Risk of cardiovascular disease in rheumatoid arthritis patients

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ABSTRACT

Despite rheumatoid arthritis (RA) therapy development has been in advance level today, its mortality remains increasing in general population. The mortality is mainly caused by early-manifested atherosclerosis and other cardiovascular complications. Available evidences show this condition appears in early stage of the disease. Thus, early detection and management of cardiovascular risk, followed by control of these factors are necessary to reduce morbidity and mortality of RA patients.

Cardiovascular disease (CVD) is a common cause of death, with higher number than cancer, chronic lower respiratory tract disease, and accident. It is estimated that 81,100,000 adults (more than a third) in US have one or more CVD. Everyday 2,300 patients die because of CVD which means one death in every 38 seconds.[1] Cardiovascular disease is the main cause of death in UK. Every year 191,000 patients die (1 of 3 deaths) because of the disease.[2] In Indonesia, 59.5% deaths caused by non-communicable diseases such as stroke (15.4%), hypertension (6.8%), diabetes mellitus (DM) (5.7%) , and ischemic heart disease (5.1%).[3]

It has been known that traditional risk factors such as hypertension, smoking, and physical inactivity are the main contributors to atherogenesis. Recently, it is proposed that inflammation may have a role in atherogenesis. The importance of inflammation in the pathogenesis of atherosclerotic CVD is supported by findings of higher prevalence of CVD in diseases related to systemic inflammation such as psoriasis, periodontitis, hypertension, DM, and rheumatoid arthritis (RA).[4]

Rheumatoid arthritis is the most common inflammatory arthritis which found in 0.5-1% adult population. Prevalence in female is twice higher than male. Prevalence becomes higher in older population and mostly found in female aged more than 65 years. It is reported that incidence of RA is approximately 5-50 per 100,000 every year.[5,6] An epidemiological study reported RA prevalence of 0.3% in Central Java.[7] Although etiology of RA is yet unknown, many studies suggested that combination of genetic and environmental factor plays role. Genes predisposing to RA are HLA-DRB1, PTPN22, STAT4, TRAF1/C5, and genes from 6q23 region.[8]

Rheumatoid arthritis is related to increase of mortality and decrease of life expectancy. Despite RA therapy development has been in advance level, mortality rate of RA patients remains high compared to general population. Higher mortality of RA patients is mainly caused by early-manifested atherosclerosis of coronary artery and cerebrovascular which is accompanied by other cardiovascular complications such as heart failure.[9] A meta-analysis concluded mortality due to CVD is 50% higher in RA patients compared to general population.[10] The CARRE study reported RA patients have similar risk of CVD to diabetic patients. This study found prevalence of CVD of 5% in non-diabetic and non-RA patients, 12.4% in type 2 DM patients, and 12.9% in RA patients.[11] Lindharsen reported risk of myocardial infarction in RA patients is similar to diabetic patients.[12] Mechanism of increased mortality caused by CVD in RA patients is thought to start very early in pathogenesis of the disease. Thus, it is important for medical doctor to understand the treatment strategy of CVD in RA patients in order to increase treatment quality.

PATHOGENESIS OF CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS

The exact mechanism lies on the relation of RA and CVD is not yet fully known. Higher prevalence of traditional risk factors can explain some parts of it, but evidence from prospective cohort study found risk of CVD in RA patients remains constant after adjustment of those traditional risk factors.[14]

Inflammation is thought to be another pathophysiologic pathway causing higher cardiovascular risk in RA patients. Inflammatory mediators in circulation can affect arterial wall where these mediators play role in every stage of atherosclerosis, starts from endothelial dysfunction, plaque formation, until plaque rupture. The similarity of inflammatory and immunologic response between RA and atherosclerosis has been revealed in recent years. Earlier atherosclerosis is suggested as a result of interaction between traditional CVD risk factors in RA patients and newly risk factors, mainly systemic inflammation.[15] It is summarized in figure 1 and table 1.

