Therapeutic Class Overview
Statins (HMG-CoA Reductase Inhibitors)

INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.
- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (*Stone et al 2014*).
- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).
- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for Altoprev (lovastatin extended-release [ER] tablet), Flolipid (simvastatin oral suspension), Zypitamag (pitavastatin tablet), and Ezallor Sprinkle (rosuvastatin capsule) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*).
- The combinations niacin/lovastatin (Advicor) and niacin/simvastatin (Simcor) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (*AbbVie Web site 2016*).
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Altoprev (lovastatin ER)	-
Crestor, Ezallor Sprinkle (rosuvastatin)	✔ -
Flolipid (simvastatin oral suspension)	-
Lescol (fluvastatin)*	✔
Lescol XL (fluvastatin ER)	✔
Lipitor (atorvastatin)	✔
Livalo, Zypitamag (pitavastatin)€	✔ -
Mevacor (lovastatin)*	✔
Pravachol (pravastatin)	✔
Zocor (simvastatin)	✔
Caduet (amlodipine/atorvastatin)	✔
Liptruzet† (ezetimibe/atorvastatin)	✔
Vytorin	✔

Drug	Generic Availability
(ezetimibe/simvastatin)	

Abbreviation: ER = extended-release.
*The brands, Lescol and Mevacor, have been discontinued, but the generic formulations are available.
€The brand Nikita was discontinued.
†The brand, Liptruzet, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was approved by the FDA; however, current market availability is unknown.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-approved indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ atorvastatin	ezetimibe/ simvastatin
Hypertriglyceridemia										
Reduce elevated TG in patients with hypertriglyceridemia							✔			
Treatment of adult patients with hypertriglyceridemia in combination with diet	✔				✔	✔ δ		✔ (atorvastatin)		
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Reduce elevated TC, LDL-C, apo B, TG, and non-HDL-C (Vytorin and rosuvastatin only) and increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia	✔	✔	✔ (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B levels in children with HeFH (Livalo, no further conditions for use) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥ 189 (lovastatin only) or 190 mg/dL or LDL-C remains ≥ 160 mg/dL and there is a positive family history of premature CVD or ≥ 2 other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)	✔ ¥	✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B in adults with HoFH						✔ δ				
Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies						✔ ₳				
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ § (IR)							

Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔ δ		✔ (atorvastatin)		
Prevention of CVD										
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔				
Reduce the risk of MI and stroke in patients with type 2 diabetes, and without clinically evident CHD, but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN	✔							✔ (atorvastatin)		
Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)		
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔					
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥ 50 years old in men and ≥ 60 years old in women, high sensitivity C-reactive protein ≥ 2 mg/L, and the presence of ≥ 1 additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔				
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD					✔					
Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary							✔			

events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease										
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD		✔								
Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels			✔							
Other										
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%								✔ (amlodipine)		
Symptomatic treatment of chronic stable angina								✔ (amlodipine)		
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)		
Treatment of HTN, to lower blood pressure								✔ (amlodipine)		

Abbreviations: ApoB = apolipoprotein B, CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, ER = extended-release, HDL-C = high-density lipoprotein cholesterol, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, IR = immediate-release, HTN = hypertension, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, TC = total cholesterol, TG = triglycerides, VLDL-C = very low-density lipoprotein cholesterol.

§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

¶In boys and postmenarchal girls 10 to 17 years of age.

#In adolescent boys and adolescents girls who are ≥ 1 year post-menarche, 10 to 16 years of age.

