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Review Article

A lipidologist perspective of global lipid guidelines and recommendations, part 2: Lipid treatment goals

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Abstract: Having knowledge of worldwide areas of harmonization and consensus regarding lipid guidelines and recommendations may provide clinicians a more global perspective on lipid management. This review examines 8 international scientific/medical organizations that have issued lipid guidelines, recommendations, and position papers: the National Lipid Association (2014), National Institute for Health and Care Excellence (2014), International Atherosclerosis Society (2013), American College of Cardiology/American Heart Association (2013), Canadian Cardiovascular Society (2013), Japan Atherosclerosis Society (2012), European Society of Cardiology/European Atherosclerosis Society (2012), and Adult Treatment Panel III (2001/2004). The focus of part 2 of this perspective was to review sentinel components of lipid guidelines and recommendations as applied to goals of lipid-altering therapy to reduce atherosclerotic cardiovascular disease (ASCVD) events. In general, lipid guidelines and recommendations have significant concordance regarding the need to reduce atherogenic lipoprotein cholesterol levels and are in general agreement on the primary lipid treatment targets. Some guidelines and recommendations differ with regard to ASCVD risk assessment and lipid treatment goals. Despite these differences, substantial agreement exists among lipid guidelines and recommendations in their emphasis on the need for aggressive treatment of hypercholesterolemia, for which the predominance of ASCVD outcomes studies suggests statins as currently the first-line treatment of choice.

Introduction

A brief history of the emergence of lipid guidelines and recommendations was discussed in part 1 of this perspective, which examined the role of atherogenic lipoprotein cholesterol levels, primary lipid and lipoprotein targets of therapy, and other primary/secondary lipid treatment targets, as well as assessment of atherosclerotic cardiovascular disease (ASCVD) risk. The purpose of Part 2 of this review was to summarize 8 worldwide lipid guidelines, recommendations, and position papers with respect to the goal of lipid-altering therapy in reducing ASCVD risk.

Do lipid-altering therapeutic agents reduce atherosclerotic cardiovascular disease risk?

According to most global lipid guidelines and recommendations, low-density lipoprotein cholesterol (LDL-C) level is the primary lipid treatment target. The rationale for

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establishing LDL-C treatment goals is 2 fold: increased LDL-C levels are a strong and independent risk predictor of coronary heart disease (CHD) and ASCVD,[1] and interventions that lower LDL-C levels often reduce CHD and ASCVD risk. Meta-analyses of randomized clinical trials of statins suggest that every 1.0-mmol/L (~40 mg/dL) reduction in LDL-C level is associated with an approximately 20% reduction in cardiovascular disease (CVD) mortality, nonfatal myocardial infarction (MI), and overall cardiovascular events.[2,3] In the Cochrane Database review of 56,934 individuals enrolled in 18 statin trials for primary prevention of CVD, statin therapy reduced the relative risk (RR) of all-cause mortality by 14% and of combined fatal and nonfatal CVD, CHD, and stroke by 25%, 27%, and 22%, respectively.[4] In an analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration of 27 randomized clinical trials of individuals grouped by predicted 5-year risk of a major vascular event and treated with statin therapy, the risk of a vascular event for patients without a history of vascular disease decreased by 15% (rate ratio per 1.0-mmol/L reduction in LDL-C) and all-cause mortality decreased by 9% (rate ratio per 1.0-mmol/L reduction in LDL-C).[3] The benefits of LDL-C lowering are generally consistent in both primary and secondary prevention and in different patient subpopulations.[2,3,5]

A question often arises about whether the ASCVD benefits noted in lipid-altering pharmacotherapy trials are due to cholesterol lowering or to some other "pleiotropic" properties of statins. However, non-statin, lipid-altering drug therapies that lower cholesterol are also associated with reduced ASCVD risk. When administered to patients without elevated triglyceride (TG) levels, fibrates can lower LDL-C levels. A number of outcomes clinical trials support fibrates as reducing ASCVD, although their benefit appears to be predominantly among patients with more elevated baseline TG levels.[6–10] Niacin is a lipid-altering agent that can lower LDL-C at higher doses. Recent ASCVD outcomes trials (AIM-HIGH, HPS2-THRIVE) have not supported niacin as reducing ASCVD risk in statin-treated patients with very low baseline LDL-C levels.[11,12] However, when administered as monotherapy to patients with higher baseline LDL-C levels, data (eg, Coronary Drug Project trial) support niacin as reducing ASCVD events.[13] Bile acid sequestrants reduce cholesterol levels, and resin therapies such as cholestyramine and colestipol reduce ASCVD.[14] Finally, in patients at very high ASCVD risk with baseline LDL-C level of ~95 mg/dL, patients who attained an LDL-C level below 70 mg/dL (mean value ~53 mg/dL) with the addition of ezetimibe to simvastatin experienced significantly reduced ASCVD risk compared with patients who attained an LDL-C level of ~70 mg/dL with simvastatin alone[15]

Thus, clinical trial evidence based on ASCVD outcomes trials supports the benefit of non-statins in reducing ASCVD risk either as monotherapy or sometimes when combined with statins, depending on the patient population studied. In fact, a meta-analysis of non-statin therapies (ie, diet, bile acid sequestrants, ileal bypass surgery) demonstrated that the degree of LDL-C lowering correlates one-to-one with reduction of CHD risk over 5 years.[16]

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The ASCVD benefits of LDL-C lowering are generally consistent in both primary and secondary prevention trials and in different patient subpopulations. However, therapeutic interventions that lower LDL-C levels do not always reduce ASCVD risk. Examples noted previously include the lack of benefit of niacin when added to statins in patients having low LDL-C levels. Also previously noted is that the ASCVD benefits of fibrates appear to be mostly among patients with baseline elevations in TG levels (and lower high-density lipoprotein cholesterol [HDL-C] levels), which is how fibrates are most often used in clinical practice. Estrogens lower LDL-C levels and increase HDL-C levels, and they have a number of other cardiovascular effects that may reduce CVD risk.[17] However, the clinical trial evidence suggests that when hormone therapy (including estrogen) is administered to postmenopausal women, CHD and thromboembolic complications may be increased, not decreased.[18] Torcetrapib was an investigational cholesteryl ester transfer protein inhibitor that lowered LDL-C and substantially increased HDL-C levels,[19] but increased (not decreased) ASCVD risk, which may or may not have been due to agent-specific, off-target effects.[20] What has emerged from these experiences is that not all interventions that lower LDL-C levels will reduce ASCVD risk. Therapeutic agents that lower LDL-C levels are most likely to reduce ASCVD if the agent has the following: (1) natural genetic mutation support,[21] (2) a validated mechanism of action, (3) a lack of off-target harmful effects that might increase ASCVD risk, and (4) favorable signaling in pooled data during phase 2 and 3 clinical trial development.

What are the potential risks and benefits of lowering LDL-C levels below 70 mg/dL?

Although many guidelines recommend lipid treatment goals of LDL-C < 70 mg/dL for patients who have the highest risk of ASCVD, the long-term clinical risks and benefits of achieving even lower levels of LDL-C < 50 mg/dL (<1.3-1.8 mmol/L) are unknown. However, data from aboriginal populations and patients with gene mutations having LDL-C levels between 30 and 70 mg/dL suggest that ASCVD mortality is very low in these subpopulations.[22–24] In Treating to New Targets (TNT), patients with ASCVD were administered atorvastatin 10 or 80 mg per day. The lowest on-treatment LDL-C levels were associated with the lowest rate of death from any cause and the lowest rate of death from ASCVD. Achievement of the lowest LDL-C levels did not result in clinically important differences in adverse experiences (eg, no increase in muscle

complaints, suicide, hemorrhagic stroke, or cancer deaths).[25] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, atorvastatin 80 mg was compared with pravastatin 40 mg per day in patients with acute coronary syndrome.[26] Atorvastatin-treated patients with on-treatment LDL-C levels < 40 and 40 to 60 mg/dL had fewer major cardiac events (ie, death, MI, stroke, recurrent ischemia, revascularization); however, they did not have significant differences in safety parameters (eg, muscle, liver, or retinal abnormalities; increased risk of intracranial hemorrhage; or death). A post hoc analysis of the JUPITER trial suggested that among adults with baseline LDL-C < 130 mg/dL and high-sensitivity C-reactive protein ≥ 2 mg/L, rosuvastatin-allocated patients who attained LDL-C levels < 50 mg/dL had lower CHD risk compared with those without LDL-C < 50 mg/dL, without evidence of an increase in reported adverse experiences.[27,28] This JUPITER analysis in conjunction with the rosuvastatin ASTEROID trial supports the safety of lower LDL-C (<50 mg/dL) in terms of statin side effects and overall safety and tolerability.[27–29]

A newer class of lipid-altering agents are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which may substantially lower LDL-C levels, especially when added to statins. When alirocumab (a fully human monoclonal antibody that inhibits PCSK9) was added to a statin in a 78-week trial of 2341 high ASCVD-risk patients with LDL-C ≥ 70 mg/dL, 37% of those who received alirocumab achieved a calculated LDL-C level < 25 mg/dL at 2 consecutive measurements. The percentage of patients with any adverse event was similar in the 2 study groups: 81.0% with alirocumab and 82.5% with placebo, with no clinically meaningful changes in fat-soluble vitamins or cortisol.[30] Although this was primarily an efficacy/safety trial (ie, not an ASCVD outcomes trial), a post hoc analysis suggested a reduction in the rate of cardiovascular events with alirocumab.[30,31] Two open-label studies evaluated 4465 patients receiving either the fully human PCSK9 inhibitor evolocumab or standard therapy for a median of 11 months.[32] Compared with those with higher LDL-C levels, rates of adverse experiences, serious adverse events, and elevations in aminotransferase or creatine kinase levels were similar among patients in the evolocumab group who had LDL-C < 40 mg/dL or <25 mg/dL. Again, although this was not an ASCVD outcome study, a prespecified exploratory analysis suggested evidence of reduction in ASCVD among patients receiving evolocumab. Finally, in a study of 354 patients receiving the humanized PCSK9 inhibitor bococizumab for 24 weeks, those who received bococizumab and who achieved LDL-C levels ≤25 mg/dL, the incidence of adverse experiences was similar to those who had higher LDL-C levels.[33]

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Patients with very low LDL-C levels due to genetic hypobetalipoproteinemia or abetalipoproteinemia (inherent lack of apolipoprotein b containing lipoproteins) have malabsorption of fat-soluble vitamins and often develop retinal disease, neurologic disorders, or other adverse complications.[34] Conversely, likely because the applicable mechanisms are entirely different, rare isolated case reports of individuals with PCSK9 loss of function may have very low LDL-C (<15 mg/dL) but can be generally healthy.[35,36] Having said this, having a PCSK9 genetic abnormality leading to lower LDL-C levels may not have the same clinical implications as therapeutically induced reductions in PCSK9. Also, although the short-term data described previously regarding very low LDL-C levels found in clinical trials of statin and PCSK9 inhibitors are encouraging, these data are neither within the context of a prospective clinical trial to determine the efficacy and/or safety of very low LDL-C levels nor are they long-term data. More definitive information regarding the safety of very low levels of LDL-C will be available from results of ongoing, more long-term ASCVD outcomes trials of PCSK9 inhibitors.

