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Title: Cardiovascular Safety of Systemic Psoriasis Treatments: a Prospective Cohort Study in the BIOBADADERM Registry.

Running head: CV Safety of Psoriasis Treatments.

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Conflicts of interest:

Dr Carrascosa has participated as a speaker, advisor, and PI/SI in clinical trials sponsored by Celgene, Janssen, Lilly, Leo Pharma, Novartis, Pfizer, MSD, Biogen, Mylan, Amgen, Abbvie, and Sandoz.

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Data availability statement: The data supporting this study's findings are available from the BIOBADADERM study group upon reasonable request.

All of the authors listed have made a substantial contribution to the study in accordance with international criteria and have revised and approved the final manuscript.

Author Contributions Statement

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ABSTRACT

Background: Psoriasis is a chronic inflammatory disease with multiple comorbidities, including an increased risk of major adverse cardiovascular events (MACE). There is limited and contradictory evidence comparing the impact of systemic treatments for psoriasis on MACE.

Objectives: To evaluate the incidence of MACE associated with each systemic treatment used for patients with psoriasis and compare these rates to those observed with methotrexate (MTX).

Methods: We conducted a prospective cohort study using data from the BIOBADADERM registry. Propensity score matching was used to adjust for baseline differences between treatment groups. We calculated the incidence rate (IR) of MACE for each systemic treatment class, including biologics (anti-TNF, IL-12/23, IL-17 and IL-23 inhibitors), conventional systemic therapies (MTX, cyclosporine, dimethyl fumarate and acitretin) and apremilast (APR). The IR for each group was compared to those observed in patients treated with MTX using Poisson regression models adjusted for potential confounders, with 95% confidence intervals (95% CI). The primary outcome

was the adjusted incidence rate ratios (IRR) for MACE between patients receiving MTX and those receiving another systemic treatment.

Results: We analysed data from 5,622 patients, 11,368 treatment cycles, and 21,762 person-years (PYs). APR (IRR=0.17; 95% CI, 0.04-0.70) and IL-17 (IRR=0.43; 95% CI, 0.20-0.91) were associated with a significant reduction in the risk of MACE compared to MTX. Cyclosporine was associated with an increased risk of MACE (IRR=3.59; 95% CI, 1.17-10.99) compared to MTX. The remaining systemic psoriasis treatments were not significantly associated with an increased or decreased risk of MACE.

Conclusions: This real-world evidence study indicates a potential association between APR and IL-17 with a lower incidence of MACE, while CYC showed a higher incidence compared to MTX. These findings underscore the importance of considering cardiovascular outcomes when selecting systemic therapies for patients with psoriasis.

Key points/Highlights

- **Why was the study undertaken?**

  - Psoriasis is a chronic inflammatory disease associated with an increased risk of major cardiovascular events (MACE). There is contradictory and limited real-world evidence (RWE) comparing the cardiovascular safety of systemic treatments for psoriasis, particularly regarding their impact on MACE.

- **What does this study add?**

  - This study provides real-world evidence of the incidence of MACE in psoriasis patients treated with systemic therapies.
  - Apremilast and IL-17 were associated with a lower risk of MACE compared to methotrexate, and cyclosporine with an increased risk.

- **What are the implications of this study for disease understanding and/or clinical care?**

  - The findings support the consideration of cardiovascular risk assessment in the selection of systemic psoriasis treatment.
  - This study provides valuable RWE to inform personalised clinical decision-making in the treatment of psoriasis.

1. Background

Psoriasis is a chronic inflammatory disease whose incidence and prevalence have increased in recent years[1] and is associated with multiple comorbidities[2].

This systemic involvement is evidenced not exclusively by a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, obesity, and dyslipidaemia among psoriasis patients but also by the increased occurrence of major adverse cardiovascular events (MACE), such as myocardial infarction, stroke and death[2–7]. This association is particularly significant in patients with severe psoriasis[6,8], even after accounting for traditional cardiovascular risk factors[5,8,9].

The heightened risk of MACE in psoriasis patients is thought to be due to systemic inflammation mediated through the Th-1, Th-17, and Th-22 pathways, which induce deregulated cytokine production, endothelial dysfunction, atherosclerosis, and subsequent cardiovascular disease (CVD) and MACE[10–13]. This theory forms the fundamental premise for proposing that systemic treatment that mitigates inflammation in psoriasis patients would decrease the risk of MACE[13]. However, some treatments might paradoxically increase that risk due to their mechanisms of action or associated adverse events. In this aspect, psoriasis therapies have shown inconsistent results[14,15]. In addition, the information of cardiovascular safety of systemic agents in patients with psoriasis is scarce in real-world evidence (RWE), most of them extrapolated from other inflammatory diseases, which are not always directly comparable to psoriasis[16,17].

1.1 Objectives

This study aims to evaluate the incidence of MACEs for the different systemic treatments used in patients with psoriasis, providing robust RWE for conventional systemic treatments, small molecules, and biologic therapy. The incidence rate of MACEs for each treatment was compared to the incidence of MACEs observed in patients treated with methotrexate (MTX).

