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CYCLE XXXV

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Real world comparative cardiovascular safety of Janus kinase inhibitors versus tumour necrosis factor inhibitors in rheumatoid arthritis

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1 - INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic, chronic, autoimmune inflammatory diseases[1]. This disease is treated nowadays with biologic synthetic disease modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi) and targeted synthetic DMARDs (tsDMARDs), such as Janus Kinase inhibitors (JAKi), either as monotherapy or in combination with other drugs[2,3]. These medications have been the key in reducing disease activity and improving quality of life, however their impact on the risk for all causes of death and cardiovascular (CV) diseases, the primary driver of mortality in these patients[4], is not clearly defined and needs to be evaluated. Given the signal of increased CV morbidity associated with tsDMARDs, recent studies have attempted to clarify the impact of these drugs on CV risk in RA.

Major highlight regarding the safety profile of tsDMARDs was the publication of ORAL Surveillance[5], randomized open label trial. Patients with active RA despite methotrexate (MTX) treatment which adds at least one additional CV risk factor were randomly assigned to receive tofacitinib at a dose of 5 mg or 10 mg twice daily or a TNFi treatment. The incidence rate (IR) of major cardiovascular events (MACE) was higher with the combined dose of tofacitinib doses (3.4%) than with TNFi (2.1%); with a 33% relative increase of the risk of MACE. This study had some limitations that include the high rates of discontinuation of treatment and the open label design. Furthermore, analyses were not adjusted for multiple comparisons. Nevertheless, the pathway by which tsDMARDs could lead to an increased risk of MACE is uncertain. Based on cytokine profile inhibition of JAK/STAT pathway, diverse biological consequences are observed. First, inhibition of JAK attached to γ-chain receptor resulting either in beneficial (high concentration mediated IL-2 transmission) or detrimental (inhibition of beneficial activity of low IL-2-impaired tissue healing and repair). Second, inhibition of JAK fused with gp130 receptor reduces IL-6 level and may contribute to the reduction of heart survival pathway activity or favourably modify heart failure pathway[6,7]. Third, inhibition of JAK results in reduction of IL-12-mediated signalling and exerts favourable effects on the cardiovascular system halting progression of atherosclerosis, reducing risk of developing ischemic cardiomyopathy and myocardial fibrosis[8]. And fourth, inhibition of JAK/STAT system transmitting signal from interferon receptor results in reduction

of activity of IFN-dependent genes that translates directly to the reduction of foam cell formation and halting progression of atherosclerosis[9]. Finally, some negative consequences may arise as the result of erythropoietin blockade with subsequent anaemia development (indirectly contributing to worsening of heart function)[10]. Blocking the JAK/STAT pathway may bring both harmful and beneficial effects depending on the pathophysiological environment. Therefore, it may be suggested that not JAK inhibition alone, but comorbidities and risk factors presented in RA patients working together may in some predisposing patients increase the risk of CVE.

A meta-analysis[11] that includes a total of 42 studies and compared 6542 tsDMARDs patient exposure years (PEYs) to 1578 placebo PEYs has highlighted, in tsDMARDs group, an incidence rate ratio (IRR) of 0.68 (95% CI 0.36 – 1.29) for venous thromboembolism (VTE), 0.44 (95% CI 0.28-0.7) for pulmonary embolism and 0.59 (95% CI 0.31 – 1.15) for deep venous thrombosis. This data, in contrast to previous study, do not provide evidence that support warning of VTE risk for tsDMARDs.

Smolen et al.[12] had evaluated long term efficacy and security of once daily baricitinib 4 mg in patients with active RA who were either naive to DMARDs or who had inadequate response to MTX; IRs per 100 PY for MACE (0.5), deep vein thrombosis (0.3), pulmonary embolism (0.2), were similar to those previously reported.

Rates of MACE, VTE and deaths were comparable between upadacitinib and adalimumab, in the long-term extension of SELECT-compare study[13].

Darwin 3[14], was an open label extension study, which included patients completing the 24-week DARWIN 1 (filgotinib + MTX) and DARWIN 2 (filgotinib monotherapy), evaluated the long-term safety and efficacy of filgotinib. The number of CV events from DARWIN 3 was small (3 MACE in patients treated with filgotinib + MTX and 2 MACE in filgotinib monotherapy) and appears comparable to the background risk observed in RA patients.

More data are available on CVE risk and treatment with TNFi. In a large meta-analysis[15], which included 28 studies of RA patients, the effect of TNFi therapy on CVE was evaluated. In RA, TNFi were significantly associated with a reduction in the risk of all CVE (RR 0.70; 95% CI 0.54 to 0.90), in stroke (RR 0.57; 95% CI 0.35 to 0.92), myocardial infarction (RR 0.59; 95% CI 0.36 to 0.97) and MACE (RR 0.30; 95% CI 0.15 to 0.57). No significant effect on heart failure was observed (RR 0.75; 95% CI 0.49 to 1.15)[15].

