

Article

Impact of Rheumatoid Arthritis Treatment Classes on Cardiovascular, Thromboembolic, Cancer Outcomes, and All-Cause Mortality: A Population-Based Cohort Study

Mohammad Movahedi ^{1,2,*} , Angela Cesta ¹, Sibel Zehra Aydin ³, Pooneh Akhavan ⁴ , Tetyana Kendzerska ³, Claire Bombardier ^{1,2,4} and Bindee Kuriya ^{4,†} on behalf of OBRI Investigators

¹ Toronto General Hospital Research Institute, University Health Network, Toronto, ON M5G 2C4, Canada

² Institute of Health Policy, Management, and Evaluation (IHPE), University of Toronto, Toronto, ON M5T 3M6, Canada

³ Department of Medicine, Faculty of Medicine, the Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON K1H 7W9, Canada

⁴ Department of Medicine, Division of Rheumatology, University of Toronto, Toronto, ON M5S 3H2, Canada

* Correspondence: mohammad.movahedi@uhn.ca

† Membership of OBRI Investigators is Provided in Acknowledgments Section.

Abstract

Background: Rheumatoid arthritis (RA) is linked to increased risks of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, and mortality. However, differences in these risks by treatment class—particularly among older adults with cardiovascular (CVD) risk factors—remain unclear. **Methods:** We conducted a population-based cohort study using Ontario administrative data. Patients aged ≥ 67 years with incident RA (2008–2013) were followed through 2023. Outcomes included health-care utilization for MACE and VTE, all-cause mortality, and cancer-related encounters. Time-varying treatment groups were: no csDMARD/advanced therapy (AT), glucocorticoids (GC) only, csDMARDs (reference), and biologic/targeted synthetic DMARDs (b/tsDMARDs). Weighted Fine–Gray models within a marginal structural framework were used, stratified by baseline CVD risk. **Results:** Among 10,058 patients, 80% had high CVD risk. Compared with csDMARDs, untreated patients (SHR 15.0; 95% CI 13.8–16.2) and GC users (SHR 1.29; 95% CI 1.13–1.47) had higher MACE risk, while AT use was associated with lower risk (SHR 0.53; 95% CI 0.37–0.77). Similar patterns were observed in low-risk patients. AT use was not associated with VTE. Untreated and GC users had increased mortality, whereas AT use reduced mortality. Increased cancer-related utilization was observed only in untreated patients. **Conclusion:** Treatment type strongly influences major outcomes in older adults with RA, underscoring the importance of integrating CVD and thrombotic risk into therapeutic decisions.



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Keywords: rheumatoid arthritis; treatment; MACE; VTE; cancer; mortality; administrative health data

1. Introduction

Rheumatoid Arthritis (RA) affects approximately 0.5–1.0% of the adult population worldwide, with prevalence varying by region and more frequently observed in developed countries [1,2], contributing substantially to morbidity and healthcare utilization. Beyond its impact on joints, RA is a systemic inflammatory condition that significantly

increases the risk of major comorbidities, including cardiovascular disease (CVD), venous thromboembolism (VTE), and certain malignancies [3–5].

Both disease-related factors—such as persistent inflammation, extra-articular manifestations, and higher rates of comorbid conditions—and treatment-related adverse effects contribute to this elevated risk. While advanced therapies (AT), including biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), have demonstrated benefits in reducing RA disease activity and overall mortality [6–9] compared to conventional synthetic DMARDs (csDMARDs), emerging safety signals have raised new concerns. In particular, Janus kinase inhibitors (JAKi), a class of tsDMARDs, have been linked to potentially increased risks of major adverse cardiovascular events (MACE) and certain cancers, especially in older patients and those with existing CVD risk factors [10–12].

Despite these concerns, there are no head-to-head studies, and existing real-world evidence remains conflicting regarding how these newer therapies compare to established RA treatments in terms of MACE, VTE, malignancy, and all-cause mortality particularly when taking into account patients' comorbidities, prior lines of therapy, and other high-risk clinical features.

