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Heart involvement in Rheumatoid Arthritis: Systematic review and meta-analysis☆,☆☆

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ABSTRACT

Objective: The aim of our study was to conduct a systematic review with meta-analysis of the current case–control studies about the valvular and pericardial involvement in patients with Rheumatoid Arthritis (RA), asymptomatic for cardiovascular diseases.
Methods: Case–control studies were identified by searching PubMed (1975–2010) and the Cochrane Central Register of Controlled Trials (CENTRAL) (1975–2010). Participants were adult patients with RA asymptomatic for cardiovascular diseases, and the outcome measure was the presence of cardiac involvement.
Results: Quantitative synthesis included 10 relevant studies out of 2326 bibliographic citations that had been found. RA resulted significantly associated to pericardial effusion (OR 10.7; 95% CI 5.0–23.0), valvular nodules (OR 12.5; 95% CI 2.8–55.4), tricuspidal valve insufficiency (OR 5.3; 95% CI 2.4–11.6), aortic valve stenosis (OR 5.2; 95% CI 1.1–24.1), mitral valve insufficiency (OR 3.4; 95% CI 1.7–6.7), aortic valve insufficiency (OR 1.7; 95% CI 1.0–2.7), combined valvular alterations (OR 4.3; 95% CI 2.3–8.0), mitral valve thickening and/or calcification (OR 5.0; 95% CI 2.0–12.7), aortic valve thickening and/or calcification (OR 4.4; 95% CI 1.1–17.4), valvular thickening and/or calcification (OR 4.8; 95% CI 2.2–10.5), and mitral valve prolapse (OR 2.2; 95% CI 1.2–4.0).
Conclusions: Our systematic review pointed out the strength and the grade of both pericardial and cardiac valvular involvement in RA patients. Our findings underscore the importance of an echocardiographic assessment at least in clinical research when RA patients are involved. Moreover, further research is needed to understand the possible relationship of our findings and the increased cardiovascular mortality.
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1. Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that affects joints causing deformities, severe disability and premature mortality [1,2]. This disease has a high social and economic burden. Indeed, about 1.3 million adults are affected by RA in the United States [3]. The world prevalence of RA might be around 0.3–1.2% [4]. Recently the Swedish patients register [5] has shown a RA cumulative prevalence of 0.77% (women 1.16% men 0.44%) confirming above mentioned assumptions. In this disease, the synovial membrane is the main target, although extra-articular manifestations can be found including the cardiac ones. Pericarditis is the cardiac manifestation most readily recognized, but myocardial disease, coronary vasculitis, diastolic dysfunction, accelerated atherosclerosis and valvular lesions of the heart have also been reported [6]. The premature mortality among patients with RA is frequently due to cardiovascular disease [7], primarily ischemic heart disease [8] and congestive heart failure [9]. A recent meta-analysis of our team showed that rheumatoid patients have a higher left ventricular mass than controls [10]. Moreover, in rheumatoid patients without overt cardiovascular disease, we previously reported pericardial, valvular, and aortic root involvement that we clinically defined as “silent rheumatoid heart disease” [11]. Recently, Yiu et al. [12] have found out a significant association between Rheumatoid Arthritis and valvular calcifications. This study used multidetector computed tomography and has also pointed out that the presence of mitral valve calcification independently predicted the occurrence of premature atherosclerosis. On the other hand, several echocardiographic studies have been published in the last two decades on this issue. So that, summarizing evidence from all these studies may be useful to understand the effect of the

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disease on cardiac structures of rheumatoid patients almost partially in the pre-biological era.

The aim of our study was to perform a systematic review and meta-analysis of the current case–control studies based on echocardiographic assessment of valvular and pericardial involvement in patients with RA.

2. Materials and methods

2.1. Search strategy for identification of studies

The review was achieved following the Cochrane Collaboration Steps [13] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standard of reporting [14].

Sources of published data included electronic database such as PubMed-Medline (1975–July 2010) [15] and the Cochrane Central Register of Controlled Trials (CENTRAL) (1975–July 2010) [16]. The search strategy was as follows: "rheumatoid arthritis AND (heart OR ventricle OR ventricular OR valvular)" without any other restriction for reaching maximum recall. We controlled for the terms "pericardial or pericardium" but it did not add any further citation recall compared to the above mentioned search string.

2.2. Criteria for considering studies for this review

Retrieved citations were screened independently by two adjudicators (SC, SM) using titles of papers and abstracts. Once pertinent studies (that is according to the aim of this systematic review) were identified, the full publication was retrieved and reviewed independently by the two investigators to determine the suitability for final inclusion.

