



**HAL**  
open science

## Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis

Benjamin Castagné, Marie Viprey, Julie Martin, Anne-Marie Schott, Michel Cucherat, Martin Soubrier

► **To cite this version:**

Benjamin Castagné, Marie Viprey, Julie Martin, Anne-Marie Schott, Michel Cucherat, et al.. Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis. PLoS ONE, 2019, 14 (8), pp.e0220178. 10.1371/journal.pone.0220178 . hal-04329176

**HAL Id: hal-04329176**

**<https://hal.science/hal-04329176>**

Submitted on 7 Dec 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## RESEARCH ARTICLE

# Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis

Benjamin Castagné<sup>1,2\*</sup>, Marie Viprey<sup>2,3</sup>, Julie Martin<sup>2,3</sup>, Anne-Marie Schott<sup>2,3</sup>, Michel Cucherat<sup>4,5</sup>, Martin Soubrier<sup>1</sup>

**1** Rheumatology Department, Gabriel-Montpied University Hospital, Clermont-Ferrand, France, **2** HESPER EA 7425, University of Lyon, Claude Bernard University Lyon 1, Lyon, France, **3** Public Health Centre, Hospices Civils de Lyon, Lyon, France, **4** University Lyon, UMR 5558, Laboratory of Biometry and Evolutionary Biology, CNRS, Villeurbanne, France, **5** Department of Pharmacology and Toxicology, Hospices Civils de Lyon, Lyon, France

\* [bcastagne@chu-clermontferrand.fr](mailto:bcastagne@chu-clermontferrand.fr)



## Abstract

### Objectives

Our objective was to compare the cardiovascular safety of tocilizumab and other biological disease-modifying antirheumatic drugs (bDMARD) in rheumatoid arthritis using a network meta-analysis (NMA).

### Methods

A systematic literature search through May 2018 identified randomized controlled trials (RCT) or observational studies (cohort only) reporting cardiovascular outcomes of tocilizumab (TCZ) and/or abatacept (ABA) and/or rituximab (RTX) and/or tumor necrosis factor inhibitors (TNFi) in rheumatoid arthritis patients. The composite primary outcome was the rate of major adverse cardiovascular outcomes (MACE, myocardial infarction (MI), peripheral artery disease (PAD) and cardiac heart failure (CHF)).

### Results

19 studies were included in the NMA, including 11 RCTs and 8 cohort studies. We found less events with RTX (5.41 [1.70;17.26]). We found no difference between TCZ and other treatments. Concerning MI, we found no difference between TCZ and csDMARD (4.23 [0.22;80.64]), no difference between TCZ and TNFi (2.00 [0.18;21.84]). There was no difference between TCZ and csDMARD (1.51[0.02;103.50] and between TCZ and TNFi (1.00 [0.06;15.85]) for stroke event.

With cohorts and RCT NMA, we found no difference between TCZ and other treatments for MACE (0.66 [0.42;1.03] with ABA, 1.04 [0.60;1.81] with RTX, 0.78[0.53;1.16] and 0.91 [0.54;1.51] with csDMARD), but the risk of myocardial infarction was lower with TCZ compared to ABA (0.67 [0.47;0.97]).

We lacked data to compare TCZ and other bDMARD for stroke and MI. Not enough data was available to perform a NMA for CHF and PAD.

## OPEN ACCESS

**Citation:** Castagné B, Viprey M, Martin J, Schott A-M, Cucherat M, Soubrier M (2019) Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis. PLoS ONE 14(8): e0220178. <https://doi.org/10.1371/journal.pone.0220178>

**Editor:** Wisit Cheungpasitporn, University of Mississippi Medical Center, UNITED STATES

**Received:** December 19, 2018

**Accepted:** July 10, 2019

**Published:** August 1, 2019

**Copyright:** © 2019 Castagné et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the manuscript and its Supporting Information files.

**Funding:** BC received financial support from the French society of rheumatology. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

## Conclusions

Despite an increase in cholesterol levels, TCZ has safe cardiovascular outcomes compared to other bDMARD.

## Introduction

Rheumatoid Arthritis (RA) is one of the most frequent chronic inflammatory rheumatism (CIR), characterized by chronic inflammation of joints, particularly hands and feet. The management of RA has been revolutionized with the development of biological disease-modifying antirheumatic drugs (bDMARD) [1,2]. Mortality is increased in RA, especially due to cardiovascular diseases (CVD) [3,4]. In a Danish population based study, the risk of CVD was similar between RA and diabetes (RR 1.7 95% CI 1.5 to 6.9 vs RR 1.7 95% CI 1.6 to 1.8, respectively,  $p = 0.64$ ) [5]. The cardiovascular risk seems to be linked with the disease's activity. In a recent study, Arts & al showed that low disease activity ( $\text{DAS28} \leq 3.2$ ) was associated with a reduced risk of CVD (HR 0.65 95% CI 0.43 to 0.99) compared with moderate or high disease activity ( $\text{DAS28} > 3.2$ ) [6].

The release of inflammatory cytokines (IL6, IL1, TNF alpha) leads to a decrease of total cholesterol (CT), especially HDL-cholesterol (HDL-C) [7,8]. Furthermore, the anti-atherogenic function of HDL-cholesterol become pro-atherogenic because of a linkage with inflammatory proteins like SAA [8]. In the recent recommendations of the European Ligue Against Rheumatism (EULAR), CVD risk assessment is recommended for all patients with RA at least once every 5 years [9].

Tocilizumab (TCZ) is a bDMARD which blockades the IL-6 receptor and has demonstrated its efficacy to control the disease activity in a phase III double-blinded randomized controlled trial (RCT): the OPTION study [10]. However, RCT and other studies showed that TCZ was associated with an increased cholesterol level [10,11]. This increase was also estimated superior compared to adalimumab (ADA) in a post-hoc analysis of the ADACTA trial [12]. TCZ interacts with CYP450 which is also implicated in atorvastatin metabolism [13]. Therefore, it has been used with caution in patients with high cardiovascular risk, particularly those with dyslipidemia. Recent studies showed reassuring data concerning major adverse cardiovascular events (MACE) with TCZ compared to other bDMARD [14–18]. Two studies conducted in American databases underscored significant decrease in cardiovascular events with TCZ [14,15]. In Zhang & al. study, TCZ reduced the risk of myocardial infarction (MI) significantly more than abatacept (ABA) (HR 0.64 95% CI 0.41 to 0.99) [14]. Kim & al. found better cardiovascular outcomes with TCZ comparing to TNF inhibitors (TNFi) (HR 0.68 95% CI 0.49 to 0.94) [15]. Furthermore, TCZ decreases inflammatory proteins like SAA, and may restore the anti-atherogenic function of HDL-C.

Given these controversial results, we aimed to assess the cardiovascular safety of tocilizumab in rheumatoid arthritis compared to other bDMARD using a network meta-analysis (NMA).

## Materials and methods

This systematic review with meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA)

guidelines (S1 File) [19]. Our protocol was recorded on PROSPERO under the registration number CRD42018097180.

### Literature search

This systematic review was performed by searching in PubMed/Medline, Science Direct, and Web of Science databases, and in Cochrane and Wiley Online libraries. We also searched abstracts in the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual meetings databases, from January 2003 until May 2018. The search equations are available in supporting information (S2 File).

### Eligibility criteria

Our eligibility criteria for qualitative analysis were: RCT or observational (cohort only) studies, wrote in French or in English, assessing cardiovascular outcomes among rheumatoid arthritis patients treated by TCZ and/or ABA and/or rituximab (RTX) and/or TNFi.

### Study selection

Studies were selected on the basis of their titles and abstracts, then on their full text, by two independent reviewers (BC, JM). Disagreements were resolved through discussion with a third reviewer (MV), when necessary.

### Data extraction and quality assessment

Two reviewers (BC and JM) assessed independently the quality of selected studies using the Cochrane Risk Of Bias tool (RoB 2.0) [20] for randomized studies and the Cochrane Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I tool) [21] for non-randomized. The two reviewers (BC and JM) also performed data extraction independently using a predetermined form. If necessary, disagreements were resolved by the third reviewer (MV). We extracted from each study: authors and publication year, country, bDMARD used in the study, number of previous bDMARD and previous csDMARD, number of patients, patient-year, follow-up period (year), number of MACE (major adverse cardiovascular events), myocardial infarction (MI), stroke, cardiac heart failure (CHF) and peripheral artery disease (PAD),

### Outcomes measures

The composite primary outcome was the rate of MACE which included stroke, MI, CHF and PAD (obliterating arteriopathy of the limbs, kidney and mesenteric artery diseases and aortic diseases). The secondary outcomes were rates of each cardiovascular event).

### Data analysis

A frequentist network meta-analysis based on a random effects model [22] was conducted for all outcomes to compute relative risk (RR) and their 95% confidence interval (95%CI). NMA allows to synthesize information from numerous studies addressing the same outcomes but involving different interventions [23,24]. NMA combines direct and indirect evidence across a network of studies into a single effect size. Forest plots were used to represent the quantitative results. For pairwise comparison, statistical heterogeneity between studies was assessed by the Cochran's Q test ( $p < 0.05$  for significance) and the  $I^2$  statistic ( $< 25\%$ : low heterogeneity,  $25\text{--}50\%$ : moderate,  $50\text{--}75\%$ : high and  $> 75\%$ : very high). All analyses were performed using R (netmeta package version 0.9–5 for treatment comparison, meta package version 4.8–2, R

Language and Environment for Statistical Computing, Vienna, Austria) [25,26]. A subgroup analysis was performed, including RCTs only and cohort studies only.

