Current Diabetes Reports (2019) 19:146
https://doi.org/10.1007/s11892-019-1246-y

MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Lowering Targeted Atherogenic Lipoprotein Cholesterol Goals for Patients at "Extreme" ASCVD Risk

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Abstract

Purpose of Review To review randomized interventional clinical and imaging trials that support lower targeted atherogenic lipoprotein cholesterol goals in "extreme" and "very high" atherosclerotic cardiovascular disease (ASCVD) risk settings. Major atherosclerotic cardiovascular event (MACE) prevention among the highest risk patients with ASCVD requires aggressive management of global risks, including lowering of the fundamental atherogenic apolipoprotein B-associated lipoprotein cholesterol particles [i.e., triglyceride-rich lipoprotein remnant cholesterol, low-density lipoprotein cholesterol (LDL-C), and lipoprotein(a)]. LDL-C has been the long-time focus of imaging studies and randomized clinical trials (RCTs). The 2004 adult treatment panel (ATP-III) update recognized that the long-standing targeted LDL-C goal of < 100 mg/dL potentially fostered substantial undertreatment of the very highest coronary heart disease (CHD) risk individuals and was lowered to < 70 mg/dL as an "optional" goal for "very high" 10-year CHD [CHD death + myocardial infarction (MI)] risk exceeding 20%. This evidence-based guideline change was supported by the observed benefits demonstrated in the high-risk primary and secondary prevention populations in the Heart Protection Study (HPS), the acute coronary syndrome (ACS) population in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial (PROVE-IT), and the secondary prevention population in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) intravascular ultrasound (IVUS) study. Subsequent national and international guidelines maintained a targeted LDL-C goal < 70 mg/dL, or a threshold for management of > 70 mg/dL for patients with CHD, CHD risk equivalency, or ASCVD.

Recent Findings Subgroup or meta-analyses of several RCTs, IVUS imaging studies, and the ACS population in IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) supported the evidence-based 2017 American Association Clinical Endocrinologist (AACE) guideline change establishing a targeted LDL-C goal < 55 mg/dL, non-HDL-C < 80 mg/dl, and apolipoprotein B (apo B) < 70 mg/dL for patients at "Extreme" ASCVD risk, i.e., 10-year 3-point-MACE-composite (CV death, non-fatal MI, or ischemic stroke) risk exceeding 30%. Moreover, with no recognized lower-limit-associated intolerance or safety issues, even more intensive lowering of atherogenic cholesterol levels is supported by the following evidence base: (1) analysis of eight high-intensity statin-based prospective secondary prevention IVUS atheroma volume regression trials; (2) a distribution analysis of on-treatment, ezetimibe and background-statin, of the very low LDL-C levels reached and CVD event risk in the IMPROVE-IT ACS population; (3) the secondary prevention Global Assessment of Pl\aque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) on background-statin; and (4) the secondary prevention population of Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER). By example, in FOURIER, the population on background-statin at a baseline median 92 mg/dL achieved median LDL-C level of 30 mg/dL and non-HDL-C to < 65 mg/dl, and apo B to < 50 mg/dL, and subgroup and post hoc analyses all demonstrated additional ASCVD event reduction benefits as LDL-C was further reduced.

This article is part of the Topical Collection on *Macrovascular Complications in Diabetes*

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Published online: 21 November 2019

Summary The level of ASCVD risk determines the degree, urgency, and persistence in global risk management, including fundamental atherogenic lipoprotein cholesterol particle lowering. "Extreme" risk patients may require extremely low targeted LDL-C, non-HDL-C and apo B goals; such efforts, implied by more recent interventional trials and analyses, are aimed at maximal atheroma plaque regression, stabilization, and MACE event reduction with the aspiration of improved quality lifespan.

Keywords ASCVD risk assessment · Extreme risk · Very high risk · 3-point-MACE-composite (CV death, non-fatal MI or ischemic stroke) risk · Secondary prevention · Atherogenic lipoprotein cholesterol particle-lowering · LDL-C-lowering, non-HDL-C, apolipoprotein B

Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
apo B	Apolipoprotein B
ARR	Absolute risk reduction
ASCVD	Atherosclerotic cardiovascular disease
ATP-III	Adult treatment panel
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
MACE	Major adverse cardiovascular events
NCEP-ATP	National Cholesterol Education Program Adult Treatment Panel III
NNT	Number needed to treat
Non-HDL-C	Non-high density lipoprotein cholesterol
RRR	Relative risk reduction
TG	Triglyceride

Acronyms

FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
GLAGOV	Global Assessment of Plaque Regression with a PCSK9Antibody as Measured by Intravascular Ultrasound
HPS	Heart Protection Study
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
ODYSSEY	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) Trial
REVERSAL	REVERSal of atherosclerosis with Aggressive lipid Lowering trial
TNT	Treating to New Targets
VOYAGER	An IndiVidual Patient Meta-Analysis Of Statin TherapY in At-Risk Groups: Effects of Rosuvastatin, Atorvastatin and Simvastatin
RCTs	Randomized Clinical Trials
IVUS	Coronary Intravascular Ultrasound
LDL-C	Low Density Lipoprotein Cholesterol
PAV	Percent Atheroma Volume

Introduction

The Atherogenic Lipoprotein Cholesterol Principle

What was once the cholesterol hypothesis is now the atherogenic lipoprotein cholesterol principle [1]. Apolipoprotein B (apo B) is the major structural protein for each lipoprotein particle that carries varying concentrations of cholesterol, triglyceride (TG), and phospholipids. These lipoprotein particles include apo B 100-associated triglyceride (TG)-rich very-low-density lipoprotein (VLDL) [TGRLP] particles, metabolized remnants of VLDL-TG lipolysis, intermediate density lipoprotein particles (IDL), low-density lipoprotein (LDL) particles of all sizes, i.e., large buoyant, intermediate or small dense LDL, and lipoprotein(a) [Lp(a)] particles. Lipoprotein cholesterol particles also include metabolized remnants of apolipoprotein B48 chylomicron (CM)-TG lipolysis. When in excess, apo B-associated lipoprotein cholesterol particles, by concentration gradient, diffuse into, and can be retained by, the arterial wall to directly initiate and cause progression of the inflammatory atherosclerotic cardiovascular disease (ASCVD) process in all mammalian species and, thus, are atherogenic [1]. Although dyslipidemias, i.e., as elevated LDL-C, elevated LDL particle numbers, elevated TGRLP remnant cholesterol particles, or elevated lipoprotein (a) or a combination, are the fundamental causal ASCVD initiators [1], progression is also influenced by a variety of other genetic and environmental factors that accelerate the atherosclerosis process. These include insulin resistance, with or without obesity, contributing to the more common dyslipidemias, and other conditions such as hypertension, diabetes, chronic kidney

disease, and factors influencing coagulation/thrombosis, inflammation, atheroma formation, vascular tone, compensatory mechanisms, and lifestyle factors, such as smoking, obesity, physical inactivity, and unhealthy diet [2–5].

For most lipid scientists and clinical experts, the cholesterol hypothesis was proven three decades ago [6, 7]. Furthermore, it became apparent, from successful clinical intervention trials of usually middle-aged and older patients with CHD, that it was "reasonable to extrapolate and expect even greater reductions if treatment is started earlier in life and continued not for just 5 years but for decades" [8]. The evidence-based criteria for apolipoprotein B-containing lipoproteins and ASCVD causality from epidemiological studies, prospective cohorts, genomic studies, and the interventional trials corroborating treatment efficacy establishing the atherogenic lipoprotein cholesterol principle have been exquisitely reviewed [1].

The recognition of this fundamental principle is the first step to understanding the imperative of lowering the concentration of atherogenic lipoprotein cholesterol particles in at-risk individuals to prevent the initiation of atheroma formation [9] and progression of the ASCVD process. Once subclinical disease has developed, an advanced primary prevention setting, obligatory tenacity is required with more aggressive lowering of atherogenic cholesterol to regress and stabilize vulnerable plaque and prevent ASCVD events. In secondary prevention settings, even more vigorous therapeutic approaches are required to stop progression and affect plaque regression and stabilization, to prolong the quality of life and lifespan of at-ASCVD-risk patients.

