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Risk of Venous Thromboembolism in Patients with Rheumatoid Arthritis Initiating Disease-Modifying Antirheumatic Drugs

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Abstract

Objectives—Recent research suggests that rheumatoid arthritis (RA) increases the risk of venous thromboembolism (VTE). This study compared the risk of VTE in newly diagnosed RA patients initiating a biologic disease-modifying anti-rheumatic drug (DMARD) with those initiating methotrexate or nonbiologic DMARDs (nbDMARDs).

Methods—We conducted a population-based cohort study using U.S. insurance claims data (2001–2012). Three mutually exclusive, hierarchical DMARD groups were used: (1) a biologic DMARD with and without nbDMARDs, (2) methotrexate without a biologic DMARD, or (3) nbDMARDs without a biologic DMARD or methotrexate. We calculated incidence rates (IR) of VTE. Cox proportional hazards models stratified by propensity score (PS) deciles after asymmetric PS trimming were used for 3 pairwise comparisons, controlling for potential confounders at baseline.

Results—We identified 29,481 RA patients with 39,647 treatment episodes. From the pairwise comparison after asymmetric PS trimming, the IR of hospitalization for VTE per 1,000 person-years was 5.5 in bDMARD versus 4.4 in nbDMARD, and 4.8 in bDMARD versus 3.5 in methotrexate initiators. The PS decile-stratified hazard ratio (HR) of VTE associated with bDMARD was 1.83 (95%CI 0.91–3.66) versus nbDMARDs and 1.39 (95%CI 0.73–2.63) versus methotrexate. The HR of VTE in bDMARD initiators was the highest in the first 180 days versus nbDMARD (2.48, 95%CI 1.14–5.39) or methotrexate (1.80, 95%CI 0.90–3.62).

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Disclosures:

Franklin and Liu have nothing to disclose.

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Conclusion—The absolute risk for VTE was low in patients with newly diagnosed RA. Initiation of a bDMARD appears to be associated with an increased short-term risk of hospitalization for VTE compared to those initiating nbDMARDs or methotrexate.

Keywords

rheumatoid arthritis; disease-modifying antirheumatic drugs; venous thromboembolism

INTRODUCTION

Several studies recently show that patients with rheumatoid arthritis have a 1.5 to 6 times increased risk of venous thromboembolism, including pulmonary embolism and deep vein thrombosis.(1–5) It is thought that active systemic inflammation may lead to development of venous thromboembolism because inflammatory cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- α activate coagulation pathways and thus alter thrombotic tendency.(6, 7) To date, limited evidence is available on whether treatment of rheumatoid arthritis with any disease-modifying antirheumatic drugs (DMARD) or with a specific type of DMARD such as biologic DMARDs (bDMARDs) including TNF- α inhibitors increases or decreases the risk of venous thromboembolism. While several studies report cases of venous thromboembolism or peripheral thrombosis following treatment with TNF- α inhibitors for rheumatoid arthritis or other inflammatory diseases,(8–12) a few small studies find that TNF- α blockade with infliximab in patients with rheumatoid arthritis decreases inflammatory and coagulation markers and reduces the inhibition of fibrinolysis.(13, 14) Furthermore, a cohort study based on the British Society for Rheumatology Biologics Register (BSRBR) shows no significant association between TNF- α inhibitors and venous thromboembolism in rheumatoid arthritis patients.(15)

Based on the potential link between DMARD treatment and thrombosis, we examined the risk of incident venous thromboembolism in newly diagnosed rheumatoid arthritis patients initiating a bDMARD, methotrexate (MTX) or other non-biologic DMARDs (nbDMARD). In addition, we investigated both short- and long-term risk of venous thromboembolism associated with the use of specific DMARD treatment.

PATIENTS AND METHODS

Data Source

We conducted a cohort study using the claims data from three commercial U.S. health plans (2001–2012) - WellPoint, United HealthCare and Aetna - which insure primarily working adults and their family members across the U.S. These databases contain longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensings. Personal identifiers were removed from the dataset before the analysis to protect subject confidentiality. Patient informed consent was, therefore, not required. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Study Cohort

Adults aged 18 years or older with at least two visits, which were seven to 365 days apart, coded with the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD 9-CM) code, 714.xx, for rheumatoid arthritis were identified. To identify newly diagnosed rheumatoid arthritis patients, patients were required to have a minimum of 12 months of continuous insurance eligibility prior to the 1st rheumatoid arthritis diagnosis and to be free of any DMARD dispensing any time before their 1st rheumatoid arthritis diagnosis. Patients were also required to have less than 365 days between the 1st rheumatoid arthritis diagnosis and the 1st DMARD dispensing. Subjects with malignancies, prior venous thromboembolism, or dispensings for an anticoagulant any time before their index date were excluded (Supplementary Table 1).

