Intensifying statin therapy to maximize cardiovascular risk reduction: is 50 the new 70? Goals are getting old

Evaluation of: Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J *et al.*: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. *Lancet* 376, 1670–1681 (2010). As the primary target of therapy in the management of dyslipidemia, LDL-C has been a central focus for practicing clinicians for more than a decade. National Cholesterol Education Program guidelines encourage physicians to lower LDL-C levels to outlined therapeutic targets on the basis of ongoing randomized controlled trials demonstrating significant benefit in cardiovascular outcomes among primary and secondary prevention individuals. Relevant epidemiologic analysis of cardiovascular outcomes in the USA reports that although statin therapy provides a relative risk reduction of 30%, many coronary heart disease patients at the LDL-C target are still having major events, of which more than half are recurrent. Although statins – the mainstay of therapy – are able to decrease LDL-C by a range of approximately 30–50% depending on the potency and dose of the statin administered, they remain underused in the clinical setting by practicing physicians. There also remains controversy as to whether more intensive lowering of LDL-C provides additional cardiovascular benefit or not. Intensive lowering of LDL-C as it pertains to the incidence of cardiovascular outcomes (including myocardial infarction, coronary revascularization and ischemic stroke) is assessed in this meta-analysis of 170,000 individuals from 26 large, randomized controlled trials. The implications of the Cholesterol Treatment Trialists' Collaboration for practicing physicians are discussed here.

KEYWORDS: cardiovascular outcomes ▪ coronary heart disease ▪ LDL-C ▪ lipids ▪ lipid-lowering therapy ▪ meta-analysis ▪ myopathy ▪ NCEP guidelines ▪ safety ▪ statins

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Background

This paper discusses the results of the recent meta-analysis by the Cholesterol Treatment Trialists' (CTT) initiative [1]. The 2010 executive summary by the American Heart Association reported that nearly a fifth of deaths in the USA are due to coronary heart disease (CHD), with approximately half a million people having recurrent acute coronary events [2]. The persistence of events despite an improvement in the control of LDL-C levels has led some physicians to more aggressively lower LDL-C. While a continuous positive linear relationship between LDL-C and coronary disease risk has been clearly demonstrated in observational studies [3–5], a growing body of evidence now exists that supports these findings in prospective randomized controlled trials (RCTs) [6–8].

Summary of methods & results

The CTT initiative is a multicycle analysis of prospective randomized trials designed to assess the benefit of further reduction in LDL-C on cardiovascular events. The most recent – second cycle – CTT meta-analysis included 26 randomized trials in total, with seven recent statin-versus-placebo trials [9–15] and five additional trials of more- versus less-intensive statin regimens [6–8,16,17]. The studies included were large scale, investigating 1000 patients or more and a treatment duration period of at least 2 years. Individual participant data were used in an intention-to-treat analysis, with 129,526 participants in the statin-versus-placebo group (84,031 men and 45,495 women; 19% Type 2 diabetes mellitus, 52% prior CHD and 15% other vascular disease) and 39,612 participants in the more-versus-less-statin group (31,945 men and 7667 women; 14% Type 2 diabetes mellitus, 100% prior CHD and 11% other vascular disease). Predetermined outcomes for the CTT initiative included all-cause mortality, major coronary events (coronary death or nonfatal myocardial infarction), coronary revascularization (balloon angioplasty or coronary artery bypass

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graft), stroke subtype (ischemic or hemorrhagic) and site-specific cancer. Cardiac mortality, in particular, was reclassified according to 'definite or likely' due to coronary disease, or noncoronary cardiac death (including sudden death, arrhythmia, heart failure and unspecified).

In the meta-analysis of the 21 statin-versus-placebo trials, the weighted mean baseline LDL-C was 142.8 mg/dl (3.70 mmol/l), the weighted mean LDL-C difference at 1 year was 41.3 mg/dl (1.07 mmol/l), and the weighted mean follow-up length was 4.8 years. Events per year in the statin-versus-placebo groups were 1.3 and 1.7% for any major coronary event (weighted relative risk [RR]: 0.76; 95% CI: 0.73–0.79; p < 0.0001), 1.2 and 1.6% for any coronary revascularization (RR: 0.76; 95% CI: 0.73–0.80; p < 0.0001), and 0.7 and 0.8% for any stroke (RR: 0.85; 95% CI: 0.80–0.90; p < 0.0001), respectively. In addition, the RR reduction for ischemic stroke was 0.80 (95% CI: 0.73–0.88; p < 0.0001) with a nonsignificant increase in hemorrhagic stroke of 1.10 (95% CI: 0.86–1.42; p < 0.0001).