Clinical Outcome Intervention Trials Have Focused on Targeting Atherogenic Lipoprotein Cholesterol, as LDL-C

While very early studies relied on correlations of total cholesterol, the large number of small and large randomized clinical trials in the past three decades has utilized LDL-C as the primary marker and correlated its lowering to CV risk reduction. LDL-C may be adequate alone, in the absence of TG-rich lipoprotein cholesterol, or elevated lipoprotein(a) [Lp(a)], but it has been argued for some time that apo B is more universal as a CVD indicator of risk and adequacy of therapy [10], because it includes an assessment of not only LDL particle numbers, but also the contribution of TGRLP remnant cholesterol particles as well as Lp(a) that better predict the total number of atherogenic cholesterol particles that diffuse by concentration gradient into the arterial wall. The association of atherosclerotic disease with the protein moiety of LDL, LDL B protein, now referred to as apolipoprotein B, even in the presence of normal cholesterol levels, has been known for over three decades [11]. Recognized in earlier investigations, the role of hypertriglyceridemia, VLDL-C, and its remnant cholesterol [12–17] and apo CIII in VLDL [18], as contributors to ASCVD have become increasingly relevant [19]. Despite the role of TG-rich lipoprotein remnant cholesterol, clinical trials of atherosclerosis have routinely focused on cholesterol, specifically within LDL particles, i.e., LDL-C, to the routine exclusion of participants with elevated TG exceeding 400 mg/dL, one population in need of evaluation. Not to ignore TG-rich lipoprotein remnant cholesterol particles, the ATP-III [20] added non-HDL-C, a calculated surrogate descriptor of all atherogenic cholesterol within all lipoproteins that contain apo B, as a second target after LDL-C. Non-HDL-C enhances risk prediction particularly when serum triglycerides are high; the sum of VLDL cholesterol plus LDL cholesterol, or the total cholesterol less the HDL-C, on a laboratory report is called non-HDL cholesterol. Non-HDL-C also includes the cholesterol content of lipoprotein(a) [Lp(a)] an independent, causal, and genetic risk factor for ASCVD and for aortic stenosis [21, 22], with atherogenic, antifibrinolytic, and pro-inflammatory effects related to its content and properties, as an LDL particle, apolipoprotein(a), and associated oxidized phospholipid [23–25]. Relative to the quantitative cholesterol content, described by non-HDL-C or LDL-C, with exceptions, e.g., lower triglyceride levels, considerable evidence supports atherogenic particle numbers or concentration, described by LDL particle numbers, LDL-P, or the more comprehensive and most potent marker of ASCVD, apo B, as the superior predictor of ASCVD risk. Targeting apo B could potentially reduce the number of ASCVD events [26, 27], but apo B has yet to replace LDL-C in clinical trials. LDL-C, non-HDL-C, and apo B have all been proposed as markers to quantitate the atherogenic damage attributable to apo B-associated cholesterol particles. While this review focuses on clinical trials, all of which have historically focused on targeting LDL-C, as a clinical risk predictor of CHD, when assessed, baseline and in-trial non-HDL-C and apo B levels achieved are also acknowledged.

Evidence-Based 2001 National Cholesterol Adult Treatment Panel Guidelines Maintained a Targeted LDL-C Goal at < 100 mg/dL for Highest Risk Patients

For the "highest risk category," CHD or CHD risk equivalents, where 10-year risk for CHD or CHD death was > 20%, the 2001 National Cholesterol Education Program Adult Treatment Panel, NCEP ATP-III, recommendations [20] described evidence from 12 statin trials, 6 dietary trials, 3 bile acid sequestrant trials, and 1 surgical trial that correlated reduction in cholesterol to reduced CHD incidence and mortality. Coronary lesion regression vs. progression and CV event rates in relatively small angiographic imaging trials of LDL-lowering therapy was described for 9 trials of various combination of statins with non-statins including BAS, niacin, and fibrates. The "achieved LDL-C levels" in those studies justified the ATP-III recommendations for a targeted LDL-C goal of < 100 mg/dL with a threshold for lifestyle management ≥ 100 mg/dL and the threshold for drug therapy

consideration ≥ 130 mg/dL. The secondary targeted non-HDL-C goal was < 130 mg/dL.

The Results of Three Randomized Clinical Trials Supported the 2004 ATP-III Targeted LDL-C Optional Goal < 70 mg/dL for Very High-Risk Patients

The 2001 NCEP ATP III guidelines [20] were updated in 2004 [28]. High-risk individuals were defined as patients with a history of CHD, stroke, or peripheral arterial disease as previously defined. Equivalent high-risk groups included patients without CHD but with multiple risk factors and diabetes or older age. High-risk patients were partitioned to recognize "very high-risk" individuals who have had an MI, stroke, or peripheral circulatory disease and in addition have multiple major risk factors, particularly if the risk factors are severe or poorly controlled, i.e., diabetes and smoking, or the metabolic syndrome (high triglycerides especially ≥ 200 mg/dL plus non-HDL-C ≥ 130 mg/dL with low HDL-C [< 40 mg/dL]) is present or the presentation is an acute coronary syndrome, including unstable angina. Thus, a targeted LDL-C goal < 70 mg/dL was "optional" for these very high-risk CHD patients [28], and the evidence base originated from both epidemiological data and 3 major clinical trials (Table 1) generating new data where lower LDL-C levels were achieved coincident with further ASCVD risk reduction.

The Heart Protection Study, HPS [32], randomized 20,536 adults, aged 40–80 years, with history of CAD, including angina, PAD as intermittent claudication, ischemic stroke, TIA, carotid artery disease, diabetes, or hypertension, and total cholesterol levels ≥ 135 mg/dL to receive 40 mg simvastatin daily or placebo. The baseline mean total cholesterol was 228 mg/dL, and mean direct LDL-C was 3.4 mmol/L (132 mg/dL). Those allocated 40 mg simvastatin achieved a mean LDL-C of 85 mg/dL. The primary outcomes were mortality for the cohort and fatal or non-fatal major vascular events for subgroups. All-cause mortality was reduced by 13%, due to an 18% RRR in coronary death rate (5.7% vs 6.9%, $p = 0.0005$), and major vascular events were reduced by 24% (19.8% vs. 25.2%, $p < 0.0001$).

Prespecified subgroup analyses demonstrated that pretreatment cholesterol levels did not influence major vascular risk reduction, i.e., there was no evidence for an LDL-C threshold, "below which lowering it would not lower risk" safely. Even the lowest tertile "subgroup" with LDL-C level of < 116 mg/dL (mean, 104 mg/dL) achieving an LDL-C < 77 mg/dL (mean 69.6 mg/dL, ~ 70 mg/dL) with simvastatin 40 mg daily resulted in a significant risk reduction compared to placebo (17.6% vs 22.2%, $p < 0.0001$). Furthermore, a "subset" of this subgroup with baseline LDL-C levels < 100 mg/dL (mean 97 mg/dL, $n = 3500$) achieved a mean LDL-C of 65 mg/dL and achieved further significant risk reduction (16.4% vs 21.0%, $p = 0.0006$).

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial [42] compared a high-intensity regimen of atorvastatin, 80 mg daily with a moderate-intensity regimen of pravastatin, 40 mg daily, to assess 18 months of treatment on the progression of atherosclerotic coronary disease in patients with known stable CAD, utilizing intravascular ultrasonography, IVUS. From a baseline mean LDL-C 150.2 mg/dL, an LDL-C of 79 mg/dL was achieved in the atorvastatin 80 mg group, relative to 110 mg/dL achieved in the pravastatin 40 mg group, for a 31 mg/dL between-group LDL-C difference ($p < 0.001$). Relative to the pravastatin group ($n = 249$), the atorvastatin group ($n = 253$) had significantly ($p = 0.02$) lower progression in terms of percentage change in atheroma volume (primary end point, $p = 0.02$), and secondary efficacy parameters, including change in percentage atheroma volume ($p < 0.001$), and change in atheroma volume in the most severely diseased 10-mm vessel sub-segment ($p < 0.01$). Compared to baseline, progression occurred in the pravastatin group (2.7%; $p = .001$), even in the subgroup attaining LDL-C < 100 mg/dL ($p < 0.01$), whereas progression did not occur in the atorvastatin group (− 0.4%; $P = .98$); progression was stopped at the mean LDL-C of 79 mg/dL.

Notably, linear regression analysis (LRA) of REVERSAL demonstrated an inverse relationship between percentage reduction in LDL-C level and progression in atheroma volume for both drugs, with each 10% or 15 mg/dL reduction in LDL-C level resulting in an approximate 1% reduction in the change in atheroma volume after 18 months. Comparing the percentage of LDL-C reduction and change in atheroma volume, regression was seen when LDL-C was reduced by > 50%, ~ 75 mg/dL, or at < 75 mg/dL, and regression was linearly greater with greater LDL-C lowering from > 50% down to 80% (reduced by 120 mg/dL) lowering, equivalent to reaching LDL-C levels from 75 mg/dL down to 30 mg/dL, respectively [42], and since atorvastatin more potently lowered LDL-C, regression was achieved with atorvastatin, but not pravastatin.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, PROVE-IT [29], randomized 4162 patients hospitalized within the preceding 10 days with an acute coronary syndrome (ACS) and baseline mean LDL-C 106 mg/dL, to either high intensity statin, atorvastatin, 80 mg, or moderate standard intensity statin, pravastatin, 40 mg. The 80 mg atorvastatin group achieved a median LDL-C level of 62 mg/dl, while the 40 mg pravastatin group achieved a median LDL-C level of 95 mg/dl. This between-group LDL-C difference of 33 mg/dL, demonstrating superiority of LDL-C lowering for the higher intensity atorvastatin, was also associated with significant superiority in reducing clinical events (16% relative risk reduction (RRR), $p = 0.005$) in these post-ACS patients, after a relatively short mean follow-up of 24 months, and clearly demonstrated that achieving the lower LDL-C was better.

