REVIEW ARTICLE

Contemporary Management of Dyslipidemia

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Abstract

The treatment of dyslipidemia continues to be a dynamic and controversial topic. Even the most appropriate therapeutic range for lipid levels—including that of triglycerides and low-density lipoprotein cholesterol—remain actively debated. Furthermore, with ever-increasing options and available treatment modalities, the management of dyslipidemia has progressed in both depth and complexity. An understanding of appropriate lipid-lowering therapy remains an essential topic of review for practitioners across medical specialties. The goal of this review is to provide an overview of recent research developments and recommendations for patients with dyslipidemia as a means of better informing the clinical practice of lipid management. By utilizing a guideline-directed approach, we provide a reference point on optimal lipid-lowering therapies across the spectrum of dyslipidemia. Special attention is paid to long-term adherence to lipid-lowering therapies, and the benefits derived from instituting appropriate medications in a structured manner alongside monitoring. Novel therapies and their impact on lipid lowering are discussed in detail, as well as potential avenues for research going forward. The prevention of cardiovascular disease remains paramount, and this review provides a roadmap for instituting appropriate therapies in cardiovascular disease prevention.

1 Introduction

Cardiovascular disease (CVD), the leading cause of mortality in the USA, had experienced a steady and robust decline throughout the later Twentieth and early twenty-first centuries (a 71% decline when adjusted for age from 1968 to 2016) [1–3]. This has been attributed largely to the proliferation of invasive and noninvasive treatment modalities over the preceding decades. Alongside an ever-growing armamentarium of therapies, there was reason to suspect that continued gains would produce ongoing improvements in cardiovascular health and wellness [4, 5]. The American Heart Association (AHA) set an Impact Goal for a 20% reduction in death from CVD and stroke by the year 2020, a high, although not unrealistic bar to reach [2].

Beginning in 2010, however, prior declines began to slow and indeed reverse, with an increase in CVD mortality seen in both cardiac events and ischemic stroke [3]. The basis for this reversal remains unclear, although is likely multifactorial including contributions from an aging population, increased rates of predisposing risk factors such as type 2 diabetes and obesity, reduced long-term adherence to medications, and healthcare disparities, among others [3]. Despite broad advancements in available medications and therapeutic modalities, population trends have yet to exhibit an abatement in CVD rates (although the rise in CVD is notably less pronounced when adjusted for age) [6]. The COVID-19 pandemic has undoubtedly contributed to this trend over the previous 2 years, posing a well-noted barrier to the access and availability of cardiovascular care [7]. Taken together, a greater focus on CVD reduction is essential to improving health and wellness in the USA and throughout the world.

How then do clinicians reestablish the downward CVD trends of prior decades? One guide outlined by the AHA for the purpose of improving cardiovascular health (CVH) is the ideal CVH score [2]. This score is based on 7 metrics, which cumulatively have been shown to lead to lower rates of CVD and adverse events: diet, physical activity, body mass index, smoking, total cholesterol, blood pressure, and fasting glucose [8, 9]. However, achievement of these goals has been

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Key Points

The contemporary management of dyslipidemia has changed substantially in the last decade with the introduction of new pharmacologic therapies that provide more approaches to the reduction of atherogenic lipoproteins in serum.

Current treatment guidelines for the management of dyslipidemia focus on low-density lipoprotein cholesterol (LDL-C) reduction. The intensity of LDL-C reduction is stratified according to risk for developing atherosclerotic cardiovascular disease (ASCVD). The higher the risk, the greater the recommended magnitude of reduction.

High-density lipoprotein cholesterol is no longer a treatment target because of a lack of evidence from clinical trials that it impacts risk for primary or secondary cardiovascular events.

Triglycerides are a treatment target when severely elevated in order to reduce risk for pancreatitis. In addition, numerous guidelines now support the treatment of triglycerides when they exceed 150 mg/dL among patients already on a statin and have established ASCVD.

limited with < 20% of US adults reaching ≥ 5 metrics and a reduced prevalence of ideal CVH over the past 20 years [9, 10]. Medication adherence—and statin use in particular—remains a major barrier to improved outcomes, with claims data suggesting under 50% ongoing adherence rates following statin initiation at 1 year, and just 19% ongoing adherence at 5 years from initiation [10]. Outlining areas of improvement for clinicians via the CVH and other metrics, therefore, remains a laudable step and provides clinicians a pathway to reducing CVD.

With barriers and goals thus defined, an understanding of the therapeutic interventions available to clinicians is crucial. Few among these tools have advanced as far or as fast in recent years as those associated with lipid-lowering therapy.

2 Lipid Measurement and Evaluation

One of the primary methods of atherosclerotic CVD (ASCVD) prevention and treatment is lipid-lowering therapy, an area of great complexity and efficacy. Measuring serum lipid levels, defining appropriate risk-stratified lipid goals, assessing response to lipid-lowering therapy, and determining individual ASCVD risk, however, has evolved

rapidly [11–13]. It is therefore essential to understand current guideline-directed goals and metrics of therapy.

The standard lipid panel is an easily accessible tool for clinicians, measured via a simple peripheral blood draw. The most frequently measured and clinically utilized components within the lipid panel include total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein (HDL-C). While not specifically noted on the standard lipid panel, very low-density lipoprotein cholesterol (VLDL-C) is an additional key component and atherogenic lipoprotein [11]. LDL-C, a focal point of guideline recommendations on lipid-lowering therapy, is only rarely measured directly and instead obtained via estimation using the Friedewald equation or the more accurate Martin-Hopkins equation [14, 15]. It is generally agreed that a non-fasting lipid panel is appropriate in the majority of patients with two notable exceptions (1) patients who have consumed a very high fat meal in the previous 8 hours, or (2) those being evaluated with a family history of premature ASCVD per guideline recommendations [11, 12].

ASCVD risk can be calculated by a number of risk estimators, although the pooled cohort equation (PCE) has taken precedence in the USA [16, 17]. The PCE incorporates data from 5 prospective, longitudinal cohorts—all NHLBI-sponsored cohorts of diverse populations, such as the Atherosclerosis Risk in Communities (ARIC) study—and provides an estimated 10-year risk of subsequent ASCVD events, including both fatal/nonfatal myocardial infarction (MI) and fatal/nonfatal stroke in adults aged 40–75 years [11, 18, 19]. However, as the PCE was developed to predict population risk, it has limitations when used for risk-assessment at the individual level. This often leads to an over- or underestimation of risk in certain patient subgroups, such as older individuals in whom risk might be overestimated given that age is a factor in the PCE and can be overly weighted in higher age groups despite otherwise relative cardiovascular wellness.

As a means of better individualizing the PCE and risk assessment for patients more broadly, 11 risk-enhancing factors were introduced in the 2018 AHA/American College of Cardiology (ACC) cholesterol guidelines [11]. These include family history, metabolic syndrome, primary hypercholesterolemia, chronic inflammatory conditions, chronic kidney disease, history of pre-eclampsia or premature menopause, high-risk ethnic groups, persistent elevation in triglycerides (TGs) ≥ 175 mg/dL, and, if measured, high sensitivity C-reactive protein (CRP) ≥ 2.0 mg/L, apolipoprotein B ≥ 130 mg/dL, lipoprotein(a) ≥ 50 mg/dL, or ankle-branchial index < 0.9. The presence of these factors would favor statin initiation in those at borderline or intermediate risk by PCE assessment [11]. It is worth noting that recent European guidelines recommend a different scoring system, the Systemic Coronary Risk Estimation (SCORE) based on European cohort data, for evaluation of CVD risk in primary

prevention cohorts (SCORE was recently updated to the SCORE2 model based on 45 European cohorts comprising 677,684 individuals to better reflect contemporary European populations) [12, 20, 21]. As the PCE is validated in US populations and recommended by AHA and ACC guideline committees, this will be the preferred risk assessment algorithm of this review.

