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ORIGINAL RESEARCH ARTICLE

Major Adverse Cardiovascular Events Related to JAK Inhibitors: A Disproportionality Analysis Using the WHO Global Individual Case Safety Database

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Abstract

Background Rheumatoid arthritis (RA) is commonly treated with Janus kinase inhibitors (JAKis) and anti-tumor necrosis factor-α (anti-TNFα), but the cardiovascular safety profiles of these drugs remain unclear.

Objective The aim of this study was to describe the individual case safety reports of major adverse cardiac events (MACE) or stroke and to determine whether there was a difference in the frequency of reporting of cardiovascular events between JAKis and anti-TNFα used in RA.

Methods A case/non-case study was conducted using the WHO VigiBase® database. Descriptive analysis was performed, the time to onset (TTO) of MACE was calculated, and the reporting odds ratio (ROR) was used to estimate the frequency of MACE reports associated with JAKis versus anti-TNFα in RA.

Results A total of 18,099 cases of MACE were identified, of which 2543 (14%) were associated with JAKis, predominantly in women (65.4%) and in patients aged ≥65 years (49.9%). The median time to onset was 210 days (IQR 60–510) for JAKis and 690 days (210–1460) for anti-TNFα. JAKis were associated with higher odds of reporting MACE (ROR 1.38 [95% CI 1.32–1.44]), mainly due to non-fatal stroke (1.65 [1.55–1.75]). Stroke as a whole showed similar results (1.62 [1.53–1.72]). The ROR of MACE was also slightly increased in patients aged <65 years treated with JAKis (1.29 [1.21–1.39]).

Conclusions Compared with anti-TNFα, JAKis were more associated with MACE, especially stroke, and with a shorter time to onset. These data support the hypothesis of a different cardiovascular reporting frequency between JAKis and anti-TNFα. In patients with identified cardiovascular risk, anti-TNFα should be preferred to JAKis until more definitive results are available.

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Key Points

Janus kinase inhibitors (JAKi) were associated with a higher frequency of reported major adverse cardiovascular events (MACE), particularly stroke, compared with anti-tumor necrosis factor-α (anti-TNFα) therapies, based on findings from VigiBase®.

The time to onset of MACE was shorter for JAKi than for anti-TNFα agents, highlighting potential differences in cardiovascular profiles between these treatments.

In patients with pre-existing cardiovascular risk, anti-TNFα therapies should be preferred over JAKis until more definitive evidence becomes available.

1 Introduction

Rheumatoid arthritis (RA) is a polygenic, multifactorial, and chronic immune-mediated disease characterized by swelling, pain, stiffness, and progressive joint damage. Without effective treatment, symptoms worsen over time, causing permanent damage to the joints and affecting both physical and psychological well-being. In addition, complications and co-morbidities of RA can reduce the life expectancy of patients [1, 2].

Numerous studies in recent decades have examined the occurrence of RA, indicating a prevalence ranging from 0.3 to 1.1%, and an incidence rate between 20 and 50 cases per 100,000 inhabitants [3, 4]. In terms of the gender distribution of RA, the disease is more common in women, with the sex ratio typically ranging from about 2:1 to 3:1 in most studies [3, 4].

Cardiovascular (CV) disease is considered the leading cause of increased mortality in patients with RA. Compared with seronegative patients, there is a 50% increased risk of death from stroke in RA [5]. This is due to the high state of systemic inflammation that characterizes RA [2], but also to damage to heart valves [6] and an increased risk of atrial fibrillation [7], which specifically increases the risk of stroke.

RA is managed with disease-modifying antirheumatic drugs (DMARDs), which can significantly reduce disability and enhance the quality of life for most patients. The usual approach is to begin with a conventional DMARD, such as methotrexate. However, in cases where the disease is not adequately controlled, further treatment with disease-modifying biologic agents, such as anti-tumor necrosis factor-α (anti-TNFα), or targeted synthetic oral DMARDs, such as Janus kinase inhibitors (JAKis), may be suggested [1].

