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Cardiovascular, Rheumatologic, and Pharmacologic Predictors of Stroke in Patients With Rheumatoid Arthritis: A Nested, Casee–Control Study

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Abstract

Objective—To determine the risk of stroke in patients with rheumatoid arthritis (RA) and risk factors associated with stroke.

Methods—We performed nested case–control analyses within a longitudinal databank, matching up to 20 controls for age, sex, and time of cohort entry to each patient with stroke. Conditional logistic regression was performed as an estimate of the relative risk of stroke in RA patients compared with those with noninflammatory rheumatic disorders, and to examine severity and anti–tumor necrosis factor (anti-TNF) treatment effects in RA.

Results—We identified 269 patients with first-ever all-category strokes and 67 with ischemic stroke, including 41 in RA patients. The odds ratio (OR) for the risk of all-category stroke in RA was 1.64 (95% confidence interval [95% CI] 1.16–2.30, $P = 0.005$), and for ischemic stroke was 2.66 (95% CI 1.24–5.70, $P = 0.012$). Ischemic stroke was predicted by hypertension, myocardial infarction, low-dose aspirin, comorbidity score, Health Assessment Questionnaire score, and presence of total joint replacement, but not by diabetes, smoking, exercise, or body mass index. Adjusted for cardiovascular and RA risk factors, ischemic stroke was associated with rofecoxib ($P = 0.060$, OR 2.27 [95% CI 0.97–5.28]), and possibly with corticosteroid use. Anti-TNF therapy was not associated with ischemic stroke ($P = 0.584$, OR 0.80 [95% CI 0.34–1.82]).

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AUTHOR CONTRIBUTIONS

Dr. Wolfe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conclusion—RA is associated with increased risk of stroke, particularly ischemic stroke. Stroke is predicted by RA severity, certain cardiovascular risk factors, and comorbidity. Except for rofecoxib, RA treatment does not appear to be associated with stroke, although the effect of corticosteroids remains uncertain.

INTRODUCTION

There is evidence that cardiovascular and cerebrovascular diseases are more common in patients with rheumatoid arthritis (RA) than in patients without RA (1–10), and 2 studies have demonstrated an increased risk of stroke among patients with RA (1,2). However, to our knowledge no studies have addressed the effect of RA severity, RA therapy, or cardiovascular risk factors on the risk of stroke in patients with RA. A number of therapies are available that influence RA activity and severity and possible long-term outcome. These include methotrexate, which may have a positive effect on outcome (11); prednisone, which has uncertain effects (12,13); and anti–tumor necrosis factor (anti-TNF) therapy, for which effects have not yet been determined, but might be promising, because it may further reduce inflammatory activity and have direct cardiovascular effects.

There is increasing evidence that inflammation is implicated in the pathogenesis of stroke (14–16). An increased serum level of C-reactive protein, which is produced in response to TNF and interleukin-6, has been shown to be an independent risk factor of myocardial infarction and stroke (17–19). In addition to initiation of C-reactive protein synthesis, TNF may activate endothelial cells, converting them into procoagulant and prothrombotic states (14,17). TNF is a key cytokine involved in all phases of stroke pathogenesis, including initiation and progression, as well as repair and development of ischemic tolerance (20). In preclinical stroke models, TNF inhibition employing anti-TNF monoclonal antibodies and TNF-binding proteins showed significant neuroprotection in animals treated with these compounds (20). However, efficacy of TNF inhibition for stroke prevention or treatment in humans has not yet been demonstrated.

In addition to possible effects of treatment, the issue of whether cardiovascular risk factors such as obesity, diabetes, and exercise are also risk factors for stroke in RA has not been determined. In the current study, we used 3 data sets to investigate the risk of stroke in patients with RA compared with those with noninflammatory disorders, identify predictors of stroke in RA, and determine the effect of anti-TNF therapy on the risk of stroke.

Because RA treatment can be confounded by RA severity and comorbidity, we used covariate control in the analysis of treatment effect. We controlled for RA severity using duration of RA, presence or absence of total joint replacement (TJR), and Health Assessment Questionnaire (HAQ) scores (21); and we used a comorbidity index and the presence or absence of individual comorbid conditions to address comorbidity confounding.

