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Incidence of Major Adverse Cardiovascular Events in Patients With Rheumatoid Arthritis Treated With JAK Inhibitors Compared With Biologic Disease-Modifying Antirheumatic Drugs: Data From an International Collaboration of Registries

Romain Aymon,[1] Denis Mongin,[1] Romain Guemara,[1] Zubeyir Salis,[2] Johan Askling,[3] Denis Choquette,[4] Catalin Codreanu,[5] Daniela Di Giuseppe,[3] Irini Flouri,[6] Doreen Huschek,[7] Kimme L. Hyrich,[8] Florenzo Iannone,[9] Tore K. Kvien,[10] Burkhard F. Leeb,[11] Dan Nordström,[12] Lucia Otero-Varela,[13] Karel Pavelka,[14] Manuel Pombo-Suarez,[15] Ana Rodrigues,[16] Ziga Rotar,[17] Prodromos Sidiropoulos,[6] Sella A. Provan,[10] Anja Strangfeld,[18] Trokovic Nina,[12] Jakub Zavada,[14] Lianne Kearsley-Fleet,[19] Delphine S. Courvoisier,[1] Axel Finckh,[20] and Kim Lauper[1]

Objective. Our objective was to assess the incidence of major adverse cardiovascular events (MACEs) in patients with rheumatoid arthritis (RA) treated with JAK inhibitors (JAKi), tumor necrosis factor inhibitors (TNFi), or biologic disease-modifying antirheumatic drugs with other modes of action (bDMARD-OMA) in a multicountry, real-world population.

Methods. Patients with RA from 15 registries in the JAK-pot collaboration were included. MACE incidence was analyzed using two approaches: a within-registry analysis aggregating country-specific estimates from registers with >25 incident MACEs through meta-analysis and an individual-level data combined analysis. We used adjusted linear mixed Poisson regression to obtain incidence rate ratios (IRRs) of MACEs between treatment groups, accounting for multiple treatment courses.

Results. The study included 73,008 treatment courses (16,417 JAKi, 35,373 TNFi, and 21,218 bDMARD-OMA) and 828 incident MACEs among 51,233 patients. Median follow-up time was 1.3 years, with most of the follow-up concentrated in the first two years of treatment. Incidence rates were 7.0, 7.6, and 11.8 per 1,000 person-years for JAKi, TNFi, and bDMARD-OMA, respectively. Compared to TNFi, JAKi (within-registry adjusted IRR 0.89, 95% confidence interval [CI] 0.63–1.25) had similar incidence rates of MACEs and bDMARD-OMA had higher rates (within-registry adjusted IRR 1.35, 95% CI 1.10–1.66). Combined analysis showed similar results.

Conclusion. Observational data from the JAK-pot collaboration show no evidence of an increase in cardiovascular events during the first two years of use with JAKi compared to TNFi in the general RA population.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder that, when suboptimally controlled, may result in chronic joint inflammation, progressive structural joint damage, and persistent pain. The disease is associated with an increased mortality rate, partly attributable to an increased risk of cardiovascular events, which occur at a higher rate in patients with RA compared to the

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[1]Romain Aymon, MSc, Denis Mongin, PhD, Romain Guemara, MD, Delphine S. Courvoisier, PhD, Kim Lauper, MD: Department of Rheumatology, Geneva University Hospital, Geneva, Switzerland; [2]Zubeyir Salis, PhD: University of Montpellier and Physiology and Experimental Medicine of the Heart and Muscles, Montpellier, France; [3]Johan Askling, MD, PhD, Daniela Di Giuseppe, PhD: Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [4]Denis Choquette, MD: Centre Hospitalier de l'Université de Montréal, Institut de Recherche en Rhumatologie, Montréal, Québec Canada; [5]Catalin Codreanu, MD, PhD: University of Medicine, Center of Rheumatic Diseases, Bucharest, Romania; [6]Irini Flouri, MD, PhD, Prodromos Sidiropoulos, MD, PhD: Rheumatology and Clinical Immunology, University Hospital of Heraklion, Crete, Greece; [7]Doreen Huschek, PhD: Deutsches Rheuma-Forschungszentrum, Programme Area Epidemiology, Berlin, Germany; [8]Kimme L. Hyrich, MD, PhD: National Institute for Health and Care Research Manchester Biomedical Research Centre, Manchester University NHS Trust, Manchester, United Kingdom; [9]Florenzo Iannone, MD, PhD: Department of Precision and Regenerative Medicine and Ionian Area, Rheumatology Unit University of Bari, Bari, Italy; [10]Tore K. Kvien, MD, PhD, Sella A. Provan, MD, PhD: Diakonhjemmet Hospital, Center

general population.[1,2] Although the elevated cardiovascular risk in RA may be partly explained by traditional cardiovascular risk factors, available evidence suggests a direct role of systemic inflammation and altered lipoprotein profiles in the development of atherosclerosis and cardiovascular events.[3,4] Accordingly, treatment with disease-modifying antirheumatic drugs (DMARDs), such as tumor necrosis factor inhibitors (TNFi) or methotrexate, has been associated with a reduction in cardiovascular events in patients with RA.[5,6]

JAK inhibitors (JAKi) are the latest treatments developed for RA. They have shown substantial promise in the management of RA and have become an important option in the therapeutic arsenal against the disease. But concerns have been raised regarding their safety. ORAL Surveillance,[7] an open-label randomized controlled safety trial, demonstrated a numerically higher incidence of major adverse cardiovascular events (MACEs) with tofacitinib (one of the licensed JAKi), compared to TNFi, with a reported hazard ratio (HR) for tofacitinib versus TNFi of 1.33 (95% confidence interval [CI] 0.91–1.94). This did not meet the study's noninferiority criteria, although the difference was not statistically significant. These findings prompted the European Medicine Agency (EMA) and the US Food and Drug Administration to issue warnings for tofacitinib use.[8,9] Recent studies[10–12] based on observational data at the national level did not confirm these signals, although one study showed a higher risk of discontinuation for adverse events with tofacitinib compared to TNFi.[13] Current management guidelines recommend that JAKi may be used after consideration of pertinent risk factors for cardiovascular disease.[14] A comprehensive understanding of the cardiovascular safety profile of JAKi is of paramount importance for the safe use of this class of medication. The primary objective of this study was to compare the incidence of MACEs in patients with RA treated with JAKi to that of alternative treatment options, such as TNFi and biologic DMARDs with other modes of action (bDMARD-OMA) in a large, multicountry, real-world population.

