

## **Drug Class Update: Statins & Combos (High Potency & Low-Medium Potency)**

**Date of Review:** April 2021

**Date of Last Review:** January 2015

**Dates of Literature Search:** 07/25/2014 – 12/31/2020

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

To search for and evaluate new comparative evidence for the efficacy and safety of statin therapy in reducing cardiovascular (CV) outcomes or mortality in adults with CV disease or at high risk for CV disease.

### **Research Questions:**

- Is there any new comparative evidence for statin lipid-lowering agents in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of CV disease?
- Is there any new comparative evidence for the harms of statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
- Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one statin agent is more effective or associated with more harm than other statin agents?

### **Conclusions:**

- There is high quality evidence that statins reduce all-cause mortality and CV events (i.e. non-fatal myocardial infarction [MI], coronary death, non-fatal stroke) compared to placebo in patients with clinical atherosclerotic cardiovascular disease (ASCVD) (i.e. acute coronary syndrome [ACS], history of MI, unstable angina, stroke, and symptomatic peripheral artery disease [PAD]).
- There is low quality evidence that high intensity statin dosing reduces non-fatal CV events compared to moderate intensity statins in patients with ASCVD, but no benefit in overall mortality or CV mortality.
- There is high quality evidence that moderate-dose statins lower CV mortality, CV events and all-cause mortality in the primary prevention of ASCVD, with greater absolute benefits in patients at higher baseline CV risk. There is insufficient evidence demonstrating a larger benefit with high-dose statins in the primary prevention population.
- There is moderate quality evidence of no difference in proportional effects of statins between men and women and low-quality evidence no differences in efficacy or safety based on other subgroups, including age, race, baseline lipid levels, presence of diabetes or hypertension.

- There is insufficient evidence of a significant difference in effectiveness on clinical outcomes between statin drugs. Instead, benefit depends on LDL-c lowering ability and baseline risk.
- There is moderate quality evidence of a higher risk of discontinuations due to adverse events, new onset diabetes mellitus and elevations in aminotransferases without reports of liver failure with high dose statins compared to control or lower dose statins.

#### **Recommendations:**

- Continue to maintain preferred statins that offer low-, moderate- and high-intensity statins for both the primary and secondary prevention of ASCVD as well as for individuals at a higher risk of statin associated adverse events.
- Combine high potency and low-medium potency PDL classes into one PDL statin class
- After evaluation of comparative costs in executive session, make rosuvastatin tablets preferred.

#### **Summary of Prior Reviews and Current Policy:**

- Evidence supports the use of statins for the primary prevention of cardiovascular disease (CVD) with a demonstrated reduction in all-cause mortality (RR 0.86, 95% CI 0.79-0.94, NNT 96), fatal CVD events (RR 0.83, 95% CI 0.72-0.96), and fatal coronary heart disease (RR 0.82, 95% CI 0.70-0.96).
- There is moderate quality evidence of an increased risk of developing diabetes mellitus (RR 1.18, 95% CI 1.01-1.39) with statin therapy compared to placebo.
- There is evidence that statin therapy is not associated with an increased risk of cancer (RR 1.16, 95% CI 0.87-1.54).
- There is insufficient comparative evidence on long term clinical outcomes or evidence that one statin agent is safer than another.

#### **Background:**

The association between hypercholesterolemia, and particularly elevated low-density lipoprotein (LDL) cholesterol, and cardiovascular disease (CVD) is well established.<sup>1</sup> In addition to optimizing a healthy lifestyle, prevention of CV events involves optimization of treatments that have proven benefits on reduction in CV events and/or cardiovascular (CV) mortality. Statins have strong and consistent evidence demonstrating CV risk reduction. For every reduction of 39 mg/dl in low density lipoprotein cholesterol (LDL-C), statins can provide relative reductions in CV events by 22% and all-cause mortality of 10%.<sup>1</sup> Statin therapy remains the pharmacologic cornerstone to lower LDL-C levels and is therefore used in the treatment of both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). However, dose escalation and/or combination with non-statin therapy to reduce ASCVD risk may be necessary for high-risk populations.<sup>2</sup>

