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Optimal lipid targets for the new era of cardiovascular prevention

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Optimal lipid targets (OLT) should be the goal for all individuals treated in the new era of cardiovascular (CV) disease prevention. Evidence supports that average LDL cholesterol (LDL-C) values in Westernized populations are not optimal. Lessons from nature and science support a physiologic LDL-C target of <70 mg/dL. Clinical trial evidence further supports optimal LDL-C targets, although several critical questions remain unanswered. Using a calculated LDL-C may have limitations in clinical practice. Non-HDL-C cholesterol may be a better predictor of outcomes, and should therefore be provided on all laboratory reports. Specific HDL cholesterol (HDL-C) targets are significantly more complicated. Although a low HDL-C predicts a less favorable outcome independent of LDL-C level, an HDL-C level > 50 mg/dL is associated with lower CV risk. Clinical trials on HDL-C have thus far been disappointing. OLT should be the goal for all individuals as an important part of addressing global CV risk.

Keywords: optimal lipid; OLT; cardiovascular; HDL; LDL; triglyceride

Background

With a growing cardiometabolic phenotype in the United States and globalization of the Westernized lifestyle, the prevalence of cardiovascular risk factors continues to increase at a rapid rate.[1–4] Risk factors, including tobacco use, dyslipidemia, diabetes, and hypertension, among others, contribute to the pathogenesis of atherosclerotic vascular disease. As such, the prevention of cardiovascular disease (CVD) takes a multifaceted approach directed toward the optimal treatment of each of these distinct factors.

Physiology and nature

In contrast to other risk factors, low-density lipoprotein cholesterol (LDL-C) has been established as the major necessary and sufficient factor for the development and progression of atherosclerosis.[5] The relevance of optimal lipid targets as they pertain to the prevention of CVD is grounded in the central role that lipids play in the initiation and development of atherothrombotic lesions. Oxidative modification of LDL-C exists within a spectrum, from minimally modified (mmLDL) to significantly oxidized (oxLDL), the latter of which is believed to initiate the process of atherogenesis by binding to scavenger receptors on macrophages and smooth muscle cells.[5,6] An imbalance between lipid burden and physiologic capacity can result in an overwhelmed protective-immunologic response, giving rise to death of foam cells and destabilization of the lipid-rich core, with subsequent increased risk of plaque rupture, thrombosis, and fatal events.

Although increased longevity of our species may unmask disease entities that otherwise may not have been described in our ancestors, atherosclerosis has been defined as a process primarily related to the lipid burden that our culture and diet has brought forth, and not our longevity. Anthropological observations, for instance, show little to no evidence of atherosclerosis among preagricultural and twentieth-century hunter-gatherers in the seventh and eighth decades of life.[7,8] In addition, the absence of atherosclerosis has been demonstrated

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across virtually all mammalian species from a spectrum of ages.[9,10]

It is likely that the low prevalence of CVD in hunter-gatherers was partially attributable to a higher level of physical activity, but also because they did not possess LDL-C levels overwhelming the physiologic capacity of the body. The LDL-C level of hunter-gatherers, neonates, wild primates, and wild mammals has been extrapolated to a range of approximately 30–70 mg/dL in several studies.[8,11–14] Compared to our predecessors, the average American adult today has an LDL-C level of 130 mg/dL (or at least two- to fourfold more than hunter-gatherers), a 50% chance of establishing atherosclerosis by the age of 50 years, and self-reports of being relatively physically inactive (∼60–65% of the U.S. population).[1,15–17] Some believe that the discordance between the Paleolithic genome and our modern day diet, with the rapid advent of processed, refined, and fat-laden products, accounts at least in part for the current endemic of CVD.[11] Others, however, argue that dietary indiscretion, independent of genetic consideration, is accountable for the current state of CVD.[17] Being that modern day humans are the only animals with an LDL-C >80 mg/dL, it is not surprising that we have the highest prevalence of atherosclerotic CVD.[11] Taken together, these findings underscore the notion that atherosclerosis is not a natural part of our physiology or of aging, but a chronic, smoldering inflammatory process that is a result of extrinsic sociocultural factors. Furthermore, these data support the concept that a lower LDL-C of less than 70 mg/dL corresponds to our physiologic level and is therefore optimal in ensuring a lifetime free of cardiovascular events.

