Familial Hypercholesterolemia

Kavita Sharma MD, FACC
Diplomate, American Board of Clinical Lipidology
Director of Prevention, Cardiac Rehabilitation and the Cholesterol Management Clinics
Assistant Professor of Internal Medicine
Division of Cardiovascular Medicine

Familial hypercholesterolemia

- Autosomal dominant genetic disease present in all racial and ethnic groups
- A cause of premature ASCVD; in the prestatin era, median age of onset for first MI in heterozygous FH was ~50 yrs in men, 60 yrs in women
- Highest prevalence of genetic defects that cause premature mortality (~1/200 to 1/500)
- 3 major genetic defects
  - LDL Receptor
  - Defects in apolipoprotein B binding to LDL-R
  - Gain of function in PCSK9, enhancing LDL-R degredation
- FH leads to elevated LDL levels in untreated adults > 190 mg/dL and untreated children > 160 mg/dL
- FH is under-treated and under-recognized. Of the theoretical estimated prevalence of 1/500 for heterozygous FH, <1% are diagnosed in most countries.[1]

1. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease
Børge G. Nordestgaard et al.
http://dx.doi.org/10.1093/eurheartj/eht273 eht273 First published online: 16 August 2013

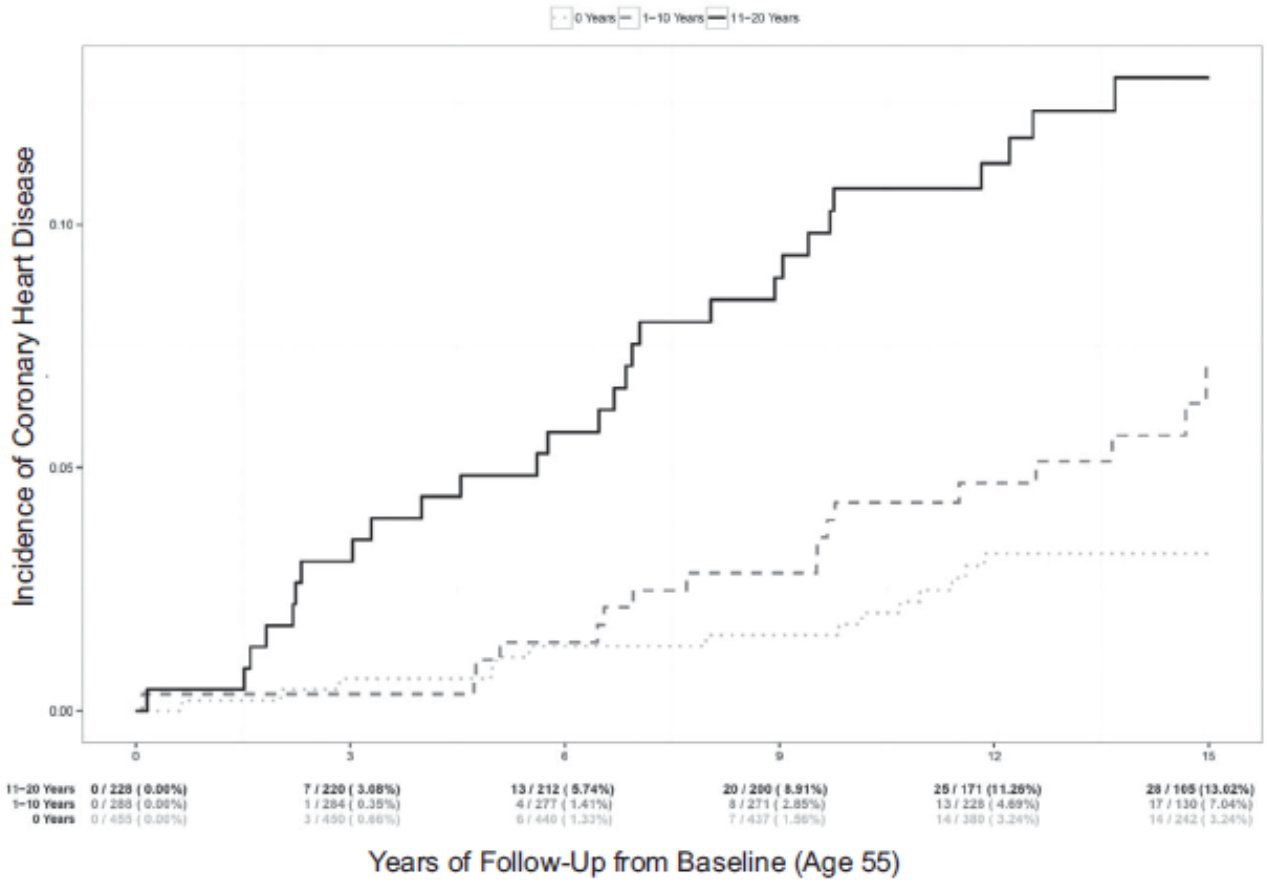


Figure 2. Time to diagnosis of CHD by number of years of hyperlipidemia at baseline among adults not recommended for statin therapy at baseline.* This figure shows Kaplan–Meier curves of future risk of CHD stratified by years of hyperlipidemia experienced by 55 years of age (age range, 53–57) among adults not recommended for statin therapy at 55 years of age. Log-rank *P* value <0.0001. *Excludes those recommended for statins: ASCVD risk ≥7.5%, LDL-C ≥190, diabetes mellitus and LDL-C ≥100. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; and LDL-C, low-density lipoprotein cholesterol.

Hyperlipidemia in Early Adulthood Increases Long-Term Risk of Coronary Heart Disease
Ann Marie Navar-Boggan, MD, PhD; Eric D. Peterson, MD, MPH; Ralph B. D'Agostino, Sr, PhD; Benjamin Neely, MS; Allan D. Sniderman, MD*; Michael J. Pencina, PhD*
(*Circulation*.
2015;131:451-458. DOI: 10.1161/CIRCULATIONAHA.114.012477.)

