Is LDL the lower the better for T2DM patients?

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In postnatal life, the serum concentration of LDL-C is low, around 30 mg/dL at birth. In adults, the level gradually increases after 20 years old and correlated with the risk of atherosclerotic cardiovascular disease (ASCVD). Accumulated data from lipid lowering trials using statins, ezetimibe, and PCSK9 monoclonal antibody showed that the average LDL-C level could be reduced to below 30 mg/dL with proportional cardiovascular benefit for the purpose of secondary prevention. In FOURIER trail, the participants with LDL-C level less than 20 mg/dL after treatment did not have more side effects, compared to those with higher LDL-C achieved levels. These evidences lead to the zero LDL-C hypothesis, which suggests that the bottom line of LDL-C level to maximally reduce cardiovascular risk would be zero.

For people with diabetes, statin trials of major primary prevention, secondary prevention and those comparing high and low dose indicated diabetic participants did not differ from non-diabetics with regard to the beneficial cardiovascular effects of statins. These included trials conducted in Asians, such as MEGA trial (primary prevention), patients with LDL-C less than 70 mg/dL post myocardial infarction in KAMIR registry (secondary prevention), and REAL-CAD trial (high versus low dose statin). However, in IMPROVE-IT study comparing simvastatin plus ezetimibe with simvastatin alone, participants with diabetes obtained significantly more benefit than non-diabetics. The phenomenon was not seen in subsequent FOURIER trial examining PCSK9 monoclonal antibody.

Current lipids management guidelines from major medical societies, including Taiwan Society of Lipids and Atherosclerosis, indicated the cardiovascular risk of diabetic people is comparable to non-diabetics having cardiovascular diseases, and therefore, the LDL-C level should be controlled, at least, below 100 mg/dL. For diabetics with cardiovascular diseases, below 70 mg/dL, and for those with extremely high risk, such as encountering acute coronary syndrome, below 55 mg/dL is recommended.

In real world practice, the administration of lipid-lowering agents should consider beneficial effects, adverse effects, and cost. For statins, ezetimibe, and PCSK9 monoclonal antibody, the beneficial effects for cardiovascular protection are well established. The major side effects for statins are myopathy, impaired liver function and new-onset DM. While myopathy and impaired liver function may be severe to lead to stop of statins, the risk of diabetic side effects is much less than the cardiovascular protective effects, and should not cause discontinuation of statins. For ezetimbe, the side effects are uncommon. For PCSK9 monoclonal antibody, no major side effected were so far reported, except injection site reaction, which is tolerable by most of the users. However, price is a

critical issue to decide its market penetration. In addition, long-term safety profile is still needed for people who may need life-long treatment.