Singh et al.[16] have conducted a meta-analysis and systematic review to estimate risk of CVE with bDMARDs and cDMARDs in patients with RA. Four studies (seven cohorts) compared risk of MACE with non-TNFi biologics vs TNFi (n = 103051 patients); exposure to tocilizumab (OR 0.59 [0.34-1.00]), but not to abatacept (OR 0.89 [0.71-1.11]), was associated with a lower risk of MACE as compared to TNFi. Exposure to csDMARDs was associated with an increased risk of MACE, as compared to treatment with TNFi (OR 1.58 [1.16-2.15]); these effects were seen in cohorts where MTX was included as csDMARD or excluded.

TNFi use may be associated with heart failure (HF), although the data are mixed. Concern about this possible adverse effect stems from randomized trials of TNF-alpha inhibitors as a potential therapy for HF[17], but other studies did not confirm this association [18,19].

There are not many studies in the literature that compare the effect on CV risk events of TNFi drugs and tsDMARDs. The overall objectives of this retrospective study were to assess and compare the effect of TNFi and tsDMARDs on CVE and mortality in patients with RA and to evaluate the differences in these outcomes considering confounding factors.

2 – OBJECTIVES

To comparatively assess the incidence risk of cardiovascular (CV) events and mortality in rheumatoid arthritis (RA) patients treated with tumour necrosis factor inhibitors (TNFi) or tsDMARDs, and to explore the interaction with age, comorbidity and frailty.

3 - PATIENTS AND METHODS

3.1 - Study design

This was a retrospective study, performed using administrative healthcare databases (AHDs). The data included beneficiaries alive at the 31st of December 2019, and cover the period from 2010 to 2022.

The data sources for the project were the AHDs of Lombardy, an Italian region with more than 10,000,000 inhabitants (about 16% of the entire Italian population). The entire Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of AHDs has been created to collect a variety of information. The source registry is an electronic database that contains fields that are built as an obligatory menu, limiting the possible errors and missing data.

This study was approved by the Brianza Institutional Review Board under the number 3356-07/08/2020 and it has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

3.2 - Population and data sources

Adults (aged 18 years and older) who were beneficiaries of the Lombardy regional health system on 31 December 2019, up to 20 May 2021 were identified from the AHD of the Lombardy Region. Fully anonymized data generated from routine health care encounters (from 2017 to 2021) for the patients thus identified was also retrieved. These data included: RA certification by a rheumatologist (ICD-9-CM code: 710.0*, 710.1*, 710.4*, 714.0-714.2*, 714.81, 725*), outpatient care, inpatient care, emergency healthcare and transports, primary care, delivery of assistive products for people with disability, mental illness care, home care services, residential care, drug prescriptions, exemptions (available since 2010) and mortality.

If someone had an exemption, it was because they suffered from certain illnesses or long-term conditions for which they are exempt from paying for healthcare.

3.3 - Follow-up to outcome

The primary outcome was any incident CVE, defined as a cardiovascular event resulting in hospitalization. The secondary outcomes included types of CVE and rates of mortality.

We used diagnostic codes (ICD-9-CM) for each CVE (**Table 1**) and identified them using primary or secondary diagnostic codes hospitalization or prescription of treatment with those diagnosis codes were captured as outcome events. The diagnosis of RA was defined as active exemption code on January 2020 or thereafter.

Table 1. The ICD-9-CM code of cardio cerebrovascular events

	ICD-9-CM code
Myocardial infarction	410*
All Coronary Revascularization	36*
Unstable Angina	411*, 413*
New Ischemic Heart Disease	414*
Stroke (fatal and non-fatal)	434*
Transient Ischemic Attack (TIA)	435*
Congestive Heart Failure (CHF)	428*
Peripheral Arterial Vascular Disease (PAVD)	441*, 444*
Deep Vein Thrombosis and embolism	451*, 453*
Pulmonary Embolism	415*
Arterial Embolism	441*, 444*
Arterial Thrombosis	441*, 444*

3.4 - Potential confounders

We assessed various covariates potentially associated with the use of TNFi or tsDMARDs and considered as a risk factor for CVE. The demographics (age and sex), duration of diseases, previous CVE (recall 10 years) and hospitalization for any cause (recall 1 year) were identified on the cohort entry date. During the study period, the Charlson Comorbidity Index (CCI)[15] and Frailty Index (FI)[16] were examined. The use of glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), MTX and use of cardiovascular drugs (lipid lowering treatments, platelet aggregation inhibitors, antithrombotic agents, cardiac therapy, anti-hypertensives) were identified as co-medications (**Table 2**). With regards to biologic DMARDs and tsDMARDs (**Table 3**), we also measured the number of different drugs prescribed before the study entry using a recall period of 10 years.

