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DOCTORAL THESIS

"STUDY OF SUBCLINICAL CARDIOVASCULAR DISEASE IN PATIENTS WITH INFLAMMATORY ARTHRITIS"

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The approval of the doctoral thesis by the Medical School of the University of Athens is not an acceptance of the author's opinions.

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«Η έγκριση της διδακτορικής διατριβής από την Ιατρική Σχολή του Πανεπιστημίου Αθηνών δεν αποτελεί παραδοχή των γνωμών του συγγραφέως»

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Dedicated to my parents

who never deprived me of anything concerning my education

αφιερωμένο στους γονείς μου

που δε μου στέρησαν ποτέ τίποτα όσον αφορά στην εκπαίδευσή μου

ΙΠΠΟΚΡΑΤΟΥΣ ΟΡΚΟΣ

ΟΜΝΥΜΙ ΑΠΟΛΛΩΝΑ ΙΗΤΡΟΝ ΚΑΙ ΑΣΚΛΗΠΙΟΝ ΚΑΙ ΥΓΕΙΑΝ ΚΑΙ ΠΑΝΑΚΕΙΑΝ ΚΑΙ ΘΕΟΥΣ ΠΑΝΤΑΣ ΤΕ ΚΑΙ ΠΑΣΑΣ ΙΣΤΟΡΑΣ ΠΟΙΟΥΜΕΝΟΣ, ΕΠΙΤΕΛΕΑ ΠΟΙΗΣΕΙΝ ΚΑΤΑ ΔΥΝΑΜΙΝ ΚΑΙ ΚΡΙΣΙΝ ΕΜΗΝ ΟΡΚΟΝ ΤΟΝΔΕ.

ΗΓΗΣΕΣΘΑΙ ΜΕΝ ΤΟΝ ΔΙΔΑΞΑΝΤΑ ΜΕ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ ΙΣΑ ΓΕΝΕΤΗΣΙΝ ΕΜΟΙΣΙ, ΚΑΙ ΒΙΟΥ ΚΟΙΝΩΣΕΣΘΑΙ ΚΑΙ ΧΡΕΩΝ ΧΡΗΖΟΝΤΙ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΕΣΘΑΙ ΚΑΙ ΓΕΝΟΣ ΤΟ ΕΞ ΑΥΤΟΥ ΑΔΕΛΦΕΟΙΣ ΙΣΟΝ ΕΠΙΚΡΙΝΕΕΙΝ ΑΡΡΕΣΙ, ΚΑΙ ΔΙΔΑΞΕΙΝ ΤΗΝ ΤΕΧΝΗΝ ΤΑΥΤΗΝ, ΗΝ ΧΡΗΙΖΩΣΙ ΜΑΝΘΑΝΕΙΝ, ΑΝΕΥ ΜΙΣΘΟΥ ΚΑΙ ΞΥΓΓΡΑΦΗΣ.

ΠΑΡΑΓΓΕΛΙΗΣ ΤΕ ΚΑΙ ΑΚΡΟΗΣΙΟΣ ΚΑΙ ΤΗΣ ΛΟΙΠΗΣ ΑΠΑΣΗΣ ΜΑΘΗΣΙΟΣ ΜΕΤΑΔΟΣΙΝ ΠΟΙΗΣΕΣΘΑΙ ΥΙΟΙΣΙ ΤΕ ΕΜΟΙΣΙ ΚΙΑ ΤΟΙΣΙ ΤΟΥ ΕΜΕ ΔΙΔΑΞΑΝΤΟΣ ΚΑΙ ΜΑΘΗΤΑΙΣΙ ΣΥΓΓΕΓΡΑΜΜΕΝΟΙΣΙ ΤΕ ΚΑΙ ΩΡΚΙΣΜΕΝΟΙΣ ΝΟΜΩ ΙΗΤΡΙΚΩ ΑΛΛΩ ΔΕ ΟΥΔΕΝΙ.

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ΟΥ ΤΕΜΕΩ ΔΕ ΟΥΔΕ ΜΗΝ ΛΙΘΙΩΝΤΑΣ, ΕΚΧΩΡΗΣΩ ΔΕ ΕΡΓΑΤΗΣΙΝ ΑΔΡΑΣΙΝ ΠΡΗΞΙΟΣ ΤΗΣΔΕ.

ΕΣ ΟΙΚΙΑΣ ΔΕ ΟΚΟΣΑΣ ΑΝ ΕΣΙΩ, ΕΣΕΛΕΥΣΟΜΑΙ ΕΠ' ΩΦΕΛΕΙΗ ΚΑΜΝΟΝΤΩΝ, ΕΚΤΟΣ ΕΩΝ ΠΑΣΗΣ ΑΔΙΚΙΗΣ ΕΚΟΥΣΙΗΣ ΚΑΙ ΦΘΟΡΙΗΣ ΤΗΣ ΤΕ ΑΛΛΗΣ ΚΑΙ ΑΦΡΟΔΙΣΙΩΝ ΕΡΓΩΝ ΕΠΙ ΤΕ ΓΥΝΑΙΚΕΙΩΝ ΣΩΜΑΤΩΝ ΚΑΙ ΑΝΔΡΕΙΩΝ, ΕΛΕΥΘΕΡΩΝ ΤΕ ΚΑΙ ΔΟΥΛΩΝ.

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ΟΡΚΟΝ ΕΝ ΟΥΝ ΜΟΙ ΤΟΝΔΕ ΕΠΙΤΕΛΕΑ ΠΟΙΕΟΝΤΙ ΚΑΙ ΜΗ ΞΥΓΧΕΟΝΤΙ ΕΙΗ ΕΠΑΥΡΑΣΘΑΙ ΚΑΙ ΒΙΟΥ ΚΑΙ ΤΕΧΝΗΣ, ΔΟΞΑΖΟΜΕΝΩ ΠΑΡΑ ΠΑΣΙΝ ΑΝΘΡΩΠΟΙΣ ΕΣ ΤΟΝ ΑΙΕΙ ΧΡΟΝΟΝ, ΠΑΡΑΒΑΙΝΟΝΤΙ ΔΕ ΚΑΙ ΕΠΙΟΡΚΕΟΝΤΙ, ΤΑΝΑΝΤΙΑ ΤΟΥΤΕΩΝ.

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Table of Contents

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ZERTIFICAT

Scientific and Research Work

Publications in International Journals:

1. **Arida A**, Vaiopoulos G, Markomichelakis N, Kaklamanis P, Sfikakis PP. Are clusters of patients with distinct clinical expression present in Behçet's disease? Clin Exp Rheumatol. 2009 Mar-Apr;27(2 Suppl 53):S48-51.
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Abstracts (as posters or oral presentations)

Greek conferences:

20th Hellenic Conference in Rheumatology (2008):

- **Arida A., Margari N., Fragkiadaki K., Giavri E., Vaiopoulos G., Kaklamanis F., Sfikakisk P.P. :** "Are there clusters with distinct clinical expression in Adamantiades-Behcet's disease?"

21th Hellenic Conference in Rheumatology (2009):

- **Arida A., Fragkiadaki K., Giavri E., Vaiopoulos G., Sfikakisk P.P** «Use of anti-TNF agents in the therapy of Adamantiades-Behcet's: systematic review of 271 patients"
- **Arida A., Vaiopoulos G., Sfikakisk P.P:** "The clinical use of ultrasound-derived the halo sign of the temporal arteries in the diagnosis of temporal arteritis: a second meta-analysis"

25th Hellenic Conference in Rheumatology (2016):

- **Arida A., Protogerou A., Konstantonis G., Fragkiadaki K., Kitas G., Sfikakis P.P.:** " Subclinical atherosclerosis is not accelerated in Rheumatoid arthritis patients with low disease activity or remission, regardless of treatment modalities: 3-year prospective study"
- **Arida A., Panopoulos S., FragkiadakiK., Pentazos G., Pitsilka D., Laskari K., Tektonidou M., Markomichelakis N., Sfikakis PP.:** "Outcome of Severe Adamantiades-Behcet's disease after anti-TNF

treatment cessation: a retrospective 15-year study in an academic reference center"

International conferences:

17th International Conference on Behcet's Disease:

- "Outcomes of biologic treatment regimens for severe Behcet's disease: current experience from a single academic center"

18th International Conference on Behcet's Disease:

- **Sfikakis P.P., Arida A., Matkomichelakis N.:** "Outcome of short-term Infliximab treatment for sight-threatening uveitis in Behcet's disease: a single center experience"

EULAR 2009:

- **G.N. Karanikolas, A. Arida, E. Komninou, K. Fragiadaki, N. Malgari, A. Zacharioudaki, J. Lasithiotakis, E. Giavri, A. Kotrotsos, E.Koukli, G. Vaiopoulos, P.P.Sfikakis** "CombinationofAdalimumab (ADL) withCyclosporine-A (CsA) againstsingletherapyinrefractoryPsoriaticArthritis: anongoing, 12-month open, three-arm, randomized study"

EULAR 2011:

- **G. N. Karanikolas, E. Koukli, A. Arida, A. Katsalira, D. Petrou, E. Komninou, I. Giavri, K. Fragiadaki, A. Zacharioudaki, J. Lasithiotakis, G. Vaiopoulos, P. P. Sfikakis** "ADALIMUMAB OR CYCLOSPORINE AS MONOTHERAPY AND THEIR COMBINATION FOR SEVERE PSORIATIC ARTHRITIS: RESULTS FROM A PROSPECTIVE, 12-MONTH, OBSERVATIONAL STUDY OF 170 PATIENTS"

EULAR 2014:

- **Arida A, Zampeli E, Konstantonis G, Fragkiadaki K, Kitas GD, Protogerou AD, Sfikakis PP** "ACCELERATED SUBCLINICAL ATHEROMATOSIS, BUT NOT ARTERIAL STIFFNESS OR HYPERTROPHY, IN RHEUMATOID ARTHRITIS PATIENTS FREE OF CLASSICAL RISK FACTORS"

EULAR 2016:

- **Arida A., Protogerou AD., Konstantonis G., Fragkiadaki K., Kitas GD., Sfikakis PP.:** "Effective control of rheumatoid arthritis disease activity prevents development of acceleration of subclinical atherosclerosis over 3 years"

EULAR 2017:

- **Sfikakis P.P, Arida A., Panopoulos S., Fragkiadaki K., Pentazos g., Laskari K., Tektonidou M., Markomichelakis N.** : "Long-term drug-free remission is feasible in severe Behcet's after cessation of successful anti-TNF treatment: a single center, retrospective longitudinal outcome study"

EULAR 2019:

- **Sfikakis PP., Arida A. Markomichelakis N:** "A single, successful Infliximab Infusion for Behcet's disease associated sight-theatening uveitis attack, followed by 2 additional imnfusions produce long-term ocular remission"

American College of Rheumatology Annual Meeting 2014:

- **Aikaterini Arida, Maria Konsta, Alex Iliopoulos, Maria Tektonidou, George Konstantonis, George D. Kitas, Athanassios D. Protogerou, Petros P. Sfikakis**: "NO EVIDENCE OF ACCELERATED ATHEROMATOSIS, INCREASED ARTERIAL STIFFNESS OR HYPERTROPHY IN ANKYLOSING SPONDYLITIS: A SYSTEMATIC CASE-CONTROL STUDY"
- **Arida A, Zampeli E, Konstantonis G,Fragkiadaki K, Kitas GD, Protogerou AD, Sfikakis PP**. "INCREASED OCCURANCE OF CAROTID AND FEMORAL PLAQUES, BUT NOT INCREASED ARTERIAL STIFFNESS OR HYPERTROPHY, IN CLASSICAL RISK FACTOR-FREE PATIENTS WITH RHEUMATOID ARTHRITIS"

American College of Rheumatology Annual Meeting 2017

- **Sfikakis P.P, Arida A., Panopoulos S., Fragkiadaki K., Pentazos g., Laskari K., Tektonidou M., Markomichelakis N.** : "Long-term remission in severe Behcet's disease following withdrawal of successful anti-TNF treatment" 2017

Turkish Greek Rheumatolgy days 2016:

- **Arida A., Korkou C., Konstantonis G., Protogerou A, Sfikakis PP., Tektonidou M.:** "Comparable prevalence of subclinical atherosclerosis in a cohort of patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis"

ECCMID:

- **K. Arida, A. Lazarini, M. Psichogiou, A. Protogerou, G. Konstantonis, A. Argyris, E. Zampeli, P. Sfikakis, G. Daikos** "Cardiovascular disease risk factors and impaired non-invasive cardiovascular disease biomarkers in acohort of HIV infected patients."

Clinical Experience

- 01/12/2008-28/02/2010: Scientific Associate of Rheumatology Unit of First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Medical School, National and Kapodostrian University of Athens
- 01/04/2011-31/6/2011: Scientific Associate of Rheumatology Unit of First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Medical School, National and Kapodostrian University of Athens

- 19/03/2010-20/3/2011: Rural Doctor of Prasino Village regional clinic and Tropaia Health Center

- 09/2011-07/2013: Resident of Internal Medicine in "Korgialeneio-Mpenakeio" Hospital in 3rd Internal Medicine Clinic

- 9/2013-7/2016: Scientific Associate of Rheumatology Unit of First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Medical School, National and Kapodostrian University of Athens

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Abbreviations

ACPA: anti-citrullinated protein/peptide antibodies, Aix: augmentation index, APS: antiphospholipid syndrome, AS: ankylosing spondylitis , ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BMI: body mass index, cDMARDs: conventional disease modifying antirheumatic drugs, CHD: coronary heart disease, cIMT: carotid intima-media thickness, CIRD: chronic inflammatory rheumatic diseases, CRP: C-reactive protein, CV: cardiovascular, CVD: cardiovascular disease, DAMPs: damage-associated molecular patterns, DM: Diabetes Mellitus, DR3: death-domain receptor 3, ds-DNA: double stranded deoxyribonucleic acid, e.g.: for example, EC: endothelial cell, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatism, FMD flow-mediated vasodilation, GM-CSF: granulocyte monocyte-colony stimulating factor, HDL: high-density lipoprotein, i.e.: id est (that is), ICAM: intercellular adhension molecule, IFN: Interferon, IL: Interleukin, IR: insulin resistance, LDL: low-density lipoprotein , Lp(a): lipoprotein a, MetS: metabolic syndrome, MI: myocardial infarction, MTX: methotrexate, NFkB: Nuclear Factor Kappa B, NLRP3: NOD-like receptor family pyrin domain containing 3, NO: nitric oxide, NSAIDs: Non-steroid antiinflammatory drugs, oxLDL: oxidised low-density lipoprotein, PAMPs: pathogen-associated molecular patterns, PGI2: prostacyclin, PRRs: pattern-recognition receptors, PsA: psoriatic arthritis, PWV: pulse wave velocity, RA: Rheumatoid arthritis, RNA: ribonucleic acid, ROS: reactive oxygen species, SLE: Systemic Lupus Erythematosus, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLICC: Systemic Lupus International Collaborating Clinics/American College of Rheumatology, SpA: Spondyloarthropathies, TC: triglycerides, TGF: transforming growth factor, Th: T-helper, TLR: Toll like receptor, TM: thrombomodulin, TNFa: Tumor necrosis factor-a, VCAM: vascular endothelial adhension molecule

THEORETICAL BACKGROUND

1. Definition, epidemiology and risk factors of CVD

The term cardiovascular disease (CVD) refers to a specific group of conditions caused changes in the arterial structure, both functional and morphological, namely arteriosclerosis and atherosclerosis. Arteriosclerosis and atheromatosis are therefore the pathogenetic substrate of all cardiovascular diseases. Atherosclerosis primarily affects the tunica intima and results in smooth muscle cell proliferation and atheromatous plaques. This causes thickening of the arterial wall and narrowing of the lumen of the vessel (arterial stenosis) that restricts blood flow and finally could result in plaque rupture. Arteriosclerosis primarily affects the tunica media and refers to loss of elasticity and stiffening of the arterial wall by loss of elastin and deposition of collagen. [1–4]

The clinical expression of atherosclerosis mainly includes Coronary Heart Disease (CHD) such as myocardial infarction (MI) and angina, Cerebrovascular Disease manifested by stroke and transient ischemic attack, and Peripheral Artery Disease. Arteriosclerosis, in terms of impaired arterial elasticity and arterial stiffness, causes microvascular damage and hemodynamic consequences that could lead to nonatherosclerotic CVD, such as myocardial ischemia and failure or damage in the kidneys or brain, or even promote atheroma formation. [1–4]

The significance of CVD lies in the fact that it is very common in the general population as it affects millions of people worldwide. It affects almost 50% of individuals over 30 years and the majority of adults over the age of 60 years. It presents with severe morbidity and mortality, and remains the leading cause of death globally with 17.3 million deaths annually estimated worldwide

Classical risk factors for developing arteriosclerosis and atherosclerosis and CVD are classified to non-modifiable risk factors, such as age, gender and family history of CVD and modifiable risk factors, such as arterial hypertension, glucose intolerance, hypercholesterolemia and smoking, as well as obesity, poor diet, anxiety and stress and excessive alcohol consumption,. [5,6] (Figure 1)

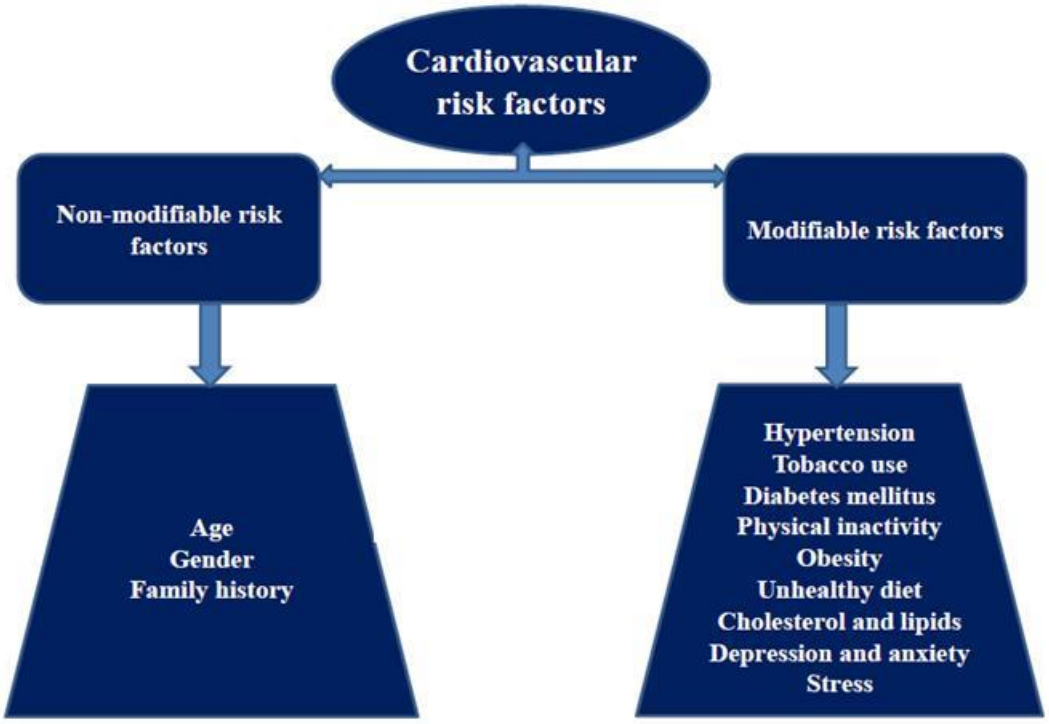

Figure 1 Classical modifiable and non-modifiable cardiovascular risk factors.

CVD is no longer considered an inevitable consequence of aging and in recent years, other conditions that appear to be related to the development of arteriosclerosis and atheromatosis have been described. The evolution of molecular biology and genetics has helped understand the mechanisms that cause arteriosclerosis and atherosclerosis and it is now known that inflammation plays an important role in all stages of atherogenesis. The causal relationship between arteriosclerosis/atherosclerosis and inflammation has been the subject of extensive investigation in recent years. Systemic markers of inflammation, such as C-reactive protein (CRP) and the proinflammatory cytokines TNFa and IL-6, are known to independently predict CVD events [7,8] and the atherosclerotic process can be modulated by anti-inflammatory molecules targeting different inflammatory pathways [9]. Moreover, several inflammatory markers are considered to be associated with classical CVD risk factors such as hypertension and metabolic syndrome [10,11] Several lines of evidence suggest that CVD, from endothelial damage and atherogenesis to plaque rupture, is an immune-mediated disease and many studies have focused on determining the exact mechanisms involved in the atherosclerotic process. (Figure 2) Alteration of lipoprotein concentrations, oxidative stress and macrophage accumulation, as well as

endothelial injury and dysfunction, activation of the innate immune system and increased circulating cytokines are few of the underlying pathogenic mechanisms.