PARTICIPANTS AND METHODS

We studied participants from the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. NDB participants are recruited from the practices of US rheumatologists, and are followed prospectively with semiannual, detailed, 28-page questionnaires, as previously described (22,23). This study used NDB data from 22,131 adult participants in nested case–control analyses, 16,990 of whom had RA, and 5,141 of whom had a noninflammatory rheumatic disorder (NIRD). Of the 16,990 RA patients, 11,225 were not members of a safety registry. Safety registry patients are those enrolled at the time they started a specific therapy (e.g., infliximab) and may be biased by increased RA severity. All patients were enrolled continuously beginning in 1999 and completed ≥2 semiannual

questionnaires between January 1999 and July 2006. Diagnoses were made by the patients' rheumatologists. NIRDs included diagnoses such as osteoarthritis, back pain syndromes, fibromyalgia, tendinitis, etc.

Case–control analysis

Cases consisted of all patients ages 25–100 years with a first-ever stroke. We included patients who had a diagnosis of stroke recorded as the cause of death if the stroke occurred within 6 months of the patient's last questionnaire. The index observation was the observation at which the stroke was noted. We matched up to 20 controls to each case at the index observation by 10 categories of age, calendar time, calendar time of entry into the cohort, and sex, using incidence density sampling (selecting controls without replacement from all persons at risk at the time of case occurrence, excluding the index case itself) (24). All controls were alive and NDB participants at the time their matched case had the stroke.

Assessment of exposure

We determined medication use based on patients' self-report in their semiannual questionnaires. Patients were classified as using a therapy if they used that therapy for any time in the index period prior to the index event. We determined the use of each nonsteroidal antiinflammatory drug (NSAID) and low-dose aspirin. We also identified use of corticosteroids and disease-modifying antirheumatic drugs (DMARDs). We classified infliximab, etanercept, and adalimumab as anti-TNF antagonists. For each medication, we identified use within each semiannual assessment period. We calculated cumulative exposure time and determined use at baseline and within 6 months of the index period.

Case definition

Possible strokes were identified from study questionnaires, hospitalization records, physician reports, and death records. Only strokes that were confirmed by medical review or death records were recognized as strokes in this study. If hospital or death records were not available, we contacted the patient's physician and/or interviewed the patient or family with a structured, preplanned interview designed to address the reported condition. Comparison of patient reports with medical records indicated agreement in >94% of cases. Death records, in which stroke was recorded, must have referred to deaths that occurred within 6 months of the last questionnaire to be included as a stroke in this study. Review of potential cases was performed by 2 trained, experienced NDB staff members. This review was followed by an independent physician review. All cases of ischemic stroke were based on hospital records.

International Classification of Diseases, Ninth Revision (ICD-9) codes were used for identification of stroke cases and were classified as follows: ischemic strokes included ICD-9 codes 433.01 through 433.80, provided the code indicated infarction, and ICD-9 codes 434 through 434.91. We combined ischemic stroke and unclassified stroke (ICD-9 code 436) into an "all-stroke" category. We excluded intracerebral, subarachnoid, subdural, and epidural hemorrhages, as well as transient ischemic attacks.

Covariates

Study variables were assessed at entry into the NDB and at every subsequent semiannual questionnaire. For use as covariates in this study, baseline and preindex (antecedent) observation values were analyzed. Demographic variables included age, sex, body mass index (BMI), and smoking history. Comorbidity was measured by a patient-reported composite comorbidity score (range 0–9) comprised of 11 present or past comorbid conditions, including pulmonary disorders, myocardial infarction, other cardiovascular disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal ulcer, other

gastrointestinal disorders, and cancer (25), and by identification of prior myocardial infarction, hypertension, and diabetes. We also identified the use of low-dose (81 mg) aspirin as an indicator of preexisting cardiovascular disease. An additional potential risk factor assessed was the amount of weekly exercise. As specific covariate measures of RA severity, we also included prior TJRs (26,27) and the HAQ disability index score (21). Duration of RA was added to assess the effect of long-term RA. Treatment variables studied included prednisone (corticosteroids), NSAIDs, and DMARDs.

Statistical analysis

In the study analyses, we used the full data set (n = 22,131) as the basis of the comparison of RA and NIRD patients for the risk of ischemic and all-cause stroke (Table 1); we used all RA patients from the full data set (n = 16,990) to form the basis of the analysis of nontreatment associations with ischemic stroke (Table 2); and we used a subset of the RA patients reduced by removal of participants in safety registries (n = 5,765) to examine the effect of treatment on ischemic stroke (Figure 1 and Figure 2). We used this last restriction to ensure absence of severity bias and immeasurable confounding.