Science and trials

Although current NCEP ATP III guidelines recommend therapeutic targeting of LDL-C to less than 70 mg/dL only in the highest-risk individuals (Table 1), emerging data continue to support the need for further reduction of LDL-C in other populations.[18–22]

O'Keefe *et al.*[11] completed multiple univariate regression analyses in which crucial points of disease and event progression relating to LDL-C were defined on the basis of several large RCTs.[23–32] In their analysis, the point limitation of atherosclerotic progression corresponded to an LDL-C of 67 mg/dL, and the coronary heart disease (CHD) event rate approached 0% at an LDL-C of 57 mg/dL and 30 mg/dL in primary and secondary prevention, respectively.[11]

Table 1. Current NCEP guidelines for LDL-C and non-HDL-C

Risk category	LDL-C goal (mg/dL)	Non-HDL-C goal (mg/dL)
Highest risk (CHD, CHD equivalent, or 10-year risk score >20%)	<100 (<70[a])	<130 (<100[a])
Moderately high risk (≥2 minor risk factors, or 10-year risk score 10–20%)	<130 (<100[b])	<160 (<130[b])
Moderate risk (≥2 risk factors, or 10-year risk score < 10%)	<130	<160
Low risk (<2 risk factors, or 10-year risk score <10%)	<160	<190

[a]Optional goal for highest-risk patients.
[b]Optional goal for higher-risk patients.
Data from Refs. 18 and 22.

Several large randomized controlled trials (RCTs) have demonstrated findings consistent with this analysis in the setting of both primary and secondary prevention.[28–31,33–36] In the West of Scotland Coronary Primary Prevention Study, for instance, 6,595 men (age, 45–64 years) were randomized to receive either 40 mg pravastatin or placebo over a mean of 4.9 years.[30] There were clinically significant event reductions in the pravastatin group for nonfatal myocardial infarction (RRR 31%, $P < 0.001$), any coronary event (RRR 31%, $P < 0.001$), and death from all cardiovascular causes (RRR 32%, $P = 0.033$).[30] In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), 6,605 men and women (age, 45–73 years) were randomized to lovastatin (20–40 mg) or placebo and followed over an average of 5.2 years.[28] Compared with placebo, the treatment group showed significant reductions in first acute major coronary events (RR: 0.63; 95% CI: 0.50–0.79; $P < 0.001$), myocardial infarction (RR: 0.60; 95% CI: 0.43–0.83; $P = 0.002$), unstable angina (RR: 0.68; 95% CI: 0.49–0.95; $P = 0.02$), coronary revascularization procedures (RR: 0.67; 95% CI: 0.52–0.85; $P = 0.001$), coronary events

Table 2. Lower is better: intensive versus conservative statin therapy in patients with ACS

Trial	*N*	Intervention arms	Baseline LDL (mg/dL)	LDL difference at 1 year (mg/dL)	Events (% per year)	
					Statin/more	Control/less
PROVE IT-TIMI 22	4162	A80, P40	101.3	25.1	11.3	13.1
IDEAL	8888	A40/80, S20/40	102.1	21.3	5.2	6.3
TNT	10001	A80, A10	97.4	24	4	5.4
A to Z	4497	S40/80, P/S20	80.8	11.6	3.6	3.8
SEARCH	12064	S80, S20	96.7	15.1	7.2	8.1

Note: Data from Refs. 31, 33–36.

(RR: 0.75; 95% CI: 0.61–0.92; $P = 0.006$), and cardiovascular events (RR: 0.75; 95% CI: 0.62–0.91; $P = 0.003$).[28] In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA),[29] 10,305 participants (age, 40–79 years) were randomized to receive either atorvastatin 10 mg or placebo over an average of 5 years. The study was stopped after a median of 3.3 years given a clinically significant reduction in total cardiovascular events (RR: 0.79; 95% CI: 0.69–0.90; $P = 0.0005$), and total coronary events (RR: 0.71; 95% CI: 0.59– 0.86; $P = 0.0005$) in the treatment arm.[29] Collectively, these trials, among others, provide clear evidence that lowering of LDL-C in the primary prevention population results in significant cardiovascular event reduction.