Although JAKis have shown comparable efficacy to biological DMARDS (bDMARDs), these drugs are relatively new and knowledge of their safety profile is still limited. In recent years, the CV safety of JAKis has been a matter of concern. In particular, a randomized, open-label study in patients with active RA despite methotrexate treatment who were aged 50 years or older and had at least one additional CV risk factor showed a higher incidence of major adverse CV events (MACE; 9.8 versus 7.3 per 1000 person-years of drug exposure), with a trend towards an increased risk in the tofacitinib group compared with the anti-TNFα group (hazard ratio [HR] 1.33 [0.91–1.94]) [8]. This risk was particularly high in patients aged ≥ 65 years (2.06 [1.08–3.93]). MACE is a composite endpoint used to assess overall CV risk, which includes non-fatal myocardial infarction (MI), non-fatal stroke, and fatal CV events. In addition, a meta-analysis showed a strong trend towards an increased risk of venous thromboembolic events (odds ratio [OR] 1.65; 95% confidence interval [CI]: 0.97–2.79), driven by trials with at least 12 months of follow-up (2.17; 1.16–4.05) [9].

On 4 February 2021, the US Food and Drug Administration (FDA) issued a public warning about preliminary results from a safety clinical trial suggesting an increased risk of serious heart problems and cancer associated with the arthritis and ulcerative colitis drug tofacitinib compared with anti-TNFα [10].

Subsequently, the European Alliance of Associations for Rheumatology (EULAR) guidelines placed JAKis on the same level as bDMARDs, but only in patients in whom cardiovascular or malignant risk factors have been excluded [11]. More recently, in Europe, the Pharmacovigilance Risk Assessment Committee (PRAC) suggested that the use of JAKis as a first alternative to methotrexate should be avoided in patients with CV risk factors, such as age ≥ 65 years [12].

Despite established recommendations, there is currently limited evidence on MACE in elderly and adult patients in real-world settings, and a lack of studies analyzing individual MACE events, such as stroke or MI, and their risk function (e.g. time to onset after drug initiation).

Therefore, the aim of this study was to describe MACE and its individual events collected in the World Health Organization (WHO) Individual Case Safety Report (ICSR) database. These data were also used to assess whether the frequency of reporting of MACE, MI, and stroke differed between JAKis and anti-TNFα. Anti-TNFα drugs were used as comparators because they are indicated in similar patient populations with comparable disease characteristics, thus providing the best possible control for confounding by indication.

2 Methods

2.1 Data Source

VigiBase® is the WHO database of adverse drug reaction (ADR) reports that may be related to the use of drugs. It currently contains more than 35 million reports from all over the world [13]. In this database, possible ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) [14]. This dictionary is divided into five levels from the most specific to the most general [15]. At the most detailed level, the Lowest Level Terms (LLTs) in MedDRA represent highly specific medical concepts. These are followed by Preferred Terms (PTs), which provide a broader representation of related concepts. High Level Terms (HLTs) group related PTs into broader categories, while High Level Group Terms (HLGTs) organize related HLTs into higher-level groupings. At the highest level, System Organ Classes (SOCs) categorize disorders based on organ systems or physiological areas. In addition, MedDRA includes Standardised MedDRA Queries (SMQs), which are predefined sets of terms designed to facilitate the identification of cases related to specific conditions (e.g. "ST segment abnormality", included in the SMQ for MI). Ethical approval and informed consent were not required as no sensitive data were available in VigiBase®.

2.2 Study Design

A case/non-case study was performed. This is a classic study design used to explore ADR databases and is used to highlight a possible association between the reporting of ADR(s) of interest and the drug(s) of interest [16]. Briefly, reports containing ADRs of interest, MACE for this study, are called *cases* and reports containing all other events are called *non-cases*. Exposure or not to the drug of interest is also sought. Despite its similarity to the case-control method, the term *non-cases* is used instead of *controls* because this group refers to patients who were all exposed to at least one drug and experienced at least one other ADR.

2.2.1 Case and Non-case Definition

The primary outcome of this study was MACE, defined as cases that included either a fatal CV event, non-fatal stroke (ischemic or hemorrhagic), or non-fatal MI [17].

ICSRs were classified as including a fatal CV event if they included at least one event classified as: a) *Cardiac Disorders* (SOC level), OR *Vascular Disorders* (SOC level), OR *Hemorrhagic Central Nervous System Vascular Disorders* (SMQ), OR *Ischemic Central Nervous System Vascular Disorders* (SMQ), AND resulting in death, either as a seriousness criterion or as an outcome. For non-fatal stroke, only reports that did not have death as a seriousness criterion or outcome and had at least one event related to *haemorrhagic central nervous system disorders* (SMQ) OR *ischaemic central nervous system disorders* (SMQ) were included. For non-fatal MI, only reports that did not result in death as a seriousness criterion or outcome and had at least one event related to *myocardial infarction* (SMQ) were included. Cases of MI and stroke were also considered as a whole. All other reports were considered as non-cases.

