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

This program applies to Commercial, Netresults A series, NetResults F series, and Health Insurance Marketplace formularies. Praluent and Repatha are preferred agents.

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 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. If the client has preferred agent(s), a preferred agent may be approved for use once criteria has been met; a non-preferred agent may be approved if the patient is currently treated with the non-preferred agent or the prescriber has documented failure of, intolerance to, FDA labeled contraindication to, or hypersensitivity to the preferred agent(s). The criteria will limit all agents to the maximum FDA approved dose for any indication.

TARGET DRUGS
Preferred Agents
Praluent® (alirocumab)
Repatha™ (evolocumab)

QUANTITY LIMIT TARGET DRUGS—RECOMMENDED LIMITS

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

INITIAL PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Praluent® (alirocumab) or Repatha™ (evolocumab) 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)
   iii. The Patient has a Dutch Lipid Clinic Network Criteria score of greater than 8 (see scoring algorithm in Table 2 below)
      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. BOTH of the following:
      i. ONE of the following:
         1. The patient is currently (for the past 90 days) on high-intensity statin therapy (i.e. rosuvastatin 20-40 mg or atorvastatin 40-80 mg)
         OR
      2. BOTH of the following:
         a. The patient has tried and is intolerant to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg and atorvastatin 40–80mg)
         AND
         b. The patient is currently (for the past 90 days) on low or moderate intensity statin therapy

AND
ii. The patient is adherent^ (for the past 90 days) to statin therapy as prescribed

OR

B. 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

C. 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 ≥100 mg/dL (≥ 2.59 mmol/L) evaluated within the past 90 days

AND

4. Praluent (alirocumab) and Repatha (evolocumab) will not be used concurrently with each other

AND

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

^Adherence is defined as filling ≥80% of therapy as prescribed in the past 90 days

Length of Approval: 6 months

Renewal Evaluation

Praluent® (alirocumab) or Repatha™ (evolocumab) 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 patient has shown a percent change of ≥ 45% in LDL-C from baseline (LDL-C before PCSK9 therapy)

   OR

   B. The patient has a current (within the past 30 days) LDL-C ≥100 mg/dL (≥ 2.59 mmol/L)

   AND

3. The patient is adherent^ (for the past 180 days) to therapy with the requested agent

AND

4. ONE of the following:
   A. ALL of the following:
      i. ONE of the following:
         1. The patient is currently (for the past 180 days) on high-intensity statin therapy (i.e. rosuvastatin 20-40 mg or atorvastatin 40-80 mg)

         OR

      2. BOTH of the following:
         a. The patient has tried and is intolerant to high-intensity statin therapy (i.e. rosuvastatin 20-40 mg and atorvastatin 40–80mg)

         AND

         b. The patient is currently (for the past 180 days) on low or moderate intensity statin therapy

      AND

ii. The patient is adherent^ (for the past 180 days) to statin therapy as prescribed

OR
B. 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
C. The patient has an FDA labeled contraindication to a statin

AND
5. Praluent (alirocumab) and Repatha (evolocumab) will not be used concurrently with each other

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

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

AND
8. 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

^Adherence to standard therapy is defined as filling ≥80% of therapy as prescribed in the past 180 days

*Adherence to PCSK9 therapy is defined as filling ≥80% of the PCSK9 therapy at an FDA approved dose in the past 180 days

Length of approval: 12 months

Non-Preferred Agent(s) – will be approved when ONE of the following additional criteria are met:

1. The patient is currently being treated with the non-preferred agent OR

2. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred agent(s) OR

3. The prescriber has submitted documentation in support of the use of the non-preferred agent(s), for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

Table 1

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Contraindication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Praluent (alirocumab)</td>
<td>History of a serious hypersensitivity reaction to Praluent (alirocumab)</td>
</tr>
<tr>
<td>Repatha (evolocumab)</td>
<td>History of a serious hypersensitivity reaction to Repatha (evolocumab)</td>
</tr>
</tbody>
</table>