**In adolescent boys and girls who are ≥ 1 year post-menarche, 10 to 17 years of age.

††In children and adolescent patients 8 to 17 years of age

₳In children and adolescents ages 7 to 17 years of age

ɣFor ER lovastatin, for patients at high risk, for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C

¥For pediatric patients ≥ 8 years of age (Livalo only)

δApproved indications for rosuvastatin capsules (Ezallor Sprinkle)

(*Prescribing information: Altoprev 2018, Caduet 2019, Crestor 2018, Ezallor Sprinkle 2020, Flolipid 2017, Fluvastatin 2017, Lescol XL 2017, Lipitor 2019, Livalo 2019, Lovastatin 2019, Pravachol 2017, Vytorin 2019, Zocor 2019, Zypitamag 2020*)
Clinical Pharmacology 2020

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Numerous clinical trials have demonstrated that the statins (single-entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Additionally, many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens (*Ai et al 2008, Alvarez-Sala et al 2008, Arca et al 2007, Avis et al 2007, Avis et al 2010, Ballantyne et al 2003, Ballantyne et al 2004, Ballantyne et al 2005, Ballantyne et al 2006, Ballantyne et al 2007, Ballantyne et al 2008, Bardini et al 2010, Bays et al 2004, Bays et al 2010, Bays et al 2013, Bays et al 2008a, Bays et al 2008b, Becker et al 2008, Betteridge et al 2007a, Betteridge et al 2007b, Braamskamp et al 2015, Brown et al 1990, Bullano et al 2006, Bullano et al 2007, Calza et al 2008, Catapano et al 2006, Charland et al 2010, Chenot et al 2007, Clearfield et al 2006, Coll et al 2006, Conard et al 2008, Constance et al 2007, Davidson et al 2002, Deedwania et al 2007a, Derosa et al 2009, Erdine et al 2009, Eriksson et al 1998, Eriksson et al 2011, Faergeman et al 2008, Farnier et al 2007, Farnier et al 2008, Farnier et al 2009, Feldman et al 2004, Feldman et al 2006, Ferdinand et al 2006, Ferdinand et al 2012, Flack et al 2008, Florentin et al 2011, Foody et al 2010, Fox et al 2007a, Fox et al 2007b, Gagné et al 2002, Gaudiani et al 2005, Goldberg et al 2004, Goldberg et al 2006, Goldberg et al 2009, Grimm et al 2010, Gumprecht et al 2011, Hall et al 2009, Harley et al 2007, Hing Ling et al 2012, Hobbs et al 2009, Hogue et al 2008, Hunninghake et al 2001, Illingworth et al1994, Insull et al 2007, Jones et al 2003, Jones et al 2009a, Jones et al 2009b, Kerzner et al 2003, Kipnes et al 2010, Knapp et al 2001, Koshiyama et al 2008, Kumar et al 2009, Lee et al 2007, Leiter et al 2007, Leiter et al 2008, Lewis et al 2007, Lloret et al 2006, Marais et al 2008, May et al 2008, Mazza et al 2008, Melani et al 2003, Meredith et al 2007, Messerli et al 2006, Milionis et al 2006, Mohiuddin et al 2009, Motomura et al 2009, Neutel et al 2009, Nicholls et al 2010, Ose et al 2007, Ose et al 2009, Ose et al 2010, Park et al 2005, Park et al 2010, Pearson et al 2007, Piorkowski et al 2007, Polis et al 2009, Preston et al 2007, Reckless et al 2008, Robinson et al 2009, Rodenburg et al 2007, Roeters van Lennep et al 2008, Rogers et al 2007, Rosenson et al 2009, Rotella et al 2010, Roth et al 2010, Saito et al 2002, Sansanayudh et al 2010, Sasaki et al 2008, Shafiq et al 2007, Stalenhoef et al 2005, Stein et al 2003, Stein et al 2004, Stein et al 2007, Stein et al 2008, Viigimaa et al 2010, Vuorio et al 2019, Winkler et al 2007, Winkler et al 2009, Wlodarczyk et al 2008, Wolffenbuttel et al 2005, Yoshitomi et al 2006, Zieve et al 2010*).
