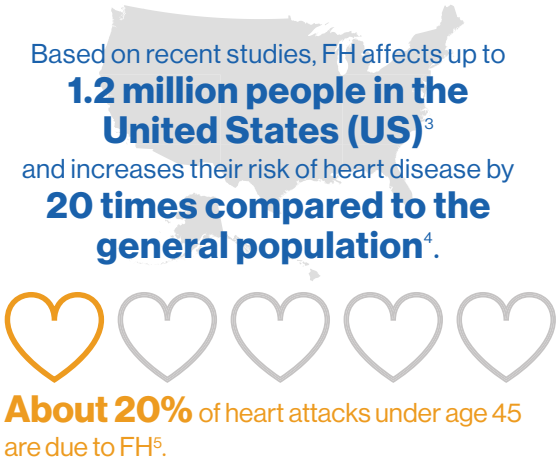
Lowering LDL-C ("bad" cholesterol) for the treatment of familial hypercholesterolemia

Patients with familial hypercholesterolemia (FH)—a genetic disorder—are exposed to elevated low-density lipoprotein cholesterol (LDL-C, also known as "bad" cholesterol) levels from a young age[1,2]. They therefore experience accelerated development of atherosclerotic cardiovascular disease (ASCVD), leaving them at particular risk of cardiovascular events—such as heart attacks or strokes—while being potentially unable to sufficiently lower their LDL-C levels with statins[2].



Based on recent studies, FH affects up to **1.2 million people in the United States (US)**[3] and increases their risk of heart disease by **20 times compared to the general population**[4].

About 20% of heart attacks under age 45 are due to FH[5].

What is FH?

FH results from a gene defect. When only one of the inherited copies of the gene is defective and the other is functional, the patient suffers from heterozygous FH (HeFH); when the patient has two defective copies of the gene, it is called homozygous FH (HoFH)[6]. With sustained exposure to elevated LDL-C levels from childhood, HoFH patients are at high risk of ASCVD events before the age of 20[6].

While HoFH is a rare disease (affecting less than 1 in 250,000 people), **HeFH has a significant prevalence** (1 in 250 people) with the **majority remaining undiagnosed,** and therefore, **undertreated**[7-10].

HeFH is estimated to affect **650,000 people** in the US[11].

Why does FH increase the risk of ASCVD?

The life-threatening effects of FH are related to the lifelong elevation of LDL-C levels, which is understood to be causal to ASCVD and leads to cardiovascular events such as heart attacks and strokes[9,12].

People with FH have over a **10-fold increased risk** of developing ASCVD[14].

Several mutations were identified as causes of FH. Most of the time, these mutations affect either LDL receptors, which are involved in clearing LDL particles from the bloodstream, or the proteins that interfere with this process[13]. As a consequence, the reduction of the number of LDL receptors available leads to a gradual increase of LDL-C levels in the blood[13,14]. Exposure to high LDL-C levels over the course of one's life could result in the development of atherosclerosis (or atherosclerotic plaques), the fatty buildup in the inner lining of the arteries. In the early stages, this is a silent process with no specific symptoms until the atherosclerotic plaque unexpectedly ruptures, causing a heart attack or stroke[12].

NOVARTIS

Why is the management of LDL-C levels crucial?

Dietary and lifestyle modifications are first line for lowering LDL-C. However, in most cases, patients will require pharmacologic therapy. Early treatment is important to avoid long-term exposure to sustained LDL-C levels[12,15].

Why are statins not enough for FH patients?

Statins are currently prescribed to over 200 million patients worldwide as LDL-C–lowering therapy[16]. Research suggests that not enough FH patients reach their recommended LDL-C target[17].

Multiple factors may impact the success of currently available treatments and clinical outcomes:

Despite high prevalence, HeFH is underdiagnosed, and therefore, undertreated[14].

Even when people take their prescribed treatment, not all reach their LDL-C goals[2]. When statins are not enough to lower LDL-C to acceptable levels and limit long-term exposure, FH patients remain at high risk of a premature ASCVD event or death[2].

This demonstrates a significant unmet need for an effective and sustained LDL-C– reducing treatment[18].

Bending the curve of life requires addressing some of society's greatest public health concerns. Committed to reimagining medicine, Novartis has a growing pipeline of potentially first-in-class molecules addressing cardiovascular, metabolic and renal diseases.

REFERENCES

1. Ruel I, et al. Imputation of baseline LDL cholesterol concentration in patients with familial hypercholesterolemia on statins or ezetimibe. *Clin Chem.* 2018;64(2):355-362. **2**. Raper A, et al. Treatment of familial hypercholesterolemia: is there a need beyond statin therapy? *Curr Atheroscler Rep.* 2012;14(1):11-16. **3.** Knowles JW, et al. Reducing the burden of disease and death from familial hypercholesterolemia: a call to action. *Am Heart J.* 2014;168(6):807-811. **4**. FH Foundation. Surprising familial hypercholesterolemia statistics. 2015. Accessed November 17, 2020. https://thefhfoundation.org/surprising-familial-hypercholesterolemia-statistics. **5**. Hopkins PN, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011;5(3 Suppl):S9-S17. **6.** Pejic RN. Familial hypercholesterolemia. *Ochsner J.* 2014;14:669-672. **7.** Bouhairie VE, et al. Familial hypercholesterolemia. *Cardiol Clin.* 2015;33(2):169-179. **8.** Kolominsky J, et al. Familial hypercholesterolemia: cardiovascular risk stratification and clinical management. Published June 1, 2020. Accessed October 2020. https://www.acc.org/latest-in-cardiology/articles/2020/06/01/13/54/familial-hypercholesterolemia. **9.** Youngblom E, et al. Familial hypercholesterolemia. In: Adam MP, et al, eds. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2020. Published January 2, 2014. Updated December 8, 2016. **10.** Repas TB, et al. Preventing early cardiovascular death in patients with familial hypercholesterolemia. *J Am Osteopath Assoc.* 2014;114(2):99-108. **11.** Vishwanath R, et al. Familial hypercholesterolemia and estimation of US patients eligible for low-density lipoprotein apheresis after maximally tolerated lipid-lowering therapy. *J Clin Lipidol.* 2014;8(1):18-28. **12.** Grundy SM, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;139(25):e1082-e1143. **13.** Goldstein JL, et al. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell.* 2015;161(1):161-172. **14.** Nordestgaard BG, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J.* 2013;34(45):3478-3490. **15**. Mach F, et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;1(41):111-188. **16.** Desai CS, et al. Non-cardiovascular effects associated with statins. *BMJ.* 2014;349:g3743. **17**. Pijlman AH, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. *Atherosclerosis.* 2010;209(1):189-194. **18.** Lansberg P, et al. Nonadherence to statins: Individualized intervention strategies outside the pill box. *Vasc Health Risk Manag.* 2018;14:911102.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

10/21 156789