow chart of study selection

Table 8. Main characteristics of the included molecular interactions studies that reported the influence of NANSAIDs on the anti-platelet action of Aspirin in human blood samples (*in vitro)*, healthy volunteers (*in vivo)* or isolated platelets (*ex vivo)* studies.

Reference	Year	Type of study (species)	Subjects	Treatments	Analyzed parameters	Conclusions
(28)	2017	*in vitro* (human)	Healthy volunteers (n = 6)	Aspirin only, ibuprofen (6 min after Aspirin) or loxoprofen (6 min after Aspirin) plus Aspirin groups were added to PRP.	Platelet aggregation by aggregometry and serum TxB_2 levels	Ibuprofen interferes with the anti-platelet effect of low-dose Aspirin; however, loxoprofen do not when given 6-12 h before Aspirin.
(26)	2013	*in vitro* (human)	Healthy volunteers (n = 6)	Aspirin, ibuprofen, loxoprofen, indomethacin, diclofenac, etodolac, mefenamic acid, naproxen, meloxicam, or flurbiprofen were added alone to PRP, then Aspirin was added before and after each NANSAID to PRP.	Platelet aggregation by aggregometry	Only ibuprofen and mefenamic acid significantly interfere with the anti-platelet effect of Aspirin when taken after.
(27)	2013	*in vitro* (human)	Healthy volunteers (n = 7)	Ibuprofen, naproxen, diclofenac, ketorolac, flufenamate, piroxicam, dipyrone, celecoxib, nimesulide, acetaminophen or oxaprozin were added alone or together with Aspirin to PRP.	Platelet aggregation (induced by AA), plasma TxB_2 concentrations by aggregometry	Celecoxib, dipyrone, ibuprofen, flufenamic acid, naproxen, nimesulide, oxaprozin, and piroxicam significantly interfere with the anti-platelet activity of Aspirin. While diclofenac, ketorolac and acetaminophen do not.
(37)	2005	*in vitro, in vivo* and *ex vivo* (human)	Healthy volunteers (aged 23-30 years, n = 4)	The volunteers received Aspirin (100 mg, once daily) for 6 days. Then they received either single or multiple doses of the combination of Aspirin 2 h before naproxen (500 mg, twice daily) for another 6 days. After a washout period of 14 days, the treatments were administered in reverse order.	Serum TxB_2, urinary 11 dehydro-TxB_2 excretion rates, platelet aggregation by aggregometry, LPS-stimulated PGE_2 production in whole blood	Naproxen interferes with the inhibitory effect of low-dose Aspirin on platelet aggregation.
(41)	2016	*in vivo* (human)	Healthy volunteers (aged 18-50 years)	Aspirin and celecoxib (alone or together) or control (saline) were added to the PRP.	Platelet aggregation (induced by AA) by aggregometry	Celecoxib interferes to a limited extent with the anti-platelet effect of low-dose Aspirin.

TABLE 8. Continued…

(34)	2014	*ex vivo* (human)	Healthy volunteers (*n* = 5)	Platelets were pre-incubated with ibuprofen, naproxen, or celecoxib for 10 min. then Aspirin was added to each group.	COX-1 acetylation, TxB_2 formation	A single therapeutic dose of ibuprofen or naproxen followed by Aspirin casue a potent drug-drug interaction, but not between celecoxib and Aspirin.
(34)	2014	*in vivo* (human)	Healthy volunteers (*n* = 7)	Subjects received a single dose of ibuprofen (600 mg), naproxen (500 mg), or celecoxib (200 mg), then a single dose of Aspirin (325 mg) was given 2 h after the NANSAID.	COX-1 acetylation, platelet aggregation (induced by AA), platelet TxB_2, urinary 11-dehydro TxB_2	
(36)	2013	*ex vivo* (human)	Healthy volunteers (*n* = 30)	The Volunteers were randomly allocated in two groups. First group received two daily doses of naproxen (500 mg), ibuprofen (600 mg) or placebo. Second group received one daily dose of meloxicam (15 mg), etoricoxib (90 mg) or placebo. Both groups received Aspirin (80 mg) 2 h after 2nd or 3rd dose of study medication.	*ex vivo* thrombocyte function, CT (seconds) was measured using the PFA-100 CT	Ibuprofen and naproxen interfere with anti-platelet effect of Aspirin, but etoricoxib and meloxicam do not.
(39)	2011	*in vivo* and *ex vivo* (human)	Healthy volunteers (aged 23-37 years, *n* = 9)	Subjects received either a combination of Aspirin (100 mg) 2 h before or after naproxen (220 mg, twice a day), or Aspirin alone for 6 days separated by 14 days of washout.	Serum TxB_2 and platelet aggregation (induced by AA and collagen)	Naproxen interferes with the anti-platelet activity of Aspirin. The interaction was similar when naproxen giving 2 h before or after low-dose of Aspirin.
(31)	2009	*in vivo* (human)	Healthy volunteers (aged 26-58 years, *n* = 12)	The volunteers were randomly assigned to either Aspirin (30 mg, once daily) for 7 days, slow release diclofenac (50 mg, three times daily) or ibuprofen (800 mg, three times daily) for 1 day. Aspirin (80 mg, once daily) was given after a washout period of 14-42 days with each treatment group for 7 days.	Serum TxB_2 levels	Only ibuprofen interferes with the anti-platelet activity of Aspirin.

