European Journal of Internal Medicine 62 (2019) 72–79

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Rheumatoid arthritis patients have higher prevalence and burden of asymptomatic coronary artery disease assessed by coronary computed tomography: A systematic literature review and meta-analysis

Peter Riis Hansen[a,b,*], Martin Feineis[c], Jawdat Abdulla[c]

[a] Department of Cardiology, Herlev and Gentofte Hospital, Hellerup, Denmark
[b] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[c] Department of Medicine, Section of Cardiology, Glostrup University Hospital, Glostrup, Denmark

ARTICLE INFO

Keywords:
Coronary artery disease
Computed tomography
Rheumatoid arthritis
Systematic review
Meta-analysis

ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with increased risk of coronary artery disease (CAD) and studies with coronary computed tomography have suggested increased rates of asymptomatic CAD determined by the coronary calcium score (CCS) in these patients. To synthesize the evidence on this topic, we conducted a systematic review and meta-analysis of the literature.

Methods: A systematic review was performed of data comparing the prevalence and burden of asymptomatic CAD in RA and controls using CCS with or without coronary computed tomographic angiography (CCTA). For the meta-analysis, pooled data provided the estimated risk ratio (RR) of CAD and weighted mean differences of CCS in patients with RA compared to controls.

Results: The search revealed 1841 results of which 1083 were screened and 26 full text papers were evaluated. Eight studies were included with data on 788 patients with RA and 1641 controls. Patients with RA had significantly increased risk of CAD (RR = 1.26 [95% CI 1.04–1.52]; $p = .021$) and increased weighted mean differences for CCS (48.25 [95% CI 26.97–69.53]; $p < .001$) compared to controls. Limited evidence suggested that patients with RA had a higher prevalence of moderate-severe (CCS > 100) CAD and more multivessel CAD, and RA duration and disease activity were associated with higher CCS, RA disease activity was linked with presence of high risk (non-calcified or mixed) coronary plaques, and treatment with methotrexate was tied to absence of CAD, respectively.

Conclusions: In patients with RA, asymptomatic CAD is more prevalent, with higher mean CCS, more multivessel disease, and more high-risk plaques compared to controls.

1. Introduction

Rheumatoid arthritis (RA) is associated with increased risk of myocardial infarction that is comparable to the risk in patients with type 2 diabetes [1,2]. Risk of subclinical atherosclerotic disease is also increased in RA, e.g. increased carotid artery intima-media thickness and reduced brachial artery flow-mediated vasodilatation [3,4]. Along this line, several small-sized studies have reported on the prevalence and burden of subclinical coronary artery disease (CAD) in patients with RA compared with controls using the coronary calcium score (CCS) and coronary angiography obtained by coronary computed tomography. However, these studies are heterogeneous and it is less clear whether CCS is increased in a large cohort of patients with RA without prior atherosclerotic disease compared with controls without RA. Perhaps unsurprisingly, traditional cardiovascular risk scores developed for the general population are inadequate for prediction of risk in RA and attempts at optimizing such risk scores, e.g. by inclusion of RA disease activity markers, have not been successful [5–7]. In patients with RA, limited evidence has suggested that CCS > 100 is linked with markedly increased risk of major cardiovascular events independent of other risk factors, as is also the case for the general population [8,9]. However, in view of the increased cardiovascular risk in RA, it is possible that assessment of CAD by computed tomography can be of more decisive importance for cardiovascular risk prediction in RA. Accordingly, to provide more accurate estimates of the prevalence and magnitude of asymptomatic CAD in RA as determined by computed tomography, we conducted a systematic review and pooled all available data from the literature in a meta-analysis.

* Corresponding author.
E-mail address: peter.riis.hansen@regionh.dk (P.R. Hansen).

https://doi.org/10.1016/j.ejim.2019.02.018
Received 16 December 2018; Received in revised form 28 January 2019; Accepted 23 February 2019
Available online 28 February 2019

Table 1
Search strategy in individual databases and manual search.