Within each of these data sets, we used conditional logistic regression for individually matched case–control studies to derive odds ratios (ORs) with 95% confidence intervals (95% CIs) as a measure of relative risk. In the treatment effect analyses we fitted 2 models. The first model assessed variables with a 0–6-month window prior to the index time. The second model analyzed covariates obtained at the baseline observation (entry into the cohort). In these 2 models, we made adjustments for possible confounding effects of prior cardiovascular disease, co-morbidity, RA severity, and treatment variables. We used Stata statistical software, version 10.0 (StataCorp, College Station, TX) for all of the analyses. We selected a *P* value of 0.05 (2-tailed) to be significant, and we reported 95% CIs.

RESULTS

Risk of ischemic and all-cause stroke in RA compared with NIRD

From the NDB research database, we identified 269 cases with a first-ever stroke between the ages of 33 and 91 years (26.8% men). We also identified 67 cases of ischemic stroke between the ages of 35 and 90 years (25.4% men). We matched all cases by age, calendar time, and sex to up to 20 controls per case. For ischemic stroke analysis, the major outcome of this study, the mean time of databank followup until the index event was 3.9 years (interquartile range [IQR] 2.0–6.0). The mean ± SD age for cases and controls at the index event was 70.0 ± 9.6 and 69.5 ± 10.6 years, respectively ($P = 0.704$), and men constituted 25.4% of cases and 25.3% of controls ($P = 0.541$). As shown in Table 1, patients with RA were at increased risk for ischemic stroke ($P = 0.012$, OR 2.66 [95% CI 1.24–5.70]) and for all categories of stroke ($P = 0.005$, OR 1.64 [95% CI 1.16–2.30]).

Stroke in RA

From all RA patients, we identified 59 cases with a first-ever ischemic stroke between the ages of 35 and 84 years. We matched these cases by age, sex, and calendar time to up to 20 controls per case (mean 19.8). The mean time of databank followup was 3.9 years (IQR 2.0–6.0). The mean ± SD age for cases and controls at the index event time was 70.0 ± 9.8 and 69.1 ± 10.6 years, respectively ($P = 0.521$), and men constituted 27.1% of cases and 25.6% of controls ($P = 0.514$).

Factors associated with ischemic stroke in RA

A number of baseline and preindex observation characteristics were associated with future ischemic strokes in RA (Table 2). The risk of stroke increased with the number of comorbid conditions, a history of hypertension (OR 1.98, 95% CI 1.16–3.37), myocardial infarction (OR 2.58, 95% CI 1.22–5.47), and the use of low-dose aspirin (OR 3.60, 95% CI 2.09–6.22). BMI, diabetes, smoking history, the amount of weekly exercise, and duration of RA were not significantly associated with the risk of ischemic stroke. RA-related factors at baseline that were associated with the risk of ischemic stroke included TJR (OR 2.13, 95% CI 1.14–3.95), baseline HAQ score ($P = 0.067$, OR 1.43 [95% CI 0.98–2.11]), and immediately antecedent HAQ score (OR 2.04, 95% CI 1.40–2.97). The 2 RA measures, however, differed in that HAQ scores can be elevated by concurrent comorbidity, but total joint assessments will be unaltered by current comorbidity. In a multivariable assessment of stroke risk with antecedent total joint assessment, HAQ score, low-dose aspirin, and comorbidity as regressors, TJR was significantly associated with stroke ($P = 0.021$, OR 2.28 [95% CI 1.13–4.58]).

The association of RA therapy and ischemic stroke in RA

Among the non-safety registry RA patients, who constituted the subjects of the effect of RA treatment on stroke risk, we identified 41 cases with a first-ever ischemic stroke between the ages of 35 and 84 years. We matched these cases by age, sex, and calendar time to up to 20 controls per case (mean 19.3, n = 791). The mean time of databank followup was 4.0 years (IQR 2.0–6.0). The mean age for cases and controls at the index event time was 69.8 and 69.9 years, respectively ($P = 0.956$), and men constituted 26.8% of cases and 25.4% of controls ($P = 0.855$).

