***BACKGROUND:*** Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by erosive synovitis that involves peripheral joints and implicates an important influence in the quality and the hope of life. In addition, on the last two decades several studies showed an increased prevalence of coronary and stroke disease and also the cardiovascular (CV) disease represents the principal mortality cause in RA patients; in both male and female subjects. Also, CV mortality prevalence is higher in patients with a younger age than in the general population; so it´s stablished an accelerated atherosclerosis in this disease.

This accelerated atherosclerosis cannot be explained only by classical CV risk factors, so several mechanism have been proposed. In fact, the inflammation that characterizes AR is probably the most important mechanism. In this way, some studies have described elevations of C reactive protein (CRP) levels in RA patients; a endothelial dysfunction marker, not only at the active RA but also at the inactive periods. Indeed, expanded populations of CD4+CD28- T cells have been demonstrated in the peripheral blood of RA patients and they have als been demonstrated in blood and atherosclerotic plaque of patients with unstable angina pectoris. In the inflammatory mechanism, multiple cytokines, including tumor necrosis factor α (TNFα) and IL-1, produced at the rheumatoid synovium have also had an important role.

These circulating cytokines produce directly endothelial dysfunction inducing adhesion molecules expression (ICAM-1, VCAM-1), oxidative stress and a prothrombotic state. After these mechanisms have been activating, the earliest cells to adhere to the endothelium are monocytes, which migrate to subendothelial layers and differentiate into macrophages. Active macrophages and T lymphocytes induce a variety of inflammatory mediators including cytokines, TNFα, growth factors, adhesion molecules and matrix metalloproteinases. This results in further recruitment of inflammatory cells, migration and proliferation of endothelial and smooth muscle cells, plateted aggregation, loss of endothelial nitric oxide and release of oxygen free radicals. On the other hand, nowadays all these stages are considered the atherosclerosis plaque formation model so it shares many features with the pathology of RA.

The drug used to the RA treatment and the new CV risk factors are two mechanisms, added to inflammation and classical CV risk factors, that contributed to accelerated atherosclerosis. In this way, is known that dislipemia is an important risk factor for atherosclerotic coronary disease heart disease in the general population, but it has also been evaluated in RA patients. The most consistent finding has been decreased levels of HDL cholesterol in active or untreated RA in both male and female subjects. Lipoprotein (a) is considered a new independent CV risk factor for coronary disease, and elevated levels have demonstrated in RA patients with both active and treated disease. Also high homocysteine levels have been detected in RA patients because of its relationship with metotrexate. A newest CV risk factor used in heart failure diagnostic is the brain natriuretic peptide (BNP); and some studies showed a relation beteween EKG changes and high levels in RA patients without previous heart disease.The prevalence of other classical CV risk factors like smoking, diabetes and hypertension are not clearly increased in RA patients.

In addition, new CV risk factors like insuline resistance, a prothrombotic state (elevate fibrinogen levels) and microalbumine elevation are also been demonstrated in RA patients. The RA treatment also increases CV risk. The conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly being replace by cyclooxigenase 2 (COX-2) in RA. This drugs have been studied in these patients in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which was designed to compare the gastrointestinal tolerability of robecoxib with that of naproxen, there was a 4-fold increase in the myocardial infarction rate in the rofecoxib group. In addition, metrotexate and cortocosteroids have a double and different CV effect. Metrotexate treatment was associated with improve survival in some studies, but on the other hand, increase homocysteine levels, so it has been associated with an increase mortalituy risk in patients with preexisting atherosclerosis. Also, corticosteroids could increase CV risk by deleterious effects on lipids, glucose metabolism and blood pressure, but in RA patients could also decrease the risk of atherosclerosis by controlling inflammation.

Early intervention studies are needed to test whether disease control and vascular risk modification will decrease atherosclerosis prevalence and CV mortality in RA patients. Statins have demonstrated decrease RA activity at the Trial of Atorvastatin In Rheumatoid Arthritis (TARA) study. Also, different diagnostic methods have test in these patients to detect vascular disease at a subclinical stage. This methods are carotid ultrasound, coronary calcium by electrom-beam computed tomography (CT) and ankle-brachial index (ABI).

Population studies have demonstrated that peripheral artery presence is related with more coronary and carotid atherosclerosis disease prevalence; so it's considered as an independent CV predictive. The ABI has been demonstrated the best subclinical lower limb arterial disease diagnostic method. Also, a high peripheral atherosclerotic disease has already established in RA patients in several studies, comparing with healthy subjects. It has been related with more accumulative glucocorticoid doses (as a disease severity marker). The arteries obstruction (ABI<=0,9) and incompressibility (ABI>1,3 or 1,4) are the two index that are been analysed in these patients.

