Effects of Therapies on Cardiovascular Events in Ankylosing Spondylitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor inhibitors (TNFi) are the most common therapies used in AS, however, the associated long-term cardiovascular risk is unclear. We performed a

systematic review and meta-analysis on the association of therapies used for ankylosing spondylitis (AS) such as NSAIDs and TNFi on cardiovascular events (CVE) in AS.

Methods: A comprehensive search was performed from database inception to May 29, 2020 to include controlled studies of AS treated with NSAIDs, oral small molecules, or biologics reporting CVE. Study-specific risk ratios (RR) were pooled using a random effects model.

Results: Nine non-randomized studies from 1570 studies screened fulfilled inclusion criteria. Among NSAID users as a whole versus no NSAIDs, no increased risk of CVE (composite outcome) was observed; however, the risk of cerebrovascular accident was significantly lower (RR 0.58, 95% CI 0.37–0.93, I^2 = 66%). Cox-2 inhibitor use was associated with reduced risk of all CVE (RR 0.48, 95% CI 0.33–0.70, I^2 = 0%). Non-selective NSAIDs were not associated with any increased/decreased risk of any CVE. Meta-analysis of three studies of MI did not show a significant association with TNFi (RR 0.88, 95% CI 0.57–1.35, I^2 = 76%).

Conclusions: In this meta-analysis of non-randomized studies, NSAID users as a whole and users of non-selective NSAIDs did not seem to have a higher risk of any CVE. Limited data suggest a lower risk of composite CVE outcome with Cox-2 inhibitors, unlike the increased risk reported in the general population. No significant association between TNFi and MI was observed. The certainty in evidence was very

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low due to all studies being observational. More studies are needed to study the association between TNFi use and CVE in general to evaluate a possible protective role in AS.

Key Summary Points

Why carry out this study?

Non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor inhibitors (TNFi) are the most common therapies used in ankylosing spondylitis (AS); however, their associated long-term effects on cardiovascular risk are unclear.

A systematic review and meta-analysis were conducted to synthesize the evidence regarding the long-term cardiovascular safety of NSAIDs and TNFi in AS.

What was learned from the study?

NSAID users as a whole and users of non-selective NSAIDs did not seem to have a higher risk of any cardiovascular events (CVE).

More data are needed on the risk of Cox-2 inhibitors in AS patients. Limited data suggest lower risk of composite CVE outcome, unlike their use in the general population.

No significant association between TNFi and myocardial infarction (MI) was observed in the limited number of studies found. More studies are needed to study the association between TNFi use and CVE in general to evaluate a possible protective role in AS.

DIGITAL FEATURES

This article is published with digital features, including summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13095602.

INTRODUCTION

Cardiovascular events (CVE) are higher in ankylosing spondylitis (AS) than the general population and are associated with higher mortality [1]. AS patients have a significantly higher risk of myocardial infarction [MI] (odds ratio [OR] 1.60) and stroke (OR 1.50) than the general population [2], comparable to the risk noted for RA patients (OR 1.63 compared to the general population) [3]. Similarly, the overall increase in mortality in AS observed (1.5 times higher than the general population) is attributed largely to CVE [4, 5]. Significantly higher risk of vascular death, cerebrovascular, and cardiovascular (CV) death was observed in a study from Ontario [6]. In the hospital setting as well, vascular disease has been reported as the most frequent cause of death in AS patients [5]. The higher CV risk in AS has been largely attributed to accelerated atherosclerosis and endothelial dysfunction in the background of inflammation [7]. CVE risk factors, such as hypertension [8] and metabolic syndrome [2], also have a higher prevalence in AS.

Therapies targeted at controlling inflammation may potentially reduce CV risk, as seen with tumor necrosis factor inhibitors (TNFi) in RA [9]. NSAIDs and TNFi are the most common therapies used in AS. While NSAIDs are known to be associated with an increased risk of CVE in the general population and RA patients [9, 10], whether the anti-inflammatory effects of NSAIDs reduce or modify CVE risk in AS is not clear. Prior studies on CV safety have been performed mostly in RA and osteoarthritis, and in patients with colorectal carcinoma [11–13]. In the context of AS, this question is even more important, as NSAIDs are the first-line therapy per American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guidelines [14]. In AS, NSAIDs are often used long term and in a continuous fashion, unlike their use in other forms of inflammatory arthritis, where they are used at times of flare

[14]. Moreover, differences in the risk of CVE with different types of NSAIDs have been well documented [12, 15]. The degree of Cox-2 inhibition with NSAIDs is hypothesized to play a role. The anti-inflammatory and analgesic effects of NSAIDs are mediated through Cox-2 inhibition, which also increases thromboxane-induced vasoconstriction and platelet activation, leading to hypertension and net-pro-thrombotic effect, respectively. Work in RA has shown that TNFi are associated with reduced risk of CVE risk likely secondary to reduced inflammatory burden [9]. Whether the same holds true for AS is unclear. Some studies demonstrate a beneficial effect of TNFi on the lipid profile, subclinical atherosclerosis, and arterial stiffness in AS [16–18]. Ascertaining if the changes in these preclinical CV risk factors translate to clinically meaningful CV benefit is an unmet need.

We aimed to perform a systematic review and meta-analysis to determine the association of therapies used for AS, such as NSAIDs and TNFi, with CVE in AS.

METHODS

Search Strategy and Study Selection

A comprehensive search of several databases from inception to May 29, 2020 was conducted. The databases included Ovid Medline In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. ACR and EULAR abstracts (without full-text publication) indexed in MEDLINE were included as well. The search strategy was designed and conducted by a medical reference librarian with input from the principal investigator (Supplementary File 1). No language restrictions were made.

We included all original reports fulfilling the following criteria:

1. Adults (≥ 18 years) with AS.

2. Participants were treated with NSAIDs, oral small molecules or biologics, and had a control group (with no drug of interest).

