Current Concepts in Management of Lipid Abnormalities in Patients With Coronary Artery Disease

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Abstract
Lipid disorders play a major pathogenic role in the development of coronary artery disease, which is the major cause of mortality worldwide. In this review, the authors discuss the role of various lipid abnormalities in the causation of coronary artery disease and also highlight the ways to manage them. The roles of a healthy lifestyle and dietary patterns have been emphasized in this regard besides the significant role of drug treatment, which mostly revolves around the statin therapy.

Keywords
Dyslipidemia, statins, coronary artery disease, current concepts

Introduction
Among cardiovascular diseases, coronary artery disease (CAD) remains the leading cause of mortality worldwide.¹ An individual is born with a low-density lipoprotein-cholesterol (LDL-C) level of 30 mg/dL, which increases as the age advances.² There exists a linear relationship between the cholesterol levels and the risk of CAD, with no apparent cut-off level below which the risk declines.² Epidemiologic studies have shown an increased risk of nonfatal myocardial infarction (MI) and death with elevated LDL-C and total cholesterol (TC) levels.³ Enough data suggest that cholesterol-lowering interventions are also likely to have an impact on CAD risk reduction.³ The fact that increased cholesterol levels have a significant pathogenic role in CAD development has made lipid-lowering therapy the most important facet of medical management of this condition.

Evidence for a Causal Relationship Between Elevated Lipid Levels and CAD
The primary role of plasma lipoproteins is to transport lipids to various tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation.⁴ Lipoproteins consist of esterified and unesterified cholesterol, triglycerides, and phospholipids, and protein components named apolipoproteins that act as structural components, ligands for cellular receptors binding, and enzyme activators or inhibitors. There are 6 major lipoproteins in the blood: chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, Lp(a), and high-density lipoprotein (HDL).⁵ Except for HDL, all other lipoproteins have ApoB moieties, which are atherogenic. All ApoB-containing lipoproteins <70 nm in diameter [VLDL, IDL, LDL, Lp(a)], and smaller triglyceride-rich (TG-rich) chylomicrons and their remnant particles, can cross the endothelial barrier, especially in the presence of endothelial dysfunction, where they can become trapped and initiate the formation of lipid-rich atheromatous plaque.² The further growth of this atheromatous plaque depends on the duration and degree of exposure to these ApoB-containing lipoproteins in a patient’s lifetime, besides the other nonlipid factors.⁴

Serum LDL-C level provides an estimate of the cholesterol mass carried by the circulating LDL particles. The latter are the most numerous ApoB-containing lipoproteins circulating in the human body.³ Various randomized controlled trials, and epidemiological studies, have demonstrated a linear causal relationship between the plasma LDL-C and atherosclerotic cardiovascular disease (ASCVD).³ This relationship is causal

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as well as cumulative and depends both on the duration of persistent increase in LDL-C and the absolute magnitude of its increase. There is enough evidence that clinical benefit is derived by therapies that lower LDL-C either by an absolute reduction in circulating LDL particles’ mass or by modification in the composition of LDL-C. The benefit in both scenarios occurs because of the absolute reduction in the ApoB levels.

As with LDL-C, a direct causal relationship has been noted between non-HDL-C (non-HDL-cholesterol) and the risk of CAD. Since the non-HDL-C comprises all atherogenic lipoproteins, and not just LDL, the former is proportionally about one-third more strongly associated with CAD compared to LDL-C for each standard deviation. Importantly, no difference has been demonstrated between the fasting and nonfasting levels of non-HDL-C with regard to risk estimation of CAD, implicating that the lipid measurements can be simplified by using non-HDL-C (the difference between TC and HDL-C) and HDL-C levels.

It is a matter of debate whether TGs are causative factors of CAD; however, conflicting data suggest that they are instead the markers of risk rather than the cause, and that risk is secondary to the concomitant low levels of HDL-C, and high levels of non-HDL-C (the latter is an estimate of the total concentration of all ApoB-containing lipoproteins). TG-rich VLDL particles and their remnants carry most of the circulating TGs. Therefore, the plasma TG concentration reflects the concentration of circulating ApoB-containing TG-rich lipoproteins. Mendelian randomization studies have suggested a causal association between plasma TGs and the risk of ASCVD; however, these studies must be interpreted with caution because nearly all the variants associated with TGs are also associated with HDL-C, LDL-C, or Lp(a). The Mendelian studies strongly suggest that the causal effect of TG-rich lipoproteins and their remnants on the risk of ASCVD is determined by the circulating concentration of ApoB-containing particles, rather than by the TG content itself. Therefore, until further data becomes available, the targets of treatment among individuals with elevated TG levels should be low HDL-C and high non-HDL-C rather than TGs. Furthermore, in the randomized trials, medications that reduce triglyceride levels, such as extended-release niacin and fibrates, have not reduced the rates of cardiovascular events when administered in addition to appropriate medical therapy, including statins. Before the results of the REDUCE-IT trial, previous trials and meta-analyses of n = 3 fatty acid products did not show a benefit in patients receiving statin therapy. REDUCE-IT trial demonstrated that among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl (IPE) twice daily than among those who received placebo. It is not known whether the lack of benefit from n = 3 fatty acids in previous trials may be attributable to the low dose or the low ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA). Both the formulation (a highly purified and stable EPA ethyl ester) and dose (total daily dose of 4 g) used in REDUCE-IT were different from those in previous outcome trials of n = 3 fatty acids. However, the exact mechanism of benefit with IPE remains unclear, and whether the observed benefit was because of its triglyceride-lowering effect or because of its anti-inflammatory, antithrombotic, or membrane-stabilizing effects remains a matter of speculation.