Subclinical coronary disease prevalence has also been analysed in our study and we had used coronary calcium by CT and the electrocardiogram (EKG). There´s accumulating evidence that coronary artery calcification may be predictive of the risk of both myocardial infarction and death due to coronary artery disease. Some studies have already used this method in patients with systemic lupus erythematous (LES) and RA; demonstrating more calcium score than in the general population.

On the other hand EKG changes have been study. The presence of a QT interval enlargement (QT value >=0,45 seconds) and QT dispersion corrected by heart rate (QTd-c) are also been established as a non invasive test predictive of sudden death. The EKG changes are been analysed in RA patients, and these studies have shown QT enlargement comparing with general population.

Finally, measurement of the intima-media thickness (IMT) and plaque presence of the far wall of the common carotid artery by high resolution ultrasonography has been established as a clinically useful index for identify early stage atherosclerosis, and both are strongly correlated with the presence of coronary artery diseases. Several studies have used this non invasive method and they demonstrated more IMT and plaques presence than in healthy subjects, mainly associated with RA evolution period.

***OBJECTIVES:*** In this study our main objective is to determinate the subclinical atherosclerosis disease prevalence at the peripheral, coronary and carotid territory by ABI, cornary calcium score by CT and EKG, and by carotid ultrasound respectively; in RA patients compared with healthy controls; and it´s relationship with disease characteristics. The secondary objectives are to investigate the presence of classical and new CV risk factors in RA patients and analysed the different non invasive diagnostic methods application.

***PATIENTS AND METHODS:*** Seventy-three unselected RA patients were enrolled in the study. Controls were patients with osteoarthritis that were been followed at our hospital rheumatology consultant. Both groups were matched by age and sex and we included patients that had been diagnosed before the study of any classical CV risk factor but we excluded those who had ever had whatever CV clinical event.

We measured clinical characteristics of the rheumatology disease and classical CV risk factors by a personal interview at the consultant. Referring the rheumatology characteristics, we asked about time of evolution, disease activity score (DAS 28), clinical systemic involvement and time and accumulative doses of the different drugs used for the RA treatment. Also, we asked about previously risk factors presence like dislipemia, diabetes mellitus, smoking, hypertension and soon family CV death; with this information we calculated the Framingham global coronary risk. In addition, we weigh and fit each patient to calculated body mass index (BMI). Systolic and diastolic pressures were also measured as the waist perimetrer analysed the central adiposity. Also we have made blood test and we analyzed cholesterol, inflammatory markers like CPR, ESR, fibrinogen, haptoglobine and new CV risk factors that included lipoprotein (a), homocysteine, and aminoterminal portion of proBNP.

Afterwards, the ABI, the IMT and plaque presence, QT enlargement and calcium score were measured. The ABI was measured at the posterior tibial and dorsal pedal arteries in both groups. We have choose the lowest and the medium ABI values; considering an ABI value <=0,9 as indicative of artery obstruction. Also, IMT and plaque presence were analysed in both groups by ultrasonographic examination of the common carotid, carotid bulb and internal carotid. We have chosen the IMT medium and maximum values between de six measures (Ross method) and also we study not only the plaque presence, but also the ultrasound plaque score and the hemodynamic plaque grade. IMT values indicate of carotid atherosclerosis disease were those similar of the 75 percentile value comparing with a study in the Spanish community; according to sex and age.

Finally, we have made an EKG and we measured calcium score to evaluated subclinical coronary atherosclerosis in both groups. Coronary artery calcification was measured by electrom beam CT and was calculated according to the Agatston and volume (Callister method) score. Values of calcium score > 100 were related with coronary atherosclerosis disease. At the EKG we analysed the presence of arrhythmias, ventricular hypertrophy, QT interval enlargement, QTd-c and also Q pathologic wave (indicates old infarction).

***RESULTS:*** Both groups were composed by 52 female and 21 male, with similar ages (54,8 years in RA group and 55,2 tears in controls). Patients with RA had a median evolution time of 7,81 years, so the majority had less than 10 years of disease evolution. In addition, we used the DAS 28 scale to measure the disease activity; and the median value was 3,2, it means a moderate disease activity. Also, the 24,6% RA patients had extraarticular affection; in this way rheumatoid nodules were the most frequent. It´s important the therapeutic intensity necessary to control RA in our patients; the 57,6% were taken NSAID at the time of the study; 64,4% were taken steroids and 59 patients were taken metotrexate and 29 levuflomida. Biological antiTNFα drugs had been used by the 31,5% of our RA patients, an important proportion because these are the newest RA therapy.

