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Review Article
The Role Of hs-CRP In Predicting The Likelihood Of Coronary Heart Disease

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Abstract. Coronary Heart Disease (CHD) is a disorder of the cardiovascular system, characterized by atherosclerotic lesions. Inflammation is a strong predictor for coronary heart disease. High sensitivity C-Reactive Protein (hs-CRP) is an important biomarker, synthesized in the liver, can predict the severity of CHD. If the hs-CRP level is found to be low 3 mg / L, a person has the potential for severe vascular risk. Therefore, hs-CRP can be used as a predictor of primary CHD prevention, especially if the hs-CRP level is still low.

Keyword: Biomarker, hs-CRP, CHD

Abstrak. *Penyakit Jantung Koroner (PJK) adalah gangguan sistem kardiovaskular, ditandai oleh lesi aterosklerotik. Peradangan adalah prediktor kuat untuk penyakit jantung koroner. High sensitivity C-Reactive Protein (hs-CRP) adalah biomarker penting, disintesis di hati, dapat memprediksi tingkat keparahan PJK. Jika level hs-CRP ditemukan rendah < 1 mg/L, mengisaratkan bahwa peradangan sistemik atau arteri koroner masih rendah dan risiko aterosklerotik masih rendah. Jika kadar hs-CRP berada di antara 1 dan 3 mg/L mengindikasikan risko vascular sedang, dan jika kadar hs-CRP > 3 mg/L, sesorang sangat potensial berisiko vaskular yang parah. Oleh karen itulah hs-CRP bisa digunakan sebagai prediktor pencegahan PJK primer, terutama jika level hs-CRP masih rendah.*

Kata Kunci: *: Biomarker, hs-CRP, PJK*

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1. Introduction

Cardiovascular disease (CVD) is a group of heart and blood vessel disorders, including coronary heart disease, vascular disease that supplies oxygen and blood to the heart muscle; cerebrovascular disease, vascular disease that supplies oxygen and blood to the brain; peripheral

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arterial disease, vascular disease that supplies oxygen and blood to the arms and legs; rheumatic heart disease, damage to the heart muscle and heart valves due to rheumatic fever, caused by streptococcal bacteria; heart disease - malformation of the structure of the heart from birth. Of the 56.9 million deaths worldwide in 2016, more than half (54%) were caused by ischemic heart disease and stroke. This disease is one of the leading causes of death globally in the last 15 years. Indonesia's 2014 Sample Registration System (SRS) shows that CHD is the second highest cause of death after stroke, which is 12.9% of all the highest causes of death in Indonesia [1, 2].

Coronary heart disease is one of the most common diseases of the cardiovascular system, characterized by atherosclerotic lesions. Atherosclerotic vascular processes are multifactorial. One factor is the inflammatory process. Platelet to lymphocyte ratio (PRL) is a marker that predicts atherosclerotic coronary load [10]. Handling of CVD, in this case, CHD is highly dependent on the ability to identify individuals who are at high risk before the disease progresses. Therefore, it is necessary to observe an accurate level of risk. Increased knowledge regarding the role of biomarkers is increasingly important for identifying and predicting cardiovascular events. Biomarkers play an important role in defining, prognosis, and decision making regarding the management of cardiovascular events. This review is aimed at biomarkers of high sensitivity C-Reactive Protein (hs-CRP) inflammation to predict CHD and death. CRP is one of the important biomarkers that reflects various aspects of the development of atherosclerosis [7].

This inexpensive and simple approach to evaluating coronary heart disease has been approved by the Centers for Disease Control and Prevention and by the American Heart Association (CDC-AHA). When measured by the hs-CRP test, CRP levels less than 1, 1 to 3, and greater than 3 mg/L can distinguish between individuals at low, moderate, and high risk of heart attack and stroke in the future. front. However, it is important to understand that CRP testing does not mean replacing cholesterol evaluation. Instead, the CRP test must be used in conjunction with cholesterol and other traditional risk factors to determine an individual's risk, possibly having CHD. Evidence also shows that individuals with high CRP levels are at higher risk of developing diabetes. This article is intended to discuss the impact of increasing CRP levels and the clinical use of CRP [9].

