抄読会

鈴木翔太郎

2022年12月15日

CLINICAL SCIENCE

Annals of the Rheumatic Diseases

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

Christina Charles-Schoeman [1], Maya H Buch [2,3], Maxime Dougados [4,5], Deepak L Bhatt [6], Jon T Giles [7], Steven R Ytterberg [8], Gary G Koch [9], Ivana Vranic [10], Joseph Wu [11], Cunshan Wang [11], Kenneth Kwok [12], Sujatha Menon [11], Jose L Rivas [13], Arne Yndestad [14], Carol A Connell [11], Zoltan Szekanecz [15]

Ann Rheum Dis . 2022 Sep 22;annrheumdis-2022-222259.

臨床の疑問

- Tofacitinibが高齢患者・心血管リスクの高い患者で
  心血管イベントの発生を増やす可能性が
  ORAL surveillance試験で指摘されたが、
  臨床の現場で使用する際に
  具体的にどのようなことに留意すればよいのか？

- もっとハイリスクな患者を正確に同定することはできないのか？

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

N Engl J Med. 2022 Jan 27;386(4):316-326.

- ランダム化オープンラベル非劣性試験
- Patients
  - MTX使用中にも関わらず活動性の関節リウマチを有する50歳以上の患者
  - 少なくとも1つ以上の心血管リスクを有する
    - 現在の喫煙, 高血圧, HDL<40, DM, 若年発症のCADの家族歴, 関節外症状, CADの既往
  - 除外基準：現在もしくは以前のガン
- Intervention
  - TOFA 5mg twice daily OR TOFA 10mg twice daily
- Exposure
  - ADA 40mg 2週おき　もしくは　ETN 50mg 毎週
- 注意事項
  - MTX併用可能
  - 2019年2月以降TOFA10mg twice dailyは5mg twice dailyに減量（肺塞栓の頻度が多いため）
- Outcome
  - MACE(心血管死, 非致死性MI, 非致死性脳卒中), ガン(非メラノーマ性皮膚腫瘍を除く)
    Major **A**dverse **C**ardiovascular **E**vents

6559人がスクリーニングされ,
4362人がランダム化・薬剤投与

観察人年
Tofa 5*2 : Tofa 10*2 : TNFi
= 5073.49 : 4773.41 : 4940.72

治療期間平均(月)
Tofa 5*2 : Tofa 10*2 : TNFi
= 41.14 ： 38.53 :40.24

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

Characteristic	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)	Total (N=4362)
Age				
Mean — yr	60.8±6.8	61.4±7.1	61.3±7.5	61.2±7.1
≥65 yr — no. (%)	413 (28.4)	478 (32.8)	462 (31.8)	1353 (31.0)
Female sex — no. (%)	1169 (80.3)	1124 (77.2)	1117 (77.0)	3410 (78.2)
Race — no. (%)‡				
White	1128 (77.5)	1126 (77.3)	1099 (75.7)	3353 (76.9)
Black	63 (4.3)	65 (4.5)	83 (5.7)	211 (4.8)
Asian	65 (4.5)	56 (3.8)	55 (3.8)	176 (4.0)
Other	199 (13.7)	209 (14.4)	214 (14.7)	622 (14.3)
Smoking status — no. (%)				
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)	2259 (51.8)
Ever smoked	720 (49.5)	704 (48.4)	679 (46.8)	2103 (48.2)
History of hypertension — no. (%)	955 (65.6)	954 (65.5)	969 (66.8)	2878 (66.0)
History of diabetes mellitus — no. (%)	243 (16.7)	261 (17.9)	255 (17.6)	759 (17.4)
History of venous thromboembolism — no. (%)§	19 (1.3)	33 (2.3)	27 (1.9)	79 (1.8)
History of extraarticular disease — no. (%)¶	532 (36.6)	521 (35.8)	552 (38.0)	1605 (36.8)
History of coronary heart disease — no. (%)	161 (11.1)	172 (11.8)	164 (11.3)	497 (11.4)
Family history of coronary heart disease — no. (%)				
First-degree male relative <55 yr of age	154 (10.6)	132 (9.1)	151 (10.4)	437 (10.0)
First-degree female relative <65 yr of age	115 (7.9)	107 (7.3)	100 (6.9)	322 (7.4)
Fasting HDL cholesterol <40 mg/dl — no. (%)	172 (11.8)	195 (13.4)	173 (11.9)	540 (12.4)

年齢 61歳
65歳以上 31%
女性 78%
白人 77%
喫煙歴あり 48%
高血圧 66%
DM 17%
VTE 2%
関節外症状 37%
冠動脈 37%
HDL低値 12%

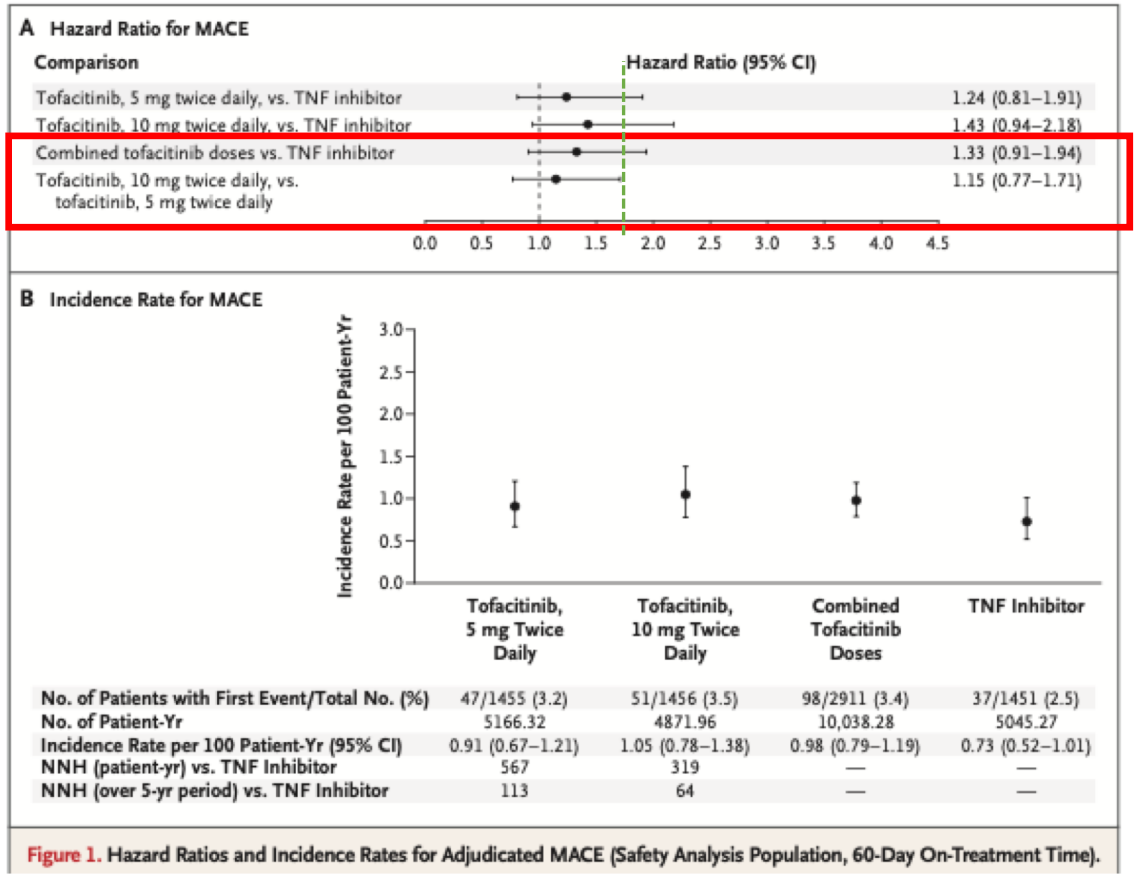


Figure 1. Hazard Ratios and Incidence Rates for Adjudicated MACE (Safety Analysis Population, 60-Day On-Treatment Time).

