



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/19/2015
LAST REVIEW DATE: 8/19/2021
LAST CRITERIA REVISION DATE: 8/19/2021
ARCHIVE DATE:

LIPID LOWERING THERAPIES:
JUXTAPID® (lomitapide) oral
PRALUENT™ (alirocumab) subcutaneous injection
REPATHA™ (evolocumab) subcutaneous injection

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)

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864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms or forms without the chart notes will be returned.

Praluent (alirocumab) subcutaneous injection
Repatha (evolocumab) subcutaneous injection

Criteria:

- **Criteria for initial therapy:** Praluent (alirocumab) and Repatha (evolocumab) is considered *medically necessary* and will be approved when of **ALL** of the following criteria are met:
1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or an Endocrinologist
 2. A confirmed diagnosis of **ONE** of the following:
 - a. Adult (18 years of age or older) with established cardiovascular disease, to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization or coronary revascularization (See Definitions section)
 - b. Adult (18 years of age or older) with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C), as adjunct to diet, alone or in combination with other lipid lowering therapies (e.g., statins, ezetimibe) (See Definitions section)
 - c. **ONE** of the following:
 - i. **For Praluent (alirocumab):** Adult (18 years of age or older) with homozygous familial hypercholesterolemia (HoFH) who requires additional lowering of LDL-C, as adjunct to diet and other lipid lowering therapies (e.g., statins, ezetimibe, LDL apheresis) (See Definitions section)
 - ii. **For Repatha (evolocumab):** An individual 13 years of age or older with homozygous familial hypercholesterolemia (HoFH) who requires additional lowering of LDL-C as adjunct to diet and other lipid lowering therapies (e.g., statins, ezetimibe, LDL apheresis) (See Definitions section)
 3. Failure, contraindication or intolerance to Zetia (either monotherapy or in combination)
 4. Combination therapy with a statin and Zetia (ezetimibe) has resulted in **ONE** of the following:
 - a. Has failed to reach LDL goal after 12-weeks of dual therapy with a moderate or high intensity statin at a maximum tolerable dose **with** Zetia (ezetimibe)
 - b. Cannot use a statin with Zetia (ezetimibe) due to current intolerance to or has prior intolerance to statin use after at least two attempts of altering dose frequency or dose re-titration or use of

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alternative statin **OR** has an FDA-label contraindication against use of a statin (see Definitions section)

- c. Cannot use Zetia (ezetimibe) with a statin due to the individual has an FDA-label contraindication against use (see Definitions section)
5. Individual is currently on and adherent with a lipid lowering diet for at least 3 months (documentation of adherence is required)
 7. Individual is currently on and adherent with exercise for at least 3 months (documentation of adherence is required)
 8. Individual is currently on and adherent with smoking cessation for at least 3 months (documentation of adherence is required)
 9. No evidence of combination therapy with Juxtapid (lomitapide), or other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
 10. There are **NO** FDA-label contraindications for use of requested agent

Initial approval duration: 3 months, renewal request must show LDL-C has reached therapeutic goal for approval

- **Criteria for continuation of coverage (renewal request):** Praluent (alirocumab) and Repatha (evolocumab) is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or an Endocrinologist
 2. Individual has reached LDL-C goal on therapy (renewal must show LDL-C has reached therapeutic goal)
 - a. LDL-C goals are defined as:
 - i. Known baseline: LDL-C decreased by 50%
 - ii. Unknown baseline and has cardiovascular disease: LDL-C < 70 mg/dL
 - iii. Unknown baseline and has no cardiovascular disease: LDL-C < 100 mg/dL
 3. Individual has been adherent with the medication, continues and is adherent with ezetimibe and statin (if tolerated) therapy, diet, exercise, and smoking cessation
 4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
 - a. Significant adverse effect such as:
 - i. Hypersensitivity reaction that require hospitalization
 - ii. Hypersensitivity vasculitis

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iii. Angioedema

5. No evidence of combination therapy with Juxtapid (lomitapide), or other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
6. There are no significant interacting drugs

Renewal duration: 12 months

➤ Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-cancer Medications**
2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Juxtapid (lomitapide)

Criteria:

