Journal of Family Medicine

Open Access

Austin Publishing Group

Review Article

Trends in Hyperlipidemia Treatments: Summary of Recommendations for Statin and Non-Statin Options

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Received: November 21, 2023

Accepted: December 18, 2023

Published: December 23, 2023

Abstract

Several treatment options and recommendations exist to guide a primary care provider to reduce overall cardiac morbidity and mortality risk through lipid control. The wealth of data from large studies, the choices of agents with varying mechanisms of action, and differing guidelines result in a challenge to keep abreast of this rapidly changing landscape. In this literature review the latest data regarding lipid management are reviewed and summarized. Current US and international cholesterol treatment guidelines recommend lifestyle modification followed by statin as first-line of therapy in management of hyperlipidemia. After optimizing statin dose if LDL remains above target goal, then the addition of ezetimibe provides added reductions in morbidity and mortality. Fibrates can be considered as an adjunct to statins therapy particularly in the diabetic population with persistent triglyceride elevations and provide modest reductions in coronary artery disease. PCSK9 inhibitors can reduce morbidity and mortality in a high-risk population when a statin or statin+ezetimibe does not bring LDL below the target goal. Some newer agents (ANGPTL3/ACL/MTP Inhibitors) are reserved for patients with a predisposition to ASCVD due to a familial genetic dyslipidemia. Cost for these adjunctive therapies is a concern for the patient and clinician and patient education along with a shared decision approach are warranted. To date, evidence for these agents is limited. Finally, there remains unclear guidance on the value between a “treat to dose” versus a “treat to target” approach to lipid management. Further research is needed to provide clarity on which strategy proves optimal for primary prevention of MACEs.

Keywords: Lipids; Statin; Fibrate; Coronary Artery Disease; Familial Hyperlipidemia; Major Adverse Cardiac Event; Coronary Artery Disease; ASCVD; Ischemic Heart Disease; Evinacumab; Cholestyramine; Colestipol; Colesevelam; Ezetimibe; Gemfibrozil; Fenofibrate; Fenofibric acid; Atorvastatin; Fluvastatin; Lovastatin; Pitavastatin; Pravastatin; Rosuvastatin; Evolocumab; Alirocumab; Bempedoic Acid; Lomitapide; Mipomersen

Abbreviations: ASCVD: Atherosclerotic Cardiovascular Disease; CAD: Coronary Artery Disease; ACS: Acute Coronary Syndrome; MI: Myocardial Infarction; MACE: Major Adverse Cardiac Event; SAMS: Statin Associated Muscle Symptoms; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; Trigs: Triglycerides; EPA: Eicosapentaenoic Acid; DPA: Docosahexaenoic Acid; IPE: Icosapent Ethyl; OM3-FA: Omega-3 Fatty Acid; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; ANGPTL3: Angiopoietin-Like Protein 3; ACL: Adenosine Triphosphate-Citrate Lyase; MTP: Microsomal Triglyceride Transfer Protein; RR: Relative Risk; NNT: Number Needed to Treat; NNTH: Number Needed to Harm; RCT: Randomized Controlled Trial; SORT: Strength of Recommendation Taxonomy; LOE: Level of Evidence; HoFH: Homozygous Familial Hypercholesterolemia; HeFH: Heterozygous Familial Hypercholesterolemia

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Citation: Schultz PA, Chaudhri P, Szymanski K, Landis E, Snyder J. Trends in Hyperlipidemia Treatments: Summary of Recommendations for Statin and Non-Statin Options. J Fam Med. 2023; 10(5): 1343.

Introduction

Lipid disorders and Cardiovascular (CV) disease are a major cause of morbidity and mortality all over the world. Over the years, many different classes of lipid lowering medications have been developed and studied- alone and in combination, with the goal of improving lipid management and decreasing CV morbidity and death. This article offers an updated source for primary care physicians in lipid management. It looks at the varying lipid lowering guidelines and the different classes of medications available to manage hyperlipidemia. The evidence of lipid lowering medications in decreasing LDL-C (low density lipoprotein cholesterol) and effects on improving CV outcomes is also discussed. Finally, it provides further context to the debate between treating LDL-C to goal or target.