In multivariable conditional logistic regression analyses that were adjusted for HAQ disability index score, TJR, RA duration, low-dose aspirin, and comorbidity index at baseline for the baseline analyses and immediately prior to the index observation for the antecedent (current) analyses, we studied the simultaneous risk of common RA treatments (Figure 1 and Figure 2).

For the preindex multivariable analyses adjusted for covariates (Figure 1), rofecoxib was associated with an increased risk of stroke ($P = 0.060$, OR 2.28 [95% CI 0.97–5.38]). Other risk associations included prednisone ($P = 0.114$, OR 1.75 [95% CI 0.87–3.53]), methotrexate ($P = 0.191$, OR 0.63 [95% CI 0.32–1.26]), and anti-TNF therapy ($P = 0.584$, OR 0.79 [95% CI 0.34–1.82]). In univariate unadjusted analyses, rofecoxib and prednisone were significantly associated with stroke: the OR for rofecoxib was 2.32 (95% CI 1.05–5.13, $P = 0.037$), the OR for prednisone was 2.03 (95% CI 1.08–3.84, $P = 0.029$), the OR for methotrexate was 0.55 (95% CI 0.30–1.04, $P = 0.066$), and the OR for anti-TNF therapy was 0.80 (95% CI 0.38–1.70, $P = 0.562$).

We also conducted analyses to determine if length of treatment exposure during the study was associated with stroke. We found a univariate (but not multivariate) exposure-time effect for prednisone ($P = 0.039$, OR 1.19 [95% CI 1.00–1.40]), and no effect for any other treatment. However, prednisone dose at the preindex assessment was also associated with the risk of stroke. Compared with 576 patients not receiving prednisone, the OR for stroke for 1–5 mg/day was 1.68 (95% CI 0.76–3.73; n = 187), the OR for 6–10 mg/day was 4.36 (95% CI 1.60–11.90; n = 56), and the OR for >10 mg/day was 4.87 (95% CI 0.85–27.77, $P = 0.075$; n = 13).

For the baseline multivariable analyses adjusted for covariates (Figure 2), rofecoxib was associated with an increased risk of stroke ($P = 0.027$, OR 3.66 [95% CI 1.16–11.60]). Other risk associations included celecoxib ($P = 0.051$, OR 2.65 [95% CI 0.99–7.08]), prednisone ($P = 0.083$, OR 1.93 [95% CI 0.92–4.07]), methotrexate ($P = 0.464$, OR 0.77 [95% CI 0.39–1.54]), and anti-TNF therapy ($P = 0.391$, OR 0.50 [95% CI 0.10–2.44]). Univariate associations

for the above variables were rofecoxib (P = 0.012, OR 3.73 [95% CI 1.34–10.38]), celecoxib (P = 0.019, OR 2.91 [95% CI 1.19–7.13]), prednisone (P = 0.014, OR 2.27 [95% CI 1.18–4.69]), methotrexate (P = 0.320, OR 0.73 [95% CI 0.39–1.36]), and anti-TNF therapy (P = 0.196, OR 0.37 [95% CI 0.18–1.66]). In evaluating the result of Figure 1 and Figure 2, it is worthwhile to note that the use of rofecoxib, celecoxib, and anti-TNF therapy increased substantially from the numbers using these treatments at baseline compared with the current use numbers ~4 years later on average.

DISCUSSION

This study contributes new information regarding pharmacologic and nonpharmacologic risk factors for stroke in RA. In addition, we provide another estimate of the risk of RA on subsequent stroke using a patient population where clinical information was available, complementing the administrative database estimates already available (1,2).

A number of studies have addressed cardiovascular risk among patients with RA (1–10). However, stroke has been the subject of only a few studies (1,2). A British Columbia administrative database cohort study of 25,385 adults with RA showed that the overall rate of stroke increased in patients with RA (rate ratio 1.9, 95% CI 1.7–2.1) (1), and an incidence sample of 527 women with RA demonstrated that the relative risk for stroke was 1.48 (95% CI 0.70–3.12) (2). The current study confirms these reports: our overall stroke risk ratio was 1.64 (95% CI 1.16–2.30), and the risk ratio for ischemic stroke was 2.66 (95% CI 1.24–5.70).

