

How current biologic therapies affect the risk of major adverse cardiovascular events in patients with plaque psoriasis? A systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction: Concerns have been raised about an increased risk of major adverse cardiovascular events (MACEs) – stroke, myocardial infarction and sudden cardiac death – in patients with plaque psoriasis receiving biologic therapies.

Aim: This review and meta-analysis of randomized controlled trials (RCTs) was to evaluate the risk difference of MACEs between experimental and comparator interventions.

Material and methods: We searched MEDLINE database for suitable trials. Prior to that we identified the search strategy and eligibility criteria. Each RCT was double-blind, placebo controlled and scored five points in Jadad scale. We calculated risk difference (RD) with use of the Mantel-Haenszel fixed-effect method with 95% confidence intervals (CIs) and calculated I^2 statistic to assess heterogeneity. A total of 43 RCTs were included, involving 19,161 patients. Overall, the risk of MACEs in the included studies was 0.1% ($n = 21$).

Results: There were no statistically significant risk differences in patients treated with biologic therapy vs. placebo ($RD = 0.0$; $Z = 1.09$; 95% CI: 0.0–0.0; $p = 0.28$); tumour necrosis inhibitors vs. placebo ($RD = 0.0$; $Z = 0.47$; 95% CI: –0.0–0.0; $p = 0.64$); anti-IL-17A agents vs. placebo ($RD = 0.0$; $Z = 1.25$; 95% CI: –0.0–0.01; $p = 0.21$); anti-IL-23 agents vs. placebo ($RD = 0$; $Z = 0.36$; 95% CI: –0.0–0.01; $p = 0.72$); anti-IL-12/23 agents vs. placebo ($RD = 0.0$; $Z = 0.73$; 95% CI: –0.0–0.0; $p = 0.46$).

Conclusions: Further trials are needed, including longer follow-up and patients with an increased cardiovascular risk, to assess the risk of MACEs.

Key words: psoriasis, biologic therapies, major adverse cardiac events.

Introduction

Plaque psoriasis is a chronic, genetically determined, non-infectious disease of the skin and joints, affecting approximately 125 million people worldwide [1]. The frequency of psoriasis is related to age, ethnicity and gender, but there are no precise data on the number of patients in total [1]. The inflammation occurs in the skin, but has also an impact on other organs, leading to psoriatic arthritis, Crohn's disease or obesity [2]. It is also associated with an increased risk of cardiovascular events, which are the most common causes of morbidity and mortality in psoriasis [3]. Patients suffering from psoriasis have a higher incidence of cardiovascular

diseases: atherosclerosis, arterial hypertension, metabolic syndrome and diabetes [4–8]. The etiopathogenesis of psoriasis and atherosclerosis are connected by several/several mechanisms such as excessive secretion of vascular endothelial growth factor (VEGF) by cells [9]. Another common process is the formation of inflammatory infiltrates with use of a similar group of cytokines: interleukin-2 (IL-2), IL-6, tumor necrosis factor- α (TNF- α), interferon γ (INF- γ) in psoriasis and early atherosclerotic lesions [10]. Major adverse cardiovascular events (MACE) include haemorrhagic and ischemic stroke, myocardial infarction and sudden cardiac death [11, 12]. The frequency of MACEs in patients with psoriasis is increased, while the potential impact of therapies used in the treatment

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of psoriasis on the risk of cardiovascular events is unknown [13–15].

Due to the anti-inflammatory effect of the biologic therapies and the similar pathogenesis of psoriasis and atherosclerosis, the influence of these treatments on the cardiovascular risk is being considered [16–19]. The currently used biologics in the treatment of plaque psoriasis are TNF- α inhibitors (TNFi), human IgG1 κ monoclonal antibodies to interleukin IL-12/23, IL-17 inhibitors and monoclonal antibodies against IL-23. There are several meta-analyses assessing the risk of MACEs occurrence while using biologic therapies during randomized controlled trials (RCTs) in this group of patients [14, 20, 21]. However, described studies did not include the latest classes of biologic therapies, approved by the European Medicines Agency (EMA), such as certolizumab, ixekizumab, or the anti-IL-23 antibody, guselkumab. Therefore, it was necessary to reassess the risk of adverse cardiovascular events in this group of patients. The aim of this review and meta-analysis of RCTs was to show whether there is a statically significant risk of occurrence of the MACEs in patients with plaque psoriasis treated with biologic therapies.