Utilizing the PCE for risk assessment, US guidelines present an easily interpretable algorithm for clinicians geared toward the primary prevention of CVD (the PCE and other risk estimation tools are not recommended in secondary prevention, which is discussed in greater depth alongside lipid-lowering therapy below) [11, 22]. For adults aged 40–75 years, a 10-year CVD risk estimation is recommended using the PCE (available at https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/). Based on this estimate, patients may be classified into four groups: low risk (< 5%), borderline risk (5% to < 7.5%), intermediate risk (≥ 7.5% to < 20%), and high risk (≥ 20%). Recommendations vary based on these categories and treatment should be planned based on shared decision making between clinicians and patients. As a result, for high-risk patients the guidelines recommend statin initiation (Class I recommendation) for those at borderline risk, the guidelines recommend evaluating risk-enhancing factors and discussing with the patient prior to initiating moderate-intensity statin (Class IIb recommendation) [11]. For clinicians and patients still uncertain on how best to proceed, the guidelines point towards further sources that might aid clinical decision making, such as coronary artery calcium scoring (Agatston score ≥ 100). Following this evaluation, therapeutic interventions such as lifestyle and pharmacologic therapies, can be initiated as indicated [23].

3 Lipid-Lowering Therapy

The primary emphasis of lipid-lowering therapy is LDL-C reduction [11]. LDL particles constitute the end product of lipoprotein metabolism and must be cleared via an endosomal pathway by hepatic lipoprotein receptors such as the LDL receptor and LDL receptor-related protein 1. While precise goals for LDL-C reduction have been a matter of intense debate, evolving data have made clear the unequivocal cardiovascular risks associated with elevated LDL-C and the benefits of lowering LDL-C well below the generally recommended 70 mg/dL for patients at high risk or with a history of prior ASCVD adverse events [24–26]. Consistent with this, recent guidelines have gone further in lipid-lowering goals, with the ESC/EAS guidelines recommending an LDL-C < 55 mg/dL for those at very high risk in primary and secondary prevention (Class I recommendation), and a goal of <40 mg/dL for those with a second atherosclerotic

CVD event within 2 years of the incident one (Class IIb) [12, 27]. Recommendations and awareness on the importance of management in high-risk groups have notably extended beyond guideline-writing committees in cardiology, with the Endocrine Society recommending an LDL-C < 55 mg/dL for patients with established cardiovascular disease or multiple risk factors in their guidelines for those with endocrine disorders [28].

Unfortunately, treatment initiation, achievement of goal LDL-C levels, and maintenance of lipid-lowering therapies remain suboptimal [29, 30]. This has been shown to be particularly the case in under-served and minority populations, and greater attention to supporting appropriate cardiovascular evaluation and goals in these communities remains important [31, 32]. This also holds for sex differences in cardiovascular care – women's health, a historically overlooked and understudied population in cardiovascular studies, as well as the impact of gender and gender identity on guideline recommendations [33]. In addition, while the pace of pharmaceutical innovation and options for lipid lowering has proceeded rapidly, the affordability and availability of these medications has lagged substantially [34, 35]. Therefore, attention to guideline-directed treatment modalities and continuity of care is crucial to long-term patient well-being. A detailed review of these is presented below.

3.1 Statins

Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis [36]. The subsequent reduction in intracellular cholesterol leads to an upregulation of LDL-receptors on the surface of hepatocytes, which augments their LDL clearing capacity. Statins have also been shown to have anti-inflammatory properties at the sites of endothelial dysfunction and atheroma, which helps to restore endothelial function and stabilize plaque [37–39]. Based on one of the most important meta-analyses of statins in the setting of secondary prevention, the Cholesterol Treatment Trialists Collaboration demonstrated that a 1 mmol/L (or 39 mg/dL) LDL-C reduction drove a 12% reduction in all-cause mortality, a 23% reduction in MI or coronary death, a 24% reduction in coronary revascularization, and a 17% reduction in nonfatal stroke [40]. Statin therapy has also been shown to reduce acute ASCVD events in primary prevention as well as in patients with diabetes mellitus, hypertension, and heightened systemic inflammatory tone (Table 1). Statin therapy is universally recommended as first-line in both primary and secondary CVD prevention [11, 12, 25, 41, 42]. Within the guidelines, the most appropriate statin dose is largely contingent upon the underlying condition or blood lipid measurement (for example an LDL-C ≥190 mg/dL is a Class Ib recommendation by the ACC/AHA cholesterol

Table 1 Prospective randomized statin trials in both primary and secondary prevention

Study	Drug	Design	Outcomes
Primary prevention studies			
AFCAPS/TexCAPS [141]	Lovastatin, 20–40 mg/day vs placebo	6605 men and women	40% reduction in fatal and nonfatal MI; 37% reduction in first ACS; 33% reduction in coronary revascularizations; and unstable angina reduced by 32%
ASCOT [142]	Atorvastatin 10 mg/day vs placebo	10,305 hypertensive men (n = 8463) and women (n = 1942) with treated high BP and no previous CAD	36% reduction in total CHD/nonfatal MI; 27% reduction in fatal and nonfatal stroke; total coronary event reduced by 29%; fatal and nonfatal stroke reduced by 27%
CARDS [143]	Atorvastatin 10 mg/day vs placebo	2838 patients with type 2 diabetes mellitus and 1 CHD risk factor(s)	37% reduction of major cardiovascular events; 27% of total mortality; 13.4% reduction of acute CVD events; 36% reduction of acute coronary events; 48% reduction of stroke
Heart Protection Study [144]	Simvastatin 40 mg/day vs placebo	20,536 high-risk (previous CHD, other vascular disease, hypertension among men aged > 65 years, or diabetes)	25% reduction in all-cause and coronary death rates and in strokes; need for revascularization reduced by 24%; fatal and nonfatal stroke reduced by 25%; nonfatal MI reduced by 38%; coronary mortality reduced by 18%; all-cause mortality reduced by 13%; cardiovascular event rate reduced by 24%
JUPITER [42]	Rosuvastatin 20 mg/day vs placebo	17,802 men (> 50 years) and women (> 60 years) with no history of CAD or DM, entry LDL < 130 mg/dL and CRP >2.0 mg/L	44% reduction in primary endpoint of major coronary events; 65% reduction in nonfatal MI; 48% reduction in nonfatal stroke; 46% reduction in need for revascularization; 20% reduction in all-cause mortality
PROSPER [145]	Pravastatin 40 mg/day vs placebo	5804 men (n = 2804) and women (n = 3000) aged 70–82 years	15% reduction in combined endpoint (fatal/nonfatal MI or stroke); 19% reduction in total/nonfatal CHD; no effect on stroke (but 25% reduction in TIA)
WOSCOPS [146]	Pravachol therapy 40 mg/day vs placebo	6595 men	CHD death of nonfatal MI reduced by 31%; CVD death reduced by 32%; total mortality 22% reduction
Secondary prevention studies			
4S [147]	Simvastatin 20 mg/day vs placebo	4444 patients with angina pectoris or history of MI	Coronary mortality reduced by 42%; myocardial revascularization reduction of 37%; all-cause mortality reduced by 30%; nonfatal major coronary event reduced by 34%; fatal and nonfatal stroke reduced by 30%
A to Z [148]	Simvastatin 40 mg/day for 1 month then 80 mg/day vs placebo for 4 months then simvastatin 20 mg/d	4497 patients with ACS	No significant difference in outcomes at 24-month follow-up, although a favorable trend toward a reduction in major adverse cardiovascular events [16.7% vs 14.4% event rates in the placebo and aggressive statin therapy arms, respectively)
AVERT [149]	Atorvastatin 80 mg/day vs angioplasty + usual care	341 patients with stable CAD	36% reduction in ischemic event; delayed time to first ischemic event reduced by 36%