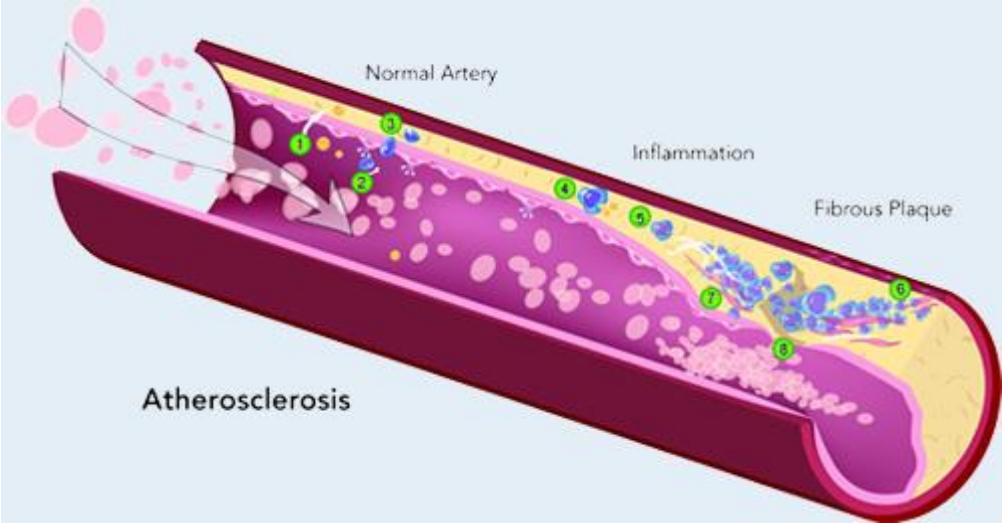

Figure 2 Progression of atherosclerosis mediated by inflammation

Given the importance of predicting and preventing the progression of CVD and CVD events, numerous studies have concentrated on non-invasive vascular biomarkers that are reliable for assessing the degree of arteriosclerosis and atherosclerosis and therefore for predicting CVD events and mortality. Pulse wave velocity (PWV) is a measure of arterial stiffness that assesses the velocity (speed) at which the blood pressure pulse (pulse wave) propagates through the circulatory system and has been found to independently predict CVD events [12–14] Augmentation index (AIx) is defined as the difference between the second and first systolic peaks on the central (aortic) pressure waveform expressed as a percentage of pulse pressure and is a measure of left ventricular afterload. Augmentation Index (AIx) represents another indirect marker of systemic arterial stiffness, as it calculates magnitude of arterial wave reflection, and has also been widely correlated with CV mortality.[12] Intima-media thickness is a measurement of the thickness of innermost two layers of the wall of an artery, usually performed by ultrasound in the carotid arteries and used to assess atherosclerosis. Carotid IMT is considered a strong predictor on CV events. [13,15] An atheromatic plaque is an abnormal deposition of material in the intima of the arterial wall, that consists of lipids, connective tissue, calcium and inflammatory cells (macrophages). Atheromatic plaques can cause narrowing of the lumen of the vessel

that could lead to restriction in blood flow, as well as plaque instability and rupture that lead to CV events. The presence of atheromatic plaques, most usually assessed in the carotid arteries, in another marker of atherosclerosis and a predictor of CV events.[13,16,17]

2. Common Inflammatory Rheumatic Diseases (CIRD)

The term CIRD refers to a group of autoimmune inflammatory disorders characterized by localized and systemic inflammation induced by dysregulation of the autoimmune system. The clinical spectrum of inflammatory rheumatic diseases is wide and heterogenic depending on the underlying condition and pathophysiology of each rheumatic disease, with involvement of the connective tissue and, in some cases, specific internal organ damage. Rheumatoid arthritis (RA) is the main representative of CIRDs and Ankylosing Spondylitis (AS) is the main type of Inflammatory Spondyloarthropathy, i.e. affecting the axial skeleton.

2.1. Rheumatoid arthritis

Epidemiology

Rheumatoid arthritis (RA) is a common autoimmune inflammatory rheumatic disease, with a prevalence of about 0.5-1% in developed countries. It is more frequent in women -three times more than men- and middle age. Etiology is still unknown and several factors are considered to contribute to the onset of the disease. Fifty percent of the disease expression is attributed to genetics factors, which is supported by the increased prevalence of RA in specific Indian populations as well as the increased familial recurrence risk, i.e. in monozygotic twins. The role of specific autoantibodies, such as Rheumatoid factor and anti-Cyclic Citrullinated Peptide (CCP) antibodies, as

well as association with specific HLA BRB1 alleles, further support the aspect of a genetic background of the disease. Environmental factors are also determinants for developing RA. Sex hormones, exposure to infectious agents, obesity, diet and smoking are thought to be implicated in disease risk.

Pathophysiology

The clinical expression of RA is the result of an inflammatory cascade, initiated by both T and B cells and subsequent production of pro-inflammatory cytokines and resulting in bone, synovial and cartilage inflammation and degradation.

Activation of various T-cell populations in the synovia, caused by arthritis-associated autoantigens, is of great importance in RA pathogenesis. T-cell activation, especially CD4+ T-cells, leads to activation of innate immune cells, activation of B-cells and production of autoantibodies and secretion of various cytokines that are responsible for synovial inflammation. B-cells produce rheumatoid factor and anti-CCP antibodies, produce cytokines such as TNF-a and IL-6 and activation T-cells via autoantigen presentation. Regarding cytokines, in RA there is an overproduction of pro-inflammatory cytokines and reduced production of anti-inflammatory cytokines. The main cytokine that is overproduced in RA and has been found elevated in the serum of RA patients is TNFa. It increases proliferation and differentiation of T and B-cells, production of pro-inflammatory cytokines and GM-CSF by synovial macrophages and expression of adhension molecules such as ICAM-1. IL-6 and IL-1, as well as Janus Kinases (JAKs) are also implicated in RA pathogenesis and synovial inflammation and joint destruction and have been targeted in RA.

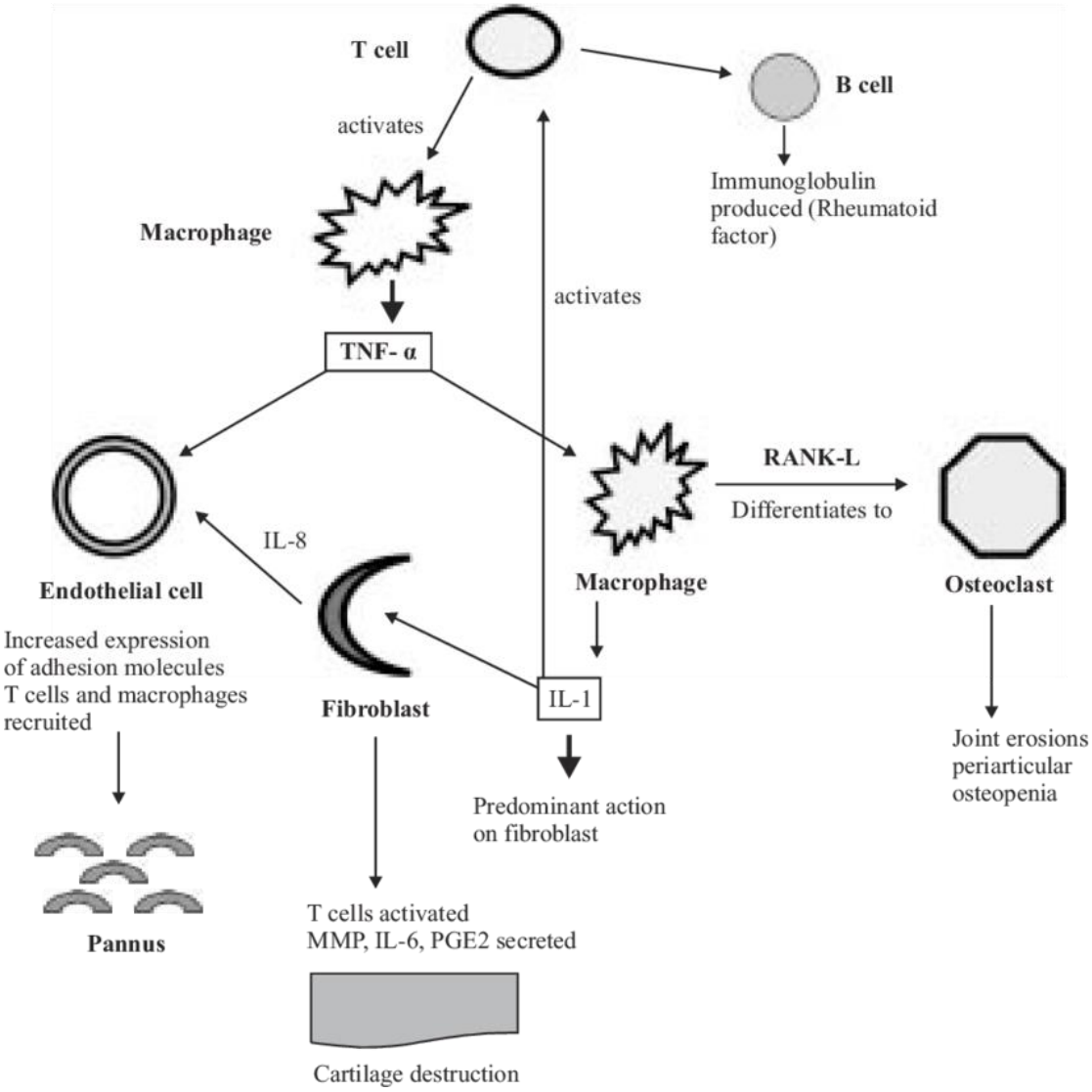

Figure 3 Pathogenesis of RA

Histopathologically, the joint in RA is characterized by new synovial blood vessels (neoangiogenesis) and hyperplasia and hypertrophy of the synovial cells and bone erosion due to osteoclast activation. Damaged is also caused in the synovium by gene products deposited by polymorphonuclear leukocytes. Moreover, there is significant cartilage degradation by proteolytic enzymes such as metalloproteinases that are secreted by synovial cells and chondrocytes. All these ultimately lead to joint destruction.

Clinical presentation and Laboratory findings

RA is typically presented as symmetrical polyarthritis, with pain, stiffness and swelling of the affected joints which affects the person's capability to perform everyday activities, although a more atypical presentation as migratory arthritis or even monoarthritis is not rare. The most commonly affected joints are the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the fingers, but other synovial joints are also usually affected, such as the wrists, elbows shoulders and knees. Disease onset is insidious in most cases and disease course varies significantly, from mild or even self-limited to aggressive and resistant to therapy disease. Mild joint deformities and joint destruction from synovitis are present early in the disease course, but characteristic deformities, such as ulnar drift, swan neck and boutonniere deformities of the fingers, are nowdays rare and the result of chronic and resistant inflammation (Figure 4).

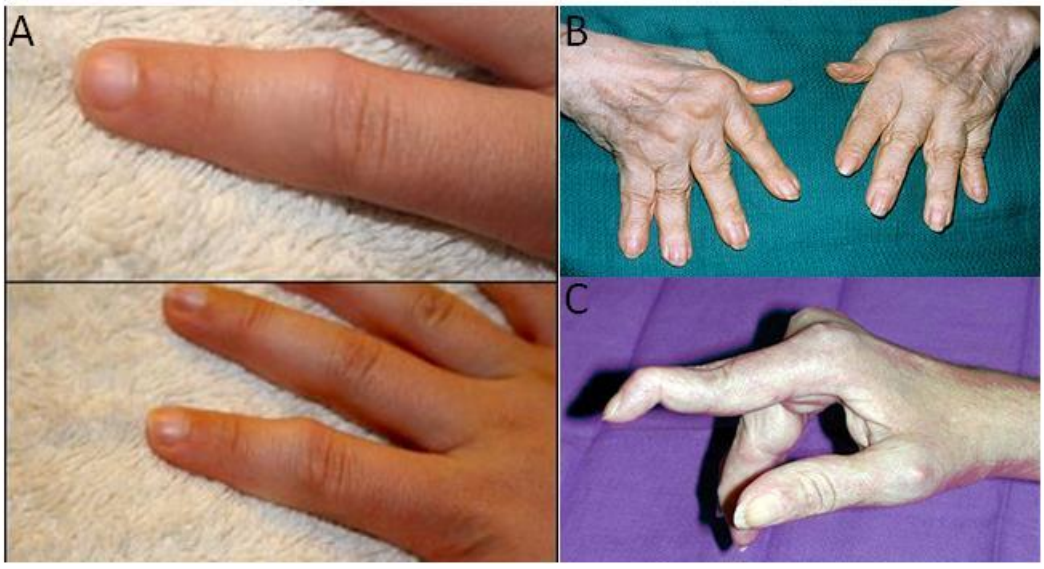

Figure 4 Hands of patients with rheumatoid arthritis A. swelling of the PIP joints in early arthritis B. ulnar drift deformity C.swan neck deformities

Many RA patients also present with systemic symptoms such as fever, fatigue, weight loss and some even with extra-articular manifestations from various organs, such as rheumatoid nodules, lung fibrosis, pleural or pericardial effusion and myocarditis, myositis, vasculitis, episcleritis etc.

RA, as many other autoimmune diseases, is characterized by the presence of specific autoantibodies. Rheumatoid factor (RF) occurs in up to 80 percent of RA patients,

however it lacks specificity, as it may be present in other infectious or autoimmune conditions such as SLE or Hepatitis C, or in elderly people. [18] High titles of RF are associated with more severe disease course or presence of extra-articular manifestations. [19,20] Anti-cyclic citrullinated antibodies (CCP) have a much higher specificity that RF and similar sensitivity and may predict a more erosive disease and radiographic progression more effectively than RF. [20–22] Patients with RA present other non-specific laboratory findings such as anemia, leucocytosis and elevated acute phase reactants, particularly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Diagnosis

RA diagnosis is clinical and can be made using of the classification criteria shown in Figure 5, created by the American College of Rheumatology and European League Against Rheumatism in 2010. The criteria are intended for patients with at least one joint with clinical synovitis and in case the synovitis cannot be explained by another disease (i.e. SLE, PsA, gout). A score of 6 or more is needed to classify a patient as having definite RA. [23]

Target population: Patients who (i) have at least 1 joint with clinical synovitis and (ii) with the synovitis not better explained by another disease.

	Score		Score
A. Joint involvement (tender/swollen)		**C. Acute-phase reactants**	
1 large joint	0	Normal CRP & ESR	0
2-10 large joints	1	Abnormal CRP & ESR	1
1-3 small joints (± involvement of large joints)	2	**D. Duration of symptoms**	
4-10 small joints (± involvement of large joints)	3	< 6 weeks	0
> 10 joints (at least 1 small joint)	5	≥ 6 weeks	1
B. Serology			
Negative RF & ACPA	0	Add score of categories A-D:	
Low-positive RF/low-positive ACPA	2	**≥ 6/10 = definite RA**	
High-positive RF/high-positive ACPA	3		

Figure 5. The ACR/EULAR 2010 classification criteria for Rheumatoid Arthritis

Specific scores have been established for the evaluation of disease activity and function. Disease Activity score (DAS) evaluates 28 joints and can be calculated using either ESR or CRP. Ranges and interpretation are shown in Figure 6. [24] Simplified disease activity index (SDAI) and Clinical disease activity index (CDAI) are two other tools of disease assessment. [25] The Health Assessment Questionnaire Disability Index (HAQ-DI) assesses patients' disability and ranges from 0 to 3 (scores <0.3 are considered normal) [26]

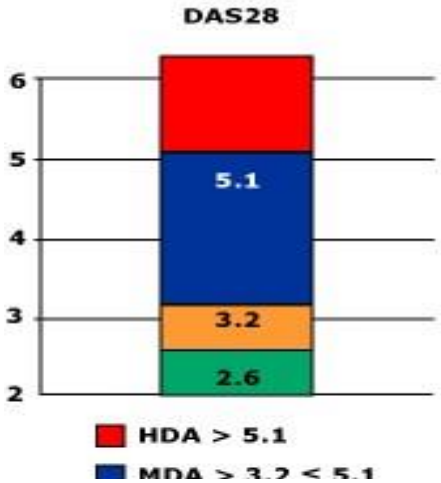

Figure 6 Ranges of DAS28. High disease activity related to >5.2 score, moderate to >3.2, low to >2.6 and remission <2.6.

Therapy

The goal of RA management is sustained remission or low disease activity in every patient with RA and therapy with conventional DMARDs, should be initiated as soon as the diagnosis is made, to avoid articular damage, with concomitant glucocorticoids in low doses for added efficacy and fast response. Methotrexate is the main and first drug used -unless contraindicated- as it has been found to be effective and safe in inducing RA remission and reduces comorbidities and mortality in RA. Other csDMARDs include leflunomide or sulfasalazine and can be used alone or in combination. The last two decades the therapeutic management of RA patients was considerably changed with the introduction and the extensive use of biologic agents, targeting molecule involved in the pathogenesis of RA. Therefore, in case of persistent disease, the therapeutic options include Jak –inhibitors, namely tofacitinib, or biologic DMARDs, namely anti-TNF agents (Infliximab, Adalimumab, Etanercept, Golimumab, Certolizumab-pegol), the anti-IL6 agent Tocilizumab, anti-IL1 agent Anakinra, the constimulation inhibitor Orencia as well as the anti-B-cell agent Rituximab. [27]

2.2 Ankylosing Spondylitis

Epidemiology

Ankylosing Spondylitis is an inflammatory disorder primarily affecting the spine and sacroiliac joints. It is categorized among the seronegative axial spondyloarthropathies (SpA). The prevalence of the disease ranges from 0.02% to 0.35% in the general polulation and there is a close association with the presence of HLA-B27.[28–30] It predominantly affects men, although the ratio of men to women has declined in recent years (male:female ratio 3:1) and the onset of the disease is typically before the age of 45 years. [31,32]

Pathophysiology

The pathophysiology of AS is still largely unknown. There seems to be a genetic background of the disease, revealed by association with the HLA-B27 gene, established many years ago. However, not all subtypes are associated with AS and while the vast majority of patients with AS are HLA-B27 positive, only 5% of HLA-B27 carriers develop AS. The role of genetic factors is also supported by the higher concordance rates in monozygotic twins positive for HLA-B27 as well as the inherited nature of the disease. [33,34] Other non-HLA genes are also suggested to be implicated in AS pathogenesis, such as IL-1 cluster genes, the ERAP1 and ERAP2 genes, Il-23 receptor gene and genes related to TNF receptor (TNFRSF1A). [33,35]

Several inflammatory cytokines play a role in the pathogenesis of AS. Firstly, IL-17A is a pro-inflammatory cytokine that induces the production of IL-1, IL-6, TNF-a and other proiflammatory chemokines. IL-17 levels are elevated in serum, synovial fluid , joints and CD4+ cells from patients with AS. Recent evidence shows that IL-23 may be involved in the pathogenesis of AS, probably by inducing the production of IL-17 by T_H17 cells. Finally, although TNF inhibitors have found to be effective in controlling AS symptoms, the exact role of TNF-a in the disease pathogenesis is not clear. [33,36,37]

In AS there is the paradox of coexistence of bone loss and bone formation. The hallmark of AS is the formation of syndesmophytes that lead to fusion of the spine, and this is along side with osteoporosis of the spine. (Figure 7) Under the effect of IL-17 and TNFa, there is bone activation of octeoclasts and bone erosion. Subsequently, there is bone formation (in the form of syndesmophytes) as a reparative process, at the periosteum-cartilage junction induced by two molecular signaling pathways, the bone morphogenetic proteins (BMPs) mediated pathway and Wnt signaling pathways.[38] Finally, environmental factors, such as gut microbioma and mechanical stress have been accused as potential pathogenetic factors.

