Original Article

Comparison of cardiorenal safety of nonsteroidal anti-inflammatory drugs in the treatment of arthritis: a network meta-analysis

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Background: Arthritis includes osteoarthritis (OA), rheumatoid arthritis (RA), and other arthritis-related disorders. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used drugs for the treatment of arthritis. However, there remains a concern that some currently used NSAIDs may increase the risk of cardiorenal adverse events in patients with arthritis. Although it has been established that some NSAIDs are associated with a higher risk of cardiovascular and renal events, their safety varies widely. To provide insight into drug use, this study systematically assessed and compared the incidence of cardiovascular and renal events in different NSAIDs by using Bayesian meta-analysis.

Methods: The PubMed, Cochrane Library, and Embase databases were searched for randomized controlled trials (RCTs) on NSAIDs. Databases were searched from the inception to April 25, 2022. Two investigators independently screened articles according to the Population, Intervention, Comparator, Outcomes, Study design (PICOS) principle, extracted data, and assessed the quality of articles using Cochrane Risk of Bias assessing tools. R software (version 4.1.3) was used for network meta-analysis (NMA).

Results: The analysis ultimately included 20 articles with a total of 144,957 patients and 13 interventions. The risk of bias in the included articles was generally moderate. Ibuprofen was associated with the highest incidence of hypertension outcomes [comparing with placebo OR (95% CI): 3.24 (1.71, 5.82)], rofecoxib with the highest incidence of renal events [comparing with placebo OR (95% CI): 4.46 (1.49, 14.73)], ibuprofen with the highest incidence of cardiovascular events [comparing with placebo OR (95% CI): 2.39 (0.82, 8.06), and naproxen with the highest incidence of edema [comparing with placebo OR (95% CI): 2.31 (1.16, 4.47)].

Conclusions: The NMA results showed that amtolmetin guacil was relatively safer, but it needs further investigation. Rofecoxib was associated with a higher incidence of cardiorenal adverse events, ibuprofen with a higher incidence of cardiovascular events and hypertension, and naproxen with a higher incidence of renal events and edema. Clinicians should weigh the efficacy of NSAIDs against renal and cardiovascular toxicity when prescribing NSAIDs for the treatment of arthritis.

Keywords: Arthritis; anti-inflammatory agents; nonsteroidal; network meta-analysis (NMA); cardiorenal safety

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Introduction

Arthritis is a common chronic joint disease that includes various types of joint disorders, such as osteoarthritis (OA) and rheumatoid arthritis (RA), and is characterized by intermittent pain. However, the pain becomes unrelenting as the disease course extends and the severity intensifies. Moreover, arthritis is more common among women and older adults (1).

Pain in arthritis patients is a multifactorial phenomenon. Different drugs are used for pain management (2). Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely adopted prescriptions for the treatment of arthritis. They have consistently shown good efficacy in relieving pain and improving function (3). In the United States alone, health care workers prescribe more than 100 million NSAIDs annually, and 50% of patients with arthritis need some type of analgesic treatment every day (4).

Nevertheless, some adverse events in recent years have raised concerns about the safety of NSAIDs (5), especially regarding their adverse effects on the heart or blood vessels, and the kidney (6,7). Some studies have also explored the potential causes of major adverse cardiac events and renal adverse events caused by the use of NSAIDs. NSAIDs mainly target cyclooxygenase (COX), which converts arachidonic acid into prostaglandins (PGs) (8,9). PGs mediate inflammation and pain. There are two isoforms of COX: COX-1 and COX-2 (10,11).

Highlight box

Key findings

- Ibuprofen was associated with the highest incidence of hypertension outcomes, rofecoxib with the highest incidence of renal events, ibuprofen with the highest incidence of cardiovascular events, and naproxen with the highest incidence of edema.

What is known and what is new?

- Some currently-in-use NSAIDs may increase the risk of cardiac and renal adverse events in arthritis patients.
- Amtolmetin guacil is associated with a low incidence of adverse renal events, hypertension, and edema. Celecoxib is not the safest drug for patients with arthritis, given the risk of adverse events, but it is safer than rofecoxib, naproxen, ibuprofen, and etoricoxib.

What is the implication, and what should change now?

- Amtolmetin guacil is a new NSAID associated with a low incidence of cardiorenal adverse events. However, there is little research in this area. Therefore, further investigation targeted toward amtolmetin guacil may benefit patients with arthritis.

Both COX-1 and COX-2 are expressed in human kidneys. COX-derived PGs play a key role in maintaining renal blood flow and glomerular filtration (12). The activation of COX-2 may impact the pathogenesis and progression of kidney disease (13). NSAIDs may cause renal adverse outcomes (14), such as the reduction of glomerular filtration rate (GFR), constriction of renal blood flow, and excretion of sodium and potassium. They can also lead to fluid retention, edema, hypertension, and hyperkalemia, and in extreme cases, can cause renal failure and tubulointerstitial nephritis (10,15).

