



Official reprint from UpToDate®

www.uptodate.com

©2011 UpToDate®

Primary disorders of LDL-cholesterol metabolism

Authors

Robert S Rosenson, MD
Sarah D de Ferranti, MD, MPH

Section Editor

Mason W Freeman, MD

Deputy Editor

Gordon M Saperia, MD, FACC

Disclosures

Last literature review version 19.3: septiembre 2011 | **This topic last updated:** junio 15, 2011

INTRODUCTION — There are a variety of different lipid disorders that can occur as either a primary event or secondary to some underlying disease [1]. (See "[Secondary causes of dyslipidemia](#)".) The primary dyslipidemias are associated with overproduction and/or impaired removal of lipoproteins ([table 1](#)). The latter defect can be induced by an abnormality in either the lipoprotein itself or in the lipoprotein receptor.

There are a number of different disorders of low density lipoprotein (LDL) metabolism, which vary according to the underlying defect and the clinical manifestations. Treatment will be reviewed for each of the disorders, while general treatment guidelines for hypercholesterolemia and possible indications for the therapy of other dyslipidemias, such as low serum HDL-cholesterol (HDL-C), hypertriglyceridemia, and elevated serum Lp(a), are discussed elsewhere. (See "[Treatment of lipids \(including hypercholesterolemia\) in primary prevention](#)" and "[Treatment of lipids \(including hypercholesterolemia\) in secondary prevention](#)" and "[ATP III guidelines for treatment of high blood cholesterol](#)".)

PREVALENCE OF LIPID ABNORMALITIES — One definition of dyslipidemia is total cholesterol, low density lipoprotein cholesterol (LDL-C), triglyceride, or Lp(a) levels above the ninetieth percentile or HDL-C or apo A-1 levels below the tenth percentile for the general population ([table 2](#)). The prevalence of dyslipidemia varies with the population being studied. The incidence is highest in patients with premature coronary heart disease (CHD), which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared to approximately 40 to 48 percent in age-matched controls without CHD ([figure 1](#)) [2,3].

The disturbance in lipoprotein metabolism is often familial. In one study, for example, 54 percent of all patients with premature CHD (and 70 percent of those with a lipid abnormality) had a familial disorder [2]. The most common familial disturbances were Lp(a) excess (alone or with other dyslipidemia), hypertriglyceridemia with hypoalphalipoproteinemia, and combined hyperlipidemia.

As a result of the frequency of familial disease and the associated risk, screening lipid analysis is recommended for first-degree relatives of patients with MI (particularly if premature). Screening begins with a standard lipid profile; if this is normal, further testing should be performed with consideration paid to the measurement of Lp(a) and

apolipoproteins B and A-I; approximately 25 percent of patients with premature CHD and a normal standard profile will have an abnormality in one of these factors. (See "[Screening guidelines for dyslipidemia](#)".)

AUTOSOMAL DOMINANT HYPERCHOLESTEROLEMIA — Autosomal dominant hypercholesterolemia (ADH) is a clinical disorder characterized by elevated plasma LDL-cholesterol (due to reduced LDL particle clearance) and premature atherosclerosis. At least three unrelated genetic mutations with an autosomal dominant mode of inheritance lead to ADH. The clinical manifestations of these mutations are indistinguishable and genetic testing is required to differentiate one from the other.

Familial hypercholesterolemia is the most common of these and is caused by defects in the LDL receptor (LDLR) gene. Familial defective apolipoprotein B-100, caused by mutations in the apolipoprotein B gene, is less common and leads to impaired binding of LDL particles to the LDL receptor. Mutations of the proprotein convertase subtilisin kexin 9 (PCSK9) gene are rare; one or more mutations lead to reduced levels of the LDL receptor.

FAMILIAL HYPERCHOLESTEROLEMIA — Familial hypercholesterolemia (FH) is a monogenic, autosomal disorder caused by defects in the gene that encodes for the apo B/E (LDL) receptor [4-7]. The associated impairment in function of these receptors results in reduced clearance of LDL particles from the circulation and an elevation in plasma LDL-C. There is also increased uptake of modified LDL (oxidized or other modifications) by the macrophage scavenger receptors, resulting in macrophage lipid accumulation and foam cell formation [8]. (See "[Lipoprotein classification; metabolism; and role in atherosclerosis](#)", section on 'Lipoproteins and atherosclerosis'.)

Over 1000 different mutations in the LDL receptor (LDLR) gene have been identified [9]. The mutations at the LDLR locus have been categorized into four classes of alleles based on the phenotypic behavior of the mutant protein [4]:

- Class I - Null, in which synthesis is defective
- Class II - Transport defective, in which intracellular transport from the endoplasmic reticulum to Golgi is impaired
- Class III - Binding defective, in which proteins are synthesized and transported to the cell surface normally, but binding of LDL is defective
- Class IV - Internalization defective, in which proteins reach the cell surface and bind LDL normally but the receptors do not cluster in the coated pits, thereby minimizing LDL internalization

Patients with FH are classified into one of two major groups based on the amount of LDLR activity: patients with less than 2 percent (receptor-negative) and patients with 2 to 25 percent of normal LDLR activity (receptor-defective) [10]. In general, plasma levels of LDL-C are inversely related to the level of residual LDLR activity.

FH is inherited with a gene dosing effect, in which homozygotes are more adversely affected than heterozygotes. In one report, for example, the fractional clearance of LDL-C was reduced by 27 percent in heterozygotes and 53 percent in homozygotes [6]. Some of the excess LDL-C is deposited in the arteries as atheroma and in the tendons and skin as xanthomata ([picture 1A-D](#)) and xanthelasma ([picture 2](#)). The prevalence of xanthomata increases with age, eventually occurring in 75 percent of FH heterozygotes.

Coronary artery calcification, a marker of coronary artery disease, can be identified as early as 11 to 23 years of age in heterozygotes [11]. (See "[Diagnostic and prognostic implications of coronary artery calcification detected by computed tomography](#)".)

Homozygotes with familial hypercholesterolemia also have a high incidence of aortic stenosis (about 50 percent) due to atherosclerotic involvement of the aortic root; the incidence is lower in heterozygotes. (See "[Supravalvar aortic stenosis](#)", section on '[Etiology](#)'.)

A clinical presentation similar to FH can be seen in a rare autosomal recessive form of FH in which the defect appears to involve an adaptor protein for the LDL receptor [12] and with mutations in apo B, the ligand on LDL for the receptor (see '[Familial defective apolipoprotein B-100](#)' below).

Determinants of CHD risk — Cardiovascular risk in patients with familial hypercholesterolemia (FH) is determined both by the LDL-cholesterol (LDL-C) concentration and by other traditional cardiovascular risk factors.

The serum LDL-C concentration is determined largely by the activity of the LDL receptor, which is genetically determined. Thus, for patients with homozygous FH, risk is related almost entirely to the severity of the genetic defect. These individuals typically have extremely low levels of LDLR activity, as discussed in the preceding section.

In patients with heterozygous FH, risk is related to both the severity of the LDLR activity defect and, to a lesser degree, other risk factors [10]. The following are examples of the variable impact of LDLR defects:

- In a study of 264 children with heterozygous FH as well as their parents and unaffected siblings, carriers of LDLR-negative mutations had, compared to carriers of LDLR-defective mutations, a significantly higher LDL-C (7.6 versus 6.7 mmol/L [295 versus 258 mg/dL]) and a significantly greater degree of carotid intima-media thickening [9]. In addition, there was a much higher prevalence of premature coronary artery disease in the first-degree relatives of LDLR-negative compared to LDL-defective patients (36 versus 7 percent) [9]. (See '[Familial hypercholesterolemia](#)' above.)
- Different mutations of the LDLR gene appear to confer varying effects on both LDL-C concentrations and on coronary heart disease (CHD) risk [13]. In a study of 399 patients with FH who were free of CHD at study entry, LDLR-negative mutations (null alleles) (ie, complete lack of the gene's normal function) were associated with more severely elevated LDL-C and higher CHD risk than the N543H/2393del9 mutation [14].

Prognosis — Prior to the widespread use of statin therapy for patients with heterozygous FH, the risk of premature CHD was very high [15]. In a 1974 study of over 1000 first and second degree relatives of 116 index patients, the risk of fatal or nonfatal CHD by age 60 was 52 percent for male and 32 percent for female relatives [16]. In relatives without FH, the comparable rates were 13 and 9 percent respectively.

Diagnosis — One useful set of diagnostic criteria for heterozygous FH categorizes patients into definite and probable FH ([table 3](#) and [table 4](#)) [17]. Definite criteria require hypercholesterolemia, usually normal serum triglycerides, and either genetic or cellular confirmation of an LDL receptor defect. The presence of tendon xanthomata in the proband

or first-degree relatives has been considered pathognomonic of FH, but these findings can also occur in familial defective apo B-100, the normal ligand for the apolipoprotein B/E (LDL) receptor [18]. Supportive findings for one of these disorders include the level of serum cholesterol and premature CHD in either a first-degree relative or two or more second-degree relatives.