HDL-C has been shown to be inversely associated with the risk of CAD, and this association persists above 70 mg/dL, albeit with some attenuation. However, whether therapeutically increasing the levels of plasma HDL-C leads to any reduction in ASCVD risk, has not been conclusively demonstrated in any of the randomized trials (namely, AIM-HIGH, dal-OUTCOMES trial, ACCELERATE trial, and REVEAL trial). In the majority of these trials showing a lack of benefit, patients were already on statin therapy with optimal LDL-C goals. The results further supported the notion that increasing HDL-C on its own is unlikely to be of mechanistic relevance unless coupled with an alternative pathway such as lowering LDL cholesterol. Additionally, there has been increasing evidence that the quality and not the quantity of HDL is important. HDL particles promote not only reverse cholesterol transport from the periphery (mainly macrophages) to the liver but also exert pleiotropic effects on inflammation, hemostasis, and apoptosis. However, there is evidence that certain forms of “dysfunctional HDL” exist that might promote inflammation and might also persist during statin therapy and despite high HDL-C levels. Whether therapies that alter the function of HDL particles will reduce the risk of ASCVD is unknown.

Lipoprotein(a) is a LDL particle containing an Apo(a) moiety, which is covalently bound to the ApoB component. Lp(a) can easily flux across the endothelial barrier because of an extremely small diameter size (<70 nm). Elevated levels of Lp(a) augment the ASCVD risk via 2 major mechanisms: first, through a prothrombotic/antifibrinolytic effect because of the structural homology of Lp(a) with plasminogen and plasmin, and secondly, through accelerated atherogenesis resulting from the free influx and intimal deposition of Lp(a) cholesterol. Enough data are suggesting a causal relationship between elevated Lp(a) levels and ASCVD; however, recent studies suggest that clinically significant reduction in the ASCVD can only be obtained by a large absolute reduction in the levels of Lp(a). This explains why earlier randomized controlled trials that evaluated therapies lowering Lp(a) by 20% to 30% (namely, niacin and CETP inhibitors) failed to demonstrate any significant reduction in the risk of adverse cardiovascular events.

### Laboratory Measurements of Lipids and Lipoproteins

The levels of plasma lipoproteins are usually derived from their cholesterol contents, instead of measuring them directly.
TC denotes 3 major classes of lipoproteins: LDL, HDL, and VLDL. Two minor lipoproteins, IDL and Lp(a), also contain smaller amounts of cholesterol. Generally, while measuring the lipid profile of a patient, the serum concentrations of TC, TG, and HDL-C are measured. Although the LDL-C can also be measured directly using enzymatic assays, it is usually indirectly derived using the Friedewald formula, as follows: LDL-C = TC – HDL-C – (TG/5) in mg/dL. For the general population, there exists a strong correlation between the derived and the direct LDL-C. However, such calculated LDL-C has certain limitations: methodological errors and inability to use in patients with TG levels >400 mg/dL, especially in the nonfasting state. An important limitation of the Friedewald formula is the assumption of a fixed ratio of triglyceride levels to VLDL cholesterol (TG: VLDL-C) of 5:1. In clinical practice, this ratio is likely to vary and may result in inaccuracies in the estimation of LDL-C, especially at high triglyceride and/or low LDL-C values. Because of this reason, many health care systems have started to endorse an alternative LDL-C estimation method (the Martin–Hopkins equation) in patients with LDL-C values below 70 mg/dL and triglycerides above 150 mg/dL. Martin–Hopkins equation replaces the fixed ratio of 5 for VLDL-C estimation by using one of 180 adaptable ratios based on a patient’s individual non-HDL-C and TG values. The ratios range from 3.1 to 11.9 and are personalized to the specific lipid panel. Martin–Hopkins equation provides distinct improvements in accuracy as compared to Friedewald estimates and has an added advantage in the nonfasting setting. In the postprandial state, triglyceride levels may be increased, but the Martin–Hopkins equation can adapt by adjusting the estimated VLDL-C ratio. However, the accuracy of the equation also starts to decrease above a triglyceride level of 400 mg/dL.

