

HMG-CoA Reductase Inhibitors (Statins) and Proprotein Convertase Subtilisin/ Kexin Type 9 (PCSK9) Inhibitors Washington Archive Report

Washington P&T Committee

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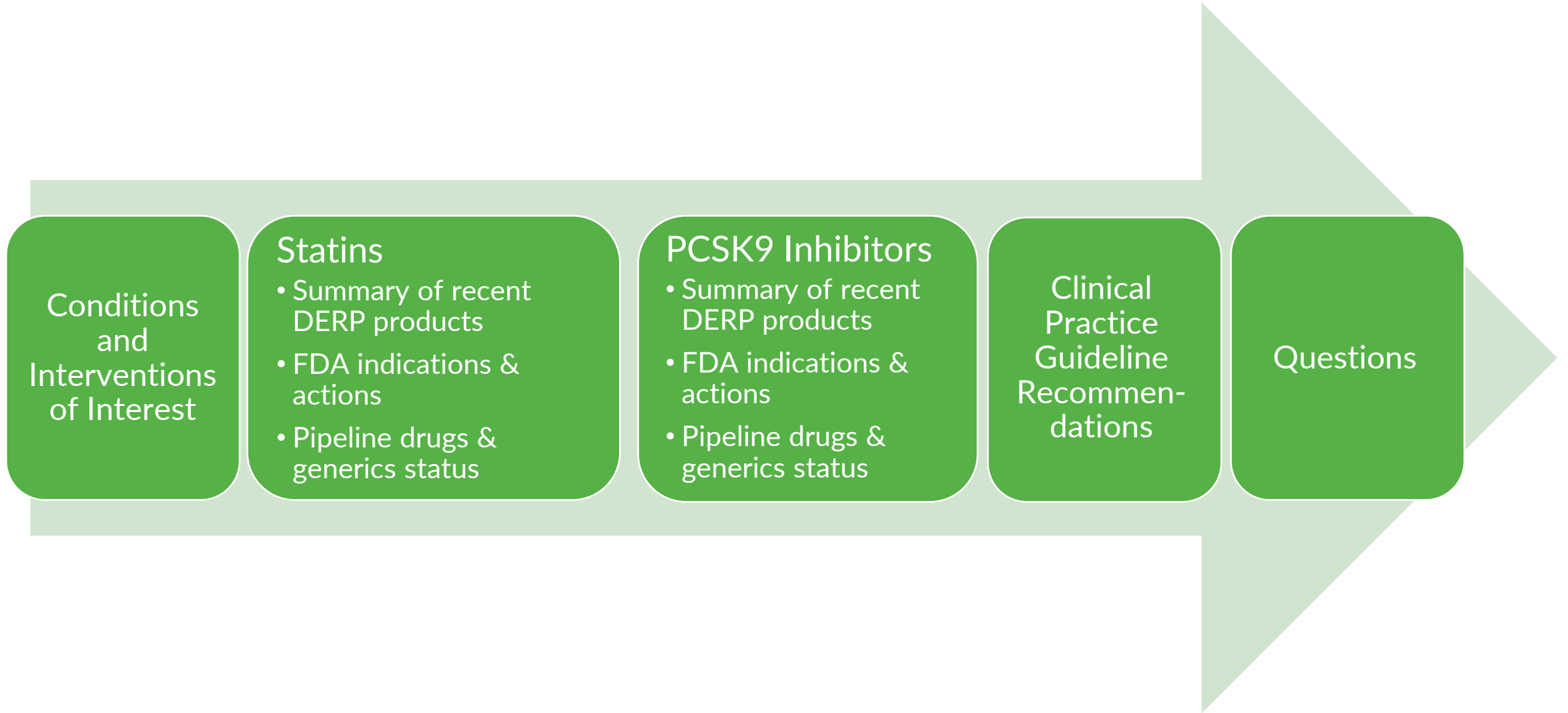


Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
 - Anticoagulants
 - Antiemetics
 - Antiplatelets
 - Asthma controllers
 - Asthma quick relief drugs
 - Long-acting opioids
 - Overactive bladder drugs
 - **PCSK9 inhibitors**
 - **Statins**