2.2.2 Exposure Definition

In this study, the following JAKis were selected as active ingredients with a primary indication in RA: baricitinib, filgotinib, peficinib, tofacitinib, and upadacitinib. Anti-TNFα was selected as a class using the Anatomical Therapeutic Chemical (ATC) classification (ATC code L04AB). All ICSRs related to JAKis as suspected drug(s) were considered exposed. All reports related to at least one anti-TNFα as a suspected drug were used as comparator for statistical analyses.

2.3 Descriptive Analyses

MACE were described in terms of patient characteristics (age, sex), administrative information (reporter qualification and countries), seriousness, and number of other suspected drugs. An event was considered serious if it resulted in death, hospitalization, or its prolongation, severe or permanent disability, or congenital anomalies/birth defects, and if it was life-threatening or a clinically relevant condition. All ICSRs were downloaded via Vigilyze and the deduplication function was used to remove duplicate reports. In addition, all MACEs were manually checked for possible further duplicates using the ADRs, suspected and concomitant drug fields.

2.4 Statistical Analyses

The dataset for the principal analyses included all reports collected from 10 July 2011 (the date of the first case related to JAKis in Vigibase) up to 23 January 2023, the date when PRAC recommendations suggested avoiding the use of JAKis as first-line treatment in patients with CV risk factors, such as age.

Time to onset (TTO) and cumulative frequency were calculated for both JAKis and anti-TNFα treatments for which event date and drug initiation were available.

The reporting odds ratio (ROR) was used to estimate the frequency of reporting of cases associated with JAKis compared with anti-TNFα. The ROR is a statistical measure comparable to the odds ratio used in case-control studies,

and it corresponds to the exposure odds among cases over the exposure odds among reported non-cases [16]. A positive ROR implies a lower 95% CI ≥1 and suggests an increased frequency of reporting cases associated with an exposure of interest [18].

RORs were calculated for the following outcomes: MACE, fatal CV events, and non-fatal MI or stroke to be as close as possible to the clinical trial definitions. RORs were also calculated for the composite of fatal and non-fatal MI or stroke.

A number of subgroup and sensitivity analyses were also performed. RORs were calculated by sex, age groups (< 65 years and ≥ 65 years), by restricting the analysis to reports from Europe only, and for individual JAKis (baricitinib, filgotinib, tofacitinib, upadacitinib) and their association with MACE. In addition, a smaller dataset was used to assess the frequency of reporting of MACE, with only reports collected from 10 July 2011 to 04 February 2021, the date of an FDA communication on potential increased CV risk [10].

Finally, latanoprost was selected as a negative control to assess the internal validity of the present study. As a prostaglandin analog used primarily topically for the treatment of glaucoma, latanoprost has no known association with MACE or any indication for a condition that increases CV risk. Its distinct mechanism of action, unrelated to the immunosuppressive and inflammatory pathways targeted by anti-TNFα drugs, makes it an appropriate comparator to ensure the reliability of Vigibase in the study of MACE [19]. Data analyses were performed using R software (version 4.2.2, R Development Core Team). This study was conducted according to the criteria of the READUS (Reporting Adverse Drug Reactions Uniformly and Systematically) checklist. The READUS-PV checklist provides a structured framework for the analysis and reporting of ADRs to ensure that reports are consistent and complete [20].

3 Results

3.1 Case and Non-case Selection

During the study period, 26,979,454 reports were collected in Vigibase. Of these, 1,410,637 had a JAKi or anti-TNFα as a suspected drug. A total of 18,099 MACE cases and 1,392,538 non-cases were retrieved. Of the cases, 2543 MACE were associated with JAKi and 15,556 with anti-TNFα (Fig. 1).

3.2 Characteristics of JAKi-Exposed MACE

Females and elderly patients were more represented in MACE exposed to JAKis than in those exposed to anti-TNFα in the most reported group (Table 1). The majority of reports came from the United States of America ($N = 1777$; 69.9%).

