
Chapter-III

THE ROLE OF INFLAMMATION IN CARDIOVASCULAR DISEASE

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Abstract--- The immune system has a major contribution to the initiation and progression of atherosclerosis, a chronic inflammatory condition. Significantly, cardiovascular diseases (CVDs), to which atherosclerosis is a major contributor, are the number one cause of death worldwide, responsible for about 31% of total deaths, and a major cause of illness globally, as per the World Health Organization (WHO). These are the world's most important health problems. Among the chronic heart conditions include arrhythmia, congestive heart failure, myocardial infarction, heart stroke, coronary artery disease, cardiac ischemia, and atrial fibrillation; early detection of these conditions may lower the death rate. Traditional diagnosis of these heart diseases is done by the physical examination of the reports related to concerned symptoms of patient with the reports of his medical history. Analysis done through these methods may not be accurate in detection of heart diseases and it also expensive and time consuming because these diseases require continuous monitoring. Low-density lipoprotein cholesterol oxidizes inside the artery wall. Furthermore, residual lipoproteins and lipoproteins high in triglycerides have pro-inflammatory properties, which is mediated by an increase in sympathetic output that releases inflammatory cytokines. Through an increase of leukocyte clones in peripheral circulation, inflammation also serves as a link between aging and cardiovascular disease Ho (2018).

Keywords--- CVDs, Anti-inflammatory, Monitoring, Myocardial.

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1. INTRODUCTION

The conversion of risk factors into CVD is largely dependent on the vascular endothelium. After entering the subendothelial region, LDL-C oxidizes and aggregates into big complexes. Selective inhibitors of cytokine pathways with anti-inflammatory drugs are able to lower the risk of myocardial infarction and stroke but in the process pose an increased risk of infections. In the environment of inflammation, lipoprotein metabolism is dysregulated, which leads to the production of sub-fractions of small dense LDL-C (sdLDL-C) having decreased affinity for the liver-specific LDL-C receptor. A higher risk of CVD is linked to elevated sdLDL-C levels. This, in turn, encourages a low-grade inflammatory response in the blood vessels, which advances atherosclerosis. Inflammation is a critical pathway that connects other cardiovascular risk factors to the pathogenesis of atherosclerosis, resulting in coronary artery disease (CAD), stroke, and cerebral aneurysms.

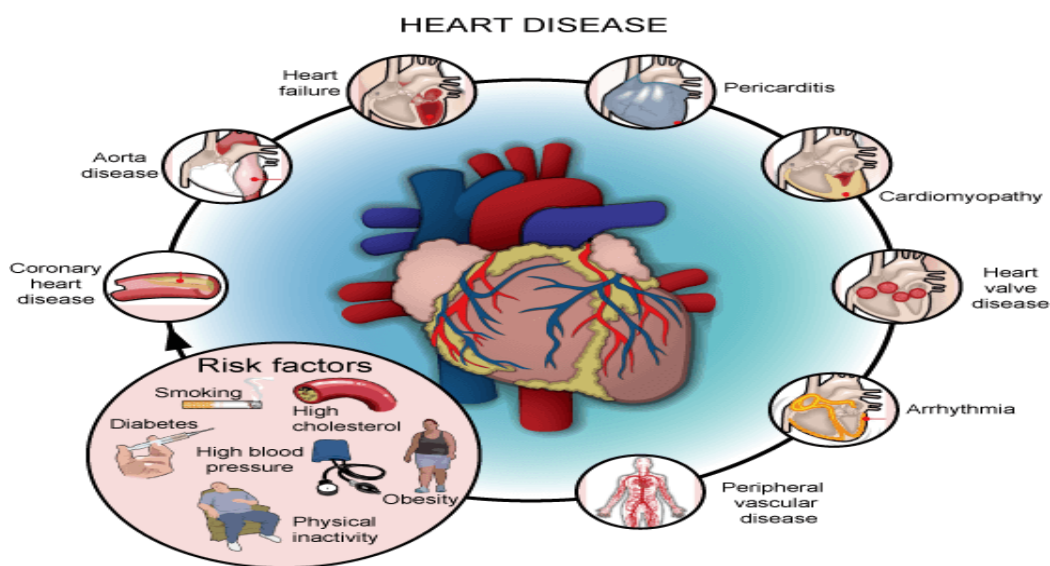


Figure 1: Cardiovascular Disease

The whole atherosclerotic process, from lipoprotein deposition to plaque development and rupture, is coordinated by a highly interconnected network that includes the immune system, bone marrow, and spleen, which control the balance between pro- and anti-inflammatory reactions through cytokines, leukocytes,

macrophages, and lymphocytes. The way that statins lower the risk of cardiovascular disease confirms the function that inflammation plays in atherosclerosis. According to a number of studies, statins' primary positive effects which are somewhat independent of their ability to lower cholesterol come from reducing vascular inflammation Kumar & Sinha (2020) (Figure 1).