Table 2. Anatomic-Therapeutic Chemical – ATC – code; co-medications

Drugs class		ATC code
Cardiovascular drugs		
	Lipid lowering treatments	C10AA*, C10BA*, C10BX*
	Platelet aggregation inhibitor	B01AC*
	Antithrombotic agents	B01AA*, B01AB*, B01AE*, B01AF*
	Cardiac therapy	C01*
	Anti-hypertensives	C02*
cDMARDs		
	Methotrexate (MTX)	L01BA01, L04AX03

Glucocorticoids		
	Methylprednisolone	H02AB04
	Prednisone	H02AB07
	Deflazacort	HO2AB13
NSAIDs		MO1A*

Abbreviations: cDMARDs, conventional synthetic disease-modifying antirheumatic; NSAIDs, Non-steroidal anti-inflammatory drugs

Table 3. Anatomic-Therapeutic Chemical – ATC – code; rheumatological treatments

Drugs class		ATC - code
bDMARDs		
	Etanercept (ETA)	L04AB01
	Infliximab (INF)	L04AB02
	Adalimumab (ADA)	L04AB04
	Certolizumb pegol (CTP)	L04AB05
	Golimumab (GOL)	L04AB06]
	Tocilizumab (TCZ)	L04AC07]
	Sarilumab (SAR)	L04AC14]
	Rituximab (RTX)	L01FA01]
	Abatacept (ABT)	L04AA24]

tsDMARDs		
	Baricitinib (BAR)	L04AA37
	Upadacitinib (UPA)	L04AA44]
	Filgotinib (FIL)	L04AA45]
	Tofacitinib (TOF)	L04AA29

Abbreviations: bDMARDs, biologic synthetic disease-modifying antirheumatic; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; cDMARDs, conventional synthetic disease-modifying antirheumatic

3.5 - Statistical analysis

Continuous characteristics are presented as median and interquartile range (IQR) or mean and standard deviation (SD), when appropriate. For proportions, absolute and relative frequencies are reported.

Incident rates of CV were estimated according to the concurring exposure to TNFi or JAKi.

The association between TNFi or JAKi exposure and CVE or death was assessed by survival models with time-dependent covariates (Cox proportional hazard models). Results were presented as hazard ratios (HR) and 95% confidence intervals (95%CI), crude and adjusted for pre-specified confounders.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc.; Cary, NC).

4 - RESULTS

A total of 4,832 therapeutic courses in RA cases were recorded between 01/01/2020 and 31/05/2021, 3,451 courses in TNFi users and 1,192 in tsDMARDs users. The mean follow-up period was 516 days with a total of 4,298 person years in TNFi and 1,497 in tsDMARDs users.

The demographic characteristic, prevalence of pre-existing CVE and the treatment of RA cases, described in terms of therapeutic courses, are reported in **Table 4**. The prevalence of pre-existing CVE was higher in the tsDMARDs compared to TNFi cases (6.6 vs. 4.9 %).

Among the RA courses, 58/3,508 (1.6%) TNFi users had at least one cardio cerebrovascular (CCV) event during the follow-up, whereas 31/1,350 (2.2%) tsDMARDs users had at least one CCV event in the same observation period. The crude incidence rate of death and CCV events was higher in the tsDMARDs compared with TNFi users 20.7 vs 13.5 (IRR 1.53) and 14 vs 10.9 respectively, (IRR 1.27). More specifically, the IRs of myocardial infarction, coronary revascularization, angina, ischemic heart disease, stroke and congestive heart failure were significantly higher in the tsDMARDs than in the TNFi users (crude IRR 1.43, 1.71, 1.71, 1.76, 2.39 and 1.76) as reported in **Table 5**. In addition, also a higher incidence of deep vein thrombosis and pulmonary embolism occurred in the tsDMARDs group (crude IRR 1.43 and 3.43 respectively).

Table 4. The demographic characteristic, prevalence of pre-existing CCV events and the treatment of RA cases, described in terms of therapeutic courses.

