Review

Incidence and risk of fatal myocardial infarction and stroke events in rheumatoid arthritis patients. A systematic review of the literature

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ABSTRACT

Background. *There is substantial evidence of excess cardiovascular morbidity and mortality in rheumatoid arthritis (RA) patients, but the related studies showed important variations in the estimation of the risk. We conducted a meta-analysis to evaluate more accurately the incidence of cardiovascular events, and the excess of cardiovascular risk in a population of RA patients.*

Methods. *The authors searched for observational studies accounting for the number of myocardial infarction or stroke events, using Medline, and congress abstracts published until February 2006. The populations studied were adults and RA diagnosis was based on the American College of Rheumatology (ACR) criteria. We calculated the incidence of myocardial infarction and cerebrovascular fatal events in RA patients and estimated the cardiovascular risk increase for RA patients compared with the control group.*

Results. *17 publications and abstracts were identified, 15 were selected for the meta-analysis (two publications were excluded because of the lack of person-years information). The incidence of fatal myocardial infarction was 13.3 for 1000 RA patients-year ($IC_{95\%}$=[13-13.6]). The incidence of fatal cerebrovascular accident was 4.5 for 1000 RA patients-year ($IC_{95\%}$=[4.3-4.7]). Risk of myocardial ischemia in RA patients was about 1.63 compared to the general population (OR=1.63, IC95%=[1.34-2]). No excess was found for the risk of stroke event in RA patients.*

Conclusion. *RA patients were reported to present an excess risk of fatal myocardial infarction compared to the general population. The prevention of*

cardiovascular complications, including management of cardiovascular risk factors and control of systemic inflammation, should be taken into account by the rheumatologist.

Introduction

Rheumatoid arthritis is the most frequent chronic inflammatory rheumatic disease, with prevalence estimates from 0.3 % to 1 % (1, 2). It affects females 2-4 times more frequently than males, with a maximal incidence between 35 and 55 years of age. This disease is characterized by synovial joint inflammation and cartilage destruction, which result in joint deformities, leading to functional disability.

Despite improvements in diagnosis and treatment of RA, this disease still reduces life expectancy (3). The increased mortality is predominantly due to cardiovascular complications (2, 4). There is substantial evidence of excess cardiovascular morbidity and mortality in RA patients, but publications show different estimations of incidence of cardiovascular complications in this population (5, 7). This heterogeneity of the data led us to conduct a systematic review of the literature on this subject.

The purpose of the present study is to investigate the association between RA and fatal and non-fatal cardiovascular events, using a review of the literature. We performed a meta-analysis of all published cohort or case-control studies which estimated rates of myocardial infarction or stroke events in RA patients. First, we determined the incidence of myocardial infarction and stroke fatal events in patients with RA. Then, we tried to estimate the risk of myocardial infarction or stroke events (fatal or not) in RA patients.

Patients and methods

Data extraction

Studies were eligible for this systematic review of the literature if all of the following criteria were met: 1. the study was based on cohort or case-control studies, accounting for the number of myocardial infarction or stroke events, 2. patients of the index cases were adults, the RA diagnosis was based on American College of Rheumatology criteria (ACR) or on physician diagnosis, and 3. results of selected studies were published in English or French. All studies which only provided odds-ratio without any exact information about the cardiovascular events frequencies were excluded from the analysis. There were no limits in the date of the publications, up to February 2006.

