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COMPARATIVE RISK OF MAJOR ADVERSE CARDIOVASCULAR EVENTS WITH JAK INHIBITORS VS. TNF ANTAGONISTS IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISORDERS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

- Janus kinase (JAK) inhibitors have emerged as an important treatment option for immune-mediated inflammatory disorders (IMIDs), offering rapid and targeted immunomodulation.[1]
- However, recent safety concerns have led to regulatory restrictions, with the U.S. FDA limiting their use to patients who have experienced prior failure of tumor necrosis factor-α (TNFα) antagonists.[2]
- This decision was largely driven by findings from a large trial conducted in older adults with RA and at least one cardiovascular risk factor, which reported an increased incidence of major adverse cardiovascular events (MACE) and malignancies with tofacitinib compared to TNFα antagonists.[3]
- While these results raise important safety considerations, their applicability across different JAKi, various IMIDs, and broader patient populations remains uncertain.

AIM

We aimed to **provide a comprehensive assessment of the safety profile of JAKi** across IMIDs and inform clinical decision-making in this evolving therapeutic landscape.

METHOD

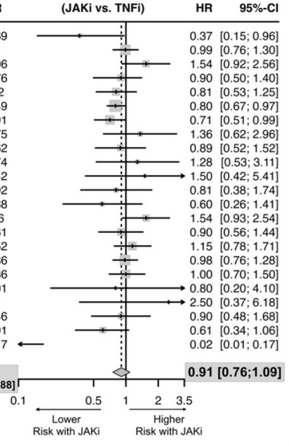
- Observational studies (cohort studies and real-world comparative studies) that met the following criteria:
  (1) Patients: adults with IMIDs, including rheumatoid arthritis, IBD, psoriasis/psoriatic arthritis (PsA), and spondyloarthropathy
  (2) Intervention: treatment with JAKi or TNFα antagonists
  (3) Comparator: alternative therapies (e.g., other JAKi, TNFα antagonists)
  (4) Outcome: risk of MACE
- Comprehensive search of multiple electronic databases through July 27, 2024 (Ovid Medline, Ovid EMBASE, Web of Science, clinical trial registries, and abstracts from relevant conferences)
- We estimated incidence rate (IR) and risk of MACE of both agents, adjusting for key confounding variables, using random effects meta-analysis.

RESULTS

- We included 23 cohorts of 293,643 patients with IMIDs, of whom 4,839 experienced MACE.
- The incidence rates (IRs) of MACE were 0.69 (95% CI, 0.51-0.93) per 100 person-years for JAKi and 0.64 (95% CI, 0.46-0.88) per 100 person-years for TNFα antagonists.
- **There was no significant difference in the risk of MACE between JAKi and TNFα antagonists** (HR: 0.91; 95% CI: 0.76–1.09), with moderate heterogeneity (I^2 = 58.8%).

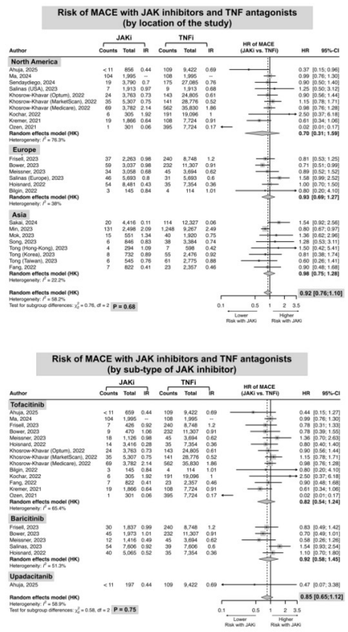
Risk of Major Adverse Cardiovascular Events (MACE) with JAK inhibitors and TNF antagonists