2. Coronary heart disease

CHD is a condition caused by the presence of atheromatous plaques the coronary arteries that cause an obstruction and gradually narrows one or more coronary arteries in epicardium [3]. This condition will cause an imbalance between myocardial oxygen supply and demand causing myocardial ischaemia/hypoxia and accumulation of residual metabolites. Symptoms will appear

with increased activity, but can also occur spontaneously and are characterized by symptoms of discomfort in the chest transiently (angina pectoris) [4, 5].

CHD is a chronic inflammatory disease that occurs gradually, influenced by environmental exposure, lifestyle factors, and genetic factors that can be described from risk factors, inflammatory biomarkers, and metabolic status [6]. Experimental and clinical evidence shows that since 1990 has established the inflammatory process as an important contributor to atherogenesis and susceptibility of atherosclerotic lesions to rupture or lesions. Based on this evidence, markers of inflammatory proteins have been studied as non-invasive indicators of underlying atherosclerosis in apparently healthy individuals. The most widely studied biomarker of inflammation in cardiovascular disease is serum CRP, through hs-CRP testing [7].

Inflammation is a strong predictor for coronary heart disease. Among the important inflammatory biomarkers intensively studied are hs-CRP, which is an acute-phase reactant, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), both inflammatory cytokines and intercellular adhesion molecule -1 (ICAM-1), which is a marker of endothelial function. CRP is produced by hepatocytes, the regulation by IL-6 and TNF-α and is found in endothelium atherosclerotic plaques, smooth muscle cells, macrophages, and adipocytes. CRP affects the endothelium by changing the bioavailability of nitric oxide, resulting in an increase in ICAM-1 [8].

3. Diagnosis of Coronary Heart Disease

The classic clinical manifestation of CHD is angina pectoris, which is a clinical syndrome of chest pain that arises when performing activities due to myocardial ischemia. This shows that there has been > 70% narrowing of the coronary arteries. Angina pectoris can be stable angina pectoris (SAP, stable angina) and this condition usually develops to become more severe and cause Acute Coronary Syndrome (ACS) or known as sudden heart attack which can cause death.

Some important definitions related to CHD are Stable Angina Pectoris (SAP) is a clinical syndrome characterized by chest, jaw, shoulder, back or arm pain, which is usually triggered by physical work or emotional stress; this complaint can subside when rested or if given nitroglycerin under the tongue. Angina Prinzmetal is chest pain caused by coronary artery spasm, often arises at rest, not related to physical activity and sometimes is periodic (at the same time every day). While Acute Coronary Syndrome (ACS) is a clinical syndrome that has the same pathophysiological basis, namely the presence of erosion, fissure, or rupture of atheroma plaque, causing intravascular thrombosis which causes an imbalance of myocardial oxygen supply and demand. Included in the ACS are unstable angina pectoris (UPS, unstable angina): characterized by sudden and more severe chest pain, and longer attacks (more than 20 minutes)

and more frequent and acute myocardial infarction (AMI) is angina pain in acute heart infarction is generally more severe and longer (30 minutes or more). However, heart infarction can occur without chest pain (20 to 25%). AMI can be in the form of non-Q waves MI (NSTEMI) and Q-waves MI (STEMI) which can be observed on ECG records [11].

Patients with suspected CHD can be diagnosed by invasive and non-invasive examinations. In patients with a diagnosis of stable CHD, especially non-invasive examination needs to be done by laboratory examination, ECG at rest, echocardiography and chest X-ray. Laboratory tests include total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, serum creatinine (glomerular filtration rate) and fasting blood sugar levels [14]. ECG examination is normal in some stable CHD patients. A normal ECG shows that left ventricular function is still good. An abnormal ECG imaging that can be found is non-specific ST-T wave changes with or without pathological Q-waves. In patients proven to have coronary lesions, ST-T segment abnormalities are associated with disease severity. Other non-invasive tests that can be performed are cardiac training, myocardial perfusion imaging, stress echocardiography, cardiac CT-scans, and cardiac magnetic resonance imaging [9, 12, 13].