Potentially eligible studies were identified by a literature search using Medline (National Library of Medicine), with MeSH terms: "RA and cerebrovascular accident or myocardial ischemia". We also searched for others terms such as "stroke", "myocardial infarction", "heart attack", "cardiovascular disease" and "cardiovascular mortality". Our search strategy yielded 414 publications. We excluded 293 articles because they were not published in English or French (n=108), because they did not concern adults (n=88) or because they were only case reports (n=97). A further 105 publications were excluded for various reasons. One publication was excluded because the results had already been published in studies already included. One paper was excluded because it provided only odds-ratio and cardiovascular event frequencies were not available. Another publication was excluded because it only concerned mortality of RA patients in a death register. We also looked for the references that identified papers to establish whether any other relevant papers exist, and one more publication was included. Moreover, we collected data from electronic abstract databases of the annual scientific meetings of the EULAR Rheumatology congress (European League Against Rheumatism) and the American College of Rheumatology. Using the terms "myocardial infarction, stroke and RA", our search
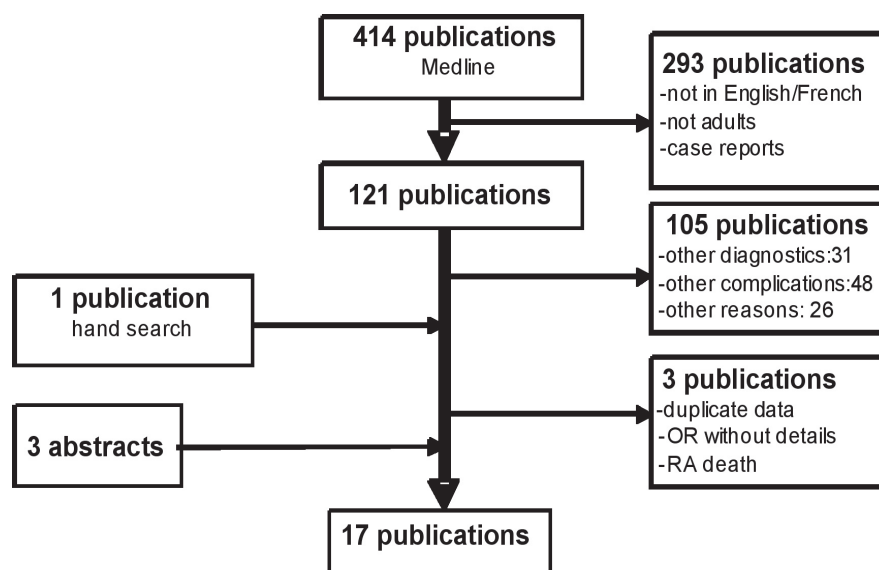
yielded 61 abstracts. We selected three abstracts using the same criteria that we have already described. All these features are described in Figure 1.

At the end of the search, 17 publications (including three abstracts) were eligible for inclusion in our review. Table I gives the clinical descriptions and ascertainment strategies of the populations of the studies.

Data analyses

We calculated the incidence of myocardial infarction and cerebrovascular fatal events in RA patients, (when the number of RA patient-years was not mentioned in the publication, we used an estimation based on the product of the number of RA patients and the mean duration of follow-up). We decided to exclude two studies from the data analyses because of the lack of person-years information (8, 9). From the information provided by the case-control studies, we tried to estimate the cardiovascular risk increase (myocardial ischemia and cerebrovascular accidents) for RA patients compared with the control group. Odds-ratio (OR) and confidence intervals (CI) were calculated using a 0.05 alpha risk.

All meta-analyses were carried out by using a fixed effects model, and combining odds-ratios from each study weighted for the size. The Mantel-Haenszel procedure was used to evaluate the association between myocardial infarction, or stroke events, and RA. This method provided a common odds-ratio estimate and 95% confidence interval, highlighting the population-wide effect of RA status (affected or not) on susceptibility to have a cardiovascular disorder. Odds-ratios and 95% confidence intervals were shown on funnel plots for myocardial infarction and stroke events.

Statistical heterogeneity of the samples considered was assessed on the basis of the Q test (χ^2), using a significance level of 0.05, and reported with the I^2 statistic (in which high values indicate high heterogeneity).

The analyses were carried out using Epiinfo 6, version 6.04 and Revman 4.2.8 software package developed by the Nordic Cochrane Center (10).

Results

We selected nine publications which were case-control studies (three retrospective and six prospective) and eight publications which were cohort studies (two retrospective and six prospective). Within these seventeen publications, ten were from northern European countries and seven from USA. Thirteen publications were focused on myocardial infarction and stroke, whereas four publications were only focused on myocardial infarction. Finally, four studies evaluated mortality and morbidity, six only morbidity and seven only mortality. The populations of interest were

Fig. 1. Flow-chart of literature selection process.

Table I. Characteristics of studies selected for meta-analysis procedure.