Table 2: Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolemia

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

<table>
<thead>
<tr>
<th>Group 2: Clinical history</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject has premature (&lt;55 years, men; &lt;60 years, women) CHD</td>
<td>2</td>
</tr>
<tr>
<td>Subject has premature (&lt;55 years, men; &lt;60 years, women) cerebral or peripheral</td>
<td>1</td>
</tr>
</tbody>
</table>
vascular disease

<table>
<thead>
<tr>
<th>Group 3: Physical examination</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>6</td>
</tr>
<tr>
<td>Corneal arcus in a person &lt;45 years</td>
<td>4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4: Biochemical results (LDL-C)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8.5 mmol/L (&gt;325 mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>6.5–8.4 mmol/L (251–325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>5.0–6.4 mmol/L (191–250 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td>4.0–4.9 mmol/L (155–190 mg/dL)</td>
<td>1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5: Molecular genetic testing (DNA analysis)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative mutation shown in the LDLR, APOB, or PCSK9 genes</td>
<td>8</td>
</tr>
</tbody>
</table>

**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

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

<table>
<thead>
<tr>
<th>Agents</th>
<th>Indications*</th>
<th>Strength(s)</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Praluent®</strong></td>
<td>Adjunctive therapy to diet and maximally tolerated statins for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease†</td>
<td>75 mg/mL pre-filled pen and syringe, 150 mg/mL pre-filled pen and syringe</td>
<td>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^</td>
</tr>
<tr>
<td><strong>Repatha™</strong></td>
<td>Adjunctive therapy to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD)^</td>
<td>140 mg/mL prefilled pen and autoinjector, 420 mg/3.5 mL Pushtronex system (infusor with pre-filled cartridge)</td>
<td>Primary hyperlipidemia with CVD or HeFH: 140 mg SC every 2 weeks or 420 mg SC monthly. HoFH: 420 mg SC once monthly</td>
</tr>
</tbody>
</table>

*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

\^ Subcutaneous

† 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.

### CLINICAL RATIONALE

**Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9)**

PCSK9 is a protein that regulates plasma concentration of LDL-cholesterol (LDL-C) through regulation of LDL receptors (LDL-R). Upon bind LDL-R, PCSK9 promote lysosomal degradation of LDL-R within hepatocytes. As a result, there is a decrease in LDL-R and consequently increased plasma LDL-C concentration. Inhibition of PCSK9 activity is therefore, a novel and viable means by which to lower plasma LDL-C. Examples of FDA approved PCSK9 inhibitors include Praluent® (alirocumab) and Repatha™ (evolocumab).

**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. 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.
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).

**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). 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 hyperlipidemia or cardiovascular disease, clinical presentation, and/or presence of identified genetic mutation affecting plasma LDL-C. 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

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

<table>
<thead>
<tr>
<th>Group 2: Clinical history</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject has premature (&lt;55 years, men; &lt;60 years, women) CHD</td>
<td>2</td>
</tr>
<tr>
<td>Subject has premature (&lt;55 years, men; &lt;60 years, women) cerebral or peripheral vascular disease</td>
<td>1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Group 3: Physical examination</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>6</td>
</tr>
<tr>
<td>Corneal arcus in a person &lt;45 years</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4: Biochemical results (LDL-C)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;8.5 mmol/L (&gt;325 mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>6.5–8.4 mmol/L (251–325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>5.0–6.4 mmol/L (191–250 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td>4.0–4.9 mmol/L (155–190 mg/dL)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5: Molecular genetic testing (DNA analysis)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative mutation shown in the LDLR, APOB, or PCSK9 genes</td>
<td>8</td>
</tr>
</tbody>
</table>

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. 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.

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. 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 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%.

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.

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
Patients who do not achieve adequate response from statins may require addition of non-statin therapy. In 2016, the ACC updated their guidelines to address the role of non-statin therapy in lowering LDL-C. The guidelines recommend ezetimibe as the first non-statin agent that should be considered in patients who require additional therapy. Bile acid sequestrants (BAS) are recommended in place of ezetimibe for patients who are ezetimibe intolerant and have triglycerides of <300 mg/dL. The ACC recommends addition of PCSK9s in patients who are not adequately managed with maximally tolerated statins and ezetimibe or BAS.

REFERENCES

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