3. Outcomes of interest: all CVE, acute coronary syndrome/ischemic heart disease (ACS/IHD), cerebrovascular accident (CVA), congestive heart failure (CHF), and the composite outcome of major adverse cardiac events (MACE; defined as acute coronary syndrome, cerebrovascular accident/ stroke, and heart failure) were reported with a particular therapy and compared to placebo or a group without the therapy of interest.

4. Duration of follow-up at least 1 year.

While cohort and case–control studies were included, case series, case reports, and non-human studies were excluded. Studies reporting data on CV risk factors (e.g., hyperlipidemia, hypertension) and subclinical or surrogate markers of atherosclerosis (e.g., arterial stiffness or intima thickness) were also excluded. The effect of combination therapy was beyond the scope of this study.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews was followed (Fig. 1) [19]. Two authors (PK and RS) screened abstracts for eligibility, retrieved full texts, and excluded irrelevant articles. The inter-rater agreement was very good (kappa statistic 0.92, 95% CI 0.89 to 0.98). Disagreements were resolved by discussion about eligibility. Bibliographies belonging to included studies, reviews, and relevant articles were screened for additional studies. Duplicate publications were avoided: full-text articles were given preference over abstracts, and when multiple studies from the same dataset were available, we included only the latest study or the report with results from the largest dataset. For example, we included data from Tsai et al. [20], in which data from the entire database was included in the main analysis, and did not include the publication from Wu et al. [21], as it included only a sample from the database (both studies used Taiwan National Health Insurance database).
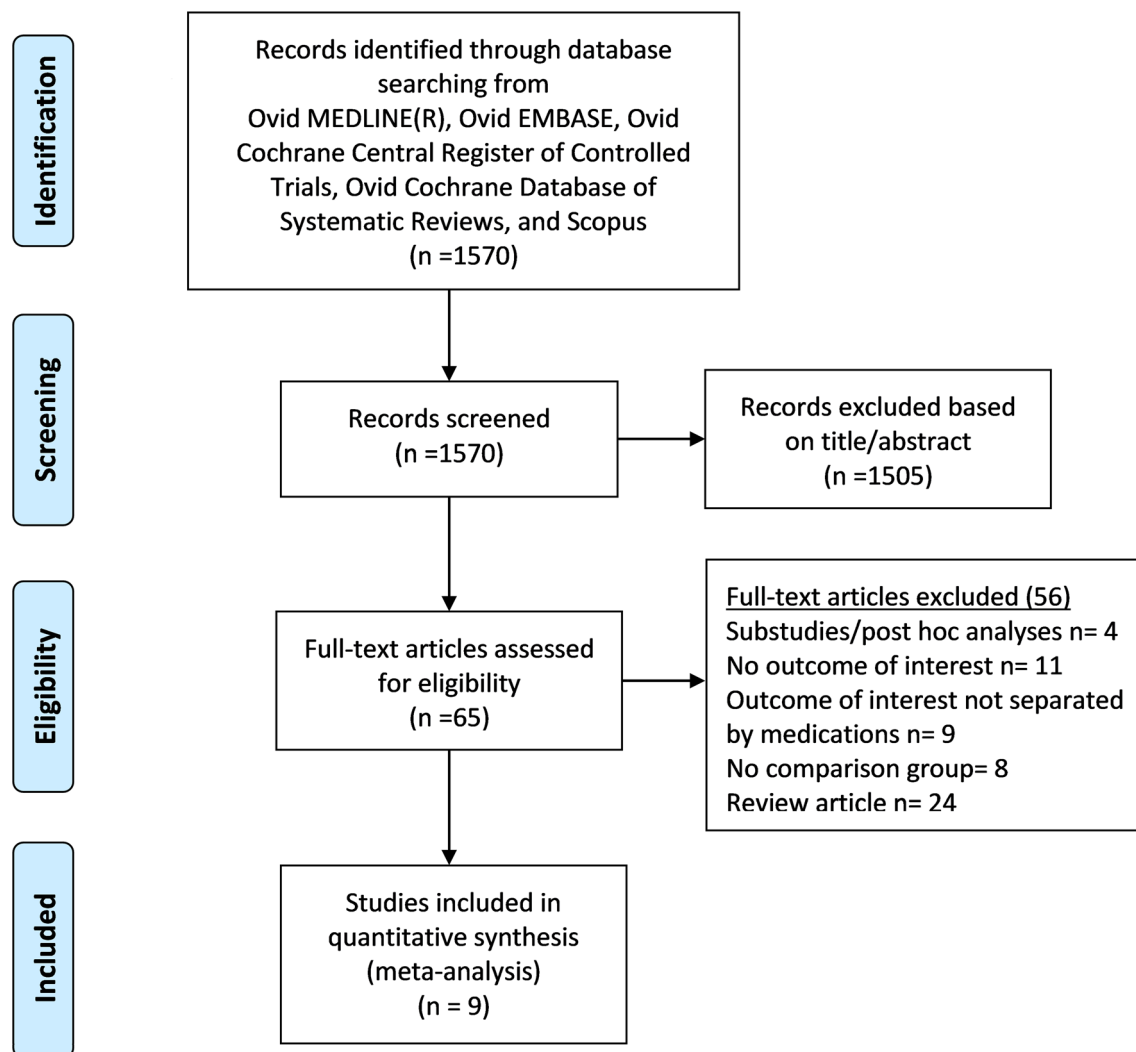
Fig. 1 Flow chart describing systematic search and study selection process

Data Extraction and Risk of Bias Assessment

Relevant data were extracted by PK, and checked by RS. Data for only AS patients were considered for studies providing CV outcomes on multiple diseases or spondyloarthritis (SpA) as a whole [22, 23]. Where no data were reported separately for the subset of patients with AS, the authors were contacted for additional data. If no specific data on AS or CVE could be obtained, the study was excluded [24]. When data at multiple time points were provided, data at the last date of follow-up in the study were used in analyses [20].

Studies were independently evaluated by two reviewers (PK and RS) for the risk of bias [25]. The New-Castle Ottawa scale was used for case–control and cohort studies (Supplementary File 2) [26]. Due to the limitation of tools assessing observational studies [27], the certainty in the evidence was evaluated using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) methodology [28]. Publication bias was assessed visually using funnel plots. Between-study heterogeneity was assessed using I^2 statistics (i.e., $I^2 < 30\%$, low heterogeneity, 30–60%, moderate, and $> 60\%$, high) [29].

