Proprotein Convertase Subtilisin/Kexin type 9(PCSK9) Inhibitors Prior Authorization with Quantity Limit Program Summary - Through Preferred Agent(s)

This program applies to Commercial, Netresults A series, SourceRx, and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the PCSK9 inhibitor Prior Authorization (PA) with quantity limit program is to appropriately select patients for therapy according to the Food and Drug Administration (FDA) approved product labeling and/or clinical practice guidelines and/or clinical studies. This program will require the patient to have a confirmed diagnosis of Homozygous Familial Hypercholesterolemia (HoFH), Heterozygous Familial Hypercholesterolemia (HeFH), or clinical atherosclerotic cardiovascular disease (ASCVD). The criteria will require the patient is currently receiving maximally tolerated statin therapy and is compliant. The program will not require use of a statin if the patient has a history of intolerance to two different statins or an FDA labeled contraindication to a statin. The program requires the use of the preferred agent, Repatha, prior to the non-preferred agent unless the prescriber has documented that the patient had an inadequate response to, intolerance to, FDA labeled contraindication to, or hypersensitivity to Repatha. The criteria will limit all agents to the maximum FDA approved dose for any indication.

TARGET DRUGS

Preferred Agent

Repatha® (evolocumab)

Non-Preferred Agent

Praluent® (alirocumab)

PRIOR AUTHORIZATION AND QUANTITY LIMIT TARGET DRUGS- RECOMMENDED LIMITS

Brand (generic)	GPI	Multisource Code	Quantity Limit
Praluent (alirocumab)			
75 mg/mL pre-filled pen	3935001000D220	M, N, O, or Y	1 package of 2 pens/28 days
75 mg/mL pre-filled syringe	3935001000E520	M, N, O, or Y	1 package of 2 syringes/28 days
150 mg/mL pre-filled pen	3935001000D230	M, N, O, or Y	1 package of 2 pens/28 days
150 mg/mL pre-filled syringe	3935001000E530	M, N, O, or Y	1 package of 2 syringes/28 days
Repatha (evolocumab)			
140 mg/mL pre-filled syringe	3935002000E520	M, N, O or Y	2 syringes/28 days
140 mg/mL pre-filled autoinjector	3935002000D520	M, N, O or Y	2 pens/28 days
420 mg/3.5 mL single-use Pushtronex system (infusor with pre-filled cartridge)	3935002000E230	M, N, O or Y	1 Pushtronex system/30 days

INITIAL PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Target Agents will be approved when ALL of the following are met:

1. The patient has ONE of the following:
   A. A diagnosis of heterozygous familial hypercholesterolemia (HeFH) confirmed by ONE of the following:

i. Genetic confirmation of one mutant allele at the *LDLR, Apo-B, PCSK9*, or *ARH* adaptor protein *1/LDLRAP1* gene locus
OR
ii. BOTH of the following:
1. ONE of the following:
a. Total cholesterol greater than 290 mg/dL (>7.5 mmol/L) (pretreatment or highest level while on treatment)
OR
b. LDL-C greater than 190 mg/dL (>4.9 mmol/L) (pretreatment or highest level while on treatment)
AND
2. History of tendon xanthomas in ONE of the following:
a. The patient
OR
b. The patient's first degree relative (i.e. parent, sibling, or child)
OR
c. The patient's second degree relative (e.g. grandparent, uncle, or aunt)
OR
iii. The Patient has a Dutch Lipid Clinic Network Criteria score of greater than 8
OR
B. A diagnosis of homozygous familial hypercholesterolemia (HoFH) confirmed by ONE of the following:
i. Genetic confirmation of two mutant alleles at the *LDLR, Apo-B, PCSK9*, or *ARH* adaptor protein *1/LDLRAP1* gene locus
OR
ii. Untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (≥7.76 mmol/L) with ONE of the following:
1. The patient had cutaneous or tendon xanthoma before age 10 years
OR
2. Untreated elevated cholesterol levels consistent with heterozygous FH in both parents [untreated LDL-C >190 mg/dL (>4.9 mmol/L) or untreated total cholesterol greater than 290 mg/dL (>7.5 mmol/L)]
OR
C. A diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) defined as having ONE of the following:
i. Acute coronary syndrome
ii. History of myocardial infarction
iii. Stable or unstable angina
iv. Coronary or other arterial revascularization
v. Stroke
vi. Transient ischemic attack
vii. Peripheral arterial disease presumed to be of atherosclerotic origin