Does clinical outcomes trial evidence support that lowering LDL-C to 70 mg/dL or less reduces ASCVD risk more than lowering LDL-C to 100 mg/dL or less?

Epidemiologically, a general principle is that the higher the cholesterol value, the higher the ASCVD risk. Conversely, the lower the cholesterol, the lower the ASCVD risk. These principles were key in the hypotheses and protocol design regarding sentinel ASCVD outcomes trials. With specific regard to lipid guidelines and recommendations, a central question is whether lowering LDL-C to 70 mg/dL reduces ASCVD risk more than lowering LDL-C to 100 mg/dL. Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) was a clinical trial wherein patients with a baseline LDL-C of 97 mg/dL (2.5 mmol/L) were randomized to simvastatin 80 or 20 mg per day.[37] Simvastatin 80 mg reduced LDL-C 13 mg/dL (0.35 mmol/L) more than simvastatin 20 mg. The further reduction in LDL-C levels was associated with a 6% proportional risk reduction for major vascular events (RR, 0.94; 95% confidence interval [CI], 0.88–1.01; $P = .10$). A subsequent CTT meta-analysis[2] (which included the SEARCH trial and the PROVE-IT, TNT, IDEAL, and A to Z trials) showed that greater LDL-C lowering in patients with baseline LDL-C of 98 mg/dL (2.53 mmol/L) with higher-dose statins significantly reduced LDL-C by 19.7 mg/dL (0.51 mmol/L) compared with lower-dose statins. The more aggressive LDL-C reduction below ~100 mg/dL with the more-intensive statin regimen resulted in a 15% additional proportional risk reduction for first major vascular event (RR, 0.85; 95% CI, 0.82–0.89; $P < .0001$). Although SEARCH and the CTT meta-analysis supported ASCVD benefit by lowering LDL-C in patients with baseline LDL-C of ~100 mg/dL, they did not specifically address the benefit of achieving specific

LDL-C treatment goals because end-of-study LDL-C values were not reported. Therefore, it may be more illustrative to focus on the 4 sentinel CHD outcomes trials that better explored the LDL-C goal hypothesis: PROVE-IT, TNT, IDEAL, and A to Z.[38–41] Table 1 summarizes randomized, controlled clinical outcomes trials supporting the hypothesis that achievement of an LDL-C of ~70 mg/dL further reduces ASCVD compared with achievement of an LDL-C of ~100 mg/dL.

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Despite the perspective advocated by some that currently available CHD outcomes trials were not designed to evaluate the value of titration of lipid-altering therapy to specific LDL-C goals, evidence from randomized, controlled, clinical ASCVD outcomes trials supports the hypothesis that achievement of an LDL-C level of ~70 mg/dL offers greater protection against ASCVD events than achieving an LDL-C level of ~100 mg/dL with a good margin of safety.

Which ASCVD outcomes evidence supports a lipid-altering drug titration approach to reduce ASCVD risk?

Results from randomized, controlled clinical trials of lipid-altering drugs support the efficacy, and especially the safety, of various lipid-altering pharmacotherapy titration approaches to achieve lipid treatment goals.[42–44]

Regarding ASCVD outcomes, perhaps the most important randomized, controlled, statin trial ever conducted was the Scandinavian Simvastatin Survival Study.[45] This secondary prevention study of 4444 patients is often considered the first study to provide convincing evidence that a statin (simvastatin) reduced not only CHD morbidity and mortality but also reduced overall all-cause mortality. In this randomized, controlled clinical trial, patients were initiated on placebo or simvastatin 20 mg/d. If subsequent total cholesterol exceeded 200 mg/dL (the lipid goal for this study), then, according to the "dosage titration" methods described in the article, the simvastatin 20 mg/d was increased ("titrated") to 40 mg/d via a computer program at the central laboratory, which allowed for dosage adjustments without revealing lipid levels or treatment allocations. Although the lipid level metric at the time was total cholesterol, and not specifically LDL-C, one could make the case that the most important historic, randomized, controlled clinical statin trial was a titration study wherein the statin dose was increased based on attempts to achieve a lipid goal. Similarly, in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Trial, pravastatin was up-titrated from 10 mg to 20 mg to achieve a total cholesterol of <220 mg/dL.[46] In this titration study, CHD was significantly lower in the diet plus pravastatin group than in the diet alone group (66 events vs 101 events; hazard ratio, 0.67; 95% CI, 0.49–0.91; $P = .01$).

In the AFCAPS-TexCAPS trial, individuals with average total cholesterol and LDL-C levels were randomized to lovastatin 20 mg or placebo.[47] The dose of lovastatin was titrated to 40 mg for individuals who did not achieve a goal LDL-C level of <110 mg/dL at 3 months. Lovastatin reduced LDL-C levels by 25% (to 115 mg/dL) from a baseline level of 150 mg/dL and decreased incidence of the first major coronary event (RR, 0.63; $P < .001$), MI (RR, 0.60; $P = .002$), unstable angina (RR, 0.68; $P = .02$), and revascularization procedures (RR, 0.67; $P = .001$).

The ALLIANCE trial evaluated patients with CHD from US managed care database records and implemented a real-world statin titration schedule wherein usual care was compared with titration of atorvastatin dose to achieve an LDL-C goal of <80 mg/dL or a maximum of atorvastatin 80 mg/d.[48] In this study, 72% of atorvastatin-treated individuals achieved goal compared with 40% of individuals receiving usual care. After an average of 51.5 months of follow-up, titration with atorvastatin significantly lowered LDL-C levels (147 mg/dL [3.8 mmol/L] to 95 mg/dL [2.5 mmol/L]) over usual care (146 mg/dL [3.8 mmol/L] to 111 mg/dL [2.9 mmol/L]). This greater LDL-C reduction was accompanied by improved ASCVD outcomes (−17% with atorvastatin vs usual care; $P = .02$).

Thus, whether it be randomized, controlled lipid-altering efficacy and safety trials or randomized, controlled ASCVD outcomes trials, the data support the efficacy—and especially the safety—of a titration strategy based on treatment to lipid goals. ASCVD outcomes trials support ASCVD risk reduction when lipid-altering drug therapy lowers LDL-C to ~70 mg/dL, compared to when the same lipid-altering drug therapy lowers LDL-C to ~100 mg/dL. Finally, as noted previously, in patients at very high ASCVD risk with baseline LDL-C level of ~ 95 mg/dL, patients who attained an LDL-C level below 70 mg/dL (mean value ~53 mg/dL) with the addition of ezetimibe to simvastatin experienced significantly reduced ASCVD risk compared with patients who attained an LDL-C level of ~70 mg/dL with simvastatin alone.[15]

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Evidence-based data such as these from randomized, clinical outcomes trials help support a lipid treatment strategy of dose titration to a specified lipid goal. These data also support the LDL-C cutoff points established by many global scientific organizations—in this latter case, the reduction of LDL-C below 70 mg/dL in patients at very high ASCVD risk. Table 1 summarizes randomized, controlled clinical outcomes trials supporting the hypothesis that achievement of an LDL-C of ~70 mg/dL further reduces ASCVD compared with achievement of an LDL-C of ~100 mg/dL.

Table 1 Randomized, controlled ASCVD outcomes trials supporting an achievement of an end-of-study LDL-C of ~70 mg/dL as having improved ASCVD outcomes compared with end-of-study LDL-C levels ~100 mg/dL

Clinical trial	Intervention	LDL-C at baseline, mg/dL (mmol/L)	LDL-C at end of study, mg/dL (mmol/L)	LDL-C reduction (%)	ASCVD outcome
PROVE-IT[38]	Atorvastatin 80 mg/d	106 (2.74)	62* (1.60)	−41.5	Compared with achievement of an LDL-C of 95 mg/dL, achievement of an end-of-study LDL-C of 62 mg/dL reduced the risk of composite of death, MI, unstable angina, vascularization, and stroke by 16% ($P = .005$ atorvastatin vs pravastatin)
	Pravastatin 40 mg/d	106 (2.74)	95* (2.46)	−10.4	
TNT[40]	Atorvastatin 80 mg/d	97 (2.51)	77† (2.00)	−20.6	Compared with achievement of an LDL-C of 101 mg/dL, achievement of an end-of-study LDL-C of 77 mg/dL resulted in a 22% relative reduction in risk of major CV events (HR, 0.78; 95% CI, 0.69–0.89; $P < .001$)
	Atorvastatin 10 mg/d	98 (2.53)	101† (2.6)	3.1	
IDEAL[41]	Atorvastatin 80 mg/d	121.6 (3.15)	80 (2.07)	−34.2‡	Compared with achievement of an LDL-C of 99.8 mg/dL, achievement of an LDL-C of 80 mg/dL reduced the risk for major coronary events by 11% (HR, 0.89; 95% CI, 0.78–1.01; $P = .07$)
	Simvastatin 20 mg/d	121.4 (3.14)	99.8 (2.58)	−17.8‡	
A to Z[39]	Simvastatin 40 mg/d then 80 mg/d	112 (2.90)	66 (1.71)	−41.1‡	Compared with an achievement of LDL-C of 81 mg/dL, an end-of-study achievement of an LDL-C of 66 mg/dL resulted in an 11% relative reduction in event rate (CV death, nonfatal MI, readmission for ACS, and stroke; HR, 0.89; 95% CI, 0.76–1.04; $P = .14$)
	Placebo then simvastatin 20 mg/d	111 (2.87)	81 (2.10)	−27.0‡	

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

To convert low-density lipoprotein to mmol/L, multiply by 0.0259.