2. THE CVD RESPONSE AND ITS ROLE

Endothelial Dysfunction

A brain aneurysm can also occur as a result of arterial remodeling brought on by WSS alterations. The plaque becomes hypoxic due to inflammatory alterations, which causes neovascularization to form from adventitial vasa vasorum. This procedure increases the susceptibility of plaque Ma et al. (2020).

Plaque Calcification

PET-based longitudinal imaging investigations have demonstrated that calcium is subsequently deposited at inflammatory arterial sites, and that the rate of calcium deposition varies within the same arterial segment depending on the degree of inflammation. These crystals can combine and embed themselves in the fibrous cap as microcalcifications that are smaller than 50 μm in diameter. Plaque calcification increases the number of nucleating sites and new calcification by further inducing macrophage infiltration. The growth of microcalcification will result from further cycles of monocyte infiltration that evolve into macrophages and then die if inflammation continues.

Furthermore, microcalcifications create a mechanical tension in the fibrous cap that exacerbates the inflammation surrounding the lesion. Death of macrophages and smooth muscle cells results in the release of vesicles, which serve as nucleating sites for hydroxyapatite crystal deposition. Biomechanical investigations indicate that plaque rupture is possible because of extreme stress at the tissue interface with varying stiffness, e.g., hard microcalcifications in the softer fibrous cap, causing a large modulus mismatch. According to this impact, the larger the interface area, the greater the chance of a plaque rupture. Microcalcifications are rare and the risk is minimal when inflammation is still in its early stages. Their

number and the size of the contact between the stiff and soft zones both grow as long as inflammation continues.

Vulnerable Plaque

Although stable plaques have also been observed to have some degree of inflammation, inflammation is a crucial characteristic of fragile plaques. The extracellular matrix (ECM), which is produced by smooth muscle cells in the artery wall and includes collagen, elastin, proteoglycan, and glycosaminoglycan, makes up the majority of atherosclerotic plaques. Plaque calcification and the ECM are intertwined, and both contribute to the stability of the plaque. Microcalcification localizes between collagen fibers and collagen-deficient areas, resulting in an inverse relationship between microcalcification and ECM proportions.

1. Key Inflammatory Mediators and Pathways

Inflammation Targeted Therapy

Changes in lifestyle, a decrease in risk factors, and lipid-lowering medication are the cornerstones of CV prevention. Acute cardiovascular events are still a significant risk for people with atherosclerosis, particularly those who are older or have comorbidities, even with the best medical care and a decrease in LDL-C levels. Observational research has demonstrated that a particular anti-inflammatory drug decreases the occurrence of atherosclerosis-related complications in patients with rheumatic disease, which is typified by elevated circulating cytokine levels. Additionally, statins reduce inflammation and cholesterol, both of which help to reduce the risk of cardiovascular disease (Townsend et al., 2016; Townsend et al., 2015).

Through the mobilization of various integrin types and other molecules, adhesion molecules play an important function in the immune system. Nevertheless, little is understood about the intricate relationships that exist between adhesion molecules and other elements of the inflammatory process when atherosclerotic plaque develops Aswathy et al., (2022) (Figure 2). It is well established that hyperlipidemia is essential to the onset and advancement of atherosclerosis. Unresolved inflammation, which is essential for atherogenesis, may result from an imbalance in cholesterol levels.