Database	Search strategy and syntaxes	Number of retrieved articles
Pubmed (Medline)	Rheumatoid arthritis and coronary calcification ((“arthritis, rheumatoid”[MeSH Terms] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields])) AND (“heart”[MeSH Terms] OR “heart”[All Fields] OR “coronary”[All Fields]) AND (“calcinosis”[MeSH Terms] OR “calcinosis”[All Fields] OR “calcification”[All Fields] OR “calcification, physiologic”[MeSH Terms] OR (“calcification”[All Fields] AND “physiologic”[All Fields]) OR “physiologic calcification”[All Fields])) AND (“loattrfull text”[sb] AND (“2000/01/01”[PDAT] : “2018/12/31”[PDAT]) AND English[lang])	68
	Rheumatoid arthritis and coronary calcium ((“arthritis, rheumatoid”[MeSH Terms] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields])) AND (“heart”[MeSH Terms] OR “heart”[All Fields] OR “coronary”[All Fields]) AND (“calcium”[MeSH Terms] OR “calcium”[All Fields])) AND (“loattrfull text”[sb] AND (“2000/01/01”[PDAT] : “2018/12/31”[PDAT]) AND English[lang])	80
	Rheumatoid arthritis and computed tomography angiography ((“arthritis, rheumatoid”[MeSH Terms] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields])) AND (“computed tomography angiography”[MeSH Terms] OR (“computed”[All Fields] AND “tomography”[All Fields] AND “angiography”[All Fields]) OR “computed tomography angiography”[All Fields])) AND (“loattrfull text”[sb] AND (“2000/01/01”[PDAT] : “2018/12/31”[PDAT]) AND English[lang])	54
	Rheumatoid arthritis and coronary artery atherosclerosis ((“arthritis, rheumatoid”[MeSH Terms] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields])) AND (“coronary artery disease”[MeSH Terms] OR (“coronary”[All Fields] AND “artery”[All Fields] AND “disease”[All Fields]) OR “coronary artery disease”[All Fields] OR (“coronary”[All Fields] AND “artery”[All Fields] AND “atherosclerosis”[All Fields]) OR “coronary artery atherosclerosis”[All Fields])) AND (“2000/01/01”[PDAT] : “2018/12/31”[PDAT]) AND (“loattrfull text”[sb] AND English[lang])	421
	Total	623
EMBASE	Rheumatoid arthritis and coronary calcification: limits “English language, year 2000–2018” Search status: all, included congress abstracts	15
	Rheumatoid arthritis and coronary calcium: limits “English language, year 2000–2018” Search status: all, included congress abstracts	38
	Rheumatoid arthritis and computed tomography angiography: limits “English language, year 2000–2018” Search status: all, included congress abstracts	24
	Rheumatoid arthritis and coronary artery atherosclerosis: limits “English language, year 2000–2018” Search status: all, included congress abstracts	171
	Total	248
Web of science	Rheumatoid arthritis and coronary calcification Refined by: WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) AND DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) AND LANGUAGES: (ENGLISH) Timespan: 2000–2018. Indexes: BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, IC, A&HCI, CPCI-SSH, CPCI-S, CCR-EXPANDED.	60
	Rheumatoid arthritis and coronary calcium Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) AND WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) Timespan: 2000–2018. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	60
	Rheumatoid arthritis and computed tomography angiography Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) Timespan: 2000–2018. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	16
	Rheumatoid arthritis and coronary artery atherosclerosis Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (RHEUMATOLOGY OR CARDIAC CARDIOVASCULAR SYSTEMS) Timespan: 2000–2018. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.	308
	Total	444
Total results of electronical search		1315
Total results of manual search	Screening of references of the retrieved eight articles and six other relevant articles	526
Overall results		**1841**

2. Material and methods

2.1. Study design and search strategy

The systematic review was conducted in accord with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [10]. We searched in electronic databases (*PubMed* via MEDLINE and *EMBASE*) for all published studies that reported the prevalence and magnitude of CAD measured by CCS in patients with rheumatoid arthritis. We combined the search term ‘rheumatoid arthritis’ in all fields with each of the following keywords: coronary calcification, coronary calcium, computed tomography angiography, and coronary artery atherosclerosis, respectively. Electronically detected published papers were all screened by titles and/or abstracts and by reviewing full papers if these were considered relevant for inclusion. All reference lists of the retrieved full text papers were also screened manually for additional eligible studies. All detected references were saved electronically in EndNote reference management program and all duplicates were identified. The literature search was restricted to papers published in English, from 1st January1990 until 31th December 2018. The systematic search was supplemented by manual review of all references in the retrieved eligible studies.

2.2. Study eligibility

Randomized or non-randomized controlled studies were considered for inclusion if they reported the prevalence of CAD and CCS in patients with RA compared with controls without RA. Eligible controlled studies had to provide at least one of the following datasets: absolute numbers of patients with prevalent CAD (CCS >0) and total patient numbers to estimate CAD prevalence and/or mean or median CCSs with standard deviations (SDs) or ranges in order to estimate the severity of the disease, respectively. We excluded all studies that did not meet these criteria or that reported insufficient data. We used the checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) for study quality assessment [11].

2.3. Data extraction

We extracted all data on demographic characteristics and key baseline clinical variables reported as means with SDs or medians with ranges from each study. We also extracted absolute numbers of patients who had CAD (CCS > 0) and means with SDs of CCSs measured as Agatston units. Additional angiographic data on coronary plaque composition characterized by cardiac computed tomographic angiography (CCTA) were also extracted whenever available. In the study by Chung [12] we excluded patients with early RA from the analysis. Studies providing data on CCS strata (<100 vs. >100) were extracted for a sub-analysis. Values reported as medians with ranges or means with standard errors were recalculated to the corresponding means with SDs. Values presented as percents were recalculated to absolute numbers.