*Median LDL-C achieved during treatment.

†Mean LDL-C levels during the study.

‡Calculated as percent change from aggregate baseline.

Table 2 Summary of guideline use of LDL-C treatment goals and associated clinical trial evidence*

Guideline† Country	Primary and secondary Goals	Evidence: Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
NLA (2014)[52] United States					• Validates and formalizes non–HDL-C <100 mg/dL and LDL-C < 70 mg/dL goal in patients at very high ASCVD risk • Therapy should continue in patients with LDL-C < 40 mg/dL based on evidence suggesting no harm from these lower levels • Advocates either Framingham risk calculator, Pooled Cohort Equations (ACC/AHA), or Framingham long-term risk calculator for quantitative risk scoring • Chronic kidney disease (stage ≥3) added as a high or very high long-term risk • Preference for first-line statin therapy, with statins broken out by intensity (superimposable with 2013 ACC/AHA guidelines) • Moderate- and high-intensity statin therapy is recommended as first line therapy for prevention of ASCVD but recommends in statin intolerant patients alternate regimens to achieve non–HDL-C and LDL-C goals. • Advocates specific goals for patients with hypertriglyceridemia: For those with TG ≥ 500 mg/dL, first priority is lowering TG to <500 mg/dL; for those with TG 200–499, non–HDL-C and LDL-C goals should be achieved in accordance with the patient's risk status
	Primary targets are non–HDL-C and LDL-C; apo B and HDL-C considered a secondary, optional target; TG not a target of therapy	Meta-analysis of 8 trials (38,153 individuals treated with statins)[54]	RCTs	Statin therapy in at least 1 study group	• The HRs for major CV events per 1-SD ↑ in LDL-C (32 mg/dL), non–HDL-C (36 mg/dL), and apo B (27 mg/dL) were 1.13 (95% CI, 1.10–1.17), 1.16 (95% CI, 1.12–1.19), and 1.14 (95% CI, 1.11-1.18), respectively • The association with future major CV events greater for non–HDL-C than for LDL-C and apo B
		Meta-analysis of 2 trials[55]	RCTs (TNT-9319 individuals with stable CHD and LDL-C < 130 mg/dL; and IDEAL- 8699 individuals with a history of myocardial infarction)	High-dose and usual-dose statin (TNT-atorvastatin 10 or 80 mg; IDEAL-simvastatin 20 to 40 mg or atorvastatin 80 mg)	• On-treatment levels of non–HDL-C and apo B had a stronger association with CV outcome than levels of LDL-C
	"Very high risk": Consider high- or moderate-intensity statin therapy, regardless of non–HDL-C or LDL-C; begin treatment at non–HDL-C ≥100 mg/dL and LDL-C ≥ 70 mg/dL. Treatment goals: non–HDL-C < 100 and LDL-C < 70 mg/dL. Optional apo B goal < 80 mg/dL.	AFCAPS/TexCAPS[47]	RCT	Lovastatin 20/40 mg or placebo	• Lovastatin ↓ LDL-C levels by 25% (to 115 mg/dL) from baseline of 150 mg/dL • Lovastatin ↓ major coronary events (37%, $P < .001$) and revascularization (33%, $P = .001$) • No significant effect on total mortality or coronary mortality
	"High risk": begin treatment at non–HDL-C ≥ 130 and LDL-C ≥ 100 mg/dL. Treatment goals: non–HDL-C < 130 and LDL-C	MEGA[46]	RCT	Diet + pravastatin 10-20 mg or diet	• Diet + pravastatin ↓ LDL-C by 18.0% vs 3.2% for diet alone

	< 100 mg/dL. Optional apo B goal < 90 mg/dL "Moderate risk": begin treatment at non–HDL-C ≥ 160 and LDL-C ≥ 130 mg/dL. Treatment goals: non–HDL-C < 130 mg/dL and LDL-C < 100 mg/dL. Optional apo B goal <90 mg/dL. "Low risk": begin treatment at non–HDL-C ≥ 190 mg/dL and LDL-C ≥ 160 mg/dL. Treatment goals: non–HDL-C < 130 mg/dL and LDL-C < 100 mg/dL. Optional apo B goal <90 mg/dL	JUPITER[28]	RCT (17,802 healthy individuals w/LDL-C < 130 mg/dL & CRP ≥2.0 mg/L)	Rosuvastatin 20 mg or placebo	• Diet + pravastatin ↓ TC by 11.5% vs 2.1% for diet alone • CHD was significantly ↓ in the diet + pravastatin group (66 events vs 101 events for diet alone; HR, 0.67; $P = .01$) • Rosuvastatin ↓ LDL-C by 50% and CRP by 37% • Mean 50% ↓ in LDL-C ↓ major CV events (HR, 0.56, $P < 00,001$) • Rosuvastatin ↓ risk of MI ($P = .0002$), stroke ($P = .002$), revascularization or unstable angina ($P < .00001$), and combined MI, stroke, or CV death ($P = .02$)
NICE Lipid Modification Guideline (2014)[56,57] United Kingdom	"Primary prevention": offer atorvastatin 20 mg to people who have a 10% or greater 10-y risk of developing CVD "Secondary prevention": start statin treatment in people with CVD with atorvastatin 80 mg "Follow-up": measure total cholesterol, HDL-C and non–HDL-C in all people who have been started on high-intensity statin treatment at 3 mo of treatment and aim for a greater than 40% reduction in non–HDL-C	—	—	—	—
		SPARCL[58]	RCT (stroke patients without evidence of heart disease)	Atorvastatin 80 mg or placebo	• Atorvastatin ↓ LDL-C by 45% to 73 mg/dL compared with a 4% change in placebo patients to 129 mg/dL • Atorvastatin ↓ risk of second stroke (fatal or nonfatal) compared with placebo over 5 y (11.2% vs 13.1%; HR, 0.84; $P = .03$) • ↓ in incidence of second stroke was specific to ischemic stroke vs hemorrhagic stroke
		ALLIANCE[48]	RCT (patients with CHD)	Atorvastatin 80 mg to achieve LDL-C < 80 mg/dL or up to 80 mg/dL or usual care	• Atorvastatin ↓ LDL-C levels by 34.3% vs 23.3% for usual care ($P < .0001$) • 72.4% and 40.0% of atorvastatin-treated and usual-care patients achieved NCEP goal of LDL-C < 100 mg/dL ($P < .001$) • Atorvastatin reduced time to first CV event compared with usual care (HR, 0.83; $P = .02$)
		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Mean on-treatment LDL-C with high-dose atorvastatin was 62 mg/dL vs 95 mg/dL for standard-dose pravastatin • 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, vascularization, and stroke in intensive treatment group ($P = .005$)
		SAGE[59]	Randomized, double-blind, active controlled (893 ambulatory coronary artery disease individuals, 65–85 y old)	Atorvastatin 80 mg or pravastatin 40 mg	• The least-squares mean absolute change from baseline in total duration of myocardial ischemia at mo 12 was_47.6 min in the atorvastatin group and 46.1 min in the pravastatin group. • 77% ↓ in all-cause mortality with atorvastatin (6 deaths) relative to pravastatin (18 deaths) over 12 mo (HR, 0.33; 95% CI, 0.13–0.83; $P = .014$) • Atorvastatin produced greater ↓ than pravastatin in total cholesterol, LDL-C, TGs, and apo B at mo 3 and 12 ($P < .001$)
		TNT[40]	Randomized, double-blind, active controlled	Atorvastatin 80 mg or atorvastatin 10 mg	• Median on-treatment LDL-C levels were 77 mg/dL in the high-dose atorvastatin group and 101 mg/dL in the 10-mg group • 22% relative ↓ in risk of major CV events in 80-mg group

(*continued on next page*)

Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence			
		Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
		SATURN[60]	Randomized, double-blind, active controlled (1039 individuals with coronary disease)	Atorvastatin 80 mg or rosuvastatin 40 mg	• Comparable overall mortality between groups • Percent atheroma volume ↓ by 0.99% (95% CI, −1.19 to −0.63) with atorvastatin and by 1.22% (95% CI, −1.52 to −0.90) with rosuvastatin ($P < .001$) • The frequency of cardiovascular events was similar in the two groups • Very low levels of LDL-C achieved in both treatment groups, with mean values ≤ 70 mg/dL; HDL-C in both groups ~50 mg/dL
		REVERSAL[61]	Randomized, double-blind active controlled trial	Atorvastatin 80 mg or pravastatin 40 mg	• LDL-C levels reduced to 79 mg/dL in atorvastatin group vs 110 mg/dL in pravastatin group ($P < .001$) • Intensive lowering of LDL-C to <100 mg/dL ↓ progression of coronary atherosclerotic lesions compared with ↓ in LDL-C to 110 mg/dL
		IDEAL[41]	Randomized, open-label, blinded	Atorvastatin 80 mg or simvastatin 20 mg	• LDL-C ↓ from 122 to 79 mg/dL in the 80-mg atorvastatin group, compared with 121 to 102 mg/dL in the simvastatin group (at 1 y) • Major coronary events occurred in 10.4% of simvastatin patients vs 9.3% of atorvastatin patients (P = NS) • No between-group difference in mortality
IAS (2013)[‡,62] Various countries outside the United States	Primary target is LDL-C (non–HDL-C expected to replace LDL-C in future guidelines) apo B considered an optional target Secondary prevention LDL-C < 70 mg/dL (1.8 mmol/L) Non–HDL-C < 100 mg/dL	TNT[40]	Randomized, double-blind, active controlled	Atorvastatin 80 mg or atorvastatin 10 mg	• Median on-treatment LDL-C levels were 77 mg/dL in the high-dose atorvastatin group and 101 mg/dL in the 10-mg group • 22% relative ↓ in risk of major CV events in 80-mg group • Comparable overall mortality between groups
		IDEAL[41]	Randomized, open-label, blinded	Atorvastatin 80 mg or simvastatin 20 mg	• LDL-C ↓ from 122 to 79 mg/dL in the 80-mg atorvastatin group, compared with 121 to 102 mg/dL in the simvastatin group (at 1 y) • Major coronary events occurred in 10.4% of simvastatin patients vs 9.3% of atorvastatin patients (P=NS) • No between-group difference in mortality
		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Median on-treatment LDL-C with high-dose atorvastatin was 62 mg/dL vs 95 mg/dL for standard-dose pravastatin • 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, revascularization, and stroke in intensive treatment group ($P = .005$)
		HPS[63]	RCT (20,536 individuals at high risk for CVD event)	Simvastatin 40 mg or placebo	• Mean difference in LDL-C between groups was ~1 mmol/L favoring active treatment (from baseline of ~3.4 mmol/L) • Statin therapy ↓ all-cause mortality (12.9% vs 14.7%, $P = .0003$)