Table 1 (continued)

Study	Drug	Design	Outcomes
CARE [150]	Pravastatin 40 mg/day vs placebo	3583 men and 576 women with history of MI	Death from CHD or nonfatal MI reduced by 24%; death from CHD reduced by 20%; nonfatal MI reduced by23%; fatal MI reduced by 37%; CABG or PTCA reduced by 27%
IDEAL [151]	Atorvastatin 80 mg/day vs simvastatin 20–40 mg/d	8888 men and women with CHD	Major cardiac events reduced by 13%, nonfatal MI reduced by 17%, revascularization reduced by 23%, peripheral arterial disease reduced by 24%
LIPID [152]	Pravachol 40 mg/day vs placebo	9014 patients	Coronary mortality reduced by 24%; stroke reduced by 19%; fatal CHD or nonfatal MI reduced by 24% fatal or nonfatal MI reduced by 29%
LIPS [153]	Fluvastatin 40 mg/day vs placebo	1667 men and women aged 18–80 years post-angioplasty for CAD	22% lower rate of major coronary events (e.g., cardiac deaths, nonfatal MI, or reintervention procedure)
MIRACL [154]	Atorvastatin 80 mg/day vs placebo	3086 patients with ACS	Reduction in composite endpoint by 16%; ischemia reduced by 26%; stroke reduced by 50%
PROVE IT [155]	Atorvastatin 80 mg/day vs pravastatin 40 mg/day	4162 patients with ACS	16% reduction of composite endpoint; 14% reduction in CHD death, MI, or revascularization; revascularizations reduced by 14%; unstable angina reduced by 29%
REVERSAL [156]	Atorvastatin 80 mg/day vs pravastatin 40 mg/day	654 patients with CAD	Atheroma: atorvastatin − 0.4%, pravastatin 2.7%, difference of − 3.1%, $p = 0.02$
TNT [157]	Atorvastatin 10 mg/day vs 80 mg/day	10,003 patients with CHD and LDL cholesterol 130–250 mg/dL	22% reduction in composite endpoint; MI reduced by 22%; stroke reduced by 25%

ACS acute coronary syndrome, *BP* blood pressure, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CHD* coronary heart disease, *CRP* C-reactive protein, *DM* diabetes myelitis, *LDL* low-density lipoprotein, *MI* myocardial infarction, *PTCA* percutaneous transluminal coronary angioplasty, *TIA* transient ischemic attack, *ial acronyms 4S* The Scandinavian Simvastatin Survival Study, *AFCAPS/TexCAPS* The Air Force/Texas Coronary Atherosclerosis Prevention Study: Implications for Preventive Cardiology in the General Adult US Population, *ASCOT* Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, *AVERT* Atorvastatin versus Revascularization Treatment Investigators, *CARDS* Collaborative Atorvastatin Diabetes Study, *CARE* Cholesterol and Recurrent Events Trial, *IDEAL* Incremental Decrease in End Points Through Aggressive Lipid Lowering Study, *JUPITER* The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, *LIPID* Long-Term Intervention with Pravastatin in Ischemic Disease, *LIPS* Lescol Intervention Prevention Study, *MIRACL* Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study, *PROSPER* Pravastatin in elderly individuals at risk of vascular disease, *PROVE IT* Pravastatin or Atorvastatin Evaluation and Infection Therapy Study, *REVERSAL* The REVERSing Atherosclerosis with Aggressive Lipid Lowering Study, *TNT* Treating to New Targets Trial, *WOSCOPS* West of Scotland Coronary Prevention Study

guidelines for initiation of maximally tolerated statin therapy) [11]. Subsequent titration should be guided by patient symptoms and medication tolerance while being mindful of the data to date suggesting that benefits derived from lower lipid levels extend far beyond levels traditionally recommended by the guidelines.

Statins are among the most intensively and comprehensively studied drug class in medical history and have an excellent risk-to-benefit profile. Despite particular focus on adverse events such as myalgia and more rarely rhabdomyolysis, multiple randomized trials have shown common symptoms occur with similar frequency across both statin and placebo arms [43, 44]. AHA/ACC cholesterol guidelines recommend a discussion of risks and benefits prior to the initiation of statin (grade I recommendation), as well as evaluation for predisposing factors to side effects, such as older age, trauma, and frequent exercise [11]. In those with objective muscle weakness, checking creatinine kinase to evaluate for rhabdomyolysis is recommended as it requires statin cessation, although this is admittedly very rare (1–3 cases per 100,000) [12]. Laboratory monitoring of serum creatine kinase after statin initiation is not recommended in those with mild/moderate symptoms or without objective muscle weakness.

Recent findings from the Self-Assessment Method for Statin Side-effects Or Nocebo (SAMSON) trial showed that in patients randomized to a 12-month treatment protocol including 4 months of atorvastatin 20 mg, 4 months of placebo, and 4 months of no treatment, patient-reported symptom scores were no different between months on statin versus those on placebo ($p = 0.388$) [45]. While acknowledging that a 4-month trial of statin may not be adequate to evaluate all cases of statin intolerance, the SAMSON investigators estimate that up to one-half of cases of statin intolerance are attributable to the nocebo effect, whereby adverse side effects develop secondary to negative expectations of a specific therapeutic intervention. Prior work has suggested that most patients (72.5%) with statin intolerance can tolerate a statin when transitioned from daily to intermittent dosing while still achieving a significant reduction in LDL-C (21.3% reduction in those with intermittent dosing vs 8.3% in those with statin discontinuation) [46]. For those with mild/moderate symptoms, guidelines recommend cessation until symptoms improve, followed by statin re-challenge at a reduced dose, or a trial of an alternative agent (which studies shows most patients will tolerate) [11]. In those unable to tolerate statin therapy with elevated ASCVD risk, transitioning to non-statin lipid-lowering therapy is recommended (grade IIa recommendation).

