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Treatment of Vulnerable Plaque

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Acute coronary syndrome (ACS) is the major cause of mortality worldwide, which results from acute thrombus formation leading to partial or complete occlusion of the coronary artery. Vulnerable plaques may be defined as those plaques prone to thrombus formation. While it remains still controversial, atherosclerotic plaques with a thin fibrous cap, a large lipid core or active inflammation are generally considered as vulnerable plaques. The primary goal of medical treatment in patients with atherosclerotic cardiovascular disease (ASCVD) is to prevent ACS by stopping the plaque destabilization and halting the formation of blood clots.

Atherosclerosis is a chronic lipid-driven inflammatory disease of the arterial wall, and cholesterol play a primary causative role. The relationships between low-density lipoprotein (LDL) cholesterol levels and the development of ASCVD as well as the effectiveness of LDL cholesterol lowering therapies in both primary and secondary prevention are well established. Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, are highly effective in lowering the LDL cholesterol levels, and the preferred treatment for lowering LDL cholesterol. A number of studies have demonstrated that statins improve the prognosis for patients with ASCVD or those at risk of developing ASCVD. Furthermore, statins are effective in inducing atherosclerotic plaque regression as well as slowing atherosclerotic plaque progression. Current guidelines recommend high-intensity statin therapy for patients with established ASCVD and familiar hypercholesterolemia, and moderate-intensity statin therapy for people with ASCVD risk > 7.5%. While statins effectively lower the LDL cholesterol levels in the majority of individuals, some individuals fail to respond to treatment (statin resistant) or are prone to developing adverse side effects (statin intolerant). In these situations, alternatives to statins including cholesterol absorption inhibitors (ezetimibe) and PCSK9 inhibitors (alrirocumab, evolucumab) are currently available. In fact, the need for more aggressive LDL cholesterol-lowering therapies, particularly for treating high-risk patients, has led to the development of PCSK9 inhibitors. These agents have shown significant mortality and morbidity benefits in patients with established ASCVD. High cost and the limited indications prohibit their wide-spread use in real-world clinical practice. Despite potent therapies of the LDL cholesterol, however, the residual risk of patients with ASCVD still remains high. Thus, clinical and basic research has continued to focus on developing remnants cholesterol (triglyceride-rich lipoproteins) lowering therapies in addition to LDL cholesterol lowering therapies. Aeveral studies have demonstrated that triglyceride-rich lipoproteins including chylomicron, VLDL and IDL also play an important role in the development of atherosclerosis. New therapeutic approaches including inhibition of angiopoietin-like 3, apo C3 or lipoprotein (a) are now under clinical investigation, and further risk reduction will be expected on top of current LDL cholesterol lowering therapies. In addition, the characteristics of vulnerable plaques by in-vivo imaging and their local therapy are not yet fully established, requiring further studies.

Finally, remnant cholesterol as well as LDL cholesterol is considered the key player in the development of atherosclerosis. Comprehensive lipid management remains the cornerstone for prevention of ACS, and new therapeutic approaches will help to abrogate the pathophysiological processes of ASCVD.

Key words: LDL cholesterol, PCSK9 inhibitors, remnant cholesterol, vulnerable plaques