Reference	Country	Type of study	Type of events	Mortality or morbidity events	Inclusion	Evaluation	Women (%)	Mean Age (years)	Number rheumatoid arthritis patients
Nicola, 2006 (15)	US	case control	myocardial infarction	morbidity	1955-1995	2001	73	58	603
Del Rincon, 2001 (16)	US	case control	myocardial infarction stroke	morbidity mortality	jan-dec 1996	1997	62	56	236
Wolfe, 2003 (20)	US	case control	myocardial infarction stroke	morbidity		1999	77	60	9093
Björnadal, 2002 (5)	Sweden	rheumatoid infarction cohort	myocardial infarction stroke	mortality	1964-1994	1995	68		46 917
Gabriel, 1999 (18)	US	case control	myocardial infarction stroke	morbidity	1965/75/85	1995	77/71/75	65/63/65	450
Wallberg-Jonsson, 1997 (8)	Sweden	rheumatoid arthritis cohort	myocardial infarction stroke	mobidity mortality	1979	1994	68	Men: 56 Women: 54	606
Goodson, 2005 (11)	UK	rheumatoid arthritis cohort	myocardial infarction stroke	morbidity mortality	1981-1996	2002	72	60	979
Turesson, 2004 (17)	Sweden	case control	myocardial infarction stroke	morbidity mortality	1997	1999	74		1022
Peltomaa, 2002 (6)	Finland	rheumatoid arthritis cohort	myocardial infarction stroke	mortality	1986-1989 1991-1993	2000	77	46.5 59	150
Lindqvist, 1999 (12)	Sweden	rheumatoid arthritis cohort	myocardial infarction stroke	mortality	1985-1989	1997	63	51	183
Krishnan, 2004 (7)	US	rheumatoid arthritis cohort	myocardial infarction	mortality	1980	1997	76	56	3862
Solomon, 2003 (19)	US	case control	myocardial infarction stroke	mobidity mortality	1976	1996	100	58	527
Erb, 2004 (21)	UK	case control	myocardial infarction	morbidity			65	61	150
Kvalvik, 1999 (13)	Norway	rheumatoid arthritis cohort	myocardial infarction stroke	mortality	1977	1992	65	58	147
Yxfeldt, 2003 (22)	Sweden	case control	myocardial infarction stroke	morbidity	1979	2001	68		640
Welsing, 2005 (9)	Netherlands	rheumatoid arthritis cohort	myocardial infarction stroke	morbidity			62	54	554
Singh, 2002 (14)	US	case control	myocardial infarction	mortality	1980	2000	76	57	6159

predominantly composed of women (approximately 70%), with a mean age of 58.1±3.4 years (range from 46.5 to 65 years). In most publications, the authors did not report the mean duration of RA.

Incidence of fatal myocardial infarction

Seven studies (including one abstract) (5-7, 11-14) reported the rate of fatal myocardial infarction and the number of patient-years follow-up (Table II). In all the studies, the cause of death was identified from death certificates and death registers. The number of RA was 562 609 patient-years follow up (women = 71%, mean age = 56.4±2.8 years), and the rate of myocardial infarction in this population was 7 492. The incidence of fatal myocardial infarction was 13.3 for 1000 RA patients-year ($IC_{95\%}$= 13.0-13.6).

Incidence of fatal cerebrovascular stroke

Five studies (5-6, 11-13) reported the rate of stroke events and the number of RA patient-years follow-up (Table II). In all the studies, the cause of death was identified from death certificates and death registers. The ACR criteria for RA were fulfilled by 506,770 patient-years follow up (women=69%, mean age=56.5±3.4 years). The number of fatal strokes was 2 259 and the incidence was 4.5 for 1000 RA patients-year ($IC_{95\%}$=4.3-4.7).

Odds-ratio for myocardial ischemia in patients with RA

Among the eight selected publications that estimated the ratio of myocardial ischemia in rheumatoid patients, some used a control group from the general population while others used osteoarthritis patients as controls (Fig. 2). As the risk of osteoarthritis patients could be different from the general population (frequently overweight, sedentary due to disability, frequent use of non steroidal anti-inflammatory drugs…), we conducted separates analyses for the first subgroup of studies, and for the whole population.
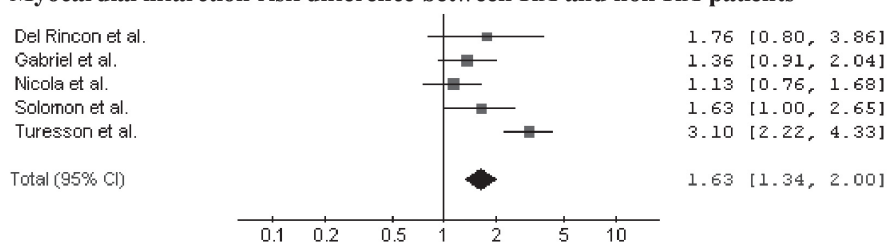
When we used only the five studies (15-19) comparing the number of myo-