Variables	Overall	TNFis	tsDMARDs
Gender (F), n (%)	3709	2750	1004
Age (years), median (IQR)	59 (49-69)	59 (48-69)	60 (52-69)
Disease duration 0-2 years, n (%)	727 (15)	463 (12.9)	264 (21.1)

Disease duration 3-5 years, n (%)	761 (15.7)	549 (1.3)	212 (16.9)
Disease duration >5 years, n (%)	3344 (69.2)	2569 (71.7)	775 (62)
Frailty Index, median (IQR)	0.05 (0.04-0.09)	0.05 (0.04-0.09)	0.06 (0.04-0.09)
Pre-existing cardio cerebrovascular events (overall), n (%)	256 (5.3)	174 (4.9)	82 (6.6)
Pre-existing myocardial infarction, n (%)	24 (0.5)	18 (0.5)	6 (0.6)
Pre-existing coronary revascularisation, n (%)	44 (0.9)	33 (0.9)	11 (0.9)
Pre-existing angina, n (%)	25 (0.5)	18 (0.5)	8 (0.6)
Pre-existing ischemic heart disease, n (%)	129 (2.7)	90 (2.5)	39 (3.1)
Pre-existing stroke, n (%)	22 (0.5)	17 (0.5)	5 (0.4)
Pre-existing transient ischemic attack, n (%)	19 (0.4)	15 (0.4)	4 (0.3)
Pre-existing congestive heart failure, n (%)	27 (0.6)	15 (0.4)	12 (1.0)
Pre-existing peripheral arterial vascular event, n (%)	51 (1.1)	33 (0.9)	18 (1.4)
Pre-existing deep vein thrombosis, n (%)	19 (0.4)	12 (0.3)	7 (0.6)
Pre-existing pulmonary embolism, n (%)	13 (0.3)	8 (0.2)	5 (0.4)
Previous hospitalizations, n (%)	669 (13.8)	471 (13.2)	198 (15.8)
Concurrent NSAIDs, n (%)	1553 (32.1)	1117 (31.2)	436 (34.9)
Concurrent csDMARDs, n (%)	2569 (53.2)	1922 (53.7)	647 (51.7)

Concurrent MTX, n (%)	1965 (40.7)	1501 (41.9)	464 (37.1)
Concurrent GCs, n (%)	1730 (35.8)	1163 (32.5)	567 (45.3)
First-line user, n (%)	700 (14.5)	467 (13)	233 (18.6)
Second-line user, n (%)	3126 (64.7)	2634 (73.6)	492 (39.3)
Third-line user, n (%)	701 (14.5)	374 (10.4)	327 (26.1)
Subsequent-line (> 2) user, n (%)	305 (6.3)	106 (3)	199 (15.9)

Abbreviations: CCV, cardio cerebrovascular; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; TNFis, Tumour Necrosis Factor inhibitors; F, female; IQR, interquartile range; GCs, glucocorticoids; NSAIDs, not steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

Table 5. Crude incidence rates of cardio cerebrovascular (CCV) events in the TNFis and tsDMARDs users (per year, per 1,000 person).

CCV events	TNFi, IR	tsDMARDs, IR	IRR
Myocardial infarction	0.93	1.34	1.43
Coronary revascularisation	2.33	4.0	1.71
Angina	1.16	2.00	1.71
Ischemic heart disease	3.03	5.34	1.76
Stroke	1.40	3.34	2.39
Transient ischemic attack	0.70	0.67	0.95
Congestive heart failure	3.03	5.34	1.76

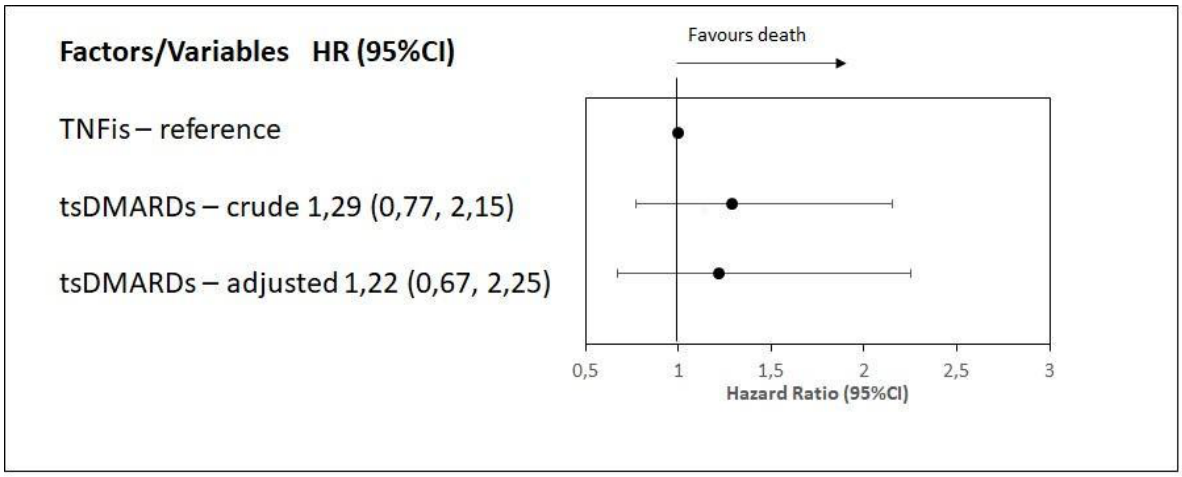
Peripheral arterial vascular event	3.96	2.00	0.51
Deep vein thrombosis	1.40	2.00	1.43
Pulmonary embolism	1.16	4.01	3.43