The measurement of ApoB has shown superiority over the measurement of non-HDL-C and LDL-C. This is because the former is a reliable measure of the number of atherogenic particles circulating in plasma (TG-rich remnant particles, LDL, and VLDL, all contain a single ApoB molecule). The available tests measuring ApoB levels are highly accurate, standardized, inexpensive, and automated, and can be done irrespective of fasting status.

It is usually recommended to obtain fasting samples for lipid analyses. However, the difference which was noted as a result of fasting versus nonfasting status was small for most of the lipid parameters. For example, the level of TG increases by 27 mg/dL on average in the nonfasting state, which is unlikely to be of clinical significance for most of the individuals. Additionally, fasting versus nonfasting status carries no prognostic value for general risk screening as well. Nonetheless, in patients with diabetes mellitus, hypertriglyceridemia, and metabolic syndrome, LDL-C calculation from nonfasting parameters should be interpreted cautiously.

### Treatment Targets

Lipid management in CAD patients primarily targets a reduction in the LDL-C levels intending to bring down CV events. Therefore, for patients with CAD or any form of ASCVD, it is recommended to achieve a ≥50% reduction in the level of LDL-C from the baseline and a LDL-C level of <55 mg/dL (class 1 A recommendation, ESC Guidelines 2019). The target LDL-C goal (<40 mg/dL) is much more stringent for the patients experiencing a repeat cardiovascular event within the first 2 years of the previous event (regardless of the type of event) while taking the maximally tolerated and recommended lipid-lowering therapy (class 2b B).

### Lifestyle Interventions

The importance of a healthy diet and lifestyle for both primary and secondary prevention of CAD cannot be underestimated. Patients should follow a dietary pattern that emphasizes the intake of fruits, vegetables, legumes, whole grains, sources of healthy protein (low-fat poultry and dairy products, nuts, and fish/seafood), and non-tropical vegetable oils. Patients should limit the intake of sugar-sweetened beverages, sweets, and red meat. The intake of calories must be restricted to prevent weight gain and to ensure a loss of weight in overweight individuals. In general, it is advisable to engage in aerobic physical activity for at least 3 to 4 days/week, lasting for at least 30 min/day.

### Drug Therapy

In addition to the healthy dietary pattern and healthy lifestyle interventions, drug treatment with statins forms the backbone of lipid-lowering treatment. Other drugs that lower the LDL-C include bile acid sequestrants, ezetimibe, proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors, inclisiran, and bempedoic acid (see Table 1). Drugs lowering triglycerides namely fibrates and niacin also cause a mild reduction in LDL-C; however, randomized trials did not provide enough evidence to support their use to lower LDL-C, in addition to statin treatment. High-intensity statins (Table 2) are usually recommended for secondary prevention of CAD with a target to achieve a reduction of 50% or more in LDL-C levels. However, if the patient cannot tolerate, it is recommended to switch to moderate-intensity statin treatment. If the levels remain 70 mg/dL or more on maximally tolerated and recommended statin therapy, it is prudent to add ezetimibe to lower the LDL-C levels further. If the level of LDL-C remains 70 mg/dL or more on statin + ezetimibe therapy, especially in high-risk CAD patients (namely patients with ACS in the preceding 1 year, history of recurrent atherosclerotic events
like MI, ischemic stroke, etc.), it is recommended to add PCSK9 inhibitors following a clinician–patient discussion about the net benefit, safety, and cost.\(^1\) In elderly CAD patients, more than 75 years of age, moderate- to high-intensity statin therapy may be initiated.\(^1,2\) However, before initiating statins in elderly patients, their potential benefits must be weighed against the associated adverse effects, and accordingly, the doses should be adjusted.\(^2\)