TABLE 8. Continued…

(38)	2009	*ex vivo* (human)	Healthy volunteers (aged 21-58 years, *n* = 11)	The volunteers received during 4 different study periods (≥10 days washout period) either acetaminophen (1 g, three times daily), diclofenac (50 mg, three times daily), naproxen (250 mg, three times daily) or placebo plus Aspirin (100 mg, once daily) for 4 days.	PFA-100 CT	Regular daily co-administration of acetaminophen, diclofenac or naproxen do not interfere with the anti-platelet activity of Aspirin.
(35)	2008	*ex vivo* (human)	Healthy volunteers (*n* = 24)	The volunteers received randomly either naproxen (550 mg), ibuprofen (400 mg), celecoxib (200 mg), indomethacin (25 mg), tiaprofenic acid SR (300 mg) or sulindac (200 mg), Aspirin (300 mg) or placebo for 2 days.	PFA-100 CT	Ibuprofen, indomethacin, naproxen, and tiaprofenic acid interfere with the anti-platelet activity of Aspirin but not sulindac or celecoxib.
(33)	2008	*in vivo* (human)	Healthy volunteers (aged 21-32 years, *n* = 10)	The volunteers were randomly assigned to receive either ibuprofen (400 mg), Aspirin (325 mg) or ibuprofen (400 mg) plus one dose of Aspirin (325 mg, 2 h later). A minimum of 6 days washout period was allowed between treatments.	Platelet aggregation by aggregometry	Administration of ibuprofen before Aspirin interferes with the inhibitory effect of Aspirin on platelet aggregation.
(32)	2006	*in vivo* and *ex vivo* (human)	Osteoarthritis and stable ischaemic heart disease patients (aged 45-73 years, *n* = 29)	The patients were undergoing long term treatment with Aspirin (100 mg, daily), and received celecoxib (200 mg, twice daily), ibuprofen (600 mg, three times daily) or placebo for 7 days.	Serum TxB_2, urinary 11 dehydro-TxB_2 excretion rates, platelet aggregation by aggregometry, LPS-stimulated PGE_2 production in whole blood	Ibuprofen interferes with anti-platelet effect of Aspirin but not celecoxib.
(49)	2005	*ex vivo* (human)	Healthy volunteers (aged 18-45 years, *n* = 28)	The volunteers were randomly assigned to receive either lumiracoxib (400 mg, once daily) or placebo for 11 days. Both treatment groups received Aspirin (75mg, once daily) from day 5 to 11 (6 days).	Platelet aggregation (induced by AA and collagen), Serum TxB_2 levels, urinary TxB_2 and prostacyclin excretion rate	Lumiracoxib does not interfere with anti-platelet effect of low-dose Aspirin.
(29)	2005	*in vivo* (human)	Healthy volunteers (aged 19-54 years, 58-100 kg, *n* = 47)	The volunteers received Aspirin (81 mg, once daily) for 8 days. On day 9, subjects received either ibuprofen (400 mg, three times daily) or placebo (three times daily) for 10 days.	Serum TxB_2 levels	No clinically meaningful loss of cardioprotection was found in healthy volunteers who received OTC doses of ibuprofen with low-dose Aspirin.