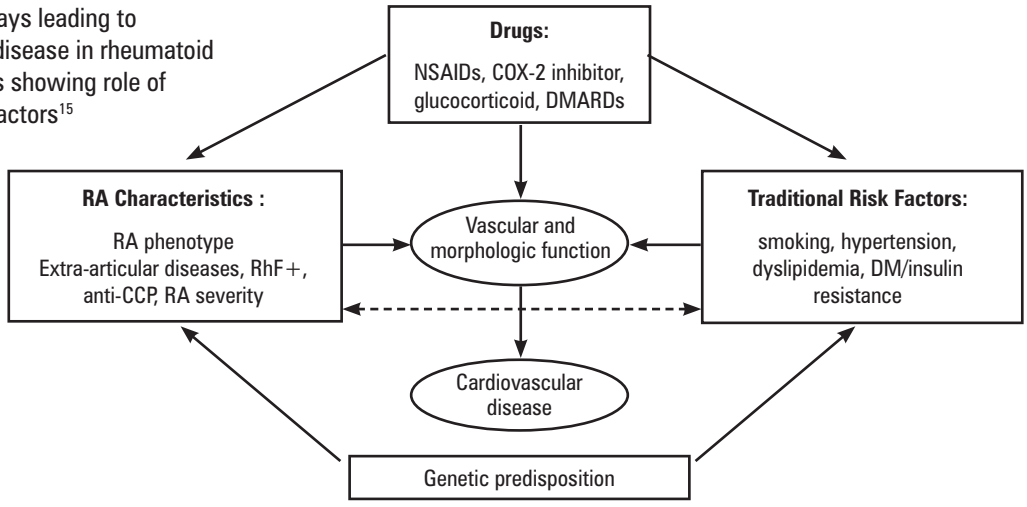

Figure 1 Pathways leading to cardiovascular disease in rheumatoid arthritis patients showing role of traditional risk factors[15]

Table 1 Atherogenesis in rheumatoid arthritis: traditional risk factors and disease-related risk factors[16]

Risk factors	
Traditional	Age, smoking, dyslipidemia, insulin resistance / diabetes mellitus, hypertension, physical inactivity, obesity
Disease related	
Inflammatory	Proatherogenic cytokine, chemokine, increasing expression of adhesion molecule, autoantibody, subset perturbation of T cells, genetic polymorphism, hyperhomocysteinemia, oxidative stress, apoptosis disorder, prothrombotic variable
Non-inflammatory	Immobilization, body weight gain
Iatrogenic	Glucocorticoid, methotrexate, NSAIDs, COX-2 inhibitors

NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclo-oxygenase-2

RHEUMATOID ARTHRITIS AND TRADITIONAL CARDIOVASCULAR RISK FACTORS

A meta-analysis reported some traditional cardiovascular risk factors such as smoking, DM, and low level of high density of lipoprotein (HDL) are more often found in RA patients.[17]

Smoking

A study stated that prevalence of smoking was increased in RA patiens with OR 1.56. Smoking can increase the risk of RA in seropositive patients who smoke ≥25 cigarettes for more than 20 years. Smoking is also related to RA with more severe manifestation. This condition may be caused by genetic and environmental factors. Combination of smoking and double-copy of allele HLA-DRB1 increases risk of RA and earlier mortality, especially caused by CVD.[17]

Diabetes

Patients with RA have higher risk to have insulin resistance. Disorder in glucose process occurs as a result of peripheral insulin resistance mediated by inflammatory response.[9] Interleukin-6 (IL-6) is suggested to be linked to insulin resistance in human.[18,19] Inhibition of IL-6 is shown to reduce risk of insulin resistance in RA patients.[20] Some studies reported no significant difference in percentage of DM between RA patients and control,[21,22] while other studies reported higher risk of DM in RA population.[17,23]

