

New Insights on Optimal Management of LDL-C in High-risk Populations

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Low-density lipoprotein cholesterol (LDL-C) is an established modifiable cardiovascular (CV) risk factor. Data from clinical trials including more than 90,000 participants evaluating lipid-lowering medications has convincingly shown that lowering LDL-C is associated with important reductions in CV morbidity and mortality. Lowering of LDL-C with statin therapy is one of the factors responsible for the reduced incidence of fatal and nonfatal cardiovascular disease (CVD) over the past 30 years.

Over the course of the past quarter century, clinical-trial data have prompted experts to recommend progressively lower targets for LDL-C; in 1988, for example, Canadian experts recommended that LDL-C be lowered to below 3.5 mmol/L for patients considered to be at high risk.¹ Clinical trial data published over the next 20 years led the authors of the 2009 Canadian guidelines to recommend treating high-risk patients (*e.g.*, those with existing vascular disease, diabetes, chronic kidney disease [CKD]) to below the threshold of 2.0 mmol/L.² Recent analyses indicate that further LDL-C lowering will result in even greater benefit. The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis³ suggests that a reduction in LDL-C of 2-3 mmol/L would reduce CVD risk by 40-50%. Consequently, we can expect even lower LDL-C therapeutic targets in the future.

The benefits of LDL-C lowering have been demonstrated in a wide range of patients at risk, including women, the elderly, patients with diabetes, and those with chronic kidney disease (CKD). Recently, the SHARP study⁶ showed that LDL-C reductions in patients with CKD led to important reductions in major CV events.

These were important findings, as the outcomes of lipid lowering in CKD were previously inconclusive.⁷

To achieve low LDL-C levels in patients at risk, the Canadian Cardiovascular Society (CCS) guidelines² recommend simultaneous initiation of lifestyle modification where appropriate, and statin medication. Failure to achieve guideline-specified goals requires either an increased dose of the statin, changing to a more powerful statin, or the addition of another class of lipid-lowering medication. As targets become progressively lower, there will be a greater need to use optimal doses of the most effective statins as well as combination therapy.

This article reviews data that have established LDL-C as one of the most important modifiable risk factors, presents the findings of recent studies showing reducing LDL-C below current recommended levels provides further benefits, and discusses treatment options for lowering LDL-C in high-risk patients.

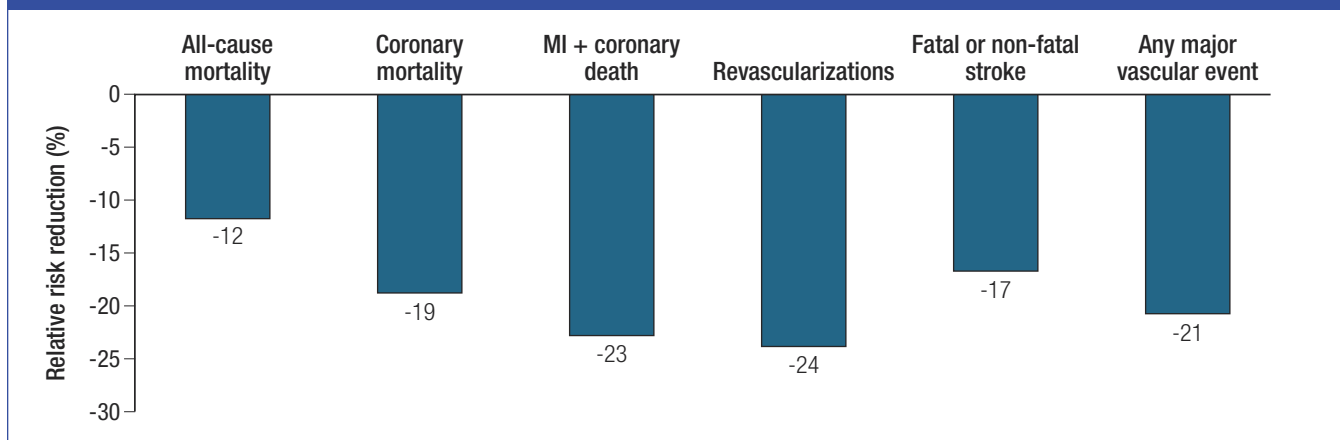
The Importance of Lowering LDL-C

The evidence showing the benefit of LDL-C reduction is compelling. Total cholesterol levels (for which LDL-C is the primary determinant) have long been known to be associated with mortality risk. Data from the MRFIT study⁸ in the 1980s showed that the risk of mortality for an individual with total cholesterol 7.5 mmol/L was more than four times higher than that for an individual with total cholesterol 3.9 mmol/L.

