Current Cardiology Reports (2019) 21: 110
https://doi.org/10.1007/s11886-019-1175-z

Optimizing Dyslipidemia Management for the Prevention of Cardiovascular Disease: a Focus on Risk Assessment and Therapeutic Options

Adam N. Berman [1] · Ron Blankstein [1]

Published online: 5 August 2019

Abstract
Primary prevention of incident atherosclerotic cardiovascular disease (ASCVD) as well as decreasing the risk of future events in those with established atherosclerosis is critical from a public health perspective. Management of dyslipidemias constitutes a key target in decreasing the risk of developing ASCVD events. While there have been great strides in the treatment of dyslipidemia over the last three decades, there are important recent developments and ongoing research that will expand the available therapeutic options and enable further cardiovascular risk reduction.

Purpose of Review The purpose of this paper is to review new developments relating to the primary prevention and management of ASCVD with a specific focus on optimizing the treatment of dyslipidemias.

Recent Findings In the realm of ASCVD risk prediction, mounting evidence over the last decade has demonstrated that coronary artery calcium testing is superior to any serum biomarker in the prediction of future ASCVD events and in discriminating future cardiovascular risk. As such, it has been incorporated into the most recent ACC/AHA primary prevention guideline to help guide management decisions in select patients. In terms of the management of dyslipidemias, PCSK9 inhibitors lower LDL-C by 50–70% and provide an additional 15% reduction in key cardiovascular events in high-risk patients with known ASCVD, as demonstrated in the ODYSSEY and FOURIER trials. Cholesteryl ester transfer protein (CETP) inhibitors, which significantly increase HDL-C levels, demonstrated mixed results in large clinical trials and have helped reframe HDL-C as a risk marker rather than a modifiable risk factor. In regard to the management of triglycerides, the REDUCE-IT trial demonstrated a nearly 5% absolute reduction in key cardiovascular events with a highly purified fish-oil derivative named icosapent ethyl in high-risk patients already on statin therapy. Finally, in regard to lipoprotein(a)—which is a strong risk factor for ASCVD—there are exciting developments in the therapeutic pipeline which reduce circulating lipoprotein(a) levels by nearly 90%.

Summary The management of dyslipidemias continues to be an exciting field with several ongoing cardiovascular outcomes trials, improvement in risk prediction models, and new therapeutic agents in the pipeline that will further mitigate residual cardiovascular risk in both primary and secondary prevention patients.

Keywords Dyslipidemia · ASCVD · Cardiovascular disease prevention · Emerging therapies · Lipoprotein(a) · LDL-C · Hypertriglyceridemia

This article is part of the Topical Collection on *Lipid Abnormalities and Cardiovascular Prevention*

✉ Ron Blankstein
rblankstein@bwh.harvard.edu

Adam N. Berman
aberman@bwh.harvard.edu

[1] Departments of Medicine (Cardiovascular Division) and Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

Introduction

Despite substantial advances in the management of cardiovascular disease over the last several decades, atherosclerotic cardiovascular disease (ASCVD) is still the leading cause of morbidity and mortality worldwide [1–4]. The average annual direct and indirect cost attributable to cardiovascular disease in the USA alone is more than 350 billion dollars [5]. It is in this light that efforts to prevent the onset of cardiovascular disease take on such monumental importance from a public policy and global health perspective. While there are a variety of modifiable risk factors which impact cardiovascular health, lipoprotein disorders play a particularly critical role in the development of atherosclerosis and incident heart disease. To underscore this point, the American Heart Association (AHA) included untreated total cholesterol of less than 200 mg/dL as one of the seven components of the "ideal cardiovascular health" [6]. Accordingly, the management of dyslipidemias is critical to both primary and secondary cardiovascular prevention efforts.

Optimizing dyslipidemia management to both prevent the onset of cardiovascular disease and mitigate the future risk in those who already have evidence of atherosclerosis requires a multidimensional approach. In this paper, we will discuss the importance of risk assessment and how it relates to treatment. Additionally, we will discuss key lipoproteins, their associated disorders, and therapeutic options for optimizing the care of individuals who are at risk of incident ASCVD.

Risk Assessment

Cardiovascular risk assessment is the foundation of primary prevention as it allows patients and practitioners to estimate future ASCVD risk and to match the intensity of therapy with the level of risk. Accordingly, there have been numerous risk-assessment models developed with the goal of providing clinicians with meaningful and actionable data points by which to encourage lifestyle recommendations and/or pharmacologic interventions. The most well-known risk assessment tools include the Framingham models, the Systemic Coronary Risk Estimation (SCORE), and the pooled cohort equations (PCE) [7–9]. Various societies rely on different risk-assessment tools with the US ACC/AHA guidelines utilizing the PCE model and the European ESC/EAS guidelines utilizing the SCORE methodology [10, 11]. Irrespective of which specific risk model is chosen, however, the underlying premise is identical: identifying and treating at-risk individuals to *prevent* the onset of ASCVD is critical from a public health perspective [12].

Another key tenant in risk assessment and subsequent management is the importance of matching the overall ASCVD risk with the intensity of treatment [12]. Although their recommendations differ slightly, both the ACC/AHA and ESC/EAS guidelines recommend more intense pharmacologic treatment to high-risk primary and secondary prevention patients while low-risk primary prevention patients may not require pharmacological therapy [4, 11]. Although both guidelines rely heavily on their respective ASCVD risk prediction tools, they nonetheless identify categories of patients who are recommended to initiate pharmacologic treatment to mitigate their cardiovascular risk irrespective of their calculated ASCVD risk score. For example, the ACC/AHA guideline indicates the need for statin therapy among individuals with diabetes or those with baseline LDL-C ≥ 190 mg/dL; in both of these patient populations, pharmacologic intervention is warranted even if the calculated ASCVD risk is below the typical threshold to warrant pharmacotherapy.