2. Methods

The patients included came from BIOBADADERM, a national, prospective multicentre cohort registry of patients with psoriasis treated with systemic therapy in clinical practice. A detailed description of BIOBADADERM has been published previously[18, 19].

All prospective data from January 2008 to November 2023 from patients with moderate-to-severe psoriasis at participating hospitals were included in the registry if they started a systemic therapy they had not received before. BIOBADADERM included safety data from 19 tertiary departments of dermatology. Additionally, a group of psoriasis patients receiving non-biologic classic systemic treatment for the first time was included. Standardised definitions of cardiovascular events or MACE events were collected during follow-up through the Medical Dictionary for Regulatory Activities (MeDRA).

BIOBADADERM is continuously monitored online, and the data are validated annually through on-site audits. The registry was approved by the Hospital 12 de Octubre Ethics Committee (216/07), and its operation complies with the Declaration of Helsinki. All patients sign informed consent to participate.

2.1 Study groups and outcomes

The time of exposure to a systemic drug was recorded from the start of treatment to the date of last administration, or November 2023 or the censor date in patients lost to follow-up. In patients who were lost to follow-up, the censor date was the last visit to the dermatologist. A MACE was temporally related to a drug if it occurred while it was being

administered or 90 days after the previous dose. Patients in combination therapy were excluded. Fatal MACE is defined as cardiovascular-related mortality.

Study groups were divided into nine categories according to the class of systemic agent they received: classical systemic treatment like acitretin (ACT), dimethyl fumarate (DMF), methotrexate (MTX), or cyclosporine (CYA); small molecules like apremilast (APR); TNFa inhibitors including adalimumab, certolizumab, etanercept, and infliximab; IL-12/23 inhibitors such as ustekinumab; IL-23 inhibitors, including guselkumab, risankizumab, and tildrakizumab; and IL-17 inhibitors, including brodalumab, ixekizumab, and secukinumab.

The primary outcome was the adjusted incidence rate ratios (IRR) for MACE between patients receiving MTX and those receiving another systemic treatment.

We used a five-point MACE definition to capture a broader range of cardiovascular events for comparison purposes and to avoid heterogeneity in MACE[20,21]. This composite includes death, myocardial infarction, stroke, unstable angina or hospitalisation for revascularisation and heart failure (supplementary table 1). We opted to include transient ischemic attack (TIA) and angina pectoris as MACE because we observed they were mainly considered as serious in our dataset. The cases of TIA were coded as a stroke outcome. Similarly, the event “angina” was included due to its seriousness and the possible lack of specificity in the coding in our dataset, which warrants its recognition as a significant cardiovascular event. Moreover, their application in previous studies supports using these MedDRA codes as MACE[20,22,23].

The decision to include a specific MACE was made after reviewing MedDRA codes only, without information about the patient (e.g., what treatment the patient was receiving).

2.2 Statistical analysis

For discrete variables, descriptive data were expressed as absolute numbers and percentages. For continuous skewed variables, medians and interquartile ranges were used.

We estimated adjusted IRR and incidence rate differences (IRD), including 95% confidence intervals (CI), for MACE, comparing MTX and each treatment using a robust Poisson regression analysis. MTX was used as the comparator with the rest of the drugs because it represents a standard therapy and the most frequently used conventional systemic therapy for psoriasis[24].

To reduce confusion bias from nonrandomised treatment assigned to patients, the propensity score of indication for each drug compared with MTX was calculated using variables associated with the exposure and the outcome[25] (sex, age, smoking, alcohol, disease duration, psoriatic arthritis, BMI, number of previous cardiovascular comorbidities, Psoriasis Area and Severity Index (PASI) and previous classic systemic treatment). These were selected based on clinical knowledge and as significant confounders identified in previous studies[17]. Cardiovascular comorbidities at baseline were ischemic heart disease, heart failure, arterial hypertension, diabetes, and hyperlipemia. All confounders were measured at a baseline. Propensity scores were included in the Poisson models as an IPTW. Hyperlipidemia was considered a possible mediator of the effect and was not included in the adjustment models.

To manage missing values, we created 20 complete datasets by means of chained equations through multiple imputation.

The incidence rate (IR) is defined as the number of new MACE occurrences per 1,000 person-years (PYs) of exposure to psoriasis treatments in our study. This measure reflects the frequency of new MACE cases in the study population over the specified period. An IRR, a measure of association equivalent to the relative risk, compares the IR of events between two groups. In our case, this comparison is between systemic psoriasis treatment and MTX (reference). The IRD, equivalent to the risk difference, refers to the incidence rate of a disease that can be attributed to a specific exposure—in our case, the psoriasis treatment—assuming a causal relationship and helps to describe the clinical relevance of the findings in absolute terms.

Several sensitivity analyses were performed using different models to improve the results' robustness. These included a multilevel analysis (with and without PS), a propensity score matching model, a propensity score variable used as a covariate, or a conventional

covariate adjustment analysis. Furthermore, sensitivity analyses were performed to evaluate the robustness of the definition of MACE by excluding less specific terms such as “angina” and “TIA”. These analyses were consistent with those of the primary analysis.