Thromboxane A2 (TXA2) and prostacyclin (PGI2) are critical for maintaining intravascular balance. COX-2's selective inhibition reduces the production of vasodilatory prostacyclin, whereas the thromboxane produced by COX-1 is not affected. The imbalance between thrombogenic and antithrombotic factors may explain the cardiovascular risk caused by NSAIDs (7,16). Study has shown that COX-2 is induced in vascular endothelial cells under normal physiological conditions and is the dominant source of PGI2. NSAID management can reduce the production of systemic PGI2 but does not affect the synthesis of platelet-derived TXA2 (17). Animal study has found that suppression of PGI2 does not cause spontaneous thrombosis, but may enhance the response to thrombosis irritants. Therefore, patients with a higher cardiovascular risk theoretically may be more prone to cardiovascular events when treated with NSAIDs (7).

However, most of the current studies are traditional head-to-head meta-analyses and few articles in network meta-analysis have systematically evaluated the cardiorenal risk of NSAIDs in the treatment of arthritis. Which of the various NSAIDs on the market can provide better efficacy with fewer cardiac and renal side effects for patients with arthritis remains an urgent question in need of answering. Network meta-analysis (NMA) is a technique used for weighting and pooling data based on meta-analysis and combining direct and indirect comparisons. This technique quantifies the effectiveness of different interventions and ranks them based on a certain outcome, which can help inform decisions on regimen selection. The present study used NMA to compare the incidence of cardiac and renal events caused by 12 different NSAIDs in order to improve the evidence base in clinical medication administration. We present the following article in accordance with the PRISMA-NMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6181/rc) (18).

Methods

This study has been registered on PROSPERO (The International Prospective Register of Systematic Reviews; No. CRD42022328467).

Literature search strategy

We searched the PubMed, Cochrane Library, and Embase databases for randomized controlled trials (RCTs) on NSAIDs in the treatment of arthritis. Databases were searched from the inception of each database to Sept 25, 2022. We searched the following key terms: anti-inflammatory agents, non-steroidal, arthritis, cardiovascular, and renal. The search process, with the search in PubMed as an example, is presented in Table S1.

Literature screening and data extraction

Two investigators independently (KW and XL) screened the literature and extracted data, and a cross-check was conducted. Disagreements were addressed by a discussion with a third investigator (Min Wan), and a consensus was reached by discussion. The eligibility criteria of Population, Intervention, Comparator, Outcomes, Study design (PICOS) are listed below.

Population

Patients were included who were over 18 years old and were diagnosed with arthritis by laboratory tests, diagnostic imaging, and detection of clinical signs and symptoms; arthritis types could include OA, RA, gouty arthritis, and other arthritis disorders. Patients who were part of an ineligible target population were excluded.

Intervention

Interventions were required to involve any of following oral NSAIDs: diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, rofecoxib, nabumetone, amtolmetin guacil, valdecoxib, paracetamol, lornoxicam, loxoprofen, and meloxicam.

Comparator

Studies need to include a control group that was treated with either placebo or one of the above-mentioned NSAIDs.

Outcomes

Reporting of the incidence of adverse cardiovascular and renal events, edema, and hypertension was required. Cardiovascular events could include palpitations, atrial fibrillation, arrhythmias, angina pectoris, heart failure, myocardial infarction, coronary artery disease, and death caused by the above causes. Renal events could include renal failure and kidney stones, as well as the elevation of serum creatinine, urea nitrogen, serum uric acid, proteinuria, and serum potassium. Edema is generally confirmed by visual inspection. Finally, A 5 mmHg increase above the baseline value or the aggravation of hypertension was considered to be an adverse event of hypertension.

Study design

The included literatures were required to be RCTs.

Risk of bias assessment

The risk of bias in included articles was independently assessed by 2 investigators (KW and XL), and a cross-check was conducted. The tool for evaluating the risk of bias of RCTs recommended by the Cochrane manual was used to assess the included studies. The risk of bias assessment of RCTs was conducted using Risk of Bias assessing tool (ROB 1.0) in Review Manager (version 5.4.1, Cochrane). The following criteria were considered: (I) random sequence generation (selection bias); (II) allocation concealment (selection bias); (III) blinding of participants and personnel (performance bias); (IV) blinding of outcome assessment (detection bias); (V) incomplete outcome data (attrition bias); (VI) selective reporting (reporting bias); and (VII) other bias. After our final evaluation, if the included study is of high risk, we will exclude it and then conduct mesh meta-analysis and sensitivity analysis to determine the impact of this study on our results.