Although the above-mentioned risk prediction tools are based on robust population data and have been validated extensively, there are still some important limitations to their practical application. Age, for instance, weighs heavily into the PCE scoring system given that it is an important risk factor for cardiovascular disease on a *population* level. However, the precise implication of age for an *individual* patient may overestimate—or in the case of young individuals, underestimate—their true risk for future ASCVD events [13–15]. In that vein, the most recent ACC/AHA guidelines stress the importance of shared decision-making along with identification of a variety of "risk-enhancing factors"—such as a family history of premature ASCVD, inflammatory diseases, elevated lipoprotein(a), and metabolic syndrome—when it comes to the initiation of pharmacologic therapy [4, 10]. Accordingly, the guideline recommends that risk-enhancing factors in a borderline-risk (10-year ASCVD risk of 5 to < 7.5%) or intermediate-risk (10-year ASCVD risk of ≥ 7.5 to < 20%) adult would increase the specificity of the calculated 10-year ASCVD risk and thereby favor the initiation of pharmacotherapy. However, if a given borderline or intermediate-risk patient has no such risk-enhancing factors, it would be reasonable to postpone institution of therapy and instead focus exclusively on lifestyle modification.

While risk-enhancing factors work to increase the specificity of the PCE calculation and favor initiating pharmacotherapy in borderline and intermediate-risk patients, there may still be uncertainty regarding the benefit of initiating therapy in select individuals. Furthermore, certain patients may have a strong preference to avoid pharmacotherapy if at all possible. It is in this light and with a strong focus on shared decision-making that the 2018 ACC/AHA guideline now recommends the use of coronary artery calcium (CAC) testing to further guide decision-making in intermediate-risk and select borderline-risk adults [4]. This recommendation is based on the substantial evidence that has accumulated over the last decade regarding the utility of CAC testing in accurately classifying cardiovascular risk by directly visualizing calcified coronary plaque [16••]. Moreover, CAC testing has been demonstrated to be superior to any serum biomarker in the prediction of future ASCVD events and in the discrimination of future cardiovascular risk [12]. Accordingly, patients with a calculated borderline or intermediate ASCVD risk who have a CAC score of zero can be reclassified to the low-risk category and pharmacotherapy can be safely deferred (unless, per the guideline, the patient has diabetes, a strong family history of early CHD, or is a current smoker), with consideration for repeat CAC testing every 5 to 10 years. However, if atherosclerosis is identified by CAC testing with any score above zero, this demonstrates an increased ASCVD risk and would justify initiating pharmacotherapy [4, 10]. In addition to CAC's ability to accurately classify risk in cases of uncertainty, it has been demonstrated to be cost-effective, a critical point within the current economics of healthcare financing and health policy [17–19]. ASCVD risk assessment—while certainly nuanced—is critical to both the management of dyslipidemia and in understanding each patient's global cardiovascular risk, establishing it as the foundation of primary prevention (Fig. 1).

Lifestyle Modification to Promote Overall Cardiovascular Health and Reduce ASCVD Risk

Lifestyle modification—including diet and exercise—forms the backbone of any intervention to reduce the risk of incident cardiovascular disease and should be recommended to all individuals. With respect to the treatment of dyslipidemia, a plant-based diet high in whole grains, fruits, vegetables, and legumes, but which minimizes processed foods and animal sources of protein, has been shown to reduce cholesterol, improve dysglycemia, lower inflammation, and in some studies even decrease lipoprotein(a) [20–24].

Low-density Lipoprotein Cholesterol

Expansive data spanning the realms of genetics, epidemiology, and randomized controlled trials (RCTs) have demonstrated the causal and pathogenic role of LDL-C in myocardial infarction, ischemic stroke, and cardiovascular death [25–30, 31••]. While the precise details that link LDL-C and plaque formation are still under active investigation, decades of vascular biology research have established that infiltration of LDL particles into the arterial wall is the inciting event that leads to the ultimate development of atherosclerosis [32]. Because of this nearly incontrovertible causal link between LDL-C and atherosclerotic heart disease, LDL-C has become the backbone of cardiovascular risk assessment and is the primary target of lifestyle and pharmacologic intervention to reduce the incidence of cardiovascular disease. Accordingly, the major US and European cardiovascular guidelines focus heavily on LDL-C as a modifiable risk factor [4, 11].

The mainstay of targeted LDL-C treatment comes in the form of HMG coenzyme A reductase inhibitors—known collectively as statins—which exert their primary therapeutic effect by upregulating the LDL receptor. Pioneering studies such as the West of Scotland Coronary Prevention Study, Air Force/Texas Coronary Atherosclerosis Prevention Study, HOPE-3, and the Scandinavian Simvastatin Survival Study demonstrated the remarkable success of statin therapy in reducing major cardiovascular events in both primary and secondary prevention [33–36]. Data from high-quality meta-analyses of statin RCTs have demonstrated that statin therapy reduces the risk of ASCVD events by more than 20% for each 1 mmol/L (38.7 mg/dL) reduction in LDL-C—all but confirming the principle that "lower is better" when it comes to LDL-C [26•, 37]. Moreover, statins are generally well-tolerated, safe, and cost-effective. It can be stated with confidence that the introduction of statin therapy to both primary and secondary prevention efforts over the last two decades has revolutionized cardiovascular medicine.

