

## Cardiovascular Disorders in Autoimmune Disease

Delcio G Silva Junior

Universidade Federal de Mato Grosso do Sul, Mato Grosso do Sul, MS, Brazil

\*Corresponding Author : Delcio G Silva Junior, Universidade Federal de Mato Grosso do Sul, Mato Grosso do Sul, MS – Brazil,

E-mail: [delcio@clinicacdc.com.br](mailto:delcio@clinicacdc.com.br)

Received date : May 13, 2019; Accepted date : June 24, 2019; Published date : June 27, 2019.

Citation : Delcio G Silva Junior. (2019) Cardiovascular Disorders in Autoimmune Disease. J.Clinical Cardiology and Cardiovascular Interventions 2(1):

DOI: [10.31579/2641-0419/015](https://doi.org/10.31579/2641-0419/015)

Copyright : © 2019 Delcio G Silva Junior. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

The presence of Cardio Vascular Disease (CVD) impacts negatively on expectation and quality of life of the population, being one of the main causes of disability. Many of those who become cardiovascular patients throughout their life could have had different evolution if preventive attitudes were taken. Since 50's decade, Framingham studies have shown the importance of predetermining factors for CVD occurrence. The classical CVD risk factors such as diabetes, metabolic syndrome, dyslipidemia, hypertension, smoking and family history are well established as predictors of cardiovascular events.

The presence of Cardio Vascular Disease (CVD) impacts negatively on expectation and quality of life of the population, being one of the main causes of disability. Many of those who become cardiovascular patients throughout their life could have had different evolution if preventive attitudes were taken. Since 50's decade, Framingham studies have shown the importance of predetermining factors for CVD occurrence. The classical CVD risk factors such as diabetes, metabolic syndrome, dyslipidemia, hypertension, smoking and family history are well established as predictors of cardiovascular events.

However, in certain clinical conditions, traditional risk factors seem not to fully explain the incidence of CVD. Coronary artery disease and early atherosclerosis in young women with Systemic Lupus Erythematosus (SLE) are one of the best examples of how chronic inflammatory diseases can affect individuals who are normally poorly exposed to traditional risk factors. Even with the plurality of extra-articular manifestations of rheumatologic diseases, such as pulmonary hypertension and SLE encephalopathy, uveitis in spondyloarthritis, or as Achalasia in scleroderma, attention is being paid to the frequent cardiovascular system involvement in these patients, especially in the vascular territory [1].

**Keywords:** cardio vascular disease; systemic lupus erythematosus; autoimmune systemic inflammatory disease; coronary artery disease

**Abbreviations:** CVD - Cardio Vascular Disease; SLE - Systemic Lupus Erythematosus; AID - Autoimmune systemic Inflammatory Disease.

### Inflammation and Cardiovascular Lesion

The involvement of the cardiovascular system in patients with Autoimmune systemic Inflammatory Disease (AID) is not limited to the arterial territory. Pericarditis, myocarditis, systolic or diastolic ventricular dysfunction, valvulopathies, aortic ectasia and pulmonary hypertension [2] are some of examples of cardiovascular extension involvement, and are not exclusively related to the presence of traditional risk factors. Gabriel, S.E. in 2010 [3] for example, has shown that traditional risk factors explain 80% of cases of heart failure in people without rheumatoid arthritis (RA), but in people with RA they would be related to only 40% of cases of heart failure.

The correlation between classic autoimmune diseases (rheumatoid arthritis, lupus and vasculitis) and CVD is well described in the literature. As raised by Van Doornum, McCool and Wicks in 2002, in RA, for example, there is a reduction of up to three times in survival, with ischemic heart disease being the leading cause of death [4]. Moreover, the risk of acute myocardial infarction in these patients is about two times higher than in the general population, and the prognosis after the event tends to be worse [5]. The meta-analysis of Avina-Zubieta et al. [6] with observational studies conducted between 1970 and 2005 gathered close to 112,000 patients with RA and found a 50% higher risk mortality in the RA group when compared to the control group. Schieir et al., in a meta-analysis involving the five major arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), gout or osteoarthritis) found a 50% greater risk of infarction when adjusted only for sex and age. Even adjusted for one of the traditional risk factors, the higher risk of infarction (30%) shows that traditional risk factors only partially explain the greater chance of infarction in this population [7].