Even though multiple classes of lipid lowering medications exist, the use of 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ("statin") medications for overall reduction of cardiac-related morbidity and mortality are well documented through several landmark studies. As a result, the use of statins with lifestyle modifications is a foundation of current hyperlipidemia and cardiac risk reduction per guidelines such as the American College of Cardiology (ACC) /American Heart Association (AHA). Since guideline publication, further studies have evaluated the additive effects of non-statins to statins in secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events, especially in those at very high risk. Several established non-statin medications can be considered as solo therapy or as adjunctive to a statin regimen. The recent development of more non-statin therapeutic agents provides more advanced options in the treatment of hyperlipidemia and the reduction of ASCVD risk.

Table 1 summarizes the major classes of lipid lowering medications, their mechanism of action, LDL lowering effects, major side effects and costs.

Statins

Statins achieve marked reductions in LDL cholesterol via the inhibition of the rate limiting step in the endogenous pathway in cholesterol synthesis. LDL reductions from 10-60% can be achieved. To a lesser degree, triglycerides are also reduced along with a modest increase in HDL [1]. Statin medications have been shown through extensive clinical research to reduce overall cardiac morbidity and mortality [2,3]. Statins not only reduce LDL cholesterol but also reduce the local inflammatory reaction found at coronary plaques. This anti-inflammatory mechanism is associated with plaque stabilization and thought to play a role in reduction of myocardial infarction (4). Statin medications continue to be the go-to agent for primary and secondary risk reduction in patients with an elevated risk for Coronary Artery Disease (CAD).

The ACC/AHA guidelines for treatment of blood cholesterol recommended moderate to high intensity statin in four groups of patients:

1. Known Atherosclerotic Cardiovascular Disease (ASCVD)
2. Diabetics
3. LDL-C ≥190 mg/dl (≥ 4.9mmol/L)
4. ASCVD 10-year risk ≥ 7.5%

Several studies have shown that muscle related symptoms attributed to statin therapy are not true statin associated muscle symptoms (SAMS). Efforts to confirm the origin of symptoms and optimize statin use are important as an increase in MACE (Major Adverse Cardiac Events) is observed in patients with an intolerance who go off statin therapy [5,6]. For the small percentage of patients with clinically presumed SAMS empiric use of either Vitamin D and/or co-enzyme Q10 have been postulated as potential treatment options to circumvent muscle symptoms. A known association exists between muscle related symptoms and vitamin D deficiency. This can benefit from supplementation. But no studies have shown that Vitamin D directly blunts or reverses SAMS. Like vitamin D, there is no clear clinical evidence to support use of co-enzyme Q10 to alleviate SAMS.

For patients with potential SAMS a reasonable first approach following the initiation of a statin is patient education and select lab testing. Informing the patient that the muscle symptoms are frequently not associated with the medication is a key initial step. Blood testing to consider can include: a serum creatinine kinase level to rule out a rare episode of rhabdomyolysis, a 25-hydroxy vitamin D level, and an inflammatory marker, ESR or CRP, to screen for polymyalgia rheumatica. Once select initial blood testing is reassuring, the patient can have statin treatment discontinued (i.e., a drug holiday). If the symptoms dissipate and the lab results are not concerning the next step would be to restart the statin under careful monitoring. If symptoms return both the clinician and patient would reasonably consider SAMS. However, a patient who has seen resolution of muscle symptoms after statin discontinuation may be reluctant to do a second trial on the medication. Overall, statins are well tolerated with the risk for a serious myositis or rhabdomyolysis being rare (<0.01%). Hepatic side effects are even less likely at <0.01%.

Fibrates

The fibrate class provides a more significant reduction of triglycerides than LDL cholesterol [1]. Thus, they are not considered a class that is utilized for LDL-C reduction. In those with severe hypertriglyceridemia, fibrates decrease triglycerides but may increase LDL-C. Among the class, gemfibrozil improves some CV outcomes but concurrent use with a statin can increase risk of severe myopathy. Although fenofibrate is the safer add on option to decrease the risk of severe myopathy, there is no evidence for it improving CV outcomes [7]. There is some moderate evidence for fibrates providing a reduction in CAD risk [8]. Fibrates are used most often for the adjunctive reduction of triglycerides when statins alone are insufficient to bring triglycerides below target levels particularly in patients with Type 2 Diabetes Mellitus [7].