TABLE 8. Continued…

(43)	2004	*in vivo* (human)	Healthy volunteers (aged 20-47 years, 55-87 kg, *n* = 16)	The volunteers received meloxicam (15 mg, once daily) alone for 4 days, then Aspirin (100 mg, once daily 2 h later) was added for another 6 days. After a washout period of 14 days, subjects received only Aspirin (100 mg, once daily) for 2 days.	Platelet aggregation by aggregometry, serum TxB_2	Meloxicam does not interfere with the inhibitory effect of low-dose Aspirin on platelet aggregation.
(40)	2002	*in vivo* (human)	Healthy volunteers (aged 18-48 years, 48.7-86 kg, *n* = 17)	The volunteers received celecoxib (200 mg, twice daily) or placebo for 4 days. On day 5, all volunteers received Aspirin (325 mg) with either celecoxib (20 mg) or placebo.	Serum TxB_2 levels, platelet aggregation (induced by ADP, AA and collagen)	Celecoxib does not interfere with anti-platelet effect of Aspirin.
(30)	2001	*ex vivo* (human)	Healthy volunteers (aged 18-65 years, *n* = 12)	The volunteers received Aspirin (81 mg) 2 h before single dose of either ibuprofen (400 mg), acetaminophen (1000 mg), or rofecoxib (25 mg) for 6 days. After a washout period of 14 days, the same medications were given in the reverse order for 6 days.	Serum TxB_2, platelet aggregation (induced by AA in PRP), LPS-stimulated PGE_2 production in whole blood, prostaglandin I_2	Only ibuprofen interferes with anti-platelet effect of Aspirin.
(30)	2001	*ex vivo* (human)	Healthy volunteers (aged 18-65 years, *n* = 10)	The volunteers received Aspirin (81 mg) 2 h before single dose of either ibuprofen (400 mg, three times daily) or delayed-release diclofenac (75 mg, twice daily) for 6 days.	Serum TxB_2, platelet aggregation by aggregometry	
(42)	2000	*ex vivo* (human)	Healthy volunteers (aged 18-38 years, 45.2-103.7 kg, *n* = 24)	The volunteers received either rofecoxib (50 mg, once daily) or placebo for 10 days and Aspirin (81 mg, once daily) for 7 days (days 4-10).	Serum TxB_2, platelet aggregation by aggregometry	Rofecoxib does not interfere with the inhibitory effect of low-dose Aspirin on platelet aggregation.
(50)	1984	*in vivo* (human)	Healthy volunteers (aged 22-32 years, *n* = 6)	The volunteers received sodium salicylate (1500 mg) and,1 h later, Aspirin (500 mg). After 2 weeks, subjects received only Aspirin (500 mg).	Serum TxB_2 concentrations	Sodium salicylate does not interfere with the inhibitory effect of Aspirin.

PRP, Platelet Rich Plasma; AA, arachidonic acid; TxB_2, thromboxane B_2; PFA, platelet function analyzer; PGE_2, prostaglandin E_2; LPS, lipopolysaccharide; COX-1, cyclooxygenase-1; h, hours; CT, closure time; OTC, over the counter; ADP, adenosine 5'-diphosphate.

Table 9. Main characteristics of the included epidemiological studies.

Reference	Year	Country	Type of study	Participants (events, *n*)	Duration	F%, age (yr), history of CV/stroke events, Aspirin use, NANSAIDs use	Comparison, *n*	Outcomes	Quality Assessment (NOS)
(17)	2015	Denmark	Cohort	61,971 patients (CV, 18,568)	3.5 yr	36.8%, 67.7 (SD, 13.6) yr, 4.9%, 18.0%, rofecoxib 0.8%, celecoxib 1.2%, diclofenac 9.9%, ibuprofen 23.1%, naproxen 1.7%, other 6.6%	Overall NANSAID use, 9,194	**Primary**: Admission or death of GI bleeding **Secondary**: CV death, nonfatal recurrent MI, and ischemic stroke, transient ischemic attack, or systemic arterial emboli	Selection: 4 stars; comparability: 2 stars; exposure: 2 stars
(18)	2008	UK	Cohort	729,294 NSAID users: 443,047 controls (MI, 5,690)	6.1:5.6 yr	54.1%, 58.0 yr: 58.2 yr, 7.4%/3.1%: 6.9%/3.4%, 76.2%, ibuprofen 31.1%, diclofenac 39.6%, naproxen 9.1%, meloxicam 3.8%, indomethacin 3.6%, piroxicam 2.0%, mefenamic acid 1.9%	Control cohort (matched by disease risk score), 443,047	MI	Selection: 4 stars; comparability: 2 stars; exposure: 2 stars
(19)	2005	Canada	Cohort	18,503 patients (AMI, 535)	239.7 days	42.3%:45.1%, 74 yr, 23.0%/6.5%: 18.9%/5.6%, NA, ibuprofen 9.1%, naproxen 30.4%, diclofenac 36.1%	Unexposed, 14,424	AMI	Selection: 4 stars; Comparability: 2 stars; Exposure: 3 stars
(24)	2003	UK	Cohort	7,107 patients (mortality, 3,813)	3.3 yr	NA, 27-100 yr, 50.5%/23.8%, 100%, ibuprofen 187, diclofenac 206, other 429	Unexposed, 6,285	All-cause mortality or CV mortality	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars

TABLE 9. Continued…

(25)	2003	USA	Cohort	70,316 patients (mortality, 12,096)	3 yr	48.3%, 75 yr (53.9%), 30.5%/13.2%, 96.1% (66,739), ibuprofen 844, other 2,733	Unexposed, 66,739	Mortality within 1 year after discharge	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
(16)	2017	UK	Case-control	9,291 cases: 30,676 controls (MI, 9,291)	13 yr	41.7%: 43.1%, 67.4 yr (±11.9): 66.3 yr (±11.6), 24.7%: 9.9%, 34.6%: 21.0%, diclofenac 1,020:2,846, meloxicam 248:655, naproxen 277: 886, other 1,246:3,843	Remote users (no exposure > 60 days prior index date but within 1 year), 4,184:15,488	MI	Selection: 3 stars; comparability: 2 stars; exposure: 2 stars
(12)	2008	UK	Case-control	8,852 cases: 20,000 controls (MI, 8,852)	4.1 yr	NA, 50-84 yr, NA, NA, celecoxib 81:144, diclofenac 353:483, ibuprofen 143:314, indomethacin 29:45, meloxicam 59:99, naproxen 54:119, refecoxib 98:139	Control cohort (matched by sex, age within 1 year, and calendar year), 20,000	MI	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
(13)	2007	Canada	Case-control	3,423 cases: 68,456 controls (MI, 3,423)	2.3 yr	52.1%:67.1%, 78.2 yr (5.4), 16.9%/2.0%: 6.2%/0.9%, 35.7%:21.8%, 71.4%	Control cohort (matched by sex, age within 1 year, and calendar year), 68,456	Nonfatal or fatal MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 3 stars
(20)	2005	UK	Case-control	8,688 cases: 33,923 controls (MI, 8,688)	7 yr	37.1%:37.2%, <50 yr 7.6%:7.7%, 50-69 yr 42.4%:42.8%, 70-89 yr 50.0%: 49.5%, 30.1%: 12.1%, NA. diclofenac 260:834, ibuprofen 176:656, naproxen 63:251, indomethacin 36:124, piroxicam 30:114, ketoprofen 18:109, fenbufen 16:19, nab-umetone 10:56, mefenamic acid 9:26, etodolac 8:43, flur-biprofen 6:34, tiaprofenic acid 6:26	Unexposed, 3,203: 13,551	The first MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars

TABLE 9. Continued…

(21)	2004	USA	Case-control	3,859 cases: 10,239 controls (MI, 3,859)	52,139 patients-months: 156,417 patients-months	97.5 % (±2.5): 97.6% (±0.15) male, NA, NA, 100%, ibuprofen 3,859	Control cohort (sex, race, age, and LDL cholesterol level), 10,239	MI	Selection: 4 stars; Comparability: 1 stars; Exposure: 1 stars
(22)	2004	USA	Case-control	1,055 cases: 4,153 controls (MI, 1,055)	1067 days	44.5%/34.4%:66.6%/54.7%, 57.01 (±9.12)/58.07 (±9.24): 51.14 (8.64)/53.16 (±9.46) yr, 15.0%/18.8%: 4.0%/3.7%, 27%, 30% (78% non-prescription NANSAID)	Control (no history of MI), 1,357:2,796	MI	Selection: 4 stars; Comparability: 2 stars; Exposure: 2 stars
(23)	2004	UK	Case-control	4,975 cases: 20,000 controls (MI, 4,975)	2 yr, 4 months	35%, 55% >70 yr, 38%/14%: 17%/8%, 27%:14%, 61%:59%	Control cohort (sex, age, and calendrer year), 20,000	MI	Selection: 3 stars; Comparability: 2 stars; Exposure: 2 stars