All analyses were performed using STATA v.17.0 (Stata Corp. 2021. Stata Statistical Software: Release 17). A P-value of less than 0.05 was considered statistically significant. The results of IRR are presented with two decimal places, while the IRD results are presented with one decimal place.

3. Results

We analysed data from 5,622 patients, 11,368 treatment cycles, 21,762 PYs, and a median duration of treatment exposure of 2.6 years (interquartile range 1-5.5 years).

3.1 Patient Characteristics

Patient characteristics are summarised by treatment group in Table 1.

TNF inhibitors were the most frequently prescribed drugs, with 2,331 cycles. Most patients were men (56%); the primary diagnosis was plaque psoriasis (88%). The mean baseline PASI was 10.5 (SD=7.3).

Comorbidities were prevalent, with hypercholesterolemia being the most common (31%), followed by arterial hypertension (27%) and diabetes (14%). The mean Body Mass Index (BMI) was 28.1 kg/m² (SD=5.7), with the mean BMI in all groups being above 25 kg/m². In total, 39% of patients presented with at least one cardiovascular comorbidity.

3.2 Incidence of MACEs in systemic therapy for psoriasis

Detailed information on IR of each treatment group can be found in Table 2

146 MACEs were reported in 21,762 PYs of exposure. The IR of MACE ranges from 20.2 cases (95% CI, 13.9-29.5) in the ACT group to 3.4 (95% CI, 1.1 to 10.5) in the APR group per 1,000 PYs. In the MTX group, we observed 19 MACE with an IR of 7 cases (95% CI, 4.5 to 11) per 1,000 PYs.

3.3 Adjusted incidence rate ratios (IRR) and incidence rate differences (IRD) of MACEs in psoriasis treatment compared to MTX

The detailed results are shown in Tables 3 and 4.

APR (adjusted IRR=0.17; 95% CI, 0.04 to 0.70) and IL-17 (adjusted IRR=0.43 95% CI, 0.20 to 0.91) were associated with a statistically significant reduction in the risk of MACE. In terms of risk reduction, APR resulted in 3.7 fewer MACEs (95% CI, -8.6 to 1.3) and IL-17 in 3.7 fewer MACEs (95% CI, -7.3 to 0.2) compared to MTX per 1,000 PYs of exposure.

In contrast, CYC was associated with an increased risk of MACE (adjusted IRR=3.59; 95% CI, 1.17 to 10.99), with an IRD of MACE being 8.9 (95% CI, -3.3 to 21.1) additional events per 1,000 PYs compared to MTX.

The remaining systemic treatments did not show a statistically higher or lower risk of MACE compared to MTX.

These results are represented in Fig. 1.

Sensitivity analyses excluding terms such as “angina” and “TIA” demonstrated no significant changes in the observed trends or outcomes.

4. Discussion

The link between psoriasis and CVD has been recognised for decades. Previous studies show that patients with psoriasis face a 6.2% higher absolute risk of experiencing a MACE within ten years of diagnosis compared to the general population[13,26,27]. In our cohort, APR and IL-17 use was associated with a significantly reduced risk of MACE compared to MTX. Conversely, CYC was associated with a significantly increased risk of MACE compared to MTX. When adjusted for confounding variables, the remaining psoriasis treatments did not show a statistically significant higher risk of MACE compared to MTX.

4.1 Conventional systemic therapies

In patients treated with MTX, we found 19 MACEs, with an incidence of 7 cases per 1,000 PYs. In previous works, MTX was associated with a reduced[14,28,29] or neutral[30] effect against CVD and MACE in patients with psoriasis. However, most of the information on MTX comes from other inflammatory diseases[14] and uses different comparators, ranging from acitretin[28] to the absence of treatment as a control[30].

CYC was associated with a significant increase in the incidence of MACE, with an additional 8.9 events per 1,000 PYs, consistent with the results of other cohorts, with topical treatments as control[30]. This increased cardiovascular risk may be due to cyclosporine's potential to elevate blood pressure, increase cholesterol and cause kidney dysfunction[31,32].

ACT showed a tendency to increase the risk of MACE compared to MTX. Nevertheless, it did not reach statistical significance when adjusted to confounding variables, suggesting that these variables and indication bias could explain the increased risk. This also aligns with the literature, which shows an elevated risk of increased serum triglycerides and cholesterol. However, it does not translate into an increased incidence of CVD in patients with psoriasis compared to those without treatment[31].

DMF was not associated with an increase in MACE risk.

4.2 Small molecules

APR was associated with a statistically significant decreased risk of total MACE in our cohort, translating clinically into 3.7 less MACE per 1,000 PYs. Other recent controlled clinical trials showed an improvement of cardiometabolic parameters in psoriasis patients treated with apremilast[32,33] and lower rates of myocardial infarction and stroke than patients with disease-modifying antirheumatic drugs, but similar to biologics users[34]. This cardioprotective effect has been linked to reductions in LDL levels, BMI, and HbA1c, particularly in patients with higher baseline levels of these parameters[33].