MACE発生率

①Tofa 5*2 vs TNFi = 3.2% vs 2.5%

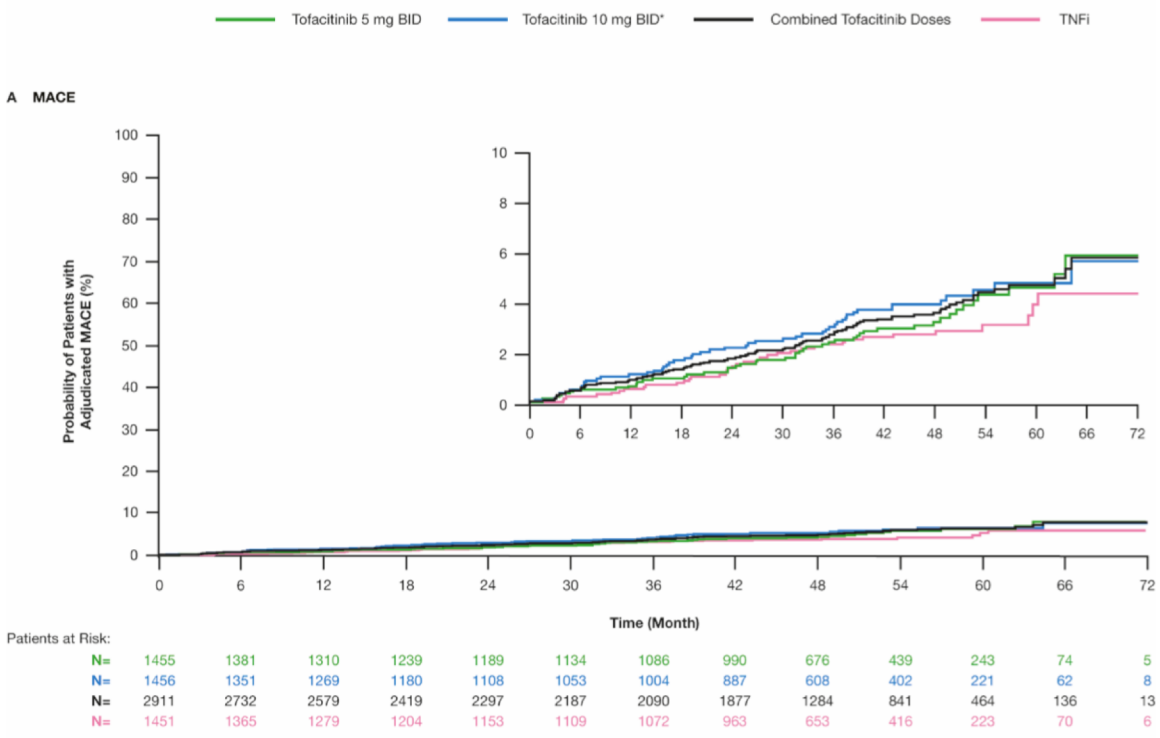
HR 1.24 [95%CI 0.81-1.91]

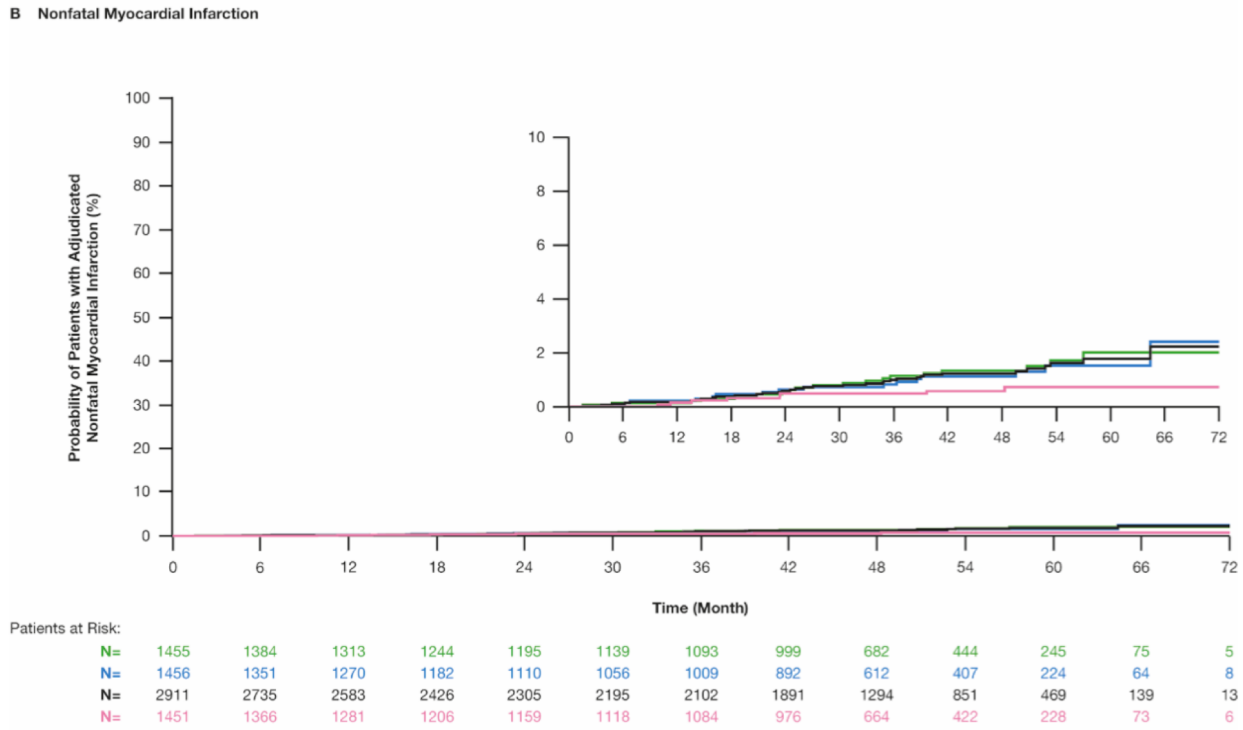
②Tofa 5*2+10*2 vs TNFi = 3.4% vs 2.5%

HR 1.33 [95%CI 0.91-1.94]
→非劣性を証明できず
※非劣性マージン 95%CI上限が1.8を超えている

③Tofa 5*2 vs Tofa 10*2

HR 1.15 [95%CI 0.77-1.71]
→非劣性が証明された
※非劣性マージン 95%CI上限が2.0を超えていない





MACE累積発生率

Tofa 5*2+Tofa10*2群 vs TNFi群

=5.8% vs 4.3%

非致死性心筋梗塞累積発生率

Tofa 5*2+Tofa10*2群 vs TNFi群

=2.2% vs 0.7%

Table 2. Adverse Events (Safety Analysis Population, 28-Day On-Treatment Time).*

Event	Tofacitinib, 5 mg Twice Daily (N=1455)	Tofacitinib, 10 mg Twice Daily (N=1456)†	TNF Inhibitor (N=1451)
Adverse event — no. (%)	1333 (91.6)	1344 (92.3)	1308 (90.1)
Serious adverse event — no. (%)	351 (24.1)	390 (26.8)	306 (21.1)
Discontinuation of trial treatment due to adverse event — no. (%)			
Permanent discontinuation‡	210 (14.4)	304 (20.9)	210 (14.5)
Temporary discontinuation§	665 (45.7)	736 (50.5)	576 (39.7)
Adverse events of special interest			
Serious infection — no. (%)	141 (9.7)	169 (11.6)	119 (8.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.17 (0.92–1.50)	1.48 (1.17–1.87)	Referent
Adjudicated opportunistic infection — no. (%)¶	39 (2.7)	44 (3.0)	21 (1.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.82 (1.07–3.09)	2.17 (1.29–3.66)	Referent
All herpes zoster, serious and nonserious — no. (%)‖	180 (12.4)	178 (12.2)	58 (4.0)
Hazard ratio vs. TNF inhibitor (95% CI)	3.28 (2.44–4.41)	3.39 (2.52–4.55)	Referent
Adjudicated hepatic event — no. (%)	46 (3.2)	72 (4.9)	35 (2.4)
Hazard ratio vs. TNF inhibitor (95% CI)	1.29 (0.83–2.00)	2.14 (1.43–3.21)	Referent
Adjudicated NMSC — no. (%)	31 (2.1)	33 (2.3)	16 (1.1)
Hazard ratio vs. TNF inhibitor (95% CI)	1.90 (1.04–3.47)	2.16 (1.19–3.92)	Referent
Adjudicated pulmonary embolism — no. (%)	9 (0.6)	24 (1.6)	3 (0.2)
Hazard ratio vs. TNF inhibitor (95% CI)	2.93 (0.79–10.83)	8.26 (2.49–27.43)	Referent
Adjudicated DVT — no. (%)	11 (0.8)	15 (1.0)	7 (0.5)
Hazard ratio vs. TNF inhibitor (95% CI)	1.54 (0.60–3.97)	2.21 (0.90–5.43)	Referent
Adjudicated VTE — no. (%)	17 (1.2)	34 (2.3)	10 (0.7)
Hazard ratio vs. TNF inhibitor (95% CI)	1.66 (0.76–3.63)	3.52 (1.74–7.12)	Referent
Adjudicated death from any cause — no. (%)	26 (1.8)	39 (2.7)	17 (1.2)
Hazard ratio vs. TNF inhibitor (95% CI)	1.49 (0.81–2.74)	2.37 (1.34–4.18)	Referent

