Chapter

Cardiovascular Risk in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA), one of the most common inflammatory rheumatic diseases. It is defined as a chronic destructive and deforming arthropathy; it also finds its expression through systemic manifestations. RA has an undulating evolution, with remissions and relapses. Atherosclerotic cardiovascular disease represents one of the most common extra-articular manifestations of RA. It is known that the cardiovascular (CV) morbidity and mortality represent one of the leading causes of reduced life expectancy in RA. Patients with RA develop a premature and accelerated atherosclerosis, explaining the high incidence and prevalence of angina, myocardial infarction, congestive heart failure, stroke, peripheral artery disease, and the need for revascularization. Traditional risk factors (arterial hypertension, obesity, smoking, dyslipidemia, insulin resistance and metabolic syndrome, diabetes mellitus, male gender, physical inactivity) interplay with RA-related risk factors, generating endothelial dysfunction, arterial stiffness, carotid plaque, and atherosclerosis. Traditional cardiovascular risk factors alone cannot explain the increased incidence of premature and accelerated atherogenesis. Chronic inflammation, hyperhomocysteinemia, and hypercoagulation act as novel cardiovascular risk factors. Rheumatoid inflammation exerts direct effects on vessels, or by means of altered traditional risk factors. Antirheumatic drugs may promote atherogenesis or by reducing systemic inflammation may decrease cardiovascular risk. EULAR recommendations require annual cardiovascular risk assessment.

Keywords: cardiovascular risk, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA), one of the most frequent rheumatic inflammatory diseases, is defined as a chronic destructive and deforming arthropathy, but it also expresses itself through systemic manifestations [1]. The incidence of RA reaches its peak around 50 years; this disease affects twice as many women than men [2]. Its evolution is undulating, marked by exacerbations and remissions, the burden being variable between patients. This fact makes long-term outcomes different between patients: some have relatively mild disease, while others have marked physical disabilities and reduced quality of life [1].

RA manifests itself in the form of a chronic symmetric polyarthritis that affects predominantly the small joints. But besides articular involvement, which generates severe disability, RA has extraarticular manifestations, which are responsible for

the increase in mortality by 1.5 times compared to that in the general population. Among these extraarticular manifestations, cardiovascular involvement generates increased morbidity and mortality in RA patients. This induces a real challenge in the treatment of these patients [2–7]. RA patients have an increased risk (50% higher than the general population) of premature mortality due to cardiovascular diseases [8–10].

In their meta-analysis, comprising 24 studies of RA mortality on 111,758 patients, Avina-Zubieta et al., reported that the cardiovascular mortality was increased by 50% in these patients. The authors identified that the RA patients with a short duration of disease evolution had had a lower risk of cardiovascular mortality compared to the patients with long evolution of RA [11]. In another study, Avina-Zubieta et al., showed that the patients with RA had a myocardial infarction relative risk of 1.68 (95% CI, 1.40–2.03), and cerebrovascular disease relative risk of 1.41 (95% CI, 1.414–1.4) [12]. Houri Levi et al., revealed in their study done on 12,000 patients with RA that the ischemic heart disease had a greater prevalence among RA patients compared with general population (16.6% versus 12.8%, $p < 0.001$) [13]. The RA patients may develop myocardial infarction at a younger age than the general population [14].

The risk of cerebrovascular events is increased by about 41% in RA patients [13]. Another atherosclerotic manifestation is represented by peripheral arterial disease. Baghdadi et al., studying 30,000 patients with RA, identified a higher incidence of peripheral arterial disease among them than the general population (HR 1.73, 95%CI 1.57–1.91). The association with high blood pressure or diabetes mellitus increased the risk of peripheral arterial disease among RA patients [15].

Heart failure is about 2 times more common in RA patients with a positive rheumatoid factor than in the general population (HR 1.87, 95% CI 1.47–2.39) [1].

In the following sections, the main aspects related to cardiovascular risk in RA are presented.

2. Cardiovascular risk in patients with RA

In European Society of Cardiology guidelines, RA is considered an independent cardiovascular risk factor [16]. Knowing the high incidence of cardiovascular diseases among RA patients, in 2016, the European League Against Rheumatism (EULAR) published a set of 10 recommendations for the screening, identification and management of cardiovascular risk factors in RA patients. These recommendations predicted that the cardiovascular risk scores obtained with the instruments used in the general population be multiplied by 1.5 in patients with RA. It is the task of the rheumatologist to identify and manage the cardiovascular risk factors in RA patients [17]. To date, the optimal control of RA inflammation has not been achieved [18].

