

Primary Prevention of Myocardial Infarction in Rheumatoid Arthritis Using Aspirin: A Case-crossover Study and a Propensity Score–matched Cohort Study

Josefina Durán, Christine Pelloquin, Yuqing Zhang, and David T. Felson

ABSTRACT. Objective. Subjects with rheumatoid arthritis (RA) are at higher risk of developing cardiovascular disease, which is their leading cause of death. Conflicting evidence exists regarding the efficacy of aspirin (ASA) as primary prevention. We evaluated whether a protective association exists between ASA and myocardial infarction (MI) in RA subjects.

Methods. In the United Kingdom, persons age ≥ 60 years receive free ASA by prescription and 75% of use is by prescription. Subjects ≥ 60 years with RA in the population-based The Health Improvement Network database constituted our study population. We excluded patients with history of MI, angina, stroke, peripheral vascular disease, or coronary artery procedures. Our main outcome was the occurrence of fatal and nonfatal MI. We performed a case-crossover study with each subject contributing a hazard period and a control period 90 days prior to the MI. In addition, to minimize confounding by indication, a propensity score (PS)–matched cohort study was performed, considering all patients with RA with an incident prescription of low-dose ASA as our exposed group.

Results. We did not find a protective effect in the case-crossover study (OR 1.83, 95% CI 0.71–4.71), with 55 subjects exposed in the hazard period and 44 in the control period. Similarly, among 1836 subjects included in the PS-matched cohort study (918 ASA users and 918 ASA non-users), we did not find a protective effect of low ASA on MI (HR 1.39, 95% CI 0.87–2.23).

Conclusion. We did not find a protective effect of ASA on MI in patients with RA when used as primary prophylaxis. (First Release March 1 2017; J Rheumatol 2017;44:418–24; doi:10.3899/jrheum.160930)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
PRIMARY PREVENTION

ASPIRIN

MYOCARDIAL INFARCTION

PROPHYLAXIS

CARDIOVASCULAR DISEASE

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint inflammation. Subjects with RA are at a high risk of developing atherosclerosis and cardiovascular (CV) disease^{1,2}. This risk is estimated to be about 1.5 \times that of the general population^{3,4,5}. Moreover, acute myocardial infarction (MI) in patients with RA has a higher

mortality compared with the general population, and CV events represent the leading cause of death in this population^{6,7}. Although studies have shown a trend toward a decrease in mortality in patients with RA with advances in therapy, CV morbidity and mortality continue to increase^{8,9}.

The European League Against Rheumatism 2010 guidelines on CV risk management recommend performing a risk assessment in patients using a 1.5-multiplication factor and then following regional guidelines for CV disease prevention¹⁰. These regional guidelines all agree on the management of comorbidity as a measure of prevention, but there is controversy regarding the use of aspirin (ASA) as a prophylactic measure.

In the general population, there is unequivocal evidence supporting ASA as secondary prophylaxis for CV events¹¹. However, its efficacy as primary prevention is not as clear¹². In 2014, the US Food and Drug Administration stated that the agency “does not believe the evidence supports the general use of aspirin for primary prevention of a heart attack or stroke^{12a}.” The issue is who should receive prophylaxis according to a balance of benefits and risks.

Patients with RA are at increased CV risk because of their disease and some of its treatments [nonsteroidal antiinflam-

From the Rheumatology Department, Pontificia Universidad Católica de Chile School of Medicine, Santiago, Chile; Clinical Epidemiology Unit, Boston University School of Medicine, Boston, Massachusetts, USA; Arthritis Research UK Epidemiology Unit, University of Manchester; Manchester UK National Institute for Health Research Biomedical Research Unit, Manchester, UK.

Supported by P60 AR047785 US National Institute of Arthritis and Musculoskeletal and Skin Diseases Multidisciplinary Clinical Research Center grant.

J. Durán, MD, MSc, Rheumatology Department, Pontificia Universidad Católica de Chile School of Medicine, and Clinical Epidemiology Unit, Boston University School of Medicine; C. Pelloquin, MPH, Clinical Epidemiology Unit, Boston University School of Medicine; Y. Zhang, DSc, Clinical Epidemiology Unit, Boston University School of Medicine; D.T. Felson, MD, MPH, Clinical Epidemiology Unit, Boston University School of Medicine, and Arthritis Research UK Epidemiology Unit, University of Manchester, and Manchester UK National Institute for Health Research Biomedical Research Unit.

