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Editorial

Residual Risk of Atherosclerotic Cardiovascular Disease; Is It Possible to Eradicate?

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Abstract

Atherosclerosis Cardiovascular disease (ASCVD) remains the number one causes of death and disability worldwide. Treatment of major traditional risk factors, including low density lipoprotein–cholesterol, smoking cessation, controlling hypertension and diabetes, enhancing physical exercise etc. are the important measures of atherosclerotic risk reduction. An LDL centric approach to risk reduction, namely with statin for decades and proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) recently have served as the foundation of primary and secondary prevention and have led to significant improvement in cardiovascular outcome. However, a considerable number of directed medically treated (GDMT) patients remain at a significantly elevated risk of having a major cardiovascular event that still remains unsolved. This is commonly referred to as residual risk. Beyond traditional risk factors, other drivers of residual risk have been postulated, these includes inflammatory, prothrombotic and metabolic factors.

Keywords: *Atherosclerosis, Cardiovascular disease, Death*

An LDL centric approach with statin and PCSK9i has driven LDL-C to very low level. PCSK9i provided further confirmation of the LDL hypothesis. Moreover, the cardiovascular outcomes trials with PCSK9i demonstrated that there was no level of achieved LDL-C that was not associated with further benefit. However, despite reduction of LDL-C levels to a mean of 30 mg/dL with the use of Evolocumab in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, the absolute risk reduction was only modestly reduced by 1.5%. In fact, the recurrent cardiovascular event rate at 3 years in those treated with a PCSK9i remained high at 9.8% [1]. A similar finding was seen in ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab), in which the composite primary end point of cardiovascular death, non-fatal myocardial infarction (MI), stroke or unstable angina occurred in 9.5% of participants receiving alirocumab, as compared to 11.1% in the placebo arm, despite reductions of LDL-C levels to a mean of 40 mg/dL in the treatment group [2]. Residual risk refers to the high observed event rate despite aggressive secondary prevention efforts defined as any sub-optimally controlled causal risk factor for ASCVD. Thus, residual risk can be attributable to many factors like hypertension, tobacco use, elevated blood glucose along with other less defined inflammatory, pro-

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thrombotic, and metabolic factors along with genetic predisposition.

Different biologic, epidemiologic, and clinical trials have shown that inflammation is animportant driver of atherosclerosis. Circulating biomarkers of inflammation, including high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6), are associated with increased risk of cardiovascular events independent of cholesterol and other traditional risk factors. Randomized trials have shown that statins reduce hsCRP, and the magnitude of hsCRP reduction is proportional to the reduction in cardiovascular risk. Additionally, these trials have demonstrated that many individuals remain at increased risk due to persistent elevations in hsCRP despite significant reductions in low-density lipoprotein cholesterol (LDL-C) levels.

The role of anti-inflammatory therapy in ASCVD risk reduction has been proven in different trials. The JUPITER trial (Justification for the Use of Statin in Prevention: an Interventional Trial Evaluating Rosuvastatin), for primary prevention and CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) [3, 4], for secondary prevention has demonstrated benefits to some extent in post MI patients. However, a potent inhibitor of Lp-PLA2, darapladib in a RCT and methotrexate in Cardiovascular Inflammation Trial (CIRT) demonstrated no benefit in cardiovascular outcomes [5].

The routine use of antiplatelet medications in primary prevention has an unfavorable risk:benefit ratio when used in those without manifest cardiovascular disease [6-8]. However, in patients with established ASCVD, antiplatelet agents are an essential component of optimal medical management. Despite appropriate antiplatelet use, usually with aspirin, risk of atherothrombosis and subsequent cardiovascular events remain in significant amount [9]. Though addition of low dose rivaroxaban to dual antiplatelet therapy in post-MI patients demonstrated the beneficial outcome, but it was offset by similar bleeding risk.Regarding the duration, the benefits of prolonged DAPT were offset by an increased risk of major though not fatal bleeding [10].

The role of Lipoprotein (a), Triglycerides and triglyceride-rich lipoproteins (TGRL, High-Density Lipoprotein-Cholesterol (HDL), Diabetes has proven in different trials.

Lipoprotein (a) (Lpa) plays an active role in vascular atherothrombosis. In the INTERHEART study, an Lp (a) level >50 mg/dL was associated with an increased risk of MI [11]. However, whether Lp (a) should be a target of therapy remains a matter of debate. Triglycerides and triglyceride-rich lipoproteins (TGRL) have also been identified as important contributors to residual risk. Trials with several triglycerides lowering therapeutics demonstrated inconsistent results. Low levels of high-density lipoprotein (HDL)-cholesterol (HDL- C) and ASCVD is proven [12]. However, though niacin and cholesterol ester transfer protein inhibitors increased HDL-C, did not lead to a reduction in major adverse cardiovascular events [13, 14]. The addition of glucagon like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) has shown substantial benefits on patients who were on optimal or near optimal background therapy as per current guidelines. Importantly, SGLT2i demonstrate benefit in individuals without diabetes as well, particularly in those with heart failure and reduced ejection fraction as demonstrated in the DAPA- HF study [15].

Conclusion

Addressing the residual risk for both primary and secondary prevention of ASCVD is the most important step towards elimination of Cardiac events. As we have an incomplete knowledge of residual risk and scanty evidences of improving CV outcome by addressing these factors, eradication of cardio vascular events remains a far target.

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