Bile Acid Sequestrants

A meta-analysis reviewed effects of additional LDL-C reduction from combining bile acid sequestrants to statin therapy. Although a thorough literature search was done, only seven articles met the final criteria of inclusion. The analysis concluded that combination of statin and bile acid sequestrant resulted in an additional 16.2-point reduction in LDL-C when compared to statins alone, this was more pronounced for patients taking maximum strength bile acid sequestrant and was not affected in a major way by type of bile acid sequestrant. The study was not powered to assess morbidity and mortality effects and found it difficult to assess adverse events, compliance, medication interaction and side effects [9].

Table 1: Summary of Lipid Lowering Agents.

Medication Class	Mechanism of Action	Agents Available in US	LDL- C Relative Reduction	Side Effects	NNT	NNTH	Cost	Strength of Recommendation
Statins	Inhibition of the rate limiting step in the endogenous pathway in cholesterol synthesis	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin	10-60% reduction	myalgia, Rare Rhabdomyolysis, Headache, dizziness, digestive changes	83-154[a]	10-50[a]	$	SORT A, Level 1
Fibrates	Stimulates peroxisome proliferator activated receptor alpha (PPARα), increasing lipolysis, activating lipoprotein lipase, and reducing apoprotein C-III	Gemfibrozil, fenofibrate, fenofibric acid	11-20% reduction, Greatest impact on Triglycerides	Abdomnial pain, Nausea and vomiting, change in taste, decreased appetite	47-100[b]	132[b]	$	SORT B, Level 2
Bile Acid Sequestrant	bind bile acids in the intestine, interrupt enterohepatic recirculation of bile acids and impede their reabsorption. Decrease bile acid pooling in liver, increase conversion of cholesterol to bile acids	Cholestyramine, Colestipol, Colesevelam	15-30% reduction	GI side effects, Triglyceridemia if Triglycerides>300mg/dl	-	-	$$	SORT B, Level 2
Cholesterol Absorption Inhibitor	inhibits cholesterol absorption from small intestine	Ezetimibe	+statin= 23-24%	Diarrhea, abdominal pain, Headache, dizziness,	59-166[c]	100[c]	$$$	SORT B, Level 1
PCSK9 Inhibitors	Monoclonal Antibodies that bind PCSK9 enzyme, avoiding the degradation of LDLRs in the liver, increasing absorption of LDL-C and decreasing serum LDL-C levels	evolocumab and alirocumab	54% to 74% reduction	injection site reaction,	67-250[c, d]	99-101[c, d]	$$$	SORT B, Level 1
Microsomal Triglyceride Transfer Protein	Act via the CYP3A4 pathway to reduce plasma levels of Apo-B lipoproteins thereby decreasing very low-density lipoprotein (VLDL)	Lomitapide, Mipomersen	40% reduction	Both agents require hepatic monitoring. injection site reaction, flu like illness, flatulence, diarrhea, nausea, and vomiting	62.5	71	$$$$	Orphan drugs, SORT C Level 2
Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors	Prodrug will reduce the production of LDL in the liver and increasing LDL receptors	Bempedoic acid	15.1 -21.4% reduction	injection cite reaction, gout flares, tendon rupture, nasopharyngitis, and urinary tract infections	62-76[e]	100[e]	$$	Orphan drugs, SORT C Level 2
Angiopoietin-Like 3 (ANGPTL3) inhibitors	inhibits hydrolysis of triglycerides and phospholipids exclusively in the liver thereby regulating plasma lipid levels	Evinacumab	56% reduction	Allergic reaction and Pregnancy category not assigned	67	100.5	$$$$	Orphan drugs, SORT C Level 2
Niacin	modulation of liver triglyceride synthesis leading to increased intracellular apo B degradation and modulating triglyceride lipolysis in adipose tissue		15 - 23% reduction	niacin-induced flushing	250[f]	100[f]	$	SORT C, level 2
Omega-3 Fatty Acids	mechanism of this claim is thought to be the blood pressure lowering effects	Vascepa and Lovaza	OM3-FA had no significant effect on LDL-C	Pruritis. dental hyperesthesia,	86[g]	0[g]	$	SORT C, level 2
Curcumin	downregulate factors in lipogenesis and stimulates lipid excretion and mobilization from adipose tissue		7.33% reduction	constipation, hot flashes, and nausea patient.	-	-	$	SORT C, level 3
Fiber	inhibits absorption of cholesterol by trapping cholesterol and bile acids in the small intestine			elevated liver enzymes, abdominal pain, leg cramps, cholelithiasis, elevated CPK and venous thromboembolus	-	-	$	SORT C, level 3