Address correspondence to Dr. J. Durán, Marcoleta 350, Santiago Centro, Santiago, Chile. E-mail: jgduran@uc.cl
Accepted for publication January 4, 2017.

matory drugs (NSAID), corticosteroids]^{13,14,15}, but at the same time have additional risks for adverse events with the use of ASA because of these same treatments (i.e., ulcers and bleeding). Moreover, subjects taking NSAID chronically, such as many persons with RA, were excluded from the majority of primary prevention studies^{16,17,18,19}. Therefore, the effectiveness of ASA has not been evaluated in this group of subjects.

As a consequence, we asked whether ASA used as primary prophylaxis decreases overall risk of MI and fatal MI among patients with RA. In the United Kingdom, ASA is provided free by prescription to persons age 60 and over and most of the use in this age group is by prescription, offering us an opportunity to examine ASA use and subsequent cardiac events. We used The Health Improvement Network (THIN) UK database to perform a case-crossover study evaluating the association of low-dose ASA use with the occurrence of MI among patients with RA, a study design that controls for time-invariant confounders and may also minimize confounding by indication.

In addition, we carried out a prospective cohort study of persons with RA receiving ASA versus those not receiving ASA matching by propensity score (PS).

MATERIALS AND METHODS

Data source. THIN is a computerized medical record database in the United Kingdom started in 1986. It contains anonymized patient data on electronic medical records of over 10 million patients from 580 general practices that are systematically recorded by general practitioners (GP)²⁰. This cohort is representative of the general population of the United Kingdom. Information collected includes demographics, GP visits, referrals, hospital admissions, laboratory test results, procedures, prescriptions (including dosage), and health information such as height, weight, blood pressure, and smoking status. Diagnoses in THIN are identified using read codes and prescriptions entered as drug codes using Multilex^{21,22}. Quality control checks are done regularly to maintain high data completion rates and accuracy. The THIN database has been validated for pharmacoepidemiology research²³. Data belonging to THIN database are deidentified; therefore, the study was regarded as exempt from review by the Institutional Review Board.

Study population. This study was performed using data recorded on individuals between January 1, 1995, and September 30, 2013, for our case-crossover analysis and between January 1, 2002, and December 31, 2012, for our PS analysis. We used a longer time period for our case-crossover analysis to increase the number of discordant pairs (subjects with a different exposure status in the hazard and the control period) and to improve power. However, a sensitivity analysis was performed with a similar followup as the PS-matched cohort study (2002–2013). Study participants were required to have ≥ 1 year of continuous enrollment in the database to be eligible.

We included subjects ≥ 60 years old with a diagnosis of RA defined as at least 1 RA read code and a disease-modifying antirheumatic drug (DMARD) code within a year. The date of the first DMARD prescription after an RA code was used as the RA diagnosis date. This RA definition has been found to have a specificity of 96% (vs the 1987 American College of Rheumatology criteria)²⁴. To analyze primary prevention, we excluded subjects with the presence of codes corresponding to MI, angina, peripheral vascular disease, ischemic stroke, transient ischemic attack, stroke, or coronary artery procedures (angioplasty, stenting, coronary artery bypass grafting) at any time prior to study entry. The date of study entry was the

later of RA diagnosis date (i.e., DMARD prescription date) or the date the subject met the age, 1-year enrollment, and calendar time criteria.

Case-crossover study. With this approach, each study subject served as his or her own control, and self-matching eliminates time-invariant confounders within a subject, confounders that would differ between study subjects. Our study design requires a transient effect such as ASA's action on platelets and exposure must be intermittent, which was the case in many THIN subjects. Such a design has been successfully used in many previous studies where the effect of transient risk factors on the risk of an acute event was evaluated (e.g., low-dose ASA use triggering gout attack)²⁵. A manual review of 100 medical records of low-dose ASA users in THIN was performed, which revealed that although prescription medications were meant for continuous use, subjects frequently used them intermittently. Therefore, a case-crossover was an appropriate study design.