To address this gap, our study aims to evaluate the risks of major adverse outcomes (including MACE, VTE, cancer, death) associated with different classes of RA therapies in a population-based cohort of older adults living with RA in Ontario. By leveraging linked provincial health administrative data, we aimed to provide real-world evidence to better inform treatment decisions and risk-benefit discussions for vulnerable RA patient populations.

2. Materials and Methods

We conducted a population-based retrospective cohort study of all adult RA between 1 January 2008 and 31 March 2013 in Ontario Canada using provincial health administrative databases. Patients with RA were identified from the Ontario Rheumatoid Arthritis Database (ORAD); a population-based registry assembled using a validated algorithm that has a 78% positive predictive value (PPV), 78% sensitivity, and ~100% specificity [13,14] in identifying a RA physician-based diagnosis.

Study population: Patients are included in ORAD if they are admitted to hospital with an RA diagnosis or have at least three RA physician service claims over two years with at least one of these claims originating from a musculoskeletal specialist. ORAD also includes physician billing diagnosis codes identified in the Ontario Health Insurance Plan (OHIP) database (with one diagnosis code representing the main reason for the visit) [13].

We included individuals aged 67 years or older diagnosed between 1 January 2008 and 31 March 2013 (Figure 1). We excluded patients who were younger than 67 years, those who did not meet OHIP eligibility at date of RA diagnosis, and those with data quality issues (e.g., birth date missing or after RA diagnosis date).

Patients were followed from index date, defined as RA diagnosis date, until death, loss of OHIP eligibility, departure from the province, or end of the study period (30 December 2023), whichever occurred first.

Data sources: We utilized the Ontario administrative healthcare databases stored at the Institute for Clinical Evaluative Sciences (ICES). ICES is an independent, not-for-profit research institute whose legal status under Ontario's health information privacy law allows them to collect and analyze health-related data without requiring patient consent. Records of publicly funded healthcare, for all residents with OHIP coverage, are captured in the ICES databases. Ethics approval for this study was obtained from the University Health Network (UHN REB# is 24-5037). Data were accessed for research purposes on 6 June 2024. For this study, the following ICES databases were used: Discharge Abstract Database (DAD), Same Day Surgery (SDS), National Ambulatory Care Reporting System

(NACRS) for emergency department visits, OHIP for physician billings (diagnostic and fee codes), Ontario Drug Benefit claims (ODB), and the Registered Persons Database (RPDB), a population registry of vital statistics. The following ICES-derived or -acquired databases were also used: Chronic Obstructive Pulmonary Disease (COPD), Ontario Asthma Dataset (ASTHMA), Ontario Hypertension Dataset (HYPER), Congestive Heart Failure (CHF) database, Ontario Diabetes Dataset (ODD), and the Ontario Cancer Registry (OCR). These datasets were linked using encrypted, unique health insurance numbers and were analyzed at ICES. A full list of used databases with their descriptions and administrative codes is included in the supplements (Tables S1 and S2).

Cohort flowchart

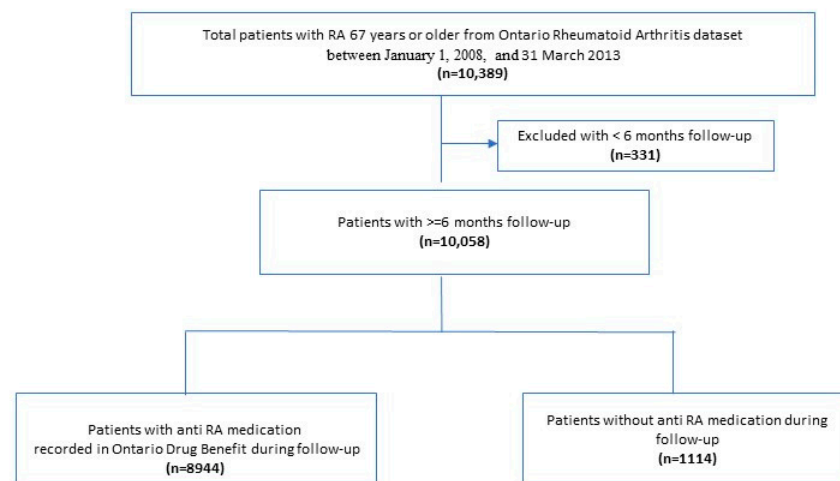


Figure 1. Cohort flowchart.