**Table 1. Commonly Used LDL-Cholesterol Lowering Drugs**

| LDL-Lowering Drug Class                  | Mechanism of Action                                                                 | Drugs         | Daily Dose (mg/d) | Dosing Frequency | Salient Features                                                                                           |
|-----------------------------------------|--------------------------------------------------------------------------------------|---------------|------------------|-----------------|-------------------------------------------------------------------------------------------------------------|
| Statins (HMG-CoA reductase inhibitors)  | • Inhibit the enzyme HMG-CoA reductase (rate-limiting step of endogenous cholesterol production) • Increase the number of LDL receptors | Atorvastatin  | 10-80            | OD              | • First-line therapy for nearly all patients • Potential LDL-C reduction is 18%-55% • Fluvastatin, lovastatin, pravastatin, and simvastatin have short half-lives. They should be administered in the evening to achieve maximum LDL-C reduction. • Atorvastatin, Fluvastatin, Pitavastatin, and Rosuvastatin can be administered anytime of the day. |
|                                         |                                                                                                                                 | Fluvastatin*  | 20-80            | OD-BD           |                                                                                                             |
|                                         |                                                                                                                                 | Lovastatin*   | 10-80            | OD/BD           |                                                                                                             |
|                                         |                                                                                                                                 | Pitavastatin  | 1-4              | OD              |                                                                                                             |
|                                         |                                                                                                                                 | Pravastatin*  | 10-80            | OD              |                                                                                                             |
|                                         |                                                                                                                                 | Rosuvastatin  | 5-40             | OD              |                                                                                                             |
|                                         |                                                                                                                                 | Simvastatin*  | 5-40             | OD              |                                                                                                             |
| Bile acid sequestrants                  | • Bind bile acids in the gut and interrupt their enterohepatic recirculation and reabsorption, • Decrease bile acid pooling in the liver • Increase conversion of cholesterol to bile acids • Increase the number of LDL receptors | Cholestyramine | 4000-24,000      | OD/BD           | • Nonsystemic add-ons to statin therapy, or used in patients with statin-associated side effects, including statin-associated muscle symptoms • Potential LDL-C reduction‡ is 15%-30% • Gastrointestinal side effects may limit use • May increase serum TG levels; avoid if TG >300 mg/dL • Can bind with other drugs and decrease their absorption |
|                                         |                                                                                                                                 | Colesevelam   | 3750             | OD/BD           |                                                                                                             |
|                                         |                                                                                                                                 | Colestipol    | 5000-30,000      | OD/QID          |                                                                                                             |
| Cholesterol absorption inhibitors       | • Block the cholesterol transport Nieman Pick C1-like 1 protein to inhibit intestinal and biliary cholesterol absorption; • Increase the number of LDL receptors | Ezetimibe     | 10               | OD              | • Evidence-based add-on to statin therapy in very high-risk patients or in patients with statin-associated side effects, including statin-associated muscle symptoms • Potential LDL-C reduction is 13% to 20% |
| PCSK9 inhibitors                        | • Fully human monoclonal antibodies that bind to PCSK9 and decrease degradation of the LDL receptor | Alirocumab    | 75-150           | 2 weekly        | • Evidence-based add-on to statin therapy in very high-risk patients • Potential LDL-C reduction‡ is 43%-64% • Lower LDL-C reduction in heterozygous FH when added to tolerated statin/ezetimibe therapy • Requires subcutaneous injection |
|                                         |                                                                                                                                 | Evolocumab    | 300              | 4 weekly        |                                                                                                             |

\(^1\) In elderly CAD patients, more than 75 years of age, moderate- to high-intensity statin therapy may be initiated.\(^1,2\) However, before initiating statins in elderly patients, their potential benefits must be weighed against the associated adverse effects, and accordingly, the doses should be adjusted.\(^2\)
### Table 2. High, Moderate, and Low Intensity Statin Therapy

| Statin | Low Intensity (LDL-C Reduction <30%) (mg) | Moderate Intensity (LDL-C Reduction 30% to <50%) (mg) | High Intensity (LDL-C Reduction ≥50%) (mg) |
|--------|-----------------------------------------|----------------------------------------------------|-------------------------------------|
| Atorvastatin | NA | 10-20 | 40-80 |
| Fluvastatin | 20-40 | 80 | NA |
| Lovastatin | 20 | 40 | NA |
| Pitavastatin | 1 | 2-4 | NA |
| Pravastatin | 10-20 | 40-80 | NA |
| Rosuvastatin | NA | 5-10 | 20-40 |
| Simvastatin | 10 | 20-40 | NA |

**Abbreviations.** LDL-C, low-density lipoprotein-cholesterol; NA, not applicable.

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**Early Trials, Statins for Secondary Prevention:**

The first 3 trials to demonstrate the safety and efficacy of lipid-lowering treatment in secondary prevention of CV events included (a) 4S trial, (b) CARE trial, and (c) LIPID trial. The 4S (Scandinavian simvastatin survival study) trial randomized 4444 patients with angina pectoris or previous MI and serum cholesterol levels of 215 to 312 mg/dL to a lipid-lowering diet or to treatment with 20 mg/day simvastatin. Over 5 years, simvastatin produced mean reductions in TC and LDL-C levels of 25% and 35%, respectively. Consequently, a 30% relative risk reduction was noted in the all-cause mortality \( P < 0.001 \). Furthermore, the CAD-related mortality was reduced by 42%, any major CAD-related event by 34%, and the need for coronary revascularization by 37%. The cholesterol and recurrent events (CARE) was a placebo-controlled trial, which also revealed similar findings, showing a significant decrease in the rates of major coronary events with pravastatin (40 mg), among patients with near-normal baseline cholesterol values. The LIPID (long-term intervention with pravastatin in ischemic disease) trial (N = 9014) replicated the results of 4S in providing mortality benefits with statin therapy, but that in a patient group with an overall lower total baseline cholesterol level (155 to 271 mg/dL). All the 3 trials established the safety and efficacy of statins for secondary prevention of CAD, and that too across a wide range of baseline cholesterol levels. Importantly, all these 3 trials had excluded patients with recent ACS (within the last 4-6 months before enrolment).

