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# 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

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## ABSTRACT

**Objectives** Evaluate risk of major adverse cardiovascular events (MACE) with tofacitinib versus tumour necrosis factor inhibitors (TNFi) in patients with rheumatoid arthritis (RA) with or without a history of atherosclerotic cardiovascular disease (ASCVD) in ORAL Surveillance.

**Methods** Patients with RA aged ≥50 years with ≥1 additional CV risk factor received tofacitinib 5 mg or 10 mg two times per day or TNFi. Hazard ratios (HRs) were evaluated for the overall population and by history of ASCVD (exploratory analysis).

**Results** Risk of MACE, myocardial infarction and sudden cardiac death were increased with tofacitinib versus TNFi in ORAL Surveillance. In patients with history of ASCVD (14.7%; 640/4362), MACE incidence was higher with tofacitinib 5 mg two times per day (8.3%; 17/204) and 10 mg two times per day (7.7%; 17/222) versus TNFi (4.2%; 9/214). HR (combined tofacitinib doses vs TNFi) was 1.98 (95% confidence interval (CI) 0.95 to 4.14; interaction p values: 0.196 (for HR)/0.059 (for incidence rate difference)). In patients without history of ASCVD, MACE HRs for tofacitinib 5 mg two times per day (2.4%; 30/1251) and 10 mg two times per day (2.8%; 34/1234) versus TNFi (2.3%; 28/1237) were, respectively, 1.03 (0.62 to 1.73) and 1.25 (0.76 to 2.07).

**Conclusions** This post hoc analysis observed higher MACE risk with tofacitinib versus TNFi in patients with RA and history of ASCVD. Among patients without history of ASCVD, all with prevalent CV risk factors, MACE risk did not appear different with tofacitinib 5 mg two times per day versus TNFi. Due to the exploratory nature of this analysis and low statistical power, we cannot exclude differential MACE risk for tofacitinib 5 mg two times per day versus TNFi among patients without history of ASCVD, but any absolute risk excess is likely low.

**Trial registration number** NCT02092467.

## INTRODUCTION

Compared with the general population, individuals with rheumatoid arthritis (RA) have a greater risk of cardiovascular (CV) disease.<sup>1,2</sup> This is attributed

## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- ⇒ ORAL Surveillance, which included patients with rheumatoid arthritis (RA) aged ≥50 years with ≥1 additional cardiovascular (CV) risk factor, was the first study to evaluate the safety of Janus kinase inhibitors in a CV risk-enriched RA population.
- ⇒ Primary findings indicated an increased risk of major adverse cardiovascular events (MACE) with tofacitinib versus tumour necrosis factor inhibitors (TNFi) (hazard ratio=1.33; 95% confidence interval (CI) 0.91 to 1.94). The non-inferiority criterion was not met (upper limit of 95% CI was >1.80).<sup>8</sup>
- ⇒ The increased risk of MACE with tofacitinib versus TNFi was more pronounced in patients aged ≥65 years than in patients aged <65 years.<sup>8</sup>
- ⇒ Risk of malignancies (excluding non-melanoma skin cancer) and infections was also higher with tofacitinib versus TNFi in ORAL Surveillance.<sup>8,26</sup>

to RA-associated systemic inflammation and traditional CV risk factors,<sup>2–7</sup> and both require effective control to mitigate the risk. The European Alliance of Associations for Rheumatology (EULAR) recommends regular CV risk assessments in patients with RA using validated risk prediction models.<sup>2</sup>

ORAL Surveillance was a post-authorisation safety study conducted, in part, due to observations of increased serum lipid levels with the Janus kinase inhibitor, tofacitinib.<sup>8–10</sup> The study was the first to evaluate the relative risk of adjudicated major adverse cardiovascular events (MACE) and malignancies with tofacitinib versus tumour necrosis factor inhibitors (TNFi) in patients with RA aged ≥50 years with ≥1 additional CV risk factor. For combined tofacitinib doses (5 mg and 10 mg two times per day) versus TNFi, non-inferiority was not shown for adjudicated MACE (incidence rate (IR) of 0.98 per 100 patient-years, 95% CI 0.79 to 1.19,

**WHAT THIS STUDY ADDS**

- ⇒ This post hoc analysis of ORAL Surveillance shows an increased risk of MACE with tofacitinib 5 mg and 10 mg two times per day versus TNFi that was primarily observed in patients with a history of atherosclerotic cardiovascular disease (ASCVD; ie, history of coronary artery disease, cerebrovascular disease or peripheral artery disease) at baseline.
- ⇒ Risk of MACE did not appear different with tofacitinib 5 mg two times per day versus TNFi in patients without a history of ASCVD; but, given the exploratory nature of the analysis and the low event rate, we cannot rule out an increased risk of MACE in patients with several CV risk factors.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

- ⇒ This exploratory analysis of MACE in ORAL Surveillance underscores the value of including patients with a history of ASCVD for appropriate risk enhancement when investigating CV safety of RA treatments.
- ⇒ Our findings emphasise the importance of rheumatologists assessing overall CV risk, including medical history of ASCVD, when considering tofacitinib as a treatment for patients with RA.

versus IR of 0.73 per 100 patient-years, 95% CI 0.52 to 1.01; hazard ratio (HR)=1.33, 95% CI 0.91 to 1.94).<sup>8</sup> For context, in the ENTRACTE study of patients with RA aged ≥50 years with ≥1 CV risk factor, rates of MACE per 100 patient-years were 1.70 with etanercept and 1.82 with tocilizumab.<sup>11</sup>

ORAL Surveillance included patients with RA and other risk factors that impact absolute risk of MACE,<sup>8</sup> and this CV-risk enriched population likely reflected a spectrum of CV risk. Guidelines on CV disease prevention distinguish between patients with or without atherosclerotic CV disease (ASCVD).<sup>12</sup> ASCVD includes a history of coronary artery disease (CAD), which was one of the eligibility criteria for the study, but also cerebrovascular disease (CeVD) and peripheral artery disease (PAD) (table 1).<sup>12 13</sup> Patients with ASCVD are generally considered to have high to very high absolute risk of MACE.<sup>12</sup> In recent CV outcome trials of patients with type 2 diabetes, MACE IRs in placebo-treated patients with ASCVD were 4.0–6.5 per 100 patient-years, compared with 1.3–3.3 per 100 patient-years, in patients without ASCVD but with multiple CV risk factors.<sup>14</sup> Here, we further evaluate risk of MACE with tofacitinib versus TNFi in the ORAL Surveillance overall population, and in patients with or without a history of ASCVD.

**METHODS****Study design and patients**

ORAL Surveillance (NCT02092467) was a phase IIIb/IV randomised, open-label, non-inferiority, safety endpoint study conducted from March 2014 to July 2020 in patients with active moderate-to-severe RA despite methotrexate treatment who were aged ≥50 years with ≥1 additional CV risk factor (current smoking, hypertension, high-density lipoprotein cholesterol (HDL-c) <40 mg/dL, diabetes mellitus, family history of premature coronary heart disease (CHD), RA-associated extra-articular disease and/or history of CAD).<sup>8</sup>

Patients were randomised 1:1:1 to receive oral tofacitinib 5 mg or 10 mg two times per day, or subcutaneous TNFi (adalimumab 40 mg every 2 weeks (North America) or etanercept 50 mg once weekly (rest of the world)). All patients continued their prestudy stable dose of methotrexate unless modification was clinically indicated. In February 2019, the tofacitinib 10 mg two-times-per-day dose was reduced to 5 mg two times per day after the Data Safety Monitoring Board noted an increased frequency of pulmonary embolism in patients receiving tofacitinib 10 mg two times per day versus TNFi and an increase in overall mortality with tofacitinib 10 mg versus 5 mg two times per day and TNFi.

**Evaluation of history of ASCVD and baseline CV risk**

A history of ASCVD was defined as the composite of history of CAD, CeVD and PAD. A history of CAD was an eligibility criterion in ORAL Surveillance (reported as ≥one of history of myocardial infarction (MI), unstable angina, stable angina pectoris, coronary artery procedures or other CHD).<sup>8</sup> A history of CeVD (including ischaemic stroke and transient ischaemic attack) and PAD was identified in patients' general medical history through Medical Dictionary for Regulatory Activities' preferred terms (online supplemental table 1).

In patients without a history of ASCVD, 10-year risk of events associated with ASCVD (ie, MACE) was calculated by ASCVD-Pooled Cohort Equations (ASCVD-PCE).<sup>15</sup> Scores were calculated based on patients' baseline age, sex, race (white/black/other), smoking status (yes/no), systolic blood pressure, anti-hypertensive treatment (yes/no), total cholesterol, HDL-c and diabetes (yes/no). In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD-PCE scores.<sup>2</sup> Based on the resulting scores, and as suggested by the American College of Cardiology/American Heart Association,<sup>16</sup> patients without a history of ASCVD were assigned to the following 10-year risk categories: high (≥20%), intermediate (≥7.5–<20%), borderline (≥5–<7.5%) and low (<5%).

**Outcomes**

MACE and its components were based on adjudicated events assessed by an external, independent adjudication committee.

**Table 1** ASCVD is defined based on events, diagnoses and procedures associated with atherosclerosis in arteries of the heart, head and neck and the periphery

