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CLINICAL RESEARCH

High risk of clinical cardiovascular events in rheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis

Polyarthrite rhumatoïde et risque d'infarctus du myocarde, d'accident vasculaire cérébral : détermination du sur-risque à partir d'une méta-analyse

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Summary
Background. — While there are convergent data suggesting that overall cardiovascular mortality is increased in patients with rheumatoid arthritis, the relative contributions of myocardial infarction and stroke remain unclear.
Aims. — We sought to clarify this issue by conducting a meta-analysis of cohort studies on myocardial infarction and stroke in patients with rheumatoid arthritis.
Methods. — A MEDLINE search from January 1960 to September 2009 and abstracts from international conferences from 2007 to 2009 were searched for relevant literature. All cohort studies reporting on standardized mortality ratio or incidence rate ratio of myocardial or stroke associated with rheumatoid arthritis, with available crude numbers, were included. STATA meta-analysis software was used to calculate pooled risk estimates.

Abbreviations: CI, confidence interval; CV, cardiovascular; IRR, incidence rate ratio; MI, myocardial infarction; RA, rheumatoid arthritis; SMR, standardized mortality ratio.
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Results. — Seventeen papers fulfilled the inclusion criteria, corresponding to a total of 124,894 patients. Ten studies reported on standardized mortality ratio for fatal myocardial infarction, which ranged from 0.99 to 3.82. The overall pooled estimate was 1.77 (95% confidence interval [CI] 1.65—1.89). Incidence rate ratio for myocardial infarction was reported in five studies; the pooled estimate was 2.10 (95% CI 1.52—2.89). Nine studies reported on fatal stroke, with standardized mortality ratio ranging from 1.08 to 2.00; the pooled estimate was 1.46 (95% CI 1.31—1.63). The pooled incidence rate ratio for stroke (three studies) was 1.91 (95% CI 1.73—2.12).

Conclusion. — Our results show that risks of myocardial infarction and stroke are increased in patients with rheumatoid arthritis. In addition, both account for the observed increased mortality in individuals with rheumatoid arthritis.

Résumé
Introduction. — La mortalité cardiaque globale est augmentée au cours de la polyarthrite rhumatoïde, mais le niveau de risque de survenue d'un infarctus du myocarde et d'un accident vasculaire cérébral demeurent incertains.
Objectif. — Préciser ce niveau de risque à l'aide d'une méta-analyse.
Méthodes. — La recherche a été effectuée sur Medline, de janvier 1960 à septembre 2009 et à partir des *abstracts* des conférences internationales de 2007 à 2009. Les études de cohorte rapportant les risques de mortalité (SMR) et les taux d'incidence (IRR) d'infarctus du myocarde ou d'accident vasculaire cérébral au cours de la polyarthrite rhumatoïde ont été inclues.
Résultats. — Dix-sept articles et/ou *abstracts* ont été retenus, ce qui correspond à une population totale de 124 894 patients. Dix études rapportent le SMR pour l'infarctus du myocarde fatal; il varie entre 0,99 et 3,82 selon les études. Le SMR global calculé est de 1,77 (IC 95% : 1,65—1,89). Le risque de survenue d'infarctus du myocarde total a été rapporté dans cinq études ; le risque global calculé est de 2,10 (IC 95% : 1,52—2,89). Neuf études ont rapporté le risque d'accident vasculaire cérébral fatal avec des SMR compris entre 1,08 et 2,00 ; le SMR global est de 1,46 (IC 95% : 1,31—1,63). Le risque d'accident vasculaire cérébral total est de 1,91 (IC 95% : 1,73—2,12).
Conclusion. — Nos résultats montrent qu'il existe un sur-risque d'infarctus du myocarde et d'accident vasculaire cérébral au cours de la polyarthrite rhumatoïde ; tous deux contribuent à la surmortalité observée au cours de la polyarthrite rhumatoïde.