## Results

### Literature search results and studies characteristics

After duplicates removal, 10 454 articles were found using PubMed/Medline, Science direct, Web of science, Cochrane library databases and ACR and EULAR conference abstracts. Of the 10 454 identified records, 10 319 were excluded at title/abstract level, leaving 135 full-text examined. Of these, we selected 29 studies, 27 original articles and two conference abstracts [18,27] for qualitative analysis (Fig 1). 106 articles did not meet the inclusion criteria for the following reasons: one was a case-control study, 55 were not controlled studies, 44 did not have clinical outcomes (biological or imaging), five because the studied population was already included, and one because the full-text could not be accessed.

Of the 29 studies included in the qualitative analysis, 13 studies were conducted in North America [11,14,15,17,28–35], 16 in Europe [10,11,17,18,29,34,36–45], five in Asia [17,32,46–48], four in South America [11,17,34,38] and two in Australia [11,32]. Study characteristics are available in Table 1. 16/29 studies were RCT [10,11,27,29,32,34–36,39,41–46,48] and 13/29 were cohort studies [14,15,17,18,28,30,31,33,37,38,40,47,49]. Of the 13 cohort studies, five [14,15,17,31,33] were performed using national health care databases and four [14,15,31,33] were propensity matched. Of the 16 RCT, four were open-label trials [27,41,43,46], the others were double-blinded.

We identify two major concerns due to confounding in two cohort studies [40,49], because of the absence of multivariate analysis. The other potential bias was selective reporting due to the absence of online recorded protocol for 8 studies. Detailed bias assessment is reported in Table 2.

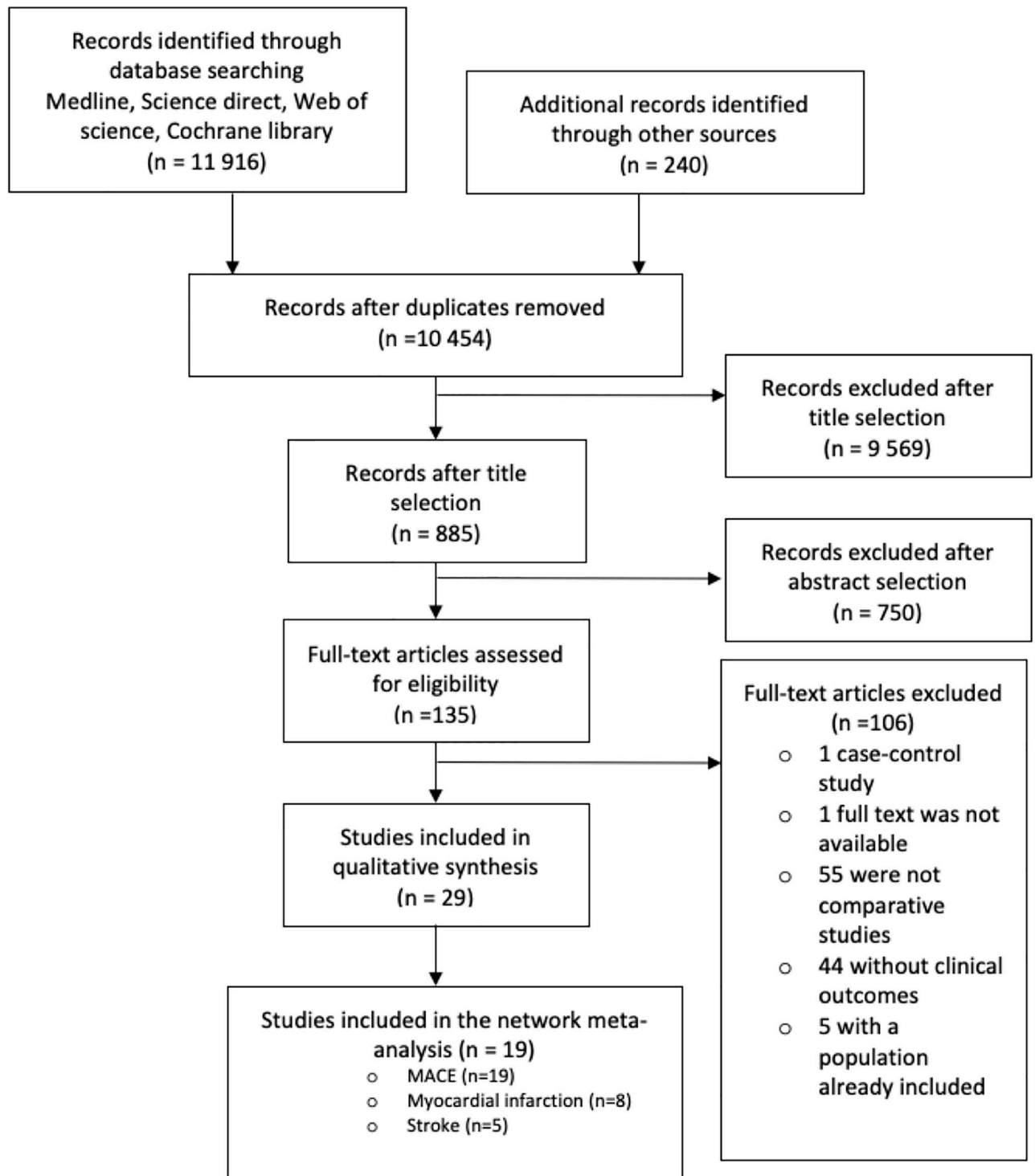
For quantitative analysis, analyzable data for NMA were available in only 19 studies for MACE outcome [10,11,14,27–30,32–34,38–40,42–44,46,48,49], eight for MI [11,14,15,27,32,34,48,49], five for stroke [11,15,27,34,38], but not enough data were available for CHF. Unfortunately, PAD was included in the MACE composite criteria in the studies but were not reported separately. Three studies [18,36,47] responded to our inclusion criteria but did not reported the number of MACE event, only Hazard Ratio (HR) or only the total number or cardiovascular events (not for each group) which have not been reported in Table 1.

### MACE risk with TCZ vs other bDMARD

The analysis of MACE outcome encompassed 19 studies (11 RCT and 8 cohorts) 12 312 patients were treated by TCZ, 8 123 with RTX, 28 728 with ABA, 45 963 with TNFi and 21 372 with csDMARD. 1 766 MACE were recorded: 125 under TCZ (1.02%), 183 under RTX (2.25%), 656 under ABA (2.28%), 1066 under TNFi (2.32%), 264 under csDMARD (1.24%).

First, we included only RCT ( $n = 11$ ) in the NMA. We found less events with RTX (TCZ vs RTX 5.41 [1.70;17.26]. We found no difference between TCZ and other treatments (1.10 [0.50;2.40] with TNFi, 4.37 [0.43;44.55] with ABA and 1.49[0.77;17.26] with csDMARD) (Fig 2). The results with only observational studies are represented in Fig 3.

When we included both designs (RCT and cohort) we found no difference between TCZ and other treatments: 0.66 [0.42;1.03] with ABA, 1.04 [0.60;1.81] with RTX, 0.78[0.53;1.16] and 0.91 [0.54;1.51] with csDMARD (Fig 4).



**Fig 1. Flow chart of the systematic literature review.** PubMed/Medline, Web of science, Cochrane library, Science direct and ACR, Annual College of Rheumatology; EULAR, European League Against Rheumatism databases.

<https://doi.org/10.1371/journal.pone.0220178.g001>

Table 1. Characteristics and results of studies on cardiovascular events (n = 29).

