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Introduction
The American College of Cardiology (ACC) annual meeting this year 2017 was held in Washington D.C. and has been denoted the hashtag #ACC17 on social media.

Among the different cardiovascular components, the highlights this year were mainly related to vascular as well valvular heart diseases, walking home with a clear safety and efficacy message on the relatively new choice of TAVR (TAVI) as an alternative to the traditional intermediate risky open heart aortic valve replacement [1].

Furthermore, the clinical utilization of PCSK9 as a new therapy to lowering LDL cholesterol has been remarkably shown by FOURIER trial investigators to be safe and effective. Two percent (~2%) absolute risk reduction is observed in clinical outcomes. In patients treated to very low levels of LDL-C, 2.9% developed acute coronary syndrome (ACS) compared to 4% in the placebo arm.

Interestingly, the word “Fourier” is the name of French mathematician and physicist (Joseph Fourier 1768-1830), who developed Fourier analysis and studied the conduction of Heat in relation to Time domain. Perhaps a friendly coincidence to remember that “time” is an important factor in the management of LDL cholesterol as a risk factor for coronary artery disease (CAD).

Despite clear efficacy of lowering serum LDL cholesterol levels to unprecedented range of 20-30 mg/dL, the clinical outcomes data are not robust enough, hence the cost remains an issue for accessibility to many patients on a large scale of population.

Fascinatingly, the novel use of injectable (subcutaneous) mRNA modulating monoclonal antibody without neutralizing antibodies has shown in FOURIER to work on maintaining those low levels of LDL-C for 26 months (~2 years) following two subcutaneous injections. Even so, the clinical outcomes of this “flawless” trial have ignited multiple queries presented with evidence based answers from basic science, lap research, and clinical trials.

What is LDL-C?
LDL (low density lipoprotein) Cholesterol structurally resembles a sphere with a core consisting for the most part of cholesteryl esters, surrounded by covering surface monolayer of phospholipids, unesterified cholesterol and apoprotein B-100 (Figure 1).

Lipoproteins and LDL transfer lipids within the blood stream in the extracellular fluid purposely for lipids to be taken up by the cells

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passing through receptor-mediated endocytosis. A single LDL particle is about 220-275 angstroms in diameter, while its molecular weight is approximately 3 million daltons, with a transporting capacity of 3,000 to 6,000 fat molecules/particle [3].

LDL cholesterol and the LDL receptors (LDLR) are combined to form a complex that is endocytosed into the intracellular matrix for release of LDL particle to lysosomes where LDL is degraded to release free cholesterol. The LDL receptors can be recycled after transportation back to the plasma membrane via transport vesicles unless intercepted by PCSK9. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme encoded by the PCSK9 gene in humans on chromosome 1 [4-6]. Moreover, PCSK9 function could reflect ancient roles in the fasting-feeding cycle and in linking lipoprotein metabolism with innate immunity. It degrades the LDL receptors and therefore LDLR are no longer recycled back to the cell membrane surface to bind more LDL-particles from the bloodstream. This process occurs mainly in the liver, which removes approximately two thirds of LDL cholesterol from the circulation (Figure 2).

Function of LDL-C

The main function of LDL cholesterol is delivering lipids to build cell membranes (phospholipids) throughout the human body. Additionally, cholesterol plays an important role in the composition of hormones as well as enzymes necessary for various body functions.

Furthermore, lipids are considered the main form of energy storage and eventually excessive storage leads to extra fat directed by forming fatty tissues in various anatomical parts. Fat surrounding major organs is beneficial in acting like cushions to prevent migration and movements of respective organs such as the kidneys, liver, and heart. Moreover, lipids are essential for brain cells (gray matter) and myelin covering cells in the white matter of nervous system.

Adipose tissue metabolism is extremely dynamic, and strictly controlled by feedback mechanism. The supply and elimination of fat substrates in the blood is in harmony according to the feedback of nutritional state. Adipose tissue possesses the ability to communicate with other body tissues in a form of biochemical signals regulating energy metabolism in accordance with the body’s nutritional state [7].

Role of LDL-C in vascular atherothrombosis

Based on current research, the function of LDL-C is directed mainly to building cell membranes. The relationship between LDL-C and atherosclerotic plaque development has been intriguing to most researchers. This has triggered a wealth of research, published and unpublished data regarding this relationship at the vascular intimal level.