Outcomes

The main outcome of interest was the association between treatment and all CVE. Secondary outcomes included MI, stroke, congestive heart failure (CHF), and the composite outcome of major adverse cardiac events (MACE).

Statistical Analysis

Data extracted from the studies were combined for meta-analysis using Review Manager (RevMan) version 5.3. For studies reporting only incident outcomes, RR were calculated. Rate ratios were calculated if person-years of follow-up were reported. Reported ORs and hazard ratios were converted to risk ratios (RR) using validated statistical formulae [30, 31]. RR were calculated using relative to the AS group with no therapy of interest if the study reported RRs with a different control group [22, 32]. Study-specific RR were pooled using a random effects model (DerSimonian and Laird) [33]. To maintain independence, data from the same administrative data from different studies were included in only separate meta-analyses. For example, data from Tsai [20] and Wu et al. [21] (both using the Taiwan National Health Insurance database) were included only in separate meta-analyses.

Compliance with Ethics Guidelines

This article is based on secondary analysis of previously conducted and published studies and does not contain any data with human participants or animals performed by any of the authors.

RESULTS

Characteristics of the Included Studies

Out of 1570 studies screened, nine non-randomized studies fulfilled our inclusion criteria (all English language): seven studies ($N = 28,314$) and four studies ($N = 47,153$) reported the association of NSAIDs and TNFi with CVE, respectively (two studies reported both drugs) [23, 34] (Fig. 1). No studies on the association of CVE pertaining to IL-17 use were found. Among the included studies, seven were published manuscripts and two were abstracts [34, 35]. Included studies were all observational, mostly retrospective cohort, and case–control studies (Table 1). Only one of the studies was a prospective cohort study [23]. While four of the studies were based on national administrative/health records [20, 21, 23, 32], the remaining five were based on other administrative or insurance claims databases [15, 22, 34–36].

The median (range) study duration was 15 (4–21) years for NSAIDs and 15 (1–23) years for TNFi. AS and CVE were defined in the included studies by International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9 and 10-CM) and Read codes (documented by general practitioners in the UK), and electronic medical record review. Most studies reported data separately for different types of NSAIDs (Cox-2 selective and non-selective), except two studies that only reported data on NSAIDs as a group. Only one study each reported data on the risk of CHF and MACE (Supplementary File 3). As for the association of CVE with TNFi in AS, only one study reported a cumulative CVE data [23]; and three other studies reported MI and ischemic heart disease events [34–36].

No studies on the CV effects of other biologic agents such as the interleukin (IL)-17A and Janus Kinase inhibitors (JAKi) on AS were found in our systematic review.

All Cardiovascular Events

In NSAID users as a whole compared to no NSAIDs, no increased risk of CVE was noted (RR 0.96, 95% CI 0.51–1.81, $I^2 = 95\%$); Cox-2 inhibitor use was associated with significantly reduced risk of all CVE (RR 0.43, 95% CI 0.26–0.71, $I^2 = 0\%$), but non-selective NSAIDs did not show a significant association (RR 0.93, 95% CI 0.41–2.11, $I^2 = 81\%$) (Fig. 2). There was only one study reporting all CVE with TNFi, which showed an increased risk (RR 1.60, 95% CI 1.05–2.41).

Table 1 Baseline characteristics of the included studies

Author, year	Study design	AS definition	Events reported (definition)	Variables adjusted	F/U in years
Kristensen, 2015 [32]	National register-based cohort study (Swedish National Patient Register)	ICD codes (the majority of patients were diagnosed and treated by a rheumatologist)	Atherosclerotic cardiac/cerebrovascular events, congestive heart failure (ICD codes) in AS subset*	Age, sex, HTN, HLD, DM, CKD, CV drugs, prednisone, anti-coagulants	4 (2006–2009)
Tsai, 2015 [20]	Nationwide case control study (Taiwan National Health Insurance Database)	Newly diagnosed AS (1997–2008) with at least 2 service claims or ambulatory/inpatient care for further confirmation	All incident CVD, CVA, MACE, CHF (ICD-9 codes)	Age, sex, CCI, AS disease duration, and other drugs	3
Essers, 2016 [22]	Retrospective, cohort study using Clinical Practice Research Datalink GOLG (CPRD)	Read Codes documented by GP	Incident IHD and acute MI (EMR)	Age, sex, BMI, smoking, alcohol use, HLD, CKD, anti-HTN, anti-DM, antiplatelet agents, statins and asthma medications	15
Wu, 2016 [21]	Nationwide population-based case–control study (Taiwan National Health Insurance Database)	Newly diagnosed AS (2001–2010) with ICD-9 720.0 and outpatient visit $\geqq 2$ or admission $\geqq 1$	Coronary artery disease (ICD-9 410–414 and had outpatient visit $\geqq 2$ or admission $\geqq 1$)	Propensity score matching on age, sex, AS duration, CCI, HTN, and HLD	10 (2001–2010)
Dubreuil, 2018 [15]	Nested case control study UK THIN database	Read codes documented by the GP	Incident MI (first recording of MI read code) in AS subset*	Age, sex, BMI, HTN, HLD, DM, GI bleed, prior IHD, CKD	21 (1994–2015)
Dubreuil (abstract), 2018 (34)	Nested case–control study (OptumLabs Data Warehouse)	Diagnostic code—AS dx after at least 6 months of claims data prior to AS dx	Incident MI (diagnostic codes)	Age, sex, BMI, smoking, obesity, DM, HTN, CKD, aspirin, anti-HTN, statins, fibrates, PPI, OSM or biologics	23 (1994–2017)
Lee, 2018 [23]	Prospective national cohort study (Australian Rheumatology Association Database)	ICD-10 codes	All CVE (angina, MI, CABG, PCI, stroke/TIA) in AS subset*	Age, sex, disease duration, alcohol use, smoking, HTN, HLD, DM, prednisone, MTX	15 (2001–2015)
Deodhar (abstract) 2018 [35]	Retrospective, cohort study from 3 insurance claim databases (claims, Truvan Market scan and Medicare)	ICD-9 codes	MI (ICD-9 codes)	Inverse probability weighting (demographic variables and comorbidities)	1 (6 months pre and 6 months post index date)
Shuster 2018 [36]	Retrospective study from "Clalit" Health Services data, Israel	Integrated EMR review (inpatient/outpatient charts)	IHD (EMR review)	Age, sex, BMI, SES, smoking, HTN, HLD, DM	2000–2017