DMARD Exposures

We defined three mutually exclusive, hierarchical groups of DMARDs: (1) a *bDMARD* with and without MTX or other nbDMARDs, (2) *MTX* with and without other nbDMARDs, or (3) one or more nbDMARDs other than MTX (Supplementary Table 2). Subjects in the MTX group could not simultaneously use a bDMARD; however, they could use other nbDMARDs (e.g., triple therapy). The nbDMARD group could not simultaneously use a bDMARD or MTX, but they could start more than one other nbDMARDs at the index date (e.g., concurrent use of hydroxychloroquine and leflunomide). The date of initiating a DMARD in one of these three exposure groups was defined as the start of follow-up (i.e., index date). Patients were also allowed to cross-over to a different DMARD category at their first switching. Therefore, all the included patients in this study were required to have had at least two rheumatoid arthritis diagnoses and at least one filled prescription for a DMARD at the start of follow-up. A previous validation study showed that rheumatoid arthritis patients can be accurately identified using a combination of diagnosis codes for rheumatoid arthritis and DMARD prescriptions in claims data with a positive predictive value over 86%.⁽¹⁶⁾

For a given DMARD category, patients were followed up until the drug discontinuation or switching to a different DMARD category (i.e. 'as treated' analysis), the occurrence of venous thromboembolism, loss of health plan eligibility, the end of study period, or death. In the case of drug discontinuation, the exposure risk window for each patient treatment episode extended until 30 days after the expiration of the supply of the last fill. Patients were allowed to enter the study cohort up to two times.

Outcome Definition

We defined the venous thromboembolism event as a hospitalization for venous thromboembolism, either deep vein thrombosis or pulmonary embolism, based on the primary discharge diagnosis code. The positive predictive value of a hospital discharge diagnosis code for venous thromboembolism listed in the Supplementary Table 1 in identifying venous thromboembolism cases was at least 93% in previous studies.^(17, 18)

Potential Confounders

Variables potentially related to initiation of DMARDs or risk factors for venous thromboembolism were assessed using data from the 12-month baseline period before the index date (i.e. the date of the 1st DMARD dispensing or switching to another DMARD category). These variables included age, sex, comorbidities such as diabetes, obesity, chronic kidney disease, heart failure, cardiovascular disease, extremity fracture and surgeries, medications including oral contraceptives, steroids, and anti-platelet drugs, and health care utilization factors (see Table 1).(19, 20) To quantify patients' comorbidities at baseline, we also calculated a comorbidity score that combined 20 medical conditions included in both the Charlson Index and the Elixhauser system based on ICD-9.(21) This comorbidity score is a summative score and ranges from -2 to 26.(21)

Statistical Analyses

We compared the baseline characteristics among initiators of each DMARD group. To control for potential confounders, we used propensity score (PS) methods.(22) The PS, a balancing score, is the conditional probability of assignment to a particular drug or treatment given a vector of observed covariates.(23) Multivariable logistic regression models that included all the baseline covariates, the index year, an indicator for a DMARD initiation versus switching, and number of days between the 1st rheumatoid arthritis diagnosis and the index date were used to estimate the PS for three pairwise comparisons, defined as the predicted probability of a patient receiving bDMARD versus nbDMARD, bDMARD versus MTX, or MTX versus nbDMARD. Prior research showed that the inclusion of variables that are unrelated to the treatment but related to the outcome in the PS model would decrease the variance of an estimated treatment effect without increasing bias.(24) For the primary analysis, patients were grouped into PS deciles after excluding those in the nonoverlapping parts of the PS distribution. We used asymmetric trimming with the cut point at the 2.5th percentiles and 97.5th percentiles of the PS distribution in the exposed and unexposed for each comparison.(25) Incidence rates (IR) of venous thromboembolism were calculated with 95% confidence interval (CI) in each group for each pairwise comparison. PS decile-stratified Cox proportional hazard models compared the risk of venous thromboembolism between each DMARD comparison.