*Drug classes in **green** are presented in this report*

Overview



Abbreviations

ACS: acute coronary syndrome

AE: adverse event

ASCVD: atherosclerotic cardiovascular disease

CABG: coronary artery bypass graft

CAD: coronary artery disease

CDC: Centers for Disease Control and Prevention

CEbP: Center for Evidence-based Policy

CHD: coronary heart disease

CNS: central nervous system

CV(D): cardiovascular disease

DERP: Drug Effectiveness Review Project

ER: extended release

FDA: US Food and Drug Administration

H2H: head-to-head

HDL-C: high-density lipoprotein cholesterol

HeFH: heterozygous familial hypercholesterolemia

HoFH: homozygous familial hypercholesterolemia

HIV: human immunodeficiency virus

HMG-CoA: hydroxymethylglutaryl-CoA

LDL-C: low-density lipoprotein cholesterol

MI: myocardial infarction

NCEP: National Cholesterol Education Program

PCSK9: proprotein convertase subtilisin/kexin type 9

PUFA: poly-unsaturated fatty acids

RCT: randomized controlled trial

TG: triglyceride

USPSTF: US Preventative Services Task Force

VA/DoD: Veteran's Affairs/Department of Defense

VLDL-C: very low-density lipoprotein cholesterol

High Blood Cholesterol: Definition & Epidemiology (slide 1 of 2)

- Elevated blood LDL-C levels have been associated with an increase in atherosclerosis and CVD
- Progression of atherosclerosis increases risks of heart attack and stroke
- Risk factors for elevated LDL-C include
 - Familial hypercholesterolemia
 - Smoking, poor diet, inactivity, overweight or obesity, excess alcohol intake, advanced age

Adult NCEP LDL-C classification:

- Optimal: < 100 mg/dL
- Near optimal: 100 to 129 mg/dL
- Borderline high: 130 to 159 mg/dL
- High: 160 to 189 mg/dL
- Very high: \geq 190 mg/dL

High Blood Cholesterol: Definition & Epidemiology (slide 2 of 2)

- The [CDC estimates](#) about 40% of adults in the US have high total blood cholesterol levels
 - Many people are unaware because there are no symptoms
 - Familial hypercholesterolemia [affects 1 in 250 people in the US](#)
- Cardiovascular event risk
 - High LDL-C may [increase risk of stroke by 10%](#)
 - In [people over 70 years](#), high LDL-C increases risk of MI by 34%
 - Lowering LDL-C by 30% may [lower a baseline 10-year CHD risk from 10.7% down to 8%](#)
- [White and Hispanic adults](#) have higher rates of elevated total cholesterol than Black adults in the US
 - [Black](#) adults have a higher prevalence of CVD and death due to CVD

Treatments (slide 1 of 3)

- Pharmaceutical agents for lowering blood cholesterol [levels](#)

Class	Mechanism	Primary Indication
Statins	Inhibits HMG-CoA reductase, reducing synthesis of cholesterol in the liver	First-line treatment for hypercholesterolemia, prevention of CVD
Selective cholesterol absorption inhibitors (ezetimibe)	Reduces dietary cholesterol absorption from intestines	People with primary hyperlipidemia and familial hypercholesterolemia
PCSK9 inhibitors	Inhibits PCSK9 proteins that limit receptors and clearance of LDL cholesterol by the liver	People with HoFM, HeFM, or with high risk of heart disease who have been unsuccessful in lowering cholesterol using other interventions
Omega-3 fatty acid esters	Reduces synthesis of VLDL-C and TGs in the liver	People with hypertriglyceridemia

Treatments (slide 2 of 3)

- Pharmaceutical agents for lowering blood cholesterol levels (cont.)

Class	Mechanism	Primary Indication
Fibric acid derivatives	Increases degradation and reduces production of VLDL cholesterol in the liver	People with hypertriglyceridemia, hyperlipidemia, or mixed dyslipidemia
Bile acid sequestrants or resins	Reduces dietary cholesterol absorption from intestines	People with primary hypercholesterolemia, who may be intolerant to statins or other treatments
Nicotinic acid	Inhibits synthesis of TGs and VLDL-C in the liver	People with primary hypertriglyceridemia and hyperlipidemia
Adenosine triphosphate-citric lyase (ACL) inhibitors	Inhibits HMG-CoA reductase, reducing synthesis and improving clearance of LDL-C in the liver	Newer class to treat primary hypercholesterolemia; may be option for people with statin-associated muscle symptoms

Treatments (slide 3 of 3)