* Shown are adverse events that emerged or worsened during the 28-day on-treatment period, which was defined as the minimum of the date of last contact or the date of the last dose of a trial treatment plus 28 days. DVT denotes deep-vein thrombosis, NMSC nonmelanoma skin cancer, and VTE venous thromboembolism.
† For patients assigned to receive tofacitinib at a dose of 10 mg twice daily who had their dose reduced to 5 mg twice daily, the data collected after patients had been switched to 5 mg twice daily were counted in the group receiving 10 mg twice daily.
‡ Data are based on the adverse-event and disposition case-report forms.
§ At the discretion of the investigator, discontinuations of trial medication were allowed, not to exceed 2 months, for safety issues.
¶ Also included are opportunistic herpes zoster and tuberculosis events.
‖ Included are herpes zoster adjudicated as an opportunistic infection and nonadjudicated herpes zoster events.

有害事象

・重症感染症
Tofa 10*2 vs TNFi HR= 1.48 (1.17-1.87)

・結核・帯状疱疹を含む日和見感染
Tofa 5*2 vs TNFi HR= 1.82 (1.07-3.09)
Tofa 10*2 vs TNFi HR= 2.17 (1.29-3.66)

・帯状疱疹
Tofa 5*2 vs TNFi HR= 3.28 (2.44-4.41)
Tofa 10*2 vs TNFi HR= 3.39 (2.52-4.55)

・非メラノーマ性皮膚腫瘍
Tofa 5*2 vs TNFi HR= 1.90 (1.04-3.47)
Tofa 10*2 vs TNFi HR= 2.16 (2.49-27.43)

・肺塞栓
Tofa 10*2 vs TNFi HR= 8.26 (2.49-27.43)

・死亡
Tofa 10*2 vs TNFi HR= 1.48 (1.17-1.87)

結論

- 50歳以上かつ心血管リスクの高い活動性関節リウマチの患者において, Tofacitinib 5mg1日2回もしくは10mg1日2回投与は TNF阻害薬と比較して
  - MACEの発生率は非劣性を証明できず (TofaとTNFiが同等か, もしくはTofaが劣っている可能性がある)

- 副次評価項目ではあるが,
  - Tofacitinib 5mg1日2回はTNF阻害薬と比較して 結核・帯状疱疹を含む日和見感染, 非メラノーマ性皮膚腫瘍 の発生率が有意に高い
  - Tofacitinib 10mg1日2回は肺塞栓発生率が有意にかつとても高い

Arthritis & Rheumatology
Vol. 72, No. 1, January 2020, pp 31–40
DOI 10.1002/art.41095

American College of Rheumatology
Empowering Rheumatology Professionals

Cardiovascular Safety of Tocilizumab Versus Etanercept in Rheumatoid Arthritis: A Randomized Controlled Trial

Jon T. Giles,[1] Naveed Sattar,[2] Sherine Gabriel,[3] Paul M. Ridker,[4] Steffen Gay,[5] Charles Warne,[6] David Musselman,[7] Laura Brockwell,[6] Emma Shittu,[6] Micki Klearman,[7] and Thomas R. Fleming[8]

Table 2. Frequency of first-occurrence events and relative hazards (tocilizumab relative to etanercept) for the primary, secondary, and exploratory end points, and sensitivity analyses of the primary end point*

	First event					
	Etanercept		Tocilizumab			
End point	No. (%) first events	No. first events/ 100 person-years (95% CI)	No. (%) first events	No. first events/ 100 person-years (95% CI)	HR†	95% CI†
Primary end point of MACE, including undetermined cause of death						
ITT population‡	78 (5)	1.70 (1.35–2.10)	83 (5)	1.82 (1.46–2.24)	1.05	0.77–1.43
On-treatment population§	52 (3)	1.28 (0.97–1.66)	57 (4)	1.44 (1.10–1.85)	1.11	0.76–1.62
Sensitivity analysis of primary end point (ITT population)						
MACE, excluding undetermined cause of death	72 (5)	1.57 (1.24–1.97)	74 (5)	1.63 (1.29–2.03)	1.01	0.73–1.40
MACE, before last direct contact	46 (3)	1.00 (0.74–1.33)	49 (3)	1.06 (0.79–1.40)	1.04	0.70–1.56
Secondary end points (ITT population)						
Nonfatal MI	31 (2)	0.65 (0.45–0.92)	28 (2)	0.59 (0.40–0.85)	0.89	0.54–1.49
Nonfatal and fatal MI	32 (2)	0.67 (0.46–0.95)	29 (2)	0.61 (0.41–0.87)	0.90	0.54–1.48
Nonfatal stroke, all types	15 (1)	0.33 (0.19–0.53)	24 (2)	0.49 (0.31–0.73)	1.53	0.80–2.92
Nonfatal and fatal stroke, all types	16 (1)	0.35 (0.20–0.56)	26 (2)	0.53 (0.35–0.78)	1.55	0.83–2.90
Cardiovascular-related death	35 (2)	0.72 (0.50–1.00)	36 (2)	0.73 (0.51–1.02)	1.03	0.64–1.63
Death from any cause	64 (4)	1.31 (1.01–1.67)	64 (4)	1.31 (1.01–1.67)	0.99	0.70–1.41
Expanded composite end point¶	84 (5)	1.98 (1.61–2.42)	84 (6)	1.90 (1.53–2.33)	0.99	0.73–1.34
Exploratory end points (ITT population)						
MACE and HHF	85 (6)	1.90 (1.53–2.33)	90 (6)	2.12 (1.73–2.57)	1.05	0.78–1.41
HHF	8 (1)	0.20 (0.10–0.38)	12 (1)	0.31 (0.17–0.50)	1.50	0.61–3.67

IL-6阻害の副次効果としての心血管イベント増加とは考えにくい…

ACR Open Rheumatology
Vol. 3, No. 3, March 2021, pp 173–184
DOI 10.1002/acr2.11232

American College of Rheumatology
Empowering Rheumatology Professionals

Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States–Based Rheumatoid Arthritis Registry

Joel M. Kremer,[1] Clifton O. BinghamIII,[2] Laura C. Cappelli,[2] Jeffrey D. Greenberg,[3] Ann M. Madsen,[4] Jamie Geier,[4] Jose L. Rivas,[5] Alina M. Onofrei,[6] Christine J. Barr,[6] Dimitrios A. Pappas,[7] Heather J. Litman,[6] Kimberly J. Dandreo,[6] Andrea B. Shapiro,[8] Carol A. Connell,[9] and Arthur Kavanaugh[10]

Corrona RA registry (CorEvitas)における
Tofa vs bDMARDsの安全性評価では
MACE, 悪性腫瘍, 死亡では
大きく差がなかった