Statistical analysis

R (version 4.1.3, The R Foundation for Statistical Computing) meta package (version 1.0) was used to conduct the NMA, and a narrative synthesis of the findings of the included studies was performed. First, the chi-squared test was performed to analyze the heterogeneity. If no apparent heterogeneity among the studies ($P>0.1$, $I^2<50\%$) was evident, a NMA could be carried out. Otherwise, the source of heterogeneity was required to be identified first, and after exclusion of obvious clinical heterogeneity, a NMA or descriptive analysis alone could be performed. If loops formed in the network diagram, the node analysis method

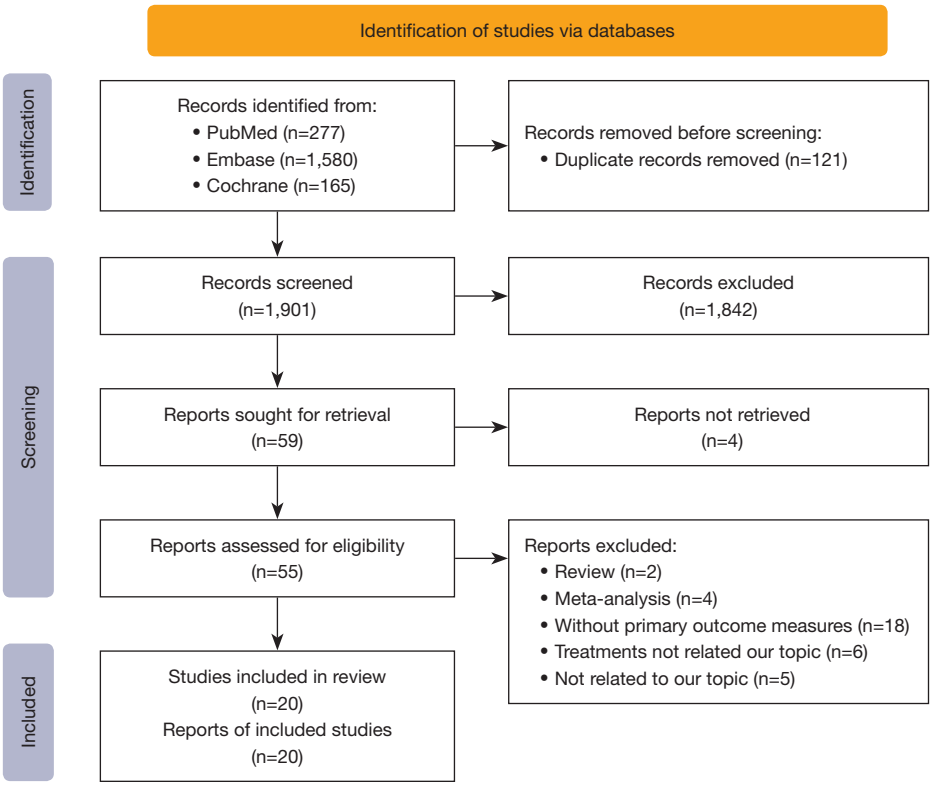

Figure 1 Flow diagram of the literature screening.

could be used to test the consistency of the results from the direct and indirect comparison of the interventions forming the loops. If the P value was >0.05, the results from the direct and indirect comparison would be considered consistent, and the consistency model (CM) could be used for NMA. Otherwise, the inconsistency model (IM) could be used. The convergence degree of the model was diagnosed by the potential scale reduction factor (PSRF). When the PSRF is close to 1, the convergence between chains is indicated. The mean value was used as the effect size for continuous variables, and the odds ratio (OR) was used for binary variables. Point estimate value and 95% confidence interval (95% CI) are presented for each effect size. The ranking diagram of probability was used to reflect the probable sequence of adverse events associated with different NSAIDs.

Results

Literature search results

We obtained 2,022 articles from the databases, and finally, 20 RCTs were included for NMA. The articles comprised 144,957 patients and 13 interventions, including oral diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, rofecoxib, nabumetone, amtolmetin guacil, valdecoxib, paracetamol, lornoxicam, and placebo. The literature search processes are presented in *Figure 1*.

Basic characteristics of the included studies and risk of bias

The basic characteristics of the included studies are summarized in *Table 1*. Assessment results of the risk of bias are presented in *Figures 2*,*3*.

In general, the risk of bias in the included articles was moderate. The risk of bias in the major included studies was low or unclear. There were certain risks in 8 studies, and the main source of risk was the high withdrawal rate caused by allocation concealment or adverse events.