| STUDY                      | TREATMENT                        | AGE (YEARS)      | GENDER (FEMALE) | HTA | DYSLIPIDEMIA | SMOKING | DIABETUS MELLEITUS | PREV CV | PREVB    | PREVCS | N      | TOTAL PY | FOLLOW-UP (YEAR) | MACE | MI  | STROKE | CHF |
|----------------------------|----------------------------------|------------------|-----------------|-----|--------------|---------|--------------------|---------|----------|--------|--------|----------|------------------|------|-----|--------|-----|
| AL-ALY & AL. [28] 2011     | TNF $\alpha$                     | 57 $\pm$ 12      | 9%              | 68% | 52%          | NS      | 31%                | 38%     | NS       | NS     | 3796   | 9 563    | 3.5              | 1460 | NS  | NS     | NS  |
|                            | cSDMARD                          | 63 $\pm$ 12      | 9%              | 68% | 52%          | NS      | 31%                | 36%     | NS       | NS     | 19899  | 65 766   | 3.5              | 7761 | NS  | NS     | NS  |
| BURMESTER & AL. [36] 2017  | TCZ                              | 50.2 $\pm$ 13.6  | 77%             | NS  | NS           | NS      | NS                 | NS      | 0        | 0      | 1 108  | 1 645    | 2                | NS   | NS  | NS     | NS  |
|                            | MTX                              | 49.6 $\pm$ 13.1  | 80%             | NS  | NS           | NS      | NS                 | NS      | 0        | 0      | 282    | 339      | 2                | NS   | NS  | NS     | NS  |
| CARDENAS & AL. [37] 2016   | IFX                              | 51.5 $\pm$ 12.7  | 80%             | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 55     | NS       | 2                | 3    | NS  | NS     | NS  |
|                            | ADA                              | 52.9 $\pm$ 14.7  | 87%             | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 31     | NS       | 2                | 1    | NS  | NS     | NS  |
|                            | ETN                              | 55.1 $\pm$ 14    | 82%             | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 44     | NS       | 2                | 3    | NS  | NS     | NS  |
| CHOY & AL. [38] 2017       | TCZ                              | 54.3 $\pm$ 12.8  | NS              | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 423    | 404      | 1                | 0    | NS  | 0      | NS  |
|                            | TNF $\alpha$                     | 55.2 $\pm$ 13.1  | NS              | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 793    | 776      | 1                | 2    | NS  | 2      | NS  |
| CURTIS & AL. [17] 2015     | TCZ (insurance claims databases) | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | 62 713 | 60 754   | NS               | 206  | 115 | 91     | NS  |
|                            | TNF $\alpha$                     | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | 19 000 | 53 360   | NS               | 676  | 308 | 368    | NS  |
|                            | TCZ (safety database)            | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | 5734   | 4 345    | NS               | 28   | 14  | 14     | NS  |
| EMERY & AL. [29] 2010      | CTZ                              | 50.4 $\pm$ 13.6  | 76%             | NS  | NS           | NS      | NS                 | NS      | 0        | 0      | 659    | NS       | 1                | 39   | NS  | NS     | NS  |
|                            | MTX                              | 51.2 $\pm$ 13    | 80%             | NS  | NS           | NS      | NS                 | NS      | 0        | 0      | 213    | NS       | 1                | 9    | NS  | NS     | NS  |
|                            | RTX                              | 51.6 $\pm$ 12.7  | 80.4%           | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 337    | 161      | 0.5              | 4    | NS  | NS     | NS  |
| EMERY & AL. [39] 2017      | MTX                              | 52.16 $\pm$ 12.4 | 85.5%           | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 172    | 79       | 0.5              | 13   | NS  | NS     | NS  |
|                            | TCZ                              | 54.4 $\pm$ 13    | 79%             | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 162    | NS       | 0.5              | 3    | 2   | 1      | NS  |
| GABAY & AL. [11] 2013      | ADA                              | 53.3 $\pm$ 12.4  | 82%             | NS  | NS           | NS      | NS                 | NS      | 0        | 1      | 162    | NS       | 0.5              | 2    | 1   | 1      | NS  |
|                            | ETN                              | 54               | 78%             | NS  | NS           | NS      | NS                 | NS      | 0        | 2      | 166    | NS       | NS               | 4    | 4   | 0      | 0   |
|                            | IFX                              | 55.4             | 79%             | NS  | NS           | NS      | NS                 | NS      | 0        | 2      | 135    | NS       | NS               | 0    | 0   | 0      | 0   |
| GEBOREK & AL. [49] 2002    | cSDMARD                          | 61.3             | 82%             | NS  | NS           | NS      | NS                 | NS      | 0        | 2      | 103    | NS       | NS               | 0    | 0   | 0      | 0   |
|                            | TCZ                              | 61               | 78%             | 71% | NS           | 29%     | 18%                | NS      | 0        | 1      | 1538   | 4900     | 3.2              | 83   | 29  | 26     | 12  |
| GOTTENBERG & AL. [18] 2016 | ETN                              | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | 0        | 12     | 1542   | 4891     | 3.2              | 78   | 32  | 16     | 8   |
|                            | TCZ                              | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | NS     | 3 441    | 2                | NS   | NS  | NS     | NS  |
|                            | ABA                              | NS               | NS              | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | NS     | 4 912    | 2                | NS   | NS  | NS     | NS  |
| HARROLD & AL. [30] 2015    | RTX                              | 57.8 $\pm$ 11.7  | 81%             | NS  | NS           | NS      | NS                 | NS      | NS       | NS     | NS     | 10 545   | 2                | NS   | NS  | NS     | NS  |
|                            | TNF $\alpha$                     | 56.1 $\pm$ 12.4  | 79%             | NS  | NS           | NS      | 10.7%              | 11.3%   | $\geq$ 1 | NS     | 265    | 242      | 1                | 5    | NS  | NS     | NS  |

(Continued)

Table 1. (Continued)

| STUDY                      | TREATMENT    | AGE (YEARS)      | GENDER (FEMALE) | HTA   | DYSLIPIDEMIA | SMOKING | DIABETUS MELLITUS | PREV CV | PREVB    | PREVCS | N     | TOTAL PY | FOLLOW-UP (YEAR) | MACE | MI | STROKE | CHF |
|----------------------------|--------------|------------------|-----------------|-------|--------------|---------|-------------------|---------|----------|--------|-------|----------|------------------|------|----|--------|-----|
| IANNONE & AL. [40] 2017    | TCZ          | 54.5             |                 | 14.3% | NS           | NS      | 3.9%              | 3.5%    | NS       | NS     | 202   | NS       | 2                | 7    | NS | NS     | NS  |
|                            | ABA          | 57.4             | 77.2%           | 15.3% | NS           | NS      | 2.9%              | 4.7%    | NS       | NS     | 230   | NS       | 2                | 11   | NS | NS     | NS  |
|                            | TNF $\alpha$ | 53.9             |                 | 23.2% | NS           | NS      | 4.9%              | 5%      | NS       | NS     | 1135  | NS       | 2                | 33   | NS | NS     | NS  |
| JIN & AL. [31] 2017        | ABA          | NS               | NS              | NS    | NS           | NS      | NS                | NS      | NS       | NS     | 6934  | NS       | NS               | 114  | NS | NS     | NS  |
|                            | TNF $\alpha$ | NS               | NS              | NS    | NS           | NS      | NS                | NS      | NS       | NS     | 6934  | NS       | NS               | 113  | NS | NS     | NS  |
| JOBANPUTRA & AL. [41] 2012 | ADA          | 55 $\pm$ 12.5    | 75%             | NS    | NS           | NS      | NS                | NS      | 0        | 2      | 60    | NS       | 1                | 5    | NS | NS     | NS  |
|                            | ETN          | 53.2 $\pm$ 12.4  | 70%             | NS    | NS           | NS      | NS                | NS      | 0        | 2      | 60    | NS       | 1                | 6    | NS | NS     | NS  |
| KAY & AL. [42] 2008        | GOL          | 54 (46-64)       | 77.4%           | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 137   | NS       | 1                | 2    | NS | NS     | 2   |
|                            | MTX          | 52 (46-66)       | 74.3%           | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 35    | NS       | 1                | 0    | NS | NS     | 0   |
| KEYSTONE & AL. [32] 2016   | GOL          | 51 (44-57)       | 89%             | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 434   | NS       | 5                | 2    | 2  | NS     | NS  |
|                            | MTX          | 52 (42-58)       | 82%             | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 105   | NS       | 5                | 0    | 0  | NS     | NS  |
| KIM & AL. [46] 2012        | ETN          | 48.4 $\pm$ 12    | 91.4%           | NS    | NS           | NS      | NS                | NS      | 0        | 0      | 137   | NS       | 0.33             | 1    | NS | NS     | 1   |
|                            | cSDMARD      | 48.5 $\pm$ 11.3  | 88.4%           | NS    | NS           | NS      | NS                | NS      | 0        | 0      | 103   | NS       | 0.33             | 0    | NS | NS     | 0   |
| KIM & AL. [15] 2017        | TCZ          | 58.9 $\pm$ 10.2  | 88.3%           | 60.6% | 45.8%        | NS      | 20%               | 12.5%   | $\geq$ 1 | NS     | 9218  | 7236     | NS               | 43   | 21 | 23     | NS  |
|                            | TNF $\alpha$ | 58.7 $\pm$ 10    | 82%             | 57.5% | 44%          | NS      | 16%               | 12.2%   | $\geq$ 1 | NS     | 18810 | 14776    | NS               | 103  | 7  | 49     | NS  |
| KIM & AL. [33] 2018        | TCZ          | 58.8 $\pm$ 10.4  | 81.4%           | 59.8% | 46.3%        | NS      | 20.1%             | 12%     | NS       | NS     | 6237  | NS       | NS               | 32   | NS | NS     | NS  |
|                            | ABA          | 59 $\pm$ 10      | 87%             | 59.1% | 45.4%        | NS      | 19.23%            | 12.6    | NS       | NS     | 14685 | NS       | NS               | 112  | NS | NS     | NS  |
| MANDERS & AL. [43] 2015    | ABA          | 56.2 $\pm$ 9.95  | 88.4%           | NS    | NS           | NS      | NS                | NS      | 1        | 1      | 43    | NS       | 1                | 1    | NS | NS     | NS  |
|                            | RTX          | 57.1 $\pm$ 11.1  | 63%             | NS    | NS           | NS      | NS                | NS      | 1        | 1      | 46    | NS       | 1                | 2    | NS | NS     | NS  |
|                            | TNF $\alpha$ | 56.3 $\pm$ 11.2  | 74%             | NS    | NS           | NS      | NS                | NS      | 1        | 1      | 50    | NS       | 1                | 2    | NS | NS     | NS  |
| SAKAI & AL. [47] 2015      | TCZ          | 59.2 $\pm$ 13    | 82.5%           | NS    | NS           | NS      | 10.9%             | NS      | NS       | NS     | 302   | 22468    | 1                | NS   | NS | NS     | NS  |
|                            | TNF $\alpha$ | 57.33 $\pm$ 15.2 | 82.8%           | NS    | NS           | NS      | 10.5%             | NS      | NS       | NS     | 304   | 23101    | 1                | NS   | NS | NS     | NS  |
| SMOLEN & AL. [44] 2015     | CTZ          | 53.6 $\pm$ 11.9  | 86.4%           | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 96    | NS       | 2                | 9    | NS | NS     | NS  |
|                            | cSDMARD      | 54 $\pm$ 12.4    | 76.4%           | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 98    | NS       | 2                | 5    | NS | NS     | NS  |
| SMOLEN & AL. [45] 2016     | CTZ          | 53.5 $\pm$ 12.3  | 79%             | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 516   | NS       | 2                | 12   | NS | NS     | 9   |
|                            | ADA          | 52.9 $\pm$ 12.8  | 79%             | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 523   | NS       | 2                | 9    | NS | NS     | 8   |
| SMOLEN & AL. [10] 2008     | TCZ          | 51.1 $\pm$ 12.3  | 83.5%           | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 418   | NS       | 1                | 29   | NS | NS     | NS  |
|                            | MTX          | 50.6 $\pm$ 12.1  | 78%             | NS    | NS           | NS      | NS                | NS      | 0        | 1      | 204   | NS       | 1                | 10   | NS | NS     | NS  |