Risk factors for stroke can be separated into 3 parts: factors associated with stroke risk in all persons regardless of RA status, factors associated with RA severity, and factors associated with RA treatment. With respect to the non-RA risk factors for stroke that were available to this study, including hypertension, cardiac disease, diabetes, smoking, lack of exercise, and obesity (28,29), we confirmed the effect of hypertension and preexisting cardiac disease, but we found no evidence for an association of stroke with diabetes, smoking, and obesity. It is not entirely clear why diabetes, smoking, and obesity had no effect in our cohort of RA patients, and confirmation of these findings is required. However, it has been previously demonstrated that elevated BMI does not predict mortality in RA (30). In data not shown, we examined the relationship between BMI and ischemic stroke using fractional polynomial regression to observe possible nonlinear effects. Although this analysis was nonsignificant, a U-shaped association between stroke and BMI could be identified. Therefore, it seems likely that the standard concept of obesity compared with nonobesity may not be appropriate in RA (31). With respect to smoking in this sample of older subjects, current smokers tend to be healthier than ex-smokers. In the current data set, for example, current smokers had comorbidity scores that were 0.6 lower than ex-smokers, and 0.34 lower than those who never smoked ($P < 0.05$). With respect to exercise, few persons reported strenuous exercise, thereby limiting somewhat the inferences that can be drawn about exercise in our study sample. However, in an analysis of myocardial infarction in the NDB cohort (32), we found that smoking and diabetes were significant univariate risks for myocardial infarction and that obesity was a possible risk ($P > 0.05$, hazard ratio 1.3 [95% CI 1.0–1.6]), but exercise was not a significant univariate risk factor.

RA severity measures (HAQ and TJR) predict stroke, as might be expected given the increased risk of RA itself. Although we did not have laboratory measures in our study, the RA severity variables in this study are effective measures of cumulative damage: the results of RA severity (33–37). The 2 measures that we used differ, however, in that HAQ score effect can be confounded by concurrent comorbidity (38), but total joint assessments are unaltered by current comorbidity. Although not shown in Figure 1 and Figure 2, TJR remained a statistically significant predictor in both analyses.

RA severity and current activity are also represented by treatment choice, with patients using corticosteroids and leflunomide having greater severity, for example, and those using methotrexate having less severity (12). Practically, this means that inclusion of RA treatments in stroke risk models also adjusts for severity of RA. In addition to reflecting RA activity and severity, individual RA treatments might contribute to the risk of stroke by contributing to atherogenesis or clotting problems (39–43), while still being measures of severity: in effect, confounders.

When we compared the univariate and multivariate treatment effects, covariate adjustment resulted in ORs moving closer to 1.0 and in a loss of statistical significance in most instances. Considering the univariate data and the results shown in Figure 1 and Figure 2, we did not find evidence to support the association of RA treatment and stroke, with the exception of rofecoxib and possibly antecedent prednisone ($P = 0.114$, OR 1.75 [95% CI 0.87–3.53]). Cumulative corticosteroid dose has been shown to be associated with atherogenesis in RA (4). Corticosteroids alter lipid metabolism (42,44,45), increase the risk of hypertension (42), and increase and are linked to carotid artery abnormalities and metabolic syndrome in non-RA patients (46,47). But as we have indicated, the interpretation of the effect of corticosteroids in RA is confounded by RA severity (4,12), and it is likely that residual confounding remains even after the adjustments used in the current study. There are limited data on the effect of corticosteroids on other cardiovascular outcomes such as myocardial infarction. In a population-based study of 5,648 subjects, current use of inhaled corticosteroids was not associated with myocardial infarction risk, but a 32% reduction in risk was noted for dosages of 50–200 μg/day (28). In another study, corticosteroids had a protective association with myocardial infarction in persons with kidney transplantation, although confounding factors limited generalizability (30). Additional or larger studies will be needed to further elucidate the prednisone association with stroke.

There are a number of caveats. The number of ischemic strokes studied was relatively small. It is possible that nonsignificant associations noted for prednisone might be statistically significant with a larger sample. In addition, if residual confounding exists for treatment effect, the associations noted might be slightly weaker than those described here. However, that would be unlikely to change the study conclusion of no treatment effect except for rofecoxib. With respect to residual confounding, we also want to note that our data set did not contain markers for joint counts, radiographic erosions, inflammatory markers, and autoantibodies, and it is possible that such data could play a role in reducing residual confounding, if present.