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, of unknown origin, that affects 0.5—1% of the adult population [1,2]. Over the past decade, several studies have shown that RA is associated with an increased cardiovascular (CV) mortality [3—6]. This has been confirmed by some meta-analyses that documented a 50—60% increase in CV mortality in RA patients [7—9]. However, although some studies specifically reported the risk of myocardial infarction (MI), there are fewer data on stroke. Additionally, it has been suggested that the impact of RA on the risk of stroke may be weaker [10]. Two meta-analyses investigated concomitantly CV mortality, MI and stroke, but these studies had some limitations [7,8]. One pooled standardized mortality ratio (SMR) and incidence rate ratio (IRR), and was not exhaustive [7]. The other meta-analysis did not include studies performed after 2005, a period of major advances in disease-modifying antirheumatic drugs [8]. Therefore, the relative impact of RA on MI and stroke remain unclear. To clarify this issue, we performed a systematic review of published studies to assess the risk of MI and stroke in RA patients.

Methods

Search methods for identification of studies

We sought studies published between January 1960 and September 2009, without restriction in settings or language. Electronic searches were performed using MEDLINE, with both keywords and free text words ''rheumatoid arthritis'' and (''mortality'' or ''myocardial infarction'' or ''cardiovascular disease'' or ''stroke'' or ''cerebrovascular accident'' or ''coronary artery disease''). We reviewed the reference lists of all included studies, any relevant guidelines, general reviews, and commentaries pertaining to the management of patients with rheumatoid arthritis. To identify recent studies not yet published as full papers, we also searched books of abstracts from 2007 to 2009 conferences (European League against Rheumatism [EULAR] and American College of Rheumatology [ACR]).

Inclusion criteria

Eligible studies were cohort studies of patients with RA diagnosed according to the recommendations available dur-

Table 1 Main characteristics of the studies reporting on standardized mortality ratio (myocardial infarction and/or stroke).

Study	Location, study period	Patients (n)	Age	Women (%)	Disease duration at inclusion	Follow-up (RA patients)	Completeness of follow-up	Validation	Consecutive
Monson	USA, 1930—1960	1035	NA	74	NA	Up to 1972	27% lost to follow-up	DC	Yes
Lewis	UK, 1966—1976	311	NA	NA	NA	11 years	Complete	DC (41% autopsy)	Yes
Allebeck	Sweden, 1971	1165	NA	46	NA	Up to 1978	Complete	Autopsy (67%) Medical records	Yes
Prior	England, 1964—1978	489	NA	65	NA	11.2 years	8.4% lost to follow-up	DC	Yes
Erhardt	UK, 1979	308	59	71	7.4 years	Up to 1985	Complete	DC	Yes
Reilly	England, 1957—1963	100	51	64	3.7 months	25 years	Adequate	Autopsy (n = 19), medical records	< 1 year duration
Wolfe [a]	USA, 1965—1990 Canada, 1966—1974	3501	53	74	NA	Canada: 15.8 US: 8.5 years	2.5, 4.5 33.6 and 10.5% lost to follow-up	DC	Yes
Wallberg-Jonsson	Sweden, 1979	606	55	68	12.5 years	15 years	Complete	Medical records and DC	No, seropositive
Bjornadal	Sweden, 1964—1994	46,917	NA	71	NA	489,048 persons—years	Complete	DC	Yes
Thomas	Scotland, 1981—2000	33,318	61.8	73	NA	6.9 years	Complete	DC	Yes
Goodson	England, 1981—1996	1010	60.4	72	Newly diagnosed	11.4 years	97%	DC	Newly diagnosed
Young	England, 1986—1997	1429	55	66	6 months	9.1 years	Complete	DC	< 2 years' duration

DC: death certificates.

[a] This study included rheumatoid arthritis patients from four centres and at different periods.

ing the study period [11]. Articles had to report either enough data to compute a SMR or an IRR for at least one of the following outcomes: fatal or non-fatal MI, fatal or non-fatal stroke. Studies that reported death related to ''ischemic heart disease'', ''arteriosclerotic heart disease'' or ''coronary artery disease'' were considered as relevant; their results were computed as fatal MI. In cases of multiple publications from the same cohort, we chose the study that provided the greatest amount of information (i.e., the largest number of patient-years).