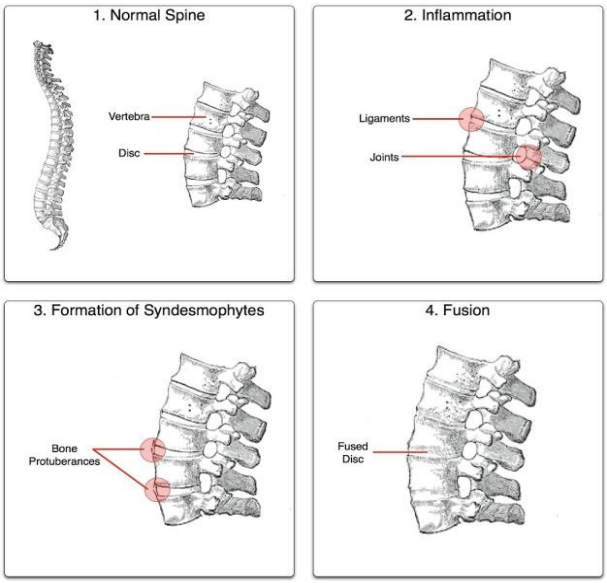

Figure 7 Formation of syndesmophytes and fusion of the spine in Ankylosing Spondylitis

Clinical presentation and Laboratory findings

AS is characterized by involvement of the spine and sacroiliac joints and typically presents as inflammatory low back pain with morning stiffness. Peripheral arthritis is seen in many AS patients with the most commonly affected joints being the hips, knees, shoulders and sternoclavicular joints. Enthesitis is also usual in AS, manifested as pain, tenderness and swelling, at the site of the enthesis and the Achilles tendon attachment is the most frequently affected. As the disease progresses, there are structural abnormalities of the vertebrae and impaired spinal mobility, with spinal fusion, reduced chest expansion and hyperkyphosis. The patients are unable to perform anterior and lateral flexion, extension of the lumbar spine and to rotate their head, thus significantly influencing their ability to perform everyday activities and their quality of life. Systemic symptoms, such as fever, weight loss, fatigue can also be present, as well as extraarticular manifestations, such as acute anterior uveitis in 40% of patients, restrictive pulmonary disease, inflammatory bowel disease/mucosal inflammation, aortic valve incompetence etc. Apart from the presence of HLA-B27,

patients with AS have non-specific laboratory findings such as anemia, leucocytosis and elevated acute phase reactants, particularly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Specific indices have been established for defining disease activity have been Disease activity, namely BASDAI [39] and ASDAS [40], and disease progression and functionality, namely BASFI [41], BASMI [42] and HAQ-S [43]

Diagnosis

The modified New York criteria have been widely used in the past to classify patients as having AS, however they require evidence of structural radiographic changes. This was the reason why the Assessment of SpA international Society (ASAS) developed new classification criteria for patients with axial SpA (with and without radiographic changes). The ASAS classification criteria for axSpA require a history of chronic back pain (pain duration ≥3 months) and an age of onset of <45 years as entry criteria. Patients can then fulfill the axSpA criteria either via the *imaging arm*, with evidence of sacroiliitis on X-ray or MRI, in addition to at least one typical clinical SpA feature, or via the *clinical arm* with the presence of HLA-B27 in addition to at least two other typical clinical SpA features. (Figure 8) [44]

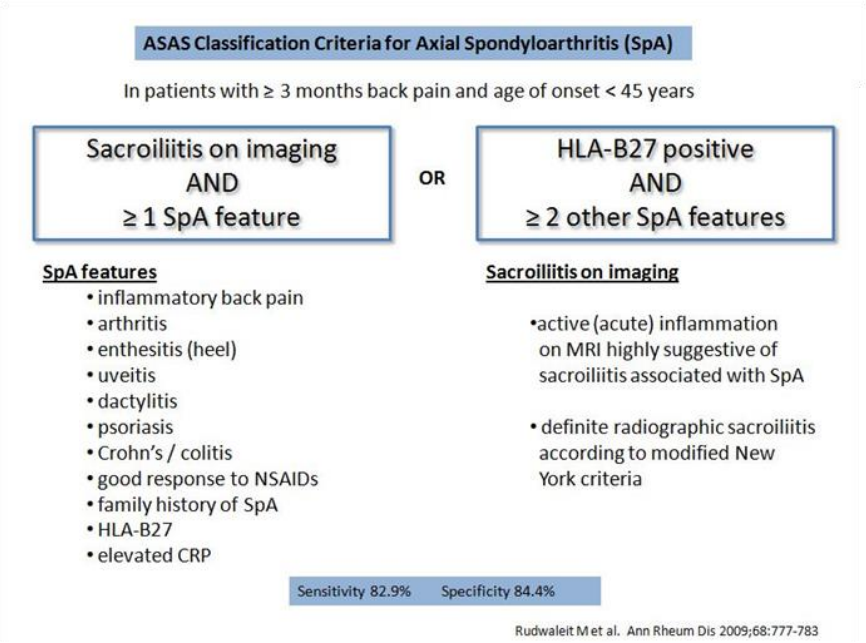

Figure 8 The ASAS classification criteria for axial Spondyloarthropathies

Therapy

According to the 2016 ASAS-EULAR recommendations for the management of SpA, the first-line drug treatment should be the use of an NSAID, with limited use of glucocorticoid injections directed to the local site of inflammation if needed. csDMARDs such as sulfasalazine can be used. Methotrexate is effective in patients with peripheral arthritis. In cases of persistent and high disease activity, biologic therapies targeting TNF or IL-17 are required. (Figure 9) Regarding nonpharmacological therapy, exercise and physical therapy are considered to be quite effective in maintaining function, even in patients responding to pharmacological treatment. [45]

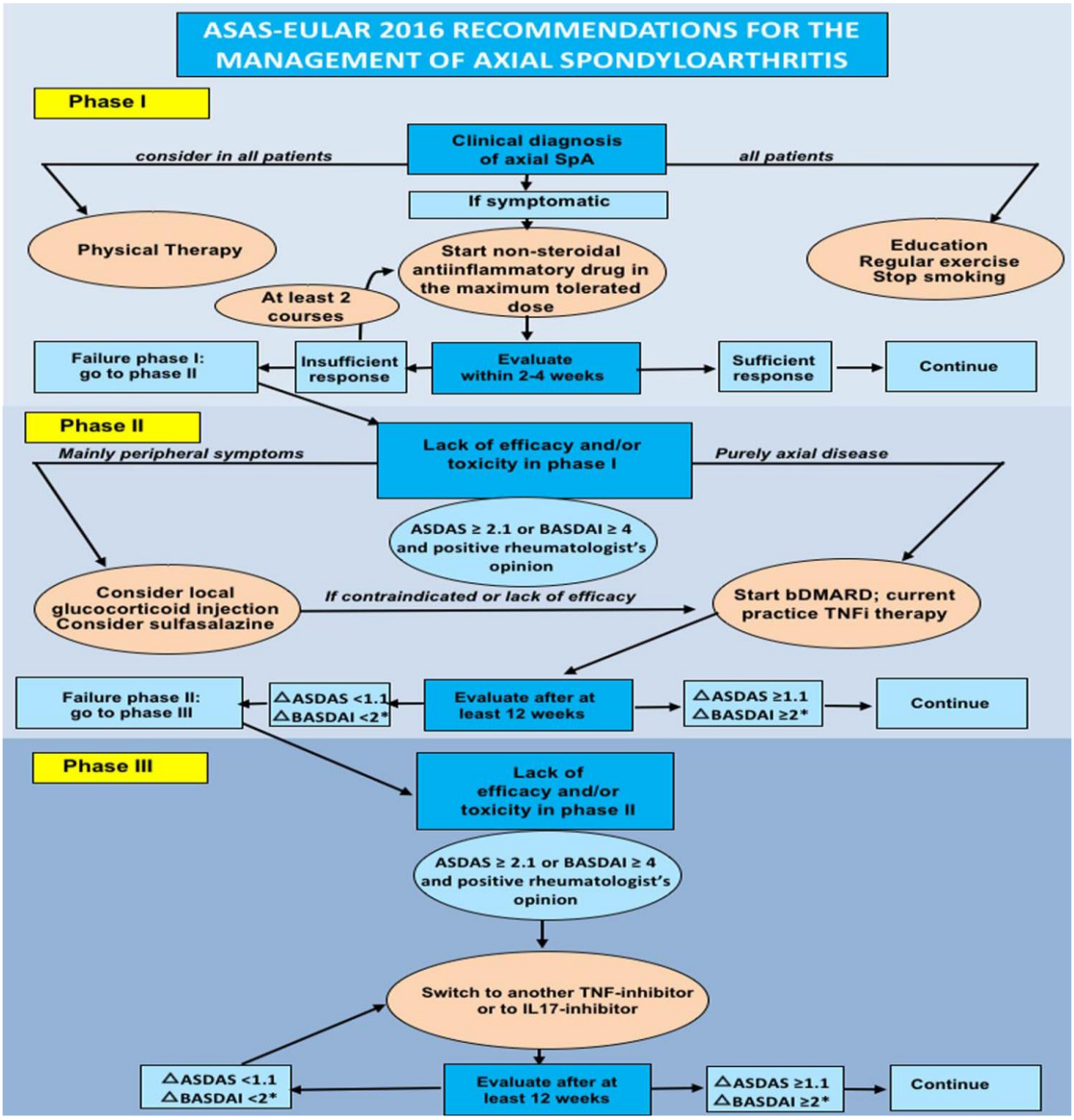

Figure 9 ASAS-EULAR recommendations for the management of SpA (van der Heijde et al. Ann Rheum Dis. 2017;76(6):978-991)

3. Association between CVD and Diseases with Systemic Inflammatory Load

3.1 Indications

This etiological association between arterial damage and inflammation could explain the high prevalence of CVD in diseases characterized with high grade of systemic inflammation, such as Chronic Inflammatory Rheumatic Diseases (i.e. Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS)). Similarities of chronic inflammatory processes and dysregulated immune response seen in CVD and CIRD, further support the association between them.[46]

In CIRD, the high prevalence of CVD leads to increased morbidity and mortality in these patients [47–50]. In these populations, accelerated cardiovascular disease is ascribed not only to classical CVD risk factors-namely arterial hypertension, glucose intolerance, sedentary life, smoking and dyslipidemia- which are in several cases more prevalent in patients with CIRD, but also to the presence of chronic inflammation and perhaps to disease-related therapies.[47,51–53] Rheumatoid arthritis patients are known to have an increased risk of CVD compared to controls, equivalent to that of diabetes mellitus (DM). Moreover, given that existing CV risk assessment models used for the general population underestimate the CVD risk in RA, in 2009 the EULAR task force recommended that the CV risk estimate should be multiplied by 1.5 when certain disease characteristics are present and this was subsequently carried over in the updated EULAR recommendations in 2017 for all patients with RA. Even though data is more limited, expanding evidence suggest an increased CVD morbidity and mortality in patients with ankylosing spondylitis (AS) although the more frequent use of NSAIDs could contribute to this increase. [50,54–58] As in RA, increased inflammatory burden, as well as immune dysregulation are thought to play a crucial role in plaque progression and promotion of CVD in these patients. Interestingly, effective disease control and effective suppression of inflammation in these patients, associates with less accelerated arterial damage, once again indicating that chronic inflammation has a detrimental effect on endothelial function, atherogenesis and arterial stiffening (arteriosclerosis). [59]

3.2. Epidemiology of CVD

Rheumatoid Arthritis

The association of CVD and RA has been widely investigated in the past years and is now well established that RA patients have an excess risk for developing CVD, comparable to that reported for patients with Diabetes Mellitus. [60–62] The increased prevalence of CVD refers to all components of arterial damage, from endothelial dysfunction and arterial stiffness to abnormal morphology and the formation of atheromatic plaques and CV events, namely myocardial infarction (MI) and stroke. A meta-analysis by Levy et al. concluded that RA patients present an excess risk of fatal MI compared to the general population and this risk was found to be similar in RA patients from a Danish cohort to that of patients with DM. [63,64] This was later verified for MI in a more recent meta-analysis [54] as well as for stroke in another meta-analysis involving 16 studies [65] (Table 1)

Ambrosino et al. in a meta-analysis concluded that RA patients have increased Pulse wave velocity (PWV) and Augmentation index (Aix) compared to controls and that alteration, present even in early-stage disease, was associated with the severity of the inflammatory status [66].The same researchers showed that RA is associated with higher carotid intima-media thickness (cIMT) and increased presence of carotid atheromatic plaques [67]. Similarly, accelerated femoral atheromatosis was found to be analogous to DM in a study by Protogerou et al. [68] IMT progression in RA was associated with systemic inflammation and classical CVD risk factors in a study by del Rincon et al. [69], however CVD progression was decelerated when RA disease inflammation was suppressed, indicating that chronic systemic inflammation alone has a substantial impact on promoting arterial disease in RA[70,71]. This is further supported by the fact that increased atherogenesis in RA has been shown to be independent of the presence of classical risk factors. [72] Finally, data from two recent meta-analyses found that endothelial function estimated by flow-mediated dilation (FMD)- considered as an independent predictor of CV events- is also impaired in patients with RA. [73,74] (Table 1)

Ankylosing Spondylitis

CVD results in increased mortality in AS reaching a hazard ratio of 1.8 [59,75–77]. Studies have reported increased risk of acute coronary syndromes and stroke in patients with AS compared to controls and this was verified in a recent meta-analysis involving 18 studies. [55,78–80]. Regarding subclinical arterial disease, several studies have shown that cIMT is increased in patients with AS compared to controls, however this is less evident in AS patients with low disease activity (mean BASDAI < 4) or in patients treated with anti-TNF [81–90]. Regarding carotid atheromatosis, there is less and contradictory data, and interestingly, overall, show that carotid plaque burden is not increased in AS patients compared to controls. [82,85,87,88] Regarding common carotid artery stiffness as well as aortic stiffness studies have shown that aortic elasticity and endothelial dysfunction, estimated by PWV and FMD respectively, are impaired. [83,91,92] Again, arterial stiffness measured by Aix, was associated with C-reactive protein and AS disease activity score (ASDAS), supporting that disease activity is related to future risk of cardiovascular disease in patients with AS. [93] (Table 1)

3.3. Classical cardiovascular risk factors and Metabolic Syndrome (MetS)

Inflammation can be a risk factor for developing MetS, as it can influence metabolic homeostasis. Metabolic syndrome can transiently occur in lean individuals during infection, where increased secretion of TNF, IL-6 and IL-1 by macrophages induces a temporary insulin-resistant state [94].

Rheumatoid arthritis

Regarding traditional risk factors such as hypertension, DM, smoking, hypercholesterolemia, obesity and physical inactivity, they are commonly present in RA and this is likely to explain at least some of the excess CV risk in these patients [95][73]. RA patients have high prevalence of arterial hypertension, ascribed partially to the use of certain antirheumatic drugs such as corticosteroids, NSAIDs, cyclosporine and leflunomide. [96–99] Interestingly, an easily modifiable risk factor such as arterial hypertension is not only under-diagnosed in RA, but also under-treated, further adding to the already excessive burden for CVD. [100,101] The increased presence of metabolic syndrome (MetS) in RA compared to controls, especially insulin resistance, is associated with disease activity and higher inflammatory markers, suggesting that inflammatory processes play a notable role in this case. [102–104] (Table 1)

Several studies have shown that TNFa and IL-6 are involved in the development of insulin resistance [105,106] and blocking of TNF-alpha activity with TNFa antagonists results is improved insulin sensitivity. [107,108] Moreover, the use of methotrexate independently correlates with a reduced propensity to MetS, whereas long-term glucocorticoid exposure does not seem to associate with a higher prevalence of the metabolic syndrome. [109,110] Of particular interest is the 'lipid paradox' of active RA, where the presence of excessive inflammatory burden leads to a decrease of total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, while their CVD risk is elevated. [111–113] (Table 1)

Moreover, chronic inflammation leads to oxidative changes that alter HDL structure, causing an impairment to the normal anti-inflammatory, antioxidant and cardioprotective function of HDL. [114] Paradoxically, anti-inflammatory therapies, especially TNFa inhibitors and methotrexate, coincide with an increase in an overall

increase of lipid components, but mostly HDL, which improves the TC/HDL ratio in patients with RA, and this lipid profile is associated with a reduction in the number of CV events, probably due to the anti-inflammatory effect and subsequent suppression of RA-associated inflammation. [115–117] The use of statins and n-3 fatty acids, apart from ameliorating the lipid profile and reducing the atherosclerotic burden, has anti-inflammatory properties that may result in an even greater CVD risk reduction. [118–120] (Table 1)

Finally, the impaired physical activity in RA patients may also affect the risk of CVD, since low physical activity in RA women is associated with increased levels of oxidized low-density lipoprotein (oxLDL) and insulin, with reduced levels of HDL and atheroprotective antibodies against phosphorylcholine, and with insulin resistance. [121] Among traditional risk factors, smoking is not only an independent risk factor of atherosclerosis, but has also been associated with increased susceptibility to and worse prognosis of RA in individuals carrying shared epitope alleles and producing anti-citrullinated protein/peptide antibodies (ACPA). [122,123]

Ankylosing Spondylitis

Although data is more limited, MetS prevalence has been found to be high in patients with AS and, as expected, was associated with disease activity, suggesting an association with the high inflammatory burden of the disease. More specifically, several studies, as well as a meta-analysis of 15 case-control studies, have shown that patients with AS have higher blood pressure levels, lower HDL and triglyceride levels, are significantly more often smokers and, therefore, have higher atherogenic indices compared to controls. [56,124,125] This is compatible with current knowledge, since evidence supports a link between inflammatory cytokines such as TNFa, which is implicated in AS pathogenesis, and key components of HDL homeostasis and therefore an altered lipid profile. [126]

4. Immunological mechanisms

4.1 Endothelial dysfunction

Endothelial dysfunction is a necessary condition for the development of arterial damage. The endothelium is the key regulator of vascular homeostasis and low oxidative stress, as it is able to respond to physical and chemical signals by the production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. The endothelium modulates vasomotion, by release of vasodilator substances, namely as nitric oxide (NO)and prostacyclin (PGI2), as well as via vasoconstrictor agents, such as endothelin, and via conversion of angiotensin I to angiotensin II at the endothelial surface. Moreover, NO normally maintains the vascular wall in a quiescent state by inhibition of inflammation, cellular proliferation, and thrombosis.

Endothelial dysfunction is basically the maladaptive response of endothelial cells to pathological stimuli, mechanical or chemical. This results in endothelial activation i.e. upregulated expression of cellular adhesion molecules(intercellular adhension molecule (ICAM)-1,ICAM-3, vascular endothelial adhension molecule (VCAM-1) at the endothelium favoring plaque formation, increased leukocyte diapedesis, increased vascular smooth muscle tone due to impaired processing of vasodilator substances, particularly NO, as well as increased production of vasoconstrictor substances, resistance to thrombosis via platelet aggregation and oxidative stress upregulation. [46,127,128] Compromised barrier function, as a result to endothelial cell damage, leads to an increase in permeability to lipoproteins and plasma constituents, resulting in penetration of lipids into the arterial wall and subendothelial lipoprotein retention. These retained lipoproteins are subsequently taken up by macrophages to form foam cells and fatty streaks within the vessel wall. [129] Moreover, endothelial dysfunction leads to accumulation of monocytes and proliferation of smooth muscle cells which migrate to the lesion and lead to the thickening of the vessel wall and formation of fibrous tissue. Ultimately, a fibrous cap develops over the plaque, which, when becoming unstable, leads to rupture and subsequent thrombosis and CV events. [130]

Endothelial dysfunction, while part of a normal immune system defense, can lead to atherogenesis and CV events as a result to prolonged and more intense inflammatory stimuli, which induces sustained endothelial activation. Both traditional and novel cardiovascular risk factors including smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, as well as obesity, elevated CRP, and chronic systemic infection, are all associated with alteration in endothelial function. [131] As previously mentioned, in CIRD, classical risk factors are more prevalent and therefore have a more injurious affect on the vasculature. Moreover, autoimmune-inflammatory mechanisms include the accumulation of inflammatory molecules (lymphocytes and macrophages), presence of autoantibodies and the secretion of pro-inflammatory cytokines, chemokines and adhesion molecules, that have systemic vascular consequences, which subsequently reduce synthesis of NO and initiate the cascade of events leading to endothelial dysfunction and CVD. [130,132]

Several studies have focused recently on the correlation between such biomarkers indicative of endothelial dysfunction and CVD in patients with CIRD, particularly RA and on how biologic therapy influences these markers associated with the development of CVD. Dessein et al. showed that serum levels of VCAM-1were associated with common cIMT and plaque presence and IL-6 was independently related to endothelial activation. [128,133,134] VCAM-1 was also partially correlated with cIMT in RA patients undergoing Infliximab therapy, but this was not evident for carotid plaques or other biomarkers of endothelial cell activation, even though anti-TNF treatment seems to reduce the serum levels of ICAM-3 and P-selectin molecules. [135,136] In another study by Kerekes et al., impaired endothelial function, measured by flow-mediated dilation (FMD), was associated with IFN-γ levels in RA patients. [137] Asymmetric dimethylarginine (ADMA) levels- an inhibitor of nitric oxide (NO) synthase and a possible marker of endothelial dysfunction- are found elevated in RA patients, and this was associated with increased inflammatory markers , even though there seems to be no correlation with in vivo assessments of vascular function and morphology. [128,138] In AS studies indicate increased levels of ICAM-1, TM and IL-6, as well as increased ADMA serum concentrations, not correlated however with disease activity. [90,139,140]

4.2 Oxidative stress

Oxidative stress reflects the imbalance between production of reactive oxygen species (ROS) and impaired antioxidant capability, which in turn causes cell injury by directly oxidizing cellular protein, lipid, and DNA or via cell death signaling pathways. Oxidative stress has been demonstrated to play an important role in the pathogenesis of arterial damage especially by promoting the oxidative modification of LDL. Oxidized LDL takes part in many phases of atherogenesis: stimulates the binding of monocytes to the endothelium, foam cell formation, the development of plaques, plaque destabilization and thrombotic complications. [46,141]

Oxidative stress and inflammation are interrelated and this interaction promotes plaque formation and rupture. Increased oxidative stress is thought to play a role in the pathophysiology of inflammatory diseases such as RA and AS, contributing to immune system dysregulation and autoimmunity. [132,142]. In RA, the overproduction of TNFa is a main contributor to increased ROS release, and this is related to disease activity. ROS conserves oxidative stress, further promoting in this way cell damage and atherogenesis. [143,144].Moreover, oxidative modification of LDL has been linked to TNFa action and HDL constituents may be altered by the inflammation, thus losing their ability to remove cholesterol from atherosclerotic lesions and reducing their antioxidant activity. Studies showed increased levels of oxidative stress markers in patients with AS [145,146] however data is limited. Interestingly, control of disease activity via the use of TNFa inhibitors in RA can reduce oxidative stress [147], probably also directly reducing in this way the risk of CVD.