One study in children of parents who had heterozygous FH found that an LDL-C concentration ≥ 135 mg/dL (3.50 mmol/L) had a positive predictive value (PPV) of 98 percent (95% CI 96 to 99 percent) [19]. This PPV would only apply to such children of parents with FH; a similar result would not be found in a general population tested for FH.

Differential diagnosis — Tendon xanthomata and premature atherosclerosis can also occur in two rare disorders not involving LDL metabolism: sitosterolemia and cerebrotendinous xanthomatosis.

- Sitosterolemia is an autosomal recessive disorder associated with hyperabsorption of cholesterol and plant sterols from the intestine [20]. The genetic defect can involve either the ABCG5 (ATP-binding cassette G5) or ABCG8 gene [21,22]. These genes are expressed primarily in the liver and intestine and are upregulated by cholesterol feeding [21]. They may normally cooperate to limit intestinal sterol absorption. [Ezetimibe](#) appears to reduce plasma plant sterol concentrations in patients with sitosterolemia [23].
- Cerebrotendinous xanthomatosis is characterized by a block in bile acid synthesis due to the absence of hepatic mitochondrial 27-hydroxylase (CYP27); it is associated with prominent neurologic abnormalities and usually normal serum cholesterol concentrations. (See "[Cerebrotendinous xanthomatosis](#)".)

FH also needs to be distinguished from the other two common causes of hypercholesterolemia described below: familial combined hyperlipidemia; and polygenic hypercholesterolemia. The clinical history and evaluation of the lipid profile are helpful in establishing the correct diagnosis ([table 3](#) and [table 4](#)).

- The lipid profile is similar in familial and polygenic hypercholesterolemia but xanthomata are not seen in the latter disorder.
- There is a reduced ratio of LDL-C to apo B (less than 1.2 versus greater than 1.4 in normals), and triglyceride levels may be above the 90th percentile in familial combined hyperlipidemia.

Management — In initial studies, heterozygotes with FH were typically treated with multidrug regimens, which included less potent statins, to adequately control serum LDL-C levels. Such regimens retarded the angiographic progression of coronary atherosclerosis [24]. At present, high-dose [atorvastatin](#), [rosuvastatin](#), or [simvastatin](#) should be the initial regimen since these drugs are more effective than other statins as monotherapy [25-27]. (See "[Statins: Actions, side effects, and administration](#)".)

The benefit of this approach was evaluated in a trial in which 325 patients with FH were randomly assigned to high-dose [atorvastatin](#) (80 mg/day) or conventional dose [simvastatin](#) (40 mg/day) for two years [25]. High-dose atorvastatin produced a larger reduction in LDL-C (308 to 149 mg/dL [8 versus 3.9 mmol/L]) than conventional dose simvastatin (321 to 185 mg/dL [8.3 to 4.8 mmol/L]). High-dose atorvastatin also produced a significant reduction in carotid intima media thickness, measured with B-mode

ultrasound, compared to an increase with simvastatin.

The role of additional therapy with other lipid altering drugs such as [ezetimibe](#), [neomycin](#), or probucol has not been established. These drugs produce a further reduction in LDL-C (the effect is greatest with ezetimibe) [[28-31](#)] but there have been no trials demonstrating either improved clinical or surrogate outcomes in patients already on high dose statin therapy.

This point was illustrated in the ENHANCE trial of 720 adult patients with heterozygous FH who were randomly assigned to treatment with [simvastatin](#) (80 mg/day) with or without [ezetimibe](#) (10 mg/day) [[32](#)]. Decreases in LDL-C were significantly greater in patients treated with combination therapy (58 versus 41 percent), but there was no statistically significant difference in the primary outcome of change from baseline in carotid intima-media thickness (0.0111 versus 0.0058 mm with simvastatin alone). (See "[Lipid lowering with drugs other than statins and fibrates](#)", section on 'Ezetimibe'.)

Homozygous children — The 2006 American Heart Association scientific statement on cardiovascular risk reduction in high-risk pediatric patients recommends that children with homozygous FH receive early initiation of combined therapy including LDL apheresis, high dose statin therapy, and a cholesterol absorption inhibitor [[33](#)]. We agree with this approach for both children and adults. Consideration can be given to the addition of a bile acid sequestrant and/or nicotinic acid as necessary, although compliance with these agents tends to be difficult [[34,35](#)].

Mipomersen, a second generation antisense oligonucleotide inhibitor of apolipoprotein B100 synthesis, lowers plasma concentrations of both apolipoprotein B and LDL-C [[36](#)]. (See "[Treatment of drug-resistant hypercholesterolemia](#)", section on 'Future approaches' and "[Novel and emerging treatment techniques in advanced prostate cancer](#)", section on 'Antisense oligonucleotides'.)

The efficacy and safety of mipomersen was evaluated in a study of 51 patients with homozygous FH, 12 years of age or older, who were being treated with maximal dose statin therapy [[37](#)]. The patients were randomly assigned in a 2:1 manner to either mipomersen 200 mg subcutaneously weekly (or 160 mg for body weight <50 kg) or placebo. The mean serum LDL-C prior to initiation of therapy 425 mg/dL (11.0 mmol/L). After 26 weeks of treatment, patients taking mipomersen had a significantly greater lowering of LDL-C (mean -24.7 versus -3.3 percent with the mean attained serum cholesterol being 330 mg/dL [8.6 mmol/L]). The most common adverse events were injection site reactions (76 versus 24 percent) and a more frequent rise in serum alanine aminotransferase concentration of more than three times the upper limit of normal (12 versus 0 percent). Mipomersen is not in general clinical use.

Heterozygous adolescents — While young subjects with homozygous FH require aggressive therapy, treatment of heterozygotes was delayed until later in life. However, this approach may be inappropriate since heterozygotes have an increased risk of premature CHD [[38,39](#)]; in one series, for example, the risk of a coronary event was 24 percent by age 40, 51 percent by age 50, and 85 percent by age 65 [[40](#)]. Thallium scanning in adolescents and young adults revealed abnormalities in 11 of 50 heterozygotes tested [[41](#)]. Autopsy reports also have demonstrated atherosclerotic lesions in children at a young age [[42,43](#)].

The American Academy of Pediatrics recommends that pharmacotherapy be considered for children as young as age eight years when the LDL-C is elevated in the range seen in

heterozygous children with FH. Dietary therapy and bile acid sequestrants have traditionally been the lipid-lowering therapies of choice in children, but the effect of both of these interventions is modest (approximately a ten percent reduction in LDL-C and total cholesterol with dietary interventions), and long-term compliance is poor [44-46].

Statins have been studied as lipid-lowering agents in children. Short-term treatment with [simvastatin](#) can reduce endothelial dysfunction in heterozygous children [47]. Two years of [pravastatin](#) therapy produced regression of carotid intima-media thickness [48].

While clinical outcomes data are limited in children, short- and medium-term randomized, placebo controlled trials have demonstrated that statins are effective in lowering LDL-C and are safe in boys and girls with heterozygous FH:

- [Lovastatin](#) (titrated up to 40 mg/day) was evaluated in 132 adolescent males, ages 10 to 17, with serum LDL-C concentrations between 189 and 503 mg/dL (4.9 and 13 mmol/L) despite dietary therapy, and at least one parent with an elevated serum LDL-C [49]. After 48 weeks, serum LDL-C fell by 25 percent in the lovastatin group compared to control. Lovastatin did not affect growth, sexual maturation, testicular volume, serum hormone concentrations (testosterone, cortisol, follicle stimulating hormone, or luteinizing hormone), or serum vitamin levels, except for a reduction in vitamin E.
- [Simvastatin](#) (10 mg/day to start, titrated at eight week intervals to 20 and then 40 mg/day) was evaluated in 173 children ages 10 to 17 [50]. After 48 weeks, treatment with simvastatin was associated with significant reductions in LDL-C compared with placebo (40.7 reduction versus 0.3 percent increase, respectively). There were no significant adverse effects noted with simvastatin therapy and no significant changes from baseline in adrenal, gonadal, or pituitary hormones.
- [Pravastatin](#) (20 mg/day in children younger than 14, 40 mg/day in older children), was evaluated in 214 children ages 8 to 18 with; the primary efficacy outcome was change in carotid intima-media thickness (IMT) [48]. After two years, children who received pravastatin showed regression of IMT (-0.10 mm) with a significant difference compared with placebo (0.014 mm). LDL-C was also reduced with pravastatin (-24.1 versus 0.3 percent). There was no evidence of adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue.
- [Rosuvastatin](#) (at doses of 5, 10, and 20 mg/day) was evaluated in 177 pubertal children ages 10 to 17 [51]. After 12 weeks, LDL-cholesterol fell from 237 to 117 mg/dL (50 percent) at the 20 mg dose. During an open-label, dose titration phase, only 40 percent of children achieved the LDL-cholesterol target of 110 mg/dl. There were no hepatic, renal, or skeletal muscle adverse events that led to permanent discontinuation of treatment and no adverse impact on growth or development was detected.

