# Journal Club 2022/7/5　　by Dr.大村

Rheumatoid arthritis

EPIDEMIOLOGICAL SCIENCE

## Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study

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## Tofacitinib and risk of malignancy: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) Study

Farzin Khosrow-Khavar, PhD;[1] Rishi J. Desai, PhD[1]; Hemin Lee, MD, MPH;[1] Su Been Lee, BA;[1] Seoyoung C. Kim, MD, ScD[1,2]

Arthritis Rheumatol 2022; online ahead of print

# 背景　Oral Surveillance（N Engl J Med 2022; 386: 316-326 ）

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

主な選択基準:
- 50歳以上
- 1つ以上の心血管リスクをもつ
- MTX-IR

デザイン
- TOFA 5mg bid or 10mg bid or TNFi（ADA 40mg or ETN 50mg）
- 無作為化非盲検非劣勢安全性試験（phase IIIb-IV）4年間観察

| Tofacitinib, 5 mg Twice Daily (N=1455) | Tofacitinib, 10 mg Twice Daily (N=1456)† | TNF Inhibitor (N=1451) |
|---|---|---|

主要評価項目：
- MACE　HR 1.24（5mg）
- 悪性腫瘍　HR 1.47（5mg）

Rheumatoid arthritis

EPIDEMIOLOGICAL SCIENCE

# Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study

Farzin Khosrow-Khavar ,[1] Seoyoung C Kim ,[1,2] Hemin Lee ,[1] Su Been Lee,[1] Rishi J Desai [1]

TOFA vs TNFiで
CV eventリスクは?

**P: 米国の3つの健康保険関連データベース*登録RA患者で、ゼルヤンツ（TOFA）もしくはTNF阻害薬（TNFI)を初めて開始された患者**
**RWE (Real World Evidence)コホート: 上記すべての患者**
**RCT-duplicateコホート: 上記のうち、Oral Surveillanceのinclusion, exclusion criteriaを適用した患者群**

**E: 上記PのうちTOFA群**

**C: 上記PのうちTNFI群**

**O: 心筋梗塞 or 脳卒中で入院（TOFA/TNFIを中止、変更、死亡、study期間終了までのイベント）**

*__Optum__: UnitedHealth Groupの健康保険部門 (2億人以上)
__MarketScan__ : IBMの運営する公的・私的な被保険者の請求データを提供するサービス（7800万人）
__Medicare__: 米国の公的健康保険（65歳以上もしくは65歳以下の障害者）

# RWEコホートRA患者背景

75-76の交絡因子で調節後

**Table 1** Select baseline characteristics of RWE RA patients initiating tofacitinib or TNFi after propensity score fine stratification weighting

| Variable | Optum | | | MarketScan* | | | Medicare | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tofacitinib (N=3761) | TNFI (N=24688) | SD (%) | Tofacitinib (N=5298) | TNFI (N=28727) | SD (%) | Tofacitinib (N=3782) | TNFI (N=35816) | SD (%) |
| Demographics | | | | | | | | | |
| Age; mean (std) | 56.8 (12.5) | 57.1 (13.2) | −2.6 | 54.7 (11.5) | 55.0 (12.0) | −1.9 | 72.1 (5.6) | 72.2 (5.6) | −1.3 |
| Female gender; n (%) | 3043 (80.9) | 20046 (81.2) | −0.7 | 4333 (81.8) | 23503 (81.8) | −0.1 | 3134 (82.9) | 29819 (83.3) | −1.0 |
| White race; n (%) | 2395 (63.7) | 15691 (63.6) | 0.3 | – | – | – | 3026 (80.0) | 28449 (79.4) | 1.4 |
| Black race; n (%) | 412 (11.0) | 2737 (11.1) | −0.4 | – | – | – | 410 (10.8) | 4051 (11.3) | −1.5 |
| Asian race; n (%) | 103 (2.7) | 643 (2.6) | 0.8 | – | – | – | 85 (2.2) | 810 (2.3) | −0.1 |
| Hispanic race; n (%) | 471 (12.5) | 3127 (12.7) | −0.4 | – | – | – | 126 (3.3) | 1224 (3.4) | −0.5 |
| RA related variables | | | | | | | | | |
| No of unique bDMARDs; mean (std) | 1.6 (0.7) | 1.6 (0.7) | 2.4 | 1.8 (0.8) | 1.8 (0.8) | 1.6 | 1.6 (0.7) | 1.6 (0.7) | 2.2 |
| Non-biologic DMARDs | | | | | | | | | |
| No of distinct csDMARDs; mean (std) | 1.0 (0.8) | 1.0 (0.8) | 0.3 | 1.0 (0.8) | 1.0 (0.8) | 1.8 | 1.1 (0.8) | 1.1 (0.8) | 0.8 |
| Any csDMARD use; n (%) | 2723 (72.4) | 17851 (72.3) | 0.2 | 3989 (75.3) | 21451 (74.7) | 1.4 | 2889 (76.4) | 27253 (76.1) | 0.7 |
| Methotrexate; n (%) | 1731 (46.0) | 11244 (45.5) | 1.0 | 2722 (51.4) | 14582 (50.8) | 1.2 | 1954 (51.7) | 18239 (50.9) | 1.5 |
| Hydroxychloroquine; n (%) | 933 (24.8) | 6143 (24.9) | −0.2 | 1254 (23.7) | 6639 (23.1) | 1.3 | 950 (25.1) | 8915 (24.9) | 0.5 |
| Leflunomide; n (%) | 799 (21.2) | 5273 (21.4) | −0.3 | 1065 (20.1) | 5756 (20.0) | 0.2 | 828 (21.9) | 7935 (22.2) | −0.6 |
| Sulfasalazine; n (%) | 388 (10.3) | 2558 (10.4) | −0.1 | 491 (9.3) | 2604 (9.1) | 0.7 | 418 (11.1) | 3988 (11.1) | −0.3 |
| Glucocorticoid use | | | | | | | | | |
| Prior use of oral glucocorticoids (365 days); n (%) | 2814 (74.8) | 18489 (74.9) | −0.2 | 3896 (73.5) | 21185 (73.7) | −0.5 | 2846 (75.3) | 26944 (75.2) | 0.1 |
| Recent use of oral glucocorticoids (60 days); n (%) | 1898 (50.5) | 12458 (50.5) | 0.0 | 2625 (49.5) | 14274 (49.7) | −0.3 | 2115 (55.9) | 20072 (56.0) | −0.2 |
| Cumulative dose of oral steroids in mg; mean (std) | 934.5 (1,485.5) | 935.6 (5,973.1) | 0.0 | 1952.8 (25,666.3) | 2094 (26,335.2) | −0.5 | 1024.5 (1,195.2) | 1019.6 (1,279.5) | 0.4 |