Use of glucocorticoid may influence glucose metabolism in RA patients. Due to the effects of chronic inflammation and glucocorticoid use to glucose metabolism, it is difficult to consider that increasing prevalence of DM is caused only by RA.[17] However, Hoes reported no difference in risk of insulin resistance between RA patients who consumed and did not consume steroid.[24]

Blood Pressure

Prevalence of hypertension in RA patients varied from 3.8 to 73%.[25] A meta-analysis reported no significant difference in blood pressure betweeen RA patients and general population.[17] A 10 year follow-up cohort study in 325 RA patients concluded that hypertension increases cardiovascular events risk (hazard ratio 3.76; 95% CI 0.99-15.06).[26]

Dyslipidemia

Dyslipidemia is found in 55-65% RA patients.[27] Dyslipidemia in RA is related to activity of inflammatory disease. Higher disease activity is related to lower level of total cholesterol, especially HDL. This condition occurs because proinflammatory cytokines—mainly tumor necrosis factor α (TNF-α)[15]—increase serum triglyceride (TG) level and decrease level of HDL.[28] Level of HDL in RA patients is lower than general population, but prevalence of hypercholesterolemia is not different in both groups.[17] Furthermore, RA patients have HDL dysfunction which causes HDL cannot prevent oxidation of low density lipoprotein (LDL).[29,30] Therapy can improve lipid profile, especially HDL which further can improve atherogenic index.

Proinflammatory cytokines can be mediator for rheumatoid cachexia, a condition where skeletal muscle is wasted and fat mass increases progressively. Consequently, RA patients have higher percentage of body fat compared to control group although body mass index (BMI) are similar. Furthermore, higher body fat mass contributes to CVD.[15] Cachexic patients have higher total cholesterol and LDL level, and also higher frequency of hypertension and metabolic syndrome compared to RA patients without rheumatoid cachexia.[31]

Physical Inactivity

Although it is not included in absolute risk estimation of CVD, this factor has been linked to higher risk of CVD in general population. Physical inactivity in RA patients occurs when disease becomes uncontrolled and/or chronic joint damage leading to disability, pain, and stiffness.

Waist circumference and higher BMI in RA patients may be also related to physical inactivity. However, no consistent findings in literature explaining BMI in RA patients. It is possible that patients with RA are reported having higher, similar, or lower BMI compared to general population. In relation to CVD, available evidences indicate patients with low BMI (<20 kg/m^2) have higher cardiovascular risk. Possibly it is related to severity of RA because systemic inflammation often causes decrease of body weight.[21]

RHEUMATOID ARTHRITIS AND NON-TRADITIONAL RISK FACTORS

Increasing risk of CVD and its mortality in RA patients which cannot be explained by traditional risk factors have been reported in literature.

Inflammation

It is thought that systemic inflammation, like in RA, has important role in premature atherosclerosis. Proinflammatory cytokines are trigger for expression of cellular adhesion molecule in endothelial cells, and also can induce atherogenic changes including dyslipidemia, insulin resistance, oxidative stress, and prothrombotic state.[16] Potential inflammatory mechanisms leading to vascular damage are: (a) endothelial dysfunction via excessive nitric oxide production; (b) activation of coagulation cascade; and (c) induction of secondary dyslipidemia with atherogenic profile.[15] Endothelial dysfunction causes change in its permeability and increases adhesion of leucocytes and thrombocytes. Furthermore, infiltration of T-cell and macrophage to arterial wall and release of inflammatory mediators induce chronic inflammation and progressive atherosclerosis.