Case definition. Our main outcome was defined as the occurrence of an incident acute MI or fatal MI. Acute MI included all ST-elevation MI (STEMI) and non-STEMI codes (echocardiogram reports alone were not considered an acute MI). Fatal MI were primarily identified by looking at medical records. If these records did not contain information for cause of death, additional health data records were used. Validity of diagnostic codes for CVD outcomes has been demonstrated in THIN²⁶.

Exposure assessment. Low-dose ASA was defined as the use of oral ASA in a dose ≤ 325 mg/day. A study performed in the United Kingdom showed that 74% of ASA use is prescription-based and over-the-counter use is more frequent in men, which represented a minority of the RA population²⁷. In addition, ASA has no cost with prescription in subjects ≥ 60 years old in the United Kingdom. Combination drugs used with analgesic purpose (such as opioids) were excluded.

We considered subjects exposed if they had an ASA prescription that covered up to 7 days before the index date (date of MI or fatal MI) because the effect of ASA on platelets may last up to 7 days (carry-over effect). The control period was 90–97 days prior to MI or fatal MI occurrence.

Covariates in the case-crossover design. We measured all covariates prior to the hazard/control period. Information on all CV risk factors was collected to describe our study population. The following covariates were collected: age, sex, body mass index (BMI), alcohol, smoking, diabetes, hypertension (HTN), dyslipidemia, peripheral vascular disease, stroke, and atrial fibrillation. Regarding drugs, we evaluated the use of NSAID, glucocorticoids, statins, nitrates, antihypertensives, anticoagulants, and antiaggregants (clopidogrel, ticlopidine). We adjusted for these covariates in our analysis because they may vary in a 3-month period.

PS-matched cohort study. For our analysis, we excluded all subjects who used ASA prior to study entry. Exposure was classified as the incident use of enteral ASA in a dose ≤ 325 mg, again excluding combination drugs used with analgesic purpose.

Our outcome was MI or fatal MI. Definition of each of the components of this outcome was similar to the one used for the case-crossover design.

Because confounding by indication is a major concern in the assessment of the effect of medication use in an observational study and there may be a potential secular trend in ASA use as well as occurrence of MI, we conducted a time-stratified PS-matched cohort study to minimize potential confounding by indication and to account for secular trends. Specifically, we divided the study followup time into 1-year blocks. Within each 1-year time block, we calculated PS for prescription of low ASA for each eligible individual using a logistic regression model. The date of prescription of ASA was used as the index date for that patient, and a random date within the 1-year block was assigned as the index date for the matched subject with RA who did not receive ASA. The variables included in the logistic regression model consisted of RA duration prior to the index date, sociodemographic factors (i.e., age and sex), BMI, lifestyle factors (i.e., smoking and alcohol consumption), comorbidities (i.e., angina, atrial fibrillation, diabetes, dyslipidemia, HTN), medication (i.e., angiotensin-converting enzyme inhibitors, antiaggregants/anticoagulants, angiotensin receptor II blockers, β blockers, calcium channel blockers, diuretics, gluco-

corticoids, lipid-lowering drugs, nitrates, NSAID), and health utilization variables (i.e., GP visits, hospitalizations).

After calculation of PS using all the listed covariates within each accrual time block, we identified a PS-matched subject who did not receive ASA (i.e., a subject in the comparison cohort) for each patient receiving his/her first ASA (i.e., a subject in the exposed cohort) using a greedy-matching algorithm^{28,29}.

Statistical analysis. Baseline characteristics were expressed as mean and SD for continuous variables and as percentages for qualitative variables.

Case-crossover analysis. A conditional logistic regression, stratified by the subject, was performed to estimate adjusted OR of ASA use and risk of MI. Medications and comorbidities listed above were adjusted for in the multivariable regression model. Considering that the duration of ASA's carry-over effect has been questioned with an interindividual variation between 2 and 5 days^{30,31,32,33}, we also conducted a sensitivity analysis to look at exposure concurrent with the index date (the same day as the index day). In this sensitivity analysis, we used the same time frame of ASA exposure for the control period.