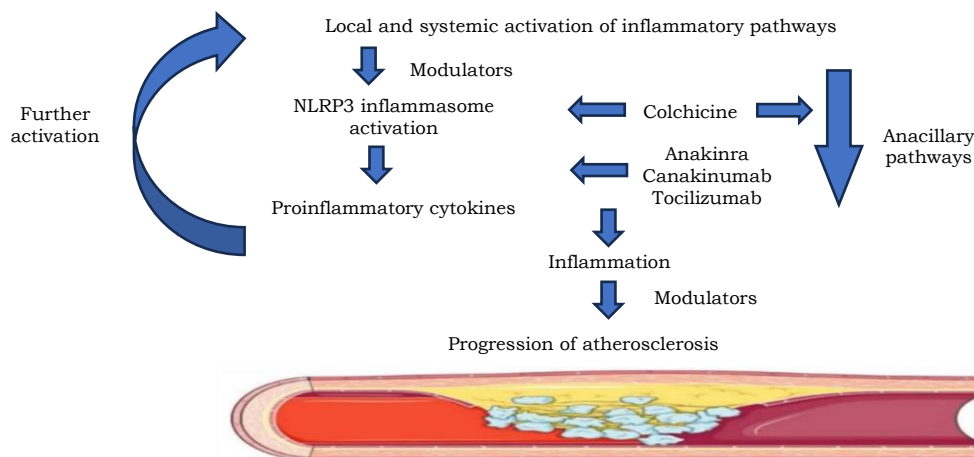


Figure 2: Inflammation in CVD

Early atheroma formation is characterized by the recruitment of many subcellular entities and the release of proinflammatory cytokines, which is an indication to exacerbate the atherosclerotic process. Prolonged inflammation exacerbates atherosclerotic plaque, which leads to myocardial infarction and thrombus development. (Tayb 2016; Libby 2002). It is possible to think of inflammation as a sequence of cellular and molecular processes that heal wounds by repairing or restoring tissue. A new humoral response for cellular growth and reformation may be produced as a result of a normal inflammatory response. When a chain reaction of inflammation fails to resolve, it eventually leads to organ damage and even death Wei-Wei et al. (2017). Reactive oxygen species, which are produced by cellular metabolism, are essential for triggering signaling pathways that change intracellular and extracellular metabolism. However, practically all of the ROS produced in the cell are produced by the mitochondrial respiratory chain. A respiratory explosion and the subsequent generation of ROS are caused by the development of an inflammatory response, which also increases the concentration of mast cells and leukocytes in the area. Along with changing inflammatory cytokines like IL-1 β , TNF- α , and IL-6 and transcription factors like NF- κ B and HIF1- α , the inflammatory cells can also create essential markers that initiate signal transduction cascades. Antioxidants are compounds that lower the inflammatory response by preventing the generation of reactive oxygen species. Antioxidants are

very helpful in preventing oxidative damage because inflammation starts a vicious cycle.

2. Therapeutic Strategies Targeting Inflammation

Cardiovascular disease (CVD) is a major global concern and one of the primary causes of death. A key element in the pathophysiology of these illnesses is the accelerated atherosclerosis process, which has been examined in relation to inflammation as a risk factor. Several inflammatory biomarkers, such as C-reactive protein (CRP), interleukins (ILs), and tumor necrosis factor-alpha (TNF- α), have been implicated in the atherosclerotic process and are associated with systemic inflammatory diseases and cardiovascular diseases (CVDs) Bhatnagar et al., (2015). The risk of CVDs may be predicted using these markers. Knowing the exact mechanisms can help develop treatment plans that focus on pro-inflammatory processes Smith & Edelman (2023) (Figure 3).