- **Criteria for initial therapy:** Juxtapid (lomitapide) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or Endocrinologist
 2. Age is 18 years or older
 3. A confirmed diagnosis of **homozygous familial hypercholesterolemia** (HoFH) by **ONE** of the following
 - a. Genetic testing confirming 2 mutated alleles at LDLR gene or alleles known to affect LDL receptor functionality
 - b. Skin fibroblast LDL receptor activity < 20% of normal
 - c. An untreated total cholesterol > 500 mg/dL and triglyceride < 300 mg/dL **and** both parents with documented untreated total cholesterol > 250 mg/dL
 4. Individual is currently on and adherent with other lipid lowering treatment
 5. Individual is currently on and adherent with a low-fat diet

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6. Individual is currently on and adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)
7. **ALL** of the following baseline tests have been obtained before initiation of treatment:
 - a. Negative pregnancy test, in females of reproductive potential
 - b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin per REMS [Note: This is waved if it is verified that Provider, Patient, and Pharmacy are enrolled in the REMS]
8. There are **NO** FDA-label contraindications, such as:
 - a. Pregnancy
 - b. Simultaneous use of moderate or strong CYP3A4 inhibitors (see Definitions section)
 - c. Moderate or severe hepatic impairment (Child-Pugh Class B or C)
 - d. Active liver disease including unexplained persistent abnormal liver function tests
9. Individual does not have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption
10. Will not be used with Praluent (alirocumab) or Repatha (evolocumab)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Juxtapid (lomitapide) is considered **medically necessary** and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Cardiologist or Endocrinologist
 2. Individual's condition responded
 - a. Response is defined as:
 - i. Achieved and maintains at least a 50% in LDL-C from baseline
 3. Individual has been adherent with the medication
 4. Individual has been adherent with other lipid lowering therapy
 5. Individual has been adherent with low fat diet
 6. Individual has been adherent with use of a supplement(s) that contains 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)

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7. Will not be used with Praluent (alirocumab) or Repatha (evolocumab)
8. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
 - a. Contraindications as listed in the criteria for initial therapy section
 - b. Significant adverse effect such as:
 - i. Liver toxicity
 - ii. Hepatic steatosis
9. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

3. **Off-Label Use of a Non-cancer Medications**
4. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Praluent (alirocumab) is 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 (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The effect of Praluent (alirocumab) on cardiovascular morbidity and mortality has not been determined.

Repatha (evolocumab) is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease; as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C; and it is indicated as an adjunct to diet and 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.

Praluent (alirocumab) and Repatha (evolocumab) are human monoclonal antibodies (IgG1 & IgG2 isotypes respectively) that inhibit PCSK9. PCSK9 is the enzyme responsible for removing LDLR from the hepatocyte surface. PCSK9 promotes the degradation of hepatic LDLR, which limits the ability of the liver to bind and remove LDL-C from the blood. Inhibition of PCSK9 increases the number of available LDLR, allowing for additional capacity to remove LDL-C from the bloodstream, leading to lowering of LDL-C levels.

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Juxtapid (lomitapide) is a microsomal triglyceride transfer protein (MTP) inhibitor indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with HoFH. Juxtapid (lomitapide) directly binds and inhibits MTP. Juxtapid (lomitapide) prevents the assembly of apo B-containing lipoproteins in enterocytes and hepatocytes. The result is inhibition of the synthesis of chylomicrons and VLDL. The inhibition of the synthesis of VLDL leads to reduced levels of plasma LDL-C.

The safety and effectiveness of Juxtapid (lomitapide) have not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH. The effect of Juxtapid (lomitapide) on cardiovascular morbidity and mortality has not been determined. Safety and effectiveness in pediatric patients have not established. Juxtapid (lomitapide) is only available through a restricted program called JUXTAPID REMS PROGRAM. They are only available from certified pharmacies that are enrolled in the program. Providers must be enrolled in the program in order to prescribe Juxtapid (lomitapide).

MTP plays a key role in the assembly and release of apo B-containing lipoproteins, including LDL-C, and inhibition of this protein significantly lowers associated plasma lipid levels. It is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Normal concentrations and function of MTP in the liver and intestine are necessary for the proper assembly and secretion of apo B-containing lipoproteins from the liver and chylomicrons from the intestine. Inhibition of MTP leads directly to decreases in circulating levels of apo B-containing lipoproteins, including LDL-C.