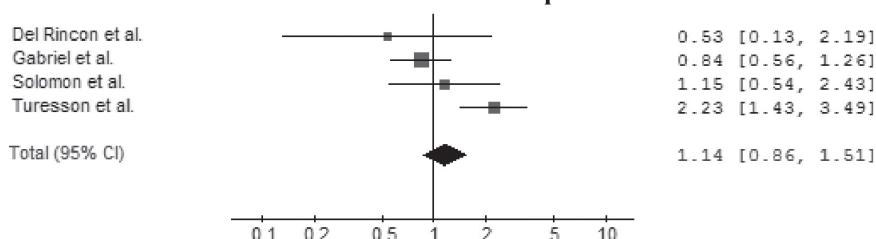**Table II.** Calculation of myocardial infarction and stroke fatal incidences.

Reference	Patients-year	Number of fatal myocardial infarctions	Number of fatal strokes	Incidence of fatal myocardial infarction (‰)	Incidence of fatal strokes (‰)
Björnadal, 2002 (4)	489 048	6 991	2 202	14.3	4.5
Goodson, 2005 (7)	11 161*	72	48	6.4	4.3
Peltomaa, 2002 (5)	2 985*	6	1	2	0.3
Lindqvist, 1999 (11)	1 793*	2	2	1.11	1.11
Krishnan, 2004 (6)	22 209	157		7	
Kvalvik, 1999 (12)	1 783	15	6	8.4	3.4
Singh, 2002 (13)	33 630	249		7.4	
TOTAL				13.1	4.5

*product of the number of rheumatoid arthritis patients and mean during of follow-up

Myocardial infarction risk difference between RA and non RA patients


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Del Rincon et al.                              1.76 [0.80, 3.86]
Gabriel et al.                                 1.36 [0.91, 2.04]
Nicola et al.                                  1.13 [0.76, 1.68]
Solomon et al.                                 1.63 [1.00, 2.65]
Turesson et al.                                3.10 [2.22, 4.33]

Total (95% CI)                                 1.63 [1.34, 2.00]

        0.1  0.2   0.5   1    2     5   10
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Stroke risk difference between RA and non RA patients


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Del Rincon et al.                              0.53 [0.13, 2.19]
Gabriel et al.                                 0.84 [0.56, 1.26]
Solomon et al.                                 1.15 [0.54, 2.43]
Turesson et al.                                2.23 [1.43, 3.49]

Total (95% CI)                                 1.14 [0.86, 1.51]

        0.1  0.2   0.5   1    2     5   10
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Fig. 2. Odds-ratios with 95% confidence intervals from each study are given, testing the association of myocardial infarction or stroke. The pooled ORs with 95% CI for overall analysis in the total population were calculated using the Maentel-Haenszel method (diamond).

cardial ischemic events (fatal or not) in RA patients to that in the general population, the total of RA patients was 2,838 (women=77%, mean age=60±3.2 years) and the number of myocardial infarction in this population was 180. Among the 327,349 non-RA patients the number of myocardial ischemia was 4,876. Moreover, the estimated RA to general population odds-ratio for myocardial ischemic event was 1.63 (IC95%=1.34-2.00).

When we included the publications of Wolfe (20) and Erb (21) and one abstract (22) which compared the RA patients to osteoarthritis patients, the odds-ratio for myocardial ischemia was similar: 1.61 (IC95%=1.41-1.84).

Odds-ratio for stroke in patients with RA

As previously, and for similar reasons, we analysed the studies differently comparing RA patients to controls from the general population and the whole (Fig. 2).