The reviewers were blinded to the names of authors, institutions or journals, and articles were independently selected for inclusion according to the prespecified selection criteria. No prejudice in study evaluation was made.

The type of studies considered to be included was controlled clinical trial with case–control design. Series of case, descriptive reports, cohort and uncontrolled studies were excluded from the analysis. Participants in the studies were adult patients with RA, asymptomatic for cardiovascular diseases.

Measured outcome was the proportion of patients with valvular and pericardial involvement.

2.3. Quality assessments

Methodological quality was assessed independently by two reviewers (SC, SM) using the STROBE (Strengthening the Reporting of Observational studies in Epidemiology Statement) recommendations [17], with special consideration on selection bias and detection bias. Performance bias was not considered because it concerns pharmacological studies. Moreover, loss to follow-up was not considered basing on the design of the included studies in this review (only case–control ones).

2.4. Data extraction and statistical analysis

Data on patients, methods, outcomes and results were extracted using a data extraction form (SM, LC). Disagreement was resolved by other adjudicator (SC). Data were analyzed using the STATA Version 9.0 and were presented as odds ratio (OR) along with their corresponding 95% confidence intervals (CI). Heterogeneity was investigated by using the I^2 statistic with significance set at $p<0.05$. Pooled ORs and 95% CIs were calculated using a random effect model or a fixed effect model according to heterogeneity. Bias of publication was evaluated by the Egger Regression Asymmetry Test and the Regression Asymmetry Plot.

3. Results

The search string that we used recalled 2326 bibliographic citations. They were screened, and 55 papers were retrieved because they were recognized as pertinent. Then, 16 studies were excluded because they were not case–control studies, 1 because it was a pharmacological study and 28 because they were not pertinent. So we identified 10 relevant papers. All of them were used for this systematic review. All the patients were asymptomatic for cardiovascular disease, and, after echocardiographic assessment, none was reported affected by more than slight–moderate hemodynamic valvular alterations (as regurgitation as stenosis). Fig. 1 shows the flow-diagram of the study selection process. Appendix 1 shows characteristics of studies that were included in this systematic review [11,18–26]. Appendix 2 shows the list of studies that were excluded.

We performed a meta-analysis for each of the following abnormalities: pericardial effusion, valvular nodules, valvular thickening and/or calcification (Fig. 2), tricuspidal valve insufficiency, aortic valve insufficiency, aortic valve stenosis, mitral valve stenosis, mitral valve prolapse

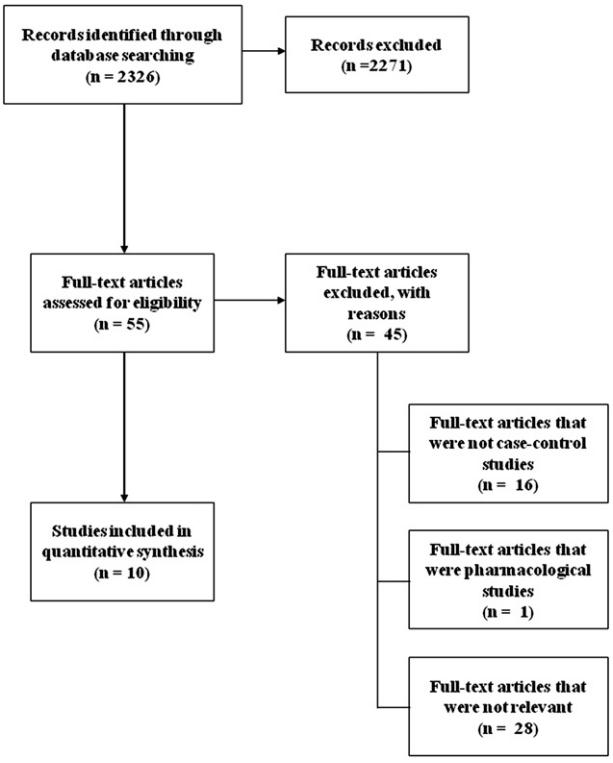

Fig. 1. Systematic review flow diagram according to the MOOSE standard: the flow chart shows the selection process regarding the retrieved citations; trials on treatment and studies not pertinent were excluded such as all the studies that were not controlled ones.