These trials demonstrate low, tolerable rates of side effects and good efficacy in LDL-C lowering. However, no longer term larger studies exist to address the question of whether there might be subtle effects on growth and development, or indeed whether LDL-C lowering during childhood will diminish or prevent future atherosclerotic disease. This effect is extrapolated from adult data and pre-clinical disease testing.

Longer-term data in children are needed. However, these studies suggest that statin therapy is safe and effective in the short term for children as young as eight years of age

and any potential risk should be balanced against the high risk of early atherosclerosis accompanying significantly elevated LDL cholesterol. (See "[Management of the child at-risk for atherosclerosis](#)", section on 'Dyslipidemia'.)

As in adults, the combination of [ezetimibe](#) plus [simvastatin](#) lowers LDL cholesterol to a greater extent than monotherapy with statin [32,52]. In a study of 248 male and female adolescents with heterozygous FH, the [ezetimibe-simvastatin](#) combination did not lead to any significant increase in adverse events compared to a similar dose of simvastatin monotherapy during up to 53 weeks of therapy [52]. However, there is as yet no evidence that lipid lowering with ezetimibe plus a statin improves clinical outcomes compared to a statin alone [32]. (See "[Lipid lowering with drugs other than statins and fibrates](#)", section on 'Ezetimibe'.)

The optimal age at which to initiate treatment of children with heterozygous FH is unknown. It is our practice, as is recommended by the American Academy of Pediatrics (AAP), to initiate cholesterol-lowering therapy in children with significant elevations of LDL cholesterol (>190 mg/dL without other risk factors, >160 mg/dL in children with family history of early atherosclerotic disease or two or more other risk factors). If the elevations are severe and the family history is particularly concerning, and lifestyle modification is not effective, treatment can be started as young as age eight years, although our preference is to wait until ten years of age in males and after the onset of menses in females. Consideration should be given to the initiation of therapy earlier in children perceived to be at particularly high risk, such as those with tendon xanthomata, aortic sclerosis, or a particularly worrisome family history, features that might be consistent with homozygous familial hypercholesterolemia or more severe forms of hyperlipidemia.

Previously, bile acid binding therapy was the first line treatment. However, compliance with these medications is particularly difficult, and statins are now an acceptable first line agent for children. Some are concerned about the theoretical risk of altering the steroid synthesis pathway by using statins in developing children; these concerns must be balanced against risks of early atherosclerotic disease; decisions about the initiation of drug therapy are best made in consultation with family members and in the context of the individual patient. We have reserved the use of cholesterol absorption inhibitors for children with intolerance to statins.

This practice is consistent with the 2006 American Heart Association scientific statement on cardiovascular risk reduction in high-risk pediatric patients [33] and the 2008 AAP guidelines noted above [53].

Resistant hypercholesterolemia — FH homozygotes and heterozygotes who are refractory to standard drug therapy have been treated with a variety of regimens. These include ileal bypass surgery, portacaval anastomosis, liver transplantation, LDL apheresis, and, in pilot studies, gene therapy. (See "[Treatment of drug-resistant hypercholesterolemia](#)".)

Investigational medical therapies include:

- Administration of L-arginine, which is converted by nitric oxide (NO) synthase to NO. In a study of mice lacking functional LDL receptor genes (a model resembling FH), L-arginine prevented xanthoma formation and reduced atherosclerosis in those animals fed a high cholesterol diet [28]. These beneficial effects of L-arginine were prevented by an inhibitor of NO synthase. The applicability of these observations to humans is unclear.

- Microsomal triglyceride transfer protein transfers triglycerides onto apolipoprotein B as part of the assembly of VLDL within the liver [29]. In a study in six patients with homozygous familial hypercholesterolemia, BMS-201038, an inhibitor of microsomal triglyceride transfer protein, decreased LDL-C by 51 percent and apolipoprotein B by 56 percent [29]. Side effects of therapy included increased aminotransferase levels and hepatic fat accumulation.

Fertile women — Fertile women with familial hypercholesterolemia present special challenges to physicians caring for them, including the potential for pregnancy while on statin therapy, the risks of pregnancy in the presence of advanced coronary artery disease or aortic stenosis, and the use of lipid lowering therapy during breast feeding.

We agree with the following recommendations made in the 2008 United Kingdom National Institute for Health and Clinical Excellence (NICE) Clinical Guidelines and Evidence Review for Familial Hypercholesterolemia [54,55]:

- FH women who are on statin therapy and anticipate becoming pregnant should stop statins three months prior to attempting to conceive. The potential risks to the fetus of statin therapy are discussed separately. (See "[Statin: Actions, side effects, and administration](#)", section on 'Risks in pregnancy and breastfeeding'.)
- Contraceptive options should be explored with fertile FH patients. For those women who choose to use an oral contraceptive, the potential for an increased risk of a cardiovascular event needs to be discussed. (See "[Risks and side effects associated with estrogen-progestin contraceptives](#)", section on 'Cardiovascular disease'.)
- An assessment of coronary artery disease and aortic stenosis risk should be made prior to conception, particularly in homozygotes. (See "[Screening for coronary heart disease](#)" and "[Acquired heart disease and pregnancy](#)", section on 'Valvular heart disease'.)
- Cholesterol measurements should not be performed during pregnancy as no therapy is indicated.
- There are no contraindications to breastfeeding in these women, but no lipid-lowering therapies should be used, with the possible exception of resin agents.

These issues should be discussed in depth with the patient well in advance of conception and should be repeated periodically.

FAMILIAL DEFECTIVE APOLIPOPROTEIN B-100 — Familial defective apo B-100 is an autosomal dominant disorder which, like FH, is associated with impaired binding of LDL particles to the apo B/E (LDL) receptor. This disorder differs from FH in that the defect is localized to the apo B-100 ligand on the LDL particle (mutation at residue 3500), not the apo B/E (LDL) receptor. The net effect is that the clearance of LDL is reduced and plasma levels increase by two- to threefold. The frequency of the apo B 3500 mutation among patients classified as FH heterozygotes is as high as 3 percent [18,56].

One study evaluated the frequency and clinical significance of the apolipoprotein B 3500 mutation in 9255 subjects from the general population, 948 patients with CHD, and 36 patients with FH [57]. The mutation was present in 0.08 percent of subjects in the general population in whom the mean serum cholesterol concentration was 100 mg/dL (2.6 mmol/L) higher than in those without the mutation. The increment in serum cholesterol

above the general population was more pronounced in the patients with CHD (154 mg/dL [4.0 mmol/L]) and those with FH (172 mg/dL [4.5 mmol/L]). Heterozygotes for the mutation were more common in patients with CHD (odds ratio 7.0) and FH (odds ratio 78) compared to the general population.

MUTATIONS IN THE PCSK9 GENE — Mutations in the gene that codes for proprotein convertase subtilisin kexin 9 (PCSK9) lead to an autosomal dominant hypercholesterolemia. PCSK9 is a protease that is highly expressed in the liver. The following observations summarize the clinical importance of PCSK9:

- Elevated levels are associated with reduced expression of the hepatic LDL receptor and increased serum LDL-cholesterol [58,59]. The mechanism(s) by which this occurs are not fully understood, but binding of PCSK9 to the LDL receptor probably enhances degradation of the receptor. There are also losses of function mutations that lead to reduced serum LDL-cholesterol.
- There are polymorphisms in the PCSK9 gene that are associated with increased severity of coronary atherosclerosis in patients with polygenic hypercholesterolemia [60]. (See '[Polygenic hypercholesterolemia](#)' below.)
- Statins appear to increase serum levels of PCSK9, thereby lessening their LDL-cholesterol lowering effect [61].

FAMILIAL COMBINED HYPERLIPIDEMIA — Familial combined hyperlipidemia (FCHL) is a relatively common lipid disorder. It occurs in 1 to 2 percent of the general population and accounts for one-third to one-half of familial causes of CHD [62] and 10 percent of cases of premature CHD [63]. One study of 63 families with FCHL found that, after adjustment for baseline covariates, 20 year cardiovascular disease mortality was increased among siblings and offspring in FCHL compared to spouse control subjects (relative risk 1.7) [64]. Baseline triglyceride concentrations were not independently associated with an increased risk.

FCHL is an autosomal disorder caused by overproduction of hepatically-derived apo B-100 associated with VLDL [65]. Apo B levels are strongly correlated with LDL phenotype B in FCHL families [66,67]; LDL phenotype B levels are inherited as a Mendelian trait that is distinct from the apo B genotype [66].

LDL phenotype B is associated with increased serum concentrations of apo B and triglycerides, reduced serum HDL ([figure 2](#)) [68], and a three-fold increase in risk of CHD (see '[Small dense LDL \(LDL phenotype B\)](#)' below) [69]. LDL phenotype A is associated with large buoyant LDL particles; in comparison, phenotype B is characterized by small, dense LDL particles.

A study of 31 extended Finnish FCHL families suggested a novel locus on chromosome 1q21-q23 [70]. A follow-up study that included an additional 29 families found that FCHL was linked and associated with the gene encoding upstream transcription factor 1 (USF1); USF1 encodes a transcription factor known to regulate several genes involved in glucose and lipid metabolism [71].

