Published in final edited form as:
Ann Rheum Dis. 2015 February ; 74(2): 326–332. doi:10.1136/annrheumdis-2014-205675.

Risk of Major Cardiovascular Events in Patients with Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis: A population-based cohort study

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DATA SHARING: Code lists and statistical coding relevant to the manuscript are available from the authors on request.

CONTRIBUTION STATEMENT: Alexis Ogdie and Joel Gelfand conceptualized and designed the study with input from YiDing Yu, Nehal Mehta, Kevin Haynes, Sean Hennessy, Andrea Troxel, Thorvardur Love, Hyon Choi. Samantha Maliha and Yihiu Jiang assisted in assignment and analysis of cause of death. All authors were integral in interpretation of the results. Alexis Ogdie and YiDing Yu performed the programming, statistical analysis, preparation of the data and the first draft of the manuscript. Kevin Haynes performed data abstraction from The Health Improvement Network and assisted in programming. All authors were involved in critical review of the data as well as drafting and revision of the manuscript, and all have approved the final version of the paper to be published.

COMPETING INTERESTS: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr. Gelfand serves as a consultant to Amgen, Abbott, Centocor, Celgene, Novartis, Eli Lily, and Pfizer and has received honoraria; He has received grants from Amgen, Abbott, Pfizer, Novartis, Eli Lily, and Genentech. Drs. Haynes and Hennessy are supported by sponsored research agreement between the University of Pennsylvania and Astra Zeneca and Bristol Myers Squibb. Dr. Hennessy has consulted for Bristol-Myers Squibb, AstraZeneca, and Bayer Healthcare, LLC, and has received institutional support for pharmacoepidemiology training from Pfizer Inc. The remaining authors do not have competing interests.
Cegedim Strategic Data (CSD) Medical Research UK is an expert in UK anonymous patient data for the healthcare industry. CSD is a commercial organization that supplies data and trains and supports researchers in the use of primary care patient data. Data are available for use in medical research in the academic setting as well as in industry for a fee which varies depending on the type of data requested. Aside from undergoing ethical review by the Scientific Review Committee at Cegedim, independent academic groups who voluntarily act as an ethical review body, this protocol was not in any way discussed with Cegedim nor were any changes made by the company. We did not receive financial support or other forms of computational or analytical support from Cegedim/THIN. The data were collected by Cegedim and the general practitioners without knowledge of the study objectives and hypotheses.

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Abstract

Objectives—We aimed to quantify the risk of major adverse cardiovascular events (MACE) among patients with psoriatic arthritis (PsA), rheumatoid arthritis (RA), and psoriasis without known PsA compared to the general population after adjusting for traditional cardiovascular risk factors.

Methods—A population-based longitudinal cohort study from 1994–2010 was performed in The Health Improvement Network (THIN), a primary care medical record database in the United

Kingdom. Patients aged 18–89 with PsA, RA, or psoriasis were included. Up to 10 unexposed controls matched on practice and index date were selected for each patient with PsA. Outcomes included cardiovascular death, myocardial infarction, cerebrovascular accidents, and the composite outcome (MACE). Cox proportional hazards models were used to calculate the hazard ratios (HR) for each outcome adjusted for traditional risk factors. A priori we hypothesized an interaction between disease status and disease modifying anti-rheumatic drug (DMARD) use.

Results—Patients with PsA (N=8,706), RA (N=41,752), psoriasis (N=138,424) and unexposed controls (N=81,573) were identified. After adjustment for traditional risk factors, the risk of MACE was higher in PsA patients not prescribed a DMARD (HR 1.24, 95%CI: 1.03 to 1.49), patients with RA (No DMARD: HR 1.39, 95%CI: 1.28 to 1.50, DMARD: HR 1.58, 95%CI: 1.46 to 1.70), patients with psoriasis not prescribed a DMARD (HR 1.08, 95%CI: 1.02 to 1.15) and patients with severe psoriasis (DMARD users: HR 1.42, 95%CI: 1.17 to 1.73).

Conclusions—Cardiovascular risk should be addressed with all patients affected by psoriasis, psoriatic arthritis or rheumatoid arthritis.