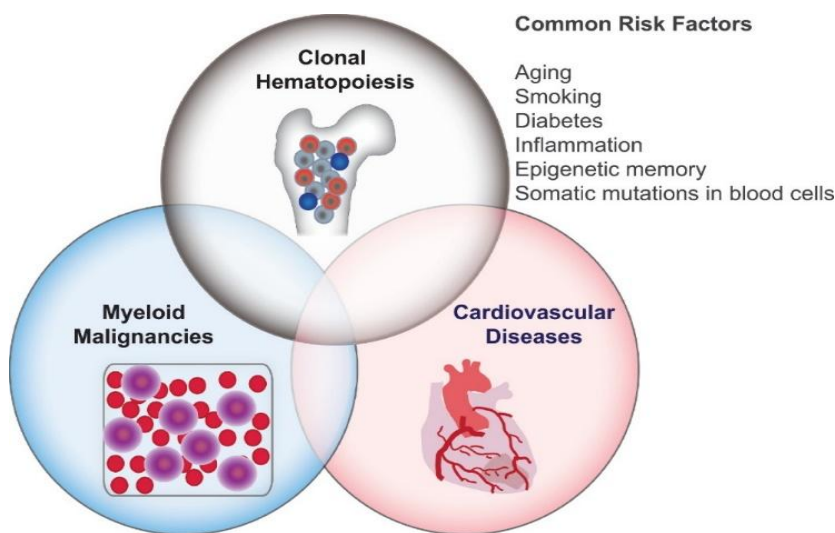


Figure 3: Clonal Hematopoiesis

Numerous families of inflammatory cytokines have been found to be responsible for endothelial dysfunction, which raises the risk of CVDs. Nonetheless, research has shown that inflammatory processes contribute to artery wall stiffness, which raises the risk of CAD. Aside from acquired risk factors including cancer, trauma, and surgery, research has also indicated that inflammation plays a part in arterial

thrombosis and VTE. The degree of VTE is known to be correlated with a number of inflammatory indicators.

Novel treatments that target these inflammatory biomarkers may result from research on the function of inflammatory processes, thereby lowering the burden of CVDs. Colchicine's function in treating pericarditis and averting atrial fibrillation following heart surgery and ablative therapy has been well investigated. In addition to evaluating the various indicators and potential treatment targets, this thorough review attempts to appraise the data currently available about the involvement of inflammation in cardiovascular illnesses. Plaque instability and a high risk of rupture are caused by the decreased NO-mediated vasodilatory response and increased arterial stiffness. In order to forecast a long-term prognosis and evaluate the risk and severity of unfavorable cardiovascular events, serum levels and gene polymorphisms in a number of markers have been employed as independent determinants. Additionally, vascular function has improved as a result of the application of anti-inflammatory medication that targets these indicators in chronic inflammatory illnesses. New anti-inflammatory treatments for improved cardiovascular outcomes may result from future research on inflammatory pathways, which will provide additional insight into the biomarkers involved Wilkins et al., (2017).

3. Therapeutic Strategies Targeting Inflammation

A complicated and highly conserved series of molecular and cellular processes make up inflammation. Known as "the fire within," inflammation is tightly controlled and essential for tissue regeneration and host defense. Inflammation is generally advantageous and has developed to aid with survival. Until recently, atherosclerosis was thought to be a condition caused by passive cholesterol buildup in the subendothelial region, despite data acquired by Virchow more than a century ago suggesting inflammatory white cells contribute to atherogenesis.

MicroRNAs

Gene expression has been demonstrated to be modulated by microRNAs, which are small non-coding RNAs. In humans, over 2000 microRNAs have been identified. According to recent studies, microRNAs play a big part in controlling inflammation.

The expression of microRNA by immune and bystander cells can contribute to an inflammatory feedback loop that, depending on the kind of microRNA generated, can either enhance or reduce inflammation. Numerous microRNAs that promote and inhibit inflammation have been identified. This enables the reduction of inflammation in locations that are experiencing active inflammation. Currently, one of the biggest obstacles is the expense of developing microRNA drugs and the methods of administering them.

Targeting the NLRP3 Inflammasome Pathway

Based on CIRT and CANTOR data, vascular risk is reduced by blocking the inflammasome-to-CRP pathway. Consequently, a number of research are looking directly at the function of NLRP3 inhibition. One potential benefit of directly inhibiting the inflammasome is that it may prevent inadvertent immunosuppression, which can occur when cytokines are systemically targeted. Numerous inflammasome inhibitors, both direct and indirect, are being studied. Compared to indirect inhibitors, direct inhibitors like CY-09, MCC950, exhibit reduced off-target immunosuppression. It has been demonstrated that IL-18 levels, can predict CVD, albeit not as well as IL-1 β or IL-6 (Figure 4).