In addition, recent large secondary prevention trials have demonstrated the benefits of further reduction of LDL-C with intensive statin therapy compared to standard dose treatment (Table 2). In the PROVE IT-TIMI 22 trial, for instance, 4,162 postacute coronary syndrome patients (mean age, 58 years) were randomized to high-dose atorvastatin versus standard-dose pravastatin and followed for an average of two years.[31] The primary endpoint was defined as a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting (if these procedures were performed at least 30 days after randomization), and stroke. There was a significant reduction of the primary endpoint in the atorvastatin group (median LDL-C, 62 mg/dL) compared with the pravastatin group (median LDL-C, 95 mg/dL; RR: 0.16; 95% CI: 0.05 to 0.26; $P = 0.005$).[31] In the IDEAL study, 8,888 secondary prevention patients (mean age, 62 years) were randomized to high-dose atorvastatin versus usual-dose simvastatin with a 5-year follow-up.[36] In this study, there was a significant reduction of coronary events (Hazard ratio (HR): 0.84; 95% CI: 0.76–0.91; $P < 0.001$) and nonfatal MI (HR: 0.83; 95% CI: 0.71–0.98; $P = 0.02$) in the atorvastatin group (mean LDL-C, 81 mg/dL) compared with the simvastatin group (mean LDL-C, 104 mg/dL). In the TNT study, 10,001 secondary prevention patients (age, 35–75 years) were randomized to low- or high-dose atorvastatin and were followed for five years.[35] The high-dose arm (mean LDL-C, 77 mg/dL) demonstrated a significant reduction of any coronary event (HR: 0.79; 95% CI: 0.73–0.86; $P < 0.001$), and any cardiovascular event (HR: 0.81; 95% CI: 0.75–0.87; $P < 0.001$) compared with the low-dose arm (mean LDL-C, 101 mg/dL).[35]

In the second-cycle of the Cholesterol Treatment Trialists' meta-analysis, Baigent *et al.*[20] collectively assessed 39,612 secondary prevention subjects (weighted mean baseline LDL-C, 97.7 mg/dL) from five RCTs of more intensive versus less intensive statin therapy (Table 2). The weighted mean difference in LDL-C at one year was 19.7 mg/dL, with significantly fewer major coronary events in the more intensive statin group compared to the less intensive statin group (RR: 0.74; 95% CI: 0.65–0.85; $P < 0.0001$). More remarkably, in the combined analysis of all 26 RCTs, which included both primary and secondary prevention individuals, there was a 22% reduction in major vascular events for every 38.6 mg/dL (1 mmol/L) decrease in LDL-C regardless of initial LDL-C level. Of note, there was a linear relationship between LDL-C reduction and relative risk reduction (RRR) of major vascular events. With a fixed RRR independent of starting LDL-C level, benefit may be further extrapolated to a 40% CV event reduction for every 2 mmol/L decrease in

LDL-C, and a 50% reduction for every 3 mmol/L decrease in LDL-C.[19,20]

A *post hoc* analysis of 17,802 healthy men and women (mean age, 66 years) from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study further supports these findings.[37] In the JUPITER study, the primary endpoint was defined as a composite of cardiovascular death, MI, stroke, arterial revascularization, and unstable angina. Hsia *et al.*[37] found a linear relationship between reduction in the primary endpoint and degree of LDL-C lowering, with fewer events in the group with an LDL-C < 50 mg/dL (HR: 0.35; 95% CI: 0.25–0.49; $P_{\text{trend}} < 0.0001$) compared to the group with an LDL-C > 50 mg/dL (HR: 0.76; 95% CI: 0.57–1.00).[37] Of note, both groups demonstrated equivalent safety outcomes with only a nonsignificant trend toward more muscle symptoms in the group with an LDL-C < 50 mg/dL. Similarly, a *post hoc* analysis of the TNT study showed a similar linear relationship between LDL-C level and CV event rate.[35] Taken together, these findings support a physiologic LDL-C target of less than 70 mg/dL not only in highest-risk individuals, but in all patients at risk for CVD.

