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

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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 stoke and MI. Not enough data was available to perform a NMA for CHF and PAD.

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 (DAS28 ≤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 (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 Ligue 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$<$0.05 for significativity) and the I^2 statistic ($<$25%: low heterogeneity, 25–50%: moderate, 50–75%: 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-test 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 cofounding 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).
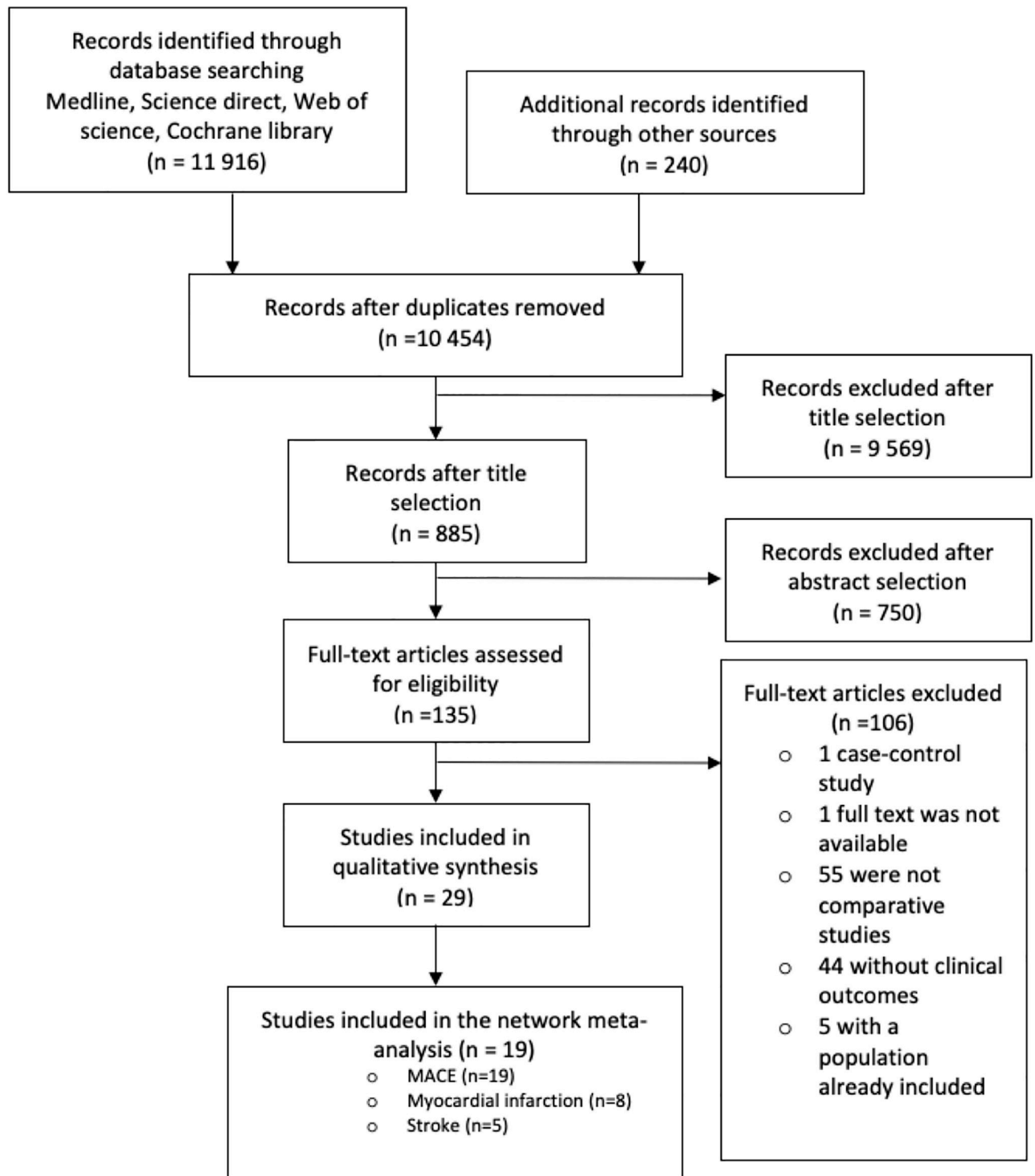
Fig 1. Flow chart of the systematic literature review. PubMed/Medline, Web of science, Cochrane library, Science direct and ACR, Annual College of Rheumatology; EULAR, European League Against Rheumatism databases.