Table 1 continued

Author, year	Treatment				Control			
	Drug (dosing)	N	Female, %	Age, mean (SD)	Drug	N	Female, %	Age, mean (SD)
Kristensen, 2015 [32]	Etoricoxib	803	37	Median 46 (IQR = 35–57)	No NSAIDs	1960	34	Median 46 (IQR = 35–57)
	Celecoxib	458	41					
	Nonselective NSAIDs (DDD)	7720	35					
Tsai, 2015 [20]	All NSAIDs	10,397 total	55	> 70% age < 55	No NSAID	10,397 total	54.87	> 70% age < 55
	Non-selective NSAIDs							
	Selective NSAIDs (MPR ≥ 80%)							
Essers, 2016 [22]	COX-2 inhibitors	287	30	NR	No NSAIDs	3353	29.88	NR
	Naproxen	291	29			3349	29.92	
	Other traditional NSAIDS	692	26			2948	30.83	
	Any NSAIDs (DDD)	1233	28			2407	31.03	
Wu, 2016 [21]	Celecoxib	198	46	55 (15)	No NSAIDs	510	45.62	55 (15)
	Etoricoxib	61				647		
	Naproxen	171				537		
	Diclofenac (DDD)	579				129		
Dubreuil, 2018 [15]	Current diclofenac	8	11	64 (12)	No NSAIDs	14	10.60	64 (12)
	Current naproxen	3				14		
	Current other NSAIDs (based on NSAID prescription recency)	12				38		

Table 1 continued

Author, year	Treatment				Control			
	Drug (dosing)	N	Female, %	Age, mean (SD)	Drug	N	Female, %	Age, mean (SD)
Dubreuil (abstract), 2018 (34)	NSAID	1282	49	59 (12)	No NSAID	21,967	48.9	59 (12)
	TNFi	~ 89			No TNFi	23,160		
Lee, 2018 [23]	NSAID	251	27	48 (13)	No NSAIDs	310	36.7	46 (12)
	TNFi	507	30	47(12)	No TNFi	54	48.1	48 (13)
	(annual self-reported questionnaire)							
Deodhar (abstract) 2018 [35]	TNFi	37,566 total	NR	NR	No TNFi	37,566 total	NR	NR
Shuster 2018 [36]	TNFi	1207	36	49 (14)	No TNFi	2869	36.1	58 (17)

F/U follow-up, CV cardiovascular, DDD defined daily doses, defined by the World Health Organization standard of exposure as the assumed average maintenance dose per day for a drug used for its main indication in adults (equivalent to 100 mg diclofenac), MPR medication possession rate, CVD cardiovascular disease, IHD ischemic heart disease, MI myocardial infarction, CV cerebrovascular accident, MACE major adverse cardiovascular events, CHF congestive heart failure, CABG coronary artery bypass grafting, HTN hypertension, HLD hyperlipidemia, DM diabetes mellitus, CKD chronic kidney disease, CCI Charlson Comorbidity Index, PPI proton pump inhibitors, OSM oral small molecules, MTX methotrexate, EMR electronic medical record, ICD International Classification of Diseases, GP general practitioner, Read codes standard clinical terminology system used in General Practice in the United Kingdom, NR not reported, MPR medication possession rate, SES socio–economic status * Additional data provided by the authors
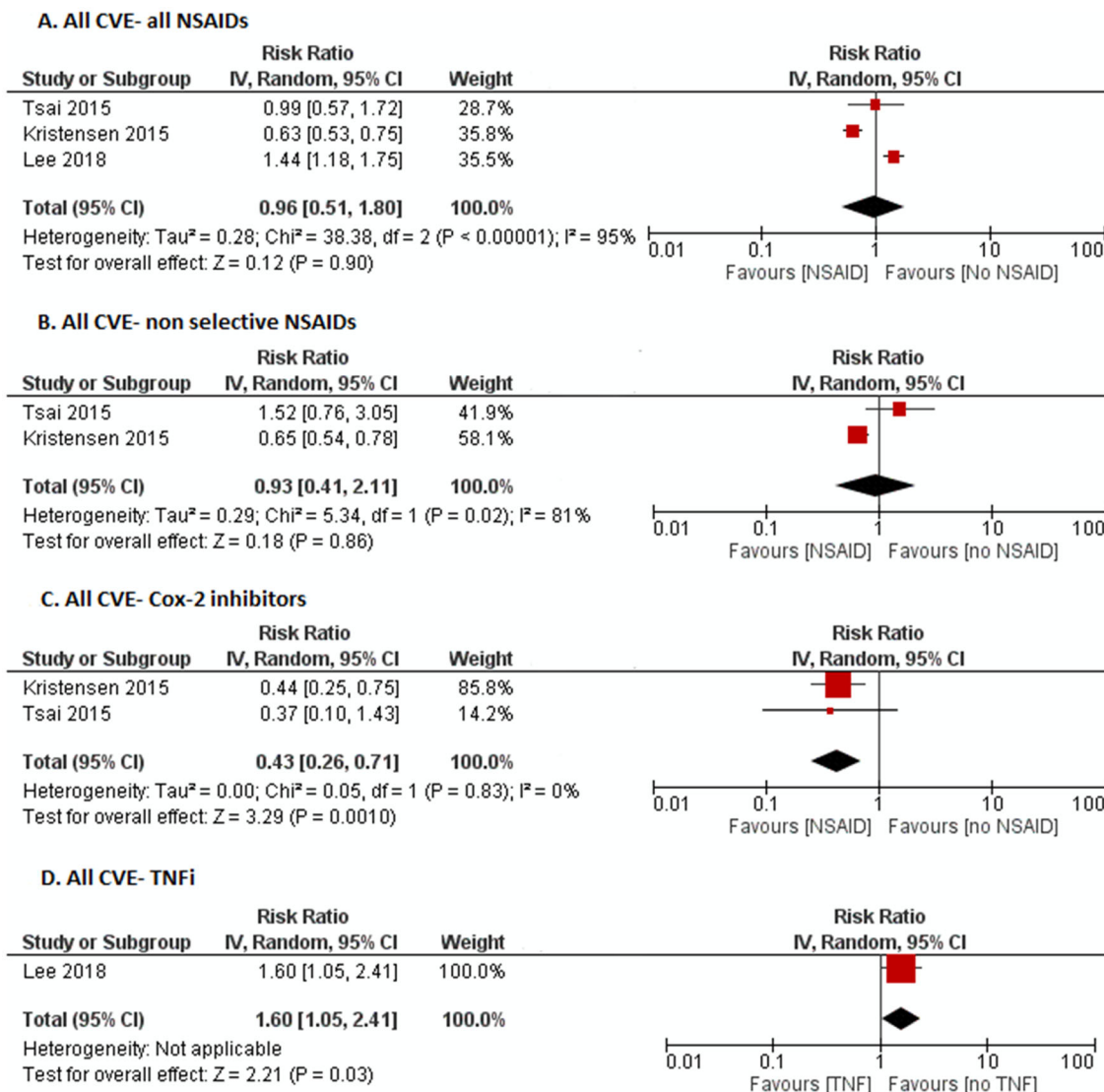
A. All CVE- all NSAIDs

