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# Factors of Progression and Occurrence of Atherosclerosis in Rheumatoid Arthritis

*Aim* To determine in a prospective study factors of progressive atherosclerotic lesion of blood vessels in patients with rheumatoid arthritis (RA).

*Material and methods* This prospective study included 124 patients with RA and suspected ischemic heart disease (IHD) and 30 patients with IHD (comparison group) aged 58 [52; 63] years. On enrollment to the study and at 3 years of follow-up, all patients underwent clinical and instrumental examination according to European and Russian guidelines for diagnosis and treatment of stable IHD (2013), including coronography as indicated. For all RA patients of the comparison group, risk factors (RF) were evaluated, including arterial hypertension, smoking, excessive body weight, family history of cardiovascular diseases (CVD), diabetes mellitus, and dyslipidemia. The following laboratory data were evaluated: blood count; biochemistry, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL–C), low-density lipoprotein cholesterol (LDL–C), triglycerides (TG), rheumatoid factor (RhF), cyclic citrullinated peptide antibodies, and high-sensitivity C-reactive protein (hsCRP). Proinflammatory cytokines, including interleukin (IL) – 1β, IL-6, and tumor necrosis factor-α (TNF- α), were measured in RA patients once, at 3 years of follow-up.

*Results* Incidence of FRs for CVD was similar in RA patients and in the comparison group. Median RA duration before inclusion into the study was 11 years, and median DAS28 index score was 3.8. Incidence of dyslipidemia due to increased TC, LDL–C, and HDL–C was higher for RA patients at baseline. The LDL–C goal (<1.8 mmol/l) was achieved only in 3 (10%) patients of the comparison group and 10 (8%) RA patients. RA patients had higher levels of the inflammation indexes, hsCRP (0.75 mg/dl vs. 0.16 mg/dl; p<0.05) and erythrocyte sedimentation rate (ESR) (15 mm/h vs. 11.5 mm/h; p<0.05). In the RA group at baseline, atherosclerotic plaques with carotid artery (CTA) stenosis of 20% or more were found in 94 (77%) patients; in 3 of them, CA stenosis was >50%. Patients with RA frequently had unchanged or slightly changed coronary arteries (CA) (47% of patients), and less frequently they had hemodynamically significant multi-arterial coronary atherosclerotic lesions (7% vs. 57% of patients in comparison group). At 37.5 months, 21 (23%) of 94 RA patients had progressive atherosclerosis in CA and/or CTA; 12 (13%) RA patients had only progressive CA atherosclerosis; 7 (8%) had only progressive CTA atherosclerosis; and 2 (2%) had simultaneous progression of CA and CTA atherosclerosis. Two groups of RA patients were formed, with the progression of atherosclerosis (n=21) and without the progression of atherosclerosis (n=69). RFs for the development/progression of atherosclerosis in RA patients included smoking, family history of CVD, and duration of the disease. Levels of lipids did not differ. Levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) were higher in RA patients with progressive atherosclerosis. No effects of the anti-rheumatic therapy on the progression of atherosclerosis were observed.

*Conclusion* Progression of atherosclerosis in RA remains in disease with low and moderate activity during the anti-rheumatic and hypolipidemic treatment. The development of atherosclerosis in RA is determined by lipid, inflammatory, and immune disorders.

*Keywords* Rheumatoid arthritis; atherosclerosis; inflammation; carotid arteries; coronary arteries; immune disorders; cytokines

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Rheumatoid arthritis (RA) is an autoimmune disease of unknown origin, manifested by chronic erosive arthritis and characterized by progressive course and clinically significant complications which lead to early disability and reduced life expectancy [1]. Despite advances in diagnosis and treatment of the disease, cardiovascular mortality in RA remains high [2, 3]. The relative risk of developing cardiovascular complications



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(CVCs) in RA due to early onset and rapid progression of atherosclerotic vascular lesions is almost 3.5-fold. The incidence of fatal CVCs is 2 times as high as in the general population [3–5], comparable to that of patients with type 2 diabetes mellitus, and is associated with the immunoinflammatory mechanisms underlying the pathogenesis of RA and atherosclerosis [6].

Vascular wall inflammation, characteristic of RA, has been shown to pave the way for the development of atherosclerotic lesions in various vascular beds. The mechanisms associated with the progression of atherosclerosis in RA are unclear. The contribution of common risk factors (RFs) of cardiovascular diseases (CVDs), systemic inflammation, immune activity, and the effects of antirheumatic drugs are discussed [7].

In order to understand the role of systemic inflammation in the development of CVDs in RA patients, a concept of similarity of the components of the pathogenesis of autoimmune inflammation and atherosclerosis is critical [8, 9].