Study selection

Two reviewers independently reviewed the studies to assess their eligibility for inclusion in the review. Disagreements were resolved by consensus. The two reviewers extracted data from the selected studies separately. Disagreements were resolved by consensus among all authors. To describe population characteristics, we abstracted the following: geographic area, mean age, female proportion, and mean duration of disease. To assess quality criteria, we abstracted the following: prospective study, consecutive enrolment, population-based study and completeness of follow-up.

Statistical analysis

SMR and IRR and their 95% confidence intervals (CIs) were calculated with crude numbers extracted from individual studies. Publication bias was assessed graphically, using a funnel plot [12].

If SMRs were reported without 95% CI, the interval was calculated using observed and expected number of deaths and assuming a Poisson distribution of observed cases. Pooled estimates of SMR for fatal MI and fatal stroke—IRR for MI and stroke—were calculated using the inverse variance method with the STATA meta-analysis program (STATA 10 software, StataCorp L, College Station, TX, USA). According to the heterogeneity test (significance at 5% level) either a fixed or a random-effects model was applied. To estimate the influence of individual studies on the summary effect estimate, meta-analysis estimates were re-computed omitting one study at a time.

Results

Among a total of 1939 references identified, 16 studies fulfilled our inclusion criteria. From abstract books of conferences we retrieved one abstract that fulfilled our inclusion criteria. Thus, we ultimately selected and included 17 studies, including one abstract, corresponding to a total population of 124,894 patients (Fig. 1). The characteristics of the studies included in the review are given in Table 1 (SMR)Table 2 (IRR). SMRs stratified by specific cohort characteristics are presented in Table 3 as highest, lowest and pooled estimates.

Funnel plots did not show evidence of publication bias (data not shown).

Table 2 Main characteristics of the studies reporting on incidence rate ratio (myocardial infarction and/or stroke).

| Study	Location, study period	Patients (n)	Age	Women (%)	Disease duration at inclusion	Follow-up (person-year)	Completeness of follow-up	Validation	Consecutive
Del Rincón	USA, 1996	236	56	62	10	252	Complete	DC, questionnaire	Yes
Solomon	USA, 1977–1996	527	58	100	NA	6259	Complete	Questionnaire, medical records	Yes
Solomon 2	USA, 1999–2003	25,385	NA	NA	NA	> 70,000	94% or 96% complete	DC, medical records	Yes
Nicola	USA, 1955–1995	603	58	73	NA	8842		Medical records	Yes
Gunnarsson[a]	Sweden, since 1995	7954	57	69	Newly diagnosed	32,247	NA	Discharge register, DC	No

DC: death certificate.
[a] This study was reported only as an abstract.

Table 3 Pooled estimates of mortality stratified by cohort characteristics.

		No. of studies	Lowest SMR	95% CI	Highest SMR	95% CI	Pooled SMR	95% CI
MI	All studies	10	0.99	0.71–1.37	3.82	2.22–6.58	1.77	1.65–1.89
	Nationality							
	Scandinavian/Scottish studies	3	0.99	0.71–1.37	1.83	1.78–1.89	1.77	1.65–1.90
	Non-Scandinavian/non-Scottish studies	7	1.42	0.88–2.28	3.82	2.22–6.58	1.83	1.54–2.16
	Disease duration							
	0–1 year	3	1.42	0.88–2.28	1.76	1.47–2.09	1.60	1.42–1.80
	> 1 year	2	0.99	0.71–1.37	3.82	2.22–6.58	1.42	1.01–1.88
Stroke	All studies	9	1.08	0.84–1.39	2.00	1.14–3.52	1.46	1.31–1.63
	Nationality	4	1.10	0.72–1.69	1.74	1.67–1.81	1.61	1.45–1.77
	Scandinavian/Scottish studies							
		5	1.10	0.83–1.46	2.00	1.14–3.52	1.37	1.01–1.72
	Non-Scandinavian/non-Scottish studies							
	Disease duration							
	0–1 year	2	1.10	0.83–1.46	2.00	1.14–3.52	1.24	0.96–1.60
	> 1 year	1	—	—	1.10	0.72–1.69	—	
	> 1 year							

