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JAK inhibitors, Cardiovascular events, Registries

Risk of cardiovascular events under Janus kinase inhibitors in patients with rheumatoid arthritis: observational data from the German RABBIT register

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Background:

In 2021, the European and US-American regulatory agencies EMA and FDA issued warnings about the cardiovascular (CV) safety of the Janus kinase inhibitor (JAKi) tofacitinib and required changes in labelling. These actions were based on results of the post-authorisation safety trial Oral Surveillance(1).

Objectives:

To analyse major cardiovascular events (MACE) under treatment with JAKi, tumor necrosis factor inhibitors (TNFi) or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs - bionaive) in patients with rheumatoid arthritis (RA) observed in daily rheumatological care.

Methods:

Data from patients enrolled in the biologics register RABBIT with treatment episodes from 01/2017 - 04/2021 were included. Incidence rates (IR) of MACE per 100 patient-years (PY) with 95% confidence intervals (CI) and adjusted risk ratios (RR) were calculated for all and for high-risk patients (age ≥ 50 years and ≥ 1 CV risk factor). Poisson regression analysis was adjusted for age, sex, smoking, disease activity, prior therapies, glucocorticoids and comorbidities.

Results:

Starting from 2017, 2030 JAKi, 2338 TNFi and 871 csDMARD initiations were documented. Patients with a JAKi start were slightly older, more often women and had a longer RA disease duration (table). The proportion with positive autoantibodies was higher than in the TNFi and csDMARD group, the physical function was lower, and they had received more previous biologic treatments. Characteristics of high-risk patients are also given in the table.

In total, 28 incident MACE were reported. Patients under treatment with JAKi, TNFi and csDMARD showed comparable IR for MACE between 0.26 and 0.41 events per 100 PY (figure). High-risk patients showed higher IRs. The median time under treatment was 10 months on JAKi and TNFi, and 12 months on csDMARDs. The majority of events were reported in the first year after treatment start. In

the adjusted analyses, JAKi (RR 0.94 [95% CI 0.39; 2.28]) and csDMARDs (RR 0.85 [0.25; 2.88]) did not show a significantly increased risk for MACE compared with TNFi in unselected patients, and also not in high-risk patients (JAKi: RR 0.90 [0.37; 2.17]; csDMARDs: RR 0.61 [0.16; 2.28]).

Conclusion:

IR of MACE in patients receiving JAKi in a real-world setting was lower than the IR reported for tofacitinib in the Oral Surveillance study. We found no evidence of an increased risk of MACE with JAKi compared to TNFi, although patients in the JAKi group were older and had longer disease duration.

References:

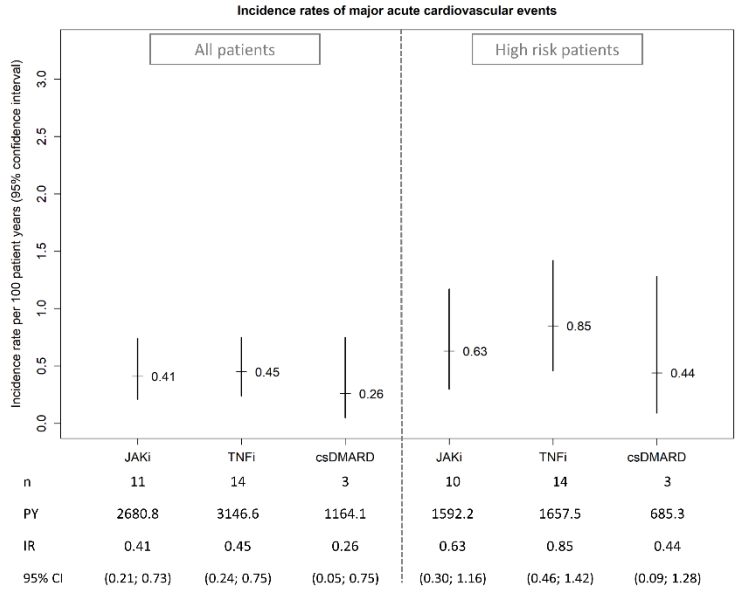
[(1)]Pfizer Press Release (27 Jan 2021): https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing

Table: Patient characteristics at the start of a JAKi, TNFi or csDMARD.

	ALL PATIENTS			HIGH RISK PATIENTS*		
	JAKi	TNFi	csDMARD	JAKi	TNFi	csDMARD
# treatment starts	2030	2338	871	1215	1254	508
Age	59.9 ± 11.6	57.6 ± 13.0	59.5 ± 12.7	64.3 ± 8.9	63.5 ± 8.9	64.4 ± 9.2
Women	1573 (77.5)	1707 (73.0)	627 (72.0)	907 (74.7)	864 (68.9)	355 (69.9)
Disease duration	12.6 ± 9.6	8.9 ± 8.5	5.7 ± 6.6	13.3 ± 9.9	9.7 ± 9.1	6.0 ± 7.0
Rheumatoid factor/ ACPA positive	1531 (79.2)	1672 (74.2)	548 (66.3)	917 (79.7)	890 (73.7)	321 (66.5)
# previous bDMARDs	2.0 ± 1.8	0.7 ± 1.2	0	2.0 ± 1.8	0.7 ± 1.2	0
DAS28-ESR	4.2 ± 1.4	4.5 ± 1.4	4.2 ± 1.3	4.4 ± 1.5	4.7 ± 1.3	4.3 ± 1.3
Percentage of full physical function	63.3 ± 24.1	68.6 ± 22.4	72.3 ± 21.9	60.3 ± 24.2	64.4 ± 23.3	69.6 ± 22.7
Glucocorticoids ≥10 mg/d	170 (17.5)	239 (21.5)	49 (12.4)	112 (18.6)	142 (22.3)	23 (10.0)
BMI >30 kg/m^2	565 (28.2)	631 (27.4)	271 (31.7)	383 (31.8)	413 (33.3)	180 (36.0)
Sum of comorbidities	2.9 ± 2.5	2.6 ± 2.4	2.2 ± 2.2	3.7 ± 2.6	3.5 ± 2.5	3.1 ± 2.3
Current smokers	461 (26.3)	617 (28.5)	274 (33.5)	355 (33.5)	466 (39.5)	202 (42.3)
Previous smokers	551 (31.4)	692 (31.9)	230 (28.1)	300 (28.3)	338 (28.6)	114 (23.9)

*Values are given as mean ± standard deviation or number (percentage). *Age ≥50 years and ≥ 1 CV risk factor (hypertension, coronary heart disease, diabetes, hyperlipoproteinaemia, current smoking)*

Figure: Incidence rates of MACE per 100 patient years by treatment group.



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