Additional side effects, such as new-onset diabetes, have garnered attention in those starting statin therapy. While there is also evidence to suggest an increased risk of incident diabetes in certain populations—particularly in trials including older participants—this risk is small and outweighed by the benefits derived by a reduction in cardiovascular events with statin use [47, 48]. The JUPITER trial showed that rosuvastatin therapy accelerated the time to new-onset type 2 diabetes by only 5.5 weeks compared to patients treated with placebo, while further studies have shown that the majority of patients who develop diabetes have underlying metabolic syndrome at baseline [42, 49]. Meta-analyses have further highlighted the benefits of intensifying statin therapy when appropriate, with a >3 times greater reduction in cardiovascular events as compared to risk of new-onset diabetes in those taking high-dose as compared to moderate-dose statin (number needed to harm for new-onset diabetes 498, number needed to treat to prevent a cardiovascular event 155) [50]. For patients with established diabetes, initiation of a moderate-intensity statin is recommended for those aged 40–75 by AHA/ACC guidelines irrespective of 10-year ASCVD risk due to significant cardiovascular benefits derived (with high-intensity recommended for those with additional risk factors) [11]. European guidelines do recommend risk assessment, and are even more aggressive in recommendations for diabetic populations with a goal LDL-C reduction $\geq 50\%$ from baseline and < 70 mg/dL in those at high risk, and LDL-C < 55 mg/dL in those at very-high risk [12].

Despite well-established benefits in guideline-recommended populations, statin therapy remains under-prescribed and under-titrated due to substantial clinical inertia [10, 51]. Recent attempts at utilizing electronic health record prompts to improve prescribing patterns among clinicians have not increased goal attainment rates, while deprescribing patterns in older adults have shown clear associations with increased CVD risk [52, 53]. Data suggest that discontinuation rates are highest in the first 30 days of initiation, further highlighting the importance of close follow-up and longitudinal monitoring [54]. Discrepancies extend to population differences as well, with data showing that women are less likely than men (56% vs 47% in one large cohort of prescription data for men and women, respectively) to fill high-intensity statin prescriptions following MI, and less likely to be prescribed the appropriate dose of a statin [55, 56]. Adherence issues are not without complications, with previous investigators suggesting a 25% increase in mortality between high-adherence and low-adherence statin groups after an MI [57]. While a comprehensive review of drug-drug interactions is outside the scope of this manuscript, evaluating for these in patients taking statins is important in order to avoid development of intolerance or serious adverse events. Thus, while recent developments in novel lipid-lowering therapies remain impressive, future work must focus on improving initiation and continuation of well-studied, affordable treatment options like statins if a reversal in population CVD trends is to occur.

3.2 Ezetimibe

Ezetimibe is an LDL-C lowering agent, primarily used to reduce LDL-C in patients above goal despite maximally tolerated statin therapy or with partial or complete intolerance to statins. Ezetimibe targets intestinal cholesterol absorption by inhibiting the Niemann-Pick C1-like protein at the jejunal brush border [58]. As a result, micelles loaded with dietary and biliary sources of lipid go unabsorbed. This leads to a reduction in hepatic cholesterol pools, an increase in hepatic LDL receptor expression, and subsequent lowering of LDL-C in the circulation. Importantly, this mechanism operates in addition to statin therapy. As statin inhibition of HMG-CoA reductase leads to a compensatory increase in intestinal cholesterol absorption, this is blocked by ezetimibe, leading to a complementary reduction in LDL-C. Similarly, as a compensatory mechanism, ezetimibe disruption of intestinal cholesterol uptake when taken as monotherapy leads to an increase in endogenous hepatic cholesterol production by increasing the activity of HMG CoA reductase. When taken in combination, this is prevented by statin administration.

The clinical efficacy of ezetimibe has been tested in multiple clinical trials. The Improved Reduction of Outcomes: Vytorin Efficacy International (IMPROVE-IT) trial, included 18,144 participants with a recent MI, and showed that ezetimibe in addition to simvastatin reduced both LDL-C (an approximately 24% incremental reduction in LDL-C vs simvastatin alone) and a composite of cardiovascular events (2% absolute risk reduction; hazard ratio [HR] 0.936; 95% CI 0.89–0.99; $p = 0.016$). It is notable that the investigators of this trial utilized a moderate-intensity statin regimen—which would not be guideline recommended at present—yet still achieved robust serum lipoprotein reductions with a mean attained LDL-C of 53.7 mg/dL in the simvastatin-ezetimibe cohort [59]. Post hoc analyses showed relative risk reductions in the primary composite endpoint of 14% for diabetic patients and 20% in patients with a history of coronary artery bypass grafting. Among patients with a prior history of stroke, relative risk reduction for a secondary stroke was 40% when comparing the combination therapy arm to the simvastatin monotherapy arm.

The SHARP trial, a study of 9270 persons with chronic kidney disease randomized to simvastatin plus ezetimibe versus placebo, demonstrated safety in this population as well as a significant reduction in major CVD events (17% reduction in major atherosclerotic cardiovascular events as compared to placebo). Although the trial was not powered to differentiate between dialysis and non-dialysis chronic kidney disease cohorts, and notably did not include a simvastatin-only trial arm, subgroup analysis did not suggest the proportional effects on atherosclerotic events differed between groups (X_1^2 1.3, $p = 0.25$) [60]. Further studies have shown the side effect and safety profile of ezetimibe to be very favorable, without significant differences in myalgias, rhabdomyolysis, gastrointestinal effects, transaminases, or creatinine kinase when added to statin monotherapy [61]. The subsequent Ezetimibe Lipid-Lowering Trial On PreventIon of Atherosclerosis in 75 or Older (EWTOPIA 75), a prospective randomized, open-label, blinded endpoint trial conducted in Japan, highlighted the benefit of ezetimibe in an older primary prevention population. In a population of 3796 participants aged ≥75 without known atherosclerotic CVD although with elevated LDL-C randomized to ezetimibe versus placebo, the ezetimibe arm exhibited a reduced rate of a composite of sudden cardiac death, MI, stroke, or coronary revascularization (HR 0.66; 95% CI 0.50–0.86; $p = 0.002$) [62]. In addition, the need for coronary revascularization was dramatically reduced among patients randomized to ezetimibe (HR, 0.38; 95% CI 0.18–0.79; $p = 0.007$).

Given the data to date, the AHA/ACC guidelines recommend the addition of ezetimibe for patients with CVD at very high risk and an LDL-C ≥70 mg/dL despite maximally tolerated statin therapy (Class IIa), as well as those being considered for therapy with a proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (class I) [11]. European guidelines are more aggressive in their recommendations for lipid-lowering, noting that ezetimibe should be added to maximally tolerated statin if necessary to meet LDL-C goals (class I) [12]. While additional work is required, particularly on the benefit of treatment in primary prevention populations, ezetimibe has emerged as a strong add-on agent for lipid lowering in addition to statin therapy.

3.3 Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibodies and Inhibitors

The PCSK9 monoclonal antibodies have dramatically improved therapeutic capacity to lower LDL-C and improve treatment target success rates [63, 64]. LDLRs on hepatocytes bind LDL-C in the extracellular milieu, and via receptor-mediated endocytosis the LDLR-LDL-C complex is internalized. While LDL-C is directed to the lysosome for further LDL digestion and processing, the LDLR is returned to the cell surface to start another cycle of LDL particle binding and uptake. However, approximately one in 500–1000 LDL particles is associated with a PCSK9 molecule. When an LDLR binds to this PCSK9/LDL complex, it is chaperoned to the lysosome for degradation, preventing LDLR recycling, reducing LDLR surface density, and as a result reducing LDL-C clearance. By inhibiting PCSK9, LDLR proteolysis is reduced and the capacity of hepatocytes to clear LDL-C from blood is increased.