High cardiovascular risk in RA patients may be explained by the interaction between traditional cardiovascular risk factors and those determined by RA [7]. But in RA patients, standard cardiovascular risk scores, like Reynold's Risk Score, Systematic Coronary Risk Evaluation (SCORE), and Framingham risk score minimizes the cardiovascular risk [19–21]. Lindharsen et al., demonstrated that the cardiovascular risk is related to the RA severity [14].

The traditional cardiovascular risk factors have a higher incidence among RA patients than in the general population, especially insulin resistance, obesity, diabetes, hypertension, and smoking; however, the presence of increased systemic inflammation has been shown to also provide a detrimental pro-atherogenic role in the RA patients [22]. It was demonstrated that the risk for cardiovascular morbidity

and mortality in RA patients keeps growing even after controlling for insulin resistance, dyslipidemia, body mass index, hypertension, and smoking. In meta-analysis published by Baghdadi et al., the cardiovascular risk induced by traditional cardiovascular risk factors is highlighted as follows: hypertension (RR 2.24, 95% CI 1.42–3.06), hypercholesterolemia (RR 1.73, 95% CI 1.03–2.44), diabetes mellitus (RR 1.94, 95% CI 1.58–2.30), smoking (RR1.50, 95% CI 1.15–1.84), and obesity (RR 1.16, 95% CI 1.03–1.29) [15]. RA-associated chronic inflammation may lead to atherosclerosis acting direct on the arterial walls, or by modifying traditional cardiovascular risk factors, especially insulin resistance and dyslipidemia [1]. Elevated levels of circulating cytokines are identified even before the onset of clinical signs of the disease [9]. Chronic systemic inflammation generates endothelial activation and dysfunction, and a pro-atherogenic and prothrombotic state, responsible of the increased cardiovascular risk in RA patients [23]. It has been identified that systemic inflammation acts on myocardial cells even before the occurrence of specific joint manifestations of RA. Therefore, it is very important that cardiovascular risk assessment be done right at the time of RA diagnosis [7].

Cardiovascular involvement in RA patients is based on two mechanisms: an ischemic one caused by accelerated atherosclerosis, as well as a non-ischemic one, produced by the structural changes of the myocardium, both of them induced by chronic inflammation [2].

3. Inflammation and cardiovascular risk in RA

The link between chronic inflammation and accelerated atherosclerosis is well known in RA patients, several studies supporting this fact [17, 21, 24–27]. Inflammation is implicated in both the development and progression of atherosclerotic plaques in the general population [1]. Chronic inflammation is associated with cardiovascular disease, independent of traditional cardiovascular risk factors [17]. In RA patients, a linear relation between chronic inflammation (elevated erythrocyte sedimentation rate, high levels of C reactive protein) and carotid intima-media thickness, independent of traditional cardiovascular risk factors, has been identified. Higher RA activity, evaluated by means of a composite index DAS28, is associated with higher cardiovascular risk [28]. In their study, carried out for a period of 10 years, Goodson et al., demonstrated the association between inflammation (evaluated by means of CRP levels) and higher cardiovascular mortality in patients with early inflammatory polyarthritis [29]. Agca el al. revealed that the RA patients presented more than twice cardiovascular events than the general population, even higher than the type 2 diabetes patients [30]. RA patients with coronary atherosclerotic disease have an unfavorable prognosis, presenting higher morbidity (recurrent ischemia episodes) and mortality than the non-RA patients [31]. RA patients are more likely to have silent myocardial ischemia and may develop heart failure and sudden death [32]. On the other hand, several studies showed that in the conditions of chronic inflammation, atherosclerotic plaques become vulnerable, unstable, with an increased risk of cardiovascular events [1].

But cardiac dysfunction may have a nonischemic origin, this dysfunction being associated with high inflammatory activity, but not rheumatoid factor positivity [33]. Cardiac dysfunction often goes undiagnosed, especially in asymptomatic patients or those with minor symptoms. Ferreira et al., studying 355 patients with RA, showed that only 7% of them were diagnosed with heart failure, but one third of RA patients met the symptoms of heart dysfunction [34]. The studies have shown that patients with high inflammatory activity (evidenced by elevated serum C-reactive protein levels) have the highest risk of developing heart dysfunction,

suggesting a role of inflammation in the cardiac dysfunction pathogenesis [1, 2]. High levels of C-reactive protein are associated with an increased risk of cardiac dysfunction, independent of the presence of traditional cardiovascular risk factors. The link between RA activity, measured by means of elevated levels of C-reactive protein and cardiovascular risk, indicates the fact that persistent systemic inflammation contributes to increased risk for cardiovascular events [35, 36].

Traditional cardiovascular risk factors acting together with systemic inflammation generate accelerated atherosclerosis and ischemic cardiac events, but systemic inflammation, even in the absence of traditional cardiovascular risk factors, determines the occurrence of cardiac dysfunction, as heart failure with preserved ejection fraction [1].