Chronic activation of the immune response is accompanied by hyper-production of pro-inflammatory cytokines: tumor necrosis factor-alpha (TNF-alpha), interleukin (IL) – 1, IL-6, etc. These are major mediators of vascular disorders, since they are associated with the effects associated with carotid and coronary atherosclerosis [10, 11]. Arterial hypertension (AH), dyslipidemia, metabolic syndrome are the most common cardiovascular RFs [12–14].

A prospective study has shown that six years after the onset of RA, there were more patients with severe atherosclerosis (increased thickness of intima-media and a higher number of patients with atherosclerotic plaques (APs)). During the observation period, certain cardiovascular FRs changed and increased the risk as assessed by the Systematic COronary Risk Evaluation (SCORE) scale. It has been suggested that RFs contribute to the progression of atherosclerosis in RA patients, as well as inflammatory activity [15]. Concurrently, Arida et al. [16], who observed patients for three years, showed that the progression of atherosclerosis was influenced by effective control of rheumatoid inflammation (decreased activity or remission).

Another study, which compared the actual and predicted 10-year progression of atherosclerosis in RA patients, has shown a reliable increase in calcification in all vascular beds: coronary (55%), carotid (29%), and the aorta (80%). At the same time, atherosclerotic vascular calcification increased and was independently associated with age and systolic blood pressure. It should be noted that the absolute increase in the actual 10-year progression of atherosclerosis was significantly higher than predicted [17].

The factors of atherosclerosis progression in RA patients have not been well studied. The development of one or another CVC is most often described in the literature. At the same time, there are few specific clinical investigation data in terms of real-world evaluation of changes in the atherosclerotic process.

## Objective

To determine the factors of progression of atherosclerotic vascular lesions in RA patients prospectively.

## Material and methods

The study was carried out under the joint program «Development of Methods of Individualized Treatment of Rheumatic Diseases with Comorbidities» of the Russian National Cardiology Research Center and V.A. Nasonova Research Institute of Rheumatology, specifically the section «Addressing Early Diagnosis, Prevention and Treatment of Cardiovascular Pathologies in Rheumatoid Arthritis».

The study protocol was approved by the ethics committee of the Russian National Cardiology Research Center and V. A. Nasonova Research Institute of Rheumatology. To be included in the study, all patients signed informed consent.

The prospective study included 124 patients with RA and suspected of coronary heart disease (CHD) (treatment group) and 30 patients with CHD without systemic diseases (control group).

Inclusion criteria for RA patients: male and female patients from 35 to 65 years old, with a more than 5-year duration of the disease, a low to moderate degree of RA activity, and suspected CHD (chest pain or shortness of breath with exercise and/or known history of myocardial infarction (MI)).

The control group included (male and female) patients comparable in sex and age to those in the main group with confirmed stable CHD and stenosing coronary atherosclerosis as shown by coronary angiogram (CAG) and no rheumatic diseases.

The study did not include individuals over 65 years old with acute coronary syndrome and a history of MI within the previous 3 months, with clinical signs of acute heart failure, and with chronic heart failure (NYHA functional class 3–4), clinically significant valvular defects, second and third-degree atrioventricular block and/or life-threatening arrhythmias, severe chronic diseases (cancer, renal and hepatic failure).

The mean observation period was 37.5 weeks.

All patients with RA were subjected to clinical investigations at the Russian National Cardiology Research Center following European and Russian guidelines for

the diagnosis and treatment of stable CHD (2013) [18], including CAG if indicated, at inclusion in the study and 3 years later.

All patients with RA and those in the control group were assessed for RFs, such as AH, smoking, excessive weight, family history of CVDs, diabetes mellitus, dyslipidemia [19]. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL–C), low-density lipoprotein cholesterol (LDL–C), triglycerides (TG) were determined using standard enzymatic methods in an ARCHITECT biochemical analyzer.

The activity of RA was determined by the DAS28 index in V. A. Nasonova Research Institute of Rheumatology.

Serum levels of high-sensitivity C-reactive protein (hs-CRP) were determined using a commercial nephelometric hs-CRP-ELISA-BEST kit following the manufacturer's protocol. The measurement was compared to a standard product with a known concentration of hs-CRP prepared using the international reference drug ECR CRM 470. The measurements were performed in a BN ProSpec blood protein analyzer.

Rheumatoid factor (IgM antibodies by nephelometry and anti-cyclic citrullinated peptide (CCP) antibodies by immunofluorescence using second- and third-generation synthetic citrullinated peptides as antigen) was determined in all RA patients in the clinical diagnostic laboratory department of V. A. Nasonova Research Institute of Rheumatology.