MATERIALS AND METHODS

Patient sample. The JAK-pot collaboration is an investigator-led, observational study that seeks to investigate the clinical characteristics of patients treated with JAKi and bDMARDs for RA.[13,15,16] Local ethics committees (when required according to local legislation) approved the collection of data in each participating registry, and the Geneva Ethics Committee approved this specific study (CCER 2017-02278, amendment 2). This analysis included treatment courses from patients aged 18 or more, initiating either JAKi or bDMARDs from the date that JAKi were commercially available in each country (as early as 2013 for some countries, see Supplementary Table S1), to avoid confounding by underlying time-trends for MACEs. Patients could contribute multiple treatment courses, on the same class or on different drugs. Individual treatment course-level data were provided by the following 14 registers: ATTRA from the Czech Republic, BIOBADASER from Spain, BIOREG from Austria, Biorx.si from Slovenia, BSRBR-RA from the United Kingdom, GISEA from Italy, NOR-DMARD from Norway, RABBIT from Germany, REUMA.PT from Portugal, RHUMADATA from Canada, ROB-FIN from Finland, RRBR from Romania, SCQM from Switzerland and UCRCR from Greece. ARTIS, from Sweden, provided aggregated data and results from local analysis based on the same statistical analysis plan. We recognized that cross-registry variability could arise from differences in populations, data collection methods, coding systems, and exposure definitions. Detailed baseline characteristics by registry (including demographics, disease duration, and comorbidities), data collection methods and coding systems, and year of JAKi introduction can be found in Supplementary Tables S2, S3, and S1 of the Supplementary material, respectively.

Exposure of interest and period. The exposure of interest was the type of treatment course: JAKi (tofacitinib, baricitinib, filgotinib, or upadacitinib), TNFi (infliximab, etanercept, adalimumab, certolizumab, or golimumab), or bDMARD-OMA (abatacept, rituximab, sarilumab, or tocilizumab). The primary exposure period spanned from the initiation of treatment (baseline) until either the first recorded MACE, three months after discontinuation, start of a new treatment defined as the start of a new biologic or targeted synthetic DMARD (b/tsDMARD) molecule (biosimilar switching was not considered as a new treatment), end of participation in the register, date of death, or the end of the study period

for Treatment of Rheumatic and Musculoskeletal Diseases, Oslo, Norway; [11]Burkhard F. Leeb, MD, PhD: BioReg, Vienna, Austria; [12]Dan Nordström, MD, PhD, Trokovic Nina, PhD: Departments of Medicine and Rheumatology, Helsinki University Hospital, The National Register of Biological Medicines, Helsinki, Finland; [13]Lucia Otero-Varela, MSc: Research Unit, Spanish Society of Rheumatology, Madrid, Spain; [14]Karel Pavelka, MD, PhD, Jakub Zavada, MD, PhD: Institute of Rheumatology, Prague, Czech Republic; [15]Manuel Pombo-Suarez, MD, PhD: NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal; [16]Ana Rodrigues, MD, PhD: NOVA Medical School, Universidade Nova de Lisboa and Reuma.pt, Sociedade Portuguesa de Reumatologia, Lisbon, Portugal; [17]Ziga Rotar, MD, PhD: Department of Rheumatology, University Medical Centre Ljubljana & Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [18]Anja Strangfeld, MD, PhD: Deutsches Rheuma-Forschungszentrum, Programme Area Epidemiology and Charité – Universitätsmedizin, Berlin, Germany; [19]Lianne Kearsley-Fleet, PhD: Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; [20]Axel Finckh, MD: Department of Rheumatology, Geneva University Hospital and Geneva Center for Inflammation Research, University of Geneva, Geneva, Switzerland.

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Address correspondence via email to Romain Aymon, MSc, at romain.aymon@hcuge.ch.

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(November 2023), whichever came first. The end of the study period was set at an earlier date for some registries who could not provide more recent data (see Supplementary Material S4). The end of the exposure period for rituximab was set at one year after the last treatment administration because of its longer-lasting effects. To further assess the robustness of our findings, we performed sensitivity analyses using two alternative exposure periods: a shorter one, ending at the time of drug cessation, and a longer one, extending to six months after discontinuation, start of a new treatment, end of participation in the register, death, or the end of the study period, whichever came first.

Study outcomes. The primary outcome was the incidence of MACE, which was operationally defined as the occurrence of a stroke, myocardial infarction (MI), or transient ischemic attack (TIA). Patients with a history of the outcome were not excluded. Secondary end points included the incidence of the individual component events of MACEs (stroke, MI, or TIA). MACE was defined operationally based on specific *International Classification of Diseases* (ICD), *9th Revision*, ICD, *10th Revision*, and Medical Dictionary for Regulatory Activities (MedDRA) codes provided to each register (see Supplementary Tables S5 and S6). Details on the coding systems used by the registries and their data collection methods are provided in Supplementary Table S3.