- Other interventions for elevated cholesterol
 - ▣ Dietary supplements
 - Omega-3 fatty acids or PUFAs
 - Niacin
 - ▣ Healthy lifestyle behaviors
 - Low-cholesterol, high fiber diet
 - Increased physical activity
 - Weight loss
 - Stopping smoking
- Combining pharmacotherapies is often considered for more intractable conditions of primary and familial hypercholesterolemia

Statins

Summary of Most Recent DERP Products (Statins)

Last Report	2009
Date Presented	November 2009
Report Title	<i>HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin</i>
Search Dates	From inception (most databases) through June 4, 2009
Authors	Oregon Evidence-based Practice Center and CEBP researchers
<u>Surveillance</u> Since Last Report	
March 2018 (last scan)	<i>HMG-CoA Reductase Inhibitors (Statins) and Fixed-Dose Combination Products Containing a Statin</i> • Search Dates: January 2016 through February 2018
Annually since 2013	<i>HMG-CoA Reductase Inhibitors (Statins) and Fixed-Dose Combination Products Containing a Statin</i>

PICOS of Most Recent DERP Report (Statins)

- *Populations*

- ❑ Outpatients (all ages) targeted for primary or secondary prevention of CHD or noncoronary forms of atherosclerotic disease with or without hypercholesterolemia
- ❑ Inpatients (all ages) with ACS or undergoing revascularization (if the statin was continued after hospital discharge and if health outcomes were reported)
- ❑ Familial hypercholesterolemia (homozygous or heterozygous)

- *Comparators*

- ❑ Another listed intervention (H2H)
- ❑ Another medication (active comparator) used to lower blood cholesterol

- *Study designs*

- ❑ RCTs, comparative effectiveness reviews

PICOS of Most Recent DERP Report (Statins)

- *Interventions (statins)*

Name	Brand Name	FDA Approval Date	Drug Class
Atorvastatin	Lipitor	December 17, 1996	HMG-CoA reductase inhibitor
Fluvastatin	Lescol	December 31, 1993	HMG-CoA reductase inhibitor
Fluvastatin ER	Lescol XL	October 6, 2000	HMG-CoA reductase inhibitor
Lovastatin	Mevacor ^c	August 31, 1987	HMG-CoA reductase inhibitor
Lovastatin ER ^a	Altoprev	June 26, 2002	HMG-CoA reductase inhibitor
Pravastatin ^{a,b}	Pravachol	October 31, 1991	HMG-CoA reductase inhibitor
Rosuvastatin ^{a,b}	Crestor	August 12, 2003	HMG-CoA reductase inhibitor
Simvastatin ^{a,b}	Zocor	December 23, 1991	HMG-CoA reductase inhibitor

Notes. Fixed-dose combination products listed in most recent report are not included here; ^a Not listed as included intervention in most recent scan, ^b but scan findings included studies with this drug; ^c Listed as **generic only** in most recent scan.

PICOS of Most Recent DERP Report (Statins)

- *Outcomes*

- ❑ Change in LDL-C
- ❑ Change in HDL-C
- ❑ CV events (e.g., nonfatal MI, stroke)
- ❑ Need for revascularization (e.g., CABG, angioplasty)
- ❑ Mortality
- ❑ AEs
 - Overall AEs
 - Serious AEs
 - Withdrawals due to AEs
 - Specific AEs (e.g., hepatotoxicity, myopathy, renal toxicity)

Key Questions in Most Recent DERP Report (Statins)

- How do statins and fixed-dose combination products (statin plus another lipid lowering drug) compare:
 1. In ability to reduce LDL-C?
 2. In ability to raise HDL-C?
 3. In ability to reduce the risk of nonfatal MI, CHD (angina), CHD mortality, all-cause mortality, stroke, hospitalization for unstable angina, or need for revascularization (CABG, angioplasty, or stenting)?
 4. In effectiveness across different demographic groups or populations with different comorbid conditions?
 5. In harms across different aged populations (i.e., children and adults)
 6. In harms in special populations (e.g., with HIV, with risk for hepatotoxicity), or with other medications (i.e., drug interactions)

Note. Red text is not of interest for this archive report, but was included in most recent report.

Summary of Findings in Most Recent DERP Report (Statins) (slide 1 of 3)

- 2009 report
 - Included 347 studies^a (102 head-to-head, 123 other RCTs, 80 observational studies, 21 systematic reviews, 21 “other”)
- Summary of key findings (adults):
 - For patients who require LDL-C reductions of up to 35% to meet their goal, any of the statins are effective
 - High-dose rosuvastatin appears to have greater LDL-C lowering and HDL-C raising effects than high-dose atorvastatin
 - In general, combination products more effective overall (decreasing LDL-C, increasing HDL-C) compared with monotherapy

Notes. *Red text* is not of interest for this archive report, but was included in most recent report; ^a Unclear if total number includes ancillary publications.