The characteristic exacerbated inflammatory process in autoimmune diseases, is intimately related to vascular lesions that contribute to the physiopathological process of several CVDs, which can be attended with vasculitis or accelerated atherosclerosis [8]. Atherosclerosis is already recognized as a consequence of the local or systemic endothelial inflammatory process, in which endothelial dysfunction, atherosclerotic plaque formation or even thrombosis begins in the expression of receptors in the endothelium, adhesion and infiltration of leukocytes and platelets [9]. Thus, accelerated atherosclerosis may be the main explanation for the high cardiovascular morbidity and mortality percentages in these patients [10].

The presence and persistence of inflammation should be seen as a key component for the occurrence of cardiovascular impairment and can be evaluated by several means, some of which are more strongly related to CVD. The C-reactive protein (CRP) is one of the most studied assessment risk factors. Its persistently increased levels constitute an independent risk factor for cardiovascular events, [11]. The late predictive value of CRP for cardiovascular events is also described in the literature, as verified in the GUSTO study [12], in which the authors showed a higher risk of mortality after 30 days of acute coronary event in patients with elevated CRP. The recent publication of the study CANTOS-Canakinumab Anti-inflammatory Thrombosis Outcomes Study [13] finally provided a proof of how the activity in the inflammatory factor is relevant to the prevention of CVD. In this double-blind randomized and controlled placebo study, in which 10061 patients after acute myocardial infarction (AMI) who persisted with elevated CRP (> 2mg) were treated with anti-IL1 monoclonal antibody, there was a 15% reduction in primary events (AMI, stroke or cardiovascular death).

Even in individuals in primary prevention, CRP can be used to stratify the risk as shown by Ridcker and collaborators in the validation of the Reynolds score [14]. Persistently increased PCR levels are associated with increased risk of myocardial infarction and stroke [15]. The plasmatic level of CRP, besides being an independent risk factor for cardiovascular events, adds risk potential to other factors such as LDL, for example, posing an associated Cardio Vascular (CV) risk increment [16]. The presence of elevated CRP is related not only to cardiovascular events but also to a worse prognosis for mortality, especially in the acute phase of ischemic heart disease, even serving as a risk assessment factor in CVD procedures [11].

The concept of the interaction between inflammation and CVD is reinforced by publications correlating other components of the inflammatory process with cardiopathy. Kaptoge et al. [17] showed that cytokines, especially interleukin 6, are independent markers for cardiovascular events, although there is still little to be affirmed about their of cause-effect relationship. IL-6 is released by Type 2 helper T lymphocytes, by antibody-presenting cells and by adipocytes, being a protein closely related to the inflammatory process and playing an important role in humoral response regulating, including PCR release, with lipid metabolism and glycemia interference, and markedly associated with metabolic syndrome. IL-6 has shown to be an attractive marker for providing information related not only to the inflammatory state but also to treatment response and future events occurrence [18].

That's clear the remarkable participation of IL-6 on cardiovascular events [19] and its intimate pathophysiology involvement in atherosclerotic disease. Endothelial dysfunction due to chronic systemic inflammation predispose LDL infiltration. From there, monocytes migrate to the middle arterial layer, phagocyte the LDL transforming into macrophages and, by signaling to T lymphocytes, amplify the inflammatory process by releasing cytokines such as PCR-S and IL-6 [9]. Increased plasma levels of IL-6 are associated with a worse cardiovascular prognosis in patients with coronary disease, and are also more relevant in acute coronary scenario [20]. Persistently high IL-6 levels late to an acute coronary syndrome episode relates to worse prognosis [21]. Therefore, the role of inflammation as a contributor in the installation and evolution process of vascular disease is well established.

### Stratification of Cardiovascular Risk in Autoimmune Disease

Although the highest incidence of CVD is recognized in patients with autoimmune disease, the investigation and risk stratification still await a better definition. While the treatments and diagnostic investigation in autoimmune diseases have evolved sharply in recent years, the approach of CVD in these patients did not have the same parallel. The existing general population risk scores for evaluation and conduct of CVD lack certification in the AID, in which the inflammatory environment can interfere in risk prediction capacity.