The involvement of systemic inflammation in heart failure with preserved ejection fraction is proved, acting by means of proinflammatory mediators [1, 35, 36]. This inflammatory environment induces endothelial activation and then dysfunction, and increased recruitment of leukocytes, especially monocytes into the cardiac tissue. In the myocardium, there is a reduction in the bioavailability of nitric oxide and consequently a reduction in cyclic guanosine monophosphate and protein kinase G. These changes lead to cardiac hypertrophy and increased resting tension, finally appearing as diastolic dysfunction [2, 33].

High levels of inflammatory cytokines (TNF-alpha, IL-1, IL-6) can be detected in patients' serum before the onset of RA symptoms [9]. They induce pro-atherogenic and pro-thrombotic states (insulin resistance, atherogenic dyslipidemia, oxidative stress, endothelium activation, and subsequent endothelial dysfunction). These cardiovascular changes appear even before the clinical RA onset [22].

The importance of systemic inflammation in cardiovascular morbidity and mortality of RA patients is revealed by the study published in 2019 by Provan et al., which showed that the RA patients diagnosed before 2003 had significantly elevated cardiovascular mortality compared with the patients diagnosed after 2004, who had a similar cardiovascular mortality risk as the general population [37].

4. Dyslipidemia

RA patients have lipid abnormalities, which promote accelerated atherogenesis. Chronic inflammation modifies lipid pattern in rheumatoid patients, favoring accelerated atherogenesis. In these patients, many studies showed a specific lipid pattern: decreased of total cholesterol, HDL-cholesterol, and LDL-cholesterol, and increased very-low density lipoprotein (VLDL), lipoprotein (a) (Lp(a)), apolipoprotein-B (apo-B), and free fatty acids (FFAs) [22, 38, 39]. Liao et al., described the "lipid paradox" in RA patients: decreased levels of total cholesterol and LDL-cholesterol are associated with high cardiovascular risk. The decreased levels of total-cholesterol are due to low levels of HDL-cholesterol [39]. Sattar et al., reported an inverse relationship between rheumatoid activity reflected by high levels of C reactive protein and low levels of total cholesterol, LDL-cholesterol and HDL-cholesterol [8]. Rheumatoid activity is associated with impaired HDL-cholesterol functions [39]. The impaired antioxidant activity of HDL-cholesterol is correlated with increased oxidized LDL-cholesterol and phagocytosis by macrophages, generating atherosclerotic plaques [40]. High levels of triglycerides are caused by VLDL increase and HDL-cholesterol decrease [8, 38, 40].

Kim et al., reported that the RA patients presented modified structure of lipoproteins, secondarily affecting their functions. The final result is represented by the increase of cardiovascular events incidence [40]. In RA patients, lipoproteins are oxidized and glycated, these processes are associated with a decrease in nitric

oxide generation, endothelial cell death, promoting endothelial dysfunction and atherosclerosis [40].

Ajeganova et al., studying the apolipoprotein pattern in RA patients, identified high levels of apo-B and a higher ratio of apo-B to apo-A, correlated with increased carotid intima-media thickness and the plaques presence [41]. Increased Lp(a) is common in patients with RA, especially when the disease is active. Lp (a) has dual actions: by binding to oxidized phospholipids, it is located in the vascular wall, contributing to atherosclerosis development, and on the other hand, by inhibition of plasmin activity, it promotes a thrombogenic effect [42].

5. Hypertension

Hypertension is known as an important cardiovascular risk factor. In RA patients, the hypertension incidence is between 4 and 73%, this incidence being dependent on the assessed patients and study design [43]. COMORA (COMOrbidities in Rheumatoid Arthritis) study reported a hypertension prevalence in RA patients of 40% [18]. Often, hypertension remains undiagnosed and consequently untreated in patients with RA, contributing to excessive cardiovascular morbidity and mortality [44, 45].

Chronic inflammation, by means of elevated levels of TNF-alpha, IL-1, IL-6, acts on the vascular endothelium, causing nitric oxide reduction, increase in endothelin, and upregulation of angiotensin II type 1 receptor, the final effect being represented by an excessive vasoconstriction and increased total peripheral resistance. Additional contributing factors for hypertension development are represented by genetic polymorphism, physical inactivity, RA medication (nonsteroidal anti-inflammatory drugs, corticosteroids, Leflunomide, Cyclosporin) [1].

6. Insulin resistance, metabolic syndrome, and diabetes mellitus

The existing data support the strong link between RA, insulin resistance and metabolic syndrome [1]. Lindhardsen et al. reported that the chronic inflammation represents the link between RA and atherogenesis [14]. In another study, Baghdadi et al., demonstrated a strong correlation between inflammatory syndrome, RA activity, insulin resistance, and subclinical atherosclerosis revealed by means of carotid intima-media thickness [15]. Metabolic syndrome and RA influence each other, the final result being represented by oxidative stress with secondary endothelial damage [1].