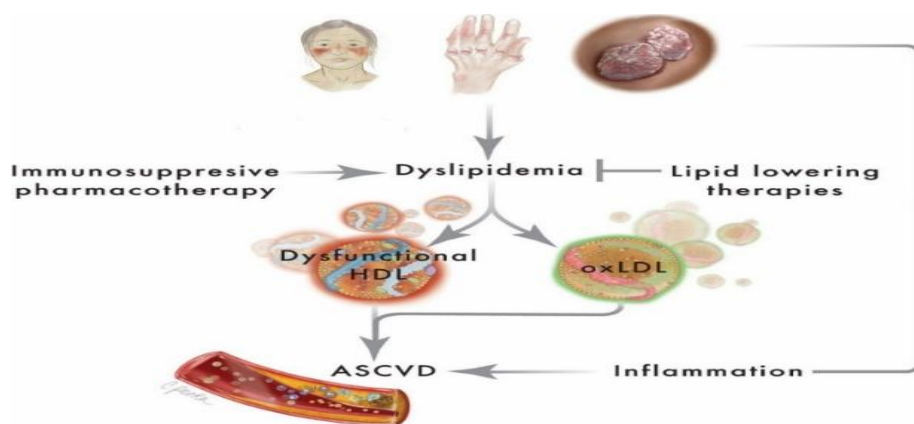


Figure 4: Inflammatory Disease

Omega-3 Fatty Acids

It's interesting to note that this positive impact happened regardless of the initial or final serum triglyceride levels. It is unclear what possible processes could be

responsible for this advantage. However, there was a significant drop in hsCRP levels among those randomly assigned to icosapent ethyl compared to placebo (median percent change from baseline, -12.6% vs. 29.9%; $P < 0.001$), indicating that EPA supplementation may have an anti-inflammatory impact. A decrease in triglyceride levels is one way that EPA may have anti-inflammatory effects. EPA also serves as a precursor to the resolvins, anti-inflammatory lipid mediators that aid in the resolution of chronic inflammation. The anti-inflammatory actions of omega-3 fatty acids, such as decreased cytokine production and endothelial and platelet activation, can be responsible for their reported benefit. Additional studies are being conducted to define the precise mechanisms by which EPA modulates inflammation. (Van de Voorde et al., 2013; Cosselman et al., 2015) (Figure 5)

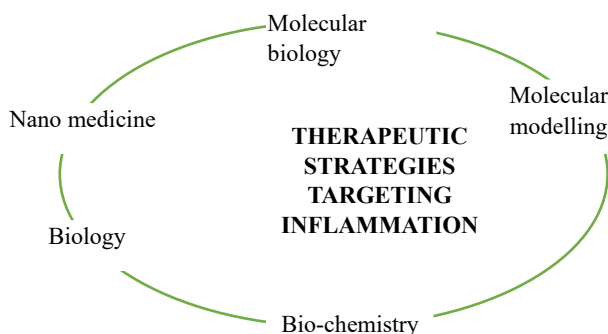


Figure 5: Therapeutic Strategies Targeting Inflammation

Microbiome Modification

The intricate relationship between the immune system, the gut, and its microbial ecology is being supported by mounting data. Alterations in the gut microbiota's makeup could put the gut at risk for inflammation, which would increase systemic inflammation. There are several levels of contact. The microbiome may be involved in regulating mucosal integrity, according to data from observational research on humans and animal models. The mucosal epithelium of the colon depends mainly on butyrate and short-chain fatty acids (SCFA) derived from the microbiome's fermentation of dietary fiber. A low-fiber diet can change epithelial metabolism, enhancing permeability and decreasing SCFA and butyrate production. This results in an inflammatory response, both locally and systemically, as a result of the transfer of bacteria and lipopolysaccharides. Studies have demonstrated that blood

hsCRP levels are inversely related to bacterial genetic markers of butyrate production in the gut. Butyrate controls the local gut inflammatory response and immunologic homeostasis by altering colonic regulatory T-cells. Gut inflammatory response alterations may result in shifts in the bacterial composition, establishing a chronic low-grade inflammatory state. The microbiome also modulates the action of a Western diet by generating TMAO precursors from choline, betaine, and carnitine, which are found in red meat, eggs, fish, and poultry. (Berry et al., 2012; Lopez et al., 2023; Bansal et al., 2020).

4. FUTURE ANALYSIS

Additional prospective research is required to validate these results. Current studies are looking into strategies to control the gut's microbial ecosystem and disrupt the possible feedback loop between systemic and intestinal inflammation. Dietary intervention and the use of prebiotics are two potential pathways being studied; these strategies seek to improve epithelial integrity and favorably change the makeup of microbial communities in order to reduce inflammation systemically.