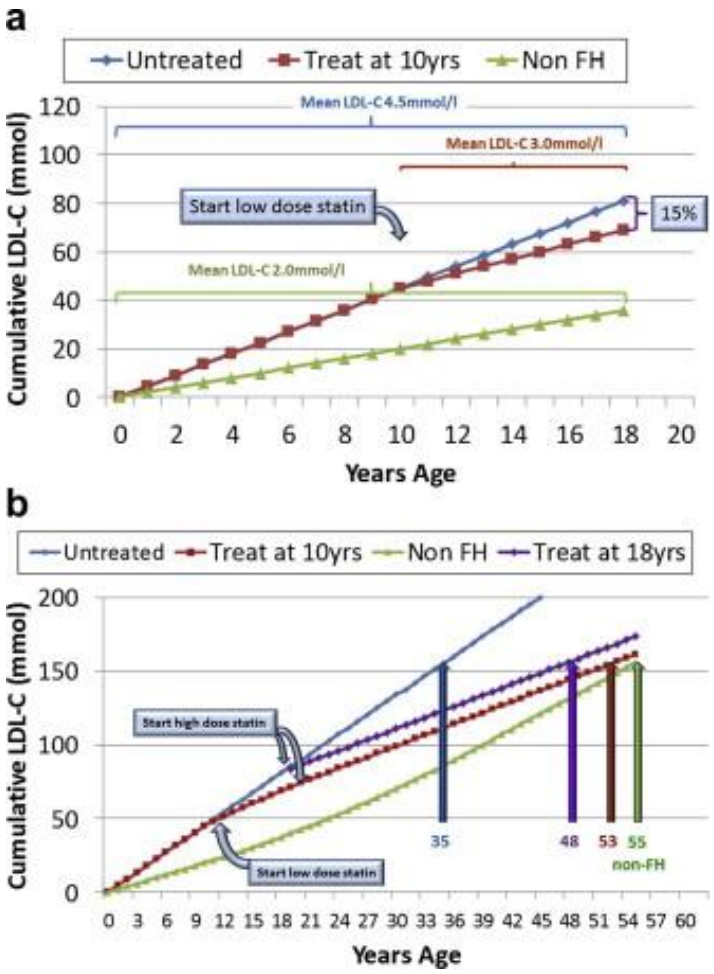


Fig. 1. LDL cholesterol (LDL-C) burden in non-FH and FH subjects depending on different age of starting statin therapy (data derived from Starr et al. [38]). For the calculation of the LDL-C burden, the following assumed mean LDL-C values were used. Non-FH sub...

Alpo Vuorio, Kieran F. Docherty, Steve E. Humphries, Jaana Kuoppala, Petri T. Kovanen