Pro-inflammatory cytokines were evaluated in RA patients once after three years of observation. The concentration was determined by means of an enzyme-linked immunosorbent assay (ELISA) using Vector-Best commercial sets in the following ranges: IL-1 beta 5–250 pg/mL, IL-65.6–300 pg/mL, TNF-alpha 0–250 pg/mL. During the control examination of RA patients, the median level of TNF-alpha was 2.30 pg/mL, IL-1 beta 3.56 pg/mL, IL-62.92 pg/mL. ELISA was performed in a Stat-Fax-2100 plate photometer.

Carotid ultrasonography was performed using a Philips IU22 ultrasound machine and a 3–9 MHz linear probe to determine the presence and severity of the atherosclerotic process and assess AP structure and surface. Entire common carotid arteries, their bifurcations, and proximal internal carotid arteries on both sides were studied using the standard method. AP was defined as the focal thickening of the vessel wall by more than 50% compared to the surrounding areas or as a focal increase in the intima-media complex thickness by more than 1.5 mm protruding into the vessel lumen. Carotid stenosis severity was determined in accordance with the ECST criteria (a ratio of the original inter-adventitial diameter at the site of stenosis to the diameter of the lumen at the site of stenosis expressed in percentage). The progression of atherosclerosis was evaluated against the baseline ultrasound results.

Angiographic examinations were performed in an Allura Xper FD-10 system using the Judkins technique by means of femoral, radial, or ulnar access. The study included patients without iodine allergy. Ioversol and iproamide non-ionic contrast media (Ultravist) were used in all cases. All angiograms were interpreted by the panel of cardiologists and interventional diagnosticians. The progression of atherosclerosis was assessed by the same panel by comparing the baseline angiograms with the results of repeat examination.

Patients with RA and control patients received statins, antiplatelet drugs, beta-blockers, antihypertensive drugs following the clinical guidelines for the treatment of stable angina [18].

Patients with RA received antirheumatic drugs: disease-modifying antirheumatic drug (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), glucocorticoids, non-steroidal anti-inflammatory drugs, and genetically engineered biological drugs. The latter include TNF-alpha inhibitors (infliximab, adalimumab, etanercept), IL-6 receptor inhibitors (tocilizumab), anti-B cell drug (rituximab), T-lymphocyte activation blocker (abatacept). Patients remained stable for three years, the activity was low to moderate, and there was no need to change the drug therapy.

The progression of atherosclerosis was interpreted by invasive and ultrasound examination as the occurrence of a ≥20% stenosis in the initially intact arterial segment, or a 10% or more increase in the available stenosis, or the progression of stenosis into occlusion [20].

The data obtained was analyzed with Statistica 7.0 software suite. Non-parametric statistics was used. The results are presented as the median and 25th and 75th percentiles. The statistical significance of differences was assessed using the Mann-Whitney test. The groups were compared by qualitative characteristics using the chi-square test with Pearson's contingency coefficient and Fisher's exact test. The correlation analysis was carried out using Spearman's rank correlation coefficient. Differences were statistically significant at $p<0.05$.

## Results

The study included 124 patients with RA. The mean age was 37.5 years. Upon inclusion, 21 patients with RA underwent a percutaneous coronary intervention (PCI). Coronary artery bypass grafting was performed in 4 cases. During that period, 3 patients with multiple coronary lesions who refused the proposed surgical treatment, died of CVCs. Another 4 patients underwent PCI for the


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**Table 1.** Baseline clinical characteristics of patients in the RA and control groups

| Indicator | Patients with RA (n=124) | Control group (n=30) |
|---|---|---|
| Age, years | 58 [52; 63] | 56 [50; 59] |
| Male/female | 41/83 (33/67) | 6/24 (20/80) |
| AH | 96 (77) | 24 (80) |
| History of MI, n (%) | 16 (13) | 16 (53)* |
| Dyslipidemia | 51 (41) | 7 (23) |
| TC, mmol/L | 5.4 [4.4; 6.2] | 4.3 [4.0; 5.5]* |
| HDL-C, mmol/L | 1.3 [1.1; 1.7] | 1.1 [0.9; 1.4]* |
| LDL-C, mmol/L | 3.4 [2.4; 4.0] | 2.5 [2.1; 2.9]* |
| TG, mmol/L | 1.37 [0.96; 1.89] | 1.57 [1.0; 2.7] |
| DM | 16 (13) | 7 (23) |
| Family history of CVDs | 45 (36) | 13 (43) |
| Smoking | 31 (25) | 14 (47) |
| DAS28, score | 3.8 [2.2; 5.0] | – |
| Duration of RA, years | 11 [6; 18] | – |
| Positive for RF | 113 (91) | – |
| Positive for anti-CCP Ab | 105 (85) | – |
| ESR, mm/h | 15 [7.3; 36] | 11.5 [11.1;18]* |
| hs-CRP, mg/dL | 0.75 [0.2; 1.7] | 0.16 [0.11;0.27]* |