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**Lipid Management in Patients With Acute Coronary Syndrome:**

Myocardial ischemia reduction with acute cholesterol lowering (MIRACL) was the first trial to demonstrate the benefits of early initiation of statins after ACS. MIRACL was a placebo-controlled randomized trial involving 3086 patients who received 16 weeks of 80 mg/day of atorvastatin, starting 24 to 96 h after ACS. There was a significant reduction in the combined primary endpoint (recurrent symptomatic myocardial ischemia, resuscitated cardiac arrest, and nonfatal acute MI). However, certain limitations of the MIRACL trial were highlighted, which involved its short-term results, the lack of long-term safety data, and the absence of any comparator drug.

The next substantial trial involving the use of statins in ACS was PROVE-IT (the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis) in MI 22 trial that compared 2 active comparators. In PROVE IT-TI MI 22 trial, 4162 ACS patients (index ACS event within preceding 10 days) were randomized to either 40 mg/day of pravastatin (standard treatment) or 80 mg/day of atorvastatin (intensive treatment). Significantly lower values of the median LDL-C levels were achieved during treatment with the intensive treatment (62 mg/dL) compared to standard treatment (95 mg/dL) \( P < .001 \). Kaplan–Meier estimates of the rates of the primary endpoint (which was a composite of all-cause death, MI, unstable angina requiring rehospitalization, revascularization, and stroke) at 2 years were 26.3% for standard therapy and 22.4% for intensive therapy, reflecting a 16% reduction in the hazard ratio in favor of intensive therapy \( P < 0.01 \). The statin-associated muscle symptoms were overall low and similar in both the treatment groups.

Furthermore, a meta-analysis was published in 2006, involving 13 randomized controlled trials, and involving 17,963 ACS patients (involving both STEMI and NSTEMI/ unstable angina), demonstrating that early intensive statin therapy was beneficial for ACS patients. In this meta-analysis, the use of early statin therapy was associated with a decreased rate of mortality and CV events over 2 years of follow-up (hazard ratio, 0.81; 95% CI [0.77, 0.87]). Importantly, on survival curves analysis, this benefit started to emerge between 4 and 12 months and became statistically significant by 12 months.
The first trial to demonstrate the added clinical benefit of adding a nonstatin therapy to the background statin treatment was the improved reduction of outcomes: vytorin efficacy international trial (IMPROVE-IT). This trial involved 18,134 stable patients who had a history of ACS and whose LDL cholesterol levels were within the guideline-recommended limits. There was a significant reduction in the median time-weighted average LDL cholesterol level in the simvastatin–ezetimibe group (53.7 mg/dL), compared to the simvastatin–monotherapy group (69.5 mg/dL, P < .001). The Kaplan–Meier analysis showed a significant decline in the event rate for the primary endpoint at 7 years in the combination group (32.7%), compared to monotherapy group (34.7%) (absolute risk reduction 2%; hazard ratio, 0.936; 95% CI [0.89, 0.99]; P < .02). No significant difference was noted in the side effect profile (including muscle-related, gallbladder, hepatic adverse effects, and cancer). The clinical benefit of the addition of ezetimibe to statin therapy was augmented in patients with prior CABG (n = 1684 out of 18,134). The absolute risk reduction in the primary endpoint, as a result of ezetimibe addition, was higher in the prior CABG patients (8.8%; 95% CI [3.1,14.6]), compared to those without prior CABG (1.3%; 95% CI [0.2,6]) (P-interaction = 0.02).

Among patients with ACS, it is recommended to obtain a lipid profile as soon as possible after admission, because LDL-C levels tend to decrease during the first days of ACS. Patients do not have to be fasting, as this has little impact on the LDL-C levels. Current recommendations suggest routine and early use of high-intensity statin therapy in patients with ACS. An additional advantage of early high-intensity statin therapy in ACS patients undergoing early invasive treatment is protection from contrast-induced nephropathy. Importantly, the lipid-lowering therapy should be continued indefinitely, without reducing the dose in patients who are tolerating the treatment, regardless of how low the LDL-C falls. The treatment goal is to reach a 50% LDL-C reduction from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). In those with recurrent events within 2 years while taking maximally tolerated statin therapy, a goal of <1.0 mmol/L (<40 mg/dL) for LDL-C should be considered. Lipid levels should be re-evaluated 4 to 6 weeks after ACS to determine whether treatment goals have been achieved and to check for any safety issues; the therapeutic regimen can then be adapted accordingly. The use of lower intensity statin therapy should be considered in patients at increased risk of adverse effects with high-intensity statin therapy, such as in the elderly, patients diagnosed with hepatic or renal impairment, or in the case of a potential risk of drug–drug interactions with other essential concomitant therapies. Nonetheless, if the target goals are not achieved or if statin intolerance occurs, Ezetimibe and PCSK9 inhibitors can be considered sequentially. Importantly, PCSK9 inhibitor can be considered early after ACS (during hospitalization, if possible), in patients who present with an ACS and whose LDL-C levels are not at goal, despite already taking a maximally tolerated statin dose and ezetimibe.