Covariates of interest. Baseline covariates were chosen a priori based on clinical knowledge and the literature. They captured various patient, disease, and treatment characteristics, including sex, age, body mass index (BMI), disease activity (Clinical Disease Activity Index [CDAI] or Disease Activity Score in 28 joints if CDAI was not available in the register), disease duration (duration from symptoms onset until baseline or from the date of diagnosis until baseline if the date of symptoms onset was not available), seropositivity (rheumatoid factors and/or anticitrullinated protein antibody), number of previously used b/tsDMARDs (0, 1, 2, or ≥3), concomitant use of conventional synthetic DMARDs (csDMARDs) (none, methotrexate, other csDMARDs without methotrexate, methotrexate, and at least one other csDMARD), concomitant use of glucocorticoids (presence or absence), use of antiplatelet and anticoagulant medications, functional status (Health Assessment Questionnaire Disability Index), and C-reactive protein. All covariates were reassessed at each new treatment initiation to account for changes in patient characteristics over time.

Because the incidence of MACEs is heavily influenced by comorbidities, a modified Rheumatic Disease Comorbidity Index (RDCI)[17] was computed and included as a baseline covariate. This modified RDCI included the following comorbidities: lung disease, cardiovascular disease, hypertension, depression, diabetes, and cancer. Data on fracture, ulcer, and stomach problems were not collected and not used in this modified RDCI.

Statistical methods. The results are presented according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18] Baseline patient demographics and disease characteristics for each treatment group are described using counts and percentages for categorical variables, means and SDs for normally distributed continuous variables, and medians and interquartile ranges (IQRs) for nonnormally distributed data. The number of patients with valid (nonmissing) data are also provided. Missing covariate data were addressed using multiple imputations with chained equations (50 samples, predictive mean matching algorithm), with all covariates used for the propensity score included in the imputation model. The outcome variable was not imputed.

Because of constraints on cross-border data sharing, one registry could only provide aggregated data. Consequently, the analyses were conducted through two different approaches:

- Within-registry analysis: Analyses were performed independently within each registry data set. The results from these analyses were then combined using random-effects meta-analysis techniques, considering the potential heterogeneity across registries. Heterogeneity among the registries was quantified using the I^2 statistic. Analyses were performed only if the number of events were ≥25 to avoid overadjustment. This analysis included data from five registries: Switzerland, Germany, Sweden, Spain, and the United Kingdom.
- Combined data analysis: Analyses were performed in a comprehensive manner, pooling data from all registries that provided individual treatment course-level data, to ensure sufficient statistical power for the analysis, particularly for more scarce outcomes. ARTIS was not included in this analysis.

The within-registry and combined analyses each involved different sets of registries, which can lead to variations in the observed results. Outcomes are reported as incidence rates, expressed as the number of events per 1,000 person-years (PYs) with 95% CIs. Unadjusted incidence rate ratios (IRRs) and 95% CIs were obtained using a Poisson regression model to compare crude incidence between treatment groups. Adjusted IRRs and 95% CIs were calculated using multivariable Poisson regression, adjusting for baseline confounders, as described previously. As rare events were analyzed, a propensity score approach with inverse probability weighting was employed to balance characteristics between treatment groups, within each register for within-registry analysis, and across combined registers for the combined data analyses. Absolute standardized mean differences before and after weighting for the combined analysis are presented in Supplementary Figures S7 and S8. We accounted for clustering resulting from patients contributing more than one treatment course and incorporated the logarithm of exposure time as an offset. The TNFi group served as the reference for

computing IRRs. All analyses were conducted using the statistics software[19] R 4.2.1 with the mice library for multiple imputation.[20]

Secondary analyses. *Randomized controlled trial duplicate cohort and history of cardiovascular disease.* A subgroup analysis was conducted focusing on patients with an increased risk of MACEs. This "randomized controlled trial (RCT)-duplicate cohort" mirrored the primary inclusion criteria of the ORAL Surveillance study, specifically targeting patients aged 50 years or older with at least one cardiovascular risk factor (hypertension, hyperlipidemia, diabetes, smoking, or a history of stroke or MI). A subgroup of patients with a history of cardiovascular disease (past stroke, past MI, or other past cardiovascular problems), drawn from the entire study cohort, was also analyzed separately.

Supplementary sensitivity analyses. Further sensitivity analyses (S9-S13), along with their methods, can be found in the Supplementary Materials, including stratification of the bDMARD-OMA group by mode of action, exclusion of rituximab, analysis by prior b/tsDMARD use (bionaive vs nonbionaive), and evaluation of MACE incidence before and after EMA safety warnings for JAKi. Additionally, an emulated trial analysis (S14-S16) using propensity score matching is detailed to assess robustness of the primary analysis.

Data sharing statement. Data are available on reasonable request. All the data belong to the registries. Anonymized data can be shared as long as agreements are made with all participating registries.