Statins are competitive inhibitors of 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibits the rate controlling step in cholesterol synthesis.<sup>1</sup> Absolute benefit of therapy with statins depends more on an individual's baseline CV risk, rather than cholesterol levels. Guidelines recommend statin therapy based on the LDL lowering ability (**Table 1**).<sup>2,3</sup> Moderate intensity statins are recommended in most patients and can lower the LDL-C by 30-49%. For high-risk individuals who may benefit from further LDL-lowering, high intensity dosing is recommended, which can lower the LDL-C by more than 50%. There does not seem to be significant differences in efficacy between different statins. The most common side effect reported with statin therapy is myalgia. However, the risk of rhabdomyolysis and serious liver injury is low and there remains debate on how much of the reported myalgia side effects are due to a nocebo effect.<sup>4</sup> For statin intolerant patients, lower doses or alternative dosing strategies of statins are recommended.

Current guidelines recommend at least moderate intensity statins as first line therapy for those with clinical ASCVD, severe hypercholesterolemia (LDL-C > 190), and in those with diabetes.<sup>2</sup> For the primary prevention of CVD in those without diabetes, there is some debate on when to initiate therapy based on the

American College of Cardiology / American Heart Association (ACC/AHA) pooled cohort equation. A shared decision-making strategy and consideration of additional risk factors is recommended prior to initiating treatment for primary prevention. Guideline recommendations vary between statin consideration with a 10-year ASCVD of at least 7.5%, 10% or 12% depending on the guideline.<sup>2,5,6</sup> However, they are all consistent with recommendations to use a shared-decision making strategy, consideration of additional risk factors and harms, and that the benefit risk profile is unclear in people 75 years and older and younger than 40 years without clinical ASCVD.

**Table 1: Statin Intensity<sup>2</sup>**

	LDL-C reduction	Drug and Dose
High-intensity	≥ 50%	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg
Moderate-intensity	30 to 49%	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40mg Pravastatin 40-80mg Lovastatin 40mg-80mg Fluvastatin 40 mg BID Pitavastatin 1-4mg
Low-intensity	<30%	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

## **New Systematic Reviews:**

After review, 11 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria)<sup>7-9, 10</sup>, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),<sup>11-13</sup> or outcome studied (e.g., non-clinical). Systematic reviews evaluating the effect on LDL-C but not cardiovascular events were not included.<sup>14-18</sup>

### Secondary Prevention

A meta-analysis included RCTs comparing either statin to placebo or standard to intensive statin treatment for the secondary prevention of CV and cerebrovascular events in patient with diabetes.<sup>19</sup> Only high quality, double-blind studies were included, and studies were assessed for quality using the Jadad score. Nine RCTs were included; five comparing standard dose statin with placebo and four comparing intensive-dose to standard dose statin. For the comparison of standard-dose statin versus placebo, the authors found a NNT of 27 over 5 years to prevent one major CV or cerebrovascular event (RR 0.85; 95% CI 0.79 to 0.91).<sup>19</sup> There was no significant difference in all-cause mortality (RR 0.78; 95% CI 0.53-1.14). Compared to standard dose-statin, there was a significant reduction in major CV events with intensive dose statin over 5 years (34.9% vs. 31.7%, respectively; RR 0.91; 95% CI 0.84 to 0.98).<sup>19</sup> Standard dose statins included pravastatin 40 mg, atorvastatin 10 mg and simvastatin 20 mg daily. The intensive-dose statin groups were treated with simvastatin 80 mg or atorvastatin 80 mg. The data were insufficient to compare standard dose to intensive dose treatment for secondary endpoints in meta-analysis, including all-cause and CV mortality.<sup>19</sup>

