The impact of biologics and tofacitinib on cardiovascular risk factors and outcomes in patients with rheumatic disease: a systematic literature review

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Introduction: Rheumatic diseases are autoimmune, inflammatory diseases often associated with cardiovascular disease, a major cause of mortality in these patients. In recent years, treatment with biologic and targeted synthetic disease modifying anti-rheumatic drugs (DMARDs), either as monotherapy or in combination with other drugs, have become the standard of treatment. In this systematic literature review, we evaluated the effect of treatment with biologic or targeted synthetic DMARDs on the cardiovascular risk and outcomes in these patients.

Methods: A systematic search was performed in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for articles reporting on cardiovascular risk and events in patients with rheumatic disease treated with a biologic agent or tofacitinib. Articles identified were subjected to two levels of screening. Articles that passed the first level based on title and abstract were assessed on full-text evaluation. The quality of randomized clinical trials was assessed by Jadad scoring system and the quality of the other studies and abstracts was assessed using the Downs and Black instrument. The data extracted included study design, baseline patient characteristics, and measurements of cardiovascular risk and events.

Results: Of the 5722 articles identified in the initial search, screening yielded 105 unique publications from 90 unique studies (33 clinical trials, 39 prospective cohort studies, and an additional 18 retrospective studies) that reported cardiovascular outcomes. A risk of bias analysis for each type of report indicated that they were of good or excellent quality. Importantly, despite some limitations in data reported, there were no indications of significant increase in adverse cardiovascular events in response to treatment with the
agents evaluated. **Conclusions:** Treatment with biologic or targeted synthetic DMARDs appears to be well tolerated with respect to cardiovascular outcomes by these patients.
**Key Points** [3-4 bullets]

- This systematic literature review evaluated 105 publications from 90 unique studies reporting cardiovascular outcomes in response to treatment with biologic or targeted synthetic DMARDs.

- There were no indications of significant increase in adverse cardiovascular events in response to treatment with the agents evaluated.

- Treatment with biologic or targeted synthetic DMARDs appears to be well tolerated with respect to cardiovascular outcomes by these patients.

- The conclusions in this review need to be interpreted with caution as quality and quantity of data vary substantially between the various drugs included, thereby limiting stringent comparisons.
1. Introduction

Rheumatic diseases are systemic, autoimmune, inflammatory diseases characterized by chronic severe pain and progressive swelling and destruction of joints resulting in functional impairment, disability, reduced quality of life, and even death [1]. Rheumatic diseases are often associated with other comorbidities, the most common of which is cardiovascular disease (CVD), a major cause for mortality in these patients [2, 3]. Clinical disease activity and systemic inflammation, as evidenced by increase in specific biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are strong predictors of increased risk of CVD [2-5], subsequent development of CVD [6, 7], and CVD-related death [2, 3, 8]. A recently published meta-analysis showed that the relative risk for myocardial infarction (MI) was significantly increased in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) [9].

Over the last decade, biologic disease modifying anti-rheumatic drugs (bDMARDs), most notably tumor necrosis factor inhibitors (TNFi), and more recently, targeted synthetic disease modifying anti-rheumatic drugs (tsDMARDs), either as monotherapy or in combination with other drugs, have become the standard of treatment for most rheumatic diseases [10, 11]. The drugs included in this review have been approved for the treatment of RA (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib), PsA (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab), ankylosing spondylitis (AS; adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and secukinumab), and juvenile idiopathic arthritis (JIA; abatacept, adalimumab, etanercept, and tocilizumab). These medications
have been key to reducing disease activity and improving patient quality of life [10, 11]. However, their impact on the risk for CVD, the primary driver of mortality in these patients, is still unclear and needs to be evaluated given the increasingly widespread use of these agents. In particular, the reports of unwanted effects on lipid profiles need to be assessed with respect to effect on risk for CVD.

The overall objectives of this systematic literature review were to assess and compare the effect of the different agents on cardiovascular (CV) events or risk outcomes and to assess differences in these outcomes according to patient and disease type.

2. Methods

A systematic literature review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12] (Appendix A) to identify studies that investigated CV risks or events in patients with rheumatic diseases treated with bDMARDs or tsDMARDs approved for the treatment of rheumatic diseases, prescribed either as stand-alone therapy or in combination.

2.1. Data sources and searches

The data sources searched included Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Databases were searched using specific search strings, which included synonyms and combinations of the following key terms: RA, JIA, PsA, AS, adalimumab, etanercept, infliximab, certolizumab, golimumab, tofacitinib, methotrexate, DMARDs, biosimilars, and CV risk factors or outcomes. The full search strings used for the electronic databases and conference proceedings, including all the search terms and the relationships between the
search terms are listed in Electronic Supplementary Material #1. Additional studies were identified from previously published SLRs or from the references of included studies. Searches were restricted to English language and limited to the time frame of January 2000 to December 2015.

2.2. Study selection

All randomized and non-randomized control trials and observational studies on adult patients diagnosed with RA, AS, PsA, and patients of any age diagnosed with JIA were included. Preclinical (animal) or studies that pooled data from different agents, case reports, case series, case studies, previously published systematic literature reviews, letters, commentaries, and editorials were excluded. Also excluded were studies that examined the effect of bDMARDs and tsDMARDs on CV risk and events but provided insufficient data to interpret findings, studies with a sample size of fewer than 30 patients, and studies assessing novel CV biomarkers not in routine clinical use.