4.3 Biologic therapy

Different meta-analyses have studied the risk of MACE in patients with psoriatic arthritis or psoriasis undergoing biologic therapy in randomised controlled trials (RCTs). In summary, these meta-analyses suggest that they are not associated with an increased risk of MACE in patients with psoriasis[35–37]. However, the characteristics of patients in registries differ from those in clinical trials[16], and the time-to-onset of MACEs - around

one year of exposure- may be longer than the follow-up period of RCTs[30,38,39]. In this context, evaluating and monitoring the incidence of MACEs in daily clinical practice and prospective cohorts is crucial. A study using RWE data from the FDA Adverse Event Reporting System found a significant association between biologic psoriasis therapies and disproportionate reporting of MACEs. However, they did not calculate the IR of adverse events and included briakinumab, a drug withdrawn precisely due to increased MACE in phase II and III RCTs[37]. The study also lacked individual patient-level data such as cardiovascular history[38]. Other RWE studies showed that biologics partially mitigate the impact of comorbidities on all-cause mortality[40].

TNFa agents did not show a statistically significant increase or decrease in the risk of MACE compared to MTX in our cohort. Results in the literature are heterogeneous. A meta-analysis found that TNF inhibitors are associated with a lower risk of cardiovascular events compared to topical/phototherapy or MTX treatment [41], which aligns with other prospective studies and meta-analyses [23, 42]. In other prospective studies, no difference was seen between MTX and TNFa [39,43], which is consistent with our results.

The IL-12/23 ustekinumab did not show a significant alteration in the risk of MACE compared to MTX in our cohort. A comprehensive study from the Psoriasis Longitudinal Assessment Registry (PSOLAR) indicated that ustekinumab treatment was not associated with an increased risk of MACE versus the topical/phototherapy cohort[44]. Other studies demonstrated similar findings[31]. In contrast, a meta-analysis found a higher rate of MACEs in patients receiving anti-IL-12/23 agents, but with the inclusion of briakinumab[44].

IL-17 treatments were associated with a significantly reduced risk of MACE with 3.6 fewer MACE 1,000 PYs than MTX. Experimental data suggest that IL-17 cytokine could play a central role in the relationship between psoriasis and cardiovascular disease[13,46]. Until now, anti-IL17 drugs have not shown a significant impact on MACE incidence in psoriasis patients[35,37,47-50].

IL-23 did not show a statistically significant increase or decrease in the risk of MACE compared to MTX. These results are consistent with the previously described absence of MACE risk for this therapeutic group[37,49,50]. However, RWE is scarce in this aspect.

5. Limitations

We acknowledge several limitations in our study. Although we adjusted for the main confounding variables related to CVD, residual confounding from unmeasured variables such as physical activity and diet cannot be excluded. Although adjustments were made for baseline comorbidities, the dataset did not include detailed information on the level of control of these conditions. MTX was used as a comparator instead of a placebo or topical treatment. MTX has been shown to reduce cardiovascular risk in patients with chronic inflammation and psoriasis, potentially underestimating the cardioprotective effect of other treatments. This approach could have facilitated the demonstration of an increase in MACE, as initially hypothesised. However, the IRR of MACE in our treatment groups further validates the safety of systemic treatments for psoriasis.

Given the observational nature of this study, indication bias in prescription or follow-up is possible due to treatment selection rather than random allocation, as seen in randomised clinical trials. We employed a propensity score model to balance these characteristics between treatment cohorts. This method ensures that comparisons between treatment groups are as unbiased and accurate as possible, enhancing the validity of our findings.

The failure to detect differences may be due to low statistical power from the small number of MACEs detected. However, the narrow 95% CI of the IRR and the infrequent nature of MACE indicate that the results likely do not reflect risks of significant clinical impact. The IRD results help evaluate this limitation, particularly in smaller patient groups.

Additionally, MACE coding depends on the reporting physician, potentially leading to errors. Nonetheless, MACE's serious or fatal nature ensures that such adverse events are always recorded, following the MedDRA classification system. Moreover, including TIA and unspecified angina as MACE reinforces the observed safety of these treatments in the study, given the conservative approach adopted.

Despite these potential sources of bias, the data represent the RWE of a considerably large cohort, making the results more feasible to generalise to routine clinical practice.

6. Strengths

This study also has several strengths. Its prospective design and the BIOBADADERM registry offer high-quality data with continuous monitoring, a rarity in observational studies. The large sample size includes patients from multiple hospitals across Spain, enhancing the study's generalisability.

All serious or fatal adverse events are closely monitored, providing robust data on mortality. Additionally, the diagnosis of MACE within the cohort was conducted without knowledge of the treatment received, thereby minimising potential bias in event classification. We transparently provided the composite MACE coding, including the five-point MACE, to capture a broader range of cardiovascular events and facilitate the comparison with similar studies. Furthermore, the sensitivity analyses demonstrated no significant changes in the observed trends or outcomes, reinforcing the validity of the chosen definition. Notably, we covered all systemic treatments used in routine clinical practice, including information about newer systemic drugs, such as IL17 and IL23, not included in other registries.

7. Conclusion

Considering the increased CVD in psoriasis patients, it is imperative to develop treatment approaches that not only address the skin symptoms but also tackle cardiovascular health. Our findings suggest a decreased risk of MACE with APR and IL-17, while CYC was associated with an increased risk compared to MTX. The remaining systemic psoriasis treatments were not significantly associated with an increased risk of MACE. Assessing CVD in psoriasis patients is crucial, as different treatments can affect MACE incidence differently. Understanding the cardiovascular impact of psoriasis treatments is essential for improving patient outcomes and reducing overall morbidity and mortality. This study provides valuable RWE to inform personalised clinical decision-making in the treatment of psoriasis.