Under normal physiological conditions, LDL-C is removed from the blood when it binds to an LDL receptor (LDLR) on the hepatocyte surface. Each LDLR binds a single LDL-C particle and is internalized into the hepatocyte. The LDL-C separates from the receptor and the unoccupied receptors are returned to the cell surface for reuse. At the same time, the lipoprotein is degraded and the released cholesterol is stored in the cell and used for a variety of cellular activities such as production of bile acids and very low density lipoproteins. The level of hepatic LDLR is controlled at the transcriptional level by proprotein convertase subtilisin kexin type 9 (PCSK9). Following its secretion, PCSK9 binds to LDLR and blocks the cholesterol-removal process by metabolizing the LDLR and breaking it up, effectively making it impossible for the LDLR to return to the surface of the cell and remove more cholesterol.

Hypercholesterolemia:

- Hypercholesterolemia is a major risk factor for ASCVD, which may result in one or more of the following: acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, revascularization procedures, stroke or transient ischemic attack, and peripheral arterial disease that is atherosclerotic in origin
- It usually results from nutritional factors such as a diet high in saturated fats combined with an underlying polygenic predisposition or it may be caused solely by a genetic disorder or a combination of other factors
 - Other risk factors include older age, early menopause in women, and family history of the condition

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Familial hypercholesterolemia (FH):

- FH is an autosomal-dominant genetic disorder, is classified as heterozygous (inherited from one parent) or homozygous (inherited from both parents).
- Characterized by very high LDL-C levels requiring aggressive lipid-lowering in order to prevent cardiovascular disease
- FH may be caused by mutations in any of several genes affecting receptor-mediated uptake of LDL-C, including the genes for the LDLR, the LDL receptor ligand (apolipoprotein B100, APOB), and PCSK9
- The vast majority of people with FH have inherited a single mutation from one parent in either of these genes
- A loss of function mutation in the LDLR gene results in absent or grossly malfunctioning LDLR and reduced uptake and clearance of circulating LDL-C by the liver
- Due to absence or abnormality in the LDLR, the liver is unable to internalize LDL-C particles, leading to elevation in serum LDL-C levels
 - Hepatic synthesis of cholesterol is not suppressed because LDL-C is not internalized by the hepatocytes
 - This leads to higher cholesterol production by the liver, despite already high levels of circulating cholesterol
 - As a result, circulating cholesterol levels increase dramatically
- The elevated serum levels of LDL-C increase a LDL-C receptor-independent cholesterol uptake pathway in non-hepatic cells
 - This scavenger pathway allows cholesterol uptake by monocytes and macrophages, leading to foam cell formation, plaque deposition in the endothelium of coronary arteries, and premature coronary heart disease

FH forms:

- There are two forms of FH: HeFH and HoFH
- HeFH is more common than HoFH, while HoFH is more severe
- HeFH is estimated to occur in 1:300 to 1:500 individuals in the United States and Europe, while HoFH occurs in 1:1,000,000
- Patients with HeFH can present with total cholesterol in the range of 350-550 mg/dL, while patients with HoFH can have total cholesterol in the range of 650-1000 mg/dL
- In all forms of FH, the phenotype is characterized by a high LDL-C level from birth, relatively normal high-density lipoprotein (HDL-C) and triglycerides, and early-onset coronary heart disease
- Findings of FH on physical examination may include arcus corneae (a white ring around the cornea), xanthelasma (sharply demarcated yellowish deposits of fat underneath the skin), and tendon or tuberous xanthomas

Management:

- Medications currently approved for the treatment of hypercholesterolemia have been extensively studied, and many have long safety and efficacy track records
- Patients with hypercholesterolemia are typically treated with statin therapy
 - Statins have been shown to reduce cardiovascular events and mortality
- However, many patients are not able to achieve LDL goals on statin therapy alone

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- Other options that can be used with or without statin therapy include Zetia (ezetimibe), fibrates, niacin, and bile acid sequestrants
- LDL apheresis is considered a standard of care in patients with HoFH, but may not be feasible due to patient access or tolerability
 - Other options for HoFH include Kynamro (mipomersen), Juxtapid (lomitapide), and Repatha (evolocumab)
 - Are typically used in patients who are not adequately controlled with or cannot receive LDL apheresis

Statin adverse effects:

- Approximately 3-10% of patients on statins may develop intolerance to the statin used
 - Intolerance is defined as an inability to take a statin because of muscle symptoms or elevated creatine kinase
 - Individuals may present with muscle weakness, aches, cramps, or flu-like symptoms
 - Other effects, such as, headache, sleep disorders, dyspepsia, nausea, rash, alopecia, erectile dysfunction, gynecomastia, and/or arthritis, may also contribute to a patient's inability to take them
 - Less than 1% of patients on statin therapy developed serious side-effects such as myopathy, myositis, or rhabdomyolysis
 - Risk factors for statin intolerance and of developing muscle-related symptoms include, female gender, advanced age, patients with significant comorbidities (such as liver failure, kidney failure, or thyroid disease), family history of myopathy, and statin dose
 - In many cases it occurs after patients are co-administered an interacting medication (such as azole antifungals, cimetidine, clarithromycin, erythromycin, or cyclosporine)
 - Some patients will respond favorably to lowering the statin dose or switching to another statin or administering statins in an unconventional (eccentric) schedule such as every other day, every second day, every third day, or even weekly instead of daily
 - Studies have shown that 92% of patients can tolerate a second statin and 72.5% can successfully tolerate a third agent
 - Use of long acting statins weekly instead of daily resulted in 74% of patients able to tolerate continued statin use
 - However, some patients cannot achieve optimal lowering of LDL-C despite these dose modifications or use of an alternative statin
 - The risk of developing statin associated muscle symptoms (SAMS) is not identical across all statins
 - Studies have suggested that the risk of developing SAMS is highest with simvastatin, atorvastatin, and lovastatin
 - The risk of myopathy has been suggested to be lowest with pravastatin and fluvastatin, possibly because they are more hydrophilic and, as a result, have less muscle penetration
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Definitions:

Risk Evaluation and Mitigation Strategies (REMS):

Use of Juxtapid is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

The goal of the Juxtapid REMS program is to mitigate the risk of hepatotoxicity associated with the use of Juxtapid

Homozygous familial hypercholesterolemia:

Loss of function mutations in both alleles of the LDLR gene

Heterozygous familial hypercholesterolemia:

Loss of function mutation in one allele of the LDLR gene

Hyperlipidemia:

Abnormal elevation of any or all lipids or lipoproteins

Types:

Primary hyperlipidemia:

Hyperlipidemia that is the result of a genetic cause such as a mutation in a receptor protein

Secondary hyperlipidemia:

Hyperlipidemia that is the result of another underlying disorder such as diabetes, drugs, hypothyroidism, etc.

Clinical atherosclerotic cardiovascular disease (ASCVD) defined as:

1. LDL > 100 mg/dL (within the last 30 days)
2. LDL-C \geq 70 mg/dL and/or non-HDL-C \geq 100 mg/dL despite high- or moderate-intensity statin therapy
3. One or more of the following clinical situations
 - Acute coronary syndrome
 - History of or diagnosis of myocardial infarction
 - Stable or unstable angina
 - Coronary or other arterial revascularization (such as percutaneous coronary intervention or coronary bypass graft surgery)
 - Diagnosis of non-hemorrhagic stroke or transient ischemic attack
 - Symptomatic Peripheral arterial disease (PAD) presumed to be of atherosclerotic origin, as evidenced by intermittent claudication with ankle-brachial index (ABI) < 0.85, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease

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- Clinically significant coronary heart disease diagnosed by invasive or noninvasive tests (e.g., coronary angioplasty, stress test using treadmill, stress echocardiography, or nuclear imaging)

Heterozygous familial hypercholesterolemia (HeFH) defined as ONE of the following:

1. World Health Organization/Dutch Lipid Network Criteria score > 8
2. Simon-Broome Register Diagnostic Criteria of Definite HeFH

Homozygous familial hypercholesterolemia (HoFH) defined by ONE of the following:

1. Genetic confirmation of **two** mutant alleles at the LDL receptor, ApoB, PCSK9, or ARH adaptor protein 1/LDLRAP1
2. An untreated LDL-C > 500mg/dl (or treated LDL-C > 300 mg/dl) with **EITHER**:
 - a. Cutaneous or tendon xanthoma before age 10
 - b. Documented evidence of HeFH in **both** biologic parents

ASCVD Pooled Cohort Risk Assessment:

The Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group, an arm of the ACC/AHA Cardiovascular Risk Guidelines, to identify appropriate candidates for statin therapy based on elevated cardiovascular risk