The data is expressed as the median and the interquartile range (Me [25%; 75%]) and the absolute and relative values (n (%)).
*, p<0.05. RA, rheumatoid arthritis; AH, arterial hypertension; MI, myocardial infarction; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; DM, diabetes mellitus; CVD, cardiovascular disease; RF, rheumatoid factor; anti-CCP Ab, anti-cyclic citrullinated peptide antibodies; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

first time. An artificial pacemaker was implanted in one case. The condition of 12 patients worsened due to RA. Eleven patients refused the repeat examination. They did not have any CVCs during the follow-up period. Seven patients were lost for follow-up. Thus, 90 (73%) patients with RA were re-examined in 3 years.

The control group included 30 patients with CHD without RA. The clinical characteristics of patients are presented in Table 1.

The groups were comparable in sex and age. Cardiovascular RFs were observed at the same rate in patients with RA and in the control group. At the same time, dyslipidemia (due to increased levels of TC, LDL–C, and HDL–C) was initially more common in RA. Statins were administered in 84 (68%) patients with RA, despite the fact that all were at high (35%) or very high (65%) cardiovascular risk. In the control group, all patients received statins. MI was more common in this group. The target level of LDL–C (<1.8 mmol/L) was reached only in 3 (10%) patients in the control group and 10 (8%) patients in the RA group.

The median duration of RA before inclusion was 11 years and the median DAS28 was 3.8. In the RA group, higher levels of hs-CRP were observed (0.75 mg/dL vs. 0.16 mg/dL; p<0.05) and ESR (15 mm/h vs. 11.5 mm/h; p<0.05).

Upon inclusion, APs with ≥ 20% carotid stenosis were identified in 94 (77%) patients with RA, three of them had >50% stenosis (Table 2). Carotid ultrasound data was not analyzed in the control patients.

During the examination, 83 patients with suspected CHD were subjected to CAG, given the clinical picture of the disease and the results of the stress test. A total of 101 (81%) patients with RA were tested. The test result was positive in 16 (16%) patients with RA, questionable in 17 (17%) patients with the typical clinical picture of angina pectoris. The stress test was not brought to the ischemia level in 36 (36%) patients with the typical and atypical clinical picture of retrosternal pain. The result of the stress test was negative in 32 (32%) patients.

According to CAG, patients with RA often had normal or almost normal coronary arteries, and hemodynamically significant multivessel coronary atherosclerosis was less frequent than in the control group (Table 3).

Over 3 years, 90 (100%) patients with RA underwent carotid ultrasound, while 14 (16%) showed progression of carotid atherosclerosis.

Repeated CAG was performed in 67 out of 90 (74%) patients with RA. The indications were deterioration or the appearance of clinical manifestations of angina pectoris combined with the results of stress test (positive, doubtful, and ischemia level not reached in 5, 3, and 10 patients, respectively), a clinical picture of retrosternal pain, shortness of breath accompanied by conditions limiting physical activity (n=35), and/or known history of coronary lesions (n=14). Progression of coronary atherosclerosis was detected in 7 (10.5%) patients with RA, of whom 4 patients were subjected to PCI. Atheroma in the initially intact coronary artery was found in 5 (7.5%) of 67 patients with RA. In 2 (3.0%) patients with stenosis at baseline, 40% and 30% stenosis progressed into occlusion.

Thus, in the 37.5 months of follow-up, 21 (23%) patients with RA formed a group of atherosclerosis progression in 1 or 2 vascular beds (coronary and/or carotid arteries). 12 (13%) patients with RA only had the progression of carotid atherosclerosis, 7 (8%) patients had progression of coronary atherosclerosis, while 2 (2%) patients had simultaneous progression of carotid and coronary atherosclerosis (Figure 1).