RESULTS

This analysis included 73,008 treatment courses from 15 registers (16,417 on JAKi, 35,373 on TNFi, and 21,218 on bDMARD-OMA) and 828 incident MACEs among 51,233 patients. Table 1 summarizes the baseline characteristics of the of 54,905 treatment courses from the 14 registers that provided treatment course-level data. ARTIS contributed with 18,103 treatment courses, for which baseline characteristics are presented in Supplementary Table S17. Patients were predominantly female (76%), seropositive (80%), and 58.4 years old, on average, with a median disease duration of 10.0 years. Most of the patients on JAKi were treated with baricitinib (44%), followed by tofacitinib (30%), upadacitinib (21%), and filgotinib (5%). Baseline characteristics were similar between the two largest JAKi groups (baricitinib and tofacitinib), whereas patients on upadacitinib and filgotinib were less often bionaive, with many (62% and 64%, respectively) having previous exposure to two or more previous b/tsDMARDs (Supplementary Table S18). Patients on JAKi had similar disease activity at baseline than patients on TNFi and slightly higher than patients on bDMARD-OMA. Other baseline characteristics, including BMI and comorbidities, were comparable for the three treatment groups. Patients starting a TNFi had shorter disease duration (8 years vs 11 years in JAKi and 12 years in bDMARD-OMA), were more often taking their first-line b/tsDMARD therapy (45% vs 20% in JAKi and 16% in bDMARD-OMA) and were less often on monotherapy (28% vs 37% in JAKi and 35% in bDMARD-OMA) compared to the other alternative treatments. A total of 78% of treatments were started in the prewarning period before the EMA safety warnings.

Incidence of MACEs. *Overall analysis.* The median follow-up from treatment start for JAKi, TNFi, and bDMARD-OMA were 1.5 (IQR 0.7–2.7), 1.5 (IQR 0.7–2.8), and 1.0 (IQR 1.0–2.0) years, respectively. Table 2 presents PYs at risk, number of MACEs, incidence rates per 1,000 PYs, and crude and adjusted IRRs for the within-registry analysis (data from 5 registries) and combined data analysis (data from 14 registries). Additionally, Supplementary Table S19 presents the PYs at risk, number of events, and crude incidence rates observed after the first and second years of treatment. When analyzing the incidence of MACEs by country (within-registry analysis) including only registries with at least 25 MACEs, there were a total of 743 MACEs recorded. The overall crude incidence was 7.0, 7.6, and 11.8 per 1,000 PYs for JAKi, TNFi, and bDMARD-OMA, respectively, and not significantly different between JAKi and TNFi (crude IRR 1.12, 95% CI 0.91–1.39), but higher for bDMARD-OMA compared to TNFi (crude IRR 1.70, 95% CI 1.45–1.99). When adjusted for baseline covariates, no difference in the incidence in MACEs was noted between JAKi and TNFi (adjusted IRR 0.96, 95% CI 0.60–1.54), but the adjusted incidence was significantly higher for bDMARD-OMA (adjusted IRR 1.35, 95% CI 1.10–1.66). The I^2 statistic, measuring the heterogeneity of the adjusted IRR was 43.5% for JAKi versus TNFi and 21.0 % for bDMARD-OMA versus TNFi, indicating moderate heterogeneity for JAKi and low heterogeneity for bDMARD-OMA.

In the combined data analysis, including data from the 14 registers who contributed individual treatment course-level data, 289 MACEs were recorded, for a crude incidence rate of 2.8 of 1,000 PYs. The crude incidence was significantly higher for bDMARD-OMA versus TNFi (crude IRR 1.49, 95% CI 1.15–1.93) and similar between JAKi and TNFi (crude IRR 0.99, 95% CI 0.73–1.34). When adjusting for confounding factors, we could not identify statistically significant differences in the incidence of MACE for bDMARD-OMA compared to TNFi (adjusted IRR 1.19, 95% CI 0.90–1.58), and the incidence of MACE remained similar between JAKi and TNFi (adjusted IRR 0.89, 95% CI 0.63–1.25).

Different exposure periods and mode of action. The results from the analyses with shorter (Supplementary Table S20) and longer (Supplementary Table S21) exposure times were consistent with the overall findings. Within-registry analysis showed the highest crude incidence rates for CTLA4-Ig and anti-CD20, both significantly higher than TNFi (Supplementary Table S9). The combined data analysis confirmed these findings, with CTLA4-Ig

Table 1. Baseline characteristics by treatment group (14 registries, individual treatment course-level data)*

Characteristic	JAKi (BARI, 44%; TOFA, 30%; UPA, 21%; FILGO, 5%)		TNFi (ETA, 40%; ADA, 30%; CZP, 9%; GOLI, 8%; INF, 6%; unspecified, 4%)		bDMARD-OMA (RITUX, 33%; TCZ, 32%; ABA, 24%; SARI, 7%; unspecified,[a] 4%)	
	Valid (%)	Value (n = 13,374)	Valid (%)	Value (n = 25,049)	Valid (%)	Value (n = 16,482)
Treatment duration, median (IQR), y	100.0	1.39 (0.58–2.66)	100.0	1.33 (0.54–2.77)	100.0	0.99 (0.79–1.88)
Age, mean (SD), y	100.0	58.29 (12.22)	100.0	57.12 (13.34)	100.0	60.48 (12.45)
Female, n (%)	100.0	10,468 (78.3)	100.0	18,906 (75.5)	100.0	12,488 (75.8)
Disease duration, median (IQR), y	93.9	10.96 (5.36–18.43)	93.6	8.35 (3.70–16.00)	93.8	11.88 (5.97–20.00)
Seropositivity (RF and/or ACPA), n (%)	83.6	9,028 (80.7)	78.8	15,237 (77.2)	79.4	11,096 (84.8)
Previous b/ts DMARD, n (%)	98.9		98.7		98.8	
0		2,667 (20.2)		11,030 (44.6)		2,617 (16.1)
1		3,192 (24.1)		6,900 (27.9)		4,219 (25.9)
2		2,570 (19.4)		3,349 (13.5)		3,640 (22.4)
3 or more		4,796 (36.3)		3,443 (13.9)		5,809 (35.7)
Concomitant csDMARD at baseline, n (%)	78.5		83.3		79.6	
MTX		3,420 (32.6)		7,305 (35.0)		4,054 (30.9)
MTX + other		890 (8.5)		2,831 (13.6)		1,326 (10.1)
Other		2,304 (21.9)		4,903 (23.5)		3,173 (24.2)
None		3,886 (37.0)		5,818 (27.9)		4,560 (34.8)
Concomitant GC, n (%)	93.9	5,542 (44.2)	92.8	7,995 (34.4)	92.0	6,362 (42.0)
CRP, mean (SD), mg/L	77.8	11.34 (21.18)	71.7	11.43 (21.51)	67.6	12.25 (27.06)
CDAI, mean (SD)	33.7	25.01 (13.74)	25.1	23.73 (13.85)	20.9	22.16 (13.97)
DAS28, mean (SD)	51.9	4.75 (1.50)	42.9	4.60 (1.58)	45.6	4.31 (1.71)
HAQ, mean (SD)	32.1	1.23 (0.72)	24.8	1.13 (0.73)	21.8	1.18 (0.75)
BMI, mean (SD)	100.0	27.07 (5.82)	100.0	27.29 (6.26)	100.0	27.25 (6.03)
Ever smoking, n (%)	74.8	3,604 (36.0)	76.5	7,388 (38.5)	75.6	4,820 (38.7)
Past myocardial infarction, n (%)	60.4	159 (2.0)	64.2	281 (1.7)	70.3	263 (2.3)
Past stroke, n (%)	62.4	112 (1.3)	69.5	265 (1.5)	68.0	218 (1.9)
Hypertension, n (%)	82.8	3,363 (30.4)	85.5	5,862 (27.4)	84.9	4,223 (30.2)
Hyperlipidemia, n (%)	70.4	1,721 (18.3)	64.7	2,306 (14.2)	65.0	1,991 (18.6)
Diabetes, n (%)	81.4	990 (9.1)	84.6	1,873 (8.8)	83.7	1,335 (9.7)