The purpose of the Pooled Cohort Equations is to estimate the risk of ASCVD within a 10-year period among patients who have never had one of these events in the past

The Pooled Cohort Equations were developed and validated among Caucasian and African American men and women who did not have clinical ASCVD. There are inadequate data in other racial groups, such as Hispanics, Asians, and American-Indian populations. Given the lack of data, current guidelines suggest to use the "Caucasian" race to estimate 10-year ASCVD risk with the knowledge that further research is needed to stratify these patients' risk. Compared to Caucasians, the risk of ASCVD is generally lower among Hispanic and Asian populations and generally higher among American-Indian populations.

The 2013 ACC/AHA guidelines recommend either a high-intensity or moderate-intensity statin regimen in patients who have an elevated ASCVD risk ($\geq 7.5\%$) for primary prevention of cardiovascular disease

Framingham Risk Score (FRS):

A validated means of predicting cardiovascular disease (CVD) risk in asymptomatic patients

It is used to determine lipid-lowering therapy for primary prevention

A 10-year risk score is expressed as a percentage

Risk is considered:

Low if the FRS < 10%

Moderate if the FRS is 10-19%

High if the FRS $\geq 20\%$

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Diagnosis of Heterozygous familial hypercholesterolemia (HeFH):
World Health Organization Criteria / Dutch Lipid Network Criteria:

		Score
Family history	First degree relative with known premature CAD &/or vascular disease (men < 55 y, woman < 60 y)	1
	First degree relative with known LDL-C > 95th percentile by age and gender	1
	First degree relative with tendon xanthomata &/or arcus cornealis	2
	Children < 18 y with LDL-C > 95th percentile by age and gender	2
Clinical history	Patient has premature CAD (male before age 55, female before age 60)	2
	Patient has premature cerebral/peripheral vascular disease (male before age 55, female before age 60)	1
Physical exam	Tendon xanthomata	6
	Arcus cornealis age < 45 y	4
LDL-C	> 330 mg/dL (> 8.5 mmol/L)	8
	250-329 mg/dL (6.5-8.4 mmol/L)	5
	190-249 mg/dL (5.0-6.4 mmol/L)	3
	155-189 mg/dL (4.0-4.9 mmol/L)	1
Genetic test	Mutation in LDLR, ApoB, or PCSK9 gene	8
Definite FH		Score > 8
Probable FH		Score 6-8
Possible FH		Score 3-5
Unlikely FH		Score < 3
First degree relative: blood relative – parents, full siblings, children Second degree relative: blood relative – grandparents, grandchildren, aunts, uncles, nephews, nieces, half siblings Third degree relative: blood relative – first cousins, great-grandparents, great grandchildren		

Simon-Broome Register Diagnostic Criteria:

A	Adult: TC > 290 mg/dL (or > 7.5 mmol/L) Child < 16 y : TC > 260 mg/dL (or > 6.7 mmol/L) OR Adult: LDL-C > 190 mg/dL (or > 4.9 mmol/L), pre-treatment or highest on treatment Child: LDL-C > 155 mg/dL (or > 4.0 mmol/L), pre-treatment or highest on treatment
B	Tendon xanthomas in the individual or first- OR second-degree relative
C	DNA-based evidence of a LDLR mutation OR a familial defective ApoB-100 OR PCSK9 mutation
D	First-degree relative with an MI before age 60 OR Second-degree relative with an MI before age 50
E	First- or second-degree relative with TC > 290 mg/dL (or > 7.5 mmol/L) OR Sibling or child < 16 years of age with TC > 260 mg/dL (or > 6.7 mmol/L)
Definite FH	(A + B) or C

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Possible FH	A + (D or E)
First degree relative: blood relative – parents, full siblings, children	
Second degree relative: blood relative – grandparents, grandchildren, aunts, uncles, nephews, nieces, half siblings	
Third degree relative: blood relative – first cousins, great-grandparents, great grandchildren	

