

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
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 ≥ 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 ≥ 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

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID (N=1456)	Combined tofacitinib doses (N=2911)
NNH vs TNFi, PY (95% CIs)			
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 ∞)
NNH vs TNFi, 5-year (95% CIs)[†]			
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 ∞)

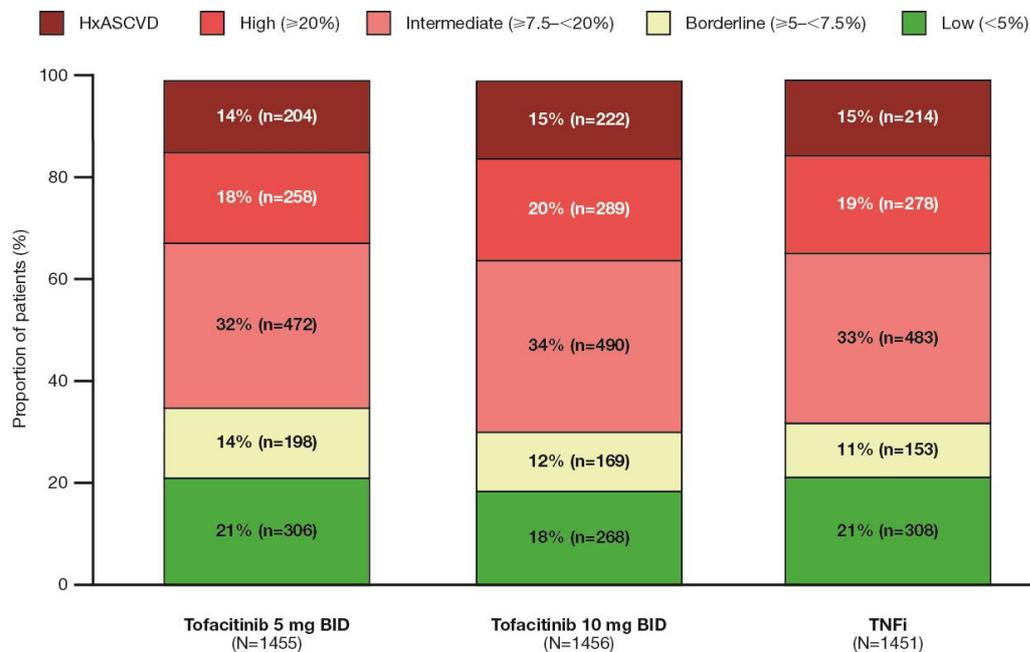
For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group.

*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). [†]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