FCHL can be represented by one of three Fredrickson phenotypes ([table 1](#)):

- Combined elevations of triglycerides and cholesterol resulting from increases in VLDL and LDL (type IIb)
- Hypercholesterolemia due to an increase in LDL (type IIa)
- Isolated hypertriglyceridemia induced by a rise in VLDL (type IV)

The phenotypic heterogeneity derives from variations in LDL subclass pattern and an associated impairment in lipoprotein lipase (mass and activity) in one-third of cases [72]. Those patients with abnormal lipoprotein lipase (LPL) function have higher levels of triglycerides (due to decreased clearance) and lower levels of HDL-C (due to reduced production from triglyceride-depleted VLDL remnants) than those with normal LPL activity. In at least some patients, a mutation in the LPL gene is responsible [73]. (See "[Approach to the patient with hypertriglyceridemia](#)".)

Because FCHL is phenotypically heterogeneous, and total cholesterol and triglyceride levels may vary within an affected individual over time [74], diagnosis of this disorder or the possible variant hyperapobetalipoproteinemia requires family data. The presence of one of these two conditions is suggested by an LDL-to-apo B ratio of less than 1.2 (normal value >1.4).

A murine model with serum lipid profiles suggestive of human FCHL may provide some insight into the pathogenesis of the human disorder. Transgenic mice were produced by crossing mice expressing human apolipoprotein C-III (which have elevated VLDL levels) with mice deficient in the LDL receptor (which have elevated LDL levels) [75]. The double transgenic animals had very high serum concentrations of VLDL, LDL, and apo B-100; elevated levels of apo B-100 were found in IDL and to a lesser extent in VLDL. The development of atherosclerotic lesions was markedly enhanced when these animals were fed a "Western diet."

Treatment — Treatment decisions are based upon the relative concentrations of LDL-C and triglycerides. As an example, patients with severe hypertriglyceridemia (triglyceride level >500 mg/dL [5.6 nmol/L]) plus moderate hypercholesterolemia will benefit more from triglyceride-lowering agents such as a fibrate or nicotinic acid. These drugs hydrolyze the triglyceride core of VLDL and convert the large, buoyant VLDL to a particle mass more easily cleared by the apo B/E (LDL) receptor. (See "[Approach to the patient with hypertriglyceridemia](#)", section on 'Pharmacologic therapy (including fish oil)').

In comparison, [gemfibrozil](#) does not reduce the level of apo B in FCHL, despite reductions in VLDL- and LDL-C and triglycerides [76]. To the contrary, gemfibrozil may actually elevate LDL-C levels when the baseline concentration of triglycerides is moderately to markedly elevated. This paradoxical response may be countered by the addition of nicotinic acid or a statin; alternatively, a bile acid sequestrant can be used if the triglyceride levels have normalized.

[Gemfibrozil](#) must be used with caution with a statin because of an increased risk of muscle injury. This risk can be minimized by using a statin that is not metabolized by CYP3A4 (eg, [pravastatin](#) or [fluvastatin](#)) [77]. (See "[Statins: Actions, side effects, and administration](#)".) Dosing of gemfibrozil and bile acid sequestrants requires separation by two hours due to sequestrant-induced impaired bioavailability of gemfibrozil [78].

HYPERAPOBETALIPOPROTEINEMIA — Hyperapobetalipoproteinemia is characterized by an overproduction of apo B and may be a variant of familial combined hyperlipidemia. The clinical manifestations include premature CHD (particularly in patients with concurrent hypertriglyceridemia), xanthelasma (in 10 percent of cases), and obesity [79]. Coexisting diabetes mellitus or impaired glucose tolerance is more common in patients who also have hypertriglyceridemia.

This condition is characterized by LDL species that are enriched in apo B-100. It is manifested clinically by an elevation in the concentration of apo B, but a normal

concentration of LDL-C. In most cases, the LDL-C level is less than 160 mg/dL (4.1 mmol/L), the LDL apo B concentration is greater than 135 mg/dL (3.5 mmol/L), and the LDL-to-apo B ratio is less than 1.2 (normal value >1.4) [80].

POLYGENIC HYPERCHOLESTEROLEMIA — Polygenic hypercholesterolemia is characterized by familial aggregation of moderate hypercholesterolemia and the premature onset of CHD. The lipid profile — hypercholesterolemia, usually normal triglyceride levels — is similar to that in heterozygous FH, but xanthomata are not seen (table 4).

Genetics — The genetics of polygenic hypercholesterolemia are poorly understood but multiple abnormalities in LDL metabolism may be involved [81]. These include mild defects in the LDL receptor, defective apo B-100, increased synthesis of apo B, and the presence of the apo E4 phenotype. Apo E is required for receptor-mediated clearance of chylomicron and VLDL remnants from the circulation. Apo E4 has a higher affinity for the LDL receptor than the other apo E isoforms. The enhanced lipid binding leads, via negative feedback, to downregulation of LDL receptor synthesis and a secondary rise in LDL-C levels. (See "[Lipoprotein classification; metabolism; and role in atherosclerosis](#)", section on '[Apolipoproteins](#)'.)

Multiple studies and reviews have evaluated the relationship between apo E genotypes (particularly the apo E4 allele) and both LDL-cholesterol and the incidence of CHD [82-84]. However, these reports may have been both underpowered to detect the true relationship and also subject to publication bias [85].

The largest meta-analysis of the impact of the presence of the apo E allele on LDL-cholesterol levels and CHD risk came to the following conclusions using the E3/E3 genotype as the reference [85]:

- There was an approximately linear relationship of apoE genotypes (when ordered E2/E2, E2/E3,E3/E3,E3/E4, and E4/E4) with LDL-cholesterol. There was a weakly inverse relationship of these genotypes with HDL-cholesterol level and a non-linear relationship with triglycerides, with the E3/E3 genotype having the lowest triglyceride levels
- There was an approximately linear relationship of apoE genotypes (when ordered E2/E2, E2/E3,E3/E3,E3/E4, and E4/E4) with CHD risk. Compared with the apo E3/E3 individual, the odds ratio for CHD was 0.8 (95% CI, 0.70-0.90) in E2 carriers and 1.06 (95% CI, 0.99-1.13) in E4 carriers.

Treatment — Therapy in polygenic hypercholesterolemia usually begins with a statin; nicotinic acid and a bile acid sequestrant are alternatives in patients who cannot tolerate a statin [30]. The 4S trial, which followed 966 survivors of a myocardial infarction for 5.5 years, found that those with the apo E4 allele had a nearly twofold increased risk of dying compared to other patients; this excess mortality was abolished by treatment with [simvastatin](#) [86]. (See "[Clinical trials of cholesterol lowering in patients with coronary heart disease or coronary risk equivalents](#)".)

Further lowering of LDL-C may be accomplished by combining a statin with nicotinic acid or a bile acid sequestrant. Low doses of nicotinic acid (1 to 1.5 g/day) will also raise HDL-C, a desirable effect in patients with hypercholesterolemia and low HDL-C. However, the concurrent use of a statin and nicotinic acid may increase the risk of liver function abnormalities and myopathy.

The Second Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II, or ATP II) had recommended that hormone replacement therapy be used as first-line therapy in women with CHD [87]. However, this recommendation was omitted in ATP III [88], as a result of clinical trials such as the HERS trial that failed to show any benefit of hormone replacement for secondary prevention of CHD (see "[Postmenopausal hormone therapy and cardiovascular risk](#)", section on 'Secondary prevention'). Thus, statins should be the first choice for lipid lowering therapy in most women with CHD. (See "[ATP III guidelines for treatment of high blood cholesterol](#)".)

SMALL DENSE LDL (LDL PHENOTYPE B) — As mentioned above, LDL particles are heterogeneous in size, density, and composition [89]. Individuals can be classified according to their predominant LDL size into one of three phenotypic patterns on gradient gel electrophoresis:

- Phenotype pattern A — Large particle size, ≥ 26.3 nm in diameter
- Phenotype pattern B — Small particle size, < 25.8 nm in diameter
- Phenotype pattern I — Intermediate particle size (mixed distribution), 25.8 to 26.3 nm in diameter

Small, dense LDL particles (phenotype B) are associated with increased serum concentrations of apo B and triglycerides, reduced serum HDL ([figure 2](#)), and an increased risk of CHD.

Determinants — LDL phenotype B levels are in part genetically determined [66]. Studies of monozygotic and dizygotic women twin pairs suggest that one-third to one-half of the variation in LDL particle diameter can be attributed to genetic factors [90]. One gene that may contribute is the gene for cholesteryl ester transfer protein (CETP), which plays a central role in reverse cholesterol transport [91]. CETP moves cholesterol from peripheral tissues to the liver by transferring cholesteryl ester from HDL-C to apo B-containing lipoproteins with triglyceride transfer in the opposite direction. Increased CETP activity may be proatherogenic and is associated with LDL phenotype B [91].