AND

2. ONE of the following:
A. The patient is currently adherent (for the past 90 days) to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg, atorvastatin 40-80 mg, or simvastatin 80 mg)
OR
B. BOTH of the following:
i. The patient has tried and is intolerant to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg and atorvastatin 40–80mg)
AND
ii. The patient is currently adherent (for the past 90 days) to low or moderate intensity statin therapy
OR
C. The patient has documented intolerance* to TWO different statins (*intolerance is defined as inability to tolerate the lowest FDA approved starting dose of a statin)

OR

D. The patient has an FDA labeled contraindication to a statin

AND

3. ONE of the following:
   A. The patient has not achieved a 50% reduction in LDL-C from baseline while on a maximally tolerated statin
   OR
   B. The patient has an LDL-C ≥70 mg/dL (≥ 1.81 mmol/L) evaluated within the past 90 days

AND

4. ONE of the following:
   A. The patient is not currently taking another PSCK9 agent
   OR
   B. The other PCSK9 agent will be discontinued before starting therapy with the requested agent

AND

5. The agent is being prescribed by a specialist in the area of practice related to the patient's diagnosis (e.g. cardiologist, endocrinologist, or lipid specialist) or in consultation with a specialist in the area of practice related to the patient's diagnosis

AND

6. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

AND

7. ONE of the following:
   A. The request is for the preferred agent, Repatha
   OR
   B. The request is for the non-preferred agent Praluent AND ONE of the following:
      i. The patient has tried and had an inadequate response to the preferred agent, Repatha
      OR
      ii. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred agent, Repatha

AND

8. ONE of the following:
   A. The quantity requested is less than or equal to the program quantity limit
   OR
   B. The quantity (dose) requested is within FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

Renewal Evaluation

Target Agents will be approved for renewal when ALL of the following criteria are met:

1. The patient has been previously approved for therapy with the requested agent through Prime Therapeutics PA process

AND

2. ONE of the following:
   A. The request is for a preferred agent, Repatha
   OR
   B. The request is for a non-preferred agent, Praluent
      i. The patient has tried and had an inadequate response to the preferred agent, Repatha
      OR
      ii. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred agent, Reptha
      AND
3. The patient has shown clinical benefit with the requested agent

AND

4. The patient is currently adherent (for the past 90 days) to therapy with the requested agent
AND
5. ONE of the following:
    A. The patient is currently adherent (for the past 90 days) to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg, atorvastatin 40-80 mg, or simvastatin 80 mg)
    OR
    B. BOTH of the following:
        i. The patient has tried and is intolerant to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg and atorvastatin 40–80mg)
        AND
        ii. The patient is currently adherent (for the past 90 days) to low or moderate intensity statin therapy
    OR
    C. The patient has documented intolerance* to TWO different statins (*intolerance is defined as inability to tolerate the lowest FDA approved starting dose of a statin)
    OR
    D.The patient has an FDA labeled contraindication to a statin
AND
6. ONE of the following:
    A. The patient is not currently taking another PCSK9 agent
    OR
    B. The patient will discontinue the current PCSK9 agent before starting therapy with the requested agent
AND
7. The agent is being prescribed by a specialist in the area of practice related to the patient's diagnosis (e.g. cardiologist, endocrinologist, or lipid specialist) or in consultation with a specialist in the area of practice related to the patient's diagnosis
AND
8. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
9. ONE of the following:
    A. The prescribed dosage is within the program limit (FDA approved labeled dosage)
    OR
    B. The quantity (dose) requested is within FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength that does not exceed the program quantity limit

Length of approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA INDICATIONS AND DOSING[19, 20]