Keywords

Psoriatic Arthritis; Psoriasis; Rheumatoid Arthritis; Myocardial Infarction; Cerebrovascular Event; Cardiovascular Disease; stroke

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in approximately 8–30% of patients with psoriasis. [1, 2] PsA has been linked to an increased prevalence of cardiovascular co-morbidities and cardiovascular risk factors. [3] However, the majority of studies performed to date have been cross-sectional. Cohort studies examining the risk of incident cardiovascular events in PsA are sparse. [4] Three population-based studies have examined the risk of cardiovascular events among patients with psoriasis and have included patients with PsA as a subgroup. [5–7] Existing studies have not examined the risk for incident major adverse cardiovascular events (MACE) including myocardial infarction (MI), cerebrovascular accidents (CVA), and cardiovascular death in PsA compared to matched internal controls from a population-based perspective after accounting for the presence of traditional cardiovascular risk factors.

Rheumatoid arthritis (RA) and severe psoriasis have been consistently linked to an increased risk for incident MACE. [3, 4, 8–16] It has been suggested that patients with PsA have a similarly elevated risk for cardiovascular disease. However, we recently demonstrated that patients with PsA did not have an increased risk of mortality compared to internal controls while patients with severe psoriasis (defined as psoriasis patients prescribed systemic therapy or phototherapy) and RA had substantially elevated mortality (HR 1.75 and 1.54–1.59, respectively). [17] This led us to question whether PsA is associated with incident cardiovascular disease from a population-based perspective.

The objective of this study was to examine the risk of incident MACE including myocardial infarction (MI), cerebrovascular accidents (CVA), and cardiovascular death controlling for traditional cardiovascular risk factors among patients with psoriatic arthritis, rheumatoid

arthritis or psoriasis compared to unexposed controls using a population-based cohort. We hypothesized similar rates of cardiovascular disease among the three groups given known associations with systemic Th1- and Th17- driven inflammation. [18, 19]

METHODS

Study Design and Setting

A cohort study was performed using data from The Health Improvement Network (THIN) in the United Kingdom (UK) between 1994 and 2010. THIN is a large medical record database in which general practitioners (GP) record routine health data about their patients. [20–22] The UK is an ideal setting for examining long-term health outcomes given the gatekeeper model, meaning that GPs are responsible for coordinating all of the patient's care. In addition, pay-for-performance measures mandate collection of data on cardiovascular outcomes and several key cardiovascular risk factors including diabetes and smoking. [23]

Study Population

All patients with PsA, psoriasis, or RA between the ages of 18 and 89 at the index date were included if they had observation time in THIN after Vision software implementation. Patients were excluded if they died or transferred out of the practice prior to the implementation of Vision software. Up to 10 unexposed controls from the general population without PsA, psoriasis, RA, or disease modifying anti-rheumatic drugs (DMARDs) prescriptions were randomly selected for each patient with PsA and were matched on practice and index date within the practice (defined as latest of registration with the practice and diagnosis date). Unexposed controls were assigned a "diagnosis date" within 6 months of the PsA patient's diagnosis date. This algorithm was designed to minimize bias by ensuring that PsA and unexposed controls are followed by similar doctors during similar time periods. For each individual outcome analysis, patients were excluded if they had the outcome of interest prior to the index date.

Exposure Definitions

PsA, psoriasis, and RA were defined by the presence of at least one READ code consistent with these diseases (READ codes are standard medical diagnosis codes used in the UK general practice system) [24]. READ codes for psoriasis (positive predictive value [PPV] 90%), [25] rheumatoid arthritis (PPV 81% for "potential cases" defined as single code without DMARD, rheumatoid factor result or rheumatology referral), [26–28] and PsA (PPV 85%) [2, 29] have been previously validated within the same or analogous large medical record databases. We have used this definition of PsA in other studies. [2, 17, 30, 31] Patients were classified as PsA if they had a code for PsA, RA if they had a code for RA but not PsA, and psoriasis if they had a code for psoriasis but did not have a code for RA or PsA.

Outcome Definitions

Outcomes were defined by READ codes representing the outcome of interest within the study period. The censoring date was the first occurrence of the outcome of interest. Patients were excluded from each analysis if they had the event of interest prior to the index date.