The INTERHEART study⁹ showed that hyperlipidemia was the most significant risk factor for myocardial infarction (MI), with a greater population impact than smoking, hypertension or diabetes.

FIGURE 1.

Reductions in Risk Associated with an LDL-C Reduction of 1.0 mmol/L: CTTC³



In 2010, the CTTC published a meta-analysis evaluating large ($n > 1,000$) trials comparing more intensive statin therapy to less intensive statin therapy (five trials, approximately 40,000 total patients) or statin vs. controls (21 trials, approximately 130,000 total patients).³ The investigators reported that, when all trials were combined, lowering LDL-C by 1 mmol/L was associated with a statistically significant 12% reduction in all-cause mortality and a 23% reduction in MI and coronary death. The risk reductions for these and a number of other important CV endpoints are shown in Figure 1.

Of note, the CTTC investigators concluded that there was no evidence of any threshold within the cholesterol range studied, and that the benefit of LDL-C lowering extended beyond the threshold currently recommended by clinical practice guidelines. Figure 2 shows the continuum of benefit, with lower LDL-C levels correlating with lower coronary event rates.¹⁰ The CTTC authors concluded that lowering LDL-C to about 1-2 mmol/L with more intensive therapy further reduces the incidence of major vascular events without compromising safety.³ The analysis confirms that the lower the LDL-C achieved with treatment, the lower the CVD event rates.

Methods of Lowering LDL-C

Does it matter how LDL-C is lowered in order to reduce CV events? Figure 3 shows the estimated effect of LDL-

C reduction on five-year risk of CHD death or nonfatal MI, from a meta-regression analysis of LDL-C reduction with bile-acid sequestrants, ileal bypass surgery or statin treatment.³¹ This analysis indicates that statin and non-statin interventions appeared to reduce CHD risk in a similar manner with a consistent relationship to the degree of LDL-C lowering. Consequently, CVD risk is reduced proportional to the degree of LDL-C lowering irrespective of the strategy used to achieve the reduction. Which particular strategy is used is of secondary importance to the need for substantial LDL-C lowering to reduce CV risk.¹¹

Lifestyle modification. Clinical practice guidelines stress the importance of lifestyle modification as part of any strategy for reducing CVD risk. However, we should not depend only upon dietary measures to reduce LDL-C. Research has shown that the lipid response to dietary changes is highly variable. Use of the U.S. National Cholesterol Education Program (NCEP) Step 2 Diet, for example, has been associated with LDL-C changes ranging from +3% to -55% in men and from +13% to -39% in women.¹² Other researchers have reported that diet alone does not have any significant benefit on LDL-C unless combined with a regimen of physical activity.¹³ Consequently, to reliably reduce LDL-C in patients at high risk, it is necessary to provide dietary counseling and simultaneously initiate pharmacologic treatment.

FIGURE 2.