Percutaneous coronary intervention (PCI) is one of the most important methods for the treatment of severe CHD, with in-stent restenosis (ISR) which will affect long-term curative effects. Selection of Coronary angiography (CAG) is the best test for the diagnosis of ISR after PCI. However, the CAG examination method is invasive, which requires time and ability to assess the severity of coronary anatomy. Coronary angiography has 2 main objectives, namely to assess the risk of cardiovascular events and death of the patient and help determine the choice of revascularization therapy [12, 13]. Biomarker indicators for predicting ISR have become the main focus in the academic and research fields. It was reported that several indicators in serum, in addition to traditional risk factors (for example, age, sex, blood pressure, blood lipids, etc.), can also be used as independent risk factors to assess CHD and are closely related to cardiovascular events. hs-CRP is a marker of inflammation, which is synthesized by the liver which can be used to predict the risk of cardiovascular disease especially CHD [12, 14].

4. Biomarkers of Coronary Heart Disease (CHD)

Biomarkers are broad subcategories of biological markers that can be measured and reproduced. In a broad sense, biomarkers are specific compounds that are measured and evaluated objectively as indications of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions. A useful biomarker must meet the following criteria: (1) accuracy: that is, the ability to identify individuals at risk; (2) reliability: that is, the stability of the results when repeated; and (3) therapeutic impact with early intervention [8].

Biomarkers are often used to detect cardiovascular-related diseases, because certain biomarkers can provide valuable information regarding diagnosis, treatment, identification of individuals at risk of heart failure, and potentially pathogenesis that causes cardiovascular disease. For biomarkers to be clinically useful, biomarkers must meet several criteria, namely biomarker levels must be accurately assessed using widely available and cost-effective methods, biomarkers must provide additional information from tests that have been carried out such as MRIs, and biomarker information must assist in taking medical decision. A number of enzymes, hormones, markers of heart stress or necrosis, cytokines, and other biological agents have been examined as biomarkers for heart failure. Although biomarkers are discussed in this review by category (for example those related to heart damage or inflammation), in fact many of these biomarkers interact or are related to each other which shows that the combination of biomarkers tends to provide the best risk assessment for cardiovascular disease [15].

Inflammation is important in the pathogenesis of many conditions that lead to heart failure. Traditionally, inflammatory biomarkers have been considered risk markers rather than risk factors because the role of these biomarkers in the pathogenesis of the disease is not always clear. Many inflammatory biomarkers found in the circulation, such as CRP, IL-6 and serum amyloid A protein (SAA), are part of the acute phase response that arises and responds to the liver and although it is strongly associated with the disease, it may simply be a conclusion inflammation. In clinical studies, inflammatory mediators in coronary arteries have been used to predict the progression of coronary artery disease to heart failure similar to biomarkers of injury and / or neuro-hormones. In animal studies and clinical observations, inflammatory biomarkers appear to be indicative of left ventricular dysfunction, increased edema, and induced endothelial dysfunction and cardiomyocyte apoptosis, and other damaging effects. A long-term study in myocarditis patients reveals that inflammation is the best predictor of predicting progression to heart failure after acute myocarditis. Viruses such as CVB3, adenovirus, parvovirus B19 and hepatitis C virus are often detected on patients' myocardial biopsy. Antiviral treatments such as interferon-reducing inflammation and heart failure in animal models and patients, this implies that viral infections are an important cause of myocarditis cases leading to heart failure. Inflammation is closely related to the etiology of the development of heart failure, and not only that, but also the consequences of chronic heart failure that have an increased concentration of inflammatory mediators, other than as a clue to a poor prognosis. There is evidence that cellular damage and auto / antibody mediated contribute to the development of dilated cardiomyopathy (DCM) and heart failure after myocarditis [15].

There are several biomarkers associated with CHD, stroke, or both, but only a few are tested for their effect on predicting risk. The most frequently studied biomarker is hs-CRP. Other biomarkers that seem promising include lipoprotein-associated phospholipase A2 (LpPLA2) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP). CRP is a non-specific marker

of inflammation. CRP was initially tested in conjunction with cardiovascular disease because scientists are aware of the role of inflammation in the pathogenesis of atherosclerosis. In several studies, scientists reported an association between hs-CRP levels and the incidence of CHD, stroke, or both [16].