2.4. Statistical methods

For assessment of the prevalence of CAD the number of RA patients with CCS >0 and the total number of RA patients were pooled and compared to similar data for controls to estimate the risk ratio (RR) for CAD. CCS means with SDs reported in the included studies were pooled to estimate the weighted mean difference between patients with RA vs. controls. Due to data heterogeneity we reported the results of analyses using the random effects model. For overall estimated RR or weighted mean difference a p-value < .05 was considered statistically significant. Heterogeneity among studies was tested using the chi-squared method where a p-value < .05 was considered statistically significant. The I^2 value indicates the percentage of variation in the pooled study results and an I^2 value above 20% was considered statistically significant. All analyses were performed using the meta-analysis package of STATA version 15 (STATA Corporation, Lakeway Drive, College Station, TX, USA).

3. Results

3.1. Results of the literature search

The PRISMA search strategy and results are shown in Table 1 and Fig. 1. Overall eight cross-sectional studies were eligible for meta-analysis. Seven studies contributed to the meta-analysis of prevalence of CAD [12–16,18,19] and seven studies contributed to the meta-analysis of mean CCS [12–15,17–19].

3.2. Study characteristics and quality assessment

All included studies were non-randomized controlled studies, where a total of 788 RA patients were compared with 1641 controls. Patients with previous CAD or stroke were excluded. One study included women only [13]. The diagnosis of RA was based on fulfillment of the American College of Rheumatology criteria [20]. For CCS quantification, two studies of older date used electron beam CT scanners [12,13], while the rest of studies used multi-slice CT scanners (Table 2). CCS was quantified using the conventional Agatston method [21]. CCTA was acquired according to recommended protocols [22]. Patients were prepared by using beta-blockers to reduce heart rates below 60/min, followed by a breath-hold and ECG-gated image acquisition using iodine contrast agents. The results of study quality assessment according to CHARMS are shown in Table 3.

3.3. Baseline characteristics

In all studies, RA patients were matched with controls at least for age and sex. Overall, there were no significant differences in mean age, sex, mean body mass index (BMI), mean total cholesterol levels and ratios of patients with current smoking, diabetes and hypertension between subjects with RA and controls (Table 4).

3.4. Meta-analysis of the prevalence of CAD and mean CCS

As shown in Fig. 2, pooling of data from eight studies showed that risk of CAD (CCS >0) was significantly higher in patients with RA than controls (373/728 [51.2%] vs. 777/1621 [47.9%]; RR = 1.26 [95% CI 1.04–1.52]; $p = .021$). Three studies provided data concerning the severity of CAD in RA patients and controls [12,14,16]. Using a threshold of CCS 100, patients were divided in mild (CCS<100) or moderate-severe (CCS > 100) CAD subgroups. A total of 147/314 (47%) RA patients vs. 245/404 (60%) controls had mild CAD (RR = 0.88 [95% CI 0.75–1.03]; $p = .11$), while a total of 103/314 (32%) RA patients vs. 73/404 (18%) controls had moderate-severe CAD (RR = 1.16 [95% CI 0.79–1.69]; $p < .001$). Limited evidence also indicated that RA duration and disease activity was associated with higher CCS [12–14,18]. Also, a steeper increase in CCS with age was observed for patients with RA compared to controls [18], whereas treatment with methotrexate was linked with absence of CAD (CCS = 0) [19]. A meta-analysis of the weighted mean difference of CCSs (Fig. 3) showed significantly higher mean Agatston units in RA compared to controls with a weighted mean difference of 48.25 (95% CI 26.97–69.53; $p < .001$) and significant heterogeneity between the studies ($I^2 = 99.5\%$, $p < .001$).

3.5. Results of CCTA

CCTA was performed in two studies. Ma et al. [16] found that the number of coronary vessels with obstructive (>50% stenosis) CAD was nominally more frequent in patients with RA than controls (19.1% vs. 6.4%; p = .06). In the study of Karpouzas et al. [18] multivessel CAD, both non-obstructive and obstructive, and numbers of all plaque types (calcified, non-calcified or mixed) were significantly more prevalent in RA compared to controls, and RA disease activity was associated with the presence of high-risk (non-calcified or mixed) plaques.

4. Discussion

In this systematic review and meta-analysis of studies where CAD was examined by computerized tomography, subjects with RA had increased prevalence of subclinical CAD and increased burden of the disease with higher mean CCS, more multivessel disease, and more high-risk plaques compared to controls. To our knowledge, this is the first meta-analysis of this topic and the results are in line with the increased risk of myocardial infarction and cardiovascular death as well as increased subclinical atherosclerosis observed in other vascular territories in RA [1–4]. Also, the clinical relevance of the results is supported by studies indicating that in subjects with new-onset CAD, patients with RA more often present with multivessel CAD on the first invasive angiogram than controls [23]. In addition, the clinical presentation of incident CAD is more severe in patients with RA than in controls, e.g. with more ST-segment elevation myocardial infarction