Linear Relationship Between LDL-C Concentration and Coronary Events¹⁰

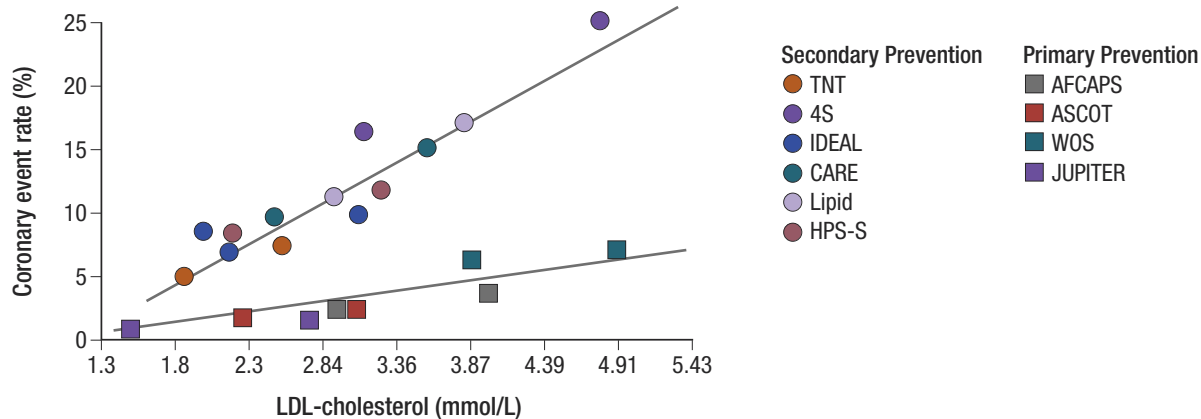
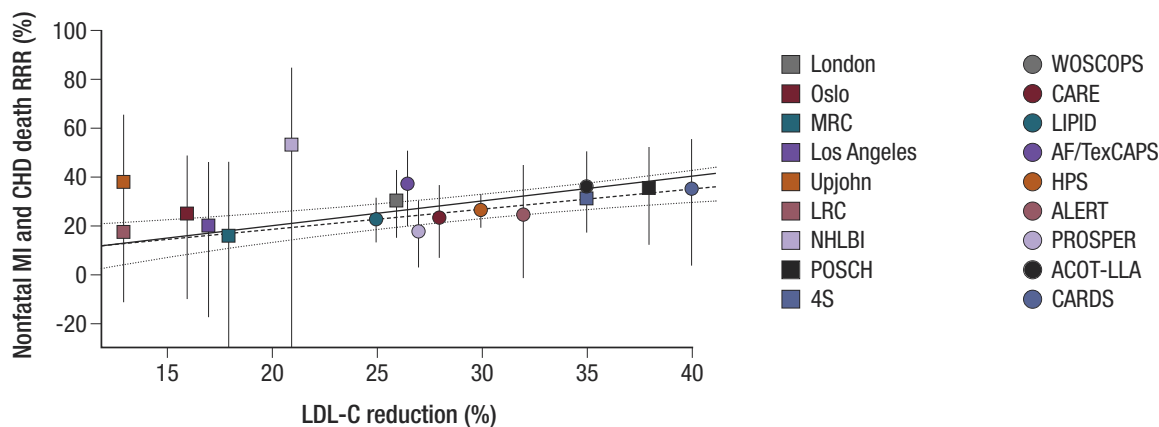


FIGURE 3.

5-Year Risk of Nonfatal MI or CHD Death and Mean LDL-C Reduction³¹



Estimated change in 5-year relative risk of nonfatal MI or CHD death associated with mean LDL-C reduction for trials of diet, bile-acid sequestrants, surgery or statins (dashed line) and 95% probability interval (dotted line). Solid line has a slope of 1.

Statin monotherapy. Clinical practice guidelines recognize the role of statins as the first pharmacotherapeutic step for lowering LDL-C.² The Canadian dyslipidemia guidelines state that the majority of patients will be able to achieve their goals with statin therapy alone, while a significant minority will require combination therapy with another lipid-lowering agent with a different mechanism of action.

Of note, the majority of patients who do not achieve their guideline-specified targets are those who would derive the most benefit from doing so: those in high-risk groups. The proportion of high-risk patients achieving guideline-specified goals has varied considerably in recent surveys, from a low of 30%¹⁴ to a high of 72%.¹⁵

Failure to achieve LDL-C targets is attributable to a number of possible factors, including high baseline

TABLE 1.
Secondary Targets Once LDL-C is at Goal²

Secondary Lipid Parameter	Recommended Target
Total cholesterol:HDL-C ratio	< 4.0
Non-HDL cholesterol	< 3.5 mmol/L
Triglycerides	< 1.7 mmol/L
apoB:apoAI ratio	< 0.80
hs-CRP	< 2 mg/L

apoB = apolipoprotein B.
apoAI = apolipoprotein AI.
hs-CRP = high-sensitivity C-reactive protein.

LDL-C, a high-cholesterol diet, the wide variability of LDL-C reduction by statins, poor adherence to treatment and an inability to tolerate higher-dose statins.