				• ~24%–25% ↓ in first event rate for nonfatal MI or coronary death (8.7% vs 11.8%, $P < .0001$), nonfatal or fatal stroke (4.3% vs 5.7%, $P < .0001$), and coronary or non-coronary revascularization (9.1% vs 11.7%, $P < .0001$)
	Meta-analysis of 4 trials (TNT, PROVE-IT, IDEAL, A to Z)[64]	RCTs	Intensive vs standard-dose statin therapy	• Higher intensity statins ↓ coronary death of MI ($P < .00001$), and 16% odds reduction of coronary death or any CV event ($P < .00001$)
Primary prevention LDL-C < 100 mg/dL (2.6 mmol/L) Non–HDL-C < 130 mg/dL	MRFIT[65]	Cohort study of 361,662 men	—	• Total cholesterol relationship with risk of CHD and death is curvilinear, with cholesterol levels above the 85th percentile ↑ RR by ~4 times • Total cholesterol ↓ to 180 mg/dL or less over 5 y substantially ↓ risk of ASCVD (primary prevention)
	Genetic (PCSK9) ARIC study[66]	Population-based samples of residents	Not taking lipid-lowering medication	• 2.6% of blacks and 3.2% of whites had sequence mutations in PCSK9 • Blacks had a 28% ↓ in LDL-C levels over 15 y and an 88% ↓ in risk of CHD ($P = .008$) • Whites had a 15% ↓ in LDL-C levels over 15 y and a 47% ↓ in risk of CHD ($P = .003$)
	Genetic (PCSK9)[67]	Myocardial Infarction Genetics Consortium and matched free controls	Individuals with early-onset MI and age- and gender-matched controls	• PCSK9 R46 L reduced risk of MI (OR, 0.40; $P = .00002$) • PCSK9 loss-of-function allele ↓ LDL-C levels and provides protection against MI
	Mendelian Genetic Analysis[68]	Meta-analysis of individuals with 9 polymorphisms in 6 different genes that ↓ LDL-C	—	• All 9 polymorphisms were associated with lower long-term LDL-C levels • Long-term exposure to lower LDL-C was associated with a 54.5% ↓ in risk of CHD for each mmol/L lower LDL-C (3-fold greater CHD risk reduction per unit lower LDL-C than achieved with statin started later in life)
	JUPITER[28]	RCT (17,802 healthy individuals w/LDL-C <130 mg/dL and CRP ≥ 2.0 mg/L)	Rosuvastatin 20 mg or placebo	• Rosuvastatin ↓ LDL-C by 50% and CRP by 37% • Mean 50% ↓ in LDL-C ↓ major CV events (HR, 0.56, $P < .00001$) • Rosuvastatin ↓ risk of MI ($P = .0002$), stroke ($P = .002$), revascularization or unstable angina ($P < .00001$), and combined MI, stroke, or CV death ($P = .00001$)
	ASCOT-LLA[69]	RCT (10,305 hypertensive individuals randomized to lipid-lowering arm or placebo)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 42 mg/dL from baseline of 131 mg/dL • Nonsignificant trend toward ↓ in total mortality (13%, $P = .16$); ↓ in fatal and nonfatal stroke (27%, $P = .024$), total CV events (21%, $P = .0005$), and total coronary events (29%, $P = .0005$)
	AFCAPS/TexCAPS[47]	RCT	Lovastatin 20/40 mg or placebo	• Lovastatin ↓ LDL-C levels by 25% (to 115 mg/dL) from baseline of 150 mg/dL • Lovastatin ↓ major coronary events (37%, $P < .001$) and revascularization (33%, $P = .001$)

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence			
		Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
					• No significant effect on total mortality or coronary mortality
		WOSCOPS[70]	RCT (6595 men with hypercholesterolemia and no history of MI)	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 26% from baseline of 192 mg/dL • Pravastatin ↓ RR of combined EP of nonfatal MI and death from CHD by 31% ($P < .001$); similar ↓ in nonfatal MI (31%, $P < .001$) and death from CHD ($P = .042$) • No effect of pravastatin on deaths from non-CV causes
		CTT collaboration meta-analysis[5]	14 large, long-term RCT outcome studies	More or less intensive statin regimens or statin vs control	• Statin therapy ↓ recurrent CHD events by ~23% (rate ratio) and ↓ stroke events by 17% (CTT) • 12% proportional ↓ in all-cause mortality per mmol/L ↓ in LDL-C (rate ratio, 0.88; $P < .0001$) • 19% ↓ in coronary mortality (rate ratio, 0.81; $P < .0001$) • Proportional ↓ in major vascular events differed significantly ($P < .0001$) according to absolute ↓ in LDL-C achieved • Unknown how much additional benefit can be attained below LDL-C levels of 70 mg/dL (1.8 mmol/L)
ACC/AHA (2013)[51] United States	"Secondary prevention" Primary target: LDL-C Non–HDL-C potential inclusion in future decision-making No recommendations are made for or against specific LDL-C targets Intensity of statin therapy considered the goal of treatment (applied to 1 of 4 major statin benefit groups): clinical ASCVD High-intensity statin therapy should be initiated or continued for adults aged ≤75 y with clinical ASCVD Moderate-intensity statin therapy should be initiated for adults aged >75 y with clinical ASCVD	4D[71]	RCT (diabetics on hemodialysis)	Atorvastatin 20 mg or placebo	• No benefit of atorvastatin on primary end point composite of death from cardiac causes, nonfatal MI, or stroke
		A to Z[72]	RCT	Simvastatin 40 mg →80 mg or placebo→ Simvastatin 20 mg	• 14.2 event rate (CV death, nonfatal MI, readmission for ACS, and stroke) in intensive simvastatin group vs 16.5 in placebo–simvastatin control group (P = NS)
		ACCORD[73]	RCT (diabetics at high risk of CVD)	Open-label simvastatin + fenofibrate or placebo	• Between-treatment first occurrences of nonfatal MI, nonfatal stroke or CV death were not different ($P = .32$) • No significant differences between groups in any secondary outcomes
		ALLIANCE[48]	RCT (patients with CHD)	Atorvastatin to achieve LDL-C < 80 mg/dL or up to 80 mg/dL or usual care	• Atorvastatin ↓ LDL-C levels by 34.3% vs 23.3% for usual care ($P < .0001$) • 72.4% and 40.0% of atorvastatin-treated and usual-care patients achieved NCEP goal of LDL-C < 100 mg/dL ($P < .001$) • Atorvastatin reduced time to first CV event compared with usual care (HR, 0.83; $P = .02$)
		ASPEN[74]	RCT (patients with DM and LDL-C at target levels)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 29% vs placebo ($P < .0001$) over 4 y from baseline of 113 mg/dL

			• No benefit of atorvastatin on primary EP of CV death, nonfatal MI and stroke, recanalization, CABG, resuscitated cardiac arrest, and angina (13.7% for atorvastatin vs 15% for placebo)
AURORA[75]	RCT (patients undergoing maintenance hemodialysis)	Rosuvastatin 10 mg or placebo	• Rosuvastatin ↓ LDL-C levels by 43% from baseline of 100 mg/dL at 3 mo • No effect on primary EP of CV death, nonfatal MI, or stroke (9.2 and 9.5 events per 100 patient-y; $P = .59$) • No effect of active treatment on all-cause mortality
CARE[76]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 32% (to 97–98 mg/dL) from baseline of 139 mg/dL • Pravastatin ↓ major coronary events (24%, $P = .003$), revascularization (26%, $P = .005$), and stroke (31%, $P = .03$) • Showed benefits of statin therapy in patients with average cholesterol levels
CORONA[77]	RCT (patients aged >60 y with systolic heart failure; NYHA II-IV)	Rosuvastatin 10 mg or placebo	• Rosuvastatin ↓ LDL-C levels by 45% (difference between groups; $P < .001$) from baseline of ~3.5 mmol/L • No effect on primary EP at 33 mo of CV death, nonfatal MI or stroke (HR, 0.92; $P = .12$) • No effect of active treatment on all-cause mortality
GREACE[78]	RCT (patients with established CHD)	Atorvastatin 10–80 mg to reach NCEP goal of LDL-C < 100 mg/dL or usual care	• Atorvastatin ↓ LDL-C and non–HDL-C levels by 46% and 44%, respectively, over 3 y • 95% and 97% of patients treated with atorvastatin achieved NCEP goals for LDL-C and non–HDL-C, compared with only 3% of usual-care patients (LDL-C) • 24.5% of usual care patients vs 12% of atorvastatin patients had a CHD recurrent event or died (RR, 0.49; $P < .0001$)
HATS[79]	RCT (patients with CHD and normal LDL-C levels)	Simvastatin 10 mg (titrated to achieve LDL-C < 90 mg/dL during first year) + niacin 1000 mg b.i.d. or antioxidants or simvastatin + niacin + antioxidants or matching placebos	• Simvastatin + niacin ↓ LDL-C by 42% and ↑ HDL-C by 26%, compared with no change in other groups • Average stenosis regressed by 0.4% in the simvastatin + niacin group, compared with progression of 3.9% (placebos), 1.8% (antioxidants), and 0.7% (simvastatin + niacin + antioxidants; $P < .001$) • Frequency of death, MI, stroke, or revascularization was lowest in simvastatin + niacin group (3% vs 14%–24% range in other groups)
HPS[63]	RCT	Simvastatin 40 mg or placebo	• Median difference in LDL-C between groups was ~1 mmol/L favoring active treatment (from baseline of ~3.4 mmol/L) • Statin therapy ↓ all-cause mortality (12.9% vs 14.7%, $P = .003$)