Abbreviations: CCV, cardio cerebrovascular; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; TNFis, Tumour Necrosis Factor inhibitors; IR, incidence rate; IRR, incident rate ratio.

4.1 - Survival analysis

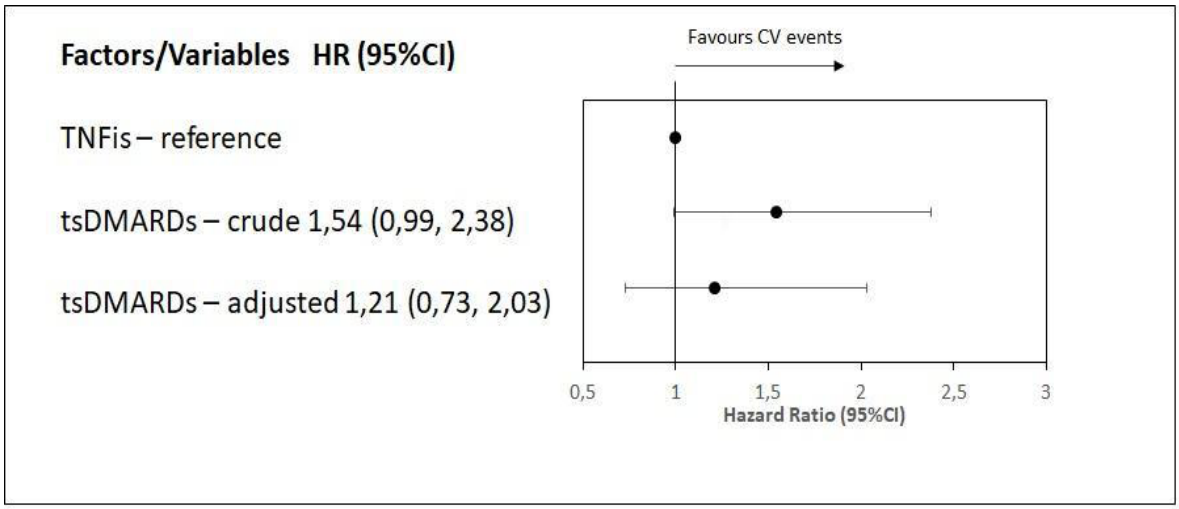
The HR (95%CI) for death was increased in treatment courses of patients treated with tsDMARDs with respect to TNFis, but without reaching statistical significance [crude HR (95%CI) 1.29 (0.77-2.15)]. The HR decreased when potential confounders were taken into account [adjusted HR 1.22 (0.67-2.25)] (**Figure 1**). Similarly, the HR (95%CI) for CCV events was non-significantly increased for tsDMARDs with respect to TNFis in crude and adjusted analyses [crude 1.54 (95%CI 0-99-2.38)]; adjusted 1.21 (0.73-2.03)] (**Figure 2**). Moreover, in adjusted analyses, Frailty Index [HR 2.00 (95%CI 1.34-3.00)], increased age [1.09 (1.06-1.11)], male gender [3.36 (2.06-5.49)], Charlson Comorbidity Index [1.26 (1.01-1.57)], glucocorticoids (GCs) [1.89 (1.13-3.14)] and CV drugs [1.84 (1.02-3.31)] significantly associated with the risk of death (**Figure 3**). Likewise, Frailty Index [HR 1.98 (95%CI 1.37-2.85)], increased age [1.06 (1.04-1.09)], male gender [2.31 (1.50-3.57)], and CV drugs [HR 1.83 (1.12-3.00)] significantly associated with subsequent CCV events (**Figure 4**). Disease duration, the line of RA treatment course and NSAIDs/MTX intake did not significantly associate with CCV events or death.

Figure 1. Crude and adjusted HR (95%CI) for death (tsDMARDs Vs TNFis).