Randomized trials have demonstrated that the PCSK9 monoclonal antibodies reduce the risk of ASCVD events.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial evaluated evolocumab versus placebo in patients already taking statin therapy [65]. The study, which included 27,564 participants with known ASCVD at 1242 sites in 49 countries, exhibited a median reduction in baseline LDL-C of 59%, from 92 to 26 mg/dL. This reduction was associated with a statistically significant reduction of 20% in the composite of cardiovascular death, stroke, and MI. Importantly, FOURIER showed that even in patients near guideline-directed LDL-C goals, further reductions in LDL-C provided benefit. In the lowest baseline LDL-C quartile, for example, a reduction in median LDL-C from 73 to 22 mg/dL was associated with a 22% reduction in cardiovascular death, stroke, and MI [65]. Subsequent analyses of the FOURIER data further support lowering LDL-C below 40 mg/dL, a target consistent with Europe guideline recommendations for patients who sustain a secondary event within two years of incident one [66]. Risk reduction was continuous even as attained LDL-C on therapy approached zero.

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab trial (ODYSSEY OUTCOMES) further demonstrated the efficacy of alirocumab [67]. This trial included 18,924 patients with acute coronary syndrome (ACS) in the previous 1–12 months and were already receiving high-intensity statin therapy. They were randomized to alirocumab versus placebo. Consistent with the results of FOURIER, reductions in LDL-C were substantial, with a mean LDL-C reduction of 62.7% (LDL-C 38 mg/dL), 61.0% (42 mg/dL), and 54.7% (53 mg/dL) at 4, 12, and 48 months, respectively. The primary endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina occurred in 9.5% in the alirocumab group and 11.1% in the placebo group. All-cause mortality was 17% lower in the alirocumab arm, with total nonfatal cardiovascular events reduced by 13% [68].

In subsequent trials, the effects of these drugs have been evaluated in the acute cardiovascular setting. In the Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients with Acute Coronary Syndrome (EVOPACS) trial, 308 patients with ACS were given evolocumab or placebo in addition to high-intensity statin. Participants in the treatment arm achieved substantial reductions in LDL-C, with 95.7% of patients achieving a guideline-directed goal LDL-C of <70 mg/dL (mean 3.61–0.79 mmol/L) versus 37.6% of patients in the placebo group (3.42 mmol/L vs 2.06 mmol/L) [69]. The Evolocumab in Acute Coronary Syndrome (EVACS) trial further assessed LDL-C reduction in patients with recent non-ST segment elevating myocardial infarction (NSTEMI), exhibiting an average LDL-C reduction of 28.6 mg/dL, which was lower in the evolocumab group at 30 days as compared to placebo. In addition, 80.5%

of patients in the evolocumab group were at or below AHA/ACC LDL-C goals at discharge as compared to 38.1% of patients randomized to the placebo arm.

Aside from robust data highlighting their effectiveness, PCSK9 antibodies have also been shown to be safe. Neither FOURIER nor ODYSSEY Outcomes exhibited any significant difference in adverse events, apart from local injection-site reactions and those classified in general as mild (erythema, pruritis, and swelling); 0.1% of participants in each group stopped the study drug for injection-site reactions) [65, 67]. Neurocognitive events were notably not different between each group. This outcome was further explored in the EBBINGHAUS trial, which assessed 1204 participants receiving evolocumab versus placebo in addition to statin therapy on a broad series of neurocognitive and executive function measures over 19 months [70]. This too showed no significant difference in measures of cognitive function between groups. Moreover, when patients completed detailed questionnaires that assessed self-perceived changes in neurocognitive features, there were no between-group differences [71].

Given these successes and the overall safety profile of PCSK9 inhibition, this therapeutic modality is an important treatment option for lipid lowering in patients with statin intolerance. In the Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects (GAUSS) study, evolocumab induced a robust 41% to 63% decline in LDL-C levels without significant side effects in patients with a history of statin intolerance [72]. These results were confirmed in the ODYSSEY ALTERNATIVE trial, in which alirocumab was compared to both ezetimibe and atorvastatin. Alirocumab therapy induced greater reductions in LDL-C than ezetimibe (mean decrease of 45% vs 15%) and was associated with a lower frequency of skeletal muscle-related side effects than patients randomized to atorvastatin (39%: 95% CI 0.38–0.99, $p = 0.042$). The trial was conducted with a statin rechallenge arm and placebo run-in to re-evaluate for statin intolerance) [73].

3.4 Inclisiran

Inclisiran therapy is a novel approach to LDL-C lowering. Inclisiran is small, synthetic interfering RNA (siRNA) conjugated to triantennary *N*-acetylgalactosamine; its target is the mRNA for PCSK9. The N-acetylgalactosamine moieties allow the inclisiran to bind very specifically to asialoglycoprotein receptors, which are highly expressed along the hepatocyte surface. Within the intracellular milieu, inclisiran binds to the RNA-induced silencing complex (RISC), allowing endonucleases to hydrolyze PCSK9 mRNA, thereby inhibiting its expression [19].

Phase I trials proved this was an effective strategy, with participants randomized to inclisiran exhibiting a mean 70%

reduction in circulating PCSK9 protein, and a 40% reduction in LDL-C compared to placebo [74]. A further advantage of inclisiran is that, as opposed to PCSK9 antibody injections, which are given every 2–4 weeks, inclisiran has shown effect when given just twice annually [75]. While the success of inclisiran in PCSK9 disruption and LDL-C reduction is clear, the ongoing A Randomized Trial Assessing the Effect of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4) trial of roughly 15,000 participants with pre-existing ASCVD randomized to inclisiran versus placebo will shed more light on the benefit of this novel therapeutic agent on cardiovascular events (https://www.clinicaltrials.gov/ct2/show/study/NCT03705234?term=Inclisiran+4&draw=2&rank=1).

3.5 Bempedoic Acid

Bempedoic acid is a novel LDL-C lowering agent and inhibits the cholesterol synthesis pathway at the level of ATP citrate lyase [76]. ATP citrate lyase acts upstream from HMG-CoA reductase and is an enzyme that integrates lipid and carbohydrate metabolism. It catalyzes the conversion of citrate to oxaloacetate and acetyl CoA. The acetyl CoA is then shunted toward either fatty acid or cholesterol biosynthesis. Bempedoic acid is a pro-drug that is activated into its biochemically active CoA thioester by very long chain acyl-CoA synthetase I. This activation reaction only occurs in the liver, potentially mitigating off-target muscle complaints widely prevalent with statin use [77].

Phase II trials of bempedoic acid as monotherapy showed a mean LDL-C reduction of up to a 27% decrease in LDL-C (17.9%, 25%, and 26.6% in daily doses of 40 mg, 80 mg, or 120 mg, respectively) in 177 patients with elevated LDL-C at baseline (130–220 mg/dL) [76]. This was not accompanied by an increase in adverse events as compared to placebo. The CLEAR Harmony trial randomized 2230 patients on maximally tolerated statin therapy to bempedoic acid versus placebo, showed an 18.1% greater reduction in LDL-C [78]. There was no statistically significant increase in the rate of any adverse event as compared to placebo ($p = 0.91$), the rate of discontinuation in the bempedoic acid arm due to adverse events was higher (0.005) as was new-onset or worsening diabetes ($p = 0.02$) and gout ($p = 0.03$). Subsequent trials have shown efficacy as a lipid-lowering agent in addition to other non-statin lipid-lowering therapies, such as ezetimibe, with bempedoic acid and ezetimibe combination in patients on maximally tolerated statin shown to be more effective than either ezetimibe or bempedoic acid in addition to statin alone [79]. The combination of bempedoic acid and ezetimibe reduces LDL-C by an average of 38% compared to placebo.