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence			
		Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
		IDEAL[41]	RCT	Atorvastatin 80 mg or simvastatin 20 mg	• ~24%–25% ↓ in first event rate for nonfatal MI or coronary death (8.7% vs 11.8%, $P < .0001$), nonfatal or fatal stroke (4.3% vs 5.7%, $P < .0001$), and coronary or non-coronary revascularization (9.1% vs 11.7%, $P < .0001$) • LDL-C ↓ from 122 to 79 mg/dL in the 80-mg atorvastatin group, compared with 121 to 102 mg/dL in the simvastatin group (at 1 y) • Major coronary events occurred in 10.4% of simvastatin patients vs 9.3% of atorvastatin patients (P=NS) • No between-group difference in mortality
		LIPID[80]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 25% from baseline of 150 mg/dL • Pravastatin ↓ RR of death from CHD (24%, $P < .001$), overall mortality (22%, $P < .001$), MI (29%, $P < .001$), coronary revascularization (20%, $P < .001$), and stroke (19%, $P = .048$) • Pravastatin ↓ risk in a broad range of baseline LDL-C levels
		LIPS[81]	RCT (patients with successful PCI and total cholesterol between 135 and 270 mg/dL)	Fluvastatin 80 mg or placebo	• Fluvastatin ↑ MACE-free survival time over ~4 y ($P = .01$) • 21.4% of fluvastatin group vs 26.7% of placebo group had at least 1 MACE (RR, 0.78; $P = .01$)
		MIRACL[82]	RCT	Atorvastatin 80 mg or placebo	• Mean LDL-C ↓ from 124 mg/dL to 72 mg/dL • Atorvastatin ↓ RR of death, nonfatal acute MI, cardiac arrest w/resuscitation, or recurrent symptomatic myocardial ischemia to 0.84 ($P = .048$) • Atorvastatin 80 mg/d ↓ recurrent ischemic events in first 16 wk
		MUSASHI-AMI[83]	RCT (Japanese patients with acute MI)	Various statins and doses vs no statin (early use after acute MI)	• Statins ↓ composite of CV death, nonfatal AMI, recurrent symptomatic myocardial ischemia, CHF, and stroke 6.1% vs 11.4% ($P = .043$) • Statins ↓ risk of CHF and symptomatic myocardial ischemia ($P = .0154$ and 0.0264, respectively) • Early lipid lowering is beneficial in reducing recurrent CV events
		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Median on-treatment LDL-C with high-dose atorvastatin was 62 mg/dL vs 95 mg/dL for standard-dose pravastatin

				• 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, vascularization, and stroke in intensive treatment group ($P = .005$)
	SPARCL[58]	RCT (stroke patients without evidence of heart disease)	Atorvastatin 80 mg or placebo	• Atorvastatin ↓ LDL-C by 45% to 73 mg/dL compared with a 4% change in placebo patients to 129 mg/dL • Atorvastatin ↓ risk of second stroke (fatal or nonfatal) compared with placebo over 5 y (11.2% vs 13.1%; HR, 0.84; $P = .03$) • ↓ in incidence of second stroke was specific to ischemic stroke vs hemorrhagic stroke
	TNT[40]	RCT	Atorvastatin 80 mg or atorvastatin 10 mg	• Median on-treatment LDL-C levels were 77 mg/dL in the high-dose atorvastatin group and 101 mg/dL in the 10-mg group • 22% relative ↓ in risk of major CV events in 80-mg group • Comparable overall mortality between groups
"Primary prevention" Primary target is LDL-C No recommendations are made for or against specific LDL-C targets Intensity of statin therapy considered the goal of treatment (applied to 3 of 4 major statin-benefit groups): 1. Primary LDL-C ≥ 190 mg/dL 2. Diabetes (40–75 y) with 3. LDL-C 70–189 mg/dL w/o ASCVD 10-y ASCVD risk ≥ 7.5% and LDL-C 70–189 mg/dL w/o ASCVD For primary LDL-C ≥190 mg/dL, use high-intensity statin therapy to achieve >50% ↓ For diabetes (40–75 y) with LDL-C 70-189 mg/dL w/o ASCVD, moderate-intensity statin therapy should be initiated or continued For patients with 10-y ASCVD risk ≥7.5% and LDL-C 70–189 mg/dL w/o ASCVD, therapy should be initiated with moderate- or high-intensity statin	AFCAPS/TexCAPS[47]	RCT	Lovastatin 20/40 mg or placebo	• Lovastatin ↓ LDL-C levels by 25% (to 115 mg/dL) from baseline of 150 mg/dL • Lovastatin ↓ major coronary events (37%, $P < .001$) and revascularization (33%, $P = .001$) • No significant effect on total mortality or coronary mortality
	ASPEN[74]	RCT (patients with DM and LDL-C at target)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 29% vs placebo ($P < .001$) from baseline of 113 mg/dL over 4 y • No benefit of atorvastatin on primary EP of CV death, nonfatal MI and stroke, recanalization, CABG, resuscitated cardiac arrest, and angina (13.7% for atorvastatin vs 15% for placebo)
	AURORA[75]	RCT (patients undergoing maintenance hemodialysis)	Rosuvastatin 10 mg or placebo	• Rosuvastatin ↓ LDL-C levels by 43% from baseline of 100 mg/dL at 3 mo • No effect on primary EP of CV death, nonfatal MI or stroke (9.2 and 9.5 events per 100 patient-years; $P = .59$) • No effect of active treatment on all-cause mortality
	CARDS[84]	RCT (patients with type 2 DM, no history of CV disease, and normal LDL-C levels)	Atorvastatin 10 mg or placebo	• 1.54 per 100 person-y at risk receiving atorvastatin experienced a major cardiovascular event vs 2.46 per 100 person-y at risk of patients allocated to placebo (rate reduction, 37%; $P = .001$) • Atorvastatin ↓ acute CHD events by 36%, coronary revascularizations by 31%, stroke by 48%, and death rate by 27% • Atorvastatin reduces risk of first CV disease event in patients with DM without high LDL-C
	JUPITER[28]	RCT (17,802 healthy individuals w/LDL-C < 130 mg/dL and CRP ≥ 2.0 mg/L)	Rosuvastatin 20 mg or placebo	• Rosuvastatin ↓ LDL-C by 50% and CRP by 37% • Mean 50% ↓ in LDL-C ↓ major CV events (HR, 0.56; $P < 00,001$) • Rosuvastatin ↓ risk of MI ($P = .0002$), stroke ($P = .002$), revascularization or

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence: Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
					unstable angina ($P < .00001$), and combined MI, stroke, or CV death ($P = .02$)
		MEGA[46]	RCT	Diet + pravastatin 10-20 mg or diet	• Diet + pravastatin ↓ LDL-C by 18.0% vs 3.2% for diet alone • Diet + pravastatin ↓ TC by 11.5% vs 2.1% for diet alone • CHD was significantly ↓ in the diet + pravastatin group (66 events vs 101 events for diet alone; HR, 0.67; $P = .01$)
CCS (2012/2013)[85] Canada	Primary target is LDL-C level Alternate lipid markers include non–HDL-C and apo B (newly added) High risk: LDL-C ≤ 2 mmol/L or ≥50% ↓ (LDL-C target of <1.8 mmol/L [70 mg/dL] is justified in some high-risk patients, in line with ATP III and ESC/EAS recommendations)[86,87] Non–HDL-C ≤ 2.6 mmol/L apo B ≤ 0.8 mmol/L	CTT collaboration meta-analysis[2]	26 large, long-term outcome studies	More or less intensive statin regimens or statin or control	• Across all 26 trials, all-cause mortality was reduced by 10% per 1 mmol/L ↓ in LDL-C • No increase in major side effect rates were observed at lower LDL-C levels
		SHARP[88] Additional clinical trials were reviewed but not cited in the guidelines	Randomized placebo-controlled trial in patients with CKD	Simvastatin 20 mg + ezetimibe 10 mg or placebo	• Simvastatin + ezetimibe produced an LDL-C difference of 0.85 mmol/L • The combination ↓ major atherosclerotic events by 17% (11.3% vs 13.4%; rate ratio, 0.83; $P = .0021$) • Significant ↓ in nonhemorrhagic stroke ($P = .01$) and arterial revascularization procedures ($P = .0036$)
	Intermediate risk: LDL-C ≤ 2 mmol/L or ≥50% ↓ Non–HDL-C ≤ 2.6 mmol/L apo B ≤ 0.8 g/L	AFCAPS/TexCAPS[47]	RCT	Lovastatin 20/40 mg or placebo	• Lovastatin ↓ LDL-C levels by 25% (to 115 mg/dL) from baseline of 150 mg/dL • Lovastatin ↓ major coronary events (37%, $P < .001$) and revascularization (33%, $P = .001$) • No significant effect on total mortality or coronary mortality
		WOSCOPS[70]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 26% from baseline of 192 mg/dL • Pravastatin ↓ RR of combined EP of nonfatal MI and death from CHD by 31% ($P < .001$); similar ↓ in nonfatal MI (31%, $P < .001$) and deaths from CHD ($P = .042$) • No effect of pravastatin on deaths from non-CV causes
		ASCOT-LLA[69]	RCT (10,305 hypertensive individuals randomized to lipid-lowering arm or placebo)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 42 mg/dL from baseline of 132 mg/dL • Nonsignificant trend toward ↓ in total mortality (13%, $P = .16$); ↓ in fatal and nonfatal stroke (27%, $P = .024$), total CV events (21%, $P = .0005$), and total coronary events (29%, $P = .0005$)
		JUPITER[28]	RCT (17,802 healthy individuals w/LDL-C <130 mg/dL and CRP ≥2.0 mg/L)	Rosuvastatin 20 mg or placebo	• Rosuvastatin ↓ LDL-C by 50% and CRP by 37% • Mean 50% ↓ in LDL-C ↓ major CV events (HR, 0.56; $P < 00,001$) • Rosuvastatin ↓ risk of MI ($P = .0002$), stroke ($P = .002$), revascularization or unstable angina ($P < .00001$), and combined MI, stroke, or CV death ($P = .02$)