Agents	Indications*	Strength(s)	Dosing and Administration
Praluent® (alirocumab)	Adjunctive therapy to diet and maximally tolerated statins for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL cholesterol[†]	75 mg/mL pre-filled pen and syringe 150 mg/mL pre-filled pen and syringe	**Atherosclerotic cardiovascular disease or HeFH:** 75 mg SC[^] once every 2 weeks. May increase dose up to 150 mg SC every 2 weeks if the LDL-C response is inadequate[±]
Repatha® (evolocumab)	To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease Adjunct to diet, alone or in combination with other lipid lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia (HeFH) to reduce low-density lipoprotein cholesterol 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	140 mg/mL prefilled pen and autoinjector 420 mg/3.5 mL Pushtronex system (infusor with pre-filled cartridge)	**Adults with established cardiovascular disease or Primary hyperlipidemia with CVD or HeFH:** 140 mg SC every 2 weeks or 420 mg SC monthly **HoFH:** 420 mg SC once monthly

*Limitation of use: The effect of Praluent on cardiovascular morbidity and mortality has not been determined

[±] LDL-C levels should be measured within 4 to 8 weeks of initiating or titrating alirocumab, to assess response and adjust the dose, if needed

[^] Sub-cutenous

[†] The American College of Cardiologists defines clinical atherosclerotic cardiovascular disease as having history of current acute coronary syndrome, myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease presumed to be of atherosclerotic origin.[29]

CLINICAL RATIONALE

Praluent (alirocumab)
Alirocumab is a monoclonal antibody PCSK9 inhibitor. Its efficacy was evaluated in five phase III clinical trials in patients with heterozygous familial hypercholesterolemia (HeFH) or non-HeFH patients with clinical atherosclerotic cardiovascular disease. All patients were receiving maximally tolerated statins with or without other lipid lowering agents and required additional LDL-C reduction.[19] All the phase III trials had the same primary efficacy outcome: mean percent change in LDL-C from baseline measured at 24 weeks of therapy.[19]

The first trial (LONG-TERM), was a double blinded placebo controlled trial evaluating alirocumab 150 mg every 2 weeks (n=1553) versus placebo (n=788). The difference in mean percent change in LDL-C at 24 weeks between alirocumab and placebo was -58% (95 CI: -61%, -56%; p-value <0.0001). A second trial (COMBO I), randomized 209 and 107 subjects to the alirocumab and placebo arms respectively. The alirocumab group received an initial dose of 75 mg every two weeks; the dose was up titrated to 150 mg every 2 weeks at 12 weeks of treatment if the patient required additional LDL-C lowering. The percent change for the alirocumab versus placebo arm was – 45% versus -1% at 12 weeks respectively and -44% versus -2% at 24 weeks respectively. The third (FH I) and forth (FH II) trials enrolled patients with HeFH and randomized them to receive either alirocumab (n= 490) or placebo (n= 245). Those in the alirocumab group received a dose of 75 mg every 2 weeks which was then up titrated to 150 mg every 2 weeks at 12 weeks if additional LDL reduction was required. 42% (n= 196) of the subjects in the alirocumab group required a titration to 150 mg every 2 weeks. The difference in primary outcome (mean percent change in LDL-C) at 24 weeks between the alirocumab and placebo was -54% (95% CI: -59%, -50%; p-value: <0.0001). The fifth efficacy trial (HIGH-FH) enrolled subjects with HeFH and LDL-C greater than or equal to 160 mg/dL while treated with maximally tolerated statins with or without other lipid lowering agents. 72 subjects were enrolled in the alirocumab group (dose: 150 mg every 2 weeks) and 35 subjects in the placebo group. The difference in treatment between the two groups at 24 weeks was -36% (95% CI: -49%, -24%; p-value: <0.0001).

Safety of alirocumab was evaluated in nine clinical trials. The most common adverse events leading to discontinuation of therapy were allergic reactions and elevated liver enzymes. These adverse events resulted in discontinuation of therapy in 5.3% of the study subjects receiving alirocumab compared to 5.1% of patients on placebo. Other adverse events reported included injection site reactions and neurocognitive impairment including confusion and memory impairment (0.8% in the alirocumab versus 0.7% in the placebo).

