Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/heart-matters/pcsk9-inhibition-ldl-cholesterol/54151/

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How PCSK9 Inhibition Lowers LDL Cholesterol

Announcer:
Welcome to *Heart Matters* on ReachMD. On this episode, we'll hear from Dr. Ann Marie Navar, an Associate Professor of Cardiology at the University of Texas Southwestern Medical Center. She'll be explaining how PCSK9 inhibition works to lower LDL levels. Let's hear from her now.

Dr. Navar:
Statins upregulate LDL receptors, so they make your body create more LDL receptors. Those live on the surface of the hepatocytes, pull LDL out of the bloodstream, and take it into the hepatocyte where it's broken down, and the cholesterol is excreted through the gut. The LDL receptor can be recycled back to the surface after it's internalized in the hepatocyte and can keep doing its job. PCSK9 protein, if it's binding to the LDL receptor, when that LDL receptor is pulled into the hepatocyte, the receptor is also degraded. And so that receptor doesn't get recycled back up to the cell surface.

So when we inhibit PCSK9, we allow the LDL receptors to live longer, and we increase the number of LDL receptors on the hepatocyte membrane. There's a few ways that we have to inhibit PCSK9. Inclisiran is a small interfering RNA. It shuts off the synthesis of PCSK9 in the hepatocytes. There's a little bit of extrahepatic PCSK9 synthesis, and so the LDL efficacy of inclisiran is a little bit less than what we see with the monoclonal antibodies, but it's over 50 percent, so very potent.

The monoclonal antibodies are injectable, and the monoclonal antibody binds to PCSK9 and prevents PCSK9 from binding to the LDL receptor, so the LDL receptor has a longer lifespan.

Enlicitide does the exact same thing. But instead of being a monoclonal antibody, it's a macrocyclic peptide. So the challenge that enlicitide was able to overcome was you can't give a monoclonal antibody through the gut, but you can get a macrocyclic peptide absorbed through the gut that then does what the mAbs do. It binds PCSK9 in the blood and prevents it from binding to the receptor.

So it's no surprise that we have almost identical lowering of LDL, non-HDL, ApoB, and Lp(a) with enlicitide as we saw with the monoclonal antibodies. If you're trying to make this simple, I think we can sort of describe this as evolocumab in a pill.

Announcer:
That was Dr. Ann Marie Navar discussing how PCSK9 inhibition works. To access this and other episodes in this series, visit Heart Matters on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!