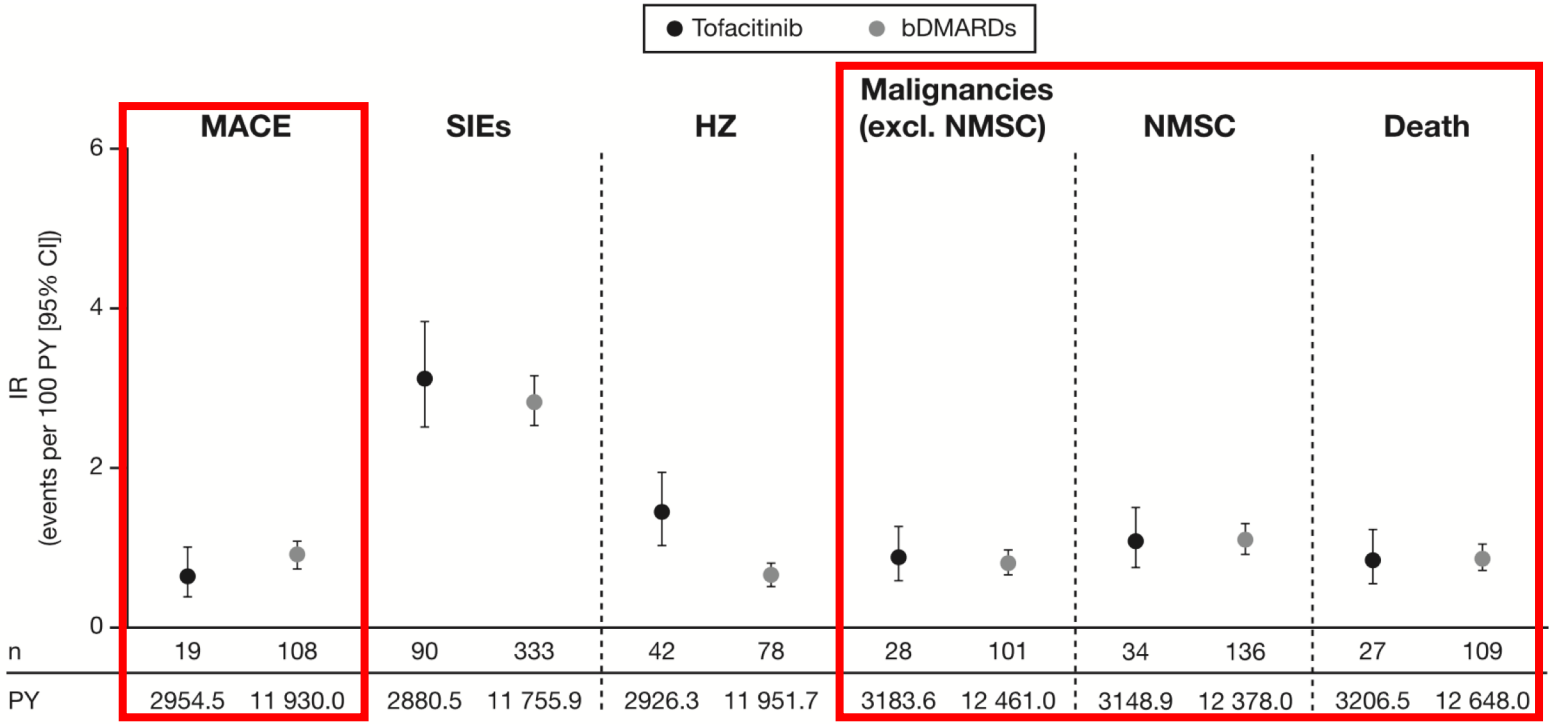
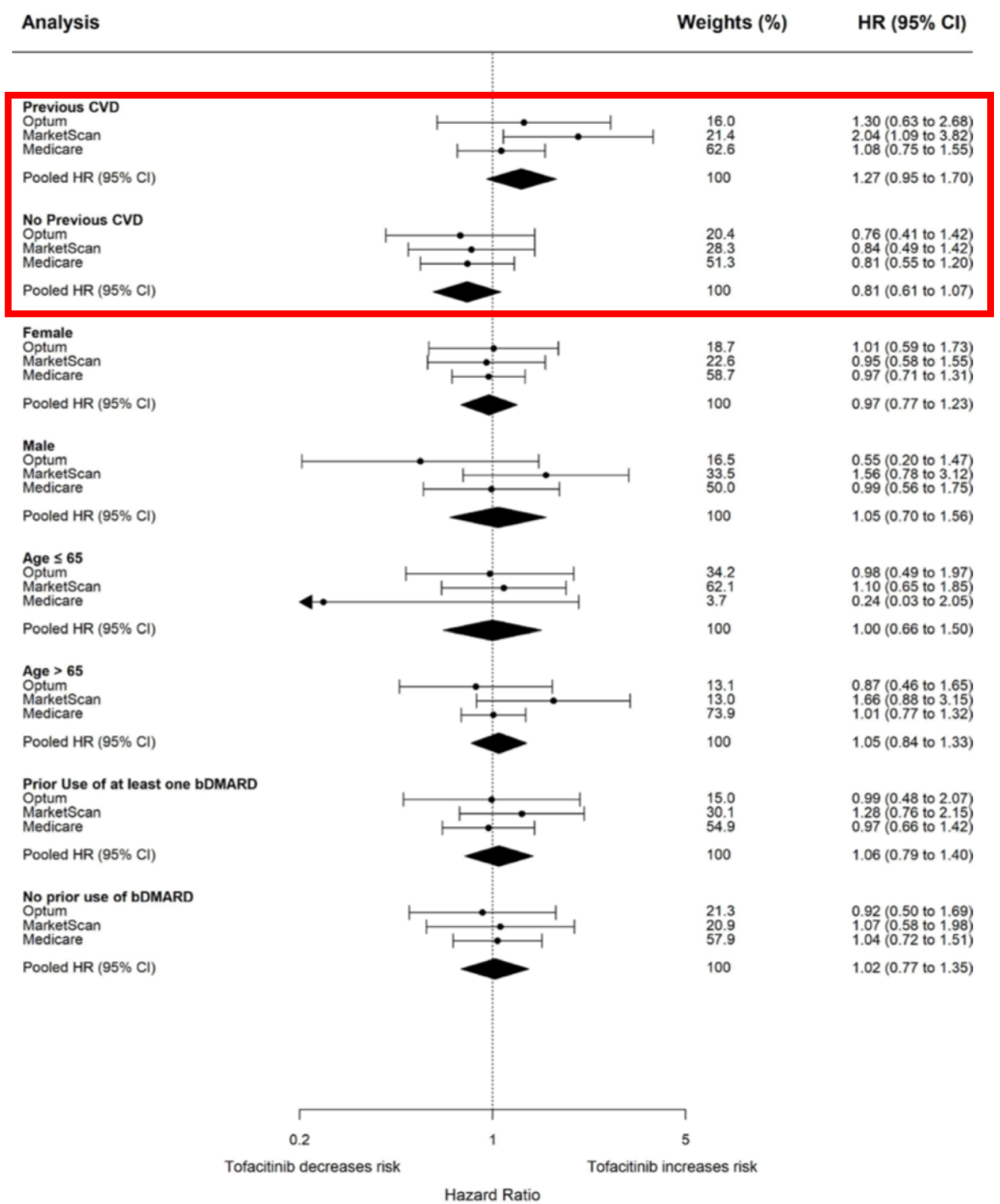


Figure 2. Incidence rates (IRs; number of first events/100 patient-years [PY]) of outcomes in the propensity score–trimmed population. IRs were based on different definitions of the risk window for outcomes with acute onset (major cardiovascular adverse events [MACE], serious infection events [SIEs], and herpes zoster [HZ]) or latent onset (malignancies and death). Tofacitinib initiators primarily received tofacitinib 5 mg twice daily. bDMARD, biological disease-modifying antirheumatic drug; CI, confidence interval; NMSC, nonmelanoma skin cancer.



USでのリアルワールドデータでは
CVDの既往のある患者では
心血管イベント発生リスクが高い傾向にはあったが
統計学的有意差はなかった

Ann Rheum Dis. 2022 Jun;81(6):798-804.