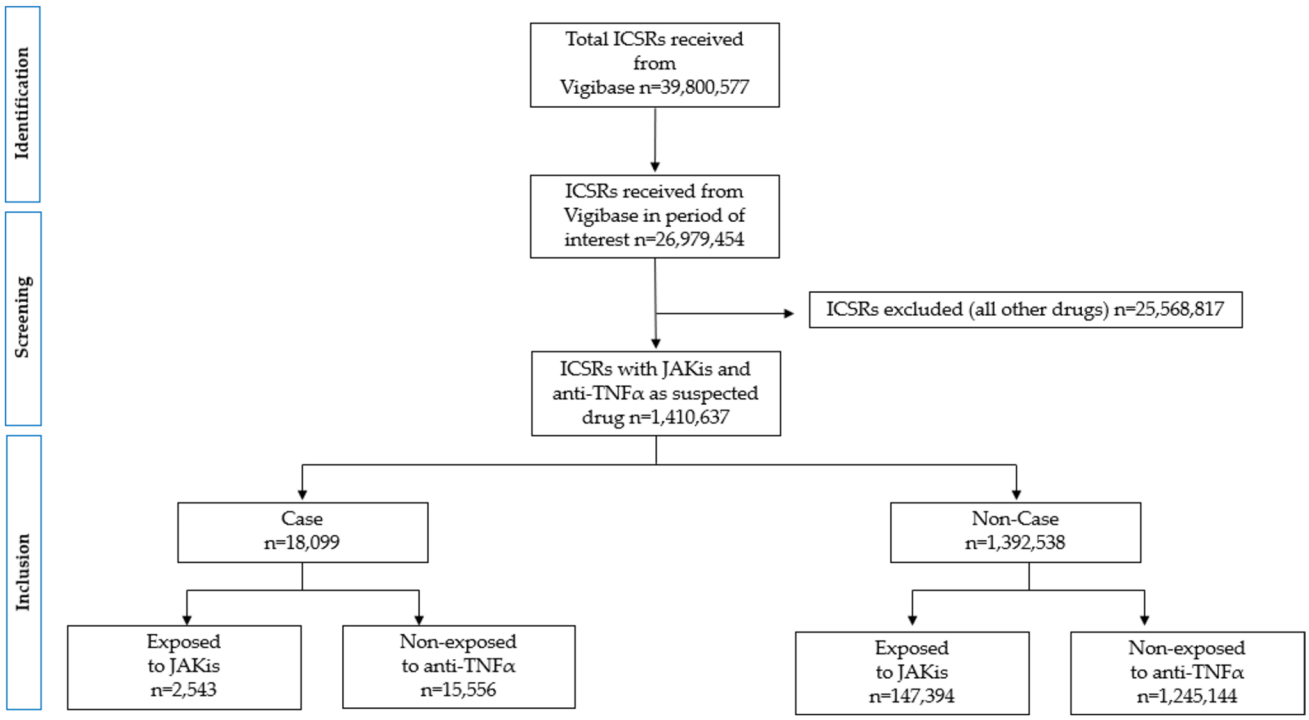

Fig. 1 Flowchart illustrating the cases and non-cases exposed or not exposed to Janus kinase inhibitors (JAKis) in the VigiBase database. *anti-TNFα* anti-tumor necrosis factor α, *ICSRs* Individual Case Safety Reports

Table 1 Characteristics of MACE cases exposed to JAKis and anti-TNFα

	MACE exposed to JAKis, *N* = 2543 (%)	MACE exposed to anti-TNFα *N* = 15,556 (%)	Overall *N* = 18,099 (%)
Sex			
Female	1663 (65.4)	8538 (54.9)	10,201 (56.4)
Male	814 (32.0)	6701 (43.1)	7515 (41.5)
Missing	66 (2.6)	317 (2.0)	383 (2.1)
Age			
Neonate		13 (0.1)	13 (0.1)
Infant		3 (0.0)	3 (0.0)
Child	5 (0.2)	15 (0.1)	20 (0.1)
Adolescent	1 (0.0)	43 (0.3)	44 (0.2)
Adult	936 (36.8)	6279 (40.4)	7215 (39.9)
Elderly	1270 (49.9)	5388 (34.6)	6658 (36.8)
Missing	331 (13.0)	3815 (24.5)	4146 (22.9)
Reporter			
Health professional	1130 (44.4)	7228 (46.5)	8358 (46.2)
Non-health professional	1252 (49.2)	7776 (50.0)	9028 (49.9)
Other	137 (5.4)	282 (1.8)	419 (2.3)
Missing	24 (0.9)	270 (1.7)	294 (1.6)
Source			
USA	1777 (69.9)	9137 (58.7)	10,914 (60.3)
Canada	85 (3.3)	1529 (9.8)	1614 (8.9)
UK	99 (3.9)	1317 (8.5)	1416 (7.8)
Germany	90 (3.5)	490 (3.2)	580 (3.2)
Seriousness			
Death	504 (19.8)	3497 (22.5)	4001 (22.1)
Congenital anomaly/birth defect		11 (0.1)	11 (0.1)
Life threatening	99 (3.9)	553 (3.6)	652 (3.6)
Disabling/incapacitating	39 (1.5)	190 (1.2)	229 (1.3)
Caused/prolonged hospitalization	868 (34.1)	6412 (41.2)	7280 (40.2)
Other medically important condition	923 (36.3)	4009 (25.8)	4932 (27.3)
Missing	110 (4.3)	884 (5.7)	994 (5.5)
Suspect drugs, (N)			
1	1828 (71.9)	10,886 (70.0)	12,714 (70.2)
2	420 (16.5)	2894 (18.6)	3314 (18.3)
3	162 (6.4)	947 (6.1)	1109 (6.1)
≥ 4	133 (5.2)	829 (5.3)	962 (5.3)