Table 1 LDL-C levels achieved in randomized clinical trials influencing changes to guidelines for the highest ASCVD risk individuals and validation of lower outcomes at intensified lower levels

LDL-C Level Achieved	<70 mg/dL, 2004 ATP III Update		<55 mg/dL, 2017 AACE/ACE		<30 mg/dL	
Trial Analysis	RCT	LDL-C, mg/dL	RCT	LDL-C, mg/dL	RCT	LDL-C, mg/dL
Level 1A RCT	PROVE-IT [29]	62	IMPROVE-IT [30••]	53.5	FOURIER [31••]	30
Prespecified or Post-Hoc Subgroup Analyses	HPS [32] - lowest tertile - sub-group <100	 69 65	PROVE-IT [33] TNT [34] VA Palo Alto Health Care [35] JUPITER [36]	40 54 40 44	IMPROVE-IT [37] FOURIER [38••]	<30 <20 <10 (7)
Meta-analyses RCT Statin Trials			8 Statin RCT Trials - divided by Quartiles [39] - divided by Septiles [40]	 Q1, <62; mean, 49 S1, <50		
Imaging (Coronary IVUS)			GLAGOV [41••]	36.6		
Coronary IVUS trial PAV changes by linear regression analysis (LRA)	REVERSAL [42] mean 73 mg/dL	LRA 83 → 30	REVERSAL [42] Mean 73 mg/dL	LRA 83 → 30	8 Statin IVUS trials [43] GLAGOV [41••]	LRA 93 → 15 LRA 90 → 20

National and International Guidelines Targeted LDL-C Goal < 70 mg/dL for the Highest Risk Patients

Thus, the ATP-III 2004 update [28] recognized that substantial undertreatment of very high-risk patients could result from the continued inadvertent utilization of a targeted LDL-C goal < 100 mg/dL, since a lower LDL-C could reduce ASCVD events even further. Subsequent to the ATP-III 2004 update [28], the AHA/ACC 2006 Update [44] concluded that a targeted LDL-C goal of < 70 mg/dL and non-HDL-C < 100 mg/dL was "reasonable" for very high-risk patients, i.e., in secondary prevention. It was also recommended that when baseline LDL-C is high and "it is not possible to attain a targeted LDL-C <70 mg/dL, reductions of >50% could be attained with either statins or LDL-C-lowering combinations", i.e., "standard dose of statin with ezetimibe, bile acid sequestrant, or niacin". And after LDL-C lowering, when non-HDL-C is elevated, intensification of LDL-C lowering or niacin or fibrate options.

Multiple national and international guidelines have since strongly recommended targeting LDL-C to a goal < 70 mg/dL for very high-risk individuals [28, 44–54, 55••]. The 2008 Consensus Statement from American Diabetes Association and the American College of Cardiology Foundation [45] recommended that patients with the highest cardiometabolic risk, e.g., those patients with known CVD or those with diabetes and one or more additional major CVD risk factor(s), should have targeted LDL-C and non-HDL-C goals of < 70 mg/dL and < 100 mg/dL, respectively, and apo B of < 80 mg/dL [45].

Controversy ensued, when the 2013 ACC/AHA guidelines removed targeted numerical atherogenic cholesterol marker "goals" per se [56], except a goal of lowering LDL-C by ≥ 50% for the highest risk patients and no longer encouraged non-statin therapies felt not to provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

The 2013 International Atherosclerosis Society (IAS) developed a new set of dyslipidemia management recommendations [50]. The optimal LDL-C in patients with established ASCVD remained < 70 mg/dL and non-HDL-C < 100 mg/dL, with maximal statin therapy as tolerated and as requires add-on drugs to statins (i.e., ezetimibe or bile acid resins or both) and those intolerant of high-dose statins, combination moderate dose statin with either ezetimibe or bile acid resin. For patients with high TG, nicotinic acid, or a fibrate as alternative add-on drugs, despite the absence of dedicated RCTs in these settings, that have yet to be done.

The 2014, 2015 patient-centered dyslipidemia recommendations of the National Lipid Association, NLA [51, 52], had low-, moderate-, and high-risk patient treatment goals for LDL-C, non-HDL-C, and apo B set at < 100 mg/dL, < 130 mg/dL, and < 90 mg/dL, respectively. Lifestyle changes were encouraged at all ASCVD risk levels, but drug therapy was not necessarily recommended, unless atherogenic cholesterol levels defined treatment thresholds within a risk category. The NLA recommended both non-HDL-C and LDL-C as primary targets of therapy and apo B as an optional, secondary target [51, 52]. For very high-risk patients' targeted LDL-C and non-HDL-C goals of < 70 mg/dL and < 100 mg/dL, respectively, and apo B of < 80 mg/dL.

Despite this interim controversy, goal attainment for the highest risk patients persisted in one form or another, either as the 2013 ACC/AHA recommended high-intensity statin-induced maximal percentage LDL-C reduction (≥ 50%) [56], or in other national and international guidelines as a desirable numerical level [49, 50, 52, 55••] or both numerical goal or ≥ 50% threshold for the initiation of, or the addition of, atherogenic cholesterol-lowering therapeutic modalities [46, 52, 53].

Achieving a Targeted LDL-C Goal < 70 mg/dL Is More Difficult than Achieving a ≥ 50% LDL-C Reduction; the Latter Is Inadequate as a Solitary Directive for the Majority of Very High- or Extreme-Risk Patients

Variability of LDL-C response to statins can be considerable and achieving a goal of LDL-C < 70 mg/dL is more difficult than achieving a goal of ≥ 50% reduction in LDL-C. By example, in the "IndiVidual patient meta-analysis Of statin therapY in At-risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin" (VOYAGER) high-risk patient database [n = 20,539] in subjects with mean baseline LDL-C 168 mg/dL, figure 3 in reference [57], even high-intensity atorvastatin 80 mg/dL resulted in approximately 60% achieving > 50% reduction in LDL-C, while only approximately 33% achieved an LDL-C level < 70 mg/dL. On high-intensity rosuvastatin 40 mg/day, approximately 76% achieved > 50% reduction in LDL-C, while only approximately 43% achieved an LDL-C level < 70 mg/dL. Such variability may contribute to considerable residual risk if a clinician limits the therapeutics to a single agent with a "goal" of ≥ 50% reduction in LDL-C, simply because that approach was utilized in a level 1 evidence-based RCT.

Identification of statin-eligible groups from the US National Health and Nutrition Examination Survey 2011–2012 and assessment of proportion on statin, proportion at recommended LDL-C levels (< 70 mg/dL for the very high risk and < 100 mg/dL for others), and adherence to lifestyle measures found that 80% of established CVD patients on any "statin therapy" did not achieve LDL-C goal < 70 mg/dL [58]. In a large administrative database of US medical and pharmacy claims with 105,269 patients with ASCVD, only 53.2% were treated with a statin and only 25.2% had achieved an LDL-C goal of < 70 mg/dL [59]. These inadequacies are particularly important since greater progression of atherosclerosis is observed in patients who fail to achieve effective reductions of LDL-C [60]. Residual ASCVD risk would be even greater if targeting LDL-C simply to < 70 mg/dL was found to be inadequate [61, 62].

Considerable Evidence Base Supported the 2017 AACE/ACE Guideline Targeting LDL-C Below 55 mg/dL

Evidence accumulated supporting a targeted LDL-C goal to even lower levels in all ASCVD risk categories. Given the unacceptably high residual risk, noted in randomized clinical trials, even in the settings of high-intensity statin monotherapy, the rationale for an "even lower is even better" atherogenic cholesterol goal may be viewed as an imperative. Substantial undertreatment of the highest risk patients could result from the inadvertent utilization of a guideline setting its goal at < 70 mg/dL, if an even lower LDL-C will reduce ASCVD events further. In each of the following studies or analyses, listed in Table 1, the lowest event rates or hazard ratio for CV disease burden or events was reached with lower levels for the markers of atherogenic cholesterol, i.e., for LDL-C far lower than just < 70 mg/dL, in the range < 55 mg/dL and down to 30 mg/dL. A sub-group analysis of the 2005 PROVE-IT study [33] found ACS individuals achieving LDL levels < 40 mg/dl and 40 to 60 mg/dl experienced the fewest major CV events. A sub-group post hoc analysis of the Treating to New Targets (TNT) trial of otherwise stable CHD patients demonstrated that those achieving LDL-C in the lowest quintile defined as LDL-C level < 64 mg/dl (mean LDL-C 54 mg/dL) [34] had the fewest CV events. An observational 2007 VA Palo Alto Health Care System study [35] demonstrated improved survival among patients placed on statins despite pre-treatment LDL levels < 40 mg/dL. In the 2011 subgroup/post hoc analysis of the primary prevention JUPITER trial [36], among individuals with inflammatory risk based on a highly sensitive CRP ≥ 2 mg/dL achieving LDL-C levels < 50 mg/dL (median 44 mg/dL) resulted in a lower risk of CV events compared to not attaining a follow-up LDL-C level < 50 mg/dL (median 69 mg/dL). Thus, based on the JUPITER trial analysis, a targeted LDL-C goal < 55 mg/dL is justified among high-risk primary prevention individuals.