**Table 2.** Changes in carotid and coronary atherosclerosis course in patients with RA after 3 years of follow-up

| Patient | Sex | Age, years | Ultrasound | | CAG | | Progression |
|---|---|---|---|---|---|---|---|
| | | | Baseline | In 3 years | Baseline, % | In 3 years | |
| 1. S. | F | 55 | AP=2, stenosis <50% | No change | LCX stenosis >75% | Occlusion | Coronary |
| 2. P. | M | 48 | AP=2, stenosis <50% | No change | LCX stenosis >75% | Occlusion | Coronary |
| 3. N. | M | 56 | AP=2, stenosis <50% | AP=2, stenosis 60% | LAD stenosis 50–75% | No change | Carotid |
| 4. M. | M | 65 | AP=2, stenosis <50% | AP=3, stenosis <50% | Not performed | Not performed | Carotid |
| 5. L. | M | 64 | AP=2, stenosis <50% | AP=3, stenosis <50% | No lesion | OM stenosis>50% | Coronary, carotid |
| 6. Z. | M | 61 | AP=2, stenosis>50% | No change | No lesion | OM stenosis<75% | Coronary |
| 7. Zi. | F | 57 | AP=2, stenosis>50% | No change | No lesion | LAD stenosis>60% | Coronary |
| 8. D. | M | 56 | AP=2, stenosis <50% | No change | RCA stenosis<50% | RCA stenosis 60–75% | Coronary |
| 9. G. | F | 48 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 10. V. | F | 58 | AP=1, stenosis <50% | AP=2, stenosis <50% | RCA stenosis>75% | No change | Carotid |
| 11. Yu. | M | 49 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 12. T. | F | 63 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 13. R. | F | 54 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 14. Pr. | F | 44 | No lesion | AP=1, stenosis <50% | No lesion | No change | Carotid |
| 15. Pro. | F | 65 | AP=2, stenosis <50% | No change | No lesion | RCA, DA stenosis 50–60% | Coronary |
| 16. Pe. | M | 65 | AP=2, stenosis <50% | No change | No lesion | LCX, OM stenosis 50–60% | Coronary |
| 17. H. | Ж. | 51 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 18. M. | Ж. | 64 | AP=1, stenosis <50% | AP=3, stenosis <50% | No lesion | No change | Carotid |
| 19. M. | Ж. | 65 | AP=2, stenosis>50% | AP=3, stenosis <60% | No lesion | RCA, DA stenosis <50% | Coronary, carotid |
| 20. H. | Ж | 46 | AP=1, stenosis <50% | AP=2, stenosis <50% | No lesion | No change | Carotid |
| 21. P. | Ж | 55 | AP=2, stenosis <50% | AP=2, stenosis <60% | No lesion | No change | Carotid |

RA, rheumatoid arthritis; CAG, coronary angiogram; AP, atherosclerotic plaque; AP=1, atherosclerotic plaque in one vessel; AP=2, atherosclerotic plaques in two vessels and more; AP=3, newly detected AP; LDA, left anterior descending artery; LCX, left circumflex artery; DA, diagonal artery; OM, obtuse marginal branch; RCA, right coronary artery; M, male; F, female.

**Table 3.** CAG findings at inclusion

| Indicator | Patients with RA (n=83) | Control group (n=30) |
|---|---|---|
| Normal arteries or mild changes | 39 (47) | 0 |
| Stenosis 50–75% | 9 (11) | 5 (17) |
| One-vessel lesion, stenosis >75% | 18 (22) | 5 (17) |
| Two-vessel lesion, stenosis>75% | 6 (7)* | 17 (57)* |
| Three-vessel lesion, stenosis>75% | 11 (13) | 3 (10) |

The data are expressed as the absolute and relative rates, n (%)
*, p<0.001. CAG, coronary angiogram;
RA, rheumatoid arthritis.

Two groups of patients with RA were formed, in order to clarify the effects of cardiovascular RFs on the development of carotid and/or coronary atherosclerosis, Group 1 included RA patients with progressing atherosclerosis (n=21), Group 2 included those without atherosclerosis progression (n=69; Table 4).

Smoking and a family history of CVDs were RFs for the development/progression of atherosclerosis in RA patients. Factors deriving from rheumatoid inflammation were analyzed in the groups of patients: duration, activity, levels of immune-inflammatory cytokines (Table 5).

The duration of the disease was longer in RA patients with progressing atherosclerosis than in those without. However, the groups did not differ in activity and hs-CRP levels. Levels of pro-inflammatory cytokines (TNF-alpha, IL-1 beta, IL-6) were significantly higher in RA patients with progressing atherosclerosis when compared to those without atherosclerosis progression.

Correlation analysis of blood lipid profile and pro-inflammatory cytokines showed an inverse relationship between TNF-alpha and LDL–C (r= –0.34), TC (r= –0.3), p<0.05 in all cases. No association with other cytokines (IL-6 and IL-1 beta) was found (p>0.05).

The analysis of the effects of antirheumatic therapy on the progression of atherosclerosis showed no significant differences in the rate of using different antirheumatic drugs.