The general approach adopted by the major US and European guidelines for the use of statin therapy centers around assessing the patient's global ASCVD risk and matching the intensity of treatment with the patient's overall risk (as detailed above). Although previous US guidelines recommended a treat-to-target LDL-C approach, this subsequently changed to the global ASCVD risk approach in the 2013 ACC/AHA guideline [9]. This overall risk-based approach remains largely unchanged in the 2018 ACC/AHA guideline, although certain LDL-C targets for initiation of more aggressive therapies are now incorporated for

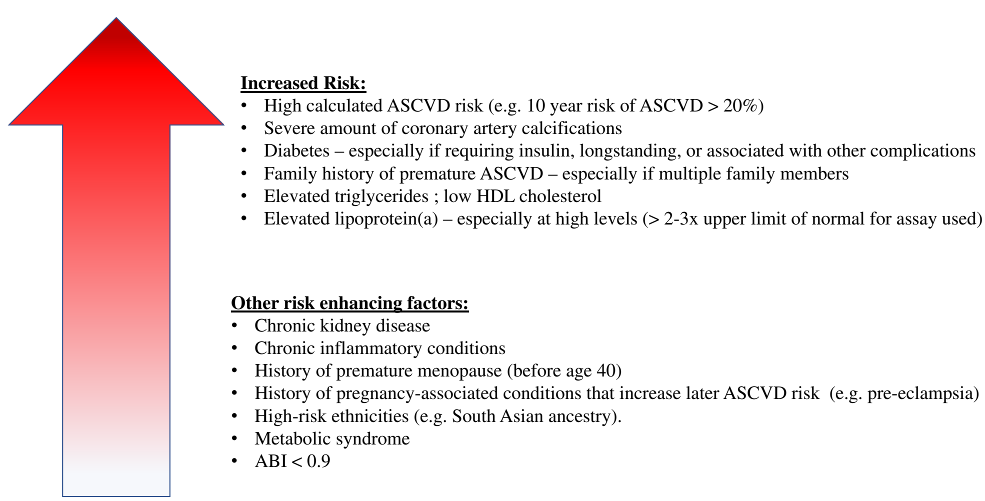

Fig. 1 Key risk factors in determining ASCVD risk in primary prevention

particularly high-risk primary and secondary prevention patients [4, 10]. The European guidelines, however, continue to advocate for treating LDL-C to specific targets given the strong compilation of data demonstrating that lower is better when it comes to LDL-C [11].

While statin-based therapy is the main agent used for lowering LCL-C, there are two additional LDL-C lowering agents which play an important role in select populations. Ezetimibe, a cholesterol absorption inhibitor, lowers LDL-C by approximately 20% and is most commonly used in high-risk secondary prevention patients but is also used selectively in certain high-risk primary prevention patients as well as in those who may be statin intolerant [4, 38]. The evidence for ezetimibe's beneficial role in the management of dyslipidemia comes primarily from two RCTs. The SHARP trial demonstrated a 17% reduction in major atherosclerotic events in patients with chronic kidney disease but with no known cardiovascular disease when ezetimibe was added to statin-based therapy [39]. Notably, the SHARP trial did *not* have a comparator statin-only arm, limiting the trial's overall generalizability in an era when statins form the backbone of ASCVD management. In contrast, the IMPROVE-IT trial demonstrated ezetimibe's independent and additive effect when combined with statin therapy in patients who recently experienced an acute coronary syndrome. Although the 2.0% absolute risk difference in major cardiovascular outcomes between the ezetimibe-treated group and the control arm was modest in nature, the IMPROVE-IT trial nonetheless demonstrated the added value of a non-statin agent in secondary prevention and further affirmed the benefits of more aggressive LDL-C reduction [40•]. Beyond its clinical utility, ezetimibe has an excellent tolerability and side-effect profile, making it an appealing choice in select, high-risk patients who have not achieved adequate LDL-C reduction with maximally tolerated statin therapy [4].

Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors now provide an effective option for the management of LDL-C and the residual cardiovascular risk in high-risk patients. PCSK9 is an enzyme which binds to the LDL receptor on hepatocytes, leading to its degradation. By blocking this enzyme, inhibitors of PCSK9 lead to higher expression of the LDL receptor on hepatocytes, thereby promoting LDL-C clearance by the liver [30]. PCSK9 inhibitors lower LDL-C by 50–70%, thus providing a substantial reduction in LDL-C levels. The outcome evidence for PCSK9 inhibitors come from two seminal RCTs: the ODYSSEY trial of alirocumab and the FOURIER trial of evolocumab which both collectively demonstrated an additional 15% reduction in key cardiovascular events in high-risk patients with known ASCVD already on statin therapy [38, 41•, 42•]. According to the latest ACC/AHA guideline, PCSK9 inhibitors are currently recommended in the following categories of patients: (a) very high-risk secondary prevention patients who are on maximally tolerated statin therapy but have LDL-C above 70 mg/dL; and (b) patients with severe primary hypercholesterolemia (LDL-C > 190 mg/dL) or heterozygous familial hypercholesterolemia (FH) who are not at goal despite maximally tolerated therapy [4]. Additionally, in clinical practice, PCSK9 inhibitors are also used in select "primary prevention" patients with multiple risk factors who have significant statin intolerance (e.g., unable to tolerate even low dose statins) as well as evidence of significant coronary atherosclerosis on non-invasive or invasive testing. Notably, given the cost of the two approved PCSK9 inhibitors, the ACC/AHA guideline recommends adding the lower-priced ezetimibe prior to the initiation of a PCSK9 inhibitor to determine whether the addition of ezetimibe alone may be able to achieve sufficient LDL-C reduction [4].