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Table 1 Patient characteristics

	TNFa	IL-12/23	IL-23	IL-17	ACI	CYC	APR	DMF	MTX	TOTAL	Missing, n (%)
Demographic data											
Number of patients, N ‡	2331	875	1003	1119	844	603	510	122	1474	5622	
Patients-years, total	7029	4134	1943	3176	1335	440	888	114	2704	21762	
Number of cycles, total	3411	1070	1082	1347	1050	738	546	134	1990	11368	
Time exposed, years. mean (sd)	3.0 (3.6)*	4.7 (3.8)*	1.9 (1.2)	2.8 (2.0)*	1.6 (2.3)	0.7 (0.9)*	1.7 (1.7)	0.9 (1.1)*	1.8 (2.2)	3.9 (3.8)	
Women, n (%)	1005 (43)*	381 (44)*	407 (41)*	489 (44)*	331 (39)*	287 (48)	274 (54)	67 (55)	717 (49)	2452 (44)	
Age at start of treatment, years. mean (sd)	45.9 (14.0)	47.4 (14.7)	52.0 (14.4)*	50.3 (13.7)*	54 (14.6)*	41.1 (14)*	55.5 (13.2)*	51.3 (14.8)*	46 (14.6)	47.7 (14.8)	20 (0.3%)
Duration of disease at start of treatment, years. mean (sd)	17.7 (13.2)*	19.9 (13)*	21.4 (13.8)*	19.1 (13.9)*	15.6 (14.8)	14.4 (11.3)	17.5 (15)*	18.6 (15.1)*	14.5 (13.2)	16.2 (13.6)	146 (2.5%)
Psoriasis Area Severity Index (PASI). mean (sd)	11.1 (7.5)*	12.7 (8.3)*	9.1 (6.4)*	10.4 (7.9)*	7.7 (5.5)	12.2 (8)*	7.7 (4.6)	6.9 (3.4)	8.2 (5.2)	10.5 (7.3)	1143 (20.3%)
Body Mass Index (BMI). mean (sd)	28.0 (5.8)*	27.9 (5.5)	29.1 (6.0)*	28.9 (5.9)*	28.2 (5.5)*	27.2 (5.4)	29.8 (6.1)*	29.1 (6.3)*	27.5 (5.4)	28.1 (5.7)	1233 (21.9%)
Diagnosis at entry in the cohort, n (% of total)											
Plaque psoriasis	2100 (90)*	826 (94)*	920 (92)*	1000 (89)	675 (80)*	527 (87)	416 (82)*	113 (93)	1293 (88)	4945 (88)	
Psoriatic arthritis	373 (16)*	120 (14)*	128 (13)*	243 (22)*	59 (7)	45 (7)	65 (13)*	11 (9)	108 (7)	736 (13)	
Comorbidities, n (% of total)											
Ischemic heart disease	48 (3)	26 (3)	36 (5)*	29 (3)	29 (4)	7 (1)	16 (4)	2 (2)	30 (2)	154 (3)	1102 (19.6%)
Heart failure	11 (1)	13 (2)	9 (1)	9 (1)	14 (2)	2 (0)	10 (2)	0 (0)	12 (1)	49 (1)	1121 (19.9%)
Arterial hypertension	442 (23)	190 (23)	243 (29)*	272 (28)*	264 (34)*	60 (11)*	145 (33)*	30 (28)	276 (22)	1280 (27)	842 (15.0%
Diabetes	247 (13)*	108 (13)*	134 (16)*	138 (15)*	131 (17)*	35 (6)	92 (21)*	11 (11)	110 (9)	666 (14)	970 (17.3%)
Hypercholesterolemia	569 (29)	218 (27)	299 (36)*	360 (38)*	290 (37)*	112 (19)*	175 (40)*	27 (25)	350 (27)	1498 (31)	863 (15.4%)
Numer of comorbidities NO CV, n (%)											