Aims

The aim of this review and meta-analysis of randomized controlled studies was to show whether there is a significant risk of occurrence of the MACEs in patients with plaque psoriasis treated with biologic therapies.

Material and methods

Eligibility criteria

We included 45 randomized, placebo-controlled, double-blind, trials of adults with plaque psoriasis that received a licensed, approved by EMA, dose of biologic therapy compared to placebo, conventional therapy or another licensed dose of the same treatment. Every included trial scored five points in Jadad scale. The study should describe safety outcome data, the number of adverse events, including major adverse cardiovascular events (Figure 1).

Study process and search strategy

We investigated the Medline database from their inception date to 30 September 2020 to find RCTs describing major adverse cardiovascular events in patients with plaque psoriasis treated with biologic therapies. While searching for suitable abstracts, we did not establish any language restriction, but we applied a filter for randomized controlled trials. The set of used phrases included psoriasis and biologic therapies or the name of the active substance or drug trade name or drug class. Each of the three combinations was used in the process of finding an appropriate abstract. Additionally, we verified the references of the included articles in search of potential new RCTs.

One investigator (S. N.) analysed the entire database searching for suitable articles and simultaneously excluding duplicates. Two investigators (S. N. and E. J.) extracted valuable information and three investigators double-checked included data (S. N., E. J. and M. P.). Other team members (Z. A., P. R., K. K.) were responsible for substantive care, resolving uncertain decisions.

Data extraction and risk of bias assessment

Each included research was assessed for completeness of the contained information using the Jadad scale. We checked whether the study was randomized and described as double-blind, as well as we overviewed the description of randomization and blinding methods. In addition, we paid attention if the information about the loss of patients from the study, their number and the reason for exclusion (including the safety outcome data) was provided. We extracted data describing study characteristics such as country, study design, length of the randomized controlled phase, number of patients in each research group, information on the active substance used and its doses, use of placebo in the control group, and number of study sites. The patient population designation included age, percentage of females and males, psoriasis area and severity index (PASI) score, percentage of body surface area (BSA) affected by psoriasis and its duration and occurrence of adverse events. We also considered the definition of MACEs used by authors.

The Cochrane Collaboration's tool for assessing the risk of bias was used to evaluate random sequence gen-