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

STUDY	TREATMENT	AGE (YEARS)	GENDER (FEMALE)	HTA	DYSLIPIDEMIA	SMOKING	DIABETUS MIELLETUS	PREV CV	PREVB	PREVCS	N	TOTAL PY	FOLLOW-UP (YEAR)	MACE	MI	STROKE	CHF
AL-ALY &AL. [28] 2011	TNFi	57 ±12	9%	68%	52%	NS	31%	38%	NS	NS	3796	9 563	3.5	1460	NS	NS	NS
	csDMARD	63 ±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 ±13.6	77%	NS	NS	NS	NS	NS	0	0	1 108	1 645	2	NS	NS	NS	NS
	MTX	49.6 ±13.1	80%	NS	NS	NS	NS	NS	0	0	282	339	2	NS	NS	NS	NS
CARDENAS &AL. [37] 2016	IFX	51.5 ±12.7	80%	NS	NS	NS	NS	NS	0	1	55	NS	2	3	NS	NS	NS
	ADA	52.9 ±14.7	87%	NS	NS	NS	NS	NS	0	1	31	NS	2	1	NS	NS	NS
	ETN	55.1 ±14	82%	NS	NS	NS	NS	NS	0	1	44	NS	2	3	NS	NS	NS
CHOY &AL. [38] 2017	TCZ	54.3 ±12.8	NS	NS	NS	NS	NS	NS	0	1	423	404	1	0	NS	0	NS
	TNFi	55.2 ±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
	TNFi	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	5 734	4 345	NS	28	14	14	NS
EMERY &AL. [29] 2010	CTZ	50.4 ±13.6	76%	NS	NS	NS	NS	NS	0	0	659	NS	1	39	NS	NS	NS
	MTX	51.2 ±13	80%	NS	NS	NS	NS	NS	0	0	213	NS	1	9	NS	NS	NS
EMERY &AL. [39] 2017	RTX	51.6 ±12.7	80.4%	NS	NS	NS	NS	NS	0	1	337	161	0.5	4	NS	NS	NS
	MTX	52.16 ±12.4	85.5%	NS	NS	NS	NS	NS	0	1	172	79	0.5	13	NS	NS	NS
GABAY &AL. [11] 2013	TCZ	54.4 ±13	79%	NS	NS	NS	NS	NS	0	1	162	NS	0.5	3	2	1	NS
	ADA	53.3 ±12.4	82%	NS	NS	NS	NS	NS	0	1	162	NS	0.5	2	1	1	NS
GEBOREK&AL. [49] 2002	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
	csDMARD	61.3	82%	NS	NS	NS	NS	NS	0	2	103	NS	NS	0	0	0	0
GILES &AL. [27] 2016	TCZ	61	78%	71%	NS	29%	18%	NS	0	1	1538	4900	3.2	83	29	26	12
	ETN		NS	NS	NS	NS			0	12	1542	4891	3.2	78	32	16	8
GOTTENBERG &AL. [18] 2016	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
	RTX	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	10 545	2	NS	NS	NS	NS
HARROLD &AL. [30] 2015	RTX	57.8 ±11.7	81%	NS	NS	NS	NS	9.8%	11.3%	≧1	NS	265	242	1	5	NS	NS	NS
	TNFi	56.1 ±12.4	79%	NS	NS	NS	NS	10.7%	7.3%	≧1	NS	205	737	1	9	NS	NS	NS

(Continued)

Table 1. (Continued)