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, and the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke (*Afilalo et al 2007, Afilalo et al 2008, Ahmed et al 2006, Amarenco et al 2009a, Amarenco et al 2009b, Asselbergs et al 2004, Athyros et al 2002, Athyros et al 2007, Baigent et al 2005, Barter et al 2007, Briel et al 2006, Bushnell et al 2006, Byington et al 1995, Cannon et al 2004, Cannon et al 2006, Cannon et al 2015, Chan et al 2010, Cholesterol Treatment Trialists' [CTT] Collaborators, 2008, Chonchol et al 2007, Colhoun et al 2004, Collins et al 2003, Crouse et al 2007, de Lemos et al 2004, Deedwania et al 2006, Deedwania et al 2007b, Downs et al 1998, Everett et al 2010, Ford et al 2007, Furberg et al 1994, Hitman et al 2007, Hulten et al 2006, Khush et al 2007, Knopp et al 2006, Koenig et al 2001, Koga et al 2018, LaRosa et al 2005, LaRosa et al 2007, Liem et al 2002, Meaney et al 2009, Mood et al 2007, Mora et al 2010, Murphy et al 2007, Nakamura et al 2006, Neil et al 2006, Nicholls et al 2006, Nissen et al 2004, Nissen et al 2005, Nissen et al 2006, No authors listed, 1994, No authors listed, 2002, No authors listed, 2007, Olsson et al 2007, O'Regan et al 2008, Pedersen et al 2005, Pitt et al 1999, Pitt et al 2012, Ray et al 2005, Ray et al 2006, Ridker et al 2008, Ridker et al 2009, Ridker et al 2010, Rossebø et al 2008, Sacks et al1996, Sakamoto et al 2007, Sato et al 2008, Schmermund et al 2006, Schoenhagen et al 2006, Schouten et al 2009, Schwartz et al 2005, Scirica et al 2006, Serruys et al 2002, Sever et al 2003, Sever et al 2005, Shah et al 2008, Shepherd et al 1995, Shepherd et al 2007, Shepherd et al 2006, Shepherd J et al 2002, Strandberg et al 2009, Tavazzi L et al 2008, Taylor et al 2013, The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002, The Long-term Intervention with Pravastatin in Ischemic Disease [LIPID] Study Group 1998, The Pravastatin Multinational Study Group for Cardiac Risk Patients [PMS-CRP] 1993, Thompson et al 2004, Tikkanen et al 2009, Waters et al 2006, Wenger et al 2007, Yu et al 2007*).
- Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events (*Downs et al 1998, Shepard et al 1995*).
- Specifically, the WOSCOPS trial (N = 6959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant reduction of 31% in the risk of the combined endpoint of CHD death and nonfatal MI ($p < 0.001$). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin (32%; $p = 0.033$) (*Shepard et al 1995*). Results of a 20-year observational follow-up of this trial continued to show beneficial