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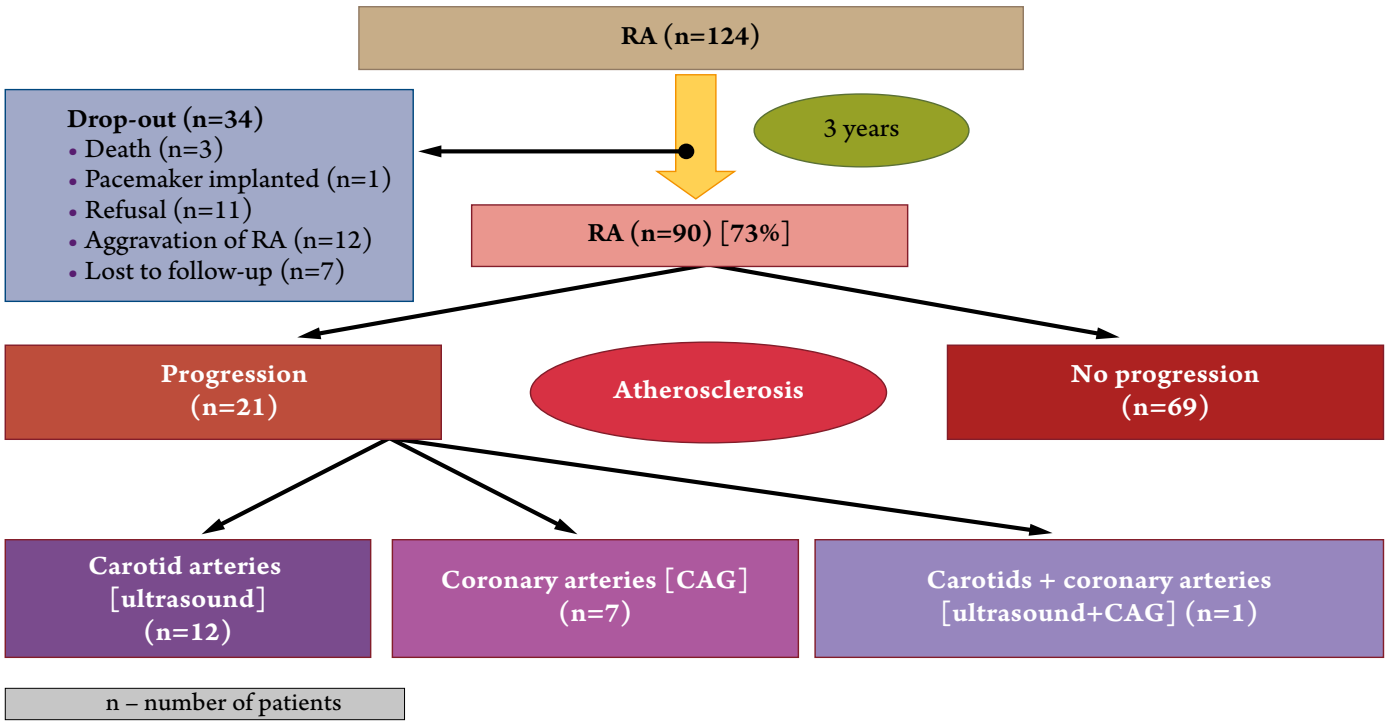
**Figure 1.** Formation of RA patient groups




RA, rheumatoid arthritis; CAG, coronary angiogram.

**Table 4.** Cardiovascular risk factors in RA patients with and without atherosclerosis progression

| Indicator | Progression of atherosclerosis (n=21) | No progression of atherosclerosis (n=69) |
|---|---|---|
| Age, years | 57 [51; 64] | 58 [52; 63] |
| Male | 8 (38) | 23 (33) |
| AH | 18 (86) | 52 (75) |
| Body mass index, kg/m² | 26 [24; 31] | 28 [25; 31] |
| TC, mmol/L | 4.6 [3.97; 5.51] | 5.5 [4.60; 6.52] |
| LDL-C, mmol/L | 2.5 [2.09; 3.30] | 3.1 [2.79; 4.16] |
| HDL-C, mmol/L | 1.4 [1.02; 1.54] | 1.3 [1.16; 1.63] |
| TG, mmol/L | 1.19 [0.96; 1.86] | 1.44 [0.96; 1.89] |
| Smoking | 12 (57) | 21 (30)* |
| Family history of CVDs | 11 (52) | 17 (25)* |

The data is expressed as the median and the interquartile range (Me [25%; 75%]) or the absolute and relative values (n (%)). *, p<0.05. CVD, cardiovascular disease; RA, rheumatoid arthritis; AH, arterial hypertension; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