Exposures: RA therapeutic class was ascertained from Ontario Drug Benefit (ODB) prescription data and modeled as a time-varying exposure. Treatments were categorized into four mutually exclusive groups: (1) No csDMARDs or AT, (2) oral glucocorticoid (GC) only, (3) csDMARDs (reference), or (4) AT including biologic disease-modifying antirheumatic drug (bDMARDs: tumor necrosis factor inhibitors [TNFi], interleukin 6 inhibitors [IL-6i], abatacept, rituximab, anakinra) or targeted synthetic disease-modifying antirheumatic drug (tsDMARD). We constructed a daily medication exposure profile for each patient using prescription start dates, quantities, and days supplied. Based on this information, we derived a time-varying daily measure of exposure to each medication throughout the follow-up period. When prescriptions for the same medication overlapped, we assumed that patients refilled their medication early and completed the existing prescription before initiating the subsequent one. The minimum at-risk period was defined as the interval from treatment initiation to treatment discontinuation. For bDMARDs, this period was extended by 90 days beyond the discontinuation date to account for residual treatment effects (lag period) [15].

Exposure status was modeled using binary time-varying indicators (on/off treatment), allowing patients to transition between treatment classes over time. Consequently, individuals could contribute person-time to multiple medication categories during follow-up if their treatment changed. Exposure periods were used to define the four comparison groups, and outcomes were attributed to the corresponding person-time accumulated within each treatment category.

Outcomes: The primary outcome was healthcare utilization, defined as hospital admission, emergency department (ED) visits, or physician encounters. This was assessed for primary outcomes including: (1) MACE (composite of myocardial infarction, stroke,

congestive heart failure, and coronary artery bypass grafting) [16] and/or (2) VTE (deep vein thrombosis or pulmonary embolism) [17]. The secondary outcomes were (1) all-cause mortality and (2) all-cause cancer requiring hospital admission, ED visits, or physician encounters.

Covariates: Pre-existing comorbidities (see details below), medications and patient demographics were determined using a two-year lookback period from the index date. Socio-demographic variables included age, sex, residency status (rural vs. urban) [18], and neighborhood income quintile. Medication profile included prior prescription of csDMARDs, bDMARDs, oral GC, and non-steroid anti-inflammatory drugs (NSAIDs).

Number of comorbidities (based on Charlson morbidity index) and individual main comorbidities included cardiovascular disease (CVD), hypertension, diabetes mellitus (DM), COPD, Chronic Kidney Disease (CKD), and cancer.

COPD, CKD, hypertension, DM, and csDMARDs combination treatments were also captured during follow-up as time-varying covariates. We used validated case ascertainment algorithms to identify hypertension [19], congestive heart failure (CHF) [20], ischemic heart disease [21], cancer [22], stroke and ischemic transient attack [21], AF [23], acute myocardial infarction [24], VTE [17], COPD [25], and CKD [26]. Where a validated algorithm did not exist, an algorithm similar to that used to derive the validated cohorts was used (i.e., at least one inpatient or two outpatient diagnoses within a two-year period) (see Table S2).

Statistical analysis: Baseline characteristics were reported as means (standard deviation (SD)) for continuous variables and as numbers and percentages for categorical variables. We calculated crude event rates and person-years of follow-up for each treatment group using unweighted data.

We estimated the causal effect of time-varying treatment (four-level medication exposure) on multiple competing outcomes (MACE, VTE, cancer, death) using marginal structural models (MSMs) with stabilized inverse-probability-of-treatment weights (IPTWs) [27]. For each person-interval we estimated the probability of the observed treatment level using multinomial logistic models. The denominator model included prior anti-rheumatic treatment, baseline covariates (age, sex, income quantile, residential area, year of diagnosis, prior comorbidity history and substance abuse 2 years prior to baseline) and time-varying confounders measured at the previous interval (COPD, CKD, hypertension, DM, and csDMARDs combination treatment) that may act as confounders affected by prior exposure. The numerator model included prior time-varying treatment and baseline covariates. The stabilized weight for each interval was formed as the ratio of the numerator probability to the denominator probability. Weighted survival models [28] were then fit to estimate hazard ratios. To account for competing risks directly, we fit weighted Fine–Gray subdistribution hazard models [29], which estimate the effect of exposures on the cumulative incidence of each outcome in the presence of competing events. Robust variance estimation clustered on patient identifiers was used to account for within-subject correlation due to repeated intervals. The cohort was stratified by CVD risk (high vs. low), with high-risk individuals defined by the presence of established CVD, DM, or hypertension at index date.