anti-TNFα anti-tumor necrosis factor α, *JAKis* Janus kinase inhibitors, *MACE* major adverse cardiac events

In contrast, reports from the European Union were sparse, with Germany being the leading country with only 3.5% of exposed cases. There were no significant differences in seriousness between JAKis and anti-TNFα. JAKis and anti-TNFα were the only suspected drugs in 71.9% and 70.0% of reports, respectively.

Concerning TTO, date of MACE, and drug start, date of start of drugs and of start of the event was available in 343 (13.5%) and 3718 (23.9%) reports related to JAKis and anti-TNFα, respectively. The cumulative frequency appeared different between JAKis and anti-TNFα, with a median TTO of 210 days (interquartile range [IQR] 60–510) for JAKis and 690 days (210–1460) for anti-TNFα (Fig. 2).

Among the 2543 cases of MACE with JAKis, 1262 cases of non-fatal stroke, 814 cases of non-fatal MI, and 510 cases of fatal CV disease were observed (Table 2). A total of 1365 cases of stroke and 906 cases of MI were retrieved.

Details of cases and non-cases associated with each sensitivity analysis are available in the electronic supplementary material (ESM) (Tables S1–S6).

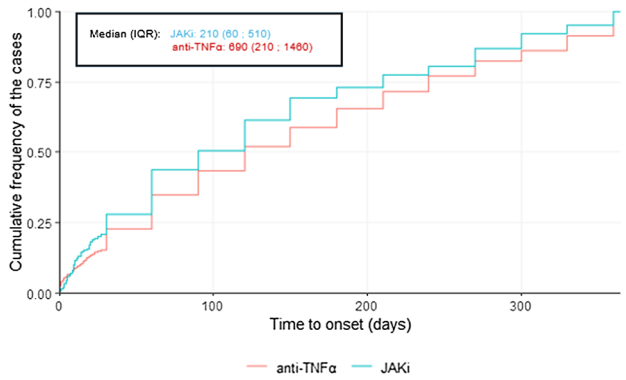

Fig. 2 Cumulative frequency of time-to-onset of major adverse cardiac events (MACE) occurrence for Janus kinase inhibitors (JAKis) and anti-tumor necrosis factor α (anti-TNFα)

3.3 Disproportionality Analyses

Compared with anti-TNFα, JAKi was significantly associated with a higher frequency of reporting MACE (ROR 1.38 [95% CI 1.32–1.44]), non-fatal stroke (ROR 1.65 [95% CI 1.55–1.75]), and total stroke (ROR 1.62 [95% CI 1.53–1.72]). In addition, the RORs for MI (ROR 1.25 [95% CI 1.16–1.34]) and fatal CV disease (ROR 1.11 [95% CI 1.01–1.22]) were significantly higher for JAKis compared with anti-TNFα (Fig. 3).

When the analysis was restricted to ICSRs from Europe, the ROR for MACE was still increased for JAKis (1.43 [95% CI 1.28–1.59]).

Regarding gender, JAKis were associated with a higher frequency of MACE reporting in both men and women. Specifically, men had an ROR of 1.58 (95% CI 1.47–1.70), while women had an ROR of 1.41 (95% CI 1.33–1.48). Concerning age, JAKis showed a significantly higher frequency of MACE reporting only in patients younger than 65 years (ROR 1.29 [95% CI 1.21–1.39]), while no significant difference was observed in patients aged 65 years and older. When analyzing individual JAKis compared with anti-TNFα, significant differences in the frequency of MACE reporting were observed. Upadacitinib had the highest ROR (2.28 [95% CI 2.09–2.50]), followed by baricitinib (ROR 1.97 [95% CI 1.77–2.20]) and tofacitinib (ROR 1.17 [95% CI 1.11–1.23]). In contrast, filgotinib showed a non-significant association with MACE (Fig. 4).