For the secondary analysis, we used the nearest neighbor PS matching method within a "caliper" of 0.05 on the PS with a variable matching ratio of 1:1 to 1:7.(26–28) To minimize potential confounding by differences in the follow-up time between the PS matched groups, we used the matched cohort methods, in which Cox regression models stratified by the PS matching set estimated the hazard ratio (HR) of venous thromboembolism from each comparison.(29, 30)

Because patients could contribute more than 1 treatment episode, we calculated robust standard errors using the robust 'sandwich' variance estimator.(31) To examine the short- and long-term effect of DMARDs on venous thromboembolism, we also conducted a separate PS decile-stratified Cox proportional hazards regression analysis for the follow-up period of 0 to 180 days, 181 to 365 days, 365 to 730 days, and 730 days or longer. The proportional hazards assumption was tested using the Kolmogorov supremum test and was

not violated in any models.(32) All analyses were done using SAS 9.2 Statistical Software (SAS Institute Inc., Cary, NC).

RESULTS

Cohort Selection

There were 272,613 patients with at least one diagnosis for rheumatoid arthritis with at least 12 months of continuous insurance eligibility in our databases. After applying exclusion criteria, our final cohort includes a total of 29,481 patients newly diagnosed with rheumatoid arthritis with 39,647 treatment episodes (5,920 treatment episodes with bDMARDs, 17,614 with MTX and 16,113 nbDMARDs) prior to asymmetric trimming based on the pairwise PS distribution (Figure 1). Of these, 27% of bDMARDs treatment episodes, 80% of MTX, and 86% of nbDMARDs were new initiation. The mean (SD) follow-up time was 1.0 (1.1) years for bDMARDs, 0.7 (0.8) for MTX and 0.6 (0.7) for nbDMARDs. On average, patients contributed to 1.34 (SD 0.48) treatment episodes.

In the secondary PS matched analysis, we compared 3,794 treatment episodes with bDMARDs versus 12,204 nbDMARDs, 3,794 treatment episodes with bDMARDs versus 12,204 MTX, and 13,904 treatment episodes with MTX versus 16,113 nbDMARDs. The mean follow-up time was similar to the main cohort prior to asymmetric trimming.

Patient Characteristics

Baseline characteristics of the study cohort per DMARD group before asymmetric trimming are presented in Table 1. The mean age was 49 years for bDMARDs and nbDMARDs and 51 years for MTX initiators. Overall, baseline demographic factors, comorbidities, medication and health care utilization were similar across the groups. However, the cumulative steroid dose and the number of total physician visits, prescription drugs, and ordered laboratory tests for acute phase reactants were the highest in bDMARDs. After the 2.5th and 97.5th asymmetric trimming for the primary PS decile-stratified analysis, baseline characteristics were more similar across each comparison pair (Supplementary Table 3a, 3b, and 3c). For the secondary PS matched analysis, all the baseline characteristics were well-balanced between the groups for each comparison (data not shown).

Risk of Venous Thromboembolism

During the follow-up, there were 31 venous thromboembolism events in bDMARDs, 46 in MTX and 47 in nbDMARDs in the entire study cohort. Twenty-nine (93.5%) of 31 venous thromboembolism events in bDMARDs occurred while on TNF- α inhibitors.

From the pairwise comparison after asymmetric trimming for the primary PS decile-stratified analysis, the IR of hospitalization for venous thromboembolism per 1,000 person-years was 5.5 in bDMARD versus 4.4 in nbDMARD initiators, and 4.8 in bDMARD versus 3.5 in MTX initiators (Table 2). In the secondary PS matched cohorts, the IR of venous thromboembolism per 1,000 person-years was 5.3 in bDMARD versus 5.3 in nbDMARD initiators, and 5.3 in bDMARD versus 3.9 in MTX initiators. The PS decile-stratified HR of venous thromboembolism was 1.83 (95% CI 0.91–3.66) for initiating bDMARD versus

nbDMARDs, 1.39 (95% CI 0.73–2.63) for bDMARDs versus MTX, and 0.78 (95% CI 0.50–1.21) for MTX versus nbDMARDs (Table 3). In the secondary PS matched analysis, similar HRs of venous thromboembolism for initiating bDMARD versus nbDMARDs or MTX were observed (Table 3).