The association between exposure and outcomes was repeated for both high- and low-CVD-risk groups. All estimates were presented as subdistribution hazard ratios (SHRs) with 95% confidence interval (CI). A p -value of <0.05 was considered statistically significant. In accordance with ICES data privacy policies, the exact count of small cell sizes was suppressed. All analyses were completed using STATA 17.0 and SAS 9.4 software. ChatGPT-5 was used to assist with word count reduction and sentence structuring; all scientific content was developed and reviewed by the authors.

3. Results

3.1. Baseline Characteristics

We identified 10,058 patients diagnosed with RA between 1 January 2008 and 31 March 2013, who met our inclusion/exclusion criteria. The mean (SD) follow-up period was 9.4 (4.2) years from index date. Patients had a mean (SD) age of 75.5 (5.8) years, with 67.3% being female and 14.1% residing in rural areas. At the time of diagnosis, 16.7% had a history of csDMARDs use, while 19.1% had been prescribed oral GC. The mean (SD) number of comorbidities was 1.09 (1.44) (Table 1). Baseline characteristics between two high- (N = 8040) and low- (N = 2018) CVD-risk groups are also shown in Table S3.

Table 1. Characteristics of ORAD patients 67 years or older at index (RA diagnosis) date.

	Sample Size	RA Medication Status During Follow-Up				
		Total N = 10,058	csDMARDs Only (With or Without Oral GC) N = 6506	Advanced Therapy (With and Without csDMARDs/Oral GC) N = 790	Oral GC Only N = 1648	No RA Medication N = 1114
Follow-up, years	Mean (SD)	9.39 (4.21)	9.6 (4.1)	11.1 (3.2)	8.5 (4.5)	8.1 (4.6)
	Median (Q1–Q3)	10.9 (5.92–12.7)	11.0 (6.3–12.8)	11.7 (9.8–13.2)	9.0 (4.5–12.3)	8.5 (3.8–12.1)
	Min–Max	0.50–15.8	0.50–15.8	0.80–15.7	0.52–15.7	0.51–15.7
Year of RA diagnosis	2008—n (%)	1874 (18.6)	1245 (19.1)	134 (17.0)	322 (19.5)	173 (15.5)
	2009—n (%)	1899 (18.9)	1246 (19.2)	115 (14.6)	327 (19.8)	211 (18.9)
	2010—n (%)	1950 (19.4)	1271 (19.5)	157 (19.9)	303 (18.4)	219 (19.7)
	2011—n (%)	2043 (20.3)	1338 (20.6)	182 (23.0)	317 (19.2)	206 (18.5)
	2012—n (%)	2292 (22.8)	1406 (21.6)	202 (25.6)	379 (23.0)	305 (27.4)
	2013—n (%)	2292 (22.8)	1406 (21.6)	202 (25.6)	379 (23.0)	305 (27.4)
Sex	Female—n (%)	6765 (67.3)	4293 (66.0)	586 (74.2)	1082 (65.7)	804 (72.2)
Age, years	Mean (SD)	75.5 (5.8)	75.0 (5.8)	72.3 (4.6)	77.1 (6.4)	77.9 (7.3)
	Median (Q1–Q3)	75 (70–80)	74 (70–79)	71 (69–75)	77 (72–82)	77 (72–84)
	Min–Max	67–97	67–95	67–92	67–97	67–97
Nearest Census Based Neighborhood Income Quintile	Missing Data—n (%)	30 (0.3%)	15 (0.23)	2 (0.24)		13 (0.47)
	1 (Lowest)—n (%)	1742 (17.4)	1129 (17.4)	109 (13.8)	299 (18.2)	205 (18.5)
	2—n (%)	2063 (20.6)	1368 (21.1)	136 (17.3)	332 (20.2)	227 (20.5)
	3—n (%)	2078 (20.7)	1329 (20.5)	174 (22.1)	354 (21.6)	221 (20.0)
	4—n (%)	2044 (20.4)	1320 (20.3)	174 (22.1)	333 (20.3)	217 (19.6)
	5 (Highest)—n (%)	2101 (21.0)	1345 (20.7)	195 (24.7)	324 (19.7)	237 (21.4)
Residence	Rural—n (%)	1415 (14.1)	1029 (15.8)	90 (11.4)	195 (11.8)	101 (9.1)
Prior csDMARDs use	n (%)	1683 (16.7)	1414 (21.7)	214 (27.1)	50 (3.0)	*
Prior bDMARDs use	n (%)	40 (0.40)	*	34 (4.3)	*	*
Prior tsDMARDs use	n (%)	*	*	*	*	*
Prior substance abuse	n (%)	10 (0.10)	*	*	*	*
Prior oral GC use	n (%)	1916 (19.1)	1344 (20.7)	160 (20.3)	408 (24.8)	*
Prior NSAIDs use	n (%)	1932 (19.2)	1315 (20.2)	201 (25.4)	251 (15.2)	165 (14.8)
Charlson morbidity index	Mean (SD)	1.09 (1.4)	1.02 (1.3)	0.60 (1.0)	1.3 (1.6)	1.2 (1.6)
	Median (Q1–Q3)	0 (0–2)	1 (0–2)	0 (0–1)	1 (0–2)	1 (0–2)
	No hospitalization (%)	72.8%	76.2%	78.9%	64.9%	67.9%
	Min–Max	0–9	0–8	0–6	0–8	0–9
Cardiovascular disease	n (%)	983 (9.8)	502 (7.7)	37 (4.7)	256 (15.5)	188 (16.9)
Hypertension	n (%)	488 (4.9)	309 (4.8)	44 (5.6)	72 (4.4)	63 (5.7)
COPD	n (%)	347 (3.5)	213 (3.3)	22 (2.8)	75 (4.6)	37 (3.3)
Cancer	n (%)	265 (2.6)	152 (2.3)	*	75 (4.6)	33 (3.0)
CKD	n (%)	381 (3.8)	192 (3.0)	11 (1.4)	111 (6.7)	67 (6.0)