7. Obesity

Obesity is known as an important traditional cardiovascular risk factor. It is important to remind that the adipose tissue is not inert but is very biologically active through the synthesis of TNF-alpha, IL-6, cytokines involved in RA pathogenesis [1].

In RA patients, the prevalence of overweight is about 60%, and the prevalence of obesity is between 18 and 31%. These patients present a higher rheumatoid activity than in RA normal weight patients. But the obesity is associated with other traditional cardiovascular risk factors, as insulin resistance, metabolic syndrome, diabetes mellitus, hypertension, atherogenic dyslipidemia, and inactive lifestyle [46].

The RA patients with low body mass index (<20 kg/m^2) present the elevated risk for cardiovascular disease development. Kremers et al., showed that patients with RA and low body mass index had a higher cardiovascular risk than those with normal weight [47]. Increased inflammatory activity, which characterized active RA, causes an increase in catabolic processes, with a consequent reduction in body weight, settling in the advanced stages of rheumatoid cachexia [1].

8. Smoking

Smoking is known as a traditional cardiovascular risk factor. But the recent data suggested that smoking is involved in RA pathogenesis. Smoking determined the increases the risk of RA. But the RA smoking patients present a higher activity of disease with RF positivity, erosions, nodules, and marked disability. In these patients, the potency of the csDMARD and bDMARDs is low, requiring higher doses of them [1].

9. RA therapy and cardiovascular risk

The therapeutic objectives are represented by the efficient control of the inflammatory process, as well as the prevention of the articular destructions [1]. By controlling the inflammatory process and its consequences on the vascular endothelium, the atherogenesis process is diminished, and consequently, the cardiovascular risk [48]. In order to diminish RA chronic inflammation, joint destruction and cardiovascular risk, EULAR recommended a sustained, aggressive control of disease activity, using several classes of drugs, as nonsteroidal anti-inflammatory drugs, glucocorticoids, csDMARD (conventional synthetic disease modifying antirheumatic drugs), bDMARD (biologic disease modifying antirheumatic drugs), tsDMARD (targeted synthetic disease modifying antirheumatic drug) [17]. All of these drugs, in addition to controlling the inflammatory process, can have side effects that can increase cardiovascular risk [48].

Nonsteroidal anti-inflammatory drugs represent a class of drugs widely used in the RA treatment. These patients used non-selective NSAIDs, or selective COX-2 inhibitors. The use of NSAIDs is associated with increased risk of cardiovascular events, especially in elderly RA patients. These drugs are associated with a high risk of arterial hypertension and atherothrombotic events development [49]. Selective-COX 2 inhibitors are contraindicated in patients with atherothrombotic risk factors, stroke, and ischemic heart disease. Therefore, Rofecoxib was withdrawn from use. But Etoricoxib can be used in RA patients in a dose of 90 mg daily. Due to side effects, these drugs should be used judiciously, but only in combination with DMARDs [1].

Corticosteroids effectively control inflammation, but they have many side effects, especially cardiovascular (uncontrolled arterial hypertension, atherogenic dyslipidemia, diabetes mellitus). The side effects of corticosteroids in RA patients have been evaluated in several studies. Del Rincon et al., demonstrated that the RA patients who received daily doses of glucocorticoids greater than 8 mg had an increase in dose-dependent cardiovascular morbidity and mortality [50]. In their meta-analysis, Roubille et al., showed that the RA patients treated with corticosteroids presented a 47% higher to develop cardiovascular events. The authors emphasized the role of inflammation in the occurrence of cardiovascular events [51]. Hazard ratios (HR) of cardiovascular mortality were 2.27 (95% CI 1.36–3.79) in RA patients who had been treated with oral corticosteroids in daily doses between 8 and

15 mg and 3.21 (95% CI 1.14–8.97) in RA patients who had been treated with doses above 15 mg [1]. The increased cardiovascular risk associated with corticosteroids is dependent on dose and time of use [49]. Based on these facts, EULAR recommends the use of glucocorticoids in RA therapy as the lowest effective dose for the shortest period of time, in order to control the inflammatory process while awaiting csDMARD onset and minimize the risk of cardiovascular side effects [17]. csDMARD (conventional synthetic disease modifying antirheumatic drug) are represented by Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine. bDMARD are classified as TNF-alpha inhibitor (tumor necrosis factor inhibitor: Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Infliximab) and non-TNF-alpha inhibitor (non-tumor necrosis factor inhibitor: Anakinra, Abatacept, Tocilizumab, Sarilumab, Rituximab). tsDMARD (targeted synthetic disease modifying antirheumatic drug) are represented by Baricitinib, Tofacitinib, Upadacitinib. All these drugs have been shown to improve the cardiovascular risk, by the amelioration of sustained inflammation, and lipid profile improvement [39, 52–55].