Comparing classical CV risk factors between both groups, the control group had significally more dyslipemic (12,3% in RA patients and 34,2% in controls)(p=0,002) and peripheral obesity (BMI 27,3 kg/m2 in RA patients and 29 in controls)(p=0,04). The controls also had more hypertension proportion; but this difference was not statistically significative. They were no differences in smoking habit, and functional kidney markers, between both groups. Only 5 patients had diabetes diagnosed before the study, 4 of then from control group. In addition, inflammatory markers (fibrinogen, ESR, haptoglobin and CRP), rheumatoid factor (RF) and homocysteine values were significally greater in RA group(p=0,001 for all); but they didn´t had any relationship with subclinical vascular disease. On the other hand, NTproBNP was significally related with more calcium score and EKG changes.

Comparing both groups, RA patients had significative less ABI lowest value (p=0,001) and ABI medium value (p=0,001) than in control group. In addition, 6,8% RA patients showed obstructive peripheral disease and only 1,4% in the control group (p=0,21). Sex and the age at the study time had significance correlation (p=0,03 and 0,009 respectively) with ABI lowest value, but none of then with artery obstruction. It´s remarkably that 23 dyslipemic patients taking statins treatment (a severity disease marker) had subclinical peripheral disease. Among RA patients, only metotrexate treatment had correlation with ABI lowest value (p=0,04); but none of antiinflammatory markers, disease duration or accumulative steroids treatment had any relationship with subclinical peripheral disease.

Subclinical atherosclerosis carotid disease has also been studied. Comparing both groups, they were no differences in IMT medium and maximum value between both groups (median of 0,7 mm for both). Control group had more IMT values indicative of vascular disease proportion (48% upon 45% in RA patients) without significance. Also, they were no differences in plaques number, but ecography ultrasound score and plaque grade were more prevalent and had strongly tendency to the significative in control group.

Among both groups, female sex (p=0,02), the age at study time (p=0,001), peripheral (p=0,002) and central (p=0,001) obesity, hypertension (p=0,005) and statin treatment (p=0,045) had correlation with pathological IMT values, so this non invasive method in our study reflects better than others the classical CV risk factors damage to the vessel. The pathological IMT value was also more prevalent in diyslipemic patients, but without significance. On the other hand, non of the RA characteristics had any relation with IMT value.

In both groups most of the patients didn´t show coronary artery calcification (Agatston and volume score=0). Also, in patients with coronary calcium score was detected, they were no differences between RA patients (median 1,8; interquartile range [IQR]=0,5-2,3) and control group (median 1,4; interquartile range [IQR]=1,2-2,1)(p=0,59). On the other hand, RA patients had more pathological Agatston and volume score (value>100 for both)(17% and 19,2% respectively) than in controls (11% for both) without significance. Only the age at the study time had a significance correlation (p=0,001) with coronary calcium score, but none of the other classical CV risk factors had any relationship in both groups. Among RA patients, disease duration (p=0,008), steroid (p=0,010) and metotrexate (p=0,049) treatment were correlated with more coronary calcium score.

Moreover, the QT interval enlargement and QTd-c were significative more prevalent (p=0,001 and 0,021 respectively) in RA patients. In addition, whatever EKG changes was also more frequent in the RA group (p=0,023). Finally, among both groups, patients with a Q pathological wave at the EKG had significative more pathological calcium score.

***CONCLUSIONS:*** 1) RA patients had lowest ABI values; they represent peripheral vascular disease. 2) It is not frequently coronary calcification in both groups; but RA patients show more calcium score related with coronary presence. 3) In RA patients EKG changes are more frequently than in controls; mainly the QT interval enlargement and QT d-c. 4) A Q pathological wave at the EKG is associated with higher calcium score values. 5) NTproBNP values are related with EKG changes and QT enlargement; also have significally relation with more coronary calcium score. 6) Carotid subclinical disease is frequent in both groups, but the rheumatoid disease impact is lower than in other vascular territories; probably because of classical CV risk factors influence. 6) Subclinical disease at whatever of the three territories, is a good predictive of vascular disease in the others. 7) In both groups the characteristic with more influence in the vascular disease is the age at the study time; in whatever vascular

territory. 8) The inflammatory markers and the rheumatoid disease activity, could be modified by the treatment anti-inflammatory effect, and explains the no relationship with vascular disease. 9) The RA characteristic that has more influence in the vascular disease is the evolution time; that also is related with the patient age.