Systemic cytokines response activates immune cells and causes phenotypical perturbation and functional subset of T-cell. Increasing level of CD4+CD28null T-cell is common in RA patients, which is autoreactive and can induce cytotoxicity of endothelial cells. Increasing subset of T-cells also can be found in patients with acute coronary syndrome and they can invade unstable atherosclerotic plaque.[16]

Genetic Influence

Cardiovascular disease in RA is suggested to be influenced by genetic factors. Functional polymorphism related to expression of major histocompatibility complex (MHC) is associated with increase of susceptibility to RA, myocardial infarction, and multiple sclerosis.[9] Despite status of autoantibody, allele of shared epitope (genotype HLA-DRB1) is associated with mortality in RA. Combination of shared epitope, smoking habit, and anti-CCP antibody will cause higher increase of premature death risk in RA patients. Shared epitope is also thought to be related to ischemic heart disease in RA with yet unknown mechanism.[9] TRAF1/C5, STAT4, and HLA-DRB1 may involve in regulation of lipid metabolism in RA patients.[32]

Hyperhomocysteinemia

Hyperhomocysteinemia, a condition frequently found in RA patients, has been considered as an independent risk factor in atherosclerotic disease. Hyperhomocysteinemia involves in endothelial dysfunction, lipoprotein oxidation, and has prothrombotic effects.[16]

Thrombotic Marker

Prothrombotic state such as increase of fibrinogen, von Willebrand factor, PAI-1, and thrombocytosis in RA patients may play a role in cardiovascular complications.[33]

RHEUMATOID VASCULITIS

RA patients possibly can suffer from rheumatoid vasculitis. Generally, it is found in small and medium blood vessels, including coronary artery. Although it is less frequently found than endothelial damage caused by systemic inflammation, rheumatoid vasculitis causes 2-3 times higher risk of ischemic heart disease in RA patients.[34]

EFFECTS OF RHEUMATOID ARTHRITIS THERAPY TO RISK OF CARDIOVASCULAR DISEASE

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs and cyclo-oxygenase-2 (COX-2) inhibitors are commonly used in RA therapy. Both drugs are thought to be related to side effects of hypertension, congestive heart failure, and kidney disorder.[35] Compared to placebo, COX-2 inhibitors group has 42% higher risk of cardiovascular events. In the same study, it is concluded that compared to naproxen, use of COX-2 inhibitors increases risk of vascular events (OR 1.57, 95% CI 1.21-2.03) and myocardial infarction twice higher (OR 2.04, 95% CI 1.41-2.96).[36] Generally, now it is recommended to use NSAIDs or COX-2 inhibitors with the lowest possible dose and the shortest possible duration. If NSAIDs should be used in therapy, naproxen is the drug of choice because cardiovascular risk of this drug seems to be lower than others.[35]

Glucocorticoid

Glucocorticoid can induce hypertension, insulin resistance, blood lipid disorder, obesity, and hypercoagulability.[9] However, it is difficult to estimate its effect to cardiovascular risk in RA patients. Glucocorticoid is thought to be linked to cardiovascular risk, but in the other hand glucocorticoid can decrease disease activity and inflammation. Until further data reported the effect of glucocorticoid, it is recommended to use it with dose as low as possible.[35]

Disease-modifying antirheumatic drugs (DMARDs)

a. Nonbiological DMARDs
   Methotrexate (MTX) is one of the main therapy of RA. It improves clinical signs of disease and slows radiologic progression.[35] A cohort study involving 1,240 RA patients reported hazard ratio of mortality in group taking MTX is

0.4 (95% CI 0.2-0.8).[37] Use of MTX is also related to lower risk of metabolic syndrome.[38] Ongoing Cardiovascular Inflammation Reduction Trial (CIRT) study is purposed to observe effect of very low dose of MTX (10 mg/week) to cardiovascular events in general population. It is expected that result of this study can provide evidence to confirm cardioprotective effect of MTX, as the agent is used widely in RA therapy.[39]

Effect of other nonbiological DMARDs to CVD risk is yet unknown. Azathioprine, cyclosporin, and leflunomide are thought to increase cardiovascular events. One of the reasons possibly because leflunomide and cyclosporin can induce hypertension.[35]

b. Biological DMARDs

In US, biological agents that have been approved today for RA therapy consist of TNF inhibitor (infliximab, etanercept, adalimumab, certolizumab pegol, dan golimumab), anakinra (antagonist of IL-1 receptor), abatacept (CTLA4-Ig protein fusion), rituximab (anti-CD20 antibody), and tocilizumab (antireceptor IL-6 antibody).[42]