For patients who do not achieve optimal LDL-C levels with their initial statin monotherapy, there are several potential options to consider.

Increase the statin dose. While titrating the dose of the statin can help many patients achieve their target LDL-C if the starting dose is inadequate, it is important to recognize that most of the benefit of statin therapy is achieved with the starting dose. The incremental benefit achieved by doubling the statin dose is approximately only a 5-6% further reduction of LDL-C.¹⁶ At higher statin doses, there is an increased risk of statin-related adverse effects (*e.g.*, muscular symptoms and abnormal liver-function tests).¹⁷

Combination therapy. In 20-30% of patients at high risk for CVD, in a Canadian Rehabilitation clinic,³⁴ the current LDL-C targets cannot be achieved with diet and statin therapy alone. The options available to help these patients attain the LDL-C target include the addition of either bile acid sequestrants, niacin or ezetimibe. Neither bile acid sequestrants nor niacin are well tolerated. Consequently, the current first-line combination for patients failing to achieve LDL-C target with statin monotherapy is ezetimibe.

Adding ezetimibe. The addition of ezetimibe to statin therapy is associated with an additional LDL-C lowering

beyond that achieved with statin therapy alone.^{18,19} In a placebo-controlled, double-blind study involving 769 patients with primary hypercholesterolemia, adding ezetimibe to existing statin therapy led to a further 25% decrease in LDL-C, compared to a 3.7% reduction with the addition of placebo.¹⁸ The use of ezetimibe has also been evaluated in high-risk subgroups, including those with diabetes²⁰ and with chronic kidney disease.^{4,21}

Adding niacin. Niacin (or nicotinic acid) has also been shown to have a favorable impact on lipid levels. Niacin at gram doses is a broad-spectrum lipid-modifying agent that increases HDL-C by up to 30% and reduces LDL-C by 20%, triglycerides by 40% and Lp(a) by up to 26%.²² Currently available clinical trials such as the Coronary Drug Project and the HDL Atherosclerosis Treatment Study suggest a potential benefit from niacin alone or in combination with a statin. However, definitive clinical trials are underway (AIM-HIGH and HPS2-THRIVE) to address CV morbidity and mortality endpoints. The results of these trials are expected in 2012 or 2013. However, niacin remains a poorly tolerated medication that will have limited application even if the trials show benefit.

Because niacin has the ability to significantly increase HDL-C levels and lower triglycerides (with a modest effect on LDL-C), it is perhaps best employed as a complementary agent when LDL-C is at goal. This strategy is in line with the Canadian guideline recommendations,² which state that secondary targets (Table 1) should only be considered after the primary goal (LDL-C) is achieved.

Adding a fibrate. Fibrate therapy may also provide benefit for patients with elevated triglycerides and low HDL-C. The impact of either fenofibrate or gemfibrozil on LDL-C is modest. Patients with high triglycerides may in fact develop an increased LDL-C when started with fibrates.

Fibrates, especially gemfibrozil, inhibit the metabolism of statins; consequently, the combination of gemfibrozil with a statin is contraindicated. In contrast, fenofibrate can be combined with a statin, however increased surveillance with CK monitoring is recommended.²³

Implications for High-risk Groups

For patients at high risk of CV events, such as those with established vascular disease, diabetes or CKD, the absolute

benefit of reducing LDL-C below the recommended targets is substantial.

The CTTC authors concluded that the primary aim for patients at high risk of vascular events should be “to achieve the largest LDL-C reduction possible without materially increasing myopathy risk.” They pointed out that this is a more aggressive position than that recommended by current guidelines, which use a specific numeric threshold. The CTTC authors stated that lowering LDL-C even further in high-risk patients who achieve guideline targets would produce additional benefits, without an increased risk of cancer or non-vascular mortality.

In light of the findings and conclusions from the CTTC meta-analysis, going below the current 2.0 mmol/L threshold and aiming for an even lower target LDL-C is a reasonable goal. Recent evidence in certain high-risk groups supports this hypothesis.