Key	Annual Cost to Patient	
$	$120-$2,000	Data derived from local Pharmacy prices in Toledo, OH. January 2023.
$$	$2,000-$6,000	
$$$	$6,001-$10,000	
$$$$	up to $700,000	
NNT: Number needed to treat		
NNTH: Number needed to harm		

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Cholesterol Absorption Inhibitors

Cholesterol Absorption inhibitors, specifically ezetimibe, have been on the US market since 2002. These are no longer considered appropriate firstline agents in management of hyperlipidemia, quite a few studies have demonstrated their effectiveness as add-on medications to statins. The IMPROVE-IT [10] trial was published in 2015 and is a landmark trial in the category affecting the ACC/AHA 2018 guidelines [11] on management of blood cholesterol. Other trials such as HIJ-PROPER [12] and RACING [13] have investigated other statin/ezetimibe combinations as well and their effects on LDL-C reduction and Acute Coronary Syndrome (ACS) outcomes. PRECISE-IVUS [14] was unique in that it looked at association between statin/ezetimibe combination therapy and percentage change in atheroma volume of plaque rather than LDL-C. The role between LDL-C and coronary plaque regression, has already been evaluated previously.

Overall, most trials have suggested that combination of a statin and ezetimibe decreases LDL-C to goal for higher risk patients, MACE, total atheroma volume and some decrease in secondary instances of cardiovascular events. These effects were present with prolonged use and observed in diabetics and age >75 years. It was also suggested that combination therapy with ezetimibe should be considered prior to statin dose maximization in those at risk for intolerance to statins at higher doses. Although HIJ-PROPER did not demonstrate a difference in MACE between combination statin-ezetimibe therapy versus statin therapy alone, it was thought to be related to the small number of overall ACS events in the study.

PCSK9 Inhibitors

PCSK9 inhibitors increase absorption of LDL-C by the liver and decrease serum LDL-C levels [15]. Network meta-analyses have shown that the PCSK9 inhibitors evolocumab and alirocumab were associated with reductions in LDL-C of 54% to 74% versus placebo and 26% to 46% versus ezetimibe in patients not adequately controlled by statins alone [16].

The FOURIER study [17] demonstrated an absolute risk reduction in patients with ASCVD for both primary endpoints of 1.5% and the NNT was 67. Additionally, those patients with a greater risk profile benefited the most from PCSK9 inhibitor use, with a NNT of 27-30 in the high-risk group.

Wang, et al, conducted a meta-analysis of PCSK9 inhibitors vs placebo and standard of care therapy in patients with ASCVD and the effects on all-cause mortality and MACE. The effects on all-cause mortality and cardiovascular mortality were not significant. However, the effect on MI was statistically significant (RR 0.78, 95% CI 0.70-0.88), NNT of 84. The effects on stroke (RR 0.78, 95% CI 0.68-0.90) with NNT of 294 and coronary revascularization (RR 0.83, 95% CI, 0.78-0.88) and NNT of 81 were also found to be significant [18].