2.3. Screening

Two levels of screening were performed. In Level I, studies were identified based on title and abstract by SL, eliminating all publications with duplication of study populations. CJ performed a quality check of 10% of all screened studies. Discrepancy ≥5% would have prompted a re-evaluation of the whole data set. All authors reviewed all studies that were eligible for Level II screening. In Level II, qualifying articles identified in Level I were assessed based on the full-text by following a standard hierarchy of evidence. Publications not meeting the inclusion criteria were excluded. CJ screened 20% of the publications excluded at the Level II screening stage and also reviewed all publications determined to be eligible for inclusion. All disagreements were resolved by consensus.
2.4. Data extracted

For each publication, the data was extracted by SL and reviewed by all authors. The information extracted included study design, baseline patient characteristics, CV risk profile, CV risk factors, CV events, and other observations, including CRP levels and lipid levels, where available, reported in patients with rheumatic diseases treated with bDMARDs or tsDMARDs. Blood lipid levels included total cholesterol (TC), low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglycerides (TG), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), and atherogenic index (ratio of TC to HDL). CV events extracted included MI, stroke, venous thrombotic events (VTE), heart failure (HF), pulmonary thromboembolism, and hypertension. Traditional, novel and disease-specific CV risk factors or markers of atherosclerosis used in disease diagnosis, included augmentation index (AIX), AIX normalized for a heart rate of 75 beats/minute (AIX@75), cardio-ankle vascular index (CAVI), carotid intima-media thickness (cIMT), pulse wave velocity (PWV), systolic and diastolic blood pressure (BP), arterial stiffness, and N-terminal pro-brain natriuretic peptide (NT-proBNP). CV risk scores included the Reynolds, Systematic COronary Risk Evaluation (SCORE), and Framingham risk scores. All CV-related mortality was also extracted.

2.5. Risk of bias

The quality of RCTs was assessed using recommendations from the National Institute for Health and Clinical Excellence (NICE) single technology appraisal (STA) manufacturer’s template. Randomized controlled trials (RCTs) were evaluated using the Jadad scoring system [13] which ranges from 0 (very poor study) to 5 (rigorous study). The quality of
all non-randomized controlled trials (nRCTs) and observational studies were assessed using the Downs and Black instrument [14] which consists of a checklist of 27 items; the score can range from 0 (very poor study) to 32 (rigorous study). Abstracts from conference proceeding were assessed using the modified-Downs and Black instrument [15] which also consists of a checklist of 27 items; however, the score ranges from 0 (very poor study) to 28 (rigorous study).

3. Results

3.1. Search
The searches of the various databases yielded 5722 articles of which 5123 were unique (Figure 1). After the Level I screening of title and abstracts, 344 articles met the inclusion criteria and 4779 articles were excluded. Level II screening of these articles based on full text analysis yielded 196 relevant articles with 148 being excluded for various criteria (Figure 1). A deeper analysis of these showed that 41 articles had insufficient CV data to interpret findings, 26 articles reported on novel CV biomarkers that were not used in routine clinical practice, and 24 articles had enrolled <30 patients in the studies, leaving 105 unique publications reporting results from 95 studies.

3.2. Risk of bias analysis
The mean Jadad score for the 22 RCTs with full publications was 3.9 with 19 (86.4%) studies being of good quality. Of the 22 studies, 13 (59.1%) scored excellent with a mean Jadad score of 4.6, and six (27.3%) scored good with a mean Jadad score of 3.2; 3 (13.6%) studies scored poor with a mean Jadad score of 2.0. The mean Downs and Black quality assessment score for the 44 nRCTs with full publications was 15.5 with 98% of
the studies being good or excellent quality. The mean modified Downs and Black quality assessment score for the 24 abstracts from conference proceedings was 5.5 with 75% of the published abstracts being of good quality.

3.3. CV Risk in RA

3.3.1. Study Characteristics

The characteristics of all the studies classified by type for all therapeutic agents are given in Electronic Supplementary Material #2 Table 1. There were a total of 25 RCTs, 32 prospective cohort studies, and 16 retrospective cohort studies. The number of patients enrolled in these studies ranged from 30 to 68,447. Treatment duration depended on the therapeutic agent being evaluated and ranged from 6 weeks to 624 weeks.

3.3.2. Patient Characteristics

The characteristics of all RA patients enrolled in these studies for all therapeutic agents evaluated are summarized in Electronic Supplementary Material #2 Table 2. Briefly, all patients enrolled in these studies were adults (range 38.0 years to 62.7 years), mostly female (range 40.8% to 100%), and had moderate to severe disease with disease duration ranging from 0.3 years to 17.6 years.

3.3.3. CV Risk analysis

The results of CV risk analysis for all therapeutic agents are summarized in Table 1. Overall, in patients with RA, there is a higher prevalence of HF, increased incidence of impaired myocardial and longitudinal deformation, and increased left ventricle circumferential apical strain. The findings for each drug are given in brief.