Two other notable LDL-C directed therapies that are currently undergoing trials include inclisiran and bempedoic acid. Inclisiran, a small interfering RNA (siRNA) molecule to the PCSK9 receptor, has been demonstrated to be safe and efficacious at decreasing LDL-C by approximately 50% in a large phase II trial [43•]. Importantly, as an siRNA molecule, inclisiran's effect on the PCSK9 receptor and circulating LDL-C levels lasts for more than 180 days, making it possible for patients to receive this therapy twice a year and reap the cardiovascular benefits of prolonged and significant LDL-C reduction. The ORION-4 trial (NCT03705234) is currently underway in a large secondary prevention setting and we look forward to its results. Bempedoic acid is an inhibitor of ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway, and has been shown to decrease LDL-C by ~ 17% in patients already on maximally tolerated statin therapy [44]. The CLEAR Outcomes trial (NCT02993406) using bempedoic acid in statin intolerant primary and secondary prevention patients is currently underway.

While the management of dyslipidemia and mitigating overall cardiovascular risk has primarily focused on therapies targeting LDL-C over the last two decades, other blood lipoproteins have been examined extensively in the context of cardiovascular risk. These lipoproteins—namely HDL-C, triglycerides, and lipoprotein(a)—play important roles in cardiovascular health and our understanding of their distinct impacts continues to grow. Moreover, there continue to be ongoing developments to specifically target these lipoproteins in an attempt to further elucidate and treat any residual cardiovascular risk in patients with otherwise well-controlled modifiable risk factors.

High-density Lipoprotein Cholesterol

Decreased levels of the cholesterol content within HDL molecules (HDL-C) are strongly correlated with the presence and development of clinically significant ASCVD [25, 45]. Conversely, every 1 mg/dL increase in HDL-C is associated with an approximate 2–4% decrease in the rates of adverse cardiovascular outcomes, promoting the concept of HDL-C as an atheroprotective molecule [46]. Accordingly, because

HDL-C is an independent and strong predictor of clinically meaningful cardiovascular events, HDL-C plays a key role in cardiovascular risk equations [47].

However, despite the body of evidence demonstrating the association between HDL-C and cardiovascular disease, the causative role of HDL-C in ASCVD has been challenged by both Mendelian randomization studies and the failure of HDL-C directed therapies to improve outcomes. For instance, lifelong reduced HDL-C levels due to mutations in the ABCA1 gene do not confer an increased risk of ischemic heart disease [48, 49]. Conversely, genetic polymorphisms which cause lifelong increased levels of HDL-C are not associated with improved cardiovascular outcomes [50]. Additionally, two large and well-designed RCTs of niacin therapy—the AIM-HIGH and THRIVE trials—did not show a cardiovascular benefit of raising HDL-C in patients with known cardiovascular disease who were on statin-based therapy [51, 52]. Furthermore, cholesteryl ester transfer protein (CETP) inhibitors, which increase HDL-C levels by more than 100%, have demonstrated mixed results and are not currently used in clinical practice. Two large CETP trials were stopped due to lack of efficacy—ACCELERATE (evacetrapib) and Dal-OUTCOMES (dalcetrapib)—while the ILLUMINATE trial with torcetrapib was terminated early due to a significant increase in the risk of cardiovascular events in the experimental arm [53–55]. Although another CETP agent, anacetrapib, successfully met its primary endpoint in the REVEAL trial, its beneficial effect was likely the result of its role in lowering non-HDL cholesterol by 18% compared with the control arm rather than its impact on raising HDL-C levels [56].

Although the classic HDL-C hypothesis that increased levels of HDL-C provide cardiovascular protection has been largely disproven, there is emerging data that a revised concept of HDL—one focusing on HDL function—may prove more fruitful in terms of therapeutic targets [47]. Evidence is accumulating that differences in HDL function in regard to promoting cholesterol efflux from cells, termed the "cholesterol efflux capacity," may be a better indicator of cardiovascular risk than HDL-C [57, 58]. Although this is a burgeoning area of research, there are currently no large-scale phase 3 clinical trials targeting therapies focused on HDL function [59]. Ultimately, while HDL-C still stands as a strong and independent risk factor for the development of ASCVD, the current data suggests that the role of HDL-C may be as a marker of overall cardiovascular risk rather than being a direct therapeutic target for the prevention of ASCVD events.

Triglycerides

Elevations in both fasting and non-fasting serum triglyceride levels are strongly associated with increased risk of MI, ischemic stroke, and all-cause mortality [60–64]. This relationship is further bolstered by data demonstrating increased incidence of ischemic heart disease in patients with triglyceride levels between 200 and 499 mg/dL who had well-controlled LDL-C while on statin therapy [65]. Although the pathogenesis of atheroma formation due to elevated triglyceride levels is not entirely clear, it likely relates to the cholesterol content of triglyceride-rich lipoproteins—also known as remnant cholesterol—rather than the distinct triglyceride particles themselves [66–68]. Until recently, there has been less of a spotlight on elevated triglyceride levels with regard to the development of ASCVD, with a greater focus placed on low HDL-C for a variety of mechanistic, epidemiologic, and conceptual reasons [68, 69]. However, as described above, with numerous failed attempts at improving cardiovascular outcomes by raising HDL-C levels as well as accumulating data regarding the role of triglycerides in ASCVD, there has been a renewed interest in pursuing targeted therapies for elevated triglyceride levels.