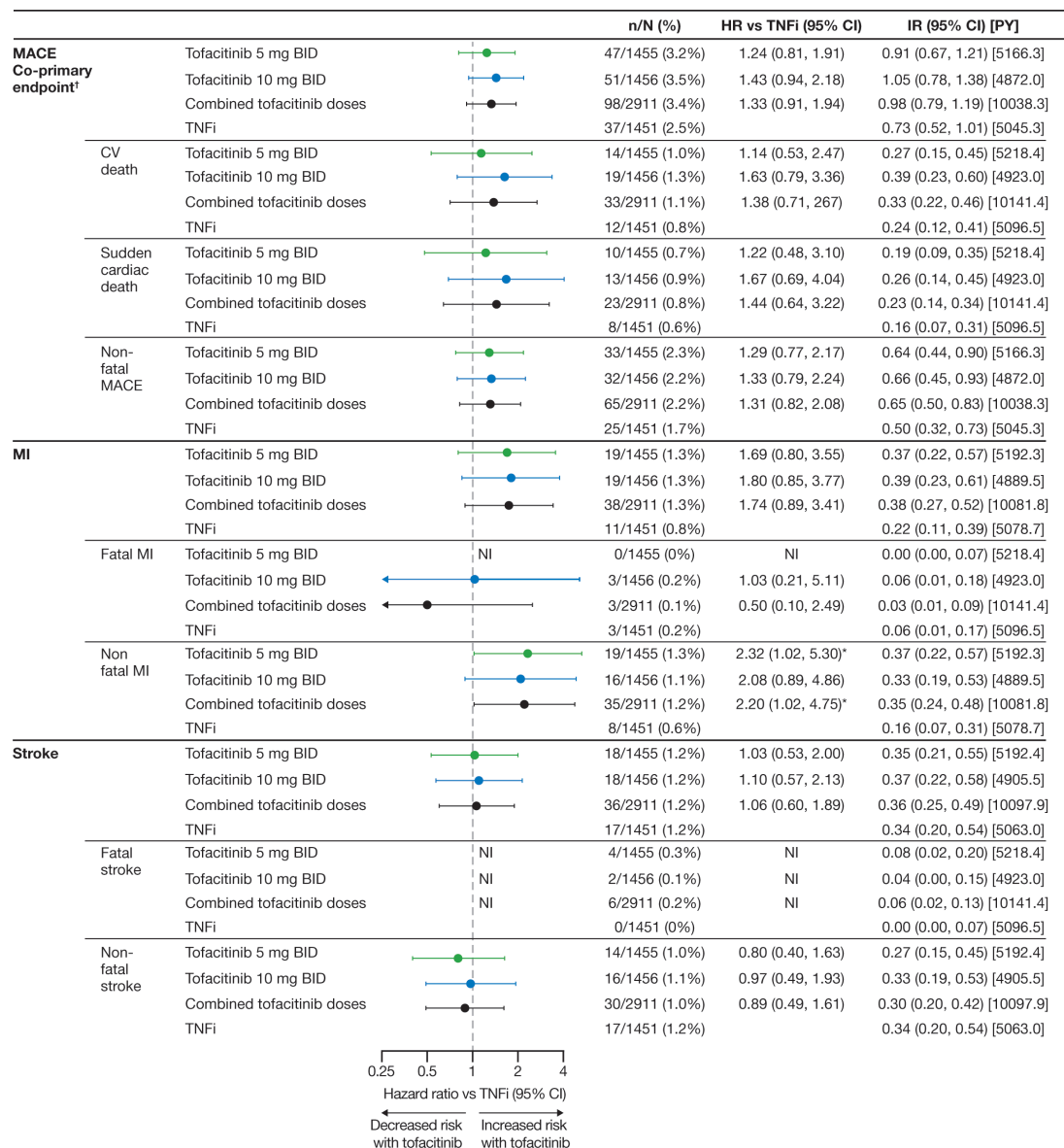
Group	Events	Diagnoses	Procedures
CAD	MI; unstable angina	CHD; stable angina pectoris	Coronary artery revascularisation; coronary artery bypass grafting
CeVD	Ischaemic stroke; transient ischaemic attack	Carotid artery stenosis; carotid atherosclerosis	Carotid endarterectomy
PAD	Peripheral artery thrombosis	Aortic atherosclerosis; intermittent claudication	Peripheral artery angioplasty

Events, diagnoses and procedures mentioned are examples, the list is not exhaustive. A complete list of terms used to define history of ASCVD in the present study is shown in online supplemental table 1.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; MI, myocardial infarction; PAD, peripheral artery disease.

**Table 2** Demographic and baseline disease characteristics in the ORAL Surveillance overall population and in patients with and without a history of ASCVD

	Overall		History of ASCVD			No history of ASCVD			
	Tofacitinib 5 mg two times per day (N=1455)	Tofacitinib 10 mg two times per day (N=1456)	TNFi (N=1451)	Tofacitinib 5 mg two times per day (N=204)	Tofacitinib 10 mg two times per day (N=222)	TNFi (N=214)	Tofacitinib 5 mg two times per day (N=1251)	Tofacitinib 10 mg two times per day (N=1234)	TNFi (N=1237)
Age (years), mean (SD)	60.8 (6.8)	61.4 (7.1)	61.3 (7.5)	63.2 (7.1)	64.7 (7.5)	65.6 (7.8)	60.4 (6.7)	60.8 (6.8)	60.6 (7.2)
Median (range)	60 (50–86)	61 (50–85)	60 (50–88)	62 (50–83)	64 (50–82)	66 (50–88)	60 (50–86)	60 (50–85)	60 (50–87)
≥65 years, n (%)	413 (28.4)	478 (32.8)	462 (31.8)	84 (41.2)	109 (49.1)	113 (52.8)	329 (26.3)	369 (29.9)	349 (28.2)
Female sex, n (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	141 (69.1)	143 (64.4)	139 (65.0)	1028 (82.2)	981 (79.5)	978 (79.1)
History of ASCVD, n (%)	204 (14.0)	222 (15.2)	214 (14.7)	204 (100)	222 (100)	214 (100)	–	–	–
History of CAD	161 (11.1)	172 (11.8)	164 (11.3)	161 (78.9)	172 (77.5)	164 (76.6)	–	–	–
History of CeVD	41 (2.8)	49 (3.4)	31 (2.1)	41 (20.1)	49 (22.1)	31 (14.5)	–	–	–
History of PAD	15 (1.0)	20 (1.4)	35 (2.4)	15 (7.4)	20 (9.0)	35 (16.4)	–	–	–
10-year risk of MACE, n (%)*									
High (≥20%)	258 (17.7)	289 (19.8)	278 (19.2)	–	–	–	258 (20.6)	289 (23.4)	278 (22.5)
Intermediate (≥7.5–<20%)	472 (32.4)	490 (33.7)	483 (33.3)	–	–	–	472 (37.7)	490 (39.7)	483 (39.0)
Borderline (≥5–<7.5%)	198 (13.6)	169 (11.6)	153 (10.5)	–	–	–	198 (15.8)	169 (13.7)	153 (12.4)
Low (<5%)	306 (21.0)	268 (18.4)	308 (21.2)	–	–	–	306 (24.5)	268 (21.7)	308 (24.9)
Smoking status, n (%)									
Current smoker	411 (28.2)	402 (27.6)	353 (24.3)	54 (26.5)	58 (26.1)	56 (26.2)	357 (28.5)	344 (27.9)	297 (24.0)
Past smoker	309 (21.2)	302 (20.7)	326 (22.5)	71 (34.8)	77 (34.7)	78 (36.4)	238 (19.0)	225 (18.2)	248 (20.0)
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)	79 (38.7)	87 (39.2)	80 (37.4)	656 (52.4)	665 (53.9)	692 (55.9)
History of diabetes mellitus, n (%)	243 (16.7)	261 (17.9)	255 (17.6)	53 (26.0)	51 (23.0)	52 (24.3)	190 (15.2)	210 (17.0)	203 (16.4)
History of hypertension, n (%)	955 (65.6)	954 (65.5)	969 (66.8)	156 (76.5)	181 (81.5)	168 (78.5)	799 (63.9)	773 (62.6)	801 (64.8)
History of hyperlipidaemia, n (%)	525 (36.1)	518 (35.6)	491 (33.8)	120 (58.8)	143 (64.4)	117 (54.7)	405 (32.4)	375 (30.4)	374 (30.2)
Family history of CHD, n (%)									
First-degree male relative <55 years	154 (10.6)	132 (9.1)	151 (10.4)	27 (13.2)	29 (13.1)	25 (11.7)	127 (10.2)	103 (8.3)	126 (10.2)
First-degree female relative <65 years	115 (7.9)	107 (7.3)	100 (6.9)	19 (9.3)	23 (10.4)	19 (8.9)	96 (7.7)	84 (6.8)	81 (6.5)
Baseline corticosteroids, n (%) <sup>†</sup>	836 (57.5)	829 (56.9)	830 (57.2)	106 (52.0)	137 (61.7)	116 (54.2)	730 (58.4)	692 (56.1)	714 (57.7)
Baseline antiplatelets including aspirin, n (%) <sup>†</sup>	226 (15.5)	244 (16.8)	237 (16.3)	110 (53.9)	124 (55.9)	107 (50.0)	116 (9.3)	120 (9.7)	130 (10.5)
Baseline statins, n (%) <sup>†</sup>	349 (24.0)	350 (24.0)	321 (22.1)	107 (52.5)	127 (57.2)	105 (49.1)	242 (19.3)	223 (18.1)	216 (17.5)
Prior use of TNFi, n (%)	115 (7.9)	110 (7.6)	105 (7.2)	15 (7.4)	15 (6.8)	14 (6.5)	100 (8.0)	95 (7.7)	91 (7.4)
For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group.									
* A 10-year risk of MACE was calculated with the ASCVD-PCE calculator and a 1.5 multiplier was applied for RA, as recommended by EULAR. <sup>2,15</sup> In the tofacitinib 5 mg two-times-per-day, tofacitinib 10 mg two-times-per-day and TNFi groups, there were 17 patients (1.2%), 18 patients (1.2%) and 15 patients (1.0%) without a history of ASCVD who had missing ASCVD-PCE scores due to missing components.									
<sup>†</sup> Based on day 1 of treatment with tofacitinib or TNFi in ORAL Surveillance.									
ASCVD, atherosclerotic cardiovascular disease; ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHD, coronary heart disease; EULAR, European Alliance of Associations for Rheumatology; MACE, major adverse cardiovascular events; n, number of patients with characteristic; N, number of patients in the safety population; PAD, peripheral artery disease; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.									



**Figure 1** Adjudicated MACE outcomes with tofacitinib versus TNFi in ORAL Surveillance. HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi, and the other for comparing tofacitinib 5 mg and 10 mg two times per day vs TNFi), with treatment as the only covariate. HRs and 95% CIs were NI when the total number of patients with events was  $\leq 2$  for the corresponding pair of treatments in the comparison or when one of the treatments in the comparison had 0 events. IRs express number of patients with first events per 100 PY. <sup>†</sup>Results reported in Ytterberg *et al*<sup>8</sup> and included for reference. \*HR 95% CI excludes 1. BID, two times per day; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; NI, non-informative; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

MACE was defined as the composite of CV death (ie, death due to MI, stroke, sudden cardiac death, heart failure, CV procedures, CV haemorrhage and other CV causes, but not death due to pulmonary embolism), non-fatal MI and non-fatal stroke (including reversible focal neurological defects with imaging evidence of a new cerebral lesion consistent with ischaemia or haemorrhage).