**Lipid Management in Patients With Chronic Stable Angina**

The landmark results from PROVE IT trial laid the foundation for all major guidelines recommending a LDL-C goal of <70 mg/dL in high-risk patients. However, it was yet to be seen whether the safety and efficacy of long-term intensive statin treatment documented in ACS patients could be replicated in stable CAD patients as well. This question was addressed by treating to new targets (TNT) and the incremental decrease in endpoints through aggressive lipid lowering (IDEAL) trials. In the TNT trial, 10,001 CAD patients from 14 countries were enrolled. All these patients had baseline LDL levels < 130 mg/dL and were administered 10 mg/day or 80 mg/day of atorvastatin in a double-blind, parallel-group design. The median follow-up duration was 4.9 years. Mean LDL-C levels were reduced to 77 mg/dL in the 80 mg group compared to 101 mg/dL in the 10 mg group. The primary endpoint, a composite of cardiovascular mortality, MI, resuscitated cardiac arrest, and stroke, occurred in 10.9% of patients in the 10 mg and 8.7% of patients in the 80 mg group (P = .0002). The benefit with 80 mg atorvastatin was much more pronounced in patients with prior CABG, diabetes mellitus, metabolic syndrome, and chronic kidney disease. The risk of hospitalization for heart failure and stroke was also significantly lower in the 80 mg group. However, no significant intergroup difference was observed in the overall mortality. Besides a higher incidence of persistent liver transaminitis with 80 mg atorvastatin (P < .001), no other significant difference in the adverse events was recorded among the 2 groups.

The results of the IDEAL trial involving 8888 patients and >20,000 patient-years of follow-up, further established the safety and benefits of intensive statin therapy in stable CAD management. Based on all this evidence, guidelines endorsed by all major societies recommend high-intensity statins in all patients with established CAD, especially in those <75 years of age.

Statin therapy is usually well tolerated in the majority of patients (85%-90%). However, in 10% to 15% of patients, statin therapy may be associated with various statin-associated symptoms (SAS), including statin-associated muscle symptoms (SAMS), diabetes mellitus, derangement in liver function tests, and central nervous system complaints. It is crucial to recognize SAS because they may prompt dose reduction or discontinuation of statins, which may hurt the outcomes. SAMS is the most frequent SAS, and mild myalgia may affect 5% to 10% of statin users. They are usually bilateral, symmetrical, and frequently involve large muscle groups. Their disappearance best recognizes true statin-induced myalgias within 2 to 4 weeks after stopping the statin therapy, and by their reappearance on restoring the statin therapy. Clinically significant muscle symptoms, including rhabdomyolysis and statin-induced necrotizing autoimmune myopathy (SINAM), are rare. Management of
SAS requires making the appropriate diagnosis, altering or discontinuing the statin treatment, and using alternative lipid-lowering therapy.41

### Table 3. A Summary of Trials Involving PCSK-9 Inhibitors in Secondary Prevention of ASCVD

| PCSK9 Inhibitor | Trial Name | Number of Patients | Number of Patients Receiving High-Intensity Statin therapy (%) | Baseline LDL-C Level (mg/dL) | Dosing of PCSK9 Inhibitor | Mean Absolute Reduction in Plasma LDL-C Level (mg/dL) | Median Follow-Up | Outcomes |
|-----------------|------------|-------------------|---------------------------------------------------------------|-----------------------------|--------------------------|-----------------------------------------------------|----------------|----------|
| Evolocumab      | FOURIER   | 27,564 patients with MI, stroke or PAD | 69 | 92 | 140 mg every 2 weeks or 420 mg every 4 weeks | 56 | 2.2 years | CV death, MI, stroke, hospitalization for unstable angina or coronary revascularization: HR 0.85 (95% CI [0.79,0.92]); CV death, MI or stroke: HR 0.80 (95% CI [0.73,0.88]) |
| Alirocumab      | ODYSSEY Outcomes | 18,924 patients with history of ACS | 89 | 87 | 75 mg every 2 weeks or 150 mg every 2 weeks | 37-48 | 2.8 years | CHD death, MI, ischemic stroke or hospitalization for unstable angina: HR 0.85 (95% CI [0.78,0.93]) |
| Bococizumab     | SPIRE-1   | 16,817 patients, secondary prevention arm (84%), primary prevention arm (16%) | 92 | 94 | 150 mg every 2 weeks | 54 | 7 months | CV death, MI, stroke or urgent revascularization: HR 0.99 (95% CI [0.80,1.22]) |
| Bococizumab     | SPIRE-2   | 10,621 patients, secondary prevention arm (84%), primary prevention arm (16%) | 73 | 134 | 150 mg every 2 weeks | 67 | 12 months | CV death, MI, stroke or urgent revascularization: HR 0.79 (95% CI [0.65,0.97]) |