CLINICAL SCIENCE

Annals of the Rheumatic Diseases

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

Christina Charles-Schoeman [1], Maya H Buch [2,3], Maxime Dougados [4,5], Deepak L Bhatt [6], Jon T Giles [7], Steven R Ytterberg [8], Gary G Koch [9], Ivana Vranic [10], Joseph Wu [11], Cunshan Wang [11], Kenneth Kwok [12], Sujatha Menon [11], Jose L Rivas [13], Arne Yndestad [14], Carol A Connell [11], Zoltan Szekanecz [15]

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- 2014年3月~
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  - 少なくとも1つ以上の心血管リスクを有する
    - 現在の喫煙, 高血圧, HDL<40, DM, 若年発症のCADの家族歴, 関節外症状, CADの既往
  - 除外基準：現在もしくは以前のガン
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  - MACE(心血管死, 非致死性MI, 非致死性脳卒中), ガン(非メラノーマ性皮膚腫瘍を除く)

15%

ASCVD (atherosclerotic cardiovascular disease) =
①冠動脈疾患=MI, 不安定狭心症
②脳血管障害=脳梗塞, TIA
③末梢血管障害の既往=末梢の動脈血栓症

を対象としたpost hoc 解析

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 (%)†	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 (%)†	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 (%)†	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)

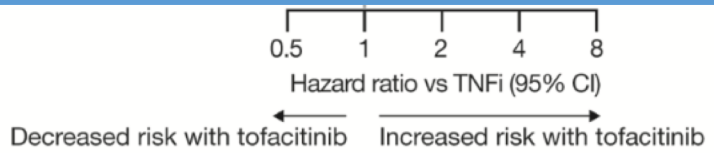
For patients randomised to the tofacitinib 10 mg two-times-per-day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two-times-per-day group.
*A 10-year risk of MACE was calculated with the ASCVD-PCE calculator and a 1.5 multiplier was applied for RA, as recommended by EULAR.[2 15] 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.
†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.

ASCVDを有する患者の背景
年齢 64歳 (65歳以上 4~5割)
女性7割
冠動脈疾患：8割
脳卒中：2割

MACE

A

			n/N (%)	HR vs TNFi (95% CI)	IR per 100 PY (95% CI) [PY]	IRD vs TNFi per 100 PY (95% CI)	NNH (PY) vs TNFi‡	NNH (5-yr) vs TNFi‡
MACE	Overall population† N=4362	Tofacitinib 5 mg BID	47/1455 (3.2%)	1.24 (0.81, 1.91)	0.91 (0.67, 1.21) [5166.3]	0.18 (–0.18, 0.53)	567	113
		Tofacitinib 10 mg BID	51/1456 (3.5%)	1.43 (0.94, 2.18)	1.05 (0.78, 1.38) [4872.0]	0.31 (–0.06, 0.69)	319	64
		Combined tofacitinib doses	98/2911 (3.4%)	1.33 (0.91, 1.94)	0.98 (0.79, 1.19) [10038.3]	0.24 (–0.06, 0.55)	412	82
		TNFi	37/1451 (2.5%)		0.73 (0.52, 1.01) [5045.3]			
	HxASCVD N=640 (14.7%)	Tofacitinib 5 mg BID	17/204 (8.3%)	1.96 (0.87, 4.40)	2.53 (1.47, 4.05) [672.7]	1.24 (–0.22, 2.71)	80	16
		Tofacitinib 10 mg BID	17/222 (7.7%)	2.01 (0.89, 4.50)	2.61 (1.52, 4.18) [651.7]	1.33 (–0.17, 2.82)	75	15
		Combined tofacitinib doses	34/426 (8.0%)	1.98 (0.95, 4.14)	2.57 (1.78, 3.59) [1324.4]	1.28 (0.08, 2.49)*	78	16
		TNFi	9/214 (4.2%)		1.28 (0.59, 2.44) [701.4]			
	No HxASCVD (CV RFs only) N=3722 (85.3%)	Tofacitinib 5 mg BID	30/1251 (2.4%)	1.03 (0.62, 1.73)	0.67 (0.45, 0.95) [4493.6]	0.02 (–0.31, 0.36)	4344	869
		Tofacitinib 10 mg BID	34/1234 (2.8%)	1.25 (0.76, 2.07)	0.81 (0.56, 1.13) [4220.2]	0.16 (–0.20, 0.52)	621	124
		Combined tofacitinib doses	64/2485 (2.6%)	1.14 (0.73, 1.78)	0.73 (0.57, 0.94) [8713.9]	0.09 (–0.21, 0.39)	1113	223
		TNFi	28/1237 (2.3%)		0.64 (0.43, 0.93) [4343.9]			



ASCVD**あり**患者に限定
Tofa 5*2 : Tofa 10*2 : TNFi =
17/204 (8.3%) : 17/222 (7.7%) : 9/214 (4.2%)

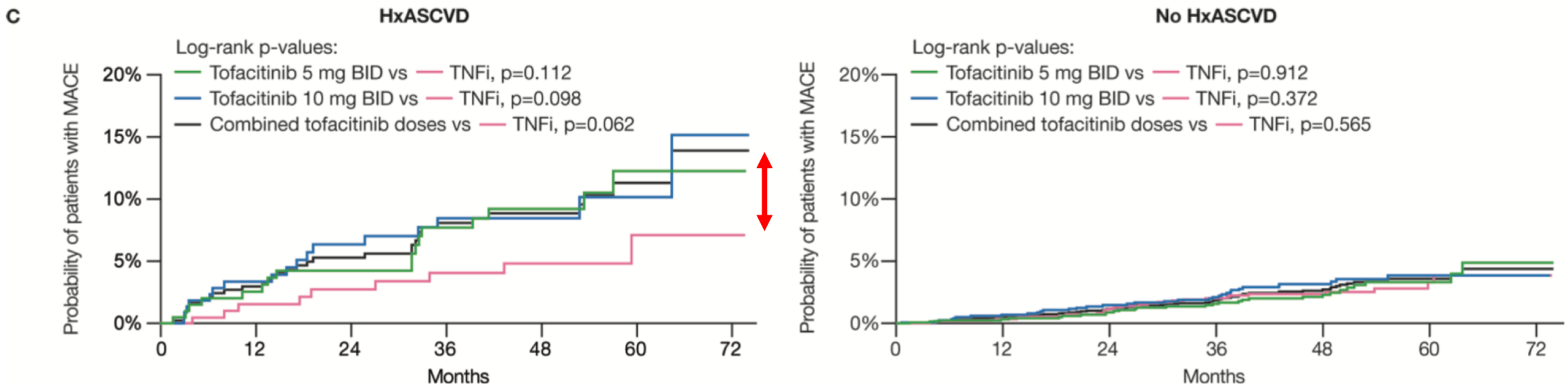
Tofa 5*2 vs TNFi
- HRs(95%CI) = 1.96 (0.87-4.40)
- NNH(95%CI) = 16