3.3.3.1. Abatacept
Data on patients with RA treated with ABA were obtained from one RCT (conference abstract) [16], one prospective cohort (PC) study (full-length article [17] and conference abstract [18]), and 6 retrospective cohort (RC) studies (all conference abstracts) [19-25]. There were no changes from baseline reported for TC [16, 17, 21, 23, 25] and TG [17, 21, 23, 25]. Saito et al reported increase in both HDLc and LDLc [24], but two other studies reported no significant change [17, 21, 23, 25]. There was no significant effect on BP [17], atherogenic index [16], augmentation index [16-18, 21, 23, 25], CAVI [18], cIMT [16], and carotid artery plaques [16]. Kume et al. reported significant reduction in CRP [16], but Provan et al. reported that there was no effect [17]. For patients with RA treated with ABA, the rate of CV events was estimated at 3.3 per 100 patient years (PY) [19] and the hazard ratio (HR) range was 1.0 – 1.6 relative to the comparator drug after adjusting for potential confounding factors [19, 20]. The Framingham 10-year CVD risk was significantly reduced from 12.7 to 10.6 (p = 0.011) [22] and the adjusted Reynolds risk score was 0.4 [21, 23, 25].

3.3.3.2. Adalimumab

Data on patients with RA treated with ADA were obtained from five RCTs (four full-length articles [26-29] and three conference abstracts [30-32]), five PC studies (four full-length articles [33-36] and one conference abstract [37]), and six RC studies (four full-length articles [38-41] and two conference abstracts [19, 24]). There was no effect on TC [27, 33, 36, 40] or TG [33, 36, 40]. In some studies, there were significant increases in HDLc [24, 26, 29, 32] and LDLc [24, 26, 32], but there were others that reported no significant change in these lipids [33, 36, 40]. There was significant reduction in CRP [27, 33, 36], augmentation index [27, 30], CAVI [27, 30], SAA [26, 32], sPLA2 [26, 32]
and arterial stiffness [30]. There were no significant effects on cIMT [27, 36], BP [34, 36], ApoB:ApoA ratio [33], or atherogenic index [27, 30]. The rate for MI was 0.3% – 0.6% and stroke 0.3%. The rate of CV events was 2.7 per 100 PY [19] and the rate of VTE was 0.3 per 100 PY [35]. The rate of thromboembolic events was greater in patients who developed ADAb at 2.7 per 100 PY compared with 0.8 per 100 PY for patients who did not develop ADAb [39]. The HR range was 0.8 – 1.8 relative to rituximab or non-biological disease modifying anti-rheumatic drugs (nbDMARDs) after adjusting for potential confounding factors [19, 35].

3.3.3.3. Certolizumab pegol

Standard CV risk outcomes were not reported in two full-length publications from a single RCT and its long-term extension on patients with RA treated with certolizumab pegol [42, 43]. However, the prevalence of hypertension was estimated to be 8.2% – 10.2%. The total of 11 deaths, six occurring in the first 12 months and five in the second 12 months corresponded to a rate of 0.73 per 100 PY. None of the deaths were considered related to treatment with CZP.

3.3.3.4. Etanercept

Data on patients with RA treated with ETN were obtained from three RCTs (two full-length articles [27, 44] and one conference abstract [30]), five PCs (all full-length articles) [35, 45-48], and five RCs (four full-length articles [38, 49-51] and two conference abstracts [19, 52]). Treatment with etanercept increased HDLc [45, 47, 48], but had no significant effect on LDLc or TG [45, 47]. Etanercept had a favorable effect on lipid profile based on a significantly lower ApoB:ApoA-I ratio, but primarily in patients exhibiting good or moderate response [47] according to the European League
Against Rheumatism (EULAR) criteria [11]; however, TC was increased significantly in these patients whereas there was no statistical difference in EULAR non-responders nor in other studies [27, 48]. Arterial stiffness [30], augmentation index [27, 30, 45, 46], DAS28 [45], CAVI [27, 30], CRP [27, 45, 46, 48], and left ventricle mass index [45] were reduced significantly in patients treated with etanercept. Small increases in CV-associated SAEs such as HF, CAD, MI, and cerebrovascular events, were reported in patients with diabetes and/or chronic pulmonary disease as comorbidities [44]. Overall, there was a reduced risk of HF in patients treated with etanercept [49, 51], and the rates of CV events and serious CV events were 3.0 per 100 PY [19] and 1.0 per 100 PY [50, 52], respectively. The risk of first VTE was 0.3 per 100 PY and the adjusted HR was 1.8 relative to nbDMARDs [35].

3.3.3.5. Golimumab

There is sparse information on the effect of golimumab treatment on CV events. What is available was reported in a conference abstract on data obtained from five clinical trials [53]. The rates of CV SAEs and ischemic CV events were reported at 0.25 per 100 PY and 0.43 per 100 PY, respectively.