性別、人種
RA治療薬
CVD risk因子
合併症
抗血栓薬
心血管薬
受診頻度
など

# RWEコホートRA患者背景（続き）

**Table 1** Select baseline characteristics of RWE RA patients initiating tofacitinib or TNFi after propensity score fine stratification weighting

| Variable | Optum | | | MarketScan* | | | Medicare | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tofacitinib (N=3761) | TNFI (N=24 688) | SD (%) | Tofacitinib (N=5298) | TNFI (N=28 727) | SD (%) | Tofacitinib (N=3782) | TNFI (N=35 816) | SD (%) |
| CVD risk factors | | | | | | | | | |
| Obesity; n (%) | 882 (23.5) | 5876 (23.8) | −0.8 | 810 (15.3) | 4392 (15.3) | 0.0 | 581 (15.4) | 5446 (15.2) | 0.4 |
| Smoking; n (%) | 749 (19.9) | 4925 (20.0) | −0.1 | 465 (8.8) | 2566 (8.9) | −0.6 | 972 (25.7) | 9180 (25.6) | 0.2 |
| Atrial fibrillation; n (%) | 154 (4.1) | 1038 (4.2) | −0.6 | 140 (2.6) | 752 (2.6) | 0.1 | 397 (10.5) | 3723 (10.4) | 0.3 |
| Coronary artery disease; n (%) | 381 (10.1) | 2564 (10.4) | −0.8 | 425 (8.0) | 2394 (8.3) | −1.1 | 904 (23.9) | 8477 (23.7) | 0.5 |
| Type 2 diabetes mellitus; n (%) | 805 (21.4) | 5353 (21.7) | −0.7 | 835 (15.8) | 4563 (15.9) | −0.3 | 1162 (30.7) | 10 918 (30.5) | 0.5 |
| Heart failure; n (%) | 192 (5.1) | 1324 (5.4) | −1.2 | 175 (3.3) | 960 (3.3) | −0.2 | 450 (11.9) | 4267 (11.9) | 0.0 |
| Hypertension; n (%) | 1966 (52.3) | 13 075 (53.0) | −1.4 | 2355 (44.5) | 12 922 (45.0) | −1.1 | 3110 (82.2) | 29 417 (82.1) | 0.3 |
| Hyperlipidaemia; n (%) | 1619 (43.0) | 10 706 (43.4) | −0.6 | 2002 (37.8) | 10 937 (38.1) | −0.6 | 2569 (67.9) | 24 187 (67.5) | 0.8 |
| Stroke or transient ischaemic attack; n (%) | 92 (2.4) | 605 (2.5) | 0.0 | 113 (2.1) | 620 (2.2) | −0.2 | 134 (3.5) | 1255 (3.5) | 0.2 |
| Peripheral vascular disease; n (%) | 163 (4.3) | 1103 (4.5) | −0.6 | 141 (2.7) | 776 (2.7) | −0.3 | 442 (11.7) | 4166 (11.6) | 0.2 |
| Venous thromboembolism; n (%) | 102 (2.7) | 699 (2.8) | −0.7 | 141 (2.7) | 765 (2.7) | 0.0 | 103 (2.7) | 996 (2.8) | −0.4 |
| Other comorbidities | | | | | | | | | |
| Chronic liver disease; n (%) | 273 (7.3) | 1792 (7.3) | 0.0 | 315 (5.9) | 1696 (5.9) | 0.2 | 317 (8.4) | 2985 (8.3) | 0.2 |
| Chronic kidney disease (Stage 3+); n (%) | 212 (5.6) | 1428 (5.8) | −0.6 | 168 (3.2) | 926 (3.2) | −0.3 | 442 (11.7) | 4207 (11.7) | −0.2 |
| COPD; n (%) | 599 (15.9) | 3992 (16.2) | −0.7 | 629 (11.9) | 3454 (12.0) | −0.5 | 1041 (27.5) | 9955 (27.8) | −0.6 |
| Inflammatory bowel disease; n (%) | 63 (1.7) | 415 (1.7) | 0.0 | 68 (1.3) | 353 (1.2) | 0.5 | 50 (1.3) | 461 (1.3) | 0.3 |
| Psoriasis; n (%) | 170 (4.5) | 1100 (4.5) | 0.3 | 169 (3.2) | 885 (3.1) | 0.6 | 119 (3.1) | 1028 (2.9) | 1.6 |
| Cancer (excluding NMSC); n (%) | 484 (12.9) | 3267 (13.2) | −1.1 | 692 (13.1) | 3783 (13.2) | −0.3 | 789 (20.9) | 7438 (20.8) | 0.2 |
| Combined Comorbidity Index; mean (std) | 1.2 (2.0) | 1.2 (2.0) | −0.8 | 0.7 (1.5) | 0.7 (1.5) | −0.7 | 1.8 (2.4) | 1.9 (2.4) | −0.4 |
| Frailty score; mean (std) | 0.2 (0.0) | 0.2 (0.0) | −0.8 | 0.1 (0.0) | 0.1 (0.0) | −1.5 | 0.2 (0.0) | 0.2 (0.0) | 0.0 |

# RWE/RCT-duplicateコホートでのCVDイベント率（背景調節なし）

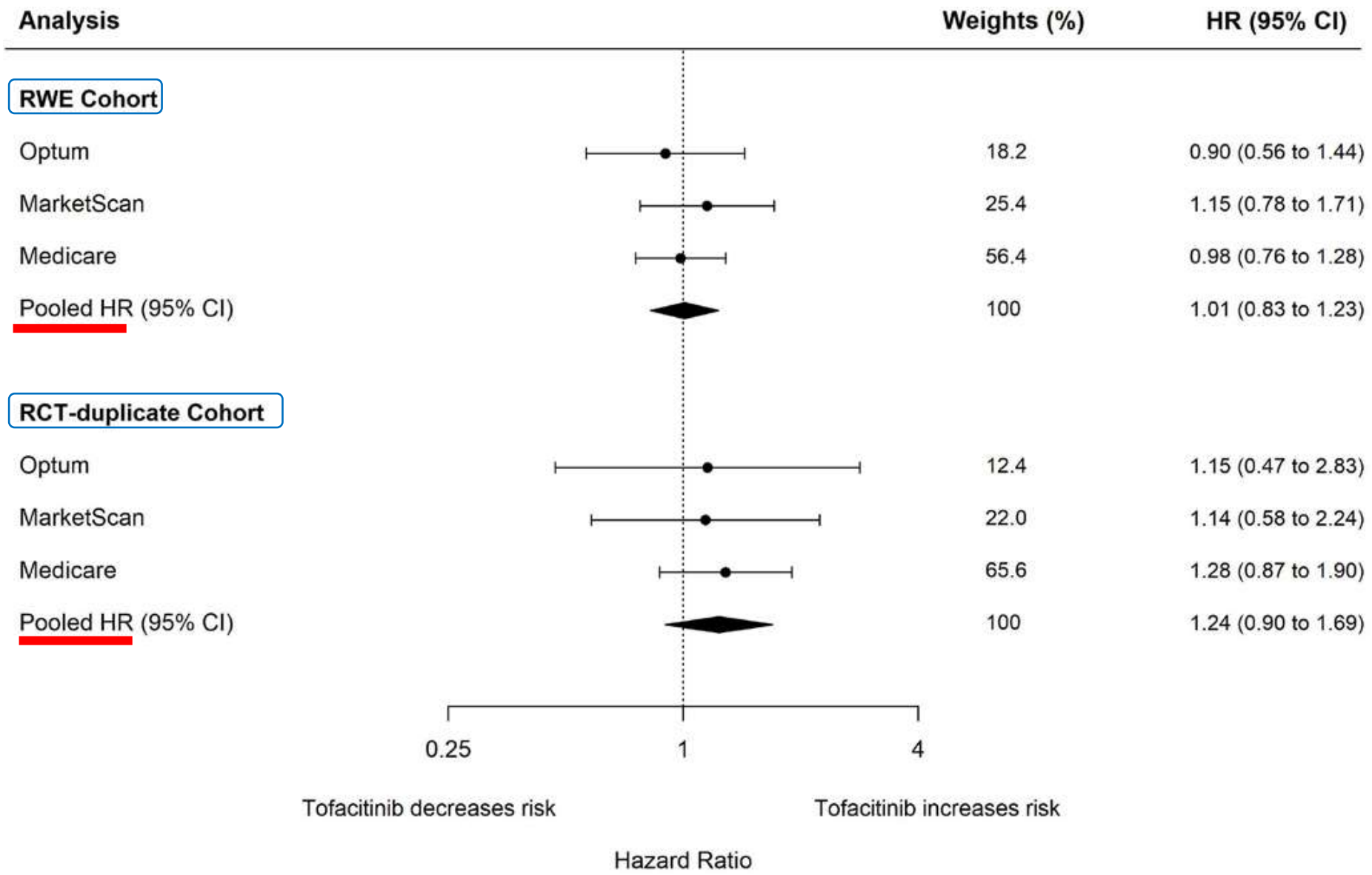
**Table 2** Incidence rate, crude HR, and corresponding 95% CIs for the primary composite cardiovascular outcome in RWE and RCT-duplicate cohort of rheumatoid arthritis patients initiating treatment with tofacitinib or TNFi