The first priority in managing those with mild to moderate hypertriglyceridemia (fasting or non-fasting TG levels between 150 and 499 mg/dL) should be lifestyle modification, treatment of secondary risk factors, and review of the current medication list [4, 11]. In regard to lifestyle modification, patients should be encouraged to lose weight, perform aerobic exercise, and limit excessive alcohol intake as each of these measures can reduce plasma triglycerides [68, 70, 71]. Additionally, treatment of secondary risk factors such as obesity, diabetes mellitus, and hypothyroidism should be optimized.

Despite the burgeoning evidence linking elevated triglyceride levels with ASCVD, pharmacotherapy for patients with mild to moderate hypertriglyceridemia has not been typically recommended in the absence of certain high-risk features or other evidence-based indications [4, 11]. The reason for this is multifactorial but primarily reflects the lack of high-quality RCT data demonstrating improved outcomes in patients with hypertriglyceridemia when treated with triglyceride lowering medications such as fibrates and niacin [11, 62]. Fibrates such as gemfibrozil and fenofibrate are typically reserved for patients with severe hypertriglyceridemia with triglyceride levels greater than 1000 mg/dL to prevent pancreatitis. Additionally, niacin has fallen out of favor given its poor side-effect profile as well as the results of the AIM-HIGH and THRIVE trials which failed to demonstrate positive cardiovascular effects when adding niacin to statin therapy [51, 52]. As such, statins are the recommended first-line agents in individuals with mild to moderate hypertriglyceridemia who are at elevated ASCVD risk by conventional metrics. In addition to their well-elucidated and beneficial cardiovascular effects, high-intensity statins are able to reduce triglyceride levels by as much as 45% [72].

With the recent publication of the REDUCE-IT trial as well as other targeted therapies in the therapeutic pipeline, the tide of triglyceride management may be evolving [62, 73•]. The REDUCE-IT trial, which randomized high-risk patients already on statin therapy to a highly purified fish-oil derivative named icosapent ethyl, is the first large-scale RCT which successfully demonstrated cardiovascular risk reduction with an agent specifically targeting patients with an elevated fasting triglyceride level. Nevertheless, the trial did not find a significant association between baseline triglyceride level and efficacy, suggesting that the mechanism of benefit—at least, in part—may be independent of the effect of triglyceride lowering. Other highly anticipated ongoing trials assessing the added cardiovascular benefit of targeting triglyceride levels include the STRENGTH trial (NCT02104817) as well as the PROMINENT trial (NCT03071692). Finally, antisense oligonucleotides and siRNA targeting apolipoprotein C-III is another novel therapeutic pathway that may further revolutionize our current management of hypertriglyceridemia [74–76].

Lipoprotein(a)

Elevated serum lipoprotein(a) [Lp(a)] levels are strongly associated with increased risk of coronary heart disease, calcific aortic valve stenosis, and stroke [77–82]. The mechanism by which Lp(a) exerts its independent effects is most likely due to its unique molecular structure [83]. First identified in 1963, Lp(a) is composed of a lipid-rich low-density lipoprotein like moiety covalently linked to a genetically heterogeneous apolipoprotein(a) molecule [84, 85]. The LDL-like moiety is thought to confer pro-atherogenic qualities while its apolipoprotein(a) component is hypothesized to be associated with pro-thrombotic properties [83]. Lp(a) concentration is primarily determined by the *LPA* gene, with the size of the gene—and the resulting size of the apolipoprotein(a) particle—strongly correlating with the serum concentration of Lp(a). Importantly, there is an inverse relationship between the *LPA* gene size and the Lp(a) serum concentration whereby individuals with larger *LPA* gene sizes (and resulting larger apolipoprotein(a) isoforms) have lower serum Lp(a) concentrations [79, 86–88]. Additionally, certain single-nucleotide polymorphisms (SNPs) within the *LPA* gene—in particular, rs10455872 and rs3798220—are strongly associated with increased levels of Lp(a) as well as increased risk of CHD and calcific aortic valve stenosis [80, 81, 88, 89].

Although the nuances of the interaction between gender and ethnic backgrounds on Lp(a)'s impact on cardiovascular disease are still being clarified, it is nonetheless clear that elevated Lp(a) levels account for a significant degree of the residual cardiovascular risk in patients with otherwise well-controlled risk factors [82, 90–94]. By most standards, Lp(a) levels above 30 mg/dL are considered abnormal, with the greatest risk conferred to those individuals with levels greater than 50 mg/dL, a value above the 80th percentile [95]. Given that the concentration of Lp(a) is explained almost entirely by the LPA gene size and certain pathogenic SNPs, elevated Lp(a) is therefore the most common inherited dyslipidemia with nearly 1 in 5 people in the USA having levels above 50 mg/dL [96]. Although Lp(a) values are not part of the current generation of ASCVD risk calculators, Lp(a) measurement has nonetheless been shown to help improve CVD risk prediction and its selected evaluation is incorporated into the ACC/AHA and ESC/EAS guidelines to help improve risk stratification [4, 11, 97].