CI: confidence interval; MI: myocardial infarction; SMR: standardized mortality rate.
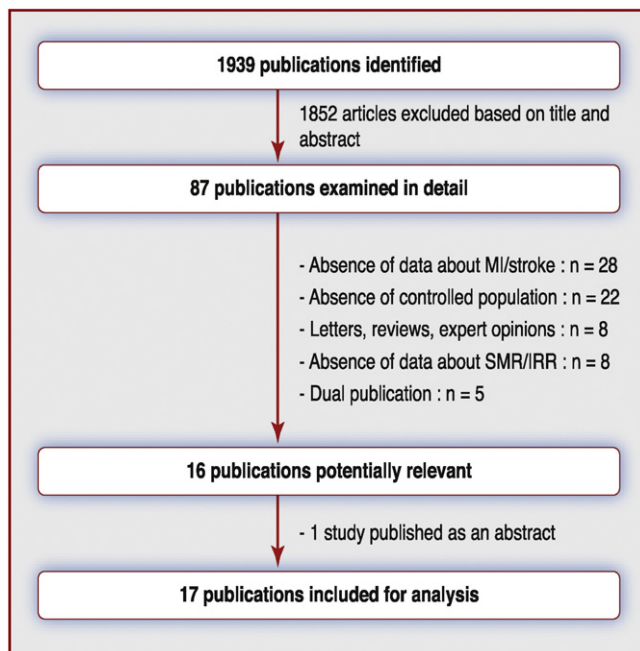
Figure 1. Study flow chart. MI: myocardial infarction; SMR: standardized mortality ratio; IRR: incidence rate ratio.

Fatal and non-fatal myocardial infarction

Ten studies reported on SMR for fatal MI, corresponding to a total of 85,323 patients [13–22] (Table 1). SMR from fatal MI ranged from 0.99 to 3.82. Seven studies demonstrated a significant increase in fatal MI [13,14,16,17,19,20,22], whereas the three remaining did not. Data were pooled by use of the random-effects model, as the heterogeneity test was significant ($\chi^2 = 31$, $P < 0.001$). The pooled SMR was 1.77 (95% CI 1.65–1.89) (Fig. 2, Table 3). The omission of one study from a subsequent analysis had no significant impact on the meta-analysis estimates.

Three studies included patients from Sweden [18,19] or Scotland [22], regions assumed to be at high risk of cardiovascular events. Mortality rates were similar in these studies conducted in Sweden/Scotland and in those performed in the USA/England (Table 3). Five studies reported mean disease duration in their cohort, which was less than 1 year in three studies [15–17] and greater than 1 year in the two remaining studies [18,20]. Pooled SMRs disclosed similar mortality in patients with less than 1-year of disease duration than in the remaining patients (Table 3).