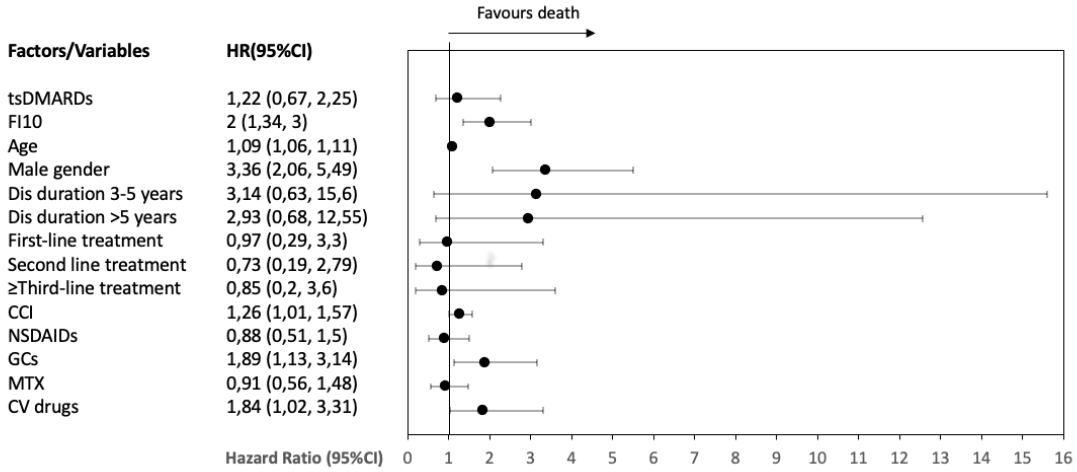
Abbreviations: HR, Hazard Ratio; TNFis, Tumor Necrosis Factor inhibitors; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs

Figure 2. Crude and adjusted HR (95%CI) for CCV (tsDMARDs Vs TNFis).



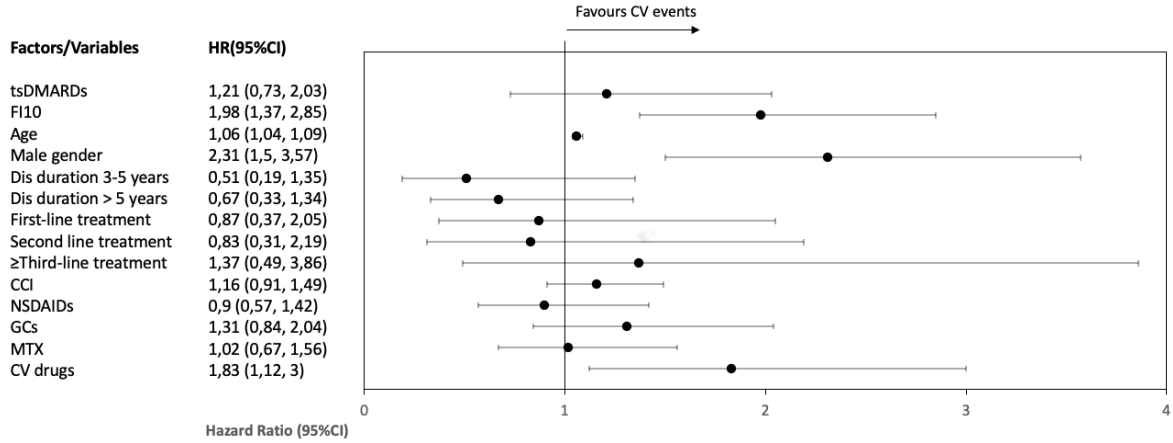
Abbreviations: HR, Hazard Ratio; CCV, cardio cerebrovascular; TNFis, Tumor Necrosis Factor inhibitors; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs

Figure 3. Adjusted HR (95% CI) for death.



Abbreviations: tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; FI10, frailty index-10; CCI, Charlson Comorbidity Index; NSAIDs, not steroidal anti-inflammatory drugs; GCs, glucocorticoids; MTX, Methotrexate; CV drugs, cardiovascular drugs.

Figure 4. Adjusted HR (95%CI) for CCV.



Abbreviations: tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; FI10, frailty index-10; CCI, Charlson Comorbidity Index; NSAIDs, not steroidal anti-inflammatory drugs; GCs, glucocorticoids; MTX, Methotrexate; CV drugs, cardiovascular drugs.

4.2 - Sensitivity analysis

When the Frailty Index was removed from the model in sensitivity analyses, the main direction of the results did not change (**Table 6**). When the model was applied only to first-line treatment courses, a non-significant reduced HR for tsDMARDs vs TNFis was highlighted for both death and CCV events occurrence (**Table 7**).

Table 6. Sensitivity analysis A (FI10 not included among confounders) - Cox proportional hazard models.