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight
Tsai 2015	0.99 [0.57, 1.72]	28.7%
Kristensen 2015	0.63 [0.53, 0.75]	35.8%
Lee 2018	1.44 [1.18, 1.75]	35.5%
Total (95% CI)	**0.96 [0.51, 1.80]**	**100.0%**

Heterogeneity: Tau² = 0.28; Chi² = 38.38, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.12 (P = 0.90)

B. All CVE- non selective NSAIDs

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight
Tsai 2015	1.52 [0.76, 3.05]	41.9%
Kristensen 2015	0.65 [0.54, 0.78]	58.1%
Total (95% CI)	**0.93 [0.41, 2.11]**	**100.0%**

Heterogeneity: Tau² = 0.29; Chi² = 5.34, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.18 (P = 0.86)

C. All CVE- Cox-2 inhibitors

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight
Kristensen 2015	0.44 [0.25, 0.75]	85.8%
Tsai 2015	0.37 [0.10, 1.43]	14.2%
Total (95% CI)	**0.43 [0.26, 0.71]**	**100.0%**

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.0010)

D. All CVE- TNFi

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight
Lee 2018	1.60 [1.05, 2.41]	100.0%
Total (95% CI)	**1.60 [1.05, 2.41]**	**100.0%**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.21 (P = 0.03)

Fig. 2 Forest plot on the risk of all cardiovascular events (CVE) in ankylosing spondylitis patients with **a** all NSAIDs, **b** non-selective NSAIDs, **c** Cox-2 inhibitors, **d** tumor necrosis factor inhibitors (TNFi)

Acute Coronary Syndrome/Ischemic Heart Disease (ACS/IHD)

Meta-analysis of five studies showed no significant effect of NSAIDs as a group (RR 1.11, 95% CI 0.81–1.53, I^2 = 80%), non-selective NSAIDs (RR 1.18, 95% CI 0.83–1.69, I^2 = 83%), or Cox-2 inhibitors (RR 0.81, 95% CI 0.41–1.60, I^2 = 69%) compared to no NSAIDs on ACS/IHD (Fig. 3). To ascertain if the CV risk was different among the different non-selective NSAIDs, we separately looked at the risk of CVE in naproxen and diclofenac users. There was no statistically significant difference in the risk of CVE in those on naproxen (RR 0.78, 95% CI 0.29–2.10, I^2 = 63%) or diclofenac (RR 1.43, 95% CI 0.91–2.26, I^2 = 36%) compared to those not on NSAIDs (Fig. 5). Meta-analysis of three studies of myocardial infarction (MI) specifically did not show a significant association with TNFi compared to those not on TNFi (RR 0.89, 95% CI 0.59–1.34, I^2 = 78%).
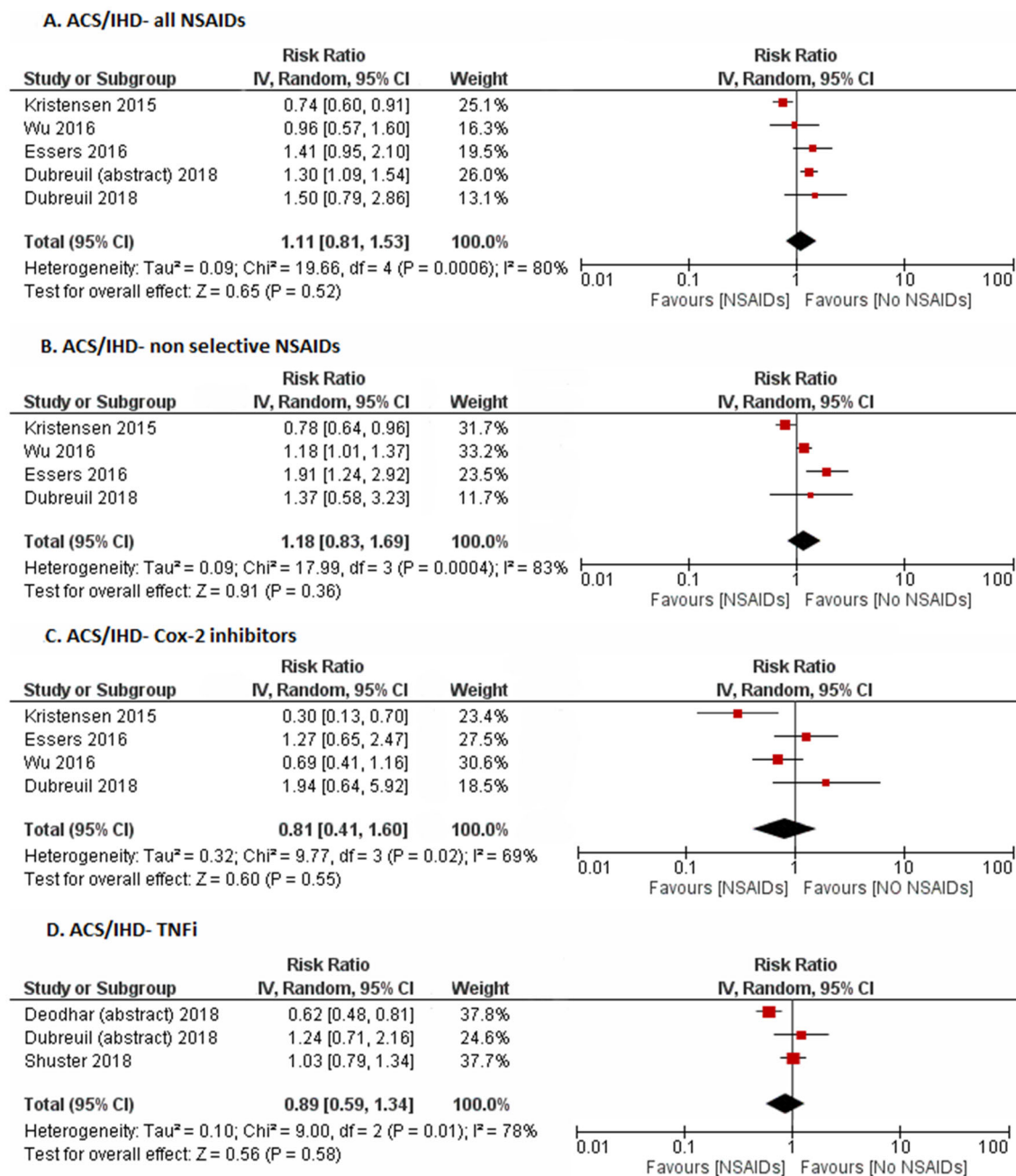
A. ACS/IHD- all NSAIDs