LDL phenotype B levels are also influenced by acquired conditions. As an example, they are associated with obesity, type 2 diabetes, and the manifestations of the acquired insulin resistance syndrome such as hypertriglyceridemia, hyperinsulinemia, increased waist-to-hip ratio, low serum HDL2, and systolic hypertension [92,93].

High hepatic lipase activity is another factor associated with an increase in small, dense LDL particles as well as a reduction in HDL2 cholesterol. Interventions that alter hepatic lipase activity can affect the concentration of small, dense LDL particles. Among patients in the FATS trial with a personal and family history of CHD and apo B levels ≥ 125 mg/dL (3.3 mmol/L), intensive lipid-lowering therapy with [lovastatin](#)-colestipol or niacin-colestipol produced a significant reduction in hepatic lipase activity and an increase in large, buoyant LDL particles [94]. These changes were associated with a significant improvement in disease severity; in a multivariate analysis, an increase in LDL buoyancy was most strongly associated with regression of CHD, accounting for 37 percent of the variance of change in coronary stenosis. (See "[Clinical trials of cholesterol lowering in patients with coronary heart disease or coronary risk equivalents](#)".)

The effect of hepatic lipase may be related to a polymorphism in the hepatic lipase gene promoter, the most common being a C to T substitution. The presence of a C allele is associated with higher hepatic lipase activity; smaller, denser, and more atherogenic LDL

particles; and lower serum HDL-C [95].

The angiographic improvement with lipid lowering is most prominent in subjects with small, dense LDL and lower serum HDL-C, suggesting that hepatic lipase polymorphism might have predictive value [96]. This hypothesis was evaluated in a study of 49 men with established coronary disease and dyslipidemia; patients with the CC genotype had the greatest decrease in hepatic lipase activity, improvement in LDL density, and regression in coronary atherosclerosis (96 versus 60 and 0 percent for TC and TT genotypes) [97].

Increase in coronary risk — Small, dense LDL particles, have been consistently associated with CHD in case-control studies [69,98-102]. As an example, the Stanford Five-City Project evaluated the association between LDL particle diameter with incident fatal and nonfatal MI in a nested case-control study [101]. The study included 124 case-control pairs (90 pairs of men and 34 pairs of women). The patients with MI had a smaller LDL size (mean 26.17 versus 26.68 nm, $p < 0.001$) and there was a graded association across quintiles of LDL size. Small LDL size was a stronger independent predictor of CHD than all other parameters except for the total cholesterol-to-HDL C ratio.

The Physicians' Health Study used a nested case-control study to evaluate whether small, dense LDL particles and nonfasting triglyceride levels were independent predictors for MI in men [102]. The study group included 266 cases and 308 controls that were matched for age and smoking status. The cases had a significantly lower average LDL diameter (25.6 versus 25.9 nm, $p < 0.001$) and higher serum triglycerides. Small, dense LDL was associated with higher triglyceride and lower HDL-C levels, and LDL diameter was not an independent risk factor after adjustment for the high triglyceride levels. (See "[Approach to the patient with hypertriglyceridemia](#)".)

It may be possible to refine the risk associated with small, dense LDL particle size. In a prospective study of over 2000 men, for example, the ability to predict CHD was improved by measuring the cholesterol concentration in the small LDL particles [103].

In addition to determining coronary risk, LDL particle size is also an important predictor of the response to risk-factor reduction. The Stanford Coronary Risk Intervention Project (SCRIP) was a four-year angiographic trial of multifactorial risk reduction versus usual care [96]. LDL particles were classified by density into a "buoyant" (density < 1.0378 g/mL) or "dense" mode (density > 1.0378 g/mL). Cholesterol-lowering therapy produced a significant treatment benefit only in the dense-mode subjects. As noted above, an improvement in LDL density and regression of atherosclerosis appear to be most prominent in patients with the CC genotype for the hepatic lipase gene promoter [97].

At any level of LDL-C, individuals with an increased number of small LDL particles have higher LDL particle (LDL-P) concentrations. In multivariate models, LDL-P size is not related to increased cardiovascular risk after adjustment for LDL-P concentration or its surrogate measure apolipoprotein B (apo B) [104,105]. Thus, LDL size represents part of the pattern of atherogenic dyslipidemia, and it is not a specific therapeutic target. In individuals with disorders of insulin resistance (obesity, metabolic syndrome, type 2 diabetes), LDL-cholesterol under-represents cardiovascular risk due to the discordance between LDL-C and LDL-P [104,106]. Thus, LDL-P, or its surrogate measure apo B, has been considered a target of therapy, as this measure is associated with a twofold higher risk of cardiovascular disease events than LDL-C. Moreover, in statin-treated patients, apo B levels are more strongly associated with residual cardiovascular risk than LDL-C [107].

Based on the high residual cardiovascular risk in metabolic syndrome and type 2 diabetes

patients who achieve current recommended LDL-C targets on statin therapy, we agree with the American Diabetes Association/American College of Cardiology Foundation issued consensus statement recommending measurement of apo B (or LDL-P concentration) in patients at high cardiometabolic risk, as well as treatment of high levels of apo B or LDL-P concentration, after therapeutic interventions have been initiated for treatment of LDL-C and non-HDL-C [108]. Treatment targets for LDL-C/non-HDL-C/LDL-P/apo B are presented in the following table (table 5).

Mechanisms of increased atherogenicity — The atherogenic potential of small LDL particles has been related to both direct and indirect mechanisms. The direct mechanisms include:

- Enhanced oxidative susceptibility [109,110]
- Reduced clearance by LDL receptors in the liver with increased LDL receptor-independent binding in the arterial wall [111,112]
- Endothelial dysfunction that is independent of the concentrations of other lipid [113]

These factors may interact. Less avid binding to the LDL receptor prolongs the half-life of small, dense LDL in the circulation, increasing the likelihood that they will undergo oxidative modification and subsequent uptake by the macrophage scavenger receptors [112].

Indirect associations between small, dense LDL and atherogenic risk include:

- Inverse relationship with HDL-C (figure 2)
- Marker for accumulation of atherogenic triglyceride remnant particles [114]
- Insulin resistance [92]

LOW LDL-CHOLESTEROL LEVELS — Two genetic disorders causing extremely low levels of LDL-cholesterol have been identified. These two, “abetalipoproteinemia” and hypobetalipoproteinemia,” are referred to as “familial hypobetalipoproteinemia.”

Abetalipoproteinemia — Abetalipoproteinemia is a rare recessive disorder caused by a mutation in the gene encoding microsomal transfer protein (MTP). MTP is responsible for the intracellular assembly of apolipoprotein B (apo B) and lipids in the liver and intestine. Consequently, no apo B-containing lipoproteins are found in the plasma (and thus LDL-C levels are near zero), and this results in impaired transport of fat-soluble vitamins (A, D, E, K). This condition is manifest in infancy, and it is characterized by mental retardation and growth abnormalities. Some patients with abetalipoproteinemia can have peripheral neuropathies. (See "[Hereditary neuropathies associated with generalized disorders](#)", section on 'Abetalipoproteinemia'.)

Hypobetalipoproteinemia — Hypobetalipoproteinemia is associated with mutations that may occur at multiple genetic loci, and the best-described cases show linkage to mutations in the gene encoding apo B [115]. The clinical manifestations include intestinal fat malabsorption, hepatic steatosis, and fat soluble vitamin deficiencies. Monitoring for symptoms of fat-soluble vitamin deficiency is recommended. Measurement of fat-soluble vitamin levels is recommended with supplementation of the deficient vitamins as dictated by the magnitude of the vitamin deficiency. Patients have very low levels of plasma apo B and LDL-cholesterol (<5th percentile of age- and sex-specific values; LDL-C levels between 25 and 40 mg/dL [0.65 and 1.03 mmol/L], as well as low levels of very low density lipoprotein (VLDL) cholesterol. (See "[Clinical features and diagnosis of malabsorption](#)".)

A 2010 report of one family with hypobetalipoproteinemia **not** linked to apo B has not only

shed light on the genetics lipid disorders, but has also raised the possibility of a new mechanism for LDL-C lowering [115]. In this family, premature coronary heart disease was absent. Four family members also had very low levels of HDL-cholesterol. Genetic analyses were performed on forty family members, including exome sequencing of two individuals with low HDL-C. The following findings were noted:

- Two independent, nonsense mutations in ANGPTL3 were found. The protein produced by ANGPTL3 region is thought to increase plasma levels of triglycerides, LDL- and HDL-cholesterol.
- Those individuals with only one affected allele had low levels of LDL-C (mean of 72 mg per deciliter [1.9 mmol/L]), compared to those without the defect, and normal levels of HDL-C (mean of 43 mg/dL [1.1 mmol per liter]).
- The four siblings with two affected alleles had very low levels of both LDL- and HDL-C (mean values of 33 mg/dL [0.9 mmol/L] and 18 mg/dL [0.5 mmol/L] respectively).

No intervention to either raise or further lower the LDL cholesterol level in these patients with mutations in ANGPTL3 is indicated.