### Statistical analyses

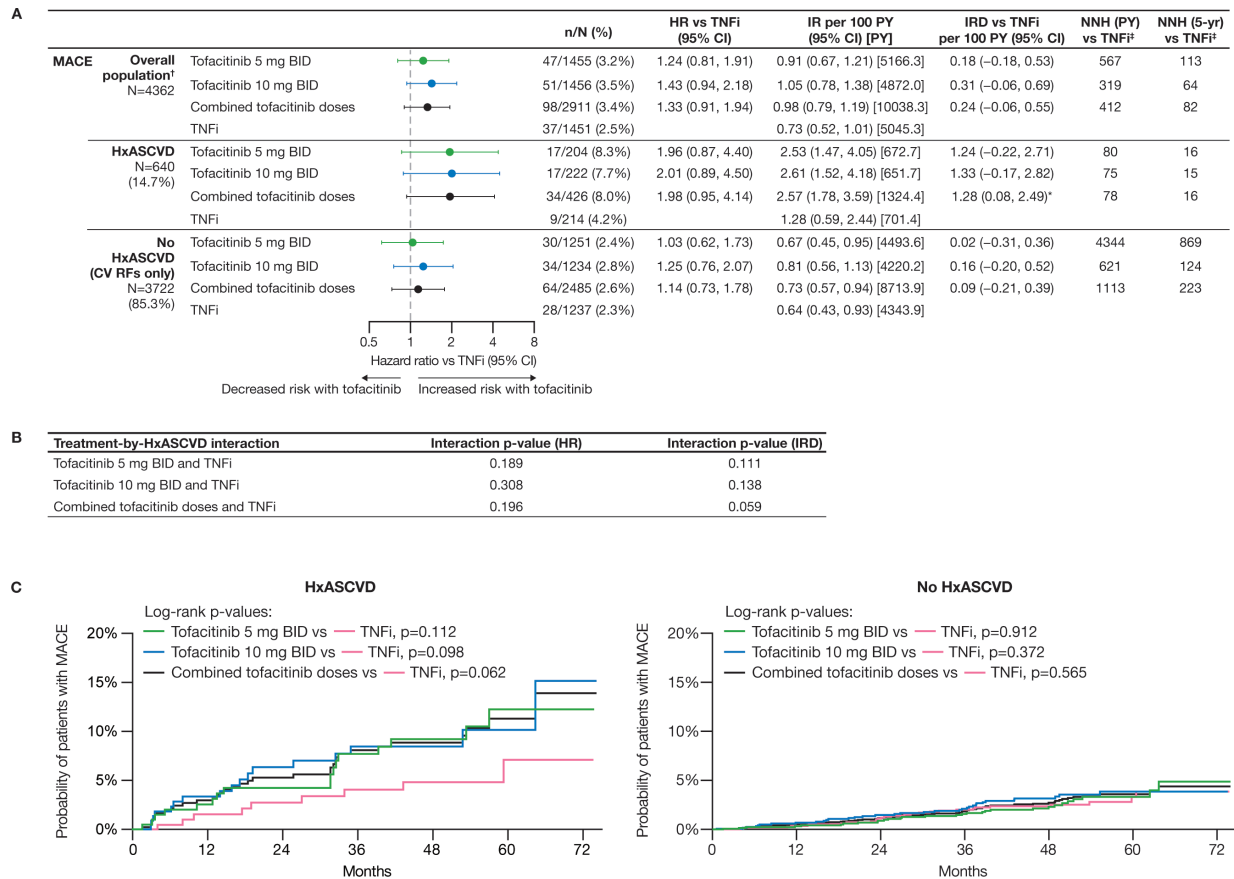
Outcomes were analysed using the safety analysis set, which included all randomised patients receiving  $\geq 1$  dose of study drug. For patients randomised to tofacitinib 10 mg two times

per day who had their dose reduced to 5 mg two times per day in February 2019, the data collected after the dose switch were counted in the tofacitinib 10 mg two-times-per-day group.

CV events were counted within the predefined risk period, based on 60-day on-treatment time, defined as time from first to last study dose +60 days or to last contact date (if a patient died, last contact date was death date), whichever was earliest. Patients without events were censored at the end of the risk period.

Crude IRs were expressed as the number of patients with first events per 100 patient-years, along with two-sided 95% CIs using the exact Poisson method.<sup>17</sup> HRs and two-sided 95% CIs for pairwise comparisons among treatment groups (tofacitinib





**Figure 2** Risk of MACE with tofacitinib versus TNFi by history of ASCVD. (A) HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses versus TNFi, and the other for comparing tofacitinib 5 mg and 10 mg two times per day vs TNFi), with treatment as the only covariate. IRs express number of patients with first events per 100 PY. NNH (PY) should be interpreted as the number of PY of exposure to tofacitinib required to have one additional MACE versus TNFi. NNH (5-year) should be interpreted as the number of patients who would need to be treated for that duration with tofacitinib rather than with a TNFi to result in one additional MACE. \*IRD 95% CI excluded 0. <sup>†</sup>Results reported in Ytterberg *et al*<sup>8</sup> and included for reference. <sup>‡</sup>NNH 95% CIs are reported in online supplemental table 2. (B) Treatment-by-HxASCVD interaction p values for HRs ( $\chi^2$  test with 1 degree of freedom) and IRD (2-sided, normal approximation of difference in IR). See supplementary material for details. (C) Cumulative probability of patients with adjudicated MACE events, calculated based on the Kaplan-Meier estimate, in patients with history of ASCVD (left panel) and without history of ASCVD (right panel). HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. BID, two times per day; CI, confidence interval; CV RF, cardiovascular risk factor; HR, hazard ratio; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; IRD, incidence rate difference; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; NNH, number needed to harm; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

doses vs TNFi) were estimated using Cox proportional hazard regression models.

Subgroup analyses were conducted to assess for an association between history of ASCVD or baseline risk of MACE (ie, categories of CV risk in patients without history of ASCVD) with risk (HRs and IRs) of MACE, MI and stroke with tofacitinib versus TNFi. Across these exploratory analyses, no multiplicity adjustments were applied. Statistical analyses of treatment by history of ASCVD interactions are described in the online supplemental material.

The number needed to harm (NNH) was calculated as the reciprocal of the difference in IRs between tofacitinib and TNFi.<sup>18</sup> Positive NNH was defined as patient-years of tofacitinib exposure needed for one more patient to report an additional event versus TNFi. Negative NNH was defined as the reverse. When the 95%CI of the IR difference includes 0, the 95%CI of the NNH has 2 disjoint (positive and negative) intervals, implying harm in either tofacitinib versus TNFi (positive) or

TNFi versus tofacitinib (negative). NNH for patients exposed for 5 years was calculated by dividing the number of patient-years needed to harm by 5.

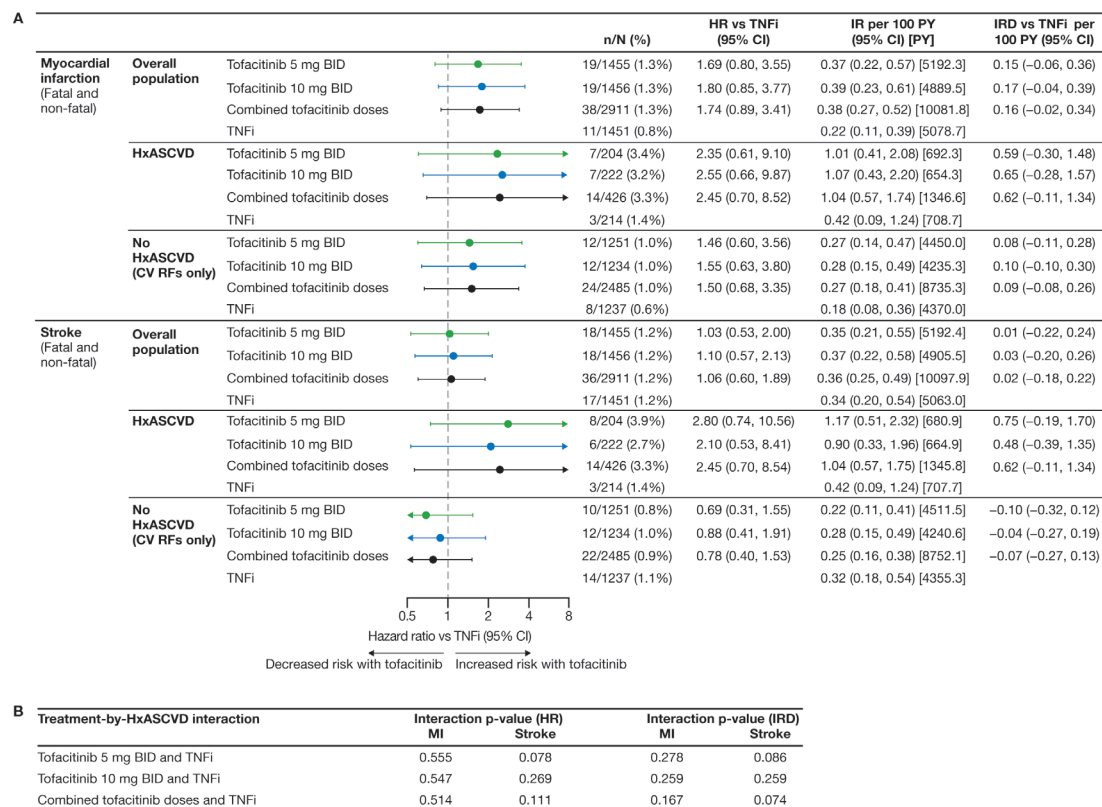
## Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

## RESULTS

### Patients

In total, 4362 patients were randomised and treated (tofacitinib 5 mg two times per day, n=1455; tofacitinib 10 mg two times per day, n=1456; TNFi, n=1451). Median follow-up was 4.0 years; 3111/4362 (71.3%) patients completed the trial and 2745/4362 (62.9%) completed trial treatment.<sup>8</sup> Full patient demographics and baseline disease characteristics are described elsewhere.<sup>8</sup> Table 2 summarises



**Figure 3** Risk of MI and stroke with tofacitinib versus TNFi by history of ASCVD. (A) HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi, and the other for comparing tofacitinib 5 mg and 10 mg two times per day vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY. (B) Treatment-by-HxASCVD interaction p values for HRs ( $\chi^2$  test with 1 degree of freedom) and IRD (two-sided, normal approximation of difference in IR). See supplementary material for details. BID, two times per day; CI, confidence interval; CV RF, cardiovascular risk factor; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; IRD, incidence rate difference; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

CV risk factors and the CV risk profile (online supplemental figure 1) of the study population versus patients with and without a history of ASCVD. These were well-balanced across treatment groups in ORAL Surveillance; 14.7% (640/4362) of patients had a history of ASCVD. Patients with a history of ASCVD were more likely to be  $\geq 65$  years, male, past smokers and have a history of diabetes mellitus, hypertension or hyperlipidaemia, compared with those with no history of ASCVD (table 2).

#### Risk of adjudicated MACE outcomes with tofacitinib versus TNFi in ORAL Surveillance

Risk of MACE, MI and sudden cardiac death were increased with both tofacitinib doses versus TNFi as reflected by HRs  $> 1.0$  and higher IRs (figure 1 and online supplemental figure 2). Risk of non-fatal MI with tofacitinib 5 mg two times per day versus TNFi was noticeably increased (HR=2.32; 95% CI 1.02 to 5.30; figure 1). Stroke HRs and IRs across treatment groups are shown in figure 1 and online supplemental figure 2.

Across treatment groups, the most frequent cause of CV death was sudden cardiac death (figure 1). One patient had fatal heart failure (tofacitinib 10 mg two times per day), and one died of other CV causes (TNFi).