Five studies, including one study as yet only published as an abstract [23], reported on IRR for total MI [4,23–26], corresponding to a total of 34,705 patients. The pooled estimate of the IRR was 2.10 (1.52–2.89; $P < 0.0001$) (Fig. 3). The exclusion of the abstract did not alter the pooled estimate of IRR.
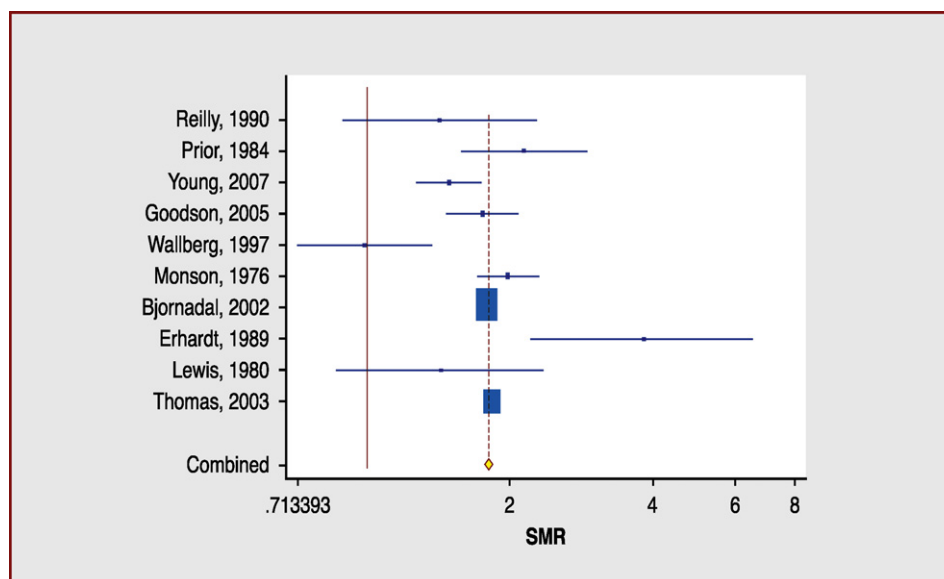
Figure 2. Forest plot of myocardial infarction standardized mortality ratio (SMR) for patients with rheumatoid arthritis. Each square represents an individual SMR estimate, the size of the square being proportional to the weight of the study. The lines represent the 95% confidence interval for the point estimate in each study.

Fatal and non-fatal stroke

The nine included studies (88,500 patients) reported SMR from fatal stroke ranging from 1.08 to 2.00 [13—16,18,19,22,27,28]. Data were pooled by use of the random-effects model, as the heterogeneity test was significant ($\chi^2 = 34$, $P < 0.001$). The pooled SMR for stroke was 1.46 (95% CI 1.31—1.63) (Fig. 4). The omission of one study in an alternative analysis had no impact on the meta-analysis estimates. Four studies reported the risk of stroke among patients from Scandinavia or Scotland [18,19,22,28]; the pooled SMR for stroke was similar in these patients from Scandinavia/Scotland than in the remaining patients from the USA/England (Table 3). Only three studies reported

mean disease duration in their cohort, which was less than 1 year in two studies [15,16] and greater than 1 year in a single cohort [18]. SMRs for stroke were similar among these studies (Table 3).

Lastly, three studies reported on IRR for total stroke (26,143 patients) [4,24,25]. The pooled estimate was 1.91 (95% CI 1.73—2.12; $P < 0.0001$) (Fig. 5).

Discussion

Our study is an update of the risk of fatal and non-fatal MI and stroke in RA. Its main result is that the risks of MI and stroke are increased in RA patients.
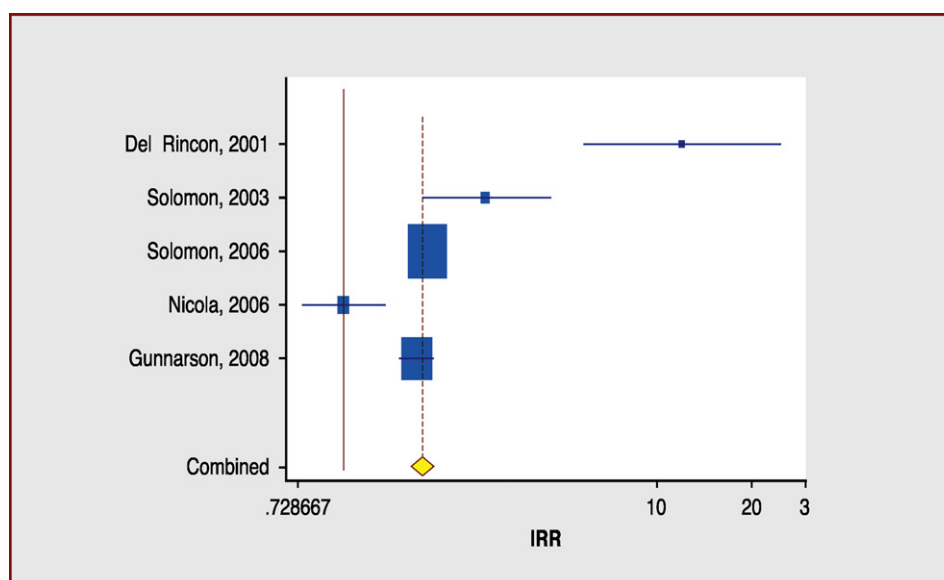