In the meta-analysis of the five more-versus-less statin trials, the weighted mean baseline LDL-C was 97.7 mg/dl (2.53 mmol/l), the weighted mean LDL-C difference at 1 year was 19.7 mg/dl (0.51 mmol/l) and the weighted mean follow-up length was 5.1 years. Events per year in the more-versus-less-statin groups were 1.9 and 2.2% for any major coronary event (RR: 0.74; 95% CI: 0.65–0.85; p < 0.0001), 2.6 and 3.2% for any coronary revascularization (RR: 0.66; 95% CI: 0.60–0.73; p < 0.0001) and 0.6 and 0.7% for any stroke (RR: 0.74; 95% CI: 0.59–0.92; p = 0.007), respectively.

In the 26 trials collectively, there were 3.2% major vascular events in the statin or more intensive statin therapy group compared with 4.0% in the control or less intensive statin therapy group (RR: 0.78; 95% CI: 0.76–0.80; p < 0.0001) **(Figure 1)**. In addition, there was a 10% reduction in all-cause mortality for every 38.6 mg/dl (1 mmol/l) LDL-C reduction, which was largely accounted for by the significant decrease in CHD events (RR: 0.80; 95% CI: 0.74–0.87; p < 0.0001). The statin/more group and the control/less group were not significantly different in cancer-related mortality (0.5 and 0.5%, respectively; RR: 0.99; 95% CI: 0.91–1.09; p = not significant [NS]), cancer incidence (1.4 and 1.4%, respectively; RR: 1.00; 95% CI: 0.96–1.04; p = NS), and stroke-related mortality (0.1 and 0.1%, respectively; RR: 0.96; 95% CI: 0.84–1.09; p = NS), per 38.6 mg/dl (1 mmol/l) decrease in LDL-C.

Discussion

Although the age-adjusted prevalence of an elevated LDL-C level in the USA has decreased over the past 30 years, it still remains high despite a significant increase in patient awareness (39.2–63.0%) and the use of lipid-lowering therapy (11.7–40.8%) [2]. While these findings partially reflect the increasing prevalence of the metabolic syndrome and specifically dyslipidemia, they also underscore suboptimal management by practicing physicians. The NCEP guidelines provide clear therapeutic targets that guide the reduction of LDL-C for patients at any given risk level. However, without definitive guidance in national guidelines on how low the LDL-C level may be safely reduced to and whether this reduction provides additional cardiovascular benefit, physicians will continue to show reluctance in aggressively decreasing LDL-C.

In both CTT meta-analysis cycles, the statin-versus-placebo cohort demonstrated cardiovascular benefit through a risk reduction of the 5-year incidence of all-cause mortality, myocardial infarction, coronary death, coronary revascularization, stroke, and any major vascular event in patients on a statin by approximately a fifth (all, p < 0.0001) without increased risk in adverse effects including cancer and rhabdomyolysis. That statin efficacy was maintained independent of age, gender, risk factor and pretreatment LDL-C directly supports the use of statins in a broader population, most notably in primary prevention.

The present meta-analysis provides a basis upon which physicians may further intensify therapy in high-risk individuals to lower LDL-C beyond the current stated goals in the NCEP III guidelines. The five recent randomized trials comparing standard versus intensive statin therapy in secondary prevention patients (100% with prior CHD) were each significantly positive with the exception of the A-to-Z trial [16] and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] trial [17]. Although the primary end point in the A-to-Z trial was not reached, it approached clinical significance in support of high-dose statin therapy (hazard ratio: 0.89; 95% CI: 0.76–1.04; p = 0.14). [16]. In the SEARCH trial, there was a 1.2% absolute risk reduction in major vascular events