effects of pravastatin on reduction of CHD. Among those with and without LDL-C ≥ 190 mg/dL (N = 5529), pravastatin reduced the risk of CHD by 27% (p = 0.002) and major adverse cardiovascular events (MACE) by 25% (p = 0.004). Among individuals with LDL-C ≥ 190 mg/dL (N = 2560), pravastatin reduced the risk of CHD-related death, cardiovascular death, and all-cause mortality by 28% (p = 0.020), 25% (p = 0.009), and 18% (p = 0.004), respectively (*Vallejo-Vaz et al 2017*).

- The AFCAPS/TexCAPs trial (N = 6605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (p < 0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (*Downs et al 1998*).
- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N = 10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and 3 additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (p = 0.0005) (*Sever et al 2003*).
- Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (p = 0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (*Colhoun et al 2004, Sever et al 2003, Sever et al 2005).*
- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N = 17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration = 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (p < 0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (p = 0.02) (*Ridker et al 2008*).
- Meta-analyses support the findings observed in the individual primary prevention trials (*Adams et al 2018, Baigent et al 2005, CTT Collaborators et al 2008, Mora et al 2010, O'Regan et al 2008, Taylor et al 2011, Nunes et al 2017*).
- The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N = 8888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; p = 0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; p = 0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; p < 0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5% vs 30.8%; HR, 0.84; p < 0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; p = 0.02), but the treatments were no different in terms of all-cause (p = 0.81) or noncardiovascular (p = 0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (p < 0.001) (Pedersen et al 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; p = 0.007) (*Stoekenbroek et al 2015*).
- Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (p = 0.02) (*Byington et al 1995, Chan et al 2010, Crouse et al 2007, Furberg et al 1994, Karlson et al 2018, Nicholls et al 2006, Nissen et al 2004, Nissen et al 2005, Nissen et al 2006, Schmermund et al 2006, Schoenhagen et al 2006*). A meta-analysis comparing the efficacy and safety of atorvastatin and pitavastatin on the regression of atherosclerosis did not find a statistically significant difference between these agents when evaluating changes in plaque volume, lumen volume, and external elastic membrane. However, atorvastatin was potentially more effective than pitavastatin at reducing LDL-C and improving HDL-C (*Liu et al 2018*).

- The majority of secondary prevention trials have evaluated the use of statins initiated 3 to 6 months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (*Briel et al 2006, Cannon et al 2004, de Lemos et al 2004, Liem et al 2002*).
- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N = 3086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (p = 0.048) (*Schwartz et al 2005*). However, a 2018 randomized, controlled trial (RCT) that included 4191 patients with ACS and planned percutaneous coronary intervention (PCI) found that 2 loading doses of atorvastatin 80 mg before and 24-hours after surgery did not reduce the rate of MACE at 30 days when compared to placebo (absolute difference, 0.85%; 95% CI, -0.70% to 2.41%; HR, 0.88; 95% CI, 0.69 to 1.11; p = 0.27) (*Berwanger et al 2018*).
- The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) investigated the efficacy of the addition of ezetimibe to simvastatin for the prevention of stroke and other adverse cardiovascular events in 18,144 patients. After 7 years, the combination of ezetimibe and simvastatin significantly reduced the risk of stroke of any etiology (HR, 0.83; 95% CI, 0.70 to 0.98; p = 0.029) and ischemic stroke (HR, 0.76; 95% CI, 0.63 to 0.91; p = 0.003) when compared to simvastatin monotherapy. Significant benefits were also observed in the subgroup of patients with prior stroke (*Bohula et al 2017*).
- Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N = 4162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After 2 years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed > 30 days after randomization, and stroke by 16% compared to pravastatin (p = 0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (p = 0.04) and unstable angina (p = 0.02). In this trial discontinuations due to adverse events were similar between the 2 treatments (p = 0.11) (*Cannon et al 2004*).
- A meta-analysis which assessed the efficacy of high dose atorvastatin in patients who underwent PCI (N = 2850) found that atorvastatin significantly reduced the risk of MI in patients with PCI compared to placebo (relative risk [RR], 0.62; 95% CI, 0.49 to 0.78) (*Lu et al 2017*).
- A meta-analysis evaluated the efficacy and safety of dosing statins on alternative days (N = 505) compared to daily dosing (N = 518). Although there were no differences in TG, the reduction in TC (p < 0.00001) and LDL-C (p = 0.003) was significantly greater in the daily dosing group (*Awad et al 2017*).
- A Cochrane review assessed the effectiveness of statins in children aged 4 to 18 years with HeFH and found that statin treatment is effective. Statin therapy was found to be safe with no significant safety issues in the short-term (*Vuorio et al 2019*). A more recent systematic review and meta-analysis involving 1191 children and adolescents with familial hypercholesterolemia (aged 13.3 ± 2.5 years) concluded similarly that statin therapy is effective in reducing TC, LDL-C, TG, and apo-B, and increasing HDL-C concentrations, with no major safety issues (*Anagnostis et al 2020*).
- A meta-analysis involving data from 28 RCTs recently assessed the efficacy and safety of statin therapy in older individuals (*Cholesterol Treatment Trialists' Collaboration 2019*). Results revealed that statin therapy was associated with a significant reduction in major vascular events regardless of age; however, there was less direct evidence of a beneficial impact among patients > 75 years who did not already have evidence of occlusive vascular disease.