These results were reinforced in the CLEAR Wisdom trial, which randomized 779 patients on maximally tolerated lipid-lowering therapy to bempedoic acid versus placebo and found a 13% increased reduction in LDL-C for patients on bempedoic acid [77]. While overall adverse event rates were similar across treatment and placebo arms, there was a noted increase in blood uric acid levels and gout as compared to placebo (hyperuricemia was seen in 2.7% of patients on bempedoic acid and 0.4% of patients on placebo). These adverse events were again identified in a pooled analysis of four prior Phase III trials of bempedoic acid including 3623 patients on maximally tolerated statin by Banach et al [80]. While observations of LDL-C reduction were again robust—an 18% decrease versus placebo in those on maximally tolerated statin and a 24% decrease in those with statin intolerance—associated increased adverse events were again seen with respect to gout (1.4% vs 0.4% in treatment and placebo arms, respectively) and uric acid levels (2.1% vs 0.5%). This trial also exhibited an association with increased hepatic enzyme levels (2.8% vs 1.3%), and a reduction in glomerular filtration rate (0.7% vs 0.15%). There is a small risk for tendon rupture (0.2%) whose etiology is not understood at present. The capacity of bempedoic acid to reduce risk for acute cardiovascular events is being evaluated in the CLEAR Outcomes trial, a study of 14,014 patients with statin intolerance, which will compare bempedoic acid to placebo against a no-statin background [81].

3.6 Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is an autosomal co-dominant disorder caused primarily by a number of mutations in the LDLR gene, although mutations in the genes for apoB100, PCSK9, and clathrin adaptor protein-1 can also give rise to phenotypic FH [82]. Heterozygous familial hypercholesterolemia is a less severe dyslipidemia defined by the inheritance of only one mutant allele [83]. Patients with HoFH frequently have LDL-C levels of 500–1000 mg/dL and have increased risk for premature onset ASCVD and cardiovascular events [83].

While well-studied lipid-lowering therapies such as statins and ezetimibe remain first-line for patient with HoFH, additional options are often necessary to lower cholesterol levels in the safest and most expeditious manner possible. As in high-risk ASCVD populations, PCSK9 monoclonal antibodies have shown great promise in patients with HoFH. In the Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities trial (TESLA Part B), patients already on stable lipid-lowering therapy were randomized to placebo versus evolocumab every 4 weeks for 12 weeks [84]. Patients in the treatment arm experienced a 30.9% reduction in LDL-C as compared to placebo. The ODYSSEY HoFH trial further supported these findings, showing in a cohort of 69 patients with HoFH randomized to alirocumab versus placebo and standard therapy (including aphesis) a 35.6%

difference in mean LDL-C for the alirocumab arm (219.9 mg/dL) versus placebo (291.6 mg/dL) at 12 weeks [85].

Mipomersen is an antisense oligonucleotide that binds to the mRNA for apoB and promotes its hydrolysis by RNase H [86]. Inhibition of the hepatic production of apoB reduces hepatic secretion of VLDL and, thereby, there is less lipoprotein from which to form LDL in serum. Mipomersen is indicated for the treatment of HoFH, and its efficacy is mechanistically independent of LDLR bioavailability. In a trial of 45 participants with HoFH over 26 weeks, Raal et al reported a 24.7% decrease in LDL-C (vs a 3.3% decrease in the placebo arm) [86]. A group of 124 patients with HoFH randomized to weekly mipomersen versus placebo over 26 weeks exhibited very similar results, with a mean LDL-C reduction of −28.0% in the mipomersen arm versus a 5.2% increase in mean LDL-C in participants receiving placebo [87]. Mipomersen treatment is associated with an increase in hepatic fat content (4.9% increase in the mipomersen arm vs 0.4% for those on placebo as well as concomitant increases in serum transaminase levels). While the drug has been approved by the US Food and Drug Administration (FDA) for the treatment of HoFH, neither US nor European guidelines recommend it as a therapeutic option at this time. Mipomersen should be used only within the context of a risk evaluation and mitigation strategy intended to reduce risk for hepatotoxicity.

Lomitapide is a small molecule inhibitor of microsomal triglyceride transfer protein, an enzyme in the endoplasmic reticulum important for the production of VLDL-C in the liver and chylomicrons by enterocytes because it lipidates apoB100 and apoB48, respectively [88]. As a result, lomitapide reduces plasma levels of apoB-containing lipoproteins, including VLDL-C and LDL-C. Trial data in 29 patients with HoFH showed this strategy to be effective, with a 50% mean LDL-C reduction at the 26-week followup when lomitapide was added to baseline lipid-lowering therapy. The primary complications were gastrointestinal, with 27/29 participants (93.1%) noting at least one gastrointestinal side effect, most categorized as mild-moderate. Mean hepatic fat content increased from 1% at baseline to 8.6% at 26 weeks. On extended follow-up of up to 126 weeks, LDL-C reduction was maintained at a 45.5% from baseline, while the incidence of reported gastrointestinal complications was also lower at 42.1%. In addition, 21.1% of patients experienced an AST or ALT elevation 5 times the upper limit of normal. The Lomitapide Observational Worldwide Evaluation Registry (LOWER) trial intends to evaluate long-term safety and cardiovascular outcomes in a large cohort and is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT02135705?term=NCT02135705&draw=2&rank=1).

Evinacumab is a monoclonal antibody directed against angiopoietin-like 3 (ANGPLT3), an enzyme that inhibits both endothelial lipase and lipoprotein lipase and is recently approved by the FDA for the treatment of HoFH [89]. Recent data from the Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE HoFH trial) showed that in 65 patients randomized to intravenous evinacumab versus placebo, this monoclonal antibody induced a 49% mean between group difference in LDL-C at 24 weeks [90]. Subsequent work showed subcutaneous administration of evinacumab was similarly effective, with a 56% between-group difference in LDL-C reduction between evinacumab 450 mg versus placebo [91]. These changes in LDL-C are attributed to increased clearance of LDL particles by hepatic remnant lipoprotein receptors.