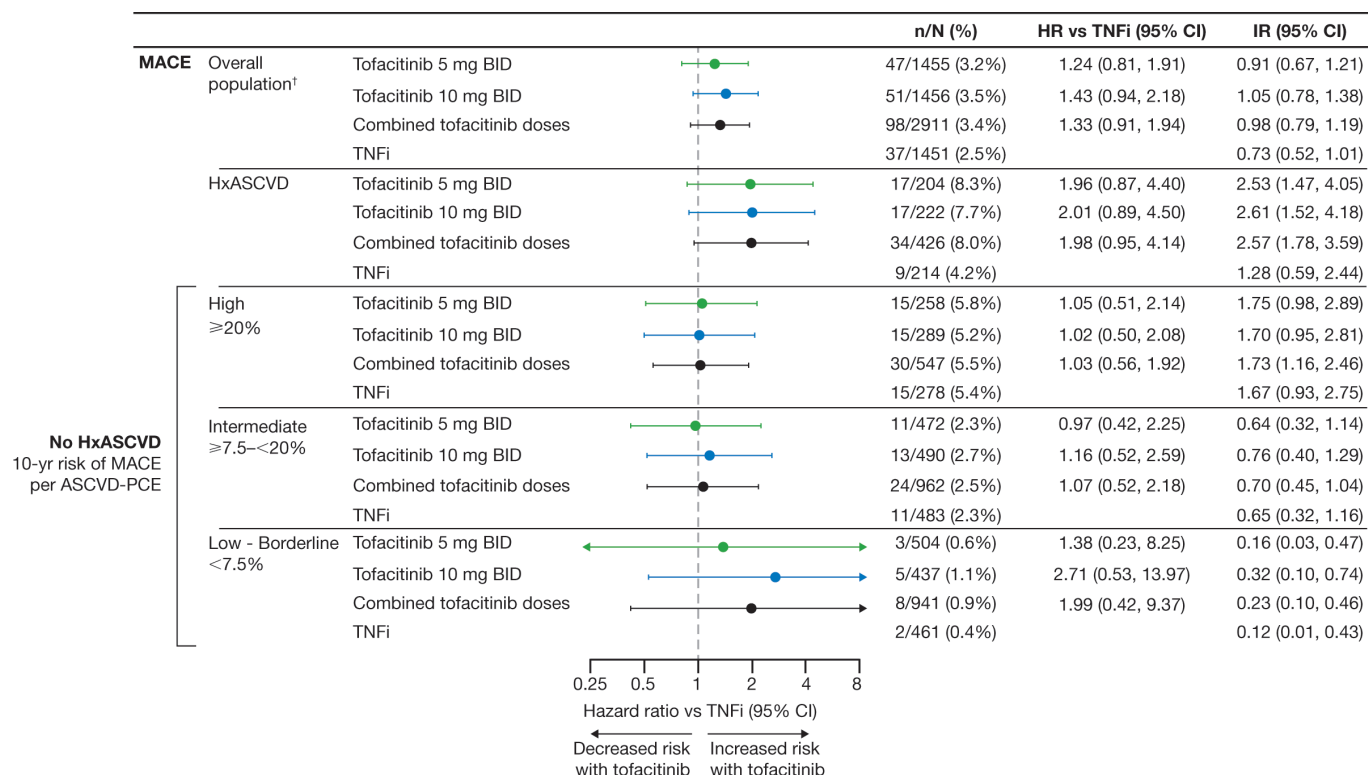
HRs for MACE with tofacitinib versus TNFi in a total time analysis, including all events up to last contact date regardless

of when study drug was discontinued, were consistent with the primary analysis (online supplemental figure 3). MACE IRs by 6-month intervals are shown in online supplemental figure 4.

#### Risk of MACE with tofacitinib versus TNFi according to a history of ASCVD

Among patients with a history of ASCVD, MACE was reported in 17/204 (8.3%), 17/222 (7.7%) and 9/214 (4.2%) of patients in the tofacitinib 5 mg two-times-per-day, tofacitinib 10 mg two-times-per-day and TNFi treatment groups, respectively. MACE HRs (95% CI) were 1.96 (0.87 to 4.40) for tofacitinib 5 mg two times per day versus TNFi, 2.01 (0.89 to 4.50) for tofacitinib 10 mg two times per day versus TNFi and 1.98 (0.95 to 4.14) for combined tofacitinib doses versus TNFi (figure 2A and online supplemental figure 5). Based on the IR differences, this corresponds to NNH of 16 (95% CI  $-\infty$  to  $-91$  and  $7$  to  $\infty$ ) and 15 (95% CI  $-\infty$  to  $-117$  and  $7$  to  $\infty$ ) patients who would need to be treated with tofacitinib 5 mg and 10 mg two times per day, respectively, versus TNFi, over 5 years to have 1 additional MACE (figure 2A; online supplemental table 2).

In patients without a history of ASCVD but with CV risk factors, MACE was reported in 30/1251 (2.4%), 34/1234 (2.8%) and 28/1237 (2.3%), in the tofacitinib 5 mg two-times-per-day, tofacitinib 10 mg two-times-per-day and TNFi treatment groups, respectively (figure 2A). HRs (95% CI) for MACE were 1.03 (0.62 to 1.73) for tofacitinib 5 mg two times per day versus TNFi,



**Figure 4** Risk of MACE with tofacitinib versus TNFi in patients without a history of ASCVD, according to CV risk categories. HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. Patients without HxASCVD were categorised according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD-PCE scores.<sup>2</sup> Because of missing ASCVD-PCE score, two MACE could not be associated with baseline CV risk (n=1 (MI) in the tofacitinib 5 mg two-times-per-day group and n=1 (stroke) in the tofacitinib 10 mg two-times-per-day group). For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi, and the other for comparing tofacitinib 5 mg and 10 mg two times per day vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY. †Results reported in Ytterberg *et al*<sup>8</sup> and included for reference. ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, two times per day; CI, confidence interval; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

1.25 (0.76 to 2.07) for tofacitinib 10 mg two times per day versus TNFi and 1.14 (0.73 to 1.78) for combined tofacitinib doses versus TNFi (figure 2A and online supplemental figure 5). Based on the IR differences, this corresponds to NNH of 869 (95% CI –∞ to –64 and 55 to ∞) and 124 (95% CI –∞ to –100 and 38 to ∞) patients who would need to be treated with tofacitinib 5 mg and 10 mg two times per day, respectively, versus TNFi, over 5 years to have 1 additional MACE (figure 2A; online supplemental table 2). P values for the treatment by history of ASCVD interaction (combined tofacitinib doses vs TNFi) for MACE were 0.196 for the HRs and 0.059 for the IR difference (figure 2B).

Kaplan-Meier curves for MACE (figure 2C) indicated separation between the tofacitinib and TNFi groups by month 3 in patients with history of ASCVD, and no separation between treatment groups in patients without history of ASCVD.

#### Risk of MI and stroke with tofacitinib versus TNFi according to history of ASCVD

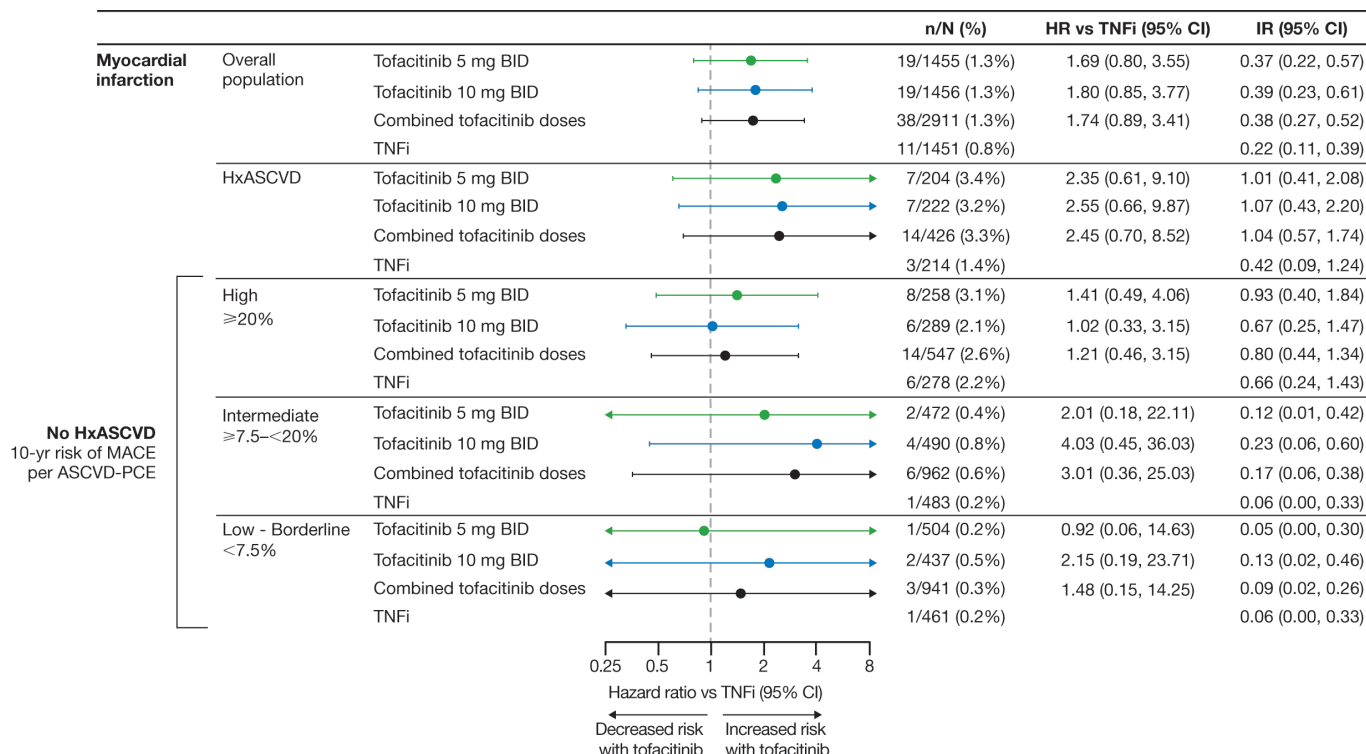
In patients with a history of ASCVD, treatment with tofacitinib 5 mg or 10 mg two times per day was associated with increased risk of MI and stroke versus TNFi (figure 3 and online supplemental figure 5). Risk of MI was also increased with tofacitinib versus TNFi

in patients without a history of ASCVD (figure 3 and online supplemental figure 5). In the assessment of MI and stroke according to history of ASCVD, the number of events overall was low, and these results should be interpreted with caution.

#### Association between baseline CV risk scores and risk of MACE, MI and stroke with tofacitinib versus TNFi in patients without a history of ASCVD

Patients without a history of ASCVD were grouped by their 10-year risk of MACE.<sup>2</sup> MACE IRs, regardless of treatment group, were highest in patients at high risk (ie, ≥20% 10-year risk of MACE) (figure 4 and online supplemental figure 6). There was no difference in risk of MACE with tofacitinib 5 mg or 10 mg two times per day versus TNFi in patients at high or intermediate risk. While HRs for tofacitinib versus TNFi were >1.0 in patients with low or borderline risk, the number of events was low.

MI IRs were highest in patients with a high CV risk score (figure 5 and online supplemental figure 7). There was an increased risk of MI with tofacitinib 5 mg two times per day versus TNFi in patients with high 10-year risk of MACE. There were fewer MIs reported in the other risk categories.