A preliminary presentation of the ODYSSEY OUTCOMES trial showed that in 18,924 post-ACS patients, after 4 years of therapy with alirocumab vs. placebo, the following were observed:[31]

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	903 (9.5)	1052 (11.1)	0.85 (0.78, 0.93)	0.0003
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
Non-fatal MI	626 (6.6)	722 (7.6)	0.86 (0.77, 0.96)	0.006
Ischemic stroke	111 (1.2)	152 (1.6)	0.73 (0.57, 0.93)	0.01
Unstable angina	37 (0.4)	60 (0.6)	0.61 (0.41, 0.92)	0.02

MACE – Major Adverse Cardiac Event
CHD – Coronary Heart Disease
MI – Myocardial Infarction

All cause death between alirocumab and placebo was only statistically significant for individuals with baseline LDL-C ≥100 mg/dL:[31]

Baseline LDL-C (mg/dL)	Alirocumab vs. Placebo Hazard Ratio (95% CI)
<80	0.89 (0.69, 1.14)
80 to <100	1.03 (0.78, 1.36)
≥100	0.71 (0.56, 0.90)

Individuals with a baseline LDL-C ≥100 mg/dL (median 118 mg/dL) showed the most absolute risk reduction vs. placebo in the following:[31]

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	0.76 (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	0.72 (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	0.69 (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	0.71 (0.56, 0.90)

Repatha (evolocumab)
Evolocumab is a fully IgG2 monoclonal antibody PCSK9 inhibitor. It is indicated for LDL-C reduction in patients with familial hypercholesterolemia (HeFH and HoFH) as well in patients with clinical atherosclerotic cardiovascular disease. Efficacy for use in patients with clinical atherosclerotic cardiovascular disease was evaluated in a double-blind, randomized controlled trial. Subjects (n=296) were randomized to receive evolocumab 140 mg every two weeks, evolocumab 420 mg once a month, or placebo. The primary outcome was mean percent change in LDL-C from baseline. The difference in the primary outcome between evolocumab and placebo at week 12 "was -71% (95% CI: -81%, -61%; p < 0.0001) and -63% (95% CI: -76%, -50%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively".[20] A second double blinded, placebo controlled, trial enrolled 139 subjects with clinical atherosclerotic cardiovascular disease; the primary outcome was to evaluate mean percent change in LDL-C from baseline. Subjects received evolocumab 420 mg once monthly or placebo. The "difference between evolocumab 420 mg once monthly and placebo in mean percent change in LDL-C from baseline at week 52 was -54 % (95% CI: -65%, -42%; p <0.0001)".[20]

Efficacy of evolocumab in HeFH and HoFH was evaluated in two separate double blinded, placebo controlled trials with 329 and 49 subjects respectively. The primary outcome in both trials was mean percent change in LDL-C from baseline. The HeFH trial randomized subjects to receive evolocumab 140 mg every two weeks, evolocumab 420 mg once monthly, or placebo. The difference in mean percent change in LDL-C between evolocumab and placebo at week 12 in the HeFH subjects was -61% (95%CI: -67%, -55%; p < 0.0001) and -60% (95%CI: -68%, -52%; p < 0.0001) for the 140 mg every 2 weeks and 420 mg once monthly dosages, respectively.[20] The HoFH trial had two groups: evolocumab 420 mg once monthly and placebo. The difference in mean percent change in LDL-C from baseline was -31% (95%CI: -44%, -18%; p < 0.0001).

The clinical benefit of evolocumab was evaluated in a phase III trial involving 27564 patients with atherosclerotic cardiovascular disease who had LDL cholesterol levels of 70 mg/dL or higher and who were receiving statin therapy. Patients were randomized to receive either evolocumab (at the FDA approved doses) or placebo. The primary endpoint was the composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina or coronary revascularization. Important secondary end points were composite cardiovascular death, MI, or stroke. Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and key secondary-end point (816[5.9%] vs. 1013 [7.4]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001).[30] The results were consistent across all key subgroups (e.g. age group, sex, and type of atherosclerotic vascular disease). There was no significant difference between the study groups with regard to adverse events. The trial authors concluded that evolocumab in combination with a statin lowered LDL levels and reduced the risk of cardiovascular events.[30]