Statin treatment of children with familial hypercholesterolemia – Trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus?

Atherosclerosis, Volume 226, Issue 2, 2013, 315–320

Diagnosis

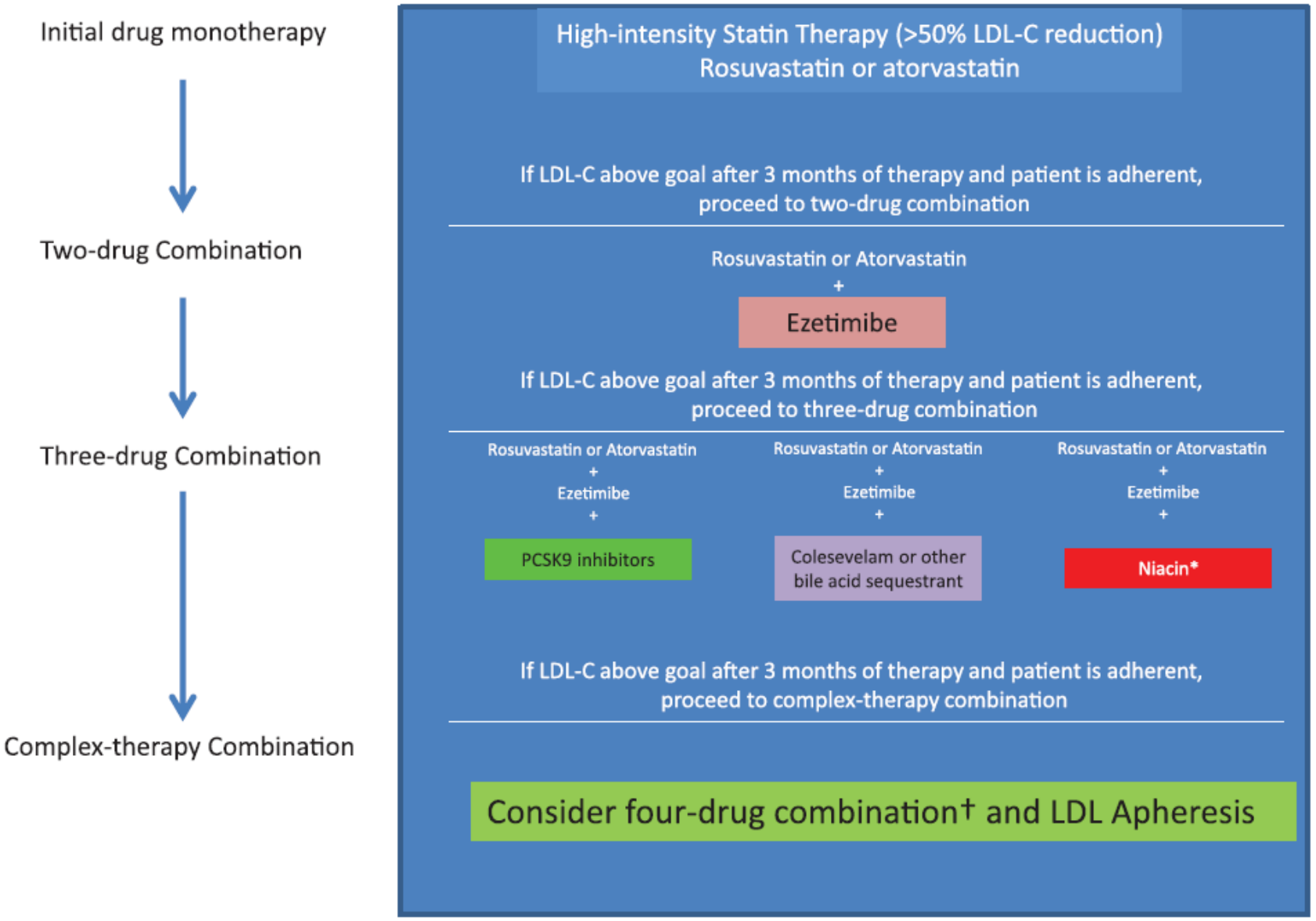
- Several methods of clinical diagnosis; no international consensus
- Dutch Lipid Clinic, Simon Broome, MEDPED
- AHA Scientific Statement proposes an ICD-10 diagnostic code for FH