(Continued)



Table 1. (Continued)

| STUDY                     | TREATMENT    | AGE (YEARS)    | GENDER (FEMALE) | HTA   | DYSLIPIDEMIA | SMOKING | DIABETUS MELLEITUS | PREV CV | PREVB | PREVCS | N      | TOTAL PY | FOLLOW-UP (YEAR) | MACE | MI  | STROKE | CHF |
|---------------------------|--------------|----------------|-----------------|-------|--------------|---------|--------------------|---------|-------|--------|--------|----------|------------------|------|-----|--------|-----|
| WESTHOVENS &AL. [34] 2006 | IFX          | 52.5 (44-60.5) | 78.9            | NS    | NS           | NS      | NS                 | NS      | 0     | 1      | 721    | NS       | 0.5              | 5    | 4   | 1      | NS  |
|                           | MTX          | 52 (44-61)     | 83.2%           | NS    | NS           | NS      | NS                 | NS      | 0     | 1      | 363    | NS       | 0.5              | 0    | 0   | 0      | NS  |
| WEISMAN &AL. [35] 2007    | ETN          | 60.6 (19-84)   | 72.2%           | 63.5% | 63.5%        | NS      | 49.7%              | 60%     | 0     | 1      | 266    | NS       | 0.33             | 7    | NS  | NS     | NS  |
|                           | Placebo      | 59.2 (23-85)   | 78.1%           | 56.1% | 66.1%        | NS      | 49.5%              | 65%     | 0     | 1      | 269    | NS       | 0.33             | 1    | NS  | NS     | NS  |
| YAMAMOTO &AL. [48] 2014   | CTZ          | 53.4 v ±10.7   | 81.9%           | NS    | NS           | NS      | NS                 | NS      | 0     | 1      | 239    | NS       | 0.5              | 2    | 2   | NS     | NS  |
|                           | MTX          | 51.9 ±11.1     | 85.7%           | NS    | NS           | NS      | NS                 | NS      | 0     | 1      | 77     | NS       | 0.5              | 0    | 0   | NS     | NS  |
| ZHANG &AL. [14] 2016      | TCZ          | 63.7           | 87%             | 27.8% | NS           | 23.59%  | 14.1%              | NS      | NS    | NS     | 3 332  | 2 728    | NS               | 17   | 17  | NS     | NS  |
|                           | RTX          | 64.9           | 84.4%           | 30%   | NS           | 21.55%  | 14.84%             | NS      | NS    | NS     | 7 475  | 8 424    | NS               | 71   | 71  | NS     | NS  |
|                           | TNF $\alpha$ | 67.5%          | 86.7%           | 27.7% | NS           | 21.19%  | 15%                | NS      | NS    | NS     | 35 718 | 44 763   | NS               | 359  | 359 | NS     | NS  |
|                           | ABA          | 65.6           | 87%             | 29.6% | NS           | 22.1%   | 13.9%              | NS      | NS    | NS     | 13 608 | 18 747   | NS               | 138  | 138 | NS     | NS  |

RTX, rituximab; ADA, adalimumab; IFX, infliximab; ETN, etanercept; CTZ, certolizumab pegol; GOL, golimumab; MTX, methotrexate; TNF $\alpha$ , TNF inhibitor; Prevcs, previous csDMARD, conventional synthetic disease-modifying antirheumatic drugs; Prevb, previous bDMARD biological disease-modifying antirheumatic drugs; PrevCV, previous cardiovascular event; NS, not specified; PY, patient year

<https://doi.org/10.1371/journal.pone.0220178.t001>

Table 2. Risk of bias assessment (n = 29).

| Randomized controlled Trial (ROB2 tool) |      |                         |                                   |  |   |                             |                         |                     |
|---|------|-------------------------|-----------------------------------|--|---|-----------------------------|-------------------------|---------------------|
| Author                                  | Year | Study acronym           | Random sequence generation        | Allocation concealment                 | Blinding of participants and personnel    | Blinding of outcome data    | Incomplete outcome data | Selective reporting |
| Burmester &al. [36]                     | 2017 | FUNCTION                | +                                 | +                                      | +   | +                           | +                       | +                   |
| Emery &al. * [29]                       | 2010 | SERENE                  | +                                 | +                                      | +   | +                           | +                       | +                   |
| Emery &al. * [39]                       | 2017 | C-EARLY                 | +                                 | +                                      | +   | +                           | +                       | +                   |
| Gabay &al. * [11]                       | 2013 | ADACTA                  | +                                 | +                                      | +   | +                           | +                       | +                   |
| Giles &al. * [27]                       | 2016 | -                       | +                                 | +                                      | ?   | ?                           | +                       | +                   |
| Jobanputra &al. [41]                    | 2012 | RED SEA                 | +                                 | +                                      | ?   | +                           | +                       | +                   |
| Kay &al. * [42]                         | 2008 | -                       | +                                 | +                                      | +   | +                           | +                       | +                   |
| Keystone &al. * [32]                    | 2016 | GO-FORWARD              | +                                 | +                                      | +   | +                           | +                       | +                   |
| Kim &al. * [46]                         | 2012 | APPEAL                  | +                                 | +                                      | ?   | +                           | +                       | +                   |
| Manders &al. * [43]                     | 2015 | DREAM-TIME              | +                                 | +                                      | ?   | +                           | +                       | +                   |
| Smolen &al. * [10]                      | 2008 | OPTION                  | +                                 | +                                      | +   | +                           | +                       | +                   |
| Smolen &al. [45]                        | 2016 | EXXELARATE              | +                                 | +                                      | +   | +                           | +                       | +                   |
| Smolen &al. * [44]                      | 2015 | CERTAIN                 | +                                 | +                                      | +   | +                           | +                       | +                   |
| Westhovens &al. * [34]                  | 2006 | -                       | +                                 | +                                      | +   | +                           | +                       | +                   |
| Weisman &al. [35]                       | 2007 | -                       | +                                 | +                                      | +   | +                           | +                       | +                   |
| Yamamoto &al. * [48]                    | 2014 | J-RAPID                 | +                                 | +                                      | +   | +                           | +                       | +                   |
| Non randomized trials(ROBINS-I tool)    |      |                         |                                   |  |   |                             |                         |                     |
| Author                                  | Year | Bias due to confounding | Bias in selection of participants | Bias in classification of intervention | Bias due to deviations from interventions | Bias in measurement outcome | Incomplete outcome data | Selective reporting |
| Al-aly &al. * [28]                      | 2011 | ?                       | +                                 | +                                      | +   | +                           | +                       | ?                   |
| Cardenas &al. [37]                      | 2016 | ?                       | +                                 | +                                      | +   | +                           | +                       | ?                   |
| Choy &al. * [38]                        | 2017 | ?                       | +                                 | +                                      | +   | +                           | +                       | +                   |
| Curtis &al. [17]                        | 2015 | ?                       | +                                 | +                                      | +   | +                           | +                       | +                   |
| Geborek &al. * [49]                     | 2002 | -                       | +                                 | +                                      | +   | +                           | +                       | ?                   |
| Gottenberg &al. [18]                    | 2016 | ?                       | +                                 | +                                      | +   | +                           | +                       | ?                   |

(Continued)

Table 2. (Continued)

|                        |      |   |   |   |   |   |   |   |
|------------------------|------|---|---|---|---|---|---|---|
| Harrold &al. *<br>[30] | 2015 | ? | + | + | + | + | + | + |
| Iannone &al. *<br>[40] | 2018 | - | + | + | + | + | + | ? |
| Jin &al. [31]          | 2017 | + | + | + | + | + | + | ? |
| Kim &al. [15]          | 2017 | + | + | + | + | + | + | + |
| Kim &al. *<br>[33]     | 2018 | + | + | + | + | + | + | + |
| Sakai &al. [47]        | 2015 | ? | + | + | + | + | + | ? |
| Zhang &al. *<br>[14]   | 2016 | + | + | + | + | + | + | ? |

RTX, rituximab; ADA, adalimumab; IFX, infliximab; ETN, etanercept; CTZ, certolizumab pegol; GOL, golimumab; MTX, methotrexate; TNFi, TNF inhibitor; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; NS, not specified, PY; patient year; IR incidence rate; RCT randomized controlled trial; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; + low risk; ? some concerns; - high risk; \*, included in NMA

<https://doi.org/10.1371/journal.pone.0220178.t002>

### MI risk with TCZ vs other bDMARD

The analysis of MI risk included eight studies (four RCT and four cohorts). 11 723 patients were treated by TCZ, 74 75 with RTX, 13 608 with ABA, 53 068 with TNFi and 648 with csDMARD. 689 MI were recorded, 58 under TCZ (0.49%), 71 under RTX (0.95%), 138 under ABA (1.01%) and 422 under TNFi (0.80%) and no MI under csDMARD. In the RCT NMA we found no difference between TCZ and csDMARD (4.23 [0.22;80.64]), no difference between TCZ and TNFi (2.00 [0.18;21.84]). We lacked data to compare TCZ and other bDMARD (Fig 2). With both designs included, the risk of myocardial infarction was lower with TCZ compared to ABA (0.67 [0.47;0.97]). There was no difference with other treatments (Fig 4).

### Stroke risk with TCZ vs other bDMARD

Five studies were included for stroke event (two RCT and three cohorts). 11 345 patients were treated by TCZ, 22 024 by TNFi and 363 by csDMARD. 119 strokes were recorded, 40 under TCZ (0.35%), 79 under TNFi (0.36%). We did not record stroke event under csDMARD only. With RCT NMA, there was no difference between TCZ and csDMARD (1.51 [0.02;103.50]) and between TCZ and TNFi (1.00 [0.06;15.85]). We lacked data to compare TCZ and other bDMARD (Fig 2). Similar results were found with the analysis that included both designs (Fig 4), and with observational studies only (Fig 3).