Safety of evolocumab was evaluated in eight placebo controlled clinical trials (n=2651). The most common side effects were those that occurred greater than or equal to 3% of evolocumab treated patients and included the following: upper respiratory tract infections, injection site reactions, musculoskeletal pain, and gastroenteritis. Injection site reactions were reported in 3.2% of patients on evolocumab. The reports of neurocognitive events were low overall (<1%) but reported more frequently in the evolocumab treated patients.[14]

Alirocumab and evolocumab are indicated for use in combination with maximally tolerated statin therapy however, their safety and efficacy has been evaluated in patients who are not receiving a statin.[25,26,27] Efficacy of alirocumab in patients who are not treated with a statin was evaluated in two double-blind, randomized, phase III clinical trials; the MONO and ALTERNATIVE trials. Both trials had a primary outcome

of mean percent change in LDL-C from baseline measured at 24 weeks of therapy. The MONO trial enrolled subjects who were on diet alone without background lipid-modifying therapy (LMT). Subjects were randomized to receive either alirocumab 75 mg every 2 weeks or ezetimibe. The ALTERNATIVE trial enrolled subjects who were statin intolerant and were receiving LMT(s) other than statin or ezetimibe. Subjects in the ALTERNATIVE trial were randomized to either alirocumab 75 mg every 2 weeks or ezetimibe. In both trials, subjects receiving alirocumab were up titrated to 150 mg every 2 weeks at treatment week 12 if they required additional LDL-C reduction. The mean reduction in LDL-C from baseline at week 24 was 45% and 47.2% for the ALTERNATIVE and MONO trials respectively.[25,26] Efficacy of evolocumab in patients not receiving a statin was evaluated in a single randomized, double blind, double dummy clinical trial (MENDEL-2). The goal of the study was to compare evolocumab (bi-weekly or monthly dose) with placebo and oral ezetimibe. Evolocumab reduced LDL-C on average by 55% to 57% more than placebo ($p<0.001$) and 38% to 40% more than ezetimibe ($p<0.001$).[27]

Familial Hypercholesterolemia (FH)

Familial Hypercholesterolemia (FH) is a genetic disorder (autosomal dominant) that causes significantly elevated level of low-density lipoprotein (LDL) and total cholesterol. FH is a deficiency or absence of the LDL-C receptors. It can also be caused by mutations of the apolipoprotein B-100 (apoB-100) binding site on LDL-C receptors. Apolipoprotein B (apo B) is a primary component of LDL-C. Apo B is responsible for carrying cholesterol to other tissues. Deficiencies of the LDL-C receptor are often caused by mutations in the *LDLR* gene. The LDLR gene is located on the short arm of chromosome 19.[3] LDL-C receptors are responsible for about 70% of the uptake of circulating LDL-C molecules into the liver.[1] Reductions in the number of LDL-C receptors leads to an accelerated deposition of cholesterol on the walls of arteries. The arteries then harden and narrow and reduce the flow of blood. This reduction in blood flow can lead to cardiovascular diseases like stroke and myocardial infarction. There are two types of FH: homozygous FH (HoFH) and heterozygous FH (HeFH). Diagnosis of HeFH and HoFH is based on "personal and family history, physical examination, and lipid concentrations".[21]

Heterozygous familial hypercholesterolemia (HeFH)

HeFH is the most common dominantly inherited disorder in human beings worldwide with an estimated prevalence between 1 in 250 and 1 in 300 people worldwide.[6] Criteria have been developed to aid in diagnosing HeFH. These include the Simon Broome Register criteria and Dutch Lipid clinic Network criteria.[21] Definitive diagnosis of HeFH according to Simon Broome diagnostic criteria requires the patient has one of the following:[13, 21]

- Total cholesterol greater than 6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) greater than 4.0 mmol/L in a child aged younger than 16 years or greater than 7.5 mmol/L or LDL-C greater than 4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) **plus** tendon xanthomas in the patient, or in first-degree relative (parent, sibling or child), or in second-degree relative (e.g. grandparent, uncle or aunt)
  Or
- DNA-based evidence of an LDL receptor mutation, familial defective Apo B-100, or a PCSK9 mutation

The Dutch Lipid Clinic Network criteria assign points based on cholesterol levels, family history of hyperlipedimia or cardiovascular disease, clinical presentation, and/or presence of identified genetic mutation affecting plasma LDL-C.[21, 22, 23] A definitive diagnosis of HeFH can be made in patients with greater than 8 points.

Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia[23]

Group 1: Family history	**Points**
• First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD)	1
• First-degree relative with known LDL cholesterol >95th percentile by age and gender for country	1
• First-degree relative with tendon xanthoma and/or corneal arcus	2
• Children <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: Clinical history	**Points**

• Subject has premature (<55 years, men; <60 years, women) CHD • Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	2 1
Group 3: Physical examination	**Points**
• Tendon xanthoma • Corneal arcus in a person <45 years	6 4
Group 4: Biochemical results (LDL-C)	**Points**
• >8.5 mmol/L (>325 mg/dL) • 6.5–8.4 mmol/L (251–325 mg/dL) • 5.0–6.4 mmol/L (191–250 mg/dL) • 4.0–4.9 mmol/L (155–190 mg/dL)	8 5 3 1
Group 5: Molecular genetic testing (DNA analysis)	**Points**
• Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Use and Interpretation	
Assign only one score, the highest applicable, per group then add the points from each group to achieve the total score Definitive FH diagnosis: > 8 points Probable FH diagnosis: 6 to 8 points Possible FH diagnosis: 3 to 5 points Unlikely FH diagnosis: 0 to 2 points	

Homozygous familial hypercholesterolemia (HoFH)

The prevalence of HoFH is about 1 case per 1 million persons in the United States.[2] There is no known cure for HoFH. Most patients do not survive adulthood beyond age 30 unless treated with liver transplantation, LDL apheresis, or ileal bypass surgery to significantly reduce their LDL-C levels.[5]

Due to the dysfunction of LDL-C receptors, changes in diet and the use of lipid lowering agents only mildly reduce circulating levels of LDL-C. The gold standard of treatment is LDL apheresis, the discriminated removal of LDL-C from the blood stream.

Guidelines advise that diagnosis of HoFH can be made on the basis of genetic or clinical criteria. Genetic confirmation of the HoFH includes confirmation of two mutant alleles at the LDL-R, APOB, PCSK9, or LDLRAP1 genes.[15,21] While genetic testing may provide a definitive diagnosis of HoFH, it is recognized that in some patients genetic confirmation remains elusive, despite exhaustive investigation; indeed, the existence of additional FH genes cannot be excluded. Historically, HoFH has been most commonly diagnosed on the basis of either an untreated LDL-C plasma concentration >13 mmol/L (>500 mg/dL), or a treated LDL-C concentration of ≥8 mmol/L (≥300 mg/dL), accompanied by the presence of cutaneous or tendon xanthomas before the age of 10 years, or the presence of untreated elevated LDL-C levels consistent with HeFH in both parents.[15,21]

The goal of treatment for FH is to reduce the risk of coronary heart disease (CHD) or risk of a CHD-equivalent condition (e.g. carotid artery disease, diabetes, peripheral arterial disease, or abdominal aortic aneurysm).[5] According the American Heart Association (AHA), initial treatment for FH should include a high intensity statin.[28] If the LDL-C is not at goal after 3 months of therapy with the high intensity statin and the patient has been adherent, AHA recommends the addition of ezetimibe. For patients who do not respond to this two-drug regimen within 3 months, AHA recommends addition of a PCKS9, a bile acid sequestrant, or niacin. Patients with HoFH who require additional therapy despite treatment with the three-drug regimen, AHA recommends addition of Juxtapid or Kynamro and LDL apheresis.[28]

Major Risk Factors[4]

- Cigarette smoking
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (< 40 mg/dL)*
- Family history of premature CHD (CHD in male first degree relative < 55 years; CHD in female first degree relative < 65 years)
- Age (men ≥45 years; women ≥55 years)

HDL cholesterol ≥ 60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

Risk categories for developing CHD include[4, 5]:

- High risk: CHD or CHD risk equivalent (10-year risk >20%)
- Moderately high risk: More than 2 risk factors (10-year risk 10-20%)
- Moderate risk: More than 2 risk factors (10-year risk 10%)
- Lower risk: 0-1 risk factor

