Clinical Policy Title: Statin use in adults and children

Clinical Policy Number: CCP.1220

Effective Date: May 1, 2016
Initial Review Date: February 17, 2016
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Related policies:
None.

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of statins in adults and children to be clinically proven and, therefore, medically necessary when the following criteria are met

1) Secondary prevention in individuals with clinical arteriosclerotic cardiovascular disease
2) Primary prevention in individuals with primary elevations of low-density lipoprotein cholesterol ≥190 mg/dL
3) Primary prevention in individuals with diabetes 40 to 75 years of age who have low-density lipoprotein cholesterol 70 to 189 mg/dL
4) Primary prevention in individual without diabetes and with estimated 10-year arteriosclerotic cardiovascular disease risk ≥7.5 percent, 40 to 75 years of age who have lipoprotein cholesterol 70 to 189 mg/dL (Stone, 2014).

For any determinations of medical necessity for medications, refer to the applicable state approved pharmacy policy.
Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of statins in adults and children are not medically necessary.

Alternative covered services:

- None.

Background

Cardiovascular disease is a major cause of morbidity and mortality in the U.S. and around the world. Currently, 28.1 million (11.5 percent) of American adults have heart disease, a figure that is 36.5 percent for adults over age 75 (Centers for Disease Control and Prevention, 2016). In 2016, a total of 840,678 Americans died of circulatory diseases (ICD-10 codes I00-I99), which represents 30.6 percent of deaths from all causes (Centers for Disease Control and Prevention, 2016).

High blood cholesterol is linked to cardiovascular disease events and is an important risk factor. Reducing high blood cholesterol is thus an important way to reduce the chances of suffering a cardiovascular disease event. Statins — lipid-lowering medications that inhibit a step used by the liver to synthesize cholesterol — (e.g. simvastatin, pravastatin, atorvastatin) are the first-line treatment for high cholesterol, and thus, heart disease (Ziaeian, 2017).

Since the early statin randomized controlled trials were reported in the 1990s, potential risks and benefits have been discussed and studied by professionals. Potential benefits include a reduction in low-density lipoprotein cholesterol levels, leading to reductions in incidence, prevalence, deaths, and hospitalizations of arteriosclerotic cardiovascular disease — along with reductions in other related conditions. Potential risks (as stated by the U.S. Food and Drug Administration) include unnecessary use in persons who don’t need statins, cognitive impairment, muscle damage (lovastatin only), along with risk for higher rates of new-onset diabetes. Moreover, some have concerns that women have been under-represented in trials (Holland, 2017; Goldfine, 2012).

Familial hypercholesterolemia is one of the most common inherited metabolic diseases; the average worldwide prevalence of heterozygous familial hypercholesterolemia is at least 1 in 500 (de Ferranti, 2016). Diagnosis of familial hypercholesterolemia in children is based on highly elevated low-density lipoprotein cholesterol level or DNA-based analysis, or both. Coronary atherosclerosis has been detected in men with heterozygous familial hypercholesterolemia as young as 17 years old and in women with heterozygous familial hypercholesterolemia at 25 years old.
Since the clinical complications of atherosclerosis occur prematurely, especially in men, lifelong hypolipidemic measures, started in childhood, are recommended to reduce the risk of cardiovascular disease. In children, hypercholesterolemia results from an alteration, genetic or acquired, in lipoprotein metabolism. It is possible to maintain a normal lipid profile in most individuals with familial hypercholesterolemia in order to reduce the risk of early onset of atherosclerosis, which is associated with serious cardiovascular complications from childhood. In children with familial hypercholesterolemia, diet is the cornerstone of treatment. Anion exchange resins, such as cholestyramine and colestipol, can be effective, but are poorly tolerated. Since the 1990s statin studies have been carried out among children with familial hypercholesterolemia (aged 7 to 17 years), based on the belief that statins reduced their serum low-density lipoprotein. More long-term studies are needed to establish safety and effectiveness.

Searches

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 21, 2018. Searched terms were: "familial hypercholesterolemia," "pediatric hypercholesterolemia" and "statin use in adults and children."

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

The American College of Cardiology/American Heart Association offers a clinical guideline on statin use. The guideline recommends statin treatment for persons with arteriosclerotic cardiovascular disease (secondary prevention); and for primary prevention in persons with 1) low-density lipoprotein cholesterol ≥190 mg/dL; 2) persons with diabetes age 40-75 with cholesterol 70 to 189 mg/dL; and 3) persons without diabetes with an estimated 10-year arteriosclerotic cardiovascular disease risk ≥7.5 percent, or those who are age 40-75 with cholesterol 70-189 mg/dL (Stone, 2014).
A U.S. Preventive Services Task Force guideline on statin use for primary prevention of arteriosclerotic cardiovascular disease recommended that statins be initiated for persons age 40-75 with no history of the disease, at least one risk factor for the disease, or a 10 year risk for the disease over 10 percent; if the 10 year risk is 7.5 - 10 percent, statins should be used selectively. Cholesterol levels and presence/absence of diabetes were not mentioned (U.S. Preventive Services Task Force, 2017).