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Kristensen 2015	0.74 [0.60, 0.91]	25.1%	
Wu 2016	0.96 [0.57, 1.60]	16.3%	
Essers 2016	1.41 [0.95, 2.10]	19.5%	
Dubreuil (abstract) 2018	1.30 [1.09, 1.54]	26.0%	
Dubreuil 2018	1.50 [0.79, 2.86]	13.1%	
Total (95% CI)	**1.11 [0.81, 1.53]**	**100.0%**	

Heterogeneity: Tau² = 0.09; Chi² = 19.66, df = 4 (P = 0.0006); I² = 80%
Test for overall effect: Z = 0.65 (P = 0.52)

Favours [NSAIDs]   Favours [No NSAIDs]

B. ACS/IHD- non selective NSAIDs

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Kristensen 2015	0.78 [0.64, 0.96]	31.7%	
Wu 2016	1.18 [1.01, 1.37]	33.2%	
Essers 2016	1.91 [1.24, 2.92]	23.5%	
Dubreuil 2018	1.37 [0.58, 3.23]	11.7%	
Total (95% CI)	**1.18 [0.83, 1.69]**	**100.0%**	

Heterogeneity: Tau² = 0.09; Chi² = 17.99, df = 3 (P = 0.0004); I² = 83%
Test for overall effect: Z = 0.91 (P = 0.36)

Favours [NSAIDs]   Favours [No NSAIDs]

C. ACS/IHD- Cox-2 inhibitors

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Kristensen 2015	0.30 [0.13, 0.70]	23.4%	
Essers 2016	1.27 [0.65, 2.47]	27.5%	
Wu 2016	0.69 [0.41, 1.16]	30.6%	
Dubreuil 2018	1.94 [0.64, 5.92]	18.5%	
Total (95% CI)	**0.81 [0.41, 1.60]**	**100.0%**	

Heterogeneity: Tau² = 0.32; Chi² = 9.77, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.60 (P = 0.55)

Favours [NSAIDs]   Favours [NO NSAIDs]

D. ACS/IHD- TNFi

Study or Subgroup	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Deodhar (abstract) 2018	0.62 [0.48, 0.81]	37.8%	
Dubreuil (abstract) 2018	1.24 [0.71, 2.16]	24.6%	
Shuster 2018	1.03 [0.79, 1.34]	37.7%	
Total (95% CI)	**0.89 [0.59, 1.34]**	**100.0%**	

Heterogeneity: Tau² = 0.10; Chi² = 9.00, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 0.56 (P = 0.58)

Favours [NSAIDs]   Favours [No NSAIDs]

Fig. 3 Forest plot on the risk of acute coronary syndrome/ischemic heart disease (ACS/IHD) with **a** all NSAIDs, **b** non-selective NSAIDs, **c** Cox-2 inhibitors, **d** tumor necrosis factor inhibitors (TNFi)

Cerebrovascular Events (CVA)