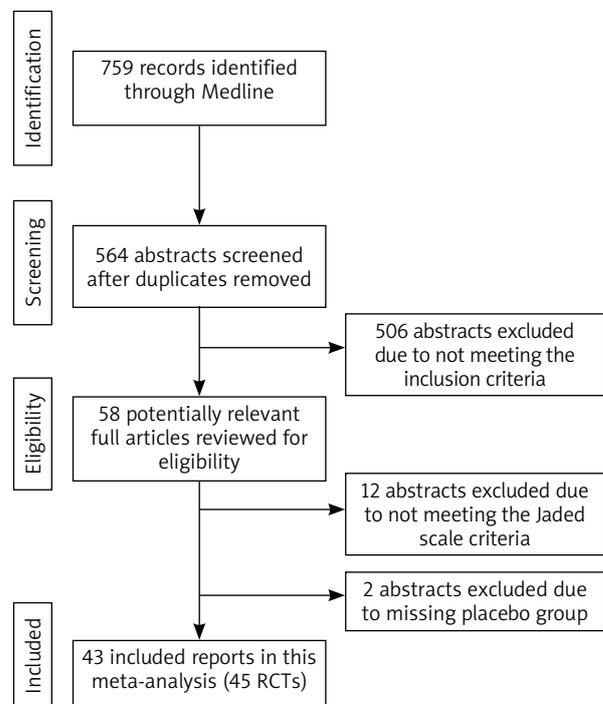


Figure 1. PRISMA

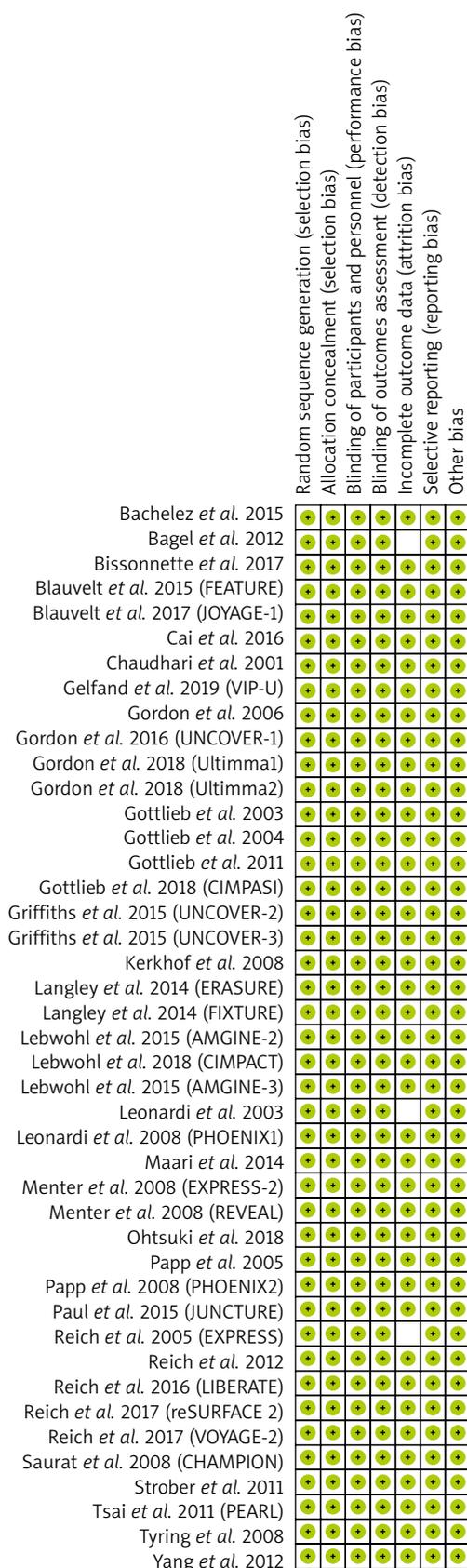


Figure 2. Risk of bias summary

eration, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The unclear risk was rated only three times (7%) in case of incomplete outcome data because studies did not include the reason for participants' exclusion. The total number of excluded patients was 1070. The most common reason for discontinuation was occurrence of the adverse event ($n = 265$; 25%), withdrawal of consent ($n = 195$; 18%), unsatisfactory response to treatment ($n = 174$; 16%), lost to follow-up ($n = 103$; 10%) and other reason ($n = 207$; 19%). Other domains of risk of bias assessment were estimated as a low risk. Funnel plot analysis using the Mantel-Haenszel fixed-effect method was used for assessing potential publication bias. In all extracted comparisons no evidence of publication bias was found (Figures 2, 3).

Data analysis

The included research data were meta-analysed using Review Manager 5.4. The Mantel-Haenszel type method was used to estimate the risk difference of MACEs in patients receiving biologic therapy versus placebo, assuming a fixed-effects model. A total of 43 RCTs (identified in 38 reports) were included in this meta-analysis as shown in Figure 1 [22–60]. The risk difference (RD) was used because, unlike the Peto OR it does not exclude RCTs without reported MACEs, in both comparisons. Additionally, interpretation of the RD between experimental and comparator interventions is straightforward. The Mantel-Haenszel method is preferable in the Cochrane Handbook for statistical properties with a few events [61]. There were four main comparisons, which included: (1) any biologic therapy (TNFi, anti-IL-17A agents, anti-IL-23 agents, anti-IL12/23 agents) vs. placebo (Figure 4); (2) TNFi (adalimumab, etanercept, infliximab, certolizumab) vs. placebo, anti-IL-17A agents (secukinumab and ixekizumab) vs. placebo; (3) anti-IL-23 agents (guselkumab) vs. placebo; (4) anti-IL-12/23 agents (ustekinumab) vs. placebo (Figure 5). χ^2 test was used to assess significance (p -value < 0.1 as statistically significant) of heterogeneity between the results of different research and presented it as I^2 test ($I^2 > 50\%$ as significant heterogeneity and $I^2 < 25$ as non-significant heterogeneity). The Number Needed to Harm was calculated to provide an alternative way of presenting the statistical results. A funnel plot was used to assess any potential risk of publication bias.

