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EDITORIAL COMMENT

Paradoxical Findings in Homozygous Familial Hypercholesterolemia in Japan

Longer Life But Still Not Totally Better!*

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In this issue of *JACC: Asia,* Takeji et al[1] give us a portrait of epidemiology and contemporary history of homozygous familial hypercholesterolemia (HoFH) in Japan. HoFH is a rare disease[2] affecting approximately 1/300,000 people in the absence of founder effects and is characterized by severely elevated concentrations of low-density lipoprotein-cholesterol (LDL-C) and early onset of atherosclerotic cardiovascular and aortic/supra-aortic valve diseases.[3] Japan has tradition on this disease and has contributed singularly for its management with development of statins[4] and lipoprotein apheresis[5] for people with HoFH.

Advances in genomic techniques for diagnosis, as well as onset of novel and efficacious therapies for LDL-C reduction, have increased interest in HoFH.[2,6] Contemporary registries from different parts of the world have been recently published[7-9] and allow us to have a better picture of the paradoxical state of the disease (**Table 1**). The paradox is that people with HoFH live longer than in the past, but disease is still ominous when cardiovascular complications are concerned, and it is particularly cruel for young people including pediatric patients. Indeed, in the study by Takeji et al[1] the mean age of the population was 54 years (median age of diagnosis: 27 years); this contrasts with data from the prestatin age when death in people with HoFH occurred on average at the second decade of life.[10] However, despite longer survival in comparison with older studies, 70% of participants had suffered coronary events, and 1 in 4 had valve disease (70% aortic valve disease). Most events were coronary revascularizations. Additionally, carotid atherosclerosis was found in 55%. One study caveat is that there is no information about how many individuals had previous myocardial infarctions or strokes or have died consequently to HoFH. This and other registries certainly present a survival bias considering that most enrolled patients were still alive when evaluated.[7-9]

In the study by Takeji et al[1] those with coronary artery disease were more likely to be older, of male sex, and had more cutaneous stigmata and polyvascular disease; however, there were no differences in LDL-C. No information was available regarding smokers/former smokers or lipoprotein(a) values that could have influenced prognosis.

Certainly, survival was facilitated by the robust reduction in LDL-C obtained during follow-up from mean 10.1 mmol/L (381 mg/dL) to 3.9 mmol/L (151 mg/dL). In addition to classic statin and ezetimibe therapies, novel therapies like PCSK9 inhibitors were used in 50% and lipoprotein apheresis in 21% of participants. Of importance, despite robust LDL-C lowering, its values were still elevated regarding current recommendations.[2,6] This shows that there is still room for improvement by use of low-density lipoprotein receptor (LDLR)-independent therapies like lomitapide and evinacumab.[2,11]

Genetic testing was available in roughly 1 in 3 patients with 52% presenting variants in the LDLR gene (*LDLR*) alone, whereas others presented combinations of digenic variants in *LDLR*, *PCSK9*, or *LDLRAP-1*. Of interest, no variants were encountered in *APOB*, apparently a rarer one in individuals

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TABLE 1 Clinical and Laboratory Characteristics of Patients From Contemporary Homozygous FH Registries

	Japan[1] (n = 201)	Iberoamerican Countries[7] (n = 134)	United States[9] (n = 67)	HICC[8] (n = 751)
Children (%)	NA	47	23.9	NA
Age at diagnosis, y	Overall 27[a] Children[b] 0[a] Adults 40.5	NA	Children 2.0 Adults 12.6	12[a]
Age at enrollment, y	54 ± 15	Children 8.8 ± 4.0 Adults 39.3 ± 15.8	Children 9.6[a] Adults 41.9[a]	NA
Sex (%)				
Males	43	38	49.3	48
Females	57	62	50.7	52
Molecular diagnosis (%)	32.3	96	65.7	75
ASCVD (%)[c]	NA	Children 52 Adults 67	NA	28.8
Age of ASCVD, y[c]	NA	NA	Children[a] 8.9 Adults[a] 30.5	31[a]
Coronary heart disease (%)	70 MI NA CABG 28 PCI 57	Children 31 Adults 88.7	Children 43.7 Adults 78.4	Angina 12.5 MI 11.9 CABG 15.9 PCI 12.1
Aortic/supra-aortic valve disease (%)	24	Children 35.4 Adults 8	Children 18.8 Adults 25.5	29
Cardiovascular death (%)	NA	NA	NA	3.7
Baseline LDL-C mmol/L	10.15 ± 2.32	14.75[a]	Children[a] 20.05 Adults[a] 13.77	14.7[a]
On treatment LDL-C mmol/L	3.9 ± 2.6	NA	Children[a] 8.19 Adults[a] 6.07	7.7[a]
Statins (%)	96	70	Children 92.3 Adults 83.7	91.9
Ezetimibe (%)	50	NA	Children 61.5 Adults 65.3	64
PCSK9 inhibitors (%)	50	5	Children 0 Adults 14.3	22.1
Lomitapide (%)	NA	7.4	Children 7.7 Adults 24.5	8.4
Lipoprotein apheresis (%)	21	8.2	Children 30.8 Adults 38.8	39.1
Liver transplantation (%)	NA	NA	Children 18.8 Adults 3.9	0.8

[a]Median. [b]In Japan children categorized by age <15 y at time of diagnosis but not at study enrollment. [c]Definition of ASCVD varied by registry.

ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft surgery; HICC = Homozygous FH International Clinical Collaboration; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention.

from Asian countries.[12] No information was also available about severity of *LDLR* defects that could influence LDL-C concentrations and consequent atherosclerotic cardiovascular disease risk.

When one looks at the available evidence, it is clear that despite great improvements HoFH is still a big challenge and early diagnosis and intensive LDL-C-lowering therapies are absolutely necessary to change its natural history. Data from Japan certainly will help in better understanding how to reduce the paradox and improve not only the amount but also the quality of lives of people living with HoFH.

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