There is also the possibility that the degree of confounding changed over time. For example, when initially prescribed, celecoxib was associated with more severe RA (48). With time, celecoxib was prescribed more generally and the association with severity was lost. This effect is suggested in the current study by the change in OR for baseline celecoxib compared with immediately antecedent celecoxib. In addition to using different time-related covariates to explore such differences, we used baseline values to explore the effect of treatment that patients may have received for long periods of time (prestudy enrollment), in order that we might better evaluate the association with methotrexate and prednisone. But no substantial differences were noted, as shown in Figure 1 and Figure 2.

In addition to the time-based approach we used to analyze the data, use of treatment exposure time is still another approach. However, if treatment immediately before the index time is central to detecting effects, as has been shown for rofecoxib (49,50), this method will fail to detect such effects, and the exposure-time method does not include time on therapy prior to enrollment. Many valid and confirmed epidemiologic associations have not shown dose-response relationships (51). As indicated in our results, we found a univariate (but not

multivariate) exposure-time effect for prednisone ($P = 0.039$, OR 1.19 [95% CI 1.00–1.40]), and no effect for any other treatment.

In summary, RA is associated with increased risk of stroke, particularly ischemic stroke. Stroke is predicted by RA severity, hypertension, myocardial infarction, low-dose aspirin, and comorbidity. Diabetes, obesity, and smoking were not risk factors for stroke among patients with RA in this study. Except for rofecoxib, RA treatment does not appear to be associated with stroke, although the effect of corticosteroids remains uncertain.

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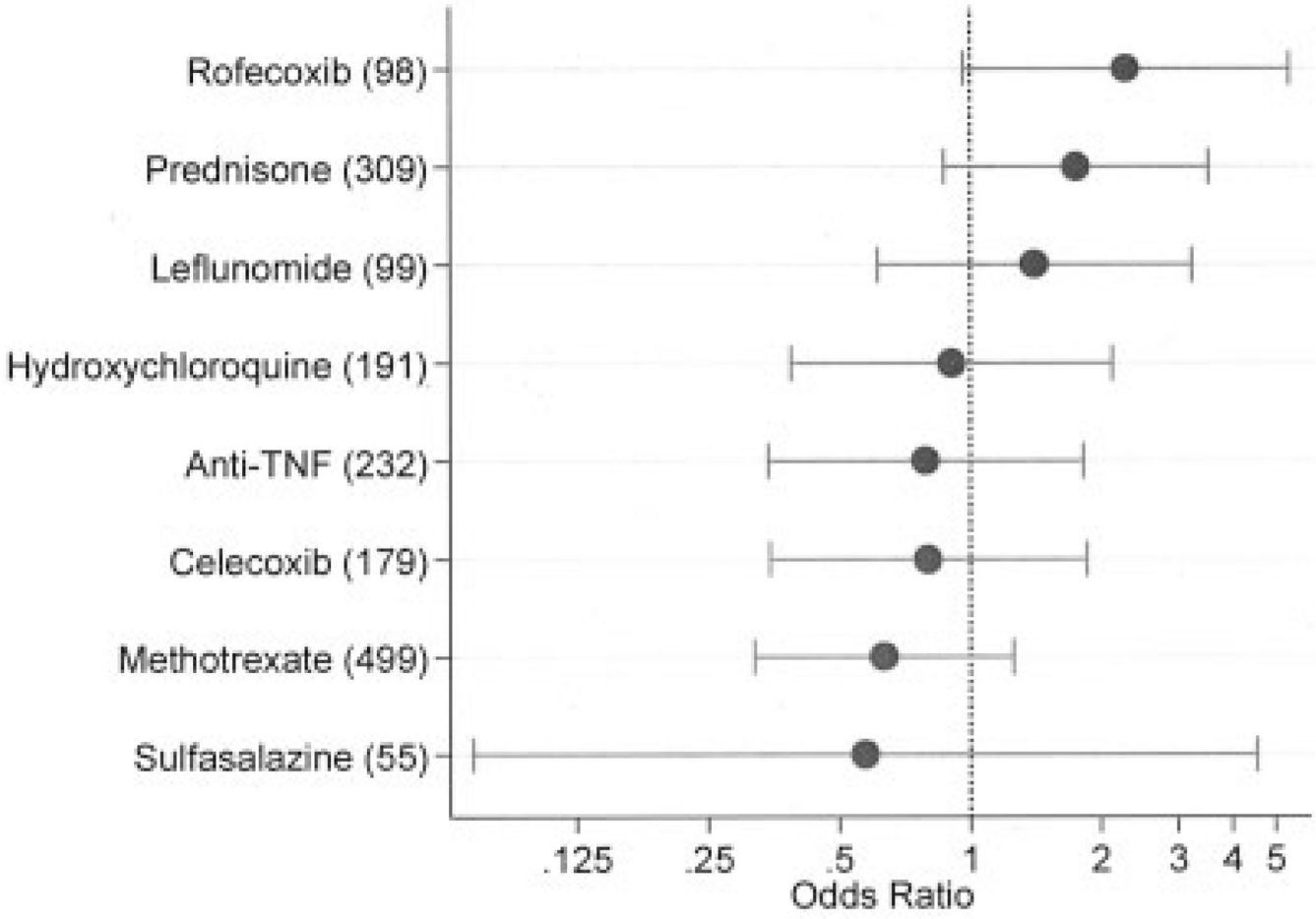