2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guideline				
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C treatment Goals				
Risk Category	Risk factor*/10-year risk†	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme	<ul style="list-style-type: none"> Progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH History of premature ASCVD (< 55 male, < 65 female) 	< 55	< 80	< 70
Very high	<ul style="list-style-type: none"> Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk > 20% Diabetes or CKD 3/4 with 1 or more risk factor(s) HeFH 	< 70	< 100	< 80
High	<ul style="list-style-type: none"> ≥ 2 risk factors and 10-year risk 10-20% Diabetes or CKD 3/4 with no other risk factors 	< 100	< 130	< 90
Moderate	<ul style="list-style-type: none"> < 2 risk factors and a 10-year risk of 10-20% 	< 100	< 130	< 90
Low	<ul style="list-style-type: none"> 0 risk factors 	< 130	< 160	--

* Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), chronic renal disease (CKD) stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

† Framingham risk scoring is applied to determine 10-year risk

Four Major Statin Benefit Groups: 2013 Recommendations AHA/ACC Cholesterol Guidelines	
Patient Category	Recommendation for Statin intensity
Secondary prevention	
-Clinical ASCVD	<ul style="list-style-type: none"> High intensity if age ≤75 y Moderate intensity if age >75 y
Primary prevention	
-LDL-C ≥190 mg/dL	High-intensity statin
-Age 40-75 y LDL-C 70-189 mg/dL +DM & no clinical ASCVD	<ul style="list-style-type: none"> Moderate intensity if low risk (10-y ASCVD risk <7.5%) High intensity if high risk (10-y ASCVD risk >7.5%)
-Age 40-75 y LDL-C 70-189 mg/dL -DM or clinical ASCVD	Moderate or high intensity (10-y ASCVD risk ≥7.5%)

Statin Treatment Categorized by Intensity Using 2013 AHA/ACC Cholesterol Guidelines

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	High Intensity	Moderate Intensity	Low Intensity
	Daily dose lowers LDL-C, on average, by about $\geq 50\%$	Daily dose lowers LDL-C, on average, by about 30% to $< 50\%$	Daily dose lowers LDL-C, on average, by about $< 30\%$
Atorvastatin	≥ 40 mg	10-40 mg	< 10 mg
Fluvastatin		80 mg	< 80 mg
Lovastatin		≥ 40 mg	< 40 mg
Pitavastatin		≥ 2 mg	< 2 mg
Pravastatin		≥ 40 mg	< 40 mg
Simvastatin	80 mg*	20 - < 80 mg	< 20 mg
Rosuvastatin	≥ 20 mg	5- < 20 mg	< 5 mg

* Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by FDA due to the increased risk of myopathy, including rhabdomyolysis.

Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
--	40 mg	20 mg	1 mg	20 mg	--	10 mg
10 mg	80 mg	40 mg	2 mg	40 mg	--	20 mg
20 mg	--	80 mg	4 mg	**	--	40 mg
40 mg	--	--	--	--	10 mg	80 mg
80 mg	--	--	--	--	20 mg	--

FDA-label contraindications of Statins and Ezetimibe:

Statins:

- Hypersensitivity to HMG-CoA reductase inhibitor (statin) or any component of the formulations
- Active liver disease or unexplained persistent elevations of serum transaminases
- Pregnancy (or women who may become pregnant [**fluvastatin, simvastatin**])
- Breastfeeding
- Co-administration of **simvastatin** with gemfibrozil or danazol
- Co-administration of **pitavastatin** or **simvastatin** with cyclosporine
- Co-administration of **lovastatin** or **simvastatin** with strong CYP3A4 inhibitors (eg, clarithromycin, cobicistat-containing products, erythromycin, HIV protease inhibitors [including boceprevir and telaprevir], itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole)

Zetia (ezetimibe):

- Hypersensitivity to ezetimibe or any component of the formulation
- Concomitant use with a statin in patients with active hepatic disease or unexplained persistent elevations in serum transaminases
- Women who are pregnant or may become pregnant
- Who are breast-feeding (when used concomitantly with a statin)

Rhabdomyolysis is documented by either:

- i. Increased creatinine kinase $> 5 \times$ ULN
- ii. Increased CK isoenzyme, MM-subunit
- iii. Increased myoglobin in blood and urine
- iv. Increased serum potassium
- v. Increased serum creatinine (or decreased CrCl)

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The Child-Pugh classification system:

	Score: 1 point	Score: 2 points	Score: 3 points
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score >9: Decompensated disease

Resources:

Juxtapid (lomitapide) product information, revised by Amryt Pharmaceuticals DAC 09-2020. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed on July 16, 2021.

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