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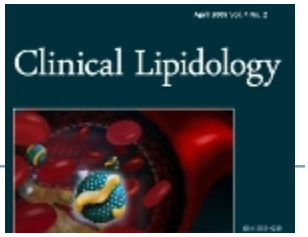
# Twenty-five Years of Statins: Where Do We Go From Here?

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## Abstract and Introduction

**Abstract**

More than 25 years of clinical trial data have established statins as first-line therapy for the prevention and treatment of atherosclerotic cardiovascular disease. With regard to low-density lipoprotein cholesterol, a wealth of evidence indicates that 'lower is better,' although recent guidelines from the American College of Cardiology and the American Heart Association take a different approach. A variety of approved and experimental lipid-lowering agents may be used as supplements or alternatives to statin therapy in patient subgroups, including those with familial hypercholesterolemia, mixed dyslipidemia or statin intolerance. Strategies to achieve further reductions in low-density lipoprotein cholesterol, target high-density lipoprotein cholesterol and triglycerides or reduce inflammation may help address residual cardiovascular risk, although early lifestyle interventions are crucial to prevention strategies.

**Introduction**

After more than 25 years in clinical use, statins have transformed the field of lipid management and cardiovascular risk reduction. Due to their proven efficacy and safety, they have become first-line therapy for individuals who are unable to manage their dyslipidemia through lifestyle changes alone. Between 1988 and 2010, average LDL-cholesterol levels fell from 129 to 116 mg/dl in the USA, and HDL-cholesterol increased from 50.7 to 52.5 mg/dl.[1] It is likely that an increase in the number of people taking lipid-lowering medications – from 3.4 to 15.5% over the same time period – contributed substantially to these favorable trends. The introduction of statins has also played an important role in the decline in cardiovascular mortality rates observed in the USA since 1970. By helping to prevent the development of atherosclerotic cardiovascular disease before it occurs and by reducing the risk of a future event in those with a clinical diagnosis, statins have had an enormous public health impact.

Still, ischemic heart disease and stroke remain leading causes of death worldwide. The release of new recommendations for cholesterol management from the American College of Cardiology (ACC) and the American Heart Association (AHA) generated considerable controversy among lipid experts and indicates that there are widely divergent views on the optimum strategy for treatment with statins. In addition, there is a pressing need for alternative therapies, particularly for patients with familial hypercholesterolemia (FH), mixed dyslipidemia or statin intolerance. Several nonstatin drugs, including ezetimibe, nicotinic acid and fibrates, have been challenged in recent years due to negative results from clinical trials. It is important that we clearly identify the patient subgroups that can achieve the greatest benefit from these medications.

This Perspective highlights some of the key issues and the most exciting new therapies in development within clinical lipidology. It begins by placing the statins in historical perspective and briefly summarizes the clinical trial data that provide robust support for the 'lower is better' approach to treating LDL-cholesterol. Although the ACC/AHA guidelines recommend a different strategy, 'lower is better' remains an important principle in the field. This Perspective also reviews existing and experimental agents designed to achieve further LDL-cholesterol reduction, as well as drugs that target HDL-cholesterol, triglycerides and inflammation. When targeted to the appropriate patient, these therapies have the potential to lower cardiovascular risk beyond the effects of statin treatment.

## Statins in Historical Perspective

The lipid hypothesis connects elevated plasma levels of cholesterol to the development of atherosclerosis and increased risk for cardiovascular disease. A series of discoveries led to the confirmation of the lipid hypothesis and underscored the primary importance of LDL-cholesterol in the pathogenesis of atherosclerotic disease. The Norwegian physician Carl Müller was one of the first to observe the association between lipids and coronary disease when studying patients with FH in the 1930s.[2] In the 1950s, John Gofman characterized the lipoproteins based on their rate of flotation in the ultracentrifuge and generated preliminary evidence suggesting that higher levels of VLDL and especially LDL were associated with increased risk for coronary heart disease (CHD), while higher levels of HDL appeared to have a protective effect.[3] Two subsequent longitudinal studies provided additional data on risk factors for heart disease. Initiated in 1948, the Framingham Heart Study identified elevated total cholesterol, LDL-cholesterol, high blood pressure and cigarette smoking as major risk factors, while HDL-cholesterol was seen to be protective against heart disease.[4,5] The Seven Countries Study, launched in 1958, showed that cardiovascular mortality rates were higher in the USA and Northern Europe than in Southern Europe.[6] These findings, which suggested that a Mediterranean-style diet low in saturated fat could lower the risk for cardiovascular disease, were recently confirmed in a randomized trial.[7] In addition to the major risk factors identified in the Framingham and Seven Countries studies, data indicate that measures of non-HDL-cholesterol and apoB, which is present in all of the pro-atherogenic lipid fractions, are also highly associated with cardiovascular risk.[8]

A major advance in the confirmation of the lipid hypothesis occurred in 1973, with the discovery of the LDL receptor by Michael Brown and Joseph Goldstein. These investigators identified a deficiency of LDL receptors in patients with FH and helped describe the role of the LDL receptor in maintaining cholesterol homeostasis.[9] Another breakthrough was the isolation of a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) from the fungus *Penicillium citrinum* by the biochemist Akira Endo.[10] This substance, called compactin or mevastatin, was the first statin to be administered to humans, although its development was soon terminated for unknown reasons. The first statin to be approved in the US was lovastatin (mevinolin) in 1987.