Network diagram

The network diagram of the comparison of different interventions is shown in *Figure 4*; part A corresponds to

Table 1 Basic characteristics of included studies

Study	Total sample size	Age (mean, SD), years	Gender (female/male)	Condition	Intervention	Outcome measure
Curtis SP, *et al.* 2004, (19)	4,770	56.66, 12.12	3,588/1,182	OA, RA, chronic low back pain	Etoricoxib (60–120 mg/d, po, 12 W), Naproxen (1,000 mg/d, po, 12 W), Ibuprofen (2,400 mg/d, po, 12 W), Placebo	1, 2, 3, 4
Truitt KE, *et al.* 2001, (20)	341	–	217/124	OA	Rofecoxib (12.5–25 mg, po, qd, 1–6 W), Nabumetone (1,500 mg, po, qd, 1–6 W, Placebo	1, 2, 4
Chan FK, *et al.* 2002, (21)	287	67.65, 13.74	161/126	OA, RA, other arthritis	Celecoxib (200 mg, po, bid, 6 M), Diclofenac (75 mg, po, bid, 6 M)	1, 3, 4
Whelton A, *et al.* 2001, (22)	811	74.05, 6.06	539/272	OA	Celecoxib (200 mg, po, qd, 6 W), Rofecoxib (25 mg, po, qd, 6W)	1, 2, 3, 4
Niccoli L, *et al.* 2002, (23)	94	72.92, 6.24	59/35	OA	Diclofenac (150 mg/d, po, 2 W), Rofecoxib (25 mg/d, po, 2 W), Amtolmetin guacil (600–1,200 mg/d, po, 2 W)	1, 3, 4
White WB, *et al.* 2004, (24)	7,934	–	5,709/2,225	OA, RA	Valdecoxib (10–80 mg/d, po, 6–52 W), Ibuprofen (800mg, po, tid, 6–52 W), Placebo	2
Birbara C, *et al.* 2006, (25)	808	60.69, 10.51	553/255	OA	Rofecoxib (12.5 mg, po, qd, 6 W), Celecoxib (200 mg, po, qd, 6 W), Placebo	1, 2, 4
Cannon CP, *et al.* 2006, (26)	34,701	63.20, 8.50	25,748/8,953	OA, RA	Etoricoxib (60–90 mg, po, qd, 4 M), Diclofenac (75 mg, po, bid, 4 M)	2
Singh G, *et al.* 2006, (27)	13,194	62.20, 10.60	10,007/3,187	OA	Diclofenac (50 mg, po, bid, 12 W), Celecoxib (100 mg, po, bid, 12 W)	3, 4
Temple AR, *et al.* 2006, (28)	571	59.30, 8.60	395/176	OA	Naproxen (750 mg/d, po, 6–12 M), Acetaminophen (4 g/d, po, 6–12 M)	3, 4
Weaver AL, *et al.* 2006, (29)	978	62.70, 10.38	685/293	OA	Rofecoxib (12.5 mg, po, qd, 6 W), Nabumetone (500 mg, po, bid, 6 W), Placebo	2
Krueger K, *et al.* 2008, (30)	4,086	60.80, 7.74	2,261/1,825	RA	Etoricoxib (90 mg, po, qd, 12 M), Diclofenac (75 mg, po, bid, 12 M)	1, 2, 3, 4
Combe B, *et al.* 2009, (31)	23,504	63.41, 8.50	17,385/6,119	OA, RA	Etoricoxib (60–90 mg, po, qd, 20 M), Diclofenac (75 mg, po, bid, 20 M)	2
Li T, *et al.* 2013, (32)	178	52.50, 14.48	12/166	Acute gouty arthritis	Etoricoxib (120 mg, po, qd), Indometacin (75 mg, po, bid)	3, 4
Gibofsky A, *et al.* 2014, (33)	305	61.60, 8.86	203/102	OA	Diclofenac (35 mg, po, tid, 12 W), Placebo	3, 4
Bickham K, *et al.* 2016, (34)	1,404	53.80, 12.00	1,172/232	RA	Etoricoxib (60–90 mg, po, qd, 6 W), Placebo	1
Chan FKL, *et al.* 2017, (35)	512	72.55, 10.25	235/277	Arthritis	Celecoxib (100 mg, po, bid, 18 M), Naproxen (500 mg, po, qd, 18 M)	2, 3
Solomon DH, *et al.* 2018, (4)	24,081	63.70, 9.41	15,445/8,636	OA, RA, AS	Celecoxib (100–200 mg, po, bid, 18 M), Ibuprofen (600–800 mg, po, tid, 18 M), Naproxen (375–500 mg, po, bid, 18 M)	2, 3
Angiolillo DJ, *et al.* 2014, (36)	2,317	–	1,521/796	OA, RA, AS	Naproxen (500 mg, po, bid, 4 M), Celecoxib (200 mg, po, bid, 4 M), Placebo	2
Nissen SE, *et al.* 2016, (37)	24,081	63.16, 9.43	15,445/8,636	Arthritis	Celecoxib (100 mg, po, bid, 20 M), Ibuprofen (600 mg, po, tid, 20 M), Naproxen (375–500 mg, po, bid, 20 M)	2, 3

1, hypertension; 2, cardiovascular events; 3, renal events; 4, Edema. SD, standard deviation; OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; W, week; M, month; d, day; qd, once daily; bid, twice daily; tid, thrice; daily; po, *per os*.