**Table 5.** RA-associated factors and immune-inflammatory cytokines in RA patients with and without atherosclerosis progression

| Indicator | Progression of atherosclerosis (n=21) | No progression of atherosclerosis (n=69) |
|---|---|---|
| Duration of RA, years | 13 [10; 18] | 12 [6;18] * |
| DAS28, score | 4.49 [3.30; 5.78] | 5.16 [3.33; 6.99] |
| hs-CRP, mg/dL | 0.64 [0.19; 1.26] | 0.99 [0.40; 3.04] |
| TNF-alpha, pg/mL | 8.08 [2.3; 8.44] | 1.22 [0.13; 8.00]* |
| IL-1 beta, pg/mL | 3.97 [3.56; 4.10] | 3.52 [0.30; 4.53]* |
| IL-6, pg/mL | 3.50 [2.92; 5.76] | 2.52 [0.92; 4.36]* |

The data is presented as the median and interquartile range (Me [25%; 75%]). *, p<0.05; RA, rheumatoid arthritis; hs-CRP, high-sensitivity C-reactive protein; TNF-alpha, tumor necrosis factor-alpha; IL, interleukin.

## Discussion

In recent decades, many clinical and epidemiological studies have shown that RA accelerates the progression of atherosclerosis and increases cardiovascular risk [1–3, 21].

In our study, a large group of RA patients who were suspected of having CHD was followed up. This was confirmed during the examination in 44 (35%) patients. Carotid ultrasound and CAG detected a high prevalence of stenosing carotid (77%) and coronary (53%) atherosclerosis in these patients at inclusion. Three years later, re-examination showed that atherosclerosis progressed in one or two vascular beds in 23% of patients. The study was limited by the fact that the major lower leg arteries had not been examined.

Pre-clinical atherosclerosis is common in RA patients regardless of traditional RFs. Roman et al. [22] noted that the progression of carotid atherosclerosis in RA patients according to ultrasound examination was 3 times as frequent as in patients without RA (44% vs. 15%, respectively; p<0.001). In our study, the progression of atherosclerosis was also often found in the carotid bed 12% versus 7% in the coronary bed. This data is consistent with the findings Pope et al. [23], who detected a high prevalence of carotid atherosclerosis (35%) in the active and long-lasting (>14 years) course of RA and cardiovascular RFs. The progression of carotid APs in SA was studied within the 24-week follow-up. APs were assessed using high-resolution 3D ultrasound (REF scanner). The progression criterion was an increase in the AP total area >0.25 $cm^2$ and/or the intima-media thickness>0.6 mm. The multifactor regression analysis showed that the progression of atherosclerosis without lipid-reducing therapy was associated with the baseline levels of hs-CRP, associated with high disease activity (r=0.443; p=0.016), LDL–C (r=0.544; p=0.007), family history of CVDs (r=0.464; p=0.011), and smoking (r=0.384; p=0.04). Dyslipidemia was detected in 68% of patients [23].

In the analysis of RFs in our cohort of patients with low- and moderate-activity RA, smoking and family history of CVDs were more common in the progression of atherosclerosis, which is consistent with other authors [24–26]. For example, Söderlin et al. [24] showed that the effectiveness of antirheumatic drugs was reduced in smokers with RA with an increased risk of CVD. In our study, the duration of RA was higher in the group of patients with progressing atherosclerosis. This is consistent with other authors, who showed that the disease duration in combination with the cardiovascular RFs contributed to the development of CVCs, and in the absence of RFs, did not affect the risk of developing CVCs [15, 27]. The rest of the RFs did not differ in groups with and without progression of atherosclerosis.

The question still remains whether which of the RFs contributes the most to the development of atherosclerosis in RA. The combined influence of cardiovascular RFs and systemic inflammation is considered the main cause of earlier development and rapid progression of atherosclerosis in patients with RA [26, 28]. Indeed, RA is primarily an immune-inflammatory disease. Numerous fundamental studies have proved the essential role of low-activity chronic inflammation in the development of all stages of the atherosclerotic process, from formation to rupture of APs and further development of thrombotic complications [29, 30]. Inflammation is the main factor which increases the cardiovascular risk 1.5 to 2.0 times in RA when compared to the general population [29–32]. Atherosclerosis and RA have many common inflammatory mechanisms. The processes underlying inflammation of the joint synovia are similar to those that cause AP instability. Pro-inflammatory cytokines (TNF-alpha, IL-1, and IL-6) play a key role in the development of RA and atherosclerosis [33]. This was taken into account in the 2019 ESC Guidelines on Dyslipidaemias (Management of), according to which the cellular and molecular mechanisms involved in the process of atherogenesis are not fundamentally different from those in chronic inflammatory conditions, such as RA [9].