Recent years have witnessed multiple cardiovascular outcome trials showing the excellent efficacy of PCSK9 inhibitors in reducing the risk of major vascular events.42 This benefit with PCSK9 inhibitors persisted in patients with a baseline LDL-C level less than 70 mg/dL, in whom the level reduced to approximately 20 mg/dL, which is well below the current guideline-recommended targets. In a randomized placebo-controlled trial of PCSK9 inhibitor evolocumab, involving 27,564 patients with established ASCVD, a 15% reduction was achieved in the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (3-year rate, 12.6% vs 14.6%, P < .001).43 A summary of trials involving PCSK9 inhibitors in secondary prevention of ASCVD is listed in Table 3. Inclisiran is a small interfering RNA (siRNA) that reduces hepatic PCSK9 synthesis.28,46 In the ORION 11 trial, inclisiran reduced LDL-C by over 50% in the patients with stable ASCVD or ASCVD-risk equivalent (type 2 diabetes, familial hypercholesterolemia, ≥20% ASCVD risk) and
elevated LDL-C despite maximum tolerated statin therapy.\textsuperscript{47} A noteworthy advantage of inclisiran is its 6-monthly dosage regimen, which has the potential to increase treatment adherence. Besides injection-site adverse events, no other significant adverse effects have been reported.\textsuperscript{46,47} The post hoc analysis of ORION 11, based on discharge summaries and adverse event reports, demonstrated a lower incidence of cardiovascular events among patients randomized to inclisiran compared to placebo.\textsuperscript{47,48} Cardiovascular outcomes of inclisiran are currently being assessed in a dedicated outcomes trial (ORION-4).\textsuperscript{49}

Bempedoic acid, a novel agent, is an oral, once-daily, nonstatin LDL cholesterol-lowering drug that inhibits ATP citrate lyase, a key enzyme linking glucose catabolism to lipogenesis by catalyzing the formation of acetyl-CoA from mitochondriald-derived citrate for de novo synthesis of fatty acids and cholesterol.\textsuperscript{29} Based on the results of recent clinical trials, bempedoic acid was approved for use by the US Food and Drug Administration in February 2020 for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD, who require additional lowering of LDL-C.\textsuperscript{49}

**Conclusion**

Statin therapy has been shown to be effective in all CAD patients. Intensive treatment with statins retards the progression of atherosclerotic disease and mitigates long-term risk of cardiovascular events in CAD patients. No threshold LDL-C level has been elucidated, below which the beneficial effects of intensive statin therapy disappear. The concept of “lower the better” has been advocated by a few authors to control LDL-C levels among patients with CAD. Besides causing a reduction in the LDL-C levels, intensive statin therapy also reduces inflammation, which is perhaps responsible for its beneficial effect among ACS, especially when started early. Beyond statin therapy, there are various other drugs that favorably alter lipid profiles, but long-term data are limited and still await validation in large-scale outcome studies. Lastly, the importance of a healthy lifestyle and dietary pattern is often neglected in lipid management among CAD patients, and should always be encouraged.

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**References**

1. Nayor M, Vasan RS. Recent update to the US cholesterol treatment guidelines: a comparison with international guidelines. *Circulation*. 2016;133(18):1795-1806.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459-2472.
3. Bandyopadhyay D, Qureshi A, Ghosh S, et al. Safety and efficacy of extremely low LDL-cholesterol levels and its prospects in hyperlipidemia management. *J Lipids*. April 23, 2018;2018:8598054.
4. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*. November 29, 2005;112(22):3375-3383.
5. Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol*. April 1, 2008;101(7):1003-1008.
6. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321:364-373.
7. Harari G, Green MS, Magid A, Zelber-Sagi S. Usefulness of non-high-density lipoprotein cholesterol as a predictor of cardiovascular disease mortality in men in 22-year follow-up. *Am J Cardiol*. 2017;119:1193-1198.
8. Doran B, Guo Y, Xu J, et al. Prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol levels on long-term mortality: insight from the National Health and Nutrition Examination Survey III (NHANES-III). *Circulation*. 2014;130:546-553.
9. Triglyceride Coronary Disease Genetics Consortium; Emerging Risk Factors Collaboration; Sarwar N, Sandhu MS, Ricketts SL, et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet*. 2010;375:1634-1639.
10. Lewis GF, Xiao C, Hegele RA. Hypertriglyceridemia in the genomic era: a new paradigm. *Endocr Rev*. 2015;36:131-147.
11. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. January 1, 2020;41(1):111-188.
12. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72:330-343.
13. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11*2. doi:10.1056/NEJMoa1812792.
14. The ORIGIN Trial Investigators. N = 3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309-318.
15. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks:
meta-analysis of 10 trials involving 77,917 individuals. *JAMA Cardiol.* 2018;3:225-234.

