

LDL-C is normally cleared from the circulation as apoprotein B100 on the surface of LDL and binds to LDL receptors on hepatic and extrahepatic tissues. While statins effectively decrease cholesterol levels, their efficacy is diminished by this increase in PCSK9 activity. As the intracellular concentration of cholesterol increases, 3 events occur, as mentioned below.[9] Decreased activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase--the rate-limiting enzyme of cholesterol synthesis. PCSK9, a product of hepatocytes, is secreted into the plasma, where it binds to the LDL receptors, facilitating their lysosomal degradation. Activation of acyl-coenzyme A:cholesterol acyltransferase (ACAT)--an enzyme that increases cholesterol storage as a cholesterol ester.