5. CURRENT SUCCESSES AND CHALLENGES

In spite of impressive therapeutic progress, cardiovascular diseases are still the predominant cause of morbidity and mortality globally. Since cardiovascular diseases tend to be inflammatory in nature, alternative treatment methods are needed. Inflammation is a normal response to tissue injury, being mediated by cytokines, chemokines, and leukocyte activation. But unchecked chronic inflammation results in tremendous tissue injury. Experimental studies point to the pivotal role of inflammation in cardiovascular disease, such as hypertension, atherosclerosis, myocardial infarction, and hypertrophic heart failure. In addition, metabolic preconditioning and cardiovascular disease have significant correlations. Inflammatory associations with disorders like diabetes and obesity have existed since the 1960s, when increased circulating fibrinogen and other acute-phase proteins were found in these conditions. People with diabetes had a higher risk of heart failure, according to the Framingham studies, regardless of age, body mass index, hypertension, or coronary disease. Higher hemoglobin A1C (HbA1c) in non-diabetic patients increases the risk of heart failure considerably, implicating that

pre-diabetic chronic hyperglycemia elevates cardiovascular risk. Obesity also raises cardiovascular disease risk, apart from diabetes, mainly through increased inflammation and reactive oxygen species. Cardiovascular inflammation is usually evidenced by elevated inflammatory cytokines, including TNF α , IL-1 β , and IL-6, secreted by immune cells, and reduced anti-inflammatory cytokines, such as TGF β and IL-10. Cardiac cells, including cardiomyocytes, cardiac fibroblasts, and endothelial cells, also secrete inflammatory cytokines in response to ischemia or hypertrophic stress. Although cardiovascular diseases trigger inflammation at cellular and systemic levels, the heart possesses inherent anti-inflammatory protection. Increasing cardiac function and diminishing inflammation following hypertrophy or ischemia stress can be done through lowering pro-inflammatory mediators or raising anti-inflammatory mediators.

The work of Gussekloo et al points up significant issues, namely that an ideal biomarker such as C-reactive protein (CRP) would ideally be a sensitive risk factor for a specific end-point, say stroke, not for a diffuse group of non-related end-points in order to maximize its positive predictive value. Future research may reveal that CRP belongs to the significant group of risk variables that are linked to a variety of outcomes, including radiation exposure and cigarette smoking. But generally speaking, an association's specificity is a crucial element that frequently indicates a causal relationship. Elevated CRP did not significantly correlate with the death risk from stroke or other cardiovascular illnesses, according to these researchers. The correlation between high CRP levels and risk of several diseases, such as cancer, cardiovascular disease, and infections, is not unexpected considering the relationship between inflammation and CRP. The research revealed a time-dependent association between CRP levels and mortality, where higher CRP levels correlated with decreasing intervals between measurement and death. This finding is consistent with the Cardiovascular Health Study in elderly populations, which differs from research in middle-aged populations. Increased CRP in the elderly could be an expression of acute pathophysiologic processes culminating in clinical disease, disability, and mortality. Subclinical conditions are frequent among the elderly, and thus increased CRP can be an indicator of developing illness, albeit not necessarily an expression of the disease etiology. Although increased CRP can be

linked to certain pathophysiologic mechanisms, including thrombosis and clotting, in cardiovascular disease, this study's results indicate that an elevated CRP is linked to a wide variety of outcomes, as opposed to one particular disease process. The correlation between CRP and outcomes suggests that increased CRP can be a marker for nonspecific underlying inflammation and risk of disease, as opposed to a distinct marker for a distinct disease process (Figure 6).