Summary of Findings in Most Recent DERP Report (Statins) (slide 2 of 3)

- Summary of key findings (adults) (continued):
 - ❑ No H2H evidence for outcomes relating to frequency of CV events
 - ❑ Statins were equally effective in men, women, and elderly patients, and rates of AEs were not different across these groups at maximum doses of simvastatin and lovastatin
 - ❑ Niacin extended-release fixed-dose combination products have increased adverse events, primarily flushing, with greater discontinuation of drug due to adverse event
 - ❑ People with diabetes did not have higher rates of AEs with statins
 - ❑ Some serious drug interactions exist with CYP 3A4 and 2C9 inhibitors

Notes. *Red text* is not of interest for this archive report, but was included in most recent report; ^a Unclear if total number includes ancillary publications.

Summary of Findings in Most Recent DERP Report (Statins) (slide 2 of 3)

- Summary of key findings (children):
 - Trials of statins in children have been conducted primarily in children with heterozygous or homozygous familial hypercholesterolemia
 - Improvement in LDL-C, but no difference in HDL-C compared with placebo across statins studied
 - In general, combination products more effective overall (decreasing LDL-C) compared with monotherapy
 - No H2H evidence for outcomes relating to frequency CV morbidity and mortality
 - No evidence for differences in effectiveness and harms in children with diabetes or obesity
 - AEs poorly reported; no significant or clinically meaningful elevations in liver or kidney function tests

Summary of Findings in Most Recent Scans/Surveillance

- Cumulative from most recent report through most recent 2018 scan (searched through February 2018)
 - ▣ 1 new drug, pitavastatin (brand name, Livalo), approved August 3, 2009
 - ▣ No new indications or serious harms
 - ▣ 55 new H2H trials (*see attached list*)
 - 16 trials comparing monotherapy with fixed-dose combined products
 - 2 studies of atorvastatin vs. pitavastatin vs. rosuvastatin
 - No new comparative studies including fluvastatin ER or lovastatin
 - 37 comparative trials for monotherapies (matrix)

	Atorvastatin	Fluvastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Atorvastatin			6	4	11	2
Fluvastatin					1	
Pitavastatin	6			5	2	2
Pravastatin	4		5		2	
Rosuvastatin	11	1	2	2		2
Simvastatin	2		2		2	

New FDA Drugs, Indications, Actions Since Most Recent DERP Report (Statins)

- **New drugs**
 - Pitavastatin (brand name, Livalo)
 - HMG-CoA reductase inhibitor FDA-approved August 3, 2009
- **No new indications or boxed warnings for statins**
- **New warnings/precautions for statins**
 - Warning for risk of immune-mediated necrotizing myopathy (an autoimmune myopathy) was listed as rare, but associated with statin use for all included statins (September 2020)
- **Warning REMOVED**
 - Atorvastatin
 - CNS toxicity/higher incidence hemorrhagic stroke in patients without CHD (December 2022)

FDA-Approved Indications (Statins)

- Indications as of November 6, 2023

	Most indications are reported as adjunct with diet				
Generic Name (Brand Name)	Reduce risk of CV events and revascularization procedures in people with risk of CHD	Reduce risk of CV events and revascularization procedures in people with established CHD, and/or slow progression of atherosclerosis	Reduce LDL-C in adults with primary hyperlipidemia, and pediatric patients with HeFH	Reduce LDL-C in adults and/or pediatric patients with HoFH	Treatment of adults with primary dysbeta-lipoproteinemia or high triglycerides
Atorvastatin (Lipitor)	✓	✓	✓	✓	✓
Fluvastatin (Lescol)		✓	✓ (HeFH only in peds)	✓	
Lovastatin (Altoprev [ER])	✓	✓	✓		
Pitavastatin ^a (Livalo)			✓		
Pravastatin (Pravachol)	✓	✓	✓		✓
Rosuvastatin (Crestor)	✓	✓	✓	✓	✓
Simvastatin (Zocor , Flolipid)	✓		✓	✓ (adults only)	✓

Note. ^a Newly approved since last report.