ORAD: Ontario Rheumatoid Arthritis Dataset; RA: rheumatoid arthritis; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; GC: glucocorticoids; bDMARDs: biologic disease-modifying antirheumatic drugs; tsDMARDs: targeted synthetic disease-modifying antirheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.

* Exact counts suppressed for privacy reasons.

In the total cohort, 8944 patients (88.9%) were prescribed RA medications, including oral GC, csDMARDs, bDMARDs, and tsDMARDs. During the follow-up period, 4663 patients (46.4%) were prescribed methotrexate (MTX), 386 (3.8%) received TNFi, 146 (1.4%) were prescribed non-TNFi biologics, and 70 (0.7%) were prescribed tsDMARDs (Table S4).

During the follow-up period, 5439 patients (54.1%) utilized healthcare services related to MACE and 906 patients (9.0%) for VTE. Out of the 10,058 patients, 5972 (59.4%) died during the follow-up, and 2103 patients (20.9%) required healthcare services related to cancer (Table S4). Crude event rates (95% CI) and person-years of follow-up for each treatment group, overall, and by CVD-risk group are shown in Table S5.

3.2. Association Between Therapeutic Class and Primary Outcome by CVD-Risk Group

A total of 10,020 RA patients were included in weighted Fine-Gray models, of whom 80% (n = 8016) were classified as having high CVD risk. Over a median follow-up of 9.4 years, the high-risk group recorded 16,643 healthcare encounters related to MACE and 2344 related to VTE, whereas the low-risk group experienced 3001 MACE-related and 497 VTE-related events. Patients receiving no treatment demonstrated substantially increased MACE healthcare encounters (SHR: 15.0; 95% CI: 13.8–16.2) compared to those treated with csDMARDs. Similarly, patients prescribed oral GC only also showed higher healthcare utilization (SHR: 1.29; 95% CI: 1.13–1.47). In contrast, receipt of AT was associated with significantly lower healthcare encounters related to MACE (SHR: 0.53; 95% CI: 0.37–0.77).