5. High sensitivity C-reactive protein (hs-CRP)

CRP was first described by William Tillet and Thomas Francis at the Rockefeller Institute in 1930. They extracted proteins from the serum of patients suffering from pneumonia pneumococcus which would form precipitation with C polysaccharides from cell walls. Pneumococcus. Because the reaction between proteins and polysaccharides causes precipitation, this protein is named C-Reactive Protein [17].

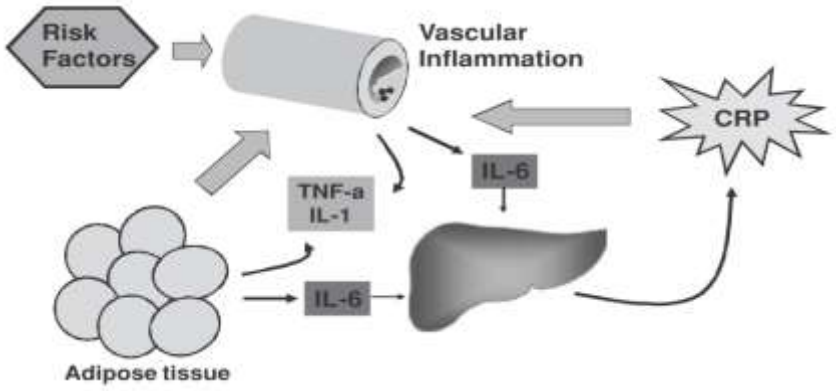

Figure 1. Mechanism of the relationship between CRP and cardiovascular events [20].

The potential mechanism of the relationship between CRP and cardiovascular events is due to risk factors for atherosclerosis which encourage atherogenesis and vascular inflammation by releasing cytokines such as interleukin 6 (IL-6), Interleukin-1 (IL-1), and Tumor Necrosis Factor-α (TNF-α)) from activated leukocytes. Furthermore, IL-6 will stimulate the release of CRP from the liver. On the other hand, adipose tissue directly promotes atherosclerosis and is also a major source of IL-6 which increases CRP levels. These events occur in parallel without a direct relationship between CRP and vascular disease. The mechanism of association between CRP and cardiovascular events can be seen in Figure 1 [20].

Recent research has shown that CRP conformations adopt two different forms, namely the pentamer isoform (pCRP) and the monomer isoform (mCRP), which have different antigenic, electrophoretic, and biological functions. Although pCRP is the main form detected in serum and is a very stable molecule, this evidence shows that the conformational subunits of pCRP can be separated, both in vitro and in vivo into a single unit of mCRP. On the other hand, free mCRP synthesis can be a major source of pCRP formation. Both forms of CRP isoform are involved in several processes: pCRP produces an inflammatory response that binds to

phosphatidylcholine on the outside of LDLox and apoptotic cell surfaces, while mCRP plays a role in the formation of aggregations that lead to complications of atherothrombosis [19]. Furthermore, the activation of this pathway contributes to the formation and development of atherosclerosis which will induce arterial smooth muscle cell proliferation and increase synthesis of IL-8 secretion and monocyte chemotactic protein (MCP-1). CRP also participates in activating Nuclear Factor kappa B (NF-κB), this transcription factor is present in cells and provides a fast response involved in immune and inflammatory reactions, thereby increasing the production of cytokines, chemokines, adhesion molecules, growth factors, and immuno receptors in several types of cells in atherosclerotic plaque. CRP will inhibit the affinity of compounds derived from factor H protein, so that the CRP isoform binds to the factor H protein as well as binds to calcium. In contrast, CFHR4 can bind pCRP through a calcium dependent mechanism. These proteins can facilitate the formation of CRP on the surface of necrotic cells, acting as a regulator that dissolves from the alternative pathway of the complement activation system. Excessive activity from this pathway will lead to the amount of C3a and C5a circulating, resulting in the potential for strong anaphylatoxins involved in the local inflammatory response. In vitro studies have shown that the expression of CR3 and CR5a in atherosclerotic arteries is the cause of plaque in coronary arteries. CR3 and CR5a support the occurrence of chemotaxis in monocytes, mast cells, and lymphocytes, adhesion of endothelial molecules, and in turn increase TNF and IL-1 release, in addition to specific reactive oxygen production based on location.