| Data source | Exposure group | Sample size | Events | Total person years of follow-up | Crude incidence rate (95% CI)* | Crude incidence rate difference (95% CI)* | Crude HR (95% CI) |
|---|---|---|---|---|---|---|---|
| RWE Cohort | | | | | | | |
| Optum | TNFI | 24805 | 143 | 23458 | 0.61 (0.51 to 0.72) | Ref | Ref |
| | Tofacitinib | 3763 | 24 | 3273 | 0.73 (0.47 to 1.09) | 0.12 (-0.19 to 0.43) | 1.21 (0.78 to 1.86) |
| MarketScan | TNFI | 28776 | 141 | 27257 | 0.52 (0.44 to 0.61) | Ref | Ref |
| | Tofacitinib | 5307 | 35 | 4655 | 0.75 (0.52 to 1.05) | 0.23 (-0.03 to 0.50) | 1.44 (0.99 to 2.09) |
| Medicare | TNFI | 35830 | 562 | 30277 | 1.86 (1.71 to 2.02) | Ref | Ref |
| | Tofacitinib | 3782 | 69 | 3229 | 2.14 (1.66 to 2.70) | 0.28 (-0.25 to 0.81) | 1.15 (0.89 to 1.48) |
| Pooled | TNFI | 89411 | 846 | 80992 | 1.24 (1.16 to 1.33) | Ref | Ref |
| | Tofacitinib | 12852 | 128 | 11157 | 1.31 (1.10 to 1.56) | 0.20 (0.01 to 0.39) | 1.23 (1.02 to 1.48) |
| RCT-duplicate cohort | | | | | | | |
| Optum | TNFI | 6077 | 56 | 5932 | 0.94 (0.71 to 1.23) | Ref | Ref |
| | Tofacitinib | 801 | 10 | 752 | 1.33 (0.64 to 2.45) | 0.39 (-0.47 to 1.25) | 1.43 (0.73 to 2.81) |
| MarketScan | TNFI | 6920 | 55 | 6857 | 0.80 (0.60 to 1.04) | Ref | Ref |
| | Tofacitinib | 1151 | 13 | 1069 | 1.22 (0.65 to 2.08) | 0.41 (-0.28 to 1.11) | 1.50 (0.82 to 2.74) |
| Medicare | TNFI | 18576 | 289 | 16241 | 1.78 (1.58 to 2.00) | Ref | Ref |
| | Tofacitinib | 1545 | 32 | 1338 | 2.39 (1.64 to 3.38) | 0.61 (-0.24 to 1.47) | 1.35 (0.93 to 1.94) |
| Pooled | TNFI | 31573 | 400 | 29030 | 1.46 (1.32 to 1.61) | Ref | Ref |
| | Tofacitinib | 3497 | 55 | 3159 | 1.83 (1.41 to 2.39) | 0.46 (0.01 to 0.92) | 1.39 (1.05 to 1.85) |

All estimates were pooled using fixed effects models with inverse variance weighting.
*Per 100 person-years.
CI, confidence interval; HR, hazard ratio; RCT, randomised controlled trial; RWE, real world evidence; TNFI, tumour necrosis factor inhibitors.

Figure 1

# RWE/RCT-duplicateコホートでのCVD risk （背景調節後）




Oral surveillanceではHR 1.33 (0.91-1.94)