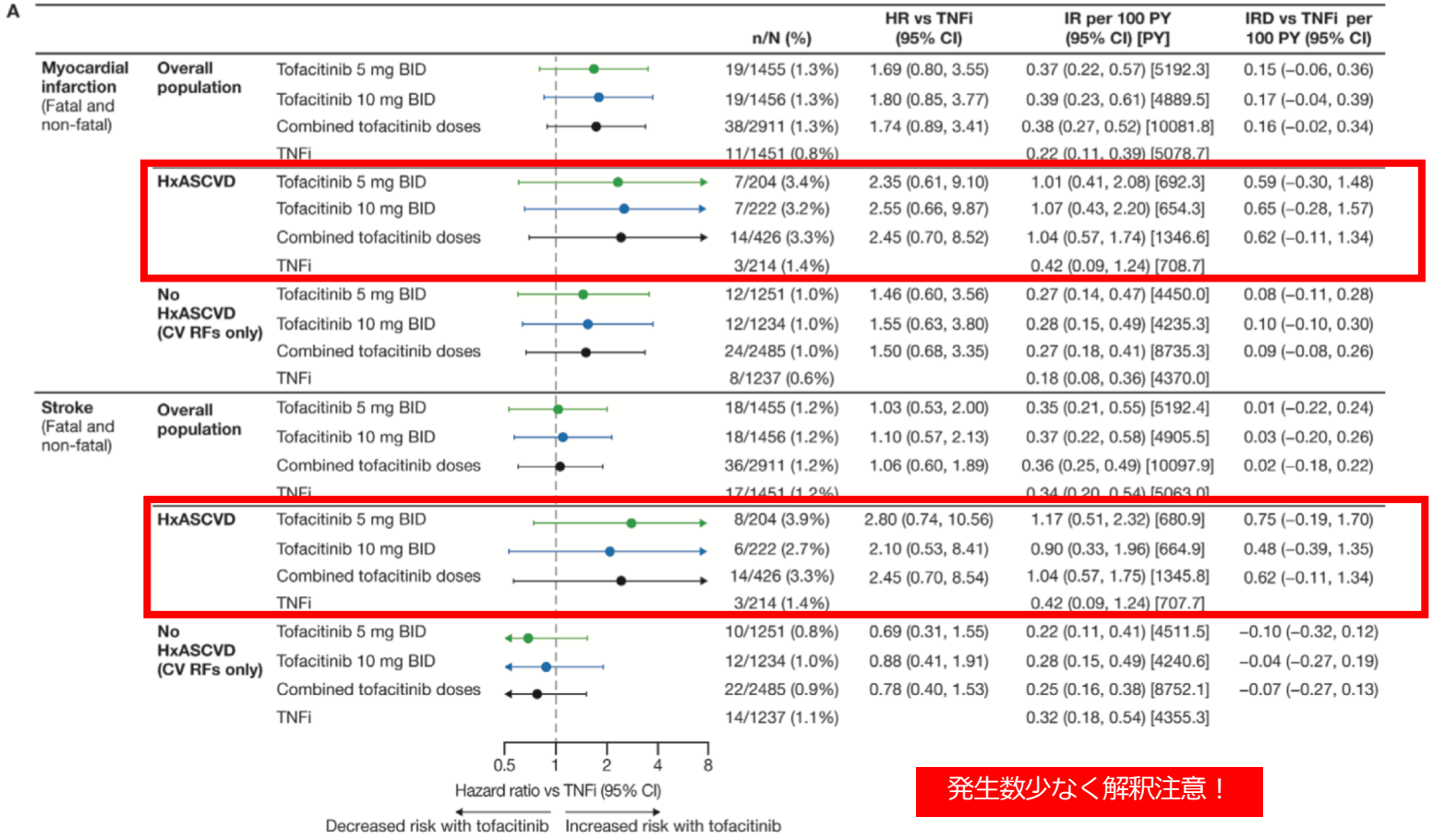
ASCVD**なし**患者に限定
Tofa 5*2 : Tofa 10*2 : TNFi =
30/1251 (2.4%) : 34/1234 (2.8%) : 28/1237 (2.3%)

Tofa 5*2 vs TNFi
- HRs(95%CI) = 1.03 (0.62-1.73)
- NNH(95%CI) = 869

ASCVDあり患者に限定

ASCVDなし患者に限定





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			n/N (%)	HR vs TNFi (95% CI)	IR per 100 PY (95% CI) [PY]	IRD vs TNFi per 100 PY (95% CI)
Myocardial infarction (Fatal and non-fatal)	**Overall population**	Tofacitinib 5 mg BID	19/1455 (1.3%)	1.69 (0.80, 3.55)	0.37 (0.22, 0.57) [5192.3]	0.15 (−0.06, 0.36)
		Tofacitinib 10 mg BID	19/1456 (1.3%)	1.80 (0.85, 3.77)	0.39 (0.23, 0.61) [4889.5]	0.17 (−0.04, 0.39)
		Combined tofacitinib doses	38/2911 (1.3%)	1.74 (0.89, 3.41)	0.38 (0.27, 0.52) [10081.8]	0.16 (−0.02, 0.34)
		TNFi	11/1451 (0.8%)		0.22 (0.11, 0.39) [5078.7]	
	HxASCVD	Tofacitinib 5 mg BID	7/204 (3.4%)	2.35 (0.61, 9.10)	1.01 (0.41, 2.08) [692.3]	0.59 (−0.30, 1.48)
		Tofacitinib 10 mg BID	7/222 (3.2%)	2.55 (0.66, 9.87)	1.07 (0.43, 2.20) [654.3]	0.65 (−0.28, 1.57)
		Combined tofacitinib doses	14/426 (3.3%)	2.45 (0.70, 8.52)	1.04 (0.57, 1.74) [1346.6]	0.62 (−0.11, 1.34)
		TNFi	3/214 (1.4%)		0.42 (0.09, 1.24) [708.7]	
	No HxASCVD (CV RFs only)	Tofacitinib 5 mg BID	12/1251 (1.0%)	1.46 (0.60, 3.56)	0.27 (0.14, 0.47) [4450.0]	0.08 (−0.11, 0.28)
		Tofacitinib 10 mg BID	12/1234 (1.0%)	1.55 (0.63, 3.80)	0.28 (0.15, 0.49) [4235.3]	0.10 (−0.10, 0.30)
		Combined tofacitinib doses	24/2485 (1.0%)	1.50 (0.68, 3.35)	0.27 (0.18, 0.41) [8735.3]	0.09 (−0.08, 0.26)
		TNFi	8/1237 (0.6%)		0.18 (0.08, 0.36) [4370.0]	
Stroke (Fatal and non-fatal)	**Overall population**	Tofacitinib 5 mg BID	18/1455 (1.2%)	1.03 (0.53, 2.00)	0.35 (0.21, 0.55) [5192.4]	0.01 (−0.22, 0.24)
		Tofacitinib 10 mg BID	18/1456 (1.2%)	1.10 (0.57, 2.13)	0.37 (0.22, 0.58) [4905.5]	0.03 (−0.20, 0.26)
		Combined tofacitinib doses	36/2911 (1.2%)	1.06 (0.60, 1.89)	0.36 (0.25, 0.49) [10097.9]	0.02 (−0.18, 0.22)
		TNFi	17/1451 (1.2%)		0.34 (0.20, 0.54) [5063.0]	
	HxASCVD	Tofacitinib 5 mg BID	8/204 (3.9%)	2.80 (0.74, 10.56)	1.17 (0.51, 2.32) [680.9]	0.75 (−0.19, 1.70)
		Tofacitinib 10 mg BID	6/222 (2.7%)	2.10 (0.53, 8.41)	0.90 (0.33, 1.96) [664.9]	0.48 (−0.39, 1.35)
		Combined tofacitinib doses	14/426 (3.3%)	2.45 (0.70, 8.54)	1.04 (0.57, 1.75) [1345.8]	0.62 (−0.11, 1.34)
		TNFi	3/214 (1.4%)		0.42 (0.09, 1.24) [707.7]	
	No HxASCVD (CV RFs only)	Tofacitinib 5 mg BID	10/1251 (0.8%)	0.69 (0.31, 1.55)	0.22 (0.11, 0.41) [4511.5]	−0.10 (−0.32, 0.12)
		Tofacitinib 10 mg BID	12/1234 (1.0%)	0.88 (0.41, 1.91)	0.28 (0.15, 0.49) [4240.6]	−0.04 (−0.27, 0.19)
		Combined tofacitinib doses	22/2485 (0.9%)	0.78 (0.40, 1.53)	0.25 (0.16, 0.38) [8752.1]	−0.07 (−0.27, 0.13)
		TNFi	14/1237 (1.1%)		0.32 (0.18, 0.54) [4355.3]	

発生数少なく解釈注意！

MI

ASCVD**あり**患者に限定
Tofa 5*2 : Tofa 10*2 : TNFi =
7/204 (3.4%) : 7/222 (3.2%) : 3/214 (1.4%)