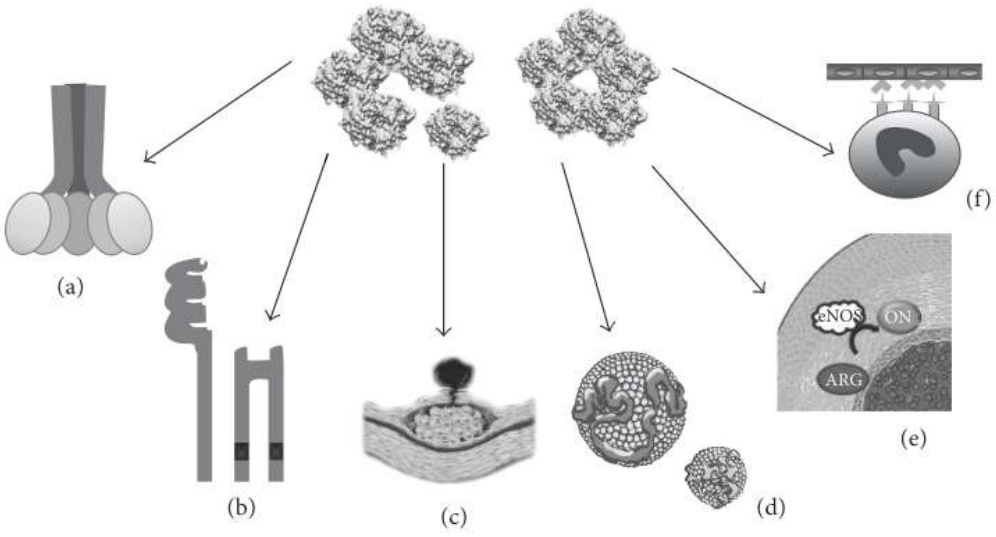

Figure 2. The key role of c-reactive protein (CRP) in atherosclerosis. (a) Activation of the complement system. (b) Activation of different receptors in inflammatory cells. (c) Changes in the shape of the extracellular matrix. (d) Interaction with lipoproteins. (e) Impaired synthesis of Nitric oxide. (f) Cell recruitment [19].

(b) Interaction with cellular receptors. The FcγR family is the main target of CRP which plays a role in the process of controlling activation, proliferation, phagocytosis, degranulation, and cytokine secretion, thereby regulating the local inflammatory process, as occurs in the formation of atherosclerotic plaque. The two forms of the CRP isoform can bind to FcγRI, FcγRIIA, and FcγRIII, thus encouraging conformational changes in the structure which in turn triggers an intracellular signaling cascade. In general, this cascade begins with sequential activation of tyrosine protein kinase (TPK) which phosphorylates tyrosine residues followed by activation of tyrosine kinase compounds which will produce multiple signaling molecules, including other kinases such as protein kinase C (PKC), extracellular signal regulating kinases (ERK) , mitogen-activating protein kinases (MAPK), and phosphatidyl inositol-3-kinase (PI3K), and phospholipase C (PLC), intracellular adaptation molecules, and second messengers such as calcium (Ca), diacylglycerol (DAG), and inositol-3- phosphate (I3P). The key role of CRP in atherosclerosis can be seen in figure 2.

(c) Changes in the shape of the extracellular matrix through selection, modulation, and activation of immune cells. pCRP is a direct regulator of endothelial cell activation and dysfunction, by inducing intracellular cell adhesion, vascular E-selectin, and monocyte chemoattractant protein-1 (MCP-1) which causes chemotaxis and binding of endothelial cell monocytes during the early stages of atherogenesis. In addition, CRP suppresses changes in the form of monocytes to the proinflammatory M1 phenotype, mediated by the Fcγ receptor and the NF-jalurB pathway, and forces a change in the cytokine secretion pattern in M2 macrophages towards the proinflammatory phenotype as in M1. In vitro studies show that when CRP concentrations <10 μg / mL there will be decreased prostaglandin F-1α synthesis, prostacyclin metabolites that regulate endothelial vasodilation, platelet aggregation, and smooth muscle cell proliferation. In addition, CRP also increases the expression of angiotensin 1 receptors (R-AT1) through MAPK and NFκB resulting in proliferation, deformation and migration of smooth muscle cells in atherosclerotic lesions [19].