STUDY	TREATMENT	AGE (YEARS)	GENDER (FEMALE)	HTA	DYSLIPIDEMIA	SMOKING	DIABETUS MIELLETUS	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
	TNFi	53.9		23.2%	NS	NS	4.9%	5%	NS	NS	1 135	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
	TNFi	NS	NS	NS	NS	NS	NS	NS	NS	NS	6934	NS	NS	113	NS	NS	NS
JOBANPUTRA &AL. [41] 2012	ADA	55 ±12.5	75%	NS	NS	NS	NS	NS	0	2	60	NS	1	5	NS	NS	NS
	ETN	53.2 ±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 ±12	91.4%	NS	NS	NS	NS	NS	0	0	137	NS	0.33	1	NS	NS	1
	csDMARD	48.5 ±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 ±10,2	88,3%	60,6%	45,8%	NS	20%	12,5%	≧1	NS	9 218	7 236	NS	43	21	23	NS
	TNFi	58.7 ±10	82%	57,5%	44%	NS	16%	12,2%	≧1	NS	18 810	14 776	NS	103	7	49	NS
KIM &AL. [33] 2018	TCZ	58.8 ±10.4	81,4%	59,8%	46,3%	NS	20,1%	12%	NS	NS	6 237	N S	NS	32	NS	NS	NS
	ABA	59 ±10	87%	59,1%	45,4%	NS	19,23%	12,6	NS	NS	14 685	NS	NS	112	NS	NS	NS
MANDERS &AL. [43] 2015	ABA	56.2 ±9.95	88.4%	NS	NS	NS	NS	NS	1	1	43	NS	1	1	NS	NS	NS
	RTX	57.1 ±11.1	63%	NS	NS	NS	NS	NS	1	1	46	NS	1	2	NS	NS	NS
	TNFi	56.3 ±11.2	74%	NS	NS	NS	NS	NS	1	1	50	NS	1	2	NS	NS	NS
SAKAI &AL. [47] 2015	TCZ	59.2 ±13	82.5%	NS	NS	NS	10.9%	NS	NS	NS	302	224,68	1	NS	NS	NS	9
	TNFi	57.33 ±15.2	82.8%	NS	NS	NS	10.5%	NS	NS	NS	304	231,01	1	NS	NS	NS	8
SMOLEN &AL. [44] 2015	CTZ	53.6 ±11.9	86.4%	NS	NS	NS	NS	NS	0	1	96	NS	2	9	NS	NS	NS
	csDMARD	54 ±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 ±12.3	79%	NS	NS	NS	NS	NS	0	1	516	NS	2	12	NS	NS	NS
	ADA	52.9 ±12.8	79%	NS	NS	NS	NS	NS	0	1	523	NS	2	9	NS	NS	NS
SMOLEN &AL. [10] 2008	TCZ	51.1 ±12.3	83.5%	NS	NS	NS	NS	NS	0	1	418	NS	1	29	NS	NS	NS
	MTX	50.6 ±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 MIELLETUS	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
	TNFi	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; TNFi, 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

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

Randomized controlled Trial (ROB2 tool)								
Author	Year	Study acronym	Random sequence generation	Allocation concealment	Blinding of particpants 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 cofounding	Bias in selection of participatnts	Bias in classification of interventio	Bias due to deviations froms 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. * [30]	2015	?	+	+	+	+	+	+
Iannone &al. * [40]	2018	−	+	+	+	+	+	?
Jin &al. [31]	2017	+	+	+	+	+	+	?
Kim &al. [15]	2017	+	+	+	+	+	+	+
Kim &al. * [33]	2018	+	+	+	+	+	+	+
Sakai &al. [47]	2015	?	+	+	+	+	+	?
Zhang &al. * [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

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).
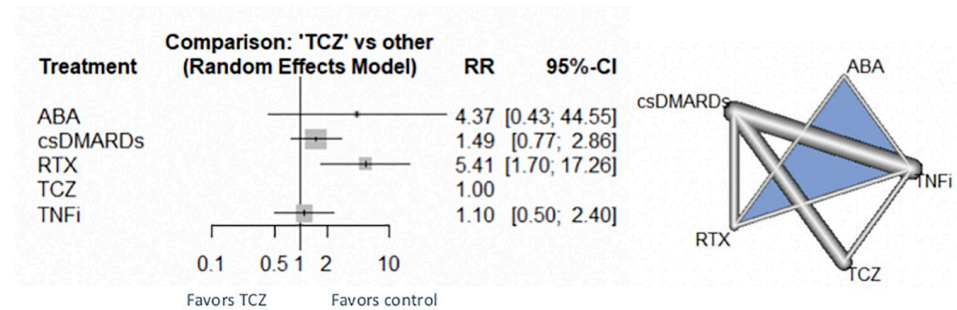
Comparison of CHF

