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ORIGINAL RESEARCH

Risk of major adverse cardiovascular events in patients with rheumatoid arthritis treated with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs: observational data from the German RABBIT register

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ABSTRACT

Objective To estimate the effects of Janus kinase inhibitors (JAKi), tumour necrosis factor inhibitors (TNFi), other biologic(b) or conventional synthetic(cs) disease-modifying antirheumatic drugs (DMARDs) on the risk of major adverse cardiovascular events (MACE) in patients with rheumatoid arthritis (RA).

Methods Cohort study analysing episodes of DMARD-treatment initiated between January 2017 and April 2022 in the biologics register Rheumatoid Arthritis: Observation of Biologic Therapy. Incidence rates (IRs) per 100 patient-years with 95% CIs were calculated for overall patients and those with cardiovascular risk (age ≥50 years and ≥1 cardiovascular risk factor). MACE risk was estimated as HRs by inverse probability of treatment weight-adjusted Andersen-Gill models.

Results A total of 154 MACE occurred among 14 203 treatment episodes (21 218 patient-years). IRs were 0.68 (0.47; 0.95), 0.62 (0.45; 0.83), 0.76 (0.53; 1.06) and 0.95 (0.68; 1.29) for JAKi, TNFi, bDMARDs and csDMARDs, respectively. IRs were higher in cardiovascular risk patients. Adjusted HRs (95% CI) comparing JAKi, bDMARDs and csDMARDs with TNFi were 0.89 (0.52 to 1.52), 0.76 (0.45; to1.27) and 1.36 (0.85 to 2.19) in overall, and 0.74 (0.41 to 1.31), 0.75 (0.45 to 1.27) and 1.21 (0.74 to 1.98) in cardiovascular risk patients. HRs were not increased in patients ≥65 years, with cardiovascular history or smokers, and also not when using csDMARD as reference instead of TNFi. IRs for baricitinib, tofacitinib and upadacitinib were 0.49 (0.25 to 0.85), 0.98 (0.58 to 1.55) and 0.53 (0.15 to 1.36), respectively.

Conclusion In this German observational cohort study, MACE did not occur more frequently with JAKi compared with other DMARDs. However, individual JAKis showed different unadjusted IRs.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Results of the ORAL Surveillance safety trial showed a numerically increased occurrence of major adverse cardiovascular events (MACE) with the Janus kinase inhibitor (JAKi) tofacitinib compared with tumour necrosis factor inhibitors (TNFi) in patients with rheumatoid arthritis (RA) and additional risk factors for cardiovascular events.

⇒ A warning has been issued by the European Medicines Agency regarding the use of all JAKi in patients with chronic inflammatory disorders at increased cardiovascular risk.

WHAT DOES THIS STUDY ADD?

⇒ Study provides evidence that the risk of MACE is not increased with JAKi compared with TNFi or conventional synthetic disease-modifying antirheumatic drugs. This applies both to the entire cohort of German patients with established RA and to those with a higher cardiovascular risk profile.

⇒ Stratification by different JAKi revealed numerically lower unadjusted incidence rates for baricitinib and upadacitinib compared with tofacitinib, but descriptive 95% CIs overlapped.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FUTURE DEVELOPMENTS?

⇒ Our study does not confirm the signal from the ORAL Surveillance safety trial. In comparison to TNFi, the risk of MACE was neither increased in the group of JAKi nor in individual substances when treatments are used in clinical practice.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a higher risk of major adverse cardiovascular events (MACE) compared with the general population, which even remains when adjusting for traditional cardiovascular risk factors.[1–4] Systemic inflammation plays a central role in increasing the risk, and adequate treatment with disease-modifying antirheumatic drugs (DMARDs) is beneficial.[5] A lower risk of MACE was observed on therapy with the more effective biologic (b)DMARDs, primarily with tumour necrosis factor inhibitors (TNFi), than with conventional synthetic (cs)DMARDs.[6–8]

Concerns have been raised about the risk of MACE associated with the targeted synthetic (ts)DMARDs Janus kinase inhibitors (JAKi). Following the observation of a numerically higher incidence of MACE among users of the JAKi tofacitinib compared with TNFi in preliminary results of the safety trial ORAL Surveillance, the US Food and Drug Administration and the European Medicines Agency (EMA) issued warnings regarding tofacitinib use.[9 10] The trial included a cardiovascular risk-enriched population of RA patients with a minimum age of 50 years and at least one cardiovascular risk factor.

So far, other clinical trials and observational studies have not confirmed these signals. Similar incidence rates (IR) or frequencies of MACE were reported in clinical trial data, including tofacitinib,[11] baricitinib,[12] filgotinib[13] and upadacitinib,[14] compared with TNFi. Incidences of MACE in association with tofacitinib exposure were neither increased in a US collaborative claims data analysis[15] nor in a US register observing patients with tofacitinib treatment since 2012.[16] French claims data showed no increased risk of MACE with tofacitinib or baricitinib compared with adalimumab, including patients at high risk.[17] In the Swedish ARTIS register, MACE did not occur more frequently with tofacitinib and baricitinib than with bDMARDs.[4] Evaluation of more than 11 million reported side effects in the global VigiBase database did not yield a higher declaration of MACE with JAKi compared with TNFi.[18] Regarding baricitinib, international collaborative analysis of two registers and several commercial and claims databases showed a numerically increased risk of MACE compared with TNFi in absence of statistical significance.[19]

After reviewing final trial and study results,[19 20] EMA endorsed the safety alerts and extended them to all JAKi approved to treat chronic inflammatory disorders. At present, they caution against the use of JAKi in patients aged 65 years or above, at increased risk of MACE, in current or past long-time smokers and in patients at increased risk of cancer.[21] These restrictions are already partly reflected in the current RA management recommendations of EULAR.[22]

To generate additional evidence based on clinical practice, the aim of this study was to estimate the effects of cs/b and tsDMARD therapies on the risk of MACE in patients with RA. Separate analyses were performed for patients at increased risk for cardiovascular events and for the different available JAKis.

METHODS

Data source

This analysis contains data from the German biologics register Rheumatoid Arthritis: Observation of Biologic Therapy (RABBIT), a nationwide prospective observational longitudinal cohort study with routine clinical care information. Adult patients with RA are consecutively enrolled into the register with the start of a b/tsDMARD or with a csDMARD after at least one prior DMARD therapy. Data are reported by rheumatologists and patients at predefined time points for at least 5 and up to 10 years. The regularly assessed information comprises demographics, disease and treatment characteristics, comorbidities and patient-reported outcomes.[23] Adverse events are reported at every follow-up visit and classified as serious or non-serious according to the International Conference on Harmonization E2A guidelines by the rheumatologist.[24] They are coded by the study centre using the Medical Dictionary for Regulatory Activities.[25] For events of interest such as MACE, the rheumatologist has to answer additional event-specific queries to provide further details. Prior to enrolment into the register, patients have to give their written informed consent.

Study population

The study included patients enrolled from 1 January 2007 in RABBIT with at least one follow-up until 30 April 2022 (figure 1). Patients were eligible for the analysis if they initiated a DMARD treatment from 1 January 2017 (overall patients). As an adaption to the ORAL Surveillance eligibility criteria,[20] an additional study cohort with a cardiovascular risk-enriched population was defined by selecting patients aged 50 years or older and with at least one cardiovascular risk factor defined as hypertension, coronary heart disease, diabetes, hyperlipoproteinemia or current smoking at treatment start (cardiovascular risk patients).

Outcomes

The endpoint of this analysis was three-point MACE, defined as the composite of non-fatal or fatal stroke or myocardial infarction, and other cardiovascular death by the rheumatologist (detailed information in the supplement).