In a 2012 meta-analysis of eight major statin trials (n = 38,153 patients), divided into quartiles of achieved LDL-C [39], the lowest CV event rate occurred in those in the lowest quartile of LDL-C < 62 (mean 49 mg/dL), non-HDL-C < 85 (mean 69 mg/dL), and apo B < 70 (mean 60 mg/dL). A second 2014 meta-analysis of the same eight statin RCTs, divided into septiles of achieved LDL-C, to evaluate even lower LDL-C levels [40] showed that patients with an LDL-C < 50 mg/dL, non-HDL-C < 75 mg/dL, or apo B < 50 mg/dL had the lowest MACE hazard rate. Thus, statin therapy is justified when extended to patients in the secondary prevention setting who already have a baseline LDL-C minimally < 70 mg/dL.

Eight prospective randomized trials, that utilized serial coronary IVUS to evaluate changes in plaque burden were analyzed [43]. Patients (n = 1,881) with established CAD were treated with high-intensity statins that produced significant reductions from baseline in LDL-C (–38.4%), non-HDL-C (33.6%), TG (–13.1%), and CRP (–33.3%), and increased HDL-C (11.7%) (p < 0.001 for all). Most patients demonstrated plaque regression (defined as any change from baseline in percent atheroma volume, PAV, or total atheroma volume, TAV, < 0, with mean coronary atheroma "regression" of PAV by 0.7% and of TAV by 8.2 mm^3 (p < 0.001, for both). Furthermore, there was a continuous relation between changes in atheroma plaque volume and achieved LDL-C level, with consistent changes across a broad range of baseline LDL (26 to 251 mg/dl). Importantly, regardless of baseline LDL-C, significant coronary regression as a reduction in PAV and TAV began below an LDL-C level of 115 mg/dL with the continuous regression curve extending down to on-treatment LDL-C levels of 15 mg/dL. Thus, patients with established

CAD and very low LDL-C obtained benefit by even achieving lower LDL levels.

In the 2015 IMProved Reduction of Outcomes: Vytorin Efficacy International Trial, IMPROVE-IT [30••], utilizing ACS patients ($n = 18,144$) with a median follow-up of 6 years, from a 93.8 mg/dL baseline LDL-C, the group allocated simvastatin 40 mg plus placebo achieved a median time-weighted average LDL-C of 69.5 mg/dL vs. 53.7 mg/dL for the group allocated simvastatin 40 mg plus ezetimibe 10 mg. The Kaplan–Meier event rate at 7 years for the primary end point (composite of CV death, major coronary event, unstable angina requiring hospitalization, non-fatal stroke) was 32.7% in the simvastatin–ezetimibe group versus 34.7% in the simvastatin plus placebo (monotherapy) group for a 6.4% RRR, $p = 0.016$, an absolute risk reduction (ARR) of 2%. Thus, the 7-year number needed to treat, NNT, was 50.

Importantly, in a pre-specified IMPROVE-IT analysis by diabetes status [30••, 63], the subgroup of ACS patients with diabetes, representing 27% of the entire cohort, allocated simvastatin plus placebo had the highest primary endpoint (45.5%) 7-year event rate, but a significantly lower primary event rate in those allocated simvastatin plus ezetimibe (40.0%), for a 15% RRR ([HR 0.85; 0.78–0.94], $p = 0.001$), p interaction 0.023, a 5.5% ARR, and an impressive NNT of 18. The 7-year 3-point MACE (CVD death, MI or stroke) event rate for the simvastatin monotherapy control group was 26.0%, an extrapolated 10-year-risk of 37.1%, consistent with "extreme" risk. The ezetimibe-simvastatin allocated group experienced a 7-year 3-point MACE event rate of 21.4%, for a 20% RRR [HR 0.80; 0.71–0.900], p interaction = 0.016, a 4.6% ARR, and therefore, NNT 22 [63].

In the pre-specified IMPROVE-IT analysis evaluating 9545 within-trial total (initial recurrent and additional recurrent) events, the 7-year 5-point MACE primary endpoint events [64], the combination of simvastatin with ezetimibe significantly reduced these total events by 9% [HR 0.91 $p = 0.007$] compared to simvastatin plus placebo. The 3-point MACE events were reduced by 12% [HR 0.88, $p = 0.002$].

Furthermore, in an exploratory analysis of IMPROVE-IT [65], ezetimibe added to statin in patients with a pre-trial history of coronary artery bypass graft surgery (CABG), $n = 1684$ or 9% of the entire cohort, following the hospitalization for ACS, the 7-year K-M rates of the primary endpoint (CV death, major coronary event or stroke) were higher in placebo-controlled patients with vs. without prior CABG at 56% vs. 32%, respectively. Patients with prior CABG receiving simvastatin/ezetimibe had a 20% reduction in the primary endpoint and absolute risk reduction of 8.8% with NNT 11. In addition, the simvastatin/ezetimibe group exhibited a more robust reduction of additional (non-first) events in the prior CABG group. These data are consistent with the concept that populations with more extreme ASCVD risk benefit from greater LDL-C lowering.

In 2015, preliminary analyses from studies with proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors evolocumab [66] after 52 weeks and alirocumab [67] after 78 weeks showed significant reductions in LDL-C from a mean baseline LDL-C of approximately 120 mg/dL to a mean LDL-C of 48 mg/dL, and although these were not long-term outcome trials, demonstrated a promising ~ 50% RRR in CV events. In a pooled analysis of 10 ODYSSEY Trials [68•], greater reductions in LDL-C and lower on-treatment LDL-C were associated with lower incidence of cardiovascular outcomes, including at levels of LDL-C < 50 mg/dL.

In the Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound, GLAGOV, coronary IVUS trial [41], with 968 patients with CAD treated with the PCSK9 inhibitor, evolocumab vs placebo, evolocumab lowered LDL-C to a mean 36.6 mg/dL versus 93.0 mg/dL with placebo and demonstrated an associated reduction in PAV (− 0.95%), i.e., regression of plaque volume, compared to placebo (+ 0.05%).

Thus, a consistent evidence base had developed for very low LDL-C levels well below the prior LDL-C goal < 70 mg/dL as associated with even lower incidence of outcomes, either assessed as atheroma volume regression by coronary IVUS, or reduced clinical ASCVD events in randomized intervention trials.

Newer Data Prompted Changes in Guidelines

The 2016 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Guidelines [53] recommended targeted LDL-C goals as follows: for patients at low or moderate risk, goal of < 3.0 mmol/L (< 115 mg/dL); at "high" risk, a goal LDL-C of < 2.6 mmol/L (< 100 mg/dL) or a minimum 50% reduction from baseline if LDL-C 100–200 mg/dL; and for those patients at very high risk, an LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) or at least 50% reduction from if baseline LDL-C ranged from 70 to 135 mg/dL.

The American College of Cardiology 2016 Task Force on Clinical Expert Consensus Documents, endorsed by the National Lipid Association, addressed optional pharmacological interventions, including addition of ezetimibe, bile acid sequestrants, and PCSK9 inhibitors, not only if the percentage LDL-C reduction was not achieved, but also in consideration of absolute LDL-C level or threshold achieved.

In the case of patients with ASCVD and comorbidities, in addition to the goal of ≥ 50% LDL-C reduction, there is consideration of a lower LDL-C threshold, i.e., < 70 mg/dL, and non-HDL-C threshold, i.e., < 100 mg/dL for patients with diabetes [54].

The American Diabetes Association (ADA) also updated its lipid recommendations in 2016 [69] to reflect the evidence

from IMPROVE-IT, recommending the addition of ezetimibe to moderate-intensity statin in ACS patients with diabetes with LDL-C levels ≥ 50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statin.

The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) in 2016, recognizing an imperative, introduced, adopted, and incorporated a consensus-generated concept of partitioning the very high-risk category to include an extreme-risk category in their guidelines for management of dyslipidemia and prevention of atherosclerosis published in January 2017 [55••] and their 2017 AACE comprehensive type 2 diabetes management algorithm [70]. To date, the AACE/ACE consensus-based "extreme-risk" category includes patients with progressive ASCVD, defined by recurrent events, multiple beds of ASCVD (polyvascular disease), or unstable angina, despite an LDL-C less than 70 mg/dL, or patients with established ASCVD, who also have DM, stage 3 or 4 CKD and/or heterozygous familial hypercholesterolemia, as well as patients with premature ASCVD (male < 55 years or female < 65 years of age). The 2017 AACE/ACE guideline and algorithm [55••] recommended desirable atherogenic cholesterol treatment goals for the very high-risk patients, as a targeted LDL-C goal < 70 mg/dL, and for the extreme-risk patients, a targeted LDL-C goal of < 55 mg/dL. When non-HDL-C and apo B are targeted, desirable goals for the very high-risk patients are < 100 mg/dL and < 80 mg/dL, respectively, and for the extreme-risk patients < 80 mg/dL and < 70 mg/dL, respectively. The extreme-risk goals were based on available data from subgroup analyses of clinical and imaging trials, including the evidence-based IMPROVE-IT clinical trial, described above.