Cohort study analysis. Followup time started from the index date until subjects experienced the outcome of interest, died, discontinued enrollment, or the study period ended, whichever occurred first. Time-stratified Cox proportional hazard models were used to estimate the HR of ASA for the MI and its 95% CI. A crude analysis and an adjusted analysis including all covariates in the PS were performed.

A sensitivity analysis excluding users of ibuprofen and/or naproxen was performed in both study designs.

A level of significance of 0.05 two-sided was used. All analyses were performed using SAS 9.3.

RESULTS

Case-crossover analysis. Our analysis included 270 patients with RA who experienced an incident MI during the study period. Mean age of MI diagnosis was 73.5 years (SD 7.4) and mean RA duration was 7.3 years (SD 5.0). There was a high frequency of comorbidities, with HTN present in 53.7% of subjects. The study participants' characteristics are described in Table 1. The frequency of the use of drugs that have a CV effect was similar in the hazard and control study periods (Table 2).

During the hazard period, 55 subjects were exposed to ASA and during the control period 44 subjects were exposed, with 27 discordant exposure statuses within subjects in the 2 observation periods. There was no significant association between ASA use and MI occurrence after adjusting for potential confounders with a crude OR of 2.37 (95% CI 1.04–5.43) and an adjusted OR of 1.83 (95% CI 0.71–4.71). Sensitivity analyses also did not show a protective effect of ASA (Table 3).

PS-matched cohort study. Our analysis included 1836 patients with RA with no previous CV events: 918 ASA initiators and 918 PS-matched subjects who had not received ASA. Prior to matching, there were 935 ASA initiators and 5819 potential comparators. Baseline characteristics were balanced in the 2 groups, with a mean age of 71 years, a high frequency of comorbidity, and a mean RA duration of 6.7 years (Table 1B).

Among ASA initiators there were 44 MI events during followup, while among ASA non-users there were 32 events

Table 1A. Study participants' characteristics: case-crossover analysis. All covariates are measured prior to the index date. Values are n (%) or mean \pm SD unless otherwise specified.

Characteristics	Values
Subjects, n	270
Age, yrs	73.5 \pm 7.4
Female	151 (55.9)
BMI, continuous	26.6 \pm 4.8
BMI, categorical	
Underweight	12 (4.4)
Normal	65 (24.1)
Overweight	96 (35.6)
Obese	46 (17.0)
Missing	51 (18.9)
Smoking	
Non-smoker	102 (37.8)
Ex-smoker	105 (38.9)
Current smoker	56 (20.7)
Missing	7 (2.6)
Alcohol	
Non-drinker	68 (25.2)
Ex-drinker	11 (4.1)
Current drinker	168 (62.2)
Missing	23 (8.5)
Diabetes	45 (16.7)
Dyslipidemia	31 (11.5)
Hypertension	145 (53.7)
Antihypertensives	179 (66.3)
Antiaggregants/anticoagulants	26 (9.6)
Glucocorticoids	133 (49.3)
Lipid-lowering drugs	68 (25.2)
Nitrates	19 (7.0)
NSAID	151 (55.9)
GP visits	11 \pm 17
Hospital visits	1 \pm 1

BMI: body mass index (underweight \leq 18.5, normal weight = 18.5–24.9, overweight = 25–29.9, obese = BMI of 30 or greater); NSAID: nonsteroidal antiinflammatory drugs; GP: general practitioner.

recorded. There was no statistically significant difference in the risk of major CV events among ASA users compared with ASA non-initiators, with a crude HR of 1.42 (95% CI 0.90–2.24). After adjusting for all covariates, the effect estimate did not change materially (HR 1.39, 95% CI 0.87–2.23; Table 3).

DISCUSSION

In our large population-based study performed among UK residents, we found that among patients with RA, the use of ASA did not provide a protective effect on the occurrence of MI. We performed 2 study designs to control for potential bias because of confounding by indication and both showed a nonsignificant association.