Myocardial infarction and stroke were defined by a previously validated set of READ codes with PPV 93% [32] and 77.5–89.3% respectively. [33, 34] Cardiovascular (CV) death was defined by a set of READ codes chosen based on the UK ICD10 codes classifying a cardiovascular death and the Centers for Disease Control (CDC) ICD9 codes classifying death as heart disease or stroke. [35, 36] These codes were extracted within the 60 days prior or 180 days following a code signifying the patient's death. Text comments in the database reporting the patient's death as cardiovascular were also used to classify CV death. This algorithm has been used previously and is the recommended method for identifying cause of death by THIN. MACE, the composite outcome, was achieved at the first of MI, CVA, or cardiovascular death.

Person Time Calculation

The index date (cohort entry) was defined as the latest date of the following events: diagnosis date, six months after initial registration with the practice, DMARD initiation (in patients utilizing DMARDs), implementation of Vision software in the patient's practice, or a practice acceptable mortality reporting. [37–40] The index data was similarly calculated in unexposed controls except for "diagnosis date" was the diagnosis date of the matched disease patient. Censoring occurred when the event of interest occurred, the patient died, the patient left the practice, the practice stopped participating in THIN, or the study ended in September 2010.

Covariates of Interest

All covariates of interest were measured prior to the index date. A priori, we hypothesized a statistical interaction between disease status and both age and DMARD use as disease severity may be reflected by DMARD use. DMARD exposure was included in the models as a binary variable for exposure at any point up to the index date. Among patients with RA and PsA, DMARDs included methotrexate, sulfasalazine, azathioprine, leflunamide, cyclosporine, mycophenolate, hydroxychloroquine, and biologic disease modifying agents including adalimumab, etanercept, and infliximab. In patients with skin psoriasis without a diagnosis of PsA or RA, methotrexate, cyclosporine, biologic disease modifying agents, phototherapy, psoralen (PUVA), retinoids (acitretin and etretinate), and hydroxyurea were considered DMARDs. In the United Kingdom, DMARDs can be prescribed by consultants (specialists) but should be captured by general practitioner records with the exception of the biologic medications, which are rarely recorded. [20] The following potential confounders were measured: age, sex, smoking, body mass index, blood pressure at baseline, year of cohort entry, Townsend deprivation score correlated with socioeconomic status [20]), urban versus rural living environment, chronic kidney disease, diabetes, hypertension, use of prescription non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids prior to index date. The Charlson comorbidity score [41] was also calculated but the typical point for RA was not included in order to better capture differences in other comorbidities among the groups.

Statistical Analysis

Covariate distribution among the groups was examined using descriptive statistics. Cox proportional hazards regression models were used to calculate the hazard ratio (HR) for each

group compared to the unexposed group after adjusting for age and sex. Hypothesized effect modifiers, use of DMARDs and age, were tested in the models and the likelihood ratio test was used to determine significance of the interactions. We then tested the hypothesized confounders in the model using a purposeful selection modeling approach [42] and kept in the model the predetermined confounders (age, sex, and traditional cardiovascular risk factors) and covariates that changed the main effects by >10% and had a p-value<0.1. Log-log survival plots and Schoenfeld residuals were used to assess the assumption of proportionality of hazards. Several sensitivity analyses were performed (more detail in Supplemental Figure 1). Statistical analysis was performed using Stata 13.0 (College Station, TX).

Sample Size Determination

Power calculations prior to the start of the study revealed that with 7,000 patients with PsA and 35,000 unexposed patients, we would have 90% power to detect a hazard ratio as small as 1.28, 1.16 and 1.19 for CV death, MI, and stroke, respectively, with an average of 5 years of follow-up per patient in an unadjusted analysis. Baseline event rates were assumed to be 0.16%, 0.49%, and 0.35% per year for CV death, MI, and stroke, respectively.

Ethics Board Approval

All data in this study was anonymous to the investigators. This study was approved by the University of Pennsylvania Institutional Review Board and Cegedim's Scientific Review Committee. This manuscript was prepared according to the STROBE statement recommendations. [43]

RESULTS

Among 8,706 patients with PsA, 41,752 patients with RA, 138,424 patients with psoriasis, and 82,258 randomly selected unexposed patients meeting the inclusion criteria, follow up time in the study period was comparable. Baseline characteristics are found in Table 1 (additional patient characteristics are found in Supplemental Table 1). Patients with RA were older and more often female. Approximately half of patients with RA and PsA were prescribed a DMARD and 3% of patients with psoriasis had been prescribed a DMARD or received phototherapy. At least 65% of patients with PsA and RA had been prescribed NSAIDs compared to 24% with psoriasis and 47% of controls. Compared to the unexposed population, the prevalences of cardiovascular risk factors, MI and stroke in the baseline period were elevated in patients with PsA, RA and psoriasis. Reasons for leaving the cohort (censoring) other than having an outcome of interest were similar among groups (data not shown).