While ACS patients meet 10-year MACE risk criteria for extreme risk, AACE/ACE decided, by consensus, for patients to be classified by the descriptor extreme risk, there had to be additional evidence that benefit would be obtained from lowering to the new targeted LDL-C goal < 55 mg/dL. At least partially, IMPROVE-IT provided such evidence, demonstrating a significant reduction in the primary outcome in the "entire cohort" of individuals recently hospitalized with ACS. However, the significant benefit in IMPROVE-IT appeared to be driven largely in patients with diabetes (14.4% risk reduction) compared to 2.3% risk reduction in individuals without diabetes. Therefore, there was a departure from the strict trialist evidence-based decision for the entire cohort and ACS patients as a cohort was maintained in the very high-risk category [56, 70], while patients with diabetes and ASCVD, which included ACS, would be described by the descriptor extreme risk. Furthermore, while patients with stage 5 CKD on dialysis and patients with congestive heart failure are conditions traditionally considered at very highest risk, consistent with extreme risk, studies to date had failed to demonstrate reduction of ASCVD events with lowering of atherogenic lipoprotein cholesterol markers in these patients. This approach, however limited, when categorizing risk has been the norm in other guidelines [51–53].

Defining 10-Year ASCVD Risk Percent Requires Standardizing a Composite Among Multiple Outcomes

Defining 10-year ASCVD risk and associated percent/incidence rates to delineate levels of risk in uniform terms can be a challenge as epidemiological data and many clinical trials utilize a variety of primary and secondary outcomes. Often in clinical trials, a primary outcome may include a composite of three to five component outcomes to assure the occurrence of a required number of events to demonstrate safety and efficacy and simultaneously maintain a shorter, less expensive, but ethical and non-controversial trial. An ideal approach would include the risk of developing all ASCVD outcomes, rather than selected or specific hard components: CHD, stroke, peripheral arterial disease, or heart failure. CHD may include components such as CHD death, or myocardial infarction, or admission due to unstable angina, or need for revascularization, either angioplasty/stent or coronary artery bypass. Ischemic stroke may be fatal or non-fatal or defined by a transient ischemic attack, or intervention, angioplasty/stent or endarterectomy. Peripheral artery disease may be defined by an ankle-brachial index measurement, diagnosis of claudication, or amputation. By modifying the Framingham CHD risk assessment tool utilized in the NCEP-ATP-III [20], a more inclusive ASCVD risk factor algorithm [71] was accomplished, but how often currently utilized is uncertain. A 3-point MACE composite (CV death, non-fatal MI, non-fatal stroke), generally fit the 2017 AACE/ACE dyslipidemia guideline definitions for all categorical levels ASCVD risk, where CV death is usually defined to include CHD death and fatal stroke and has become a favored primary end point for many contemporary safety and efficacy CVOTs in common with the recommendation by the 2013 ACC/AHA guideline in its the assessment of ASCVD risk [72].

Evidence Now Supports an Even Lower Targeted LDL-C Goal for Extreme ASCVD Risk

Evidence-based analyses and RCTs now support an even lower is better or lowest is best atherogenic lipoprotein cholesterol markers, LDL-C, non-HDL-C, and apo B (Table 1).

In the 2014 analysis [43] of eight intravascular ultrasound (IVUS) trials, described above, studies of patients with stable CAD demonstrated attenuation of progression and plaque regression utilizing high-intensity statins, rosuvastatin 40 mg, or atorvastatin 80 mg. A continuous relation between changes in plaque volume versus achieved LDL-C was noted; those achieving LDL-C levels 15 to 30 mg/dL (mean 26 mg/dL) achieved progressively more regression defined as changes

from baseline coronary percentage atheroma volume (PAV) or total atheroma volume (TAV).

In the IMPROVE-IT prespecified subgroup analysis to evaluate the long-term safety and efficacy at very low LDL-C levels [37], a distribution curve was generated of all ACS patients according to LDL-C level at 1 month with the following distributions: < 30 mg/dL, $n = 971$ (6.4%); 30–49 mg/dL, $n = 4780$ (31%); 50–69, $n = 5504$ (36%); ≥ 70 mg/dL, $n = 4026$ (26%). Similar safety profiles were noted at all LDL-C levels. The patients achieving an in-trial LDL-C level of < 30 mg/dL [6%, $n = 969$] had numerically the lowest rate of cardiovascular events, a 21% RRR in the primary efficacy composite of CV death, major coronary events, or stroke over the median 6-year period, as compared with patients achieving higher LDL-C concentrations the reference LDL-C level 70 mg/dL or greater; adjusted HR, 0.79; 95% CI, 0.69–0.91; $p = 0.001$.

In the GLAGOV trial [41••], in patients with stable CAD, taking background statin therapy, treatment with a non-statin, the PCSK9 inhibitor, evolocumab, lowered LDL-C to less than 37 mg/dL, mean 36.6 mg/dL, compared to 93.0 mg/dL for the placebo. Other atherogenic lipoprotein cholesterol biomarkers, non-HDL-C and apo B, were significantly lowered to < 58 mg/dL and < 43 mg/dL, respectively. The percent atheroma volume (PAV) assessed by IVUS was reduced (− 0.95%) in the evolocumab-allocated group, i.e., regression of plaque volume, but not in the placebo-allocated group (+ 0.05%). Notably, the post hoc linear regression analysis as a LOESS plot [41••] in GLAGOV demonstrated a linear and continuous relationship of evolocumab-induced regression of coronary disease plaque volume in proportion to the magnitude of LDL-C reduction, with maximum plaque regression reached at an LDL-C of 20 mg/dL.

In Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) [31••], a double-blind, placebo-controlled randomized controlled trial, 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of ≥ 70 mg/dL while on statin therapy were randomly assigned to evolocumab, 140 mg q 2 weeks or 420 mg monthly, or matching placebo subcutaneous injections. The primary efficacy end point was the 5-point MACE composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the 3-point MACE composite (CV death, MI, or stroke). At the median 2.2-year duration of follow-up, median LDL-C was reduced by evolocumab 59% from 92 to 30 mg/dL (the between-group difference in LDL-C 48 weeks was 53.4 mg/dL). Non-HDL-C was reduced by 51.2% (from baseline 124 mg/dL to 60.5 mg/dL, between-group difference 50.8%), apo B was reduced by 46% (baseline not reported, between-group difference − 48.7%), and TG was reduced by − 16.2% (from baseline 134 mg/dL to 112 mg/dL; between-group difference 15.5%). The primary end point was experienced by 11.3% in the placebo group versus 9.8% in the evolocumab group, for a 15% RRR [HR 0.85, 0.79–0.92, $p < 0.001$].

For the purpose of applying the 2017 AACE guideline partitioning of very high risk to recognize those at extreme risk, FOURIER results are herein discussed in terms of the 3-point composite MACE (CV death, MI, or ischemic stroke) > 30%. This key secondary endpoint was experienced by 7.4% in the placebo group versus 5.9% in the evolocumab group, for a 20% RRR [HR 0.80, 0.73–0.88, $p < 0.001$]. Thus, the extrapolated 10-year 3-point MACE risk was 33.6% for the placebo group, consistent with extreme risk for the entire cohort studied, and was reduced to 26.8% or very high risk in those receiving evolocumab.

In the prespecified secondary analysis of 25,982 patients from FOURIER, the relationship between achieved LDL-C at 4 weeks and subsequent MACE events at 3-year follow-up was evaluated [38••]. Relative to LDL-C > 100 mg/dL (7.8%, referent), for each level lower of LDL-C in mg/dL, the secondary 3-point MACE (CV death, MI, or stroke), Kaplan–Meier event rates and adjusted risk reduction [38••] were for 70 to < 100 mg/dl (6.7%, − 10%); 50 to < 70 mg/dL (6.5%, − 13%); 20 to < 50 mg/dL (5.7%, − 25%); and < 20 mg/dL (5.0%, − 31%). In a post hoc analysis for achieved ultra-low LDL-C < 15 mg/dL, the event K-M event rate was the lowest at 4.9% and risk reduction was − 34%, and for ultra-low LDL-C < 10 mg/dL (mean LDL-C 7 mg/dL), the event K-M event rate was the lowest at 4.4% and risk reduction was − 41%. Thus, there was no threshold below which there was no additional clinical benefit in terms of risk reduction in ASCVD events.

In FOURIER, Both Extreme-Risk and Very High-Risk Groups Benefit

The participant patient background history in FOURIER [31••] was clinical ASCVD in 100%, MI in 81%, ischemic stroke in 19.5%, and PAD in 13%. Single morbidity or very high-risk participants represented 85% of the cohort, i.e., those at 10-year 3-point MACE risk exceeding 20%, while a smaller portion (15%) of participants had polyvascular disease or extreme risk, i.e., 10-year 3-point MACE risk exceeding 30%. These estimates are confounded by co-morbidities, i.e., a history of diabetes among 40% of the participants, CKD in 16%, increasing the proportion of multi-morbidities and those with extreme risk. Furthermore, it could be argued that PAD, even in the absence of a history of a stroke or MI, is a polyvascular disease or extreme-risk category considering the bilateral nature and extent of this arterial bed. The level of risk for participants with PAD is further confounded by the 43% who had diabetes in FOURIER.