### Comparison of CHF

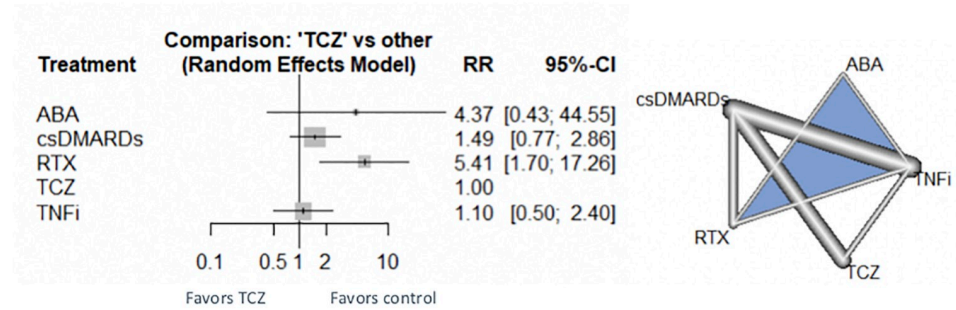
There was not enough data available to perform a network meta-analysis.

### Discussion

We performed the first network meta-analysis comparing the cardiovascular outcomes of TCZ and other biologics. However, we found a lower risk of MACE with RTX in the RCT NMA, which is not significant when we included only cohorts or both designs. This study showed that TCZ has similar cardiovascular outcomes comparing with other bDMARD and csDMARD.

TCZ significantly increases lipids levels more than TNFi [12], ABA and RTX [50]. This is one of the reasons why TCZ was initially used with a particular attention in patient with a high

### Analysis with only RCTs MACE



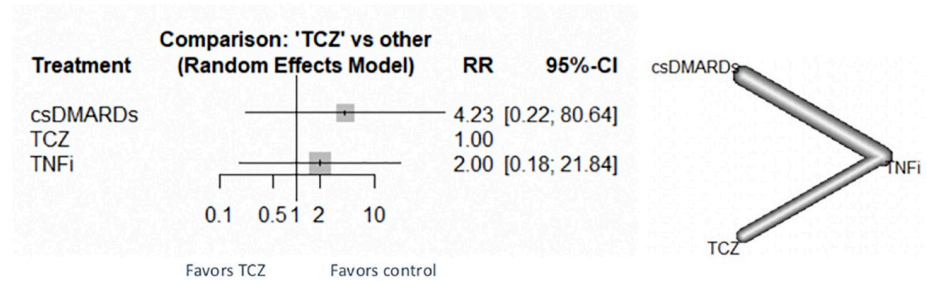
Tau<sup>2</sup> = 0; Cochran's Q = 5.42; p=0.71 I<sup>2</sup> = 0%; k= 11 studies

|          | P-Score (random) |
|----------|------------------|
| RTX      | 0.89             |
| TCZ      | 0.16             |
| csDMARDs | 0.49             |
| TNFi     | 0.21             |
| ABA      | 0.76             |

Direct vs indirect comparison (random effects model)

| Comparison       | k | prop | nma  | direct | indirect | RoR   | p-value |
|------------------|---|------|------|--------|----------|-------|---------|
| ABA vs csDMARDs  | 0 | 0    | 0.34 | .      | 0.34     | .     | .       |
| ABA vs RTX       | 1 | 0.88 | 1.24 | 0.54   | 707.40   | <0.01 | 0.04    |
| TCZ vs ABA       | 0 | 0    | 4.37 | .      | 4.37     | .     | .       |
| ABA vs TNFi      | 1 | 0.88 | 0.25 | 0.58   | <0.01    | 1299  | 0.04    |
| csDMARDs vs RTX  | 1 | 0.76 | 3.64 | 6.37   | 0.60     | 10.62 | 0.04    |
| TCZ vs csDMARDs  | 1 | 0.88 | 1.49 | 1.42   | 2.10     | 0.68  | 0.70    |
| csDMARDs vs TNFi | 7 | 0.88 | 0.74 | 0.67   | 2.36     | 0.27  | 0.09    |
| TCZ vs RTX       | 0 | 0    | 5.41 | .      | 5.41     | .     | .       |
| RTX vs TNFi      | 1 | 0.29 | 0.20 | 1.09   | 0.10     | 10.62 | 0.04    |
| TCZ vs TNFi      | 1 | 0.19 | 1.09 | 1.50   | 1.01     | 1.48  | 0.67    |

### Myocardial infarction



Tau<sup>2</sup> = 0; Cochran's Q = 0.42; p=0.82; I<sup>2</sup> = 0%; k= 4 studies

Direct vs indirect comparison (random effects model)

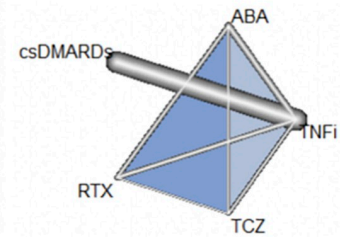
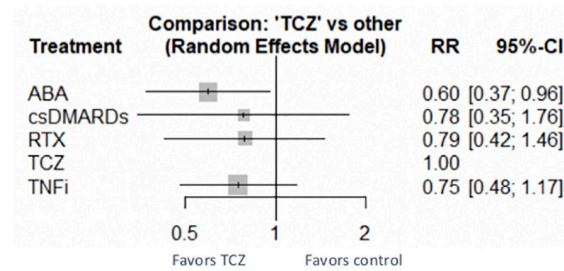
| Comparison       | k | prop | nma  | direct | indirect | RoR | p-value |
|------------------|---|------|------|--------|----------|-----|---------|
| TCZ vs csDMARDs  | 0 | 0    | 4.23 | .      | 4.23     | .   | .       |
| csDMARDs vs TNFi | 3 | 1.00 | 0.47 | 0.47   | .        | .   | .       |
| TCZ vs TNFi      | 1 | 1.00 | 2.00 | 2.00   | .        | .   | .       |

**Fig 2. NMA with RCT on major adverse cardiac events, myocardial infarction and stroke with TCZ vs other treatments.** comparison—Treatment comparison, k—Number of studies providing direct evidence, prop—Direct evidence proportion, nma—Estimated treatment effect (RR) in network meta-analysis, direct—Estimated treatment effect (RR) derived from direct evidence, indirect—Estimated treatment effect (RR) derived from indirect evidence, RoR—Ratio of Ratios (direct versus indirect), p-value—p-value of test for disagreement (direct versus indirect), TCZ—tocilizumab; csDMARDs—conventional synthetic disease-modifying antirheumatic drugs; TNFi—tumor necrosis factor inhibitor; ABA—abatacept; RTX—rituximab.

<https://doi.org/10.1371/journal.pone.0220178.g002>

### Analysis with only cohort studies

#### MACE



Tau<sup>2</sup> = 0.1251; Cochran's Q = 20.42; p=0.005; I<sup>2</sup> = 65.7%; k= 8studies

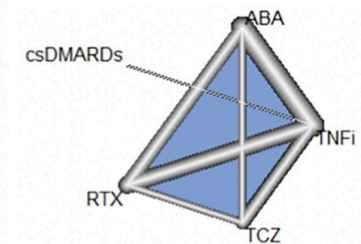
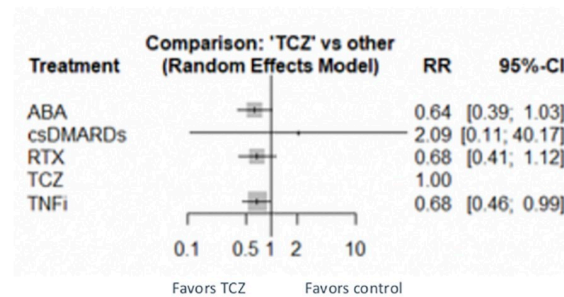
P-Score (random)

|          |      |
|----------|------|
| RTX      | 0.53 |
| TCZ      | 0.85 |
| csDMARDs | 0.51 |
| TNFi     | 0.45 |
| ABA      | 0.16 |

#### Direct vs indirect comparison (random effects model)

| Comparison       | k | prop | nma  | direct | indirect | RoR  | p-value |
|------------------|---|------|------|--------|----------|------|---------|
| ABA vs csDMARDs  | 0 | 0    | 1.31 | .      | 1.31     | .    | .       |
| ABA vs RTX       | 1 | 0.76 | 1.32 | 1.18   | 1.89     | 0.62 | 0.5189  |
| TCZ vs ABA       | 3 | 0.90 | 0.60 | 0.55   | 1.26     | 0.44 | 0.32    |
| ABA vs TNFi      | 2 | 0.76 | 1.25 | 1.26   | 1.23     | 1.03 | 0.96    |
| csDMARDs vs RTX  | 0 | 0    | 1.01 | .      | 1.01     | .    | .       |
| TCZ vs csDMARDs  | 0 | 0    | 0.78 | .      | 0.78     | .    | .       |
| csDMARDs vs TNFi | 2 | 1.00 | 0.96 | 0.96   | .        | .    | .       |
| TCZ vs RTX       | 1 | 0.64 | 0.79 | 0.48   | 1.90     | 0.25 | 0.04    |
| RTX vs TNFi      | 2 | 0.87 | 0.95 | 0.78   | 3.54     | 0.22 | 0.08    |
| TCZ vs TNFi      | 4 | 0.89 | 0.75 | 0.76   | 0.65     | 1.17 | 0.83    |