Reducing inflammation very effectively, Methotrexate (MTX) is the gold standard of RA treatment, showing a reduction of cardiovascular events by 28% [51]. MTX influences the lipid profile, as increase the serum levels of HDL-cholesterol, total cholesterol, and LDL-cholesterol, decrease of lipoprotein (a) level, while the levels of apo-B and triglycerides remain unchanged [7].

Another csDMARD with similar efficacy as MTX in RA treatment is Leflunomide. But this drug is associated with arterial hypertension in 6–10% of treated RA patients. Therefore, it is very important to monitor blood pressure values at the initiation and then during treatment with this drug [56]. The use of this drug is not contraindicated in RA therapy, but it should be avoided in RA patients with uncontrolled arterial hypertension [48].

By interfering with platelet function, SSZ provides cardioprotection in RA patients. HDL-cholesterol levels are increased during treatment with SSZ alone, or in combination with MTX. On the other side, triple therapy with MTX, SSZ and Hydroxychloroquine confers a better lipid profile, consisting of higher HDL-cholesterol levels and lower total cholesterol and LDL-cholesterol levels [7].

By using Hydroxychloroquine (HCQ) in RA therapy, the risk of cardiovascular events has been reduced by 72%. This drug determined an anti-atherosclerotic lipid profile, consisted of lower total cholesterol, LDL-cholesterol and triglycerides, and higher HDL-cholesterol. A rare complication associated with HCQ therapy is cardiotoxicity, manifested in the form of dilated or restrictive cardiomyopathy, or atrioventricular block and bundle branch block. In order to avoid this condition, it is necessary to conduct regular screening using cardiac ultrasound and electrocardiography [7].

Active RA is characterized by increased cytokine levels. By effectively controlling inflammation and reducing cytokine levels, bDMARDs reduce the risk of cardiovascular events [48]. Among them, TNF-alpha has a very important role. Naerr et al., reported that by using anti TNF-alpha therapy, both the RA activity and cardiovascular risk decreased [57]. Halacoglu et al., showed a reduction of 30% in the risk of major cardiovascular events. The beneficial effects of anti TNF-alpha drugs are the consequence of blocking the actions that TNF-alpha has in the atherogenesis appearance [7]. Bergström et al., showed that the anti TNF-alpha therapy increased HDL-cholesterol, total cholesterol, and apo-B, and decreased the levels of Lp(a) [58]. But these drugs can cause or exacerbate heart failure; therefore, they are not indicated in moderate and severe forms of heart failure [59].

Abatacept is associated with the reduction of cardiovascular risk. The study performed by Jin Y et al., showed that the patients treated with Abatacept presented a 20% greater reduction in CV risk compared with TNF-alpha inhibitors [60].

The patients treated with Abatacept presented a significant increase in HDL-cholesterol [61].

Rituximab determined a significant increase in total cholesterol and HDL-cholesterol, and a significant decrease in inflammation (C reactive protein, ESR) and disease activity (evaluated by means of DAS28 score). The levels of LDL-cholesterol have not undergone significant changes [56]. Hsue et al., reported that the therapy with Rituximab had been associated with endothelial function improvement [62].

Tocilizumab decreases inflammation, has a favorable effect on serum fibrinolytic activity and left ventricular systolic function in RA patients, but arterial hypertension is one of side effects of this drug [1, 63, 64]. Curtis et al., analyzing cardiovascular events in RA patients treated with Tocilizumab and anti-TNF-alpha agents, did not identify significant differences between the two groups in terms of myocardial infarction incidence and sudden cardiac death [65].

By using small molecule inhibitors of Janus kinase (JAK), lipid profile pattern is modified in the following manner: levels of total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and apo-B levels are increased, and lipoprotein (a) is reduced (by baricitinib) or unchanged (by Tofacitinib) [53]. It is very important to note that with a dose of tofacitinib 10 mg twice daily, the risk of thrombosis has increased, this risk is not being noticed when reducing the dose at 5 mg twice daily [7].

In their meta-analysis, Ozen et al., showed that the risk of cardiovascular events was reduced by 28% by the use of MTX and by 30% by the use of anti-TNF-agents (Infliximab and Etanercept) use, while corticosteroid therapy increased the cardiovascular risk by 47% [66]. The use of Abatacept has also been associated with a reduction in cardiovascular risk [60].

It is important to note that in order to have cardioprotective effects, the dose of MTX must be higher than 15 mg/week [51]. These high doses of MTX reduce cardiovascular risk by controlling RA activity, but possibly also by direct effects on vascular endothelium [66].