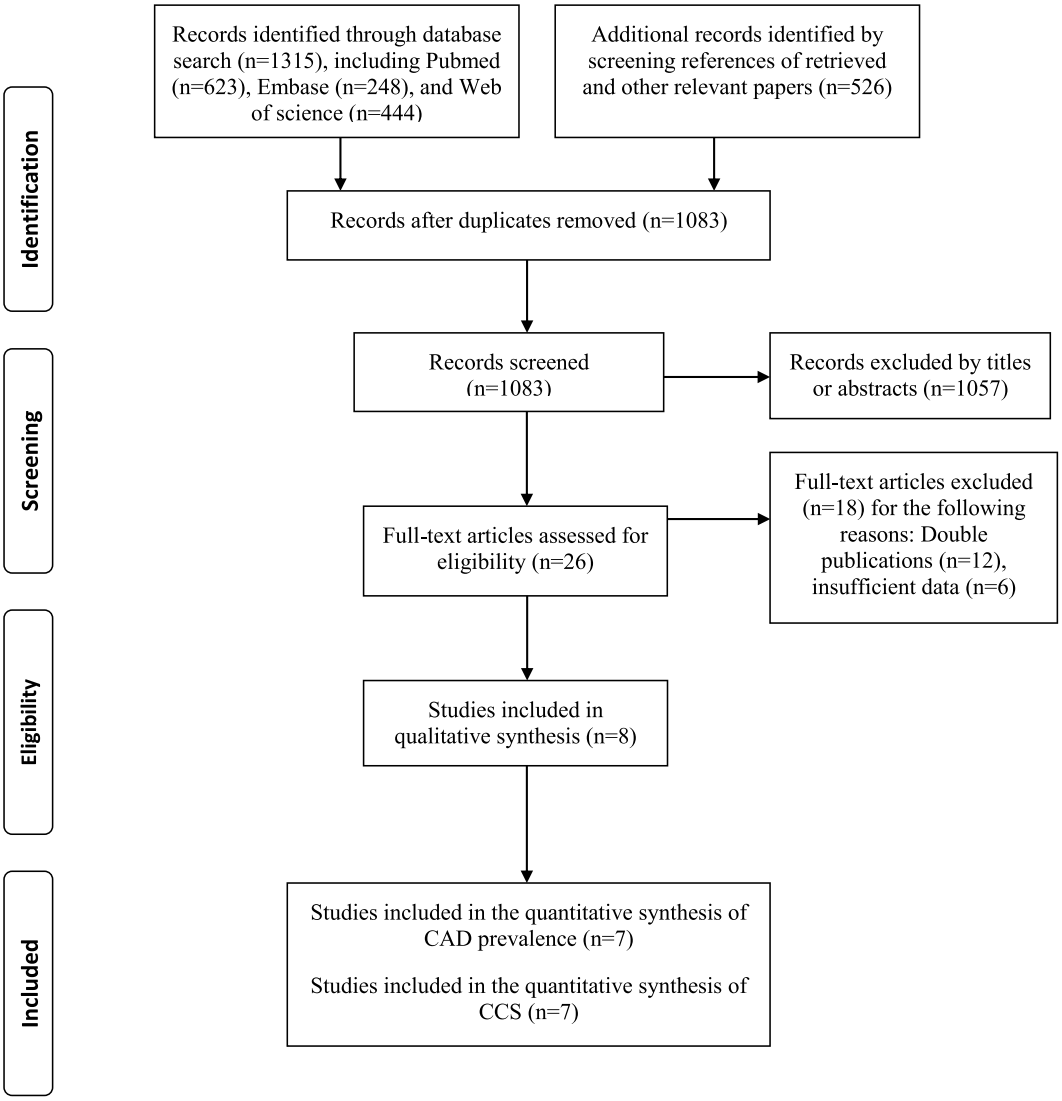

Fig. 1. Flow chart depicting the selection process of the systematic review. CAD = coronary artery disease; CCS: coronary artery calcium score.

and higher short-term mortality [24].

Increased mortality in patients with RA is mainly driven by CAD and the risk of myocardial infarction in RA is comparable to that of subjects with type 2 diabetes or individuals without RA that are 10 years older [1,2]. The risk is correlated with RA duration and activity, and treatment with methotrexate, a disease-modifying antirheumatic agent, and tumour necrosis factor-α (TNF) antagonists, respectively, have been associated with reduced risk of myocardial infarction, stroke and cardiovascular death [1,25,26]. In agreement with these observations, studies included in the present systematic review found that in RA patients without prior CAD, the duration and activity of RA were associated with higher CCS and use of methotrexate was linked with absence of CAD [12–14,18,19]. Also, CCS > 100 was observed more frequently in patients with RA and it is notable that in comparison with patients with CCS = 0, CCS > 100 has been associated with increased independent risk of major cardiovascular events in subjects with RA and systemic lupus in excess of the increased risk linked with CCS > 100 in the general population [8,9]. In addition, a report included in the present review showed that RA disease activity was associated with the presence of high-risk (non-calcified or mixed) coronary artery plaques [18]. Such plaques are characterized by increased inflammation and in patients dying from acute myocardial infarction, culprit coronary arteries from individuals with RA display increased lymphocyte and mast cell infiltration compared to controls [27]. Unstable plaque characteristics are also more prevalent in carotid arteries of patients with active RA compared to those with RA in remission and demonstration by CCTA of more unstable coronary plaques in patients with active RA compared to controls without RA provides both a link between RA disease activity and risk of CAD, and support for the role of shared inflammatory mechanisms in the two diseases [1,28].