(Fig. 3), and combined valvular alterations (Fig. 4). Fig. 5 shows other four meta-analyses that were preformed about mitral valve thickening/calcification, aortic valve thickening/calcification, mitral valve prolapse, and mitral valve insufficiency. Pulmonary valve insufficiency and aortic valve prolapse were reported by only one study [18]. Thus, in this case, we did not perform any meta-analysis.

The fixed model was used for the following abnormalities: pericardial effusion, valvular nodules, valvular thickening and/or calcification, tricuspidal valve insufficiency, aortic valve insufficiency, aortic valve stenosis, mitral valve stenosis, and combined valvular alterations.

The random model was used for the following abnormalities: mitral valve insufficiency, mitral valve thickening and/or calcification, aortic valve thickening and/or calcification.

We preferred to use fixed and random models for mitral valve prolapse since the high I^2 (51.8%; $p<0.081$) even if not significant.

Table 1 shows the summary data of all the performed meta-analyses, including the Egger's test statistic for evaluation of the publication bias. Only in the case of aortic valve stenosis, we found a significant p value by the Egger's test (this test states a probable publication bias in this field of knowledge).

Our meta-analyses showed a higher risk of pericardial effusion and valvular nodules more than ten times in patients with RA compared with controls. Concerning data about tricuspidal valve insufficiency, aortic valve stenosis, and mitral valve thickening/calcification, meta-analyses showed an increased risk about five times more in patients with RA compared with controls. Moreover, data about valvular thickening and/or calcification, combined valvular alterations, and aortic valve thickening and/or calcification showed an increased risk about four times in patients with RA compared with controls. Data about mitral valve insufficiency showed an increased risk about three times in patients with RA compared with controls. A risk about twice in patients with RA compared with controls emerged from data about aortic valve insufficiency. Finally, data of meta-analyses did not show an increased risk about mitral valve stenosis,

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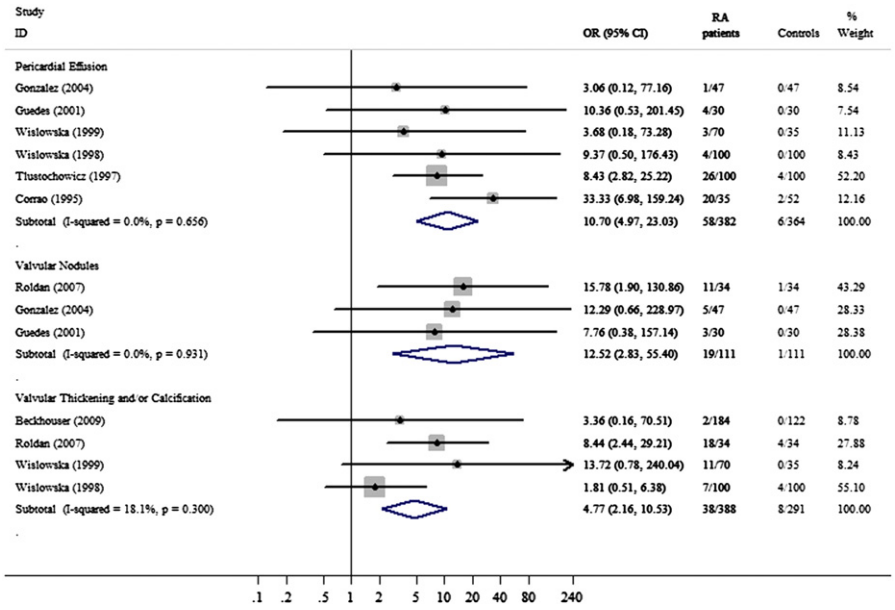

Fig. 2. Forest plot summarizing meta-analyses of pericardial effusion, valvular nodules and valvular thickening and/or calcification; the pooled odds ratios, represented by the diamonds, show a higher risk, in RA patients, of pericardial effusion, valvular nodules and valvular thickening and/or calcification (all the diamonds are on the right side to the equality line).