Author	JAKi Counts	JAKi Total	JAKi IR	TNFi Counts	TNFi Total	TNFi IR	HR of MACE (JAKi vs. TNFi)	95%-CI
Ahuja, 2025	< 11	856	0.44	109	9,422	0.69	0.37	[0.15; 0.96]
Ma, 2024	104	1,995	--	108	1,995	--	0.99	[0.76; 1.30]
Sakai, 2024	20	4,416	0.11	114	12,327	0.06	1.54	[0.92; 2.56]
Sendaydiego, 2024	19	3,790	0.7	175	27,085	0.76	0.90	[0.50; 1.40]
Frisell, 2023	37	2,263	0.98	240	8,748	1.2	0.81	[0.53; 1.25]
Min, 2023	131	2,498	2.09	1,248	9,267	2.49	0.80	[0.67; 0.97]
Bower, 2023	59	3,037	0.98	232	11,307	0.91	0.71	[0.51; 0.99]
Mok, 2023	15	551	1.34	40	1,920	0.75	1.36	[0.62; 2.96]
Meissner, 2023	34	3,058	0.68	45	3,694	0.62	0.89	[0.52; 1.52]
Song, 2023	6	846	0.83	38	3,384	0.74	1.28	[0.53; 3.11]
Tong (Hong-Kong), 2023	4	294	1.09	7	598	0.42	1.50	[0.42; 5.41]
Tong (Korea), 2023	8	732	0.89	55	2,476	0.92	0.81	[0.38; 1.74]
Tong (Taiwan), 2023	6	545	0.76	61	2,775	0.88	0.60	[0.26; 1.41]
Salinas, 2023	54	7,606	0.92	39	7,606	0.6	1.54	[0.93; 2.54]
Khosrow-Khavar (Optum), 2022	24	3,763	0.73	143	24,805	0.61	0.90	[0.56; 1.44]
Khosrow-Khavar (MarketScan), 2022	35	5,307	0.75	141	28,776	0.52	1.15	[0.78; 1.71]
Khosrow-Khavar (Medicare), 2022	69	3,782	2.14	562	35,830	1.86	0.98	[0.76; 1.28]
Hoisnard, 2022	54	8,481	0.43	35	7,354	0.36	1.00	[0.70; 1.50]
Bilgin, 2022	3	145	0.84	4	114	1.01	0.80	[0.20; 4.10]
Kochar, 2022	6	305	1.92	191	19,096	1	2.50	[0.37; 6.18]
Fang, 2022	7	822	0.41	23	2,357	0.46	0.90	[0.48; 1.68]
Kremer, 2021	19	1,866	0.64	108	7,724	0.91	0.61	[0.34; 1.06]
Ozen, 2021	1	301	0.06	395	7,724	0.17	0.02	[0.01; 0.17]
Pooled summary	**726**	**57,259**	**0.69 [0.51;0.94]**	**4,113**	**236,384**	**0.64 [0.46;0.88]**	**0.91 [0.76;1.09]**	
Heterogeneity: I^2 = 58.8%								

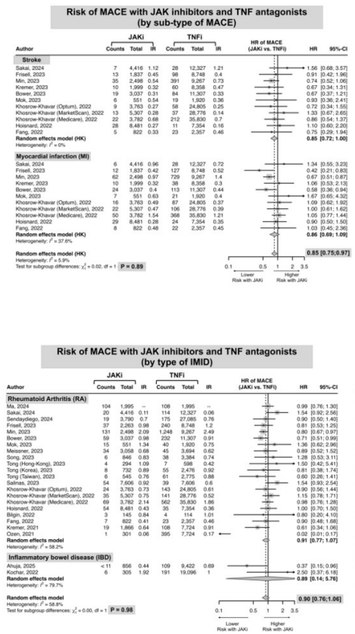


- **Overall findings remained stable in subgroup analyses** stratified by type of JAKi, disease type, atherosclerotic cardiovascular disease (ASCVD) subtype, study location, and age group.
- In meta-regression, concomitant steroid use, concomitant immunomodulators, diabetes, age, sex, midpoint of study recruitment, smoking status, hypertension, hyperlipidemia, and prior CAD did not significantly influence the association, whereas obesity did (p = 0.03).

Risk of MACE with JAK inhibitors and TNF antagonists (by location of the study)



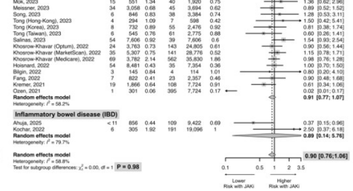
Risk of MACE with JAK inhibitors and TNF antagonists (by sub-type of MACE)



Risk of MACE with JAK inhibitors and TNF antagonists (by sub-type of JAK inhibitor)

Risk of MACE with JAK inhibitors and TNF antagonists (by type of IMID)

Risk of MACE with JAK inhibitors and TNF antagonists (by type of IMID)



CONCLUSIONS

- On meta-analysis of real-world comparative studies, **JAK inhibitors were not associated with increased risk of MACE compared with TNF antagonists** across IMIDs.
- The risk of premature atherosclerosis in patients with IMID might be influenced more by effective control of systemic inflammation than by the specific type of therapy used (JAKi or TNFα antagonists). In other words, both JAKi and TNFα antagonists may reduce systemic inflammation, which could, in turn, help mitigate the development of atherosclerosis.
- Our subgroup analyses, stratified by cardiovascular risk factors such as ASCVD, did not reveal significant differences in MACE risk, although obesity emerged as a factor influencing the risk of cardiovascular events.

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