Diabetes is a major risk factor for CVD. The Framingham study showed that the lifetime risk for coronary artery disease in patients with diabetes from age 50 is 67% for men and 57% for women.²⁴ Diabetes is the CV risk factor with the greatest impact on the lifetime development of CVD. CV events are the cause of death for more than three quarters of patients with diabetes.²⁵ Consequently, there is a need for an aggressive CV risk management strategy in these patients. The STENO 2 trial²⁸ showed that an intensive multifactorial approach, which included aggressive control of LDL-C, blood pressure and glucose, halved combined CV events after eight years. After a further five years of follow-up, mortality was also reduced 50% in the group that had received intensive risk factor management. Furthermore, of the risk modalities modified, cholesterol reduction had the greatest impact on CV risk.

While statin monotherapy reduces CV risk in patients with diabetes with or without established CVD, the residual risk for CV events remains high. Furthermore, a substantial number of individuals fail to achieve current recommended LDL-C targets. The recently published DYSIS study³² showed that more than 40% of Canadian patients with diabetes fail to achieve the current LDL-C target of < 2.0 mmol/L. In one study, the addition of ezetimibe to statin monotherapy in patients

with diabetes resulted in an additional 30.9% reduction of LDL-C beyond that achieved with simvastatin 40 mg alone.²⁰ Yet, in the DYSIS study, from data collected in 2008-9, only 14% were taking combination therapy (11% ezetimibe).

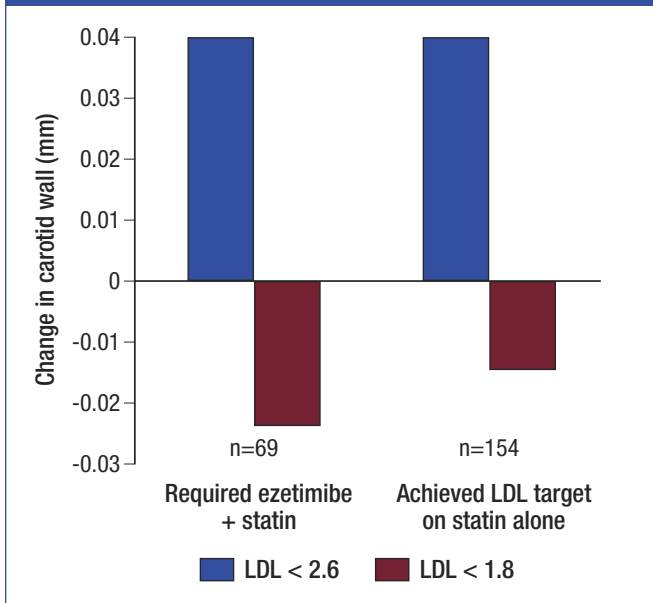
Achieving an LDL-C level lower than the currently recommended target may have additional benefits in patients with type 2 diabetes. The SANDS trial^{4,5} examined the impact of aggressive cholesterol and blood-pressure lowering on the surrogate outcomes of carotid artery intimal-medial thickness (IMT) and left ventricular mass in patients with type 2 diabetes. In this study, 497 patients were randomized to standard intervention for LDL-C and systolic blood pressure (LDL-C target of < 2.6 mmol/L and SBP target of ≤ 130 mmHg) or more aggressive intervention (LDL-C tar-

For patients at high risk of CV events, such as those with established vascular disease, diabetes or CKD, the absolute benefit of reducing LDL-C below the recommended targets is substantial.

get < 1.8 mmol/L, SBP target ≤ 115 mmHg). For the LDL-C goals, patients were initially treated with simvastatin, and ezetimibe was added if the LDL-C goals were not achieved with statin therapy alone. Using this strategy, 31% of patients in the aggressively treated group and 10% in the standard group required ezetimibe (Figure 4). The change in IMT related to the cholesterol modification and not to blood-pressure manipulation. For the standard-treatment group, IMT increased, whereas the aggressively treated patients had a significant regression in IMT. This suggested that the aggressive LDL-C target resulted in a regression of the atherosclerotic plaque. The benefit of the lower LDL-C

FIGURE 4.

Change in Carotid IMT Related to LDL-C Reduction: SANDS^{4,5}



target was observed whether or not ezetimibe was required to achieve the aggressive LDL-C target. Furthermore, the IMT progressed in the standard-treatment group whether or not ezetimibe was required to achieve the LDL-C target. This study confirms that it is the achieved LDL-C target that matters, and not the strategy for achieving that target.

