

Familial Hypercholesterolemia and PCSK9 Inhibitors: A Cautious Comment.

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Accepted on February 06, 2017

We have read with much interest the recent expert consensus by Lloyd-Jones et al. [1] on the role of non-statin therapies for LDL^ϕ-cholesterol lowering. They have reinforced and expanded the recommendations for the use of non-statin therapies for patients with high LDL from their earlier published guidelines in 2013. In particular, the role of genetically determined disease is plainly stated and emphasized in the subgroup of patients with high risk for cardiovascular disease. Those patients have primary severe elevations of LDL-C ≥ 190 mg/dL, and are more likely to have genetic heterozygous (HeFH) or homozygous (HoFH) familial hypercholesterolemia. In the opinion of the Expert Consensus Writing Committee, in such patients who fail statin mono-therapy (<50% reduction in LDL-C), it is reasonable to take advantage of the greater LDL-C lowering effect of PCSK9 inhibitors as a first step treatment. Inadequate response to such therapies supports the use of mipomersan, lomitapide or LDL apheresis. This allows the use of the PCSK9 inhibitor (evolocumab) before committing to LDL apheresis in phenotypic HoFH patients unless a “receptor negative” mutation has been documented.

The notion of “receptor negative” practically means a non-functioning LDL receptor - patients with less than 2% of LDL uptake – as classified by Raal et al. [2]. Homozygous *receptor negative* familial hypercholesterolemia patients do not respond to PCSK9 treatment – the LDL cholesterol in those patients even show slight increase compared to baseline levels. Homozygous non-negative (with 2-25% LDL uptake) mutations are amenable to evolucumab therapy [2]. Heterozygous or compound heterozygous familial hypercholesterolemia patients have a significant mean reduction in LDL levels [3,4]. The mean reduction in LDL cholesterol reached 40.8% in those with one or two defective alleles, and no response in double *receptor negative* alleles. The opinion of the expert consensus written committee on *receptor negative* homozygous familial hypercholesterolemia is derived from this finding and is based on one Lebanese patient with the p.C681X “Lebanese Allele” homozygous mutation.

In Lebanon, most of the familial hypercholesterolemia patients have a founder *LDLR* mutation with high demographic burden for the disease. We have previously identified in one cohort 18 different families with the homozygous mutations c.2043 C>A (p.C681X) in *LDLR* accounting for almost 50% of all families with clinically identified FH (Table 1) [5].

These patients presented with an average LDL-C level of 493 mg/dl (ideal below 100 mg/dl) and typical signs and symptoms of familial hypercholesterolemia. They were managed with apheresis after their failure to respond adequately to statin therapy. Our finding on the genetic basis of the disease in Lebanon puts a red flag on the consensus’s opinion to provide non-statin therapy before going into apheresis. We expect failure of therapy to occur in 45% of the clinically identified

FH patients in Lebanon, who will harbor an underlying homozygous “*negative receptor*” mutation (Figure 1).

Table 1. Clinical indicators by type of mutation. (TC: total cholesterol, LDL: low density lipoprotein). Adapted from Fahed et al.

	Any LDLR mutation			No LDLR mutation
	Heterozygous any Allele	Homozygous Leb Allele	Homozygous other Allele/s	
Number of patients	29	18	6	11
Average Years	26.3	24.1	23.3	26.1
Average Lipid Levels (mg/dl)	TC	567	600	500
	LDL	467	493	380

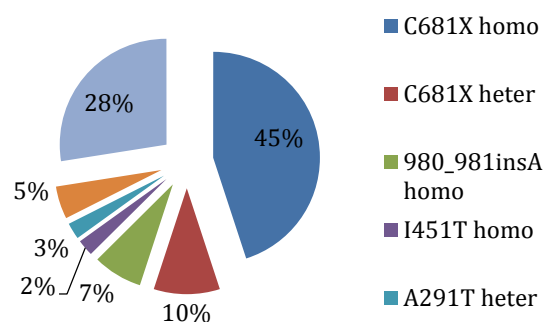


Figure 1. Mutations in the *LDLR* gene in forty Lebanese patients with clinically diagnosed Familial hypercholesterolemia. Adapted from Fahed et al.

This effect might not be seen in other countries as population studies in South Africa, Netherlands and Italy failed to show such a drastic disease-linked mutation [6-8]. We recommend population based understanding of the disease prior to drug use. In populations where there is high risk of therapy failure, and where a recurrent founder mutation is of the *negative receptor* type, genetic screening on individual basis before therapy trial should thus be indicated.

ϕ Low Density Lipoprotein

Ψ Proprotein Convertase Subtilisin/Kexin type 9

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