Atherosclerotic Cardiovascular Disease (ASCVD) – Secondary Prevention

The American College of Cardiology and the American Heart Association Prevention Guidelines focus recommendations on ASCVD risk reduction and identify 4 groups of patients that would benefit from statin therapy (see diagram below). These groups are 1) secondary prevention in patients with *clinical* ASCVD (defined as acute coronary syndrome, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin), 2) primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL, 3) primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and 4) primary prevention in individual without diabetes with an estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL. Evidence supports the risk versus benefit in these patient populations.[16,29]

These guidelines define high, moderate, and low intensity statin therapy for use in secondary and primary prevention (see table below).[16]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Boldface type indicates specific statins and doses that were evaluated in RCTs[16–18,46–49,64–75,77] included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3.[20] All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.[47]

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

BID indicates twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

High intensity statin therapy is anticipated to lower LDL-C levels by approximately ≥50% and moderate intensity statin therapy is anticipated to lower LDL-C levels by approximately 30% to < 50%.[17] According to the 2014 National Committee of Quality Assurance (NCQA) *state of Health Care Quality Report* on cholesterol management, the proportion of patients at high CV risk achieving an LDL-C target of less than 100 mg/dL was in the range of 50% to 59%. Only 1 in 4 achieves an LDL-C below 70 mg/dL. Therefore, there may be between 4-12 million Americans who are a very high or high CV risk who fail to achieve adequate LDL-C reduction with statins with or without other lipid-lowering therapy. This number may be misleading as this number includes those who may not be receiving adequate dose level of statin or are nonadherent to statins.[18]

Practitioners are familiar with treating patients to a specific LDL-C or non-HDL-C target. Several guidelines recommend LDL-C goals of < 100 mg/dL (2.8 mmol/L) or < 70 mg/dL (1.8 mmol/L) depending on level ACC-AHA guidelines recommend the appropriate intensity of statin therapy be used to reduce ASCVD risk in patients most likely to benefit citing a lack of randomized controlled trials supporting the use of a specific LDL-C/non-HDL-C target.