CV, cardiovascular; GI, gastrointestinal; MI, acute myocardial infarction; LDL, low-density lipoprotein; NA, not available; NOS, Newcastle-Ottawa quality scale.

SUPPLIMENTARIES

Appendix 1: List of search terms and key words used

MEDLINE

1. acetylsalicylic acid.mp. or exp Aspirin/ (47960)
2. Aspirin.mp. or exp Aspirin/ (65534)
3. ASA.mp. (24069)
4. 1 or 2 or 3 (87880)
5. exp Anti-Inflammatory Agents/ or exp Anti-Inflammatory Agents, Non-Steroidal/ or NSAID*.mp. or exp Cyclooxygenase Inhibitors/ (500344)
6. nonsteroidal antiinflammatory.mp. (4610)
7. nonsteroidal anti-inflammatory.mp. (15647)
8. non-steroidal antiinflammatory.mp. (913)
9. non-steroidal anti-inflammatory.mp. (15062)
10. (Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (90791)
11. (cyclooxygenase* or cyclo-oxygenase* or COX*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (196883)
12. 5 or 6 or 7 or 8 or 9 or 10 or 11 (683969)
13. cardiovascular.mp. (517392)
14. myocardial infarction.mp. or exp Myocardial Infarction/ (241926)
15. exp Stroke/ or stroke*.mp. or exp Cerebrovascular Disorders/ (481036)
16. (cardioprotect* or cardio-protect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (19351)
17. 13 or 14 or 15 or 16 (1140235)
18. exp Platelet Aggregation/ or platelet*.mp. (262607)
19. blood platelets.mp. or exp Blood Platelets/ (78062)
20. exp Platelet Aggregation Inhibitors/ or exp Platelet Aggregation/ or platelet aggregation inhibit*.mp. or exp Blood Platelets/ (186906)
21. anti platelet effect*.mp. (264)
22. 18 or 19 or 20 or 21 (324684)
23. 17 or 22 (1419931)
24. Interaction.mp. (724108)
25. Drug interaction.mp. or exp Drug Interactions/ (164791)
26. Interact*.mp. (1503338)
27. 24 or 25 or 26 (1563966)
28. 4 and 12 and 23 and 27 (3728)
29. ((NSAID* or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15311)
30. ((cyclooxygenase* or cyclo-oxygenase* or COX*) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (36297)
31. ((aspirin or ASA or acetylsalicylic acid) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4517)
32. 29 or 30 or 31 (45379)
33. 28 and 32 (1161)
34. remove duplicates from 33 (1079)

EMBASE

1. acetylsalicylic acid.mp. or exp acetylsalicylic acid/ (194594)
2. Aspirin.mp. or exp acetylsalicylic acid/ (200287)
3. ASA.mp. or exp acetylsalicylic acid/ (225835)
4. 1 or 2 or 3 (235264)
5. exp nonsteroid antiinflammatory agent/ or NSAID*.mp. (537163)
6. nonsteroidal antiinflammatory.mp. (5560)
7. exp antiinflammatory agent/ or nonsteroidal anti-inflammatory.mp. (1643638)
8. non-steroidal antiinflammatory.mp. (1926)
9. non-steroidal anti-inflammatory.mp. (19822)
10. mefenamic acid.mp. or exp mefenamic acid/ (5640)
11. meclofenamic acid.mp. or exp meclofenamic acid/ (2834)
12. (ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (166401)
13. (cyclooxygenase* or cyclo-oxygenase* or COX*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (284223)
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1876062)
15. cardiovascular.mp. (874842)
16. myocardial infarction.mp. or exp heart infarction/ (378320)
17. stroke*.mp. (370234)
18. Cerebrovascular.mp. or exp cerebrovascular disease/ (556732)
19. (cardioprotect* or cardio-protect).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (25495)
20. 15 or 16 or 17 or 18 or 19 (1726649)
21. platelet*.mp. (291091)
22. blood platelets.mp. or exp thrombocyte/ (104209)
23. Platelet Aggregation Inhibitors.mp. or exp antithrombocytic agent/ (314999)
24. Platelet Aggregation.mp. or exp thrombocyte aggregation/ (61352)
25. platelet aggregation inhibit*.mp. (2390)
26. anti platelet effect*.mp. (421)
27. 21 or 22 or 23 or 24 or 25 or 26 (586844)
28. 20 or 27 (2171471)
29. exp drug interaction/ or Interaction.mp. (1524352)
30. Interact*.mp. (1914430)
31. 29 or 30 (2067908)
32. 4 and 14 and 28 and 31 (17752)
33. ((NSAID* or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (17171)
34. ((cyclooxygenase* or cyclo-oxygenase* or COX*) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (43788)
35. ((aspirin or ASA or acetylsalicylic acid) adj3 (interact* or inhibit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (5681) 33 or 34 or 35 (55160)
36. 32 and 36 (3017)
37. remove duplicates from 37 (2965)