[OR (95% CI): 2.1 (0.7–6.9); p = 0.199], pulmonary valve insufficiency [OR (95% CI): 3.1 (0.1–79.2); p = 0.494], and aortic valve prolapse [OR (95% CI): 2.1(0.2–24.1); p = 0.561] in patients with RA compared with controls. About mitral valve prolapse, the meta-analysis showed a high grade of heterogeneity ($I^2 = 51.8\%$) even though it did not result significant [OR (95% CI): 2.2(0.8–6.1); p = 0.081]: in this case, we performed a

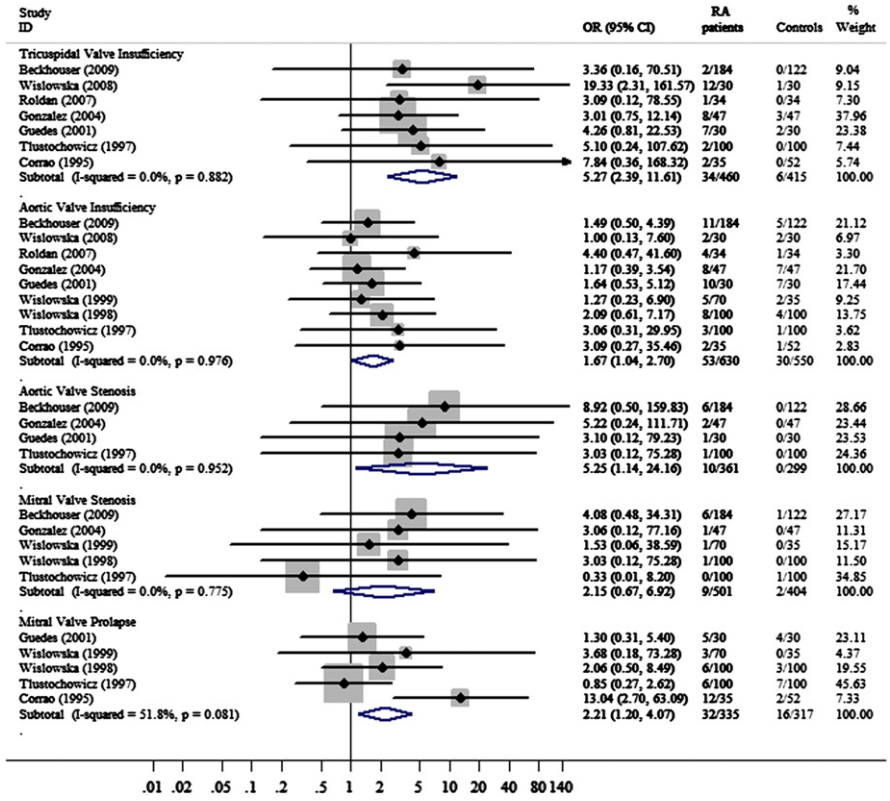

Fig. 3. Forest plot summarizing meta-analyses of tricuspidal valve insufficiency, aortic valve insufficiency, aortic valve stenosis, mitral valve stenosis and mitral valve prolapse; the pooled odds ratios, represented by the diamonds, show a higher risk, in RA patients, of tricuspidal and aortic valve regurgitation; the risk of aortic valve stenosis resulted higher in RA patients than controls such as the risk of mitral valve prolapse (however in this last case the I-squared resulted large even though not significant for heterogeneity; see Fig. 5 for the same meta-analysis on mitral valve prolapse applying the random-effect model).

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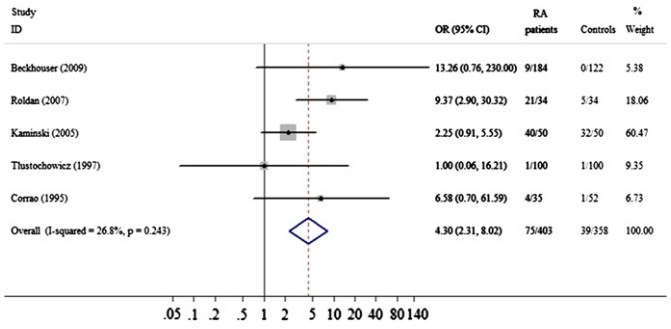

Fig. 4. Forest plot of combined valvular alteration; the pooled odds ratio, represented by the diamond, shows a higher risk, in RA patients, of combined valvular alteration (the diamond is on the right side to the equality line).

sensitive analysis using both the models (fixed and random); the two analyses showed different results with a potentially double risk in patients with RA compared with controls (Table 1).

4. Discussion

Various significant cardiac alterations have been detected by echocardiography in RA patient with no cardiac symptoms and/or clinical evidence of extra cardiac complaints. The extra-articular inflammatory process seems to involve the pericardium frequently and insidiously, even in the absence of symptoms. In fact, pericardial effusion is the most frequent abnormality, and it has been described as minimal pericardial effusion (end-diastolic pericardial–epicardial separation up to 4 mm) or overt pericardial effusion (end-diastolic pericardial–epicardial separation more than 4 mm) [11].