SUMMARY

- The primary dyslipidemias are associated with overproduction and/or impaired removal of lipoproteins ([table 1](#)). The latter defect can be induced by an abnormality in either the lipoprotein itself or in the lipoprotein receptor. (See ['Introduction'](#) above.)
- The prevalence of dyslipidemia varies with the population being studied. The incidence is highest in patients with premature coronary heart disease (CHD), which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared to approximately 40 to 48 percent in age-matched controls without CHD ([figure 1](#)). (See ['Prevalence of lipid abnormalities'](#) above.)
- Autosomal dominant hypercholesterolemia, familial hypercholesterolemia, and familial combined hyperlipidemia are three of the most common types of primary dyslipidemia. (See ['Autosomal dominant hypercholesterolemia'](#) above and ['Familial hypercholesterolemia'](#) above and ['Familial combined hyperlipidemia'](#) above.)

Use of UpToDate is subject to the [Subscription and License Agreement](#).

REFERENCES

1. Durrington P. Dyslipidaemia. *Lancet* 2003; 362:717.
2. Genest JJ Jr, Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation* 1992; 85:2025.
3. Roncaglioni MC, Santoro L, D'Avanzo B, et al. Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators. *Circulation* 1992; 85:2065.
4. Hobbs HH, Russell DW, Brown MS, Goldstein JL. The LDL receptor locus in familial

- hypercholesterolemia: mutational analysis of a membrane protein. *Annu Rev Genet* 1990; 24:133.
5. Ishibashi S, Brown MS, Goldstein JL, et al. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. *J Clin Invest* 1993; 92:883.
 6. Grossman M, Rader DJ, Muller DW, et al. A pilot study of ex vivo gene therapy for homozygous familial hypercholesterolaemia. *Nat Med* 1995; 1:1148.
 7. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004; 160:407.
 8. Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 1989; 320:915.
 9. Guardamagna O, Restagno G, Rolfo E, et al. The type of LDLR gene mutation predicts cardiovascular risk in children with familial hypercholesterolemia. *J Pediatr* 2009; 155:199.
 10. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest* 2003; 111:1795.
 11. Gidding SS, Bookstein LC, Chomka EV. Usefulness of electron beam tomography in adolescents and young adults with heterozygous familial hypercholesterolemia. *Circulation* 1998; 98:2580.
 12. Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* 2001; 292:1394.
 13. Koeijvoets KC, Rodenburg J, Hutten BA, et al. Low-density lipoprotein receptor genotype and response to pravastatin in children with familial hypercholesterolemia: substudy of an intima-media thickness trial. *Circulation* 2005; 112:3168.
 14. Umans-Eckenhausen MA, Sijbrands EJ, Kastelein JJ, Defesche JC. Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population. *Circulation* 2002; 106:3031.
 15. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004; 160:421.
 16. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation* 1974; 49:476.
 17. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol* 1993; 72:171.
 18. Defesche JC, Pricker KL, Hayden MR, et al. Familial defective apolipoprotein B-100 is clinically indistinguishable from familial hypercholesterolemia. *Arch Intern Med* 1993; 153:2349.
 19. Wiegman A, Rodenburg J, de Jongh S, et al. Family history and cardiovascular risk in familial hypercholesterolemia: data in more than 1000 children. *Circulation* 2003; 107:1473.
 20. Gregg RE, Connor WE, Lin DS, Brewer HB Jr. Abnormal metabolism of shellfish sterols in a patient with sitosterolemia and xanthomatosis. *J Clin Invest* 1986; 77:1864.
 21. Berge KE, Tian H, Graf GA, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000; 290:1771.

22. Lee MH, Lu K, Hazard S, et al. Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. *Nat Genet* 2001; 27:79.
23. Salen G, von Bergmann K, Lütjohann D, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation* 2004; 109:966.
24. Kane JP, Malloy MJ, Ports TA, et al. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 1990; 264:3007.
25. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357:577.
26. Davidson MH, Stein EA, Dujovne CA, et al. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. *Am J Cardiol* 1997; 79:38.
27. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998; 81:582.
28. Aji W, Ravalli S, Szabolcs M, et al. L-arginine prevents xanthoma development and inhibits atherosclerosis in LDL receptor knockout mice. *Circulation* 1997; 95:430.
29. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med* 2007; 356:148.
30. Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. *Arch Intern Med* 1994; 154:1586.
31. Yamamoto A, Matsuzawa Y, Yokoyama S, et al. Effects of probucol on xanthomata regression in familial hypercholesterolemia. *Am J Cardiol* 1986; 57:29H.
32. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358:1431.
33. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006; 114:2710.
34. Colletti RB, Neufeld EJ, Roff NK, et al. Niacin treatment of hypercholesterolemia in children. *Pediatrics* 1993; 92:78.
35. McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr* 1997; 130:266.
36. Kastelein JJ, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. *Circulation* 2006; 114:1729.
37. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous

- familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; 375:998.
38. Yuan G, Wang J, Hegele RA. Heterozygous familial hypercholesterolemia: an underrecognized cause of early cardiovascular disease. *CMAJ* 2006; 174:1124.
 39. Mabuchi H, Koizumi J, Shimizu M, Takeda R. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989; 79:225.
 40. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet* 1969; 2:1380.
 41. Mouratidis B, Vaughan-Neil EF, Gilday DL, et al. Detection of silent coronary artery disease in adolescents and young adults with familial hypercholesterolemia by single-photon emission computed tomography thallium-201 scanning. *Am J Cardiol* 1992; 70:1109.
 42. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 1999; 281:727.
 43. McGill HC Jr, McMahan CA, Zieske AW, et al. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation* 2000; 102:374.
 44. Tonstad S, Knudtson J, Sivertsen M, et al. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr* 1996; 129:42.
 45. Groot PH, Dijkhuis-Stoffelsma R, Grose WF, et al. The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-I concentrations in children heterozygous for familial hypercholesterolemia. *Acta Paediatr Scand* 1983; 72:81.
 46. Lauer RM, Obarzanek E, Hunsberger SA, et al. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. *Am J Clin Nutr* 2000; 72:1332S.
 47. de Jongh S, Lilien MR, op't Roodt J, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol* 2002; 40:2117.
 48. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004; 292:331.
 49. Stein EA, Illingworth DR, Kwiterovich PO Jr, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; 281:137.
 50. de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation* 2002; 106:2231.
 51. Avis HJ, Hutten BA, Gagné C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. *J Am Coll Cardiol* 2010; 55:1121.
 52. van der Graaf A, Cuffie-Jackson C, Vissers MN, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous

- familial hypercholesterolemia. *J Am Coll Cardiol* 2008; 52:1421.
53. Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008; 122:198.
 54. Thorogood M, Seed M, De Mott K, Guideline Development Group. Management of fertility in women with familial hypercholesterolaemia: summary of NICE guidance. *BJOG* 2009; 116:478.
 55. www.nice3.org.uk/nicemedia/pdf/CG071FullGuideline.pdf (Accessed on March 18, 2009).
 56. Tybjaerg-Hansen A, Gallagher J, Vincent J, et al. Familial defective apolipoprotein B-100: detection in the United Kingdom and Scandinavia, and clinical characteristics of ten cases. *Atherosclerosis* 1990; 80:235.
 57. Tybjaerg-Hansen A, Steffensen R, Meinertz H, et al. Association of mutations in the apolipoprotein B gene with hypercholesterolemia and the risk of ischemic heart disease. *N Engl J Med* 1998; 338:1577.
 58. Peterson AS, Fong LG, Young SG. PCSK9 function and physiology. *J Lipid Res* 2008; 49:1152.
 59. Abifadel M, Rabès JP, Devillers M, et al. Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. *Hum Mutat* 2009; 30:520.
 60. Chen SN, Ballantyne CM, Gotto AM Jr, et al. A common PCSK9 haplotype, encompassing the E670G coding single nucleotide polymorphism, is a novel genetic marker for plasma low-density lipoprotein cholesterol levels and severity of coronary atherosclerosis. *J Am Coll Cardiol* 2005; 45:1611.
 61. Dubuc G, Chamberland A, Wassef H, et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2004; 24:1454.
 62. Williams RR, Hopkins PN, Hunt SC, et al. Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah. *Arch Intern Med* 1990; 150:582.
 63. Goldstein JL, Schrott HG, Hazzard WR, et al. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973; 52:1544.
 64. Austin MA, McKnight B, Edwards KL, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. *Circulation* 2000; 101:2777.
 65. Venkatesan S, Cullen P, Pacy P, et al. Stable isotopes show a direct relation between VLDL apoB overproduction and serum triglyceride levels and indicate a metabolically and biochemically coherent basis for familial combined hyperlipidemia. *Arterioscler Thromb* 1993; 13:1110.
 66. Jarvik GP, Brunzell JD, Austin MA, et al. Genetic predictors of FCHL in four large pedigrees. Influence of ApoB level major locus predicted genotype and LDL subclass phenotype. *Arterioscler Thromb* 1994; 14:1687.
 67. DeJager S, Bruckert E, Chapman MJ. Dense low density lipoprotein subspecies with diminished oxidative resistance predominate in combined hyperlipidemia. *J Lipid Res* 1993; 34:295.

68. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990; 82:495.
69. Austin MA, Breslow JL, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA* 1988; 260:1917.
70. Pajukanta P, Nuotio I, Terwilliger JD, et al. Linkage of familial combined hyperlipidaemia to chromosome 1q21-q23. *Nat Genet* 1998; 18:369.
71. Pajukanta P, Lilja HE, Sinsheimer JS, et al. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). *Nat Genet* 2004; 36:371.
72. Babirak SP, Brown BG, Brunzell JD. Familial combined hyperlipidemia and abnormal lipoprotein lipase. *Arterioscler Thromb* 1992; 12:1176.
73. Yang WS, Nevin DN, Peng R, et al. A mutation in the promoter of the lipoprotein lipase (LPL) gene in a patient with familial combined hyperlipidemia and low LPL activity. *Proc Natl Acad Sci U S A* 1995; 92:4462.
74. Veerkamp MJ, de Graaf J, Hendriks JC, et al. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. *Circulation* 2004; 109:2980.
75. Masucci-Magoulas L, Goldberg IJ, Bisgaier CL, et al. A mouse model with features of familial combined hyperlipidemia. *Science* 1997; 275:391.
76. Hokanson JE, Austin MA, Zambon A, Brunzell JD. Plasma triglyceride and LDL heterogeneity in familial combined hyperlipidemia. *Arterioscler Thromb* 1993; 13:427.
77. Athyros VG, Papageorgiou AA, Hatzikonstandinou HA, et al. Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. *Am J Cardiol* 1997; 80:608.
78. Forland SC, Feng Y, Cutler RE. Apparent reduced absorption of gemfibrozil when given with colestipol. *J Clin Pharmacol* 1990; 30:29.
79. Kwiterovich PO Jr, Coresh J, Bachorik PS. Prevalence of hyperapobetalipoproteinemia and other lipoprotein phenotypes in men (aged < or = 50 years) and women (< or = 60 years) with coronary artery disease. *Am J Cardiol* 1993; 71:631.
80. Teng B, Thompson GR, Sniderman AD, et al. Composition and distribution of low density lipoprotein fractions in hyperapobetalipoproteinemia, normolipidemia, and familial hypercholesterolemia. *Proc Natl Acad Sci U S A* 1983; 80:6662.
81. Grundy SM. George Lyman Duff Memorial Lecture. Multifactorial etiology of hypercholesterolemia. Implications for prevention of coronary heart disease. *Arterioscler Thromb* 1991; 11:1619.
82. Walden CC, Hegele RA. Apolipoprotein E in hyperlipidemia. *Ann Intern Med* 1994; 120:1026.
83. Wilson PW, Myers RH, Larson MG, et al. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. *JAMA* 1994; 272:1666.
84. Frikke-Schmidt R, Tybjaerg-Hansen A, Steffensen R, et al. Apolipoprotein E genotype: epsilon32 women are protected while epsilon43 and epsilon44 men are susceptible to ischemic heart disease: the Copenhagen City Heart Study. *J Am Coll Cardiol* 2000; 35:1192.
85. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA* 2007; 298:1300.

86. Gerdes LU, Gerdes C, Kervinen K, et al. The apolipoprotein epsilon4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction : a substudy of the Scandinavian simvastatin survival study. *Circulation* 2000; 101:1366.
87. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993; 269:3015.
88. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143.
89. Otvos JD, Jeyarajah EJ, Bennett DW, Krauss RM. Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. *Clin Chem* 1992; 38:1632.
90. Austin MA, Newman B, Selby JV, et al. Genetics of LDL subclass phenotypes in women twins. Concordance, heritability, and commingling analysis. *Arterioscler Thromb* 1993; 13:687.
91. Talmud PJ, Edwards KL, Turner CM, et al. Linkage of the cholesteryl ester transfer protein (CETP) gene to LDL particle size: use of a novel tetranucleotide repeat within the CETP promoter. *Circulation* 2000; 101:2461.
92. Selby JV, Austin MA, Newman B, et al. LDL subclass phenotypes and the insulin resistance syndrome in women. *Circulation* 1993; 88:381.
93. Siegel RD, Cupples A, Schaefer EJ, Wilson PW. Lipoproteins, apolipoproteins, and low-density lipoprotein size among diabetics in the Framingham offspring study. *Metabolism* 1996; 45:1267.
94. Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. *Circulation* 1999; 99:1959.
95. Zambon A, Deeb SS, Hokanson JE, et al. Common variants in the promoter of the hepatic lipase gene are associated with lower levels of hepatic lipase activity, buoyant LDL, and higher HDL2 cholesterol. *Arterioscler Thromb Vasc Biol* 1998; 18:1723.
96. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. *Circulation* 1996; 94:2146.
97. Zambon A, Deeb SS, Brown BG, et al. Common hepatic lipase gene promoter variant determines clinical response to intensive lipid-lowering treatment. *Circulation* 2001; 103:792.
98. Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis* 1994; 106:241.
99. Tornvall P, Karpe F, Carlson LA, Hamsten A. Relationships of low density lipoprotein subfractions to angiographically defined coronary artery disease in young survivors of myocardial infarction. *Atherosclerosis* 1991; 90:67.
100. Lamarche B, Tchernof A, Mauriège P, et al. Fasting insulin and apolipoprotein B levels

and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA* 1998; 279:1955.

101. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* 1996; 276:875.
102. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 1996; 276:882.
103. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. *Circulation* 2001; 104:2295.
104. Rosenson RS, Davidson MH, Pourfarzib R. Underappreciated opportunities for low-density lipoprotein management in patients with cardiometabolic residual risk. *Atherosclerosis* 2010; 213:1.
105. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation* 2009; 119:931.
106. Kathiresan S, Otvos JD, Sullivan LM, et al. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. *Circulation* 2006; 113:20.
107. Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation* 2000; 101:477.
108. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care* 2008; 31:811.
109. de Graaf J, Hak-Lemmers HL, Hectors MP, et al. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. *Arterioscler Thromb* 1991; 11:298.
110. Chait A, Brazg RL, Tribble DL, Krauss RM. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med* 1993; 94:350.
111. Galeano NF, Al-Haideri M, Keyserman F, et al. Small dense low density lipoprotein has increased affinity for LDL receptor-independent cell surface binding sites: a potential mechanism for increased atherogenicity. *J Lipid Res* 1998; 39:1263.
112. Nigon F, Lesnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. *J Lipid Res* 1991; 32:1741.
113. Vakkilainen J, Mäkimattila S, Seppälä-Lindroos A, et al. Endothelial dysfunction in men with small LDL particles. *Circulation* 2000; 102:716.
114. Slyper AH. Low-density lipoprotein density and atherosclerosis. Unraveling the connection. *JAMA* 1994; 272:305.
115. Musunuru K, Pirruccello JP, Do R, et al. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. *N Engl J Med* 2010; 363:2220.

GRAPHICS**Fredrickson classification of lipid disorders**

Frederickson phenotype	Lipoprotein abnormality	Typical lipid levels
I	Chylomicrons	Triglycerides (TG) >99th percentile
IIa	LDL	Total cholesterol (TC) >90th percentile; depending upon type, may also see TG and/or apolipoprotein B ≥90th percentile
IIb	LDL and VLDL	Depending upon type, TC and/or TG ≥90th percentile and apolipoprotein B ≥90th percentile
III	Remnants of VLDL and chylomicrons	TC and TG >90th percentile
IV	VLDL	TC >90th percentile; depending upon type, may also see TG >90th percentile or low HDL
V	Chylomicrons and VLDL	TG >99th percentile

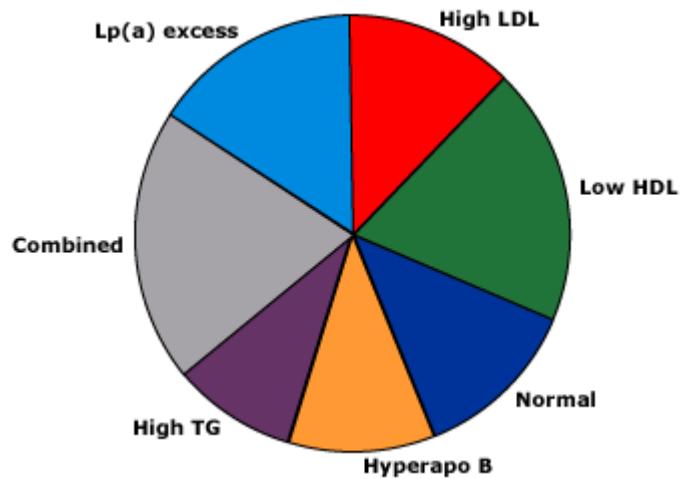
Adapted from Fredrickson, DS, Ann Intern Med 1971; 75:471.