Comparable patterns were observed in the low-CVD-risk group, where the absence of csDMARD or AT prescriptions (SHR: 20.8; 95% CI: 17.1–25.3) and the presence of oral GC prescriptions (SHR: 1.59; 95% CI: 1.14–2.22) were similarly linked to increased MACE-related healthcare utilization.

For VTE-related healthcare utilization within the high-CVD-risk group, patients who did not receive csDMARDs or AT had markedly elevated rates (SHR: 25.1; 95% CI: 19.1–32.9), as did those prescribed oral GCs (HR: 2.42 95% CI: 1.69–3.47), compared to patients receiving csDMARDs. Use of ATs was not significantly associated with VTE-related healthcare utilization in this group (SHR: 1.30; 95% CI: 0.55–3.08). Similar trends were evident in the low-CVD-risk group, where lack of csDMARD or AT therapy (SHR: 26.2; 95% CI: 15.5–44.3) and oral GC use (SHR: 3.01; 95% CI: 1.49–6.11) were associated with increased VTE-related healthcare utilization (Table 2).

Table 2. Subdistribution hazard ratios (SHRs) [±] and 95% confidence intervals are estimated from weighted marginal structural models for healthcare utilization (outpatient or inpatient visits) due to major adverse cardiovascular events (MACE) or venous thromboembolism (VTE) by RA therapeutic class and baseline cardiovascular (CVD) risk.

	High-CVD-Risk Group	Low-CVD-Risk Group
MACE		
csDMARD prescription	Reference	Reference
No csDMARD/AT/Oral GC prescription	15.0 (13.8, 16.2)	20.8 (17.1, 25.3)
Oral GC prescription only	1.29 (1.13, 1.47)	1.59 (1.14, 2.22)
AT prescription	0.53 (0.37, 0.77)	0.27 (0.11, 0.68)
VTE		
csDMARD prescription	Reference	Reference
No csDMARD/AT prescription	25.1 (19.1, 32.9)	26.2 (15.5, 44.3)

Table 2. *Cont.*

	High-CVD-Risk Group	Low-CVD-Risk Group
Oral GC prescription only	2.42 (1.69, 3.47)	3.01 (1.49, 6.11)
AT prescription	1.30 (0.55, 3.08)	0.11 (0.01, 2.64)

[±] Reported SHRs represent subdistribution hazard ratios comparing each treatment group to the reference category, interpreted as the relative rate of the cumulative incidence function for the event of interest, accounting for competing outcomes. MACE: major adverse cardiovascular events, VTE: vein thromboembolism, csDMARD: conventional synthetic disease modifying antirheumatic drug; AT: advanced therapy; GC: glucocorticoid.

3.3. Association Between Therapeutic Class and Secondary Outcomes by CVD-Risk Group

During the follow-up period, there were 5101 deaths and 1780 healthcare encounters related to cancer in the high-CVD-risk group, compared with 871 deaths and 439 healthcare encounters related to cancer in the low-CVD-risk group. Among patients at high CVD risk, absence of csDMARD or AT prescriptions (SHR: 1.94; 95% CI: 1.77–2.12) and oral GC use (HR: 1.72; 95% CI: 1.51–1.95) were significantly associated with increased all-cause mortality compared to csDMARD treatment, while AT use was linked to lower mortality risk (SHR: 0.05; 95% CI: 0.02–0.15). Similar associations were observed in the low-risk group, where no csDMARD/AT treatment (SHR: 1.94; 95% CI: 1.58–2.38) and oral GC use (SHR: 1.75; 95% CI: 1.30–2.35) were also associated with higher mortality, whereas AT prescription conferred a reduced risk (SHR: 0.08; 95% CI: 0.02–0.38).

For cancer-related healthcare utilization, patients without csDMARD or AT prescriptions had markedly higher rates of hospitalizations, emergency department visits, or physician consultations for cancer in both the high- (SHR: 41.2; 95% CI: 28.4–59.7) and low- (SHR: 37.9; 95% CI: 19.6–37.9) CVD-risk groups, relative to csDMARD users. No significant associations were observed between oral GC or AT use and cancer-related healthcare utilization (Table 3).