The other main alterations are mitral and aortic valve thickening, mitral valve prolapse with or without insufficiency, isolated valvular insufficiency and aortic root abnormalities [11], (i.e. enlargement of almost one sinus of Valsalva). Abnormal valve echoes in RA patients might be due to fibrosis of the valve structures for extra-articular inflammatory process [11]. Beyond these valvular alterations, left ventricular diastolic filling abnormalities have been observed in spite of normal left ventricular systolic function. This might be clinically very important because diastolic dysfunction has been recognized as a primary cause of congestive heart failure that is highly prevalent in RA patients. In these patients, diastolic dysfunction seems to be related with structural abnormalities of the left ventricle, in particular with changes regarding left ventricular mass, interventricular septum thickening and posterior wall thickening [27]. Also, Rudominer et al., in a recent study, have described the association between AR and an increased left ventricular mass [28], and this increase has been confirmed by our recent meta-analysis [10].

Thus, five alterations at least seem to be typical of RA patients without any symptom of cardiac disease: 1) pericardial effusion, 2) valvular thickening and nodules, 3) isolated valvular insufficiency, 4) aortic root alteration, and 5) structural (increased left ventricular mass) and functional (diastolic dysfunction) left ventricular changes. These changes are variously combined in each patient. Hence, we believed that it is possible to represent this heart involvement such as "silent rheumatoid heart disease". On the other hand, abnormalities in left ventricular myocardial structure and diastolic function are clinically very important. Indeed, these abnormalities are also correlated to a higher risk of both cardiac failure and cardiovascular mortality in patients with RA. However, these

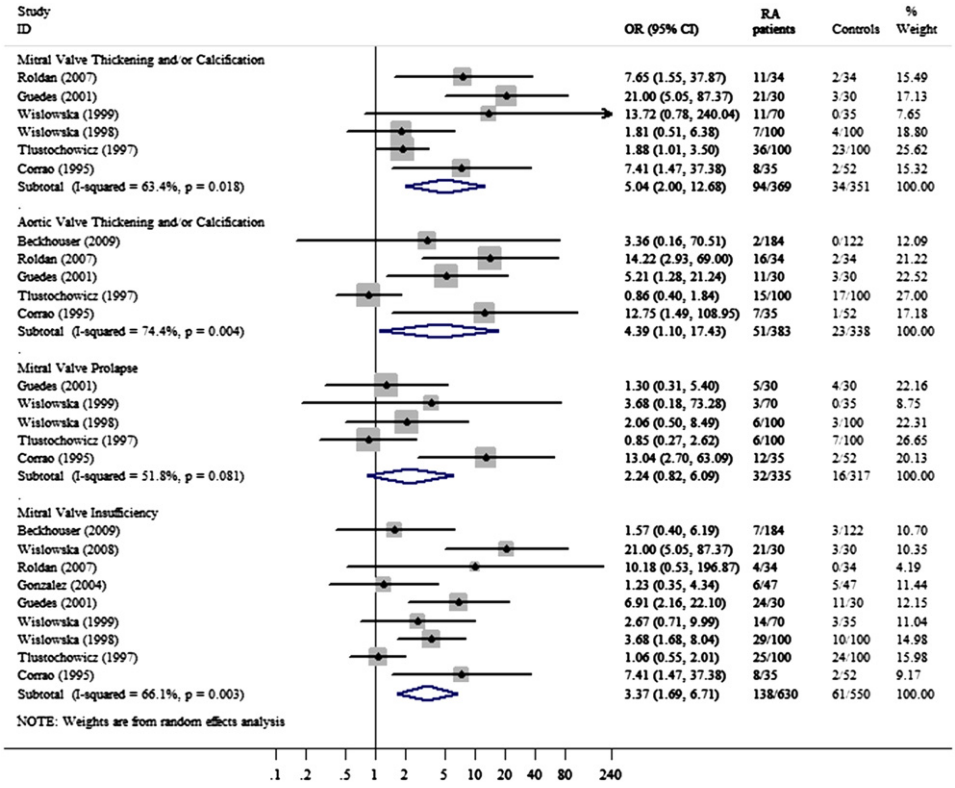

Fig. 5. Forest plot summarizing meta-analyses of mitral prolapse, mitral valve insufficiency, mitral valve thickening and/or calcification and aortic valve thickening and/or calcification; the pooled odds ratios, represented by the diamonds, show a higher risk, in RA patients, of mitral valve insufficiency, mitral valve thickening and/or calcification and aortic valve thickening and/or calcification except for mitral valve prolapse (note that in this plot the random effect model was applied even though heterogeneity for all the included studies did not result to a statistical significance; see Fig. 3 for the same meta-analysis on mitral valve prolapse applying the fixed-effect model).