Figure 2.1

# RWEコホートのサブグループ解析でのCVD risk （背景調節後）

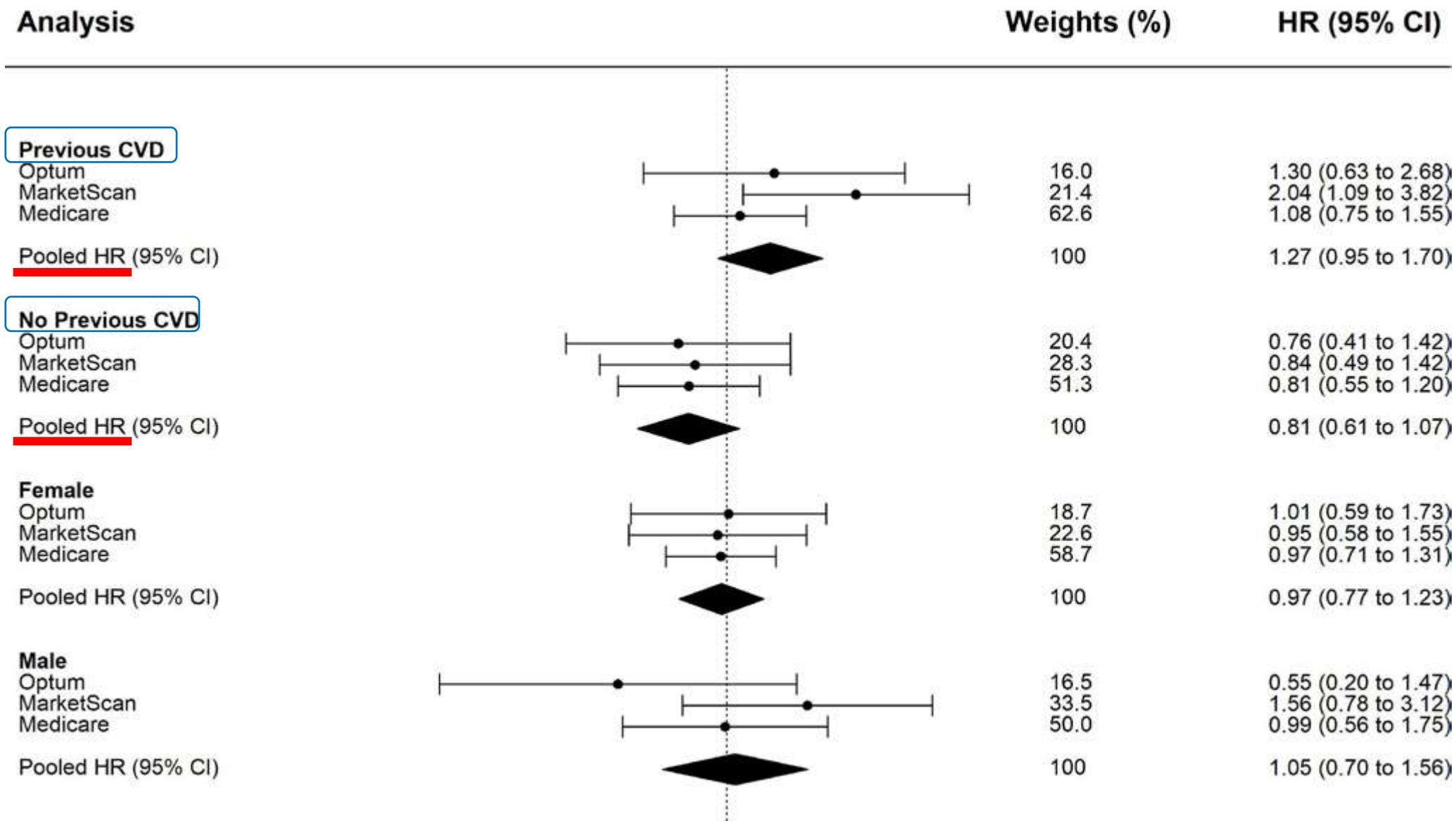
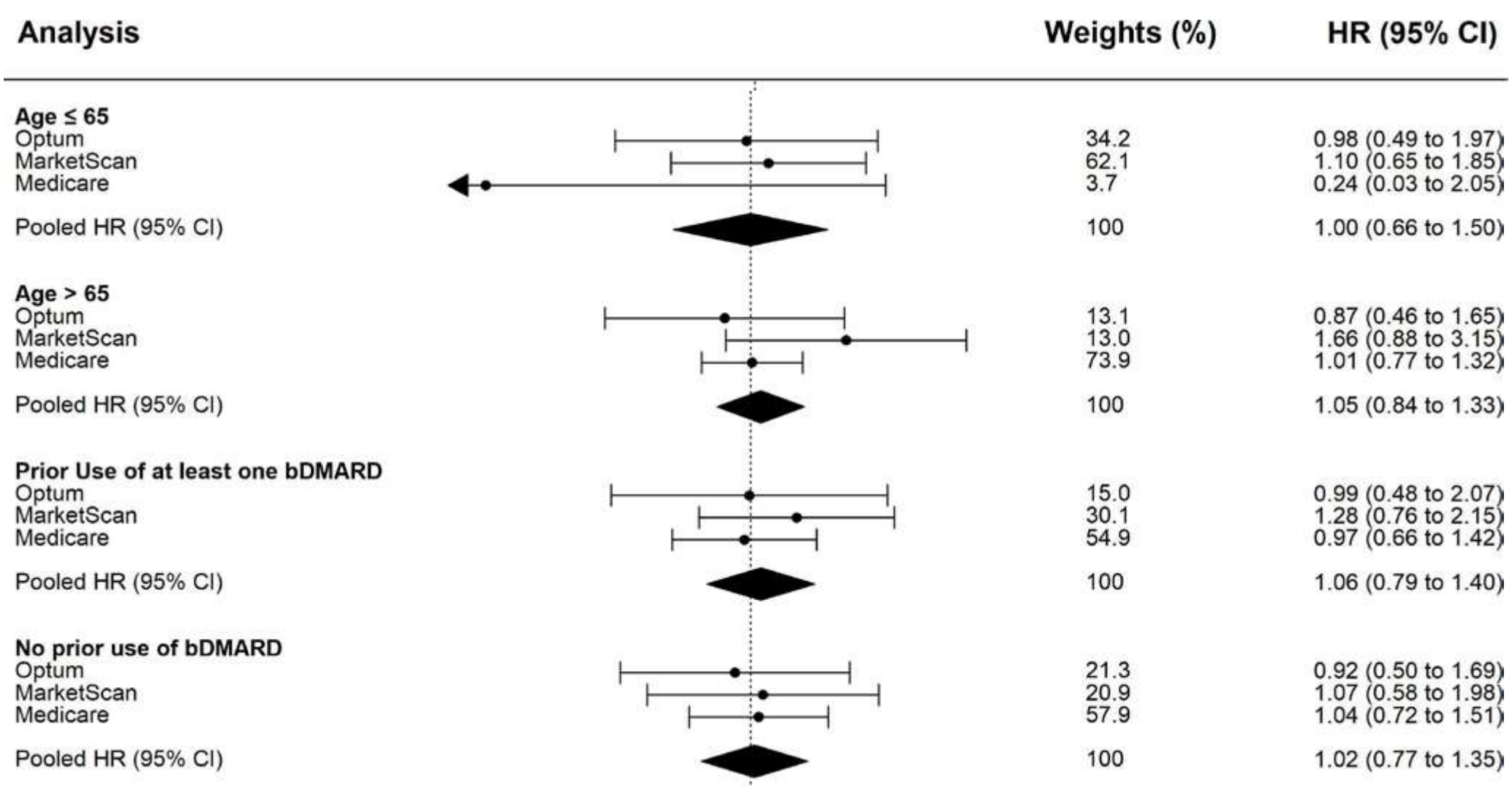
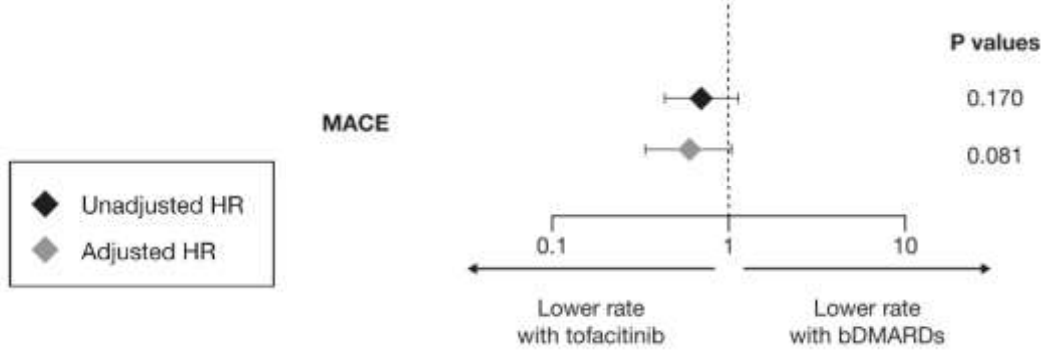


Figure 2.2

# RWEコホートのサブグループ解析でのCVD risk （背景調節後）



# Discussion




- CORRONA RA registryでTOFA vs b-DMARDでもTOFAはMACEのリスクを上げなかった（ACR Open Rheumatol 2021;3:173）
- Limitationとして
  1. RA活動性などの交絡因子が調節できていない
  2. 薬剤のアドヒアランスなどは確認できていない
  3. 他のJAK阻害薬の評価はできていない

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TOFA vs TNFiで
悪性腫瘍リスクは?