		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Median on-treatment LDL-C with high-dose atorvastatin was 62 mg/dL vs 95 mg/dL for standard dose pravastatin • 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, vascularization, and stroke in intensive treatment group
		TNT[40]	Randomized, double-blind	Atorvastatin 80 mg or atorvastatin 10 mg	• Median on-treatment LDL-C levels were 77 mg/dL in the high-dose atorvastatin group and 101 mg/dL in the 10-mg group • 22% relative ↓ in risk of major CV events in 80-mg group • Comparable overall mortality between groups
		A to Z[72]	Randomized, double-blind, controlled	Simvastatin 40 mg →80 mg or placebo→ Simvastatin 20 mg	• 14.2 event rate (CV death, nonfatal MI, readmission for ACS, and stroke) in intensive simvastatin group vs 16.5 in placebo-simvastatin control group (P = NS)
		IDEAL[41]	Randomized, open-label, blinded	Atorvastatin 80 mg or simvastatin 20 mg	• LDL-C ↓ from 122 to 79 mg/dL in the 80-mg atorvastatin group, compared with 121 to 102 mg/dL in the simvastatin group (at 1 y) • Major coronary events occurred in 10.4% of simvastatin patients vs 9.3% of atorvastatin patients (P = NS) • No between-group difference in mortality
		SEARCH[37]	Randomized, double-blind	Simvastatin 80 mg or simvastatin 20 mg	• 0.35 mmol/L greater ↓ in LDL-C in intensive statin group • 6% proportional ↓ in major vascular events (P=NS)
	Low risk: ≥50% ↓ in LDL-C	JUPITER[28]	RCT (17,802 healthy individuals w/LDL-C <130 mg/dL & CRP ≥2.0 mg/L)	Rosuvastatin 20 mg or placebo	• Rosuvastatin ↓ LDL-C by 50% and CRP by 37% • Mean 50% ↓ in LDL-C ↓ major CV events (HR, 0.56; P < 00,001) • Rosuvastatin ↓ risk of MI (P = .0002), stroke (P = .002), revascularization or unstable angina (P < .00001), and combined MI, stroke, or CV death (P = .02)
		CTT collaboration meta-analysis[3]	27 RCTs	Various statins or placebo	• 1 mmol/L ↓ in LDL-C ↓ major CV events by ~11 per 1000 over 5 y (5%–9% FRS)
JAS-G (2012)[89] Japan	History of CAD: LDL-C < 100 mg/dL No mention of using secondary lipid markers including apo B and non–HDL-C[89]	4S[45]	RCT	Simvastatin 10/40 mg or placebo	• Simvastatin ↓ LDL-C levels by 35% from baseline of 188 mg/dL • Simvastatin ↓ RR of death by 30% (P = .0003) • Significant (P < .05 or lower) ↓ in risk for major coronary events (35%), revascularization (37%), coronary mortality (42%), and total mortality (30%)
		CARE[76]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 32% (to 98–99 mg/dL) from baseline of 139 mg/dL • Pravastatin ↓ major coronary events (24%, P = .003), revascularization (26%, P = .005), and stroke (31%, P = .03) • Showed benefits of statin therapy in patients with average cholesterol levels
		LIPID[80]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 25% from baseline of 150 mg/dL

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence: Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
					• Pravastatin ↓ RR of death from CHD (24%, $P < .001$), overall mortality (22%, $P < .001$), MI (29%, $P < .001$), coronary revascularization (20%, $P < .001$), and stroke (19%, $P = .048$) • Pravastatin ↓ risk in a broad range of baseline LDL-C levels
		MIRACL[82]	RCT (post-ACS)	Atorvastatin 80 mg or placebo	• Mean LDL-C ↓ from 124 mg/dL to 72 mg/dL • Atorvastatin ↓ RR of death, nonfatal acute MI, cardiac arrest w/resuscitation, or recurrent symptomatic myocardial ischemia to 0.84 ($P = .048$) • Atorvastatin 80 mg ↓ recurrent ischemic events in first 16 wk
		PACT[90]	RCT (post-acute MI or unstable angina)	Pravastatin 20-40 mg or placebo	• Pravastatin ↓ RR of death, recurrence of MI, or readmission to hospital for unstable angina (within 30 d) by 6.4% (11.6% vs 12.4%; P=NS)
		A to Z[39]	Randomized, double-blind, controlled	Simvastatin 40 mg →80 mg or placebo → Simvastatin 20 mg	• 14.2 event rate (CV death, nonfatal MI, readmission for ACS, and stroke) in intensive simvastatin group vs 16.5 in placebo-simvastatin control group (P=NS)
		RIKS-HIA[91]	Prospective cohort study from Swedish Register of Cardiac Intensive Care	Various statin or no statin therapy	• At 1 y, adjusted mortality was 9.3% in the no-statin group and 4.0% in the statin group • Early statin treatment ↓ 1-y mortality (RR, 0.75; $P = .001$)
		Ext-ESTABLISH[92]	RCT (post-acute coronary syndrome)	Atorvastatin 20 mg or standard care	• 6 mo after PCI, patients were treated to achieve LDL-C of <100 mg/dL • Early statin administration is a good predictor of MACCE (HR, 0.46; $P = .015$) • Cumulative event-free survival significantly higher in atorvastatin group ($P = .041$)
		Meta-analysis[93]	13 RCTs started within 14 d of hospitalization for acute coronary syndrome	Various statins at different dose intensities	• Early statin therapy for ACS ↓ rate of death and CV events over 2-y follow-up period (HR, 0.81; $P < .001$) • Survival benefits were evident within first 12 mo
	"Primary prevention"[94] Category I (<0.5% risk of CAD death) LDL-C < 160 mg/dL Category II (≥0.5%, <2.0% risk of CAD death) LDL-C < 140 mg/dL Category III (≥2% risk of CAD death) LDL-C < 120 mg/dL	MEGA[46]	RCT	Diet + pravastatin 10–20 mg or diet	• Diet + pravastatin ↓ LDL-C by 18.0% vs 3.2% for diet alone • Diet + pravastatin ↓ TC by 11.5% vs 2.1% for diet alone • CHD was significantly ↓ in the diet + pravastatin group (66 events vs 101 events for diet alone; HR, 0.67; $P = .01$)
ESC/EAS (2011/2012)[86] Europe, Mediterranean Region	Primary target is LDL-C level Secondary targets include non–HDL-C and apo B Very high risk: LDL-C < 1.8 mmol/L (70 mg/dL) or ≥50% ↓ apo B < 80 mg/dL	CTT collaboration meta-analysis[2]	26 large, long-term outcome studies	More or less intensive statin regimens or statin vs control	• Every 1 mmol/L (~40 mg/dL) ↓ in LDL-C is associated with a 22% ↓ in CVD mortality and morbidity • Absolute ↓ to LDL-C level <1.8 mmol/L) or at least a 50% relative ↓ provides the best reduction in CVD

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	non–HDL-C <100 mg/dL (~30 mg/dL ↑ than LDL-C)	TNT[40]	Randomized, double-blind	Atorvastatin 80 mg or atorvastatin 10 mg	• Median on-treatment LDL-C levels were 77 mg/dL in the high-dose atorvastatin group and 101 mg/dL in the 10-mg group • 22% relative ↓ in risk of major CV events in 80-mg group ($P < .001$) • Comparable overall mortality between groups
		IDEAL[41]	Randomized, open-label, blinded	Atorvastatin 80 mg or simvastatin 20 mg	• LDL-C ↓ from 122 to 79 mg/dL in the 80-mg atorvastatin group, compared with 121 to 102 mg/dL in the simvastatin group (at 1 y) • Major coronary events occurred in 10.4% of simvastatin patients vs 9.3% of atorvastatin patients who had previously had an MI (P=NS) • Major CV events and nonfatal MI occurred less frequently in the atorvastatin group • No between-group difference in all-cause mortality
	High risk: LDL-C < 2.5 mmol/L (100 mg/dL) apo B < 100 mg/dL non–HDL-C <130 mg/dL	CTT collaboration meta-analysis[2]	26 large, long-term outcome studies	More or less intensive statin regimens or statin or control	• Every 1 mmol/L (~40 mg/dL) ↓ in LDL-C is associated with a 22% ↓ in CVD mortality and morbidity • Absolute ↓ to LDL-C level <1.8 mmol/L) or at least a 50% relative ↓ provides the best reduction in CVD
		Meta-analysis of 10 trials of 70,388 patients[95]	RCTs (risk factors for CVD but no established CVD)	Various statins and dose intensities tested in large trials	• Statin therapy ↓ risk of all-cause mortality (OR, 0.88), major coronary events (OR, 0.70), and major cerebrovascular events (OR, 0.81)
		Pooled analysis of 20 trials of >65,000 patients[96]	RCTs (primary prevention)	Various statins and dose intensities compared with standard therapy or placebo	• Statin therapy ↓ RR of all-cause mortality (RR, 0.93; $P = .03$), CVD deaths (RR, 0.89; $P = .01$), and MI-attributable mortality (RR, 0.46; $P = .005$)
	Moderate risk: LDL-C < 3.0 mmol/L (115 mg/dL) Low risk: LDL-C < 4.9 mmol/L (190 mg/dL)	—	—	—	—
ATP III (2002 and 2004 update)[87,97] United States	Primary target is LDL-C level Secondary targets include non–HDL-C "Very-high risk" LDL-C < 70 mg/dL (recommended as a therapeutic option)	HPS[63]	RCT (20,536 individuals at high risk for CVD event)	Simvastatin 40 mg or placebo	• Simvastatin ↓ all-cause mortality by 13% ($P = .0003$) • Reductions in major vascular events (24%), coronary death rate (18%), nonfatal MI + coronary death (27%), nonfatal or fatal strokes (25%), and CV revascularization (24%) • Available clinical trial evidence supports an LDL-C goal of <70 mg/dL when risk is very high • LDL-C goal of <70 mg/dL extends to patients with baseline LDL-C < 100 mg/dL
		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Atorvastatin LDL-C, 62 mg/dL vs 95 mg/dL with pravastatin • 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, vascularization, and stroke in intensive treatment group ($P < .005$)
		REVERSAL[61]	Randomized, double-blind active controlled trial	Atorvastatin 80 mg or pravastatin 40 mg	• LDL-C levels reduced to 79 mg/dL in atorvastatin group vs 110 mg/dL in pravastatin group ($P < .001$)