A systematic review attempted to evaluate the impact of more-intensive vs. less-intensive LDL-C lowering with pharmacologic treatment, including statins, in patients with established ASCVD.<sup>20</sup> A literature search was done to identify trials with > 500 patients evaluating CV outcomes during at least 1-year follow up. The Cochrane risk of bias assessment tool was used to evaluate the risk of bias among included trials. A total of 19 trials met inclusion criteria, including 15 trials of statins. Risk of bias was rated as low in all studies. Overall, there was a significant reduction in major vascular events with more-intensive treatment compared to less-intensive treatment (RR 0.81; 95% CI 0.77-0.86).<sup>20</sup> More intensive vs. less-intensive included statin vs. no statin, more-statin vs. less-statin and non-statin in combination with statin compared to statin plus placebo. The benefit was greater in trials comparing statin vs. no statin (RR 0.77; 95% CI 0.71-0.83) than in trials of more-statin vs. less-statin (RR 0.88; 95% CI 0.82-0.93) or in trials of non-statin vs. placebo (RR 0.85; 95% CI 0.77-0.95).<sup>20</sup> There was a significant reduction in all-cause (RR 0.85; 95% CI 0.78 to 0.92) and CV mortality (RR 0.78; 95% CI 0.73 to 0.84; I<sup>2</sup> 3%) with statin compared to no statin. However, there was no survival benefit with more intensive statin compared to less intensive statin treatment.

Authors of a recent meta-analysis searched all RCTs comparing more- (intensive statin therapy or combination therapy with ezetimibe or PCSK9 inhibitor on top of statin) and less-intensive therapy on CV outcomes.<sup>21</sup> The Cochrane risk of bias tool was used to assess quality of each trial. The primary outcome was major adverse cardiovascular events (MACEs) or equivalent. Twenty-three studies (n=133,037) studies were included. Twelve evaluated more intensive versus less intensive statins and will be the focus of this review. The majority of included patients had coronary artery disease (CAD) and follow up duration ranged from 0.8 to 6.7 years. Overall, more intensive therapy (intensive statin, ezetimibe, or PCSK9 inhibitor) reduced the odds of MACE compared to less intensive therapy (odds ratio [OR] 0.84; 95% CI 0.79 to 0.88).<sup>21</sup> Additionally, more intensive statin therapy reduced the odds of MACE compared to less intensive statin therapy (OR 0.83; 95% CI 0.76 to 0.90).<sup>21</sup> For safety outcomes, there was no significant difference in rhabdomyolysis (RR 1.72; 95% CI 0.52 to 5.68) between higher-dose statin and lower dose, with a wide confidence interval. There was an increase in elevation of aminotransferases (RR 2.89; 95% CI 1.51 to 5.53).<sup>21</sup> There was moderate heterogeneity among the trials for MACE.

### Primary Prevention

A systematic review and evidence report to inform the US Preventive Services Task Force (USPSTF) guidelines reviewed the benefits and harms of statins for prevention of CVD in adults without prior CV events (primary prevention).<sup>22</sup> Studies were limited to those in which fewer than 10% of the participants had a history of CV events. Studies comparing statin to placebo or no statin, and studies evaluating the effects of statin therapy intensity were included. Nineteen RCTs were identified comparing statins on clinical outcomes in adults without a history of CV events (n=71,344).<sup>22</sup> Mean ages ranged from 51 to 66 years and duration of follow-up ranged from 6 months to 6 years. All trials enrolled patients at increased CV risk (i.e. presence of dyslipidemia, early cerebrovascular disease, diabetes, or hypertension). Six trials were rated as good quality, 12 of fair quality and one trial was poor quality because it did not report attrition. Statins were associated with reduced risk in all-cause mortality compared to placebo (RR 0.86; 95% CI 0.80 to 0.93; absolute risk difference [ARD] -.4%; 95% CI -0.64%--0.17%; I<sup>2</sup>=0%) and CV mortality (RR 0.82; 95% CI 0.71 to 0.94; ARD -.2%; 95% CI -0.35%--0.05%; I<sup>2</sup>=0%).<sup>22</sup> There were no differences in relative risk estimates based on sex, age, race/ethnicity, or baseline lipid levels, but absolute benefits were greater in subgroups at higher risk for events. There was no significant difference in withdrawals due to adverse events with statins compared to placebo (RR 0.95; 95% CI 0.75 to 1.21; I<sup>2</sup>=86%).<sup>22</sup> There was also no significant difference in serious adverse events, any cancer, fatal cancer, myalgias, rhabdomyolysis or elevated aminotransferase levels. Statins were not associated with increased risk of diabetes compared to placebo (RR 1.05; 95% CI 0.91 to 1.20). However, most studies did not include high intensity dosing because of the low baseline risk of the population. The studies comparing different intensities were underpowered to evaluate clinical outcomes.