Results

Study characteristics

Of the 759 abstracts searched on MEDLINE, only 43 met the inclusion criteria [22–60]. A total of 19,161 patients with plaque psoriasis participated in the included studies. Only of these trials were not multi-centre ones [28, 29, 44, 55, 56]. The mean duration of the randomized phase was 14 weeks. Inclusion criteria

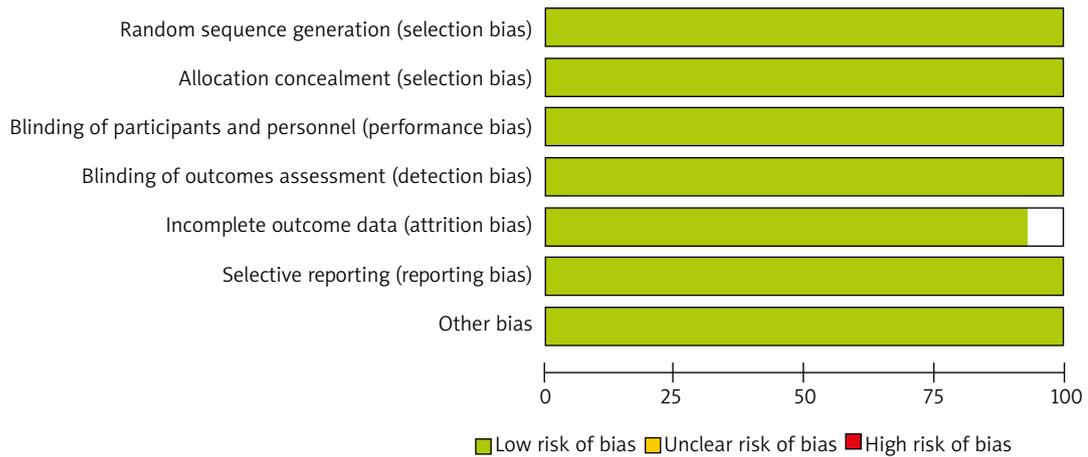


Figure 3. Risk of bias graph

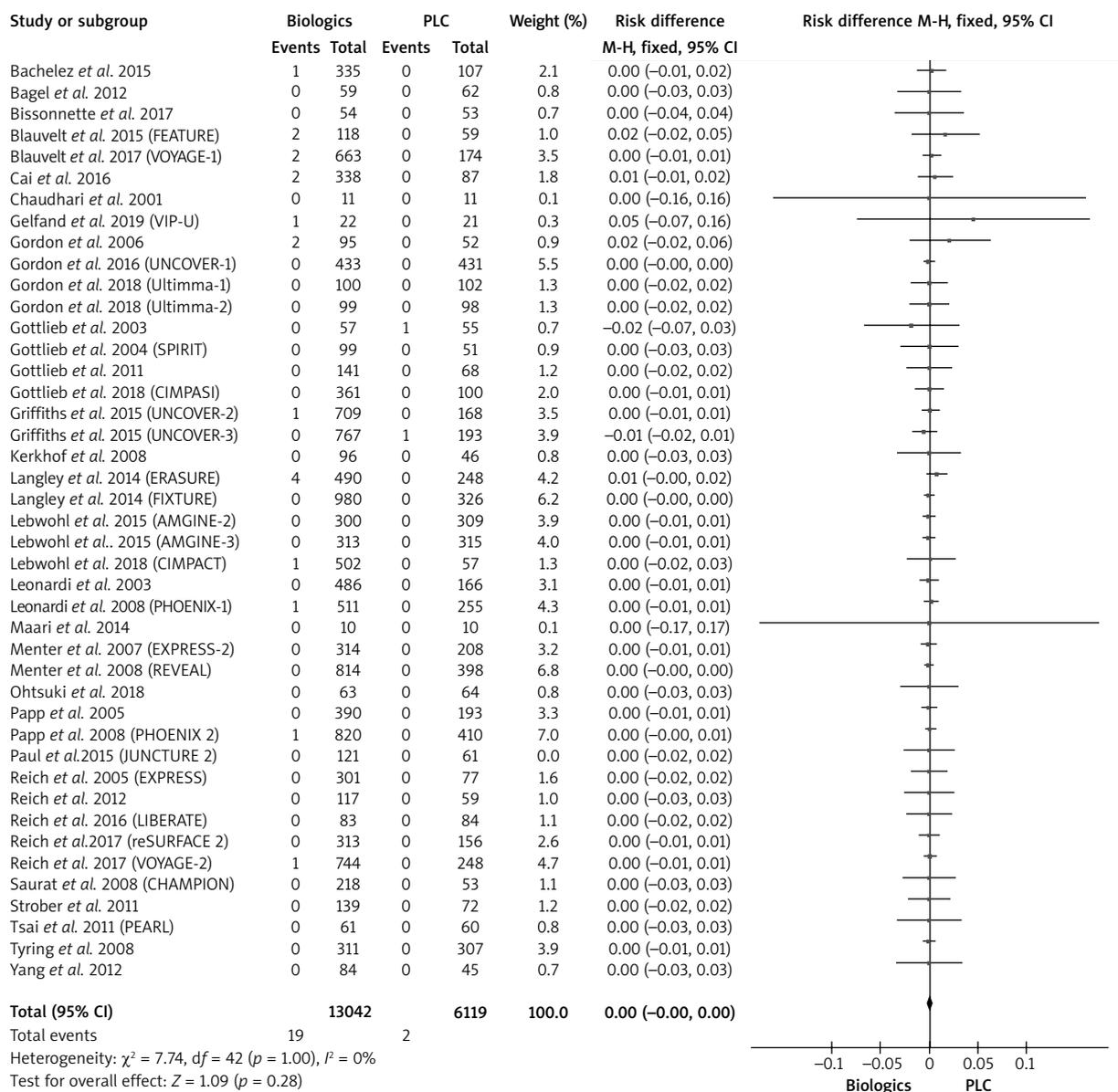


Figure 4. Forest plot for biologics

for the RCTs were minimum duration of psoriasis range 6 to 12 months (10 studies did not specify these criteria), minimum BSA range 5–10% (1 study did not specify these criteria), and PASI range 10–12 points (6 studies did not specify this criterion). Those studies included 20 to 1306 participants, with a male percentage range of 54.35–90.0%, mean age range of 40.1–55.7 years, mean duration of psoriasis range of 11.9–20.8, and PASI score range of 10.12–28.2.

Overall, the risk of MACEs in the included studies was 0.1% ($n = 21$), with 2 cases in the control group. Thirty-one trials compared TNFi (8 adalimumab, 3 certolizumab,

5 infliximab, 15 etanercept), and eleven MACEs were reported [22–24, 27, 28, 31–40, 43–45, 48, 51, 52, 54–59]. Three RCTs compared the anti-IL-23 agent (guselkumab) with placebo, and there was just one MACE [25, 47, 60]. Seven trials reported six MACEs, comparing anti-IL-17A agents (secukinumab, ixekizumab) with placebo [31, 37, 39, 50, 61, 62]. Eight RCTs compared ustekinumab versus placebo, and three MACEs were reported [29, 30, 41, 42, 49, 53]. The MACE rates were 0.15% for TNFi (7266 total patients), 0.1% for anti-IL-23 agents (888 total patients), 0.2% for anti-IL-17A agents (2552 total patients) and 0.1% for anti-IL-12/23 agents (2226 total patients) (Figure 5).