Continuing to aggressively treat dyslipidemia beyond achieving the initial LDL-C goal is a particularly important consideration in diabetes, where the predominant lipid abnormality often involves elevated triglycerides, low HDL-C, and often “normal” or modestly elevated LDL-C. Yet, patients with diabetes have highly atherogenic small-particle LDL, recognized by the association of low HDL-C and modestly elevated triglycerides. These individuals will have an increased apoB lipoprotein, a measure of LDL particle number. Consequently, it is likely not adequate to just reduce LDL-C to below 2.0 mmol/L, especially when the baseline LDL-C is not very high. It is preferable to target the CCS guideline alternative targets of LDL-C reduced by > 50%, or apoB < 0.8 g/L.

Reducing the residual CVD risk in patients with diabetes might be achieved by targeting alternative lipid targets.

However, as yet there are no clinical trials to support strategies other than LDL-C lowering. Lipid abnormalities observed in patients with diabetes such as low HDL-C and increased triglyceride levels might be improved with niacin or a fibrate, after LDL-C targets are achieved. The combination of a statin and a fibrate (simvastatin and fenofibrate) vs. statin alone was evaluated in the ACCORD trial in patients with type 2 diabetes.²⁶ In this trial, the addition of fenofibrate to the statin did not reduce the composite outcome of nonfatal MI, stroke, or CV death. Subgroup analysis suggested that fenofibrate might be more beneficial for men (and potentially harmful for women) and for patients with a high baseline triglyceride level and low baseline HDL-C.

Chronic kidney disease is recognized as being a major CV risk factor; patients with CKD experience higher mortality and CV event rates independent of other conventional CV risk factors.²⁷ Although two major trials (4D³⁰ and AURORA²⁹) in patients with end-stage dialysis-dependent renal failure had failed to show benefit from statin therapy, a meta-analysis³³ has indicated a benefit.

The findings of the recently reported SHARP trial^{6,21} confirm predictions of the meta-analysis. This large, landmark study involved 9,438 patients with advanced CKD (blood creatinine $\geq 150 \mu\text{mol/L}$ in men or $\geq 130 \mu\text{mol/L}$ in women) with no known history of MI or coronary revascularization. They were randomized to receive ezetimibe 10 mg + simvastatin 20 mg daily (in a combination tablet not available in Canada), simvastatin 20 mg daily, or placebo. After one year, when the safety of the simvastatin + ezetimibe combination in this population was confirmed, subjects in the simvastatin group were re-randomized to receive addition of ezetimibe 10 mg daily or placebo.

The baseline mean LDL-C in the SHARP cohort was 2.87 mmol/L. After one year of follow-up, the combination-therapy group experienced a mean LDL-C change of -1.09 mmol/L (*i.e.*, down to a mean of 1.78 mmol/L), compared to -0.75 mmol/L (down to a mean of 2.12 mmol/L) with simvastatin alone and -0.15 mmol/L (down to a mean of 2.72 mmol/L) in the placebo group.⁶

After five years of treatment, there was a 17% reduction of major vascular events in the ezetimibe + simvastatin