P: 米国の3つの健康保険関連データベース*登録RA患者で、ゼルヤンツ（TOFA）もしくはTNF阻害薬（TNFI)を初めて開始された患者
RWE (Real World Evidence)コホート: 上記すべての患者
RCT-duplicateコホート: 上記のうち、Oral Surveillanceのinclusion, exclusion criteriaを適用した患者群

E: 上記PのうちTOFA群

C: 上記PのうちTNFI群

O: 悪性腫瘍リスク（NMSC=non-melanoma skin cancer除く）

*Optum Clinformatics (2012-2020)
MarketScan (2012-2018)
Medicare (2012-2017)

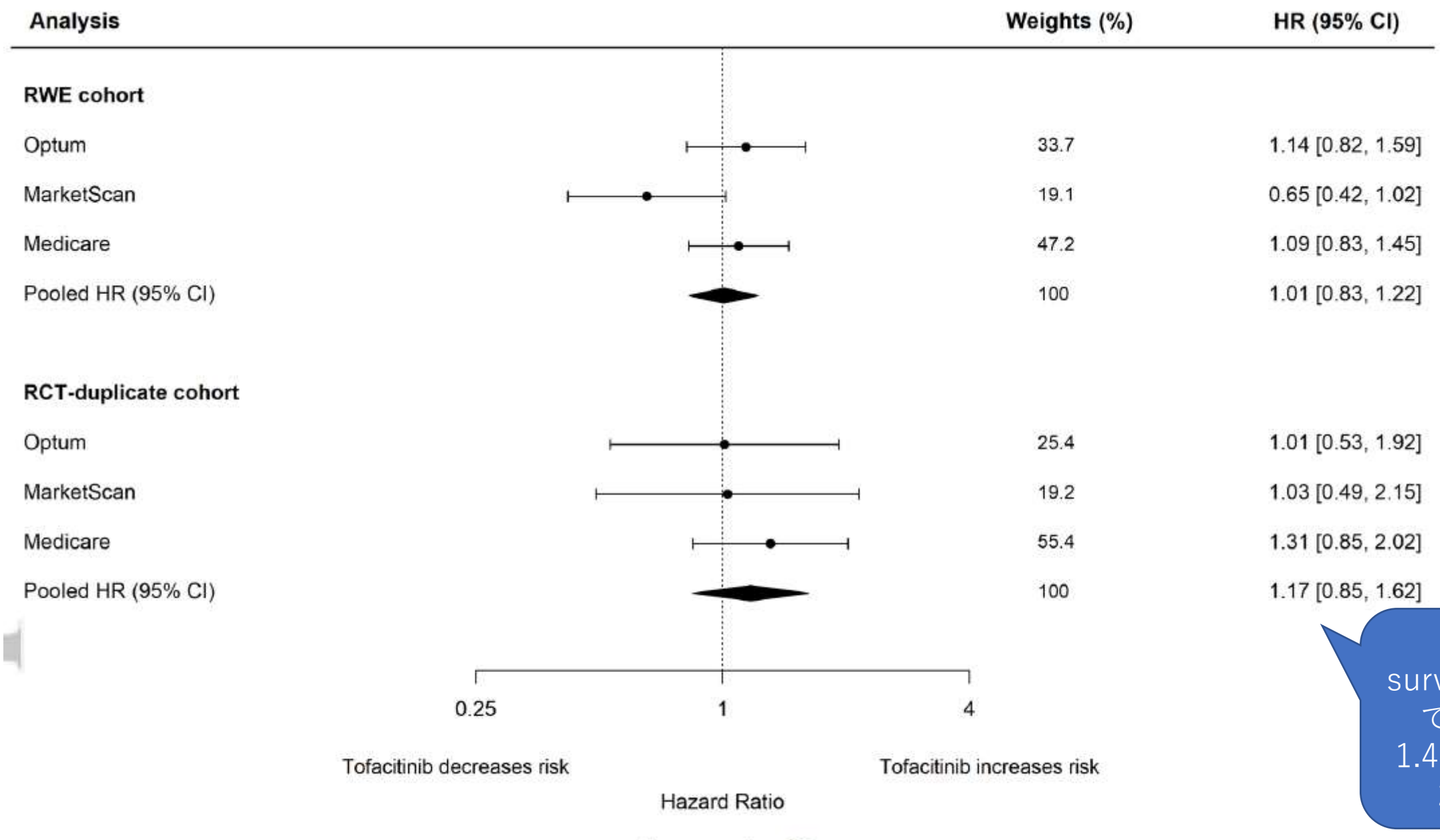
# RWEコホートRA患者背景（CV riskとほぼ同じ）

| Variables | Optum | | | MarketScan | | | Medicare | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tofacitinib (n=3,301) | TNFI (n=21,934) | SD (%) | Tofacitinib (n=4,499) | TNFI (n=24,960) | SD (%) | Tofacitinib (n=2,689) | TNFI (n=25,673) | SD (%) |
| Demographic variables | | | | | | | | | |
| Age; mean (std) | 55.8 (12.4) | 56.1 (13.1) | -2.3 | 53.8 (11.4) | 54.0 (11.7) | -1.8 | 71.3 (5.4) | 71.4 (5.3) | -1.3 |
| Female; n (%) | 2,690 (81.5) | 17,963 (81.9) | -1.0 | 3,699 (82.2) | 20,562 (82.4) | -0.4 | 2,300 (85.5) | 22,082 (86.0) | -1.4 |
| White; n (%) | 2,069 (62.7) | 13,683 (62.4) | 0.6 | - | - | - | 2,064 (76.8) | 19,537 (76.1) | 1.5 |
| Black; n (%) | 368 (11.1) | 2,473 (11.3) | -0.4 | - | - | - | 344 (12.8) | 3,397 (13.2) | -1.3 |
| Asian; n (%) | 98 (3.0) | 613 (2.8) | 1.1 | - | - | - | 73 (2.7) | 710 (2.8) | -0.3 |
| Hispanic; n (%) | 426 (12.9) | 2,903 (13.2) | -1.0 | - | - | - | 100 (3.7) | 980 (3.8) | -0.5 |
| RA related variables | | | | | | | | | |
| Number of unique bDMARDs; mean (std)* | 1.6 (0.7) | 1.6 (0.7) | 2.1 | 1.8 (0.8) | 1.8 (0.8) | 1.5 | 1.6 (0.7) | 1.6 (0.7) | 2.9 |
| *Non-biologic DMARDs* | | | | | | | | | |
| Number of distinct csDMARDs; mean (std) | 1.0 (0.8) | 1.0 (0.8) | 0.1 | 1.0 (0.8) | 1.0 (0.8) | 2.0 | 1.1 (0.8) | 1.1 (0.8) | 0.7 |
| Any csDMARD use; n (%) | 2,402 (72.8) | 15,971 (72.8) | -0.1 | 3,374 (75.0) | 18,576 (74.4) | 1.3 | 2,075 (77.2) | 19,725 (76.8) | 0.8 |
| Methotrexate; n (%) | 1,523 (46.1) | 10,037 (45.8) | 0.8 | 2,303 (51.2) | 12,618 (50.6) | 1.3 | 1,403 (52.2) | 13,214 (51.5) | 1.4 |
| Hydroxychloroquine; n (%) | 829 (25.1) | 5,528 (25.2) | -0.2 | 1,053 (23.4) | 5,711 (22.9) | 1.2 | 679 (25.3) | 6,425 (25.0) | 0.5 |
| Leflunomide; n (%) | 703 (21.3) | 4,702 (21.4) | -0.3 | 893 (19.8) | 4,917 (19.7) | 0.4 | 605 (22.5) | 5,845 (22.8) | -0.6 |
| Sulfasalazine; n (%) | 343 (10.4) | 2,287 (10.4) | -0.1 | 424 (9.4) | 2,287 (9.2) | 0.9 | 314 (11.7) | 3,025 (11.8) | -0.3 |
| Prior use of oral glucocorticoids (365 days); n (%) | 2,432 (73.7) | 16,177 (73.8) | -0.2 | 3,284 (73.0) | 18,275 (73.2) | -0.5 | 2,018 (75.0) | 19,258 (75.0) | 0.1 |
| Concurrent use of oral glucocorticoids (60 days); n (%) | 1,633 (49.5) | 10,825 (49.4) | 0.2 | 2,192 (48.7) | 12,188 (48.8) | -0.2 | 1,505 (56.0) | 14,329 (55.8) | 0.3 |
| Cumulative dose of oral steroids in mg; mean (std) | 901.4 (1277.6) | 911.5 (6555.1) | -0.2 | 1,754.5 (21873.2) | 1,859.6 (20903.4) | -0.5 | 1023.3 (1202.8) | 1,015.8 (1262.7) | 0.6 |
| Comorbidities | | | | | | | | | |
| Obesity; n (%) | 767 (23.2) | 5,139 (23.4) | -0.5 | 691 (15.4) | 3,844 (15.4) | -0.1 | 430 (16.0) | 4,118 (16.0) | -0.1 |
| Smoking; n (%) | 654 (19.8) | 4,292 (19.6) | 0.6 | 382 (8.5) | 2,146 (8.6) | -0.4 | 665 (24.7) | 6,377 (24.8) | -0.2 |
| Atrial fibrillation; n (%) | 116 (3.5) | 783 (3.6) | -0.3 | 94 (2.1) | 533 (2.1) | -0.3 | 246 (9.1) | 2,324 (9.1) | 0.3 |
| Coronary artery disease; n (%) | 296 (9.0) | 1,986 (9.1) | -0.3 | 326 (7.2) | 1899 (7.6) | -1.4 | 593 (22.1) | 5,641 (22.0) | 0.2 |
| Type 2 diabetes mellitus; n (%) | 702 (21.3) | 4,672 (21.3) | -0.1 | 683 (15.2) | 3,835 (15.4) | -0.5 | 821 (30.5) | 7,801 (30.4) | 0.3 |
| Heart failure; n (%) | 154 (4.7) | 1,073 (4.9) | -1.1 | 131 (2.9) | 733 (2.9) | -0.2 | 292 (10.9) | 2,791 (10.9) | 0.0 |
| Hypertension; n (%) | 1,671 (50.6) | 11,226 (51.2) | -1.1 | 1,928 (42.9) | 10,842 (43.4) | -1.2 | 2,207 (82.1) | 21,048 (82.0) | 0.2 |
| Hyperlipidemia; n (%) | 1,371 (41.5) | 9,201 (42.0) | -0.8 | 1,643 (36.5) | 9,215 (36.9) | -0.8 | 1,780 (66.2) | 16,896 (65.8) | 0.8 |
| Stroke or transient ischemic attack; n (%) | 81 (2.5) | 554 (2.5) | -0.5 | 81 (1.8) | 473 (1.9) | -0.7 | 88 (3.3) | 830 (3.2) | 0.2 |
| Peripheral vascular disease; n (%) | 137 (4.2) | 936 (4.3) | -0.6 | 106 (2.4) | 611 (2.4) | -0.6 | 268 (10.0) | 2,542 (9.9) | 0.2 |
| Venous thromboembolism; n (%) | 76 (2.3) | 518 (2.4) | -0.4 | 99 (2.2) | 559 (2.2) | -0.3 | 72 (2.7) | 694 (2.7) | -0.2 |