In addition to drug therapy, apheresis plays an important role in patients with HoFH. The history of plasma exchange and plasmapheresis for patients with familial hypercholesterolemia is a long one, with impressive data substantiating its use in lipid lowering for decades [92, 93]. As opposed to plasma exchange where the entire plasma compartment is removed and replaced thereby removing LDL-C as well as beneficial plasma components such as immunoglobin, apheresis targets LDL-C for plasma removal quite specifically [94]. Apheresis reduces LDL-C in patients with HoFH by approximately 57%–75% [95]. Unfortunately, rebound is rapid, requiring frequent treatment for effective LDL-C lowering (weekly or biweekly) treatment. While limited, small study data are available in HoFH, the data on apheresis with respect to cardiovascular outcomes, remain mixed, with recent studies showing progression of disease despite apheresis (ranging from progression of disease in 30% of those on apheresis to 86% in varying studies) [94, 96, 97]. In contrast, the German Lipoprotein Apheresis Registry reported a 78% reduction in major acute coronary events after two years of apheresis therapy [98]. Additional studies of novel therapeutics, in place of or in addition to apheresis, remain to be seen, although data from a recent small cohort study of lomitapide versus apheresis suggest that lomitapide may be more successful in LDL-C reduction than apheresis (additional 58% LDL-C reduction on lomitapide vs 37.1% on apheresis when added to conventional lipid-lowering therapy) [99, 100].

4 Triglyceride-Lowering Therapies Treatment

4.1 Hypertriglyceridemia as a Risk Factor for ASCVD

Low-density lipoprotein reduction is not the only component of lipid-dependent ASCVD risk mitigation, and significant residual risk is associated with elevated triglyceride levels [101–103]. For some time, the evaluation of risk associated with elevated triglycerides was largely overlooked, with studies in the era following the discovery of statins more

focused on LDL, and even low HDL as a risk factor for cardiovascular disease (a hypothesis that has since largely been disproven) [104, 105].

Triglycerides are carried in VLDL particles and chylomicrons. On a lipid panel, elevated triglycerides primarily act as a proxy for apoB-lipoproteins like VLDL, and contribute to cardiovascular risk/disease. Similar to LDL, triglyceride-enriched lipoproteins enter the arterial intima, where they are scavenged by activated macrophages and contribute to foam cell and fatty streak formation [106, 107]. An interesting quirk is that hyperchylomicronemia is not associated with increased risk for ASCVD but is highly associated with risk for pancreatitis. Chylomicrons appear to be too large to enter the intima and be scavenged by macrophages [108]. This highlights the essential feature of elevated triglycerides on increased ASCVD risk, which is the entrance through the arterial wall. Hypertriglyceridemia is also associated with metabolic syndrome, increased serum levels of apo CIII, hypercoagulability, endothelial dysfunction, and heightened intravascular inflammation, all of which contribute to ASCVD risk.

Much recent data have supported elevated triglycerides as an independent risk factor for ASCVD. In a post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial, low triglyceride levels in 4162 patients with recent ACS were associated with a reduced rate of recurrent cardiac events, irrespective of attained LDL-C levels [109]. Among participants in the Study of RO4607381 in Stable Coronary Heart Disease Patients With Recent Acute Coronary Syndrome (dal-OUTCOMES) and Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) cohorts, triglyceride levels correlated with both short- and long-term cardiovascular risk. In a cohort of 29,039 participants, the Copenhagen General Population study exhibited not only increased risk in association with elevated triglycerides, but also showed that on a per-particle basis, VLDL was more atherogenic than alternative apoB-containing lipoproteins such as IDL or LDL [110]. In the Progression of Early Subclinical Atherosclerosis study, participants with TGs > 150 mg/dL experienced a significantly increased risk for subclinical atherosclerosis as well as for the number of noncoronary vascular territories affected [111]. In addition, arterial inflammation and the number of inflamed plaques increased as triglyceridess increased. High triglyceride levels doubled the risk of arterial inflammation. As a result of these studies and others, elevated triglycerides warrant therapeutic intervention [11, 12, 41].

4.2 Treatment and Therapy

Lifestyle modification with increases in exercise and adjustments to dietary needs are first-line therapy for hypertriglyceridemia [11, 12]. Additional consideration must be given to evaluating secondary factors that may lead to elevated triglycerides, such as obesity, insulin resistance, diabetes mellitus, chronic kidney disease, liver disease, cigarette smoking, and hypothyroidism. Certain drugs can also induce or worsen hypertriglyceridemia, such as thiazide diuretics, oral estrogens, retinoids, protease inhibitors, glucocorticoids, among others [11, 112]. Finally, statin therapy is largely considered to be first-line treatment of ASCVD risk for patients with elevated triglycerides by guideline-writing committees, and offer substantial reductions in triglyceride levels in parallel with increasing intensity of statin (class I recommendation in 2019 ESC/EAS dyslipidemia guidelines, Class IIa AHA/ACC 2018 cholesterol guidelines) [11, 12, 113].

4.2.1 Fibrates

The fibric acid derivatives (fibrates) are peroxisome proliferator-activated receptor-α agonists, which effects nuclear gene transcription and downstream lipoprotein metabolism and, ultimately, a reduction in serum triglycerides [12]. The fibrates increase expression of lipoprotein lipase, reduce apo CIII (an inhibitor of lipoprotein lipase), and stimulate production of apo CII (an activator of lipoprotein lipase). They also promote the production of apo AI and the biogenesis of HDL. Early randomized trials in the Helsinki Heart Study and the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) conducted in the 1980s and 1990s, respectively, notably including predominately White men, exhibited reductions of 34% and 24%, respectively, in cardiovascular events with the use of gemfibrozil [114, 115]. Despite these results, gemfibrozil has been severely limited by the fact that it should not be used in combination with a statin. Gemfibrozil inhibits multiple glucuronosyltransferases, which impedes the glucuronidation and elimination of the statins, leading to a substantial rise in risk for rhabdomyolysis [116, 117].

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, a large cohort of 9795 participants with type 2 diabetes mellitus randomized to fenofibrate or placebo, did not the meet primary endpoint for reduction of cardiovascular events (HR 0.89, $p = 0.16$) [118]. Despite this, FIELD showed a 24% reduction in nonfatal MI and 21% reduction in coronary revascularization, as well as reductions in microvascular events such as proliferative retinopathy (HR 0.70%; CI 0.52–0.93; $p = 0.015$), macular edema (HR 0.69; 95% CI 0.54–0.8; $p = 0.002$), or lower extremity amputation (HR 0.64; CI 0.44–0.94; $p = 0.020$) [120, 121]. The subsequent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of 5518 patients with type 2 diabetes mellitus on simvastatin randomized participants to fenofibrate versus placebo, finding no significant

difference in cardiovascular events (HR 0.92, $p = 0.32$) or any secondary outcomes [119]. Notably, trials that have nonsignificant reductions in the primary composite of endpoints with fibrate therapy have almost uniformly not used hypertriglyceridemia as an inclusion criterion for entry into the trial (only 52% of patients in the FIELD trial had hypertriglyceridemia, and median triglyceride levels were just 162 mg/dL for all participants in the ACCORD trial). Post hoc analysis of the ACCORD trial, which included patients with the highest tertile of triglycerides (≥ 204 mg/dL), showed a trend toward benefit from fenofibrate therapy, although this finding was nominally significant (primary outcome 12.4% in the fenofibrate group vs 17.6% in the placebo arm, $p = 0.06$) [119]. Meta-analysis of major trials on the benefit of fibrates in subgroups with elevated triglyceride levels showed a significant reduction in cardiovascular events as compared to those without elevated triglycerides (pooled relative reduction HR 0.72 vs HR 0.94, $p = 0.002$) [122].

The ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study in a cohort of approximately 10,000 participants with type 2 diabetes mellitus, elevated triglycerides (200–499 mg/dL), and low HDL-C ≤ 40 mg/dL) randomized to pemafibrate 0.2 mg twice daily versus placebo will help to further define where fibrate therapy may show clinical efficacy [123]. In the interim, guideline committees remain tentative in their recommendations on fibrate therapy. The 2018 AHA/ACC cholesterol guidelines give a IIa recommendation for fibrates only in patients with severe hypertriglyceridemia (triglycerides ≥ 1000 mg/dL) and primarily as a mechanism to prevent acute pancreatitis (and even in this the guidelines recommend fenofibrate over gemfibrozil due to the risk of severe rhabdomyolysis) [11]. European guidelines are also mixed, although slightly more liberal in their recommendations, giving IIb recommendations for the use of fibrates—fenofibrate and bezafibrate specifically—for primary prevention or those at high-risk at LDL-C goal with triglycerides remaining > 200 mg/dL (bezafibrate is not available in the USA at this time) [12].

4.2.2 Omega-3 Fatty Acid Therapy

Interest in the relationship between omega-3 fatty acids and cardiovascular disease has been ongoing for decades [124–126]. Although produced endogenously to a small extent, dietary sources of omega-3s are key, and underlie variation in fatty acid blood levels. The two most important omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are derived primarily from fish intake (plant-derived essential fatty acid alpha-linolenic acid [ALA] has also been studied to some extent, although with less obvious cardiovascular benefit) [127–129]. The primary mechanism of benefit from these is believed to be a reduction in plasma triglycerides, although there exist many additional effects, such as cell membrane stabilization and anti-inflammatory properties, that likely contribute above and beyond triglyceride reduction to varying degrees [101]. Indeed the prevention of cardiac arrythmia was originally thought to play a large role via the inhibition of voltage-dependent sodium and L-type calcium channels, subsequently reducing the arrhythmogenic potential of cardiac myocytes [130].

Initial trials of omega-3 supplementation seemed to support these considerations. The GISSI-Prevenzione trial, which compared daily gel capsule of 850–882 mg EPA and DHA in an average ratio of 1:2 versus placebo in participants with recent MI, showed a significant reduction in the primary outcome of nonfatal MI, stroke, or death for those taking omega-3 (10% reduction), and a 17% reduction in cardiovascular death [131]. A major criticism of this trial is that it was done prior to the statin era, and hence only a small percentage of patients were receiving statin therapy. The subsequent Japan EPA Lipid Intervention Study (JELIS) trial of 18,645 participants randomized to 1800 mg EPA ethyl ester daily plus low-dose statin therapy versus statin alone exhibited a 19% reduction in major coronary events in the EPA group [132]. Most recently in REDUCE-IT, a trial that included 8179 patients with established ASCVD or diabetes mellitus and one additional risk factor, who had been randomized to receive icosapent ethyl (EPA ethyl ester) 2 g twice daily versus placebo, found a significant 25% ($p < 0.001$) reduction in major coronary events in the EPA arm, 31% reduction in fatal or nonfatal MI, ($p < 0.001$), 27% reduction in fatal or nonfatal stroke ($p = 0.02$), 35% reduction in urgent or emergent revascularization ($p < 0.001$), and 20% ($p = 0.03$) reduction in cardiovascular death [133]. These findings were independent of baseline triglyceride status or triglyceride lowering. Vascepa (icosapent ethyl) has the following indications: (1) as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization in adult patients with elevated triglyceride levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease; and 2) as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. The results of REDUCE-IT support risk reduction by mechanisms other than triglyceride reduction. These may include increased production of E-series resolvins (small downstream metabolites of EPA, which actively resolve inflammation, increased interleukin-10 [an anti-inflammatory cytokine]; improved endothelial cell function; and reductions in cell membrane oxidation, oxidized LDL-C, apo CIII, hsCRP, and matrix metalloproteinases, among other injurious mediators of atherogenesis) [134, 135].

Other studies of omega-3 fatty acid intake, and EPA-DHA combination therapies in particular, have all been negative. There are no clinical trials that have tested the impact of DHA monotherapy on cardiovascular events. The Alpha-Omega trial, which studied low-dose EPA-DHA combination therapy (400 mg), 2 g of ALA daily, or both EPA-DHA and ALA in 4837 participants with prior MI, showed no significant reduction in major cardiac event in any treatment arm [128]. Similarly negative results for EPA-DHA combination therapy were found in numerous subsequent trials, including ASCEND trial (15,480 participants with diabetes and no known ASCVD) and the recent STRENGTH trial (13,078 participants at high ASCVD risk) [136, 137]. Atrial fibrillation rates were notably higher in omega-3–treated participants in both the recent REDUCE-IT (3.1% vs 2.1%, $p = 0.004$) and STRENGTH (2.2% vs 1.3%, nominal $p < 0.001$) trials, the mechanism for which remains unknown [133].

Data to date suggest a dichotomy between pure EPA ethyl ester supplementation, and that of DHA-EPA combination therapy, although the underlying reason for this inconsistency remains unclear. Two possible hypotheses as relates to such differences in trial findings—that blood EPA levels were not high enough in the STRENGTH trial to achieve benefit or that the DHA component of therapy in STRENGTH led to negative effects that superseded the benefits of EPA—have predominated. Post hoc analysis of the results of the STRENTH trial that worked to address these concerns are neutral even among those in the highest tertile of EPA blood level—on par with median levels achieved in REDUCE-IT—while also demonstrating no additional harm in participants at highest DHA level [138]. Irrespective of causation, we have two randomized trials showing therapeutic benefit with EPA monotherapy. In contrast, there are no trials of combination EPA/DHA therapy that have shown benefit. At the present time, the use of combination EPA/DHA therapy to treat hypertriglyceridemia cannot be encouraged. Furthermore, we now have evidence to actively counsel patients against commonly used over-the-counter combination EPA/DHA products. Finally, the Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) trial provides evidence that EPA is anti-atherogenic, as indicated by a substantial reduction in total atherosclerotic plaque burden (15% vs 26%, $p = 0.0004$) by coronary computed tomography angiography [139].

Current guidelines remain mixed in their recommendations on omega-3 therapy, many having yet to incorporate recently released trial data [11, 12, 41]. While no recommendation is given in the 2018 AHA/ACC cholesterol guidelines, 2019 ACC/AHA primary prevention guidelines, or 2021 ESC guidelines on cardiovascular prevention, the 2019 EAS/ESC dyslipidemia guidelines recommend the addition of icosapent ethyl 2 g twice daily in high-risk patients with elevated triglyceride levels (135–499 mg/dL) to statin therapy (Class IIa, Level B), a recommendation also endorsed by the Canadian Cardiovascular Society, the National Lipid Association, and the Endocrine Society [12, 13, 28, 33, 140].

5 Conclusion

As research continues to progress, a wide and growing range of modalities is available for the treatment of dyslipidemias, despite a proliferation of therapeutic options, atherosclerotic CVD rates have risen, while the initiation and maintenance of already accessible treatment options remain underutilized. By practicing in a guideline-directed manner, clinicians can impact and reverse these trends, improving the well-being and longevity of their patients. While this review provides a brief roadmap on available therapeutic options and their implementation in a guideline-directed manner, the treatment of dyslipidemia remains dynamic and ever-changing. It is therefore incumbent on clinicians to remain informed as recommendations progress and maintain focus on providing their patients the best evidence-based medications and therapies available.

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