In 2010, the EULAR (European League against Rheumatism) has published an interesting document about it. EULAR, considering the most common forms of autoimmune disease like RA, SLE, psoriatic arthritis (PsA), suggests considering, besides the traditional risk factors for CVD, the inflammatory disease time, the presence of persistent inflammatory activity, and the occurrence of extra-articular manifestations [22]. Some patients should have their risk score multiplied by 1.5 for repunctuation (RA for more than 10 years, positive rheumatoid factor and extra-articular involvement). The document also recommends great control of the inflammatory scenario and caution when adopting NSAID and high doses of corticosteroids, reinforcing the importance of using statins and ACE inhibitors/ABRs in these individuals. Such recommendations have higher evidence in patients with SLE and RA, and are less significant in patients with SpA [22].

However, it has recently been shown that there is higher CV risk also in the SpAs (ankylosing spondylitis, PsA, reactive arthritis and enteropathy associated arthritis) even when considering the traditional risk factors.

So that the presence of these diseases may also be considered additional risk factor for the occurrence of CVD. In an eight years follow-up, Bengtsson et al. compared almost 22 thousand patients with AS, PsA and SpAs with approximately 270 thousand control subjects, and found higher prevalence of CVD in the group with articular rheumatic disease. In general, the risk in SpAs was between 36% and 76% higher for ACS, and 50% higher for venous thromboembolism. The CVA risk was also higher in the spondyloarthritis group, with average risk ratio of 1.29 (from 1.06 to 1.48). These data reinforce the EULAR recommendations of considering SpAs also as CV risk aggravating [23].

We can see the best comprehension of what occurs in the publication of Crowson et al. [24], which shows that these risk factors explain just 70% of the CV events in patients with RA, being the last 30% of the events related to autoimmune disease and inflammatory activity.

Thus, the challenge when classifying the real risk for CVD in this population still needs to be better defined. The broad spectrum of immunological response, the variability of the inflammatory activity in each one of them and the use of medication with modifier role in the evolution of diseases interfere in the interpretation of studies, showing conflicting results in the topic.

Despite the recommendation of EULAR taskforce, there are still more recent arguments showing that it is necessary to better search for the presence of cardiopathy, especially of accelerated atherosclerosis, in patients with AID. Gomez-Vaquero et al. has shown that the European risk score SCORE and the Spanish risk score REGICOR, despite being good predictors of mortality and CV events in the general population, lose this potential in patients with RA, particularly when assessed by the presence of subclinical atherosclerosis [25].

In these patients, the general population risk scores have a less desired accuracy. Almost 50% of low risk SpAs patients classified by the Framingham score are reclassified to high risk when submitted to carotid ultrasound [26].

In order to achieve better stratification, other scores were developed to refine the risk assessment of CV in autoimmune diseases, such as the Expanded Cardiovascular Risk Prediction Score for RA (ERS-RA) that re-stratifies the impact of factors using information on AR activity level, disability, corticosteroid use and disease time, and the QRISK2, which considers the presence of RA as an independent risk factor.

These scores have failed to correctly assess the CV risk, especially when confronted with traditional scores [27]. As example, the ACC/AHA score proved to be incapable of identifying 55% of high-risk individuals when carotid ultrasound was used as an additional research method [28].

### Approach and Investigation

The challenging CV risk assessment in AID patients does not seem to be enough attended by the available scores. Early stages of cardiovascular impairment may be observed in several autoimmune diseases and different complementary methods. Moreover, the cardiovascular system involvement is not limited to the arterial territory and can be present in various forms such as vasculitis, myocarditis, pericarditis, endocarditis, valvulopathies and arrhythmias. Aneurysmal dilatation of the aorta, aortic insufficiency and right bundle branch blocks are possibilities in AE. Myopericarditis and endocarditis are classic complications in SLE. Systolic heart failure and diastolic dysfunction can be found in RA. Thus, there are several forms of cardiovascular abnormality manifestation, that can be seen by different investigation methods.