FIGURE 5.
SHARP Study: Major Vascular Events²¹

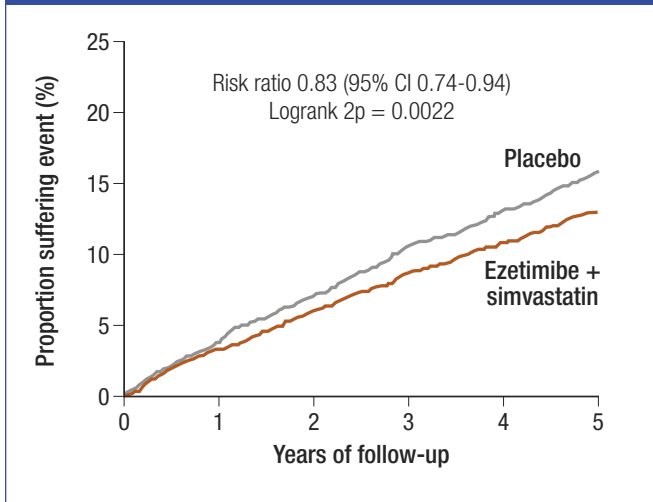
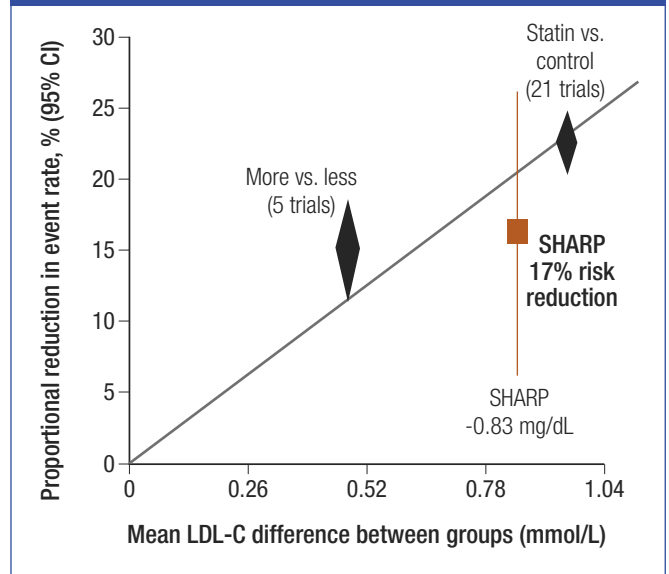


FIGURE 6.
Effects of LDL-C Lowering on Major Atherosclerotic Events: SHARP²¹



group compared to those randomized to placebo (risk ratio 0.83; 95% confidence interval [CI] 0.74-0.94; Figure 5). In this population, only two thirds of the study group remained adherent to medication. Thus, it is likely that the benefit would be considerably greater than that observed, if adherence were better. Consequently, the trial investigators indicated that the combination of simvastatin 40 mg and ezetimibe 10 mg reduces the risk of CV events by a quarter; this translates into avoiding 30-40 events per 1,000 treated for 5 years. The results show how lowering LDL-C to the current targets results in a reduction of events consistent with the predictions of the CTTC meta-analysis discussed above (Figure 6). Similar benefits were observed for patients receiving dialysis as for those with moderately severe renal insufficiency.

Of note, the SHARP trial did not observe any increase in risk of myopathy, liver and biliary disorders, cancer, or nonvascular mortality with treatment using the combination of ezetimibe and simvastatin compared to placebo.²¹

Conclusions


Aggressively targeting CV risk factors in patients at high risk for CV events, such as with established atherosclerotic vascular disease (coronary artery disease, cerebrovascular

disease or peripheral vascular disease) and with diabetes or CKD provides the greatest absolute benefit.

Lowering LDL-C has consistently been associated with improved outcomes in a variety of patient populations at high CV risk. Clinical-trial data has led to a gradual lowering of the LDL-C treatment target recommendation in clinical-practice guidelines. Evidence from a 2010 CTTC meta-analysis has indicated that treatment to LDL-C levels even lower than the currently recommended target of < 2.0 mmol/L likely provides additional benefit.

To achieve these low levels of LDL-C is a challenge. However, clinicians have a number of tools at their disposal to help meet the challenge. Lifestyle modifications in combination with powerful statins such as atorvastatin or rosuvastatin can provide substantial benefit in many cases and achieve LDL-C targets in a majority. For patients who do not reach these goals—and when aiming for even lower LDL-C targets—combination therapy with additional pharmacotherapeutic options should be employed. Both ezetimibe and niacin favorably alter the lipid profile in patients taking statin therapy. However, ezetimibe is most likely to be tolerated in a majority of patients.

Recent evidence in diabetes (e.g., the SANDS study) and CKD (e.g., the SHARP study) illustrates the potential benefit to be gained from lowering LDL-C levels below the 2.0 mmol/L threshold, with and without ezetimibe. Ongoing trials with ezetimibe and with niacin in addition to statin therapy will provide further insight in high-risk groups and

help clinicians make treatment decisions to optimally reduce CV risk through the reduction of LDL-C. 

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