Two important intracoronary ultrasound studies assessing the differential effects of standard- and intensive-dose statins on atheroma morphology and volume further support the findings of recent RCTs. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, 502 secondary prevention subjects (age, 30–75 years) were randomized to receive either pravastatin 40 mg or atorvastatin 80 mg over the course of 18 months, with baseline and posttreatment intravascular ultrasound (IVUS) assessment of atheroma volume and changes thereof.[13] In this study, Nissen *et al.*[13] found a significantly lower rate of atherosclerotic progression as measured by percentage change in atheroma volume in the atorvastatin group (mean LDL-C achieved, 79 mg/dL) compared with the pravastatin group (mean LDL-C achieved, 110 mg/dL; pravastatin: +1.9%; atorvastatin: +0.6%; $P < 0.001$).[13] Similarly, in the ASTEROID study,[38] 349 individuals (mean age, 58.5 years) received rosuvastatin 40 mg (mean LDL-C achieved, 60 mg/dL) and were followed for two years. IVUS assessment at two years showed significant regression of atheroma lesions by all three prespecified IVUS points of measure (–0.98% mean atheroma volume for the entire vessel; –6.1 mm^3 for the most diseased 10-mm segment; –14.7 mm^3 in total atheroma volume; all $P < 0.001$).[38] This study, however, did not include a control group or paired IVUS measurements, which may limit data utility. Consistent evidence from several large RCTs[28–31,33,34,36] showing a reduction in cardiovascular events with a linear relationship to LDL-C and independent of starting level, as well as findings of limited progression or regression of atheromas with statin therapy provide compelling evidence to support that optimal LDL-C is likely below 70 mg/dL.

Although accumulating evidence strongly supports a more aggressive LDL-C goal in primary and secondary prevention patients, it remains unclear as to how low the LDL-C may be safely reduced. Physiologic observations indicate that some cholesterol is a necessary part of our basic function, with necessary roles in cellular membrane composition, steroid hormone synthesis, vitamin synthesis, and neuronal myelination.[9,17] Importantly, the adverse effects of lipid lowering with statins have been assessed in several RCTs, with a recent meta-analysis reporting no significant effect on cancer incidence (RR: 1.00, 95% CI: 0.96–1.04, $P = 0.9$), or cancer and nonvascular mortality (RR: 0.97, 95% CI: 0.92–1.03; $P = 0.3$) in 170,000 participants from 26 RCTs.[20] Among the recent more intensive versus less intensive RCTs, PROVE IT-TIMI 22,[31] TNT,[35] and IDEAL[36] each reported minimal and equal rates of rhabdomyolysis in high and low-dose statin arms (all $< 0.1\%$, $P =$ NS). One study analyzed 309,506 person-years of follow-up from 23 statin arms and found that there was no significant correlation between percent of LDL-C lowering and rates of elevated liver enzymes ($R^2 < 0.001$, $P = 0.91$) or rhabdomyolysis ($R^2 = 0.05$, $P = 0.16$).[39] Although the effects of statin therapy on specific adverse outcomes have been evaluated, the long-term effects of a very low LDL-C have yet to be investigated.

With the growing cardiometabolic phenotype globally, there is a need to better characterize residual risk in the population. Statin therapy at the current intensity provides a 30% risk reduction of cardiovascular events, still leaving a large window for potential events. Given the significant risk of events despite LDL-C at "optimal goal" by current standards, it is clear that improvement in

cardiovascular risk assessment is warranted. Non-HDL-C and apoB are among the two foremost emerging biomarkers in CVD risk stratification. Non-HDL-C has been shown to correspond to characteristics of the metabolic syndrome better than LDL-C, is twice as good as LDL-C in predicting cardiovascular risk reduction and has cutpoints based on well-established LDL-C goals (Table 1).[40,41] Although apoB offers comparable performance benefit, it carries an additional cost of 33.7% more than non-HDL-C and takes up to three times longer to result, with only negligible net reclassification benefit.[3] These practical limitations make non-HDL-C a strong biomarker to better stratify the globally emerging cardiometabolic phenotype.[3] In patients who have achieved LDL-C goal, therapeutic targeting to non-HDL-C is likely to be beneficial.