The electrocardiogram is certainly the simplest and most economical complementary exam. It can be interesting in the follow-up of patients with spondyloarthritis where the branch blocks are more frequent, or in ischemia and necrosis identification in other kinds of AID. Despite its low cost and simplicity, it has very low specificity.

Echocardiography is a simple, low-cost and risk-free exam that can add valuable information on systolic and diastolic function, valvulopathies and pericardiopathies, common conditions in several AIDs. With Doppler method, it's able to identify ventricular dysfunction in early AID phases and related to the activity, severity and treatment response, especially in RA and SLE.

Myocardial scintillography can be used to assess coronary perfusion in patients with AID.

Despite the possibility of abnormalities found due to classical atherosclerosis and their high sensitivity, the endothelial dysfunction of microcirculation can often cause non-specific alterations confounding with the presence of obstructive coronary artery disease. The radioactive concerns and higher cost add limitations on this method.

Angiotomography is well defined as a coronary lesions assessing method. It allows to evaluate beyond the coronary anatomy, the presence of plaques and calcium quantification score, which has a strong correlation with the cardiovascular risk prognostic. Patients with RA and SLE have a higher prevalence of valvular and coronary calcification, with higher prevalence and complexity of coronary plaques than controls [29]. It also allows scars and fibroses identification, as well as effusion and pericardial thickening. However, in addition to the high radioactivity employed, the method has lower tissue definition capacity, losing to magnetic resonance in fibrosis or amyloid infiltration differentiation for example, and both common in AID patients.

Magnetic resonance imaging (MRI) is particularly special in autoimmune diseases. Besides the advantages of not being radioactive and having less dependence on the operator evaluation, the method is able to identify characteristic myocardial edema in acute conditions, localized or focal fibrosis, damage in the epicardial, subendocardial or transmural region. It may identify obstructive atherosclerosis or microvascular disease. It can also differentiate fibrosis from other types of muscular infiltrates, reveal changes in contractility and diagnose pulmonary hypertension, common in autoimmune disease with prognostic relevance [30].

Therefore, in this diverse scenario of the AID, a well-performed echocardiogram may be enough. Carotid Doppler can contribute to a risk rescore at low cost in most cases, and make changes in the conduction of cardiovascular protection goals. Sometimes, the identification of perfusion by scintigraphy or stable chronic coronary atherosclerosis by CT may be preferable. On the other hand, the differentiation between acute inflammatory conditions, infiltrative cardiomyopathy or pulmonary hypertension by MRI should be taken into account.

Finally, like on other cardiopathies, the best complementary exam to evaluate the cardiovascular impairment depends not only on the AID type with its typical form of CV manifestation but also on the CV risk profile of each patient. Thus, the multiple assessing possibilities of CVD in AID patients may depend on available resources, experience of the service and what is intended to be evaluated. The multifaceted cardiovascular compromise in the AID aggregates chronic inflammation, specific evolution of each autoimmune disease, lifestyle components, genetics and medications effects. These factors can lead to varying degrees and types of CVD [31].

## Conclusion

Autoimmune diseases are an independent risk factor for occurrence of cardiovascular disease. The association between traditional risk factors and inflammation is complex and multifarious, leading to different degrees of cardiovascular impairment. The best approach of CVD in the AID patients requires a broad evaluation of the autoimmune pathology with quantification of intensity and persistence of inflammation allied to traditional CVD risk factors stratification and different investigation methods.