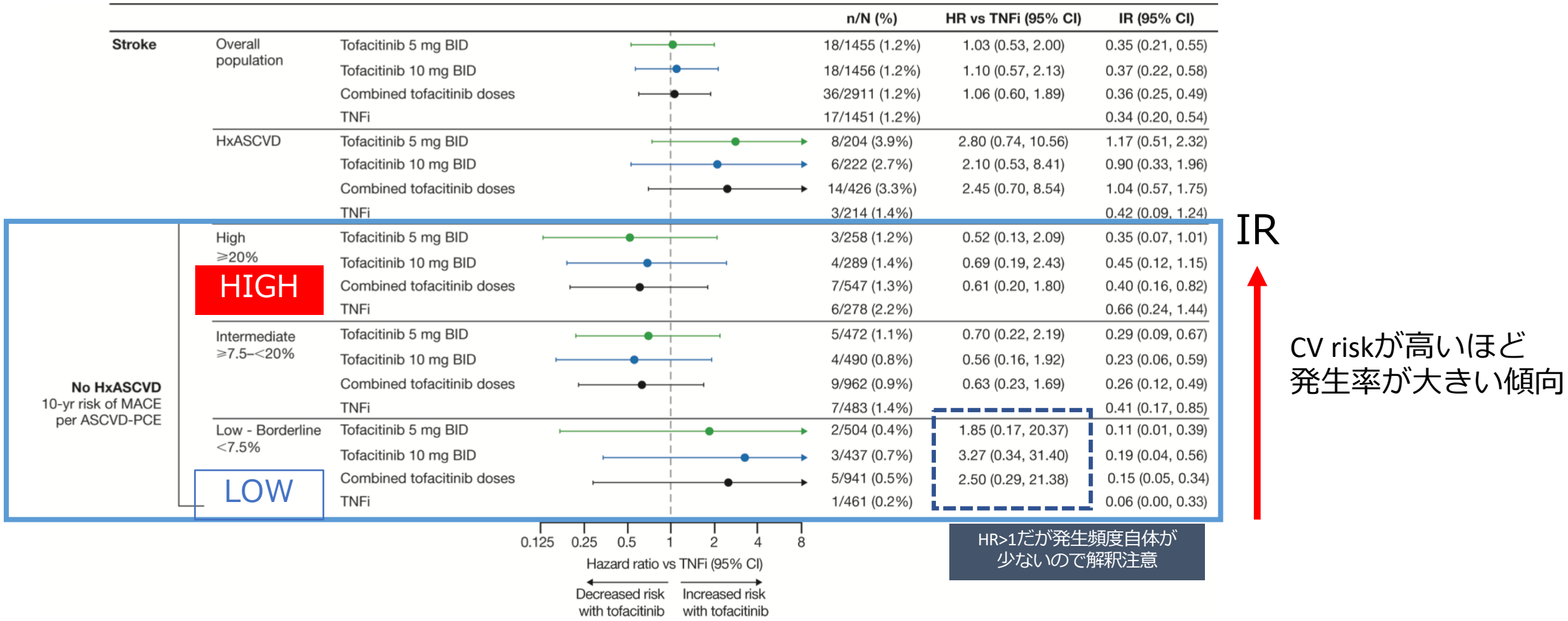
Tofa 5*2 vs TNFi
- HRs(95%CI) = 2.35 (0.61-9.10)

Stroke

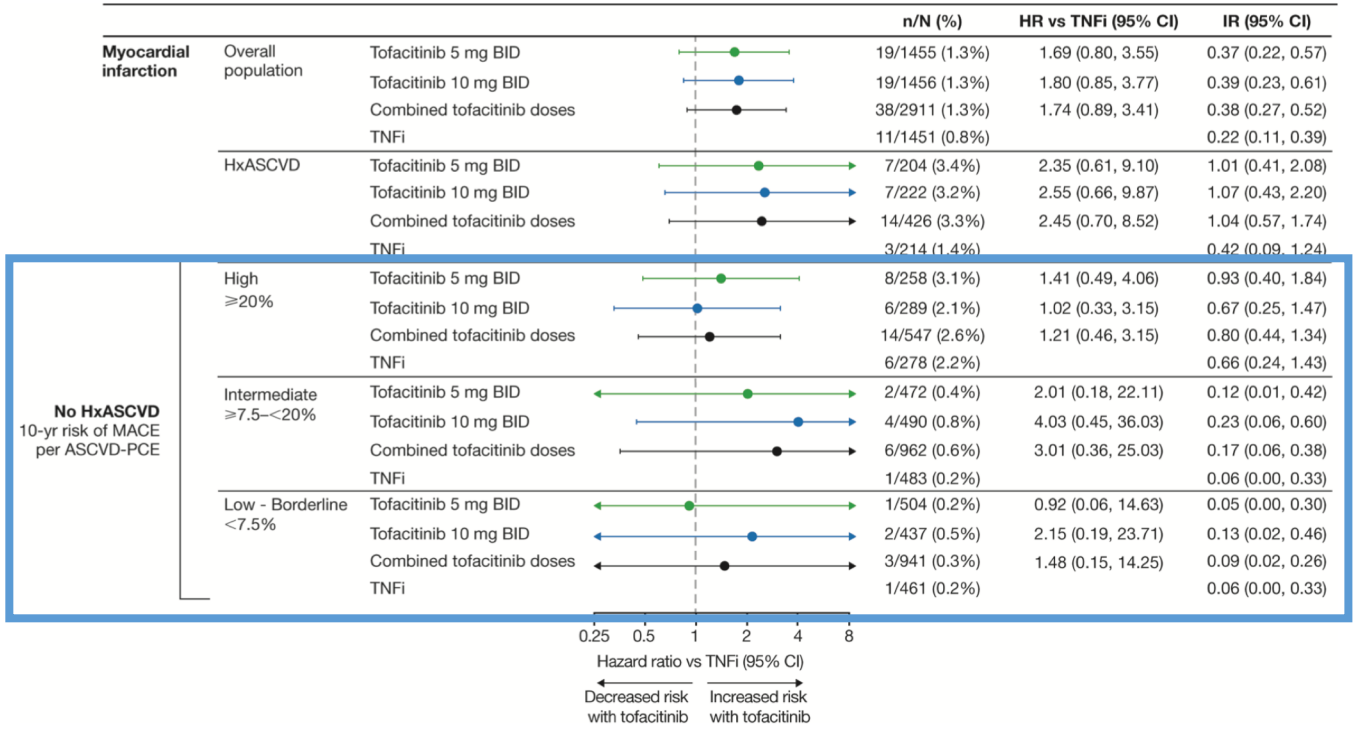
ASCVD**あり**患者に限定
Tofa 5*2 : Tofa 10*2 : TNFi =
8/204 (3.9%) : 6/222 (2.7%) : 3/214 (1.4%)

Tofa 5*2 vs TNFi
- HRs(95%CI) = 2.80 (0.74-10.56)