* ABA, abatacept; ACPA, anticitrullinated protein antibody; ADA, adalimumab; BARI, baricitinib; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, classical synthetic disease-modifying antirheumatic drug; CZP, certolizumab; DAS28, Disease Activity Score in 28 joints; ETA, etanercept; FILGO, filgotinib; GC, glucocorticoid; GOLI, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; IQR, interquartile range; JAKi, JAK inhibitor; MTX, methotrexate; OMA, other modes of action; RF, rheumatoid factor; RITUX, rituximab; SARI, sarilumab; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor; TOFA, tofacitinib; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; UPA, upadacitinib.
[a] Because of internal regulation, one of the registries could only provide the category of the bDMARD (bDMARD-OMA or TNFi) but not the specific type of bDMARD-OMA or TNFi.

Table 2. Crude and adjusted incidence and IRRs of MACEs for within-registry and combined data analysis*

	PYs	MACEs	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Within-registry analysis[a]					
TNFi	45,432	344	7.57 (6.79–8.42)	1 (ref)	1 (ref)
JAKi	16,786	117	6.97 (5.76–8.35)	1.12 (0.91–1.39)	0.96 (0.60–1.54)
bDMARD-OMA	23,951	282	11.77 (10.44–13.23)	1.70 (1.45–1.99)[b]	1.35 (1.10–1.66)[b]
Combined data analysis[c]					
TNFi	50,042	125	2.50 (2.08–2.98)	1 (ref)	1 (ref)
JAKi	25,113	62	2.47 (1.89–3.16)	0.99 (0.73–1.34)	0.89 (0.63–1.25)
bDMARD-OMA	27,428	102	3.72 (3.03–4.51)	1.49 (1.15–1.93)[b]	1.19 (0.90–1.58)

* Adjusted analyses adjusted for sex, age, body mass index, disease activity, disease duration, seropositivity, number of previously used bDMARDs or targeted synthetic DMARDs, concomitant use of conventional synthetic DMARDs, concomitant use of glucocorticoids, use of antiplatelet and anticoagulant medications, functional status, C-reactive protein, and Rheumatic Disease Comorbidity Index. bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; JAKi, JAK inhibitor; MACE, major adverse cardiovascular event; OMA, other modes of action; PY, person-year; ref, reference; TNFi: tumor necrosis factor inhibitor.
[a] Within-registry unadjusted and adjusted analysis included data from registries with at least 25 MACEs: Switzerland, Germany, Sweden, Spain, and United Kingdom.
[b] P value < 0.05.
[c] Combined data analysis included all 14 registries excluding Sweden.

Table 3. Crude and adjusted incidence and IRRs of secondary outcomes for the combined data analysis*

	Within-registry analysis[a]					Combined data analysis[b]				
	PYs	Events, n	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)	PYs	Events, n	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Stroke										
TNFi	NA	NA	NA	NA	NA	49,532	38	0.77 (0.54–1.05)	1 (ref)	1 (ref)
JAKi	NA	NA	NA	NA	NA	24,790	17	0.69 (0.40–1.09)	0.89 (0.50–1.58)	0.78 (0.42–1.46)
OMA	NA	NA	NA	NA	NA	27,068	25	0.92 (0.60–1.36)	1.20 (0.74–1.96)	0.97 (0.57–1.65)
Myocardial infarction (includes DE, SE, SP, and UK)										
TNFi	29,409	138	4.69 (3.94–5.54)	1 (ref)	1 (ref)	50,193	75	1.49 (1.18–1.87)	1 (ref)	1 (ref)
JAKi	11,075	57	5.15 (3.90–6.67)	1.23 (0.91–1.66)	0.90 (0.61–1.32)	25,190	39	1.55 (1.10–2.12)	1.04 (0.70–1.52)	0.91 (0.60–1.39)
OMA	16,173	125	7.73 (6.43–9.21)	1.76 (1.40–2.22)[c]	1.72 (1.07–2.78)[c]	27,533	62	2.25 (1.73–2.89)	1.51 (1.08–2.11)[c]	1.31 (0.91–1.89)
Transient ischemic attack										
TNFi	NA	NA	NA	NA	NA	34,376	16	0.46 (0.27–0.76)	1 (ref)	1 (ref)
JAKi	NA	NA	NA	NA	NA	14,149	8	0.56 (0.24–1.11)	1.21 (0.52–2.84)	1.36 (0.51–3.61)
OMA	NA	NA	NA	NA	NA	17,470	17	0.97 (0.57–1.56)	2.09 (1.06–4.13)[c]	1.57 (0.74–3.35)