## References

- Doria A, Puttini PCS, Shoenfeld Y (2004) Heart, rheumatism and autoimmunity: Milan, Italy. February 5–7, 2004 3(4): 337-354.
- Knockaert DC (2007) Cardiac involvement in systemic inflammatory diseases. *Eur Heart J* 28(15): 1797-1804.
- Gabriel SE (2010) Heart disease and rheumatoid arthritis: understanding the risks. *Ann Rheum Dis* 69(S1): 61-64.
- Van Doornum S, Mc Coll G, Wicks IP (2002) Accelerated atherosclerosis: an extra articular feature of rheumatoid arthritis? *Arthritis & Rheumatism. Cardiol Res Pract* 46(4): 862-873.
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, et al. (2012) European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 33: 1635-1701.
- Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, et al. (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta analysis of observational studies. *Arthritis Rheum* 59: 1690-1697.
- Schieir O, Tosevski C, Glazier RH, Johnson SH, Badley EM, et al. (2017) Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. *Ann Rheum Dis* 76: 1396-1404.
- Mason JC, Libby P (2014) Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. *Eur Heart J* 21(36): 482-489.
- Bisoendial RJ, Kastelein JJP, Stroes ESG (2007) C-reactive protein and atherogenesis: From fatty streak to clinical event. *Atherosclerosis* 195(2): 224-436.
- Van Doornum S, Mc Coll G, Wicks IP (2002) Accelerated atherosclerosis: an extra articular feature of rheumatoid arthritis?. *Arthritis & Rheumatism* 46(4): 862-873.
- Biasucci LM (2004) CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice Clinical Use of Inflammatory Markers in Patients With Cardiovascular Diseases A Background Paper, Available 110: 560-567.
- James SK, Armstrong P, Barnathan E, Califf R, Lindahal, et al. (2003) GUSTO IV ACS Investigators. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. *J American College Cardiol* 41: 916-924.
- Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, (2017) Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 377(12): 1119-1131.
- Ridker PM, Buring JE, Rifai N (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds Risk Score. *JAMA* 297: 611-619.
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336(14): 973-979.
- Ridker PM (2003) Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention. *Circulation* 107(3): 363-369.
- Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, et al. (2014) Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J* 35: 578-589.
- Fisman EZ, Tenenbaum A (2010) The ubiquitous interleukin-6: a time for reappraisal. *Cardiovasc Diabetol* 9: 62.
- Fisman EZ, Adler Y, Tenenbaum A. (2008) Biomarkers in cardiovascular diabetology: interleukins and matrixins. *Adv Cardiol* 4: 44 -64.
- Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, et al. (1996) Elevated Levels of Interleukin6 in Unstable Angina. *Circulation* 94(5): 874-877.
- Fisman EZ, Benderly M, Esper RJ, Behar S, Boyko V, et al. (2006) Interleukin-6 and the risk of future cardiovascular events in patients with angina pectoris and/or healed myocardial infarction. *Am J Cardiol* 98: 14-18.
- Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, et al. (2010) Eular evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 69: 325-331.



23. Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, et al. (2017) S Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Res Ther* 19: 102.
24. Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, Van Riel PL, et al. (2018) On behalf of A Trans-Atlantic Cardiovascular Consortium for Rheumatoid Arthritis (ATACC-RA) Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 77: 48-54.
25. Gómez-Vaquero C, Corrales A, Zacarías A, Rueda-Gotor J, Blanco R, et al. (2013) SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis. *Arthritis Res Ther* 15(4): R91.
26. Eder L, Chandran V, Gladman DD (2014) The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis* 73: 1990-1996.
27. Hippisley-Cox J, Coupland C, Vinogradova, Sheikh A, Brindle P, et al. (2008) Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 336(7659): 1475-1482.
28. Ozen G, Sunbul M, Atagunduz P, Direskeneli H, Tigen K, et al. (2016) The 2013 ACC/AHA 10-year atherosclerotic cardiovascular disease risk index is better than SCORE and QRisk II in rheumatoid arthritis: is it enough? *Rheumatology (Oxford)* 55(3): 513-522.
29. Raggi P, Achenbach S (2010) Computed tomography for atherosclerosis and coronary artery disease imaging. *Discov Med* 9: 98-104.
30. Mavrogeni SI, Sfrikakis PP, Koutsogeorgopoulou L, Markousis-Mavrogenis G, Dimitroulas T, et al. (2017) Cardiac Tissue Characterization and Imaging in Autoimmune Rheumatic Diseases. *JACC Cardiovasc Imaging* 10(11): 1387-1396.
31. Zegkos T, Kitas G, Dimitroulas T (2016) Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps. *Ther Adv Musculoskelet Dis* 8(3): 8-101.