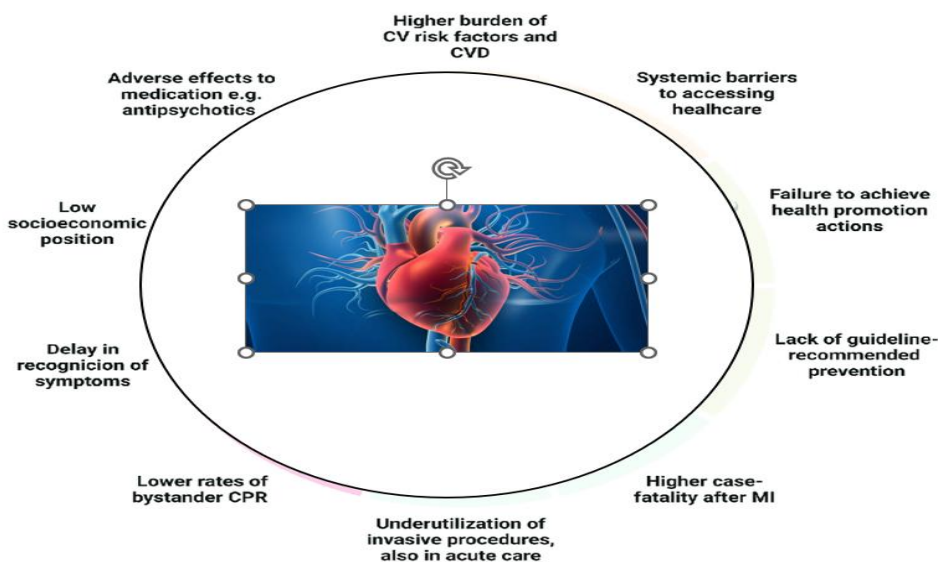


Figure 6: Current Successes and Challenges

CRP may indicate a developing subclinical illness in younger and middle-aged people that is not picked up by standard clinical assessment methods. This subclinical condition could develop into a clinical ailment years later. CRP can be a marker of the severity and progression of unmeasured subclinical disease, but not necessarily a direct causative agent. Elevated CRP is, however, linked with augmented production of proinflammatory cytokines, like interleukin-6, which can directly or indirectly affect disease pathophysiology through their associations with other inflammatory, thrombotic, or fibrinolytic elements.

It would be absurd to assume that CRP and related acute-phase proteins are mechanistic risk factors for disease and that lowering the CRP level will lower the risk of disease without the appropriate data to support such a claim. In spite of the importance of the study of CRP and other acute-phase proteins, as yet there is no

firm evidence that CRP is a unique mechanistic risk factor for cardiovascular disease. Moreover, CRP does not seem to indicate the severity or the degree of disease, nor is there evidence to suggest that it is causative. In addition, there is no evidence that lowering CRP or other acute-phase reactants will retard the progression of disease or prevent recurrent disease events. This assertion has been reviewed and approved by the CDC and the American Heart Association's Science Advisory and Coordinating Committee, on the basis of the key findings and conclusions of the Workshop. The argument is supported by the strongest evidence to date associating cardiovascular disease and inflammatory markers. The study utilized the US Surgeon General's standards for causality, such as consistency, biological plausibility, dose-response relationship, timeliness, and strength. The American College of Cardiology/American Heart Association classification scheme was employed to evaluate strength of evidence supporting the association. In addition, advice on the use of inflammatory markers for screening was assessed employing an evidence-based method, taking into account issues including randomized trial evidence, benefits and harms, performance in various populations, screening methods, and cost-effectiveness.

6. CONCLUSIONS

Atherosclerosis and its clinical consequences are thought to be caused by systemic inflammatory and immunological pathogenesis, according to recent epidemiological, clinical, and imaging research. There is no clinical significance in using atherosclerotic plaque vulnerability traits to predict significant cardiovascular events. A thorough evaluation of atherosclerosis should emphasize a qualitative assessment of a patient's susceptibility rather than anatomical imaging studies of atherosclerotic lesions. Present inflammatory markers are not very specific, and they do not reliably represent underlying biological processes. But longitudinal follow-up of circulating, cellular, and imaging markers could potentially allow identification of high-risk individuals and direct individualized treatment, potentially altering CVD risk. A viable treatment strategy might be to modulate the early stages of atherosclerosis formation and target inflammation upstream. A deeper comprehension of the inflammatory pathways involved in atherosclerosis

could result in the development of more targeted therapies without sacrificing the immune system's ability to fight against infections.

Even with effective lipid-reducing medications, residual inflammatory risk persists because methods that target lowering apoB/LDL-C alone do not adequately address the varying inflammatory and/or atherogenic potential across diverse apoB profiles. This emphasizes the necessity of addressing all factors that contribute to atherosclerosis risk, including inflammation, as opposed to evaluating and treating a single marker like apoB/LDL-C. Pharmacological research is being done on a number of medications, specifically those that target the NLRP3-IL1- β /IL-6 pathway. High-risk post-MI patients, who are best identified by an elevated inflammatory load, may benefit most from these medications. However, there is still uncertainty regarding the commencement date and duration of treatment. The prevention of cardiovascular disease could be completely transformed by an all-encompassing approach to residual risk management. However, we are only at the start of this adventure, and there are still many unanswered questions.

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