In the general population, studies evaluating ASA as a primary prophylaxis have shown conflicting results, probably related to the study population characteristics and composite endpoints. Initial results were highly encouraging. Particu-

Table 1B. Study participants' characteristics: propensity score–matched cohort study. All covariates are measured prior to the index date. Values are n (%) or mean ± SD unless otherwise specified.

Characteristics	ASA Initiators	ASA Non-users
Subjects, n	918	918
Demographic characteristics		
Age, yrs	71.5 ± 7.2	71.3 ± 7.2
Female	608 (66.2)	601 (65.5)
BMI	26.9 ± 4.9	27.1 ± 4.9
Alcohol		
Non-drinker	237 (25.8)	227 (24.7)
Ex-drinker	38 (4.1)	40 (4.4)
Current drinker	643 (70.0)	651 (70.9)
Smoking		
Non-smoker	445 (48.5)	406 (44.2)
Ex-smoker	309 (33.7)	322 (35.1)
Current smoker	164 (17.9)	190 (20.7)
RA duration	6.7 ± 4.8	6.7 ± 4.7
Comorbidities		
Angina	40 (4.4)	29 (3.2)
Atrial fibrillation	73 (8.0)	67 (7.3)
Diabetes	128 (13.9)	117 (12.7)
Dyslipidemia	119 (13.0)	132 (14.4)
Hypertension	489 (53.3)	512 (55.8)
Cardiovascular disease drugs		
Antiaggregants/anticoagulants	41 (4.5)	46 (5.0)
Antihypertensive drugs		
ACE inhibitors	228 (24.8)	261 (28.4)
ARB	101 (11.0)	112 (12.2)
β-blockers	180 (19.6)	180 (19.6)
Calcium channel blockers	222 (24.2)	234 (25.5)
Diuretics	359 (39.1)	379 (41.3)
Lipid-lowering drugs		
Nitrates	39 (4.2)	33 (3.6)
Antiinflammatory drugs		
NSAID	510 (55.6)	520 (56.6)
Glucocorticoids	322 (35.1)	311 (33.9)
Health service use variables		
GP visits	9 ± 8	10 ± 11
Hospital visits	1 ± 1	1 ± 1

ASA: aspirin; BMI: body mass index (underweight ≤ 18.5, normal weight = 18.5–24.9, overweight = 25–29.9, obese = BMI of 30 or greater); RA: rheumatoid arthritis; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; NSAID: nonsteroidal antiinflammatory drugs; GP: general practitioner.

Table 2. Frequency of potential time-varying confounders between hazard periods and control periods in the case crossover analysis. Values are n (%) unless otherwise specified.

Variables	Case Period	Control Period
Subjects, n	270	270
Antihypertensives	168 (62.2)	157 (58.1)
Antiaggregants/anticoagulants	24 (8.9)	19 (7.0)
Glucocorticoids	105 (38.9)	111 (41.1)
Lipid-lowering drugs	60 (22.2)	62 (23.0)
Nitrates	14 (5.2)	8 (3.0)
NSAID	119 (44.1)	113 (41.9)

NSAID: nonsteroidal antiinflammatory drugs.

larly, the Physicians Health study found a decrease in risk of MI of more than 40% with the daily use of 325 mg of ASA; however, no significant association was seen for stroke. These were men, mainly healthy subjects who did not take NSAID¹⁶. A slightly lower but still clearly beneficial effect was seen for ASA 100 mg administered to male and female high-risk patients in the Primary Prevention Project with a 31% reduction in MI and a 23% reduction in total CV events, again with no protective effect for stroke¹⁸.

However, in the Women's Health Study, no association was found for ASA for their main composite outcome of major CV events, or for MI, whereas a protective effect was found for stroke (RR 0.76). In a subgroup analysis of women 65 years of age or older, the risk of major CV events was reduced by 26% with ASA use¹⁷. Similarly, studies performed in patients with diabetes with asymptomatic peripheral artery disease and Japanese individuals failed to show any benefit of ASA^{19,34,35}. A metaanalysis that was recently published showed a protective effect of ASA for primary prevention for nonfatal MI. However, studies were heterogeneous and no benefit was found for CVD mortality³⁶.