Biologic DMARDs are associated with a lower risk of atherosclerotic cardiovascular disease than csDMARD [66]. Zhang et al., studying the risk of atherosclerotic cardiovascular disease in the RA elderly patients, showed that the risk is higher in patients treated with anti-TNF-agents compared to Abatacept and Tocilizumab [67]. By improving endothelial function, Rituximab would reduce the incidence of atherosclerotic cardiovascular disease [66].

In order to reduce the cardiovascular risk in RA patients, it is necessary to take some steps; at the time of RA diagnosing, the patient must be evaluated in order to detect subclinical atherosclerosis and cardiovascular risk factors. NSAIDs and corticoids should be used at the lowest doses, for the shortest period, and always associated with csDMARD. MTX dose should be over 15 mg/week. Administration of other csDMARDs (non-MTX csDMARD) will take into account the presence of cardiovascular risk factors. bDMARDs should be administered without delay, to control systemic inflammation and, implicitly, cardiovascular risk. But in the case of these drugs, the presence of cardiovascular risk factors will also be taken into account [48, 66, 67].

These are just a few aspects of cardiovascular risk in RA patients. Subsequent research will bring new data that will explain aspects related to cardiovascular risk in RA and will implement new therapeutic strategies to reduce it.

Conflict of interest

None.

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References

[1] D Dimitroulas T, Sandoo A, Skeoch S, et al. Rheumatoid arthritis. In: Nussinovitch U, editor. The Heart in Rheumatic, Autoimmune and Inflammatory Diseases. London: Elsevier Inc.; 2017. pp. 129-165

[2] Chen J, Norling LV, Cooper D. Cardiac dysfunction in rheumatoid arthritis: The role of inflammation. Cell. 2021;**10**:881. DOI: 10.3390/cells10040881

[3] Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis and Rheumatism. 2003;**48**:54-58

[4] Lassere M, Rappo J, Portek IJ, et al. How many life years are lost in patients with rheumatoid arthritis? Secular cause-specific and all-cause mortality in rheumatoid arthritis, and their predictors in a long-term Australian cohort study. Internal Medicine Journal. 2013;**43**:66-72

[5] Widdifield J, Bernatsky S, Paterson JM, et al. Trends in excess mortality among patients with rheumatoid arthritis in Ontario, Canada. Arthritis Care & Research. 2015;**67**:1047-1053

[6] van den Hoek J, Boshuizen HC, Roorda LD, et al. Mortality in patients with rheumatoid arthritis: A 15-year prospective cohort study. Rheumatology International. 2017;**37**:487-493

[7] Halacoglu J, Shea LA. Cardiovascular risk assessment and therapeutic implications in rheumatoid arthritis. Journal of Cardiovascular Translational Research. 2020;**13**(5):878-890. DOI: 10.1007/s12265-020-09964-9

[8] Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation. 2003;**108**(24): 2957-2963

[9] Bag-Ozbek A, Giles JT. Inflammation, adiposity, and atherogenic dyslipidemia in rheumatoid arthritis: Is there a paradoxical relationship? Current Allergy and Asthma Reports. 2015;**15**(2):497

[10] Siebert S, Lyall DM, Mackay DF, et al. Characteristics of rheumatoid arthritis and its association with major comorbid conditions: Cross-sectional study of 502 649 UK Biobank participants. RMD Open. 2016;**2**(1):e000267

[11] Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis and Rheumatism. 2008;**59**:1690-1697

[12] Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies. Annals of the Rheumatic Diseases. 2012;**71**(9): 1524-1529

[13] Houri Levi E, Watad A, Whitby A, et al. Coexistence of ischemic heart disease and rheumatoid arthritis patients—A case control study. Autoimmunity Reviews. 2016;**15**(4): 393-396

[14] Lindhardsen J, Ahlehoff O, Hilmar Gislason G, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: A Danish nationwide cohort study. Annals of the Rheumatic Diseases. 2011;**70**:929-934

[15] Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. The impact of traditional cardiovascular risk factors

on cardiovascular outcomes in patients with rheumatoid arthritis: A systematic review and meta-analysis. PLoS One. 2015;**10**:e0117952

[16] Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal. 2016;**37**:2315-2312

[17] Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Annals of the Rheumatic Diseases. 2017;**76**:17-28

[18] Dougados M, Soubrier M, Antunez A, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: Results of an international, cross-sectional study (COMORA). Annals of the Rheumatic Diseases. 2014;**73**:62-68

[19] D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. Circulation. 2008;**117**(6):743-753

[20] Crowson CS, Matteson EL, Roger VL, et al. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. The American Journal of Cardiology. 2012;**110**(3):420-424