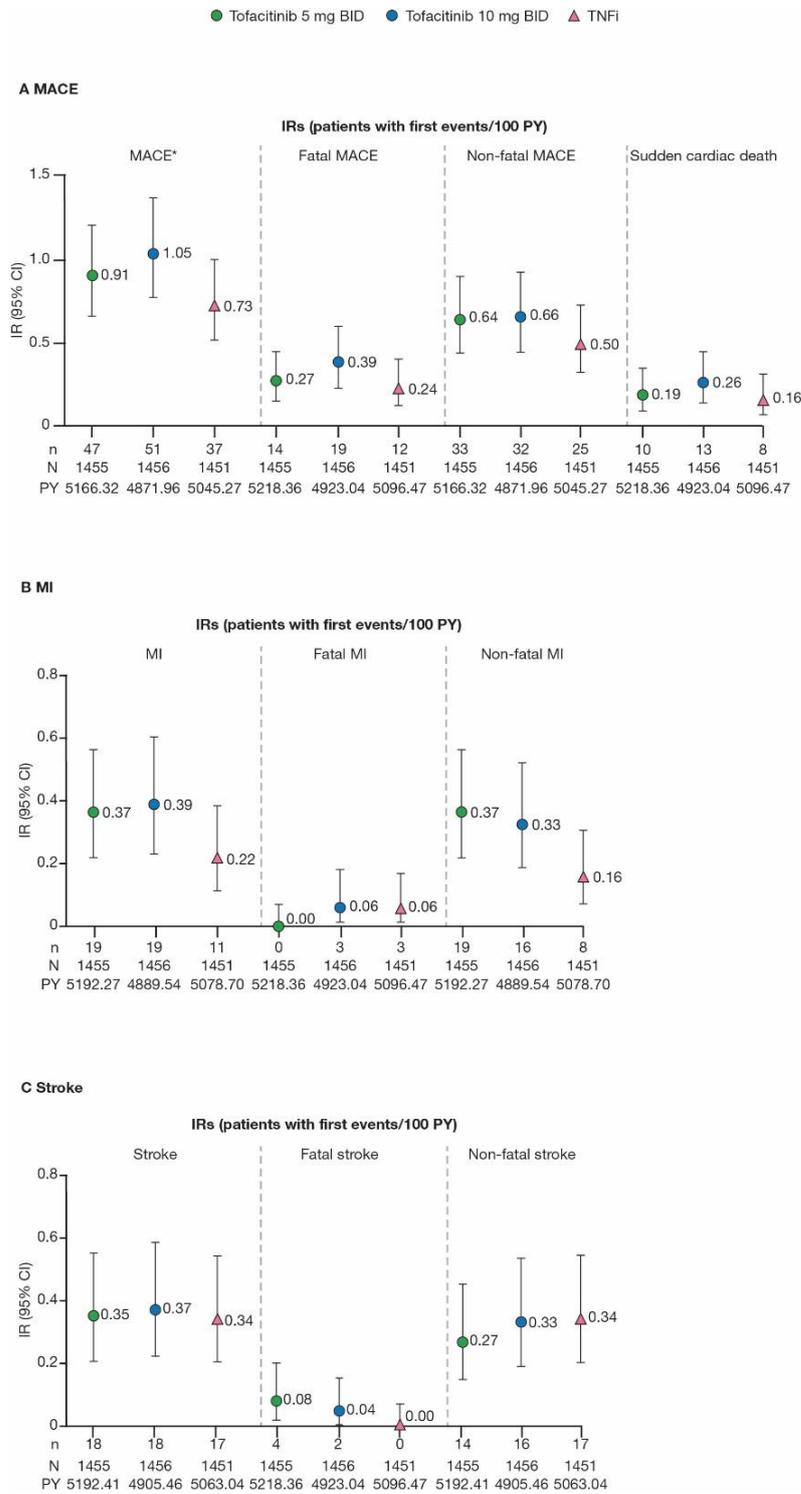
Proportions of patients with and without history of ASCVD were categorised according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator, in ORAL Surveillance. In line with EULAR recommendations, a 1.5 multiplier was applied to all ASCVD-PCE scores.[1] ASCVD was defined as any of CAD, CeVD 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



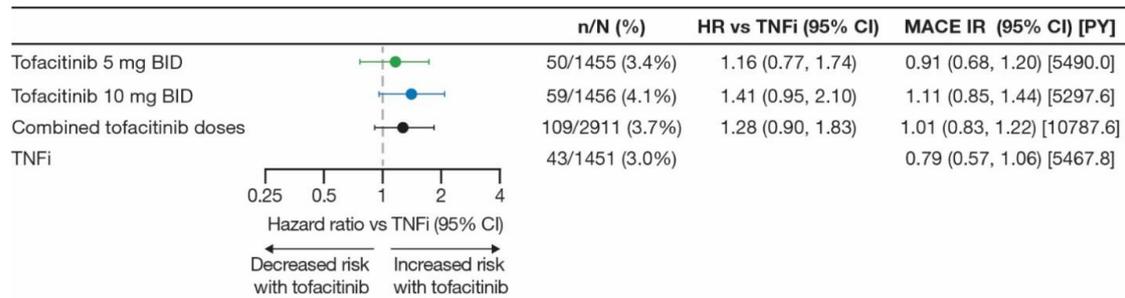
Panels display adjudicated (A) MACE, (B) MI and (C) stroke according to total number of events, fatal events and non-fatal events. Sudden cardiac death is included in fatal MACE.