ANGPTL3 Inhibitors/ ACL Inhibitors/ MTP Inhibitors

Homozygous Familial Hypercholesterolemia (HoFH) is a rare genetic condition characterized by markedly elevated LDL cholesterol causing premature cardiovascular disease. Starting in 2012 there have been several new treatments of different classes and modalities to get FDA approval. None of the medications to treat HoFH have been studied in human pregnancy studies and many are contraindicated based on animal studies. Evinacumab is a monthly intravenous infusion human monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3) which was FDA approved in 2021 for ages twelve and older [1]. The Adenosine Triphosphate-Citrate Lyase (ACL) inhibitor Bempedoic acid (FDA approved 2020) is the only drug in this class and is intended to be used in conjunction with lifestyle modification and statin therapy or ezetimibe, and recently received FDA approval for treatment resistant ASCVD [19-21]. Recent data shows bempedoic acid alone reduces MACE in statin intolerant patients [22]. Microsomal Triglyceride transfer Protein (MTP) inhibitors Lomitapide and Mipomersen are another class approved by the FDA to treat HoFH. Lomitapide is an oral agent (FDA approved 2012) for ages eighteen and older. Mipomersen (FDA approved 2013) administered subcutaneously is for ages twelve and older but is contraindicated in liver or severe renal disease. Both agents are metabolized in the liver and require hepatic monitoring. These medications have shown promising results and further study may expand their indications for treatment [1,23,24].

Niacin

Studies demonstrated no advantageous outcomes in MACE in patients with known atherosclerosis and well-controlled LDL-C levels on statin therapy when niacin was added [25,26]. Niacin may be beneficial in specific cases of severe hypertriglyceridemia at doses of 1000-2000 mg; however, a 2017 Cochrane Systematic Review concluded with moderate to high evidence that niacin did not reduce the number of deaths, heart attacks, or stroke [27,28].

Supplements

The addition of omega-3 fatty acids (OM3-FAs) to statin

therapy in patients with residual hypertriglyceridemia has been shown to be effective in lowering triglycerides to target goal, however if there is concern for LDL-C levels, high-purity EPA products such as Icosapent Ethyl (IPE) are more beneficial than those containing DHA [29-31]. The effect of OM3-FAs on MACE is unclear. The REDUCE-IT trial studied patients with a history of coronary artery bypass grafting and found that IPE was associated with an absolute risk reduction of 6.2% in first ischemic events, with a number needed to treat of 16 [32]. In the STRENGTH trial, patients with high cardiovascular risk who were already on statin therapy were administered a carboxylic acid formulation of EPA and DHA. When compared with corn oil, there was no significant difference in MACE [33].

Phytosterols are also believed to reduce cholesterol and the FDA claims that 1.3g of plant sterol esters and 3.4g of plant stanol esters consumed daily with a diet low in saturated fat and cholesterol may reduce the risk of heart disease [34]. The NATCOL study examined the effectiveness of a combined nutraceutical of phytosterols, red yeast rice, niacin and policosanols which demonstrated statistically significant reduction in LDL-C, TC, non-HDL-C and apoB [35].

Curcumin was shown to be superior compared to either coenzyme Q10 or curcumin + coenzyme Q10 [36]. At 1000 mg/day and 2100 mg/day Curcumin was shown to improve the lipid profile in patients with metabolic syndrome and T2DM, however data is lacking in the role of curcumin in ASCVD risk reduction [37,38].

Fiber is encouraged by the FDA as part of diet low in saturated fat and cholesterol to reduce the risk of heart disease, however no trials have demonstrated the effect of fiber on cardiovascular morbidity and mortality [39] (Table 2).

Table 2: Summary of Major Lipid Management Trials.