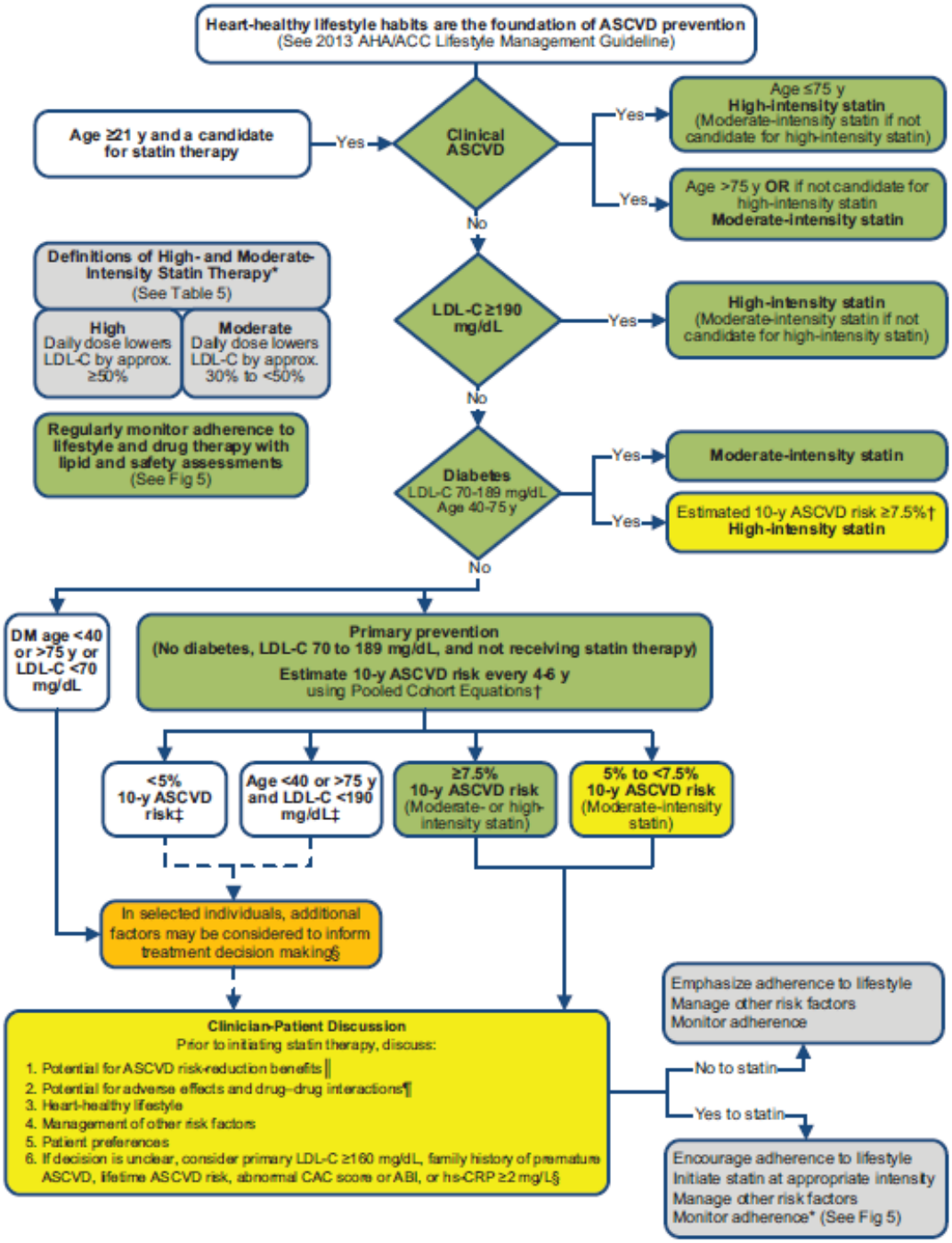

Figure 2. Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults (See Figures 3, 4, and 5 for More Detailed Management Information). Colors correspond to the Classes of Recommendation in Table 1. Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the *framework* for clinical decision making incorporating patient preferences. *Percent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal. †The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin. ‡Consider moderate-intensity statin as more appropriate in low-risk individuals. §For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future. ‖Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential

ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. ¶Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated (see Table 8, Safety Recommendation 8). ABI indicates ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and RCT, randomized controlled trial.

The 2017 Focused Update of the 2016 American College of Cardiology (ACC) Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for Low-Density Lipoprotein Cholesterol (LDL-C) Lowering in the Management of Atherosclerotic Cardiovascular Disease (ASCVD) Risk recommends the following:

- The addition of non-statin therapy, as either ezetimibe or a PCSK9 inhibitor, to maximally tolerated statin therapy in patients with clinical ASCVD with comorbidities and baseline LDL-C 70-189 mg/dL is reasonable. The additional percent LDL-C reduction desired, patient preferences, route of administration, and other factors should be considered. Clinicians should preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk reduction benefits that outweigh the potential for adverse effects and drug-drug interactions, and consider patient preference.
- If patients with clinical ASCVD and comorbidities require > 25% additional LDL-C lowering, a PCSK9 inhibitor may be the preferred non-statin agent. The clinician-patient discussion should consider the extent of available scientific evidence for net ASCVD risk reduction, benefit, administration by SC route, and storage requirements.
- If patients with clinical ASCVD without comorbidities, who are on maximally tolerated statin–ezetimibe or non-statin combination therapy (if documented statin intolerance) achieve a less-than-anticipated response with < 50% reduction in LDL-C (may consider LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL), it is reasonable to engage in a clinician–patient discussion with consideration of the net benefit of a PCSK9 inhibitor (in addition to or in place of ezetimibe) as a second step to achieve further LDL-C reduction. If a PCSK9 inhibitor is prescribed, clinicians should continue maximally tolerated statin and monitoring for adherence to medications and lifestyle, side effects, and ongoing LDL-C response to therapy.
- In the absence of ASCVD or baseline LDL-C ≥ 190 mg/dL, the committee judges that at present, PCSK9 inhibitors do not have an established role for primary prevention of ASCVD in patients with diabetes.
- No data exist examining the use of non-statin therapies in heart failure patients, and heart failure is an exclusion criterion in recent PCSK9 inhibitor trials.

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