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



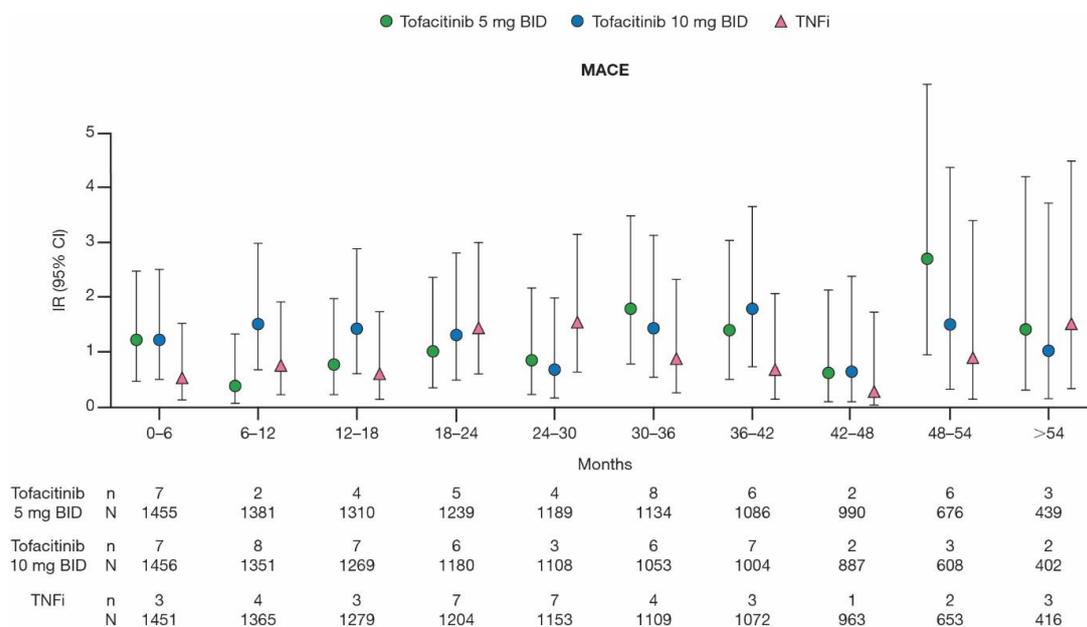
HRs are shown on a logarithmic scale.