The unadjusted incidence rates of MI, CVA, and MACE (composite outcome) are reported in Table 2. Hazard ratios for myocardial infarction, stroke, cardiovascular death, and MACE are presented in Table 3. There was a significant interaction between DMARD status (ever vs never prescribed) and exposure (disease) group ($p<0.001$ for CV death, CVA, and MACE and $p=0.01$ for MI). Therefore, the stratified results are presented. The risk of any major adverse cardiovascular event (composite outcome) was elevated in patients with PsA

without a DMARD prescription (HR 1.24, 95% CI 1.03–1.49), RA (No DMARD: HR 1.39, 95%CI 1.28–1.50 and DMARD user: 1.58, 95%CI 1.46–1.70) and severe psoriasis (defined as patients prescribed a DMARD; HR 1.42, 95%CI 1.17–1.73).

Patients with PsA had an elevated risk for incident MI (HR 1.36, 95%CI 1.04–1.77 and HR 1.36, 95%CI 1.01 to 1.84 for no DMARD and DMARD respectively). The risk for MI was similarly elevated in patients with RA without a DMARD prescription (HR 1.33, 95%CI 1.17–1.51) and patients with severe psoriasis (HR 1.26, 95%CI 0.92–1.72) but was substantially higher in patients with RA who had been prescribed a DMARD (HR 1.96, 95%CI 1.75–2.19).

The risk of incident stroke was also significantly elevated in patients with PsA without a DMARD prescription (HR 1.33, 95%CI: 1.03–1.71) which was similar to patients with RA and severe psoriasis. Finally, cardiovascular death was only significantly elevated in RA (No DMARD: HR 1.43, 95%CI 1.28–1.59 and DMARD: HR 1.66, 95%CI 1.48–1.86) and severe psoriasis (HR 1.54, 95%CI 1.15–2.05).

A third interaction with age as a continuous variable was tested and found to be significant ($p<0.001$ for all four outcomes). The three way interactions are presented in Figure 1. The relative risk is highest in the younger age groups where the absolute risk is low. Few events occurred in patients younger than 50 years of age (13% of MI, 8% of stroke, 3% of CV death, and 10% of composite outcomes).

Our results were robust to several sensitivity analyses (Supplemental Figure 1) varying definitions of the outcomes, restricting to only patients followed regularly, utilizing multiple imputation for smoking and body mass index, and imputing additional DMARD users. However, in examining the role of death as a competing risk factor for cardiovascular events, all previously significant associations in PsA were null whereas the HR in the other groups remained unchanged. Finally, adjusting for potentially cardiovascular-protective medication use (e.g., antihypertensives, lipid lowering medications, and antiplatelet agents listed in Supplemental Table 1) during the one year prior to start date in the cohort and health care utilization in the baseline period (number of GP visits) did not significantly change the results. One such model is illustrated in Supplemental Table 2.

DISCUSSION

To our knowledge, this is the first population-based study dedicated to examining MACE in PsA which may be an independent risk factor for major cardiovascular events including myocardial infarction and stroke, although this was only statistically significant for patients who were not prescribed a DMARD. Additionally, this is the first longitudinal population-based study dedicated to the simultaneous examination of the incidence of MACE in PsA, psoriasis and RA after adjusting for traditional cardiovascular risk factors. All three diseases had statistically similar risks for the development of incident cardiovascular events after adjustment for age, sex, calendar year of cohort entry, and traditional cardiovascular risk factors.