Assignment of treatment exposure

Four treatment exposure groups were evaluated in this analysis: (I) JAKi (baricitinib, filgotinib, tofacitinib or upadacitinib), (II) TNFi (adalimumab, certolizumab, etanercept, golimumab or infliximab), (III) other bDMARD (abatacept, rituximab, sarilumab or tocilizumab) and (IV) csDMARD without or with prior b/tsDMARD exposure. Groups (I) to (III) could have been applied as monotherapy or in combination with csDMARD. Treatment episodes were analysed. Switching

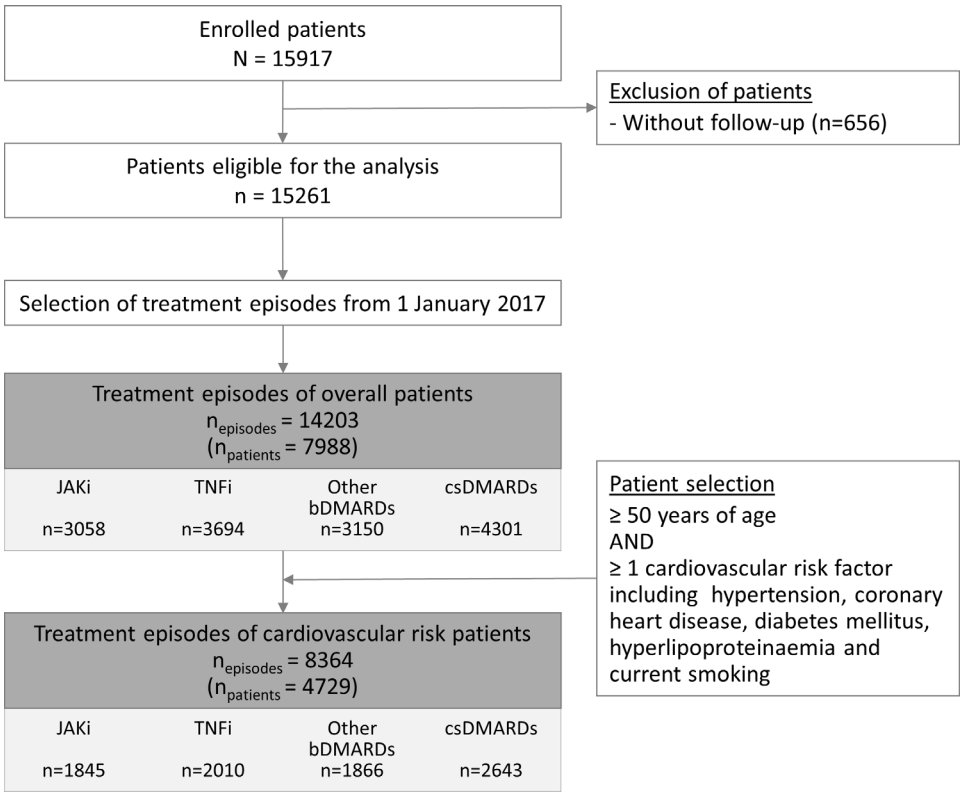


Figure 1 Flowchart of patient and treatment episode selection. bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor.

across different exposure groups was allowed, and one patient could contribute to more than one exposure group. The day of initiation of any drug from one exposure group was defined as index date for each treatment episode. Treatment episodes lasted from index date until treatment stop (unless another drug from the same treatment exposure group was initiated, that is, switching within the same exposure group did not trigger a new treatment episode), end of individual patient observation or study period, whichever came first. For IR calculation, exposure to a treatment was censored after the first occurrence of MACE. For HR calculation, treatment episodes were artificially split at the occurrence of an event in order to analyse recurrent events with Cox methodology, that is, treatment episodes always ended at the occurrence of an event. Exposure in group IV was censored at the time of starting a b/tsDMARD. For b/tsDMARDs (groups I–III), an additional risk window of 90 days (270 days for rituximab) was added after treatment discontinuation. For overlaps between treatment episodes, the overlap in exposure time (including associated events) was assigned to both treatment groups for IR calculation and the previous treatment group for regression models.

Statistical analyses

Patient characteristics were summarised per treatment group at the index date (=baseline) either as mean with SD, median with IQR or number and percentages. Number of first reported events, patient years (PY) at risk and crude IRs per 100 PY, including a descriptive 95% CI were calculated per treatment group assuming a Poisson distribution for observed event numbers.[26]

The Andersen-Gill model, a simple extension of the standard Cox proportional hazard regression model developed to consider recurrent events and the complete follow-up time, was applied.[27–30] By using treatment episodes instead of patients as unit of observation, it better adjusts for treatment switches than the standard Cox model. Adjusted HRs with 95% CIs were calculated to investigate the risk of first and subsequent MACE associated with JAKi, other bDMARD and csDMARD treatment in comparison to TNFi. Models were adjusted for treatment decisions via stabilised and winsorised inverse probability of treatment weighting (IPTW). Weights were estimated using propensity scores calculated by logistic regression including the baseline covariates age, sex, current smoking, Clinical Disease Activity Index (CDAI), C reactive protein (CRP), number of previous DMARDs, number of comorbidities associated with cardiovascular risk (hypertension, coronary heart disease, diabetes, hyperlipoproteinemia, stroke and obesity defined as body mass index ≥30 kg/m^2), dose of concomitant glucocorticoid therapy, functional status assessed by Hannover Functional Capacity Questionnaire (FFbH),[31] type of enrolling institution (clinic vs practice) and year of index date (until 2020 or thereafter, to account for preliminary

safety warnings). IPTW was additionally carried out to adjust for selective dropout, applying logistic regression with the covariates age, sex, FFbH, CDAI and CRP. Both weights were multiplied to obtain a final weight for each treatment episode. If a covariate of the IPTW model showed a mean standardised difference of >0.1 or <−0.1, indicating insufficient balance between treatment groups, it was additionally included as covariate to the Andersen-Gill model. HRs are presented for treatment groups with at least five events in order to guarantee stable results. The CIs of the HRs were calculated using robust sandwich estimates.[32]

Tenfold imputation of missing values via full conditional sampling was applied. Since CRP distribution was strongly skewed, this covariate was logarithmised prior to analysis. All analyses were conducted in SAS (V.9.4) and R (V. 4.2.1).

Subgroup and secondary analyses

Subgroup analyses were stratified by sex (female vs male), age (≥65 years vs <65), prior cardiovascular disease (CVD) defined as coronary heart disease or stroke (history of CVD vs no history CVD), smoking (current smokers vs non-smokers including former smokers, never smokers and patients with missing information) and prior b/tsDMARD use (bionaive vs non-bionaive). Crude IRs and adjusted HRs were calculated for each subgroup of overall and cardiovascular risk patients. Secondary analyses comprised two different Andersen-Gill models: in the first, csDMARD group was used as reference category instead of TNFi, in the second, IPTW covariates were included in the regression. Furthermore, the risk of first MACE events was addressed by Cox proportional hazard regression that censored exposure at the first event, therapy switch or end of observation, whichever occurred first. Eventually, individual JAKi drugs were examined (baseline characteristics, IRs and HRs), with the exception of filgotinib due to the low number of episodes and events (n=125 and n=1, respectively). For upadacitinib, only IRs were calculated due to the low number of events (n=4).

RESULTS

From 1 January 2017 onwards, a total of 14 203 treatment episodes were eligible for the analysis, thereof 3058 with JAKi, 3694 with TNFi, 3150 with other bDMARDs and 4301 with csDMARD (overall patients, figure 1). After selecting patients with cardiovascular risk factors, 1845, 2010, 1866 and 2643 episodes remained in the groups of JAKi, TNFi, other bDMARDs and csDMARDs, respectively (cardiovascular risk patients). PYs for individual substances are given in online supplemental table S1.