RORs and their 95% CIs were calculated for individual events with 95% CIs and presented both graphically (black square with line) and numerically. An ROR with a lower 95% CI > 1 indicates an increased frequency of reporting a CV event with JAKis compared with anti-TNFα.

Table 2 Distribution of cardiovascular events of interest in patients treated with JAKis and anti-TNFα, as reported in the VigiBase database from 10 July 2011 to 23 January 2023

	JAKi		Anti-TNFα	
	Cases, *N*	Non-cases, *N*	Cases, *N*	Non-cases, *N*
MACE	2543	147,394	15,556	1,245,144
Fatal cardiovascular disorders	510	149,427	3860	1,256,840
Non-fatal stroke	1262	148,675	6450	1,254,250
Non-fatal myocardial infarction	814	149,123	5487	1,255,213
Stroke	1365	148,572	7107	1,253,593
Myocardial infarction	906	149,031	6405	1,254,295

anti-TNFα anti-tumor necrosis factor α, *JAKis* Janus kinase inhibitors, *MACE* major adverse cardiac events

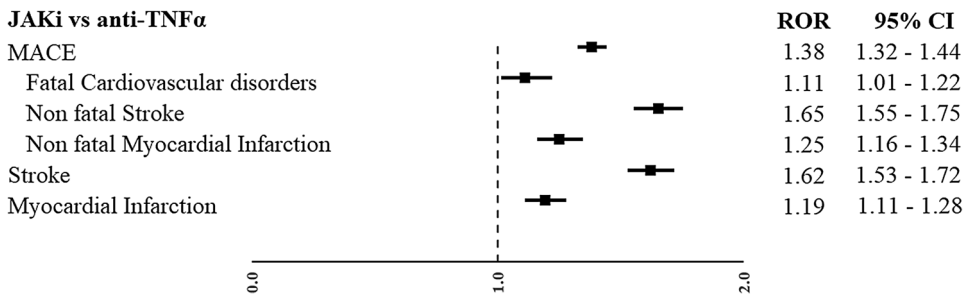

Fig. 3 Forest plot of RORs of MACE, stroke (fatal and non-fatal), and myocardial infarction (fatal and non-fatal), comparing JAKis versus anti-TNFα. RORs and their 95% CIs were calculated for individual events with 95% CIs and presented both graphically (black square with line) and numerically. An ROR with its lower 95% CI > 1 indicates an increased probability of reporting a cardiovascular event with JAKi vs anti-TNFα. *anti-TNFα* anti-tumor necrosis factor α, *CI* confidence interval, *JAKis* Janus kinase inhibitors, *MACE* major adverse cardiac events, *RORs* reporting odds ratios

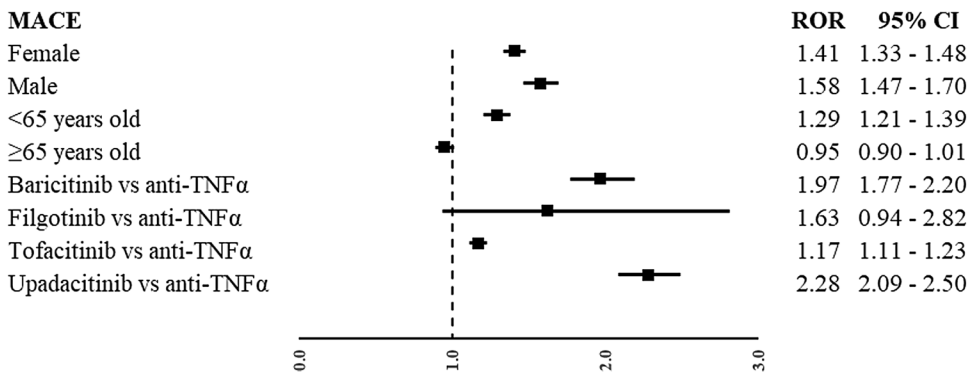

Fig. 4 RORs of MACE by sex and age groups, comparing JAKis with anti-TNFα. Additionally, RORs of MACE for each JAKi compared with anti-TNFα. *anti-TNFα* anti-tumor necrosis factor α, *CI* confidence interval, *JAKis* Janus kinase inhibitors, *MACE* major adverse cardiac events, *RORs* reporting odds ratios

In addition, the frequency of MACE reporting was also higher for JAKi drugs compared with anti-TNFα in the period before the FDA communication (ROR estimates of around 1.18; see Fig. S1 in the ESM).