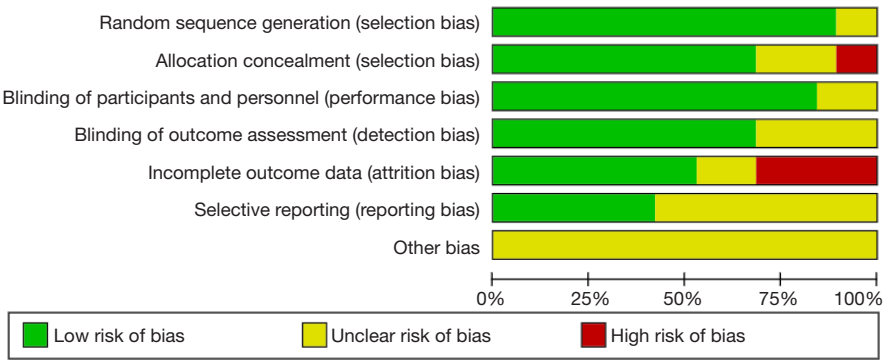

Figure 2 Risk of bias.

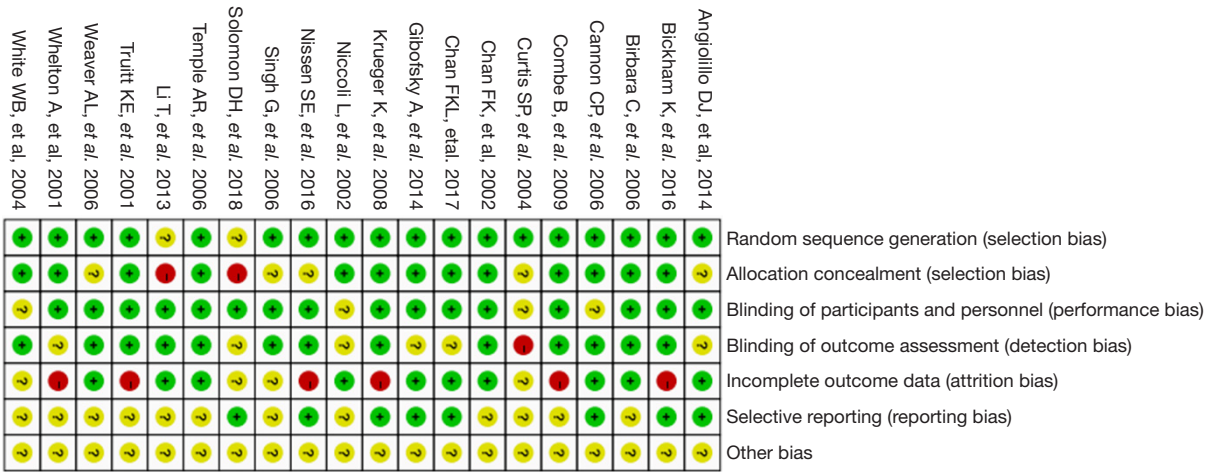

Figure 3 Summary of risk of bias.

hypertension, part B renal events, part C cardiovascular events, and part D edema; the number of studies for direct comparisons between interventions is positively correlated with the thickness of edges.

Inconsistency test

As shown in *Figure 4*, there are 7 closed loops in the diagram for hypertension, 6 for renal events, 7 for cardiovascular events, and 7 for edema. Therefore, the node analysis method was used for the inconsistency test. The results showed that there was no significant difference between the direct and indirect comparison of interventions forming the loops (P>0.05). Therefore, the CM was used for the NMA of cardiorenal risk.

Meta-analysis results

Hypertension

A total of 8 studies (19-23,25,30,34) with a total of 12,601 patients evaluating 9 NSAIDs (including etoricoxib, naproxen, ibuprofen, placebo, rofecoxib, nabumetone, celecoxib, amtolmetin guacil, and diclofenac) contributed to the analysis of the adverse events of hypertension (*Figure 4*). The PSRF was 1, indicating great convergence. Although the league table showed that there was no significant difference between the different interventions, the analysis of the probability ranking diagram and surface under the cumulative ranking (SUCRA) values indicated that amtolmetin guacil was associated with the lowest incidence of hypertension, while ibuprofen was associated with the