In current guidelines for cardiovascular disease risk management in individuals with RA, optimal disease control is recommended to achieve risk reduction and screening for asymptomatic atherosclerotic plaques by use of carotid artery ultrasound examination may be considered as part of the risk evaluation, whereas potential utility of cardiac computed tomography is not mentioned [29]. Although carotid plaques predict incident acute coronary syndromes in patients with RA, a recent study of patients with inflammatory joint disease (mostly RA) referred for CCTA showed that the presence of carotid plaques was not sufficient to reliably identify RA patients with CAD [30,31]. Along this line, evidence suggests that in patients with axial spondylarthritis, carotid plaques are observed in a considerable number of subjects with CCS = 0, indicating that carotid artery ultrasound examination may be more suitable for cardiovascular risk stratification in these patients [32]. Notably, although the increased risk of acute coronary syndrome in subjects with RA has declined in recent years in the wake of new

Table 2
Characteristics of included studies.

Author and publication year	N (RA/ controls)	Type of controls without RA	Ethnicity RA%/ controls%	RA duration (median [range] or mean ± SD years)	Medications used for RA	Type of CT scanner
Chung 2005	71/86	Age-, sex-, and race- matched volunteers	White 84.5/86.1	>10	Corticosteroids Methotrexate Hydroxychloroquine	EBCT
Kao 2008	105/105	Age-, and race-matched healthy women	Caucasian 96.2/ 96.2	15.7 ± 10.4	Corticosteroids 44% Hydroxychloroquine 22% Immunosuppresants 60% Anti-TNF-α 41% NSAID 71%	EBCT
Giles 2009	195/1073	Patients from a population study	Caucasian 85.8/ 54 African American 8.2/49.7	9 (4–17)	Glucocorticoids 38% Conventional DMARD 48% Biologic DMARD 10% NSAID 65%	MDCT
Wang 2009	85/85	Age- and sex-matched subjects from community health screening programme	Chinese 100/100	12.6 ± 10.8	Corticosteroids 17% Methotrexate 61% NSAID 22%	MDCT
Ma 2010	47/47	Age-, sex-, and traditional CV risk factors-matched subjects screened for CAD	Chinese: 40.4/ 63.8 Malay: 25.5/23.4 Iban: 17%/2.1 Bidayuh: 15/6.3	3 (interquartile range 5.5)	NA	MDCT
Abdel-Khalek 2011	60/20	Age- and sex-matched healthy controls	NA	10.25 ± 3.13	NA	MDCT
Karpouzas 2014	150/150	Age- and sex-matched subjects screened for CAD	NA	11 ± 8	Prednisolone 35% DMARD Methotrexate	MDCT
Paccou 2014	75/75	Age- and sex-matched subjects	NA	12.9 ± 9.2	Glucocorticoids 29% Conventional DMARD 83% (incl. methotrexate 76%) Biologic DMARD 67% (incl. anti-TNF-α 41%) NSAID 28%	MDCT

CAD = coronary artery disease; CV = cardiovascular; DMARD = Disease-modifying anti-rheumatic drugs; EBCT = electron beam computed tomography; MDCT = multi-detector computed tomography; NA = not available; NSAID = Non-steroidal anti-inflammatory drugs; RA = rheumatoid arthritis; SD = standard deviation; TNF = tumour necrosis factor.

therapeutic options and aggressive treatment aimed at prompt RA remission, the excess relative risk of acute coronary syndrome has remained unchanged [33]. Therefore, there is a continuing need to improve CAD risk stratification in RA and the potential of CCS and CCTA to refine such risk algorithms remains to be defined.

4.1. Limitations

The present systematic review and meta-analysis has inherent limitations including, for example, studies with small-sized patient populations with differences in RA duration, activity and treatment history. Our results may also have been skewed by use of RA patients and/or controls with (potentially divergent) clinical indication for coronary computerized tomography and by inclusion of RA patients treated with methotrexate and biological agents, e.g. TNF antagonists (Table 2). Indeed, methotrexate has been linked to reduced risk of myocardial infarction and was associated with absence of CAD in one study [19], while on the other hand, such treatment could potentially allow for inclusion of more RA patients without prior history of clinical CAD despite having prevalent disease [25]. In patient with psoriasis, another chronic inflammatory disease, TNF antagonists have been associated with reduced progression of both CCS and plaque volume [34]. Also, use of statins and antithrombotic agents can reduce risk of clinical CAD and influence CCS and CCTA findings, e.g., statin therapy is associated with increased CCS, reduced plaque progression and reduction of high risk low attenuation (lipid rich and/or with necrotic core) plaques [35]. However, most included studies had no information on statins and aspirin, and in the few that did [12,13], use of these agents was very limited in agreement with the notion that included subjects had no history of CAD. Moreover, some unmeasured CAD risk confounders that are known to be more prevalent in subjects with RA, e.g., depression, low socio-economic status, and low cardiorespiratory fitness, may lead to overestimation of the effect of RA per se [36–38]. Finally, more studies examining the incremental prognostic value of CAD assessment by cardiac computed tomography in RA patients are warranted.