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Table 1
Summary data of all the performed meta-analyses. Odds ratios (ORs) and their 95% confidence intervals, p values concerning statistical significance of ORs, the I^2 statistic, p values concerning heterogeneity, and p values of the Egger's test are shown. The Egger's test represents the statistic to evaluate publication bias.

Ecocardiographic abnormalities	Pooled OR[a] (95% CI[b])	p	I^2[c] (%)	p (heterogeneity)	Egger's test[d] p
Pericardial effusion	10.698 (4.969–23.033)	0.000	0.0	0.656	0.746
Valvular nodules	12.518 (2.828–55.404)	0.001	0.0	0.931	0.283
Valvular thickening and/or calcification	4.773 (2.163–10.534)	0.000	18.1	0.300	0.702
Mitral valve insufficiency	3.369 (1.691–6.710)	0.001	66.1	0.003	0.178
Tricuspidal valve insufficiency	5.265 (2.388–11.609)	0.000	0.0	0.882	0.727
Aortic valve insufficiency	1.673 (1.036–2.703)	0.035	0.0	0.976	0.069
Pulmonary valve insufficiency[e]	3.102 (0.121–79.228)	0.494	n.a.[f]	n.a.[f]	n.a.[f]
Aortic valve stenosis	5.249 (1.140–24.165)	0.033	0.0	0.952	0.009
Mitral valve stenosis	2.151 (0.669–6.916)	0.199	0.0	0.775	0.153
Mitral valve prolapse (fixed effect model)	2.208 (1.200–4.065)	0.011	51.8	0.081	0.613
Mitral valve prolapse (random effect model)	2.241 (0.825–6.091)	0.114	51.8	0.081	0.613
Aortic valve prolapse[e]	2.071 (0.178–24.148)	0.561	n.a.[f]	n.a.[f]	n.a.[f]
Combined valvular alterations	4.303 (2.310–8.018)	0.000	26.8	0.243	0.552
Mitral valve thickening and/or calcification	5.038 (2.002–12.680)	0.001	63.4	0.018	0.182
Aortic valve thickening and/or calcification	4.386 (1.104–17.430)	0.036	74.4	0.004	0.212

[a] OR: odds ratio.
[b] CI = confidence interval.
[c] I^2 = as a measure of statistical heterogeneity.
[d] Egger's test for publication bias.
[e] Only one study was recognized.
[f] n.a. = not assessable.

aspects related to the left ventricle structure and function, although very important, were not the object of this systematic review, but further investigation about this issue is hoped for completing the whole picture of the heart involvement in RA.

The results of this systematic review with meta-analysis have shown some unclear areas of literature about pulmonary valve insufficiency and aortic valve prolapse (investigated by only one study), and aortic valve stenosis (publication bias was detected). Another gray zone regards mitral valve prolapse. Indeed, we found an intermediate grade of heterogeneity that involved contrasting results when different meta-analysis models were applied. While, according to the findings of this systematic review, data are substantially strong concerning an increased risk of both pericardial involvement and aortic and mitral valvular alterations in RA patients compared to healthy controls. In particular, there was a strong evidence of pericardial effusion and mitral or aortic regurgitation as well as valvular nodules and isolated or combined valvular thickening/calcifications. Moreover, our systematic review fits with clinical studies recruiting patients mainly followed-up in the pre-biological drug era. This represents a chance to evaluate actual effects on the heart of the underlying phlogistic rheumatoid process without shadowing by the powerful biological drugs. On the other hand, the paramount importance of our findings lies in the fact that the presence of aortic and mitral valvular calcifications has been associated with cardiovascular events in the general population [29,30]. Indeed, Yiu et al. recently [12] demonstrated that cardiac valvular calcifications in patients with RA and Systemic Lupus Erythematosus predict the occurrence of premature atherosclerosis with arterial calcification. For the first time, our systematic review has documented the grade and strength of the association between pericardial and cardiac valvular alterations, in particular valvular calcifications, and RA. These findings could be very useful for further research that would explain the highest cardiovascular morbidity and mortality in this kind of patients.