Table 3. Subdistribution hazard ratios (SHR) and 95% confidence intervals are estimated from weighted marginal structural models for all-cause mortality and all-cause cancer-related outpatient or inpatient visits by RA therapeutic class and baseline cardiovascular (CVD) risk.

	High-CVD-Risk Group	Low-CVD-Risk Group
All-Cause Mortality		
csDMARD prescription	Reference	Reference
No csDMARD/AT prescription	1.94 (1.77, 2.12)	1.94 (1.58, 2.38)
Oral GC prescription only	1.72 (1.51, 1.95)	1.75 (1.30, 2.35)
AT prescription	0.05 (0.02, 0.15)	0.08 (0.02, 0.38)
All-Cause Cancer		
csDMARD prescription	Reference	Reference
No csDMARD/AT prescription	41.2 (28.4, 59.7)	37.9 (19.6, 47.9)
Oral GC prescription only	1.40 (0.75, 2.62)	1.19 (0.35, 4.09)
AT prescription	n/a	2.03 (0.44, 9.36)

Reported SHRs represent subdistribution hazard ratios comparing each treatment group to the reference category, interpreted as the relative rate of the cumulative incidence function for the event of interest, accounting for competing outcomes. CVD: cardiovascular disease; csDMARD: conventional synthetic disease modifying antirheumatic drug; AT: advanced therapy; GC: glucocorticoid; n/a: not applicable.

4. Discussion

In this large population-based cohort study of older adults with RA, we investigated the association between RA therapeutic classes and major adverse health outcomes, stratified by cardiovascular risk. By evaluating the total burden of key outcomes including MACE, VTE, all-cause mortality, and cancer-related healthcare utilization, we aimed to address common patient concerns regarding the perceived risks associated with RA therapies. Rather than isolating a single adverse event, our objective was to capture the outcomes most relevant to patients' long-term health. Notably, patients who did not receive csDMARDs or AT experienced significantly higher rates of adverse outcomes, whereas those treated with more intensive therapeutic regimens demonstrated lower risks, even among the highest-risk patients. These findings underscore the importance of effective disease control in mitigating systemic inflammation and align with prior evidence documenting the deleterious effects of prolonged glucocorticoid use, including increased cardiovascular events and mortality [8,30,31].

Importantly, we found that AT, including bDMARD and tsDMARD prescriptions, was associated with reduced rates of healthcare utilization related to MACE and lower all-cause mortality in both CVD-risk groups. These findings align with other studies' findings on cardiovascular risk [10,11,32–35] and mortality [8,36].

For VTE-related outcomes, both oral GC use and absence of csDMARD therapy were associated with significantly increased healthcare utilization, suggesting that inadequate inflammatory control or failure to initiate DMARD treatment may contribute to elevated thrombotic risk in RA. Although VTE rates were higher among AT users in the high-CVD-risk group, this association was not statistically significant and should be interpreted cautiously. This finding may reflect confounding by indication, greater baseline disease severity, reduced mobility, or residual confounding from unmeasured factors such as obesity, smoking, or genetic risk [32]. Additionally, certain AT, such as JAK inhibitors, have been linked to increased VTE risk, and closer clinical monitoring of AT users may lead to higher detection rates [37,38]. These considerations underscore the complexity of evaluating VTE risk in this population and highlight the need for further study. However, our findings align with other studies which showed similar results with no increased risk of VTE in tsDMARDs users [10,33].

There are several limitations to our study. This study was limited to elderly individuals because ICES prescription drug data originate from the ODB program, which only captures medication claims for Ontarians aged 65 and older. This limitation suggests that these findings may not be readily generalized to the broader, younger RA patient population encountered in routine clinical practice.

We observed an exceptionally high SHR for MACE in the no-treatment group compared with the csDMARD group, even after applying marginal structural models intended to mitigate confounding by indication. For example, patients not receiving csDMARDs may represent a heterogeneous group that includes individuals with comorbidities, frailty, contraindications to treatment, or prior treatment intolerance, all of which may independently increase healthcare utilization. Thus, the persistence of such a large effect suggests that additional biases are likely to remain.