* Adjusted analyses adjusted for sex, age, body mass index, disease activity, disease duration, seropositivity, number of previously used biologic disease-modifying antirheumatic drugs (DMARDs) or targeted synthetic DMARDs, concomitant use of conventional synthetic DMARDs, concomitant use of glucocorticoids, use of antiplatelet and anticoagulant medications, functional status, C-reactive protein, and Rheumatic Disease Comorbidity Index. CI, confidence interval; DE, Germany; IR, incidence rate; IRR, incidence rate ratio; JAKi, JAK inhibitor; NA, number of events considered too low to perform the analysis; OMA, other mode of action; PY, person-year; ref, reference; SE, Sweden; SP, Spain; TNFi, tumor necrosis factor inhibitor; UK, United Kingdom.

[a] Within-registry unadjusted and adjusted analysis included data from registries with at least 25 major adverse cardiovascular events: CH, DE, SE, SP, and UK.

[b] Combined data analysis included all 14 registries excluding SE.

[c] *P* value < 0.05.

and anti-CD20 demonstrating significantly higher crude IRRs compared to TNFi.

Previous b/tsDMARD use. Adjusted IRR for patients using JAKi as first-line treatment were marginally lower than for patients having already been treated with a b/tsDMARD (Supplementary Table S11). However, the small number of events in the bionaive group limits the statistical power to draw definitive conclusions from this analysis.

Effect of the EMA warnings and emulated targeted trial. Patients taking JAKi after the EMA warnings tended to be younger than before, but other characteristics were similar (Supplementary Table S12 and S13). Crude rates for the combined analysis of MACEs were lower after the EMA warnings for the three treatment groups, and adjusted IRRs for JAKi versus TNFi were higher after than before. The analysis of the emulated trial design (see Supplementary Tables S14-S16) provided similar results to the main analysis.

Incidence of secondary end points. When looking at the specific end points of stroke, MI, and TIA, the incidence of stroke across treatment groups did not differ (Table 3). Specifically, the combined data analysis adjusted IRRs suggest that, after accounting for confounding factors, the incidence of strokes associated with JAKi is similar to that of TNFi and bDMARD-OMA. The crude incidence rates for MI was not statistically different for JAKi, although the point estimate was higher, especially in the within-registry analysis (crude IRR 1.23, 95% CI 0.91–1.66), and significantly higher for bDMARD-OMA compared to TNFi (crude IRR 1.76, 95% CI 1.40–2.22); a significant difference that was still observed after adjusting for confounding factors (adjusted IRR 1.72, 95% CI 1.07–2.78). The unadjusted IRR for TIA was significantly higher for bDMARD-OMA, but adjusted analyses mitigated these differences.

Subgroup analyses. *RCT-duplicate cohort.* The cohort referred to as the RCT-duplicate represented 45% of all treatment courses (n = 32,877). Supplementary Table S22 presents the baseline characteristics of this cohort from the 14 registries that provided individual treatment-level data, accounting for 23,217 treatments. Although the cohort shares some selection criteria with the ORAL Surveillance (older age and cardiovascular risk factor), it is important to note that patients in this cohort generally had lower baseline disease activity compared to those included in the ORAL Surveillance study. Outside these selection criteria, patients in the RCT-duplicate cohort were similar to the general cohort. A total of 573 MACEs were recorded in the within-registry data analyses (five registries), for a crude incidence of 13.0 of 1,000 PYs, notably higher than in the overall cohort. Comparative analyses in this elevated-risk group revealed consistent results with the overall JAK-pot population (adjusted IRR JAKi compared to TNFi 0.57, 95% CI 0.12–2.66 for within-registry analyses; adjusted IRR bDMARD-OMA compared to TNFi 1.11, 95% CI 0.43–2.94 for within-registry analyses) (Table 4). However, the wide CI for the adjusted IRR suggests considerable uncertainty in the estimate, due to the relatively small number of events in this subgroup.

History of cardiovascular disease. In the subpopulation of patients with a history of cardiovascular disease (12% of the population), 86 MACEs were recorded in the combined data analyses, for a crude incidence of 6.9 of 1,000 PYs, higher than in both the overall cohort and the RCT-duplicate cohort. Only

Table 4. Crude and adjusted incidence and IRRs of MACEs for within-registry and combined data analysis in the randomized controlled trial duplicate cohort (aged ≥50 years and with at least one cardiovascular risk factor)

	PYs	MACEs	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Within-registry analysis[a]					
TNFi	21,628	258	11.93 (10.52–13.48)	1 (ref)	1 (ref)
JAKi	9,027	91	10.08 (8.12–12.38)	1.02 (0.80–1.32)	0.57 (0.12–2.66)
bDMARD-OMA	13,256	224	16.90 (14.76–19.26)	1.46 (1.22–1.75)[b]	1.11 (0.43–2.94)
Combined data analysis[c]					
TNFi	21,136	94	4.45 (3.59–5.44)	1 (ref)	1 (ref)
JAKi	11,440	41	3.58 (2.57–4.86)	0.81 (0.56–1.17)	1.11 (0.55–2.22)
bDMARD-OMA	12,933	70	5.41 (4.22–6.84)	1.22 (0.89–1.66)	1.36 (1.07–1.72)[b]

* Adjusted analyses adjusted for sex, age, body mass index, disease activity, disease duration, seropositivity, number of previously used bDMARDs or targeted synthetic DMARDs, concomitant use of conventional synthetic DMARDs, concomitant use of glucocorticoids, use of antiplatelet and anticoagulant medications, functional status, C-reactive protein, and Rheumatic Disease Comorbidity Index. bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; JAKi, JAK inhibitor; MACE, major adverse cardiovascular event; OMA, other mode of action; PY, person-year; ref, reference; TNFi, tumor necrosis factor inhibitor.