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence			
		Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
					• Intensive lowering of LDL-C to <100 mg/dL ↓ progression of coronary atherosclerotic lesions compared with ↓ in LDL-C to 110 mg/dL
	High-risk CHD or CHD risk equivalents (10-y risk > 20%) LDL-C < 100 mg/dL	HPS[63]	RCT (20,536 individuals at high risk for CVD event)	Simvastatin 40 mg or placebo	• Simvastatin ↓ all-cause mortality by 13% ($P = .0003$) • Reductions in major vascular events (24%), coronary death rate (18%), nonfatal MI + coronary death (27%), nonfatal or fatal strokes (25%), and CV revascularization (24%) • Benefits in older persons
		PROSPER[98]	RCT (5804 individuals aged 70–82 y with history of vascular disease or CVD risk factors)	Pravastatin 40 mg or placebo	• Composite EP of coronary death, nonfatal MI, and fatal or nonfatal stroke ↓15% ($P = .014$) in pravastatin group • Reductions in major coronary events (19%, $P = .006$) and CHD mortality (24%, $P = .043$) in pravastatin group; no significant change in stroke occurrence • Benefits in older persons
		ASCOT-LLA[69]	RCT (10,305 hypertensive individuals randomized to lipid-lowering arm or placebo)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 42 mg/dL from baseline of 132 mg/dL • Nonsignificant trend toward ↓ in total mortality (13%, $P = .16$); ↓ in fatal and nonfatal stroke (27%, $P = .024$), total CV events (21%, $P = .0005$), and total coronary events (29%, $P = .0005$)
		PROVE-IT[38]	RCT (4162 individuals hospitalized for ACS)	Atorvastatin 80 mg or pravastatin 40 mg	• Atorvastatin LDL-C, 62 mg/dL vs 95 mg/dL with pravastatin • 16% ↓ in composite of death, MI, unstable angina resulting in hospitalization, vascularization, and stroke in intensive treatment group ($P < .005$)
		4S[45]	RCT (4444 patients with CHD)	Simvastatin 10/40 mg or placebo	• Simvastatin ↓ LDL-C levels by 35% from baseline of 188 mg/dL • Simvastatin ↓ RR of death by 30% ($P = .0003$) • Significant ($P < .05$ or lower) ↓ in risk for major coronary events (35%), revascularization (37%), coronary mortality (42%), total mortality (30%), and stroke (27%)
		CARE[76]	RCT	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 32% (to 98–99 mg/dL) from baseline of 139 mg/dL • Pravastatin ↓ major coronary events (24%, $P = .003$), revascularization (26%, $P = .005$), and stroke (31%, $P = .03$)

LIPID[80]	RCT	Pravastatin 40 mg or placebo	• Showed benefits of statin therapy in patients with average cholesterol levels • Pravastatin ↓ LDL-C levels by 25% from baseline of 150 mg/dL • Pravastatin ↓ RR of death from CHD (24%, $P < .001$), overall mortality (22%, $P < .001$), MI (29%, $P < .001$), coronary revascularization (20%, $P < .001$), and stroke (19%, $P = .048$) • Pravastatin ↓ risk in a broad range of baseline LDL-C levels
MIRACL[82]	RCT	Atorvastatin 80 mg or placebo	• Mean LDL-C ↓ from 124 mg/dL to 72 mg/dL • Atorvastatin ↓ RR of death, nonfatal acute MI, cardiac arrest w/resuscitation, or recurrent symptomatic myocardial ischemia to 0.84 ($P = .048$) • Atorvastatin 80 mg ↓ recurrent ischemic events in first 16 wk
AVERT[99]	RCT (341 patients with stable CAD referred for percutaneous revascularization)	Atorvastatin 80 mg or percutaneous revascularization followed by usual care	• 13% of patients in the atorvastatin group (↓ LDL-C by 46% to 77 mg/dL) had ischemic events, compared with 21% of patients who underwent angioplasty/ usual care (36% ↓ over 18 mo; $P = .048$) • Atorvastatin was associated with a significantly longer time to the first ischemic event ($P = .03$)
MARS[100]	RCT (270 patients with angiograph-ically defined CAD)	Diet + lovastatin 80 mg or diet + placebo	• No difference in percent diameter stenosis between groups ($P > .20$) • For lesions ≥50%, average percent diameter ↓ 4.1% in lovastatin patients compared with an ↑ in stenosis diameter in the placebo group ($P = .005$) • Lovastatin + diet slows the rate of progression and ↑ frequency of regression in coronary artery lesions
LAARS[101]	RCT (42 patients with severe hypercholesterolemia and extensive coronary artery disease)	Simvastatin 40 mg with or without LDL apheresis	• Simvastatin ↓ LDL-C by 47% to 4.1 mmol/L compared with 63% to 3.0 mmol/L for simvastatin plus biweekly LDL-C apheresis • There was no change in hyperemic mean transit time in the simvastatin group, compared with a ↓ hyperemic mean transit time in the simvastatin plus apheresis group • Aggressive reduction in LDL-C has a favorable effect on regional myocardial perfusion and alleviates ischemia
Post-CABG[102]	RCT (1351 patients who had undergone bypass surgery and LDL-C between 130 and 175 mg/dL)	Lovastatin 40 mg (titrated to 80 mg to achieve LDL-C < 85 mg/dL) or lovastatin 5 mg (moderate-treatment group)	• Aggressive lovastatin doses ↓ LDL-C levels to 93–97 mg/dL vs 132–136 mg/dL for moderate-dose lovastatin ($P < .001$) • Percentage of grafts with progression to atherosclerosis was ↓ in the aggressive dosing group relative to moderate-dose group (27% vs 39%, respectively, $P < .001$)

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Table 2 (*continued*)

Guideline[†] Country	Primary and secondary Goals	Evidence: Clinical trials	Design	Treatments/ regimens	Selected outcomes/recommendations
					• Aggressive LDL-C lowering to <100 mg/dL reduced progression of atherosclerosis in grafts
		FATS extension[103]	RCT (29 patients with coronary artery disease and hyperlipidemia)	Triple therapy with lovastatin 20 mg b.i.d., niacin 500 mg q.i.d., and colestipol 10 g b.i.d.	• Target LDL-C level of ≤100 mg/dL at 8 mo achieved by 83% of patients (controlled-release niacin) vs 52% receiving regular niacin ($P < .01$) • High proportion of patients achieved target goal of ≤100 mg/dL • Controlled-release niacin preferred to standard niacin
		HATS[79]	RCT (patients with CHD and normal LDL-C levels)	Simvastatin 10 mg (titrated to achieve LDL-C <90 mg/dL during first year) + niacin 1000 mg b.i.d. or antioxidants or simvastatin + niacin + antioxidants or matching placebos	• Simvastatin + niacin ↓ LDL-C by 42% and ↑ HDL-C by 26%, compared with no change in other groups • Average stenosis regressed by 0.4% in the simvastatin + niacin group, compared with progression of 3.9% (placebos), 1.8% (antioxidants), and 0.7% (simvastatin + niacin + antioxidants; $P < .001$) • Frequency of death, MI, stroke, or revascularization was lowest in simvastatin + niacin group (3% vs 14%–24% range in other groups)
	Moderately high risk 2 + risk factors (10-y risk 10%–20%) LDL-C < 130 mg/dL "Moderate risk" "2 + risk factors (10-y risk <10%)" LDL-C < 130 mg/dL "Low risk (0–1 risk factors)" LDL-C < 160 mg/dL	ASCOT-LLA[69]	RCT (10,305 hypertensive individuals randomized to lipid-lowering arm or placebo)	Atorvastatin 10 mg or placebo	• Atorvastatin ↓ LDL-C levels by 42 mg/dL from baseline of 132 mg/dL • Nonsignificant trend toward ↓ in total mortality (13%, $P = .16$); ↓ in fatal and nonfatal stroke (27%, $P = .024$), total CV events (21%, $P = .0005$), and total coronary events (29%, $P = .0005$) • Clinical trial evidence suggests that an LDL-C goal < 100 mg/dL is an option • LDL-C goal of <100 mg/dL extends to patients with baseline LDL-C of 100 to 129 mg/dL
		ALLHAT-LLT[104]	RCT (10,355 hypertensive individuals with moderate hypercholester-olemia)	Pravastatin or usual care	• 6-y CHD event rates were similar between groups (9.3% for pravastatin and 10.4% for usual care) • CHD events were significantly reduced in the African-American subgroup
		WOSCOPS[70]	RCT (6595 men with hyper-cholesterolemia and no history of MI)	Pravastatin 40 mg or placebo	• Pravastatin ↓ LDL-C levels by 26% from baseline of 192 mg/dL • Pravastatin ↓ RR of combined EP of nonfatal MI and death from CHD by 31% ($P < .001$); similar ↓ in nonfatal MI (31%, $P < .001$) and deaths from CHD ($P = .042$) • No effect of pravastatin on deaths from non-CV causes
		Meta-analysis[105]	5 trials of 30,817 men and women	Various treated and control populations	• Statin treatment ↓ LDL-C by 28% • Statin treatment ↓ major coronary events (31%) and all-cause mortality (21%)
		AFCAPS/TexCAPS[47]	RCT	Lovastatin 20/40 mg or placebo	• Lovastatin ↓ LDL-C levels by 25% (to 115 mg/dL) from baseline of 150 mg/dL

- Lovastatin ↓ major coronary events (37%, $P < .001$) and revascularization (33%, $P = .001$)
- No significant effect on total mortality or coronary mortality

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACS, acute coronary syndrome; AHA, American Heart Association; apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; b.i.d., twice daily; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CTT, Cholesterol Treatment Trialists; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; EP, end point; ESC, European Society of Cardiology; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; JAS-G, Japan Atherosclerosis Society Guidelines; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac event; MI, myocardial infarction; NCEP, National Cholesterol Education Program; NICE, National Institute for Health and Care Excellence; NLA, National Lipid Association; NS, not significant; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; q.i.d., 4 times daily; RCT, randomized controlled trial; RR, relative risk; SCORE, Systemic Coronary Risk Estimation; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

*Does not include an exhaustive review of various patient populations and demographic factors, including review of guidelines for diabetes, familial hypercholesterolemia, hemodialysis and CKD, peripheral artery disease, and considerations for gender, ethnicity, and age (eg, persons aged older than 75 years).