Strengths of this study include the large cohort of patients, an average of 5 years of follow up, simultaneous comparison among three disease cohorts in a population-based study, and the use of THIN in which the exposures (psoriasis, RA, PsA) and outcomes (MI, CVA) have been validated. The incidences of MI and CVA in our unexposed population are similar to UK National Statistics [44], lending credence to our algorithms to identify these outcomes and the validity of our unexposed population. These statistics are based on inpatient hospitalizations but support our assumption that we have captured the majority of the outcomes of interest. Furthermore, the increased risk of cardiovascular disease in RA and psoriasis are similar to those reported in recent meta-analyses, lending internal validity to our results in PsA. [14, 16]

Our study has limitations including lack of disease activity measures in THIN, generally absent biologic medication records, possible missing DMARD prescriptions, and the inability to account for over-the-counter NSAID use. THIN does not include data on disease activity in psoriasis or inflammatory arthritis, limiting our ability to examine the effect of disease severity on the incidence of MACE. However, we have shown that simple GP categorization of body surface area affected by psoriasis is positively correlated with the prevalence of atherosclerotic disease in a prospective study we are conducting nested within the THIN population. [45] Use of a systemic DMARD or phototherapy in patients with psoriasis has previously been used as a proxy for severe psoriasis. [5, 10, 46] However, DMARDs are less likely to represent a pure marker of disease severity in patients with PsA or RA due to confounding by indication and a potential healthy user effect in patients with PsA (i.e., fewer comorbidities in PsA and psoriasis patients prescribed a DMARD). In contrast, patients with RA prescribed a DMARD could have had more events because their disease was more severe. However, we are unable to test this hypothesis. In patients with PsA who were prescribed a DMARD, the point estimates were nearly the same as patients without a DMARD prescription but the confidence interval crossed 1.0. This may be due to a lack of statistical power after stratification by DMARD status. It could also be the result of a healthy user effect, the anti-inflammatory effect of medications on atherosclerosis, or closer follow up in patients using DMARDs with more attention to cardiovascular risk reduction given more frequent physicians visits. [47, 48]

NSAIDs have been associated with the development of cardiovascular disease, [49] although this is less clear in patients with RA. [12] Over-the-counter NSAID use may be prevalent among our arthritis cohorts, particularly given that the majority of patients with arthritis have received a prescription NSAID. This should not substantially affect our results, however, as adjustment for prescription NSAID use did not change the main effects (results not shown). Similarly, GPs often do not record the use of biologic DMARDs as these are prescribed directly by rheumatology consultants in the hospital setting. [20] However, according to NICE guidelines in the UK, all patients must first fail at least one oral DMARD in order to receive a biologic DMARD prescription, [50] so these patients should have been captured in the "DMARD" group. However, in some cases, the rheumatology consultant will directly prescribe an oral DMARD and the GP may not record this. In a recent validation study, we examined the agreement between GP and medical record report of DMARD use and found that while agreement is overall good, 20 of 53 (38%) patients without a code for a DMARD were reported by the GP to have received a DMARD at some point. In the study, a

total of 51 of 87 patients (59%) had either a code for a DMARD or GP report of DMARD use. [29] Therefore, in a sensitivity analysis, we augmented the number of DMARD users by first deriving a propensity score (a treatment prediction model) and then assigning those in the top three quintiles a DMARD prescription; this did not change the results. Finally, there may be patients with PsA in the "psoriasis only" cohort who have not yet been diagnosed with inflammatory arthritis or whose diagnosis was not recorded. This concern is not unique to population-based studies but a general issue that makes comparison of cohorts of patients with psoriasis and PsA challenging. [51] The goal of this study was to examine PsA with high specificity and without physical examination or direct questioning of the patients; we did not seek to identify patients with subclinical or undiagnosed PsA.

In conclusion, we report an increased incidence of major adverse cardiovascular events in PsA, psoriasis and RA. The hazard ratios for RA and psoriasis were similar to risk estimates in previous studies providing internal validity for the study results in patients with PsA and external validity for the study as a whole. These results suggest the need for improved screening and management of traditional cardiovascular risk factors in patients with inflammatory diseases. Future prospective randomized controlled studies are needed to better understand the impact of systemic therapy in decreasing the risk of major adverse cardiovascular events in these diseases. Additionally, studies addressing the impact of interventions for traditional cardiovascular risk factors on reducing the risk for MACE in patients with inflammatory diseases are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We would like to thank Peter Merkel, MD, MPH for helpful discussions and Ronac Mamtani, MD MSCE, James Floury MD MSCE, and Joy Wan, MD for assistance in assembling code lists.