Table 4. FH Diagnostic Categories

ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect
		Diagnosed as heterozygous FH if gene-raising defect positive and LDL-C <160 mg/dL (4 mmol/L)
		Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes
		Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type
	If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 y of age, homozygous FH highly likely	Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

apoB indicates apolipoprotein B; FH, familial hypercholesterolemia; *ICD-10*, *International Classification of Diseases, 10th Revision*; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtulisin/kexin type 9.

Gidding et al. The Agenda for Familial Hypercholesterolemia:
A Scientific Statement from the American Heart Association. Circulation. 2015;132:00-00.



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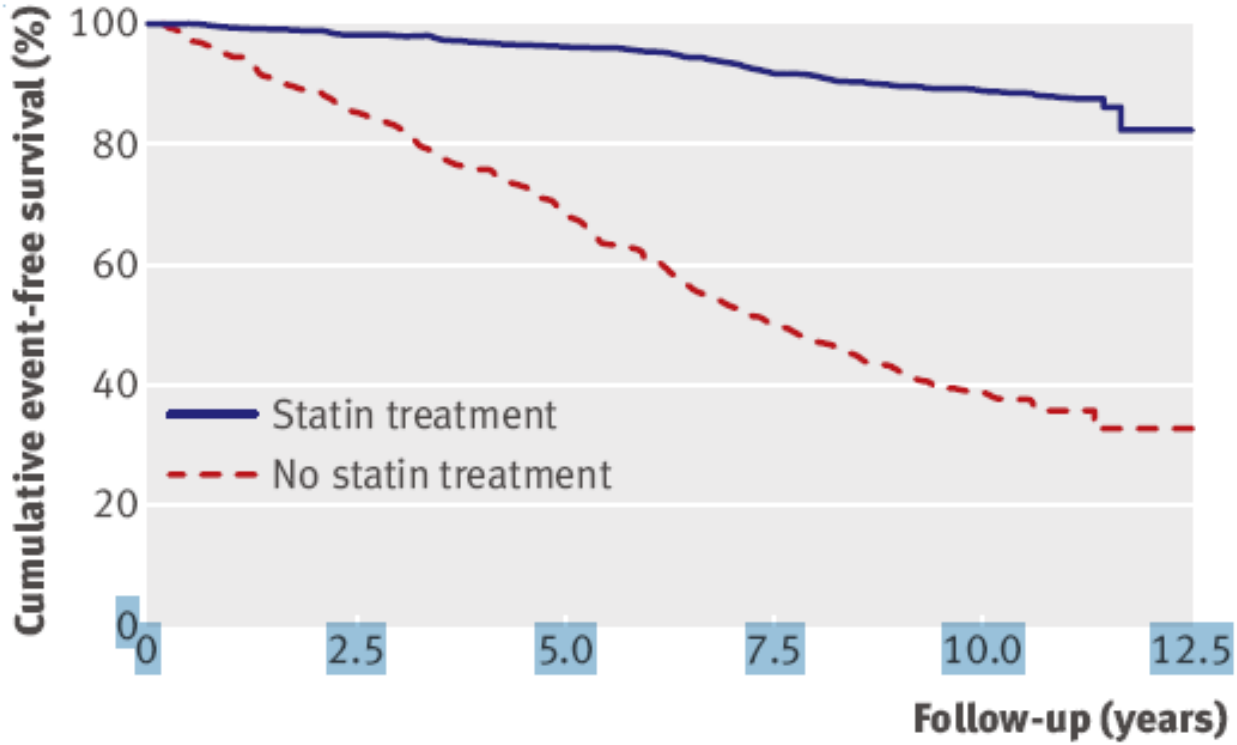

Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment ($P<0.001$ for difference)

Efficacy of statins in familial hypercholesterolaemia: a long termcohort study. Versmissen et al BMJ 2008;337:a2423 doi:10.1136/bmj.a2423

Screening

- **Pediatric Screening** [1,2]
- Universal screening at age 9 to 11 years with a fasting lipid profile or nonfasting non-HDL cholesterol measurement is recommended to identify all children with FH. This age identifies individuals at the potential onset of advanced atherosclerosis, and provides the best discrimination between those with and without inherited dyslipidemias by avoiding confounding due to changes in lipid levels associated with puberty.
- If a nonfasting non-HDL cholesterol concentration of ≥145 mg/dL is detected, then a fasting lipid profile should be performed.
- Screening should occur earlier (≥2 years of age) in the presence of a positive family history for hypercholesterolemia or premature CHD or the presence of other major CHD risk factors.

1. Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Anne C. Goldberg, MD, FNLA, ChairJournal of Clinical Lipidology, Vol 5, No 3S, June 2011
2. NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

PCSK9 inhibitors

- Two FDA approved PCSK9 inhbitors
- Praluent and Repatha
- Praluent is a PCSK9 inhibitor antibody indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C)
- The effect of Praluent on cardiovascular morbidity and mortality has not been determined.

- Repatha is a PCSK9 inhibitor antibody indicated as an adjunct to diet and:
  - Maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).
  - Other LDL-lowering therapies (e.g. statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
  - The effect of REPATHA on cardiovascular morbidity and mortality has not been determined.
  - COST ~$14,000

Lipoprotein Apheresis

- Extracorporeal treatment that removes apoB-containing lipoproteins
- Goal to reduce LDL by 65%

CCMD

LDL-Apheresis Recommendations for Treatment of FH

NLA criteria*

Consider when subjects do not have an adequate response to drug therapy after *6 months*

- Functional HoFH with LDL ≥300 (non-HDL ≥330)
- Functional HeFH with LDL ≥300 (non-HDL ≥330) and 0-1 risk factors
- Functional HeFH with LDL ≥200 (non-HDL ≥230) and 2 risk factors or Lp(a) ≥50
- Functional HeFH with LDL ≥160 (non-HDL ≥190) and very high risk (established CVD, CHD, diabetes)

FDA-approved indications (US)

Initiate when individuals have failed diet and max drug therapy from ≥2 classes of antihyperlipidemic drugs for ≥6 months

- HoFH with LDL ≥500
- HeFH with LDL ≥300
- Functional HeFH with LDL ≥200 and CAD

*NLA recommendations broader than FDA-approved indications; clinicians must be aware of this distinction for reimbursement

FH=familial hypercholesterolemia; HeFH=heterozygous FH; HoFH=homozygous FH; Lp(a)=lipoprotein(a)

Jacobson TA, et al. *J Clin Lipidol*. 2014;8:473-488.