In the prespecified analysis of FOURIER by diabetes (DM) status [73], 3-year Kaplan–Meier (K-M) cumulative incidence rates for the primary outcome of the ASCVD and DM patients on placebo was 17.1% and 14.4% in the evolocumab group, while for the ASCVD patients without DM on placebo 13% and 11.4% in the evolocumab group. For the 3-point MACE composite, the 3-year K-M incidence for the ASCVD + DM was 12.2% (extrapolated extreme risk 40.7% 10-year 3-point MACE) risk and 10.2% on evolocumab or 18% RRR. For the ASCVD group without DM, the placebo group experienced very high risk 8.4% (extrapolated 28% 10-year 3-point MACE risk) and 6.4% on evolocumab (extrapolated 10-year risk is lowered to 25.6%) or 2.0% ARR, 22% RRR.

In the FOURIER analysis by MI proximity status [74], placebo-allocated patients with more recent MI, within 2 years of initiating the trial, experienced a 3-year 10.8% cumulative incidence or extrapolated 10-year 3-point MACE of 36% consistent with extreme risk. Placebo-allocated patients with MI ≥ 2 years of initiating the trial experienced a 3-year 9.3% cumulative incidence or extrapolated 10-year 3-point MACE of 31% consistent with extreme risk. Those patients with ≥ 2 prior MIs experienced a 3-year 15.0% cumulative incidence or extrapolated 10-year 3-point composite MACE of 50% consistent with extreme risk, compared to those with a single MI experienced a 3-year 8.2% cumulative incidence or extrapolated 10-year 3-point MACE of 27.3% consistent with very high risk. Patients identified with residual multivessel disease, defined as ≥ 40% stenosis in ≥ 2 large vessels, experienced a 3-year 12.6% cumulative incidence or extrapolated 10-year 3-point MACE of 42% consistent with extreme risk, relative to those with no multivessel disease who experienced a 3-year 8.9% cumulative incidence or extrapolated 10-year 3-point MACE of 29.6% consistent with very high risk. The relative and absolute risk reductions in cardiovascular outcomes when evolocumab (either 140 mg every 2 weeks or 420 mg monthly) reduced LDL-C to ~ 30 mg/dL were greater in the extreme-risk groups, more recent MI, within the past 2 years, multiple prior MIs, and residual multivessel coronary disease.

In the prespecified analysis of FOURIER by PAD status [75], 2.5-year K-M cumulative incidence rates for 3-point MACE (CV death, MI, stroke) were 13.0%, or extrapolated 10-year risk of 52% among the placebo group, and evolocumab reduced the 10-year risk dramatically to 38%, an ARR 3.5%, and NNT of 29. Of note, 43.4% of patients with PAD had history of diabetes. Among those placebo-allocated patients with PAD without prior MI or stroke, 2.5-year K-M cumulative incidence rates for 3-point MACE were 10.3% or extrapolated 10-year risk of 41%, and evolocumab reduced the 3-point MACE event rate to 5.5%, an ARR 4.8%, and NNT of 21. Among those placebo patients with prior MI or stroke, but without PAD, the 2.5-year K-M cumulative incidence rates for 3-point MACE were 7.6% or an extrapolated 10-year risk of 30.4%. Of note, 35.5% of those placebo patients without PAD had a history of diabetes. Evolocumab reduced the 3-point MACE event rate to 6.2%, an ARR 1.4% and NNT of 71.

In the prespecified analysis of FOURIER [76] by CKD status, the safety and efficacy of evolocumab in those participants with mild-to-moderate CKD ($n = 4443$, 16.1% of the entire cohort) was evaluated. Similar LDL-C reductions were obtained for CKD and preserved renal function patients, 58.7% and 58.2%, respectively. The key secondary end point at 3-point MACE (CV death, MI and ischemic stroke) at 3-year K-M curves was evaluated. For patients with preserved renal function, the placebo group was 7.1% (extrapolated 10-year 3-point MACE risk of 23.7%) and the evolocumab group 5.4%. For patients with CKD stage > 3, the incidence was 12.8% in the placebo group (extrapolated 10-year 3-point MACE risk of 42.7%), and in the evolocumab-allocated group, the incidence was 10.3%. Thus, patients on evolocumab with more advanced (stage ≥ 3) CKD had greater absolute risk reduction (ARR) for 3-point MACE (CV death, MI, and ischemic stroke); 2.5% ARR in patients with CKD compared to 1.7% ARR in patients with preserved kidney function at year 3.

Based on these New Data, New Goals for Targeted Atherogenic Cholesterol Markers (LDL-C, Non-HDL-C, and apo B) Are Justified at All Levels of Risk

These data demonstrate additional benefit for the highest risk ASCVD patients in targeting LDL-C to very low levels even well below the previous AACE/ACE established extreme-risk targeted atherogenic lipoprotein cholesterol marker goals, i.e., targeted LDL-C goal level < 55 mg/dL for the management of dyslipidemia. FOURIER was designed to explore the very low LDL-C realm, among patients with stable ASCVD, and these results, taking LDL-C down to 30 mg/dL, represent the level 1A evidence from a large randomized CVOT utilizing a PCSK9 inhibitor, evolocumab, on the background of statins. From a baseline of 124 mg/dL, non-HDL-C was reduced by 51.2% (see supplement [31••]) to 60.5 mg/dL, suggesting a new goal for non-HDL-C in extreme-risk patients to be < 65 mg/dL.

The baseline apo B in FOURIER has yet to be reported, but the reduction in apo B was reported as − 46%. Baseline apo B can be estimated utilizing a published validated formula [77] utilized when TG levels are ≤ 270 mg/dL; apo B = (0.65)(total cholesterol) minus (0.59)(HDL-C) plus (0.01)(TG) [77]. In FOURIER [31••], the baseline lipoproteins/lipids were as follows: total cholesterol, 168 mg/dL; TG, 134 mg/dL; and HDL-C, 44 mg/dL. Therefore, the estimated baseline apo B = (0.65)(168 mg/dL) minus (0.59)(44 mg/dL) plus (0.01)(134 mg/dL) = 85 mg/dL and the estimated in-trial apo B level, in the evolocumab group, at 45.7 mg/dL, suggesting a new targeted apo B goal at < 50 mg/dL.

In FOURIER, the cohort inclusion criteria comprised age 40 to 85 years with clinically evident ASCVD, defined as a history of MI, non-hemorrhagic stroke, or symptomatic PAD, as well as additional characteristics that placed them at higher CV risk. The FOURIER cohort and subgroup analyses demonstrated that patients with ASCVD, as multi-morbidities, peripheral arterial disease, previous historical MI, more recent MI (< 2 years), CKD, or diabetes, exhibit extreme 10-year 3-point MACE (ASCVD) risk > 30% and yet benefit from reaching very low LDL-C levels at 30 mg/dL, suggesting the possibility of a new targeted LDL-C goal. Furthermore, the prespecified analysis demonstrated the linearity from > 100 mg/dL to very low < 20 mg/dL and the post hoc analysis taking LDL-C to an extremely low < 10 mg/dL (< 7 mg/dL) and demonstrated no safety issues and no lower limit; the lowest is best. This analysis clearly lends support to the "Zero-LDL hypothesis" [78]. Thus, newer evidence-based data supports targeted atherogenic cholesterol marker treatment goals as follows: LDL-C, ≤ 30 mg/dL; non-HDL-C, < 65 mg/dL; and apo B < 50 mg/dL, for patients satisfying the criteria of extreme-risk category. The FOURIER inclusion criteria sought out patients that would satisfy at least the very high-risk criteria described by the 2017 AACE/ACE guidelines, and these patients also benefitted from the very low levels atherogenic lipoprotein cholesterol levels. Thus, patients with a single ASCVD event or ASCVD risk equivalents deserve at a minimum the prior goals attributed to extreme risk described by the 2017 AACE/ACE guidelines or the modified characteristics of the very high-risk group as follows: LDL-C, < 55 mg/dL; non-HDL-C, < 80 mg/dL; and apo B < 70 mg/dL (Table 1).

ODYSSEY Outcomes Was Not Designed to Explore the Lowest Targeted LDL-C Goal to Achieve the Greatest Benefit

The pooled analyses of the PCSK9 monoclonal antibody, alirocumab, in ODYSSEY Trials clearly demonstrated the safety [79] and practicability of reducing atherogenic cholesterol markers to very low levels, i.e., LDL-C, 25 mg/dL; apo B, 40 mg/dL; and non-HDL-C, 50 mg/dL [80].

ODYSSEY Outcomes [81••] included 18,924 patients at 1315 sites in 57 countries who had a recent ACS within the previous 12 months. Trial inclusion required residual LDL-C levels ≥ 70 mg/dL, non-HDL-C ≥ 100 mg/dL, or apolipoprotein B ≥ 80 mg/dL after 2 to 16 weeks of intensive or maximally tolerated statin therapy (atorvastatin or rosuvastatin). Patients were randomized to either subcutaneous injections of alirocumab 75 mg every 2 weeks ($n = 9462$) or placebo ($n = 9462$). Mean baseline LDL-C was 92 mg/dL, non-HDL-C was 122 mg/dL, and apo B was 83 mg/dL.

