



## How low can you go?

### The promise of a new class of cholesterol lowering drugs

Laura Dean, MD<sup>1</sup>

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Cardiovascular disease is the leading cause of death in the United States, accounting for 40% of all deaths (1). And cholesterol, transported in the blood in the form of LDL (Low Density Lipoprotein), is at the heart of the fatty plaques that narrow critical arteries in the heart and nervous system, increasing the risk of heart attack and stroke.

Cholesterol, however, is essential to health. It is an important structural component of cell membranes, and it is also a sterol from which steroid hormones such as testosterone, estrogen, and progesterone are made. The liver is responsible for synthesizing most of the cholesterol found in the blood via the HMG Co-A (3-hydroxy-3-methylglutaryl-coenzyme A) reductase pathway, but a diet that is high in saturated fats can increase cholesterol levels further, as can inheriting a genetic tendency towards having higher lipid levels.

LDL normally circulates in the bloodstream for 2 – 3 days before being removed. The lipid-binding protein, Apo-B-100, is the only protein found in LDL and it contains a binding domain that interacts with LDL receptors, mainly found on the surface of the liver, triggering endocytosis. Endosomes form, containing the LDL, which fuse with transport vesicles carrying lysosomal hydrolases from the Golgi apparatus to become lysosomes leading to the hydrolysis of LDL to cholesterol, fatty acids, and amino acids.

Cholesterol can then be recycled and used in the synthesis of new cell membranes, for hormone synthesis, or be transformed back in to esters and stored. But some individuals have dyslipidemia, which refers to an abnormal amount (high or low) of any or all lipids in the blood. The most common form is hyperlipidemia, an abnormally high level of any lipid, associated with an increased risk of heart disease and stroke.

The management of hyperlipidemia often begins with a recommendation to change lifestyle factors and to reduce any other cardiovascular risk factors, such as giving up smoking and treating hypertension. The next step is usually treatment with lipid-lowering drugs. By far the most commonly prescribed class of drugs are HMG-CoA reductase inhibitors, known as statins (2). Statins are effective for people with known heart disease, significantly reducing the risk of another cardiovascular event and death. However, the benefits of statins are less clear for people who do not have known heart disease, and about 1 in 5 people who take statins report side effects such as muscle pain, memory loss, sexual dysfunction, and in women, there is an increased risk of diabetes (3).

Rarely, high cholesterol levels are caused by a single genetic mutation, a condition known as familial hypercholesterolemia (FH). Cholesterol levels are usually extremely high and are less responsive to lifestyle changes or statin therapy. In affected individuals, LDL receptors are either absent or have a reduced function, and as a result, LDL is left for longer to circulate in the bloodstream. The most common causes of FH are a

mutation in the LDL receptor (affects about 1 in 500), and a mutation in the Apo B protein (about 1 in 1000) (4-6).

A less common cause of FH is a mutation in *PCSK9*, (proprotein convertase subtilisin/kexin type 9). This newly identified subtilase (an enzyme that resembles a serine protease) is highly expressed in the liver where it has an important role in cholesterol homeostasis. PCSK9 binds to the LDL receptor and induces its degradation, thereby controlling the number of LDL receptors available to remove LDL from the circulation. It is generally thought that polymorphisms in *PCSK9* contribute towards the natural variation in cholesterol levels seen in populations (7).

The first mutations to be discovered in *PCSK9* conferred a gain of function—a switch of a single amino acid increased the protease activity of PCSK9 so it could reduce the numbers of LDL receptors more quickly (8). This led to FH, specifically, familial hypercholesterolemia type 3 (9, 10).

More recently, several nonsense mutations of *PCSK9* have been reported. Here, the switch of a single amino acid results in the introduction of a premature stop codon in to the DNA sequence, leading to the translation of a shorter, incomplete protein product. The lucky individuals with nonsense mutations in *PCSK9* have unprecedented *low* levels of cholesterol, together with a much lower risk of cardiovascular disease (11, 12).