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

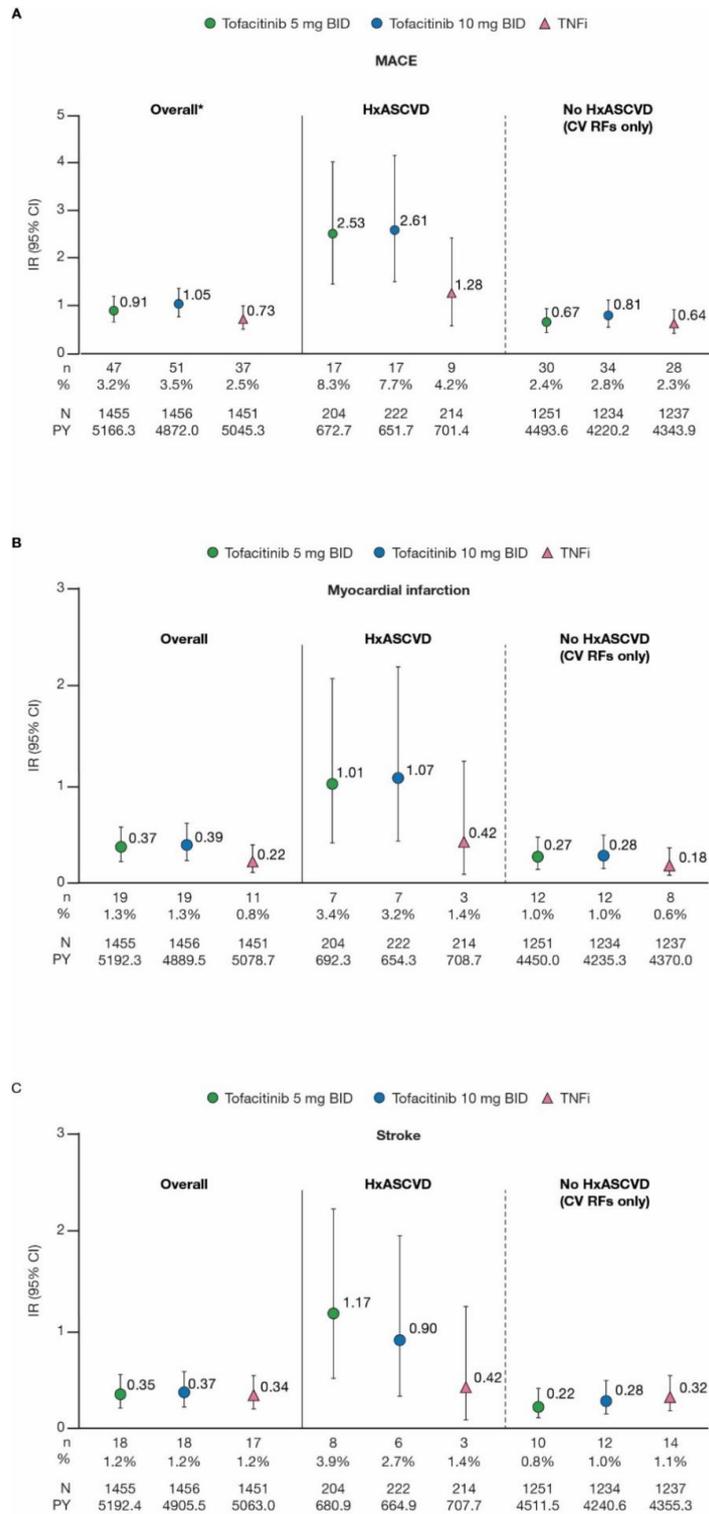


In this analysis, the risk period was defined as time from first study dose to last study dose +60 days or to the last contact date (if a patient died, the last contact date was death date), whichever was earliest. Patients without events were censored at the end of the risk period.

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



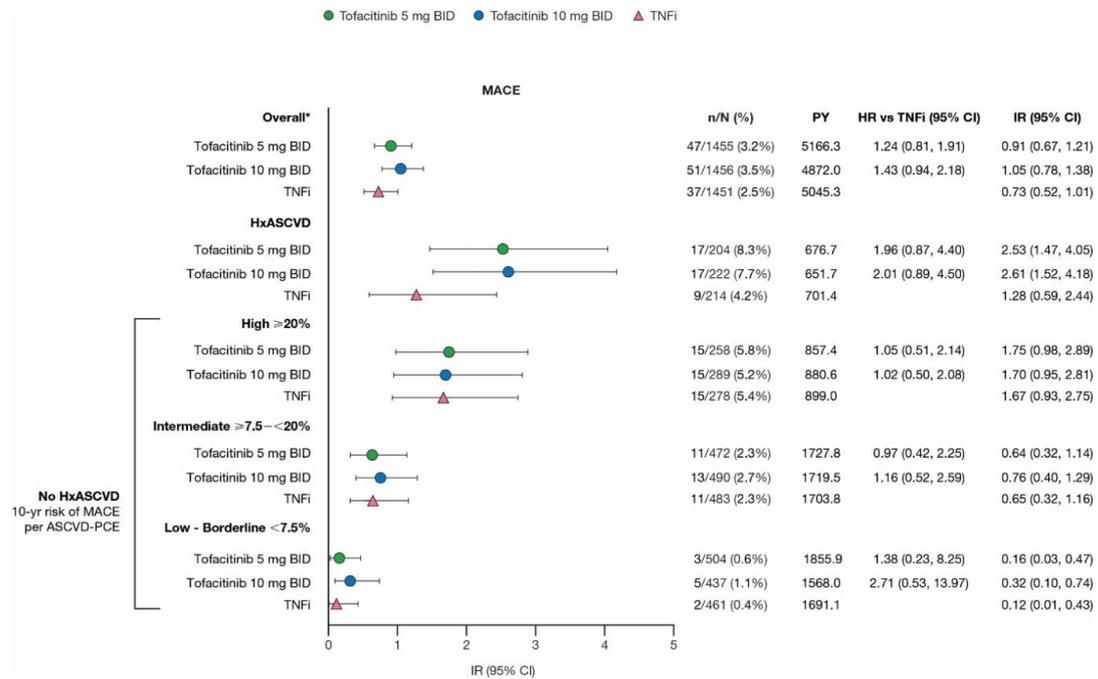
Panels display adjudicated (A) MACE, (B) MI and (C) stroke in overall population, and in patients with and without HxASCVD.

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.