ODYSSEY Outcomes was not designed, however, to target LDL-C to the lowest possible achievable level or goal, but rather a prespecified treat-to-target goal range set at 25 to 50 mg/dL, with acceptable 15 to 25 mg/dL on lowest-dose alirocumab. To maximize the number of patients in the specific goal range, blinded dose up-titration or down-titration algorithms were in place for targeted LDL-C. In patients with higher LDL-C ≥ 50 mg/dL, alirocumab was up-titrated from 75 to 150 mg every 2 weeks. For patients with consistent lower LDL-C levels, < 25 mg/dL, alirocumab was down-titrated, 2 consecutive LDL-C values < 25 mg/dL, with tapering of 150 to 75 mg. For patients with persistent LDL-C values < 15 mg/dL, alirocumab was permanently discontinued and switched to placebo. The blinded switch to placebo occurred for 730 (7.7%) in the alirocumab-allocated group. The number or percent dose-tapered from 150 to 75 mg is not reported. These maneuvers would be expected to widen between-group LDL-C difference in the patient group allocated to alirocumab at the highest LDL and narrow the between-group LDL-C difference in those achieving the lowest in-trial LDL-C levels. Such differences would be expected to skew ASCVD benefits favorably for those with higher baseline LDL-C and unfavorably for those with lower baseline LDL-C. Premature treatment discontinuation occurred for an additional 1343 (14.2%) of the alirocumab-allocated group.

The "intention-to-treat" analysis demonstrated an LDL-C reduction in alirocumab vs. placebo at 4 months was 40 mg/dl vs. 93 mg/dl and at 48 months was 66 mg/dL vs. 103 mg/dl. The intention-to-treat time-averaged LDL-C, by inspection of figure 1 in reference [81••], appears to be at ~ 53 mg/dL for the alirocumab arm. The "on-treatment" analysis demonstrated an LDL-C reduction in alirocumab vs. placebo at 4 months was 38 mg/dl vs. 93.3 mg/dl, or 62.7% reduction, and at 48 months was 53.3 mg/dL vs. 101.4 mg/dl or 54.7% reduction. The on-treatment time-averaged LDL-C, by inspection of figure 1 in reference [81••], appears to be at ~ 45 mg/dL for the alirocumab arm. The drift upward throughout the course of the trial for both the intention-to-treat and the on-treatment analyses, the former more rapidly than the latter, was likely due to the premature discontinuation of treatment, dose reduction or substitution of placebo for alirocumab under blinded conditions, and attenuation of the intensity of statin treatment. The on-treatment time-averaged non-HDL-C was < 75 mg/dL and apo B < 50 by inspection of figure S4 supplement reference [81••].

At the 2.8-year median follow-up duration, the primary 5-point MACE endpoint composite of CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization was significantly lower in the alirocumab group versus the placebo group (9.5 vs. 11.1%); HR 0.85 (0.78–0.93), $p < 0.001$; or a relative risk reduction (RRR) for the primary end point of 15% and absolute risk reduction (ARR) of 1.6%, for a NNT 63. Components of any CHD event, any CV event, or the composite of death from any cause, not fatal MI or nonfatal stroke for similarly significantly reduced.

In the prespecified post hoc analysis by baseline LDL-C level, patients with an LDL-C ≥ 100 mg/dL experienced reductions in all end points and the ARR was greater than among patients who had a lower baseline LDL-C levels; for 5-point MACE 24% RRR and ARR of 3.4%, for a NNT 29. For CHD death RRR 28%, and ARR 0.9%; for CV death RRR 31% and ARR 1.3%, and all-cause death RRR 28% and ARR of 1.7%.

While the typical 3-point MACE (CV death, non-fatal MI or non-fatal stroke) was not precisely presented [81••], the 2.8-year median estimate from supplied information for the placebo group in ODYSSEY was at least 10.5% or an extrapolated 37.5% 10-year risk, consistent with extreme risk.

Thus, the post-ACS setting of ODYSSEY OUTCOMES, by its design and on-treatment results, lends the evidence-based level 1A guidance for a targeted atherogenic lipoprotein cholesterol marker goals [LDL-C goal < 55 mg/dL, non-HDL-C < 75, and apo B < 50], for the extreme ASCVD risk patients, similar to the 2017 AACE/ACE dyslipidemia guidelines. Despite ODYSSEY OUTCOMES not being designed to explore the lowest targeted LDL-C level to achieve the greatest benefit, patients in the alirocumab group had a significant graded relationship of LDL-C level to subsequent mortality, apparent to an achieved LDL-C level of approximately 30 mg/dL [82].

In the ODYSSEY OUTCOMES analysis by diabetes status, 5444 patients (28.8%) had diabetes. The incidence of "primary endpoint" by the end of the median 2.8-year follow-up was 16.4% in the control (alirocumab-placebo) and was 14.1% in the alirocumab group for a 16% RR reduction (HR 0.84 0.74–0.97) or ARR 2.3% and 2.8-year NNT 43 [83].

In summary, alirocumab is quite capable of safely [79] reaching LDL-C well below 30 mg/dL [80], and while ODYSSEY OUTCOMES was not designed to evaluate a targeted LDL-C goal at the lowest possible level, subgroup or subset analyses may reveal the similar guidance afforded by the results of FOURIER that lower targeted atherogenic lipoprotein cholesterol goals confer lower CV event risk.

Standard of Care Approaches Influencing Outcomes and 10-Year ASCVD Risk

The meaningful definition of incidence or percent associated with categorical risk levels in secondary prevention, i.e., very high risk or extreme risk, should include an understanding of the extent of contemporary standard-of-care therapy utilization, each proven to beneficially influence outcomes and thus reduce ASCVD risk and event incidence. The secondary prevention clinical trials in the past three decades have increasingly utilized a background of statin, ACE inhibitors or ARB and beta blockade for blood pressure control and aspirin or dual antiplatelet therapies, all of which should additively reduce residual risk and thus the percent 10-year MACE risk, regardless of the defined components and composite outcomes. Other cornerstones or pillars of therapy have been demonstrated in selected settings, although have not yet received regulatory recognition, including the cholesterol absorption inhibitor, ezetimibe; peroxisome proliferator-activated receptor gamma agonist, pioglitazone, in prediabetes and diabetes; and peroxisome proliferator-activated receptor alpha agonists, fibrates, in moderate hypertriglyceridemia; high-dose eicosapentaenoic acid (icosapent ethyl) in mild to moderate hypertriglyceridemia; as well as established standard-of-care therapies, PCSK9i in secondary prevention, and others in selected settings, i.e., glucagon-like peptide-I receptor agonists and sodium-glucose co-transporter 2 inhibitors in diabetes, renin-angiotensin-aldosterone system inhibition-natriuretic peptide enhancement (angiotensin receptor-neprilysin inhibitors) in stage C heart failure with reduced ejection fraction failure; their use may need to be considered in influencing estimating ASCVD risk.

Thresholds for Therapy Versus Goals of Therapy

The utilization of a threshold appears based on RCT design, i.e., utilization of LDL-C level ≥ 70 mg/dL as a signal that the highest ASCVD risk individuals need therapeutic intervention, and simultaneously recognizing that a goal < 70 mg/dL is preferred. However, a threshold alone does not pay homage to the LDL-C level achieved and the level of incident MACE reduced by the intervention, which is dependent on therapeutic potency of the intervention(s). The 2018 AHA/ACC/Multi-society guideline [84] states, importantly, that the more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction and clinicians should use a high-intensity statin therapy or maximally tolerated statin to lower LDL-C levels by ≥ 50% to reduce LDL-C in patients with "clinical ASCVD." The implication is the recognition that the more LDL-C is reduced by combinations of lipid-lowering therapy, the greater will be subsequent risk reduction. An advancement in 2018 AHA/ACC/Multi-society guideline [84], relative to the 2013 ACC/AHA guideline [56], was the re-introduction of the treatment "threshold" of an LDL-C ≥ 70 mg/dL to consider the addition of non-statins to statins. In the 2018 AHA/ACC/Multi-society guideline for the very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C remains ≥ 70 mg/dL, and for patients at very high risk if LDL-C level remains ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable. A threshold for treatment is not necessarily a goal of treatment. The threshold implies that treatment, whether it be lifestyle or drug therapy, is initiated when above the threshold, i.e., if just above 70 mg/dL the atherogenic marker level

achieved for ezetimibe may be just below 70 mg/dL or for a PCSK9i far below the threshold.

The rationale for using numerical treatment goals has been elucidated [52, 55••]. Thus, the 2018 AHA/ACC/Multi-society guidelines do recognize that lower is even better and utilizing standard-of-care lipid-lowering agents charges the clinician to reduce LDL-C below 70 mg/dL for the highest risk categories. Since there is considerable variability in LDL-C lowering, the higher the LDL-C is at baseline, the less likely LDL-C will end up below the 70 mg/dL threshold [57]. The ability to reduce LDL-C below a threshold ultimately depends on the baseline LDL-C level and the potency of the interventional drug.

While the 2 clinical guidelines, 2017 AACE/ACE [55••] and 2018 AHA/ACC/Multi-society guideline [84], may appear to differ in method, they are both designed to provide the practicing clinician with recommendations that ultimately have the greatest impact on the reduction of ASCVD events, and the more the LDL-C is reduced, the greater the likelihood of that accomplishment. The utilization of both atherogenic lipoprotein cholesterol thresholds for initiation and/or addition of therapy as well as goals of therapy, based on ASCVD risk, is likely to harmonize all national and international guidelines.