[a] Within-registry unadjusted and adjusted analysis included data from registries with at least 25 MACEs: Switzerland, Germany, Sweden, Spain, and United Kingdom.

[b] P value < 0.05.

[c] Combined data analysis included all 14 registries excluding Sweden.

Table 5. Crude and adjusted incidence and IRRs of MACEs for within-registry and combined data analysis in patients with a history of cardiovascular disease*

	PYs	MACEs	IR per 1,000 PYs (95% CI)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Within-registry analysis[a]					
TNFi	2,841	52	18.30 (13.67–24.00)	1 (ref)	NA
JAKi	1,607	26	16.18 (10.57–23.71)	1.00 (0.62–1.60)	NA
bDMARD-OMA	2,623	67	25.54 (19.80–32.44)	1.49 (0.77–2.88)	NA
Combined data analysis[b]					
TNFi	5,517	32	5.80 (3.97–8.19)	1 (ref)	1 (ref)
JAKi	2,827	19	6.72 (4.05–10.50)	1.16 (0.67–2.00)	1.06 (0.56–2.02)
bDMARD-OMA	4,068	35	8.60 (5.99–11.97)	1.48 (0.91–2.42)	1.40 (0.80–2.43)

* Adjusted analyses adjusted for sex, age, body mass index, disease activity, disease duration, seropositivity, number of previously used bDMARDs or targeted synthetic DMARDs, concomitant use of conventional synthetic DMARDs, concomitant use of glucocorticoids, use of antiplatelet and anticoagulant medications, functional status, C-reactive protein, and Rheumatic Disease Comorbidity Index. *P* value < 0.05. bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; JAKi, JAK inhibitor; MACE, major adverse cardiovascular event; NA, number of events considered too low to perform the analysis; OMA, other mode of action; PY, person-year; ref, reference; TNFi, tumor necrosis factor inhibitor.
[a] Within-registry unadjusted and adjusted analysis included data from registries with at least 25 MACEs: Switzerland, Germany, Sweden, Spain, and United Kingdom.
[b] Combined data analysis included all 14 registries excluding Sweden.

combined data analyses were performed because of the insufficient sample size in individual registers (Table 5).

DISCUSSION

In this large, international, collaborative study, we did not observe an increased incidence of MACEs in patients treated with JAKi compared to patients treated with other bDMARDs, with a point estimate of approximately 1 between JAKi and TNFi (adjusted IRR 0.96, 95% CI 0.60–1.54). We further did not observe an increased rate of any individual cardiovascular outcome. Although the combined and within-registry analyses differed in design, both yielded point estimates that support similar risk profiles for JAKi and TNFi. When restricting our analysis to an "at risk" population for cardiovascular events, the overall incidence of MACEs was higher, but the relative risk of MACEs between the treatment groups remained similar, whether in patients with similar inclusion criteria to the ORAL Surveillance study[7] or in patients with a history of cardiovascular disease or using an emulated trial design.

Our study contributes important data to the ongoing debate regarding cardiovascular safety profile of JAKi, sparked by the publication of the ORAL Surveillance study results. This randomized, open-label, noninferiority, event-driven, safety trial enrolled more than 4,000 patients with RA aged 50 years or more and with at least one cardiovascular risk factor. Patients were randomly assigned to receive either tofacitinib at a dosage of 5 mg or 10 mg twice daily or a TNFi. Although the difference was not statistically significant, tofacitinib did not meet the noninferiority criteria for MACEs, as the 95% CIs of the HRs exceeded the prespecified upper boundary of 1.8 (HR 1.24, 95% CI 0.81–1.91 for the 5-mg dose). In our study, the upper range of uncertainty is lower than this upper boundary of 1.8 when comparing JAKi to TNFi (adjusted IRR 0.96, 95% CI 0.60–1.54).

Our approach is characterized by the inclusion of a broad, real-world population of patients with RA across multiple registries, reflecting routine clinical practice. In contrast to single-country studies, our cross-registry collaboration encompasses diverse RA populations across several nations, broadening the generalizability of our findings and enabling more comprehensive subgroup analyses. The eligibility criteria differed from ORAL Surveillance. Although we performed analyses that mimicked the two of the inclusion criteria (aged more than 50 years and at least one cardiovascular risk factor), another main criterion in the ORAL Surveillance study was related to inadequate RA disease control, a factor we did not replicate in our analysis. In addition, other specific criteria, including cotreatment regimens, were not part of our study's design. Our study focused on a broader comparison across JAKi rather than looking at individual JAKi. ORAL Surveillance only studied tofacitinib, whereas our study included all commercially available JAKi, with a nearly equal distribution between baricitinib and tofacitinib. Additionally, our study population is mostly European. Although ORAL Surveillance included European patients, almost all of them were from Poland, with only 3% included from non-Polish countries. Polish patients have a very low access to second-line therapy (3% of patients) and are treated mainly with non–anti-inflammatory drugs and methotrexate in contrast to the majority of other countries in Europe.[21] The difference in health care coverage should also be considered when comparing the studies, as most European countries have an inclusive health coverage, which has been shown to associate with fewer untreated cardiovascular comorbidities or risk factors.[22,23]