In conclusion, we found a significant valvular and pericardial involvement in RA patients compared with control samples. All seems to represent the cardiac expression of the same underlying phlogistic process typical of RA disease. This should be considered a cornerstone for future research in the field of RA where echocardiographic assessment should be considered as part of the instrumental assessment of the recruited patients. However, further research is needed to understand the possible relationship of our findings and the increased cardiovascular mortality in this kind of patients. Finally, we think that the knowledge of presence and kind of unrecognized cardiac abnormalities in asymptomatic patients might be important for the correct management of RA patients.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

Appendix 1. Characteristics of the studies included in the quantitative synthesis

Author, publication year, country	Design	Study's objective	Participants
Beckhauser AP et al. 2009, Brazil	Case–control	To verify the frequency of valvular heart involvement in Rheumatoid Arthritis patients by trans-thoracic echocardiographic examination.	184 rheumatoid patients (17 men, 167 women; mean age 48.2 ± 13.9 yrs; mean duration of disease 8.4 ± 7.4 yrs) from the Rheumatology Unit of Hospital Evangelico de Curtiba; 122 controls (18 men, 104 women; mean age 51.5 ± 14.4 yrs).
Wislowska M et al. 2008, Poland	Case–control	To assess systolic and diastolic function of the left ventricle in Rheumatoid Arthritis patients, by trans-thoracic echocardiographic examination, and also estimate whether there is a correlation between the duration and severity of Rheumatoid Arthritis and the degree of left ventricle diastolic dysfunction.	30 rheumatoid patients (5 men, 25 women; mean age 51.8 ± 7.6 yrs; mean duration of disease 12.5 ± 9.3 yrs) from the Rheumatologic Outpatient Department of the central clinical hospital in Warsaw; 30 controls (5 men, 25 women; mean age 51.7 ± 7.6 yrs).

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Appendix 1 (*continued*)

Author, publication year, country	Design	Study's objective	Participants
Roldan CA et al. 2007, New Mexico	Case–control	To characterize valvular heart disease associated with Rheumatoid Arthritis by trans-esophageal echocardiography.	34 rheumatoid patients (15 men, 19 women; mean age 50 ± 10 yrs; mean duration of disease 13 ± 7 yrs) from the University of New Mexico Health Science Center in Albuquerque; 34 controls (16 men, 18 women; mean age 42 ± 6 yrs).
Kamiński G et al. 2005, Poland	Case–control	To assess the effect of rheumatoid process on the heart in patients with Rheumatoid Arthritis without clinically over features of heart disease by trans-thoracic echocardiographic examination.	50 rheumatoid patients (6 men, 44 women; mean age 59.4 ± 11.1 yrs; mean duration of disease 10.7 ± 8.7 yrs) in Warsaw; 50 controls (6 men, 44 women; mean age 59.2 ± 11.2 yrs).
Gonzalez-Juanatey C et al. 2004, Spain	Case–control	To assess the frequency of structural and functional abnormalities in long-term treated Rheumatoid Arthritis patients without clinically evident cardiovascular manifestation, by trans-thoracic echocardiographic examination.	47 rheumatoid patients (11 men, 35 women; mean age 59.2 ± 12.5 yrs; mean duration of disease 15.5 ± 8.5 yrs) from the Hospital Xeral-Calde, Lugo, in Northwest Spain; 47 controls (11 men, 36 women; mean age 58.6 ± 12.4 yrs).
Guedes C et al. 2001, France	Case–control	To assess the frequency and type of heart lesions in Rheumatoid Arthritis, coupling trans-thoracic echocardiography with trans-esophageal one.	30 rheumatoid patients (4 men, 26 women; mean age 57.8 ± 15.1 yrs; mean duration of disease 11 ± 8.7 yrs) from the Rheumatology Department of the Bobigny-Avicenne Teaching Hospital, France; 30 controls (4 men, 26 women; mean age 57.8 ± 15.0 yrs).
Wislowka M et al. 1999, Poland	Case–control	To assess cardiac abnormalities in two groups of Rheumatoid Arthritis patients, nodular and non nodular, by trans-thoracic echocardiographic examination.	35 nodular rheumatoid patients and 35 non nodular ones (14 men, 56 women; mean age 53.4 ± 9.4 yrs; mean duration of disease 9.4 ± 6.7 yrs) from the Rheumatology Outpatient Department of the Central Clinical Hospital in Warsaw; 35 controls with osteoarthrosis and spondyloarthrosis (7 men, 28 women; mean age 53.3 ± 9.4 yrs).
Wislowska M et al. 1998, Poland	Case–control	To assess cardiac abnormalities in Rheumatoid Arthritis patients by echocardiographic examination.	100 rheumatoid patients (18 men, 82 women; mean age 49.9 ± 11.3 yrs; mean duration of disease 9.4 ± 6.7 yrs) from the Rheumatology Outpatient Department of the Central Clinical Hospital in Warsaw; 100 controls with osteoarthrosis (n.8) and spondyloarthrosis (n.92) (18 men, 82 women; mean age 49.8 ± 11.1 yrs).
Tlustochowicz W et al. 1997, Poland	Case–control	To assess the clinical significance of heart lesions in Rheumatoid Arthritis patients by trans-thoracic echocardiographic examination.	100 rheumatoid patients (23 men, 77 women; mean age 55.7 ± 12.5 yrs; mean duration of disease 8.3 ± 8.0 yrs) from the University Hospital of Warsaw; 100 controls (23 men, 77 women; mean age 55.7 ± 12.7 yrs).
Corrao S et al. 1995, Italy	Case–control	To determine the nature and extent of cardiac involvement in Rheumatoid Arthritis patients with no symptoms of cardiac disease by trans-thoracic echocardiographic examination.	35 rheumatoid patients (5 men, 25 women; mean age 51 ± 11 yrs; mean duration of disease 5 ± 8 yrs) from Rheumatological outpatient clinic in Palermo; 52 controls (7 men, 45 women, mean age 51 ± 12 yrs).