Generic Drug & Pipeline Status (Statins)

Name	Generic Availability	Status
Atorvastatin	Yes	Already available as generic since most recent report • <i>Lipitor brand discontinued</i>
Fluvastatin	Yes	Already available as generic since most recent report (both original and ER formulations)
Lovastatin	Yes	Already available as generic since most recent report • <i>Mevacor brand discontinued</i> • <i>ER formulation (Altoprev brand) does not appear to be available as a generic</i>
Pitavastatin	No	Estimated date of generic launch August 2024, or sooner ^a
Pravastatin	Yes	Already available as generic since most recent report • <i>Pravachol brand discontinued</i>
Rosuvastatin	Yes	Already available as generic since most recent report
Simvastatin	Yes	Already available as generic since most recent report • <i>Oral suspension formula (Folipid brand) to lose exclusivity February 2030</i>

- No new HMG-CoA reductase inhibitor (statin) pipeline therapies since the most recent report

PCSK9 Inhibitors

Summary of Most Recent DERP Products (PCSK9s)

Most Recent Report	2018
Date presented	December 6, 2018 (DERP Governance call)
Report Title	<i>Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors</i>
Search Dates	From inception (most databases) through July 2018
Authors	Center for Evidence-based Policy researchers
<u>Surveillance</u> Since Most Recent Report	
February 2020	<i>Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors</i> <ul style="list-style-type: none">• Search dates: July 2018 through December 2019

PICOS of Most Recent DERP Report (PCSK9s)

- *Population*

- Patients with HeFH or HoFH
- Patients with nonfamilial hypercholesterolemia who are intolerant to or unsuccessful with statin therapy

- *Interventions*

Name	Brand Name	FDA Approval Date	Delivery	Doses Available
Alirocumab	Praluent	July 24, 2015	Injection	75 to 150 mg biweekly
				300 mg monthly
Evolocumab	Repatha	August 27, 2015	Injection	140 mg biweekly
				420 mg monthly

PICOS of Most Recent DERP Report (PCSK9s)

- *Comparators*

- H2H comparisons of included interventions
- Active pharmacological treatments (e.g., statins), including trials of add-on therapy that provide comparative data on an included drug vs. another active treatment
- Placebo if with CVD outcomes

- *Outcomes*

- Health events and survival (e.g., MI, mortality)
- Change in blood cholesterol levels (e.g., LDL-C, HDL-C)
- AEs (serious AEs, withdrawals due to AEs, specific AEs)

- *Study designs*

- RCTs, systematic reviews

Key Questions in Most Recent DERP Report (PCSK9s)

Comparative benefits and harms of PCSK9 inhibitors in patients with:

1. Heterozygous and homozygous familial hypercholesterolemia?
2. Hypercholesterolemia who are unable to use statins because of intolerance or for any other reasons?
3. Nonfamilial hypercholesterolemia who have not achieved LDL-C < 100 mg/dl or < 70 mg/dl with their current lipid-lowering regimen?
4. Effectiveness of PCSK9 inhibitor monotherapy or adjunct therapy with other lipid-lowering agents or other cardiovascular risk reduction methods on cardiovascular risk in patients with hypercholesterolemia?
5. Differences in comparative benefits and harms of PCSK9s across patient subgroups?

Summary of Findings in Most Recent DERP Report (PCSK9s) (slide 1 of 2)

- 2018 Report
 - Included 13 RCTs, 1 systematic review, 2 pooled data analyses
- Summary of key findings
 - PCSK9 inhibitors were more effective than other lipid-lowering therapies at reducing LDL-C levels in various populations with familial or nonfamilial hypercholesterolemia; participants with statin intolerance experienced substantial reductions in LDL-C levels
 - Incidences of AEs were, in general, similar between PCSK9s and other lipid-lowering agents

Summary of Findings in Most Recent DERP Report (PCSK9s) (slide 2 of 2)

- Summary of key findings (continued)
 - ▣ In people with nonfamilial hypercholesterolemia:
 - Alirocumab or evolocumab demonstrated significant reductions in cardiovascular risks compared with placebo (with statin background therapy) during follow-up periods of at least 2 years (absolute risk reductions in events were small)
 - All-cause mortality incidence was lower for alirocumab and evolocumab compared with placebo after 34 and 26 months, respectively, but only significantly different with evolocumab