A National Institute for Health and Care Excellence policy addressed cardiovascular disease risk assessment, listing tests that should be performed before starting statin treatment (National Institute for Health and Care Excellence, 2014). The Canadian Cardiovascular Society guideline for prior testing and management of cardiovascular disease with statins featured advocacy for low-density lipoprotein targets for patients using statins (Anderson, 2016). A European Society of Cardiology/European Atherosclerosis Society guideline acknowledged that statins were the gold standard of treating high cholesterol, but that lifestyle changes could be more beneficial than statins for mild cases of hypercholesterolemia (European Society of Cardiology/European Atherosclerosis Society, 2016).

The American Academy of Pediatrics has a guideline recommending that statins be used as a first-line agent in children as young as eight years old. Studies show stating monotherapy in children is effective, well tolerated and safe; long-term studies are needed to confirm these findings (Lamaita, 2013).

The new American College of Cardiology/American Heart Association guidelines would raise the number of U.S. adults receiving or eligible for statins from 43.2 million to 56.0 million, mostly among adults without cardiovascular disease with a 10-year risk of a cardiovascular event (Pencina, 2014).

In a meta-analysis of eight studies (n=24,674), elderly patients taking statins or placebo were followed for an average of 3.5 years. Statins significantly reduced risk of myocardial infarction (39.4 percent, \( P = 0.003 \)), and of stroke (23.8 percent, \( P = 0.006 \)). Reductions in risk of all-cause death (-5.9 percent, \( P = 0.21 \)) and cardiovascular death (-9.3 percent, \( P = 0.49 \)) were not significant (Savarese, 2013).

A systematic review to assess the effects, both in terms of benefits and harms of statins, for the primary prevention of CVD found 18 randomized controlled trials with 19 trial arms (56,934 patients) dating from 1994 to 2008. All were randomized control trials comparing statins with usual care or placebo. The mean age of the participants was 57 years (range 28 — 97 years), 60.3% were men, and of the eight trials that reported on ethnicity, 85.9 % were Caucasian. Duration of treatment was a minimum one year and with follow-up of a minimum of six months. All-cause mortality and fatal and non-fatal cardiovascular disease events were reduced with the use of statins as was the need for revascularization (the restoration of an adequate blood supply to the heart) by means of surgery (coronary artery bypass graft) or by angioplasty. Of 1000 people treated with a statin for five years, 18 would avoid a major cardiovascular disease event which compares well with other treatments used for preventing cardiovascular disease. Taking statins did not increase the risk of serious adverse effects such as cancer. Statins are likely to be cost-effective in primary prevention (Pencina, 2014).
A systematic review examined eighteen randomized control trials (19 trial arms; 56,934 participants) that recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria) to study the effect of statins on primary prevention of cardiovascular disease. All-cause mortality was reduced by statins (Odds Ratio 0.86); as was combined fatal and non-fatal cardiovascular disease risk ratio 0.75, combined fatal and non-fatal coronary heart disease events (Risk Ratio 0.73) and combined fatal and non-fatal stroke (Risk Ratio 0.78). Reduction of revascularization rates (Risk Ratio 0.62) was also observed. The evidence suggests that primary prevention with statins is likely to be cost-effective and may improve patient quality of life (Huffman, 2013).

A systematic review/meta-analysis of 34 trials (n=270,288) compared undergoing more- or less-intensive statin therapy for elevated low-density lipoprotein cholesterol. No difference was observed between the high- and low-intensity groups (7.08 versus 7.70 percent). Significantly greater reductions were reported in patients with high baseline cholesterol levels (P <.001). Cardiovascular mortality was lower for the high- and low-intensity group (3.48 versus 4.07 percent). Those with a baseline cholesterol level over 100 mg/dL benefited most (Navarese, 2018).

A systematic review/meta-analysis of 24 randomized controlled trials of heart failure patients (n=11,464) compared outcomes for statins to placebo or controls. Statins did not significantly reduce rates of sudden cardiac death events (relative risk 0.92) or all-cause mortality, but significantly reduced hospitalization for worsening heart failure (0.79) (Al-Gobari, 2017).