### Primary and Secondary Prevention

A meta-analysis of studies included in the Cholesterol Treatment Trialists' (CTT) Collaboration aimed to evaluate the effects of statin therapy on CV outcomes in men and women in both primary and secondary prevention.<sup>23</sup> Estimates of the mean effect on lipid concentration between women and men were compared using a t-test. Individual participant data were available from 27 trials of statin therapy. Twenty-two trials compared statin therapy to control and 5 trials compared more-intensive statin therapy to less-intensive. Overall, 26.8% (n=46,675) of all participants were women. The mean duration of follow up was 4.9 years (ranging from 2 to 7 years). Mean concentrations of total and LCL-C at baseline were similar in men and women but all baseline characteristics differed significantly. Women were older and had a higher prevalence of hypertension and diabetes and were less likely to smoke. Statins reduced the risk of major CV events by 21% for each 1 mmol/L (38.8 mg/dl) reduction in LDL-C with significant reductions in both women and men (rate ratio 0.79; 95% CI 0.77-0.81).<sup>23</sup> After adjusting for other differences in baseline characteristics, there was no heterogeneity (p=0.331) between proportional effects of statins in women (RR 0.84; 99% CI 0.78 to 0.91) and men (RR 0.78; 99% CI 0.75 to 0.81).<sup>23</sup> Effects in participants without a history of vascular disease were slightly greater in men (RR 0.72; 99% CI 0.66 to 0.80) than women (RR 0.85; 99% 0.72 to 1.00) but were similar in those treated for secondary prevention.

A systematic review was done to compare standard-dose statin and high-dose statin treatment for stroke prevention in adults with and without ASCVD (primary and secondary prevention).<sup>24</sup> Only RCTs with masked assessment of outcomes were included. Standard treatment was defined as doses less than or equal to atorvastatin 20mg, simvastatin 60 mg, rosuvastatin 10 mg or any dose of pravastatin, lovastatin or fluvastatin. Seventeen RCTs (n=120,970) were included in the analysis. Seven trials compared placebo or standard-dose statin with intensive-dose statin treatment and 10 studies compared standard-dose treatment with placebo. No studies included lovastatin as a treatment arm and the majority included atorvastatin (n=9). Intensive-dose statin treatment resulted in a significant reduction in all-stroke incidence (RR 0.79; 95% CI 0.71 to 0.87) compared to placebo or standard dose (2.4% vs. 3.1%, respectively) with nonsignificant heterogeneity and no significant reporting bias. There was also a significant reduction in fatal stroke with intensive-dose statin (RR 0.61; 95% CI 0.39 to 0.96).<sup>24</sup> There was an increase in the risk of elevated aminotransferases with intensive-dose statin treatment compared to standard dose or placebo (RR 5.45; 95% CI 3.81 to 7.81).<sup>24</sup>

### Familial Hypercholesterolemia

A Cochrane Collaboration systematic review assessed the effectiveness and safety of statins in children with heterozygous familial hypercholesterolemia (HeFH).<sup>25</sup> Since mortality and non-fatal CV events are rare in children, the primary outcomes were surrogate outcomes, including change in serum LDL-C, change in carotid intima-media thickness and change in measures of growth maturation. Secondary outcomes included liver dysfunction, myopathy and rhabdomyolysis. Nine RCTs met inclusion criteria (n=1177). Median follow up time was only 24 weeks (range from 6 weeks to 2 years). Age of study participants ranged from 6 to 18 years. Five studies reported change in serum LDL-C (high quality evidence) and demonstrated a 32.15% (95% CI 34.9%-29.4%) mean reduction with statins compared to placebo.<sup>25</sup> Despite some risk of bias concerns, evidence was rated high quality due to the large effect size. There was low quality evidence in no difference in the number of cases of either liver dysfunction (increase in aminotransferase levels greater than 3 times the upper limit of normal) or myopathy between statins and placebo. However, the confidence intervals of pooled results were wide due to very low number of events. There were no reported cases of rhabdomyolysis. There was moderate quality evidence of no difference in adverse events at 1 year between statins and placebo (RR 1.01; 95% CI 0.81 to 1.26).<sup>25</sup>