| Variables | Optum | | | MarketScan | | | Medicare | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tofacitinib (n=3,301) | TNFI (n=21,934) | SD (%) | Tofacitinib (n=4,499) | TNFI (n=24,960) | SD (%) | Tofacitinib (n=2,689) | TNFI (n=25,673) | SD (%) |
| Chronic liver disease; n (%) | 238 (7.2) | 1,582 (7.2) | 0.0 | 246 (5.5) | 1,341 (5.4) | 0.4 | 209 (7.8) | 1,987 (7.7) | 0.1 |
| Chronic kidney disease (Stage 3+); n (%) | 164 (5.0) | 1,090 (5.0) | 0.0 | 135 (3.0) | 753 (3.0) | -0.1 | 287 (10.7) | 2,776 (10.8) | -0.4 |
| COPD; n (%) | 490 (14.8) | 3,302 (15.1) | -0.6 | 501 (11.1) | 2,804 (11.2) | -0.3 | 693 (25.8) | 6,674 (26.0) | -0.5 |
| Inflammatory bowel disease; n (%) | 58 (1.8) | 388 (1.8) | -0.1 | 48 (1.1) | 258 (1.0) | 0.3 | 34 (1.3) | 324 (1.3) | 0.0 |
| Psoriasis; n (%) | 146 (4.4) | 960 (4.4) | 0.2 | 140 (3.1) | 749 (3.0) | 0.7 | 81 (3.0) | 728 (2.8) | 1.0 |
| Combined Comorbidity Index; mean (std) | 1.0 (1.8) | 1.0 (1.8) | -0.1 | 0.6 (1.4) | 0.6 (1.4) | -0.8 | 1.6 (2.2) | 1.6 (2.3) | -0.4 |
| Frailty index; mean (std) | 0.2 (0.0) | 0.2 (0.0) | -0.4 | 0.1 (0.0) | 0.1 (0.0) | -1.6 | 0.2 (0.0) | 0.2 (0.0) | 0.3 |

Figure 1

# RWE/RCT-duplicateコホートでの悪性腫瘍リスク（背景調節後）




Oral surveillanceではHR 1.48 (1.04-2.09)