5. Conclusion

This systematic review and meta-analysis indicated that in patients with RA, subclinical CAD is more prevalent, with higher mean CCS, more multivessel disease, and more high-risk plaques compared to controls.

Financial support

PRH is supported by the LEO Foundation and a Borregaard Clinical Scientist Fellowship from the NOVO Nordisk Foundation. JA has received speaker fees from Novartis-Health Care. The funding sources did not have influence on any part of the work.

Author contributions

PRH conceived the study, contributed to the literature search, and wrote the first draft; JA conducted the literature search and data extraction; MF validated the search results. All authors contributed to the final manuscript.

Table 3
Study quality assessment using the checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS).

Author and publication year	Source of data	Sampling	Number of variables	Loss of follow-up%	Missing data %	Blinding of imaging analysis	Statistics and modelling methods	Discussion of concerns leading to possible bias
Chung 2005	Cross-sectional design comparing non-randomized RA patients with matched control subjects	Consecutive	12	0%	0%	Yes	Participant power calculation, logistic regression	1. Lack of temporal relationship between exposures and outcomes 2. Lack of information about risk factors
Kao 2008	Cross-sectional design comparing RA patients and matched controls recruited from institutional registries	Non-selective recruitment	26	0%	0%	Unclear	Logistic regression	1. Lack of information about risk factors 2. Lack of information on non-calcified plaques 3. Most subjects were Caucasians
Giles 2009	Cross-sectional design comparing RA cohort and matched cohort of controls	Unclear	13	0%	0%	Yes	Participant power calculation, Poisson regression	1. Possibility that some controls with rheumatic diseases were not excluded 2. Selection bias due to different referral patterns
Wang 2009	Cross-sectional design comparing non-randomized RA patients with matched controls	Consecutive	23	0%	0%	Yes	Logistic regression	1. Lack of temporal relationship between exposures and outcomes 2. Severity of RA was not well-assessed
Ma 2010	Cross-sectional design comparing non-randomized RA patients with matched controls	Consecutive	13	0%	0%	Yes	Chi-square test and Spearman correlation	1. Small population with short period of disease 2. Larger study needed
Abdel-Khalek 2011	Cross-sectional design comparing RA patients selected from outpatient clinic with matched healthy volunteers	Unclear	22	0%	0%	Unclear	ANNOVA	Study limitations were not discussed
Karpouzas 2014	Cross-sectional design comparing RA patients with matched controls	Prospective single centre	25	0%	0%	Yes	Logistic regression	1. Causal relationships cannot be inferred 2. Predominant (90%) female population
Paccou 2014	Cross-sectional design comparing RA patients with matched volunteers	Unclear	15	0%	0%	Unclear	Logistic regression	1. Causal relationships cannot be inferred 2. Non-calcific plaques could not be identified.

Assessment using the checklist for Critical Appraisal.

Table 4
Characteristics of rheumatoid arthritis (RA) study populations compared with controls.

Characteristics	Number of studies providing data	n RA vs. controls (means ± SDs or n [%])	p-Values
Age (years)	8	53.7 ± 8.9 vs. 53.8 ± 8.0	0.99
Gender (Female)	8	632/788 (80%) vs. 996/1641 (60.0%)	0.17
BMI (kg/m^2)	6	26.5 ± 4.5 vs. 26.9 ± 4.3	0.14
Total cholesterol (mg/dL)	6	4.9 ± 0.7 vs. 4.5 ± 0.6	0.08
Smoking	6	81/680 (11.9%) vs. 203/1523 (13.3%)	0.77
Diabetes	5	46/552 (8.0%) vs. 178/1430 (12.4%)	0.37
Hypertension	6	289/653 (44.2%) vs. 762/1546 (49.2%)	0.63
Prevalence of CAD	7	373/728 (51.2%) vs. 777/1621 (47.9%)	0.021

BMI = body mass index; CAD = coronary artery disease; SD = standard deviation.