Four articles (16-19) compared the number of cerebrovascular events in RA patients to that in the general population. The total number of RA patients was 2,235 (women=78%, mean age=60±3 years), and the number of strokes was 79. The total of non-RA patients was 326 746 and the number of strokes was 3,290. The odds-ratio of strokes in patients with RA compared with those without RA was 1.14 (IC95%=0.86-1.51).

The odds-ratio did not change when we included the Wolfe (20) and Erb (21) publications: 1.13 (IC95%=0.94-1.36).

Statistical heterogeneity of samples

The test for heterogeneity highlights a significant difference between studies with I^2=78% (p=0.001) for the myocardial infarction risk, and I^2=75.1% (p=0.007) for the risk of stroke in RA patients.

Risk factors for myocardial infarction and stroke

The authors could not study the effect of rheumatologic treatments, disease characteristics (such as inflammation) and conventional cardiovascular risk factors on myocardial infarction or stroke incidence, because of the heterogeneity of related data in the selected publications.

Discussion

In the present meta-analysis we report a high incidence of fatal myocardial infarction (13.3 for 1000 RA patients-year, $IC_{95\%}$=13.0-13.6). The incidence of fatal cerebrovascular accident was three times less (4.5 for 1000 RA patients-year, $IC_{95\%}$=4.3-4.7). We also report that the risk of myocardial infarction (fatal or not) was increased in RA patients compared with the general population OR=1.63 (IC95%=1.34-2.00). Conversely, our results do not reveal a significant increase of stroke risk OR=1.14 (IC95%=0.86-1.51).

The Q-test revealed high heterogeneity between the different studies on myocardial infarction and stroke risks in RA patients. From a statistical point of view, this test informs whether there is more variation in the results of the studies than would be expected by random. The use of this test is rather limited: if there are few studies it is not very sensitive for detecting excess variation, and if there are many studies it is too sensitive to detect negligible variation. In our case, we can suppose that the small number of studies considered, and low number of patients and controls in some of them could lead to heterogeneity in studies combination. One way to try to deal with heterogeneity is to apply a random-effect model. The Mantel-Haenszel method performs a fixed-effect analysis which assumes that all study samples are derived from a single population with a common effect size. By contrast, random-effect analysis assumes that the samples included come from a distribution of populations. To confirm this feature, the meta-analysis was performed without the largest study, which is Turesson *et al*. (17). The results showed the same conclusion as before with an excess risk of myocardial infarction in RA patients (OR=1.34; IC95%=[1.06;1.70], p=0.01), and no variation observed for risk of stroke in RA patients (OR=0.87; IC95%=[0.61;1.22], p=0.41), but the test for heterogeneity allowed the combination of such studies (data not shown). So the addition of the study performed by Turesson *et al*. did not provide more information, but only increased the heterogeneity between studies leading to confusion in the results.

From a population point of view, the heterogeneity observed in our results could be explained by the admixture of various populations with exposure to different environmental conditions. No consideration of environmental exposure variations between studies selected was made. Heterogeneity between populations in this study could also be explained by the different impact of environmental factors in each study, such as nutrition, exposure to cigarette smoking or individual factors, such as sex, which might influence the risk of cardiovascular events.

In addition, some limits and criticisms can be addressed to this study. First of all, we were surprised to notice that in most of the publications the definition of myocardial infarction and stroke events was not clearly specified, leading to a possible selection bias.

The populations studied came from Northern countries, where the cardiovascular risk factors are much more important than elsewhere, so our results may not be directly applicable to Southern countries.

The relative low incidence of cerebrovascular accidents in our population can be explained because of the lower mean age of the RA patients selected compared to the traditional mean age of patients affected by cerebrovascular events.

Unfortunately, in our meta-analysis we could not study the factors underlying this increased risk of myocardial infarction and stroke for persons with RA. Data such as: already known risk factors, anti-rheumatic treatments, biomarkers of inflammation (ESR, CRP…) were not available in each publication studied.