Summary of Findings in Most Recent Scans/Surveillance

- 2020 surveillance (searched through December 2019)
 - No new drugs
 - 1 new indication for alirocumab
 - Expanded to include adults who are hospitalized with established CVD to reduce risk of MI, stroke, and unstable angina
 - No new serious harms
 - 2 new RCTs
 - 1 trial for alirocumab vs. standard of care in patients with ACS
 - 1 trial for evolocumab vs. ezetimibe in statin-intolerant patients

New FDA Drugs and Indications Since Most Recent DERP Report (PCSK9s)

- **New drugs**

- ▣ Inclisiran (brand name, Leqvio)

- A PCSK9 inhibitor approved on December 22, 2021
 - Injection administered every 3 months for 2 doses, then every 6 months thereafter

- **New indications**

- ▣ Alirocumab (Praluent)

- Expanded to include hospitalized patients with CVD to reduce risks of MI, stroke and unstable angina (April 2019)
 - Expanded to include patients with HoFH (April 2021)

- ▣ Evolocumab (Repatha)

- Expanded to include younger pediatric patients at least 10 years for HoFH (from at least 13 years) and HeFH (February 2021)

FDA-Approved Indications (PCSK9s)

- Indications as of November 3, 2023

Generic Name (Brand Name)	Reduce LDL-C in adults with primary hypercholesterolemia or HeFH, adjunct to diet or with other cholesterol-lowering therapies	Reduce LDL-C in adults with HoFH, adjunct to other cholesterol-lowering therapies	In adults with CVD (with* or without hospitalization), to reduce risk of MI, stroke, and unstable angina or coronary revascularization	In pediatric patients aged 10 years and older with HeFH or HoFH
Alirocumab (Praluent)	✓	✓	✓*	
Evolocumab (Repatha)	✓	✓	✓	✓
Inclisiran ^a (Legvio)	✓		✓	

Note. ^a Newly approved since most recent surveillance.

Abbreviations. CVD: cardiovascular; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction.

New FDA Actions Since Last DERP Report (PCSK9s)

- **New boxed warnings**
 - No new boxed warnings
- **New warnings/precautions/contraindications**
 - Warning for hypersensitivity expanded to include excipients (inactive substances in product) in addition to the active drugs for:
 - Alirocumab (April 2021)
 - Evolocumab (February 2021)

Pipeline Therapies and Generics Status (PCSK9s)

- 2 new pipeline PCSK9 inhibitor therapies are in phase 3 trials
 - ▣ Lerodalcibep (LIB003)
 - Subcutaneous delivery
 - For patients with HeFH, HoFH, and atherosclerosis due to hypercholesterolemia
 - ▣ MK-0616
 - Oral delivery
 - For patients with HeFH, HoFH, and to reduce cardiovascular events in patients with elevated lipoprotein “a”
- Generics are not available for any of the approved PCSK9 inhibitors at this time; no other information about future generic status identified

Other New Treatments

- Highlighted new treatments that are neither statins nor PCSK9s
 - Icosapent ethyl ([Vascepa](#)) expanded indication of reducing risk for CV events (December 2019)
 - As adjunct to statins to reduce risk of CV events in adults with high triglycerides and other risk factors
 - [Bempedoic acid](#) ([Nexletol](#), [Nexlizet](#) [plus ezetimibe])
 - Both approved February 2020 for the indication of HeFH in adults or for established atherosclerotic CVD in adults who require additional lowering of LDL-C

Clinical Practice Guidelines (slide 1 of 6)

- Treatment of hypercholesterolemia as primary prevention of CVD^a
 - Counsel all patients on healthy lifestyle behaviors and healthy weight
 - LDL-C > 190 mg/dL, start high-dose statin (atorvastatin, rosuvastatin)
 - LDL-C < 190 mg/dL, depends on 10-year CVD risk of > 10%
 - High risk: initiate statin therapy (moderate dose)
 - Intermediate risk: may initiate statins based on patient preference
 - Low risk: no statin therapy
 - PCSK9 inhibitors considered with statin-intolerance, but typically limited to patients with existing atherosclerotic cardiovascular disease (or familial hypercholesterolemia), or with statin-resistant hypercholesterolemia
 - [VA/DoD](#) strongly recommends **against** using PCSK9s for primary prevention due to unknown long-term safety, inconclusive evidence for benefit, and high cost

Clinical Practice Guidelines (slide 2 of 6)