No comorbidities	1983 (85)*	724 (83)*	776 (77)*	875 (78)*	633 (75)*	542 (90)	345 (68)*	102 (84)	1330 (90)	4591 (82)	
1 comorbidities	283 (12)*	116 (13)*	171 (17)*	193 (17)*	164 (19)*	49 (8)	122 (24)*	17 (14)	130 (9)	806 (14)	
2 comorbidities	55 (2)*	26 (3)*	45 (4)*	40 (4)*	38 (5)*	11 (2)	33 (6)*	3 (2)	13 (1)	184 (3)	
3 or more comorbidities	10 (0)*	9 (1)*	11 (1)*	11 (1)*	9 (1)*	1 (0)	10 (2)*	0 (0)	1 (0)	41 (1)	
Numer of comorbidities CV, n (%)											
No comorbidities	1499 (64)	541 (62)*	581 (58)*	622 (56)*	410 (49)*	451 (75)*	245 (48)*	76 (62)	968 (66)	3408 (61)	
1 comorbidities	495 (21)	182 (21)*	219 (22)*	270 (24)*	232 (27)*	104 (17)*	139 (27)*	26 (21)	302 (20)	1214 (22)	
2 comorbidities	209 (9)	94 (11)*	120 (12)*	155 (14)*	122 (14)*	33 (5)*	85 (17)*	16 (13)	145 (10)	630 (11)	
3 or more comorbidities	128 (5)	58 (7)*	83 (8)*	72 (6)*	80 (9)*	15 (2)*	41 (8)*	4 (3)	59 (4)	370 (7)	
Alcohol consumption, n (%)											1668 (29.7%)
Current	441 (26)*	171 (26)*	190 (26)*	181 (22)	139 (22)	113 (25)	79 (26)	23 (29)	225 (21)	992 (25)	
Previous	19 (1)*	11 (2)*	17 (2)*	14 (2)	6 (1)	5 (1)	6 (2)	0 (0)	10 (1)	63 (2)	
Smoker, n (%)											1309 (23.3%)
Current	706 (39)	265 (38)	338 (43)*	331 (37)	282 (41)*	217 (45)*	139 (39)*	31 (36)	425 (37)	1692 (39)	
Previous	226 (12)	86 (12)	137 (17)*	136 (15)	100 (15)*	56 (11)*	76 (21)*	15 (17)	137 (12)	605 (14)	
Previous treatments, n (%)											
Systemic treatments	1848 (79)*	773 (88)*	805 (80)*	925 (83)*	400 (47)*	368 (61)*	376 (74)*	89 (73)*	578 (39)	2988 (53)	
Phototherapy	885 (38)*	430 (49)*	376 (37)*	415 (37)*	210 (25)	163 (27)	192 (38)*	37 (30)	387 (26)	1878 (33)	

‡ The total number of patients reported for each group does not equal the total number of patients in the study because some patients belong to more than one treatment group.

* P value (P<0.05).

TNFa (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-23 (guselkumab, risankizumab, tildrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); ACT, acitretin; CYA, cyclosporine; APR, apremilast; DMF, dimethyl fumarate; MTX, methotrexate; PASI, Psoriasis Area Severity Index; BMI, Body Mass Index; SD, standard deviation; CV, cardiovascular.

Table 2. Adverse events incidence rates.

Systemic therapy for psoriasis	Number of person years of exposure	**All MACE events**		**Fatal MACE events**	
		Number of events	Incidence (95% CI)	Number of events	Incidence (95% CI)
TNFa	7029	39	5.5 (4.1 ; 7.6)	4	0.6 (0.2 ; 1.5)
IL-12/23	4134	30	7.3 (5.1 ; 10.4)	1	0.2 (0 ; 1.7)
IL-23	1943	9	4.6 (2.4 ; 8.9)	0	NA
IL-17	3176	11	3.5 (1.9 ; 6.3)	0	NA
ACI	1335	27	20.2 (13.9 ; 29.5)	6	4.5 (2 ; 10)
CYC	440	7	15.9 (7.6 ; 33.3)	0	NA
APR	888	3	3.4 (1.1 ; 10.5)	0	NA
DMF	114	1	8.8 (1.2 ; 62.5)	0	NA
MTX	2704	19	7 (4.5 ; 11)	1	0.4 (0.1 ; 2.6)

Incidences rates (per 1000 person-years). MACE, Major Adverse Cardiovascular Events; CI, confident interval.
TNFa (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-23 (guselkumab, risankizumab, tildrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); ACT, acitretin; CYA, cyclosporine; APR, apremilast; DMF, dimethyl fumarate; MTX, methotrexate

Table 3. Incidence Risk Difference of MACE compared to MTX.

Systemic therapy for psoriasis	**All MACE events**	**Fatal MACE events**
	Risk Difference (95% CI)	Risk Difference (95% CI)
TNFa	-1.5 (-5.1 ; 2.1)	0.2 (-0.7 ; 1.1)
IL-12/23	0.2 (-3.9 ; 4.3)	-0.1 (-1 ; 0.7)
IL-23	-2.4 (-6.8 ; 2.0)	-0.4 (-1.1 ; 0.4)
IL-17	-3.6 (-7.3 ; 0.2)	-0.4 (-1.1 ; 0.4)
ACI	13.2 (4.9 ; 21.5)	4.1 (0.5 ; 7.8)
CYC	8.9 (-3.3 ; 21.1)	-0.4 (-1.1 ; 0.4)
APR	-3.7 (-8.6 ; 1.3)	-0.4 (-1.1 ; 0.4)
DMF	1.8 (-15.8 ; 19.3)	-0.4 (-1.1 ; 0.4)
MTX	Reference incidence: 7 (4.5 ; 11)	Reference incidence: 0.4 (0.1 ; 2.6)

Risk Difference (per 1000 person-years). MACE, Major Adverse Cardiovascular Events; CI, confident interval.
TNFa (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-23 (guselkumab, risankizumab, tildrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); ACT, acitretin; CYA, cyclosporine; APR, apremilast; DMF, dimethyl fumarate; MTX, methotrexate