Appendix 2. Excluded studies and the reason of exclusion

	Author, publication year	Title	Reason of exclusion
1	Berisha I, Berisha B, Krasniqi X, 2010	Cardiac and pulmonary alterations in patients with Rheumatoid Arthritis.	Not case–control study
2	Obradović-Tomasević B, Vujasinović-Stupar N, Tomasević R, 2009	The assessment of diastolic function in patients with Rheumatoid Arthritis.	Not case–control study
3	Sugiura T, Kumon Y, Kataoka H, Matsumura Y, Takeuchi H, Doi Y, 2008	Asymptomatic pericardial effusion in patients with Rheumatoid Arthritis.	Not case–control study
4	Dawson JK, Goodson NG, Graham DR, Lynch MP, 2000	Raised pulmonary artery pressures measured with Doppler echocardiography in Rheumatoid Arthritis patients.	Not case–control study
5	Nemchinov EN, Kanevskaia MZ, Chichasova NV, Telepneva LM, Krel' AA, 1994	Heart defects in Rheumatoid Arthritis patients (the results of a multiyear prospective clinico-echocardiographic study).	Not case–control study
6	Rowe IF, Gibson DG, Keat AC, Brewerton DA, 1991	Echocardiographic diastolic abnormalities of the left ventricle in inflammatory joint disease.	Not case–control study
7	Kelly CA, Bourke JP, Malcolm A, Griffiths ID, 1990	Chronic pericardial disease in patients with Rheumatoid Arthritis: a longitudinal study.	Not case–control study
8	Mody GM, Stevens JE, Meyers OL, 1987	The heart in Rheumatoid Arthritis: a clinical and echocardiographic study.	Not case–control study
9	Badui E, Jiménez J, Saldivar C, Mintz G, Lavalle C, Fraga A, 1987	The heart and Rheumatoid Arthritis. Prospective study of 100 cases.	Not case–control study
10	Kozáková M, Hradec J, Petrásek J, Kölbel F, Urbanová M, Dostál C, 1985	Cardiac involvement in progressive polyarthritis: an echocardiographic study.	Not case–control study
11	Svantesson H, Björkhem G, Elborgh R, 1983	Cardiac involvement in juvenile Rheumatoid Arthritis. A follow-up study.	Not case–control study
12	Nomeir AM, Turner RA, Watts LE, 1979	Cardiac involvement in Rheumatoid Arthritis. Follow-up study.	Not case–control study

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Appendix 2 (*continued*)

	Author, publication year	Title	Reason of exclusion
13	Devlin AB, Goldstraw P, Caves PK, 1978	Aortic valve replacement in rheumatoid aortic incompetence.	Not case–control study
14	David-Chaussé J, Blanchot P, Warin J, Dehais J, Bullier R, Texier JM, 1976	Atrioventricular blocks and Rheumatoid Arthritis.	Not case–control study
15	Thadani U, Iveson JM, Wright V, 1975	Cardiac tamponade, constrictive pericarditis and pericardial resection in Rheumatoid Arthritis.	Not case–control study
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