A steady stream of clinical trial data proceeded to establish the safety and efficacy of cholesterol reduction using statins. The first major study to demonstrate that lowering cholesterol could increase the probability of survival was the Scandinavian Simvastatin Survival Study (4S), a secondary prevention study of 4444 patients with existing CHD and a mean cholesterol level of 272 mg/dl.[11] Treatment with simvastatin reduced LDL-cholesterol by 38%, and it decreased coronary events by 34% and total mortality by 30%. The first primary prevention study with statins was the West of Scotland Coronary Prevention Study (WOSCOPS) with pravastatin, which showed a reduction in coronary events but no significant effect on all-cause mortality.[12] The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) in primary prevention was the first to show cardiovascular benefit when treating individuals at lower risk.[13] Over a 5-year period, treatment with lovastatin reduced the risk for a first acute major coronary event by 37% in individuals with cholesterol levels considered average.

Other statin trials confirmed and extended these findings in diverse patient populations, including women and the elderly.[14,15] Studies with intensive statin therapy also support the view that, with regards to LDL-cholesterol, 'lower is better'.[16] Although clinical trial data suggest that this axiom may not apply to variables such as blood pressure or glycated hemoglobin, the corresponding evidence for lipids appears quite robust.[17,18] Meta-analyses further demonstrate that larger reductions in LDL-cholesterol confer greater cardiovascular benefit.[19,20] Based on data from over 170,000 subjects treated with statins in primary and secondary prevention, the Cholesterol Treatment Trialists found a 22% relative reduction in risk for major vascular events and a 10% decrease in all-cause mortality for every 39 mg/dl (1 mmol/l) reduction in LDL-cholesterol, with no attenuation of this relationship even at low LDL-cholesterol levels.[19] Additionally, it showed that the risk for each type of major vascular event is reduced with statin treatment, except for a non-significant excess of hemorrhagic stroke.

Currently, there are seven commercially available statins. Lovastatin, pravastatin and simvastatin are fungal derivatives, while atorvastatin, fluvastatin, rosuvastatin and pitavastatin are synthetic compounds. Their primary effect is to reduce LDL-cholesterol by 20–63%, although they can also modestly increase HDL-cholesterol by 5–15% and reduce triglycerides by 10–37%. In addition, they are associated with a high degree of safety and are not associated with an increased incidence of cancer.[19–21] Cerivastatin was withdrawn worldwide because of

reports of rhabdomyolysis, but this serious adverse reaction is very low and nonsignificant with other drugs in this class (absolute excess 0.01% [SE: 0.01]; p = 0.4).[21] Statins have been found to increase the risk for incident diabetes by 9%, which translates into one extra case of diabetes per 255 patients treated with statins for 4 years.[22] This excess risk is outweighed by the cardiovascular benefits of statin therapy since 5.4 coronary events would be prevented over the same patient treatment period.

## Further Reductions in LDL-cholesterol

### ACC/AHA Guidelines for Cholesterol Management

At the end of 2013, the ACC and the AHA issued new guidelines that emphasize the importance of statin therapy in reducing risk for atherosclerotic cardiovascular disease, which includes CHD, stroke and peripheral arterial disease.[23] These recommendations improve on previous guidelines in important ways, although they also diverge from the cumulative body of evidence in eliminating lipid targets.

The guidelines identify three categories of high-risk patients who should receive statin therapy: individuals with established atherosclerotic cardiovascular disease, a likely diagnosis of FH, or diabetes. They also create a fourth category of individuals in primary prevention who are likely to benefit from statin therapy, namely middle-aged people with an estimated 10-year risk for atherosclerotic cardiovascular disease of at least 7.5% and with LDL-cholesterol levels of at least 70 mg/dl. Compared with the previous Adult Treatment Panel (ATP) III guidelines, the ACC/AHA version increases the number of individuals eligible for statin therapy in the USA from 43.2 million to 56.0 million.[24] Most of this increase is seen among adults aged 60–75 years without existing cardiovascular disease who now fall into the primary prevention category of statin benefit. The extension of statin therapy to individuals with a 10-year risk of at least 7.5% is an appropriate and beneficial strategy that will help reduce the incidence of atherosclerotic cardiovascular disease.