Drug Class	Major Trials	Study Overview	CV Outcomes	LDL-C outcomes
Statins, Cholesterol absorption inhibitors	IMPROVE-IT [10]	Multicenter RCT	Combination therapy decreased:	LDL- C at the time of index event- 93.8 mg/dl
		18,000 patients, followed for 6 years	- LDL- C additional 24%	
			- first CV events	mean LDL- C in combination group- 53.7 mg/dl versus 69.5 mg/ dl in statin alone.
		9545 total events (1st and subsequent)	No mortality benefit, reduction in other MACE events	
		Patients with ACS: simvastatin 40 mg vs simvastatin 40 mg + ezetimibe 10 mg	Subgroup analysis showed combination therapy benefits in diabetics, those older than age 75	Greater percentage in combination therapy achieved LDL-C < 70 and High sensitivity CRP < 2
	HIJ- PROPER [47]	Multicenter RCT in Japan:2010-2013.	No difference in all-cause mortality, non-fatal MI, and non-fatal stroke in the two groups	Combination therapy + aggressive revascularization lowered LDL-C < 70 mg/ dl but no difference in CV events in both groups
		- 19 hospitals		
		- 1733 patients		
		- 2003 events		
		- Followed for 3 years		
		Patients with ACS + dyslipidemia:		
		pitavastatin 2mg vs pitavastatin 2mg + ezetimibe 10mg		
	RACING [13]	Multicenter RCT in South Korea from 2017- 2018	Combination therapy non inferior to monotherapy in MACE occurrence	Combination therapy group (sustained over 3 years)
		- 25 centers		- 70% of patients achieved LDL-C < 70
		- 3779 patients		- 40% patients with LDL-C< 55
		- 2 year follow up		Monotherapy
		Patients with CVD		- 55% of patients achieved LDL-C < 70
		Rosuvastatin 20 mg vs Rosuvastatin 10 mg + ezetimibe 10 mg		- 25% patients with LDL-C< 55
	PRECISE-IVUS [14]	RCT	Combination therapy showed greater percent atheroma volume regression (78% vs 55%)	Combination therapy- greater percentage reduction in LDL-C
		Patients with CAD post cath./ PCI		No change in CRP, cholesterol absorption markers
		Atorvastatin titrated to LDL-C< 70 vs atorvastatin + ezetimibe 10 mg		

Lipid Management Guidelines

Various organizations have guidelines addressing lipid management. However, a cohesive guideline that addresses LDL-C targets along with outcome information for the varied class of lipid lowering medications does not exist currently. Guidelines currently recommend treating LDL-C level with variance in the goal value based upon organization and disease state. The following table highlights the guidelines from some major organizations in this area (Table 3).

Further recommendations for screening and/or treatment strategies are provided for specific populations of patients including pediatric, geriatric, and those with familial hyperlipidemias.

Pediatric

There is variability on recommendations for screening of lipid disorders in the pediatric population.

The USPSTF 2016 guidelines have an "I" recommendation for lipid screening in children and adolescents age <20 years. This is not a recommendation against screening, but that there is insufficient evidence for or against lipid screening in this population [40].

In 2011, the American Academy of Pediatrics and the National Heart Lung and Blood Institute 2011 published guidelines recommending universal screening for lipid disorders in children between ages 9-11 with either a fasting lipid profile or non-fasting testing to evaluate non-HDL-C (SOR: B) [41]. The aim of this one-time screening was to capture children with an underlying genetic predisposition for elevated cholesterol (familial or non-familial) and begin a treatment strategy prior to the advent of ASCVD in later years.

Fibrates	ACCORD [7,48]	RCT Patients treated with statin or statin+fibrate	No difference in MACE with combination therapy	
PCSK9 Inhibitors	FOURIER [17]	Patients with ACSVD and LDL>= 70 on statin + evolocumab	15% reduction in primary endpoint (AMI, stroke, coronary revascularization, hospitalization for unstable angina and CV mortality)	LDL reduction by 60%
	ODYSSEY [49]	alirocumab + statin vs statin monotherapy	15% reduction in all-cause mortality	LDL reduction by 54.7%
Microsomal Triglyceride Transfer Protein	Pivotal Phase 3 trial	Lomitapide was treated in a multi-center, 78-weeks single arm open label study on 29 adults	Unable to assess due to limited number of participants	More than 50% achieved >50% reduction in LDL-c levels.
	FOCUS	Mipomersen phase 3 trial with double blinded then open label treatment of 309 adults	Unable to assess due to limited number of participants	LDL-C reduction of 28-36%
Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors	CLEAR [22]	Phase 3 Randomized control, double blinded, placebo controlled multisite study for 24 weeks.		Significant reduction in LDL-c from baseline within 12 weeks.
		All patients had a history of statin intolerance		Most common side effect of Myalgia was more common in placebo than treatment group.