Figure 1.
Multivariable ischemic stroke risk (odds ratios and 95% confidence intervals on log scale) associated with rheumatoid arthritis (RA) treatment in a 6-month window before the index stroke, adjusted for Health Assessment Questionnaire score, total joint replacement, RA duration, and for low-dose aspirin and comorbidity index immediately prior to index observation. Numbers in parentheses represent the number of patients using that therapy (cases and controls). Analysis included 41 RA patients with ischemic stroke and 791 RA patients without ischemic stroke. Anti-TNF = anti–tumor necrosis factor.

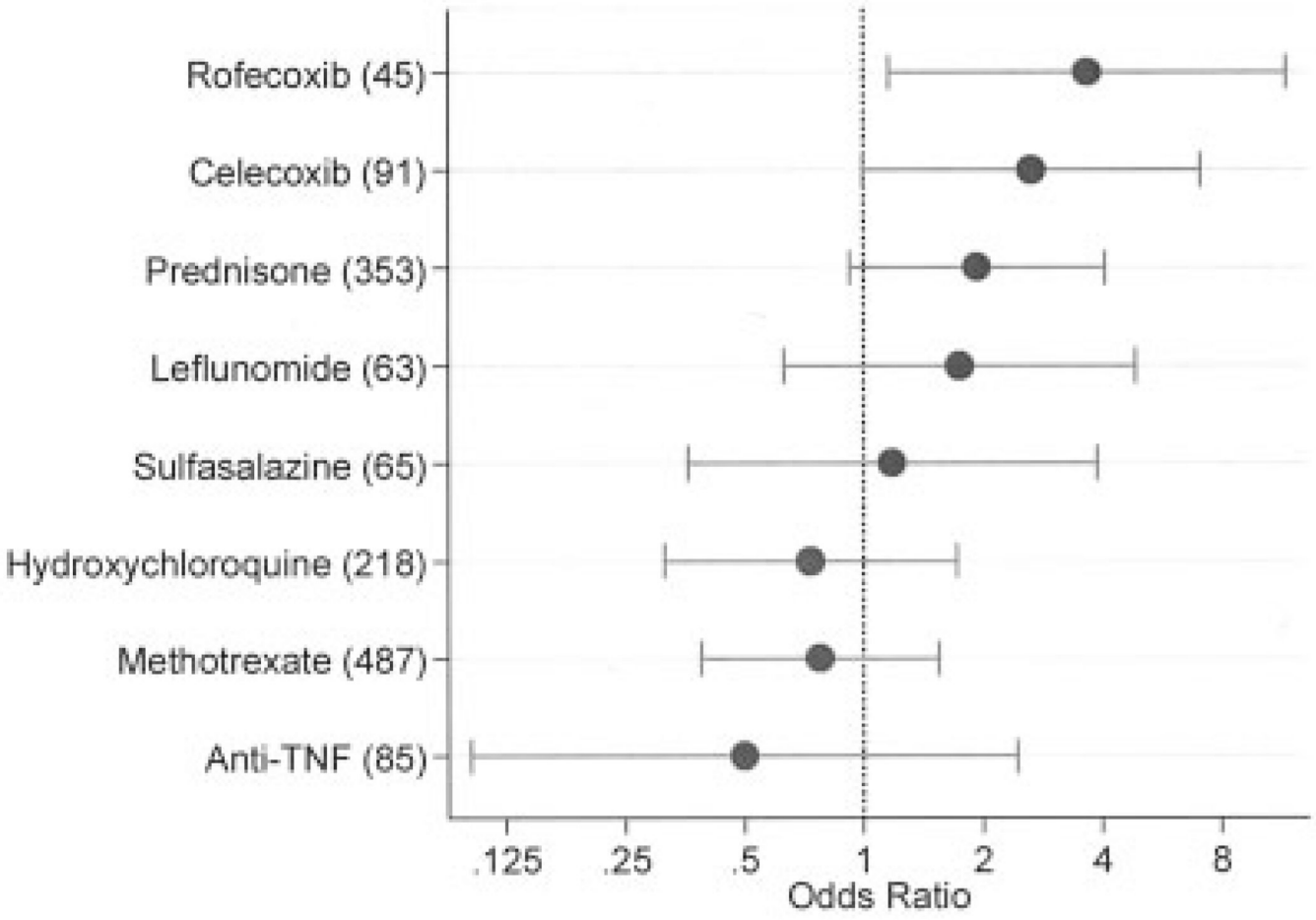

Figure 2.
Multivariable ischemic stroke risk (odds ratios and 95% confidence intervals) associated with baseline rheumatoid arthritis (RA) treatment, adjusted for Health Assessment Questionnaire score, total joint replacement, RA duration, and for low-dose aspirin and comorbidity index at baseline. Numbers in parentheses represent the number of patients using that therapy in cases and controls. Analysis included 41 RA patients with ischemic stroke and 791 RA patients without ischemic stroke. Anti-TNF = anti–tumor necrosis factor.

Table 1

Stroke risk in patients with RA*

	No. strokes	No. patients	RA cases/ noncases	NIRD cases/ noncases	OR (95% CI)†	*P*
All strokes	269	5,640	226/4,125	43/1,246	1.64(1.16–2.30)	0.005
Ischemic strokes	67	1,405	59/996	8/342	2.66(1.24–5.70)	0.012

*RA = rheumatoid arthritis; NIRD = noninflammatory rheumatic disorder; OR = odds ratio; 95% CI = 95% confidence interval.

†Comparison group consists of patients with NIRDs, matched for age, sex, and time of study entry.