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation; however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- A recent review concluded that statin-induced hepatotoxicity occurs rarely and that concern that hepatic damage may occur should not be a reason to avoid statin therapy in patients with appropriate clinical indications for use (*Meurer et al*

2020). The authors recommended liver function testing at statin initiation and as clinically indicated while on therapy; however, ongoing routine monitoring was not recommended. Additionally, statins should be avoided in patients with liver failure, acute liver injury, and decompensated cirrhosis.

- In December 2018, the American Heart Association (AHA) published its first scientific statement specifically aimed at reviewing statin harms. Approximately 10% of patients stop taking a statin because of subjective complaints, most commonly muscle symptoms without raised creatinine kinase. Randomized clinical trials, however, have found that the difference in the incidence of muscle symptoms without significantly raised creatinine kinase in statin-treated compared with placebo-treated participants is < 1%, and it is even smaller (0.1%) for patients who discontinued treatment due to muscle symptoms. This suggests that muscle symptoms are usually not caused by pharmacological effects of the statin. Restarting statin therapy in these patients, especially those at high risk of cardiovascular events, should be prioritized, as the benefits of these agents outweigh their risks (*Newman et al 2019*).
- Increases in hemoglobin A1c (HbA1c) and fasting serum glucose have been reported with statins. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients on metformin and a sulfonylurea, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in atherosclerotic cardiovascular disease (ASCVD) (*Jellinger et al 2017*).
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (*Wiggins et al 2016*).
- The 2016 scientific statement written by the AHA stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
  - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
  - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker, amlodipine.
  - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
  - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (eg, digoxin) (*Wiggins et al 2016*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single-Entity Agents				
Atorvastatin	Tablet: 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial 10 to 40 mg once daily; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Dosage adjustments may be necessary in	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	patients taking cyclosporine, clarithromycin, itraconazole, or certain protease inhibitors.	
Fluvastatin	Capsule: 20 mg 40 mg ER tablet: 80 mg	Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Patients requiring LDL-C reductions ≥ 25% should initiate fluvastatin therapy at 40 mg once daily or 80 mg in divided doses of the 40 mg capsule given twice daily. Patients requiring LDL-C reductions < 25% should initiate a starting dose of 20 mg. ER tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily ER tablet: 80 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after 4 weeks and dosage adjusted accordingly. Max dose is 20 mg twice daily when used with cyclosporine or fluconazole.	Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in 2 divided doses (IR capsule). May be administered with or without food. Tablets may be taken at any time during the day (ER tablet). Tablets should be swallowed whole. (ER tablet).
Lovastatin	ER tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg	Hyperlipidemia: ER tablet: initial 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial 20 mg once daily; maintenance, 10 to 80 mg/day in single or 2 divided doses; maximum, 80 mg/day Prevention of CVD: ER tablet: initial 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial 20 mg once daily; maintenance, 10 to 80 mg/day in single or 2 divided doses; maximum, 80 mg/day	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	ER tablet should be taken at bedtime. ER tablets should be swallowed whole. IR tablet should be taken with an evening meal.
Pitavastatin	Tablet: 1 mg 2 mg	Hyperlipidemia:	After initiation and/or upon titration, lipid	May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	4 mg	Tablet: initial 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day <u>Reduce TC, LDL-C and apo B in patients with HoFH (ages 8 years and older):</u> Tablet: initial 2 mg once daily; maximum, 4 mg/day	levels should be analyzed after 4 weeks and dosage adjusted accordingly. Do not exceed 4 mg once daily dosing due to increased risk of severe myopathy Max dose is 1 mg/day when used with erythromycin. Max dose is 2 mg/day when used with rifampin. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	Tablets may be taken at any time during the day.
Pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	<u>Hyperlipidemia:</u> Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily <u>Prevention of CVD:</u> Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily <u>Pediatric patients</u>: Ages 8 to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after 4 weeks and dosage adjusted accordingly. Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.	May be administered with or without food. Tablets may be taken at any time during the day.
Rosuvastatin	Tablet: 5 mg 10 mg 20 mg	<u>Tablets:</u> <u>Hyperlipidemia:</u> Initial 10 to 20 mg once daily; maintenance, 5 to 40 mg/day	After initiation and/or upon titration, lipid levels should be	May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	40 mg Capsule: 5 mg 10 mg 20 mg 40 mg	 <u>Reduce TC, LDL-C and apo B in patients with HoFH:</u> Initial 20 mg once daily; Ages 7 to 17 years: 20 mg once daily <u>Reduce TC, LDL-C and apo B in pediatric patients with HeFH:</u> Aged 8 to less than 10 years: maintenance, 5 to 10 mg/day Aged 10 to 17 years: maintenance, 5 to 20 mg/day <u>Capsules:</u> Initial 10 to 20 mg once daily; usual starting dose in HoFH is 20 mg once daily Maximum dose: 40 mg once daily	analyzed within 2 to 4 weeks and dosage adjusted accordingly. Dosing in Asian patients: initial 5 mg once daily. Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/ ritonavir, lopinavir/ritonavir, or simeprevir.	May be taken at any time during the day.
Simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg Oral suspension: 20 mg/5 mL 40 mg/5 mL	<u>Hyperlipidemia:</u> initial 10 or 20 mg once daily; maintenance, 5 to 40 mg/day <u>Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable:</u> 40 mg once daily <u>Prevention of CVD:</u> initial 10 or 20 mg once daily; maintenance, 5 to 40 mg/day <u>Reduce TC, LDL-C and apo B in pediatric patients with HeFH:</u> Aged 10 to 17 years: initial 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after 4 weeks and dosage adjusted accordingly. Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g. for 12 months or more) without evidence of muscle toxicity)	Tablets should be taken in the evening. The oral suspension should be taken on an empty stomach. Shake oral suspension bottle for at least 20 seconds. Use accurate measuring device. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who have been taking the 80 mg dose chronically without