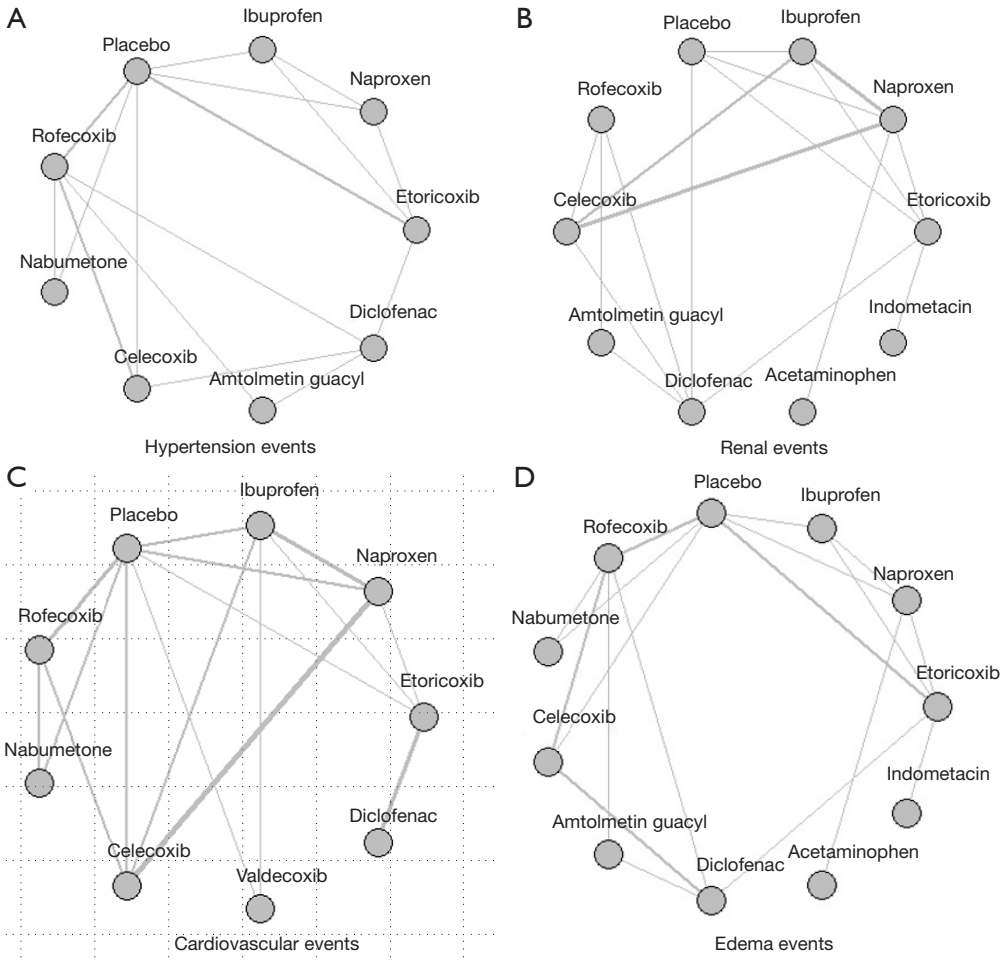

Figure 4 Network diagram of outcome measures.

highest incidence of hypertension. The ranking diagram of probability and SUCRA rankings are presented in the Figure S1 and OR value for the incidence is presented in the Figure S2.

Renal adverse events

A total of 12 studies (4,19,21-23,27,28,30,32,33,35,37) comprising 72,970 patients and evaluating 10 NSAID types (including etoricoxib, naproxen, ibuprofen, placebo, rofecoxib, celecoxib, amtolmetin guacil, diclofenac, acetaminophen, and indomethacin) contributed to the analysis of renal adverse events (*Figure 4*). The PSRF was 1, indicating great convergence. Although the league table showed that there was no significant difference between the different interventions, the analysis of the probability ranking diagram and SUCRA values suggested that amtolmetin guacil was associated with the lowest incidence of renal adverse events, while rofecoxib was associated with the highest incidence of renal adverse events. The ranking diagram of probability and SUCRA rankings are presented in the Figure S3 and OR value for the incidence is presented in the Figure S4.

Cardiovascular events

A total of 13 studies (4,19,20,22,24-26,29-31,35-37) comprising 128,924 patients and evaluating 9 NSAID types (including etoricoxib, naproxen, ibuprofen, placebo, rofecoxib, nabumetone, celecoxib, valdecoxib, and indomethacin) contributed to the analysis of cardiovascular events (*Figure 4*). The PSRF was 1, indicating great convergence. Although the league table showed that there was no significant difference between different interventions, the analysis of the probability ranking diagram and SUCRA values revealed that nabumetone was associated with the

lowest incidence of cardiovascular events, while ibuprofen was associated with the highest incidence of cardiovascular events. The ranking diagram of probability and SUCRA rankings are presented in Figure S5 and OR value for the incidence is presented in the Figure S6.

