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High incidence of cardiovascular events in patients with rheumatoid arthritis

Rheumatoid arthritis (RA) is associated with higher risk for cardiovascular disease (CVD) in comparison with the general population.[1] Traditional cardiovascular (CV) risk factors only partially explain the higher risk for CVD.[2] There is increasing evidence that inflammation explains the enhanced CV risk in RA, as inflammation has a pivotal role in the development of atherosclerotic disease and this might be the link between increased atherosclerotic CVD and RA.[3] Other RA-related factors might be undertreatment of CV comorbidity,[1] and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclo-oxygenase 2 inhibitors.[4 5]

The objective of this prospective observational study was to determine the incidence of CV events in patients with RA in comparison to the general Dutch population, where the incidence of CV events is 1% per year.[6]

Between September 2003 and August 2004 three questionnaires were sent to all patients with RA of the Departments of Rheumatology of the Jan van Breemen Institute and of the VU University Medical Center, Amsterdam, The Netherlands.

A total of 12 532 questionnaires were sent to 4125 patients with RA. In all, 2099 patients (51%) returned at least 1 questionnaire and 1036 patients (25%) returned 3 questionnaires, comprising 1557 patient years. The annual incidence of CV events was 2.6 (95% CI 1.8 to 3.4) per 100 patient years. CV events occurred in 41 patients: 19 patients experienced coronary events, 14 patients experienced cerebrovascular events and 8 patients experienced peripheral arterial events (table 1).

We observed a more than twofold increase in the incidence of CV events in RA in comparison to the general Dutch population. The age-adjusted incidence of ischaemic heart and cerebrovascular diseases in the general Dutch population was 1.0%,[7] versus 2.6% in our RA population. As the RA population encompassed relatively more women than the general population our findings probably underestimate the true CV risk in RA. As expected, established CV risk factors as higher age, male gender, smoking and (family) history for CVD as well as statin use, were associated with a higher risk for CVD.

Patients with CV events used a lower dose of methotrexate than patients without CV events, which is in line with other studies,[8] demonstrating the CV protective effect of methotrexate, probably mediated by inflammation suppression.[9]

The observed association between acetaminophen use and antihypertensive use, might be due to the induction of hypertension mediated by cyclo-oxygenase 2 inhibition.[10] This observation confirms earlier literature findings and necessitates prospective investigations.

Cyclo-oxygenase 2 inhibitors and most NSAIDs are associated with an increased CV risk.[6] In the present study patients with CV events used less NSAIDs prior to the event in comparison to the patients without CV events. This is probably the result of restrained prescriptions of cyclo-oxygenase 2 inhibitors and NSAIDs to patients who were high risk for CVD and demonstrates the potentially strong effects of unmeasured confounding in observational studies.

Two limitations of this study should be discussed. Firstly, the relatively low response rate of 51% could result in a selection bias. Therefore, we compared the baseline characteristics between the responders and non-responders and found no differences rendering this bias unlikely. Secondly, the small number of events in our case-control substudy makes it difficult to reach final conclusions about CV risk factors. Future studies are needed to further elucidate these topics.

Altogether, this study reveals a doubled incidence of CV events in RA in comparison to the general Dutch population, strengthening the case for CV risk management in RA.

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Table 1 Characteristics of patients with rheumatoid arthritis (RA) with and without cardiovascular (CV) events

	Patients with CV events	Patients without CV events	p Value
No. of patients with RA	41	2058	
Mean age, years (range)	72 (56–84)	61 (19–94)	<0.001
No. aged 60 years or older	36 (88)	1083 (53)	<0.001
No. of females (%)	23 (56)	1157 (73)	0.02
Duration of RA in years (%):			
<2	1 (4)	76 (5)	1.000
2–10	12 (43)	676 (49)	0.53
>10	15 (54)	631 (46)	0.40
Unknown	13 (32)	675 (33)	
No. of patients with history of GI event(s) (%)	7 (22)	175 (11)	0.04
No. of patients without history of GI event(s)	25 (78)	1362 (89)	
Unknown	9 (22)	521 (25)	
No. of high risk patients* (%)	38 (93)	1148 (56)	<0.001
NSAIDs and cyclo-oxygenase 2 inhibitors (%):			
No NSAIDs	25 (61)	747 (36)	<0.001
NSAIDs with low-dose aspirin	3 (7)	98 (5)	0.45
NSAIDs without low-dose aspirin	6 (15)	966 (47)	<0.001
Cyclo-oxygenase 2 inhibitors with low-dose aspirin	0	30 (1)	1.00
Cyclo-oxygenase 2 inhibitors without low-dose aspirin	7 (17)	257 (12)	0.38
Acetaminophen (%)	14 (34)	624 (30)	0.60
Low-dose aspirin alone (%)	13 (32)	102 (5)	<0.001
Low-dose aspirin, clopidogrel, dipyridamole†	18 (44)	236 (11)	<0.001
Anticoagulants‡ (%)	13 (32)	103 (5)	<0.001
Family history of CV events, no. (%)	22 (71)	824 (55)	0.07
Treatment for RA (%):			
No DMARDs	8 (20)	307 (15)	0.38
Methotrexate	14 (34)	1224 (59)	<0.001
Corticosteroids	16 (39)	432 (21)	0.01
Other DMARDs	9 (22)	373 (18)	0.53
Combination of DMARDs§	10 (24)	501 (24)	1.00
Biologicals¶	5 (12)	322 (16)	0.06
Gastroprotection** (%)	19 (46)	895 (43)	0.73
Current or previous smoker (%)	32 (78)	1308 (64)	0.06
Antihypertensive drugs (%)	25 (61)	666 (32)	<0.001
Oral diabetic drugs or insulin (%)	4 (10)	130 (6)	0.33
Statins (%)	18 (44)	251 (12)	<0.001

*High risk: higher age and/or previous GI event.
†Low-dose aspirin, clopidogrel and dipyridamole are used in secondary prevention for CV event.
‡Anticoagulants: aspirin not included.
§Combination of DMARDs: two or more DMARDs, corticosteroids included.
¶Biologicals: adalimumab, infliximab, etanercept and anakinra.
**Gastroprotection: proton pump inhibitors (PPIs), prostaglandin analogue and high dose of H_2 antagonists (other: PA or H2A) and cyclo-oxygenase 2 inhibitors.
DMARDs, disease-modifying antirheumatic drugs; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.

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