CINAHL

EBSCOhost

Wednesday, November 01, 2017 4:53:55 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S5	(Interaction OR Drug interaction OR Interact*) AND (S1 AND S2 AND S3 AND S4)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	142
S4	Interaction OR Drug interaction OR Interact*	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	117,174
S3	cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelets	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	256,163
S2	NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR (Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib) OR (cyclooxygenase* OR cyclo-oxygenase* OR COX*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	66,609
S1	acetylsalicylic acid OR aspirin OR ASA	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus with Full Text	15,169

Web of Science

Set	Results	Save History / Create Alert · Open Saved History	Edit Sets	Combine Sets (AND OR) Combine	Delete Sets Select All · Delete
# 5	460	#4 AND #3 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 4	2,772,324	**TOPIC:** (Interaction) *OR* **TOPIC:** (Drug interaction) *OR* **TOPIC:** (Interact*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 3	1,135,107	**TOPIC:** (cardiovascular) *OR* **TOPIC:** (myocardial infarction) *OR* **TOPIC:** (stroke*) *OR* **TOPIC:** (cerebrovascular) *OR* **TOPIC:** (cardioprotect*) *OR* **TOPIC:** (cardio-protect*) *OR* **TOPIC:** (platelet*) *OR* **TOPIC:** (platelet aggregation) *OR* **TOPIC:** (platelet aggregation inhibit*) *OR* **TOPIC:** (antiplatelet effect*) *AND* **TOPIC:** (blood platelets) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 2	283,167	**TOPIC:** (NSAID*) *OR* **TOPIC:** (nonsteroidal antiinflammatory) *OR* **TOPIC:** (nonsteroidal anti-inflammatory) *OR* **TOPIC:** (non-steroidal antiinflammatory) *OR* **TOPIC:** (non-steroidal anti-inflammatory) *OR* **TOPIC:** (Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib) *OR* **TOPIC:** (cyclooxygenase* OR cyclo-oxygenase* OR COX*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
# 1	79,382	**TOPIC:** (acetylsalicylic acid) *OR* **TOPIC:** (Aspirin) *OR* **TOPIC:** (ASA) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
				AND OR Combine	Select All · Delete

EBM Reviews search (via Wiley)

Search Name: acetylsalicylic acid or Aspirin or ASA in Title, Abstract, Keywords and NSAID* or nonsteroidal antiinflammatory or nonsteroidal anti-inflammatory or non-steroidal antiinflammatory or non-steroidal anti-inflammatory or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib or cyclooxygenase* or cyclo-oxygenase* or COX* and cardiovascular or myocardial infarction or stroke* or cerebrovascular or cardioprotect* or cardio-protect* or platelet* or platelet aggregation or platelet aggregation inhibit* or antiplatelet effect* or blood platelets and Interaction or Drug interaction or Interact* (Word variations have been searched)