The discovery of these lipid-lowering variants ignited a race to find a new type of drug that could mimic the effects. And currently a number of potential drugs are progressing through clinical trials (13).

The drugs Alirocumab (REGN727/SAR236553), Evolocumab (AMG145), and PF-04950615 (RN316) have completed phase 1 trials (small, short trials enrolling healthy volunteers, to determine whether the drug is safe and to determine drug doses) and phase 2 trials (larger, longer-term trials designed to see if a drug is both safe and effective). They are currently in various stages of phase 3 trials. These trials are typically very large, involving several thousand patients, and last for several years—they aim to see how well drugs work in real patients.



[New drugs that lower LDL are in clinical trials—are any of the trials near you?](#)

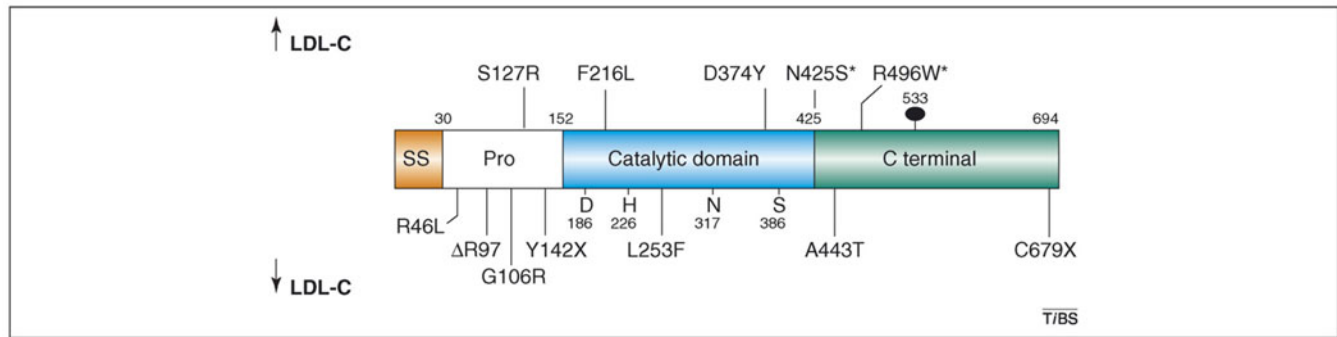
All three drugs are monoclonal antibodies that have been designed to be highly specific for PCSK9 and once bound, they prevent its interaction with the LDL receptor. Another type of drug class is the small interfering RNAs (siRNAs), which work by “gene-silencing.” The drug ALN-PCS is one example that is currently in Phase 1 trials; it works by binding to *PCSK9*-specific messenger RNA and prevents the production of protein (14).

One thing that all these drugs designed to target PCSK9 share in common is that they need to be taken in the form of an injection, typically 2 weeks between doses. And it will take many years to determine how well they reduce the risk of future cardiovascular events.

But starting today, what can be done to reduce these risks is very simple and extremely effective—enjoying a heart healthy diet with a daily dose of exercise.

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**Figure 1. Mutations in PCSK9 that result in elevated or reduced plasma levels of LDL.** Abbreviations: LDL-C, Low Density Lipoprotein Cholesterol, SS, signal sequence; Pro, prodomain.

A schematic of PCSK9 with the location of naturally occurring mutations associated with elevated (top) or reduced (bottom) plasma levels of LDL-C. The mutations included are limited to those associated with significant differences in plasma levels of LDL-C in at least two independent populations or those that co-segregate consistently with hypercholesterolemia in families. Mutations associated with elevated plasma cholesterol levels found only in families who also have mutations in the LDLR are indicated by with an asterisk (\*). The major domains of PCSK9 are delineated using different colors. The location of the aspartic acid (D), histidine (H) and serine (S) comprising the catalytic triad and the site of binding of the single N-linked sugar (Asn533) are shown. The oxyanion hole is located at Asn317.

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