Figure 3. Incidence rate ratio (IRR) for myocardial infarction in rheumatoid arthritis with 95% confidence intervals and the combined IRR.
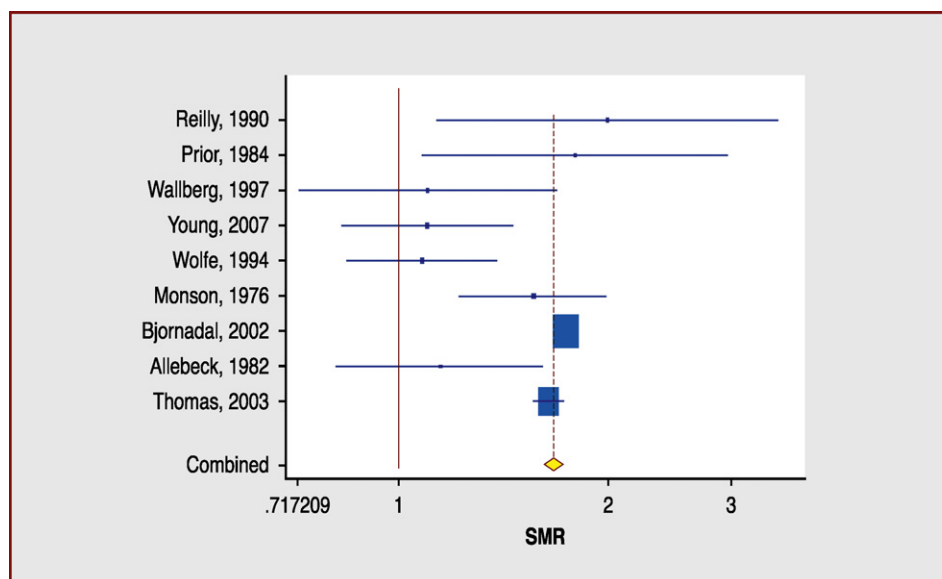
Figure 4. Forest plot of stroke standardized mortality ratio (SMR) for patients with rheumatoid arthritis. Each square represents an individual SMR estimate, the size of the square being proportional to the weight of the study. The lines represent the 95% confidence interval for the point estimate in each study.

The primary strengths of our study are the inclusion of recent studies, the application of strict search and inclusion criteria, and the assessment of population-based cohort studies only. In addition, all included studies reported data on patients with RA defined according to recommendations available at the moment of the study.

It has been suggested that the impact of RA on the risk of stroke may be weaker possibly because of the longer time to occurrence of cerebrovascular events [10]. Our study shows that both MI and stroke are more frequent in RA patients than in the general population, and suggest that both MI and stroke account for a similar extent in the observed mortality and CV events observed in RA. Our results are consistent with both our knowledge of atherosclerosis as a systemic disease [29], and the hypotheses that

have been generated to explain such an increase in CV events in RA patients. Traditional risk factors for atherosclerosis should be considered as important contributors to CV events in RA patients [6,30—32]. Indeed, atherogenic lipid profile may warrant special consideration, as previous studies have demonstrated that RA patients have raised low-density lipoprotein, and do have an atherogenic lipid profile when compared with controls, even before the onset of articular involvement [33,34]. Inflammation by itself may promote atherosclerotic plaque development, increase their vulnerability and promote thrombosis [18,35—38]. As a consequence, one may expect that all forms of atherosclerotic disease should be increased in RA.