Edema

A total of 11 studies (19-23,25,27,28,30,32,33) comprising 25,445 patients and evaluating 11 NSAID types (including etoricoxib, naproxen, ibuprofen, placebo, rofecoxib, nabumetone, celecoxib, amtolmetin guacil, diclofenac, acetaminophen, and indomethacin) contributed to the analysis of edema (*Figure 4*). The PSRF was 1, indicating great convergence. Although the league table showed that there was no significant difference the between different interventions, the analysis of the probability ranking diagram and SUCRA values indicated that acetaminophen was associated with the lowest incidence of cardiovascular events, while naproxen was associated with the highest incidence of cardiovascular events. The ranking diagram of probability and SUCRA rankings are presented in Figure S7 and OR value for the incidence is presented in the Figure S8.

Discussion

NSAIDs are widely used for the treatment of OA. This study evaluated the safety of 12 different NSAIDs based on the incidence of cardiovascular and renal adverse events, hypertension, and edema.

The NMA results showed that rofecoxib was associated with a higher incidence of adverse cardiovascular and renal events and edema outcomes, which is consistent with the conclusion of Sooriakumaran's study in 2006 (38). In the study by Whelton *et al.* (22), rofecoxib, which selectively inhibits COX-2, resulted in a significant increase in body weight, blood pressure, and serum sodium, as well as a reduction in the 24-hour urine volume. This indicates that rofecoxib mainly affects the sodium-water exchange mechanism in the body, which is consistent with the observation that COX-2 is constitutively expressed by the kidney and represents the critical enzyme for sodium excretion and renin release (39). In Garner *et al.*'s study (10), rofecoxib was associated with a greater risk of myocardial infarction, but the exact significance and pathophysiology of this possible relationship are unclear (10,40). A possible reason for this association is that rofecoxib interferes with prostacyclin synthesis and disrupts the balance between thrombogenic and antithrombotic effects, thereby increasing the risk of cardiovascular events (41,42). Rofecoxib was discontinued worldwide at the end of September 2004 since long-term use of rofecoxib (more than 18 months) may increase the risk of heart attack and stroke (10,40).

Amtolmetin guacil was associated with a low incidence of adverse renal events, hypertension, and edema. In 2002, Niccoli *et al.* (23). compared the renal tolerance of amtolmetin guacil, diclofenac, and rofecoxib, 3 commonly used NSAIDs. The study pointed out that both diclofenac and rofecoxib significantly damaged renal function, while amtolmetin guacil had a renal-protective effect, but the exact mechanism is not clear. Experimental study on rats showed that amtolmetin guacil stimulates the activity of inducible nitrous oxide synthase (NOS) with a consequent increase in NO. NO plays a major role in regulating the renal blood flow, inducing an increase in the GFR (43). NO seems to act synergically with PG in the regulation of the renal blood flow, and renal function impairment due to COX inhibition by NSAIDs is significantly reduced in the presence of elevated levels of NO (44). In particular, diclofenac reduces renal blood flow, which manifests as a significant increase in serum creatinine, potassium, uric acid, and urea nitrogen, and a decrease in 24-hour urine volume and creatinine clearance. Rofecoxib, as a COX-2 selective NSAID, affects renal function mainly by increasing salt and water reactions. However, compared with traditional NSAIDs, COX-2 inhibitors may have no advantages due to their effects on renal function. COX-2 is central to sodium excretion and renin release. Its inhibition can cause sodium retention, hyperkalemia, and water poisoning. In clinical practice, these effects lead to the development of peripheral edema and hypertension. Amtolmetin guacil appears to not do obvious harm to renal function, but its potential mechanism is not clear. However, study has shown that amtolmetin guacil does not affect the GFR rate or water-sodium balance (23). Special attention should be paid to the fact that the drug is currently included in only 1 study (23), and further clinical trials are needed to investigate this drug.

In the treatment of patients with arthritis, celecoxib is not the safest drug as it relates to the risk of adverse events of hypertension, edema, and cardiovascular and renal outcomes, but it is safer than rofecoxib, naproxen, ibuprofen, and etoricoxib (45,46). In 2005, Moore *et al.* (47) reported that edema, heart failure, and death occurred at a lower rate in a celecoxib group than in the other NSAIDs groups, which is consistent with some of our conclusions. Coxibs are different from other NSAIDs in their cardiovascular safety profiles. This may be because of their

specific effects on COX-2, which is not highly related to the time of drug exposure and the extent of relative selectivity. Among coxibs, celecoxib is associated with a relatively lower risk of cardiovascular events, which may be due to its low specificity for COX-2 (38,48). Johnsen *et al.*'s 2005 study (49) also supported this idea, but conflicted in another regard. They found elevated risk estimates for myocardial infarction among current and in particular new users of rofecoxib and celecoxib. Elevated risk estimates were also found among current and new users of another COX-2 selective inhibitor, naproxen as well as other conventional nonaspirin NSAIDs. For current users, the lowest risk estimates were found for celecoxib and the highest for rofecoxib and other nonaspirin NSAIDs (50).

