

## So Far, PCSK9 Inhibitors Work for All Heterozygous FH Patients

Markey C. McNutt, MD, PhD; Zahid Ahmad, MD

Two proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies have obtained approval by the United States Food and Drug Administration: evolocumab (Amgen) and alirocumab (Sanofi/Regeneron). Per their package inserts, both are "indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein-cholesterol (LDL-C)." Evolocumab has an additional indication for homozygous FH patients.

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Several issues cloud the use of PCSK9 inhibitors in FH (also referred to as autosomal dominant hypercholesterolemia) patients and may be causing confusion for both clinicians and payers.

First, what does "maximally tolerated statin" refer to? It may be interpreted as no statin in patients with complete statin intolerance or it may imply high-intensity statin therapy (atorvastatin 40 or 80 mg daily and rosuvastatin 20 or 40 mg daily). Second, which patients require additional lowering of LDL-C? Recent guidelines de-emphasize LDL-C goals, although many clinicians likely continue to treat to LDL-C target levels. Third, how should FH be diagnosed? No standard FH diagnostic criteria—or even International Classification of Diseases-9 or -10 codes—exist in the United States. FH can be clinically diagnosed with elevated LDL-C levels (usually >190 mg/dL) plus a suspicious family history. Or more complex scoring systems, like the Dutch Lipid Clinic Network Scoring criteria, stratify patients into unlikely, possible, probable, or definite FH. Fourth, should specialists (eg, cardiologists, endocrinologists, or lipid specialists) be required to diagnose FH or prescribe PCSK9 monoclonal antibodies? Fifth, is there a role for genetics in predicting how heterozygous FH patients respond to PCSK9 monoclonal antibodies?

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In homozygous FH patients with biallelic null mutations, evolocumab fails to reduce LDL-C.<sup>1</sup> Does something similar occur in heterozygous FH patients with *PCSK9* mutations? *PCSK9* mutations affect PCSK9's affinity for the LDL receptor (LDLR). Could they also result in variable affinities for a PCSK9 monoclonal antibody?

Although studies of alirocumab and evolocumab have already been done in heterozygous FH patients, they did not require genetic screening for inclusion.<sup>2,3</sup> In the current issue of *Circulation: Cardiovascular Genetics*, Hopkins et al<sup>4</sup> describe the results of an interventional study of alirocumab (150 mg every 2 weeks) administered to 13 FH patients harboring *PCSK9* gain-of-function mutations. The study represents the first such investigation in humans with gain-of-function *PCSK9* mutations.

Alirocumab achieved 50% to 70% LDL-C reductions—with 12 of 13 patients getting to an LDL-C <70 mg/dL—similar to prior studies, including those of heterozygous FH patients (Figure).<sup>1-3,5,6</sup> The high affinity of monoclonal antibodies to PCSK9 and the high therapeutic concentrations of antibody likely overwhelm any difference in affinity that a *PCSK9* mutation may cause.

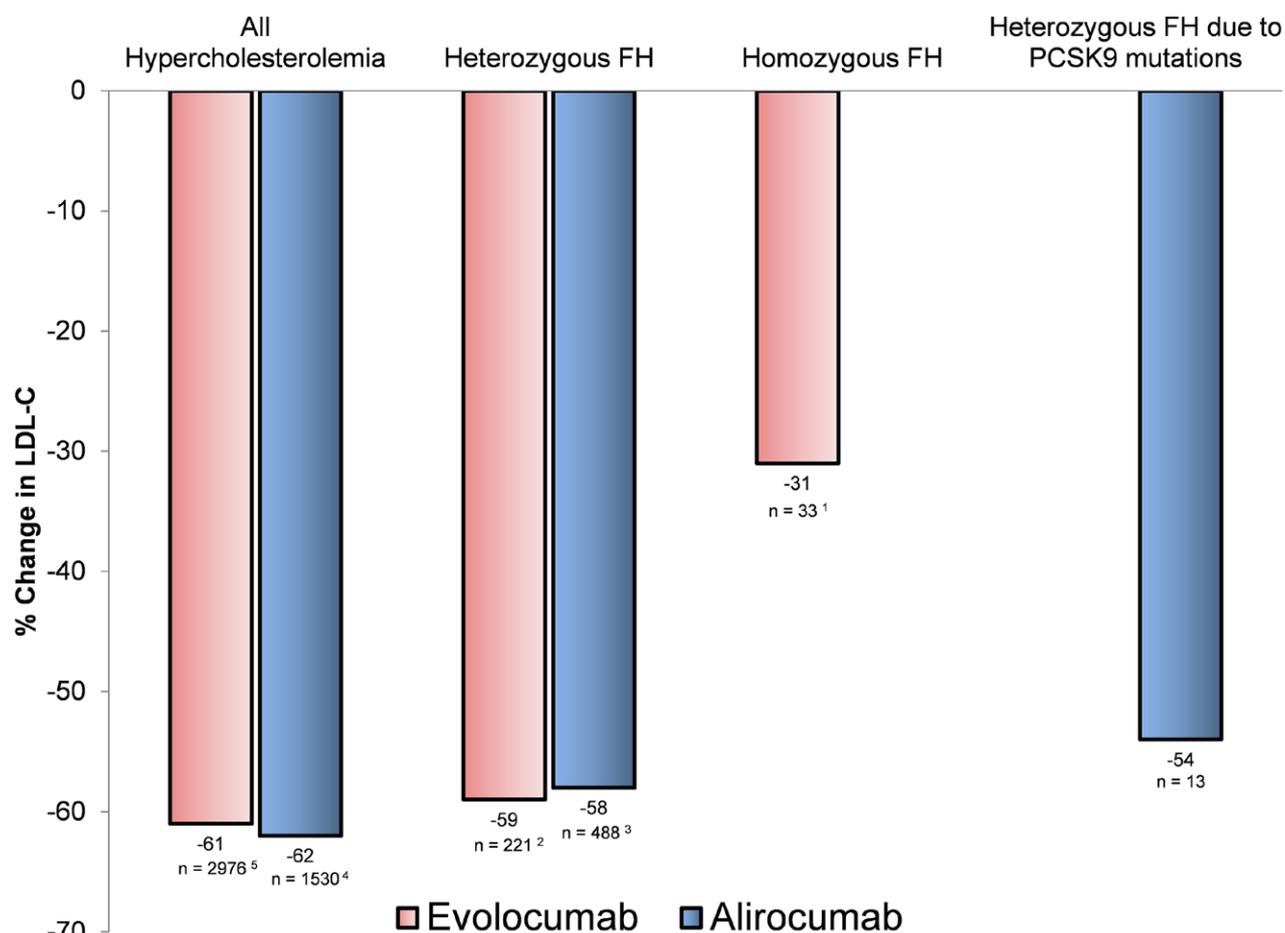
Clearly, as long as interference occurs in the PCSK9:LDLR interaction, a therapeutic response results. In fact, previous *in vitro* studies showed that mutant PCSK9 proteins can be blocked by a peptide that inhibits the PCSK9:LDLR interaction.<sup>7</sup>