16. Schwartz GG, Olsson AG, Abt M, et al; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012;367:2089-2099.

17. AIM-HIGH Investigators; Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy [published correction appears in *N Engl J Med.* July 12, 2012;367(2):189]. *N Engl J Med.* 2011;365(24):2255-2267. doi:10.1056/NEJMoai107579.

18. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med.* 2017;376:1933-1942.

19. HPS/TIMI/REVEAL Collaborative Group; Bowman L, Hopewell JC, Chen F, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med.* 2017;377:1217-1227.

20. Verdonia M, Schaffer A, Suryapranata H, De Luca G. Effects of HDL-modifiers on cardiovascular outcomes: a meta-analysis of randomized trials. *Nutr Metab Cardiovasc Dis.* 2015;25(1):9-23. doi:10.1016/j.numecd.2014.09.003.

21. Van der Valk FM, Bekkering S, Kroon J, et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. *Circulation.* August 23, 2016;134(8):611-624.

22. O’Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation.* 2019;139:1483-1492.

23. Parish S, Hopewell JC, Hill MR, et al; HPS2-THRIVE Collaborative Group. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE study. *Circ Genom Precis Med* 2018;11:e001696.

24. Jialal I, Inn M, Siegel D, Devaraj S. Underestimation of low density lipoprotein cholesterol with the Friedewald equation versus a direct homogenous low density lipoprotein cholesterol assay. *Lab Med.* 2017;48:220-224.

25. Cartier LJ, St-Coeur S, Robin A, Lagace M, Douville P. Impact of the Martin/Hopkins modified equation for estimating LDL-C on lipid target attainment in a high risk patient population. *Clin Biochem.* 2020;76:35-37. doi:10.1016/j.clinbiochem.2019.12.002.

26. Langlois MR, Chapman MJ, Cobbaert C, et al. Quantifying Atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM. *Clin Chem.* July, 2018;64(7):1006-1033.

27. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation.* June 18, 2019;139(25):e1082-e1143.

28. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med.* 2017;376(15):1430-1440. doi:10.1056/NEJMoai1615758.

29. Honigberg MC, Natarajan P. Bempedoic acid for lowering LDL cholesterol. *JAMA.* 2019;322(18):1769-1771. doi:10.1001/jama.2019.16598.

30. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). 1994. Atheroscler Suppl. October, 2004;5(3):81-87.

31. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med.* October 3, 1996;335(14):1001-1009.

32. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* November 5, 1998;339(19):1349-1357. doi:10.1056/NEJM199811053391902. PMID: 9841303.

33. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA.* April 4, 2001;285(13):1711-1718.

34. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* April 8, 2004;350(15):1495-504.

35. Hulten E, Jackson JL, Douglas K, George S, Villines TC. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med.* September 25, 2006;166(17):1814-1821.

36. Blazing MA, Giugliano RP, Cannon CP, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. *Am Heart J.* August 2014;168(2):205-212.e1.

37. Eisen A, Cannon CP, Blazing MA, et al. The benefit of adding ezetimibe to statin therapy in patients with prior coronary artery bypass graft surgery and acute coronary syndrome in the IMPROVE-IT trial. *Eur Heart J.* December 21, 2016;37(48):3576-3584.

38. Marenzi G, Cosentino N, Werba JP, Tedesco CC, Veglia F, Bartorelli AL. A meta-analysis of randomized controlled trials on statins for the prevention of contrast-induced acute kidney injury in patients with and without acute coronary syndromes. *Int J Cardiol.* March 15, 2015;183:47-53.
39. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. April 7, 2005;352(14):1425-1435.

40. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. November 16, 2005;294(19):2437-2445.

41. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol*. 2016;67(20):2395-2410. doi:10.1016/j.jacc.2016.02.071.

42. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. *Annu Rev Pharmacol Toxicol*. 2014;54:273-293.

43. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713-1722.

44. Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097-2107.

45. Ridker PM, Revkin J, Amarenco P, et al; SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. April 20, 2017;376(16):1527-1539.

46. Ray KK, Stoeckenbroek RM, Kallend D, et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. *JAMA Cardiol*. November 1, 2019;4(11):1067-1075.

47. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387.

48. Ray KK, Wright S, Kallend D, et al. Inclisiran and cardiovascular outcomes: analyses from ORION-11. *JACC*. March, 2020;75(11, Suppl 1). doi:10.1016/S0735-1097(20)30865-2.

49. FDA approves bempedoic acid for treatment of adults with HeFH or established ASCVD. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/02/24/10/09/fda-approves-bempedoic-acid-for-treatment-of-adults-with-hefh-or-established-ascvd