4.3. Innate immunity, Toll like receptor (TLR) signaling and NLRP3 inflammasome activation

Innate immune mechanisms play a central role in atherogenesis, involving activation of pattern-recognition receptors (PRRs), especially damage-associated molecular patterns (DAMPs), on the surface of ECs, and induction of inflammatory processes and atherogenesis. [148] Scavenger receptors expressed by macrophages, recognize specific epitopes of oxidized LDL and mediate clearance of lipoproteins and intracellular cholesterol accumulation, thereby promoting foam cell formation.

Signaling through the Toll like receptor (TLR) pathway has been implicated in the pathogenesis of autoimmune diseases including RA, as well as in arteriosclerosis and atherosclerosis. TLRs are membrane glycoprotein PRRs that recognize both PAMPs and DAMPs and initiate complex signal transduction pathways that mediate strong inflammatory responses. They are widely expressed on many cell types such as ECs, macrophages, dendritic cells, lymphocytes, and vascular smooth muscle cells, all of which are implicated in atherosclerotic lesion development. Atherosclerotic lesions, display enhanced expression of specific TLRs, especially TLR2 and TLR4, on the surface of ECs. In atherosclerosis oxidized LDL can trigger TLR signaling thus mediating macrophage accumulation and infiltration, induction of proinflammatory cytokines, activation of inflammatory cells and decreased presence of regulatory T cells in the atherosclerotic lesions, conditions which are known to promote atherogenesis. [130,149,150]

In RA, there is the pathogenic expression of inflammatory cytokines- including TNF-α, IL-1, and IL-6-by synovial macrophages and an increasing body of evidence supports the role of TLRs in the persistent, progressive activation of macrophages. Several studies have shown an increased expression of different TLRs by cells within the RA joint, as well as an increased responsiveness of RA synovial fibroblasts and RA synovial macrophages to microbial TLR ligands. [151–153] Therefore, both RA and atherosclerosis are characterized by chronic inflammation, the accumulation of macrophages, dendritic cells, and B and T lymphocytes caused by the local expression of TLRs and potential endogenous TLR ligands. Moreover, the release of endogenous TLR ligands as well as cytokines, such as TNFa and IL-6, from the inflamed synovial tissue might further activate macrophages in the atherosclerotic plaque and partly explain the increased occurrence and severity of atherosclerosis in RA. [151]

Regarding AS, emerging evidence indicate that TLRs play a potential role in the pathogenesis of SpA, which is supported by the fact that certain TLRs have been found to be overexpressed in patients with AS. De Rycke et al showed increased TLR4 expression in peripheral blood mononuclear cells from patients with AS, as well as increased TLR2 and -4 expression in the inflamed synovium of patients with SpA (including PsA, AS and undifferentiated spondyloarthritis) compared with osteoarthritis or RA synovium, which was sharply reduced by TNFa blockade. [154] Similarly, Assassi et al. showed upregulation of gene expression of TLR4 and 5 in AS but not healthy controls. [155] As in RA, it is probable that engagement of TLRs

activates inflammatory cells and promotes secretion of pro-inflammatory cytokines such as IL-6, TNFa and type I IFNs, which not only drive inflammation in AS, but also could further activate macrophages in the atherosclerotic plaques and thus promote atherogenesis.

Recently, there is much interest in the possible role of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in arterial damage. The NLRP3 inflammasome is an intracellular signaling molecule that, after being stimulated by TLRs and NFkB, activates caspase-1, which in turn cleaves the pro-inflammatory cytokines IL-1β and IL-18 to their active forms, known to play a vital role in promoting the development of lipid plaques and destabilizing the plaques. [156,157] In a study by Altaf et al. NLRP3 and downstream cytokine expression was increased in the peripheral blood of patients with acute MI and unstable angina compared to controls and this was modulated by high dose rosuvastatin. [158] High expression of NLRP3 was also evident in carotid atherosclerotic plaques and this was associated with plaque vulnerability. [159] The implication of NLRP3 in atherogenesis is further supported by the fact that inhibition of NLRP3 reduced plaque formation and decelerate atherosclerosis in mice. [160] Studies have shown NLRP3 is activated by cholesterol crystals and releases IL-1β [161,162], also demonstrating that the deposition of crystalline cholesterol in arteries or elsewhere is an early cause rather than a late consequence of inflammation.

NLRP3 inflammasome, being an important component of the inflammatory process, has also been shown to have major involvement in the development of CIRD. Several studies have implicated activation of NLRP3 and subsequent IL-1β secretion in the pathogenesis of RA, as NLRP3 gene expression and caspase-1 and IL-1β levels were elevated in patients with active RA. [163,164] Finally, a study by Kastbom et al. showed that Genetic variants of the NLRP3 inflammasome increased the risk of stroke/transient ischemic attack in RA patients [165] In AS, data is scarce and contradictory concerning the role of NLRP3 inflammasome in pathogenesis. A recent study by Kimet al. showed that there was higher mRNA expression and protein expression of NLRP3 suggesting a potential pathogenic role of NLRP3 in AS. [166] Similarly, Zhao et al. reported association with AS susceptibility and Kim et al [167], whereas Kastbom A et al. found no association between them. [165]

4.4 Macrophage accumulation

Macrophages are fundamental contributors in the development and progression of atherosclerosis. Atherosclerosis begins with a fatty streak, which is made up almost entirely of monocyte-derived macrophages. Macrophages and monocytes ingest oxidized LDL, transform into foam cells, and recruit additional monocytes and macrophages to the vessel wall. The development of an atheroma continues as other inflammatory cells are recruited to the intima and as smooth muscle cells proliferate, thereby increasing the lesion size. [46,168]

The accumulation of macrophages at the site of inflammation producing inflammatory mediators, serve as a prominent feature in both systemic inflammation and atherosclerosis. In RA, macrophage activation, as reflected by serum neopterin concentrations –a derivative of pyrimidine metabolism produced by activated monocytes, macrophages, and dendritic cells upon stimulation by interferon gamma produced by T-lymphocytes-, is increased compared to controls, with a significant correlation with disease activity and anti-CCP positivity and even methotrexate use. [169,170] However, other studies suggest that neopterin levels are not correlated with disease duration or activity and are independent from methotrexate therapy. [171,172] In another study by Voloshyna et al. [173], the presence of RA plasma induced pro-atherogenic changes in gene expression and was associated with augmented lipid accumulation and foam cell formation by macrophages, suggesting that chronic exposure to RA plasma adversely affects the capacity of monocytes/macrophages in the arterial wall to metabolize cholesterol and maintain lipid homeostasis, thereby contributing to the development of premature atherosclerosis.

Regarding AS, Yanuz et al. found that neopterin levels and human chitotriosidase levels (which is also produced by macrophages when activated) are significantly elevated in AS patients with active disease compared with inactive AS patients and the latter were correlated with BASDAI scores and ESR and CRP levels. [174]

4.5 Pro-inflammatory cytokines

Proinflammatory cytokines are involved in all stages of arterial disease and therefore are considered key mediators in the pathogenesis of CVD. From activation of the endothelium and recruitment of immune cells, to monocyte differentiation,

foam cell formation and plaque rupture and thrombosis, cytokines orchestrate the whole inflammatory process, both the innate and adaptive immune response. [175,176]

Dyslipidemia is promoted by sustained inflammation as certain cytokines, namely TNFa and IL6, have been shown to influence lipid levels, shifting them towards an atherogenic profile. [177,178] Other cytokines, such as IFN-γ and TNF-α can modulate the permeability of vascular endothelial cells to macromolecules such as LDL and activated endothelial cells release chemokines and other cytokines in order to recruit immune cells, particularly monocytes and T-lymphocytes, in the lesion. [179]

Cytokines are also responsible for the differentiation of monocytes to macrophages in the arterial intima and the macrophage differentiation to phenotypes. T-helper-1 (Th1) cytokines such as IFN-γ and IL-1β favor M1 phenotype, which produces pro-inflammatory cytokines such as IL-6, IL-12 and TNF-α, whereas Th2 cytokines such as IL-4 and IL-13 are required for M2 phenotype, which produces anti-inflammatory cytokines such as IL-10 and TGF-β. TNF-a, IL-4 and IL-13 are also known to promote LDL oxidation by monocytes/macrophages and IFN-γ stimulates macrophage foam cell formation by increasing the uptake of modified LDL and decreasing cholesterol efflux. A recent review highlighted the cellular and oxidative mechanisms of IL-6 signaling in the vasculature, including endothelial activation, vascular permeability, immune cell recruitment, endothelial dysfunction, as well as vascular hypertrophy and fibrosis. [180,181]

TL1A is another inflammatory cytokine, member of the TNF superfamily of ligands, whose impact on atherogenesis has recently been a topic of interest. TL1A, via binding to death-domain receptor 3 (DR3) expressed in lymphocytes, is important for T-cell costimulation and Th1 polarization, induction of pro-inflammatory cytokines/chemokines and promotes macrophage foam cell formation. [182,183] Furthermore, various growth factors, produced by macrophages, ECs and T-cells, control the migration and proliferation of smooth muscle cells and other pro-inflammatory cytokines, such as IFN-γ and TNFa, affect plaque vulnerability by stimulating the apoptosis of macrophages and of smooth muscle cells. Finally, certain pro-inflammatory cytokines, including TNF-a and IL-6, may also induce coagulation, by activation of coagulation factors, such as factor X, prothrombin and thrombin-antithrombin 3 complexes.

As in arteriosclerosis and atherosclerosis, it is well known that aberrations in cytokine expression and signaling have pivotal pathogenetic roles in CIRD. In RA, many of the local and systemic manifestations appear to result from the production of a variety of cytokines within the inflamed synovium, particularly TNF-α, IL-1 and IL-6 [184],and inhibition of these cytokines with biologic agents is currently a main therapeutic option for patients with RA. Interestingly, between the proinflammatory cytokines involved in the pathogenesis of RA, TNFa and IL6 are independently predictive of subsequent CV event, suggesting a more direct effect of these cytokines on the endothelium. [185] The overexpression of these proinflammatory cytokines in RA could be responsible for the accelerated CVD risk. Increased production of IFNγ in RA, as a result to a significant amount of $CD4^{+}CD28^{-}$ cells which promoteTh1cell activation, could also have a critical role in accelerated cardiovascular disease [186,187].

Regarding TL1A, recent studies have demonstrated that this cytokine is overexpressed in synovial fluids and synovial tissue, as well as serum of rheumatoid factor (RF)-seropositive RA patients, and this expression is correlated with disease activity. [188,189] In addition, individual serum levels of TL1A correlated with the progression of carotid atheromatic plaque height and the formation of new plaques, indicating that the dysregulated TL1A induced signaling may be associated with risk for accelerated arterial damage in RA. [190]

Finally, cytokine-induced metabolic effects could induce atherosclerosis by alteration of classical CVD risk factors. Cytokines such as TNFa and IL-6, favor insulin resistance in RA patients, as well as a more atherogenic lipid profile. [105,191,192] This is amplified by the fact that anti-TNF treatment improves insulin resistance, increases the levels or atheroprotective HDL, however does not seem to ameliorate overall atherogenic index in the long term, while anti-IL6 treatment seems to improve insulin resistance but increases levels of total cholesterols, LDL and triglycerides [111,193]

Data on the pathogenic role of cytokines and atherosclerosis in AS is more limited. As previously mentioned, among pro-inflammatory cytokines, TNF-α is a key pathogenic factor in AS. As in RA, TNF-a may also have a harmful effect on lipid profile in patients with AS, results from studies examining the impact of TNF inhibitors on lipid profiles in AS are controversial and may present only a minor effect. [194–196] Regarding IL17, data from different studies are contradictory, as IL-

17 has been thought to be atheroprotective as well as proatherogenic. IL-17 seems to inhibit the development of Th1 cells by activation of IL-17 receptors. On the other hand, higher IL-17 expression in human carotid plaques was associated with a more stable phenotype. Apart from the direct effect on the vasculature,IL17 is known to be elevated in obese individuals and are implicated in the development of MetS, as they increase IR. [197,198]

5. What it all means for treatment of patients with Inflammatory Arthritis

The therapeutic effect of different biologic and non-biologic antirheumatic drugs on CVD has been widely investigated in the recent years. Firstly, antirheumatic therapies seem to differently affect classical CVD risk factors and MetS. In RA there is evidence from systematic reviews and large observational studies that MTX therapy may decrease CV morbidity and mortality [199]. The use of MTX is associated with a reduced chance of having MetS [110] but increases total cholesterol, LDL, HDL and triglycerides in RA. However, these lipid increases are possibly due to the inflammatory-dampering effect and essentially reflect normalization of the lipid levels to those seen in the general population [112,113] [203,204] and therefore not generally believed to increase CV risk. We should point out that the pathophysiologic mechanisms causing increased prevalence of MetS differ between rheumatic diseases, therefore it is possible that each condition requires a more customized management for prevention of CVD.

On the other hand, established therapies classically used for the management of traditional risk factors, such as statins or *angiotensin-converting-enzyme* inhibitors, could have a favorable impact on CIRD by bearing an anti-inflammatory effect. A recent review by Soulaidopoulos et al. reported evidence on the angioprotective, antioxidative and anti-inflammatory properties of statins and their efficacy in reducing RA-disease activity, supporting that RA patients should be screened via non-invasive methods for increased subclinical CVD –namely by cIMT evaluation- in order to receive lipid-lowering therapy when needed. [47,50,119]

Numerous studies have demonstrated that the use of biologic agents in CIRD blocking cytokines, such as TNF and IL6, can decelerate the atherogenic process and

even improve endothelial function, arterial stiffness or arterial wall hypertrophy. A recent meta-analysis focusing on the impact of TNFa inhibitors showed that TNF-a antagonist treatment induced a significant improvement in aortic PWV and Aix and therefore on CV risk. [200] The same stands for IL-6 receptor inhibition, as the use of the anti-IL-6 receptor antibody tocilizumab improved endothelial dysfunction and aortic stiffness in patients with RA. [201] A review by Tam et al concluded that the use of biologic agents in RA probably is effective in preventing the progression of subclinical atherosclerosis and improving arterial stiffness, although results from different studies are contradictory, and it cannot be clear whether this effect beyond that of controlling inflammation irrespective of the disease modification strategy by which this is achieved. [202]

In a large British cohort patients with RA receiving TNF inhibitors have a decreased risk of MI compared with patients receiving cDMARDs. [203] Finally, a meta-analysis examining the association between CV events and antirheumatic drugs concluded that TNFa inhibitors and MTX are both associated with a reduced risk of CV events [204] Data on other therapies is more limited. A recent review by Ketelhuth et al found evidence from preclinical and clinical studies on the therapeutic effect of various immunomodulatory therapies on CVD, including IFNγ and IL17. [205] Koga et al. argued that postnatal blocking of IFN-γ function by gene transfer of a soluble mutant of IFN-γ receptor in adult mice prevented the progression of established plaques that remodeled toward a more stable and less inflammatory phenotype [206], thus implying that IFN-γ blockade could reduce CV events. Importantly, a recent secondary CVD prevention multicenter placebo-controlled study revealed that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering. [207] Such a claim paves the way for the use of biologic agents specifically for the management of CVD.

The use of biologic agents in the majority of studies was not associated with significantly increased infections compared to the placebo-treated group. However, the potential risk of the development of opportunistic infections due to immunosuppression should be noted, and the expected benefit from any biologic treatment should be considered in the context of this risk.

Recently, the chemoattractant chemerin, which is considered an independent predictor of cardiovascular disease risk, was associated with endothelial activation

and arterial damage in RA, and blockade of TNFa and IL-6 seems to reduce chemerin concentrations in RA patients. [208,209] Similarly to classical risk factors, there is heterogeneity with respect to autoimmune-inflammatory risk factors between rheumatic diseases. Cytokines, such as TNF-α and immune complexes are primarily involved in arthritides, such as RA and AS, whereas other cytokines are involved in other autoinflammatory diseases, i.e. interferons and autoantibodies are rather involved in SLE-associated vascular conditions. Therefore, the therapeutic management of CVD in each condition should be customized.

6. Practical implications

The pathogenetic association between inflammation and CVD could provide valuable insights on the development and progression of CVD in patients with CIRD, such as RA and AS, who by default are characterized by high grade inflammation,. More importantly, better understanding of the common underlying pathogenic conditions and the revelation of the exact process and molecules implicated, could provide new therapeutic targets and options for these patients. In other words, if we are able to adequately understand the association between the inflammatory process and the development of CVD in each of these conditions, we could be able to effectively manage both arterial damage and CIRD with therapies targeting molecules and specific pathways that are implicated in the shared pathogenesis.

As previously mentioned, inflammation per se plays a role in the development of CVD only to a certain degree. To ameliorate the impact of CVD in morbidity and mortality of patients with CIRD, such as RA and AS, it is also important to promptly recognize and effectively manage classical modifiable CVD risk factors, as studies have shown that they are under-diagnosed and under-treated despite a more close and regular monitoring. [100,101] As outlined above, inflammation alters the metabolic profile in these patients and effective treatment normalizes this metabolic state, however, anti-hypertensive treatment and especially lipid-lowering therapy should be initiated in each patient in such need early in the disease course. Since the decision to start drug treatment of high blood pressure and lipids is based on total CV risk levels as assessed by international algorithms (e.g. the EU score), it is expected that the multiplication of these scores in e.g. RA will have substantial impact on the

management of CV risk factor in RA. Moreover, we should always take into account before initiation of therapies, the demographic characteristics of each CIRD and each patient individually. For example, the age of disease onset for RA patients is usually greater than AS patients and AS patients are usually men, thus adding to the already increased CV burden. Lastly and more importantly, disease duration, apart from disease activity, seems to be an important factor determining CVD. This is more documented for RA [47] and several studies indicate that it applies for other CIRD.

We should point out that despite all advances and research on the management of CVD in CIRD, studies still denote an increased prevalence of CV events and mortality in rheumatic diseases compared to the general population. however, awareness has lead to a decline in the prevalence of CV events compared to previous years, as denoted by a recent meta-analysis by Mathieu et al. that found a reduction in the prevalence and risk of MI and stroke in AS compared with a previous meta-analysis by the same researchers [55,210] probably attributed to improvements in the control of cardiovascular risk in AS.

The possible role of cytokine measurement in the diagnosis and prevention of CV events should be also considered. Wainstein et al. showed that IL-6 levels are predictive of significant coronary artery disease in patients referred for coronary angiography and Lin et al. concluded that IL-6 demonstrated a notable prognostic value for predicting cardiovascular mortality. [211,212]

To conclude, CIRD and arteriosclerosis and atherosclerosis share common pathogenic mechanisms and this raises the possibility of a common therapeutic strategy. Apart from adequate management of cardiovascular comorbidities, which still remains insufficient, therapeutic options could include blockade of proiflammatory cytokines implicated in both diseases. Whether the low relative risks of CVD in CIRD justify further research in the biomedical field to broaden therapeutic options remains open to debate. Future studies should focus on other potential targets implicated in atherosclerosis pathogenesis, i.e. the NLRP3 inflammasome or specific or multiple chemokines.

EXPERIMENTAL

AND

CLINICAL DATA

1. Rationale and Purpose of the study

Cardiovascular disease remains the main cause of morbidity and mortality worldwide. Classical risk factors for developing CVD –namely arterial hypertension, dyslipidemia, smoking and glucose intolerance- have been extensively studied and can now be effectively managed, thus significantly reducing CVD risk in the general population. However, when it comes to diseases characterized by chronic systemic inflammation, such as CIRD, the prevalence of CVD remains accelerated despite adequate control of classical risk factors. The answer to this lies in the common pathogenic background of CVD and CIRD, i.e. chronic inflammation and dysregulation of the immune system, which in turn generates new questions regarding the degree, extent and type of arterial damage seen in each disease and more importantly the proper management for preventing the acceleration of cardiovascular disease.