Alirocumab seems safe for *PCSK9* FH patients. No serious adverse events directly attributable to the study drug and no reports of myalgia or neurocognitive disorders—both of which have been noted in other studies<sup>5,6</sup>—occurred.

A few questions still remain. Will evolocumab have similar efficacy for PCSK9 FH patient? It has a different epitope and, thus, the potential exists for variable affinity to mutant PCSK9. Also, the study by Hopkins et al lacks comparator groups of FH patients with *LDLR* or apolipoprotein B (*APOB*) mutations, so no direct comparison of the efficacy of PCSK9 monoclonal antibodies has been reported thus far.

More than 10 variants are associated with FH, with the p.S127R and p.D374Y mutations being most studied functionally. The aspartic acid residue at position 374 lies in the binding interface between the LDLR and PCSK9, and its substitution to tyrosine results in increased affinity between PCSK9 and LDLR at the cell surface. The substitution of serine residue at position 127 to arginine does not affect binding affinity at the cell surface; how it results in downregulation of LDLR from the surface remains unclear.

Because of the rarity of gain-of-function *PCSK9* mutations (<2% of genetic hypercholesterolemias<sup>8</sup>), few descriptions exist of their phenotype, especially in comparison with the more common genetic causes of FH (*LDLR* and *APOB*).



**Figure.** Low-density lipoprotein cholesterol (LDL-C) reduction achieved with PCSK9 inhibitors. FH indicates familial hypercholesterolemia.

Previous studies with a single gain-of-function mutation in *PCSK9* (D374Y) have noted higher levels of LDL-C and earlier onset of coronary heart disease than heterozygous mutations in either *LDLR* or *APOB*.<sup>9</sup>

Hopkins et al<sup>4</sup> assembled clinical characteristics of the largest cohort (n=160) to date of patients with FH-causing *PCSK9* mutations. A few issues may limit the interpretation of their data. Controls were not selected from the same population as cases; because coronary heart disease rates vary throughout the world, some bias may have been introduced into their analysis of premature coronary heart disease. Also, some of the mutations had LDL-C levels lower than typical for FH (156 mg/dL in 6 patients with Pro71Leu mutations from the Netherlands, for example) making it unclear whether these are true disease-causing mutations.

Overall, it seems that *PCSK9* gain-of-function mutations cause more severe hypercholesterolemia than *LDLR* mutations. Such information may be useful for ongoing FH genetic screening studies<sup>10</sup> and future bio-banking efforts, where sequencing of *PCSK9* can be reserved for patients with the highest LDL-C who lack any mutations in *LDLR* or *APOB*.

Although several questions remain unanswered about the use of PCSK9 inhibitors, they seem safe and efficacious at lowering LDL-C levels in most patients, regardless of the

underlying genetics. Of course, the results of ongoing cardiovascular outcome studies will ultimately have the largest effect on both prescriber and payer practices.

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Dr Ahmad has received honorarium for educational talks sponsored by Sanofi, is on speakers' bureaus for Amgen and Genzyme, and participated in advisory board meetings sponsored by Genzyme and Regeneron. The other author reports no conflicts.

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