Treatment Duration and Risk of Venous Thromboembolism

Figure 2 presents the effect of DMARD treatment duration on the risk of venous thromboembolism in the PS decile-stratified analyses. The short-term use of bDMARDs up to 180 days appears to be associated with an increased risk of venous thromboembolism compared to nbDMARDs (HR 2.48, 95% CI 1.14–5.39) and MTX (HR 1.80, 95% CI 0.90–3.62). The use of bDMARDs for longer than 1 year was not associated with an increased risk of venous thromboembolism compared to either nbDMARDs or MTX, but the confidence intervals were very wide due to the small number of events.

DISCUSSION

We found that the incidence of venous thromboembolism in newly diagnosed rheumatoid arthritis patients initiating bDMARDs, MTX, or nbDMARDs was low, but the risk of hospitalization for venous thromboembolism was possibly increased in bDMARD initiators compared to nbDMARD initiators, particularly in the first 180 days of follow-up, after controlling for a number of potential confounders. If systemic inflammation is in the causal pathway between rheumatoid arthritis and venous thromboembolism,(6, 7, 33, 34) one might expect to find a reduced risk of venous thromboembolism with more intensive treatment with bDMARDs. Although the exact mechanism is not well-demonstrated in the literature, it is possible that initiation of bDMARDs might acutely cause a paradoxical pro-coagulating phase. Production of both IgM and IgG anti-cardiolipin antibodies as well as other auto-antibodies has been reported in patients treated with etanercept and infliximab.(35–37) Another study suggested increased risks of thromboembolic events during treatment with adalimumab in patients who developed anti-adalimumab antibodies.(38) Nonetheless, more data are needed to determine the benefits and risks of prophylactic anticoagulation in patients with rheumatoid arthritis initiating bDMARD therapy.

Could a difference in rheumatoid arthritis severity or systemic inflammation between the bDMARD and nbDMARD groups explain such an increase in the risk of venous thromboembolism? Our study may be still subject to residual confounding by unmeasured risk factors. However, unless there are strong risk factors that are prevalent in only one of the groups are unmeasured and uncontrolled, it is unlikely that the observed HR of 2.48 in our study would be completely moved to the null.(39) A previous study, arguing against residual confounding, did not find a significant association between venous thromboembolism risk and rheumatoid arthritis disease activity such as presence of rheumatoid factor, elevated erythrocyte sedimentation rates, presence of joint erosions or destructive changes, or rheumatoid nodules.(3) Furthermore, we used both PS decile-stratification and PS matching methods to simultaneously account for known risk factors of venous thromboembolism, comorbidities, medication, and health care utilization patterns and found similar risks associated with bDMARDs.(19, 40)

The prior BSRBR study did not find an increased risk of venous thromboembolism in TNF inhibitor initiators.(15) A number of differences exist between our study and the BSRBR study should be noted. First, we examined a large population-based cohort of newly diagnosed rheumatoid arthritis patients initiating a DMARD in one of the three DMARD categories whereas the BSRBR study examined the risk of venous thromboembolism in initiators of a TNF inhibitor compared to prevalent users of nbDMARDs for prevalent rheumatoid arthritis. Because rheumatoid arthritis disease duration could be a risk factor for venous thromboembolism, having the cohort limited to new diagnosis and including the number of days between the 1st rheumatoid arthritis diagnosis and the index date could potentially decrease the bias. The overall venous thromboembolism IRs in our study were similar to the IRs of clinically validated venous thromboembolism events reported in the BSRBR study, but the IR for bDMARD initiators was higher in our study. Our patients were younger and likely had a shorter duration of rheumatoid arthritis, but a greater proportion of patients with comorbidities such as diabetes were included in our study. Given the lack of information on rheumatoid arthritis disease activity in claims data, we utilized several approaches to minimize confounding by indication. First, we had a comprehensive list of potential confounders including age, sex, comorbidities, medications, surgical history, and health care utilization patterns. A broad category of diagnosis codes combined with the use of disease-specific drugs was used to identify comorbidities. Second, PS methods were utilized to select patients with similar distributions of baseline covariates from each DMARD group.

Other strengths of this study are the new-user design which includes initiators but not prevalent users of a DMARD to minimize issues with healthy users or survivor bias and time-varying hazards and to control for baseline confounders appropriately.(41) The present study also illustrated the effect of different treatment duration on the risk of venous thromboembolism for each DMARD comparison.