Increased rates of several traditional cardiovascular risk factors have been reported in populations with RA. Del Rincon *et al*. reported in their prospective study, that the incidence rate of cardiovascular events associated with RA decreased only slightly after adjusting for traditional cardiovascular risk factors (16). Incidence of cardiovascular events in RA patients is not entirely explained by the classical cardiovascular risk factors. In this regard, several mechanisms, different from the traditional atherosclerosis risk factor, have been put forward as responsible for the accelerated atherosclerosis observed in patients with RA (23). Among them, endothelial dysfunction, an early step in the atherogenesis process, is observed in RA (24), in RA young patients with low disease activity (25), and long-standing actively treated patients (26).

Although the intimate cause of atherosclerosis is unknown, many investigators have suggested that the underlying systemic inflammation gives rise to endovascular inflammation and atherosclerosis (27-29). Deleterious effects resulting from persistent chronic inflammation may lead to endothelial dysfunction, insulin resistance and a dyslipidemic pattern (23). According to this assumption, we could explain the higher than expected rate of cardiovascular diseases in patients affected by chronic inflammatory diseases such as RA (30). It seems that RA and cardiovascular disease share some critical items in their pathogenesis. It has long been supposed that T cells play a critical role in the pathogenesis of RA, and more recent data suggest that it also play an important role in acute coronary syndromes and atherosclerotic plaque instability (31). Inflammatory markers, (cytokines, C-reactive protein…) which are increased in

RA are also known to be elevated in patients with coronary artery disease. Wallberg-Jonsson found that extensive inflammation and high disease activity is an important risk indicator for cardiovascular disease and mortality in RA (32). Maradit-Kremers *et al.* revealed that markers of systemic inflammation confer statistically significant additional risk for cardiovascular death among RA patients, after adjusting for traditional cardiovascular risk factors and comorbidities (33). Interestingly, a significant linear trend for increased carotid intima-media thickness (another surrogate marker of atherosclerosis) associated with increasing C-reactive protein levels was also reported in RA patients without classic atherosclerosis risk factors or clinically evident cardiovascular disease (34). Most of the publications studied highlighted that the information on inflammatory makers was missing and we were unable to examine the role of inflammatory makers on cardiovascular disease.

The effect of the anti-rheumatic treatments on cardiovascular complications is likely to be complex. Corticosteroids could increase the risk of cardiovascular events by deleterious effects on blood pressure, lipids and glucose metabolism (35). However, in some studies based on "homogeneous" series of patients, the evidence for accelerated atherosclerosis mediated by prolonged steroid therapy has not been unanimously supported (36). Non-steroidal anti-inflammatory drugs are also known to increase blood pressure and to generate cardiovascular complications (37, 38). Methotrexate treatment increase homocysteine level which is an independent risk factor for cardiovascular disease (39). Folic acid supplementation reduces homocysteine level but we don't know the real effect on cardiovascular disease. In Choi *et al.* (39), significant survival benefit, largely by reducing cardiovascular mortality, has also been observed following methotrexate therapy. TNF plays a role in the development of atherosclerosis by recruiting the inflammatory cells to the site of injury, and it also plays a role in plaque rupture (40). Progression of subclinical atherosclerosis has

been observed in patients treated with anti-TNF-alpha monoclonal antibody infliximab (41, 42), contrary to the fully human monoclonal antibody adalimumab which has been reported to improve endothelial function in patients with RA (43).

On the one hand, all these drugs lead to cardiovascular complications as side effects, but on the other hand, they could also reduce the cardiovascular morbidity in RA by controlling inflammation.

We think that rheumatologists should not only focus on the arthritis, but they also have to prevent the cardiovascular complications in RA patients. This prevention includes the screening and the management of traditional cardiovascular risk factors and the control of systemic inflammation.

Conclusion

This meta-analysis confirms that patients with RA may have increased morbidity and mortality from cardiovascular disease compared with people not affected. RA patients have a more important risk of myocardial infarction (but not stroke) compared with the general population. It is important that rheumatologists are aware of this increased cardiovascular risk in RA patients. Mechanisms underlying the increase of cardiovascular events in RA are not exactly elucidated: it seems that inflammation plays an important role, but the respective weight of all classical risk factors is not clearly determined. A better control of inflammation and also a better control of the traditional cardiovascular risk factors could decrease the cardiovascular risk in RA patients. Further studies are needed to determine the impact of the control of inflammation by anti-rheumatic treatments and the exact impact of the control of traditional cardiovascular risk factors in the prevention of cardiovascular complications in RA patients.

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