**Figure 5** Risk of MI with tofacitinib versus TNFi in patients without history of ASCVD, according to CV risk categories. HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. Patients without HxASCVD were categorised according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD-PCE scores.<sup>2</sup> Because of missing ASCVD-PCE score, one MI in the tofacitinib 5 mg two-times-per-day group could not be associated with baseline CV risk. For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi, and the other for comparing tofacitinib 5 and 10 mg two times per day vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY. ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, two times per day; CI, confidence interval; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HR, hazard ratio; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

The association between baseline CV risk and stroke IRs was less apparent than observed for MACE and MI (figure 6 and online supplemental file 8). Overall, event numbers in each risk category were low.

## DISCUSSION

Primary analyses of ORAL Surveillance, which included patients aged ≥50 years with ≥1 additional CV risk factor and was the first study to evaluate tofacitinib safety in a CV risk-enriched RA population, found an increased risk of MACE with tofacitinib versus TNFi.<sup>8</sup> In this post hoc analysis, increased risk of MACE was primarily identified in patients with a history of ASCVD (ie, pre-existing CAD, CeVD or PAD). In patients without a history of ASCVD but with CV risk factors, there did not appear to be a detectable difference in risk of MACE with tofacitinib 5 mg two times per day or the combined tofacitinib doses versus TNFi.

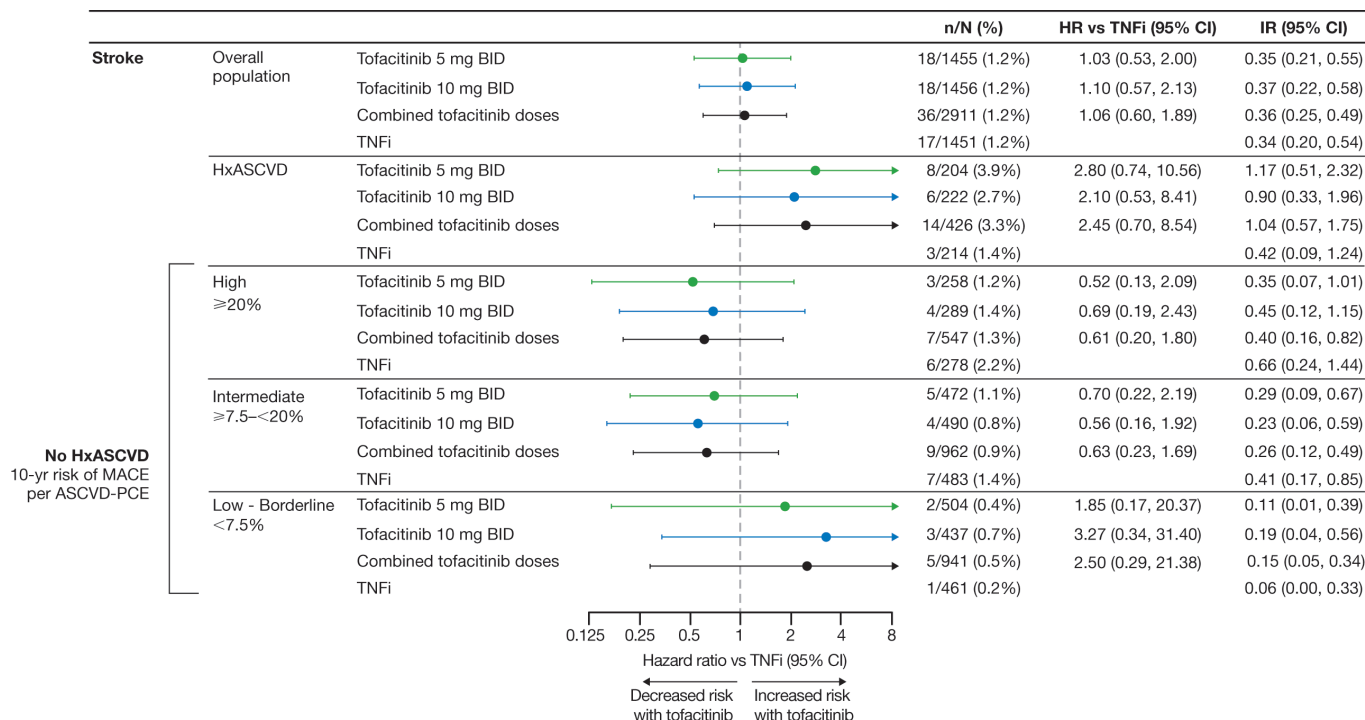
ORAL Surveillance was powered to assess non-inferiority for risk of MACE with combined tofacitinib doses versus TNFi and not powered to compare individual MACE components across treatment groups.<sup>8</sup> The exploratory analyses on CV outcomes and subgroup analyses we provide, therefore, need to be interpreted cautiously and as hypothesis-generating. Notwithstanding, our analysis of the overall study population supplements the primary analysis of the study and shows increased risk of MI and sudden

cardiac death with tofacitinib versus TNFi in this CV risk-enriched population.

Almost 15% of the patients in ORAL Surveillance had a history of ASCVD. In this subgroup, we found increased risk of MACE, MI and stroke with tofacitinib versus TNFi. In the remaining 85% of patients without a history of ASCVD, who nevertheless had CV risk factors, we did not find increased relative risk of MACE with tofacitinib versus TNFi. This observation is supported by our assessment of relative risk across categories of predicted MACE risk; there was no clear difference in risk of MACE in patients without a history of ASCVD who had high (≥20%) or intermediate (≥7.5–<20%) predicted 10-year risk at baseline. Approximately one-third of the ORAL Surveillance population had low or borderline absolute risk of MACE, and the low number of MACE in this group makes assessment of relative risk less certain.

A large observational study that used USA claims data to assess risk of CV outcomes (composite of hospitalisation for MI or stroke) with tofacitinib versus TNFi in patients with RA (Safety of Tofacitinib in Routine care patients with Rheumatoid Arthritis; STAR-RA) was recently published.<sup>19</sup> Evidence for an increased risk of CV outcomes with tofacitinib was not identified in this real-world evidence cohort. However, STAR-RA included a cohort that mirrored ORAL Surveillance inclusion





**Figure 6** Risk of stroke with tofacitinib versus TNFi in patients without a history of ASCVD, according to CV risk categories. HRs are shown on a logarithmic scale. Arrows indicate that the CI extends beyond the graph axis. Patients without history of ASCVD were categorised according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD-PCE scores.<sup>2</sup> Because of missing ASCVD-PCE score, one stroke in the tofacitinib 10 mg two-times-per-day group could not be associated with baseline CV risk. For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses versus TNFi, and the other for comparing tofacitinib 5 mg and 10 mg two times per day vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY. ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, two times per day; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

and exclusion criteria (randomised controlled trial (RCT)-duplicate cohort). The primary outcome of the RCT-duplicate cohort aligned with the increased risk of MACE with tofacitinib versus TNFi observed in ORAL Surveillance (ie, approximately 25% relative risk increase with tofacitinib 5 mg two times per day vs TNFi).<sup>8,19</sup> STAR-RA also prespecified subgroup analyses of patients with or without previous CV disease. These results were also similar to ORAL Surveillance; risk of CV outcomes appeared to be increased with tofacitinib versus TNFi in patients with, but not in those without, pre-existing CV disease.<sup>19</sup>

Our analysis of MACE in ORAL Surveillance underscores the importance of investigating the long-term safety of RA treatments in appropriately designed, prospective, randomised and comparative trials of sufficient size and duration to adequately evaluate safety events of interest, including CV adverse events. Consequently, for ORAL Surveillance to be declared complete, ≥1500 patients had to be followed for 3 years and the study was conducted in a CV risk-enriched population to ensure accumulation of a sufficient number of CV events. To the best of our knowledge, the only similar studies in RA are the ENTRACTE and PRECISION trials that assessed CV safety of tocilizumab versus etanercept and celecoxib versus naproxen versus ibuprofen, respectively.<sup>11,20</sup> In ENTRACTE and PRECISION, 11% (347/3080) and 24% (584/2436) of patients with RA had previous CV disease diagnoses, events and procedures consistent with ASCVD.<sup>11,21</sup> In contrast, the wider tofacitinib RA clinical trial programme included 1.3% (100/7964) of patients with

a history of MI and 0.4% (30/7964) with a history of CHD, and 39% (3126/7964) of tofacitinib-treated patients met the CV risk-enrichment criteria of ORAL Surveillance.<sup>22</sup> Similarly, a recent report on the baricitinib RA clinical trial programme found that 35% (1325/3770) of patients met ORAL Surveillance inclusion criteria, and 2.3% had a history of ASCVD.<sup>23</sup> The non-CV risk-enriched wider tofacitinib clinical trial programme did not identify the increased risk of MACE with tofacitinib versus TNFi that was observed in ORAL Surveillance. Based on our data, future trials with objectives overlapping with ORAL Surveillance should include sufficient patients with high absolute CV risk and history of ASCVD, and even prespecify the analysis we present herein.

Overall, limitations of ORAL Surveillance have been published previously.<sup>8</sup> The exploratory nature and the lack of statistical evidence (ie, nominally significant p values) of a treatment by history of ASCVD interaction limits our conclusions on this subgroup analysis. This analysis points to a need for more data on risk of MACE with tofacitinib versus other advanced RA treatments in patients with increased CV risk but no history of ASCVD. The subgroup distribution was also uneven (14.7% with vs 85.3% without history of ASCVD). In the history of ASCVD group, across treatment arms, there were relatively few patients (N=204–222) and patients with MACE events (n=9–17). Accordingly, IRs and HRs should be regarded as statistically uncertain, as reflected in the wider 95% CIs, and be interpreted with caution. In addition, substantial literature supports the atheroprotective effects of TNFi, effects that

likely extend to other immunomodulators via their ability to modulate synovial and systemic inflammation.<sup>3 6 24 25</sup> These treatment-associated effects cannot be assessed in ORAL Surveillance given the lack of an untreated control group, but the results we present should be interpreted in this context.

## CONCLUSION

Our post hoc analysis of ORAL Surveillance showed that increased risk of MACE with tofacitinib 5 mg and 10 mg two times per day versus TNFi was found in patients with a history of ASCVD. Among patients without a history of ASCVD, who all had prevalent CV risk factors, risk of MACE did not appear to be different comparing tofacitinib 5 mg two times per day and TNFi. Due to the exploratory nature of this analysis and low statistical power, we cannot exclude any differential MACE risk for tofacitinib 5 mg two times per day versus TNFi among patients without HxASCVD, but any absolute risk excess is likely low.

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CAC was an employee and stockholder of Pfizer Inc at the time of this analysis. ZS has acted as an advisor for AbbVie, Eli Lilly, Gedeon Richter, Novartis, Pfizer Inc and Roche, a consultant for AbbVie, Eli Lilly, Novartis, Pfizer Inc, Roche and Sanofi, has received grant/research support from Pfizer Inc and UCB, and is a member of the speakers' bureau for AbbVie, Eli Lilly, MSD, Novartis, Pfizer Inc, Roche, Sanofi and UCB.

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**Patient consent for publication** Not applicable.