The ACC/AHA guidelines incorporate a risk prediction algorithm that includes all of the variables of the ATP III version (age, total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for hypertension and cigarette smoking), in addition to race. The new risk assessment formula is an improvement on the ATP III one, which drew on data from the largely male and Caucasian cohort tracked in the Framingham Heart Study. The ACC/AHA version is based on studies in more diverse patient populations and provides a better estimate of cardiovascular risk in African Americans and in women, who may need to be treated more aggressively than previously thought. There is still room for improvement though, particularly when assessing risk in Hispanic, Asian American and American Indian patients, who make up approximately one-fifth of the US population. Estimates of risk for these individuals are made by categorizing them as non-Hispanic whites, which can lead to overestimates for some (e.g., people of East Asian ancestry, Mexican Americans) and underestimates for others (e.g., people of South Asian heritage, Puerto Ricans).[23]

The ACC/AHA guidelines also depart from the previous version in eliminating specific lipid targets. The authoring committee maintained that randomized clinical trials have not established that 'lower is better' since most were fixed-dose trials comparing two statin regimens, rather than titration trials targeting a specific LDL-cholesterol or non-HDL-cholesterol goal. As a result, the guidelines recommend that patients be treated either with a high-intensity statin, which can be expected to lower LDL-cholesterol by at least 50%, or a moderate-intensity statin, which typically reduces LDL-cholesterol by 30–50%. Factors such as age, tolerance of side effects and concomitant medications guide the choice between high- or moderate-intensity treatment. In 2014, the National Institute for Health and Care Excellence (NICE) in the UK issued evidence-based guidelines that similarly recommend treatment according to statin intensity, rather than specific lipid targets.[25]

Arguably, the decision to forgo a numerical goal for LDL-cholesterol, such as 70 mg/dl for high-risk patients or 100 mg/dl for those at moderate risk, disregards at least 25 years of clinical trial evidence. What these trials have shown through individual *post hoc* analyses and large-scale meta-analyses is that intensive statin therapy resulting in lower attained LDL-cholesterol levels leads to improved clinical outcomes, such as reduced mortality and vascular events.

[16,19–21] In addition, the hypothesis of the Treating to New Targets study, one of the landmark trials of intensive statin therapy, was that reducing LDL-cholesterol to well below the existing target of 100 mg/dl would yield greater benefit in patients with acute coronary syndromes.[26] The goal was for the high-dose arm to achieve an average LDL-cholesterol level of 75 mg/dl, compared with an average level of 100 mg/dl in the arm allocated to standard treatment. In this trial, intensive treatment with atorvastatin to a mean LDL-cholesterol level of 77 mg/dl resulted in a 22% relative reduction in the risk for major cardiovascular events, compared with patients in the standard treatment arm who achieved a mean LDL-cholesterol of 101 mg/dl. This trial, along with other studies that have been designed with the aim of patients achieving low LDL-cholesterol levels, such as the secondary prevention Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and the primary prevention Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), provide incontrovertible evidence that 'lower is better'.[27,28] In addition, having a clear lipid target can help motivate patients to make lifestyle changes, such as exercising more and improving their diet, and it can also enhance medication adherence.

As the ACC/AHA guidelines acknowledge, some patients require a greater degree of LDL-cholesterol reduction than can be achieved with statin therapy alone. Those with severe primary hypercholesterolemia or FH in particular often require add-on therapy to statins to maintain adequate lipid control. In addition, despite the efficacy of high-dose statin therapy, residual risk remains unacceptably high among the general population, especially with the staggering rise in rates of obesity, metabolic syndrome and diabetes. Atherogenic dyslipidemia, defined as an imbalance between proatherogenic apoB-containing lipoproteins and antiatherogenic apoA-I lipoproteins, is a major contributor to this residual risk, particularly in individuals with insulin resistance.[29] Therapies that further reduce LDL-cholesterol and that raise triglycerides and HDL-cholesterol may confer additional benefit beyond the effects of statin therapy, even though their body of evidence is not as robust as for statins. Nonstatin treatments may also be required for patients who are intolerant of statin therapy due to muscular or other side effects.