FUNDING: This project was funded by the American College of Rheumatology (AO), R01HL089744 (JMG), K24AR064310 (JMG). Data from The Health Improvement Network is supported by the Clinical and Translational Science Award at the University of Pennsylvania (8UL1TR000003 from the National Center for Research Resources). Dr. Ogdie was supported by the American College of Rheumatology Research and Education Foundation and is now supported by NIH K23AR063764. Dr. Yu was supported by a grant from the Doris Duke Charitable Foundation and a grant from the Center for Clinical Epidemiology and Biostatistics. Dr. Hennessy was supported by R01AG025152. Dr. Love was supported by The Icelandic Research Fund, #120433021. Dr. Mehta was supported by K23HL097151-01. This work was completed independent of the funders.

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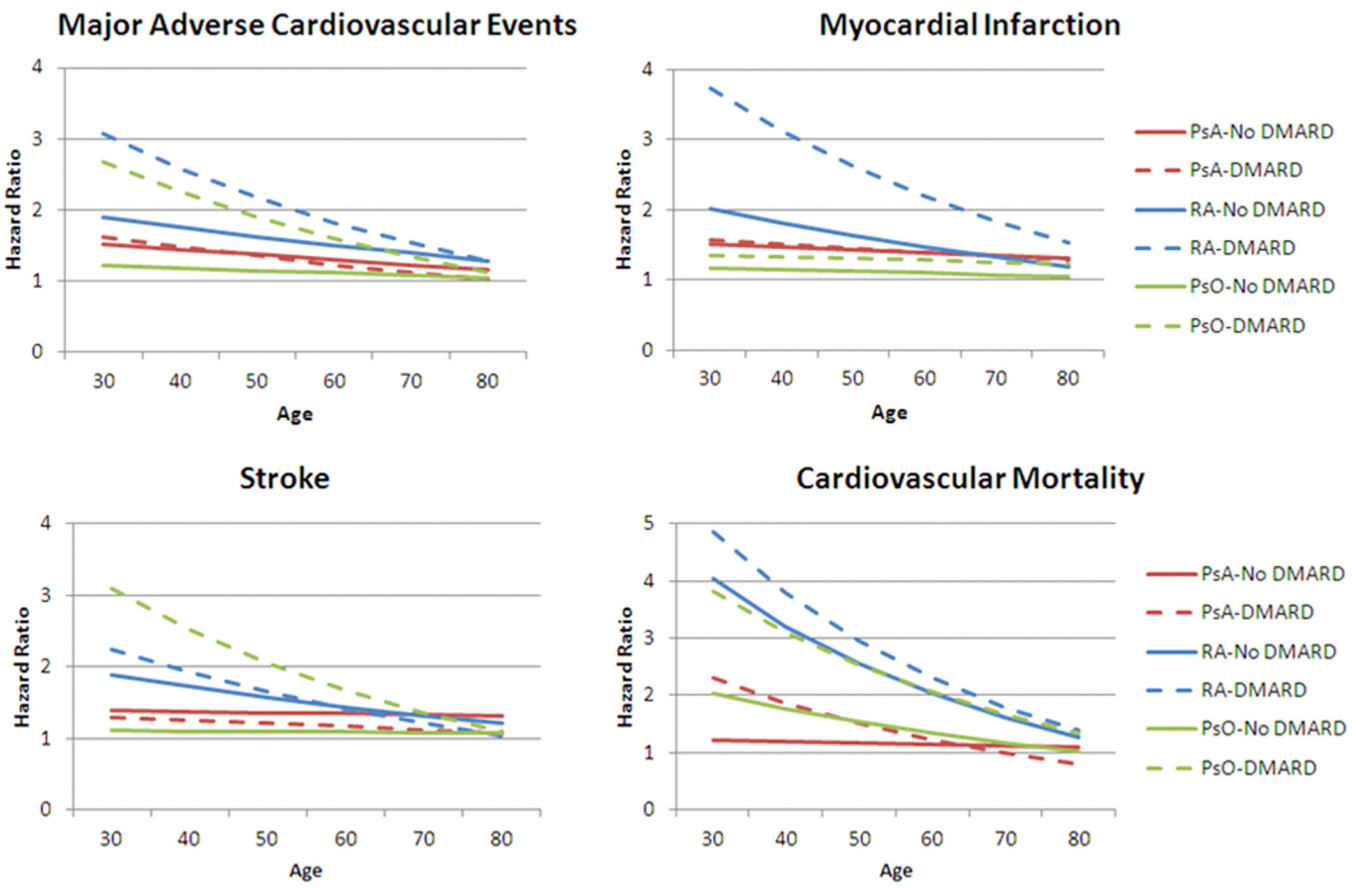

Figure 1. Hazard Ratios by Age

These graphs incorporate the age interaction into the fully adjusted models for major adverse cardiovascular events, cardiovascular mortality, myocardial infarction, and stroke. The fully adjusted models include age, sex, hypertension, diabetes, hyperlipidemia, and smoking status (never, past, current).