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## SUPPLEMENTAL MATERIAL

### SUPPLEMENTARY METHODS

#### **Statistical analyses of treatment-by-history of atherosclerotic cardiovascular disease (ASCVD) interactions**

Two approaches were followed to assess the treatment-by-HxASCVD interaction for major adverse cardiovascular events (MACE), myocardial infarction (MI) and stroke. First, for the Cox proportional hazard regression models (ie, hazard ratios [HRs]), two Cox interaction models, including treatment group, HxASCVD and treatment-group-by-HxASCVD interaction, as covariates (one model using tofacitinib 5 mg twice daily [BID], 10 mg BID and tumour necrosis factor inhibitors [TNFi]; another model using combined tofacitinib doses and TNFi) were performed to assess whether the treatment effect (tofacitinib vs TNFi) on the time to MACE, MI or stroke differed between HxASCVD Yes vs No (ie, differential effect). A small interaction p-value (Chi-square test with 1 degree of freedom) would be suggestive of the presence of such a differential treatment effect between HxASCVD Yes vs No. Second, the differential effect (tofacitinib vs TNFi) between HxASCVD Yes vs No was assessed using the difference of the incidence rates (IRD) between HxASCVD Yes vs No and its standard error. The 2-sided interaction p-value was calculated assuming normal approximation to the difference of IRD. A small interaction p-value would suggest the presence of such a differential treatment effect between HxASCVD Yes vs No.



## SUPPLEMENTAL TABLES

**Supplemental table 1** List of preferred terms/code to identify history of CeVD, PAD and ASCVD

Classification	Preferred Term (MedDRA v24.1)	Preferred Term Code
CeVD	Ischaemic stroke	10061256
	Transient ischaemic attack	10044390
	Cerebrovascular accident	10008190
	Cerebral ischaemia	10008120
	Cerebral infarction	10008118
	Carotid endarterectomy	10007692
	Carotid artery stent insertion	10066102
	Carotid artery disease	10061744
	Carotid artery occlusion	10048964
	Carotid artery stenosis	10007687
	Carotid arteriosclerosis	10067116
	Cerebral arteriosclerosis	10065559
	Brachiocephalic arteriosclerosis	10075449
PAD	Peripheral artery thrombosis	10072564
	Peripheral artery angioplasty	10057518
	Peripheral artery bypass	10072561
	Peripheral artery stent insertion	10072562
	Arterial occlusive disease	10062599
	Peripheral arterial occlusive disease	10062585
	Intermittent claudication	10022562
	Aortic arteriosclerosis	10065558
ASCVD	Arterial stent insertion	10061657
	Arterial stenosis	10060965
	Arteriosclerosis	10003210
	Stent placement	10048561
	Vascular stent insertion	10063382
	Endarterectomy	10014648

Patients who had  $\geq 1$  of the preferred terms in their general medical history (provided at trial inclusion) were classified to have either history of CeVD or PAD. History of CAD was captured directly in electronic case report form by the investigator, who provided this based on history of MI, unstable angina, stable angina

pectoris, coronary artery procedures or other CHD. Patients who had  $\geq 1$  of CAD, CeVD or PAD were classified as patients with history of ASCVD.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; CeVD, cerebrovascular disease; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; PVD, history of peripheral vascular disease.

**Supplemental table 2** NNH (95% CIs)\* for adjudicated MACE based on IR difference, overall and by HxASCVD

	<b>Tofacitinib 5 mg BID (N=1455)</b>	<b>Tofacitinib 10 mg BID (N=1456)</b>	<b>Combined tofacitinib doses (N=2911)</b>
<b>NNH vs TNFi, PY (95% CIs)</b>			
Overall	567 (-∞ to -571 and 189 to ∞)	319 (-∞ to -1708 and 146 to ∞)	412 (-∞ to -1603 and 182 to ∞)
HxASCVD	80 (-∞ to -453 and 37 to ∞)	75 (-∞ to -584 and 35 to ∞)	78 (40 to 1234)
No HxASCVD	4344 (-∞ to -318 and 277 to ∞)	621 (-∞ to -500 and 192 to ∞)	1113 (-∞ to -478 and 257 to ∞)
<b>NNH vs TNFi, 5-year (95% CIs)<sup>†</sup></b>			
Overall	113 (-∞ to -114 and 38 to ∞)	64 (-∞ to -342 and 29 to ∞)	82 (-∞ to -321 and 36 to ∞)
HxASCVD	16 (-∞ to -91 and 7 to ∞)	15 (-∞ to -117 and 7 to ∞)	16 (8 to 247)
No HxASCVD	869 (-∞ to -64 and 55 to ∞)	124 (-∞ to -100 and 38 to ∞)	223 (-∞ to -96 and 51 to ∞)

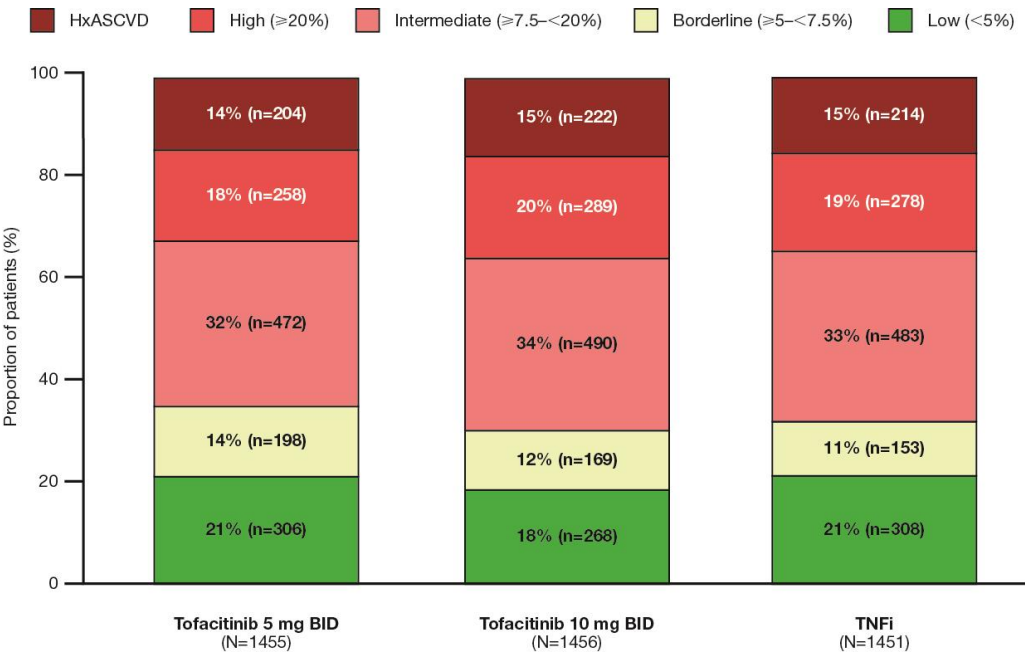
For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group.

\*Positive NNH refers to the number of PY of tofacitinib exposure needed to have one additional patient with an event compared to TNFi. Negative NNH refers to the reverse. When the 95% CI of the IR difference includes zero, the 95% CI of the NNH has two disjoint (positive and negative) intervals, implying harm in either tofacitinib versus TNFi (positive) or TNFi versus tofacitinib (negative). <sup>†</sup>Number of patients who would need to be treated with tofacitinib for 5 years to have one additional event compared to TNFi.

BID, twice daily; CI, confidence interval; HxASCVD, history of atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; N, number of evaluable patients; NNH, number needed to harm; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

SUPPLEMENTAL FIGURES

Supplemental figure 1 Baseline CV risk profile of ORAL Surveillance



Proportions of patients with and without history of ASCVD were categorised according to their 10-year risk of MACE, per the ASCVD–PCE risk calculator, in ORAL Surveillance. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD–PCE scores.[1] ASCVD was defined as any of CAD, CeVD or PAD. The proportions of patients who had no HxASCVD and were missing ASCVD-PCE risk category data are not shown (tofacitinib 5 mg BID, n=17 [1.2%]; tofacitinib 10 mg BID, n=18 [1.2%]; TNFi, n=15 [1.0%]).

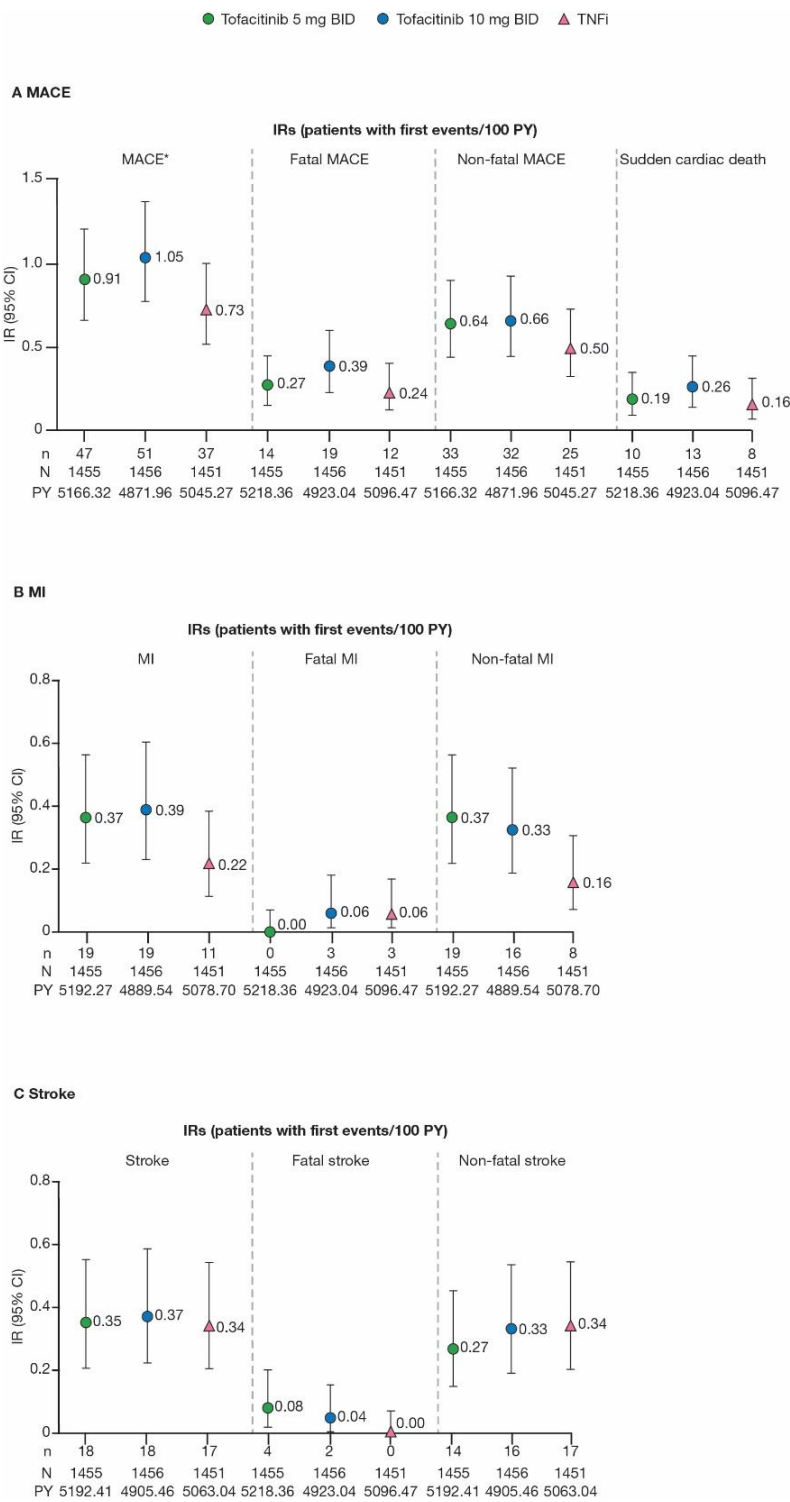
ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, twice daily;

CAD, coronary artery disease; CeVD, cerebrovascular disease; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HxASCVD, history of atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular events; PAD, peripheral artery disease TNFi, tumour necrosis factor inhibitor.