Baseline characteristics

Compared with patients starting a TNFi, patients with JAKi, other bDMARD or csDMARD were older on average, showed signs of a more long-standing RA disease, eg, longer disease duration, higher number of prior b/tsDMARDs, lower physical capacity and higher prevalence of comorbid conditions (table 1). Disease activity measures were lowest in the csDMARD group. Restricting the cohort to patients with a minimum age of 50 years and at least one cardiovascular risk factor (cardiovascular risk patients) led to a lower percentage of female patients, higher mean age and disease duration and slightly elevated disease activity at treatment start (table 1).

Crude IRs and HRs of MACE (main analysis)

A total of 154 events (including 148 first events) were reported in individual patients, of which 65 (42%) were non-fatal or fatal myocardial infarctions, 64 non-fatal or fatal strokes (42%) and 25 fatal MACE (16%). This outcome distribution was similar in the TNFi and csDMARD group. In the other bDMARD group, 46% myocardial infarctions, 29% strokes and 26% fatal MACE were registered. More strokes (53%, n=18) than myocardial infarctions (38%, n=13) occurred with JAKi, and three of the events were fatal MACE (9%). Of the 18 strokes that occurred in JAKi-treated patients, three were ruptured aneurysms, two were haemorrhagic and 13 were ischaemic or unknown.

The IR overall (95% CI) per 100 PYs for MACE was 0.73 (0.61 to 0.85). For individual exposure groups, IRs were 0.68 (0.47 to 0.95), 0.62 (0.45 to 0.83), 0.76 (0.53 to 1.06) and 0.95 (0.68 to 1.29) for JAKi, TNFi, other bDMARDs and csDMARDs, respectively (table 2). Compared with TNFi, HRs (95% CI) were 0.89 (0.52 to 1.52), 0.76 (0.45 to 1.27) and 1.36 (0.85 to 2.19) for JAKi, other bDMARDs and csDMARDs, in the group of overall patients (figure 2).

Higher IRs were observed in cardiovascular risk patients with 1.11 events per 100 PY (0.93 to 1.32) overall, and 0.92 (0.62 to 1.33), 1.03 (0.74 to 1.40), 1.17 (0.80 to 1.65) and 1.48 (1.05 to 2.01) with JAKi, TNFi, other bDMARDs and csDMARDs, respectively (table 2). HRs were 0.74 (0.41 to 1.31), 0.75 (0.45 to 1.27) and 1.21 (0.74 to 1.98) for JAKi, other bDMARDs and csDMARDs compared with TNFi (figure 2). In all Andersen-Gill models, the number of previous DMARDs was added as covariate due to exceeding the mean standardised difference threshold.

Subgroup and secondary analyses

Across all exposure groups, subgroup analyses of overall patients revealed considerably higher IRs in male patients compared with female patients, in patients aged ≥65 years compared with <65 years and in patients with CVD history compared with no CVD history (table 2). Differences in IRs were not as pronounced in smokers compared with non-smokers and in patients with versus without prior b/tsDMARD use, except for the csDMARD exposure group. No significantly altered HRs of MACE in association with JAKi, other bDMARD or csDMARD treatment in comparison to TNFi were observed in any

Table 1 Patient characteristics at the time of starting treatment with JAKi, TNFi, other bDMARDs or csDMARD given for overall and cardiovascular risk patients

	Overall patients				Cardiovascular risk patients			
	JAKi	TNFi	Other bDMARDs	csDMARDs	JAKi	TNFi	Other bDMARDs	csDMARDs
Number of treatment episodes	3058	3694	3150	4301	1845	2010	1866	2643
Treatment start before 2021	2457 (80.4)	3100 (83.9)	2793 (88.7)	3700 (86.0)	1475 (80.0)	1675 (83.3)	1658 (88.9)	2282 (86.3)
Time on treatment in months	18.2±14.3	19.2±15.3	16.5±13.7	12.6±13.6	18.4±14.2	18.6±14.8	15.8±13.2	12.7±13.7
Age in years	60.2±11.8	57.7±13.3	60.4±11.9	61.3±12.3	64.7±8.9	64.0±9.0	65.2±8.8	66.0±9.1
Age≥65 years	1023 (33.5)	1122 (30.4)	1116 (35.4)	1722 (40.0)	826 (44.8)	869 (43.2)	874 (46.8)	1372 (51.9)
Male patients	721 (23.6)	962 (26.0)	842 (26.7)	1111 (25.8)	491 (26.6)	598 (29.8)	570 (30.6)	764 (28.9)
Disease duration in years	12.5±9.5	9.6±8.7	13.6±9.7	12.4±9.8	13.3±9.8	10.5±9.5	14.5±10.1	13.3±10.0
Positive rheumatoid factor or ACPA	2315 (78.9)	2622 (73.6)	2586 (85.6)	3161 (77.2)	1396 (79.4)	1406 (72.6)	1531 (85.3)	1953 (77.5)
Joint erosions	1405 (47.7)	1429 (39.8)	1664 (55.0)	1917 (46.8)	890 (49.8)	825 (42.1)	1016 (56.6)	1236 (49.0)
DAS28-ESR	4.2±1.4	4.3±1.4	4.0±1.5	3.6±1.4	4.4±1.4	4.5±1.3	4.1±1.5	3.7±1.4
CDAI	20.0±12.3	21.0±11.7	17.9±12.1	14.8±10.7	20.6±12.5	21.8±11.7	18.1±12.2	15.1±10.7
CRP in mg/L, median (IQR)	4.7 (1.9–12.0)	5.0 (2.0–13.0)	4.7 (2.0–11.4)	3.9 (1.7–9.6)	5.0 (2.0–12.4)	5.6 (2.3–13.6)	5.3 (2.5–13.0)	4.5 (2.0–10.7)
% of full physical function (0–100)	64.2±23.9	68.6±22.6	65.5±23.6	67.8±23.9	60.7±24.1	63.9±23.3	62.3±24.4	63.9±24.6
Number of prior b/tsDMARDs	2.3±2.0	0.9±1.6	2.4±1.6	1.8±1.7	2.4±2.1	0.9±1.6	2.4±1.6	1.9±1.7
Number of prior csDMARDs	2.2±1.0	2.0±1.0	2.3±1.0	2.1±1.1	2.3±1.0	2.0±1.0	2.4±1.1	2.2±1.1
Concomitant corticosteroids	1482 (52.2)	1759 (50.6)	1344 (46.2)	1788 (45.3)	926 (53.8)	1045 (54.9)	823 (47.9)	1147 (47.3)
Corticosteroids≥10 mg/d	283 (10.0)	354 (10.2)	229 (7.9)	235 (6.0)	185 (10.8)	217 (11.5)	142 (8.3)	149 (6.2)
Sum of cardiovascular comorbidities	1.1±1.1	1.0±1.1	1.2±1.2	1.2±1.2	1.6±1.1	1.6±1.1	1.7±1.2	1.7±1.1
Hypertension	1456 (47.6)	1534 (41.5)	1484 (47.1)	2126 (49.4)	1357 (73.6)	1431 (71.2)	1390 (74.5)	2027 (76.7)
Coronary heart disease	251 (8.2)	257 (7.0)	310 (9.8)	423 (9.8)	246 (13.3)	254 (12.6)	299 (16.0)	415 (15.7)
History of stroke	72 (2.4)	81 (2.2)	91 (2.9)	124 (2.9)	63 (3.4)	73 (3.6)	85 (4.6)	113 (4.3)
Hyperlipoproteinaemia	392 (12.8)	336 (9.1)	461 (14.6)	535 (12.4)	371 (20.1)	318 (15.8)	443 (23.7)	519 (19.6)
Diabetes mellitus	425 (13.9)	429 (11.6)	420 (13.3)	596 (13.9)	386 (20.9)	387 (19.3)	390 (20.9)	559 (21.2)
Obesity (BMI≥30 kg/m^2)	749 (28.4)	941 (28.0)	724 (28.0)	1075 (29.8)	510 (32.3)	623 (34.3)	516 (33.9)	766 (34.9)
Sum of all comorbidity	2.3±2.0	2.0±1.8	2.4±2.1	2.4±2.1	3.1±2.0	2.7±1.9	3.3±2.1	3.2±2.1
Osteoporosis	578 (18.9)	486 (13.2)	666 (21.1)	838 (19.5)	418 (22.7)	354 (17.6)	501 (26.9)	633 (24.0)
History of malignancy	137 (4.5)	138 (3.7)	190 (6.0)	282 (6.6)	99 (5.4)	109 (5.4)	140 (7.5)	210 (8.0)
Current smoking	792 (25.9)	963 (26.1)	783 (24.9)	1086 (25.3)	619 (33.6)	723 (36.0)	601 (32.2)	858 (32.5)
Enrolling institution: rheumatology clinic*	560 (18.3)	533 (14.4)	807 (25.6)	851 (19.8)	344 (18.6)	266 (13.2)	502 (26.9)	528 (20.0)