Numerous studies worldwide have examined the different aspects of accelerated CVD in inflammatory disorders and current data on the subject is extensive. It is well established that such patients with CIRD present with more CVD events and more extended atherosclerosis than the general population, reaching the conclusion that they require more aggressive treatment not only of the classical risk factors but also of the underlying condition.

Nonetheless, many of these studies present methological issues and leave some questions unanswered. Only very few studies examined the presence of plaques in femoral arterial beds, which is important in assessing multifocal disease and has been shown to be accelerated in patients with RA. [213,214] No study has examined patients with inflammatory load without classical CVD risk factors, in order to clarify in what extend inflammation affects the arteries and which aspect of arterial disease in more evident. In the same notion, limited studies have examined the progression of subclinical CVD in patients with a history of CIRD without inflammatory load during the follow-up period, i.e. eliminating the "inflammation factor" and examining if other aspects/ pathogenetic mechanisms influence CVD progression.

Moreover, not all studies used strict 1:1 matching between patients and controls for all classical CVD risk factors as well as demographic characteristics, which could be regarded as an important limitation and could lead to inaccurate results. Similarly,

even though statistical analysis allows comparison of patients and controls after adjustment for classical risk factors, such results could be still biased, since differences in the severity and duration of comorbidities are not taken into account.

In this notion, the present research aims to investigate subclinical CVD in two different inflammatory diseases. More specifically patients with Rheumatoid Arthritis and Ankylosing Spondylitis will be tested for established vascular biomarkers of subclinical CVD and the results will be compared to those of apparently healthy controls. Analysis of the results will include strict 1:1 matching as well as comparison of specifically selected patient and control populations characterized by the absence of hypertension, diabetes, dyslipidemia and smoking, to determine how *disease per se* differentially affects different aspects/components of arterial disease, namely intraluminal plaque formation (atheromatosis) and intra-arterial wall changes (arterial stiffening and/or hypertrophy).

More importantly, the present study examines not only the increased CVD burden in these disorders, but also the progression of arteriosclerosis and atheromatosis after an adequate period of time. This will provide valuable information on the way and the degree residual inflammation in treated patients further affects the arteries and in this manner, how the management of each disease affects the progression of CVD and indicate therapeutic directions and goals. Moreover, prospective re-evaluation will allow better understanding of the impact of each of the diseases' components, that is chronic systemic inflammation, genetic substrate and drugs, when adequate control of the other classical CVD risk factors is achieved.

2. Study population and Methodology

2.1 Study population

In the present study we included consecutive individuals attending the Laikon Hospital's outpatient clinics, over the age of 18 years, with:

- RA patients who met the ACR/EULAR 2010 classification criteria for Rheumatoid Arthritis [23]
- AS patients diagnosed according to the ASAS classification criteria for axSpA [44]
- Apparently healthy individuals who were referred for evaluation of suspected arterial hypertension, and who served as controls

Exclusion criteria included: known clinical CVD, malignancy, chronic renal failure or other concomitant chronic or acute inflammatory disease. Exclusion criteria also included diabetes mellitus (already diagnosed by a physician or 2 fasting plasma glucose levels on different days >125 or HbA1c>6.5%).

The study was approved by our Institutional Scientific Board and all cases and controls signed informed consent according to the Helsinki Declaration.

All patients enrolled in the study were re-evaluated after a minimum of 3 years and a maximum of 3.5 years (follow-up time). RA and AS patients lost to follow-up or not regularly followed-up (i.e. at least every 4 months during the whole follow-up period) were excluded from the analysis.

2.2. **Recording of clinical parameters**

2.2.1 D**emographics and p**hysical, laboratory and clinical markers

Age, gender and race were recorded for all subjects. Personal as well as family history of CVD, history of arterial hypertension and hyperlipidemia, smoking (current or previous as well as calculation of pack-years) and alcohol consumption, as well as medications were recorded.

All patients and controls underwent body weight, height, waist and hip circumference and arterial pressure measurement and subsequently Body Mass Index (BMI) and waist-hip ratio were calculated.

Laboratory tests within 3 months, after 12hour fasting, were recorded including: full blood count**,** glucose, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides, liver and kidney function tests (AST, ALT, γGT, serum Creatinine, Urea), as well as Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) were performed in all subjects. Moreover Rheumatoid factor (RF) and Anti-cyclic citrullinated peptide antibody (anti-CCP) were measuredin RA patients.

Indices of disease activity were calculated for patients with RA and AS. More specifically, RA disease activity and severity were assessed by the Disease Activity Score on 28 joints (DAS28) [24] and Health Assessment Questionnaire score (HAQ-DI) respectively [26] and AS disease activity and function were calculated by namely Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [39] and Bath Ankylosing Spondylitis Functional Index. [41]

All parameters were inquired, measured and calculated and recorded both at study initiation (baseline) and follow-up time.

2.2.2 **Re-evaluation of classical CVD risk factors and re-classification of patients**

In all patients without DM and with fasting glucose of ≥110mg/dl, glucose was re-evaluated and in case of hyperglycemia they were excluded from the analysis.

In case where a diagnosis of hyperlipidemia had not been made, and fasting LDL levels were ≥160mg/dl, subjects were considered to have hyperlipidemia.

In case of known arterial hypertension, subjects were instructed do a 7-day home BP monitoring or to use a 24-hour monitoring device and they were further categorized as well controlled or poorly controlled according to mean blood pressure levels (systolic BP/diastolic BP: ≤130/80 mmHg or >130/80mmHg respectively). Similarly, in cases where a diagnosis of hypertension had not been made and subjects presented with AP

≥130/80mmHg, they were also instructed to do an out-of –office 7-day home BP monitoring or use a 24-hour monitoring device and were considered to have hypertension if they presented with mean SBP ≥130mmHg or mean DBP≥80mmHg. [100]

Evaluation was performed both at baseline and follow-up time.

2.3Assessment of subclinical Cardiovascular Disease

All patients and controls abstained from food, drink or any medication and smoking for 12 hours prior to examination. All measurements were conducted between 8:30am and 12:30pm, in a quite environment with a stable temperature of about 26ºC. Subjects were comprehensively studied at baseline and follow-up for:

a) aortic stiffness by carotid to femoral pulse wave velocity (PWV) and pressure wave reflections by augmentation index (AIx) –an indirect marker of arterial stiffness- using pulse wave analysis methodology (Figure 10)

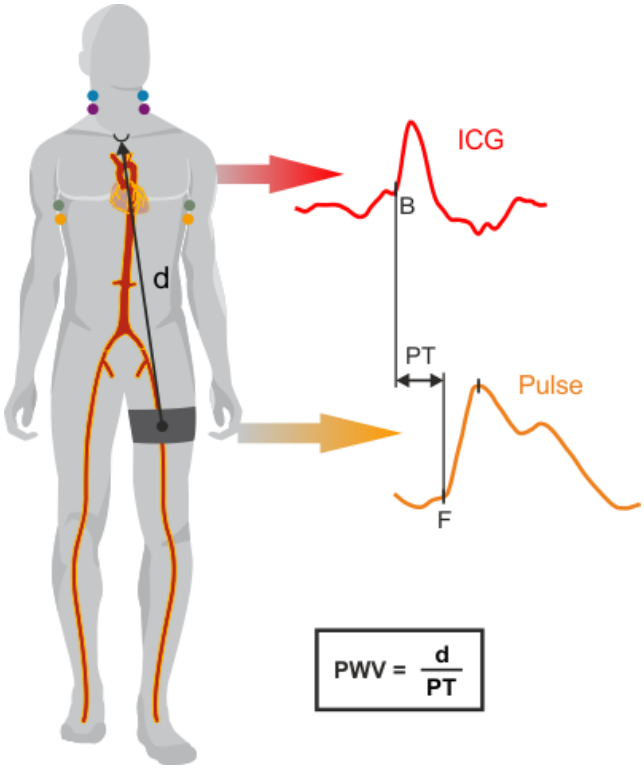

Figure 10 Pulse wave velocity measurement

b) carotid hypertrophy, by intimal-medial thickness (IMT, adjacent to plaques when present) and cross sectional area (CSA) in both the right and left common carotid arteries. (Figures 11 and 12)

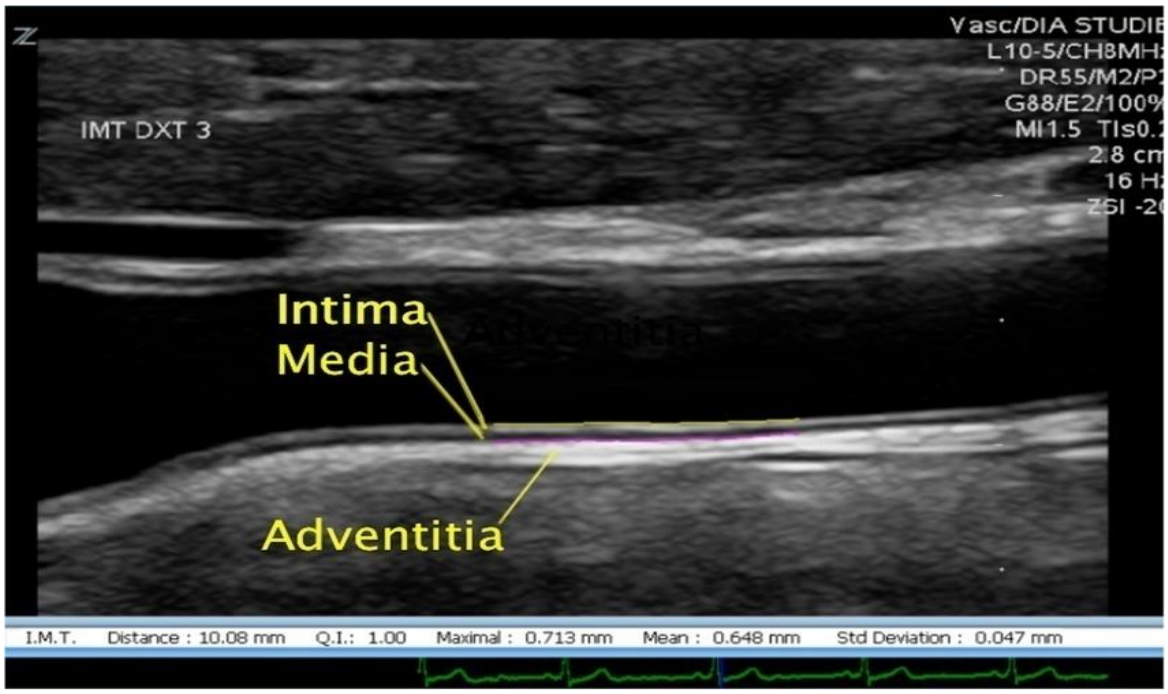

Figure 11 IMT measured as the distance between lumen-intima (yellow line) and media-adventitia (pink line) interfaces

c) subclinical atheromatosis namely the presence of atherosclerotic plaques in a total of 8 arterial beds both in carotid and femoral arteries (left and right common and internal carotid arteries and carotid bulb and both common femoral arteries). (Figure 12)

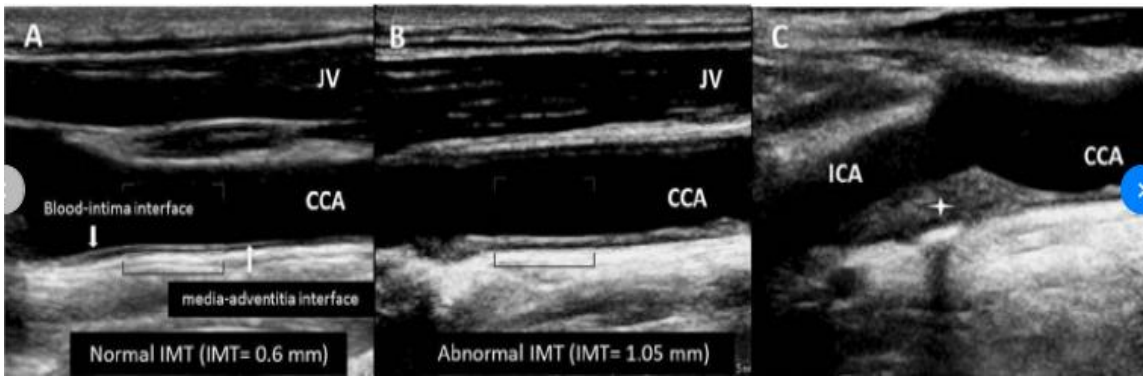

Figure 12 Noninvasive vascular ultrasound of the carotid arteries A)Normal IMT measurement at the posterior level of the common carotid artery B)Abnormal IMT (cut-off value for abnormality >0.9mm) C) Large atherosclerotic plaque at the birfurcation and internal

PWV and Aix were assessed using the Sphygmocor device (AtCor Medical, Australia). PWV was calculated by application of 2 sensors on the common carotid and femoral artery. The mean score of 2 consecutive measurements was recorded; if the 2 measurements differed by >0.5, a third measurement was performed and the mean value of all 3 measurements was used. The measurement of each individual was categorized as normal or abnormally high based on both a cutoff value of 10 m/s and age-adjusted normal range curves. [215,216]

Measurements were performed by a single technician using high-resolution B-mode ultrasound (Vivid 7 Pro, GE Heathcare) with a 14-MHz multi-frequency linear transducer. The common carotid arteries were scanned in both transverse and longitudinal plane and IMT measurements were performed using automatic IMT measurement software. ccIMT (common carotid IMT) measurements >0.9mm were considered pathological regardless of age and gender. Atheromatic plaques were defined as local increase of the intima-media thickness (IMT) of >50% compared to the surrounding vessel wall, an IMT >1.5 mm, or local thickening >0.5 mm. [217,218]

2.4 Statistical analysis

Normality of sample distribution was examined by the Shapiro-Wilk test. Continuous variables are presented as mean±standard deviation (SD) when sample had a normal distribution, or median and 25^{th} and 75^{th} percentile values (interquartile range (IQR)) for non-normally distributed samples. Frequency of categorical variables was computed by percentiles. For comparison of continuous or categorical variables we used paired t-test or chi-square test, respectively. We used multivariate logistic regression models, before and after correcting for the presence of intermediates/confounders, to compare the probability for the formation of new atheromatic plaques or the yearly progression rate of IMT between the two groups.

The selection of CVD risk factors as potential intermediates/confounders was based on their clinical use as suggested by worldwide recommendations for screening for total CVD risk. [61] Moreover, RA disease duration, family history of CVD, difference in Body Mass Index (BMI), antihypertensive and lipid-lowering drugs, as well as baseline vascular status, were further included in the analysis. Stata version 12 was used for all analyses and $p<0.05$ was considered as the level of statistical significance in all cases.

3. Results

3.1 Baseline

3.1.1 Demographics and clinical characteristics of studied subjects

Overall, 982 subjects fulfilled inclusion criteria and were enrolled in the study (Table 1):

- 674 controls, aged 52.2±12.7 years, 53% men
- 227 patients with RA, aged 57.8±12.4years, 17.6% men
- 81 patients with AS, aged 46.7±13.2 years, 85.4% men

Demographics, clinical characteristics and prevalence of classical CVD risk factors are shown in Table 2.

As expected, patients with AS were younger compared to controls and most of them were men whereas the vast majority of patients with RA were women.

Studied groups presented significant differences compared to controls regarding the prevalence of classical CVD risk factors.

One hundred eighteen controls (17%) were reclassified as having arterial hypertension –as defined in study protocol- as opposed to 22 with RA (10%) and 10 with AS (12%).This difference is due to the fact that most control subjects were referred to the Cardiovascular Research Laboratory after being referred to the Laikon Hospital Outpatient Clinic for suspected hypertension. Consequently, a greater proportion of controls were classified as having arterial hypertension compared to the other studied groups.

Similarly, 63 controls (9%), 15 patients with RA (7%) and 3 patients with AS (4%) were reclassified as having hyperlipidemia, according to serum LDL levels.

Finally, specific indices indicative of disease activity were as follows:

- for RA patients, median CRP was 4.5mg/l (IQR 2.2-9) and median ESR was 21.5mm (IQR 12-39).
- for AS patients, median CRP was 4mg/l (IQR 2-12), median ESR was 15mm (IQR 9-25), median BASDAI was 1.4 (IQR 0.4-3.1) and median BASFI was 2.3 (IQR 1-3.1)

In regards to therapies

- 158 RA patients were receiving cortisone, 127 methotrexate, 41 leflunomide and 76 were receiving biologic therapy (22 Adalimumab, 16 Etanercept, 15 Tocilizumab, 9 Anakinra, 7 Golimumab, 3 Abatacept, 2 Rituximab, 1 Infliximab and 1 Certolizumab pegol)
- 51 AS patients were receiving biologic therapy (23 Adalimumab, 16 Infliximab, 8 Etanercept, 4 Golimumab) and 14 were receiving NSAIDs.

3.1.2 Vascular indices of studied subjects

As regards to subclinical cardiovascular disease, all vascular indices examined are presented in Table 3.

Univariate analysis showed RA patients presented similar IMT of both carotid arteries as controls. As expected AS patients had less IMT values than controls, which can be attributed to the younger age as well as significantly smaller prevalence of arterial hypertension.

As to arteriosclerosis, AS had better outcomes than controls, whereas RA patients showed a worst arteriosclerotic profile

Regarding atheromatosis, RA patients had more plaques than controls, as expected. Interestingly, univariate analysis did not reveal significant differences regarding femoral atheromatosis between controls and any of the study groups.

When taking into account pathological IMT and PWV values, the proportion of RA and AS patients that had abnormal arterial hypertrophy and arteriosclerosis indices was similar to controls, except for PWV age reference values in RA patients (Table 4).

Rheumatoid arthritis

Multivariate analysis revealed differences between RA patients and control subjects as to carotid atheromatosis, hypertrophy of the LCCA and AIx, reflecting arterial stiffness. Even though statistical analysis allows comparison of RA patients and controls after adjustment for classical risk factors, such results could be still biased, since specific parameters, such as severity, duration a defective management of risk factors, are not taken into account. In order to determine whether RA disease *per se* has the same impact on atheromatosis, arterial stiffening and/or hypertrophy, another analysis was performed utilizing specifically selected RA and control populations characterized by the absence of hypertension, diabetes, dyslipidemia and smoking, to test the hypothesis that *RA disease per se* differentially affects atheromatosis, arteriosclerosis, and arterial hypertrophy in distinct arterial sites.

Only 48 of RA patients (18%) were never-smokers, had no hypertension (defined by absence of antihypertensive treatment and elevated out-of-office blood pressure, assessed by home BP monitoring or 24-hour ambulatory BP monitoring) [100], diabetes mellitus (use of antidiabetic drug and/or abnormal glucose and/or HbcA1) and dyslipidemia (use of statins and/or LDL>160mg/dL) and were eligible for analysis. Of them 41 (aged 49±13 years, 36 women, median disease duration of 7 (3-19) years) **(Table 5)** could be matched effectively 1:1 for age and gender to eligible healthy control subjects, also free of clinical CVD and classical CVD risk factors.

RA patients had more than 2-fold higher prevalence of carotid and/or femoral atheromatic plaques than healthy controls (29% vs. 12%, p=0.039) **(Table 5)**. All patients with plaques had an acceptable functional status of class I or II (mean HAQ-DI = 0.80±0.73). Moreover, body mass index, blood pressure and family history of CVD, were similar between patients with plaques and their matched controls.

More RA patients than controls had plaques at both the carotid and femoral artery (n=6 vs n=1, respectively). Multi-arterial preclinical atheromatosis, defined as plaque presence at more than 1 of the 8 arterial sites evaluated, was by far more prevalent in RA patients than controls (22% vs. 2%, p=0.026) **(Table 5).** The presence of arterial plaques in RA patients was not significantly associated with rheumatoid factor or anti-CCP positivity, C-Reactive Protein level at the time of study (5 IQR [2.1-8.5]), or HAQ-DI score. DAS-28 was significantly higher in RA patients with atheromatosis than those without (4.38±1.31 vs 3.45±1.30 respectively, p=0.045).Plaque burden in the subgroup of RA patients with less than 5 years of disease duration was not significantly different to their matched controls (2.4% vs 4.9%, p=1.000). In contrast, atheromatosis was clearly accelerated in RA patients with disease duration of more than 5 years versus their controls (27% vs. 7%, p=0.005). In this subgroup of RA patients multi-arterial atheromatosis was also significantly increased (p=0.030) **(Table 6).** Notably, CRP levels between the 2 groups of RA patients with less or more than 5 years of disease duration were comparable (8.99±9.72 for less than 5 years and 7.87±11.05 for more than 5 years respectively, p=0.779).