Supplemental figure 2 IRs of adjudicated MACE outcomes with tofacitinib vs TNFi in

ORAL Surveillance



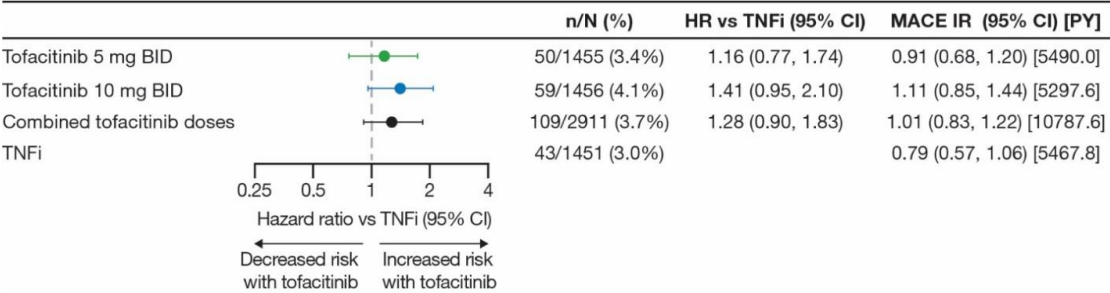
Panels display adjudicated (A) MACE, (B) MI and (C) stroke according to total number of events, fatal events and non-fatal events. Sudden cardiac death is included in fatal MACE.

In this analysis, the risk period was defined as time from first study dose to last study dose +60 days or to the last contact date (if a patient died, the last contact date was death date), whichever was earliest. Patients without events were censored at the end of the risk period.

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. IRs express the number of patients with first events per 100 PY.

\*Results reported in [2] and included for reference. BID, twice daily; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

**Supplemental figure 3** Risk of MACE with tofacitinib vs TNFi in ORAL Surveillance in total time analysis



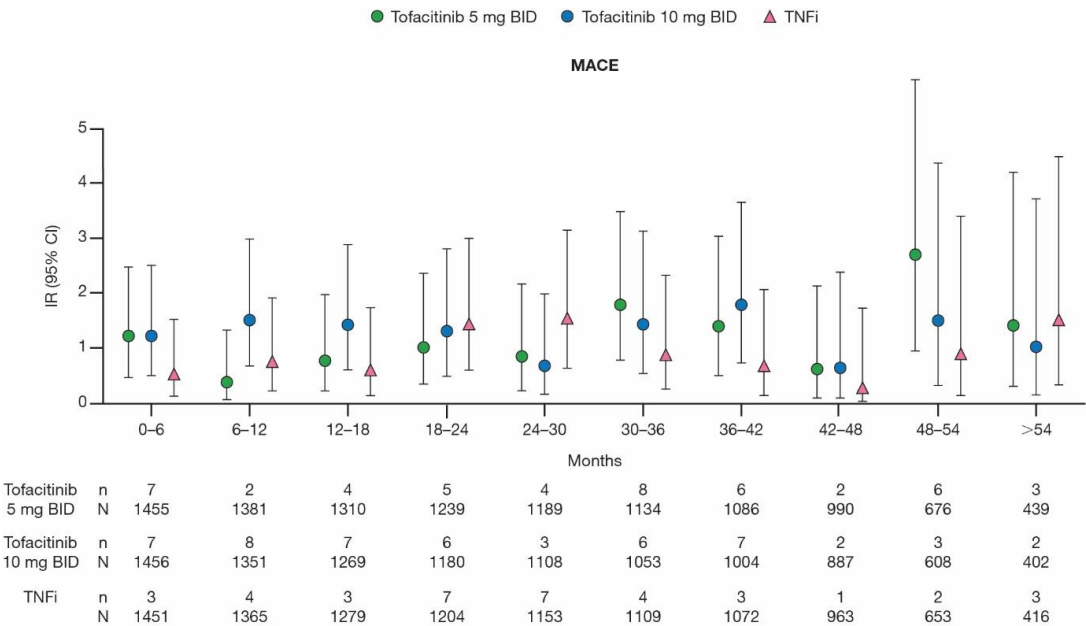
HRs are shown on a logarithmic scale.

In this analysis, the risk period was defined as time from first study dose to last contact date (if a patient died, the last contact date was death date). Patients without events were censored at the last contact date.

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi and the other for comparing tofacitinib 5 and 10 mg BID vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY.

BID, twice daily; CI, confidence interval; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

Supplemental figure 4 MACE IRs with tofacitinib vs TNFi in ORAL Surveillance by 6-month intervals



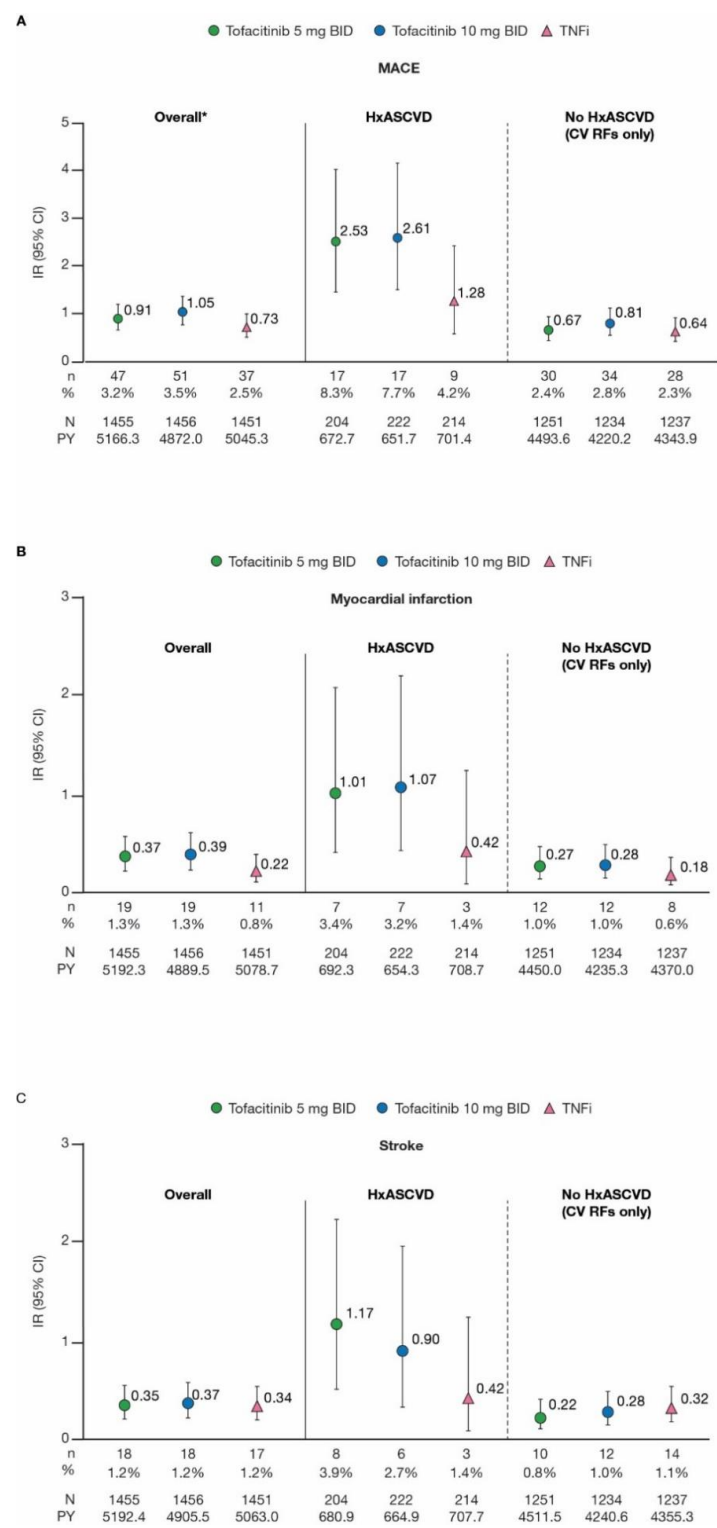
In this analysis, the risk period was defined as time from first study dose to last study dose +60 days or to the last contact date (if a patient died, the last contact date was death date), whichever was earliest. Patients without events were censored at the end of the risk period.

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. IRs express the number of patients with first events per 100 PY.

BID, twice daily; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; TNFi, tumour necrosis factor inhibitor.



**Supplemental figure 5** IRs of adjudicated MACE, MI and stroke with tofacitinib vs TNFi by history of ASCVD



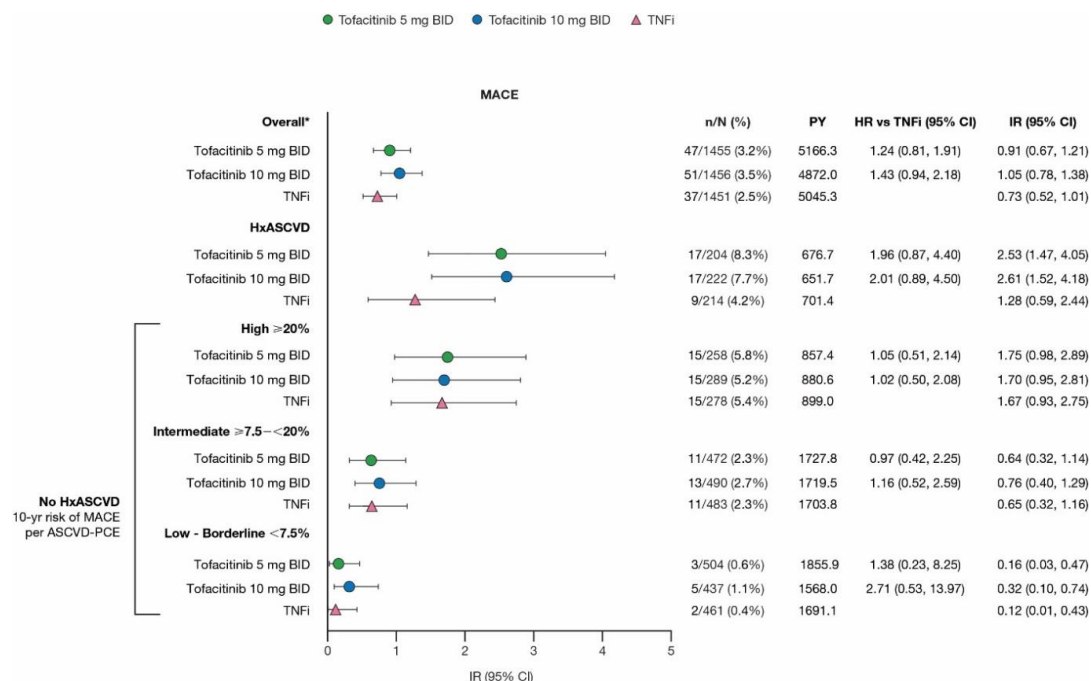
Panels display adjudicated (A) MACE, (B) MI and (C) stroke in overall population, and in patients with and without HxASCVD.