#### Ezetimibe

One option for patients with statin intolerance or elevated LDL-cholesterol levels despite therapy is ezetimibe, which effectively reduces LDL-cholesterol levels as monotherapy and in combination with statins.[30,31] The Study of Heart and Renal Protection (SHARP) with simvastatin/ezetimibe was of particular interest since it was the first to show cardiovascular benefit with lipid-lowering therapy in high-risk patients with renal disease, although it was not designed to assess the relative contributions of ezetimibe and simvastatin.[32] Compared to placebo, treatment for 4.9 years reduced the risk of major atherosclerotic events by 17% in 9270 patients with advanced chronic kidney disease ($p = 0.0021$). However, high-profile imaging studies failed to show atherosclerotic improvement with ezetimibe, which led to doubts concerning the drug's efficacy in nonrenal patients.[33,34] The recent results of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which compared ezetimibe/simvastatin with simvastatin alone in patients with acute coronary syndromes, have helped establish the incremental benefit of treatment with ezetimibe on cardiovascular outcomes in secondary prevention. In this large-scale trial, the addition of ezetimibe to simvastatin reduced the risk of cardiovascular events by 6.4% over 7 years, compared to treatment with simvastatin alone ($p = 0.016$). Participants in the ezetimibe/simvastatin group achieved an average LDL-cholesterol levels of 53.2 mg/dl, while those in the simvastatin group reached a level of 69.9 mg/dl. These results support the 'lower is better' approach to lipid modification, and they confirm that ezetimibe can be a viable alternative or supplement to statin therapy.[35]

#### Mipomersen & Lomitapide for Homozygous Familial Hypercholesterolemia

Patients with homozygous FH represent a major unmet need in clinical lipidology since most require LDL apheresis and LDL-cholesterol levels remain extremely elevated even with adjunctive, aggressive statin therapy. The traditional estimate of FH prevalence has been 1 in 1 million, but a recent analysis from The Netherlands suggests that its frequency could be as great as 1 in 300,000.[36] In addition to having severe elevations in LDL-cholesterol, patients with FH experience greater reductions in coronary mortality compared with members of the general population when their cholesterol is reduced.[37] Two new orphan drugs for the treatment of homozygous FH,

mipomersen and lomitapide, take novel approaches to LDL-cholesterol reduction () and are an important new treatment option for this population. Mipomersen, an antisense oligonucleotide, is the first agent of its kind to target apoB. By blocking the synthesis of apoB-100, a primary component of all pro-atherogenic lipoproteins, it decreases the production of VLDL particles in the liver, which then results in reduced levels of LDL-cholesterol in the plasma.[38]

**Table 1. Comparison of lomitapide and mipomersen for homozygous familial hypercholesterolemia.**

| Criteria | Lomitapide | Mipomersen |
|---|---|---|
| Administration | Oral; daily | Weekly; subcutaneous injection |
| Dosage | Initial 5 mg per day titrated to 60 mg per day | 200 mg per week |
| Reduction in LDL-cholesterol | 50% after 26 weeks in 23 patients on aggressive lipid-lowering therapy, including LDL apheresis; 38% after additional 52 weeks with six patients discontinuing LDL apheresis | 25% after 26 weeks in 51 patients on maximal lipid-lowering therapy without LDL apheresis |
| Site of action | Liver and intestines | Liver |
| Adverse effects | Gastrointestinal in 93% of patients | Injection site reactions in 84% of patients; flu-like symptoms in 30% of patients |
| Contraindications | Pregnancy, CYP3A4 inhibitors, hepatic impairment or active liver disease | Hepatic impairment or active liver disease |
| Access | Restricted to Juxtapid® (Aegerion Pharmaceuticals, Inc., MA, USA) REMS program owing to risk of hepatotoxicity | Restricted to Kynamro® (Genzyme Corporation, MA, USA) REMS program owing to risk of hepatotoxicity |

CYP3A4: Cytochrome P450 3A4; FH: Familial hypercholesterolemia; REMS: Risk evaluation and mitigation strategy.

Mipomersen is administered by a weekly subcutaneous injection at doses of 200 mg per week. In a Phase III trial with 51 homozygous FH patients already on maximal lipid-lowering therapy without LDL apheresis, it has been shown to reduce LDL-cholesterol by 24.7% from a baseline mean of 441 mg/dl, compared with placebo ($p = 0.0003$).[39] It has also been evaluated in three additional Phase III trials: in patients with heterozygous FH and coronary artery disease on maximal lipid-lowering therapy, those with severe hypercholesterolemia while receiving maximal therapy and patients with statin intolerance.[40–42] Significant reductions in LDL-cholesterol of up to 37% while on statin therapy, apoB, total cholesterol, non-HDL-cholesterol, lipoprotein(a), triglycerides and VLDL-cholesterol were observed in all three trials with mipomersen compared with placebo.

In the four Phase III trials, common adverse events in patients treated with mipomersen included injection site reactions (84.3%), primarily mild erythema and abnormal hepatic transaminases (16%) that resolved following treatment discontinuation.[42,43] Flu-like symptoms may also occur, but typically resolve within a couple of days. No cases of severe hepatotoxicity occurred, although mipomersen caused a median 9.6% increase in hepatic fat fraction in two of the trials. After 24 weeks following mipomersen cessation, measures of hepatic fat fraction returned to baseline, but it is uncertain what the long-term effect of hepatic steatosis with mipomersen might be. Use of mipomersen is limited to homozygous FH patients, and only healthcare providers and pharmacies that have been certified regarding the drug's potential to cause hepatotoxicity may prescribe or carry it. Given the very high risk for premature atherosclerotic disease in patients with homozygous FH, mipomersen should be considered as an adjunct to LDL apheresis in this population.