Results are given as mean ± standard deviation or number (percentage) unless otherwise indicated.
*In contrast to private rheumatology practice.
ACPA, anti-citrullinated protein autoantibodies; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-ESR, Disease Activity Score based on erythrocyte sedimentation rate and 28 joints; IQR, interquartile range; JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Table 2 Crude incidence rates of major adverse cardiovascular events per 100 patient-years in main and subgroup analyses given for overall and cardiovascular risk patients

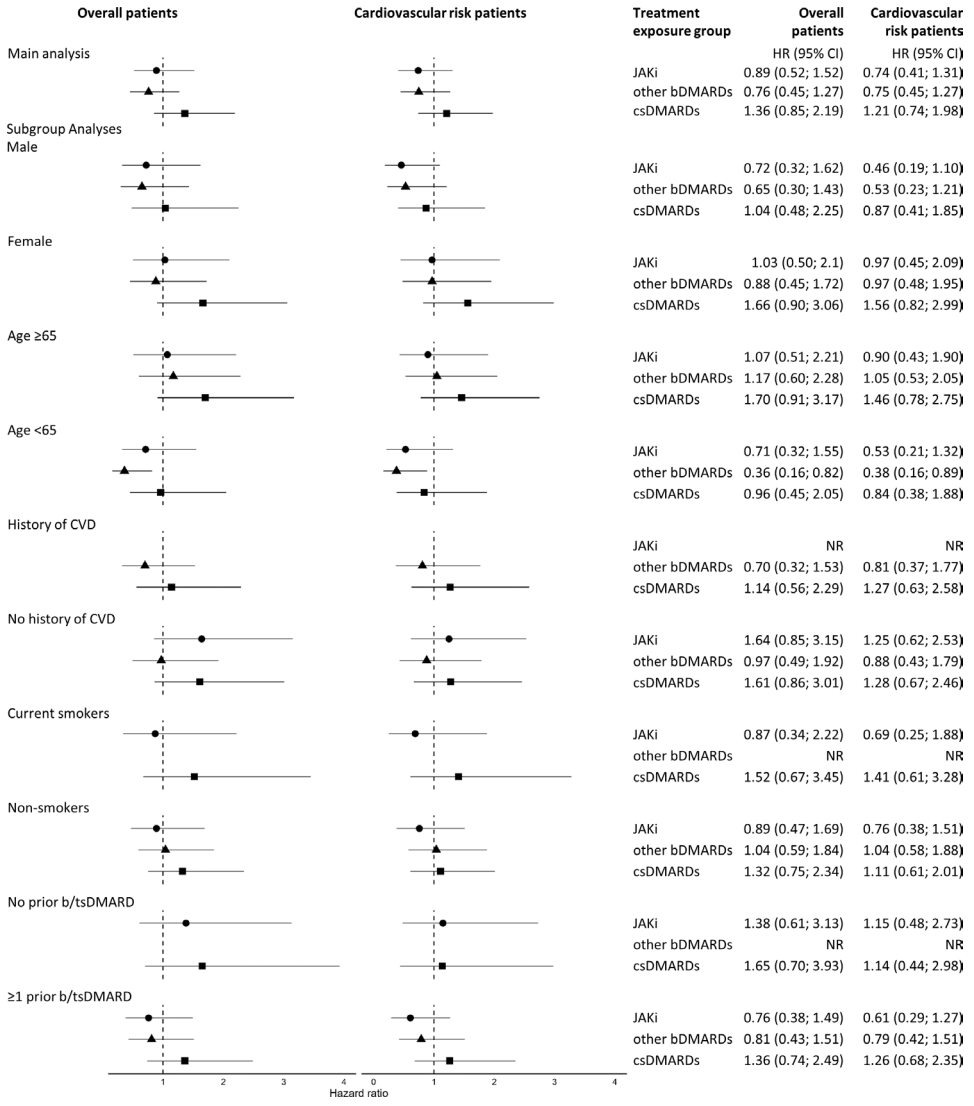
		Overall patients				Cardiovascular risk patients			
	Treatment exposure group	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)
Main analysis									
	JAKi	3058	5013.17	34	0.68 (0.47 to 0.95)	1845	3142.75	29	0.92 (0.62 to 1.33)
	TNFi	3694	7264.00	45	0.62 (0.45 to 0.83)	2010	3985.58	41	1.03 (0.74 to 1.40)
	Other bDMARDs	3150	4615.92	35	0.76 (0.53 to 1.06)	1866	2746.83	32	1.17 (0.80 to 1.65)
	csDMARDs	4301	4326.58	41	0.95 (0.68 to 1.29)	2643	2712.17	40	1.48 (1.05 to 2.01)
Subgroup analyses									
Male	JAKi	721	1226.08	15	1.22 (0.69 to 2.02)	491	862.33	12	1.39 (0.72 to 2.43)
	TNFi	962	1959.67	20	1.02 (0.62 to 1.58)	598	1234.08	18	1.46 (0.86 to 2.31)
	Other bDMARDs	842	1223.17	13	1.06 (0.57 to 1.82)	570	815.00	11	1.35 (0.67 to 2.42)
	csDMARDs	1111	1103.00	17	1.54 (0.90 to 2.47)	764	733.42	17	2.32 (1.35 to 3.71)
Female	JAKi	2337	3787.08	19	0.50 (0.30 to 0.78)	1354	2280.42	17	0.75 (0.43 to 1.19)
	TNFi	2732	5304.33	25	0.47 (0.31 to 0.70)	1412	2751.50	23	0.84 (0.53 to 1.25)
	Other bDMARDs	2308	3392.75	22	0.65 (0.41 to 0.98)	1296	1931.83	21	1.09 (0.67 to 1.66)
	csDMARDs	3190	3223.58	24	0.75 (0.48 to 1.11)	1879	1978.75	23	1.16 (0.74 to 1.74)
Age≥65 years	JAKi	1023	1798.42	19	1.06 (0.64 to 1.65)	826	1440.75	18	1.25 (0.74 to 1.98)
	TNFi	1122	2322.42	24	1.03 (0.66 to 1.54)	869	1777.00	23	1.29 (0.82 to 1.94)
	Other bDMARDs	1116	1640.17	25	1.52 (0.99 to 2.25)	874	1298.58	23	1.77 (1.12 to 2.66)
	csDMARDs	1722	1887.00	28	1.48 (0.99 to 2.15)	1372	1484.00	28	1.89 (1.25 to 2.73)
Age<65 years	JAKi	2035	3215.75	15	0.47 (0.26 to 0.77)	1019	1703.00	11	0.65 (0.32 to 1.16)
	TNFi	2572	4942.67	21	0.43 (0.26 to 0.65)	1141	2209.67	18	0.82 (0.48 to 1.29)
	Other bDMARDs	2034	2978.83	10	0.34 (0.16 to 0.62)	992	1450.17	9	0.62 (0.28 to 1.18)
	csDMARDs	2579	2440.08	13	0.53 (0.28 to 0.91)	1271	1228.67	12	0.98 (0.51 to 1.71)
History of CVD	JAKi	310	517.58	7	1.35 (0.54 to 2.79)	297	500.50	7	1.40 (0.56 to 2.88)
	TNFi	322	632.25	18	2.85 (1.69 to 4.50)	311	614.17	17	2.77 (1.61 to 4.43)
	Other bDMARDs	371	504.25	16	3.17 (1.81 to 5.15)	354	484.75	16	3.30 (1.89 to 5.36)
	csDMARDs	513	501.58	20	3.99 (2.44 to 6.16)	494	481.25	20	4.16 (2.54 to 6.42)
No history of CVD	JAKi	2748	4499.25	27	0.60 (0.40 to 0.87)	1548	2645.92	22	0.83 (0.52 to 1.26)
	TNFi	3372	6640.00	27	0.41 (0.27 to 0.59)	1699	3379.17	24	0.71 (0.46 to 1.06)