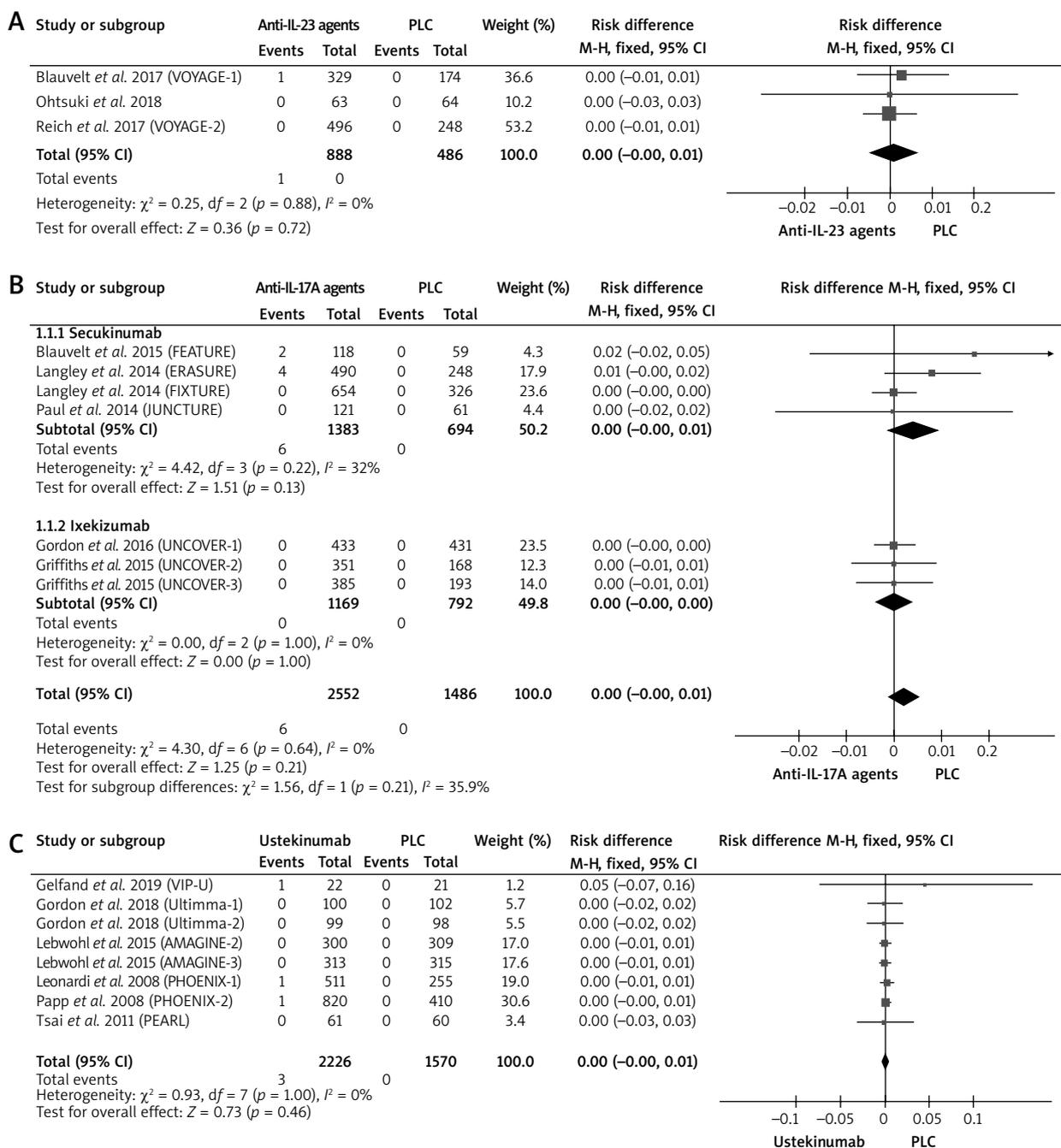


Figure 5. Risk difference (RD) of major adverse cardiovascular events in patients treated with (A) anti-IL-23 agents vs. placebo; (B) anti-IL-17A agents vs. placebo; (C) ustekinumab vs. placebo