### Harms

A systematic review evaluated evidence for an association between statin therapy and impaired cognition from RCTs.<sup>26</sup> RCTs comparing statin therapy to placebo or standard therapy and reported cognitive outcomes were included. Cochrane risk of bias tool was used to determine study quality. Twenty-five RCTs were included and all were placebo-controlled. Duration varied between 2 weeks and 260 weeks. The majority of studies included participants with normal cognition at baseline and risk of bias ranged from low to moderate for most studies. Sixteen studies reported cognitive test outcomes using various tests and data from 14 of the studies was able to be combined in meta-analysis. There was no statistically significant difference between statin and no statin groups on cognitive outcomes (standard mean difference [SMD] 0.01; 95% CI 0.01 to 0.03).<sup>26</sup> However, effect sizes were combined across various cognition domains, which is difficult to interpret.

A systematic review and meta-analysis was done to compare the tolerability and safety of long-term (>6 weeks) treatment with high-intensity atorvastatin 80 mg daily.<sup>27</sup> RCTs published through 2015 reporting safety outcomes with atorvastatin 80 mg were identified and the Cochrane risk of bias tool was used to assess quality. Seventeen studies met selection criteria and were included in the meta-analysis. Mean age in the trials ranged from 43 to 75. Thirteen studies provided moderate evidence that atorvastatin 80 mg/day was significantly less well-tolerated leading to discontinuations due to adverse events compared with the control (placebo or lower dose atorvastatin) (8.8% vs. 6.8% RR 1.29; 95% CI 1.17-1.42) with no significant heterogeneity.<sup>27</sup> There was high quality evidence of a higher risk of elevations in liver transaminases (1.6% vs. 0.3%; RR 4.59; 95% CI 3.26-6.48) and low quality evidence of no difference in myalgia (RR 1.06; 95% CI 0.93-1.20).<sup>27</sup> There were few older participants > 75 years of age, limiting the generalizability to this population at higher risk of adverse events.

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## New Guidelines:

### Department of Veterans Affairs

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work group updated the guidelines for the management of dyslipidemia for cardiovascular risk reduction in 2020.<sup>3,6</sup> This is a high-quality guideline designed to assist primary care providers in managing dyslipidemia for the purpose of CVD risk reduction. Similar to ACC/AHA guidelines for the management of cholesterol, statins are the recommended first-line therapy for patients with CVD and for those at high risk of CVD. They also recommend treating based on target medication doses used in clinical trials rather than treating toward target LDL-C levels. The following recommendations regarding statin therapy are included in the update:

- For secondary prevention, at least a moderate-dose statin is recommended (Strong Recommendation)
  - This recommendation came from three meta-analyses from the CTT Collaborators showing fixed-dose moderate intensity statins (simvastatin 20-40 mg, pravastatin 40 mg, lovastatin 20-80, and atorvastatin 10 mg) led to a reduction in all-cause mortality, non-fatal MI, coronary death and non-fatal stroke when compared to placebo.
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest offering high-dose statins for reducing non-fatal CV events after discussion of the risk of high dose statins and an exploration of the patient's values and preferences (Weak recommendation)
  - This recommendation differs from the ACC/AHA guidelines and is supported by meta-analyses that only demonstrated an incremental benefit for a reduction in non-fatal events (e.g., MI, stroke), but no significant reduction in CV or all-cause mortality when comparing high-dose statins to lower doses statins.
  - There is a high risk of statin-related adverse events and more discontinuations due to adverse events with high dose statins compared to lower dose statins.
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest adding ezetimibe to either moderate- or high-dose statins for reducing non-fatal cardiovascular events following a discussion of the risks, additional benefits, and an exploration of the patient's values and preferences (Weak recommendation)
- For secondary prevention in higher risk patients who are willing to intensify treatment, they suggest offering a PCSK9 inhibitor in addition to a maximally tolerated statin dose with ezetimibe for reducing non-fatal cardiovascular events following a discussion of their uncertain long-term safety, additional benefits, and an exploration of the patient's values and preferences (Weak recommendation)
- For primary prevention, a moderate-dose statin is recommended for those with a 10-year CV risk greater than 12% or LDL-C  $\geq$  190 mg/dl or diabetes (Strong recommendation)
- For primary prevention, they suggest offering a moderate-dose statin for patients with a 10-year cardiovascular risk between 6% and 12% following a discussion of risks, limited benefit, and an exploration of the patient's values and preferences (Weak recommendation)

