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Updates in LDL-Cholesterol Management-The Lower, The Better - For Longer

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Abstract

Low-density lipoprotein cholesterol (LDL-C) is a validated marker for the amount of plasma LDL and primary drivers of atherosclerosis. At least 25% of ASCVD-related deaths are directly attributed to elevated LDL-C as the primary marker of dyslipidemia. LDL-C is the primary target of lipid-lowering therapies. Targets of LDL-C depend on CV risk categorization. For primary prevention desirable level of LDL-C should be less than 100mg/dl (2.6mmol/L) for the patient with moderate risk; less than 70mg/dl(1.8mmol/L) for high risk patient ; less than 55mg/dl(1.4mmol/L) for very high risk patient . The goal of drug treatment for any patient with LDL-C greater than 190mg/dl (4.9mmol/L). Dietary intervention, moderate exercise, and weight loss, are first-line therapies. Statins are the cornerstone of therapy to lower LDL-C and reduce LDL-C by 20% to 60%, increase HDL-C by 2% to 16%. Statins are safe and generally well tolerated. Subtle adverse events are more frequent due to the nocebo effect. Rhabdomyolysis is rare. Ezetimibe inhibits cholesterol absorption from ileum and lowers LDL by 14% to 25% when used alone or in combination with statins and reduce CVD events. Uncommon side effects are diarrhea and abnormal liver function. Bile acid sequestrants (Cholestyramine, colestipol, and cole sevelam) were the first LDL-C lowering drug class shown to reduce CVD. As monotherapy, sequestrants lower LDL-C by 5% to 30%. GI disturbances are common. Bempedoic acid reduces cholesterol synthesis by inhibiting ATP citrate lyase and especially useful in statin-intolerant patients and reduces LDL-C by 18% to 30%, either alone or in combination with other LDL-lowering agents with very limited musculoskeletal-related side effects. PCSK9 inhibitors (alirocumab and evolocumab), alone or in conjunction with statins, further reduces 60% of circulating LDL-C beyond that achieved by statins alone. Administered alongside high- intensity statin therapy (with or without ezetimibe), PCSK9 inhibitors significantly reduces MACE in patients with DM with ASCVD. It is especially useful in FH. Side effects are injection site reactions. Inclisiran, a small interfering RNA (siRNA), inhibit hepatic synthesis of PCSK9, decreases LDL-C levels by 51% and is associated with a 24% lower risk of MACE. ANGPTL3 Inhibitors, Evinacumab is a monoclonal antibody against ANGPTL3166 and reduces up to a 50% LDL-C in patients with HoFH, with good safety and tolerability. LDL apheresis cornerstone of therapy in HoFH and produces an acute decrease in LDL-C by 50% to 60%. *[J Assoc Clin Endocrinol Diabetol Bangladesh, 2025;4(Suppl 1): S24]*

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