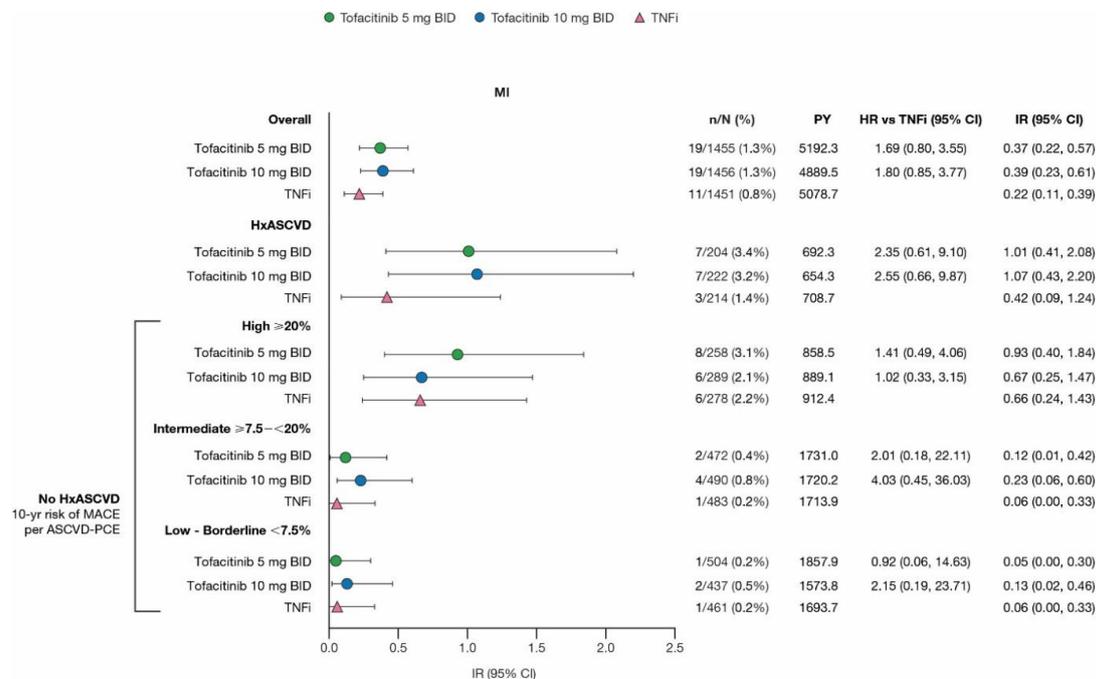
Supplemental figure 6 MACE IRs with tofacitinib vs TNFi in patients without history of ASCVD, according to CV risk categories



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.

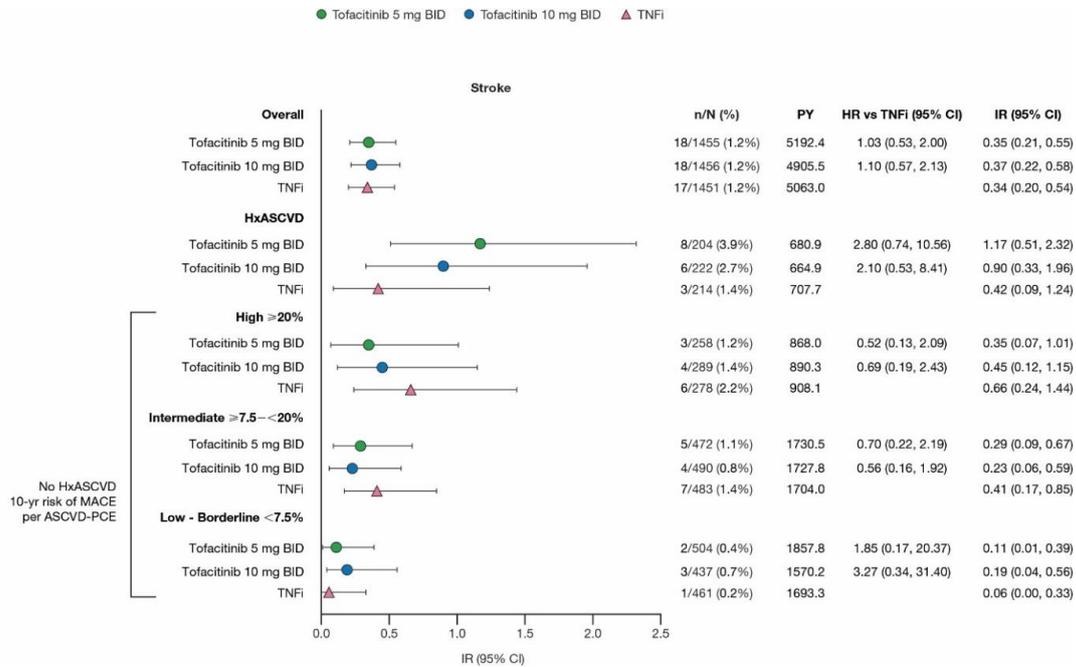
Supplemental figure 7 MI IRs with tofacitinib vs TNFi in patients without history of ASCVD, according to CV risk categories



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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- 1 Agca R, Heslinga SC, Rollefstad S, *et al.* EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;76:17–28.
- 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.