Figure 2.1 RWEコホートのサブグループ解析での悪性腫瘍リスク（背景調節後）

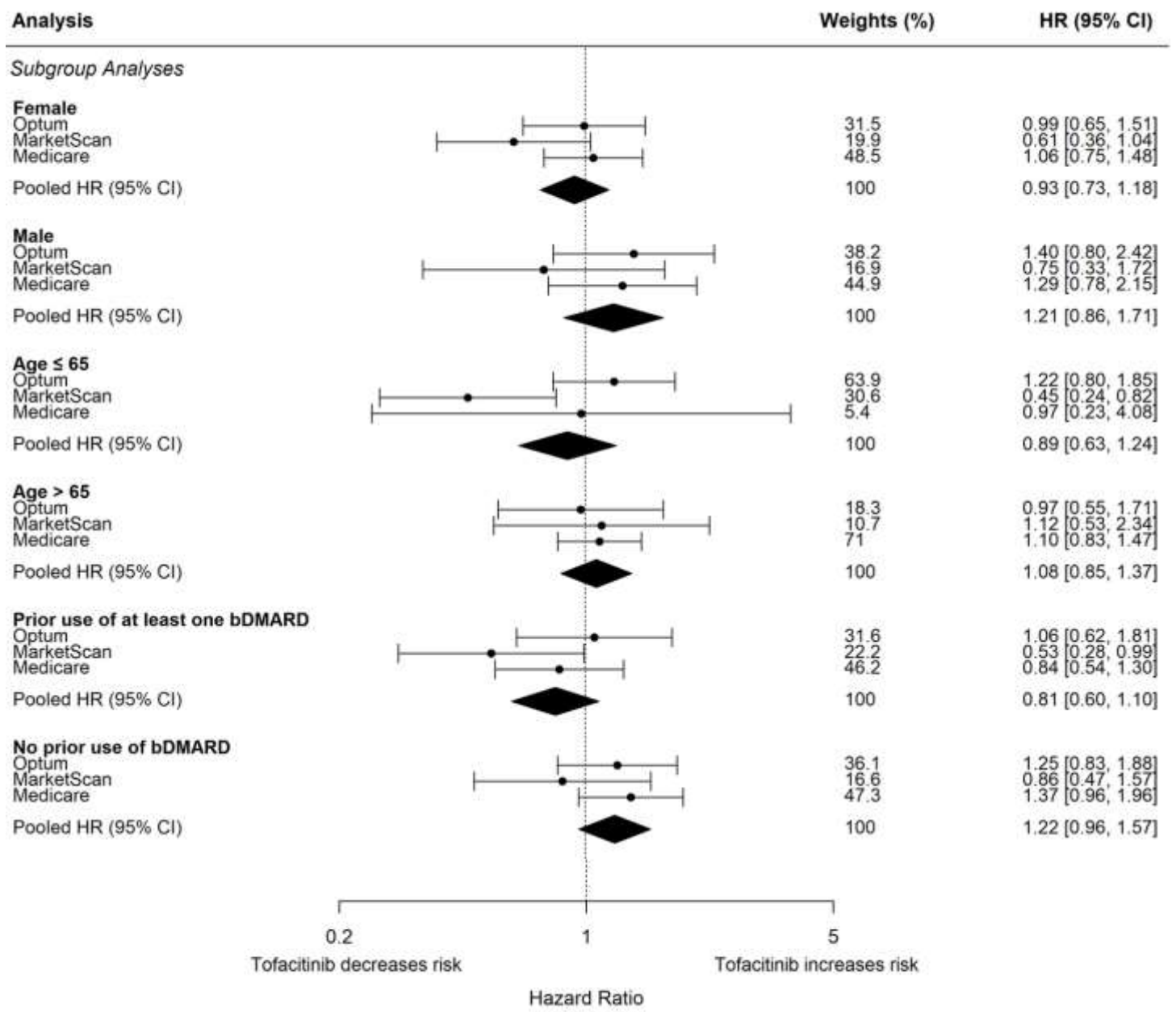


Figure 2.2

# RWEコホートの感度解析での悪性腫瘍リスク（背景調節後）

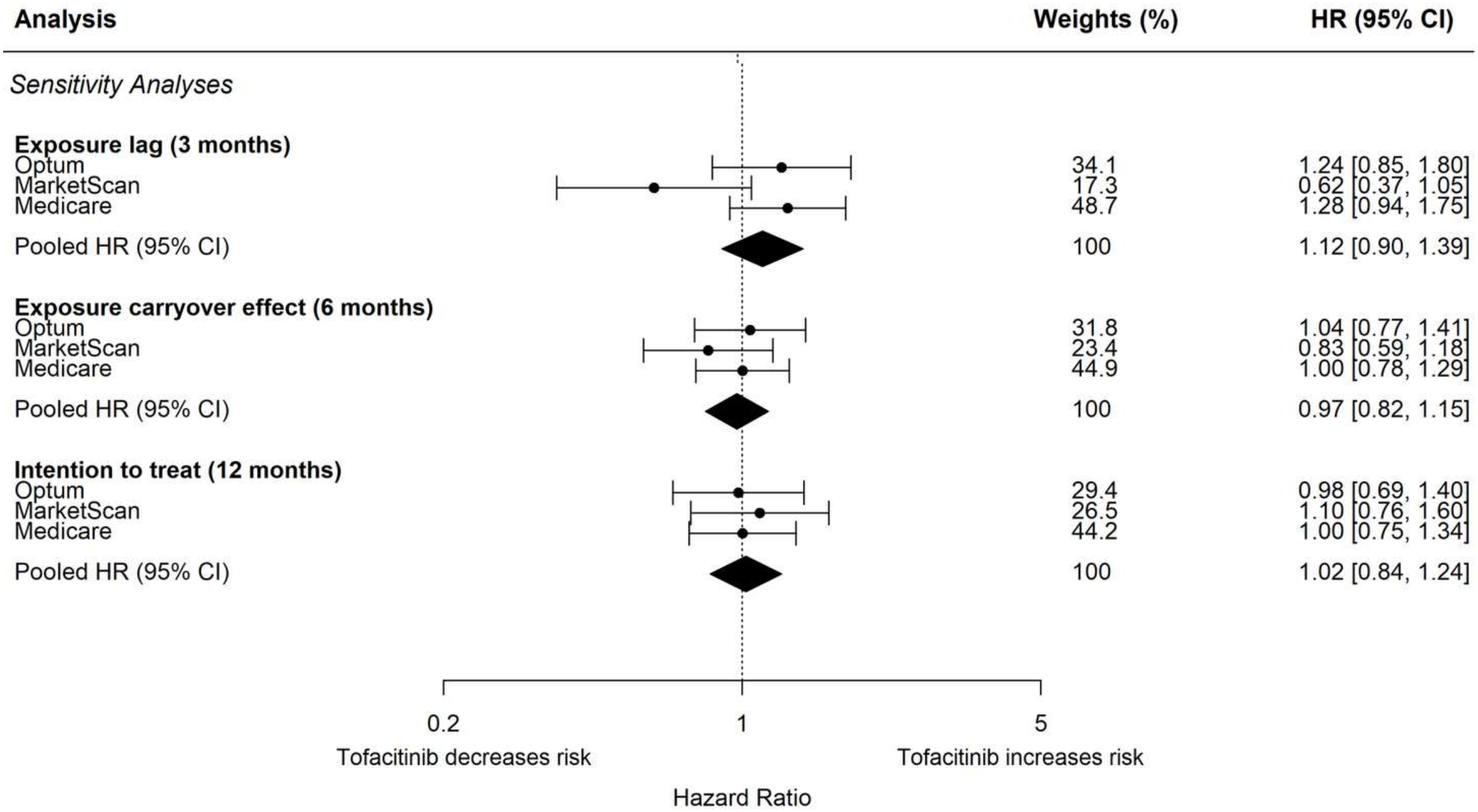


Figure 3.1 RWEコホートの悪性腫瘍種類別解析での悪性腫瘍リスク（背景調節後）

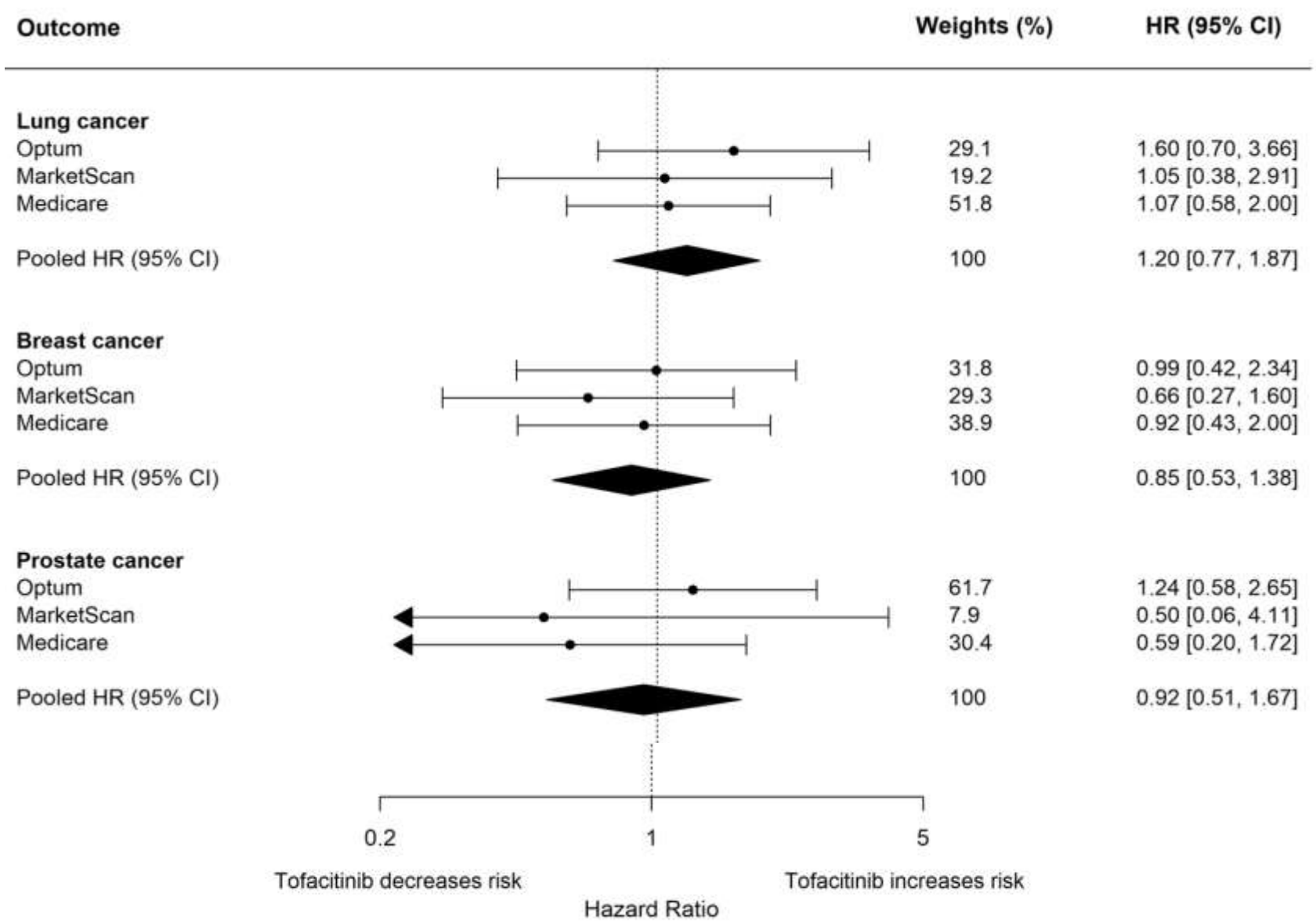
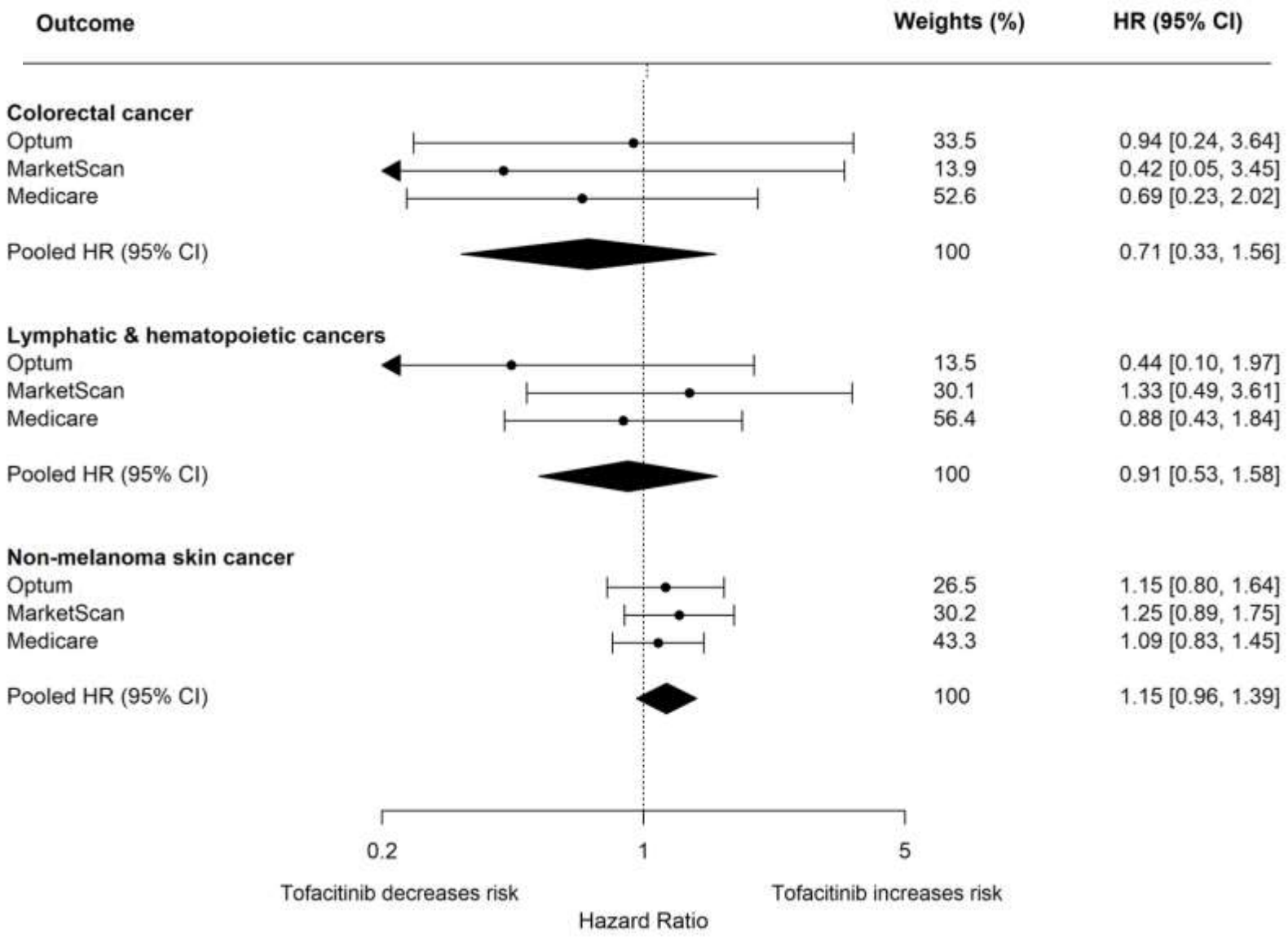


Figure 3.2 RWEコホートの悪性腫瘍種類別解析での悪性腫瘍リスク（背景調節後）



# Discussion

- ORAL Surveillance，本研究以外に３つのスタディでTOFAの悪性腫瘍リスクを検討されている
  1. P2,P3,LTEのメタ解析 0.85 events per 100人年（本研究 1.74）
  2. CORRONA RA registry HR 1.04 (95%CI 0.68-1.61)
  3. Swedish Rheumatology Quality Register (Bio/JAKi vs no Bio/JAKiでリスク増加なし)
- Limitations
  1. follow up timeが短い（平均1年未満）。11%（9237人）は2年以上フォロー（ORAL Surveillanceより多い人数）。ただし、ORAL Surveillanceは中央値4年のfollow up。
  2. 他のJAKIは検討していない
  3. 白血病やリンパ腫などの評価には十分なサンプルサイズとは言えない
  4. outcome misclassificationの可能性
  5. 診断と治療情報はcodeに頼っている
  6. 他の交絡因子の可能性（RA 活動性など）

# 結論

- 米国の保険情報大規模データによるTOFAのTNFiと比較したMACE risk、malignancy riskは認められなかった。ORAL Surveillanceと同様のinclusion/exclusion criteriaの患者に絞ったRCT-duplicateコホートでもリスク上昇は認めなかった