There are limitations to our study. First, we assessed a number of variables potentially related to a future venous thromboembolism event using the data from the 12-month baseline period, but this time period might not be long enough to capture all the information on potential confounders. In addition, no data were available on race, disease severity and duration, physical activity level, use of over-the-counter-drugs, and body mass index. Second, our study has weak statistical power, limited by the relatively small total number of patients initiating a bDMARD. Third, because our primary outcomes were based on a hospital discharge diagnosis of venous thromboembolism, not an admission diagnosis, some of the venous thromboembolism cases might have occurred during the hospitalization for a different reason. Lastly, as the mean follow-up was less than a year for the majority of patients, the results on the long-term effect of DMARD use on venous thromboembolism risk should be interpreted with caution.

In conclusion, among newly diagnosed rheumatoid arthritis patients, initiating a bDMARD may be associated with an increased risk of hospitalization for venous thromboembolism, particularly in the first 180 days of follow-up, compared to those initiating nbDMARDs. The absolute risk of venous thromboembolism was low in rheumatoid arthritis patient initiating biologic or nonbiologic DMARDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

- Initiation of a bDMARD appears to be associated with an increased short-term risk of hospitalization for VTE compared to those initiating nbDMARDs or MTX.
- The absolute risk of hospitalization for VTE was low in RA patient initiating biologic or nonbiologic DMARDs.

Figure 1. Cohort selection flow

Our final study cohort included a total of 39,647 treatment episodes: 5,920 with bDMARDs, 17,614 with methotrexate and 16,113 with nbDMARDs.

RA: rheumatoid arthritis, DMARD: disease-modifying antirheumatic drug, bDMARD: biologic DMARD, nbDMARD: non-biologic DMARD

Figure 2. Duration of DMARD treatment and the risk of venous thromboembolism: Propensity score decile-stratified analysis
bDMARD: biologic DMARD, nbDMARD: non-biologic DMARD, HR: hazard ratio, CI: confidence interval
Propensity score models included age, sex, comorbidities such as diabetes, obesity, chronic kidney disease, heart failure, cardiovascular disease, extremity fracture and surgeries, medications including oral contraceptives, steroids, and anti-platelet drugs, and health care utilization factors (listed in Table 1) and index year.

Table 1

Baseline characteristics of the study cohort in 12 months before DMARDs initiation

	Biologic DMARDs	Methotrexate	Non-biologic DMARDs
Treatment episodes	5,920	17,614	16,113
<i>N (%) or mean $\pm$ SD</i>			
Follow-up periods, years	1.0 $\pm$ 1.1	0.7 $\pm$ 0.8	0.6 $\pm$ 0.7
Demographic			
Age, years	48.9 $\pm$ 12.1	50.7 $\pm$ 11.9*	49.2 $\pm$ 12.3
Female	69.5*	72.0*	76.4
Comorbidities			
Comorbidity Index	0.3 $\pm$ 1.1	0.2 $\pm$ 1.0*	0.3 $\pm$ 1.2
Diabetes	695 (12)	2,207 (13)*	1,853 (12)
Obesity	393 (7)	1,171 (7)	1,048 (7)
Smoking	601 (10)	1,755 (10)	1,649 (10)
Varicose vein	54 (1)	195 (1)	187 (1)
Chronic kidney disease	137 (2)	331 (2)*	394 (2)
Liver disease	303 (5)	614 (3)*	851 (5)
Hypertension	2,002 (34)	6,532 (36)	5,648 (35)
Cardiovascular disease	340 (6)	1,140 (6)	972 (6)
Stroke	148 (3)*	555 (3)	540 (3)
Lung disease	825 (14)*	2,398 (14)*	2,490 (15)
Heart failure	94 (2)	281 (2)	295 (2)
Pregnancy	118 (2)	305 (2)*	357 (2)
Hyperlipidemia	1,962 (33)*	6,420 (36)	5,759 (36)
Extremity fractures	218 (4)*	513 (3)	513 (3)
Surgery, musculoskeletal	292 (5)*	754 (4)*	620 (4)
Surgery, cardiovascular	113 (2)	323 (2)	288 (2)
Surgery, intra-abdominal	360 (6)	954 (5)*	1,012 (6)
Medications			
Anti-platelet drugs	132 (2)	476 (3)	400 (2)
Statins	903 (15)*	3,060 (17)	2,704 (17)
Hormone replacement therapy	415 (7)*	1,388 (8)*	1,454 (9)
Oral contraceptives	501 (8)*	1,276 (7)*	1,566 (10)
Non-oral contraceptives	65 (1)	152 (1)*	201 (1)
Recent steroid use ^a	2,421 (41)*	7,262 (41)*	5,233 (32)