Ann Rheum Dis. Author manuscript; available in PMC 2015 June 01.

Table 1

Baseline Characteristics

		Control	Psoriatic Arthritis		Rheumatoid arthritis		Psoriasis	
		N=81,573	**No DMARD N=4,174**	**DMARD N=4,532**	**No DMARD N=17,912**	**DMARD N=23,840**	**No DMARD N=134,095**	**DMARD N=4,329**
Demographics	Age (Mean(SD))	49.86 (18.25)	51.63 (14.95)	49.80 (13.70)	63.48 (16.15)	59.76 (14.34)	47.56 (17.73)	49.27 (16.52)
	Male N (%)	36,806 (45.1%)	2,121 (50.8%)	2,329 (51.4%)	5,185 (28.9%)	7,129 (29.9%)	65,280 (48.7%)	2,201 (50.8%)
	Disease Duration[1] (Mean Years(SD))	N/A	5.75 (7.93)	4.39 (6.92)	8.70 (11.42)	5.98 (8.78)	7.10 (10.51)	12.20 (12.04)
	Cohort time (Mean(SD))	5.24 (3.92)	5.55 (4.02)	5.02 (3.77)	5.40 (3.99)	5.36 (3.80)	5.41 (3.99)	4.33 (3.40)
Baseline Event Rates[2]	Myocardial infarction N (%)	1,925 (2.36%)	104 (2.49%)	88 (1.94%)	818 (4.57%)	983 (4.12%)	3,193 (2.38%)	116 (2.68%)
	Stroke N (%)	1,265 (1.55%)	59 (1.41%)	48 (1.06%)	625 (3.49%)	531 (2.23%)	2,015 (1.50%)	80 (1.85%)
	Transient Ischemic Attack N (%)	433 (.53%)	20 (.48%)	19 (.42%)	209 (1.17%)	165 (.69%)	627 (.47%)	20 (.46%)

Additional baseline characteristics are found in Supplemental Table 1.

[1]Disease duration was calculated from the diagnosis date to start date.

[2]Note that patients with baseline event rates were excluded from the relevant analyses (e.g. patients with a previous MI were excluded from the incident MI analysis and the composite outcome analysis).

Table 2

Incidence Rate of Cardiovascular Death, Myocardial Infarction, Stroke and MACE

		CV Death	PY*	Incidence Rate per 1000 PY	MI	PY	Incidence Rate per 1000 PY	Stroke	PY	Incidence Rate per 1000 PY	MACE	PY	Incidence Rate per 1000 PY
Unexposed		902	427,554	2.1	838	415,547	2.0	1,010	419,573	2.4	2,055	408519	5.0
PsA	All	86	45,889	1.9	123	44,496	2.8	119	45,037	2.6	249	43710	5.7
	No DMARD	57	23,149	2.5	70	22,339	3.1	73	22,643	3.2	148	21882	6.8
	DMARD	29	22,740	1.3	53	22,158	2.4	46	22,394	2.1	101	21829	4.6
RA	All	1,258	224,336	5.6	1,032	212,904	4.8	1,094	216,806	5.0	2,504	206264	12.1
	No DMARD	672	96,662	7.0	409	91,782	4.5	569	92,952	6.1	1,198	88494	13.5
	DMARD	586	127,674	4.6	623	121,122	5.1	525	123,854	4.2	1,306	117770	11.1
Psoriasis	All	1,695	744,257	2.3	1,643	721,708	2.3	1,810	729,470	2.5	3, 864	708554	5.5
	No DMARD	1, 645	725,493	2.3	1, 603	703,652	2.3	1,753	711,187	2.5	3, 749	690931	5.4
	DMARD	50	18,764	2.7	45	18,056	2.5	57	18,283	3.1	115	17623	6.5