Finally, the incidence of MACEs in absolute terms was lower in our study's combined analysis, likely reflecting patient

selection, with patients on average having less active disease compared to those enrolled in ORAL Surveillance and probably less at risk of cardiovascular. However, when focusing on the within-registry analysis, which included data from five countries with a higher number of recorded events, the incidence rate of MACEs for patients treated with TNFi (7.6 per 1,000 PYs) was comparable to that reported in ORAL Surveillance (7.3 per 1,000 PYs). The possibility of underreporting MACEs in observational settings, particularly in registries with less frequent or incomplete follow-up, remains a consideration. Nevertheless, the incidence rates reported herein align with the ranges reported in existing observational studies on patients with RA and similar to ORAL Surveillance in the within-registry analysis.[3,24]

The absence of an increased incidence of MACEs in patients with RA treated with JAKi corroborates the results of other observational studies on the topic. A population-based cohort study[25] of the French national health system compared a group of patients initiating JAKi and a group initiating adalimumab, and found similar risk of MACEs (weighted HR 1.0, 95% CI 0.7–1.5) between the two groups. In the United States, the STAR-RA study[26] pooled three claims databases to analyze the cardiovascular outcome of more than 100,000 patients with RA, 12% of whom had initiated tofacitinib. They found no evidence of increased risk of cardiovascular outcome with tofacitinib versus TNFi both in the overall RA population (pooled weighted HR 1.01, 95% CI 0.83–1.23) and in the RCT-duplicate cohort (pooled weighted HR 1.24, 95% CI 0.90–1.24). Another real-world retrospective observational study[27] used Korean health insurance data to investigate the risk of MACE, and found no significant differences between JAKi and TNFi in the rate of MACEs. In the Netherlands, a cohort study[11] using prescription database also found no difference between JAKi and bDMARDs (IRR 0.99, 95% CI 0.70–1.41) for cardiovascular events. Finally, data from the ARTIS register[10] in Sweden and the RABBIT register[12] in Germany, both of which are part of the present JAK-pot study, have independently published very similar conclusions, reporting no increased risk with JAKi treatment. Their inclusion in our current analysis builds on these previously reported findings, reinforcing the consistency of the observed results.

Although the results of these studies occasionally vary and not all JAKi are always considered, these studies provide reassurance regarding the cardiovascular risk for patients currently receiving JAKi therapy. However, these studies, such as ours, may also be limited by the duration of follow-up (less than one-third of PYs were observed beyond two years), preventing us from drawing conclusions on long-term risks. Despite this limitation, our study, which includes 13,000 JAKi treatments and all available b/tsDMARDs in clinical practice, also likely represents the most significant collaborative effort of this kind to date, aimed at investigating the real-world implications of JAKi.

Our study has several limitations. First, despite our best efforts to harmonize cardiovascular events based on exhaustive lists of the different coding (MedDRA, ICD coding, or text) used by the registries, some differences in reporting between registries might persist. Indeed, some registries are linked to hospitalization data, whereas others have adverse events only documented by the patient's rheumatologist. The resulting differences in incidence between registries, similar to what has been observed elsewhere,[28] can be a topic of concern if events are reported selectively by treatment groups. If the report of MACEs between treatment arms within each registry was to be expected, it would likely increase the incidence for JAKi, given the novelty of the treatment and the concerns raised by the ORAL Surveillance study. Such a difference was not observed here, and if existing, this bias would tend to overestimate the true relative risk of JAKi. The dual approach we adopted for the analysis, comprising both within-registry and pooled analyses, was designed to account for the difference of MACE incidence between registries and address possible differences in reporting.

A second limitation is the overall limited number of events, especially for secondary outcomes and subgroups analyses. Although we considered analyzing each JAKi agent individually, the event count was insufficient for reliable subgroup analyses. Additionally, we did not adjust the combined analysis for countries, as including this factor would have increased the complexity of the model and led to overfitting. As a result, the low number of events also prevented us from comparing specific JAKi to bDMARDs. Furthermore, only approximately 30% of the follow-up time extends beyond two years, with 20% of MACEs occurring after the two-year mark. This limited long-term follow-up may have prevented us from observing the significant differences observed in ORAL Surveillance, that appeared mostly after two years, although disparities in nonfatal MI rates were already evident during the second year. Finally, despite our best effort to account for confounding factors through propensity score inverse probably weighting adjustment, and a sensitivity analysis using propensity score matching (emulated trial), we cannot exclude residual confounding.

Despite these limitations, our study includes a large sample size, with the use of multiple registries across Europe and Canada, allowing us to adjust for a wide range of confounders. The larger pooled cohort also enhances the statistical precision of MACE risk estimates, particularly for these rarer outcomes. Although RCTs are the gold standard for assessing efficacy and safety in controlled conditions, real-world evidence complements these data by reflecting broader, more diverse patient populations and practice patterns. Finally, the extended follow-up in our real-world setting provides important long-term insights that complement the relatively shorter duration of RCTs. The robustness of our statistical approach, together with the consistency of the results yielded by the sensitivity and subgroup analyses strengthen our results. Our results suggest that, overall, patients with RA treated with JAKi do not incur an increased risk of MACEs

compared to those treated with alternative bDMARDs, particularly within the first two years of therapy.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Aymon confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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AbbVie, Galapagos, Pfizer, and Eli Lilly had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AbbVie, Galapagos, Pfizer, and Eli Lilly.

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