These conflicting results suggest that primary prophylaxis may be applied only to a selected group of patients. Subjects with RA are a group that might require a low threshold for prescribing ASA because of their accelerated atherosclerosis linked to a dysfunctional endothelium, increased lipoprotein A, low-density lipoprotein oxidation, and altered high-density lipoprotein^{37,38,39}. In addition, there is a high use of NSAID and corticosteroids among these patients, further increasing their risk of CV events^{13,15,40}. However, these medications simultaneously put these patients at higher risk of events from ASA⁴¹. Our findings fail to show a protective effect of ASA in patients with RA in spite of their high-risk profile. It is possible that the prothrombotic risk conferred by chronic inflammation such as RA fails to be controlled by ASA, with additional factors in play, such as the use of corticosteroids (half of the patients were receiving oral corticosteroids).

Although a PS-matched analysis seemed like the most appropriate observational study for our study question, it is vulnerable to confounding by indication because of potential unmeasured confounders. A case-crossover analysis avoids interindividual variability of time-invariant confounders, so it theoretically better controls unmeasured time-invariant confounders. When looking at ASA exposure patterns over time in subjects of our study, we found that intermittent use of ASA was common; in addition, given that ASA's protective effect disappears a few days after interruption, we believe that a case-crossover analysis is an appropriate study design to assess the transient effect of ASA on the risk of MI. Further, most chronic risk factors for MI, such as HTN, are unlikely to change in a 3-month timespan, therefore we separated our index and control date by 90 days.

If ASA had a chronic effect on MI risk, a PS analysis

Table 3. Study results from both study designs. Association of ASA with cardiovascular events in RA.

Study Design	Subjects, n	Hazard Period	Control Period	Crude OR (95% CI; case-crossover) Crude HR (95% CI; PS-matched analysis)	Adjusted OR (95% CI; case-crossover) Adjusted HR (95% CI; PS-matched analysis)
Case-crossover: 7-day exposure ASA users	270	55	44	2.37 (1.04–5.43)	1.83* (0.71–4.71)
Case-crossover: 2002–2012 time period, 7-day exposure ASA users	219	47	38	2.29 (0.94–5.56)	1.96* (0.69–5.55)
Case-crossover: concomitant exposure with index date ASA users	270	52	42	2.00 (0.94–4.27)	1.52* (0.65–3.59)
		ASA User	ASA Non-user		
PS-matched cohort	1836				
MI cases, n		44	32		
Total followup time, PY		3531	3668		
Mean followup time, yrs		3.85	4.0		
Incidence rate, per 1000 PY		12.46	8.72	1.42 (0.90–2.24)	1.39** (0.87–2.23)

* Adjusted for atrial fibrillation, diabetes, dyslipidemia, hypertension, peripheral vascular disease, stroke, NSAID, glucocorticoids, statins, nitrates, antihypertensives, anticoagulants, and antiaggregants. ** Adjusted RA duration, age, sex, body mass index, smoking, alcohol, angina, atrial fibrillation, diabetes, dyslipidemia, hypertension, angiotensin-converting enzyme inhibitors, antiaggregants/anticoagulants, angiotensin receptor II blockers, β -blockers, calcium channel blockers, diuretics, glucocorticoids, lipid-lowering drugs, nitrates, NSAID, general practitioner visits, hospitalizations. ASA: aspirin; RA: rheumatoid arthritis; PS: propensity score; PY: patient-years; NSAID: nonsteroidal antiinflammatory drugs.

would give a different result from the case-crossover analysis because the latter is looking at the immediate and transient effect of ASA⁴². This does not seem to be the case according to our results, and this is concordant with studies showing a high risk of MI after ASA interruption⁴³.

There are some limitations to our study. First, our study used a GP cohort report of RA, and our definition of RA required that DMARD use was listed, but RA drugs may not always be listed. Therefore, we may have missed RA subjects in the population. This could lead to selection bias if, for example, subjects with listed DMARD were those with more aggressive RA, a higher inflammatory state, and therefore higher CV risk. However, there is no reason to think that there is differential report of DMARD related to CV risk, so this should not invalidate our findings. In addition, owing to lack of reliable information on DMARD, we could not adjust for these drugs, which may modify CV risk^{44,45}. We also lacked information regarding RA activity, which is relevant given that inflammation may lead to a higher CVD risk⁵.