Table 3: Summary of Major Guidelines for Lipid Screening, Targets, and Medication Therapy.

Guideline Organization	LDL Goals for high CV risk	Recommendations	Strength of Recommendation (*SOR*) & Level of Evidence (*LOE*)
2019 ESC/EAS Guidelines for the Management of Dyslipidemia [50]	55 mg/dl (1.4 mmol/L)	For patients at very high risk (ESC/EAS criteria):	Primary prevention: SOR- IIb, LOE- C
		LDL-C remains ≥1.4 mmol/L (≥55 mg/dL) on maximally tolerated statin, first add ezetimibe	
		LDL-C remains ≥1.4 mmol/L (≥55 mg/dL), a combination with a PCSK9 inhibitor is recommended	Secondary prevention: SOR- I, LOE- A
2018 AHA/ACC Multi-Society Cholesterol Guideline [25]	70 mg/ dl (1.8mmol/L)	For patients at very high risk (AHA/ACC criteria):	SOR- I to IIA, LOE- A to B- NR
		LDL-C remains ≥70 mg/dL on maximum tolerated statin: consider adding ezetimibe	
		LDL-C remains ≥70 mg/dL (or non–HDL-C ≥100 mg/dL), consider adding PCSK9 inhibitor	
		>75 years of age with ASCVD, potential benefits versus adverse effects of statin therapy should be considered before initiation of statin therapy	
Canadian CV Society Guidelines for Management of Dyslipidemia for Prevention of CV disease in Adult in 2021	70 mg/ dl (1.8mmol/L)	For all secondary prevention Patients with CV disease in whom LDL-C ≥70 mg/dl (1.8mmol/L) on maximally tolerated statin, Intensify therapy with ezetimibe and/or PCSK9 Inhibitor	SOR: "High quality evidence"
		If ezetimibe is used initially and LDL-C remains ≥70 mg/dl (1.8mmol/L), PCSK9 inhibitor is recommended	
National Lipid Association	LDL-C >70 or non-HDL-C > 100 mg/dL	HoFH despite ASCVD status. LDL-C >70 treat with maximized statin +/- ezetimibe	
	Baseline LDL-C > 190 mg/dL and LDL-C > 100 mg/dL or non-HDL-C > 130 mg/dL.	HeFH age 18-39 with uncontrolled ASCVD, or age 40-79 with controlled ASCVD: Treat with maximized statin +/- ezetimibe	
	Baseline LDL-C > 190 mg/dL and LDL-C > 70 mg/dL or non-HDL-C > 100 mg/dL.	HeFH age 40-79 with uncontrolled ASCVD: Treat with maximized statin +/- ezetimibe	
American Geriatric Society [43]		Discussion with patient of risk-benefit and life expectancy	LOE- C
USPSTF [40]	No LDL-C goal	Only apply to those >40 years who do not have CVD or symptoms of CVD and have an LDL-C <190 mg/dL. Does not apply to those with FH	
		≥40-75 with 1 or more CVD risk factors and an estimated 10-year CVD risk of ≥10%: Initiate statin	Grade B
		≥40-75 with 1 or more CVD risk factors and an estimated 10-year CVD risk of 7.5%-10%: Selectively offer statin	Grade C

Statins are recommended as a first line agent for children/adolescents age >10: a) LDL-C >190 or b) LDL-C >60 mg with 1 high level or c) >2 moderate-level risk factors [42].

The AHA/ACC Cholesterol Clinical Practice Guidelines 2018 recommend universal screening for dyslipidemia between ages 9-11 and then at ages 17-21 (LOE: B and SOR IIb). It also recommends screening based on family history (LOE: B and SOR: IIa).

Treatment recommendations are lifestyle approaches (LOE: A). for children/adolescents age >10 with LDL-C above 190 or above 160 with clinical presentation consistent with familial hypercholesterolemia with inadequate response to 3-5 months of lifestyle changes a statin is recommended (LOE: B; SOR: IIIa).