Although Lp(a)'s impact on cardiovascular disease outcomes has been well established for more than a decade, targeted therapeutic options have been limited. Currently, the most recent ACC/AHA and ESC/EAS guidelines recommend intensified risk factor modification as well as aggressive management of LDL-C for patients with elevated Lp(a). However, there are a variety of promising developments that may revolutionize targeted Lp(a) management [98••]. First, recent

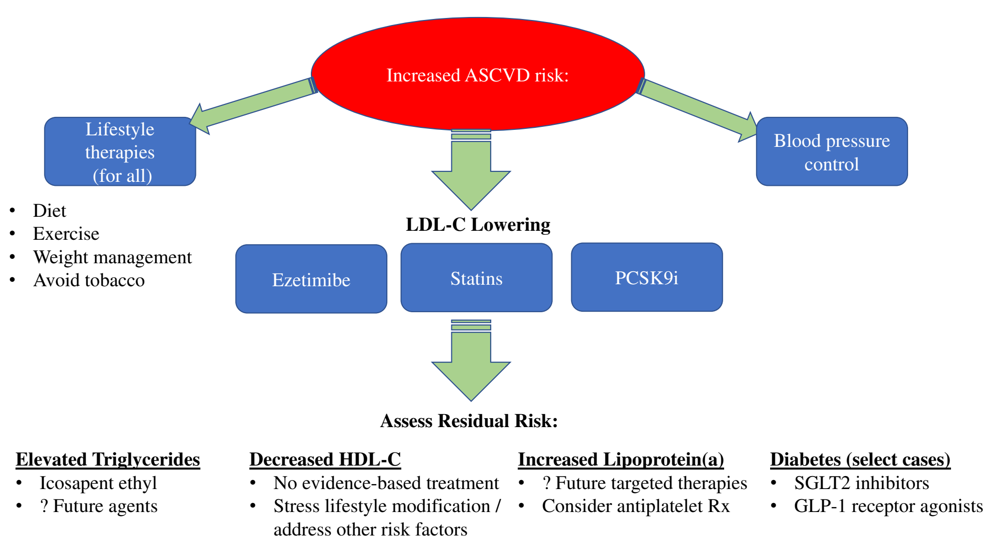

Fig. 2 Assessing and treating individuals with increased ASCVD risk requires both a primary focus on LDL-C and consideration of other residual risk/modifiable risk factors

evidence has demonstrated that PCSK9 inhibitors both significantly lower Lp(a) levels and potentially provide even greater cardiovascular benefit to patients with elevated baseline Lp(a) levels. In an analysis of the FOURIER trial, which investigated the cardioprotective role of the PCSK9 inhibitor evolocumab, the investigators demonstrated that evolocumab tended to reduce the risk of major cardiovascular events by a greater degree in patients with an elevated Lp(a) as compared with those with Lp(a) levels below the median. Overall, evolocumab reduced the incidence of the primary cardiovascular endpoints in the study population by 16%. However, when stratified by Lp(a) level, those patients with Lp(a) above the median experienced a 23% reduction in the primary endpoints versus a 7% reduction in those patients with Lp(a) levels below the median [99•]. Although these findings were observational, they are nonetheless important for two reasons. For one, they are the first to support the concept of Lp(a) being a *modifiable* risk factor and bolster the development of evermore targeted therapies. Second, they provide potential insight into which patients may derive the most benefit from PCSK9 inhibitors, a finding which could influence practice patterns if confirmed in other analyses of PCSK9 inhibitors [96].

An important development in the Lp(a) pipeline, however, involves antisense oligonucleotides (ASOs) targeting components of the Lp(a) molecule. In particular, there is much anticipation around ASOs directed against apolipoprotein(a) production in the liver, thereby inhibiting the production of Lp(a). ASOs are single-stranded DNA molecules, typically under 30 nucleotides in length, which are engineered to be complementary to a specific messenger RNA or a regulatory RNA sequence. Once administered, these designer molecules enter the patient's cells and bind to the intended native RNA, preventing transcription into a functional protein [75, 100]. Currently, there are ongoing early phase trials of different ASO molecules targeting apolipoprotein(a) which have demonstrated dose-dependent reductions in Lp(a) levels of up to 90% [75, 98••, 101, 102]. Given these early findings, we eagerly await large-scale phase III trials of these molecules, which have the potential to revolutionize the treatment of elevated Lp(a) and improve our ability to treat residual cardiovascular risk in patients with otherwise well-controlled risk factors.

Conclusions

Although there have been tremendous strides in the management of dyslipidemias over the last three decades, there are still many areas that are under active research and investigation. Key questions revolve around how to further identify and reduce the risk of incident cardiovascular disease in primary prevention and how to decrease the rate of future events in those with known cardiovascular disease who are currently optimally managed. Given the exciting developments in this field as a whole as well as particular developments in triglyceride management and ongoing trials in Lp(a), we anticipate that there will be meaningful advances in the coming years which will impact the management of dyslipidemias and how we optimize the cardiovascular risk profiles of our patients (Fig. 2).

Compliance with Ethical Standards

Conflict of Interest Adam Berman declares that he has no conflict of interest.