Because ours is an observational study based in a healthcare database, it is subject to potential confounding by indication. In the cohort study design, we may not have identified all potential risk factors for CV disease, such as family history of MI, despite the use of a PS that included all known CV risk factors and potential contraindications to ASA use. Incomplete reporting of some factors such as medications or smoking could have contributed to a further

residual confounding effect. Using a case-crossover design minimizes this potential bias because it eliminates confounding by time-invariant factors. In our analysis, we compared 2 time periods within the same subject with relatively short interval (i.e., 90 days) so that the risk profile is likely to be similar in both hazard and control periods. Most CV risk factors are chronic diseases such as diabetes, HTN, and dyslipidemia, and it was unlikely for them to change in the 3 months that separated our 2 observation periods. Even so, we adjusted for any new medication use or comorbidities that differed between hazard and control periods. Still, some level of variation may exist in the severity of comorbidities, which may not be identified in this kind of database, such as an acute rise in blood pressure or a high frequency arrhythmia, which may lead to some residual confounding.

Using a case-crossover design, our crude analysis showed an increased risk for CV disease among ASA users and this may indicate confounding by indication because we do not expect ASA to increase risk given its biologic effect on platelets. It is likely that the drugs for which we adjusted not only had a confounding effect by themselves, but were proxies of the disease for which they were prescribed, which generated confounding by indication (HTN, diabetes, dyslipidemia). Therefore, adjusting for these drugs helped control for this type of confounding.

Our study is subject to potential misclassification of the

exposure. It is likely there was poor adherence to ASA among RA subjects given that it is a population with polymedication with a high use of drugs with frequent gastrointestinal intolerance (DMARD, NSAID, glucocorticoids). A study performed in the United Kingdom showed that the odds of discontinuing ASA were 58% higher in patients with RA versus non-RA⁴⁶. In addition, studies have shown that CV risk may increase when ASA is discontinued⁴². In our case-crossover design, we looked at ASA use close in time to the CV event. In addition, we looked at 2 time frames prior to the index date as ASA that may have a residual effect up to 7 days after discontinuation. Still, misclassification may exist given that our exposure status is based on prescriptions and we cannot be certain how regularly the medication was taken. Also, case-crossover studies are at risk of “persistent user bias” when looking at chronic drug prescriptions such as ASA given that subjects who are prescribed the drug just before the event are more numerous than subjects who stop taking the drug before the event⁴⁷. This bias may lead to an increased risk estimation and may explain the lack of a protective effect seen in our study. Cohort studies are not susceptible to this bias.

Finally, comedication with ibuprofen and naproxen has been shown to interact with ASA³⁰. We performed an analysis excluding all subjects who were taking these 2 NSAID and obtained similar results (data not shown).

Strengths of our study were its prospective collection of data over a prolonged timespan and its population base. The use of 2 study designs suggests that our findings are unlikely due to bias. To our knowledge, ours is the first study to evaluate primary prophylaxis in patients with RA, a population at high risk of CV events.

Our study did not detect a primary protective effect of ASA against MI among patients with RA.

REFERENCES

- Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. *Ann Rheum Dis* 2004;63:952–5.
- Peters MJ, van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum* 2009;61:1571–9.
- Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1608–12.
- Meune C, Touzé E, Trinquart L, Allanore Y. High risk of clinical cardiovascular events in rheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253–61.
- Mackey RH, Kuller LH, Deane KD, Walitt BT, Chang YF, Holers VM, et al. Rheumatoid arthritis, anti-cyclic citrullinated peptide positivity, and cardiovascular disease risk in the women's health initiative. *Arthritis Rheum* 2015;67:2311–22.
- Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 2003;48:54–8.
- Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum* 2002;46:2010–9.
- Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2009;48:1309–13.
- Widdifield J, Bernatsky S, Paterson JM, Tomlinson G, Tu K, Kuriya B, et al. Trends in excess mortality among patients with rheumatoid arthritis in Ontario, Canada. *Arthritis Care Res* 2015;67:1047–53.
- Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
- Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209–16.
- US Food and Drug Administration. Use of aspirin for primary prevention of heart attack and stroke. Available from: www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm390574.htm
- Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
- Davis JM 3rd, Maradit Kremers H, Crowson CS, Nicola PJ, Ballman KV, Therneau TM, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2007;56:820–30.
- Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, et al. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. *Rheumatology* 2013;52:68–75.
- Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;321:129–35.
- Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293–304.
- de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet* 2001;357:89–95.
- Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA* 2014;312:2510–20.
- NHS Digital. Attribution dataset GP registered populations scaled to ONS population estimates, 2011. [Internet. Accessed January 19, 2017.] Available from: content.digital.nhs.uk/pubs/gpregpop11
- Chisholm J. The Read clinical classification. *BMJ* 1990;300:1092.
- First Databank. Multilex. [Internet. Accessed January 6, 2017.] Available from: www.fdbhealth.co.uk/solutions/multilex
- Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2007;16:393–401.

24. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? *Arthritis Rheum* 2008;59:1314-21.
25. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi H. Low-dose aspirin use and recurrent gout attacks. *Ann Rheum Dis* 2014;73:385-90.
26. García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation* 2004;109:3000-6.
27. Bedson J, Whitehurst T, Lewis M, Croft P. Factors affecting over-the-counter use of aspirin in the secondary prophylaxis of cardiovascular disease. *Br J Gen Pract* 2001;51:1001-3.
28. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. *Pharmacoepidemiol Drug Saf* 2005;14:465-76.
29. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399-424.
30. Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809-17.
31. Jámor C, Weber CF, Gerhardt K, Dietrich W, Spannagl M, Heindl B, et al. Whole blood multiple electrode aggregometry is a reliable point-of-care test of aspirin-induced platelet dysfunction. *Anesth Analg* 2009;109:25-31.
32. Lee J, Kim JK, Kim JH, Dunuu T, Park SH, Park SJ, et al. Recovery time of platelet function after aspirin withdrawal. *Curr Ther Res Clin Exp* 2014;76:26-31.
33. Gulpinar K, Ozdemir S, Ozis E, Sahli Z, Demirtas S, Korkmaz A. A preliminary study: aspirin discontinuation before elective operations; when is the optimal timing? *J Korean Surg Soc* 2013;85:185-90.
34. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
35. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134-41.
36. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016;164:804-13.
37. Chatterjee Adhikari M, Guin A, Chakraborty S, Sinhamahapatra P, Ghosh A. Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritis as evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. *Semin Arthritis Rheum* 2012;41:669-75.
38. Vaudo G, Marchesi S, Gerli R, Allegrucci R, Giordano A, Siepi D, et al. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis* 2004;63:31-5.
39. Sandoo A, Veldhuijzen van Zanten JJ, Metsios GS, Carroll D, Kitas GD. Vascular function and morphology in rheumatoid arthritis: a systematic review. *Rheumatology* 2011;50:2125-39.
40. del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum* 2014;66:264-72.
41. Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1819-28.
42. Maclure M. 'Why me?' versus 'why now?' — differences between operational hypotheses in case-control versus case-crossover studies. *Pharmacoepidemiol Drug Saf* 2007;16:850-3.
43. Rodríguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011;343:d4094.
44. Kisiel B, Kruszewski R, Juskiewicz A, Raczekiewicz A1, Bachta A, Tlustochowicz M, et al. Methotrexate, cyclosporine A, and biologics protect against atherosclerosis in rheumatoid arthritis. *J Immunol Res* 2015;2015:759610.
45. van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. *Arthritis Res Ther* 2006;8:R151.
46. Martín Merino E, Johansson S, Nagy P, García Rodríguez LA. Effect of baseline gastrointestinal risk and use of proton pump inhibitors on frequency of discontinuation of aspirin for secondary cardiovascular prevention in United Kingdom primary care. *Am J Cardiol* 2013;112:1075-82.
47. Hallas J, Pottegård A, Wang S, Schneeweiss S, Gagne JJ. Persistent user bias in case-crossover studies in pharmacoepidemiology. *Am J Epidemiol* 2016 Oct 25 (E-pub ahead of print).