The risk of cerebrovascular accident (CVA) was significantly lower (RR 0.52, 95% CI 0.37–0.73, I^2 = 6%) for NSAIDs as a whole, but did not reach significance individually for Cox 2-inhibitors (RR 0.59, 95% CI 0.33–1.08, I^2 = 0%) or non-selective NSAIDs (RR 0.65, 95% CI 0.26–1.64, I^2 = 95%) (Fig. 4).
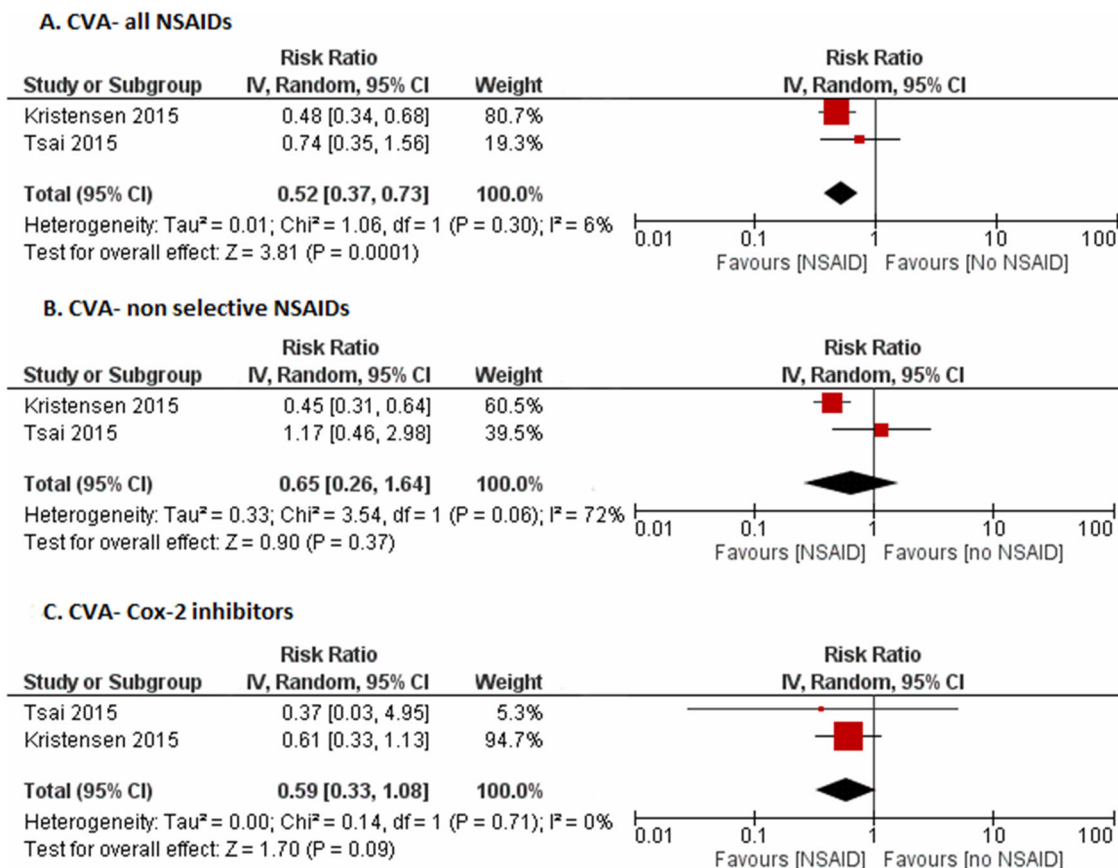
Fig. 4 Forest plot on the risk of cerebrovascular accidents (CVA) with **a** all NSAIDs, **b** non-selective NSAIDs, **c** Cox-2 inhibitors

Other Cardiac Outcomes

Only one study reported risk of CHF with NSAIDs; the study showed a lower risk with NSAIDs as a group (RR 0.28, 95% CI 0.20–0.37), and individually with Cox-2 inhibitors (RR 0.27, 95% CI 0.10–0.60) and non-selective NSAIDs (RR 0.28, 95% CI 0.20–0.37). Similarly, there was no difference in MACE with NSAIDs as a group (RR 0.52, 95% CI 0.13–2.10), or with Cox-2 inhibitors (RR 1.43, 95% CI 0.08–25.09) or non-selective NSAIDs (RR 1.38, 95% CI 0.23–8.45) in the only study reporting this specific outcome.

Risk of Bias

Assessment of overall risk of bias for the included studies is summarized in supplementary file 2. All the included studies were judged to have a low risk of bias as per the New-Castle Ottawa scale for observational studies [26]. All the included studies were observational, therefore the certainty in evidence evaluated using the GRADE approach methodology was low to very low [28]. Publication bias was unable to be assessed accurately as we had fewer than ten eligible studies (Supplementary file 4).

DISCUSSION

This systematic review, including nine non-randomized studies, found no increased risk of any CVE with NSAIDs as a whole and lower risk with NSAIDs as a group for CVA in the limited number of studies found. Limited data suggested a possible lower risk of composite outcome of CVE with Cox-2 inhibitors. No

significant association between TNFi and MI was observed, and studies on other CV outcomes with TNFi were limited.

While long-term NSAIDs use has been associated with increased risk of CVE in the general population [12], we found a limited number of studies on the effects of NSAIDs on the CVE risk in AS where they are used as first-line therapy. Studies in inflammatory polyarthritis and RA suggest that the effect of NSAIDs on CV outcomes might be different for inflammatory arthritis. The UK Norfolk Arthritis Register (NOAR) data for an inception cohort of inflammatory polyarthritis and the Danish RA cohort both did not show higher CVE or all-cause mortality with NSAIDs [37, 38]. Our review found similar results in AS patients, with no increased risk of any CVE (composite CVE outcome, ACS/IHD, or CVA) with NSAIDs as a whole. In fact, a significantly lower risk of CVA seen was seen with NSAIDs as a whole. Similarly, non-selective NSAIDs as a group were not found to have increased risk of a composite CVE outcome, ACS/IHD, or CVA. Some prior studies have shown that the risk within individual non-selective NSAIDs might differ as well [15]. Meta-analysis of the included studies, however, did not find any difference in the risk of CVE with naproxen or diclofenac (Fig. 5). While

diclofenac was noted to be associated with a higher risk of ACS in data from the UK THIN database, data from Taiwan was reassuring [15, 21]. Although the pooled estimate was numerically higher in diclofenac users, it was not statistically significant.