Table 4. Adjusted* incidence rate ratios compared to MTX

Systemic therapy for psoriasis	Number of person years of exposure	All MACE events		Fatal MACE events	
		IRR adjusted (95% CI)	p-value	IRR adjusted (95% CI)	p-value
TNFa	7029	0.98 (0.51 ; 1.91)	0.956	3.01 (0.42 ; 21.75)	0.276
IL-12/23	4134	0.85 (0.43 ; 1.68)	0.636	NA	
IL-23	1943	0.68 (0.23 ; 2.03)	0.494	NA	
IL-17	3176	0.43 (0.20 ; 0.91)	0.028‡	NA	
ACI	1335	1.85 (0.94 ; 3.64)	0.075	7.18 (0.83 ; 62.01)	0.073
CYC	440	3.59 (1.17 ; 10.99)	0.025‡	NA	
APR	888	0.17 (0.04 ; 0.70)	0.014‡	NA	
DMF	114	1.76 (0.63 ; 4.93)	0.284	NA	
MTX	2704	Reference: 1		Reference: 1	

*Adjusted by sex, age, smoking, alcohol, disease duration, psoriatic arthritis, BMI, number of previous cardiovascular comorbidities, Psoriasis Area and Severity Index (PASI) and previous classic systemic treatment.

‡ P value (P<0.05).

TNFa (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-23 (guselkumab, risankizumab, tildrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); ACT, acitretin; CYA, cyclosporine; APR, apremilast; DMF, dimethyl fumarate; MTX, methotrexate.

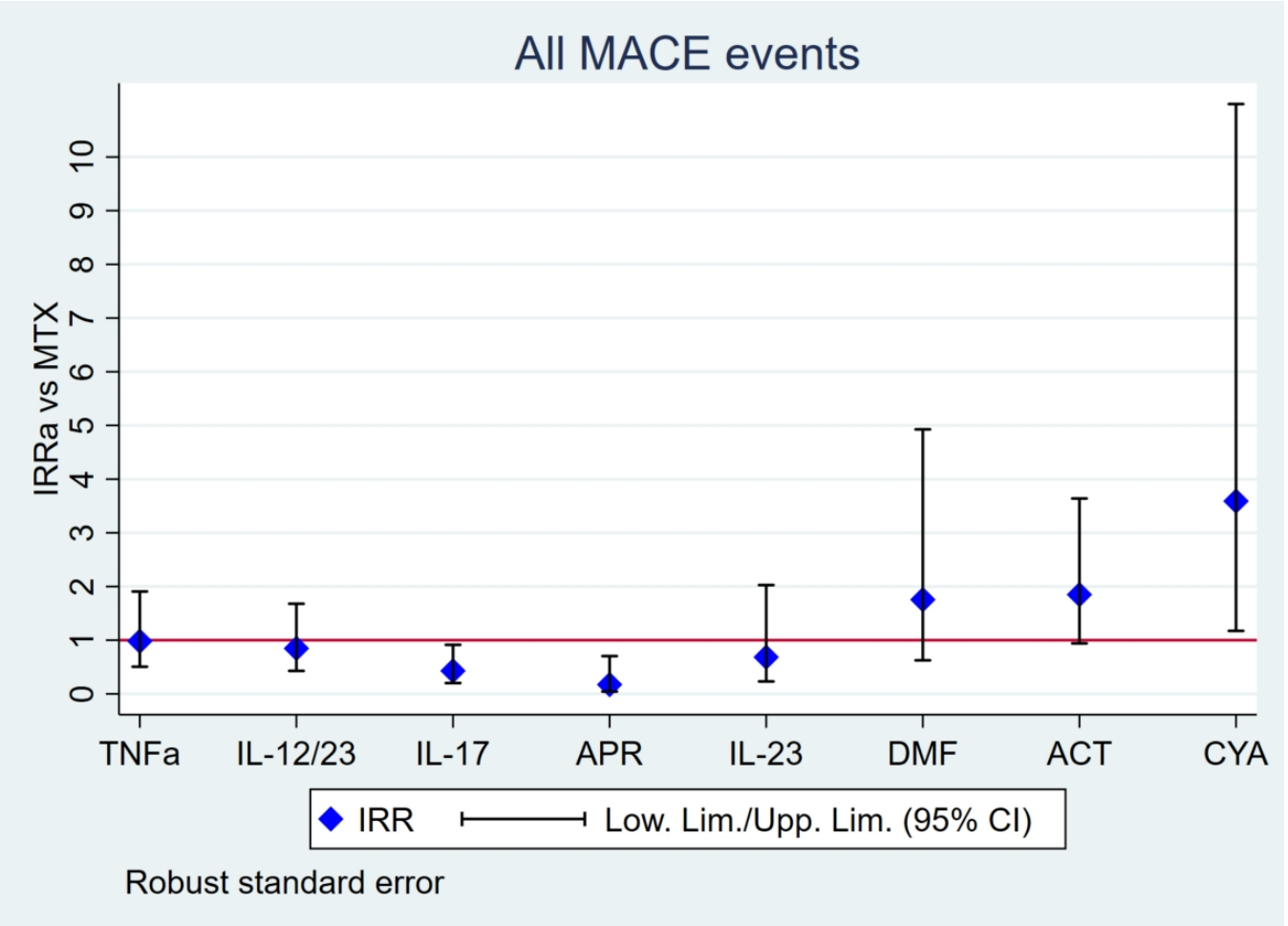
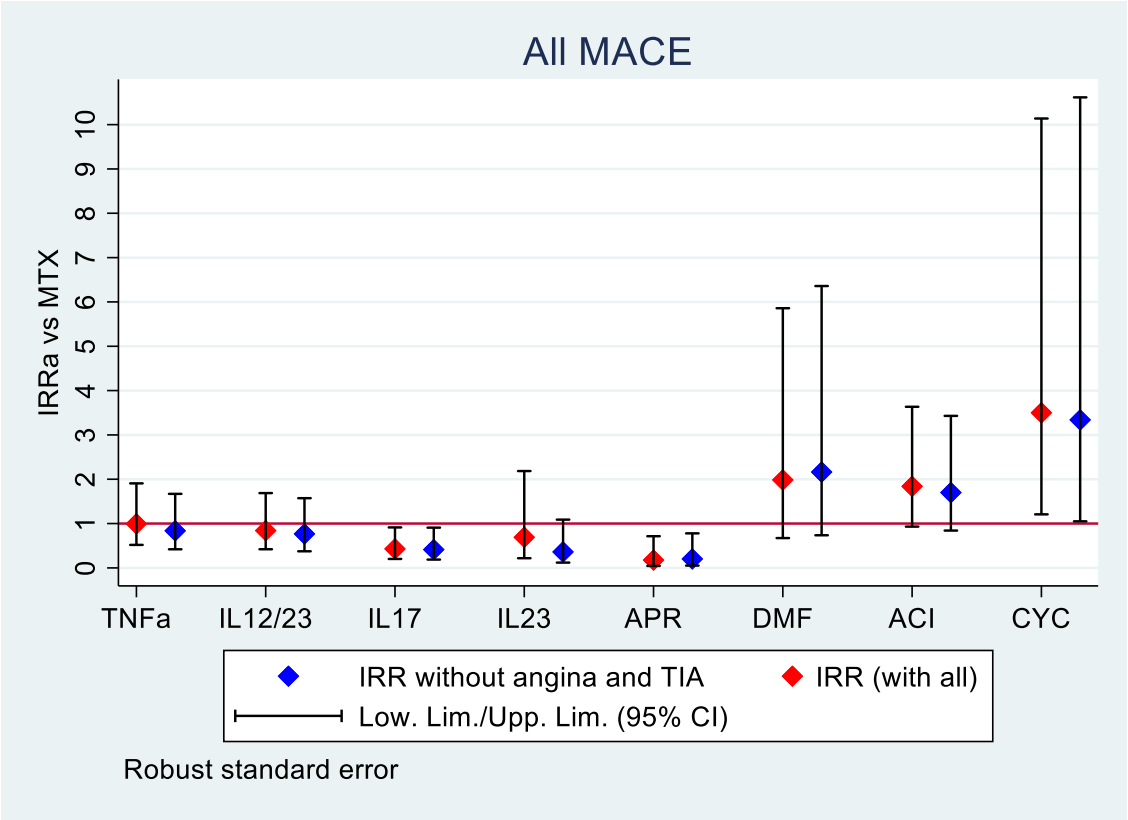