(d) Activation of the metalloproteinase enzyme. Metalloproteinases are proteolytic enzymes responsible for reshaping extracellular matrix (ECM), which are involved in atherogenesis and rupture of atherosclerotic plaque.

(e) Synthesis of nitric oxide. (NO) is a simple gas produced by the enzyme NO-synthase (eNOS). NO is widely distributed in several tissues, especially in endothelial cells, NO plays a role in the process of vasodilation, antioxidants, and antithrombotic effects. In vitro and in vivo studies show that CRP can interfere with NO synthesis by inhibiting endothelial eNOS through various pathways, all of which cause endothelial dysfunction.

(f). Lipoprotein. mCRP selectively binds to low density lipoproteins (LDL) and, in small proportions, binds to very low density lipoproteins (VLDL). Whereas pCRP interacts mainly

with immunopatogen lipoproteins that are highly immunogenic, such as LDL-ox, enzymatic LDL (E-LDL) and minimally modified LDL (mmLDL). The acidity of the microenvironment at the site of inflammation plays a key role in binding CRP to lipoproteins, because the binding site for LDL-ox only occurs after modification in CRP structures that are triggered in an acidic atmosphere. In vivo testing shows that CRP not only increases LDL-ox absorption, but also stimulates the accumulation of cholesterol esters in human macrophages [19].

Some drugs like Colchicine and statins are reported to be able to inhibit its production. CRP has a long half-life in plasma and is known to be a mediator and marker of atherothrombotic disease. CRP levels tend to increase significantly 6-8 hours after initial release, maximum at 24-48 hours, with a half-life of around 19 hours. The concentration of CRP in circulation is mainly determined by the rate of synthesis. A research report, has measured CRP in healthy women and men, to see the relationship of CRP and cardiovascular events from other cardiovascular risk factors. In the meta-analysis, which included more than 160,000 subjects, nearly 28,000 incidents of cardiovascular events; each increase in standard deviation of values is associated with an increase in the relative risk of 1.37 for CAD (95% CI: 1.27-1.48) and 1.55 (95% CI: 1.37-1.76) for mortality caused by CVD . In addition, in patients undergoing percutaneous coronary intervention (PCI), higher CRP levels at the time of examination are predictors of 10-year mortality due to myocardial infarction (MI) [8, 20].

Based on the evidence obtained, the European Society of Cardiology (ESC) and the CDC-AHA recommend a grouping and state that hs-CRP can be measured as part of a moderate or moderate cardiovascular risk assessment. As such, interpretations of the hs-CRP result are elaborated with: levels < 1 mg/L are desirable levels and reflect lower systemic inflammatory status and lower atherosclerotic risk; levels between 1 to 3 mg/L indicate moderate vascular risk; levels of > 3 mg/L indicate a higher vascular risk in the context of other risk factors and a value of > 10 mg/L may reflect a transient infectious process or other acute phase response, so it must be repeated two to three weeks later. Despite having a direct relationship with cardiovascular events, recent research has confirmed that CRP values are predictors of cardiovascular events, CRP is not a causative factor for CVD [8, 18].

However, the most important use of CRP today is primary prevention, namely in detecting risks among individuals who are not yet known to have a problem. Individuals with high CRP levels have a risk of about 2 to 3 times higher than individuals who have low CRP levels. Because CRP is an "acute phase reactant" and increases during major trauma and infections. However, several studies have shown that the role of CRP, when properly measured by high sensitivity tests in stable individuals, is specific enough to predict future cardiovascular events. In a recent study, it was produced that an increase in CRP levels was associated with an 8-fold increase in cardiovascular mortality, but it did not have a predictive value of death from other causes. CRP can also be a predictor of heart attack and stroke, but not in individuals with cancer or other

major disorders. Thus, an ever-increasing CRP level is an indication of the risk of heart disease and accelerated atherosclerosis [9].

6. Conclusion

Based on research evidence that there is a hs-CRP biomarker in CHD to date is a predictor in primary prevention of disease. Individuals with high CRP levels have a risk of about 2 to 3 times higher than individuals who have low CRP levels in CVD.

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