3.3.3.6. Infliximab

Data on patients with RA treated with INF were obtained from four RCTs (three full-length articles [54-56] and two conference abstracts [57, 58]), 11 PCs (11 full-length articles [35, 59-68] and one conference abstract [69]), and 5 RCs (four full-length articles [38, 49, 51, 70] and one conference abstract [19]). Data from several studies showed that treatment with infliximab resulted in significant increase in TC [54, 57-63, 65, 67, 68, 70], HDLc [57-65], and TG [61, 63, 65, 70]. Results with LDLc and atherogenic index
were mixed. In three PC studies, there was significant increase in LDLc for at least the first 12 weeks [60, 61, 64], whereas data from two RCTs [54, 57, 58] and two PC studies [65, 67, 68] showed no significant change. Significant improvement in atherogenic index was reported in one RCT [57, 58], but significant worsening was reported three PC studies [61, 63, 65], and no significant change was reported in one RCT [56] and two PC studies [59, 60]. Several studies reported significant reduction in inflammation as determined by decreased CRP levels [56, 60, 64, 67, 68, 70]. In one RCT [55], augmentation index worsened in response to INF treatment, but showed no significant change in another [56]. Treatment with INF resulted in higher aortic stiffness index, aortic strain, and aortic distensibility [69], but a lower risk of HF [51], decreased arterial stiffness as indicated by decreased PWV [56], and decreased aortic beta index [69]. There were no changes reported in BP and cIMT. Long-term treatment may improve myocardial deformation and normalize left ventricular torsion [67, 68]. Insulin resistance [57, 58], HOMA-IR [57, 58], and aortic elasticity [69] all improved with INF treatment. There was no significant change in N-terminal pro-brain natriuretic peptide [57, 58, 63]. SAEs were reported in 68.2% of patients who experienced CVD-related mortality [66]. The rates of CV events and VTE were 2.1 per 100 PY [19] and 0.5 per 100 PY [35], respectively. The adjusted HR for CV events was 1.1–1.3 relative to rituximab or nbDMARDs [19, 35].

3.3.3.7. Rituximab

Data on patients with RA treated with RTX were obtained from six PC studies (four full-length articles [17, 71-73] and two conference abstracts [74, 75]) and four RC studies (two full-length articles [28, 76] and six conference abstracts [19-21, 23, 25, 31]. There
was no significant effect on LDLc [17, 21, 23, 25, 71-74], TG [17, 71-74], augmentation index [17, 71, 72], PWV [17], or systolic BP [17]. Significant increases in TC, HDLc, and decrease in atherogenic index were reported in two PC studies [71, 74] and no significant change in three PC studies [17, 72, 73] and one RC study [21, 23, 25]. Significant decrease in CRP was reported in two PC studies [71, 74], whereas no significant change was reported in another [17]. In addition, there were significant decreases in ESR and DAS28 [74]. The rate of MI, the most common cardiac AE [28, 31, 76], was 0.39–0.6 per 100 PY [28, 31, 75, 76], and similar to that in the general RA population (0.48–0.59 per 100 PY) [28, 31, 76]. The overall rate of CV events was 2.4 per 100 PY. However, there were more CV-related deaths among patients treated with rituximab than those treated with placebo for over 11 years [28, 31, 76]. The rates of stroke, pulmonary embolism, DVT, and death per 100 PY were 0.5, 0.3, 0.4, and 1.6, respectively [75]. The adjusted HR for CV events was 1.0 relative to abatacept [19, 20] and the adjusted Reynolds risk score was 0.1 [21, 23, 25].

3.3.3.8. Secukinumab

In the two conference abstracts from a single RCT [77, 78], there were no significant changes in TC, HDLc, LDLc, atherogenic index, ApoB:ApoA-1 ratio, and no CV events reported.

3.3.3.9. Tocilizumab

Data on patients with RA treated with TCZ were obtained from 10 RCTs (seven full-length articles [26, 27, 79-83] and five conference abstracts [16, 30, 32, 84, 85]), seven PC studies (six full-length articles [17, 37, 72, 86-88] and one conference abstract [89]), and six RC studies (one full-length article [90] and seven conference abstracts [20-25,
Most studies reported significant increases in TC [16, 21, 23, 25, 27, 79-81, 83-86, 90, 91], HDLc [22, 24, 26, 32, 79, 85, 92], LDLc [21, 23-26, 32, 81, 85, 92], and TG [21, 23, 25, 79, 86, 92], although two PC studies reported no significant change from baseline [17, 72] and one RCT reported that the increase in TC was reversible [79]. When measured, there was significant reduction in CRP levels [16, 17, 27, 80, 84, 90], CAVI [16, 27, 30], atherogenic index [79], augmentation index [16, 22, 27, 30], and Framingham 10-year CVD risk [22]. There were no changes reported in cIMT [16, 27] or BP [17]. Compared with patients treated with methotrexate, hypertension and vascular disorders were more common in patients treated with tocilizumab [81]. The rates per 100 PY of serious cardiac dysfunction, HF, ischemic heart disease, MI, angina pectoris, stroke, and death were 1.11, 0.47, 0.43, 0.09–0.2, 0.16, 0.15, and 0.07, respectively [88]. The rates of cardiac AEs, CV-related death, and cerebrovascular-related death were 0.4% [80, 84], 6.7%–9.0% [80, 84, 88], and 5.6% [88], respectively, both higher than the rates for patients receiving placebo (0.2% and 5.1%, respectively) [80, 84]. The proportion of patients with serious cardiac dysfunction did not increase over time with treatment [88]. The adjusted HR was 0.4 [87].