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			while taking lomitapide. Use caution in Chinese patients receiving doses > 20 mg with niacin-containing products. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when used with amiodarone, amlodipine, or ranolazine. Simvastatin is contraindicated for use with strong CYP3A4 inhibitors. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Use caution in patients receiving ≥ 1 gram daily of	evidence of muscle toxicity.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			niacin-containing products.	
Combination Products				
amlodipine/ atorvastatin	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of HTN/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is amlodipine 10 mg daily and atorvastatin 80 mg daily. Patients requiring large LDL-C reductions (> 45%) should initiate atorvastatin therapy at 40 mg once daily. <u>HeFH in pediatric patients 10 to 17 years old:</u> *Atorvastatin* Tablet: initial dose 10 mg/day, maximum dose 20 mg/day *Amlodipine [age 6 to 17 years old]* Tablet: initial dose 2.5 to 5 mg maximum dose 5 mg	After initiation and/or upon titration, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood pressure goals. In general wait 7 to 14 days between titration steps. Titration may proceed more rapidly if clinically warranted, provided the patient is assessed frequently.	May be administered with or without food. Tablets may be taken at any time during the day.
ezetimibe/ atorvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	<u>Usual starting dose:</u> 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/40 mg once daily. May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (> 55%). <u>HoFH:</u> 10/40 mg once daily.	After initiation or titration of doses, lipid levels may be analyzed after ≥ 2 weeks. For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenair alone or with	Tablets may be taken at any time of the day. May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			ritonavir: Do not exceed 10/20 mg once daily. For patients taking nelfinavir: Do not exceed 10/40 mg once daily.	
ezetimibe/ simvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B, TG, and non-HDL-C levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: initial 10/10 or 10/20 mg once daily; maintenance, 10/10 to 10/40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within ≥ 2 weeks and dosage adjusted accordingly. Decrease dose of Vytorin by 50% if initiating lomitapide. Vytorin dosage should not exceed 10/20 mg once day (or 10/40 mg once daily for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with	May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy, particularly during the first year of treatment, use of the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			amiodarone, amlodipine, or ranolazine. Vytorin is contraindicated for use with strong CYP3A4 inhibitors. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	