The internal validity of these results was strengthened by the results of the negative control, in which all RORs related to latanoprost were negative or nonsignificant (see Fig. S2 in the ESM for details).

4 Discussion

This is the largest study to assess the CV safety of JAKis compared with anti-TNFα using clinical data from the WHO Global Drug Safety Database. The present data suggest that stroke, both fatal and non-fatal, may be the key event for the increased frequency of reported MACE seen with JAKis. Secondly, it suggests that the occurrence of these events in JAKi-treated patients is shorter than that in anti-TNFα-treated patients, supporting a real difference in their CV safety profile.

Although affected by the usual limitations of studies conducted in databases collecting ICSRs, several elements suggest that the results are reliable. First, among the exposed cases, JAKis were the only suspected drug in 71.9% of patients.

Second, the dataset did not include any reports collected after the FDA announcement, thus avoiding a notoriety bias either due to massive *a posteriori* reporting of cases that occurred before an alert (i.e., the *seesaw* effect) or because new events are relatively more likely to be reported after an alert than before [21]. Third, all sensitivity analyses showed comparable results to the main analyses. Fourth, the negative ROR for latanoprost supported the idea that these data may discriminate between drugs that can be associated with real reporting frequency and drugs that cannot.

The current study is the first to look at TTO for MACE and shows relevant differences between JAKi and anti-TNFα. MACE associated with JAKi tends to occur much earlier than with anti-TNFα (median TTO of 210 days vs 690 days), with lines of difference starting very early (around 30 days). However, as approximately 77.5% of reports do not provide this information, this analysis must be considered exploratory and these results should be interpreted with caution. Nevertheless, these results may be related to a real difference in the occurrence of MACE between JAKis and anti-TNFα, which merits further investigation.

A noteworthy finding from this study is that stroke emerged as a primary event among MACE. To date, there is a lack of studies comparing JAKis and anti-TNFα for each MACE event. One study with limited sample size and a very limited number of events did not reveal a difference between JAKis and anti-TNFα. It is thus likely to be too underpowered to be considered reassuring [22].

The mechanisms underlying the increased reporting of MACE or stroke are not well understood. Evidence in the literature suggests a possible increase in circulating lipid levels, which may induce atherosclerotic plaques [23]. JAKis may be associated with a small increase in low-density or high-density lipoproteins (LDL and HDL, respectively) [24], but this increase is of limited clinical relevance [25]. Furthermore, dyslipidemia is not a clear risk factor for stroke [26], especially in the short term.

Heart valve disease may also increase the risk of stroke and is a known potential long-term complication of RA. However, inhibition of the TNFα or JAK pathways appears to be protective [27, 28].

There may be an increased risk of atrial fibrillation in patients with RA [7]. To date, atrial fibrillation has not been recognized as an ADR of JAKi, although other protein kinase inhibitors may have off-target effects that can induce atrial fibrillation [29].

Another hypothesis is an increased risk of arterial hypertension. This is reported as common in the summary of product characteristics for tofacitinib, but not for etanercept, for example. Hypertension is probably the more relevant predictor of stroke [30], which may explain the results of the present study, both for stroke and for short TTO.

In the present study, although a slight majority of reports (49.9%) occurred in patients over 65 years of age, younger

patients were found to be more frequent to report a MACE, which was quite unexpected. This could be due to reporting biases inherent in the reporting of ADRs, where, for example, a stroke occurring in a young patient after drug therapy may be more frequently suspected and reported as drug-related than the same event occurring in an older patient with other known risk factors. Furthermore, this result is not consistent with a recent study in which the hazard ratio for MACE was 2.06 (1.08–3.93) for those aged ≥ 65 years and 1.07 (0.60–1.89) for those aged < 65 years [8].

Regarding the potential frequency of reporting in patients aged ≥ 65 years, the confidence interval of the ROR for this age group is < 1, suggesting a lower frequency of reporting of MACE for JAKis compared with anti-TNFα in this population. However, this finding should be interpreted with caution due to the spontaneous reporting nature of the data, in which the unexpected events (e.g. MACE in the adult population) may be more frequently reported than the expected events (e.g. MACE in the elderly). Furthermore, it is important to emphasize that missing data on age are 4 times higher in ICSRs related to anti-TNFα than to JAKis, which may have influenced the results by age.