In this analysis, the risk period was defined as time from first study dose to last study dose +60 days or to the last contact date (if a patient died, the last contact date was death date), whichever was earliest. Patients without events were censored at the end of the risk period.

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. IRs express the number of patients with first events per 100 PY.

\*Results reported in [2] and included for reference. BID, twice daily; CI, confidence interval; CV RF, cardiovascular risk factor; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

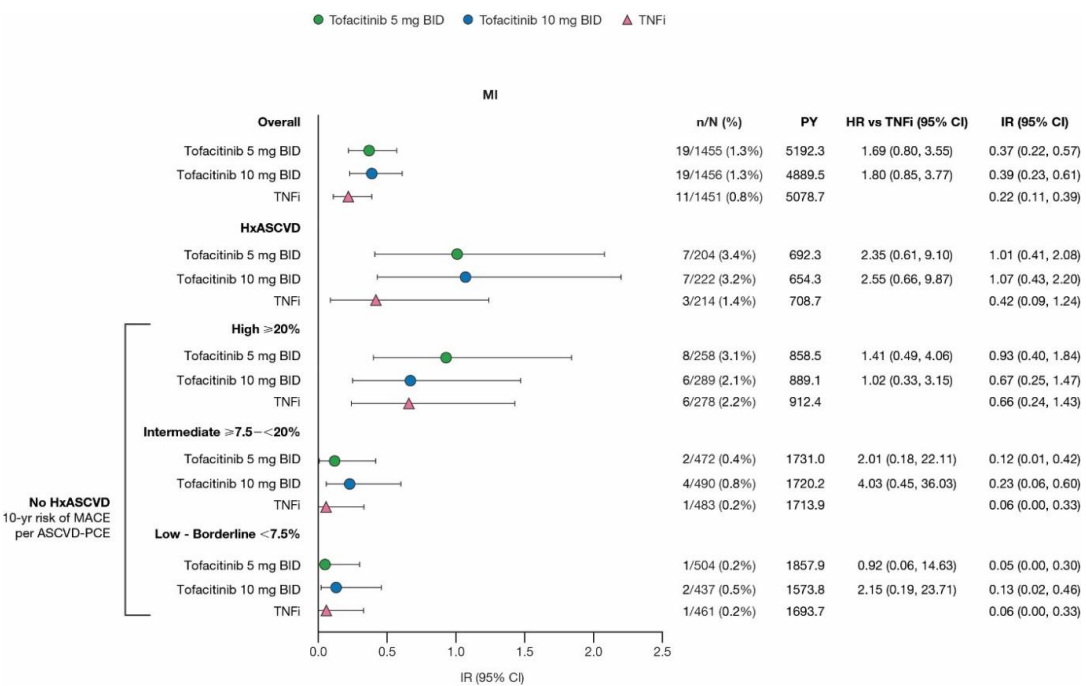
**Supplemental figure 6** MACE IRs with tofacitinib vs TNFi in patients without history of ASCVD, according to CV risk categories



Patients without HxASCVD were categorised according to their 10-year risk of MACE, per the ASCVD–PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD–PCE scores.[1] Because of missing ASCVD–PCE scores, two MACE could not be associated with baseline CV risk (n=1 [MI] in tofacitinib 5 mg BID arm and n=1 [stroke] in tofacitinib 10 mg BID arm). For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi and the other for comparing tofacitinib 5 and 10 mg BID vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY.

\*Results reported in [2] and included for reference. ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, twice daily; CI, confidence interval; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HR, hazard ratio; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

Supplemental figure 7 MI IRs with tofacitinib vs TNFi in patients without history of ASCVD, according to CV risk categories

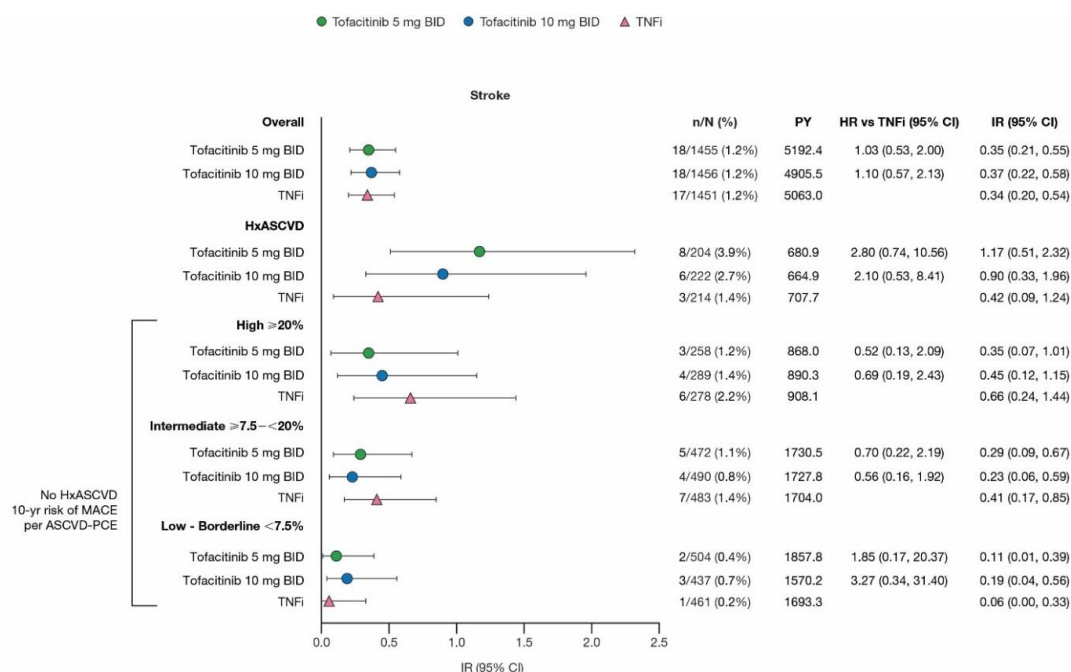


Patients without HxASCVD were categorised according to their 10-year risk of MACE, per the ASCVD–PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD–PCE scores.[1] Because of missing ASCVD–PCE scores, one MI in tofacitinib 5 mg BID arm could not be associated with baseline CV risk. For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi and the other for comparing tofacitinib 5 and 10 mg BID vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY.

ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, twice daily; CI, confidence interval; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HR, hazard ratio; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.



## Supplemental figure 8 Stroke IRs with tofacitinib vs TNFi in patients without history of ASCVD according to CV risk categories



Patients without HxASCVD were categorised according to their 10-year risk of MACE, per the ASCVD–PCE risk calculator. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD–PCE scores.[1] Because of missing ASCVD–PCE scores, one stroke in tofacitinib 10 mg BID arm could not be associated with baseline CV risk. For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group. HRs (95% CIs) are based on two simple Cox proportional hazard models (one for comparing combined tofacitinib doses vs TNFi and the other for comparing tofacitinib 5 and 10 mg BID vs TNFi), with treatment as the only covariate. IRs express the number of patients with first events per 100 PY.

ASCVD-PCE, atherosclerotic cardiovascular disease-Pooled Cohort Equations; BID, twice daily; CI, confidence interval; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; HR, hazard ratio; HxASCVD, history of atherosclerotic cardiovascular disease; IR, incidence rate; MACE, major adverse cardiovascular events; n, number of patients with events; N, number of evaluable patients; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

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- 2 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.

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10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>													

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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Maxime Dougados

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Carol A Connell

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Jon T Giles

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Gary G Koch

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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8	Patents planned, issued or pending	<input checked="" type="checkbox"/> <b>None</b>	
9	Participation on a Data Safety	<input checked="" type="checkbox"/> <b>None</b>	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	Monitoring Board or Advisory Board		
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/> None	
		Pfizer Inc	Member of the Steering Committee for ORAL Surveillance
11	Stock or stock options	<input type="checkbox"/> None	
		IQVIA	Shareholder
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input type="checkbox"/> None	
		University of North Carolina at Chapel Hill	Employee
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Kenneth Kwok

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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<b>2</b>	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						
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4	Consulting fees	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>									
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>									
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9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>									
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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<b>11</b>	Stock or stock options	<input type="checkbox"/> <b>None</b>	
		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input checked="" type="checkbox"/> <b>None</b>	
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Sujatha Menon

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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<b>Time frame: past 36 months</b>								
<b>2</b>	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						
<b>3</b>	Royalties or licenses	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						



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<b>11</b>	Stock or stock options	<input type="checkbox"/> <b>None</b>	
		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input checked="" type="checkbox"/> <b>None</b>	
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Jose L Rivas

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None <table border="1"> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>									
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<b>11</b>	Stock or stock options	<input type="checkbox"/> <b>None</b>	
		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input checked="" type="checkbox"/> <b>None</b>	
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Zoltán Szekanecz

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

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<b>2</b>	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None <table border="1"> <tr> <td>Pfizer Inc</td> <td>Grant/research support</td> </tr> <tr> <td>UCB</td> <td>Grant/research support</td> </tr> <tr> <td></td> <td></td> </tr> </table>	Pfizer Inc	Grant/research support	UCB	Grant/research support		
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	advocacy group, paid or unpaid								
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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Ivana Vranic

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

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		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input checked="" type="checkbox"/> <b>None</b>	
<p><b>Please place an "X" next to the following statement to indicate your agreement:</b></p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Joseph Wu

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

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		Pfizer Inc	Employee and shareholder
<b>12</b>	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> <b>None</b>	
<b>13</b>	Other financial or non-financial interests	<input checked="" type="checkbox"/> <b>None</b>	
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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Arne Yndestad

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Steven R Ytterberg

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** Click or tap here to enter text.

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## ICMJE DISCLOSURE FORM

**Date:** 1/27/2022

**Your Name:** Cunshan Wang

**Manuscript Title:** Risk factors for major adverse cardiovascular events with tofacitinib vs tumour necrosis factor inhibitors in patients with rheumatoid arthritis: results from ORAL Surveillance

**Manuscript Number (if known):** [Click or tap here to enter text.](#)

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