Residual and unmeasured confounding may still be present for factors that were not captured, were poorly measured, or were incompletely recorded in administrative data. For example, we did not have reliable measures of RA disease severity or extra-articular disease manifestations, both of which could act as important confounders. We also lacked information on other relevant risk factors that may influence outcomes, including smoking history, obesity, lifestyle factors, and family history of CVD or cancer. This big effect size

may also suggest frailty bias or sick-user bias. Patients receiving no DMARDs are likely too sick, frail, or in palliative care to receive treatment.

In our study, tsDMARD users were combined with bDMARD users due to the limited number of individuals receiving tsDMARD therapy. As a result, the findings from this AT-group analysis may not fully capture or represent outcomes specific to tsDMARD users. For example, this limitation prevented us from assessing the association between tsDMARDs, particularly tofacitinib, and the risks of MACE and cancer reported in the ORAL Surveillance study [12] which subsequently led to regulatory safety warnings. A recent Italian study compared prescription rates of tsDMARDs across three time periods defined according to the date of the first European Medicines Agency (EMA) safety warning. The study reported an absolute reduction of 32% in the number of patients prescribed a tsDMARD between Group 1 and Group 2, and a reduction of 16% between Group 1 and Group 3. In contrast, there was a 19% increase in tsDMARD prescriptions between Group 2 and Group 3 [39].

Our analyses were also restricted to an overall composite of MACE and did not include cause-specific mortality or detailed cancer subtype data, which may limit the interpretation of these outcomes. Lack of all-cause mortality analysis includes non-medical deaths (e.g., accidents, trauma), which could introduce noise into the data and affect the comparisons between treatment groups.

Some degree of misclassification of RA diagnosis may have occurred; however, this is likely minimized as we used the ORAD algorithm, which has demonstrated good validity with a 78% positive predictive value, 78% sensitivity, and approximately 100% specificity [14].

A key strength of this study was its ability to account for changes in patient treatment over time, which is critical when evaluating long-term outcomes such as mortality and cancer in patients with RA. By incorporating longitudinal data and capturing treatment modifications, this study provides a more accurate and nuanced understanding of how therapeutic strategies influence long-term risks. This dynamic approach enhances the validity of the findings compared to analyses relying solely on baseline treatment information. Additionally, the large sample size improved statistical power and allowed for robust stratification by CVD-risk groups. The use of validated outcome definitions further strengthened the reliability of our results. Finally, conducting this study within a universal healthcare setting supports its generalizability to other publicly funded healthcare systems.

5. Conclusions

In conclusion, these findings underscore significant disparities in treatment patterns and long-term outcomes among older adults with RA, particularly for those not receiving csDMARDs or AT. Our results indicate that the absence of disease-modifying treatment and a greater reliance on glucocorticoids are associated with higher risks of healthcare utilization for MACE and increased mortality. These observations reinforce the critical need to integrate comprehensive cardiovascular and thrombotic risk assessment into RA management strategies. Optimizing the use of effective RA therapies while minimizing prolonged glucocorticoid exposure is essential to improving both disease control and long-term safety outcomes for this vulnerable population.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/inflammj1010002/s1>, Table S1. ICES Data Sources used for this study; Table S2. Definition of clinical conditions; Table S3. Characteristics of ORAD patients over 67 years old at index (RA diagnosis) date by CVD-risk group; Table S4. Primary and secondary outcomes and every use of RA medication during follow-up; Table S5. Crude event rate by RA medication and CVD-risk group.

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Informed Consent Statement: ICES does not require patient consent for its activities under the Personal Health Information Protection Act (PHIPA) and the Coroners Act. This means that ICES can collect and use personal health information without individual consent or research ethics board approval for the purposes of health planning, management, and evaluation of the healthcare system.

Data Availability Statement: We are unable to share our data publicly due to ethical and legal restrictions. This study made use of de-identified data from the ICES Data Repository, which is managed by the Institute for Clinical Evaluative Sciences. Therefore, the authors are not the custodians of this data.

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