Although emerging biomarkers like non-HDL-C and apoB are better than LDL-C at CV risk stratification, defining the VLDL or triglyceride (TG) fraction is an important component related to appreciating comprehensive risk. Given an increase in the prevalence of the metabolic syndrome over the past decade, it is likely that aggressive management of elevated triglycerides will play a key role in optimizing individuals at risk for CV disease.[3] On the basis of recent large randomized clinical trials,[35,31] normal and optimal fasting TG levels have been defined as $<$150 mg/dL and $<$100 mg/dL, respectively, in the most recent AHA Scientific Statement.[42] Of note, proper therapeutic lifestyle counseling and implementation may decrease triglycerides by up to 50%.[42]

HDL-C and cardiovascular disease: still aiming high?

In keeping with the need to better risk stratify and optimize patients at risk for CVD, high-density lipoprotein cholesterol (HDL-C) has recently become a point of therapeutic focus. HDL-C plays a complex role in lipid metabolism involving multiple pathways including antiinflammatory, antithrombotic, antioxidative, and antiapoptotic processes. Although these mechanistic roles are individually well described, the composite effect of raising HDL-C on atherosclerotic lesions and clinical outcomes is still unclear.

A dominant role of HDL-C is in reverse cholesterol transport, whereby potentially proatherogenic lipid is transferred to HDL-C from LDL-C. HDL-C is taken up by hepatocytes via SRB1-receptor binding and endocytosis, allowing for proatherogenic lipid clearance.[43–46] Significant antioxidative effects of HDL-C are attributed to the presence of paraoxonase (PON) and platelet-activating factor acetylhydrolase (PAF-AH).[47] In addition, HDL-C inactivation of lipid hydroperoxides (LOOH) and oxidized phospholipids of LDL-C is carried out by activity of lecithin–cholesterol acyltransferase (LCAT), which transfers lipid hydroperoxides from LDL-C to HDL3.[45,48,49] Finally, the antithrombotic properties of HDL-C include inhibition of factor Va and VIIa, as well as inhibition of platelet aggregation and adhesion via upregulation of endothelial nitric oxide synthase (eNOS).[50–53] Although these biologic effects of HDL-C are well described, the clinical relevance of raising HDL-C and effects thereof still remain poorly defined in part because of limited assay specificity.[54]

Epidemiologic studies have shown that a low HDL-C level is an independent predictor of CVD.[55–59] Importantly, there is an inverse relationship between risk of atherosclerosis and HDL-C level independent of LDL-C level, which is consistent with the observation that HDL-C confers benefit through multiple pathways.[56,60] Gordon *et al.*[56] analyzed four prospective trials in which they found a 2–3%[55,56] reduction in cardiovascular events for every 1 mg/dL increase in HDL-C. More recently, a *post hoc* analysis of TNT[35] showed that even individuals with an LDL-C $<$ 70 mg/dL demonstrated a 25% reduction in the 5-year rate of CV events with an HDL-C in the highest quintile compared with the lowest quintile.