Lomitapide is the first microsomal triglyceride transfer protein inhibitor, also approved as an orphan drug for the treatment of homozygous FH. An oral agent, it inhibits microsomal triglyceride transfer protein, which plays a key role in the assembly of VLDL in the liver and of chylomicrons in the intestines. Its actions result in a decrease in all apoB-containing lipoproteins, including LDL-cholesterol. Individuals with abetalipoproteinemia, which is characterized in part by the absence of all apoB-containing lipoproteins, carry mutations in the gene for microsomal triglyceride transfer protein. In a Phase III trial, 29 homozygous FH patients on aggressive lipid-lowering therapy and a low-fat diet received increasing doses of lomitapide up to a maximum of 60 mg/day.[44] During this initial 26-week efficacy phase, six patients withdrew. Remaining participants received a median 40 mg/day dose of lomitapide, and mean LDL-cholesterol decreased by 50% from a baseline of 336 mg/dl ($p < 0.0001$). A total of 23 patients continued lomitapide for a 52-week safety phase of the study, and six permanently stopped or decreased the frequency of LDL apheresis during that time. At the end of the study, LDL-cholesterol levels were significantly reduced by 38% from baseline ($p < 0.0001$). HDL-cholesterol was significantly reduced at 26 weeks but returned to baseline at week 78. Mild-to-moderate adverse events, primarily gastrointestinal, were reported by nearly all patients. Gastrointestinal side effects can be managed by adhering to a low-fat diet (<20%). Ten patients experienced clinically relevant elevations in hepatic enzymes that resolved following dose modification, and levels of mean hepatic fat increased from 1.0 to 8.6% between weeks 0 and 26. As with mipomersen, only homozygous FH patients have access to lomitapide, and prescribing healthcare providers and pharmacies must be certified regarding its potentially harmful effects on the liver. As with mipomersen, the risk-to-benefit profile with lomitapide is favorable for patients with homozygous FH, who generally require multiple approaches, including LDL apheresis, in order to achieve significant reductions in LDL-cholesterol. While LDL apheresis remains the first line of treatment for homozygous FH, clinical trial experience with lomitapide indicates that some patients may be able to reduce the frequency of or discontinue apheresis treatment while still maintaining adequate control of LDL-cholesterol.[45]

#### PCSK9 Inhibitors

An important new target for therapy is proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that regulates the removal of LDL receptors from cell surfaces. Gain-of-function mutations in the gene encoding PCSK9 decrease the number of LDL receptors, resulting in a phenotype similar to FH. Loss-of-function mutations increase the number of LDL receptors, resulting in lifelong hypocholesterolemia.[46] In the Dallas Heart Study, African–American participants with loss-of-function PCSK9 mutations that were associated with a 28% reduction in mean LDL-cholesterol had an 88% reduction in the risk for CHD.[47] Caucasians with similar PCSK9 mutations that were associated with a mean reduction in LDL-cholesterol levels of 15% had a 47% decrease in risk for CHD. Such findings have fueled intense research into the pharmacological inhibition of PCSK9. Numerous approaches to inhibiting PCSK9 expression, including by antisense oligonucleotides, small interference RNAs, antibodies and other small molecules, are now in development.[48]

Currently, the monoclonal antibody approach, administered through subcutaneous injections, appears the most promising. Published Phase II data with two monoclonal antibodies, evolocumab (AMG145) and alirocumab, (REGN727/SAR236553), show broadly similar effects.[49–51] In short-term studies, both agents showed reductions in LDL-cholesterol between 35 and 65%, plus moderate reductions in lipoprotein(a), when administered as monotherapy or in conjunction with statins or ezetimibe in patients with elevated LDL-cholesterol levels. For example, 12 weeks of treatment with evolocumab monotherapy reduced LDL-cholesterol by 51% in 406 patients with baseline levels between 100 and 190 mg/dl.[50] Results of this study also suggested that monthly dosing with evolocumab might be clinically equivalent to biweekly injections. Another 12-week study in patients with hypercholesterolemia already on a statin and/or ezetimibe found a maximal 66% reduction in LDL-cholesterol with evolocumab.[51] One 8-week study in 92 patients with hypercholesterolemia receiving atorvastatin at 10 mg/day showed a 66% reduction in LDL-cholesterol with alirocumab, compared with a 17% reduction after increasing the statin dose to 80 mg/day.[49] In these small-scale studies, both evolocumab and alirocumab exhibited no significant signs of toxicity. They are undergoing further evaluation in large-scale Phase III clinical development programs in multiple patient populations, including those with primary hypercholesterolemia, statin intolerance and FH.