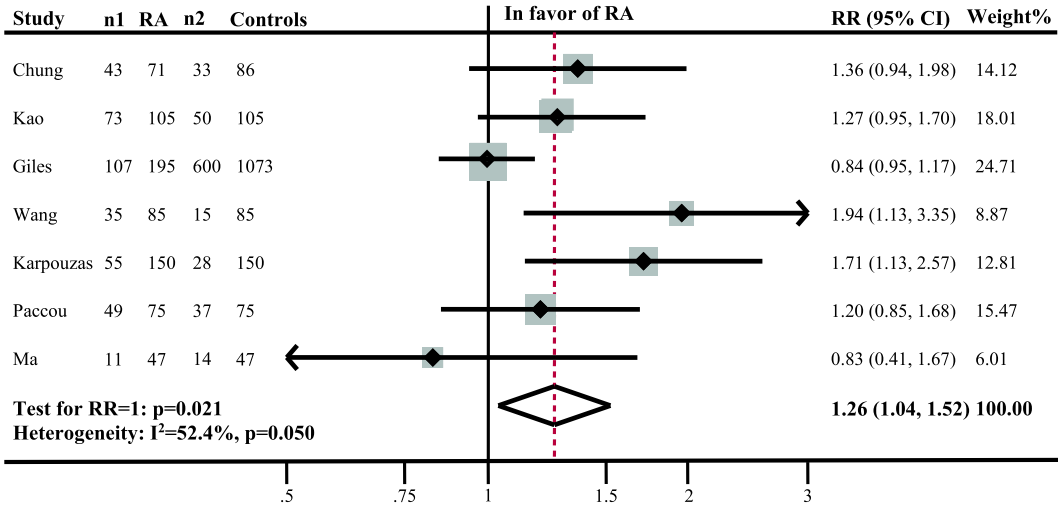

Fig. 2. Meta-analysis of prevalence of asymptomatic coronary artery disease (CAD) in patients with rheumatoid arthritis (RA) compared with controls. n1 = number of psoriasis patients with CAD; n2 = number of controls with CAD; RR = risk ratio; CI = confidence interval.

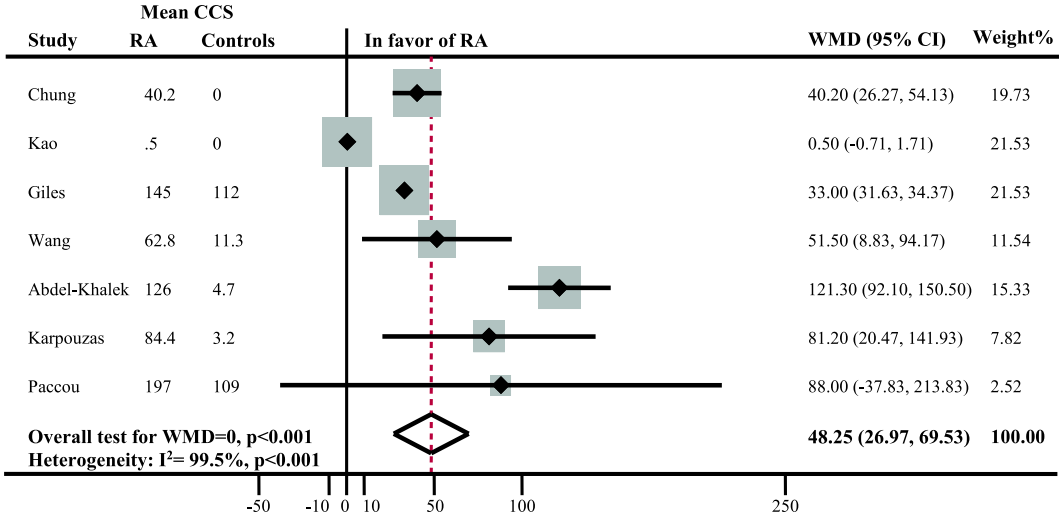

Fig. 3. Meta-analysis of the weighted mean differences (WMDs) of coronary calcium score in patients with rheumatoid arthritis (RA) compared with controls. CCS = coronary calcium score (Agatston units); CI = confidence interval.

Acknowledgements

The LEO Foundation and the NOVO Nordisk Foundation are acknowledged for support.

Declaration of interest

None.

References

[1] Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheum 2015;11:693–704.
[2] Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus – A Danish nationwide cohort study. Ann Rheum Dis 2011;70:929–34.
[3] Wang P, Guan SY, Xu SZ, Li HM, Leng RX, Li XP, et al. Increased carotid intima-media thickness in rheumatoid arthritis: an update meta-analysis. Clin Rheumatol 2016;35:315–23.