Similarly, data regarding the risk of CVE with selective Cox-2 inhibitors were also limited. Pooled data from two of the included studies [20, 32] showed a lower risk of the composite CVE outcome with Cox-2 inhibitors in AS. With respect to the risk of ACS/IHD, studies showed discordant results with Cox-2 inhibitors in AS with no overall increased risk (Fig. 3). The difference in study designs could also have led to different results: two cohort studies and one case–control study. Even among the two cohort studies from the UK and Sweden, respectively, Essers et al. [22] reported incidence rates (excluding patients with pre-existing ACS/IHD) and Kristensen et al. [32] reported RRs adjusted for prior CVE (did not exclude patients with pre-existing ACS/IHD). Sensitivity analysis excluding the case–control study by Wu et al. did not change the results. As all the studies were from national administrative databases, AS-specific characteristics such as disease activity were not available. Differences in disease characteristics could have further accounted for the different

Fig. 5 Forest plot on the risk of ACS/IHD with specific non-selective NSAIDs **a** naproxen and **b** diclofenac

results. Nonetheless, Cox-2 was associated with a lower risk for different CV outcomes studied in the pooled analyses of a limited number of studies.

The differential effects of NSAIDs have been well documented in the literature, and are believed to be related to the degree of Cox-2 selectivity. Increased in CVE with the selective Cox-2 inhibitor, rofecoxib lead to its withdrawal from the market [39]. Similarly, celecoxib was noted to be associated with a dose-related increased risk of CVE (composite endpoint of CV death, MI, stroke, and heart failure) in colon cancer patients [13]. In the more recent PRECISION trial, no increase in CVE risk with celecoxib was seen as compared to other traditional NSAIDs in a subgroup of patients with RA. This trial, however, had a low adherence rate and a relatively low dose of Cox-2 inhibitors [11]. The beneficial effect of Cox-2 inhibitors seen in our meta-analysis of the included studies might be specific to AS, as Cox-2 inhibitors have also been shown to be associated with lower radiographic progression in AS patients when used in conjunction with TNFi, as opposed to traditional NSAIDs [40]. The reason for the noted differential benefit of Cox-2 inhibitors in AS is not clear. However, the effect of confounding cannot be ruled out, especially given that all the included studies were observational. For example, clinicians may avoid Cox-2 inhibitors in patients perceived to have high CV risk (channeling bias), or alternatively patients whose symptoms are controlled on celecoxib at lower doses (200 mg per day) may have milder AS than those who require "high" doses of traditional NSAIDs. While statistical methods may be used to attempt to adjust for such confounding in observational studies, such methods were not used in all of the studies included in this meta-analysis. AS disease duration was adjusted for in few of the included studies [20, 21, 23], however, other disease-related factors such as disease activity were not accounted for. Therefore, the safety of higher doses of Cox-2 inhibitors remains uncertain.

While TNFi are associated with decreased risk of CVE in RA [9], the risk in AS remains unclear. Our review found only limited data on the effects of TNFi on CVE in AS. Studies have shown a beneficial effect of TNFi on CV parameters such as lipid profile, atherosclerosis, and CV function. Van Eijk et al. showed improvement in lipid profile after 3 months of etanercept therapy in AS patients [16]. Similarly, significantly lower intima-media thickness on carotid sonography was seen in AS patients on TNFi compared to healthy matched controls, and improvement in endothelial function was noted [17, 18]. Reduction in subclinical myocardial inflammation and improved CV function was found in cardiac magnetic resonance imaging in RA, AS, and psoriatic arthritis patients on TNFi [41]. More recent studies have also shown that TNFi led to significantly lower complement activation in SpA [42]. However, it is unclear whether these subclinical changes lead to clinically meaningful change in CV outcomes in AS. In the limited number of studies included, no difference was observed in the risk of acute coronary syndrome/ischemic heart disease (ACS/IHD) in AS patients with and without TNFi. While a minimally increased risk of composite CVE was noted with TNFi in the only study reporting this [23], there was no increase in ACS/IHD. These findings support the current guidelines recommending long-term use of NSAIDs and do not show any safety concerns in the limited data for TNFi in AS [14].

This systematic review has several limitations and strengths. The certainty in evidence in all estimates was very low due to the studies being non-randomized. Moreover, there were only a few studies examining some of the CV outcomes. Heterogeneity was high for some CV outcomes, which is likely related to different study designs, and different definitions of NSAIDs use and doses in the studies. While the comparator arm was uniformly no NSAIDs (for NSAIDs) and no TNFi (for TNFi), respectively, there were differences in the CV outcome definitions across studies. Subgroup analyses to explore the cause of heterogeneity could not be performed due to the overall low number of studies. Results from the included observational studies might be limited due to confounding by indication as those with a higher risk of CVE such as ischemic heart disease or heart failure are less likely to be treated with NSAIDs.

However, most studies adjusted for multiple factors including baseline demographic characteristics, traditional CV risk factors, comorbidities, and other medications (Table 1). We note that only a few studies included glucocorticoid use as a potential confounder [23, 32], however we assume that the use of glucocorticoids would be relatively rare, as efficacy in AS is lower compared to other inflammatory arthritides such as RA. Moreover, setting up a randomized controlled trial to study the risk of NSAIDs would require a very large number of patients, as the event rate is low (assuming an annual event rate of approximately 2% followed for approximately 3 years, a sample size of 20,000 patients would be required). For example, the PRECISION trial in RA included 24,222 patients from 926 centers with a mean follow-up of 34.1 ± 13.4 months [11]. Most studies relating to TNFi exposure were cross-sectional, hence the results should be interpreted with caution. While the reported major adverse cardiac events with secukinumab were low in clinical trial and post-marketing surveillance data, controlled data are lacking [43]. We also did not find any studies on the CV effects of IL-17A or JAKi on CVE in AS. Longitudinal analysis of CVE in TNFi and IL-17A trials on AS might provide more data on the association of TNFi with CVE in AS. Similarly, the effect of combined therapy of NSAIDs and biologics on CVE must be explored.

CONCLUSIONS

This systematic review suggests that NSAID users as a whole and users of non-selective NSAIDs did not seem to have a higher risk of any CVE. Limited data suggest possibly lower risk of composite CVE outcome in AS patients on Cox-2 inhibitors, unlike their use in the general population. These results provide some reassurance for use of NSAIDs in AS. No association between TNFi and MI was observed in a limited number of observational studies.

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