*PY = person years

For comparison, according to United Kingdom National Statistics between 2000–2009, the incidence of MI for men of all ages was 2.05–3.34/1,000 and for women of all ages was 0.84–1.52/1,000. The incidence of stroke for men of all ages was 1.78–2.77/1,000 and for women of all ages was 1.39–2.08/1,000. [44]

Table 3

Hazard Ratios and 95% Confidence Intervals for Major Adverse Cardiovascular Events

COMPOSITE OUTCOME				
		Unadjusted	Age-Sex Adjusted	Fully Adjusted*
Unexposed		Ref	Ref	Ref
PsA	No DMARD	1.34 (1.13–1.58)	1.33 (1.13–1.58)	1.24 (1.03–1.49)
	DMARD	0.93 (0.76–1.13)	1.17 (.96–1.43)	1.17 (.95–1.46)
RA	No DMARD	2.62 (2.44–2.81)	1.43 (1.33–1.53)	1.39 (1.28–1.50)
	DMARD	2.17 (2.02–2.32)	1.62 (1.51–1.74)	1.58 (1.46–1.70)
Psoriasis	No DMARD	1.07 (1.02–1.13)	1.16 (1.10–1.23)	1.08 (1.02–1.15)
	DMARD	1.30 (1.08–1.57)	1.41 (1.17–1.71)	1.42 (1.17–1.73)
MYOCARDIAL INFARCTION				
		Unadjusted	Age-Sex Adjusted	Fully Adjusted
Unexposed		Ref	Ref	Ref
PsA	No DMARD	1.55 (1.21–1.98)	1.46 (1.14–1.86)	1.36 (1.04–1.77)
	DMARD	1.19 (0.90–1.57)	1.35 (1.03–1.79)	1.36 (1.01–1.84)
RA	No DMARD	2.20 (1.96–2.48)	1.36 (1.21–1.53)	1.33 (1.17–1.52)
	DMARD	2.55 (2.30–2.83)	2.02 (1.82–2.24)	1.96 (1.75–2.19)
Psoriasis	No DMARD	1.13 (1.04–1.23)	1.19 (1.09–1.29)	1.08 (.98–1.18)
	DMARD	1.25 (.92–1.68)	1.30 (.96–1.76)	1.26 (.92–1.72)
STROKE				
		Unadjusted	Age-Sex Adjusted	Fully Adjusted
Unexposed		Ref	Ref	Ref
PsA	No DMARD	1.34 (1.05–1.69)	1.36 (1.08–1.73)	1.33 (1.03–1.71)
	DMARD	0.85 (0.64–1.15)	1.12 (.83–1.50)	1.13 (.83–1.55)
RA	No DMARD	2.54 (2.29–2.81)	1.29 (1.16–1.43)	1.29 (1.15–1.45)
	DMARD	1.76 (1.59–1.96)	1.27 (1.14–1.41)	1.24 (1.10–1.39)
Psoriasis	No DMARD	1.02 (0.95–1.11)	1.13 (1.05–1.22)	1.08 (.99–1.17)
	DMARD	1.31 (1.00–1.71)	1.45 (1.11–1.90)	1.45 (1.10–1.92)
CARDIOVASCULAR DEATH				
		Unadjusted	Age-Sex Adjusted	Fully Adjusted
Unexposed		Ref	Ref	Ref

PsA	No DMARD	1.16 (0.89–1.52)	1.30 (.99–1.70)	1.07 (.79–1.44)
	DMARD	0.61 (0.42–0.88)	.98 (.68–1.42)	0.96 (.64–1.43)
RA	No DMARD	3.29 (2.97–3.63)	1.55 (1.40–1.71)	1.43 (1.28–1.59)
	DMARD	2.18 (1.96–2.42)	1.69 (1.53–1.88)	1.66 (1.48–1.86)
Psoriasis	No DMARD	1.07 (0.99–1.16)	1.22 (1.13–1.34)	1.09 (1.00–1.20)
	DMARD	1.29 (0.97–1.71)	1.49 (1.12–1.98)	1.54 (1.15–2.05)

* The fully adjusted models include age, sex, hypertension, diabetes, hyperlipidemia, smoking status (never, past, current), and start year in the cohort.