3.3.3.10. Tofacitinib

Data on patients with RA treated with TOFA were obtained from nine RCTs (nine full-length articles [29, 83, 93-99] and two conference abstracts [100, 101]). Most studies reported significant increases in TC [83, 93, 95, 98, 99], HDLc [29, 83, 93-101], LDLc [29, 83, 93-101], and TG [83, 97, 100, 101], and a significant decrease in CRP [95, 97, 100, 101]. Treatment with statin can normalize cholesterol levels. There were no changes in atherogenic index [83, 93] and BP [95].
3.4. CV Risk in PsA

3.4.1. Study Characteristics

The characteristics of all the studies classified by type for all therapeutic agents are given in Electronic Supplementary Material #2 Table 3. There were a total of three RCTs [102-105], two PC studies [62, 106], and two RC studies [41, 107]. The number of patients enrolled in these studies ranged from 60 to 23,458. Treatment duration depended on the therapeutic agent being evaluated and ranged from 24 weeks to 624 weeks.

3.4.2. Patient Characteristics

The characteristics of all PsA patients enrolled in these studies for all therapeutic agents evaluated are summarized in Electronic Supplementary Material #2 Table 4. Briefly, all patients enrolled in these studies were adults (range 42.5 years to 49.6 years), the proportion of female patients ranged from 29.8% to 60.0%, and the disease duration ranged from 0.9 years to 14.6 years.

3.4.3. CV Risk analysis

Overall, all PsA patients have higher prevalence of CV comorbidities including diabetes and hypertension than the general population [105]. Furthermore, women have higher CV risk compared with men, due to higher prevalence of metabolic syndrome and elevated BP [105]. There were no studies reporting CV events or biomarkers for patients with PsA treated with abatacept, certolizumab pegol, golimumab, rituximab, tocilizumab, or tofacitinib. The results of CV risk analysis for all therapeutic agents are summarized in Table 2.

3.4.3.1. Adalimumab
Data on patients with PsA treated with ADA were obtained from two RC studies, both full-length articles [41, 107]. Costa et al. reported that HDLc was increased and TG was decreased [107]. Burmester et al. reported that the rate of CHF per 100 PY was zero.

3.4.3.2. Etanercept

Data on patients with PsA treated with ETN were obtained from one full-length article on a retrospective analysis of data from a RCT [105], one PC study (conference abstract) [106], and one full-length article for a RC study [107]. There was a significant increase in HDLc [105, 107], although the PC study reported no change [106]. There was significant reduction in CRP [105, 106]. Costa et al. reported decrease in TG [107], but the other two studies reported no significant change [105, 106]. There were no significant effects on TC [105], LDLc [105, 106], atherogenic index [106], or ApoB:ApoA-1 ratio [105, 106]. However, the favorable CV effects could not be attributed to lipid profile [106].

3.4.3.3. Infliximab

In the single prospective cohort study evaluating the effect of infliximab treatment on CV risk factors in patients with PsA [62], there was a sustained increase in TC and HDLc, but no significant effect on LDLc or TG. There was also a significant decrease in atherogenic index and CRP levels.

3.4.3.4. Secukinumab

Among patients treated with secukinumab, the reported incidence rate for major cardiac AEs was 0.7 per 100 PY based on data from a single clinical trial [103, 104]. No other CV-related events or biomarkers were reported.
3.4.3.5. Ustekinumab

In patients treated with ustekinumab, as reported in a conference abstract on a single clinical trial [102], the rate of major CV AEs was 0.7 per 100 PY. No other CV-related events or biomarkers were reported.

3.5. CV Risk in AS

3.5.1. Study Characteristics

The characteristics of all the studies classified by type for all therapeutic agents are given in Electronic Supplementary Material #2 Table 5. There were a total of two RCTs [108-110], eight PC studies [54, 55, 62, 111-115], and one RC study [41]. The number of patients enrolled in these studies ranged from 30 to 23,458. Treatment duration depended on the therapeutic agent being evaluated and ranged from 7 to 624 weeks.

3.5.2. Patient Characteristics

The characteristics of all AS patients enrolled in these studies for all therapeutic agents evaluated are summarized in Electronic Supplementary Material #2 Table 6. Briefly, all patients enrolled in these studies were adults (range 34.2 years to 43.1 years), the proportion of female patients ranged from 3.1% to 46.7%, had moderate to severe disease with a mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ranging from 4.9 to 7.0, and disease duration ranging from 1.5 years to 13.0 years.

3.5.3. CV Risk analysis

The results of CV risk analysis for all therapeutic agents are summarized in Table 3. There were no studies reporting CV events or biomarkers for patients with AS treated with abatacept, certolizumab pegol, rituximab, tocilizumab, ustekinumab, or tofacitinib.
3.5.3.1. Adalimumab

In a full-length article on a RC study on patients treated with ADA [41], the rate of CHF was reported to be 0.1 per 100 PY. No other CV events were reported.

3.5.3.2. Etanercept

Data on patients with AS treated with ETN were obtained from two PC [111, 112], both full-length articles. van Eijk et al. reported that in response to ETN, there was a significant increase in TC, HDLc, LDLc, and TG accompanied by a significant decrease in SAA particles in HDLc, atherogenic index, ApoB:ApoA-1 ratio, and CRP [111]. On the other hand, van Halm et al. reported that in patients treated with ETN, there were negative correlations between disease parameters and TC, HDLc, and TG although there were no significant changes in the levels of these lipids [112]. No other CV events were reported.