Age at inclusion and disease duration may be important parameters to consider when analysing the literature. How-
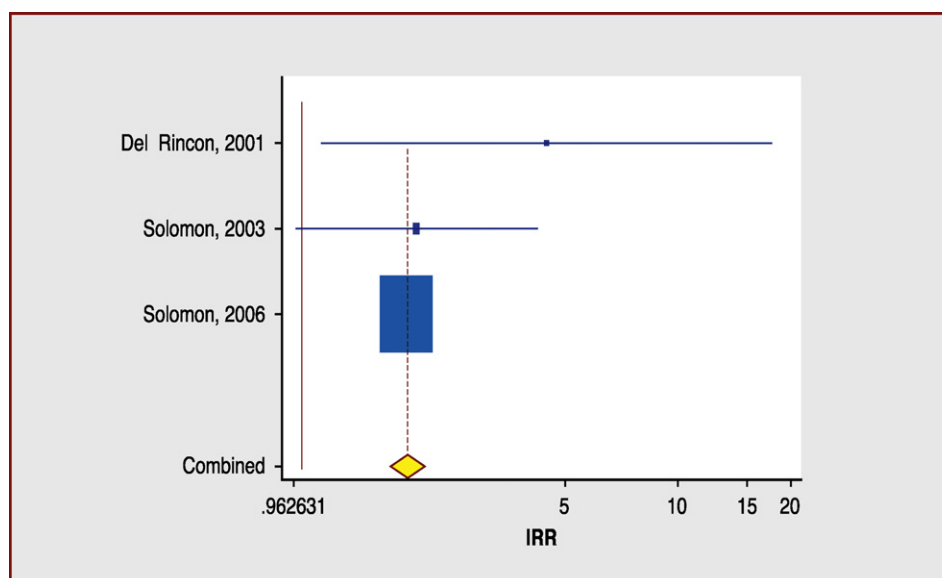

Figure 5. Incidence rate ratio (IRR) for stroke in rheumatoid arthritis with 95% confidence intervals and the combined IRR.

ever, age ranged from 51 to 61.8 years in the studies included in our analysis, with most patients aged 50—55 years at inclusion. Therefore, we cannot derive any conclusion concerning the influence of age in our study. Pooled SMR were similar in studies that focused on patients with disease duration less than 1 year than in studies that reported patients with more prolonged disease duration (Table 3). In their study, Gunnarsson et al. documented that RA patients were not reported to have increased MI by the time of the diagnosis whereas the risk of MI increased significantly during follow-up. This may be interpreted as a progressive risk over time, possibly due to prolonged disease, older age or both [23]. We must, however, acknowledge that disease duration may be hard to ascertain in some patients and was not reported in many studies.

In our analysis, we did not find any association between the time of the study and both the quality of the studies (i.e., adequate follow-up, validation of events) or the existence of increased risk of MI or stroke. This is in accordance with our previous report that mortality was not significantly altered during the past 50 years [9]. Such results could be regarded as in conflict with advances in both the management of RA and cardiovascular disease. In fact, there is strong evidence that TNFα inhibitors may alter the CV risk of these patients. TNFα inhibitors increase high-density lipoprotein (HDL) cholesterol, may reverse metabolic insulin resistance, reduce C-reactive protein concentration [10], and ultimately reduce the rate of first CV events according to a longitudinal observational study [39]. However, one should keep in mind that SMR is the ratio of observed versus expected mortality. Adequate interpretation should be that MI and stroke have decreased in both the general population and RA patients with a similar extra risk in RA patients [9].

Our study has some limitations. Our analysis showed heterogeneity among study results for MI and stroke. However, we analysed population-based cohort studies that allowed the determination of SMR and IRR and used strict inclusion criterion. In addition, we used a random-effect model to include an estimate of the between-studies variability [40] and therefore assume that our results should be considered as robust. Most of the studies evaluated the prognosis of patients with disease onset in the 1980s or early 1990s, a period when disease-modifying antirheumatic drugs were poorly prescribed and only minimal attention was paid to control of inflammation and prevention of cardiovascular events. Some studies do support the beneficial effect of these drugs on mortality; their impact upon MI and stroke remain to be demonstrated. Lastly, SMR and IRR evaluated the association between RA and measured outcomes (MI, stroke) adjusted for age and sex and not for traditional risk factors.

Conflict of interest statement

None.

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