## Raising HDL-cholesterol & Lowering Triglycerides

Although the epidemiological Framingham Heart Study established an association between higher HDL-cholesterol levels and decreased cardiovascular risk, recent clinical trials with niacin, fibrates and experimental cholesteryl ester transfer protein (CETP) inhibitors have called into question the hypothesis that pharmacological elevation of HDL-cholesterol is always cardioprotective. In addition, a Mendelian randomization study found that genetically elevated levels of HDL-cholesterol are not associated with decreased risk for myocardial infarction, raising the possibility that the relationship between HDL-cholesterol and cardiovascular risk may be more complicated than previously thought.[52] One explanation is that the functionality of HDL particles may have a bigger impact on risk than plasma levels alone.[53,54]

Recent epidemiological and genetic studies are also driving increasing interest in triglycerides as a marker or target for cardiovascular risk.[55] In observational studies, elevated triglycerides have been associated with increased risk for CHD, although they often occur along with low HDL-cholesterol, obesity and other metabolic syndrome components.[56,57] It can thus be difficult to tease out the independent contribution of elevated triglycerides. While existing drugs that raise HDL-cholesterol and/or lower triglycerides remain important therapeutic options, careful patient selection is crucial in determining who is most likely to be helped by treatment with these nonstatin agents. Trials with a variety of experimental drugs will provide additional valuable evidence on whether specifically targeting these lipid fractions reduces the risk of atherosclerotic cardiovascular disease.

### Existing Therapies

The primary effects of niacin and the fibrates are to reduce triglycerides and increase HDL-cholesterol. With the exception of the fibrate gemfibrozil, they may be used in combination with statins in patients with mixed dyslipidemia. Classic trials such as the Coronary Drug Project with niacin and the Helsinki Heart Study and the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) with the fibrate gemfibrozil have demonstrated clinical event reduction with both agents.[58–60] Another option for the treatment of severe hypertriglyceridemia is prescription-strength omega-3 fatty acids. Niacin has traditionally been the primary drug for hypertriglyceridemia since the fibrates and fish oils can often increase LDL-cholesterol levels in patients with high triglycerides, but its use is limited by the common side effect of flushing. One fish oil formulation in development, which contains eicosapentaenoic acid ethyl ester with no docosahexaenoic acid, has been shown to reduce triglycerides without adversely affecting LDL-cholesterol levels in two Phase III studies.[61,62]

Two clinical trials have generated doubts regarding the safety and efficacy of niacin. Both the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trials found no benefit with niacin in patients optimally treated with other lipid-lowering therapies to low LDL-cholesterol levels.[63,64] Although AIM-HIGH may have been underpowered, HPS2-THRIVE was a well-designed trial that enrolled more than 25,000 patients with a history of atherosclerotic cardiovascular disease. Prior to randomization, participants were treated with simvastatin and/or ezetimibe to a mean LDL-cholesterol level of 63 mg/dl and a mean HDL-cholesterol of 44 mg/dl.[64] They were then randomized to placebo or to treatment with niacin and laropiprant, a drug approved in Europe to inhibit flushing.

After a median of 3.9 years, HDL-cholesterol increased by 6 mg/dl and LDL-cholesterol decreased by 10 mg/dl in the active treatment arm. There was no effect on the primary end point of major vascular events (13.2% vs 13.7%; rate ratio, 0.96; 95% confidence interval, 0.90 to 1.03; p = 0.29). Niacin/laropiprant was also associated with a 55% proportional increase in serious disturbances in diabetes control and a 32% proportional increase in new-onset diabetes compared with placebo. Serious adverse events including infection and bleeding were also reported for the first time with the niacin/laropiprant combination, although it is unclear which drug contributed to the significant excesses of these reactions. Participants from China, who constituted 43% of the study participants, experienced higher rates of myopathy and of major vascular events in both the active treatment and placebo study groups, lesser degrees of alterations in lipids with niacin/laropiprant and no effect on the primary end point, compared with

participants from Europe. It is possible that Chinese patients may react differently to treatment with niacin, which complicates interpretation of the safety and efficacy findings of this trial. Still, what AIM-HIGH and HPS2-THRIVE indicate is that individuals already treated to low LDL-cholesterol levels did not benefit from the addition of niacin to incrementally raise HDL-cholesterol levels. However, niacin remains one of the most effective HDL-raising agents and has considerable utility in lowering triglycerides. Its use is appropriate in high-risk patients with abnormal levels of these lipid fractions.

Fenofibrate has also fared poorly in recent large-scale trials. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, conducted in patients with Type 2 diabetes, both failed to reach their primary end points.[65,66] In FIELD, many patients began taking statins during the course of the study, and in ACCORD, all participants were receiving statins. Arguably, the statins have set a high bar for efficacy, and it can be difficult to show cardiovascular benefit with other agents, such as the fibrates or niacin, when used in combination. Nevertheless, *post hoc* analyses of the FIELD and ACCORD trials suggested possible cardiovascular benefit in diabetic individuals with high triglycerides and low HDL-cholesterol.[66,67] These findings indicate that treatment with fenofibrate may best be reserved for high-risk individuals with diabetes who also have mixed dyslipidemia.