In contrast to atheromatosis, all indices indicative of either arterial stiffness or arterial wall hypertrophy in RA patients were similar compared to their matched controls, even in patients with disease duration more than 5 years (**Table 6).** IMT measurements were found to be abnormal (i.e. >0.9mm), in either carotid artery, in 7 RA patients (age 60.71±6.9, disease duration 17.57±13.55) versus 9 controls (age 59.78±7.82) (p=0.577). Mean disease duration of RA treatment, including use of anti-TNF therapy, was not associated with any of the studied indices of arterial disease (data not shown).

Ankylosing Spondylitis

Results of the multivariate analysis did not reveal any differences between AS patients and controls for any of the vascular disease indices, namely arterial plaques, IMT of RCCA and LCCA and PWV and AIx. In order to confirm these results, a second analysis was performed using strict 1:1 matching of AS patients and controls for each of the classical CVD risk factors. More specifically, 67 were effectively matched 1:1 with apparently healthy controls for age (± 3 years), gender, smoking, dyslipidemia (defined as diagnosis by a physician or LDL fasting plasma levels >160 mg/dL) and hypertension (defined as diagnosis by a physician or blood pressure levels >130/80 using a 24-hour monitoring device). Mean age of patients and cases was 47.5±12.5 and 48.8±12.7 respectively (Table 7). Thirty-three percent of patients had hypertension, 15% had dyslipidemia and 55% were smokers. Mean blood pressure levels and BMI were also similar between the two groups. AS patients were of low disease activity and good functional class (BASDAI=1.8 IQR[0.4-3.6] and BASFI=2 IQR[0.9-2.8] respectively) and the majority (66%) were receiving anti-TNF treatment.

These AS patients and very-well age-, gender- and risk factors-matched controls had similar arterial hypertrophy and arteriosclerosis indices, whereas atheromatosis was slightly increased in healthy controls, albeit not reaching significance. More specifically, carotid and/or femoral plaques were present in 23 and 32 patients and controls respectively (p=0.114, Table 7). Mean IMT, the main parameter of arterial hypertrophy, was 0.79±0.22 and 0.80±0.20 in left CCA and 0.73±0.16 and 0.75±0.21 in right CCA, for patients and controls respectively (p=0.724 for left CCA and 0.303 for right CCA). PWV was 7.64±1.7 in patients and 7.65±1.9 m/s in controls (p=0.238) and AI was 18.6±13.2 and 17.5±14 % (p=0.642). None of the disease parameters, such as disease duration and activity or anti-TNF treatment, were associated to any of the studied vascular indices.

3.2 **Three-year follow-up**

3.2.1 Demographics and clinical characteristics of studied subjects

Overall, 531 subjects were assessed after a 3-year period (Table 8):

- 293 controls, aged 54.2±13.5 years, 48.8% men
- 177 patients with RA, aged 59.5±11.6 years, 17%men
- 61 patients with AS, aged 49.6±12.8 years, 85.3% men

Demographics, clinical characteristics and prevalence of classical CVD risk factors after 3 years are shown in Table 8.

Overall 7 patients died due a CV event (6 patients had a myocardial infarction and 1 patients a stroke) and 7 patients due to non-CVD related causes.

Moreover, 4 more patients experienced a CV event (2 experienced a MI and 2 a stroke). One patient underwent a coronary artery bypass and 2 patients a peripheral artery stent.

The remaining patients were either lost to follow up or refused to undergo examination at follow-up time due to personal reasons.

Seven control subjects, 10 patients with RA and 1 patient with AS who were re-evaluated after three years, were reclassified as having Diabetes Mellitus (either a diagnosis had been made during the follow-up period or they were reclassified if they presented with HbA1c >6.5%) and were subsequently excluded from the follow-up analysis.

Finally, specific indices indicative of disease activity were as follows:

- for RA patients, median CRP was 3.17 mg/l (IQR 2.7-4.3) and median ESR was 14 mm (IQR 8-24). Mean DAS28crp was 2.4±0.9 and mean DAS28esr was 2.8±1.
- for AS patients, median CRP was 3.26mg/l (IQR 3.2-8.3), median ESR was 10 mm (IQR 5-16), median BASDAI was 1.5 (IQR 0.2-2.8) and median BASFI was 2.3 (IQR 1-3.2)

In regards to therapies

- 108 RA patients were receiving cortisone, 86 methotrexate, 27 leflunomide and 74 were receiving biologic therapy (11 Adalimumab, 7 Etanercept, 23 Tocilizumab, 5 Anakinra, 7 Golimumab, 3 Abatacept, 7 Rituximab, 1 Infliximab and 10 Certolizumab pegol)
- 44 AS patients were receiving biologic therapy (17 Adalimumab, 6 Infliximab, 13 Etanercept, 4 Golimumab, 4 certolizumab pegol) and 3 were receiving NSAIDs.

3.2.2 Vascular indices of studied subjects

As regards to subclinical cardiovascular disease, all vascular indices examined are presented in Table 9.

Univariate analysis showed that RA patients presented similar IMT of both carotid arteries as controls. As expected AS patients had less IMT values than controls, which can be attributed to the younger age as well as significantly smaller prevalence of arterial hypertension. Progression of IMT during follow-up period was similar between the study groups.

As to arteriosclerosis, RA patients increased PWV compared to controls, whereas AS patients did not differ significantly. Moreover, when considering progression of arterial damage, more controls subjects improved PWV compared to all the other three study groups. This is anticipated, given that most of control subjects where referred to our center due to elevated blood pressure levels and were subsequently treated, whereas RA and AS patients may have not been monitoring BP levels so closely.

Interestingly, univariate analysis did not reveal significant differences regarding atheromatosis between controls and any of the study groups.

Rheumatoid arthritis

We were able to demographically match 1:1 a total of 139 RA patients, aged 56.7±11.7 years, 16% men, with median disease duration of 7 years at baseline (IQR 2-13 years) who were re-evaluated by ultrasound after 3.2±0.2years **(Table 10)**. During the follow-up period disease remission or low activity had been achieved with the target to treat approach; at follow-up end 56 patients were receiving biologic therapy, combined with methotrexate (n=23), other synthetic DMARDs (n=6), or given as monotherapy (n=27). Of the remaining patients, 49 were receiving methotrexate (8 of whom combined with hydroxychloroquine), 14 leflunomide (3 of whom combined with hydroxychloroquine), 6 patients were receiving hydroxychloroquine and 14 low dose prednisolone only. Prednisolone, always at doses lower than 7.5 mgs, had been used at follow-up end by 58% of patients and none of the controls.

The burden of classical CVD risk factors, such as family history of CVD, smoking, arterial hypertension and hyperlipidemia, was comparable between RA patients and non-RA controls, both at baseline and follow-up end **(Table 10).** Moreover, numbers of subjects under anti-hypertensive or lipid-lowering treatment were comparable between groups; a marginal difference was only noted regarding the number of subjects in whom anti-hypertensive was added during follow-up which was higher among controls **(Table 10).** Body mass index was almost similar between RA patients and controls **(Table 10).**

Vascular indices under study at baseline and at follow-up end in RA patients and their matched non-RA controls are shown in **Table 10.** The median yearly PWV change was 0.07 m/s (IQR -0.15-0.27) for RA patients versus -0.06 m/s (IQR -0.26 – 0.13) in controls. Carotid intima-media thickness in the LCCA increased per year by 0.009 mm (IQR: 0.001-0.023) in RA patients versus 0.011 mm (IQR 0-0.022) in controls. New atheromatic plaques in carotid and/or femoral arterial beds were seen in 22% of RA patients vs 25% of controls. By multivariate analysis models, no statistically significant differences for any of the evaluated markers of subclinical CVD were found between RA patients and controls (**Table 10**). Two patients versus 1 control developed clinical CVD during follow-up.

A further subgroup analysis was performed of the progression of arteriosclerosis and atherosclerosis indices in patients treated with biologic versus synthetic DMARDs. The two RA subgroups did not differ in terms of traditional CVD risk factors **(Table 11)**; proportions of RF and CCP positivity were lower in the DMARDs-treated, than the biologic-treated group, albeit not significantly. After correction for possible confounders no difference was evident in any of the vascular indices examined between the 2 subgroups. Multivariate analysis did not reveal any significant effect of disease duration, low dose prednisolone or methotrexate treatment, any modification of antihypertensive or lipid-lowering therapies, as well as of RF or anti-CCP status on any of the evaluated vascular indices.

Ankylosing Spondylitis

In the same notion as for patients with RA, analysis of AS patients at follow-up end included AS patients being in remission or low disease activity (BASDAI<4) for at least 75% of the follow-up period, in order to examine whether CVD progression is accelerated in the absence of inflammation in these patients. We were able to demographically match 1:1 a total of 40 AS patients who were re-evaluated by ultrasound after 3.2±0.2years, with 40 healthy controls. Demographics and vascular indices at baseline and follow-up end are shown in Table 12. As expected, more AS patients were receiving biologic therapy compared to RA patients, both at baseline and follow-up end. The remaining patients were in remission with the help of physical activity or the use of NSAIDs.

The burden of classical CVD risk factorswas comparable between AS patients and controls, both at baseline and follow-up end, except for family history of CVD which was higher in AS patients. **(Table 12).** Moreover, numbers of subjects under anti-hypertensive or lipid-lowering treatment were comparable between groups. Multivariate analysis between AS patients in remission or low disease activity and their matched controls did not reveal significant differences regarding the progression in any of the examined vascular indices, i.e. the progression of PWV and IMT in the LCCA or the formation of new atherosclerotic plaques. **(Table 12)**

4. Discussion

4.1 Baseline assessment

Rheumatoid arthritis

Regarding the baseline assessment in RA patients, this is the first time that arterial properties, namely atheromatosis, arteriosclerosis and hypertrophy, were assessed comprehensively in a population of RA patients free of any classical CVD risk factor. Perhaps the lack of such studies is due to the fact that the vast majority of RA patients present with at least one classical CVD risk factor. In the present analysis, it was shown that RA *per se* is sufficient to cause atheromatosis, defined as the presence of carotid and/or femoral plaques. Accelerated atheromatosis was not evidenced during the first 5 years after disease onset and therefore seems to be associated with longer RA disease duration. Moreover, RA patients with plaques had more extensive subclinical atheromatosis than controls, as shown by the presence of multiple plaques in various arterial segments. Surprisingly, however, in the absence of traditional CVD risk factors, both arterial stiffening and hypertrophy were not increased in RA patients compared to 1:1 matched healthy controls.

Previous studies have shown that increased arterial stiffness and increased carotid IMT are common in RA patients and relate to disease duration and activity. [219–222] In fact, the presence of carotid arterial abnormalities is considered a good predictor of CVD events in RA. [223–225] Other studies, however, have shown higher prevalence of carotid plaques but not increased IMT in RA compared to controls. [226] In the present study there were no differences between RA patients and controls regarding either arterial elasticity or hypertrophy in the absence of classical CVD risk factors. The discordance with previous studies may have various, partly complementary explanations. First, it might be attributed to the fact that all patients were free of arterial hypertension, meticulously defined on the basis of out-of-office BP recordings and that they were well-matched to healthy controls for the BP level. This is also in line with the fact that a comprehensive systematic review of the evidence accumulated so far has shown that age and BP level are the main determinants of arterial stiffness [227], whereas other factors have a more restricted impact on atherosclerosis. Second,

it is possible that arterial elasticity and arterial hypertrophy are within normal limits in the current era of RA management due to effective inflammatory disease control. This is supported by studies reporting a beneficial effect of biologic therapy on aortic stiffness [201,228–231] and impaired endothelial function [232,233], as well as reduction of progression or even reversion of arterial IMT [222,234,235]. In accordance to such studies, the findings presented herein could be attributed to effective control of RA, as indicated by the moderate disease activity in our population. Finally, previous studies evaluating IMT in RA patients include plaque presence in measurement of IMT [222–224], therefore cannot differentiate atheromatosis and hypertrophy. It is reasonable to speculate that IMT reversal can take place at early stages of RA before the development of plaques.

The present data provide the first clear evidence that RA disease *per se* is associated with atheromatosis. However, the exact pathophysiological links cannot be clear at this stage. These might include systemic inflammation, RA related treatments (e.g. corticosteroids), the genetic background related to RA, amongst several other factors. As previously stated, there is a significant positive association between CVD risk, atheromatosis and inflammatory markers in RA patients, as well as in healthy individuals. [72,236] Moreover, atheromatosis and RA seem to share similarities in inflammatory and autoimmune response, with activation of inflammatory cells (monocytes and helper T lymphocytes) and chronically increased levels of proinflammatory cytokines. [131,186,237] Longterm corticosteroid treatment has also been linked to increased carotid atherosclerosis and plaque formation in RA patients. [222,237,238] However, such an association remains unclear, given the concurrent impact of inflammation itself, which in contrast is suppressed by corticosteroid use, and the relatively low doses of corticosteroids given for RA. Also, genetic factors associated with RA are thought to play a part in developing CVD, possibly through LDL-cholesterol levels [72] or elastic vascular properties [4].

The European League Against Rheumatism task force recommends adapting general populations CVD risk algorithms with a 1.5 multiplication factor for all patients with RA, as opposed to previous recommendations that proposed the application of this multiplication factor when certain RA-specific criteria were present, i.e. disease duration of more than 10 years or RF or actiCCP positivity. [50] In accordance to this,

in the present study it was shown that preclinical atheromatosis may appear earlier in the disease course (5 years from disease onset) and seems to be independent of RF and anti-CCP positivity, being associated with the level of disease activity expressed by DAS28, as also shown in other studies. [239,240] Taken together the above findings suggest that early Treat to Target trials in RA should include both aggressive inflammation control, as well as subclinical arterial disease by more aggressive prevention CVD strategies, the latter potentially guided rather by atheromatic plaque presence than IMT or arterial stiffness. Future trials should ideally include vascular subclinical endpoints and not only RA remission and inflammation control since plaque formation appears to be intimately involved as a relatively early feature of RA.

One limitation of the analysis in the RA study group at baseline is the relatively small sample size, as a result of the strict study design and exclusion criteria. This, however, is an unavoidable consequence of the high prevalence of classical CVD risk factors seen in patients with RA. Subsequently, this could be the reason why, even though some aspects of subclinical arterial damage are considered to be more prevalent in RA patients, this was not evident herein. Interestingly, PWV was found to be 0,4m/sec higher in the subgroup of RA patients of more than 5 years disease duration than their matched controls. This observation could be of clinical importance, and maybe statistical significance in a larger sample size. Finally, effect of type and duration of RA treatment could have biased results, even though no direct correlation between indices of subclinical cardiovascular disease examined and type of treatment was found.

Ankylosing Spondylitis

The original data presented herein show that subclinical cardiovascular disease- in terms of atheromatosis, carotid hypertrophy and arterial stiffness- in not increased in well-controlled AS patients compared to the healthy individuals. These results cannot be directly compared with previous studies, since none had used a strict 1:1 matching of AS patients and controls for each of the classical CVD risk factors. Notably, previous studies involving patients with low disease activity present similar results, as carotid IMT was found to be similar between AS patients with BASDAI <4 and controls. [81,87,90] The lack of increased plaque burden may be also explained

mainly by the relatively young age of AS patients examined. In other studies, AS was associated with increased IMT[83–85,89], however the presence of arterial hypertrophy, but not atheromatosis, may indicate that increased IMT is attributed to subclinical vasculitis rather than atherosclerosis. Such a mechanism of arterial dysfunction has been described in patients with rheumatoid arthritis, where active disease was accompanied with increased aortic inflammation compared to healthy subjects. [231]

In the notion that disease activity and persistent systemic inflammation are associated with subclinical vasculitis, absence of advanced carotid hypertrophy in well-controlled AS patients could also be attributed to dissolution of vessel wall inflammation. Anti-TNF therapy appears to play an important role in ameliorating vascular properties. In rheumatoid arthritis anti-TNF therapy succeeded in reducing aortic inflammation along with disease activity, thus decreasing aortic stiffness measured by PWV. [231] Apart from the probable direct impact of TNF inhibitors on vascular inflammation, they are claimed to have an effect on lipid profile [116] and anti-oxidative capacity of HDL [241], and even a specific direct effect on arterial wall. Most importantly, however, reduction of systemic inflammation induced by anti-TNF agents seems to be the main reason for similar arterial features between patients with systemic inflammatory diseases and healthy individuals and, therefore, can explain the lack of increased carotid hypertrophy in well-controlled AS patients. A recent review by Tam et al. [202] examining the effect of TNF antagonists on the progression of cardiovascular disease and in reducing CV risk, concluded that anti-TNF agents are probably effective in preventing or even reversing the progression of IMT in systemic rheumatic diseases responding to treatment. Moreover, according to another study, long-term anti-TNF therapy seems to induce a persistent stable vascular function after some period of time. [242]

Progression of arterial stiffness by systemic inflammation in general, is well established. In AS patients in particular, published studies, while diverse, suggest that active disease causes impaired vascular elasticity and function. [243–248] However, these original data, as well as results from other studies, indicate that effective disease control, particularly through the use of TNF inhibitors, seems to reverse arterial

stiffness and ameliorate functional arterial indices concurrent with reduction in clinical and laboratory inflammatory markers. [87,249,250]

Overall published data from numerous studies, as well as a recent meta-analysis from our center, suggests that, even though AS could be a novel independent CV risk factor, its impact on developing CVD is more limited than that of rheumatoid arthritis. This disparity could be attributed to the higher level of systemic inflammation seen in rheumatoid arthritis compared to AS. Furthermore, long-term use of corticosteroids in rheumatoid arthritis, which is not considered a first line treatment in AS, could have an important detrimental effect on vascular damage and subsequent atherosclerosis, as well as on classical CVD risk factors. Frequent and more intensive exercise seen in AS patients, acknowledged to have a protective cardiovascular effect, is another reason why they present with less impaired vascular indices. Finally, the more extended CVD noted in rheumatoid arthritis might be explained by the older age of patients throughout studies compared to the mean age patients with AS, which reflects a more advanced level of arterial damage.

4.2 Three-year follow-up assessment

Regarding the analysis in RA patients at follow-up end, this is the first time shown that sufficient control of inflammation in patients with RA associates with rates of arterial disease progression seen in people without RA and otherwise similar CVD risk factor burden. Moreover, the progression rate of three different parameters of subclinical cardiovascular disease were evaluated i.e. arterial stiffness, common carotid artery hypertrophy and carotid and femoral atheromatic plaques, the combination of which may predict CVD event in these patients. [68,251] Although the rate of IMT progression in this study is lower when compared to rates reported elsewhere, it should be noted that patients and controls studied herein were regularly followed-up, therefore, classical CVD risk factors were under strict control. In any case, distribution of IMT values is too heterogeneous between studies so that reference values cannot be defined. [15]

Indeed, observational studies suggest that the higher the inflammatory load, the more accelerated the processes of atherosclerosis become. [252] Other studies have shown that mediators participating in inflammatory pathways, such as TNF and IL-6, are associated with acceleration of arteriosclerosis and atherosclerosis and could be markers of arterial disease, even implying a common etiologic pathway between RA and CVD. [190,253] This may well be true for active RA. [252] The results of the present study demonstrate that in the presence of low disease activity and/or remission, the development of arterial damage is not accelerated, suggesting that any further development may be largely due to classical risk factors. These results are in accordance with the results described above for AS patients, concluding that control of inflammation associates with arterial damage progression rates seen in people without Ankylosing Spondylitis.

The use of biologic DMARDs has been associated with improved arterial morphology and function [202] and better CVD outcomes [254] in patients with RA. It remains unclear whether this is indirectly attributed to effective control of inflammation or to neutralization of specific cytokine effects implicated in atherogenesis, such as TNF and IL-6, the levels of which are known to predict cardiovascular mortality, independently of cardiovascular risk factors [187,255] Interestingly, in this study, differences in all examined vascular indices were similar between RA patients receiving biologic therapy and those under conventional DMARDs, suggesting that acceleration of atherosclerosis is abrogated regardless of treatment modalities used to suppress inflammation.

Based on the current treat-to-target approach for RA, early disease diagnosis and optimized treatment are essential for achieving long-term health-related quality of life, not only regarding directly related disease symptoms, but also induced comorbidities. In this notion, early control of RA disease activity, as well as classical cardiovascular risk factors, could minimize risk for developing CVD. In this cohort of RA patients in remission or with low disease activity, there was no acceleration of subclinical CVD, ensuring minimum impact of RA disease.

Regarding the study limitations, as previously mentioned, it should be again noted that some control subjects had been referred to our center for suspected arterial hypertension, while patients had been already followed up in our center, thus having probably more effective control of traditional CVD risk factors. Thus, a larger proportion of control subjects than patients either initiated or changed their anti-hypertensive or lipid-lowering therapy after the baseline evaluation (Table 10). This could explain differences between the two groups, especially regarding PWV which is predominantly affected by arterial pressure.