- Statins considered cornerstone of lipid-lowering therapy

Estimated LDL-C Lowering Intensity		
High ($\geq 50\%$)	Moderate (30% to 49%)	Low ($< 30\%$)
Atorvastatin (40 mg and 80 mg) Rosuvastatin (20 mg and 40 mg)	Atorvastatin (10 mg and 20 mg) Rosuvastatin (5 mg and 10 mg) Simvastatin (20 to 40 mg) Pravastatin (40 mg and 80 mg) Lovastatin (40 mg and 80 mg) Fluvastatin XL (80 mg) Fluvastatin (40 mg twice daily) Pitavastatin (1 to 4 mg)	Simvastatin (10 mg) Pravastatin (10 to 20 mg) Lovastatin (20 mg) Fluvastatin (20 to 40 mg)

Source. Adapted from Table 3, [2018 AHA/ACC Guideline on the Management of Blood Cholesterol](#)

Note. Different doses are from different RCT study results.

Clinical Practice Guidelines (slide 3 of 6)

- USPSTF recommendations for statins
 - For primary prevention of CVD, statins are recommended for adults aged 40 to 75 years with ≥ 1 CVD risk factor and (selectively offer) 7.5% to $< 10\%$, or (prescribe) $\geq 10\%$ risk of CV event within 10 years
 - Insufficient evidence to recommend statins for adults aged > 75 years for primary prevention of CVD
- Treatment of familial hypercholesterolemia^a
 - Intense LDL-C lipid lowering treatment reduces risk for CAD, MI, and all-cause mortality
 - Lifestyle behavioral counseling (including weight loss if appropriate) for all patients

Clinical Practice Guidelines (slide 4 of 6)

- Treatment of familial hypercholesterolemia^a (continued)
 - Pharmacologic treatment for majority adults with HoFH^b:
 - High-dose statin (atorvastatin or rosuvastatin) + ezetimibe
 - Add PCSK9 inhibitors for “many patients”
 - Pharmacologic treatment for majority adults with HeFH:
 - High-dose statin therapy → measure LDL-C after 6 to 12 weeks
 - If not at goal (target < 55 mg/dL with highest risk), start ezetimibe; PCSK9 inhibitors are third-line therapies
 - NICE guidelines recommend [alirocumab](#) or [evolocumab](#) if LDL-C ≥ 3.5 mmol/L (135 mg/dL) with CVD or ≥ 5 mmol/L (193 mg/dL) without

Clinical Practice Guidelines (slide 5 of 6)

- Treatment of familial hypercholesterolemia^a (continued)
 - In pediatric FH, more likely to require a second lipid-lowering agent in addition to statins; PCSK9s generally limited to patients with persistently elevated LDL-C (e.g., HoFH) despite intense statin therapy or with statin intolerance
- Treatment of hypercholesterolemia as secondary prevention in adults with ASCVD^a
 - Statin therapy is recommended for all adults
 - Decision to include PCSK9 inhibitors depends on these factors:
 - Risk of future ASCVD events (high and very-high risk)
 - Level of baseline LDL-C levels (e.g., ≥ 190 mg/dL)
 - Familial hypercholesterolemia
 - Diabetes status
 - Statin-resistance
 - Statin intolerance

Clinical Practice Guidelines (slide 6 of 6)

- Treatment of hypercholesterolemia as secondary prevention in adults with ASCVD^a (continued)
 - Typically, ezetimibe is recommended as initial nonstatin therapy with maximally tolerated statin therapy; PCSK9s are next in line
 - Example: patient with ASCVD and LDL-C \geq 70 mg/dL (on highest statin dose), initiate ezetimibe, and include PCSK9s if patient considered very *high risk*

Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
American College of Cardiology (ACC)		
Nonstatin therapies for lowering LDL-C	2022	<u>Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic CVD Risk</u>
American College of Cardiology (ACC) / American Heart Association (AHA)		
Reduce CV risk	2018	<u>Management of Blood Cholesterol</u>
National Institute for Health and Care Excellence (NICE)		
Familial hypercholesterolemia	2019	<u>Familial hypercholesterolemia: identification and management</u>
US Department of Veterans Affairs/Department of Defense (VA/DoD)		
Reduce CV risk	2020	<u>Management of Dyslipidemia for Cardiovascular Risk Reduction</u>
US Preventive Services Task Force (USPSTF)		
Prevent CV disease	2022	<u>Statin Use for the Primary Prevention of Cardiovascular Disease in Adults</u>

Questions?