[21] Arts EEA, Popa CD, Den Broeder AA, et al. Prediction of cardiovascular risk in rheumatoid arthritis: Performance of original and adapted SCORE algorithms. Annals of the Rheumatic Diseases. 2016;**75**(4):674-680

[22] Khalid U, Egeberg A, Ahlehoff O, et al. Incident heart failure in patients with rheumatoid arthritis: A nationwide cohort study. Journal of the American Heart Association. 2018;**7**(2):e007227

[23] Meyer PW, Anderson R, Ker JA, Ally MT. Rheumatoid arthritis and risk of cardiovascular disease. Cardiovascular Journal of Africa. 2018;**29**(5):317-321

[24] Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: Scientific rationale for the cardiovascular inflammation reduction trial (CIRT). Journal of Thrombosis and Haemostasis. 2009;**7**(Suppl. 1):332-339

[25] Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1 inhibition and the prevention of recurrent cardiovascular events: Rationale and Design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). American Heart Journal. 2011;**162**:597-605

[26] Libby P. Inflammation in atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012;**32**:2045-2051

[27] Geraldino-Pardilla L, Zartoshti A, Ozbek AB, et al. Arterial inflammation detected with 18 F-fluorodeoxyglucose–positron emission tomography in rheumatoid arthritis. Arthritis & Rhematology. 2018;**70**:30-39

[28] Innala L, Möller B, Ljung L, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: A five year prospective study. Arthritis Research & Therapy. 2011;**13**:R131

[29] Goodson NJ, Symmons DPM, Scott DGI, et al. Baseline levels of

C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: A ten-year follow-up study of a primary care-based inception cohort. Arthritis and Rheumatism. 2005;**52**:2293-2299

[30] Agca R, Hopman LH, Laan KJ, et al. Cardiovascular event risk in rheumatoid arthritis compared with type 2 diabetes: A 15-year longitudinal study. The Journal of Rheumatology. 2020;**47**: 316-324

[31] McCoy SS, Crowson CS, Maradit-Kremers H, et al. Longterm outcomes and treatment after myocardial infarction in patients with rheumatoid arthritis. The Journal of Rheumatology. 2013;**40**:605-610

[32] Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. The American Journal of Medicine. 2008;**121**(10):S9-S14

[33] Mantel Ä, Holmqvist M, Andersson DC, et al. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. Journal of the American College of Cardiology. 2017;**69**:1275-1285

[34] Ferreira MB, Fonseca T, Costa R, et al. Prevalence, risk factors and proteomic bioprofiles associated with heart failure in rheumatoid arthritis: The RA-HF study. European Journal of Internal Medicine. 2021;**85**:41-49

[35] Meissner Y, Zink A, Kekow J, et al. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis. Arthritis Research. 2016;**18**:183

[36] Mong N, Tarjanyi Z, Tothfalusi L, et al. Accelerated arterial aging in rheumatoid arthritis is associated with inflammatory activity and smoking in the early stage of the disease. Frontiers in Pharmacology. 2020;**11**:523962

[37] Provan SA, Lillegraven S, Sexton J, et al. Trends in all-cause and cardiovascular mortality in patients with incident rheumatoid arthritis: A 20-year follow-up matched case-cohort study. Rheumatology. 2019;**59**: 505-512

[38] Khovidhunkit W, Memon RA, Feingold KR, Grunfeld C. Infection and inflammation-induced proatherogenic changes of lipoproteins. The Journal of Infectious Diseases. 2000;**181**(Suppl. 3): S462-S472

[39] Liao KP, Playford MP, Frits M, et al. The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. Journal of the American Heart Association. 2015;**4**(2):e001588

[40] Kim JY, Lee EY, Park JK, et al. Patients with rheumatoid arthritis show altered lipoprotein profiles with dysfunctional high-density lipoproteins that can exacerbate inflammatory and atherogenic process. PLoS One. 2016;**11**(10):e0164564

[41] Ajeganova S, Ehrnfelt C, Alizadeh R, et al. Longitudinal levels of apolipoproteins and antibodies against phosphorylcholine are independently associated with carotid artery atherosclerosis 5 years after rheumatoid arthritis onset—A prospective cohort study. Rheumatology. 2011;**50**(10): 1785-1793

[42] García-Gómez C, Bianchi M, de la Fuente D, et al. Inflammation, lipid metabolism and cardiovascular risk in rheumatoid arthritis: A qualitative relationship? World Journal of Orthopedics. 2014;**5**(3):304-311

[43] Panoulas VF, Metsios GS, Pace AV, et al. Hypertension in rheumatoid arthritis. Rheumatology (Oxford). 2008;**47**:1286-1298

[44] Panoulas VF, Douglas KMJ, Milionis HJ, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. Rheumatology (Oxford). 2007;**46**:1477-1482