3.5.3.3. Golimumab

Data on patients with AS treated with GLM were obtained from a single full-length article on a RCT [110]. There were significant increases in TC, HDLc, and TG, but not in LDLc. There was also a significant decrease in CRP. There were no significant changes in augmentation index, BP, cIMT, and PWV. No other CV events were reported.

3.5.3.4. Infliximab

Data on patients with AS treated with INF were obtained from six PC studies, all full-length articles [54, 55, 62, 113-115]. Some studies reported significant increases in TC [54, 62], HDLc [54, 62], and TG [54], whereas Ersozlu Bozkirli et al. reported no significant changes in these lipids [113]. There was no significant change in LDLc [54, 62, 113] or augmentation index [115]. There was significant reduction in CRP [55, 62,
113, 115] and the Framingham 10-year CV risk [113]. The results were mixed for atherogenic index and BP; Spanakis et al. [62] and Ersozlu Bozkirli et al. [113] reported significant decrease in atherogenic index and BP, respectively, but others reported no significant changes in these parameters [54, 55, 115]. CV-related AEs reported included palpitations (11.4%), hypertension (20.0%), chest pain (2.9%), and premature ventricular contraction (2.9%), all of which were short term [114]. There were no long-term CV related AEs reported.

3.5.3.5. Secukinumab

The clinical trial evaluating the effect of secukinumab on patients with AS [108, 109] reported that the exposure-adjusted incidence rate for major cardiac AEs was 0.4 per 100 PY. No other CV events were reported.

3.6. CV Risk in JIA

3.6.1. Study Characteristics

The characteristics of all the studies classified by type for all therapeutic agents are given in Electronic Supplementary Material #2 Table 7. There were a total of two RCTs (including a long-term extension) [116-119], one PC study [120], and two RC studies [41, 121]. The number of patients enrolled in these studies ranged from 30 to 23,458. Treatment duration depended on the therapeutic agent being evaluated and ranged from 6 weeks to 624 weeks.

3.6.2. Patient Characteristics

The characteristics of all JIA patients enrolled in these studies for all therapeutic agents evaluated are summarized in Electronic Supplementary Material #2 Table 8. Briefly, the mean age of patients enrolled in these studies ranged from 6.9 years to 13.1 years, the
proportion of female patients ranged from 71.0% to 86.0%, and the disease duration ranged from 2.5 years to 4.7 years.

3.6.3. CV Risk analysis

The results of CV risk analysis for all therapeutic agents are summarized in Table 4. There were no studies reporting CV events or biomarkers for patients with JIA treated with abatacept, certolizumab pegol, golimumab, infliximab, rituximab, secukinumab, tofacitinib, or ustekinumab.

3.6.3.1. Adalimumab

The single retrospective cohort study evaluating the effect of adalimumab in patients with JIA reported no CHF events [41].

3.6.3.2. Etanercept

Data on patients with JIA treated with ETN were obtained from one PC study (full-length article [120] and one RC study (conference abstract) [121]. Among children with JIA, treatment with ETN significantly decreased TC, LDLc, TG, and CRP, but not HDLc [120]. However, this overall improvement in lipid profile and inflammation did not translate into improvement in atherogenic index. Among adult patients with JIA who received ETN during childhood, the prevalence of CVD of 10.8% [121], which was similar to that observed in the general population. However, patients with systemic JIA had significantly higher rate of CVD.

3.6.3.3. Tocilizumab

In the CHERISH trial [116, 117], treatment with TCZ resulted in 34.6% and 11.4% patients having TC levels ≥170 mg/dL and LDLc levels ≥110 mg/dL, respectively. Levels of cholesterol exceeding the upper limit of normal for TC or LDL were observed
at least once in 31% of the patients who received TCZ. In the TENDER trial [118], patients with JIA and insulin resistance treated with TCZ showed significant reductions in HOMA-IR at week 6 which was associated with improvement in Juvenile Arthritis Disease Activity Score and active joint count. In the long-term extension study [119], there was no change in mean TC, but 11.9% patients reported grade 2 elevation.

4. Discussion

This systematic literature search for the effect of bDMARDs and tsDMARDs on CV events among patients with rheumatic diseases resulted in 105 publications from 95 separate studies. The risk of bias analyses demonstrated that the methodological rigor of the studies included in this review was fairly high indicating that information obtained from these reports was reliable.

Of the 95 studies, 73 (76.8%) included patients with RA, 7 (7.4%) included patients with PsA, 11 (11.6%) included patients with AS, and 5 (5.3%) included patients with JIA; the total is greater than 100% as some studies included multiple indications. The information available was heavily skewed towards CV effects in patients with RA, with some data published on 10 of the 11 therapeutic agents being evaluated. By comparison, information was available from only five therapeutic agents each for patients with PsA and AS, and three therapeutic agents for patients with JIA. Sufficient relevant data were available for only ETN for all four rheumatic diseases being evaluated; although data for ADA were available for all four diseases, the information was primarily for RA with scant information on the other three diseases. Data for INF were available for RA, PsA, and AS. Data on the other eight therapeutic agents were essentially limited to one disease, seven for RA and one (GLM) for AS. Furthermore, not all studies
reported the same parameters. Thus, the patchwork of data available poses a challenge when comparing therapeutic agents across diseases and derive definitive conclusions regarding their effects.