### **Guidelines included for clinical context only:**

#### American College of Cardiology / American Heart Association

Updated recommendations for reducing ASCVD risk were released following from the American College of Cardiology (ACC) / American Heart Association (AHA) in 2018.<sup>2</sup> Guidelines were updated based on a systematic review that identified 10 new RCTs in patients with clinical ASCVD or at high risk of ASCVD. The prespecified primary outcome was a composite of fatal CV events, nonfatal MI, or nonfatal stroke. RCTs were assessed for bias using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis was not done, and direct comparisons of the included RCTs could not be performed. This guideline was evaluated and reviewed in previous reviews for the non-statin dyslipidemia PDL class in in May 2019.

Overall, statins are recommended in all patients with ASCVD and at high risk for ASCVD. Statins are recommended in the four patient management groups, which were modified from previous guidelines to allow for more personalized care and more detailed risk assessments (**Table 2**).

**Table 2: Patient Management Groups**

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin ( $\leq 75$ y/o); moderate- to high-intensity statin if $> 75$ y/o
Severe Hypercholesterolemia (LDL-C $\geq 190$ mg/dl)	Maximally tolerated statin
Diabetes age 40-75 and LDL-C $\geq 70$ mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
Primary Prevention (Adults 40-75 years with LDL-C $\geq 70$ )	Moderate- intensity statin based on risk discussion, 10-year ASCVD risk, and ASCVD risk enhancers
<b>Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; y/o: years old</b>	

A significant change in the guidelines is the addition of an LDL-C threshold of 70 mg/dl to consider adding a non-statin in clinical ASCVD. This recommendation comes from the general idea that “lower is better” for LDL-C, particularly in high-risk patients. Very high-risk ASCVD is a new category and includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a PCSK9 inhibitor if LDL-C remains  $\geq 70$  mg/dl on both statin and ezetimibe therapy for very high-risk patients only.

**New Formulations or Indications:**

In 2017, the FDA approved pitavastatin magnesium (Zypitamag®) for use in adults with primary hyperlipidemia or mixed dyslipidemia. The magnesium salt formulation was considered bioequivalent to pitavastatin calcium (Livalo®).<sup>28</sup>

In November 2015, rosuvastatin was FDA approved for pediatric patients age 8 to 17 years with heterozygous familial hypercholesterolemia.<sup>29</sup> Previously it was only approved for age 10 years and up. In 2016, the label was further expanded to include pediatric patients aged 7 to 17 years with homozygous familial hypercholesterolemia.<sup>29</sup> These approvals were based on studies demonstrating safety and LDL-C lowering ability in this pediatric populations.<sup>30,31</sup>

**New FDA Safety Alerts:**

**Table 1. Description of new FDA Safety Alerts**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Simvastatin <sup>32</sup>	Zocor	3/2019	Warnings	Chinese patients may be at a higher risk of myopathy
Rosuvastatin Fluvastatin Simvastatin	Crestor Lescol Zocor	9/2020	Warnings and Precautions	Immune-mediated necrotizing myopathy

**Randomized Controlled Trials:**

A total of 266 citations were manually reviewed from the initial literature search and 11 were evaluated more carefully for inclusion. After further review, 10 citations were excluded because of wrong study design (eg, observational)<sup>33-35</sup>, comparator (eg, no control or placebo-controlled)<sup>36-39</sup>, or outcome studied (eg, non-clinical)<sup>40-42</sup>. The remaining 2 trials are summarized in the table below and systematic reviews were summarized above. Full abstracts are included in **Appendix 2**.