Ron Blankstein reports grants from Astellas Inc. and Amgen Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–88.
2. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief. 2018(328):1–8.
3. Weir HK, Anderson RN, Coleman King SM, Soman A, Thompson TD, Hong Y, et al. Heart disease and cancer deaths - trends and projections in the United States, 1969-2020. Prev Chronic Dis. 2016;13:E157.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. Circulation. 2018;0(0):CIR0000000000000625.
5. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–e528.
6. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. Circulation. 2010;121(4):586–613.
7. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743–53.
8. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003.

9. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2935–59.
10. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. Circulation. 2019;0(0): CIR0000000000000678.
11. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37(39):2999–3058.
12. Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC Jr, Sperling LS, Virani SS, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease. Circulation. 2018;0(0):CIR0000000000000638.
13. Karmali KN, Goff DC Jr, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64(10):959–68.
14. DeFilippis AP, Young R, McEvoy JW, Michos ED, Sandfort V, Kronmal RA, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J. 2017;38(8):598–608.
15. Singh A, Collins BL, Gupta A, Fatima A, Qamar A, Biery D, et al. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. J Am Coll Cardiol. 2018;71(3):292–302.
16.•• Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66(15):1657–68 **This important analysis underscores the utility of coronary artery calcium testing in accurately classifying ASCVD risk**.
17. Hong JC, Blankstein R, Shaw LJ, Padula WV, Arrieta A, Fialkow JA, et al. Implications of coronary artery calcium testing for treatment decisions among statin candidates according to the ACC/AHA cholesterol management guidelines: a cost-effectiveness analysis. JACC Cardiovasc Imaging. 2017;10(8):938–52.
18. Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips KA, Auer R, et al. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes. 2014;7(2):276–84.
19. Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, et al. Cost-effectiveness of coronary artery calcium testing for coronary heart and cardiovascular disease risk prediction to guide statin allocation: the Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One. 2015;10(3):e0116377.
20. Blanco Mejia S, Messina M, Li SS, Viguiliouk E, Chiavaroli L, Khan TA, et al. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. J Nutr. 2019;149:968–81.
21. Martinez-Gonzalez MA, Sanchez-Tainta A, Corella D, Salas-Salvado J, Ros E, Aros F, et al. A provegetarian food pattern and reduction in total mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. Am J Clin Nutr. 2014;100(Suppl 1):320S–8S.
22. Najjar RS, Moore CE, Montgomery BD. A defined, plant-based diet utilized in an outpatient cardiovascular clinic effectively treats hypercholesterolemia and hypertension and reduces medications. Clin Cardiol. 2018;41(3):307–13.
23. Shah B, Newman JD, Woolf K, Ganguzza L, Guo Y, Allen N, et al. Anti-inflammatory effects of a vegan diet versus the American Heart Association-Recommended Diet in Coronary Artery Disease Trial. J Am Heart Assoc. 2018;7(23):e011367.
24. Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and plasma lipids: a systematic review and meta-analysis. Nutr Rev. 2017;75(9):683–98.
25. Emerging Risk Factors C, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993–2000.
26.• Trialists CT. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81 **This large meta-analysis demonstrated the safety and efficacy of further LDL-C lowering, without evidence of a threshold effect.**
27. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60(25):2631–9.
28. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol. 2004;160(5):421–9.
29. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J. 2016;37(17):1384–94.
30. Ridker PM. LDL cholesterol: controversies and future therapeutic directions. Lancet. 2014;384(9943):607–17.
31.•• Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–72 **This wide-ranging analysis demonstrated the nearly incontrovertible causal relationship between LDL-C and ASCVD.**
32. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004–13.
33. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333(20): 1301–7.
34. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279(20):1615–22.
35. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2021–31.
36. Scandinavian Simvastatin Survival Study G. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383–9.
37. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316(12):1289–97.
38. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 focused update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin

Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70(14): 1785–822.

39. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.

40.• Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97 **The IMPROVE-IT trial demonstrated the ability of a non-statin agent to both reduce LDL-C and recurrent ASCVD events in secondary prevention.**

41.• Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–22 **The FOURIER trial with the PCSK9 inhibitor evolocumab demonstrated the therapeutic role of these agents in secondary prevention.**

42.• Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097–107 **The ODYSSEY trial with the PCSK9 inhibitor alirocumab demonstrated the therapeutic role of these agents in secondary prevention.**

43.• Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2017;376(15): 1430–40 **This large phase II trial of the siRNA molecule inclisiran demonstrated the tolerability and efficacy of this unique molecule in reducing LDL-C via the PCSK9 receptor.**

44. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. N Engl J Med. 2019;380(11):1022–32.

45. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. Am J Med. 1977;62(5):707–14.

46. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989;79(1):8–15.

47. Rader DJ, Hovingh GK. HDL and cardiovascular disease. Lancet. 2014;384(9943):618–25.

48. Frikke-Schmidt R, Nordestgaard BG, Stene MC, Sethi AA, Remaley AT, Schnohr P, et al. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. JAMA. 2008;299(21):2524–32.

49. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, et al. Mendelian randomization of blood lipids for coronary heart disease. Eur Heart J. 2015;36(9):539–50.

50. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. Lancet. 2012;380(9841):572–80.

51. Group HTC, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371(3):203–12.

52. Investigators A-H, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67.

53. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med. 2017;376(20):1933–42.

54. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367(22):2089–99.

55. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357(21):2109–22.

56. Group HTRC, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med. 2017;377(13):1217–27.

57. Mody P, Joshi PH, Khera A, Ayers CR, Rohatgi A. Beyond coronary calcification, family history, and C-reactive protein: cholesterol efflux capacity and cardiovascular risk prediction. J Am Coll Cardiol. 2016;67(21):2480–7.

58. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014;371(25):2383–93.

59. Bhatt A, Rohatgi A. HDL cholesterol efflux capacity: cardiovascular risk factor and potential therapeutic target. Curr Atheroscler Rep. 2016;18(1):2.

60. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299–308.

61. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298(3):309–16.

62. Madsen CM, Varbo A, Nordestgaard BG. Unmet need for primary prevention in individuals with hypertriglyceridaemia not eligible for statin therapy according to European Society of Cardiology/ European Atherosclerosis Society guidelines: a contemporary population-based study. Eur Heart J. 2018;39(7):610–9.

63. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, et al. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013;45:1345–52.

64. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. Eur Heart J. 2013;34(24):1826–33.

65. Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S. Increased cardiovascular risk in hypertriglyceridemic patients with statin-controlled LDL cholesterol. J Clin Endocrinol Metab. 2018;103(8):3019–27.

66. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626–35.

67. Ginsberg HN. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. Circulation. 2002;106(16):2137–42.

68. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Boren J, Catapano AL, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32(11):1345–61.

69. Libby P. Triglycerides on the rise: should we swap seats on the seesaw? Eur Heart J. 2015;36(13):774–6.

70. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56(2):320–8.

71. Brunzell JD. Clinical practice. Hypertriglyceridemia. N Engl J Med. 2007;357(10):1009–17.

72. Bakker-Arkema RG, Davidson MH, Goldstein RJ, Davignon J, Isaacsohn JL, Weiss SR, et al. Efficacy and safety of a new HMG-

CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA. 1996;275(2):128–33.

73.• Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380(1):11–22 **The REDUCE-IT trial demonstrated the added cardiovascular benefit of targeted triglyceride lowering with a highly purified fish-oil derivative named icosapent ethyl.**

74. Graham MJ, Lee RG, Bell TA 3rd, Fu W, Mullick AE, Alexander VJ, et al. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. Circ Res. 2013;112(11):1479–90.

75. Tsimikas S. RNA-targeted therapeutics for lipid disorders. Curr Opin Lipidol. 2018;29(6):459–66.

76. Schmitz J, Gouni-Berthold I. APOC-III antisense oligonucleotides: a new option for the treatment of hypertriglyceridemia. Curr Med Chem. 2018;25(13):1567–76.

77. Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009;302(4):412–23.

78. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. 2008;117(2):176–84.

79. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009;301(22):2331–9.

80. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368(6):503–12.

81. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol. 2014;63(5):470–7.

82. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. Lancet. 2018;392(10155):1311–20.

83. Koschinsky ML, Marcovina SM. Structure-function relationships in apolipoprotein(a): insights into lipoprotein(a) assembly and pathogenicity. Curr Opin Lipidol. 2004;15(2):167–74.

84. Berg K. A new serum type system in man—the Lp system. 1963;59(3):369–82.

85. Ballantyne CM. Clinical lipidology: a companion to Braunwald's heart disease. Philadelphia: 2nd edition; 2015.

86. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest. 1992;90(1):52–60.

87. Rader DJ, Cain W, Ikewaki K, Talley G, Zech LA, Usher D, et al. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. J Clin Invest. 1994;93(6):2758–63.

88. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361(26):2518–28.

89. Wei W-Q, Li X, Feng Q, Kubo M, Kullo IJ, Peissig PL, et al. LPA variants are associated with residual cardiovascular risk in patients receiving statins. Circulation. 2018;138(17):1839–49.

90. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. J Am Coll Cardiol. 2018;72(3): 287–96.

91. Paré G, Çaku A, McQueen M, Anand Sonia S, Enas E, Clarke R, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. Circulation. 2019;139(12):1472–82.

92. Cao J, Steffen BT, Budoff M, Post WS, Thanassoulis G, Kestenbaum B, et al. Lipoprotein(a) levels are associated with subclinical calcific aortic valve disease in White and Black individuals: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2016;36(5):1003–9.

93. Virani SS, Brautbar A, Davis BC, Nambi V, Hoogeveen RC, Sharrett AR, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in Black and White subjects: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2012;125(2):241–9.

94. Guan W, Cao J, Steffen BT, Post WS, Stein JH, Tattersall MC, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(4):996–1001.

95. Nordestgaard BG, Chapman MJ, Ray K, Boren J, Andreotti F, Watts GF, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.

96. Thanassoulis G. Screening for high lipoprotein(a). Circulation. 2019;139(12):1493–6.

97. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol. 2014;64(9):851–60.

98.•• Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2017;69(6):692–711 **This comprehensive review of lipoprotein(a) and cardiovascular disease synthesizes important insights into the lipoprotein(a) and its future as a therapeutic target.**

99.• O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation. 2019;139(12):1483–92 **This analysis of the FOURIER trial demonstrated that the PCSK9 inhibitor evolocumab reduced the risk of major cardiovascular events by a greater degree in patients with an elevated Lp(a) as compared with those with Lp(a) levels below the median. This analysis supported Lp(a) as a modifiable risk factor and provides insight into which patients may benefit the most from PCSK9 inhibition.**

100. Levin AA. Treating disease at the RNA level with oligonucleotides. N Engl J Med. 2019;380(1):57–70.

101. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016;388(10057): 2239–53.

102. Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. Lancet. 2015;386(10002):1472–83.