Although the overall effects on the lipid profiles were mixed, some patterns were discernable. Six of the therapeutic agents (ETN, GLM, INF, RTX, TCZ, and TOFA) caused significant increase in TC, with an additional three (ABA, ADA, and SEC) indicating no change; significant decrease was only reported in patients with JIA treated with ETN. Significant increase in HDLc was reported for eight (ABA, ADA, ETN, GLM, INF, RTX, TCZ, and TOFA) of the therapeutic agents regardless of disease; only SEC did not increase HDLc and no data were reported for CZP or UST. The results with LDLc, TG, and atherogenic index were mixed depending on the study/investigators with about an equal number reporting significant increase or no change; significant decrease was only reported in patients with JIA treated with ETN. The ApoB:ApoA-I ratio was significantly decreased only in patients with RA and AS treated with ETN; there was no effect on patients with RA treated with ADA or SEC or patients with PsA treated with ETN. The apparent increase in HR for CVD among patients with RA treated with biologics seemed counterintuitive. Further examination of the publications revealed that these HRs were determined relative to a comparator biologic or nbDMARDs. Thus, these values do not indicate the real HRs of these drugs. Consequently, it cannot be concluded that there was an increase in CV risk when treated with biologics.

Consistently, CRP was significantly decreased across eight of therapeutic agents (there were no data for CZP, SEC, or UST) and diseases. The data for surrogate markers was mixed. When reported, there was significant decrease in CAVI (ADA, ETN and
TCZ, but not ABA) and augmentation index (ADA, ETN, and TCZ, but not ABA, GL or RTX; there was either no change or increase in response to INF treatment). There was generally no significant effect on cIMT or BP.

4.1. Limitations

The main limitation of this review is the variability in reporting of CVD events and CV risk factors in the publications identified. This has resulted in many gaps in data making it difficult for direct comparison between drugs within the same disease. Furthermore, the same risk factors and CV events were not reported for a given drug across all four rheumatic diseases making it difficult to evaluate whether or not there was a consistent pattern of response that could be attributed to that drug. In some cases, the only data available was from a published conference abstract or a single study, adding to the difficulty of this analysis. Thus, the conclusions drawn from this analysis need to be interpreted with caution.

5. Conclusions

There were no reports of significant increases in rates of CV outcomes when treated with these drugs. The data analyzed and reported in this paper indicate treatment with bDMARDs or tsDMARDs do not appear to be associated with adverse CV outcomes.
Compliance with Ethical Standards

**Funding:** The systematic literature review to support the manuscript and medical writing assistance was sponsored by Pfizer.

**Conflicts of Interest:** Dr. Michael Nurmohamed has received grants, consulting fees, support for travel to meetings, and speaker bureau fees from AbbVie, BMS, Celgene, Eli Lilly, Janssen, Menarini, MSD, Mundipharma, Pfizer, Roche, Sanofi, and UCB; fees for participating in review activities from AbbVie; and provision of writing assistance from Pfizer. Dr. Ernest Choy has received grants from Novimmune, Pfizer, Roche, and UCB; consulting fees from Abbott Laboratories, Amgen, Biogen, BMS, Celgene, Chugai Pharma, Eli Lilly, GSK, Hospira, Janssen, MedImmune, Napp, Novimmune, Novartis, Pfizer, Regeneron, Roche, R-Pharm, and Sanofi-Aventis; fees for participating in review activities from AB2 Bio Ltd; speaker bureau fees from Amgen, BMS, Boehringer Ingelheim, Chugai Pharma, Eli Lilly, Hospira, MSD, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis, and UCB. Mr. Sadiq Lula was an employee of Envision Pharma Group which was paid by Pfizer to perform the systematic literature review. Drs. Blerina Kola, Ryan DeMasi, and Paola Accossato are employees of Pfizer and own stock in the company.

**Acknowledgements**

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References


Table 1. Summary of CV risk assessment for patients with RA

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<th>tsDMARD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABA</td>
<td>ADA</td>
</tr>
<tr>
<td>TC</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>HDLc</td>
<td>↑/↔</td>
<td>↑/↔</td>
</tr>
<tr>
<td>LDLc</td>
<td>↑/↔</td>
<td>↑/↔</td>
</tr>
<tr>
<td>TG</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>ApoB:ApoA-1</td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>CAVI</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>cIMT</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>CRP</td>
<td>↑/↔</td>
<td>↓</td>
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<tr>
<td>sPLA2</td>
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</tr>
<tr>
<td>SAA</td>
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### Draft Revision 1.0

**Nurmohamed, et al.**

**Drug Safety**

<table>
<thead>
<tr>
<th>MI</th>
<th>0.3%–0.6%</th>
<th>0.8%</th>
<th>0.2%</th>
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<tbody>
<tr>
<td>Stroke</td>
<td>0.3%</td>
<td></td>
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<td>0.3%</td>
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<tr>
<td>Carotid artery plaque</td>
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<td>↔</td>
</tr>
<tr>
<td>FMD</td>
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<tr>
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<tr>
<td>Rate of CV SAE, per 100 PY</td>
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<td></td>
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<tr>
<td>Adjusted HR*</td>
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<td>0.8–1.8</td>
<td>1.8</td>
<td>1.1–1.3</td>
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</table>

Blank shaded cells indicate that data were not reported in original publications. *Relative to the comparator in that study.