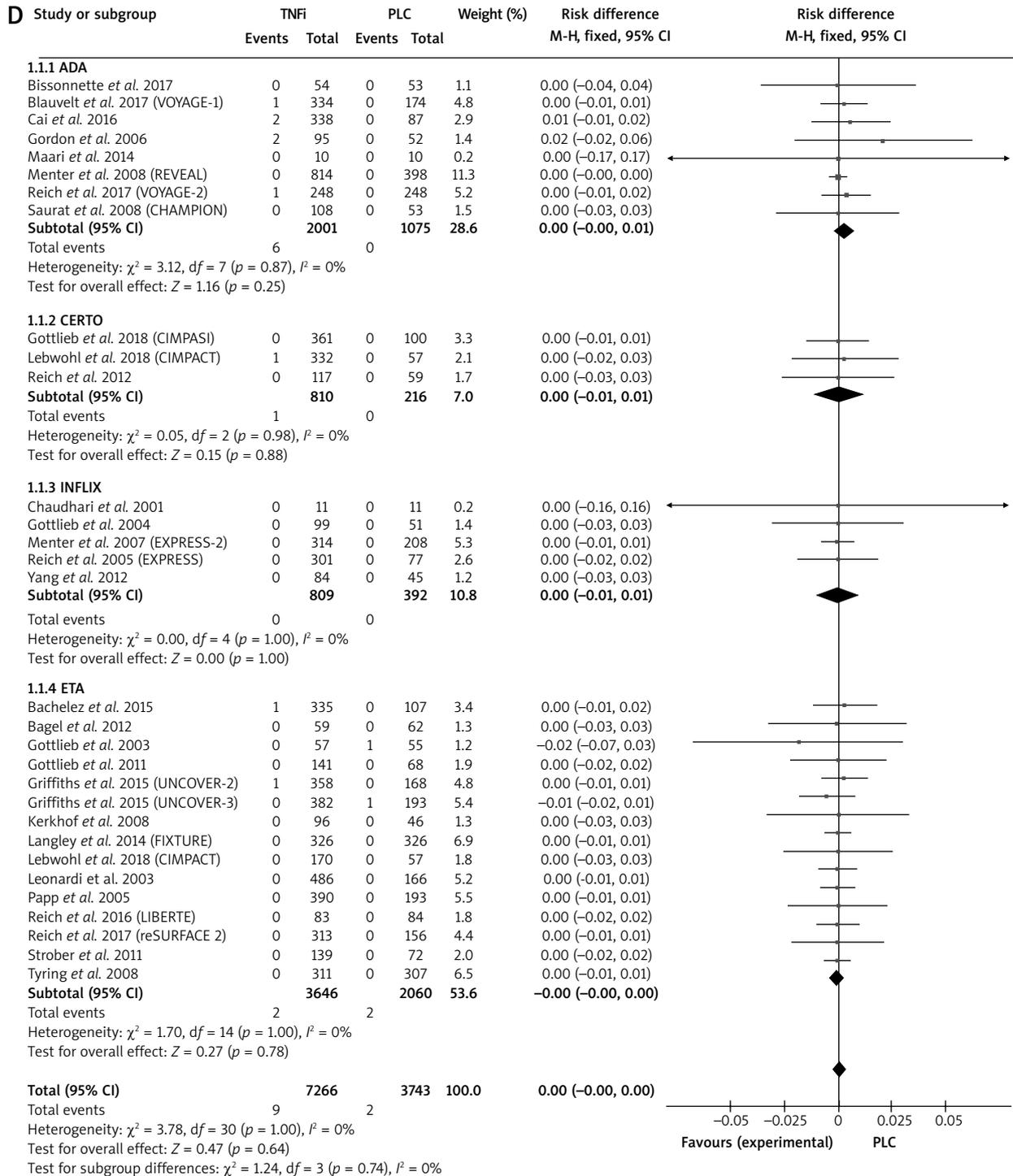


Figure 5. Cont. (D) tumour necrosis factor- α inhibitors (TNFI) vs. placebo. CI – confidence interval, df – degrees of freedom

Meta-analysis

From 43 RCTs comparing biologic therapy with placebo only 14 (identified in 13 publications) reported MACEs, the total number of MACEs, during randomized

controlled studies, was 21 [22, 25, 27, 29, 32, 35, 37, 39, 40, 42, 49, 60, 61] (Figure 4). Analysis including any biologic therapy in comparison to placebo found that there was no statistically significant risk difference of MACEs

occurrence in the treatment group ($RD = 0.0$; $Z = 1.09$; 95% CI: $-0.0-0.0$; $p = 0.28$; fixed-effect model). The heterogeneity between included RCTs was rated as low ($\chi^2 = 7.74$; $df = 42$; $p = 1.00$; $I^2 = 0\%$) (Figure 4).

Individual analysis has also shown that there was no statistically significant risk difference for patients receiving TNFi, including adalimumab, certolizumab, infliximab, etanercept ($RD = 0.0$; $Z = 0.47$; 95% CI: $-0.0-0.0$; $p = 0.64$; fixed-effect model) vs. placebo; for anti-IL-23 antibodies – guselkumab ($RD = 0$; $z = 0.36$; 95% CI: $-0.0-0.01$; $p = 0.72$; fixed-effect model) vs. placebo; for anti-IL-17A agents, including secukinumab and ixekizumab ($RD = 0.0$; $Z = 1.25$; 95% CI: $-0.0-0.01$; $p = 0.21$; fixed-effect model) vs. placebo; for anti-IL-12/23 antibodies – ustekinumab ($RD = 0.0$; $Z = 0.73$; 95% CI: $-0.0-0.0$; $p = 0.46$; fixed-effect model) vs. placebo. The overall heterogeneity of particular analysis was low for TNFi ($\chi^2 = 3.78$; $df = 30$; $p = 1.0$; $I^2 = 0\%$); anti-IL-23 antibodies ($\chi^2 = 0.25$; $df = 2$; $p = 0.88$; $i^2 = 0\%$); anti-IL-17A antibodies ($\chi^2 = 4.30$, $df = 6$; $p = 0.64$; $I^2 = 0\%$); anti-IL-12/23 antibodies ($\chi^2 = 0.93$, $df = 7$; $p = 1.00$; $I^2 = 0\%$) (Figure 5).