The gender differences observed in this study with regard to the incidence of MACE associated with JAKi are striking. While there was an increased frequency of reported MACE in both groups, men had a higher ROR compared with women. This finding suggests that while women have a higher prevalence of RA and are generally more frequent to report ADRs [31, 32], men may be more frequent to report MACEs associated with treatment with JAKi. This discrepancy may reflect gender-specific cardiovascular risk factors. Men have an inherently higher risk of cardiovascular disease, which may contribute to the higher reporting of MACE in this group [33].

Although all JAKis show an increased frequency of reporting MACE, significant differences in ROR between upadacitinib, baricitinib, and tofacitinib suggest that the frequency is not uniform within the class. In particular, upadacitinib has the highest ROR, followed by baricitinib and tofacitinib. The lack of a significant association with MACE for filgotinib further highlights that these differences may be due to the specific characteristics of each JAKi rather than a common class effect. Therefore, the variability in results suggests that each JAKi may carry different risks.

The results of the comparison between JAKis and anti-TNFα revealed a higher ROR when analyzing MACE events in Europe compared with the ROR obtained from all global MACE reports. This observation may be elucidated by potential variations in prescribing protocols, differences in patient characteristics compared with other countries, or increased attention of European prescribers before the PRAC risk reduction recommendation.

4.1 Strengths and Limitations

This study has some limitations. As with any other study based on reports mostly submitted voluntarily, its main weakness is underreporting; in routine pharmacovigilance, the reporting rate is on average 6% of the actual ADRs. However, a systematic review has shown that underreporting tends to be higher for non-serious ADRs, especially in general practice settings [34]. While the underreporting of serious ADRs remains significant, the impact on this work is likely limited since the case definition almost exclusively concerns serious cases. Nevertheless, it is likely that the present results underestimate the number of cases of MACE occurring in patients exposed to JAKis. On the one hand, while it is possible that clinicians' attention to CV events may have influenced the number of reported cases to some extent compared with anti-TNFα, any particular attention to stroke was found prior to this study, which greatly reduces the possibility of a notoriety bias [21]. The potential for a notoriety bias was limited as much as possible by including only cases reported up to January 2023, the date of the EMA restriction on JAKi in elderly populations in European countries.

Another limitation is the incomplete data in the Vigibase ICSRs regarding the indication of use, such as RA, as these drugs are also used for other conditions. However, in order to reduce as much as possible the effect of different indications on the results of this study, the JAKis and anti-TNFα selected for this study were those that are primarily indicated in patients with RA.

An additional limitation of this analysis is the inclusion date for anti-TNFα, which was based on the first MACE report associated with tofacitinib in the VigiBase database, rather than the launch date of each drug. Although anti-TNFα agents were introduced before JAKis, this approach may have introduced some bias, as anti-TNFα agents were monitored for a longer period, whereas the reporting profile of JAKis may be more affected by the Weber effect [35]. In the context of the present disproportionality analysis, this choice could be considered conservative, as a potential Weber effect could relatively reduce the frequency of serious events, such as MACE, more for JAKis than for anti-TNFα, thus limiting the ability to detect significant differences in CV safety profiles between the two drug classes.

Another important limitation of this study, due to the nature of large observational data, is the inability to adjust for confounding factors such as severity of underlying disease. JAKis may be prescribed to a population with more severe disease compared with anti-TNFα, which could influence the observed results. Nevertheless, there is no apparent reason to believe that pre-existing CV risk factors could have influenced the choice of JAKis or anti-TNFα, particularly prior to the FDA or EMA communication.

The TTO analysis was based on < 22% of cases exposed to JAKis or anti-TNFα, thus reducing its absolute value. Nevertheless, the observed difference in median values is impressive and suggests a real difference between drug classes in the occurrence of MACE. Finally, the mechanism for the risk of CV events is not fully understood and a possible protective role of anti-TNFα should be considered.

5 Conclusions

The present analysis of the WHO global pharmacovigilance database is consistent with previous studies suggesting an increased frequency of reporting of MACE with JAKis compared with anti-TNFα. The CV profile of these two classes was different, with JAKis being more associated with stroke with a shorter TTO. It also points to the need for further studies in adult patients.

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Declarations

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Author contributions Conceptualization, F.S. and. A.C; formal analysis, investigation, and methodology R.D.N.; supervision, A.M., C.C., C.R., A.S., M.D.; validation, F.S. and A.C., writing original draft, R.D.N.; writing review and editing, F.S. and C.R. All authors have read and agreed to the published version of the manuscript.

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