A study of outcomes comparing high-compliance and low-compliance of statin use in persons with no prior cardiovascular disease found greater reductions of 18, 47, 26, and 49 percent in ischemic heart disease risk, cardiovascular disease, cerebrovascular event, and mortality, all highly significant (Martin-Ruiz, 2018).

In a double-blind case-control study of patients starting with relatively low-density lipoprotein cholesterol levels (as low as a median of 63 mg/dL) a consistent risk reduction in major vascular events, and reduction to levels as low as a median of 21 mg/dL were observed. Results suggest further lowering of cholesterol beyond current targets would also improve cardiovascular safety (Sabatine, 2018).

A narrative review of statin among the elderly found the association of adverse effects with intensive doses of statin and their interactions with other drugs may be more problematic in older adults. Statin therapy appears cost-effective for individuals with higher cardiovascular disease risk but this is dependent on the assumptions used. The authors concluded that evidence remains limited regarding the overall benefit of starting statin therapy in adults ages 80 years and older; thus, clinical judgment remains necessary in making this decision (Desai, 2012).

A Cochrane systematic review evaluated the long-term safety of statin use in the pediatric age group of children with heterozygous familial hypercholesterolemia (n=1177). In general, follow-up short (median 24 weeks). Statins use reduced average low-density lipoprotein cholesterol at each point studied
Authors conclude that children using statins should be carefully monitored by pediatricians and (later) adult lipidologists after age 18 (Vuorio, 2017).

A systematic review of 21 studies, of which eight were randomized placebo-controlled studies (1074 children) found that statins reduced the mean low-density lipoprotein cholesterol concentration at all time points from six weeks to two years. The risks of myopathy and clinical adverse events were very low in both groups. In one study simvastatin was shown to improve flow-mediated dilatation of the brachial artery, and in another study treatment with pravastatin for two years induced a significant regression in carotid intima media thickness. The authors concluded that statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia. No significant safety issues were identified; however, long-term safety is unknown (Vuorio, 2014).

A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia aged 8 to 18 years examined six pertinent studies (n=798 children) inclusive of 12 to 104 weeks of treatment. Total cholesterol, LDL cholesterol, and apolipoprotein B were significantly reduced, whereas high-density lipoprotein cholesterol and apolipoprotein A1 were significantly increased by statin therapy. No statistically significant differences were found between statin- and placebo-treated children for adverse events, sexual development, muscle toxicity, or liver toxicity. Authors contend the results support the safety of statins in children (Avis, 2007).

A meta-analysis of 12 randomized controlled trials (n=1023) explored outcomes for patients taking statins daily versus every other day. Findings of the study included no significant difference between the two groups in low-density lipoprotein cholesterol level and triglycerides changes. Reductions in triglycerides were both significant ($P < .00001$ for daily use, $P < .002$ for alternate-day use. Both were generally well tolerated with good adherence (Awad, 2018).

Some statins may be more effective than others. In terms of reducing the risk of coronary heart disease morality, fluvastatin (77.3 percent), atorvastatin (72.3) and lovastatin (68.4) had higher probability than other statins. In terms of reducing all-cause mortality, atorvastatin (78.6), fluvastatin (77.1) and pitavastatin (74.1) had higher probability than other statins (Lu, 2016).

A systematic review/meta-analysis of the effects of statins on reducing mortality in persons with chronic obstructive pulmonary disease was the topic of 20 articles (n=303,981). All-cause mortality declined by 35 percent, significant at ($P < 0.001$). Exacerbation of the condition with or without hospitalization declined 42 percent, significant at $P < 0.001$ (Li, 2017).

A systematic review of 21 articles (n=65,196) documented that those subjects taking statins had a relative risk of 0.97 for developing cancer, compared to those who were not taking statins, indicating that statins pose no elevated risk for cancer (Kim, 2017).