Variable	HR (Death)	95%CI	HR (CCV events)	95%CI
tsDMARDs	1.11	0.61-1.99	1.27	0.77-2.09
Age	1.09	1.07-1.12	1.07	1.05-1.09
Male gender	3.25	1.99-5.29	2.35	1.53-3.63
First-line treatment	1.14	0.34-3.78	0.75	0.33-1.69
Second line treatment	0.93	0.25-3.52	0.72	0.28-1.84
≥Third-line treatment	1.25	0.30-5.13	1.20	0.44-3.22
CCI	1.38	1.13-1.68	1.30	1.06-1.61
NSAIDs	0.87	0.51-1.50	0.90	0.57-1.43
GCs	1.98	1.20-3.28	1.43	0.93-2.21
MTX	0.85	0.52-1.38	1.00	0.65-1.53

CV drugs	2.44	1.40-4.28	2.28	1.43-3.64

Abbreviations: FI10, frailty index-10; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; CCI, Charlson Comorbidity Index; NSAIDs, not steroidal anti-inflammatory drugs; GCs, glucocorticoids; MTX, Methotrexate; CV drugs, cardiovascular drugs.

Table 7. Sensitivity analysis B (restricted to first-line treatment course) - Cox proportional hazard models.

Variable	HR (Death)	95%CI	HR (CCV events)	95%CI
tsDMARDs	0.95	0.44-2.05	0.93	0.46-1.91
FI10	1.71	1.01-2.89	2.03	1.32-3.13
Age	1.09	1.06-1.13	1.06	1.03-1.09
Male gender	3.32	1.88-5.85	2.69	1.59-4.56
CCI	1.07	0.74-1.55	1.12	0.84-1.51
NSAIDs	0.89	0.48-1.68	0.91	0.51-1.60
GCs	2.02	1.13-3.59	1.86	1.09-3.14
MTX	0.65	0.36-1.14	0.67	0.39-1.15
CV drugs	2.09	1.06-4.12	1.95	1.06-3.60

Abbreviations: tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; FI10, frailty index-10; CCI, Charlson Comorbidity Index; NSAIDs, not steroidal anti-inflammatory drugs; GCs, glucocorticoids; MTX, Methotrexate; CV drugs, cardiovascular drugs.

4.3 - Interaction between frailty index and treatment on the outcomes of interest

While Frailty Index significantly correlated with death and CCV events (Wald Chi Square 6.19, p=0.0128 and 10.04, p=0.0015, respectively), the interaction between FI and treatment did not (Wald Chi Square 0.88, p=0.3477 and 0.01, p=0.9373, respectively) (**Table 8**).

Table 8. Interaction among variables on the outcomes of interest.

Effect	Wald chi-square (death)	p	Wald chi-square (CCV)	p
Therapy	0.30	0.5220	0.37	0.5434
FI10	6.19	0.0128	10.04	0.0015
FI10 / Therapy	0.88	0.3470	0.01	0.9373
Age	35.62	<0.0001	29.90	<0.0001
Male gender	23.09	<0.0001	14.74	0.0001
Treatment line	0.57	0.9054	1.58	0.6647
CCI	3.67	0.0555	1.68	0.1956
NSAIDs	0.22	0.6398	0.19	0.6615
GCs	5.23	0.0221	1.65	0.1994
MTX	0.29	0.5929	0.03	0.8671
CV drugs	4.48	0.0342	5.49	0.0190

Abbreviations: FI10, frailty index-10; CCI, Charlson Comorbidity Index; NSAIDs, not steroidal anti-inflammatory drugs; GCs, glucocorticoids; MTX, Methotrexate; CV drugs, cardiovascular drugs.

5 - DISCUSSION

The present study was designed to examine the effect of tsDMARDs, compared with TNFi, on CVE risk in a large RA population, adjusted for potential confounders. Our findings provide suggestive evidence that the use of tsDMARDs was associated with increased risk of CVE compared to TNFi drugs, on the edge of statistical significance. When adjusting for confounding factors, there were no significant differences in the risk of developing CVE in RA patients treated with tsDMARDs compared with the TNFi group. These findings were consistent with results from previous studies[11–14,22].

The overall crude incidence rates (100 person-years) of CVE were 2.07 and 1.35 in the tsDMARDs and anti-TNFi groups, respectively. In a previous study on RA patients, the rate of major adverse CVE was found to be 0.4 per 100 person-years[23]; Charles-Schoeman et al. evaluated the risk for CVE with tofacitinib using pooled data from six phase III studies and two long term efficacy studies over 7 years in RA patients, the IR for MACE was 0.4 per 100 PYs[24]; in the TNFi-treated RA patients, the adjusted incidence rate of first MACE was 0.46 PYs[25]; the discrepancy between our results is related to the fact that, in our study, all CVE were examined.