**New Approaches**

A variety of investigational approaches seek to raise HDL-cholesterol by increasing the activity of apoA-I, the major protein component of HDL. These include infusions of recombinant HDL[68,69] or apoA-I Milano,[70] mimetic peptides[71,72] and oral small molecules.[73,74] Inhibition of apoC-III, a protein that slows the clearance of triglycerides from the blood, is one exciting strategy under investigation for lowering triglycerides and cardiovascular risk.[75] This approach is supported by findings indicating that rare mutations that disrupt the function of the gene coding for apoC-III are associated with lower levels of triglycerides and reduced risk for CHD.[76]

CETP inhibitors have reached the furthest stage of clinical development among agents designed to raise HDL-cholesterol and show the most promise at the moment. These drugs target CETP, a protein secreted by the liver that facilitates the transfer of cholesteryl ester from HDL to the apoB-containing lipoproteins, which are subsequently cleared through hepatic LDL receptors.[77] Four CETP inhibitors have reached Phase III clinical trials, but the development of two of them, torcetrapib and dalcetrapib, was terminated due to negative study results. Torcetrapib had an off-target effect that raised systolic blood pressure, resulting in an increase in cardiovascular events and all-cause mortality.[78] Dalcetrapib did not negatively affect blood pressure, but its Phase III cardiovascular outcomes study was terminated early due to futility.[79]

Current hopes for CETP inhibitors center on anacetrapib and evacetrapib, which both raise HDL-cholesterol and lower LDL-cholesterol. Both agents are being evaluated in large-scale cardiovascular outcomes trials following the successful completion of smaller studies. The primary purpose of the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) trial was to confirm the safety of treatment with anacetrapib in 1623 statin-treated patients with or at high risk for CHD, and results in this regard were strongly favorable.[80] DEFINE demonstrated a 138% increase in HDL-cholesterol and a 40% decrease in LDL-cholesterol with anacetrapib compared with placebo ($p < 0.001$ for both), and no significant adverse events were reported. Residual effects on lipids and residual plasma levels of anacetrapib were observed twelve weeks and up to 4 years following cessation of treatment with anacetrapib, although the clinical significance of these findings have yet to be determined.[81,82]

Evacetrapib was evaluated as monotherapy and in combination with statins in a 12-week study conducted in patients with dyslipidemia.[83] HDL-cholesterol levels increased by 79–89% and LDL-cholesterol levels decreased by 11–14% with evacetrapib in patients taking statins. At a maximal dose of 500 mg/d, evacetrapib monotherapy increased HDL-cholesterol by 129% and decreased LDL-cholesterol by 36%. No significant adverse effects were reported, although the study was underpowered to rule them out. The Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) and A Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE) are ongoing and will provide important information on the clinical efficacy of CETP inhibitors in

addressing residual risk in statin-treated patients.

## Inflammation

Another promising area of investigation centers on the inflammatory reaction that occurs within the atherosclerotic plaque.[84] The process begins when circulating LDL particles penetrate the arterial wall. A variety of lipases, including lipoprotein lipase, hepatic lipase, secretory phospholipase $A_2$ and lipoprotein-associated phospholipase $A_2$, attack the LDL and expose positively charged amino acid residues on them. These amino acids then bind to negatively charged regions on proteoglycans within the arterial wall and are retained by them.[85] Retained LDL particles are attacked by additional lipases, resulting in oxidation or chemical modification. Oxidized or modified LDL triggers an inflammatory cascade characterized by an accumulation of macrophages and activated T-lymphocytes and the production of cytokines. The release of cytokines then leads to an increase in adhesion molecules that promote the entry of monocytes into the arterial wall. In a series of steps, monocytes eventually become lipid-filled foam cells, narrowing the arterial lumen and signaling the progression of atherosclerotic disease.

C-reactive protein (CRP) is a marker of the inflammatory response in atherosclerosis and a risk factor for cardiovascular disease, as confirmed by results from the JUPITER trial. This landmark study enrolled participants with a median baseline LDL-cholesterol level of 108 mg/dl and a median CRP level of 4.3 mg/l.[28] Subjects were randomized to rosuvastatin 20 mg or placebo, and the study was stopped early after 1.9 years due to clear evidence of benefit with rosuvastatin. Median LDL-cholesterol levels were reduced by 50% to 55 mg/dl, and CRP decreased by 37% with rosuvastatin. The primary composite end point of myocardial infarction, stroke, unstable angina, cardiovascular death and revascularization was reduced by 44%, and all-cause mortality was decreased by 20% with active treatment compared with placebo. Based on these very strong results, rosuvastatin was the first statin to receive an indication on the basis of CRP. The agent may now be used in primary prevention for middle-aged individuals with CRP levels of at least 2 mg/l and at least one additional cardiovascular risk factor.