Animal studies have shown clearly that the intimal layer of vessel is made out of a single mono-cellular layer which represents the inner part of the tunica intima [8]. This part of cell layer is seen as a transparent membrane when experimentally stripped from other vascular endothelial components. The problem with this membrane being a mono-cellular layer is the difficulty to strip the membrane completely intact due to friability, however, extracted parts of this endothelial layer has been studied extensively under microscopic evaluation.

Results

The anatomy of the intimal layer was amazing in confirming the presence of a single layer that’s activated pathologically upon interruption (injury) in order to repair the endovascular wall. Activation process usually triggers many factors, biochemically, hemodynamically, as well as cellular recruitment of macrophages and Foam cells, providing a proper inflammatory response rich medium.

The exposure of the sub-intimal endothelium to the bloodstream following interruption of the intimal cell layer results in recruitment of thrombotic reaction utilizing foam cells, LDL-C, platelets, fibrin, as well as other adhesive and clotting factors [9-22]. Vascular smooth muscle cells in the media produce proteoglycans, collagen and elastin found in extra-cellular matrix (ECM) of the intima. Structural as well as functional changes in the LDL-C particle are produced upon interaction with components of ECM that lead to deposition of LDL-C in atherosclerotic lesions. During this process, LDL-C is deposited at the site of intimal interruption and further aggregates forming a core of the thrombus. Excess levels of LDL-C available for aggregation is synergistically working with other components of thrombus formation, has been demonstrated to be incriminated in forming the highly thrombogenic lipid core of the atherosclerotic lesion.

Another area of medical research is atherosclerotic plaque lipid homeostasis between ‘Bad’ and ‘Good’ cholesterol, reaching the exact target amount required for endothelial repair, utilizing LDL-C without causing further excessive accumulation thru the function of HDL-C. Nonetheless, this was not confirmed loudly in clinical outcome trials focused on elevating HDL-C levels [23].

Clearly, the lower levels of LDL-C has been confirmed to reduce the burden of atherothrombosis, as well as further reduction in atheromatous plaque that is vulnerable, along with further reduction in cardiovascular morbidity and mortality. It is important to emphasize that the longer duration of developing atherothrombosis requires longer duration of therapy as well to see robust translation into clinical survival outcomes.

Data from published studies performed on pediatric and adolescent age groups evaluating the level of LDL-C prior to development of atherosclerosis, the target healthy level is in the range of 30 to 50 mg/dL. At this low level of LDL-C, the longitudinal follow up of those individuals, revealed lack of atherosclerosis in the absence of other known risk factors, enforcing the pivotal role of LDL-C in the development of atherothrombosis.

Figure 2: LDL receptors.
There have been several debates about the healthy target level of LDL-C, however, an agreement on the notion that the lower LDL-C the better, has not been reached. Concerns of increased incidence of diabetes as well as alteration in cognitive functions as a result of very low levels of LDL-C has ignited a search for confirming or refuting such claims.

It is of note, conceivably, that the mechanism of lowering LDL-C may result in different outcomes. The novel mechanism of PCSK9 inhibitors in lowering LDL-C is acting by enhancing cellular uptake of LDL-C thru LDLR, hence functions based on the availability of LDL-C as an intracellular substrate remains intact. However, the mechanism of action of Statins, (HMG-CoA reductase inhibition to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol), is to halt the production of LDL-C depriving intracellular lysosomes from utilizing LDL-C at very low levels.

Perhaps, one may speculate that the lowering ability of PCSK9 inhibitors is safely and effectively done by reaching target low levels of LDL-C without interfering with intra-cellular abundance of LDL-C as a substrate for utilization by lysosomes in contrast to a different mechanism in the case of Statins.

Conclusion

A leap in the quantum of LDL-C reveals that risk factors for CAD are synergistically additive with each other to produce the burden of the disease. Moreover, patient selection remains the most influential factor in implementing new therapeutic modalities, as one size doesn’t fit all. Clearly, adopting healthy lifestyle preventive strategy is more appropriate, in addition to medical intervention either primary or secondary risk factors management as per guidelines to avoid unnecessary harmful CAD effects including cost of healthcare.

References