Continued

Table 2 Continued

		Overall patients				Cardiovascular risk patients			
	Treatment exposure group	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)
	Other bDMARDs	2779	4120.75	19	0.46 (0.28 to 0.72)	1512	2267.58	16	0.71 (0.40 to 1.15)
	csDMARDs	3788	3828.67	21	0.55 (0.34 to 0.84)	2149	2234.58	20	0.90 (0.55 to 1.38)
Current smoker	JAKi	792	1313.67	9	0.69 (0.31 to 1.30)	619	1052.58	8	0.76 (0.33 to 1.50)
	TNFi	963	1835.83	16	0.87 (0.50 to 1.42)	723	1399.42	16	1.14 (0.65 to 1.86)
	Other bDMARDs	783	1172.67	5	0.43 (0.14 to 1.00)	601	888.67	5	0.56 (0.18 to 1.31)
	csDMARDs	1086	1070.67	16	1.49 (0.85 to 2.43)	858	857.75	16	1.87 (1.07 to 3.03)
Non-smoker	JAKi	2266	3700.67	25	0.68 (0.44 to 1.00)	1226	2091.33	21	1.00 (0.62 to 1.54)
	TNFi	2731	5434.67	29	0.53 (0.36 to 0.77)	1287	2592.67	25	0.96 (0.62 to 1.42)
	Other bDMARDs	2367	3443.25	30	0.87 (0.59 to 1.24)	1265	1858.17	27	1.45 (0.96 to 2.11)
	csDMARDs	3215	3258.33	25	0.77 (0.50 to 1.13)	1785	1856.83	24	1.29 (0.83 to 1.92)
No prior b/tsDMARD treatment	JAKi	770	2579.33	22	0.85 (0.54 to 1.29)	450	1586.75	18	1.13 (0.67 to 1.79)
	TNFi	2311	5480.08	29	0.53 (0.35 to 0.76)	1250	2993.08	26	0.87 (0.57 to 1.27)
	Other bDMARDs	451	1967.17	11	0.56 (0.28 to 1.00)	266	1122.50	10	0.89 (0.43 to 1.64)
	csDMARDs	1170	1922.33	10	0.52 (0.25 to 0.96)	670	1149.92	10	0.87 (0.42 to 1.60)
≥1 prior b/tsDMARD treatment	JAKi	2288	3538.42	21	0.59 (0.37 to 0.91)	1395	2248.58	20	0.89 (0.54 to 1.37)
	TNFi	1383	1777.00	16	0.90 (0.52 to 1.46)	760	988.00	15	1.52 (0.85 to 2.50)
	Other bDMARDs	2699	2644.17	24	0.91 (0.58 to 1.35)	1600	1620.17	22	1.36 (0.85 to 2.06)
	csDMARDs	3131	1388.58	19	1.37 (0.82 to 2.14)	1973	901.17	18	2.00 (1.18 to 3.16)

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CVD, cardiovascular disease; JAKi, Janus kinase inhibitor; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs.



Treatment exposure group	Overall patients	Cardiovascular risk patients
	HR (95% CI)	HR (95% CI)
Main analysis		
JAKi	0.89 (0.52; 1.52)	0.74 (0.41; 1.31)
other bDMARDs	0.76 (0.45; 1.27)	0.75 (0.45; 1.27)
csDMARDs	1.36 (0.85; 2.19)	1.21 (0.74; 1.98)
Subgroup Analyses		
Male		
JAKi	0.72 (0.32; 1.62)	0.46 (0.19; 1.10)
other bDMARDs	0.65 (0.30; 1.43)	0.53 (0.23; 1.21)
csDMARDs	1.04 (0.48; 2.25)	0.87 (0.41; 1.85)
Female		
JAKi	1.03 (0.50; 2.1)	0.97 (0.45; 2.09)
other bDMARDs	0.88 (0.45; 1.72)	0.97 (0.48; 1.95)
csDMARDs	1.66 (0.90; 3.06)	1.56 (0.82; 2.99)
Age ≥65		
JAKi	1.07 (0.51; 2.21)	0.90 (0.43; 1.90)
other bDMARDs	1.17 (0.60; 2.28)	1.05 (0.53; 2.05)
csDMARDs	1.70 (0.91; 3.17)	1.46 (0.78; 2.75)
Age <65		
JAKi	0.71 (0.32; 1.55)	0.53 (0.21; 1.32)
other bDMARDs	0.36 (0.16; 0.82)	0.38 (0.16; 0.89)
csDMARDs	0.96 (0.45; 2.05)	0.84 (0.38; 1.88)
History of CVD		
JAKi	NR	NR
other bDMARDs	0.70 (0.32; 1.53)	0.81 (0.37; 1.77)
csDMARDs	1.14 (0.56; 2.29)	1.27 (0.63; 2.58)
No history of CVD		
JAKi	1.64 (0.85; 3.15)	1.25 (0.62; 2.53)
other bDMARDs	0.97 (0.49; 1.92)	0.88 (0.43; 1.79)
csDMARDs	1.61 (0.86; 3.01)	1.28 (0.67; 2.46)
Current smokers		
JAKi	0.87 (0.34; 2.22)	0.69 (0.25; 1.88)
other bDMARDs	NR	NR
csDMARDs	1.52 (0.67; 3.45)	1.41 (0.61; 3.28)
Non-smokers		
JAKi	0.89 (0.47; 1.69)	0.76 (0.38; 1.51)
other bDMARDs	1.04 (0.59; 1.84)	1.04 (0.58; 1.88)
csDMARDs	1.32 (0.75; 2.34)	1.11 (0.61; 2.01)
No prior b/tsDMARD		
JAKi	1.38 (0.61; 3.13)	1.15 (0.48; 2.73)
other bDMARDs	NR	NR
csDMARDs	1.65 (0.70; 3.93)	1.14 (0.44; 2.98)
≥1 prior b/tsDMARD		
JAKi	0.76 (0.38; 1.49)	0.61 (0.29; 1.27)
other bDMARDs	0.81 (0.43; 1.51)	0.79 (0.42; 1.51)
csDMARDs	1.36 (0.74; 2.49)	1.26 (0.68; 2.35)

Figure 2 Adjusted HRs with 95% CIs and TNFi as reference treatment group in overall (left) and cardiovascular risk (right) patients given for main and subgroup analyses. Risk of major adverse cardiovascular events estimated from the Andersen-Gill model applying inverse probability weighting. In all Andersen-Gill models, the number of previous DMARD substances was used as covariate in addition to the treatment effect due to exceeding the mean standardised difference threshold. bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CVD, cardiovascular disease; JAKi, Janus kinase inhibitor; NR, not reported due to a low number of events; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

subgroup, except for a significantly reduced risk with other bDMARDs in patients<65 years (figure 2).