Summary data from a large-scale analysis of safety showed that celecoxib had a good renal safety profile (51). Although the risk of renal adverse events after celecoxib treatment is higher than that after placebo treatment, celecoxib is better and more effective than are conventional NSAIDs. There is no evidence that time or dose-related events occur after celecoxib treatment. In addition, patients who are highly sensitive to the adverse renal outcomes of NSAIDs have good tolerance to celecoxib (51). Celecoxib was not found to affect GFR at the treatment dose of 200 mg BID and 400 mg BID, while naproxen significantly reduced GFR at the standard treatment dose for adult arthritis (500 mg BID). Although no significant changes in creatinine levels were observed in the 10-day study, additional interval monitoring of serum creatinine levels is necessary for long-term treatment, especially during the use of NSAIDs. Patients receiving naproxen may need to modify their medication regimen according to changes in renal function (52). The nephrotoxicity of traditional NSAIDs is attributed to the nonspecific inhibition of COX-1 and COX-2, and the therapeutic benefits of conventional NSAIDs stem from inhibiting the function of COX-2 at inflammatory sites. Celecoxib inhibits COX-2 without simultaneously affecting COX-1, which can achieve anti-inflammatory and analgesic effects without negatively impacting the gastrointestinal tract, platelets, or renal function (51).

In addition, this study found that naproxen was associated with renal adverse events and edema, while ibuprofen was associated with a high incidence of adverse cardiovascular events and hypertension, which may be related to its greater reduction of ibuprofen in PG and renin levels than other NSAIDs. Previous studies have revealed that NSAIDs can significantly lower PG and renin levels, undermining the therapeutic effects of antihypertensive drugs, which complicate hypertension management (53-55). Patients with controlled hypertension can increase their blood pressure by 3 to 6 mmHg (56) during the treatment with NSAIDs, which significantly increases the risk of subsequent stroke, end-stage renal disease, or congestive heart failure (5,54). In clinical trials using NSAIDs, sodium retention and edema were observed in 2% to 5% of patients, and patients prone to edema also experienced aggravation of edema when taking conventional NSAIDs (52). The main reason for edema and sodium retention associated with naproxen may be the blocking of the following PG-mediated properties induced by naproxen: regulation of the reabsorption of sodium and water by distal renal tubules, antagonism of the diuretic hormone, and the redistribution of blood flow from the cortex to the proximal femoral medullary region. The main causes of renal adverse events associated with naproxen may be as follows: the decrease of PGs, the disturbance of hemodynamic stability of the kidney, increased lymphocyte recruitment, and activation related to leukotriene. The main symptoms of renal adverse events may include increased blood urea nitrogen, serum creatinine, and potassium; weight gain; and decreased urine volume (53,57).

Considering these findings cumulatively, we believe clinicians should weigh the efficacy of NSAIDs against renal and cardiovascular toxicity when prescribing NSAIDs for the treatment of arthritis. They need to evaluate the risk-benefit profiles of each option to select the most suitable one for treatment. Moreover, clinical monitoring should be strengthened and greater attention paid to the dosage and duration of pharmaceutical use (58,59). When taking NSAIDs, patients should be informed of the risks of these drugs in plain language, and patients should be guided to use them reasonably. We recommend celecoxib and amtolmetin guacil as preferable options.

This research has some limitations. First, the risk of bias in the included articles was generally moderate. the quality of some the included studies was low, as the random allocation, hiding method, and blinding method were not explained. This might have affected the accuracy of the results. Second, this meta-analysis included a small number of studies on NSAIDs, such as amtolmetin guacil, valdecoxib, acetaminophen, and indomethacin, so future research with a larger sample size is needed. Third, we did not separately analyze patients with common arthritis, patients with arthritis and confirmed cardiovascular or renal disease, and patients with arthritis at high cardiovascular or renal risk. This might have influenced the accuracy of the

analysis results. Fourth, we only searched English literature, which may have language bias. In the future, we need to supplement relevant studies in other languages. Finally, the small number of events analyzed in some of the included studies limited the risk evaluation of different COX-2 inhibitors and conventional NSAIDs in specific clinical circumstances (9).

Conclusions

The current results reflect the relative safety of amtolmetin guacil in the treatment of arthritis, but this conclusion should be investigated further. Rofecoxib is associated with a higher risk of cardiorenal events, ibuprofen with cardiovascular events and hypertension, and naproxen with renal adverse events and edema.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6181/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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