The incidence rate ratios of deep vein thrombosis (IRR: 1.43) and pulmonary embolism (IRR: 3.43) in tsDMARDs were increased compared to TNFi groups. These findings correspond with recent reports of thromboembolic events in RA patients using tofacitinib[5]. However, long-term extension studies and phase III studies have not shown an increased risk of VTE with tofacitinib[23]. In a recent meta-analysis, treatment with baricitinib was associated with significantly increased risk of VTE compared to TNFi (IRR 1.55; 95% CI 1.10 to 2.08)[22].

In the present study, the IRR of myocardial infarction, chronic heart failure and stroke in tsDMARDs were increased compared to TNFi groups. Findings from previous studies examining the association between JAKi and CVE risk have not been consistent. Results from the ORAL Surveillance (ORALSURV) randomized trial identified a 1.33-fold (95% CI; 0.91, 1.94) greater risk of MACE with tofacitinib versus TNFi treatment in a cohort of patients with active RA despite methotrexate treatment who are 50 years of age or older and had at least one additional CV risk factor, this elevated risk was present for both the doses (5 and 10 mg), although not statistically significant given the low incidence[5]. Interestingly, the IR of MACE for TNFi inhibitors in ORALSURV was markedly lower than that seen for etanercept

(1.70 per 100 patient-years) in a similar trial evaluating patients with RA and CV risk factors[26].

The observational STAR-RA study, which compared tofacitinib with TNFi, detected 1.24-fold (CI 95%; 0.90 to 1.69) risk of MACE in a cohort designed to emulate the high-risk ORAL Surveillance population; however, no difference (HR = 1.01; 95% 0.83, 1.23) in risk was detected when the comparison was made on the same data, but in an unselected real-world cohort consisting of routine care patients. The authors hypothesize that the association between tofacitinib and CV outcomes is modified by baseline cardiovascular risk[27].

In the subgroup analysis, we observed a significant difference in the risk of CVE between the sexes. A higher CVE risk in male patients may be due to sex-based differences in susceptibility to CVE: in RA patients, a higher burden of atherosclerosis was found in males than in females[28]. Furthermore, women with RA have significantly better endothelial function than men with RA. It means that women are more protected from atherosclerotic coronary artery disease and cardiac events[29].

A 0.1-point increment of Frailty Index score was associated with a doubled risk of CVE, as reported in previous studies[30]. In our study, the use of CV drugs, as expected, was associated with increased risk of CVE in tsDMARDs. These findings are related to the fact that patients taking these drugs have more CV comorbidities. The treatment with tsDMARDs was not significantly associated with increased all causes of mortality compared to the treatment with TNFi, even when adjusted to the confounding factors. Our data support evidence from previous observations [23,31,32]. In the ORALSURV study, there was a statistically significant increase in overall mortality for the 10-mg dose (HR 2.37; 95% CI 1.34 to 4.18) and non-statistically significant trend for the 5-mg dose (HR 1.49; 95% CI 0.81 to 2.74) compared with TNF inhibitor-treated patients; these data were reflective to the differential rates of MACEs and malignancy observed in the trial[5].

The strengths of this study included a large patient cohort (4832 patients) with a prolonged median observation time of 516 days and the absence of selection bias. Furthermore, this study has structural characteristics similar to other works that have proven validity[33]. The main limitation is linked by the retrospective design of an administrative database. The use of data extracted from the administrative databases lacks some clinical information that could influence the CV risk (e.g., disease activity, some concomitant drugs and biomarkers). We did not have

information on clinical measures or laboratory values for RA disease severity or activity (e.g., DAS-28). However, the difference in the RA disease activity between the two groups may not be large as both groups started or switched to a treatment indicated for active RA.

The utilization of disease exemption codes to define patients with RA may have resulted in a diagnostic misclassification. To overcome this, we additionally used a record of specific drug prescriptions for the identification of patients with RA. The processing of administrative registers to evaluate therapeutic prescriptions is well established in pharmaco-epidemiological studies, however, the data acquired are limited to the prescriptions dispensed and no information is available on the reasons for the suspension of therapies. Another limitation is represented by the lack of analysis of possible unmeasured or unknown confounding variables, which could have influenced the results. There is also a bias related to the fact that the risk for CVE is affected by the age of patients. These limitations mean that study findings need to be interpreted cautiously.

In conclusion, our results suggest that the use of tsDMARDs were not associated with the increased risk of CVE, when adjusted for confounding factors, compared with TNFi. Overall, this study provides more reassuring real-world evidence on the comparative safety of tsDMARDs versus TNFi among RA patients.

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