#### Myocardial infarction



Tau<sup>2</sup> = 0.279; Cochran's Q = 2.63; p=0.2691; I<sup>2</sup> = 23.8%; k= 4 studies

#### Direct vs indirect comparison (random effects model)

| Comparison       | k | prop | nma  | direct | indirect | RoR  | p-value |
|------------------|---|------|------|--------|----------|------|---------|
| ABA vs csDMARDs  | 0 | 0    | 3.29 | .      | 3.29     | .    | .       |
| ABA vs RTX       | 1 | 1.00 | 1.07 | 1.07   | .        | .    | .       |
| TCZ vs ABA       | 1 | 0.64 | 0.64 | 0.50   | 0.96     | 0.52 | 0.21    |
| ABA vs TNFi      | 1 | 0.95 | 1.06 | 1.01   | 3.12     | 0.32 | 0.21    |
| csDMARDs vs RTX  | 0 | 0    | 0.32 | .      | 0.32     | .    | .       |
| TCZ vs csDMARDs  | 0 | 0    | 2.09 | .      | 2.09     | .    | .       |
| csDMARDs vs TNFi | 1 | 1.00 | 0.32 | 0.32   | .        | .    | .       |
| TCZ vs RTX       | 1 | 0.66 | 0.68 | 0.54   | 1.07     | 0.50 | 0.21    |
| RTX vs TNFi      | 1 | 0.96 | 0.10 | 0.94   | 3.58     | 0.26 | 0.21    |

**Fig 3. NMA with cohort studies on major adverse cardiac events, myocardial infarction and stroke with TCZ vs other treatments.** comparison—Treatment comparison, k—Number of studies providing direct evidence, prop—Direct evidence proportion, nma—Estimated treatment effect (RR) in network meta-analysis, direct—Estimated treatment effect (RR) derived from direct evidence, indirect—Estimated treatment effect (RR) derived from indirect evidence, RoR—Ratio of Ratios (direct versus indirect), p-value—p-value of test for disagreement (direct versus

indirect), TCZ—tocilizumab; csDMARDs—conventional synthetic disease-modifying antirheumatic drugs; TNFi—tumor necrosis factor inhibitor; ABA—abatacept; RTX—rituximab.

<https://doi.org/10.1371/journal.pone.0220178.g003>

cardiovascular risk. Despite this increase, our results show the cardiovascular safety profile of TCZ comparing to the other biologics, especially when we included only RCT in the NMA. We also found less myocardial infarction with TCZ than ABA and TNFi in observational studies. This beneficial effect on myocardial infarction could be explained by the fact that TCZ decreases more lipoprotein A levels, and SAA-HDL than adalimumab in the ADACTA study [12]. Indeed, lipoprotein-A has been associated with MI [51] and the HDL linkage by SSA protein could be responsible for HDL-C loss anti atherogenic function [12,50,52,53]. Furthermore, inflammatory cytokines, particularly IL-1 and IL-6 seem to play a determinant role in the atherosclerotic process. Recently, the CANTOS trial performed in general population shown a significantly lower rate of recurrent cardiovascular events with canakinumab than placebo [54]. A cohort study found an improvement of the endothelial function in high risk patients with RA with TCZ but not with TNFi [55]. IL-6 seems strongly involved in the coronary heart disease (CHD), especially via the trans-signaling pathway [56–58]. Mendelian randomization studies showed that IL-6 up-regulation increases CHD risk [59,60]. Conversely, the variant Asp358 causes an increase in the soluble IL-6 receptor (IL-6Rs) and is associated with a reduced risk of coronary artery disease [61,62]. Indeed, in a placebo-RCT in general population with MI, a single dose of TCZ decreases more troponin levels than placebo at day 3 [63]. In an observational study Kobayashi & al. found that TCZ treatment in RA patients significantly increased left ventricular ejection fraction and decreased left ventricular mass index comparing to healthy controls [64]. Finally, in high-risk population of CHD, high IL-6 levels were associated with MI risk, cardiovascular death and all causes death [65].

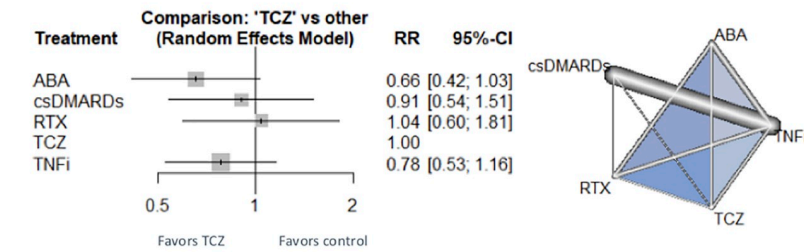
This systematic review and meta-analysis have several strengths. Indeed, we performed an exhaustive review, through four international databases, and two international meetings databases. The included studies showed high quality. RCT were at low risk of bias except for which who were open-label. However, one of these had MACE as primary outcome with an open-label design. Furthermore this study is not published and was found in the 2016 ACR meetings abstract [16]. Most of the cohort studies were at “moderate risk of bias” only because of their non-randomized design. We realized a network meta-analysis which allowed us to make indirect comparisons of multiple treatments and thus to analyze a large amount of studies including placebo RCT. Due to multiple comparators, heterogeneity had to be measured which was possible with this technique. Furthermore, we used random effects model even if the heterogeneity test was no statistically significant because it considers fluctuations of sampling and also treatment effect fluctuations due to multiple covariates. Finally, although we restricted our research to English and French languages, no article was excluded because of the language.

However, our studies showed some limits. The heterogeneity test was significant for MACE outcome which was controlled by using a random effects model. The transitivity hypothesis has not been tested, which is a limitation of the study. Unfortunately, the baseline CV risk was not specified in the included studies, we were unable to carry out an analysis to determine whether this risk was an effect modifier.

Our network meta-analysis illustrates the indication bias in observational studies. Indeed, the beneficial effect of TCZ for MI could be explained by a lesser use of TCZ in high CV risk patients because of the cholesterol increase under treatment. The fact that TCZ is under used in high-risk CV patients is not supported by the literature, the indication bias due to the prudent use of TCZ in high-risk patients is therefore purely hypothetical, not supported by the

### Analysis with all studies

#### MACE



Tau<sup>2</sup> = 0.1184; Cochran's Q = 38.52; p=0.005; I<sup>2</sup> = 50.7%; k= 19 studies

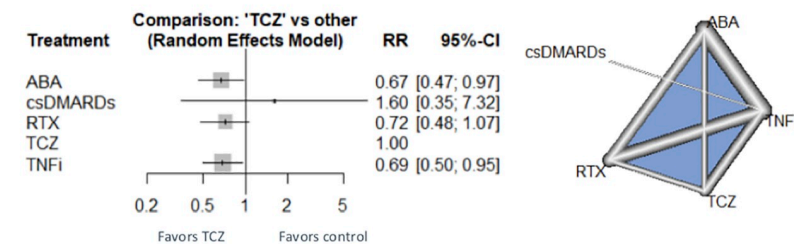
P-Score (random)

|          |      |
|----------|------|
| RTX      | 0.76 |
| TCZ      | 0.74 |
| csDMARDs | 0.57 |
| TNFi     | 0.31 |
| ABA      | 0.11 |

#### Direct vs indirect comparison (random effects model)

| Comparison       | k | prop | nma  | direct | indirect | RoR  | p-value |
|------------------|---|------|------|--------|----------|------|---------|
| ABA vs csDMARDs  | 0 | 0    | 1.38 | .      | 1.38     | .    | .       |
| ABA vs RTX       | 2 | 0.72 | 1.59 | 1.11   | 3.93     | 0.28 | 0.05    |
| TCZ vs ABA       | 3 | 0.86 | 0.66 | 0.55   | 1.90     | 0.29 | 0.06    |
| ABA vs TNFi      | 3 | 0.73 | 1.19 | 1.21   | 1.13     | 1.07 | 0.90    |
| csDMARDs vs RTX  | 1 | 0.21 | 1.15 | 6.37   | 0.72     | 8.81 | 0.01    |
| TCZ vs csDMARDs  | 1 | 0.28 | 0.91 | 1.41   | 0.76     | 1.86 | 0.29    |
| csDMARDs vs TNFi | 9 | 0.77 | 0.86 | 0.76   | 1.30     | 0.59 | 0.29    |
| TCZ vs RTX       | 1 | 0.53 | 1.04 | 0.47   | 2.52     | 0.19 | 0.01    |
| RTX vs TNFi      | 3 | 0.75 | 0.75 | 0.80   | 0.61     | 1.31 | 0.65    |
| TCZ vs TNFi      | 5 | 0.77 | 0.78 | 0.79   | 0.76     | 1.04 | 0.93    |

#### Myocardial infarction



Tau<sup>2</sup> = 0; Cochran's Q = 3.88; p=0.69; I<sup>2</sup> = 0% k= 8 studies

#### Direct vs indirect comparison (random effects model)

| Comparison       | k | prop | nma   | direct | indirect | RoR  | p-value |
|------------------|---|------|-------|--------|----------|------|---------|
| ABA vs csDMARDs  | 0 | 0    | 2.39  | .      | 2.39     | .    | .       |
| ABA vs RTX       | 1 | 1.00 | 1.068 | 1.07   | .        | .    | .       |
| TCZ vs ABA       | 1 | 0.52 | 0.67  | 0.51   | 0.92     | 0.55 | 0.10    |
| ABA vs TNFi      | 1 | 0.99 | 1.023 | 1.01   | 7.01     | 0.14 | 0.10    |
| csDMARDs vs RTX  | 0 | 0    | 0.45  | .      | 0.45     | .    | .       |
| TCZ vs csDMARDs  | 0 | 0    | 1.60  | .      | 1.60     | .    | .       |
| csDMARDs vs TNFi | 4 | 1.00 | 0.43  | 0.43   | .        | .    | .       |
| TCZ vs RTX       | 1 | 0.57 | 0.72  | 0.54   | 1.05     | 0.51 | 0.10    |
| RTX vs TNFi      | 1 | 1.00 | 0.96  | 0.95   | 24.62    | 0.04 | 0.10    |
| TCZ vs TNFi      | 4 | 1.00 | 0.67  | 0.67   | .        | .    | .       |

**Fig 4. NMA with both designs (RCT and cohorts) on major adverse cardiac events, myocardial infarction and stroke with TCZ vs other treatments.** comparison—Treatment comparison, k—Number of studies providing direct evidence, prop—Direct evidence proportion, nma—Estimated treatment effect (RR) in network meta-analysis, direct—Estimated treatment effect (RR) derived from direct evidence, indirect—Estimated treatment effect (RR) derived from indirect evidence, RoR—Ratio of Ratios (direct versus indirect), p-value—p-value of test for disagreement (direct versus indirect), TCZ—tocilizumab; csDMARDs—conventional synthetic disease-modifying antirheumatic drugs; TNFi—tumor necrosis factor inhibitor; ABA—abatacept; RTX—rituximab.