In subgroup analyses, as already observed in the main analysis, the vast majority of MACE occurred in cardiovascular risk patients, which is reflected in higher IRs compared with the overall group of patients (table 2). However, in cardiovascular risk patients, IRs in the subgroups age ≥65 years, CVD history and current smokers were more comparable to the group of overall patients. No increase in MACE risk was found in subgroups of cardiovascular risk patients treated with JAKi, other bDMARD or csDMARD using TNFi as reference (figure 2). Only patients aged <65 years and treated with other bDMARDs had a significant reduction of MACE risk.

Using csDMARDs as reference in the regression model resulted in a statistically significant lower risk of MACE for other bDMARDs and in numerically lower HRs for TNFi and JAKi, in overall and cardiovascular risk patients (table 3). Adjustment for covariables in the main regression model (in addition to IPW) showed a significant association with the occurrence of MACE for age ≥65 years, male sex, CRP, number of cardiovascular comorbidities and current smoking in the group of overall patients. The Cox proportional hazard model, that investigated the risk of first MACE, revealed HRs comparable to the main analysis of the Andersen-Gill model for JAKi versus TNFi (table 3).

Baseline characteristics for treatment episodes with baricitinib (n=1416), tofacitinib (n=1126) and

Table 3 Secondary analyses of adjusted HRs of major adverse cardiovascular events estimated by Andersen-Gill model given for overall and cardiovascular risk patients

	Overall patients				Cardiovascular risk patients			
	HR	LCL	UCL	P-value	HR	LCL	UCL	P-value
csDMARD as reference category								
Reference: csDMARDs	1.00				1.00			
JAKi	0.73	0.46	1.18	0.20	0.82	0.50	1.34	0.44
TNFi	0.65	0.40	1.05	0.08	0.61	0.36	1.03	0.06
Other bDMARDs	0.56	0.35	0.88	0.01	0.62	0.39	1.00	0.048
(II) Adjustment for covariables								
Reference: TNFi	1.00				1.00			
JAKi	0.84	0.47	1.48	0.54	0.71	0.38	1.31	0.27
Other bDMARDs	0.74	0.44	1.24	0.25	0.74	0.43	1.26	0.26
csDMARDs	1.28	0.78	2.08	0.33	1.19	0.72	1.97	0.50
Treatment episode start≥2021 (vs.<2021)	0.79	0.40	1.54	0.49	0.89	0.46	1.75	0.74
Number of prior csDMARDs	1.19	1.02	1.40	0.03	1.24	1.05	1.46	0.01
Number of prior TNFi	1.00	0.77	1.29	0.99	0.92	0.71	1.20	0.55
Number of prior other b/tsDMARDs	1.14	0.98	1.32	0.09	1.18	1.00	1.38	0.049
Corticosteroid dose<10 mg/d (vs 0 mg/d)	1.39	0.95	2.04	0.09	1.29	0.86	1.95	0.22
Corticosteroid dose≥10 mg/d (vs 0 mg/d)	1.56	0.85	2.86	0.15	1.35	0.72	2.53	0.35
Age 50–64 years (vs.<50 years)	1.93	0.73	5.14	0.19				
Age 65–74 years (vs.<50 years)	3.21	1.17	8.85	0.02	1.65	1.05	2.58	0.03
Age≥75 years (vs.<50 years)	6.78	2.43	18.95	< 0.01	3.40	2.08	5.55	< 0.01
Male sex (vs female sex)	1.74	1.19	2.55	< 0.01	1.73	1.16	2.59	0.01
Log CRP (per point)	1.21	1.03	1.43	0.02	1.23	1.03	1.46	0.02
% of full physical function (per 10%)	0.96	0.87	1.06	0.43	0.94	0.85	1.04	0.22
CDAI≥22 (vs.<22)	0.95	0.64	1.42	0.81	0.88	0.59	1.31	0.53
Number of cardiovascular comorbidities*	1.58	1.38	1.80	< 0.01	1.45	1.23	1.70	< 0.01
Current smokers (vs non-smokers)†	2.12	1.39	3.24	< 0.01	0.94	0.59	1.49	0.78
Enrolling institution: rheumatology clinic (vs private praxis)	1.24	0.80	1.93	0.33	1.30	0.82	2.06	0.27
(III) Cox proportional hazard model‡								
Reference: TNFi	1.00				1.00			
JAKi	0.96	0.49	1.91	0.92	0.79	0.38	1.64	0.54
Other bDMARDs	0.72	0.35	1.51	0.38	0.82	0.40	1.71	0.61
csDMARDs	1.82	1.00	3.29	0.049	1.55	0.85	2.82	0.16

In the Andersen-Gill model inverse probability weighting was applied and sensitivity analysis (I) was additionally adjusted for prior DMARD treatments. In sensitivity analysis (II), all covariates used of inverse probability of treatment weights were additionally added to the regression model.
*Comprises hypertension, coronary heart disease, diabetes mellitus, hyperlipoproteinemia, stroke and obesity.
†Comprises never smokers, previous smokers and patients with missing smoking status.
‡Patients were censored at first event or therapy switch.
bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; JAKi, Janus kinase inhibitor; LCL, lower confidence limit; RR, relative risk; TNFi, tumour necrosis factor inhibitor; UCL, upper confidence limit.

upadacitinib (n=768) are reported in online supplemental table S2. Mean age and disease duration were comparable. Patients with upadacitinib were more often male and had a markedly shorter time on treatment (9.8±6.2 months), compared with tofacitinib (18.1±13.9) and baricitinib (19.2±15.1), caused by the later marketing authorisation.

A total of 34 MACE events occurred during JAKi therapy, 18 assigned to tofacitinib (IR 0.98 (95% CI 0.58 to 1.55)), 12 to baricitinib (0.49 (0.25 to 0.85)) and four

Table 4 Crude incidence rates per 100 patient years and HRs of major adverse cardiovascular events stratified by Janus kinase inhibitors

	Overall patients					Cardiovascular risk patients				
	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)	HR* (95% CI)	Number of treatment episodes	Patient years of follow-up	Number of events	Incidence rate (95% CI)	HR* (95% CI)
Baricitinib	1416	2460.17	12	0.49 (0.25 to 0.85)	0.58 (0.26 to 1.26)	862	1543.25	11	0.71 (0.36 to 1.28)	0.54 (0.24 to 1.22)
Tofacitinib	1126	1836.92	18	0.98 (0.58 to 1.55)	1.36 (0.70 to 2.63)	671	1145.75	14	1.22 (0.67 to 2.05)	1.04 (0.48 to 2.23)
Upadacitinib	768	750.67	4	0.53 (0.15 to 1.36)	NR	459	469.50	4	0.85 (0.23 to 2.18)	NR

*HR of major adverse cardiovascular events were estimated from the Andersen-Gill model applying inverse probability weighting. In all Andersen-Gill models, the number of previous DMARD substances was used as covariate in addition to the treatment effect due to exceeding the mean standardised difference threshold. Tumour necrosis factor inhibitors were selected as reference category.
DMARD, biologic disease-modifying antirheumatic drug; NR, not reported due to a low number of events.

to upadacitinib (0.53 (0.15 to 1.36)) in overall patients (table 4). The majority of events occurred in cardiovascular risk patients (29/34) with numerically lower IR for baricitinib (0.71 (0.36 to 1.28)) and upadacitinib (0.85 (0.23 to 2.18)) compared with tofacitinib (1.22 (0.67 to 2.05)). HRs for MACE with TNFi as reference were 0.58 (0.26 to 1.26) for baricitinib and 1.36 (0.70 to 2.63) for tofacitinib in overall patients. In cardiovascular risk patients, HRs for MACE were 0.54 (0.24 to 1.22) for baricitinib and 1.04 (0.48 to 2.23) for tofacitinib.