5. Conclusion

The purpose of the present thesis was to examine the prevalence and progression of subclinical cardiovascular disease, namely arterial stiffness, arterial hypertrophy and athromatosis, in patients with Rheumatoid arthritis and Ankylosing Spondylitis, compared to apparently healthy controls. The thing that differentiates the present study from previous studies examining subclinical CVD in CIRD is the careful selection of patients and strict 1:1 matching of classical CVD risk factors.

Regarding RA, only patients free of any classical CVD risk factor burden were analyzed at baseline in order to determine the impact of RA disease *per se* on the different components of cardiovascular disease. RA patients had more atheromatic plaques than controls and multi-arterial atheromatosis was more prevalent in RA. However, in patients with less than 5 years disease duration, plaque burden was comparable to their matched controls. In contrast, all indices of arterial stiffness and hypertrophy were similar between controls and RA patients, even in those with long-standing disease. These findings suggest that in the same way that the various CVD risk factors are considered to have a differential impact on arterial morphology, elasticity and plaque formation [61,233], this analysis of RA patients free of classical CVD risk factors suggests that RA disease, potentially a novel CVD risk factor in its own right, causes arterial damage mainly via potentially irreversible plaque formation

but does not affect arterial stiffness or hypertrophy in the absence of classical CVD risk factors.

Analysis of RA patients at follow-up end was limited to RA patients who had been in remission or low disease activity (DAS28<3.2) for at least 75% of the follow-up period. Comparison with demographically matched controls, with comparable classical CVD risk factor burden, demonstrated no significant differences between patients and controls in any of the subclinical CVD indices. Moreover, further subgroup analysis within the selected RA cohort, revealed that changes in all arterial cardiovascular disease indices from baseline to end of follow-up were comparable between patients treated with biologic DMARDs and demographically matched patients treated with synthetic DMARDs. Therefore, effective inflammation control, which may not be drug-specific, seems to de-accelerate the progression of CVD in RA to the rate observed in non-RA controls. Whether early and sustained disease control also translates to the expected for the general population rates of cardiovascular morbidity and mortality in RA patients remains to be proven in large prospective cohort studies. Nevertheless, the current therapeutic strategy, based on the treat-to-target approach, should include prompt control of joint disease, as well as of cardiovascular risk factors.

Finally, concerning AS, the analysis only included AS patients and very-well (1:1) age-, gender- and risk factors-matched controls. Atheromatic plaques were less prevalent compared to controls, albeit not reaching significance, while carotid hypertrophy and stiffness and aortic stiffness were similar between patients and their matched controls. Notably, none of the disease parameters, such as disease duration and activity or anti-TNF treatment, were associated to any of the studied vascular indices. Thus, it seems that subclinical CVD- in terms of atheromatosis, carotid hypertrophy and arterial stiffness- is not accelerated in well-controlled AS and prompt and effective disease control can stop progression of atherosclerosis and improve arterial hypertrophy and stiffness in AS patients.

Summary

Backgroung/Aim: Cardiovascular disease remains the main cause of morbidity and mortality worldwide. The development of arteriosclerosis and atheromatosis is the pathogenetic substrate of all cardiovascular diseases and is characterized by functional and morphological abnormalities in the wall of the arteries. Patients with Inflammatory Arthritis, such as Rheumatoid Arthritis (RA and Ankylosing Spondylitis (AS), present with increased prevalence of CVD, which leads to increased morbidity and mortality in these patients. In RA and AS, accelerated arterial disease is ascribed not only to classical CVD risk factors -namely arterial hypertension, glucose intolerance, smoking and dyslipidemia- which are known to be more prevalent in patients with CIRD, but also to the presence of chronic inflammation and perhaps to disease-related therapies. The aim of the present dissertation was to assess the prevalence as well as the acceleration of subclinical cardiovascular disease in patients with RA and AS and, in particular, define the degree, extent and type of arterial damage in each condition.

Methods: Overall, 227 RA patients (aged 57.8±12.4years, 17.6% men), 81 AS (aged 46.7±13.2 years, 85.4% men) and 674 controls (aged 52.2±12.7 years 53% men), without known CVD and/or Diabetes Mellitus, were enrolled. All subjects were assessed for subclinical cardiovascular disease, namely a) arterial stiffness by pulse wave velocity (PWV) and augmentation index (AIx), b)carotid hypertrophy, by intimal-medial thickness (IMT, adjacent to plaques when present) and cross sectional area (CSA) in both the right and left common carotid arteries and c) subclinical atheromatosis, i.e. the presence of atherosclerotic plaques in a total of 8 arterial beds both in carotid and femoral arteries (left and right common and internal carotid arteries and carotid bulb and both common femoral arteries). Re-assessment of all vascular indices was performed after a 3-year period in 177 patients with RA (aged 59.5±11.6 years, 17% men), 61 patients with AS (aged 49.6±12.8 years, 85.3% men) and 293 controls (aged 54.2±13.5 years, 48.8% men). Multivariate analysis of patients with RA or AS compared to controls was performed after adjusting for classical CVD risk factors and disease specific characteristics.

Results: Multivariate analysis of specifically selected RA and control populations characterized by the absence of hypertension, diabetes, dyslipidemia and smoking, revealed that RA patients had more than 2-fold higher prevalence of carotid and/or femoral atheromatic plaques than healthy controls (29% vs. 12%, p=0.039) and multi-arterial preclinical atheromatosis was more prevalent in RA. Interestingly plaque burden in the subgroup of RA patients with less than 5 years of disease duration was comparable to their matched controls. In contrast to atheromatosis, all indices indicative of either arterial stiffness or arterial wall hypertrophy were similar between RA and controls, even in patients with disease duration more than 5 years. In AS, strict 1:1 age-, gender- and risk factors-matching of 67 AS patients and controls showed that they had similar arterial hypertrophy and atherosclerosis indices, whereas atheromatosis was slightly increased in healthy controls, albeit not reaching significance. Moreover, none of the disease parameters, such as disease duration and activity or anti-TNF treatment, were associated to any of the studied vascular indices. Regarding evaluation of progression of subclinical CVD, comparison of RA patients in remission or low disease activity versus 1:1 demographically matched controls with comparable classical CVD risk factor burden, demonstrated no statistically significant differences for any of the evaluated markers of subclinical CVD. A further subgroup analysis between RA patients treated with biologic versus synthetic DMARDs showed that no difference was evident in any of the vascular indices examined between the two subgroups.

Conclusion: RA disease per se is sufficient to cause atheromatosis but not arterial stiffness or hypertrophy in the absence of classical CVD risk factors and this is evident in patients with more than 5 years disease duration. However, effective inflammation control, which may not be drug-specific, seems to de-accelerate the progression of atherosclerosis in RA to the rate observed in non-RA controls. Nevertheless, the current therapeutic strategy, based on the treat-to-target approach, should include prompt control of joint disease, as well as of cardiovascular risk factors. In contrast, subclinical arterial disease- in terms of atheromatosis, carotid hypertrophy and arterial stiffness- is not accelerated in well-controlled AS and thus, prompt and effective disease control can stop progression of arterial damage and improve arterial hypertrophy and stiffness in AS patients.

Περίληψη

Υπόστρωμα / Στόχος: Η καρδιαγγειακή νόσος παραμένει η κύρια αιτία νοσηρότητας και θνησιμότητας παγκοσμίως. Η αρτηριοσκλήρυνση και η αθηρωμάτωση είναι τα παθογόνα υποστρώματα όλων των καρδιαγγειακών παθήσεων και χαρακτηρίζονται από λειτουργικές και μορφολογικές ανωμαλίες στο τοίχωμα των αρτηριών. Οι ασθενείς με φλεγμονώδη αρθρίτιδα, όπως η ρευματοειδής αρθρίτιδα (ΡΑ) και η αγκυλοποιητική σπονδυλίτιδα (ΑΣ), παρουσιάζουν αυξημένο επιπολασμό καρδιαγγειακής νόσου, προκαλώντας έτσι αυξημένη νοσηρότητα και θνησιμότητα σε αυτούς τους ασθενείς. Στη ΡΑ και την ΑΣ, η αυξημένη αρτηριοπάθεια δεν οφείλονται μόνο στην παρουσία κλασσικών παραγόντων καρδιαγγειακού κινδύνου, δηλαδή αρτηριακής υπέρτασης, δυσανεξίας στη γλυκόζη, καπνίσματος και δυσλιπιδαιμίας, που είναι γνωστό ότι είναι πιο διαδεδομένες σε ασθενείς με φλεγμονώδη αρθρίτιδα, αλλά και στην παρουσία χρόνιας φλεγμονής και ίσως σε θεραπείες σχετιζόμενες με τη νόσο. Σκοπός της παρούσας διατριβής ήταν να εκτιμηθεί ο επιπολασμός καθώς και η επιτάχυνση της υποκλινικής καρδιαγγειακής νόσου σε ασθενείς με ΡΑ και ΑΣ και συγκεκριμένα να καθοριστεί ο βαθμός, η έκταση και ο τύπος της αρτηριακής βλάβης για κάθε νόσημα.

Μέθοδοι: Συνολικά, 227 ασθενείς με ΡΑ (ηλικίας 57,8 ± 12,4 ετών, 17,6% άνδρες), 81 με ΑΣ (ηλικίας 46,7 ± 13,2 ετών, 85,4% άνδρες) και 674 μάρτυρες (ηλικίας 52,2 ± 12,7 ετών 53% άνδρες), χωρίς γνωστή καρδιαγγειακή νόσο ή Σακχαρώδη Διαβήτη, έλαβαν μέρος στη μελέτη. Όλοι οι συμμετέχοντες αξιολογήθηκαν για υποκλινική καρδιαγγειακή νόσο, συγκεκριμένα α) αρτηριακή σκληρία μέσω ταχύτητας σφυγμικού κύματος (PWV) και δείκτη ενίσχυσης ανακλώμενων κυμάτων (AIx), β) καρωτιδική υπερτροφία, με πάχος έσω-μέσου χιτώνα (IMT, προσαρμοσμένο σε αθηρωματικές πλάκες όπου υπάρχουν) και επιφάνεια διατομής (CSA) και στην αριστερή και δεξιά κοινή καρωτίδα και γ) αθηρωμάτωση, δηλ. παρουσία αθηρωματικών πλακών σε συνολικά 8 αρτηριακά σημεία τόσο στις καρωτιδικές όσο και στις μηριαίες αρτηρίες (αριστερή και δεξιά κοινή και έσω καρωτίδα και βολβό και αμφότερες κοινές μηριαίες αρτηρίες). Η επαναξιολόγηση όλων των αγγειακών δεικτών πραγματοποιήθηκε μετά από τριετία σε 177 ασθενείς με ΡΑ (ηλικίας 59,5 ± 11,6 ετών, 17% άνδρες), 61 ασθενείς με ΑΣ (ηλικίας 49,6 ± 12,8 ετών, 85,3% άνδρες) και 293 μάρτυρες (ηλικίας 54,2 ± 13,5 ετών, 48,8% άνδρες). Η πολυπαραγοντική

ανάλυση των ασθενών με ΡΑ ή ΑΣ συγκριτικά με τους μάρτυρες πραγματοποιήθηκε μετά από στάθμιση για τους κλασσικούς παράγοντες καρδιαγγειακού κινδύνου καθώς και συγκεκριμένα χαρακτηριστικά ειδικά για την κάθε νόσο.

Αποτελέσματα: Πολυπαραγοντική ανάλυση ειδικά επιλεγμένων ασθενών με ΡΑ και μαρτύρων που δεν παρουσίαζαν υπέρταση, διαβήτη, δυσλιπιδαιμία και κάπνισμα, έδειξε ότι οι ασθενείς με ΡΑ είχαν περισσότερο από 2 φορές υψηλότερη παρουσία καρωτιδικών και/ή μηριαίων αθηρωματικών πλακών από τους υγιείς μάρτυρες (29% 12%, p = 0,039) και η πολυεστιακή υποκλινική αθηρωμάτωση ήταν πιο συχνή στη ΡΑ. Είναι ενδιαφέρον ότι παρουσία αθηρωματικών πλακών στην υποομάδα των ασθενών με διάρκεια νόσου μικρότερη των 5 ετών ήταν συγκρίσιμη με τους αντίστοιχους μάρτυρες. Σε αντίθεση με την αθηρωμάτωση, όλοι οι δείκτες αρτηριακής σκληρίας ή υπερτροφίας αρτηριακού τοιχώματος ήταν παρόμοιοι μεταξύ ασθενών με ΡΑ και μαρτύρων, ακόμη και σε ασθενείς με διάρκεια νόσου μεγαλύτερη από 5 έτη. Στην ΑΣ, αυστηρή 1:1 αντιστοίχιση 67 ασθενών με ΑΣ και μαρτύρων για ηλικία, φύλο και κλασσικούς παράγοντες καρδιαγγειακού κινδύνου έδειξαν ότι είχαν παρόμοιους δείκτες αρτηριακής υπερτροφίας και αρτηριακής σκληρίας, ενώ η αθηρωμάτωση ήταν ελαφρά αυξημένη στους υγιείς μάρτυρες, αν και δεν έφτασε σε στατιστική σημαντικότητα. Επιπλέον, καμία από τις παραμέτρους της νόσου, όπως η διάρκεια και η ενεργότητα ή η θεραπεία με αντι-TNF παράγοντα, δεν συσχετίστηκε με κανένα από τους εξεταζόμενους αγγειακούς δείκτες. Όσον αφορά την αξιολόγηση της εξέλιξης της υποκλινικής καρδιαγγειακής νόσου, η σύγκριση ασθενών με ΡΑ που βρίσκονταν σε ύφεση ή χαμηλή ενεργότητα νόσου σε σχέση με 1:1 δημογραφικά αντιστοιχισμένους μάρτυρες με παρόμοια επιβάρυνση κλασσικών καρδιαγγειακών παραγόντων, δεν κατέδειξε στατιστικά σημαντικές διαφορές για κανένα από τους εξεταζόμενους αγγειακούς δείκτες.

Συμπέρασμα: Η ΡΑ είναι αυτή καθαυτή επαρκής για να προκαλέσει αθηρωμάτωση αλλά όχι αρτηριακή σκληρία ή υπερτροφία, απουσία κλασικών παραγόντων καρδιαγγειακού κινδύνου και αυτό είναι πιο εμφανές σε ασθενείς με διάρκεια νόσου άνω των 5 ετών. Εντούτοις, ο αποτελεσματικός έλεγχος της φλεγμονής, ο οποίος δεν εξαρτάται από το είδος της θεραπείας, φαίνεται να επιβραδύνει την εξέλιξη της υποκλινικής αρτηριοπάθειας στην ΡΑ στο επίπεδο αυτής των υγιών μαρτύρων. Ωστόσο, η τρέχουσα θεραπευτική στρατηγική, που βασίζεται στην προσέγγιση "treat-to-target", θα πρέπει να περιλαμβάνει τόσο την αποτελεσματική αντιμετώπιση της

αρθρίτιδας, όσο και των παραγόντων καρδιαγγειακού κινδύνου. Αντίθετα, η υποκλινική αγγειοπάθεια – υπό την έννοια της αθηρωμάτωσης, της καρωτιδικής υπερτροφίας και της αρτηριακής σκληρίας – δε φαίνεται να επιταχύνεται σε ασθενείς με ΑΣ που βρίσκονται σε ύφεση και επομένως ο άμεσος και αποτελεσματικός έλεγχος της νόσου μπορεί να σταματήσει την εξέλιξη της αρτηριακής βλάβης και να βελτιώσει την αρτηριακή υπερτροφία και σκληρία σε αυτούς τους ασθενείς.

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TABLES

Table 1 Cardiovascular mortality and morbidity, subclinical cardiovascular disease and classical cardiovascular risk factors in Rheumatoid arthritis and Ankylosing spondylitis

		RA	AS
CVD risk or mortality		Comparative risk to DM[8,9,29] 1.5-fold risk compared to the general population[1] More than 1.5 risk of fatal CV event[31]	↑ vs controls[32-34]
CV events	CHD	Similar risk as DM[10] 1.6-2.1 rate ratio for MI[17,30,31]	1.4 relative risk of MI[18,36]
	Stroke	1.9 rate ratio[31]	1.3-1.4 relative risk[18,36]
Subclinical CVD	cIMT	↑ vs controls[38]	↑ vs controls[23]
	PWV	↑ vs controls[40]	↑ vs controls[44,45]
	FMD	↓ vs controls[48,49]	↓ vs controls[45]
	Aix	↑ vs controls[40]	Similar to controls[23]
	Plaques	↑ carotid vs controls[38] femoral analogous to DM[52]	Similar to controls[23]
Classical Risk factors		• ↑prevalence of HTN, which underdiagnosed and undertreated. • ↑ IR, associated with disease activity TNFa and IL6 levels • "Lipid Paradox" • Oxidative changes to HDL structure • ↓ physical activity • smoking	• ↑ BP levels • ↓ HDL and TC levels, probably associated with TNFa • smoking • male gender

Table 2. Demographics, clinical characteristics and prevalence on classical CVD risk factors in studied subjects

		Controls (n=674)	**Rheumatoid Arthritis (n=227)**	**Ankylosing Spondylitis (n=81)**
Age, years		52.2±12.7	57.8±12.4 *	46.7±13.3 *
Gender, men (%)		53	17.6 *	85.2 *
BMI (kg/ m^2)		27.9±5.0	26.9±5.2*	25.9±4.3 *
Systolic BP (mmHg)		132.2±16.6	131.9±20.1	126.3±14.7 *
Diastolic BP (mmHg)		81.2±10.7	78.4±11.1*	77.7±9.2*
Disease duration (years, range)		--	10.5±9.9	11.5±12.0
Family History of CVD, Y/N (%)		14.2	14.2	21*
Smoking, Y/N (%)	Never Smokers	44.6	49.3	17.3*
	Cuurent smokers	31.5	29.1	60.5*
	Ex-Smokers	23.9	21.6	22.2*
Hypertension, Y/N (%)		64.2	46.7*	29.6*
Dyslipidemia, Y/N (%)		36.1	29.5	16.1*

Data are presented as mean +/- standard deviation or percentages as appropriate. *: significant difference to controls

BMI: Body Mass Index, BP:Blood Pressure, CVD: Cardiovascular disease, Y/N:yes/no

Table 3.Vascular indices of subclinical CVD of each study group at baseline.

			Controls (n=674)	**Rheumatoid Arthritis (n=227)**	**Ankylosing Spondylitis (n=81)**
Atheromatosis indices	Number of subjects with plaques (%)	Carotid and/or Femoral	47	56.8*	35.8
		Carotid	29.1	42.3*	21*
		Femoral	36.9	38.1	30.9
	Plaque localisation	Unilateral carotid	17.2	17.6	11.1
		Bilateral carotid	12	24.7*	9.9
		Only one site	15.4	13.7	12.4
		More than one sites	30.7	43.2*	23.5
Arterial hypertrophy indices	Intima-Media Thickness (mm)	LCCA	0.715±0.170	0.711±0.152	0.661±0.179*
		RCCA	0.666±0.146	0.676±0.135	0.602±0.130*
	CSA (mm^2)	LCCA	14.13±3.9	13.47±3.15*	12.79±4.02*
		RCCA	14.23±4.26	13.54±3.22*	12.95±3.63*
Arterial Stiffness indices	Augmentation Index (%)		24.3±12.6	31.4±10*	17.0±13.7*
	Pulse Wave Velocity (m/s)		8.4±1.9	8.6±1.9	7.6±1.7*

Data are presented as mean +/- standard deviation or percentages as appropriate, *: significant difference to controls

LCCA: left common carotid artery, RCCA: right common carotid artery

Table 4. Proportion of subjects under study with pathological IMT and PWV values.