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
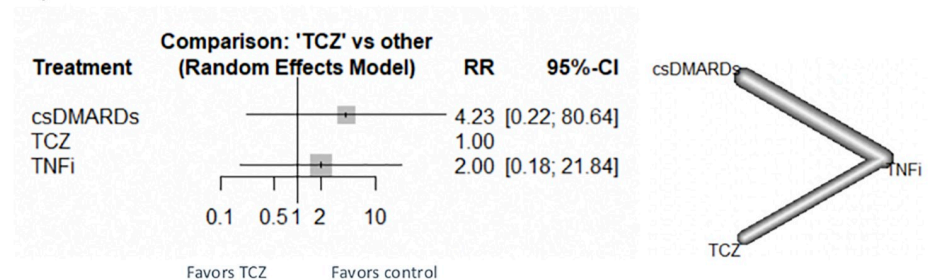
Analysis with only RCTs
MACE

Treatment	Comparison: 'TCZ' vs other (Random Effects Model)	RR	95%-CI
ABA		4.37	[0.43; 44.55]
csDMARDs		1.49	[0.77; 2.86]
RTX		5.41	[1.70; 17.26]
TCZ		1.00	
TNFi		1.10	[0.50; 2.40]

0.1 0.5 1 2   10

Favors TCZ   Favors control

Tau² = 0; Cochran's Q = 5.42; p=0.71 I² = 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

Treatment	Comparison: 'TCZ' vs other (Random Effects Model)	RR	95%-CI
csDMARDs		4.23	[0.22; 80.64]
TCZ		1.00	
TNFi		2.00	[0.18; 21.84]

0.1 0.5 1 2   10

Favors TCZ   Favors control

Tau² = 0; Cochran's Q = 0.42; p=0.82; I² = 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.

Analysis with only cohort studies

MACE

Treatment	Comparison: 'TCZ' vs other (Random Effects Model)	RR	95%-CI
ABA		0.60	[0.37; 0.96]
csDMARDs		0.78	[0.35; 1.76]
RTX		0.79	[0.42; 1.46]
TCZ		1.00	
TNFi		0.75	[0.48; 1.17]

Favors TCZ   Favors control
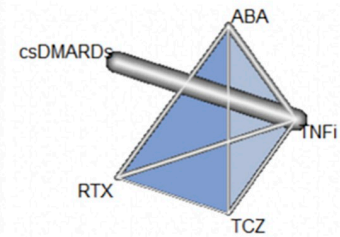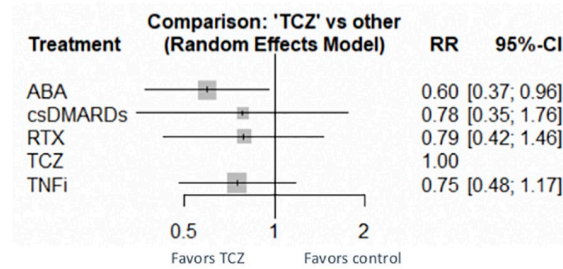
Tau² = 0.1251; Cochran's Q = 20.42; p=0.005; I² = 65.7%; k= 8 studies

	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

Treatment	Comparison: 'TCZ' vs other (Random Effects Model)	RR	95%-CI
ABA		0.64	[0.39; 1.03]
csDMARDs		2.09	[0.11; 40.17]
RTX		0.68	[0.41; 1.12]
TCZ		1.00	
TNFi		0.68	[0.46; 0.99]

Favors TCZ   Favors control
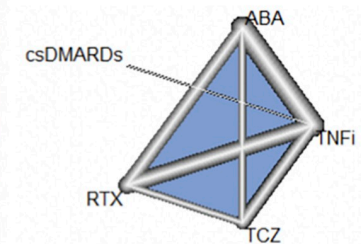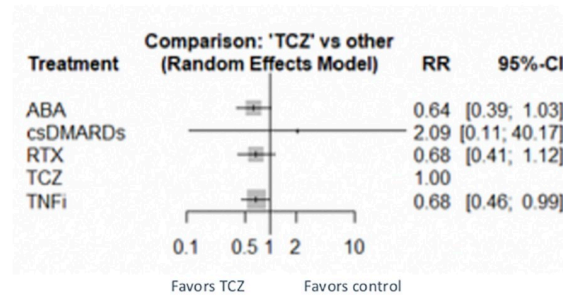
Tau² = 0.279; Cochran's Q = 2.63; p=0.2691; I² = 23.8%; k= 4 studies

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.

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 transivity 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

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

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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. Lindhardsen 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

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

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. Bellosta 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, Multicenter, 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, Hroacute 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, Multicenter, 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-α 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 Corrona 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

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 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