DISCUSSION

This analysis of the German observational RABBIT register included more than 14 000 real-world treatment episodes with JAKi, TNFi, other bDMARDs and csDMARDs started between 2017 and 2022 from approximately 8000 RA patients. The results provide real-world evidence that the incidence of MACE in patients with RA is not increased with JAKi therapy compared with TNFi, and that the hazard of MACE is also not increased. Our findings apply equally to patients with existing cardiovascular risk factors, who were selected from the study cohort in intentional adaption to the eligibility criteria of the ORAL Surveillance trial.

The randomised ORAL Surveillance safety trial included 4362 patients with active RA aged 50 years or older with at least one cardiovascular risk factor.[20] They were randomised to receive either 5 mg or 10 mg tofacitinib two times per day or a TNFi, either adalimumab (North America) or etanercept (rest of the world). The HR of MACE was non-significantly higher for tofacitinib at a dose of 5 mg two times per day compared with TNFi (HR 1.24 (95% CI 0.81 to 1.91)) but did not meet the non-inferiority criteria defined in the study design as an upper confidence limit of less than 1.8.

The safety trial's IR for the group receiving tofacitinib 5 mg two times per day, which is the recommended dose in Germany, was the same as for the JAKi group in our analysis—both 0.9/100 PY. Looking at baseline characteristics, it is obvious that cardiovascular risk patients in our analysis are a highly selected group with many risk factors. Their proportions are often even higher in real-world practice than reported in the safety trial, for example, for male gender, age ≥65 years and comorbidities such as hypertension, coronary heart disease and diabetes. Obesity, however, was more common in safety trial patients than in RABBIT patients (42% vs 32–35%).

The adjusted relative risk measured as HR in our observational data was 0.74 (0.41 to 1.31) for cardiovascular risk patients and, thus, lower than in the safety trial. The ORAL Surveillance trial recruited patients from more than 30 countries, and, therefore, regional and ethnic inequalities that translate into different risk profiles may not have been fully adjusted for. Only 3% of the ORAL Surveillance study population (n=147 patients) were recruited in Europe, the portion of German patients is not available. Therefore, a one-to-one transfer of the trial results to the European or even German RA patient population is questionable. Most of the European countries have a high healthcare quality and universal coverage of a core set of health services, which is not comparable to many other countries in the world.[33 34]

Furthermore, eligibility criteria of ORAL Surveillance were selective and may not correspond to the real-world treatment population. Beyond that, differences in MACE risk between our study and the safety trial may not be explainable by measured and available variables. In the RABBIT study, the treatment decision of the rheumatologist may have been influenced by other factors, for example, family history of CVD or characteristics and burden of the rheumatic disease and is in contrast to a randomisation of treatment.

Moreover, in our study, patients with JAKi had a longer disease duration, more prior therapies and more signs of

consequential damage such as loss of function compared with TNFi. Comorbidities were also more frequent. A higher proportion of high-risk patients is, therefore, subsumed in the JAKi group, which needs to be taken into account when comparing therapy risks, especially since the number of cardiovascular comorbidities showed up as relevant risk factor for MACE in the adjusted models.

A post hoc analysis of ORAL Surveillance identified that high-risk patients, defined as age ≥65 years and current or previous smokers, who received 5 mg or 10 mg tofactinib two times per day have a significant 2.7-fold higher risk of MACE in comparison to TNFi.[35] Other stratifications, eg, by history of CVD or smoking and age separately, showed higher estimates, which did not reach statistical significance.[35 36] In our study, we performed several subgroup analyses, especially to explore the impact of individual cardiovascular risk factors. While IRs clearly showed higher absolute risks in those patients with existing risk factors like male sex, higher age or CVD history, the treatment comparison in the adjusted regression provided no evidence of an effect of DMARD therapy on the risk of MACE. Moreover, in the main analysis and in all the subgroups, the vast majority of events was registered in the cardiovascular risk patient population, implicating no elevated risk in patients not fulfilling the applied selection criteria. As for age, the cut-off of 65 years seems more reasonable as cardiovascular risk factor than the ORAL Surveillance cut-off of 50 years, since in our analysis, IRs doubled in older patients of both groups, overall and cardiovascular risk patients.

Our findings are in line with results from other observational studies and do not support the warnings that were raised based on results of the ORAL surveillance trial.[21] The STAR-RA study, which used data of three US claims databases, showed a numerically increased risk of MACE with tofacitinib versus TNFi in a selected cohort adapted to ORAL surveillance, but not in an unselected cohort of RA patients.[15] French claims data revealed a risk estimate of 1 for baricitinib and tofacitinib together versus adalimumab in an overall and also in a selected population.[17] Within the US CorEvitas register, 5-year IRs for MACE were comparable between patients initiating tofacitinib and bDMARDs, and no increase of the hazard of MACE was observed.[16] In the Swedish ARTIS register, MACE were assessed individually for baricitinib and tofacitinib, and hazards were not increased compared with etanercept, although the evidence for tofacitinib is limited due to the small number of events and PY.[4] The collaborative data analysis of an EU PAS study including 14 data sources with the largest share of patients from ARTIS showed a numerically greater risk for MACE when comparing baricitinib to TNFi.[19]

Stratifying individual JAKi in the overall patient population of our analysis showed a numerically higher risk estimate for tofacitinib compared with TNFi (HR 1.36 (0.70 to 2.63)), but not for baricitinib (0.58 (0.26 to 1.26)). The HR for tofacitinib was lower for patients with cardiovascular risk (1.04 (0.48 to 2.23)). This might be due to the selection by cardiovascular risk factors, which reduces the amount of residual confounding. In the overall cohort, residual confounding, however, might still be present despite adjustment, and it could be partly responsible for the differences seen between substances. Our observation is in contrast to the French claims data, which reported a numerically higher risk for baricitinib versus adalimumab, but not for tofacitinib,[17] and also to the ARTIS register, which showed comparable IRs and HRs for the two JAKi.[4] These discrepancies may be caused by different data sources, study designs including outcome definition and prescription behaviours in the individual countries.

Effective suppression of disease activity is an essential factor in minimising cardiovascular risk.[5] Therapy selection according to current EMA warnings should take into account that if a JAKi is discontinued for precautionary reasons, returning to a less effective therapy may result in increased inflammatory activity and in the additional need for higher dosages of glucocorticoids. Both contribute to higher cardiovascular risk. All results from observational data available up to now, including our register data, do not support a general recommendation to avoid or discontinue JAKi therapy in patients with cardiovascular risk factors. Heterogeneous IRs among individual JAKi need to be further monitored though.

In the JAKi group of our study, we observed an unusual distribution within the composite outcome of MACE with a higher proportion of reported strokes than myocardial infarctions as compared with all other DMARD groups. A comparable distribution of events within the JAKi group was also reported in the ORAL Surveillance trial[20] and by Hoisnard *et al* using French claims data.[17] This unexpected finding needs to be explored further.

Strengths of this study include the large nationwide cohort with data on all available DMARDs in routine care. More than 5000 PY of follow-up with JAKi and the comparison to more than 16000 PY with cs/bDMARDs from the past 5 years considerably contribute to existing safety data. The application of the Anderson-Gill models enabled to adjust for multiple confounders, such as clinical measures of disease activity, disease duration, treatment history, cardiovascular comorbidity and smoking. Anderson-Gill models conveniently extend standard Cox regression analysis to account for recurrent events, using treatment episodes as the unit of observation instead of patients. This is particularly important when investigating JAKi since in the RABBIT register about two-thirds of JAKi patients are switchers coming from other therapies, which is a much higher percentage than in other DMARD classes. Focusing only on the first treatment episode, as in an intention-to-treat analysis, for example, the question of favouring JAKi would arise. However, as it turned out in our data, censoring patients at the first event or treatment switch did not give JAKi an advantage and did not lead to considerable changes in HR. In addition, Andersen-Gill models improve adjustment for time-varying confounding by performing propensity score

adjustment at the beginning of each treatment episode, in contrast to at enrolment into the study, which is the case when using standard Cox models. Compared with standard adjustment, the use of IPW is less susceptible to overfitting due to a small number of events, even in stratified analyses. This is because the adjustment in the propensity score model uses treatment assignment (or dropout) as the outcome. Numbers of the treatment assignment variable are usually much larger than event numbers.