			Controls (n=674)	**Rheumatoid Arthritis (n=227)**	**Ankylosing Spondylitis (n=81)**
Arterial hypertrophy indices	Intima-Media Thickness	LCCA >0.9mm (%)	14.5	11.6	11.5
		RCCA>0.9mm (%)	7	6.8	2.5
Arterial Stiffness indices	Pulse Wave Velocity≥10 m/s (%)		15.9	18.2	10.3
	Pulse Wave Velocity ≥ 90th age reference value (%)		32.5	20.2*	33.3

LCCA: left common carotid artery, RCCA: right common carotid artery

*: significant difference to controls

Table 5. Characteristics and preclinical vascular indices of RA patients and 1:1 age- and gender-matched healthy controls without traditional cardiovascular risk factors

			RA(n=41)	Controls (n=41)	P*
Age (years)			49.12±12.95	49.17±13.35	0.844
Women (%)			88	88	
BMI (kg/m^2)			25.73±5.0	24.89±4.46	0.309
Systolic BP (mmHg)			123.05±15.62	118.76±10.42	0.131
Diastolic BP (mmHg)			74.12±9.86	72.24±7.51	0.296
Glucose (mg/dl) (n=25)****			94.32±14.00	91.20±12.39	0.430
Low Density Lipoprotein (mg/dl) (n=26)****			113.12±29.92	128.49±20.38	0.064
CRP (mg/dl)			5 (2.1-8.5)		
Disease duration (years, range)			7 (3.5-19.0)	-	-
DAS28			3.72±1.35	-	-
HAQ-DI			0.625(0.000-1.125)	-	-
Medication					
	Biologic therapy**		17 (41.5%)	-	-
	Low dose steroids***		31 (75.6%)	-	-
	Methotrexate		31 (75.6%)	-	-
	Leflunomide		3 (7.3%)	-	-
Atheromatosis					
	Number of subjects with plaques	Carotid and/or Femoral	12	5	0.039
		Carotid and Femoral	6	1	
		Only Carotid	4	3	
		Only Femoral	2	1	
	Plaque localisation				0.145
		Unilateral carotid	8	4	
		Bilateral carotid	2	0	
		Only one site	3	4	0.026
		More than one sites	9	1	
Arterial hypertrophy indices	Intima-Media Thickness (mm)	LCCA	0.72±0.17	0.74±0.15	0.550
		RCCA	0.72±0.13	0.71±0.16	0.315
	CSA (mm^2)	LCCA	12.59±3.62	12.16±3.12	0.450
		RCCA	11.62±2.63	11.89±3.22	0.623
Arterial Stiffness indices	Augmentation Index (%)		25.96±10.95	30±14.16	0.670
	Pulse Wave Velocity (m/s) (n=37)		7.65±1.37	7.54±1.32	0.678

Data are presented as mean +/- standard deviation or median (interquartile range) or percentages as appropriate. **Adalimumab: 4 patients, Etanercept: 3 patients, Tocilizumab: 7 patients, Anakinra: 2 patients, Golimumab:1 patient, ***<7.5 mgs, CSA: cross sectional area; LCCA: left common carotid artery; RCCA: right common carotid artery ****measured within 3 months from the time of the study (number in parenthesis represents number of patients with available data)

Table 6. Subclinical vascular indices of RA patients stratified by disease duration and 1:1 and gender-matched healthy controls without traditional cardiovascular risk factors

Less than 5 years disease duration			**RA (n=11)**	**Controls(n=11)**	P
Mean age 41.00±12.84 CRP	Number of subjects with plaques	Carotid and/or Femoral	1	2	1.000
		Carotid and Femoral	0	0	
8.99±9.72		Only Carotid	0	1	
		Only Femoral	1	1	
	Plaque localisation				0.306
		Unilateral carotid	0	1	
		Bilateral carotid	0	0	
					0.217
		Only one site	0	2	
		More than one sites	1	0	
Arterial hypertrophy indices	Intima-media Thickness (mm)	LCCA	0.71±0.14	0.66±0.15	0.789
		RCCA	0.65±0.12	0.68±0.17	0.477
Arterial Stiffness indices	PWV (m/s) (n=8)		7.06±1.17	6.97±0.69	0.753
More than 5 years disease duration			**RA(n=30)**	**Controls(n=30)**	**P**
Mean age52.13±11.91 CRP	Number of subjects with plaques	Carotid and/or Femoral	11	3	0.009
		Carotid and Femoral	6	1	
7.87±11.05		Only Carotid	4	2	
		Only Femoral	1	0	
					0.070
	Plaque localisation	Unilateral carotid	8	3	
		Bilateral carotid	2	0	
					0.030
		Only one site	3	2	
		More than one sites	8	1	
Arterial hypertrophy indices	Intima-media Thickness (mm)	LCCA	0.77±0.17	0.78±0.14	0.496
		RCCA	0.73±0.13	0.75±0.15	0.440
Arterial Stiffness indices	PWV (m/s) (n=28)		7.82±1.42	7.40±1.44	0.632

Data are presented as mean +/- standard deviation or median (interquartile range) as appropriate

Table 7. Characteristics and vascular indices in AS patients and 1:1 age- and gender- and classical CVD risk factor- matched healthy controls

			AS (n=67)	Controls (n=67)	P*
Age (years)			47.54±12.47	47.78±12.69	0.952
Women (%)			18	18	
BMI (kg/m^2)			26.45±4.22	26.96±3.62	0.187
Systolic BP (mmHg)			126.99±14.94	127.21±15.32	0.788
Diastolic BP (mmHg)			78.60±9.11	77.31±10.11	0.123
Disease duration (years, range)			12 (3-25)	-	-
BASFI			2 (0.9-2.8)	-	-
BASDAI			1.8 (0.4-3.6)	-	-
Medication					
	Biologic therapy*		44 (66%)	-	-
Smoking					
	Never Smokers		14	14	
	Current smokers		37	37	
	Ex-Smokers		16	16	
Hypertension			22	22	
Dyslipidemia			10	10	
Atheromatosis					
	Number of subjects with plaques	Carotid and/or Femoral	23	32	0.114
		Carotid and Femoral	10	17	
		Only Carotid	3	3	
		Only Femoral	10	12	
	Plaque localisation				0.366
		Unilateral carotid	8	13	
		Bilateral carotid	5	7	
		Only one site	10	8	0.104
		More than one sites	13	24	
Arterial hypertrophy indices	Intima-Media Thickness (mm)	LCCA	0.79±0.22	0.80±0.20	0.724
		RCCA	0.73±0.16	0.75±0.21	0.303
	CSA (mm^2)	LCCA	13.60±4.38	13.38±4.33	0.801
		RCCA	12.84±3.79	12.61±4.14	0.741
Arterial Stiffness indices	Augmentation Index (%)		18.58±13.21	17.49±14.05	0.642
	Pulse Wave Velocity (m/s)		7.64±1.71	7.65±1.92	0.238

Data are presented as mean +/- standard deviation or median (interquartile range) or percentages as appropriate. *Adalimumab: 19 patients, Etanercept: 15 patients, Remicade: 6 patients, Golimumab: 4 patient, CSA: cross sectional area; LCCA: left common carotid artery; RCCA: right common carotid artery

Table 8. Demographics, clinical characteristics and prevalence on classical CVD risk factors in studied subjects

		Controls (n=293)	**Rheumatoid Arthritis (n=177)**	**Ankylosing Spondylitis (n=61)**
Age, years		54.2±13.5	59.5±11.6	49.6±12.8
Gender, men (%)		48.8	17	85.3 *
Time to follow-up (years)		3.2±0.4	3.2±0.2	3.2±0.2
BMI (kg/ m^2)		27.2±4.9	26.7±5	26.9±4.5
Systolic BP (mmHg)		124.9±16.1	125.5±16.4	123.3±12.9
Diastolic BP (mmHg)		76.2±8.6	75.5±8.1	76.3±9.2
Disease duration (years, range)		--	13.4±9.9	14.9±12.4
Family History of CVD, Y/N (%)		13.5	14.9	24.6
Smoking, Y/N (%)	Never Smokers	45.4	47.5	18
	Current smokers	31.7	28.3	54.1
	Ex-Smokers	22.9	24.3	27.9
Hypertension, Y/N (%)		53.2	40.7	24.6
Dyslipidemia, Y/N (%)		46.1	41	23

Data are presented as mean +/- standard deviation or percentages as appropriate. *: significant difference to controls

BMI: Body Mass Index, BP:Blood Pressure, CVD: Cardiovascular disease, Y/N:yes/no

Table 9. Vascular indices of subclinical CVD of each study group at follow-up end, as well as progression of subclinical CVD during follow-up period

			Controls (n=293)	**Rheumatoid Arthritis (n=177)**	**Ankylosing Spondylitis (n=61)**
Atheromatosis indices	Number of subjects with plaques (%)	Carotid and/or Femoral	53.6	58.2	42.6
		Carotid	40.6	46.3	24.6*
		Femoral	41.6	42.4	37.7
	Plaque localisation	Unilateral carotid	24.8	20.3	11.5*
		Bilateral carotid	18.8	26	13.1
		Only one site	17.1	12.4	11.5
		More than one sites	36.5	45.8	31.2
	Change in plaques (Y/N) (%)		20.5	24.3	19.7
	Increase of plaques	1	16	20.3	13.1
		2	4.4	3.4	6.6
		3	0	0.6	0
Arterial hypertrophy indices	Intima-Media Thickness (mm)	LCCA	0.732±0.154	0.735±0.146	0.693±0.184
		RCCA	0.695±0.158	0.700±0.133	0.646±0.131*
	CSA (mm^2)	LCCA	14.3±3.8	13.8±3.4	13.3±3.5
		RCCA	14.7±4.3	14±3.3	13.4±3.7*

			Controls (n=293)	Rheumatoid Arthritis	Ankylosing Spondylitis
Arterial hypertrophy indices	Difference in IMT	LCCA	0.035 (0.0025-0.07)	0.035 (0.005-0.08)	0.04 (0.015-0.08)
		RCCA	0.035 (-0.005-0.075)	0.035 (0.005-0.08)	0.0475 (0.005-0.075)
Arterial Stiffness indices	Augmentation Index (%)		25.5±11.9	33.7±9.2*	20.1±11.9*
	Pulse Wave Velocity (m/s)		8.2±1.8	8.6±1.9*	7.8±1.8
	Difference in PWV	m/s	-0.017 (-0.65 - 0.6)	0.25 (-0.475 – 0.925)	0.2 (-0.15 -0.75)*
		Stable (%)	3.7	2.5	0
		Amelioration (%)	50.1	40*	36.8*
		Deterioration (%)	46.2	57.5*	63.2*

*: significant difference to controls

Table 10. Characteristics and vascular indices studied at baseline and/or follow-up end of 139 RA patients being in remission or low disease activity during 3.2years, as well as of their 139 demographically matched controls studied in parallel

			RA (n=139)	CONTROLS (n=139)	p
Age at BSL (years)			56.7±11.7	55.6±13.4	0.461
Women (%)			84.2	84.1	
Disease duration at BSL (years)			7 (2-13)	--	
CRP levels at BSL/ FU end (mg/dl)			3.7 (2.1-7.5)/ 3.2 (2.2-3.5)	2.82 (1.2-3.00) / 3.1 (1.5-3.2)	
RA medication at BSL	Biologics		47*	--	
	DMARDs		108	--	
RA medication at FU end	Biologics		56**	--	
	DMARDs		94	--	
Family History of CVD (%)			17.3	11.7	0.190
Smokers at BSL (%)	Current		27.3	31.2	0.694
	Ex		21.6	16.7	0.388
Smokers at FU end(%)	Current		26.6	30.4	0.617
	Ex		22.3	18.8	0.607
Smoking during FU period(py)			0.61±1.3	0.69±1.2	0.594
Aver SBP at BSL/ FU end (mmHg)			131.9±20.2/ 124.8±16.7	132.8±20.3/ 125.1±18.2	0.305
LDL at BSL/ FU end (mg/dl)			129.9±35.3/ 122±29.4	136.9±36.7/ 123.9±33.2	0.153
Antihypertensive drug at BSL (%)			33.8	39.1	0.385
Addition of antihypertensive drug (%)			10	18	0.057
Lipid lowering drug at BSL (%)			12.2	16.7	0.295
Addition of Lipid lowering drug (%)			20.1	22.5	0.637
BMI at BSL/ FU end (kg/m^2)			27.4±4.7/ 27.5±4.4	27.3±5.1/27.3±5.1	0.385
PWV (m/s)	BSL		8.4±1.8	8.7±2.2	0.165/0.152***
	FU end		8.5±1.8	8.4±2.0	0.816/0.933***
	Difference per year		0.07 (-0.15-0.27)	-0.06 (-0.26-0.13)	0.221***
IMT LCCA (mm)	BSL		0.699±0.147	0.708±0.161	0.632/0.725***
	FU end		0.734±0.152	0.742±0.156	0.674/0.565***
	Difference per year		0.009(0.001- 0.023)	0.011(0 - 0.022)	0.972***
Presence of Plaques at BSL/ FU end (%)			52.5/ 57.6	44.9/ 56.5	0.207/0.862 0.084***/0.566***
Presence of Carotid Plaques at BSL/ FU end (%)			38.1/45.3	37/44.9	0.840/0.940 0.781***/0.810***
Presence of Femoral Plaques at BSL/ FU end (%)			33.8/ 40.3	32.6/ 40.6	0.832/0.961 0.895***/0.716***
Difference in Plaques (%)		1	26 (18.7)	28 (20.3)	0.714/0.891***
		2	4 (2.88)	5 (3.6)	0.703/0.764***
		3	1	1	0.979/0.464***
Change in plaques (Y/N, %)			31 (22.30)	34 (24.64)	0.647/0.511***
Difference in Carotid Plaques (%)		1	15 (10.8)	20 (14.5)	0.343/0.427***
		2	2	3	0.614/0.570***
Difference in Femoral Plaques (%)		1	14 (10.1)	13 (9.4)	0.839/0.834***
		2	2	1	0.569/0.799***

Data are presented as mean +/- standard deviation or median (interquartile range) or percentages as appropriate.
RA: rheumatoid arthritis; BSL: baseline; FU: follow up; py: pack years; SBP: systolic blood pressure; LDL: low-density lipoprotein; BMI: body mass index; PWV: pulse wave velocity; IMT: intima-media thickness; LCCA: left common carotid artery; Y/N: yes/no *29 anti-TNF, 10 Tocilizumab, 6 Anakinra, 1 Abatacept, 1 Rituximab ** 29 anti-TNF, 19 Tocilizumab, 5 Anakinra, 1 Abatacept, 2 Rituximab***by multivariate analysis, after adjusting for Age, Hypertension, Dyslipidemia, smoking during follow-up period, family history of CVD, difference in BMI, baseline status and antihypertensive and lipid-lowering therapy

Table 11. Clinical characteristics and vascular indices of 56 RA patients with biologic-treatment induced remission/low disease activity during follow-up, and their 56 demographically matched patients with remission/low disease activity induced by non-biological DMARDS

			Biologics (n=56)	**DMARDS (n=56)**	**p**	**p***
Age at BSL			53.7±13	53.6±8	0.962	--
Women (%)			82.1	82.1	--	--
Family History of CVD (%)			14.3	19.6	0.452	--
Disease duration at baseline			8.5 (3-15)	4 (1-10.5)	0.032	--
CRP levels at BSL/ FU end (mg/dl)			4.9 (3-8.1)/ 3.2 (0.9-3.3)	4.4 (2.1-9)/ 3.2 (3.1-3.8)	0.525/0.095	--
Smoking (py) during FU			0 (0-0.2)	0 (0-1.5)	0.331	--
Aver SBP at BSL/ FU end (mmHg)			130.6±18.9/122.9±16.1	127.7±20.6/122.4±13.8	0.455/0.860	--
LDL at BSL/ FU end (mg/dl)			130.3±36.8/119.8±30.2	130.2±36.9/121.1±28.9	0.987/0.822	--
Clinical CVD during FU period (n)			1	0	--	--
PWV	BSL/ FU end		7.9±1.2/ 8.0±1.3	8.1±1.5/ 8.2±1.6	0.384/0.306	0.674/ 0.187
	change per year		0.029 (-0.16-0.22)	0.064 (-0.13 - 0.27)	0.400	0.202
IMT LCCA	BSL/ FU end		0.70±0.14/0.74±0.16	0.67±0.14/0.70±0.14	0.285/ 0.116	0.121/0.035
	change per year		0.01 (0.003 - 0.022)	0.009 (-0.0008 - 0.022)	0.270	0.102
Presence of Plaques at BSL/ FU end (%)			50/ 55.4	44.6/ 48.2	0.570/ 0.450	0.455/0.234
Presence of Carotid Plaques at BSL/ FU end (%)			39.3/ 46.4	26.8/ 30.4	0.162/ 0.082	0.075/0.124
Presence of Femoral Plaques at BSL/ FU end (%)			35.7/ 39.3	25/ 32.1	0.210/0.431	0.390/0.438
Difference in Plaques, n		1	8	9	0.824	0.921
		2	2	0	0.991	0.999
		3	0	1	0.993	0.999
Change in plaques (Y/N), n			10	10	1.000	0.795
Difference in Carotid Plaques,n		1	4	6	0.529	0.944
		2	1	0	0.994	
Difference in Femoral Plaques,n		1	6	4	0.529	0.569
		2	0	0	0.94	1000

Data are presented as mean +/- standard deviation or median (interquartile range) or percentages as appropriate.

RA: rheumatoid arthritis; BSL: baseline; FU: follow up; SBP: systolic blood pressure; LDL: low-density lipoprotein; PWV: pulse wave velocity; IMT: intima-media thickness; LCCA: left common carotid artery; Y/N: yes/no

*by multivariate analysis, after adjusting for Age, Hypertension, Dyslipidemia, smoking during follow-up period, family history of CVD, difference in BMI, baseline status and antihypertensive and lipid-lowering therapy

Table 12. Characteristics and vascular indices at baseline and/or follow-up end of 40AS patients being in remission as well as of their 40 demographically matched controls studied in parallel

			CONTROLS (n=40)	AS (n=40)	p
Age at BSL (years)			46.9±11.1	47.1±11.2	0.954
Men (%)			82.5	82.5	1.000
Disease duration at BSL (years)			--	9 (2-25.5)	
CRP levels at BSL/ FU end (mg/dl)			1.3 (0.6-6.5) / 3.4±1	3.3 (1.9-6.1) / 3.7±2	0.279 / 0.169
BASDAI AT BSL/FU end			--	1.55 (0.3-3) / 1.2 (0.9-2.5)	
Biologics at BSL			--	70*	
Biologics at FU end			--	80*	
Family History of CVD (%)			7.5	30	0.016
Smokers at BSL (%)		Current	52.5	52.5	NS
		Ex	25	25	NS
Smokers at FU end(%)		Current	50	45	NS
		Ex	27.5	32.5	NS
Smoking during FU period(py)			0.15 (0-3)	0.2 (0-3)	0.780
Aver SBP at BSL/ FU end (mmHg)			130.3±17.0 / 123.4±14	127.0±16.5 / 125.2±12.7	0.379 / 0.554
LDL at BSL/ FU end (mg/dl)			128.7±28 / 130.1±33.2	118.7±26.8 / 120.6±26	0.139 / 0.182
Antihypertensive drug at BSL (%)			17.5	22.5	0.576
Addition of antihypertensive drug (%)			12.5	17.5	0.531
Lipid lowering drug at BSL (%)			7.5	7.5	1.000
Addition of Lipid lowering drug (%)			20	12.5	0.363
BMI at BSL/ FU end (kg/m^2)			26.7±3.8 / 27.1±3.9	27.0±4.7 / 27.6±4.6	0.705 / 0.581
PWV (m/s)	BSL		8.0±1.7	7.5±1.6	0.195
	FU end		8±1.5	8±2	0.936
	Difference per year		-0.015 (-0.15 – 0.13)	0.13 (-0.08 – 0.26)	0.551***
IMT LCCA (mm)	BSL		0.698±0.162	0.678±0.179	0.607
	FU end		0.731±0.150	0.722±0.190	0.823
	Difference per year		0.010 (0.002-0.019)	0.013 (0.003-0.023)	0.730***
Presence of Plaques at BSL/ FU end (%)			57.5 / 60	37.5 / 47.5	0.073/ 0.262
Presence of Carotid Plaques at BSL/ FU end (%)			37.5 / 42.5	17.5 / 30	0.045 / 0.245
Presence of Femoral Plaques at BSL/ FU end (%)			52.5 / 55	32.5 / 42.5	0.070 / 0.263
Difference in Plaques (%)		1	15	17.5	0.105***
		2	5	10	0.706***
Change in plaques (Y/N, %)			20	27.5	0.107***
Difference in Carotid Plaques (%)		1	12.5	15	0.103***
		2	2.5	5	0.635***
Difference in Femoral Plaques (%)		1	5	7.5	0.377***
		2	0	2.5	1.000***

Data are presented as mean +/- standard deviation or median (interquartile range) or percentages as appropriate.

AS: ankylosing Spondylitis; BSL: baseline; FU: follow up; py: pack years; SBP: systolic blood pressure; LDL: low-density lipoprotein; BMI: body mass index; PWV: pulse wave velocity; IMT: intima-media thickness; LCCA: left common carotid artery; Y/N: yes/no

*12 Adalimumab, 10 Etanercept, 4 Infliximab, 3 Golimumab** 12 Adalimumab, 10 Etanercept, 4 Infliximab, 3 Golimumab, 1 Certolizumabpegol

***by multivariate analysis, after adjusting for Age, Hypertension, Dyslipidemia, smoking during follow-up period, family history of CVD, difference in BMI, baseline status and antihypertensive and lipid-lowering therapy