	Biologic DMARDs	Methotrexate	Non-biologic DMARDs
Cumulative steroid dose ^b (milligrams)	596.0 ± 1080.7 *	361.8 ± 751.7 *	298.1 ± 646.9
NSAIDs	3,401 (57)	10,660 (61) *	9,098 (56)
Coxibs	866 (15) *	2,363 (13)	2,072 (13)
Opioids	3,027 (51) *	8,676 (49) *	7,715 (48)
Health care utilization			
No. of total physician visits	12.1 ± 7.5 *	9.8 ± 6.6 *	10.6 ± 7.2
No. of hospitalizations	0.2 ± 0.6	0.2 ± 0.5 *	0.2 ± 0.6
Length of hospitalizations, days	5.8 ± 18.4	7.1 ± 36.9	6.3 ± 25.9
No. of prescription drug	10.5 ± 6.5 *	9.0 ± 6.2 *	9.7 ± 6.6
No. of emergency room visits	0.4 ± 1.0	0.4 ± 1.0	0.4 ± 1.0
No. of ordered CRP tests	1.7 ± 1.9 *	0.9 ± 1.1 *	1.0 ± 1.2
No. of ordered ESR tests	2.3 ± 2.1 *	1.4 ± 1.3 *	1.5 ± 1.4

SD: standard deviation, NSAID: non-selective anti-inflammatory drug, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate

^a Steroid use in the 30 days prior to the index date,

^b cumulative steroid dose in the 180 days prior to the index date

* P-value is less than 0.05 compared to nbDMARDs

Table 2

Incidence rates of venous thromboembolism per 1,000 person-years after asymmetric PS trimming*

Exposure	Treatment episodes	VTE events	PY	IR (95% CI)
<i>bDMARDs</i>	4488	23	4157.9	5.53 (3.67–8.32)
<i>nbDMARDs</i>	12859	32	7720.1	4.43 (3.13–6.26)
<i>bDMARDs</i>	4597	21	4368.2	4.81 (3.14–7.38)
<i>Methotrexate</i>	13912	32	9258.1	3.46 (2.45–4.89)
<i>Methotrexate</i>	16352	42	11075.6	3.79 (2.80–5.13)
<i>nbDMARDs</i>	14618	41	8250.0	4.97 (3.66–6.75)

CI: confidence interval, IR: incidence rate, VTE: venous thromboembolism, PY: person-years, PS: propensity score, bDMARD: biologic DMARD, nbDMARD: non-biologic DMARD

* Asymmetric trimming with the cut point at the 2.5th percentiles and 97.5th percentiles of the PS distribution in the exposed and unexposed for each comparison

Table 3

Hazard ratios and 95% confidence intervals for venous thromboembolism

Exposure	Hazard ratios (95% CI)
Propensity score decile-stratified^a	
<i>bDMARDs</i>	1.83 (0.91–3.66)
<i>nbDMARDs</i>	Reference
<i>bDMARDs</i>	1.39 (0.73–2.63)
<i>Methotrexate</i>	Reference
<i>Methotrexate</i>	0.78 (0.50–1.21)
<i>nbDMARDs</i>	Reference
Variable ratio up to 1:7 propensity score-matched	
<i>bDMARDs</i>	1.34 (0.74–2.44)
<i>nbDMARDs</i>	Reference
<i>bDMARDs</i>	1.73 (1.04–2.88)
<i>Methotrexate</i>	Reference
<i>Methotrexate</i>	0.81 (0.54–1.22)
<i>nbDMARDs</i>	Reference

bDMARD: biologic DMARD, nbDMARD: non-biologic DMARD, HR: hazard ratio, CI: confidence interval

^a Asymmetric trimming with the cut point at the 2.5th percentiles and 97.5th percentiles of the PS distribution in the exposed and unexposed for each comparison.

Propensity score models included age, sex, comorbidities such as diabetes, obesity, chronic kidney disease, heart failure, cardiovascular disease, extremity fracture and surgeries, medications including oral contraceptives, steroids, and anti-platelet drugs, and health care utilization factors (listed in Table 1) and index year.