Abbreviations: ER = extended-release, IR = immediate-release.
*Pravachol 10 mg is no longer available; however, generic pravastatin 10 mg remains available.

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SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses of > 20 mg have not been studied in this population. Safety and efficacy in children < 10 years of age have not been established.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.
Fluvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 9 to 16 years of age for the treatment of HeFH. Safety and efficacy in children for other approved indications have	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in women who are pregnant or may become pregnant. Potential excretion into

		not been established.	severe renal dysfunction; doses above 40 mg per day have not been studied.		breast milk; contraindicated during breastfeeding
Lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin ER should not exceed 20 mg/day (Altoprev).	Approved for use in children 10 to 17 years of age for the treatment of HeFH (Mevacor); maximum dose of 40 mg/day. Safety and efficacy in children < 10 years of age have not been established (Mevacor). Safety and efficacy in children have not been established (Altoprev).	Renal dosage adjustment is required; for creatinine clearances < 30 mL/minute, use with caution and carefully consider doses > 20 mg/day.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X (Mevacor) No data on excretion in breast milk; not recommended (Mevacor) Unclassified† (Altoprev) Contraindicated in pregnant women (Altoprev). Contraindicated during breastfeeding (Altoprev)
Pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 years of age and older for the treatment of HeFH (Livalo). Safety and efficacy in children have not been established (Zypitamag).	Renal dosage adjustment is required; for creatinine clearances 15 to 59 mL/ minute or end-stage renal disease receiving hemodialysis, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women Contraindicated during breastfeeding
Pravastatin	No evidence of overall differences in safety or efficacy observed between elderly	Approved for use in children 8 to 18 years of age for the treatment of HeFH. Safety and efficacy in children	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast

	and younger adult patients.	< 8 years of age have not been established.			milk; contraindicated during breastfeeding.
Rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children < 7 years of age have not been established. Pediatric dosing is approved for Crestor; however, due to marketing exclusivity rights, Ezallor Sprinkle is not labeled with similar pediatric dosage information.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances < 30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Limited data indicate that the drug is in breast milk; contraindicated during breastfeeding.
Simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses greater than 40 mg have not been studied in this population. Safety and efficacy in children < 10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required for severe renal impairment: an initial dose of 5 mg/day with close monitoring is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Contraindicated in active liver disease.	Unclassified† Contraindicated for use during pregnancy and in women who may

	Elderly patients have decreased clearance of amlodipine; lower initial doses of amlodipine may be required.	Safety and efficacy of atorvastatin in children < 10 years and amlodipine in children < 6 years of age have not been established			become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ atorvastatin	The maximum dosage limit is 10/80 mg once daily for most patients.	Safety and efficacy have not been established.	No dosage adjustment is needed.	Contraindicated in patients with active hepatic disease or unexplained transaminase elevations.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients; prescribe with caution.	Safety and efficacy in children < 10 years old have not been established.	Use with caution doses exceeding 10/20 mg in patients with moderate to severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.

Abbreviation: ER=extended-release.

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

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CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (Caduet [amlodipine/atorvastatin], ezetimibe/atorvastatin, and Vytorin [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.
- Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.
- All products in this review are now available in a generic formulation except for Altoprev (lovastatin ER), Flolipid (simvastatin oral suspension), Zypitamag (pitavastatin), and Ezallor Sprinkle (rosuvastatin capsule) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*).
- In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.