Extreme LDL-C Lowering Is But One Aspect of Atherogenic Lipoprotein Cholesterol-Lowering, and Additional Residual ASCVD Risk Reduction Considerations

This review was limited in scope, focusing largely on studies targeting LDL-C lowering and based on levels achieved that demonstrated the greatest ASCVD impact/benefit in RCTs involving participating patients at very high or extreme risk, utilizing pharmacologic lipid-lowering management. Beyond the scope of this article was a discussion of low-, moderate-, or high-risk settings and targeted atherogenic cholesterol particle goals for primary prevention. The most practical primary prevention approach, so often historically discussed, but underemphasized, is to begin management of risks long before fatty streaks and pl\aque processes are initiated [8, 85] and long before the time-dependent subclinical-diseased arterial system becomes calcified; this torch with its rationale is being carried forward [9, 86–89].

Lifestyle change has always been the first line of therapy for all patients at all levels of ASCVD risk and is particularly important and impactful for smokers, physically inactive individuals, and those with insulin resistance (metabolic) syndrome characteristics, particularly the overweight and obese.

Targeting residual lipid/lipoprotein residual risk should include other genetic causal, fundamental atherogenic lipoprotein targets. Significant TG-lowering in moderate hypertriglyceridemia states by reducing VLDL-C production or clearance may be an important step to expose the otherwise cryptic apolipoprotein B-associated cholesterol within TG-rich lipoprotein (TGRL) remnants. Remnant cholesterol represents 9 to 43% of the cholesterol content at non-fasting TG concentration from < 89 to 443 mg/dL. Such remnant cholesterol within TGRLs appears to be more atherogenic, associated with greater inflammation and higher mortality rates relative to LDL-C [90]. Clearing TGs converts chylomicrons to smaller chylomicron remnants that are more readily cleared by hepatic receptors and VLDL to LDL-C that may then require further cholesterol lowering.

By several mechanisms, pharmacologic dosed omega-3 polyunsaturated fatty acid enrichment, particularly eicosapentaenoic acid, may favorably off-set the otherwise unfavorable saturated fatty acid composition of phospholipids and triglycerides [91]. High dose, 4 g, of highly purified non-oxidized eicosapentaenoic acid, icosapent ethyl, significantly reduced the primary outcome MACE by 24.8%, ARR 4.8%, NNT = 21 (p = 0.00000001) in the recent Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [92]. The secondary outcome 3-point composite hard MACE (CV death, myocardial infarction, or stroke) was experienced by 20% of the control (placebo) group at 5.7-year median follow-up, a 10-year 35% ASCVD risk, consistent with the AACE/ACE ''Extreme'' risk. Of those participants receiving iIcosapent ethyl, 16.2% experienced the secondary outcome, for a RRR of 26.5%, ARR 3.6%, NNT = 28 (p = 0.0000006). Thus, icosapent ethyl (IPE) enrichment represents a new strong evidence-based pillar of therapy for very high and extreme-risk patients recruited to have well-controlled LDL-C (40–100 mg/dL) and TG levels 150 to 499 mg/dL, and median baseline LDL-C of 74 mg/dL and actual in-trial TG ranging 135 to 1074 mg/dL.

Lipoprotein(a), a genetic causal factor in 20% of the general population and over 30% of patients with ASCVD, possesses at least 3 inherent atherogenic properties: (1) proatherogenic LDL-like particle that infiltrates into atheroma, (2) apo(a) with plasminogen homology inhibits fibrinolysis increasing thrombosis, and (3) carrier of pro-inflammatory oxidized phospholipids (OxPL). Lp(a) has yet to become an officially recognized target of therapy in most guidelines, because only moderate reductions have been achieved with selected agents, and a large CVOT has yet to be completed [93]. A requirement for significant Lp(a) lowering has been implied from Mendelian randomization and is currently accomplished only by cumbersome and frequent apheresis [94].

Other non-lipid targets of therapy include blood pressure, blood glucose and A1C, or platelet aggregation. Furthermore, other therapeutic approaches, including PPAR gamma activation, GLP-1 RA, and SGLT2 inhibition, can significantly reduce or prevent ASCVD risk.

Conclusions

MACE prevention among very high- and extreme-risk patients requires aggressive global risk reduction. Targeting of LDL-C has evolved based on studies performed in primary and secondary patient cohorts with increasingly intensive therapies from low- to moderate-dose monotherapy statin +/− low efficacy non-statins, to high-intensity statin, to add-on ezetimibe, and to the more recent added potent PCSK9 inhibitors, each new technology allowing for lower achieved LDL-C levels. The lowering of fundamental atherogenic lipoprotein cholesterol particles [i.e., low-density lipoprotein cholesterol (LDL-C), triglyceride-rich lipoprotein remnant cholesterol (TGRLR-C), and lipoprotein(a)] has been and remains an evolving matter.

With a focus on LDL-C lowering, several lines of evidence justified the 2017 AACE/ACE guideline [55] change for a targeted LDL-C goal < 55 mg/dL, non HDL C< 80 mg/dL, and apo B< 70 mg/dL for the extreme-risk category. These included four subgroup analyses within RCTs utilizing statins [33–36] and meta-analyses of 8 statin RCTs [39, 40], and a metaanalysis of coronary IVUS imaging studies utilizing high-intensity statin [43]. In addition, the evidence included a RCT of add-on non-statin, ezetimibe, on background IMPROVE-IT [30••] and an IVUS trial, GLAGOV [41••], with add-on PCSK9i, evolocumab, on a statin background, achieving a mean LDL-C of 36.6 mg/dL, provided significant atheroma regression in secondary prevention setting..

The evidence base has more recently emerged that validates lower LDL-C levels and possibly supports achieving even lower atherogenic lipoprotein markers, i.e., LDL-C levels ≤ 30 mg/dL non-HDL-C < 65 mg/dL and apo B < 50 mg/dL for extreme-risk patients, with no recognized lower-limit associated safety issues. The coherent and consistent evidence base discussed herein arise from (1) a meta-analyses of statin-based intravascular ultrasound (IVUS) trials [43]; (2) a generated distribution curve analysis of on-treatment LDL-C levels reaching below 30 mg/dL and associated reduced outcomes in the cohort taking ezetimibe on background statin IMPROVE-IT [37]; (3) a post hoc LOESS plot of the IVUS imaging study, GLAGOV, utilizing the PCSK9 inhibitor (evolocumab) on background statin therapy [41••], demonstrating induction of coronary atheroma regression in proportion to the magnitude of LDL-C reduction down to 20 mg/dL; (4) level 1A evidence from a large randomized clinical PCSK9i (evolocumab) on background statin trial, FOURIER [31••], achieving a mean LDL-C at 30 mg/dL associated with low MACE outcomes, and subgroup analyses demonstrating even lower MACE outcomes for LDL-C < 20 mg/dL and even < 10 mg/dL; and (5) despite the limitations of its design, ODYSSEY OUTCOMES was able to demonstrate a reduction in all-cause mortality down to an LDL-C of 30 mg/dL [93].

In FOURIER, a clinical ASCVD event history was basic to the inclusion criteria along with other morbidities. Despite the extensive use of well-established and proven standard-of-care ASCVD prevention pharmacology, relative to those at very high risk, those with extreme risk had the greatest benefit. Utilizing the cumulative 3-year incidence of 3-point MACE (CV death, non-fatal MI, or ischemic stroke) in its control arm, 55% and 40% of the cohort had extrapolated 10-year MACE AACE/ACE defined very high and extreme risk, respectively [55••, 95], when estimated using the TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2P), the simple 10-point risk stratification tool [96]. Relative to those at very high risk, those at extreme risk demonstrated greater patterns of ARR and lower 3-year NNT.

Based on these results, in the settings of very high and extreme risk, guidelines should reflect an avoidance of undertreatment with LDL-C lowering goals, far lower than just below a 70 mg/dL threshold.

The landmark REDUCE-IT [92] demonstrated a highly significant MACE risk reduction due to multifactorial effects of high dose pharmacologic enrichment with highly purified, unoxidized, eicosapentaenoic acid. Clinical trials continue to investigate methods to reduce the highly atherogenic TG-rich lipoprotein remnant cholesterol particles and lipoprotein(a) needed to further eradicate lipid and lipoprotein residual risks.

In order to eradicate ASCVD, future clinical trials will need to (1) better assess future risk potential in younger individuals, (2) determine the optimal risk-based age to begin treatment, and (3) the optimal atherogenic lipoprotein cholesterol levels to avoid the initiation of the atherosclerosis process. The degree and urgency of atherogenic cholesterol lowering and global risk management are dictated by levels of ASCVD risk; the aspiration is improved quality lifespan.

Acknowledgments The author would like to thank Dr. Vanita R. Aroda for critical review, feedback, and edits of earlier and current drafts of this review.

Compliance with Ethical Standards

Conflict of Interest Paul D. Rosenblit received clinical trial research site funding from Amgen, Dexcom, GlaxoSmithKline, Ionis, Lilly, Mylan, and Novo Nordisk; speaker faculty honoraria from Akcea, Amgen, and Merck; and advisory board honoraria from Akcea, Esperion, and Novo Nordisk.

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

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- • Of importance
- •• Of major importance

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