Geriatrics

Outside of drug reactions, the ACC/AHA currently do not have guideline recommendations to discontinue statin therapy in the older population. The American Geriatric Society recommends discussion of risk-benefit and life expectancy with patients [43].

Familial Hyperlipidemia

The National Lipid Association Guideline prerequisite for use of PCSK9 inhibitors in patients with ASCVD, HoFH, or HeFH (heterozygous familial hyperlipidemia):

1. Patients who have maximized statin therapy with or without adjunctive ezetimibe.

2. Patients with ASCVD or at increased risk for ASCVD who have not achieved target LDL-C levels.

3. Initiation of therapy in statin-intolerant patients with ASCVD or at increased risk for ASCVD.

PCSK9 inhibitors are indicated when statin-only or statin+ezetimibe treatment has been maximized and LDL targets have not been achieved in this high-risk population (Table 2).

Conclusion

With the emergence of more potent lipid lowering medications, trials focused on CV outcomes combining various statins with adjunctive medications have attempted to define optimal LDL-C targets for primary and secondary prevention. A continued focus of lipid management is to address whether to 'treat to dose' or 'treat to target'. And, whether the addition of another agent to a statin regimen provides meaningful benefit for ASCVD morbidity and mortality.

PROVE-IT-TIMI 22, Treating to New Targets, ASTEROID trial, Cholesterol Treatment Trialists (CTT) Collaboration meta-analysis [44], and IMPROVE-IT were all major driving forces for "treat to target" guidelines recommending a LDL-C goal of lower than 70 mg/ dl with meta-analysis also suggesting a linear relationship between LDL-C and CVD outcomes. Population based subanalysis and clinical trials looking at varying intensities of statins as well as add-on medications to statins, further led to guideline amendments recommending percent LDL-C reduction with a target of >50% reduction for higher risk patients [45]. While these studies do provide data indicating a MACE risk reduction in people with a lower LDL-C, it is important to note that none were designed to initially randomize participants into target LDL-C groups for a more direct correlation of MACE outcomes of a treat to target approach. Further investigations designed to help answer this question are needed. For now, continued use of a shared decision-making approach tailored to the individual regarding treatment goals and including a cost to benefit analysis of continued lab testing remains prudent. Table 2 summarizes some of these key studies.

In the US, the current ACC/AHA guidelines employ a risk calculator derived from population-data that is applied to individuals. The resultant 'ASCVD Risk Score' helps determine whether a statin may be beneficial to reduce a patient's 10-year risk for primary ASCVD. The ACC/AHA treatment algorithm selectively supports 'treating to target' in a subset of patients with a higher risk for ASCVD (diabetes; past ASCVD history; LDL-C > 190). In addition to a patient's cholesterol profile, the 10-year risk calculation uses other significant risk factors for ASCVD (e.g., tobacco use status, history of hypertension, diabetes status, and age). Prior to the advent of the ASCVD risk calculator in the 2013 ACC/AHA guideline, the decision for statin use was based on an LDL target goal.

This strategy was easier for both patients and providers to grasp. Using the current model, a patient with an LDL-C once considered acceptable under previous guidelines, e.g., Adult Treatment Panel (ATP-III) may still benefit from a statin therapy. Conceptually, this can lead to patient's questioning the need for treatment as they perceive they are at or near a target LDL-C goal. This provides an opportunity for patient education to aid understanding that the goal is a reduction in ASCVD risk and that our current risk calculators acknowledge but cannot account for variation of risk across population subgroups. LDL-C reduction, while important, is only part of the overall strategy. In these scenarios, with patients in the select high risk categories, the patient is both being treated 'to dose' and 'to target'. The benefit of a decreased ASCVD risk is achieved through the anti-inflammatory and plaque stabilization benefits of the statin and not solely on LDL-C reduction.

Which direction we will go in the future remains to be determined as studies comparing the two approaches in head-to-head trials are starting to come out [46]. Until then, we continue to follow the current the ACC/AHA guidelines employing a combination of a "treat to dose" approach with some risk stratification focusing on a "treat to target" approach (Table 3).

Author Statements

Disclosures/Conflicts of Interest

The authors have no financial disclosure or conflicts of interest.

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