Our findings showed that RA patients with progressing atherosclerosis in different vascular beds had higher levels of TNF-alpha, IL-6, and IL-1 beta than in RA patients without progression of atherosclerosis with no differences in the lipid profile between the groups. This is due to the fact that these cytokines are involved in the pathogenesis of RA, and the hyperproduction in the inflamed synovial fluid activates macrophages in APs, which partially explains the progression of atherosclerosis and the development of CVCs [34].

Modern engineered biological treatments for RA allow for the effective suppression of autoimmune inflammation by targeting pro-inflammatory cytokines [35]. This therapy is also possible in patients without rheumatic diseases, in order to prevent the development of CVCs. It was clearly demonstrated in CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) that the use of IL-1 beta inhibitor canakinumab, in addition to the best possible therapy for patients with a history of MI, reduces the risk of developing repeat CVCs compared to a placebo without changing plasma lipid levels, and has positive effects on immune-inflammatory markers. One of the inclusion criteria was hs-CRP >2 mg/L. This study has shown for the first time that reducing inflammation can reduce the risk of CVD [36].

At the same time, we have established a negative correlation between the concentration of cytokines and the levels of TC and LDL–C. This confirms the essential role of the immunological component in the development of atherosclerosis in RA [37, 38]. Other studies have shown that dyslipidemia is stimulated by persistent inflammation caused by pro-inflammatory cytokines, namely TNF-alpha and IL-6, which affect lipid levels by shifting them toward the atherogenic profile [37, 39].

We also tested the lipid profile in RA patients. Serum levels of TC and LDL–C were found to be higher at inclusion in RA patients than in the control group. The mechanism of such changes may be explained by the fact that all the RA patients included had a low level of activity (median DAS28=3.8) and received antirheumatic treat-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ments. The correlation of increasing lipid levels with decreasing inflammation parameters in RA is described as a «lipid paradox» [40]. It should be noted that 68% of RA patients received statins at baseline.

Inflammation in RA can reduce TC, while paradoxically associated with an increased cardiovascular risk. As the inflammation reduces, anti-atherogenic LDL–C increases by contrast. However, the use of certain anti-rheumatic drugs is associated with increased levels of TC, LDL–C, and even more HDL–C, which improves the TC to HDL–C ratio. In this case, the risk of developing CVCs is reduced. Lipid levels in RA should be measured when the disease activity is stable or in remission because they can be modified by disease activity and anti-inflammatory therapy.

However, statins remain the first-line therapy for patients with RA with elevated levels of LDL–C and cardiovascular risk factors [37, 41, 42].

All patients included in our study received statins during the follow-up period. However, the lipid targets were not reached. There was no difference in lipid levels in RA patients with and without atherosclerosis progression. Recently, Svanteson et al. [43] published the results of 5-year follow-up of patients with CHD and inflammatory joint diseases, including RA, receiving statin therapy. According to these results, when the level of LDL–C <1.8 mmol/L was reached, atherosclerosis progression slowed down by reducing the AP calcification index in CT and total plaque volume determined by the same method, compared to patients with LDL–C >1.8 mmol/L: 21 [2; 143] $mm^3$ vs. 69 [16; 423] $mm^3$ (p=0.006) and 0.65 [–1.0; 13.9] $mm^3$ vs. 13.0 [0.0; 60.8] $mm^3$ (p=0.019), respectively. Moreover, the plaque structure changed: the volume of soft/mixed APs reduced. Authors also noted that only 50% of patients had LDL–C ≤1.8 mmol/L by the end of the follow-up period [43].

The contribution of RA-associated factors in the development of CVDs is currently being studied. In this regard, the Trans-Atlantic Cardiovascular Risk Consortium for Rheumatoid Arthritis (ATACC-RA) was established. The study included 5,638 RA patients without signs of CVDs from 13 rheumatology centers around the world. The follow-up period was 5.8 years. The work showed that the 10-year cumulative cardiovascular risk was 20.9 and 11.1% in male and female patients, respectively. In this large international cohort of patients with RA, 30% of cardiovascular events were associated with the underlying disease characteristics: DAS28 index, positive serostatus [44].

However, we have found no association between baseline disease activity and progression of atherosclerosis in RA patients. This is probably due to the fact that patients in our cohort had low or moderate baseline RA activity while receiving adequate antirheumatic treatment.

## Conclusion

Our findings show that the progression of atherosclerosis in rheumatoid arthritis persists with low- to moderate disease activity during antirheumatic and hypolipidemic therapy. Atherosclerosis develops in rheumatoid arthritis due to lipid, inflammatory, and, to a greater extent, immune disorders, which should be considered to stratify and manage cardiovascular risks in rheumatoid arthritis.

## Limitations

The major lower leg arteries were not examined in the RA patients included.

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