Of note, there are several genetic syndromes—in particular, LCAT deficiency, ApoA-I Paris mutation, and Tangier disease, among others—that predispose patients to a chronically very low HDL-C in which low rates of cardiovascular events are still reported.[63–63] This observation speaks to the likelihood of differential effects of HDL-C as a result of its variability as a substrate. HDL-C exists within a spectrum of subfractions, each class exhibiting a unique combination of lipids, apolipoproteins, enzymes, and transfer proteins.[54,64] Some experts argue that the current standard of measurement—HDL-C mass, rather than subfraction or functional capability—may be contributing to our limited understanding of its benefits and role in CVD prevention.[54]

Table 3. Optimal lipid targets

	Optimal goals (mg/dL)			
Risk level	LDL-C	Non-HDL-C	Fasting TG	HDL-C
Highest risk	<70	<90	<100	>50
Moderate risk				
Low risk				

As such, findings in intervention trials have been equivocal to date. The Veterans Affairs HDL Intervention Trial (VA-HIT),[65] for instance, was the first trial to demonstrate CV benefit with raising of HDL-C in secondary prevention in patients with normal LDL-C levels (RR: 0.78, 95% CI: 0.65–0.93, $P < 0.006$). The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events trial,[66] however, found an increase in cardiovascular events (HR: 1.25, 95% CI: 1.09–1.44, $P = 0.001$) and all-cause mortality (HR: 1.58, 95% CI: 1.14–2.19, $P = 0.006$) despite a 72% increase in HDL-C in subjects treated with torcetrapib, a CETP inhibitor, in addition to atorvastatin. These findings, however, have raised several questions given the described off-target effects of torcetrapib that may have accounted for the adverse outcomes. Most recently, the Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) trial assessed 3,414 secondary prevention men and women (mean age, 64 years) over a mean of 32 months.[67] Patients maintained at an LDL-C goal of < 80 mg/dL on simvastatin were randomized to receive either niacin or placebo in addition to statin therapy. The study was stopped early given no significant difference in the primary endpoint—time to first occurrence of CV event or ischemic stroke—at 32 months between the two groups despite a significant difference in HDL-C levels.[67] Similarly, the Treatment of HDL-C to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) trial is an ongoing study that aims to assess whether there exists any benefit to raising HDL-C with niacin in 25,000 secondary prevention individuals at LDL-C goal on statin therapy. The results of this study are pending study completion. In addition, several ongoing clinical trials with CETP inhibitors such as anacetrapib and dalcetrapib anticipate results within the next three to five years.[35]

The Framingham Study defined the HDL-C threshold points of 40 mg/dL in men and 50 mg/dL in women, below which there was a significant increase in cardiovascular events.[60] These findings in the setting of recent studies suggesting a dose-dependent relationship between HDL-C and cardiovascular events support an optimal HDL-C goal of >50 mg/dL. As assays better delineate functional HDL-C, rather than mass of HDL-C, it is likely that optimal levels will become better defined and more established in clinical practice.

Conclusion

Current epidemiologic data for the United States and globally demonstrate a growing cardiometabolic burden despite better implementation of therapeutic lifestyle counseling and aggressive pharmacologic intervention on the part of physicians.[1,3] Given the significant risk of cardiovascular events even in patients who are considered to be "optimized" by current standards, factors associated with residual risk likely contribute to atherosclerotic disease persistence and progression.

Lessons from nature, science, as well as clinical trials support a physiologic LDL-C target of <70 mg/dL in not only high-risk patients, but all individuals (Table 3). Furthermore, therapeutic targeting to a non-HDL-C goal once an LDL-C goal is achieved may allow clinicians to better optimize comprehensive approaches to care as this risk marker accounts for the total proatherogenic lipid volume rather than just LDL-C with no additional cost. Given the low cost of generic statins in the present era, the cost-effectiveness of aggressive statin therapy in an expanded statin-prescribing model has been demonstrated to confer a $430 million annual reduction in healthcare costs and additional health benefits for $9,900 per quality-adjusted life-year.[68] The demonstrated cost-effectiveness of statins should enable physicians to aggressively initiate and titrate statin therapy to evolving stated goals in all individuals with less reservation.

A further decrease in triglycerides is warranted in individuals who have fasting levels >150 mg/dL but who are otherwise optimized. An ideal fasting TG level has been defined as <100 mg/dL on the basis of recent data. Finally, an HDL-C >50 mg/dL may be ideal for all individuals on the basis of predominately epidemiologic data, however,

a better understanding of HDL-C function and its role in CV prevention is needed.

Conflicts of interest

The authors declare no conflicts of interest.

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