**Table 2. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results
Stoekenbroek et al. <sup>43</sup>	Atorvastatin 80 mg/day (high dose) vs. simvastatin 20-40 mg/day (usual dose)	Post – MI patients	Incident PAD or recurrent PAD requiring hospitalization	<u>Incident PAD</u> Atorvastatin: 94 (2.2%) Simvastatin 135 (3.2%) HR 0.70; 95% CI 0.53 to 0.91
Berwanger, et al. <sup>44</sup> RCT, MC, PC	Atorvastatin 80 mg x 1, 40 mg daily x 7 days vs. placebo	Statin-naïve patients scheduled for a noncardiac surgery	Composite of all-cause mortality, nonfatal MI, and stroke at 30 days	<u>Composite CV outcome:</u> Atorvastatin: 54 (16.6%) Placebo: 59 (18.7%) HR 0.87; 95% CI 0.60-1.26 P=0.46

Abbreviations: CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; MC = multicenter; PAD = peripheral artery disease; PC = placebo-controlled; RCT = randomized clinical trial.

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**Appendix 1: Current Preferred Drug List****High-Potency**

<b>Generic</b>	<b>Brand</b>	<b>Route</b>	<b>Form</b>	<b>PDL</b>
atorvastatin calcium	ATORVASTATIN CALCIUM	ORAL	TABLET	Y
atorvastatin calcium	LIPITOR	ORAL	TABLET	Y
simvastatin	SIMVASTATIN	ORAL	TABLET	Y
simvastatin	ZOCOR	ORAL	TABLET	Y
ezetimibe/simvastatin	EZETIMIBE-SIMVASTATIN	ORAL	TABLET	N
ezetimibe/simvastatin	VYTORIN	ORAL	TABLET	N
pitavastatin calcium	LIVALO	ORAL	TABLET	N
pitavastatin magnesium	ZYPITAMAG	ORAL	TABLET	N
rosuvastatin calcium	EZALLOR SPRINKLE	ORAL	CAP SPRINK	N
rosuvastatin calcium	CRESTOR	ORAL	TABLET	N
rosuvastatin calcium	ROSUVASTATIN CALCIUM	ORAL	TABLET	N

**Low-Medium Potency**

<b>Generic</b>	<b>Brand</b>	<b>Route</b>	<b>Form</b>	<b>PDL</b>
lovastatin	LOVASTATIN	ORAL	TABLET	Y
pravastatin sodium	PRAVACHOL	ORAL	TABLET	Y
pravastatin sodium	PRAVASTATIN SODIUM	ORAL	TABLET	Y
fluvastatin sodium	FLUVASTATIN SODIUM	ORAL	CAPSULE	N
fluvastatin sodium	FLUVASTATIN ER	ORAL	TAB ER 24H	N
fluvastatin sodium	LESCOL XL	ORAL	TAB ER 24H	N
lovastatin	ALTOPREV	ORAL	TAB ER 24H	N

## Appendix 2: Abstracts of Comparative Clinical Trials

- Stoekenbroek, et al. High-dose atorvastatin is superior to moderate-dose simvastatin in preventing peripheral arterial disease. *Heart*. 2015 Mar;101(5):356-62

**Objectives:** To study whether high-dose versus usual-dose statin treatment reduces the incidence of peripheral artery disease (PAD) and what is the effect of high-dose statin treatment on cardiovascular disease (CVD) outcome in patients with PAD.

**Methods and results:** In the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial, 8888 post-myocardial infarction patients were randomised to high-dose or usual-dose statin therapy (atorvastatin 80 mg/day vs simvastatin 20-40 mg/day). We investigated the effect of high-dose versus usual-dose statins on the pre-specified outcome PAD incidence, and additionally performed a posthoc analysis of the efficacy of high-dose statins in reducing CVD risk among patients with PAD. During a median follow-up of 4.8 years, 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed PAD (HR=0.70, 95% CI 0.53 to 0.91; p=0.007). The risk of major coronary events was almost twofold higher in patients with PAD at baseline, but was no longer significant after adjusting for the adverse cardiovascular risk profile. In PAD patients, major coronary events occurred in fewer patients in the atorvastatin group (14.4%) than in the simvastatin group (20.1%), but the difference did not reach statistical significance. (HR=0.68, 95% CI 0.41 to 1.11; p=0.13). Atorvastatin treatment significantly reduced overall cardiovascular (p=0.046) and coronary events (p=0.004), and coronary revascularisation (p=0.007) in these patients.