Figure 1: Adjusted incidence rate ratio of all Major Adverse Cardiovascular Events with systemic psoriasis treatment compared to methotrexate. TNFa (adalimumab, certolizumab, etanercept, infliximab); IL-12/23, ustekinumab; IL-23 (guselkumab, risankizumab, tildrakizumab); IL-17 (brodalumab, secukinumab, ixekizumab); ACT, acitretin; CYA, cyclosporine; APR, apremilast; DMF, dimethyl fumarate; MTX, methotrexate.

Supplementary Table 1: Codification of the MACE in BIOBADADERM

MACE category in the five-point MACE composite	Codification of the MACE in BIOBADADERM
Death	sudden cardiac death, cardiac arrest, cardiorespiratory arrest, death
Myocardial infarction	ischemic cardiomyopathy, severe coronary artery disease, infarction, acute myocardial infarction, myocardial infarction, myocardial ischemia, acute ischemic cardiomyopathy, acute coronary syndrome
Stroke	cerebrovascular accident, transient ischemic attack, ischemic neurological deficit, embolic stroke, ischemic stroke, thrombotic stroke, cerebellar infarction, cerebral infarction, cerebral ischemia, haemorrhagic transformation due to stroke
Unstable angina or hospitalisation	unstable angina, severe angina pectoris, arterial catheterisation, cardiac catheterisation, trans myocardial revascularisation, angina.
Heart Failure	heart failure, acute heart failure, congestive heart failure, acute pulmonary oedema, severe chronic heart failure

MACE, Major Adverse Cardiovascular Events.



Supplementary figure 1: sensitivity analysis where "angina" and "transient ischaemic attack (TIA)" were excluded as MACE. The results of this analysis indicate minimal changes in the overall trends and outcomes, as observed in the incidence rate ratios (IRRs) across treatment groups