- In 2018, American College of Cardiology (ACC)/AHA and a variety of other organizations released a new guideline on the management of blood cholesterol (*Grundy et al 2019*). Statins remain the cornerstone of therapy; however, this guideline also contains very specific recommendations for clinicians in a newly defined "very high risk of ASCVD" category, which refers to patients who continue to have LDL-C levels ≥ 70 mg/dL after maximizing statin therapy. In these patients, the guideline recommends considering the addition of a non-statin medications, such as ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.
- The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease incorporates the 2018 management of blood cholesterol guideline recommendations into their guidance (*Arnett et al 2019*). The guideline also discusses the importance of having patient-clinician risk discussions prior to initiating pharmacologic treatment for reducing ASCVD risk. Statins remain first-line treatment for primary prevention of ASCVD for those with LDL-C elevations ≥ 190 mg/dL, those with diabetes mellitus, and those who have determined to be at sufficient risk for ASCVD after a patient-clinician discussion.
- The 2013 ACC/AHA Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary ASCVD risk reduction in adults (*Stone et al 2014*).
  - These guidelines established 4 statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C > 190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk > 7.5%
  - Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.
  - A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to 189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥ 190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al 2014).
  - Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.
- The 2015 AHA Scientific Statement on Familial Hypercholesterolemia recommends aggressive pharmacological treatment for patients with HeFH beginning at age 8 to 10 years. Pharmacological treatment may also be considered in younger patients (less than 8 years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after 3 months, then ezetimibe may be added. If LDL-C continues to be above goal after 3 months of 2-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (*Gidding et al 2015*).
- The 2019 AHA Scientific Statement on Cardiovascular Risk Reduction in High-Risk Pediatric Patients recommends initiating both lifestyle interventions and statin therapy for those at high risk, which includes patients with HoFH (*de Ferranti et al 2019*). For patients at moderate risk, including those with HeFH, statin therapy should be initiated if LDL-C goals are not met after 3 months of lifestyle interventions. Respective LDL-C goals for high risk and moderate risk pediatric patients are < 100 mg/dL and < 130 mg/dL. Lastly, the statement also notes that patients with HoFH will also require nonstatin therapies such as LDL apheresis or a PCSK9 inhibitor.
- The 2016 United States Preventive Services Task Force (USPSTF) recommendations for statin use for the primary prevention of cardiovascular disease in adults note the following:
  - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 years (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, HTN, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
  - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of < 10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a

history of CVD when all of the following criteria are met: (1) they are aged 40 to 75 years (2) they have ≥ 1 CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
  - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥ 76 years without a history of MI or stroke (*US Preventative Task Force 2016).*
- In 2017, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended the addition of another agent when statin therapy alone does not achieve therapeutic goals; their guidance offers cholesterol absorption inhibitors, bile acid sequestrants, and PCSK9 inhibitors as options (*Jellinger et al 2017*). The recommendations for statin therapy for managing dyslipidemia and prevention of cardiovascular disease are stated as the following:
  - Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials.
  - For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset type 2 diabetes mellitus associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.
  - In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered.
  - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least 1 additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of < 70 mg/dL.
  - Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal < 55 mg/dL.
- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.
- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.
- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1% to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase. A recent review concluded that statin-induced hepatotoxicity occurs rarely and that concern that hepatic damage may occur should not be a reason to avoid statin therapy in patients with appropriate clinical indications for use (*Meurer et al 2020*).
- The 2018 AHA scientific statement regarding statin safety emphasized restarting statin therapy in patients who have discontinued due to muscle-related complaints, as the benefits of these agents outweigh their risks (*Newman et al 2019*).
- Pravastatin is the only statin that does not undergo CYP 450 metabolism and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.
- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

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