TARGETING PCSK9 IN DYSLIPIDEMIA

Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors regulate one of the same functional targets that statins do—both work by indirectly increasing the levels of low-density lipoprotein (LDL) receptor surface expression on hepatocytes, promoting LDL cholesterol (LDL-C) clearance. Their similar mechanism of action suggests the possibility that blocking PCSK9 will not only lower LDL-C, but may also reduce cardiovascular risk. However, long-term outcomes studies are not yet available.

Mechanism of Action of PCSK9 Inhibitors

- LDL particles bind to the LDL receptor. Under normal circumstances, the LDL particle–LDL receptor complex is concentrated in clathrin-coated pits along the hepatocyte surface. The LDL particle–LDL receptor complex is taken up into the cell.
- If conjugated with PCSK9, the LDL particle–LDL receptor complex is directed into the endosomal compartment, where the LDL receptor undergoes proteolytic degradation.
- If the LDL particle–LDL receptor complex is not conjugated with PCSK9, then the LDL receptor is recycled to the cell surface so that it can reinitiate another cycle of LDL particle binding and uptake, resulting in a decrease of circulating LDL-C.
- Monoclonal antibodies to PCSK9 bind to PCSK9 and induce steric hindrance so that PCSK9 can no longer bind to the LDL receptor and target the LDL receptor for destruction.

ASO = antisense oligonucleotide; LDL-R = LDL receptor; mAb = monoclonal antibody; siRNA = small interfering RNA; SREBP = sterol regulatory element-binding protein.