Discussion

Due to the increasing use of biologic therapies in the treatment of plaque psoriasis and the creation of new medicinal products, it is necessary to assess the risk of adverse events. Complications of biologic treatment depend on the type of used antibodies. Major adverse cardiovascular events are one of the rarest complications but are directly life-threatening. Therefore, in assessing the difference in the risk of MACEs in experimental and comparator interventions, we used a statistical method intended for uncommon events. We found no statistically significant risk difference of MACEs in patients with plaque psoriasis treated with any biologic therapy or placebo in this meta-analysis of RCTs.

The previously performed meta-analysis ambiguously define the risk of MACEs in patients treated with biologic agents. Additionally, they did not include all currently used treatments of plaque psoriasis, approved by EMA. An earlier meta-analysis which included 22 RCTs, reported no association of MACEs between TNFi (adalimumab, etanercept and infliximab) and anti-IL-12/23 agents [14]. This study, like ours, used the Mantel-Haenszel fixed-effect method to assess the risk difference, which is recommended for those type of events [14, 61]. Another meta-analysis has examined patients receiving anti-IL-12/23 agents (ustekinumab and briakinumab), and shown a significant association of the increased risk of MACEs in this group [20]. Authors of this trial also used the Mantel-Haenszel fixed-effect method. The meta-analysis including the biggest number of RCT (38 trials), with use of the Peto's method, found no increased risk of MACEs occurrence between experimental and comparator interventions [21]. The advantage of our study is that it includes all currently used therapies approved for the treat-

ment of plaque psoriasis. Contrary to the previous analysis we did not include experimental therapies (as briakinumab), unlicensed doses and did not use the Peto's method which is not recommended for assessing the risk of events such as MACEs. Several limitations should be considered while interpreting this meta-analysis. The search strategy did not include Cochrane or EMBASE. Some of the included trials had a small sample size (the smallest number of study participants was 20). Most of the included trials had a short duration of randomized controlled phase (10–30 weeks). Although we included all currently approved therapies, we did not compare different dosages of the same drugs. Most included trials did not report MACEs separately but compared them with other adverse events. The significant limitation of our meta-analysis is due to lack of information about cardiovascular risk factors, which may have influenced the risk of MACEs independently. Furthermore, the inclusion criteria of the majority of studies practically exclude patients with previously diagnosed cardiovascular diseases. These studies also tend to exclude elderly patients, who have a higher cardiovascular risk (mean age range: 40.1–55.7). It is important to state that in the general population these therapies may be used by patients with cardiovascular risk factors, cardiovascular diseases and other comorbidities or patients of elder age. The risk of MACEs in these groups cannot be assessed based on this meta-analysis and requires further studies.

In conclusion, gathered evidence suggests no significant impact on the risk of MACEs in adult patients with plaque psoriasis over the short term. The limitations of this study such as short duration of the randomized controlled phase or patient characteristics should be regarded. Our recommendations for future studies are to include assessment of cardiovascular risk factors, involve a larger number of patients and extend the time of treatment exposure reflecting the clinical practice for better safety assessment of biologic therapies. Further studies are required to evaluate the impact of biologic therapies on the risk of MACEs in patients with cardiovascular risk factors or cardiovascular comorbidities.

Conclusions

The risk of MACEs in patients with plaque psoriasis receiving biologic therapies is still undefined. An unknown risk of MACEs is related to the fact that most RCTs have a short randomized controlled phase (10–30 weeks), exclude patients with an increased cardiovascular risk and the participants are mainly people under 50 years of age. No statistically significant risk difference in patients treated with any biologic therapy vs. placebo; TNFi vs. placebo; anti-IL-17A agents vs. placebo; anti-12/23 agents vs. placebo; anti-IL-23 agents vs. placebo, has been reported. Further trials are needed, including longer follow-up and patients with an increased cardiovascular risk, to assess the risk of MACEs.

Conflict of interest

The authors declare no conflict of interest.

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