ABA abatacept, ADA adalimumab, Apo apolipoprotein, boDMARD biological originator disease-modifying anti-rheumatic drug, BP blood pressure, CAVI cardio-ankle vascular index, cIMT carotid inter-media thickness, CRP C-reactive protein, CV cardiovascular, ETN etanercept, FMD flow-mediated dilation, GLM golimumab, HDLc high-density lipoprotein cholesterol, HR hazard ratio, INF infliximab, LDLc low-density lipoprotein cholesterol, MI myocardial infarction, PY person year, RA rheumatoid arthritis, RTX rituximab, SAA serum amyloid A, SAE serious adverse event, SEC secukinumab, sPLA2 secretory phospholipase A2, TC total cholesterol, TCZ tocilizumab, TG triglycerides, TOFA tofacitinib, tsDMARD targeted synthetic disease-modifying anti-rheumatic drug

↑ significantly increased, ↓ significantly decreased, ↔ no significant effect
### Table 2. Summary of CV risk assessment for patients with PsA

<table>
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<th>Risk Factor</th>
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<tr>
<td></td>
<td>ADA</td>
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<tr>
<td>TC</td>
<td>↔</td>
</tr>
<tr>
<td>HDLc</td>
<td>↑</td>
</tr>
<tr>
<td>LDLc</td>
<td>↔</td>
</tr>
<tr>
<td>TG</td>
<td>↓</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>↔</td>
</tr>
<tr>
<td>ApoB:ApoA-1</td>
<td>↔</td>
</tr>
<tr>
<td>CRP</td>
<td>↓</td>
</tr>
<tr>
<td>Rate of major CV AEs, per 100 PY</td>
<td></td>
</tr>
</tbody>
</table>

Blank shaded cells indicate that data were not reported in original publications.


↑ significantly increased, ↓ significantly decreased, ↔ no significant effect
Table 3. Summary of cardiovascular risk assessment for patients with AS

<table>
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<tr>
<th>Risk Factor</th>
<th>boDMARD</th>
</tr>
</thead>
<tbody>
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<td>ADA</td>
</tr>
<tr>
<td>TC</td>
<td>↑</td>
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<tr>
<td>HDLc</td>
<td>↑</td>
</tr>
<tr>
<td>LDLc</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td>↑</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>↔</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>↔</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>↓</td>
</tr>
<tr>
<td>ApoB:ApoA-1</td>
<td>↓</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>↔</td>
</tr>
<tr>
<td>cIMT</td>
<td>↔</td>
</tr>
<tr>
<td>CRP</td>
<td>↓</td>
</tr>
<tr>
<td>SAA</td>
<td>↓</td>
</tr>
<tr>
<td>CHF per 100 PY</td>
<td>0.1</td>
</tr>
<tr>
<td>Rate of major CV AEs, per 100 PY</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Blank shaded cells indicate that data were not reported in original publications.

ADA adalimumab, AE adverse event, Apo apolipoprotein, AS ankylosing spondylitis, 
boDMARD biological originator disease-modifying anti-rheumatic drug, BP blood pressure, CHF congestive heart failure, cIMT carotid inter-media thickness, CRP C-reactive protein, CV cardiovascular, ETN etanercept, GLM golimumab, HDLc high-density lipoprotein cholesterol, INF infliximab, LDLc low-density lipoprotein cholesterol,
PY person year, SAA serum amyloid A, SEC secukinumab, TC total cholesterol, TG triglycerides

↑ significantly increased, ↓ significantly decreased, ↔ no significant effect
Table 4. Summary of cardiovascular risk assessment for patients with JIA

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>boDMARD</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ADA</td>
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<td>TCZ</td>
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<tr>
<td>TC</td>
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<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>HDLc</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLc</td>
<td></td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Atherogenic index</td>
<td></td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blank shaded cells indicate that data were not reported in original publications.

ADA adalimumab, boDMARD biological originator disease-modifying anti-rheumatic drug, CHF congestive heart failure, CRP C-reactive protein, CV cardiovascular, ETN etanercept, HDLc high-density lipoprotein cholesterol, LDLc low-density lipoprotein cholesterol, TC total cholesterol, TCZ tocilizumab, TG triglycerides

↑ significantly increased, ↓ significantly decreased, ↔ no significant effect
Figure 1. PRISMA Flow diagram

Level I, studies identified based on title and abstract; Level II, articles identified in Level I assessed based on full-text analysis.
### Appendix A: PRISMA Checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>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.</td>
<td>2</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>6</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>6</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>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.</td>
<td>No protocol exists</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>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.</td>
<td>7</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>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.</td>
<td>6</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>ESM#1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>7</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>Checklist item</td>
<td>Reported on page #</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>7-8</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>7-8</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>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.</td>
<td>8-9</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>8</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>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.</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>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.</td>
<td>9</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>10, 17, 19, 21</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>8-9</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>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.</td>
<td>10-16; 17-19; 19-21; 22-23</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>8-9</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----</td>
<td>---------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>Not applicable</td>
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</table>

**DISCUSSION**

<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>24</th>
<th>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).</th>
<th>23-25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>25</td>
<td>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).</td>
<td>25</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
<td>25</td>
</tr>
</tbody>
</table>

**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. | 26 |


For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).