Anti TNF-α agent is a potent drug to decrease inflammation and slow radiologic progression in RA patients. Thus, possibly this drug can give cardiovascular benefit. British Society for Rheumatology Biologics Register observed myocardial infarction in 8,670 RA patients administered with anti TNF-α agent compared with 2,170 RA patients treated with traditional DMARDs. This study did not find reduction of myocardial infarction incidence in patients treated with anti TNF-α agent (hazard ratio 1.44; 95% CI 0.56-3.67). However, in group which gave response to therapy in six months, incidence of myocardial infarction was 3.5 per 1,000 patient-year compared to 9.4 per 1,000 patient-year in non-responsive group.[40] Another study reported lower risk of cardiovascular events in group treated with TNF-α antagonist compared to non-biological DMARDs group.[41]

Effect of other biological agents to CVD risk is not known thoroughly. Anakinra, the IL-1 antagonist, was reported to improve vascular and left ventricular function in RA population.[43] Rituximab was reported to have beneficial effect to endothelial function and plasma cholesterol level. A 16 week-research involving five RA patients treated with rituximab found decrease of total cholesterol and increase of HDL level.[44] Use of tocilizumab causes slight increase of TG, LDL, and HDL level, but it could decrease lipoprotein (a).[20] Monotherapy of tocilizumab could reduce arterial sclerosis. Similar effect were found in etanercept and adalimumab.[45] The effect of abatacept to CVD risk is still unknown yet.

TREATMENT

Medical treatment for RA patients including management of joint disease and related comorbidities such as osteoporosis, depression, CVD, and malignancy. These comorbidities have significant impacts to quality of life, work disability, and mortality.[15] Preventive strategy to decrease CVD risk in RA patients should be initiated immediately after diagnosis of RA is made. Cardiovascular evaluation in RA patients is initiated by detecting comorbidities such as hypertension, tobacco use, hyperglycemia, dyslipidemia, increased BMI, central obesity, physical inactivity, and family history of CVD.[9]

In 2010, The European League Against Rheumatism (EULAR) released a recommendation for treatment of cardiovascular risk in RA and other inflammatory arthritis diseases.

Table 3 Ten recommendations for treatment of cardiovascular risk in rheumatoid arthritis[46]

No.	Recommendation	Level of evidence	Strength of recommendation
1.	RA should be considered as a condition related to higher risk of CVD. Increasing risk possibly due to increase of traditional risk factors and inflammatory burden	2b-3	B
2.	Proper control of disease activity is necessary to reduce cardiovascular risk	2b-3	B
3.	Assessment of cardiovascular risk using national recommendation is recommended for all RA patients. Risk assessment should be repeated if antirheumatic therapy changes	3-4	C
4.	Model of risk assessment should be adapted to RA patients by using multiplication factor of 1.5. This multiplication factor should be used in RA patients who fulfill minimally 2 of 3 following criteria: disease duration >10 years, positive RF or anti-CCP, and having extra-articular manifestation	3-4	C
5.	Ratio of total cholesterol/HDL should be used if SCORE model is utilized	3	C
6.	Intervention should be performed based on national guideline	3	C
7.	Statin, ACE-I, and/or AT-II blocker are drugs of choice	2a-3	C-D
8.	Role of COX-2 inhibitor and most NSAIDs in the cardiovascular risk are not yet well-understood and need further investigation. Thus, physician should be thoughtful to prescribe them, especially in patients with CVD or having risk factors	2a-3	C
9.	Use glucocorticoid with the lowest possible dose	3	C
10	Tell the patient to stop smoking	3	C

RA, rheumatoid arthritis; CVD, cardiovascular disease; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; ACE-I, angiotensin converting enzyme inhibitor; AT, angiotensin; COX, cyclo-oxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs

Although pathologic mechanism of cardiovascular system in RA has been known widely, the treatment remains unclear. It is not yet known neither at what level of lipid and blood pressure should pharmacological therapy be started, nor the intervention can improve cardiovascular risk. Beside, although DM and RA has similar risk of CVD, it is not clear whether guideline for DM can reduce CVD risk significantly in RA patients.[9] It is also necessary to evaluate whether the drugs usually used for CVD can be used in RA patients. Type of drugs and its risk-benefit is summarized in table 4.