A limitation, however, is that residual confounding may persist, particularly in case of long treatment episodes when the time interval between covariate measurement (at the start of a treatment episode) and potential events is large. In addition, relevant but unmeasured confounders such as family history of CVD and reasons for initiating a DMARD treatment could not be considered. Furthermore, the low number of PY with upadacitinib and filgotinib prevented a robust analysis of all four approved JAKi.

To conclude, the data from RABBIT are comparable with other available observational data and do not confirm the signal of MACE interpreted from the ORAL surveillance trial results. Treatment with JAKi in routine care was not associated with increased risk of MACE, not even in subgroups with higher risk profiles. This study emphasises the value of real-world observational data in providing robust evidence on drug safety. The results should help to cautiously reassure rheumatologists and patients in the joint decision-making process on a therapy start or continuation with JAKi. Further data in the long-term will help us to better classify the safety aspects of individual JAKi and to refine individual risk profiles of patients with RA.

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REFERENCES

1 Avina-Zubieta JA, Thomas J, Sadatsafavi M, *et al*. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012;71:1524–9.
2 Ogdie A, Yu Y, Haynes K, *et al*. Risk of major cardiovascular events in patients with Psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;74:326–32.
3 del Rincón ID, Williams K, Stern MP, *et al*. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737–45.
4 Frisell T, Bower H, Morin M, *et al*. Safety of biological and targeted synthetic disease-modifying Antirheumatic drugs for rheumatoid arthritis as used in clinical practice: results from the ARTIS programme. *Ann Rheum Dis* 2023;82:601–10.
5 Meissner Y, Zink A, Kekow J, *et al*. Impact of disease activity and treatment of Comorbidities on the risk of myocardial infarction in rheumatoid arthritis. *Arthritis Res Ther* 2016;18:183.
6 Ozen G, Pedro S, Michaud K. The risk of cardiovascular events associated with disease-modifying Antirheumatic drugs in rheumatoid arthritis. *J Rheumatol* 2021;48:648–55.

7 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;63:522–9.
8 Singh S, Fumery M, Singh AG, *et al*. Comparative risk of cardiovascular events with biologic and synthetic disease-modifying Antirheumatic drugs in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Arthritis Care & Research* 2020;72:561–76. 10.1002/acr.23875 Available: https://acrjournals.onlinelibrary.wiley.com/toc/21514658/72/4
9 Food & Drug Administration. Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib). 2021. Available: https://www.fda.gov/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis
10 European Medicines Agency. Xeljanz (tofacitinib): initial clinical trial results of increased risk of major adverse cardiovascular events and malignancies (excluding NMSC) with use of tofacitinib relative to TNF— alpha inhibitors. 2021. Available: https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-initial-clinical-trial-results-increased-risk-major-adverse-cardiovascular
11 Giles JT, Sattar N, Gabriel S, *et al*. Cardiovascular safety of Tocilizumab versus Etanercept in rheumatoid arthritis: A randomized controlled trial. *Arthritis Rheumatol* 2020;72:31–40.
12 Taylor PC, Keystone EC, van der Heijde D, *et al*. Baricitinib versus placebo or Adalimumab in rheumatoid arthritis. *N Engl J Med* 2017;376:652–62.
13 Combe B, Kivitz A, Tanaka Y, *et al*. Filgotinib versus placebo or Adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021;80:848–58.
14 Fleischmann RM, Genovese MC, Enejosa JV, *et al*. Safety and effectiveness of Upadacitinib or Adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019;78:1454–62.
15 Khosrow-Khavar F, Kim SC, Lee H, *et al*. Tofacitinib and risk of cardiovascular outcomes: results from the safety of tofacitinib in routine care patients with rheumatoid arthritis (STAR-RA) study. *Ann Rheum Dis* 2022;81:798–804.
16 Kremer JM, Bingham CO III, Cappelli LC, *et al*. Postapproval comparative safety study of tofacitinib and biological disease-modifying Antirheumatic drugs: 5-year results from a United States-based rheumatoid arthritis Registry. *ACR Open Rheumatology* 2021;3:173–84. 10.1002/acr2.11232 Available: https://acrjournals.onlinelibrary.wiley.com/toc/25785745/3/3
17 Hoisnard L, Pina Vegas L, Dray-Spira R, *et al*. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus Adalimumab: a nationwide cohort study. *Ann Rheum Dis* 2023;82:182–8.
18 Montastruc F, Flumian C, Degboe Y, *et al*. Op0268 COMPARISON OF MAJOR CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS IN SAFETY REPORTS BETWEEN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH JAK INHIBITORS VERSUS ANTI-TNF: RESULTS FROM Vigibase. *Ann Rheum Dis* 2022;81:178.
19 Salinas CA, Louder A, Polinski J, *et al*. Evaluation of VTE, MACE, and serious infections among patients with RA treated with Baricitinib compared to Tnfi: A multi-database study of patients in routine care using disease registries and claims databases. *Rheumatol Ther* 2023;10:201–23.
20 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386:316–26.
21 European Medicine Agency. EMA CONFIRMS measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders (EMA/27681/2023). 2023. Available: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki
22 Smolen JS, Landewé RBM, Bergstra SA, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying Antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
23 Richter A, Meißner Y, Strangfeld A, *et al*. Primary and secondary patient data in contrast: the use of observational studies like RABBIT. *Clin Exp Rheumatol* 2016;34(5 Suppl 101):S79–86.
24 Branch SK. Guidelines from the International conference on Harmonisation (ICH). *J Pharm Biomed Anal* 2005;38:798–805.
25 Mann RD, Andrews EB. Pharmacovigilance. In: *Medical Dictionary for Regulatory Activities (MedDRA®)*. Pharmacovigilance: John Wiley & Sons, Ltd, 2006: 168–83.
26 Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol* 1990;131:373–5.
27 Cheung YB, Xu Y, Tan SH, *et al*. Estimation of intervention effects using first or multiple episodes in clinical trials: the Andersen-Gill model re-examined. *Stat Med* 2010;29:328–36.
28 Guo Z, Gill TM, Allore HG. Modeling repeated time-to-event health conditions with discontinuous risk intervals. an example of a longitudinal study of functional disability among older persons. *Methods Inf Med* 2008;47:107–16.
29 Sagara I, Giorgi R, Doumbo OK, *et al*. Modelling recurrent events: comparison of statistical models with continuous and discontinuous risk intervals on recurrent malaria episodes data. *Malar J* 2014;13:293.
30 Andersen PK, Gill RD. Cox's regression model for counting processes: A large sample study. *Ann Statist* 1982;10:1100–20.
31 Lautenschläger J, Mau W, Kohlmann T, *et al*. Comparative evaluation of a German version of the health assessment questionnaire and the Hannover functional capacity questionnaire. *Z Rheumatol* 1997;56:144–55.
32 Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *Journal of the American Statistical Association* 1989;84:1074–8.
33 Access GBDH, Quality Collaborators. Electronic address cue, Access GBDH. Healthcare access and quality index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990-2015: a novel analysis from the global burden of disease study 2015. *Lancet* 2017;390:231–66.
34 OECD/European Union. *Health at a Glance: Europe 2022: State of Health in the EU Cycle*. Paris: OECD Publishing, 5 December 2022.
35 Kristensen LE, Danese S, Yndestad A, *et al*. Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL surveillance. *Ann Rheum Dis* 2023;82:901–10.
36 Charles-Schoeman C, Buch MH, Dougados M, *et al*. Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of Atherosclerotic cardiovascular disease: a post hoc analysis from ORAL surveillance. *Ann Rheum Dis* 2023;82:119–29.