Reference values for lipid levels

	Age	Total cholesterol (90)	LDL cholesterol (90)	Triglycerides (90)	HDL cholesterol (10)
White men	20-34	236	165	199	34
	35-44	258	176	241	30
	45-54	268	187	228	31
	55-64	274	194	280	31
	65-74	270	185	256	31
	≥75	257	186	219	32
White women	20-34	229	155	164	38
	35-44	242	155	209	37
	45-54	279	182	212	38
	55-64	291	189	213	37
	65-74	290	192	253	37
	≥75	287	197	248	39
Non-Hispanic white men		260	179	248	30
Non-Hispanic white women		271	176	228	37
Mexican-American men		257	172	266	33
Mexican-American women		258	166	240	37
Non-Hispanic black men		252	186	171	35
Non-Hispanic black women		262	174	162	40

Reference values in the United States for the ninetieth percentile for total and LDL-cholesterol and triglycerides and for the tenth percentile for HDL-cholesterol. Values are shown according to age for white men and women, and mean values are given for different groups. (Units are mg/dL; divide cholesterol values by 38.5 to convert to mmol/L; divide triglyceride values by 88.5 to convert to mmol/L.) *Data from: National Health and Nutrition Examination Survey (NHANES) III.*

Lipoproteins and and premature coronary heart disease



Incidence of different lipid abnormalities in men with premature coronary disease (<60 years of age). Patients with more than one disturbance (eg, low HDL plus hypertriglyceridemia) are noted in the combined group. Only 12.5 percent of subjects were normal in this study versus 58.5 percent of age-matched controls without coronary disease. *Data from Genest, JJ, McNamara, JR, Ordovas, JM, et al, J Am Coll Cardiol 1992; 19:792.*

Tendon xanthomata



Tendon xanthomata on the dorsum of the hand in a patient with heterozygous familial hypercholesterolemia. *Reproduced with permission from: Durrington, P. Dyslipidaemia. Lancet 2003; 362:717. Copyright © 2003 Elsevier.*

Achilles tendon xanthoma



A xanthoma of the Achilles tendon in a patient with heterozygous familial hypercholesterolemia. *Reproduced with permission from: Durrington, P. Dyslipidaemia. Lancet 2003; 362:717. Copyright © 2003 Elsevier.*

Subperiosteal xanthomata



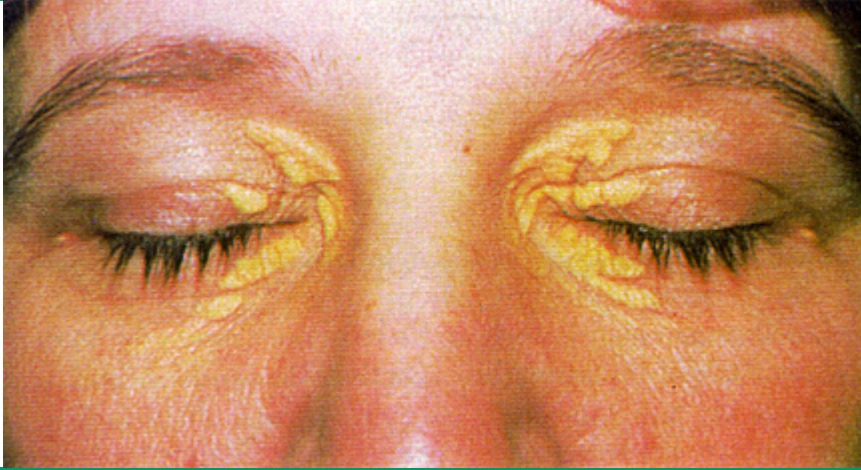
Subperiosteal xanthomata in a patient with heterozygous familial hypercholesterolemia. *Reproduced with permission from: Durrington, P. Dyslipidaemia. Lancet 2003; 362:717. Copyright © 2003 Elsevier.*

Planar xanthoma



Planar xanthoma in the antecubital fossa of a patient with homozygous familial hypercholesterolemia. *Reproduced with permission from: Durrington, P. Dyslipidaemia. Lancet 2003; 362:717. Copyright © 2003 Elsevier.*

Xanthelasma



Yellow plaques are present bilaterally. *With permission from Slomovits, TL (Ed), Basic and clinical science courses section, American Academy of Ophthalmology, San Francisco 1996.*

Cholesterol criteria for heterozygous FH

Age, years	First-degree relative	Second-degree relative	Third-degree relative	General population
<18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
≥40	290 (205)	300 (215)	310 (225)	360 (260)

Total cholesterol and LDL-cholesterol (in parentheses) levels expected to diagnose heterozygous familial hypercholesterolemia (FH) with 98 percent specificity by demonstrating high cholesterol levels in family members; the general population column refers to levels that need to be seen in a patient with no evaluable family members. Units are mg/dL; divide by 38.5 to convert to mmol/L. Second-degree relatives refers to aunts, uncles, grandparents, nieces, or nephews; third-degree relatives refers to first cousins, siblings, or siblings of grandparents. *Data from Williams, R, Hunt, SC, Schumacher, C, et al, Am J Cardiol 1993; 72:171.*

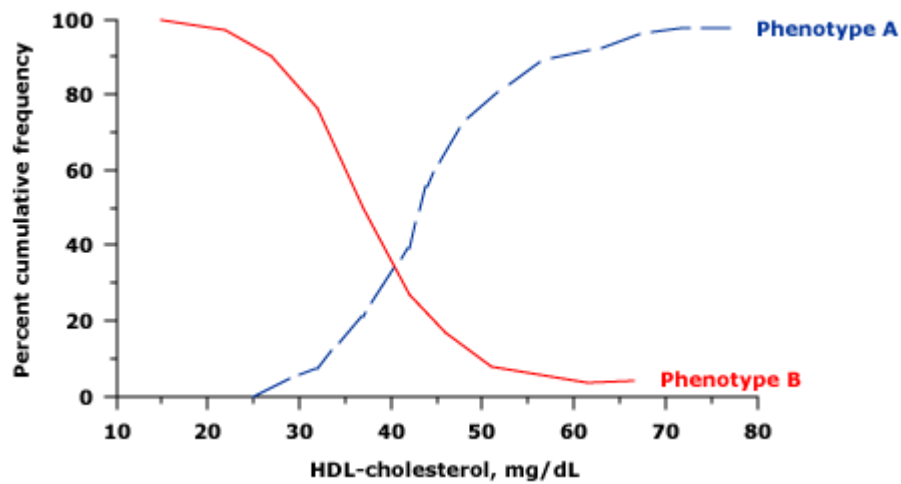
Primary disorders of cholesterol metabolism

Disorder	Lipid levels	Confirmatory studies	Physical findings
Familial hypercholesterolemia (definite)*	High TC; TG usually normal	LDL receptor defect by cell studies or DNA mapping	Tendon xanthomata in patient or one first or second degree relative
Familial hypercholesterolemia (probable)*	High TC; TG usually normal	Exclusions include secondary disorders of cholesterol metabolism; tendon xanthomata in patient or relative	Corneal arcus; xanthelasma
Familial combined hyperlipidemia	TC and/or TG \geq 90th percentile in patient and in one first or two second-degree relatives; apo B \geq 90th percentile	LDL-cho/ apo B $<$ 1.2	Xanthelasma; corneal arcus
Familial hyperapobeta-lipoproteinemia	Apo B $>$ 90th percentile; at least two first- or second-degree relatives with similar profile	LDL-cho/ apo B $<$ 1.2	Xanthelasma
Polygenic hypercholesterolemia	TC $>$ 90th percentile; TG $<$ 90th percentile		Exclusions: tendon xanthomata in patient or family members

Summary of diagnostic criteria for the different forms of hypercholesterolemia. TC: total cholesterol; TG: total triglycerides; apo B: apolipoprotein B.

* The laboratory and clinical manifestations of familial defective apolipoprotein B-100 are identical to those of familial hypercholesterolemia; the distinction can be made only by molecular biology techniques. *Summary of diagnostic criteria for the different forms of hypercholesterolemia. Data from Rosenson, RS, Fraumeni, WA, Tangney, CC, Dis Mon 1994; 40:369.*

LDL phenotypes and HDL-cholesterol



Percent cumulative frequency of HDL-cholesterol levels according to LDL phenotypes A and B. Phenotype B (solid line) is associated with lower HDL levels and a higher risk of coronary heart disease. *Data from Austin, MA, King, MC, Vranizan, KM, Krauss, RM, Circulation 1990; 82:495.*

Suggested apolipoprotein B or LDL-P treatment goals

apo B, mg/dL	LDL-C, mg/dL	Non-HDL-C, mg/dL	LDL-P, nmol/L
	<70	<80	
<80	<100	<120	<1100
<100	<130	<150	<1400

Reproduced with permission from: Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Disease Division Working Group on Best Practices. Clinical Chemistry 2009; 55:407. Copyright © 2009 American Association for Clinical Chemistry. All rights reserved.

© 2011 UpToDate, Inc. All rights reserved. | [Subscription and License Agreement](#) | Support Tag:
[ecapp1004p.uptd.com-217.12.16.56-83B4630F79-234261.14]
Licensed to: **Biblioteca Virtual del SSPA**