Last Saved: 01/11/2017 22:00:04.558

ID Search

#1 acetylsalicylic acid or Aspirin or ASA:ti,ab,kw and NSAID* or nonsteroidal antiinflammatory or nonsteroidal anti-inflammatory or non-steroidal antiinflammatory or non-steroidal anti-inflammatory or Ibuprofen or naproxen or ketoprofen or flurbiprofen or fenoprofen or oxaprozin or etoldolac or tolmetin or diclofenac or ketorolac or nabumetone or indomethacin or sulindac or piroxicam or meloxicam or mefenamic acid or meclofenamic acid or rofecoxib or celecoxib or veldecoxib or paracoxib or etoricoxib or lumaricoxib or cyclooxygenase* or cyclo-oxygenase* or COX* and cardiovascular or myocardial infarction or stroke* or cerebrovascular or cardioprotect* or cardio-protect* or platelet* or platelet aggregation or platelet aggregation inhibit* or antiplatelet effect* or blood platelets and Interaction or Drug interaction or Interact* (Word variations have been searched)

Results: 160

1. Cochrane Database of Systematic Reviews (25)
2. Database of Abstracts of Reviews of Effect (1)
3. Cochrane Central Register of Controlled Trials (134)
4. Cochrane Methodology Register (0)
5. Health Technology Assessment Database (0)
6. NHS Economic Evaluation Database (0)
7. About the Cochrane Collaboration (0)

PubMed (March 15, 2018)

This searched aimed to screen for any relevant studies published after October 2017. We, therefore, carried out PubMed search using the following keywords “NSAID AND Aspirin” and restricted to publication date from 2017/11/01 to 2018/03/15. We found 88 studies, and none met the inclusion criteria of this review. On May 1, 2018 another search was carried out that resulted in no eligible study.

Grey Literature Search					
Database/ Website Name	**URL or Path**	**Date searched**	**Search terms used**	**# of Relevant Documents**	**Comments**
Cochrane Central Register of Controlled Trials (CENTRAL)	http://onlinelibrary.wiley.com /cochranelibrary/search	01-Nov-17	acetylsalicylic acid OR Aspirin OR ASA in Title, Abstract, Keywords and NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX* and cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelets and Interaction OR Drug interaction OR Interact*	**134**	We added this to the Cochrane library search results as the CENTRAL is one database included in Cochrane library
ProQuest Dissertations & Theses Global	https://search-proquest-com.login. ezproxy.library.ualberta.ca/ pqdtglobal/results/ D2EEE14FBB414B59PQ/ 1?accountid=14474	02-Nov-17	all(acetylsalicylic acid OR Aspirin OR ASA) AND all(NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX*) AND all(cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelet) AND all(Interaction OR Drug interaction OR Interact*)	**16**	We added all 16 to the additional records identified through other sources
Health Canada's Clinical Trials Database	https://health-products.canada.ca/ ctdb-bdec/search-recherche.do; jsessionid=1D954BB5AFD48D4326 64B0D0818697F4	02-Nov-17	**Medical Condition**: cardiovascular OR cerebrovascular **Drug Name**: acetylsalicylic acid OR Aspirin AND NSAID	**0**	

PROSPERO International prospective register of systematic reviews	https://www.crd.york.ac.uk/PROSPERO/#searchadvanced	06-Nov-17	acetylsalicylic acid OR Aspirin OR ASA AND NSAID* OR nonsteroidal antiinflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR non-steroidal anti-inflammatory OR Ibuprofen OR naproxen OR ketoprofen OR flurbiprofen OR fenoprofen OR oxaprozin OR etoldolac OR tolmetin OR diclofenac OR ketorolac OR nabumetone OR indomethacin OR sulindac OR piroxicam OR meloxicam OR mefenamic acid OR meclofenamic acid OR rofecoxib OR celecoxib OR veldecoxib OR paracoxib OR etoricoxib OR lumaricoxib OR cyclooxygenase* OR cyclo-oxygenase* OR COX* AND cardiovascular OR myocardial infarction OR stroke* OR cerebrovascular OR cardioprotect* OR cardio-protect* OR platelet* OR platelet aggregation OR platelet aggregation inhibit* OR antiplatelet effect* OR blood platelet AND Interaction OR Drug interaction OR Interact*	**2**	Both records were not relevant

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**1-2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**1-2**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**2**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**2**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**3**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**2-3**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**25-30**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**3-4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**3**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**3**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**4**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**3**

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**NA**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**4**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**NA**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**4-5**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**18-24**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**22-24**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**5-9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**NA**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**22-24**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16).	**NA**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**5-9**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**12**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**12-13**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**13**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097