Table 4 Type of drugs and its function for cardiovascular treatment in rheumatoid arthritis patients[35]

Focus to cardiovascular	
Statin	Having statistically significant antiinflammatory activity, but no clinically significant effect was reported
	Its use should follow general recommendation for cardiovascular treatment
Antihypertensive drugs	Its use should be based on general recommendation
	Whether ACE-I or ARB become drug of choice still needs further investigation
Aspirin	In patients with unclear cardiovascular disease, benefit-risk consideration is necessary
	General recommendation may help decide whether indication exists or not. Consider interaction with NSAIDs
Focus to anti-inflammation	
DMARDs	Methotrexate seems to give benefit
	Leflunomide, azathioprine, and cyclosporine may be related to inadequate cardiovascular outcome
TNF-α inhibitor	It may reduce cardiovascular events incidence, especially in patients giving clinical response
Glucocorticoid	It is related to higher cardiovascular morbidity and mortality in general population. Its role in RA treatment should be defined. Use with the lowest possible dose
NSAIDs, COX-2 inhibitors	It is related to higher cardiovascular risk. Naproxen shows smallest effect making it as drug of choice

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factors; RA, rheumatoid arthritis; COX, cyclo-oxygenase

Statin

Benefits of statin to CVD has been proved. Statin also has been tested in RA patients, but there has not been large enough study to conclude its effect to cardiovascular events.[35] Statin effect may be more obvious in RA patients because of its potency as antiinflammatory agent. The Trial of Atorvastatin in Rheumatoid Arthritis (TARA) study compared administration of atorvastatin 40 mg and placebo in 116 RA patients for six months. Significant improvement of disease activity score (DAS) of 28 was found in atorvastatin group. C-reactive protein level and erythrocyte sedimentation rate was reduced by 50% and 28%, respectively.[47] Similar study by El-Barbary reported decreased level of cholesterol, LDL, and TG; increased level of HDL; and improvement of disease activity parameter in atorvastatin group.[48] However, number of subjects in these studies are too small to show therapy effect to cardiovascular events. Another ongoing study, The Trial of Atorvastatin in the Primary Prevention of Cardiovascular Endpoint in Rheumatoid Arthritis (TRACE RA) involving 3,800 subjects is expected to answer this question.

Antihypertensive drugs

Hypertension is commonly found in RA patients. Therefore, control of blood pressure becomes target in the management of RA. At present, no available data can be used to determine a target for blood pressure control in RA patients. Therefore, recommendation for general population still can be used.[35] ACE-inhibitor and AT-II blocker may give beneficial effect to inflammation and endothelial function in RA patients. Thus, these two agents are drug of choice for RA patients, if indication exists to prescribe it.[46]

DMARDs

Literature has mentioned cardioprotective effect of DMARDs, especially MTX and biological agents. However, strategy to control disease activity and progression of CVD remains unclear. It is not known the limit to control inflammation in order to decrease cardiovascular risk and at what extent the therapy for RA patients can reduce cardiovascular risk.[6]

CONCLUSION

Higher risk of CVD has a great role to increase morbidity and mortality in RA patients. Evidences show this condition started early in disease activity. Early identification and management of cardiovascular risk, followed by control of these factors are necessary to decrease cardiovascular events risk. These risk factors are smoking habit, physical inactivity, nutrition, body weight, and blood pressure.

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