**Conclusions:** High-dose statin therapy with atorvastatin significantly reduced the incidence of PAD compared with usual-dose statin therapy with simvastatin. Patients with a history of PAD at baseline were at higher risk of future coronary events and this risk was reduced by high-dose atorvastatin treatment.

- Berwanger O, de Barros ESPG, Barbosa RR, et al. Atorvastatin for high-risk statin-naïve patients undergoing noncardiac surgery: The Lowering the Risk of Operative Complications Using Atorvastatin Loading Dose (LOAD) randomized trial. *American heart journal*. 2017;184:88-96

**Methods:** We randomized 648 statin-naïve patients who were scheduled for noncardiac surgery and were at risk for a major vascular complication. Patients were randomized to a loading dose of atorvastatin or placebo (80 mg anytime within 18 hours before surgery), followed by a maintenance dose of 40 mg (or placebo), started at least 12 hours after the surgery, and then 40 mg/d (or placebo) for 7 days. The primary outcome was a composite of all-cause mortality, nonfatal myocardial injury after noncardiac surgery, and stroke at 30 days.

**Results:** The primary outcome was observed in 54 (16.6%) of 326 patients in the atorvastatin group and 59 (18.7%) of 316 patients in the placebo group (hazard ratio [HR] 0.87, 95% CI 0.60-1.26, P=.46). No significant effect was observed on the 30-day secondary outcomes of all-cause mortality (4.3% vs 4.1%, respectively; HR 1.14, 95% CI 0.53-2.47, P=.74), nonfatal myocardial infarction (3.4% vs 4.4%, respectively; HR 0.76, 95% CI 0.35-1.68, P=.50), myocardial injury after noncardiac surgery (13.2% vs 16.5%; HR 0.79, 95% CI 0.53-1.19, P=.26), and stroke (0.9% vs 0%, P=.25).

**Conclusion:** In contrast to the prior observational and trial data, the LOAD trial has neutral results and did not demonstrate a reduction in major cardiovascular complications after a short-term perioperative course of statin in statin-naïve patients undergoing noncardiac surgery. We demonstrated, however, that a large multicenter blinded perioperative statin trial for high-risk statin-naïve patients is feasible and should be done to definitely establish the efficacy and safety of statin in this patient population.

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### Appendix 3: Medline Search Strategy

[Database: Ovid MEDLINE(R) ALL <1946 to February 04, 2021>

Search Strategy:

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- 1 statins.mp. or Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (44334)
- 2 Ezetimibe, Simvastatin Drug Combination/ or Simvastatin/ or simvastatin.mp. (11241)
- 3 atorvastatin.mp. or Atorvastatin/ (10049)
- 4 rosuvastatin.mp. or Rosuvastatin Calcium/ (4025)
- 5 pitavastatin.mp. (1029)
- 6 lovastatin.mp. or Lovastatin/ (6013)
- 7 Fluvastatin/ (1402)
- 8 Pravastatin/ (3440)
- 9 Myocardial Infarction/ or Cardiovascular Diseases/ or cardiovascular events.mp. (338329)
- 10 cardiovascular mortality.mp. (14227)
- 11 stroke.mp. or Stroke/ (307809)
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (57745)
- 13 Percutaneous Coronary Intervention/ or major adverse cardiovascular events.mp. (23545)
- 14 9 or 10 or 11 or 13 (633526)
- 15 12 and 14 (14026)
- 16 limit 15 to (english language and full text and yr="2015 -Current" and (clinical trial, phase iii or comparative study or meta analysis or randomized controlled trial or "systematic review")) (266)
- 17 from 16 keep 6,9,18-19,23,25,29,54,82,87,102,106,114-115,120-121,130,133,139,164,170,180,221 (23)

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**Appendix 4: Key Inclusion Criteria**

<b>Population</b>	<b>Patients with atherosclerotic cardiovascular disease (ASCVD) or high risk for ASCVD</b>
<b>Intervention</b>	Statins or high intensive statin therapy
<b>Comparator</b>	Placebo or less intensive statin therapy
<b>Outcomes</b>	All-cause mortality, cardiovascular mortality, cardiovascular events (i.e. myocardial infarction, stroke, revascularization)
<b>Timing</b>	≥ 1 year
<b>Setting</b>	Outpatient