Although JUPITER established the benefits of simultaneous reductions in LDL-cholesterol and CRP, it remains unclear whether targeting inflammation alone independently reduces cardiovascular event rates. Two novel anti-inflammatory approaches, inhibition of secretory phospholipase $A_2$ and of lipoprotein-associated phospholipase $A_2$, have not proven successful in Phase III clinical trials.[86,87] Other agents being tested in ongoing large-scale studies will provide further data on the viability of anti-inflammatory strategies for cardiovascular risk reduction. The Cholesterol Inflammation Reduction Trial is evaluating low-dose methotrexate in postmyocardial infarction patients with either diabetes or metabolic syndrome, while the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study is assessing an inhibitor of the cytokine interleukin-1β in patients with stable coronary disease.[88]

## Conclusion

With all of these exciting developments in the field of clinical lipidology, it is essential to keep in mind what we can accomplish with lifestyle changes, including a healthy diet, regular exercise and smoking cessation. In a recent clinical trial. consumption of a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events by an impressive 30% over 4.8 years, compared with a low-fat diet.[7] In addition, a Mendelian randomization analysis found that lifelong low LDL-cholesterol would have a threefold greater benefit per 39 mg/dl (1 mmol/l) decrease in LDL-cholesterol than statin treatment started later in life.[89] Both studies highlight the importance of early lifestyle interventions to improve risk factors and prevent the development of atherosclerotic cardiovascular disease well before it occurs. Although we have a robust array of pharmacological agents to help correct lipid abnormalities, as well as many more in development, our primary strategy should be to improve diet, physical activity and smoking habits within the population.

## Future Perspective

Due to their well established safety and efficacy, statins will remain the primary lipid-lowering therapy for individuals

at increased cardiovascular risk. Guidelines regarding their optimal use and the role of non-statin alternatives will continue to evolve as additional data accumulate. Ongoing clinical trials will help clarify the therapeutic viability of new and approved agents designed to further decrease LDL-cholesterol, increase HDL-cholesterol, lower triglycerides, or reduce inflammation beyond the effects of statin therapy.

## Sidebar

**Executive Summary**

**Background**

- Statins have had an enormous impact on the public health over the past 25 years due to their demonstrated efficacy and safety.
- There is still a pressing need for alternative lipid-modifying therapies, particularly for patients with familial hypercholesterolemia, mixed dyslipidemia or statin intolerance.

**Statins in historical perspective**

- A series of discoveries led to the confirmation of the lipid hypothesis and underscored the central role played by LDL-cholesterol in the pathogenesis of atherosclerotic disease.
- Clinical trials with statins support the view that 'lower is better' with regards to LDL-cholesterol.

**Further reductions in LDL-cholesterol**

- Although the American College of Cardiology/American Heart Association guidelines take a different approach, 'lower is better' remains an important principle of cholesterol management.
- The results of the IMPROVE-IT trial have confirmed that ezetimibe confers modest benefit when added to statin therapy in secondary prevention and lend further support to the 'lower is better' hypothesis.
- Two new orphan drugs for the treatment of homozygous familial hypercholesterolemia, mipomersen and lomitapide, provide additional lipid control for this subgroup of patients at very high cardiovascular risk.
- PCSK9 inhibition is a promising area under investigation for achieving further reductions in LDL-cholesterol among a wider patient population.

**Raising HDL-cholesterol & lowering triglycerides**

- Recent studies have stimulated renewed examination of the independent contributions made by HDL-cholesterol and triglycerides in the development of atherosclerotic cardiovascular disease.
- Careful patient selection is crucial in determining who is most likely to be helped by treatment with niacin, fibrates and prescription-strength omega-3 fatty acids.
- Cardiovascular outcomes trials with experimental cholesteryl ester transfer protein inhibitors will provide crucial data on the viability of pharmacological strategies to raise HDL-cholesterol.

**Inflammation**

- C-reactive protein is a marker and risk factor for atherosclerotic cardiovascular disease, but validation of anti-inflammatory strategies to reduce cardiovascular risk await the results of trials with agents that do not also lower LDL-cholesterol.

**Conclusion & future perspective**

- As a complement to the statins, there are a variety of pharmacological agents to help correct lipid abnormalities, as well as many more in development that may help reduce residual cardiovascular risk.
- The importance of early lifestyle interventions to improve diet, increase physical activity and promote nonsmoking cannot be overstated when optimizing strategies for cardiovascular risk reduction.

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** Shows importance of early lifestyle interventions in cardiovascular risk reduction.

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