MACE　ASCVDなし患者に限定

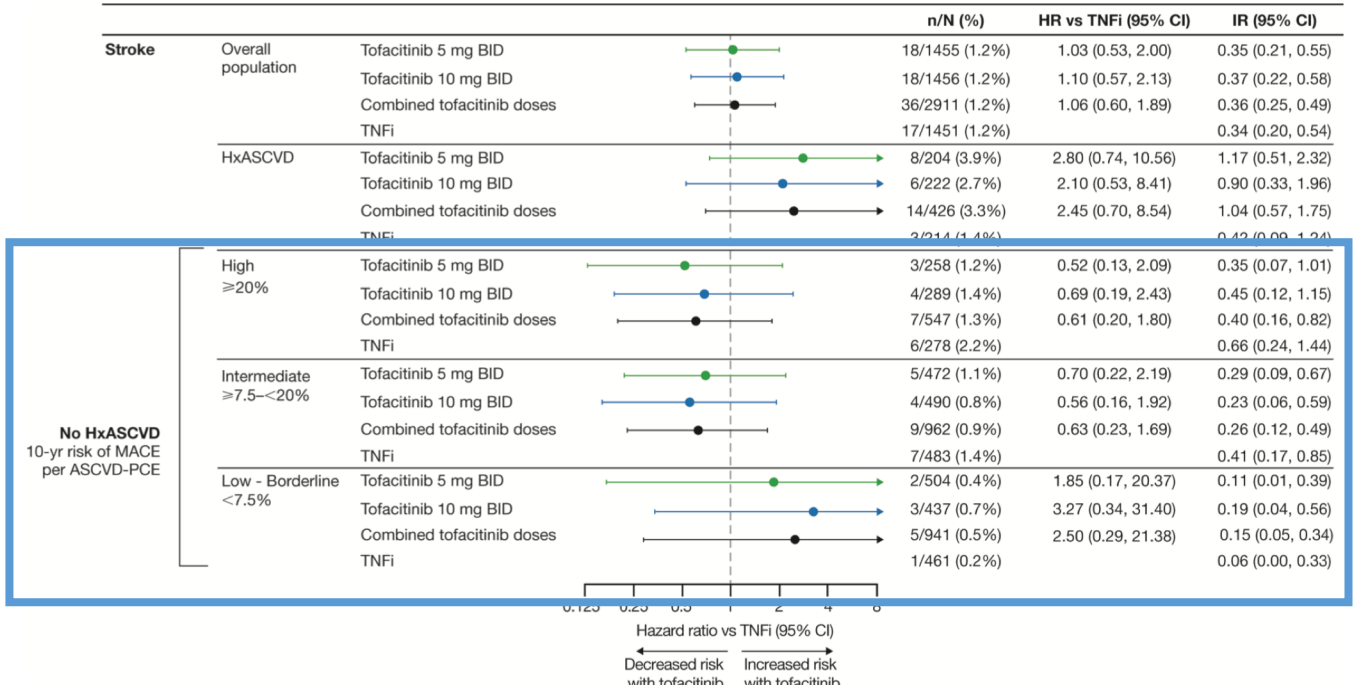


MI



			n/N (%)	HR vs TNFi (95% CI)	IR (95% CI)
Myocardial infarction	Overall population	Tofacitinib 5 mg BID	19/1455 (1.3%)	1.69 (0.80, 3.55)	0.37 (0.22, 0.57)
		Tofacitinib 10 mg BID	19/1456 (1.3%)	1.80 (0.85, 3.77)	0.39 (0.23, 0.61)
		Combined tofacitinib doses	38/2911 (1.3%)	1.74 (0.89, 3.41)	0.38 (0.27, 0.52)
		TNFi	11/1451 (0.8%)		0.22 (0.11, 0.39)
	HxASCVD	Tofacitinib 5 mg BID	7/204 (3.4%)	2.35 (0.61, 9.10)	1.01 (0.41, 2.08)
		Tofacitinib 10 mg BID	7/222 (3.2%)	2.55 (0.66, 9.87)	1.07 (0.43, 2.20)
		Combined tofacitinib doses	14/426 (3.3%)	2.45 (0.70, 8.52)	1.04 (0.57, 1.74)
		TNFi	3/214 (1.4%)		0.42 (0.09, 1.24)
No HxASCVD 10-yr risk of MACE per ASCVD-PCE	High ≥20%	Tofacitinib 5 mg BID	8/258 (3.1%)	1.41 (0.49, 4.06)	0.93 (0.40, 1.84)
		Tofacitinib 10 mg BID	6/289 (2.1%)	1.02 (0.33, 3.15)	0.67 (0.25, 1.47)
		Combined tofacitinib doses	14/547 (2.6%)	1.21 (0.46, 3.15)	0.80 (0.44, 1.34)
		TNFi	6/278 (2.2%)		0.66 (0.24, 1.43)
	Intermediate ≥7.5–<20%	Tofacitinib 5 mg BID	2/472 (0.4%)	2.01 (0.18, 22.11)	0.12 (0.01, 0.42)
		Tofacitinib 10 mg BID	4/490 (0.8%)	4.03 (0.45, 36.03)	0.23 (0.06, 0.60)
		Combined tofacitinib doses	6/962 (0.6%)	3.01 (0.36, 25.03)	0.17 (0.06, 0.38)
		TNFi	1/483 (0.2%)		0.06 (0.00, 0.33)
	Low - Borderline <7.5%	Tofacitinib 5 mg BID	1/504 (0.2%)	0.92 (0.06, 14.63)	0.05 (0.00, 0.30)
		Tofacitinib 10 mg BID	2/437 (0.5%)	2.15 (0.19, 23.71)	0.13 (0.02, 0.46)
		Combined tofacitinib doses	3/941 (0.3%)	1.48 (0.15, 14.25)	0.09 (0.02, 0.26)
		TNFi	1/461 (0.2%)		0.06 (0.00, 0.33)

Stroke



			n/N (%)	HR vs TNFi (95% CI)	IR (95% CI)
Stroke	Overall population	Tofacitinib 5 mg BID	18/1455 (1.2%)	1.03 (0.53, 2.00)	0.35 (0.21, 0.55)
		Tofacitinib 10 mg BID	18/1456 (1.2%)	1.10 (0.57, 2.13)	0.37 (0.22, 0.58)
		Combined tofacitinib doses	36/2911 (1.2%)	1.06 (0.60, 1.89)	0.36 (0.25, 0.49)
		TNFi	17/1451 (1.2%)		0.34 (0.20, 0.54)
	HxASCVD	Tofacitinib 5 mg BID	8/204 (3.9%)	2.80 (0.74, 10.56)	1.17 (0.51, 2.32)
		Tofacitinib 10 mg BID	6/222 (2.7%)	2.10 (0.53, 8.41)	0.90 (0.33, 1.96)
		Combined tofacitinib doses	14/426 (3.3%)	2.45 (0.70, 8.54)	1.04 (0.57, 1.75)
		TNFi	3/214 (1.4%)		0.42 (0.09, 1.24)
No HxASCVD 10-yr risk of MACE per ASCVD-PCE	High ≥20%	Tofacitinib 5 mg BID	3/258 (1.2%)	0.52 (0.13, 2.09)	0.35 (0.07, 1.01)
		Tofacitinib 10 mg BID	4/289 (1.4%)	0.69 (0.19, 2.43)	0.45 (0.12, 1.15)
		Combined tofacitinib doses	7/547 (1.3%)	0.61 (0.20, 1.80)	0.40 (0.16, 0.82)
		TNFi	6/278 (2.2%)		0.66 (0.24, 1.44)
	Intermediate ≥7.5–<20%	Tofacitinib 5 mg BID	5/472 (1.1%)	0.70 (0.22, 2.19)	0.29 (0.09, 0.67)
		Tofacitinib 10 mg BID	4/490 (0.8%)	0.56 (0.16, 1.92)	0.23 (0.06, 0.59)
		Combined tofacitinib doses	9/962 (0.9%)	0.63 (0.23, 1.69)	0.26 (0.12, 0.49)
		TNFi	7/483 (1.4%)		0.41 (0.17, 0.85)
	Low - Borderline <7.5%	Tofacitinib 5 mg BID	2/504 (0.4%)	1.85 (0.17, 20.37)	0.11 (0.01, 0.39)
		Tofacitinib 10 mg BID	3/437 (0.7%)	3.27 (0.34, 31.40)	0.19 (0.04, 0.56)
		Combined tofacitinib doses	5/941 (0.5%)	2.50 (0.29, 21.38)	0.15 (0.05, 0.34)
		TNFi	1/461 (0.2%)		0.06 (0.00, 0.33)

ASCVDなし患者に限定

IR

CV riskが高いほど
発生率が大きい傾向

CV riskと発生率には
一定の傾向認めず

結果のまとめ

MACE in patients with ASCVD
Tofa 5*2 vs TNFi
- HRs(95%CI) = 1.96 (0.87-4.40)
- NNH(95%CI) = 16

- ORAL surveillanceの被検者(高齢・心血管リスクあり)のうち<u>ASCVDを持つ患者ではMACE riskが増加する傾向にあった</u>
  - MIやstrokeのいずれも増加傾向であったが
    イベント発生率が少なく解釈には注意が必要

- 一方で心血管リスクを有するのみでASCVDの既往がない場合にはMACE riskは増加しない傾向があった

DISCUSSION

- ORAL surveillanceではMACE発生リスクを高くするためにCVリスクの高い患者を組入れた

- このような患者を対象としない限り長期的なCVリスクの安全性は見えてこない可能性が示唆された

LIMITATIONS

- post hoc analysisなので, ASCVDを有する高齢RA患者においてTofaがTNFiと比較してMACEを増やす可能性については仮説の域を出ない

- ASCVD患者が少なかったため, HRsやIRsの信頼区間が大きくなっており解釈には注意が必要

臨床への応用

- まだ仮説の域は出ないが…以下の患者はJAK阻害薬は避ける
  - 50～65歳を超える患者
  - 特に虚血性心疾患, 脳梗塞, 末梢動脈疾患がある患者
  - DVT/PEを有する患者

FDAはTofa, Bari, Upaの全てにblack box warning

- IL-6阻害薬であるTCZでは心血管イベントの増加は認められていないが(ENTRACTE study), BariやUpaも今のところはTofaと同様に扱う方が無難
- pure TYK2阻害薬のdeucravacitinibなどで同様の傾向が見られるかは気になるところ