[45] Chung CP, Giles JT, Petri M, et al. Prevalence of traditional modifiable cardiovascular risk factors in patients with rheumatoid arthritis: Comparison with control subjects from the multiethnic study of atherosclerosis. Seminars in Arthritis and Rheumatism. 2012;**41**:535-544

[46] Bray GA, Bellanger BT. Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine. 2006;**29**:109-117

[47] Kremers HM, Nicola PJ, Crowsonet CS, et al. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis and Rheumatism. 2004;**50**:3450-3457

[48] Vicente GNS, Pereira IA, de Castro GRW, et al. Cardiovascular risk comorbidities in rheumatoid arthritis patients and the use of anti-rheumatic drugs: A cross-sectional real life study. Advances in Rheumatology. 2021;**61**:38

[49] Danelich IM, Wright SS. Safety of nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease. Pharmacotherapy. 2015;**35**:520-535

[50] del Rincon I, Battafarano DF, Restrepo JF, et al. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis & Rhematology. 2014;**66**:264-272

[51] Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, nonsteroidal antiinflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: A systematic review and meta-analysis. Annals of the Rheumatic Diseases. 2015;**74**:480-489

[52] Micha R, Imamura F, von Ballmoos M, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. The American Journal of Cardiology. 2011;**108**(9):1362-1370

[53] Charles-Schoeman C, Wang X, Lee YY, et al. Association of triple therapy with improvement in cholesterol profiles over two-year follow-up in the treatment of early aggressive rheumatoid arthritis trial: Triple therapy and cholesterol profiles in early RA. Arthritis & Rhematology. 2016;**68**(3):577-586

[54] Widdifield J, Abrahamowicz M, Paterson JM, et al. Associations between methotrexate use and the risk of cardiovascular events in patients with elderly-onset rheumatoid arthritis. The Journal of Rheumatology. 2019;**46**(5): 467-474

[55] Agca R, Blanken AB, van Sijl AM, et al. Arterial wall inflammation is increased in rheumatoid arthritis compared with osteoarthritis, as a marker of early atherosclerosis. Rheumatology (Oxford). 2021;**60**(7):3360-3368

[56] Nurmohamed MT, van Halm VP, Dijkmans BA. Cardiovascular risk profile of antirheumatic agents in patients with osteoarthritis and rheumatoid arthritis. Drugs. 2002;**62**(11):1599-1609

[57] Naerr GW, Rein P, Saely CH, Drexel H. Effects of synthetic and biological disease modifying antirheumatic drugs on lipid and lipoprotein parameters in patients with rheumatoid arthritis. Vascular Pharmacology. 2016;**81**:22-30

[58] Bergström U, Jovinge S, Persson J, et al. Effects of treatment with

adalimumab on blood lipid levels and atherosclerosis in patients with rheumatoid arthritis. Current Therapeutic Research, Clinical and Experimental. 2018;**89**:1-6

[59] Low ASL, Symmons DPM, Lunt M, et al. Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017;**76**:654-660

[60] Jin Y, Kang EH, Brill G, et al. Cardiovascular risk after initiation of abatacept versus TNF inhibitors in rheumatoid arthritis patients with and without baseline CV disease. The Journal of Rheumatology. 2018;**45**(9): 1240-1248

[61] Mathieu S, Couderc M, Glace B, et al. Effects of 6 months of abatacept treatment on aortic stiffness in patients with rheumatoid arthritis. Biologics. 2013;**7**:259-264

[62] Hsue PY, Scherzer R, Grunfeld C, et al. Depletion of B cells with rituximab improves endothelial function and reduces inflammation among individuals with rheumatoid arthritis. Journal of the American Heart Association. 2014;**3**(5):e001267

[63] Tanaka T, Ogata A, Narazaki M, et al. Tocilizumab for the treatment of rheumatoid arthritis. Expert Review of Clinical Immunology. 2010;**6**:843-854

[64] McInnes IB, Thompson L, Giles JT, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo controlled study. Annals of the Rheumatic Diseases. 2015;**74**(4):694-702

[65] Curtis JR, Perez-Gutthann S, Suissa S, et al. Tocilizumab in rheumatoid arthritis: A case study of safety evaluations of a large postmarketing data set from multiple data sources. Seminars in Arthritis and Rheumatism. 2015;**44**:381-388

[66] Ozen G, Pedro S, Michaud K. The risk of cardiovascular events associated with disease-modifying antirheumatic drugs in rheumatoid arthritis. The Journal of Rheumatology. 2021;**48**(5): 648-655. DOI: 10.3899/jrheum.200265

[67] Zhang J, Xie F, Yun H, et al. Comparative effects of biologics on cardiovascular risk among older patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2016;**75**:1813-1818