Table 2

The association of univariate baseline demographics, cardiovascular risk factors, and RA risk factors with ischemic stroke in RA (n = 1,230)*

	Value	OR (95% CI)	*P*
Non-RA variables			
Low-dose aspirin	25.8	3.60 (2.09–6.22)	< 0.001
Myocardial infarction	6.9	2.58 (1.22–5.47)	0.013
Hypertension	41.8	1.98 (1.16–3.37)	0.012
First comorbidity index (range 0–9), mean ± SD†	1.6 ± 1.4	1.69 (1.44–1.99)	< 0.001
Index comorbidity index (range 0–9), mean ± SD†	1.7 ± 1.5	1.42 (1.20–1.64)	< 0.001
College graduate	24.1	1.42 (0.80–2.55)	0.235
Moderate or greater aerobic exercise	9.6	1.29 (0.57–2.91)	0.535
Diabetes	10.1	1.22 (0.54–2.76)	0.636
Any aerobic exercise	21.8	1.12 (0.62–2.01)	0.706
BMI, mean ± SD kg/m^2	26.9 ± 5.5	1.00 (0.95–1.05)	0.825
Ever smoked	56.9	1.00 (0.58–1.72)	0.888
Current smoker	10.8	0.96 (0.40–2.32)	0.930
Non-Hispanic white	94.0	0.86 (0.30–2.45)	0.777
RA variables			
Lifetime TJR	17.5	2.13 (1.14–3.95)	0.017
Index HAQ score, mean ± SD (range 0–3)	1.08 ± 0.73	2.04 (1.40–2.97)	< 0.001
HAQ score, mean ± SD (range 0–3)	1.04 ± 0.70	1.43 (0.98–2.11)	0.067
Disease duration, mean ± SD years	15.9 ± 13.5	1.02 (1.00–1.03)	0.100

*Values are the percentage unless otherwise indicated. Variables represent baseline values except as described. RA = rheumatoid arthritis; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; TJR = total joint replacement; HAQ = Health Assessment Questionnaire.

†Conditions in the comorbidity index include pulmonary disorders, myocardial infarction, other cardiovascular disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal ulcer, other gastrointestinal disorders, and cancer.