Policy updates:
A total of eight guidelines/other and 12 peer-reviewed references were added to, and three peer-reviewed references removed from this policy in August 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Vuorio (2017) Statins for children with familial hypercholesterolemia | **Key points:**  
  - A systematic review evaluated the long-term safety of statin use in the pediatric age group of children with heterozygous familial hypercholesterolemia (n=1177).  
  - In general, the intervention and follow-up time was short (median 24 weeks; range from six weeks to two years).  
  - Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points (moderate quality evidence).  
  - Serum aspartate and alanine aminotransferase, as well as creatinine kinase concentrations, did not differ between treated and placebo groups at any time point (low quality evidence).  
  - The risks of myopathy (low quality evidence) and clinical adverse events (moderate quality evidence) were very low and also similar in both groups.  
  - In one study simvastatin was shown to improve flow-mediated dilatation of the brachial artery (low quality evidence), and in another study treatment with pravastatin for two years induced a significant regression in carotid intima media thickness (low quality evidence).  
  - The authors concluded that statin treatment is an effective and safe lipid-lowering therapy in children with familial hypercholesterolemia.  
  - Children treated with statins should be carefully monitored and followed up by their pediatricians and their care transferred to an adult lipidologist once they reach 18 years of age. |
| Pencina (2014) Hypercholesterolemia -a disease with expression from childhood | **Key points:**  
  - A systematic review to assess the effects, both in terms of benefits and harms of statins, for the primary prevention of cardiovascular disease found 18 randomized controlled trials with 19 trial arms (56,934 patients) dating from 1994 to 2008.  
  - All were randomized control trials comparing statins with usual care or placebo.  
  - The mean age of the participants was 57 years (range 28 — 97 years), 60.3 percent (%) were men, and of the eight trials that reported on ethnicity, 85.9 % were Caucasian.  
  - Duration of treatment was a minimum one year and with follow-up of a minimum of six months.  
  - All-cause mortality and fatal and non-fatal cardiovascular events were reduced with the use of statins as was the need for revascularization (the restoration of an adequate blood supply to the heart) by means of surgery (coronary artery bypass graft) or by angioplasty.  
  - Of 1000 people treated with a statin for five years, 18 would avoid a major cardiovascular disease event which compares well with other treatments used for preventing cardiovascular disease.  
  - Taking statins did not increase the risk of serious adverse effects such as cancer.  
  - Statins are likely to be cost-effective in primary prevention. |
| Vuorio (2014) Statins for children | **Key points:**  
  - A systematic review of 21 studies, of which eight were randomized placebo-controlled studies (1074 participants,) found that statins reduced the mean low-density lipoprotein cholesterol concentration at all time points from six weeks to two years.  
  - The risks of myopathy and clinical adverse events were very low in both groups. In one study simvastatin was shown to improve flow-mediated dilatation of the brachial artery, and |
in another study treatment with pravastatin for two years induced a significant regression in carotid intima media thickness.

- The authors concluded that statin treatment is an efficient lipid-lowering therapy in children with familial hypercholesterolemia.
- No significant safety issues were identified; however, long-term safety is unknown.

**Huffman (2013)**

**Statins for the primary prevention of cardiovascular disease**

**Key points:**

- Eighteen randomized control trials (19 trial arms; 56,934 participants) were included.
- Fourteen trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria).
- All-cause mortality was reduced by statins (Odds Ratio (OR) 0.86, 95% Confidence Interval (CI) 0.79 to 0.94); as was combined fatal and non-fatal cardiovascular disease Risk Ratio (RR) 0.75 (95% CI 0.70 to 0.81), combined fatal and non-fatal coronary heart disease events RR 0.73 (95% CI 0.67 to 0.80) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89).
- Reduction of revascularization rates (RR 0.62, 95% CI 0.54 to 0.72) was also seen.
- Total cholesterol and low-density lipoprotein cholesterol were reduced in all trials but there was evidence of heterogeneity of effects.
- There was no evidence of any serious harm caused by statin prescription.
- Evidence available to date showed that primary prevention with statins is likely to be cost-effective and may improve patient quality of life.
- Recent findings from the Cholesterol Treatment Trialists study using individual patient data meta-analysis indicate that these benefits are similar in people at lower (< 1% per year) risk of a major cardiovascular event.

**Desai (2012)**

**A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia**

**Key points:**

- Only a few studies of statin use have included older individuals, particularly ages 80 years or older.
- A recent narrative review of statin in this population found the association of adverse effects with intensive doses of statin and their interactions with other drugs may be more problematic in older adults.
- Statin therapy appears cost-effective for individuals with higher cardiovascular disease risk but this is dependent on the assumptions used.
- The authors concluded that evidence remains limited regarding the overall benefit of starting statin therapy in adults ages 80 years and older; thus, clinical judgment remains necessary in making this decision.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determination:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<td>Statin therapy prescribed or currently being taken (CAD)</td>
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<td>Patients who are currently statin therapy users or received an order (prescription) for statin therapy</td>
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<td>G9963</td>
<td>Any fasting or direct LDL-C laboratory test result = 190 mg/dl</td>
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<tr>
<td>G9966</td>
<td>The highest fasting or direct LDL-C laboratory test result of 70/189 mg/dl in the measurement period or two years prior to the beginning of the measurement period</td>
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