<https://doi.org/10.1371/journal.pone.0220178.g004>

literature, but remains likely. Another explanation is that observational studies were designed to study cardiovascular events, with high sample sizes, unlike RCTs.

## Conclusion

Despite these limits, our study showed a good cardiovascular safety profile of TCZ compared to other bDMARD, with potential benefit on MI compared to other bDMARD. Further studies are needed to corroborate these data.

## Supporting information

### S1 File. PRISMA checklist.

(DOC)

**S2 File. Research equations.** Medline, Cochrane library, Web of science, Science Direct, EULAR and ACR databases.

(DOCX)

## Acknowledgments

BC thanks the French Society of Rheumatology (SFR) because this work has been possible thanks to their financial support.

## Author Contributions

**Conceptualization:** Benjamin Castagné, Marie Viprey.

**Data curation:** Benjamin Castagné, Marie Viprey, Julie Martin.

**Formal analysis:** Benjamin Castagné, Marie Viprey, Michel Cucherat.

**Methodology:** Benjamin Castagné, Marie Viprey, Michel Cucherat.

**Project administration:** Anne-Marie Schott.

**Supervision:** Marie Viprey, Julie Martin, Anne-Marie Schott, Michel Cucherat, Martin Soubrier.

**Validation:** Marie Viprey, Julie Martin, Anne-Marie Schott, Michel Cucherat, Martin Soubrier.

**Writing – original draft:** Benjamin Castagné.

**Writing – review & editing:** Julie Martin, Anne-Marie Schott, Michel Cucherat, Martin Soubrier.

## References

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017; 76: 960–977. <https://doi.org/10.1136/annrheumdis-2016-210715> PMID: 28264816
2. Guillemin F, Saraux A, Guggenbuhl P, Roux CH, Fardellone P, Le Bihan E, et al. Prevalence of rheumatoid arthritis in France: 2001. *Ann Rheum Dis*. 2005; 64: 1427–1430. <https://doi.org/10.1136/ard.2004.029199> PMID: 15800010
3. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum*. 2008; 59: 1690–1697. <https://doi.org/10.1002/art.24092> PMID: 19035419



4. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis*. 2015; 74: 326–332. <https://doi.org/10.1136/annrheumdis-2014-205675> PMID: 25351522
5. Lindhardtsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis*. 2011; 70: 929–934. <https://doi.org/10.1136/ard.2010.143396> PMID: 21389043
6. Arts EEA, Fransen J, den Broeder AA, Popa CD, van Riel PLCM. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. *Ann Rheum Dis*. 2015; 74: 998–1003. <https://doi.org/10.1136/annrheumdis-2013-204531> PMID: 24458537
7. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurol*. 2012; 12: 41. <https://doi.org/10.1186/1471-2377-12-41> PMID: 22708578
8. Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, Boy M, Geier J, Luo Z, et al. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. *Semin Arthritis Rheum*. 2016; 46: 71–80. <https://doi.org/10.1016/j.semarthrit.2016.03.004> PMID: 27079757
9. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2017; 76: 17–28. <https://doi.org/10.1136/annrheumdis-2016-209775> PMID: 27697765
10. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet Lond Engl*. 2008; 371: 987–997. [https://doi.org/10.1016/S0140-6736\(08\)60453-5](https://doi.org/10.1016/S0140-6736(08)60453-5)
11. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet Lond Engl*. 2013; 381: 1541–1550. [https://doi.org/10.1016/S0140-6736\(13\)60250-0](https://doi.org/10.1016/S0140-6736(13)60250-0)
12. Gabay C, McInnes IB, Kavanaugh A, Tuckwell K, Klearman M, Pulley J, et al. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016; 75: 1806–1812. <https://doi.org/10.1136/annrheumdis-2015-207872> PMID: 26613768
13. Bellosa S, Corsini A. Statin drug interactions and related adverse reactions: an update. *Expert Opin Drug Saf*. 2018; 17: 25–37. <https://doi.org/10.1080/14740338.2018.1394455> PMID: 29058944
14. Zhang J, Xie F, Yun H, Chen L, Muntner P, Levitan EB, et al. Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016; 75: 1813–1818. <https://doi.org/10.1136/annrheumdis-2015-207870> PMID: 26792814
15. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. *Arthritis Rheumatol Hoboken Nj*. 2017; 69: 1154–1164. <https://doi.org/10.1002/art.40084> PMID: 28245350
16. Giles JT, Sattar N, Gabriel SE, Ridker PM, Gay S, Warne C, et al. Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multi-center, Noninferiority, Phase 4 Clinical Trial. *Arthritis Rheumatol*. 2016; 68.
17. Curtis JR, Perez-Gutthann S, Suissa S, Napalkov P, Singh N, Thompson L, et al. Tocilizumab in rheumatoid arthritis: a case study of safety evaluations of a large postmarketing data set from multiple data sources. *Semin Arthritis Rheum*. 2015; 44: 381–388. <https://doi.org/10.1016/j.semarthrit.2014.07.006> PMID: 25300699
18. Gottenberg J-E, Morel J, Constantino A, Bardin T, Cantagrel A, Combe B, et al. Similar Rates of Death, Serious Infections, Cancers, Major Cardiovascular Events in Patients Treated with Abatacept, Rituximab and Tocilizumab: Long-Term Registry Data in 4498 Patients with Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016; 68. Available: <http://acrabstracts.org/abstract/similar-rates-of-death-serious-infections-cancers-major-cardiovascular-events-in-patients-treated-with-abatacept-rituximab-and-tocilizumab-long-term-registry-data-in-4498-patients-with-rheumatoid/>
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; 339: b2535. <https://doi.org/10.1136/bmj.b2535> PMID: 19622551
20. Higgins JPT, Sterne JAC, Savović J, Page MJ, Hroacutae bjartsson, Boutron I, et al. Appraising the risk of bias in randomized trials using the Cochrane Risk of Bias Tool. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). 2016.

21. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016; i4919. <https://doi.org/10.1136/bmj.i4919> PMID: 27733354
22. Senn S. Trying to be precise about vagueness. *Stat Med*. 2007; 26: 1417–1430. <https://doi.org/10.1002/sim.2639> PMID: 16906552
23. Dias S, Welton NJ, Sutton AJ, Ades AE. Evidence synthesis for decision making 1: introduction. *Med Decis Mak Int J Soc Med Decis Mak*. 2013; 33: 597–606. <https://doi.org/10.1177/0272989X13487604> PMID: 23804506
24. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Mak Int J Soc Med Decis Mak*. 2013; 33: 641–656. <https://doi.org/10.1177/0272989X12455847> PMID: 23804508
25. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*. 2012; 3: 312–324. <https://doi.org/10.1002/jrsm.1058> PMID: 26053424
26. Rücker G, Schwarzer G, Krahn U, Koenig J. Netmeta. Network meta-analysis using frequentist methods. 2017; <https://CRAN.R-project.org/package=netmeta>.
27. Giles JT, Sattar N, Gabriel SE, Ridker PM, Gay S, Warne C, et al. Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multi-center, Noninferiority, Phase 4 Clinical Trial. In: ACR Meeting Abstracts [Internet]. 9 May 2018 [cited 9 May 2018]. <http://acrabstracts.org/abstract/comparative-cardiovascular-safety-of-tocilizumab-vs-etanercept-in-rheumatoid-arthritis-results-of-a-randomized-parallel-group-multicenter-noninferiority-phase-4-clinical-trial/>
28. Al-Aly Z, Pan H, Zeringue A, Xian H, McDonald JR, El-Achkar TM, et al. Tumor necrosis factor- $\alpha$  blockade, cardiovascular outcomes, and survival in rheumatoid arthritis. *Transl Res*. 2011; 157: 10–18. <https://doi.org/10.1016/j.trsl.2010.09.005> PMID: 21146146
29. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis*. 2010; 69: 1629–1635. <https://doi.org/10.1136/ard.2009.119933> PMID: 20488885
30. Harrold LR, Reed GW, Magner R, Shewade A, John A, Greenberg JD, et al. Comparative effectiveness and safety of rituximab versus subsequent anti-tumor necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti-tumor necrosis factor therapies in the United States Corona registry. *Arthritis Res Ther*. 2015; 17: 256. <https://doi.org/10.1186/s13075-015-0776-1> PMID: 26382589
31. Jin Y, Kang EH, Brill G, Desai RJ, Kim SC. Comparative Cardiovascular Safety of Abatacept and Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis Patients with and Without Cardiovascular Disease: A Population-Based Cohort Study. *Ann Rheum Dis*. 2017; 76: 544–544. <https://doi.org/10.1136/annrheumdis-2017-eular.2727>
32. Keystone EC, Genovese MC, Hall S, Bae S-C, Han C, Gathany TA, et al. Safety and Efficacy of Subcutaneous Golimumab in Patients with Active Rheumatoid Arthritis despite Methotrexate Therapy: Final 5-year Results of the GO-FORWARD Trial. *J Rheumatol*. 2016; 43: 298–306. <https://doi.org/10.3899/jrheum.150712> PMID: 26669912
33. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, et al. No difference in cardiovascular risk of tocilizumab versus abatacept for rheumatoid arthritis: A multi-database cohort study. *Semin Arthritis Rheum*. 2018; <https://doi.org/10.1016/j.semarthrit.2018.03.012> PMID: 29673963
34. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum*. 2006; 54: 1075–1086. <https://doi.org/10.1002/art.21734> PMID: 16572442
35. Weisman MH, Paulus HE, Burch FX, Kivitz AJ, Fierer J, Dunn M, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatol Oxf Engl*. 2007; 46: 1122–1125. <https://doi.org/10.1093/rheumatology/kem033> PMID: 17470434
36. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Blanco R, et al. Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. *Ann Rheum Dis*. 2017; 76: 1279–1284. <https://doi.org/10.1136/annrheumdis-2016-210561> PMID: 28389552
37. Cárdenas M, de la Fuente S, Font P, Castro-Villegas MC, Romero-Gómez M, Ruiz-Vílchez D, et al. Real-world cost-effectiveness of infliximab, etanercept and adalimumab in rheumatoid arthritis patients:

- results of the CREATE registry. *Rheumatol Int*. 2016; 36: 231–241. <https://doi.org/10.1007/s00296-015-3374-2> PMID: 26494567
38. Choy EH, Bernasconi C, Aassi M, Molina JF, Epis OM. Treatment of Rheumatoid Arthritis With Anti-Tumor Necrosis Factor or Tocilizumab Therapy as First Biologic in a Global Comparative Observational Study. *Arthritis Care Res*. 2017; <https://doi.org/10.1002/acr.23303> PMID: 28622454
  39. Emery P, Bingham CO, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. *Ann Rheum Dis*. 2017; 76: 96–104. <https://doi.org/10.1136/annrheumdis-2015-209057> PMID: 27165179
  40. Iannone F, Ferraccioli G, Sinigaglia L, Favalli EG, Sarzi-Puttini P, Atzeni F, et al. Real-world experience of tocilizumab in rheumatoid arthritis: sub-analysis of data from the Italian biologics' register GISEA. *Clin Rheumatol*. 2018; 37: 315–321. <https://doi.org/10.1007/s10067-017-3846-8> PMID: 28980085
  41. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years. *Bmj Open*. 2012; 2: e001395. <https://doi.org/10.1136/bmjopen-2012-001395> PMID: 23148339
  42. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum*. 2008; 58: 964–975. <https://doi.org/10.1002/art.23383> PMID: 18383539
  43. Manders SHM, Kievit W, Adang E, Brus HL, Moens HJB, Hartkamp A, et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Res Ther*. 2015; 17: 134. <https://doi.org/10.1186/s13075-015-0630-5> PMID: 25997746
  44. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Ann Rheum Dis*. 2015; 74: 843–850. <https://doi.org/10.1136/annrheumdis-2013-204632> PMID: 24431394
  45. Smolen JS, Burmester G-R, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *The Lancet*. 2016; 388: 2763–2774. [https://doi.org/10.1016/S0140-6736\(16\)31651-8](https://doi.org/10.1016/S0140-6736(16)31651-8)
  46. Kim H-Y, Hsu P-N, Barba M, Sulaiman W, Robertson D, Vlahos B, et al. Randomized comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. *Int J Rheum Dis*. 2012; 15: 188–196. <https://doi.org/10.1111/j.1756-185X.2011.01680.x> PMID: 22462423
  47. Sakai R, Cho S-K, Nanki T, Watanabe K, Yamazaki H, Tanaka M, et al. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. *Arthritis Res Ther*. 2015; 17: 74. <https://doi.org/10.1186/s13075-015-0583-8> PMID: 25880658
  48. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Mod Rheumatol*. 2014; 24: 715–724. <https://doi.org/10.3109/14397595.2013.864224> PMID: 24313916
  49. Geborek P, Crnkic M, Petersson IF, Saxne T, South Swedish Arthritis Treatment Group. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis*. 2002; 61: 793–798. <https://doi.org/10.1136/ard.61.9.793> PMID: 12176803
  50. Pappas AN 2827 EOBAOL and CRIRAPDA, John A, Curtis JR, Reed GW, Greenberg JD, Shewade A, et al. Effect Of Biologic Agents On Lipids and Cardiovascular Risk In Rheumatoid Arthritis Patients. In: ACR Meeting Abstracts [Internet]. [cited 2 May 2018]. <http://acrabstracts.org/abstract/effect-of-biologic-agents-on-lipids-and-cardiovascular-risk-in-rheumatoid-arthritis-patients/>
  51. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009; 301: 2331–2339. <https://doi.org/10.1001/jama.2009.801> PMID: 19509380
  52. Virone A. Comparison of Changes in Cardiovascular Risk-Associated Biomarkers in RA Patients Treated with Anti-TNF or Other Biological Agents: A Metabolic Study from a Randomized Trial. In: ACR Meeting Abstracts [Internet]. [cited 2 May 2018]. <http://acrabstracts.org/abstract/comparison-of-changes-in-cardiovascular-risk-associated-biomarkers-in-ra-patients-treated-with-anti-tnf-or-other-biological-agents-a-metabolic-study-from-a-randomized-trial/>

53. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis*. 2015; 74: 694–702. <https://doi.org/10.1136/annrheumdis-2013-204345> PMID: 24368514
54. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med*. 2017; 377: 1119–1131. <https://doi.org/10.1056/NEJMoa1707914> PMID: 28845751
55. Bacchiega BC, Bacchiega AB, Usnayo MJG, Bedirian R, Singh G, Pinheiro G da RC. Interleukin 6 Inhibition and Coronary Artery Disease in a High-Risk Population: A Prospective Community-Based Clinical Study. *J Am Heart Assoc*. 2017; 6. <https://doi.org/10.1161/JAHA.116.005038> PMID: 28288972
56. Morieri ML, Passaro A, Zuliani G. Interleukin-6 “Trans-Signaling” and Ischemic Vascular Disease: The Important Role of Soluble gp130. *Mediators Inflamm*. 2017; 2017: 1396398. <https://doi.org/10.1155/2017/1396398> PMID: 28250574
57. Anderson DR, Poterucha JT, Mikuls TR, Duryee MJ, Garvin RP, Klassen LW, et al. IL-6 and its receptors in coronary artery disease and acute myocardial infarction. *Cytokine*. 2013; 62: 395–400. <https://doi.org/10.1016/j.cyto.2013.03.020> PMID: 23582716
58. Moreno Velásquez I, Golabkesh Z, Källberg H, Leander K, de Faire U, Gigante B. Circulating levels of interleukin 6 soluble receptor and its natural antagonist, sgp130, and the risk of myocardial infarction. *Atherosclerosis*. 2015; 240: 477–481. <https://doi.org/10.1016/j.atherosclerosis.2015.04.014> PMID: 25910182
59. Omicron Hartaigh B, Thomas GN, Bosch JA, Hemming K, Pilz S, Loerbroks A, et al. Evaluation of 9 biomarkers for predicting 10-year cardiovascular risk in patients undergoing coronary angiography: findings from the LUdwigshafen Risk and Cardiovascular Health (LURIC) study. *Int J Cardiol*. 2013; 168: 2609–2615. <https://doi.org/10.1016/j.ijcard.2013.03.043> PMID: 23601216
60. Niu W, Liu Y, Qi Y, Wu Z, Zhu D, Jin W. Association of interleukin-6 circulating levels with coronary artery disease: a meta-analysis implementing mendelian randomization approach. *Int J Cardiol*. 2012; 157: 243–252. <https://doi.org/10.1016/j.ijcard.2011.12.098> PMID: 22261689
61. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *The Lancet*. 2012; 379: 1205–1213. [https://doi.org/10.1016/S0140-6736\(11\)61931-4](https://doi.org/10.1016/S0140-6736(11)61931-4) PMID: 22421339
62. Jansen H, Samani NJ, Schunkert H. Mendelian randomization studies in coronary artery disease. *Eur Heart J*. 2014; 35: 1917–1924. <https://doi.org/10.1093/eurheartj/ehu208> PMID: 24917639
63. Kobayashi Y, Kobayashi H, Giles JT, Hirano M, Nakajima Y, Takei M. Association of tocilizumab treatment with changes in measures of regional left ventricular function in rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. *Int J Rheum Dis*. 2016; 19: 1169–1174. <https://doi.org/10.1111/1756-185X.12632> PMID: 26480957
64. Kobayashi H, Kobayashi Y, Giles JT, Yoneyama K, Nakajima Y, Takei M. Tocilizumab Treatment Increases Left Ventricular Ejection Fraction and Decreases Left Ventricular Mass Index in Patients with Rheumatoid Arthritis without Cardiac Symptoms: Assessed Using 3.0 Tesla Cardiac Magnetic Resonance Imaging. *J Rheumatol*. 2014; 41: 1916–1921. <https://doi.org/10.3899/jrheum.131540> PMID: 25128513
65. Chen S-L, Liu Y, Lin L, Ye F, Zhang J-J, Tian N-L, et al. Interleukin-6, but not C-reactive protein, predicts the occurrence of cardiovascular events after drug-eluting stent for unstable angina. *J Intervent Cardiol*. 2014; 27: 142–154. <https://doi.org/10.1111/joic.12103> PMID: 24588086