†Guidelines are generally listed in chronological order from most recent to least current.

‡International Atherosclerosis Society is a position statement.

What are other potential advantages of lipid treatment goals, from a patient-centered perspective?

Beyond the scientific support for recommending lipid goals are practical and behavioral patient care considerations. In collaboration with the National Committee for Quality Assurance, American Society of Health-System Pharmacists, and American Medical Association, the American College of Cardiology (ACC), American Heart Association (AHA), American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Family Physicians, and American Nurses Association have outlined concepts for clinician–patient shared accountability in performance measures.[49] The goal-related concepts included the following: (1) patients who are more actively engaged in self-care, defined as the ability to perform the activities necessary to achieve, maintain, or promote optimal health, are more likely to successfully achieve their treatment goals; (2) the general framework of shared accountability is predicated on partnerships between patients and clinicians, in which patients play an active role in setting goals, making treatment decisions, and assessing outcomes; (3) key conceptual issues for shared accountability are (a) shared goal setting, (b) shared decision-making, (c) shared care planning and monitoring, including patient feedback and self-care, and (d) assessment of patients' longitudinal outcomes; (4) in management of other metabolic diseases, such as hypertension, specific blood pressure goals are useful, as they allow for process measures, such as "treatment intensification or alteration by clinician(s) in response to elevated blood pressure levels;" if the first medication choice or dose titration does not achieve the desired goal, several iterations of this process may be required; (5) defining the appropriate period of evaluation is an important technical feature of performance measures and should be meaningful from both patient and provider perspectives; performance measures must define a discrete period of measurement consistent with the actual treatment goals for the measures; and (6) as a principle of shared accountability, performance on these measures should be reported back to both clinicians and patients in a timely fashion to facilitate shared care management and achievement of best outcomes. Thus, having lipid goals may enhance patient self-care and accountability, improve monitoring of the patient's response to treatment and clinical progress, and better allow for patient/clinician partnership in making treatment adjustments for the duration of lipid therapy.

Perhaps an unintended consequence of the removal of lipid treatment goals in the ACC/AHA guidelines was the proposed recommendation of "retirement" (or removal) of LDL-C measures for screening or assessment of lipid control (http://www.ncqa.org/Portals/0/HomePage/CMC.pdf, accessed December 15, 2014). The guidance that lipid levels should no longer be measured and the subsequent potential

reaction from payers that such lipid measures will not be reimbursed may severely impair the ability of clinicians to assess not only the lipid response to therapy but also the persistence of use of lipid-altering interventions within the context of clinical practice. It is based on challenges presented by the ACC/AHA guidelines, compared with other existing international guidelines that some European authors conclude that existing lipid guidelines and recommendations having lipid treatment goals (eg, European Society of Cardiology/European Atherosclerosis Society guidelines) "seem to be the most wide-ranging, pragmatic, and appropriate choice for European countries."[50]

Author perspective

With regard to the clinical utility of LDL-C and non–HDL-C levels in the management of dyslipidemic patients, the ACC/AHA Guideline authors stated: "This guideline does not recommend their use as performance measures."[51] However, ACC/AHA Guideline authors also recommended that a fasting lipid panel be performed 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter. Conversely, the National Lipid Association (NLA) recommendations recommend routine post-treatment lipid testing, because lipid "treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives, thus supporting efforts to maximize long-term adherence to the treatment plan."[52] Finally, with the continued development of novel lipid-altering drugs, some of those most involved in pharmaceutical administration have advocated for specific LDL-C goals, which serve to facilitate a stepwise approach and rational clinical decision-making, intended to enhance efficacy, safety, and evidence quality.[53]

How do global lipid guidelines, recommendations, and position papers compare regarding primary and secondary treatment goals?

The previous discussion outlines the historical perspective of data supporting guidelines and recommendations. The clinical application of these data is reflected in the 8 international major lipid guidelines and recommendations summarized in Table 2.[51,52,56,62,85,86,89,97]

Regardless of baseline lipid levels, patients at high or very high ASCVD risk may benefit from high-intensity statin therapy.[106] The ACC/AHA cholesterol guidelines (see in the following section) define specific statin benefit groups. Organizations such as the NLA recommend the consideration of moderate- to high-intensity statin for patients with ASCVD or diabetes mellitus, irrespective of baseline lipid levels.[52]

In addition to the general recommendation of statin therapy for patients at high or very high ASCVD risk, 6 of 8 guidelines also provide explicit LDL-C goals aligned with appropriate risk categories.[51,57,62,85,86,89,97] Consistent with the principle that achievement of lower cholesterol levels results in greater ASCVD reduction, an optional goal for LDL-C of <70 mg/dL (<1.8 mmol/L) for individuals at very high ASCVD risk is recommended in 3 guidelines (NLA, "European Society of Cardiology/European Atherosclerosis Society," National Cholesterol Education Program Adult Treatment Panel III),[52,62,86,97] and LDL-C < 2 mmol/L (<77 mg/dL) in 1 lipid guideline (Canadian Cardiovascular Society).[85] The Japanese Atherosclerosis Society guidelines also have established explicit LDL-C goals; however, the lower level of LDL-C was set at <100 mg/dL (<2.6 mmol/L) for patients at high risk.[89]

The NLA has dual lipid treatment goals, with respect to non–HDL-C and LDL-C, with non–HDL-C listed first to emphasize its primary importance (Table 2). The National Institute for Health and Care Excellence (NICE) recommends the use of non–HDL-C, rather than LDL-C, and sets a >40% reduction in non–HDL-C as the primary therapy goal.[56] Percentage reduction of LDL-C is used only to group statins into 3 different intensity levels: low intensity if the produced LDL-C reduction is 20% to 30%; medium intensity if the reduction is 31% to 40%; and high intensity if the reduction is >40%. According to NICE, individuals who have a 10-year risk of developing CVD ≥ 10% (estimated with the QRISK2 algorithm [a registered trademark of the University of Nottingham and EMIS] assessment tool) should be initiated with atorvastatin 20 mg for primary prevention. Statin treatment in people with CVD should be started with atorvastatin 80 mg for secondary prevention. Individuals with non–HDL-C concentration ≥ 7.5 mmol/L are advised to be assessed by a specialist.

In contrast to the other 7 sets of guidelines and recommendations, the ACC/AHA guidelines do not have lipid treatment goals.[51] Rather, the ACC/AHA guidelines provide expectations regarding the percent LDL-C reduction with moderate- or high-intensity statins. A stated justification is that the use of LDL-C goals, and other risk assessment tools has the potential to undertreat some patients at high ASCVD risk,[107–109] although some analyses suggest that most of the increased statin usage would be among older individuals without ASCVD.[110] For individuals who require a 30% to <50% reduction in LDL-C levels, moderate-intensity statin therapy is used. High-intensity statin therapy is initiated in individuals to achieve LDL-C reductions of ≥50%. Instead of setting lipid treatment goals, ACC/AHA guidelines identify 4 major statin benefit groups that include individuals with: (1) clinical ASCVD, (2) primary elevations of LDL-C ≥ 190 mg/dL, (3) diabetes aged 40 to 75 years with LDL-C of 70 to 189 mg/dL and without clinical ASCVD, or (4) without clinical ASCVD or diabetes with LDL-C 70

to 189 mg/dL and estimated 10-year ASCVD risk ≥ 7.5%.[51] In this case, the 10-year risk of ASCVD is determined from the Pooled Cohort Equations.

Author perspective

Recommendations for the 4 statin benefit groups described previously are among the most practical and clinically useful recommendations of the ACC/AHA guidelines. One of the listed statin benefit groups is individuals with untreated primary LDL-C levels ≥ 190 mg/dL. Within the ACC/AHA Guideline document, the National Heart and Lung Blood Institute Grade for this recommendation is "Expert Opinion." Thus, among the most sentinel and clinically useful recommendations made by the ACC/AHA Guidelines, allowance is given for Expert Opinion for clinical recommendations, presumably based on interpretation of available data and clinical judgment.

Conclusion and Summary

Part 2 of this review examined 8 illustrative, international lipid guidelines, and recommendations as they pertain to the goal of lipid-altering therapy in reducing ASCVD risk. These lipid guidelines and recommendations share a high degree of harmonization with respect to emphasizing the importance of treating LDL-C (primary target) and achieving lower LDL-C goals, whether through the approach of managing to an explicit goal, achieving a percentage reduction, or administering to treatment intensity based on the evidence of benefits. With the exception of the treatment–intensity approach recommended in the 2013 ACC/AHA[51] and NICE[56] guidelines, all other assessed guidelines (including 2 US-based guidelines) suggest treatment to specific LDL-C goals (based on risk assessment). Despite some differences, the overall message is that cholesterol lowering, especially with statins, is beneficial in reducing ASCVD risk. Ultimately, the decision as to which guideline or recommendation the clinician chooses to follow should be based on which best fits the priorities of the patient.

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