[4] Di Minno MN, Ambrosino P, Lupoli R, De Minno A, Tasso M, Peluso R, et al. Clinical assessment of endothelial function in patients with rheumatoid arthritis; a meta-analysis of literature studies. Eur J Clin Med 2015;26:835–42.
[5] Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol 2012;110:420–4.
[6] Crowson CS, Rollefstad S, Kitas GD, van Riel PL, Gabriel SE, Semb AG, et al. Challenges of developing a cardiovascular risk calculator for patients with rheumatoid arthritis. PLoS One 2017 Mar 23;12(3):e0174656.
[7] Crowson CS, Gabriel SE, Semb AG, van Riel PL, Karpouzas G, Dessein PH, et al. Rheumatoid arthritis-specific cardiovascualr risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatol 2017;57:1102–10.
[8] Yiu KH, Mok MY, Wang S, Ooi GC, Khnog PL, Lau CS, et al. Prognostic role of coronary calcification in patients with rheumatoid arthritis and systemic lupus erythromatosus. Clin Exp Rheumatol 2012;30:345–50.
[9] Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial groups or ethnic groups. N Engl J Med 2008;358:1336–45.
[10] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015 Jan 1;4:1.
[11] Moons KGM, de Groot JAH, Bouwmeester W, Vergouwe Y, Mallett S, et al. Critical appraisal and data extration for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med 2014;11:e1001744.
[12] Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis – relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;52:3045–53.
[13] Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am J Cardiol 2008;102:755–60.
[14] Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison with the multi-ethnic study of atherosclerosis. Arthritis Res Ther 2009;11(2):R36.
[15] Wang S, Yiu KH, Mok MY, Ooi GC, Khong PL, Mak KF, et al. Prevalence and extent of calcification over aorta, coronary and carotid arteries in patients with rheumatoid arthritis. J Intern Med 2009;266:445–52.
[16] Ma NH, Teh CL, Rapaee A, Lau KB, Fong AY, Hi S, et al. Subclinical coronary artery disease in Asian rheumatoid arthritis patients who were in remission: a pilot study. Int J Rheum Dis 2010;13:223–9.
[17] Abdel-Khalek MA, El-Barbary AM, Essa SA, Ghobashi AS. Serum hepcidin: a direct link between anemia of inflammation and coronary artery atherosclerosis in patients with rheumatoid arthritis. J Rheumatol 2011;38:2153–9.
[18] Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis 2014;73:1797–804.
[19] Paccou J, Renard C, Liabeuf S, Kamel S, Fardellone P, Massy ZA, et al. Coronary and abdominal aorta calcification in rheumatoid arthritis: relationships with traditional cardiovascular risk factors, disease characteristics, and concomitant treatments. J Rheumatol 2014;41:2137–44.
[20] Arnett FC, Edworthy S, Bloch D, McShane D, Fries J, Cooper N, et al. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
[21] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed-tomography. J Am Coll Cardiol 1990;15:827–32.
[22] Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of cardiovascular computed tomography guidelines committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr 2016;10:435–49.
[23] Aubry MC, Maradit-Kremers H, Reinalda MS, Crowson CS, Edqards WD, Gabriel SE. Differences in atherosclerotic coronary heart disease between subjects with and without rheumatoid arthritis. J Rheumatol 2007;34:937–42.
[24] Mantel Ä, Holmqvist M, Jernberg T, Wållberg-Jonsson S, Askling J. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term prognosis. Eur Heart J 2015;36:3413–22.
[25] Micha R, Imumura F, Von Ballmoos W, Solomon DH, Hernán MA, Ridker P, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 2011;108:1362–70.
[26] Westlake SL, Colebatch AN, Blaird J, Curzen N, Kiely P, Quinn M, et al. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology 2011;50:518–31.
[27] van den Oever IAM, Van Sijl AM, Baylan U, ter Wee MM, Schalkwijk CG, Krijen PAJ, et al. Comparing inflammatory cell density in the myocardium and coronary arteries in rheumatoid arthritis patients versus controls with myocardial infarction: a post-mortem case-control study. Int J Cardiol 2016;209:74–6.
[28] Semb AG, Rollefstad S, Provan SA, Kvien TK, Stranden E, Olsen IC, et al. Carotid plaque characteristics and disease activity in rheumatoid arthritis. J Rheumatol 2013;40:359–68.
[29] Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, et al. Södergren A, et al. EULAR recommendations for cardiovascular disease risk mangement in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17–28.
[30] Evans MR, Escalente A, Battafarano DF, Freeman GL, O'Leary DH, del Rincón I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011;63:1211–20.
[31] Svanteson M, Rollefstad S, Kløw NE, Hisdal J, Ikdahl E, Semb AG, et al. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. RMD Open 2017;3:e000544https://doi.org/10.1136/rmdopen-2017-000544.
[32] Rueda-Gotor J, Llorca J, Corrales A, Parra JA, Portilla V, Genre F, et al. Cardiovascular risk stratification in axial spondylarthritis: carotid ultrasound is more sensitive than coronary artery calcification score to detect high-cardiovascular risk axial spodyloarthritis patients. Clin Exp Rheumatol 2018;36:73–80.
[33] Holmqvist M, Ljung L, Askling J. Acute coronary syndrome in new-onset rheumatoid arthritis: a population-based nationwide cohort study of time trends in risks and excess risks. Ann Rheum Dis 2017;76:1642–7.
[34] Hjuler KF, Bøttcher M, Vestergaard C, Bøtker HE, Iversen L, et al. Association between changes in coronary artery disease progression and treatment with biological agents for severe psoriasis. JAMA Dermatol 2016;152:1114–21.
[35] Andelius L, Mortensen MB, Nørgaard BL, Abdulla J. Impact of statin therapy on coronary plaque burden and composition assessed by computed tomographic angiography: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imag 2018;19:850–9.
[36] Murphy LB, Sacks JJ, Brady TJ, Hootman JM, Chapman DP. Anxiety and depression among US adults with arthritis: prevalence and correlates. Arthritis Care Res 2012;64:968–76.
[37] Shih M, Hootman JM, Kruger J, Helmick CG. Physical activity in men and women with arthritis National Health Interview Survey, 2002. Am J Prev Med 2006;30:385–93.
[38] Jacobs P, Bisonette R, Guenther LC. Socioeconomic burden of immune-mediated inflammatory diseases-focusing on work productivity and disability. J Rheumatol Suppl 2011;88:55–61.