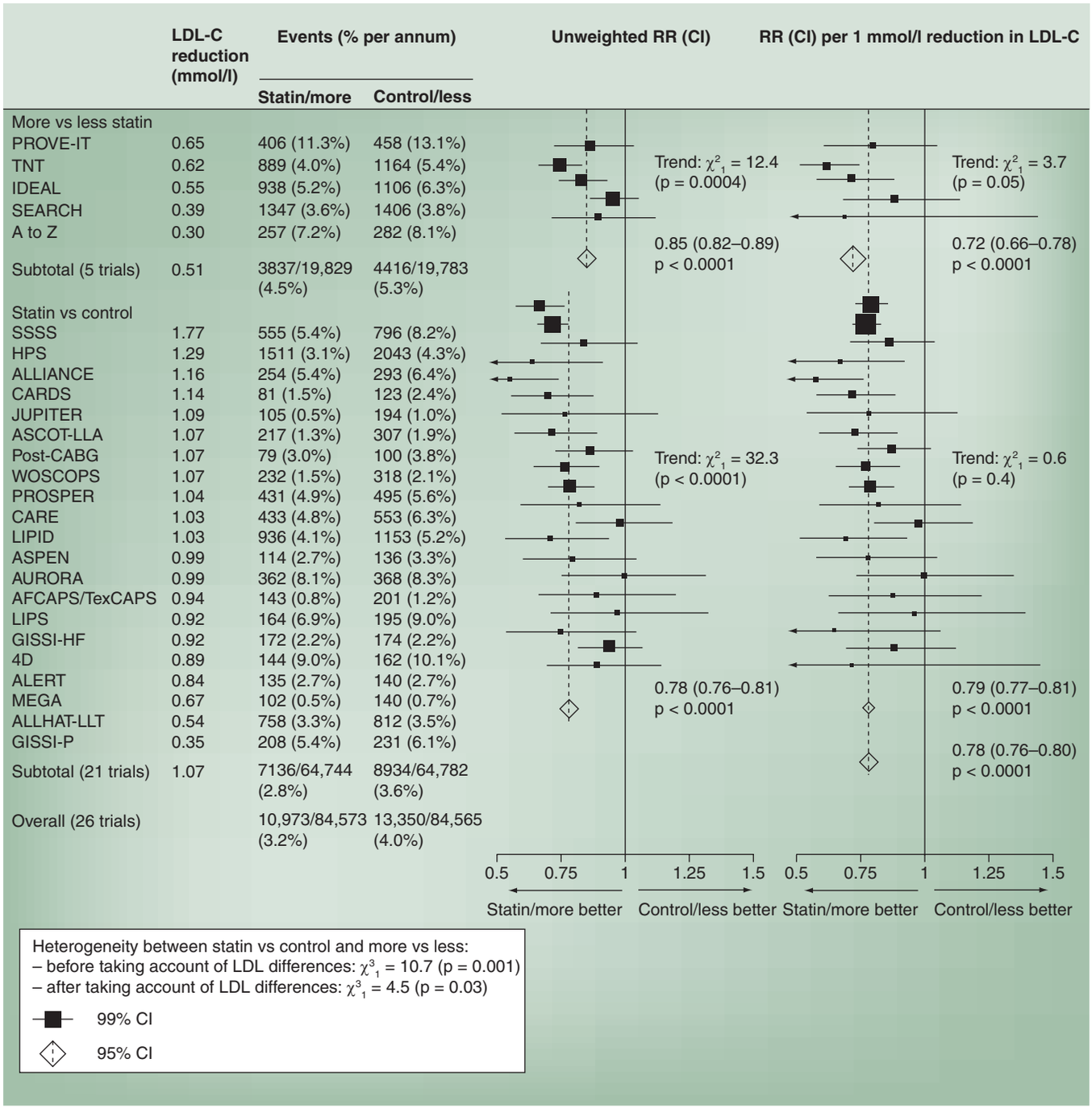

Figure 1. Weighted and unweighted relative risk ratios for any major vascular events by individual trial.
RR: Relative risk.
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between high-dose (80 mg) and standard-dose (20 mg) simvastatin therapy with a nonsignificant difference in vascular and nonvascular death rates. Although not a statistically significant decrease, the 6% risk reduction in major vascular events corresponds to a 13.5 mg/dl (0.35 mmol/l) LDL-C reduction, which is proportionally consistent with the findings of the other pooled statin trials (i.e., a 20% risk reduction per 1 mmol/l [38.6 mg/dl] LDL-C reduction).

Importantly, in the standard versus intensive statin cohort, even individuals who were within the lowest tier baseline LDL-C (<77 mg/dl or 2 mmol/l, mean 66 mg/dl) demonstrated a significant risk reduction of 29% in major vascular

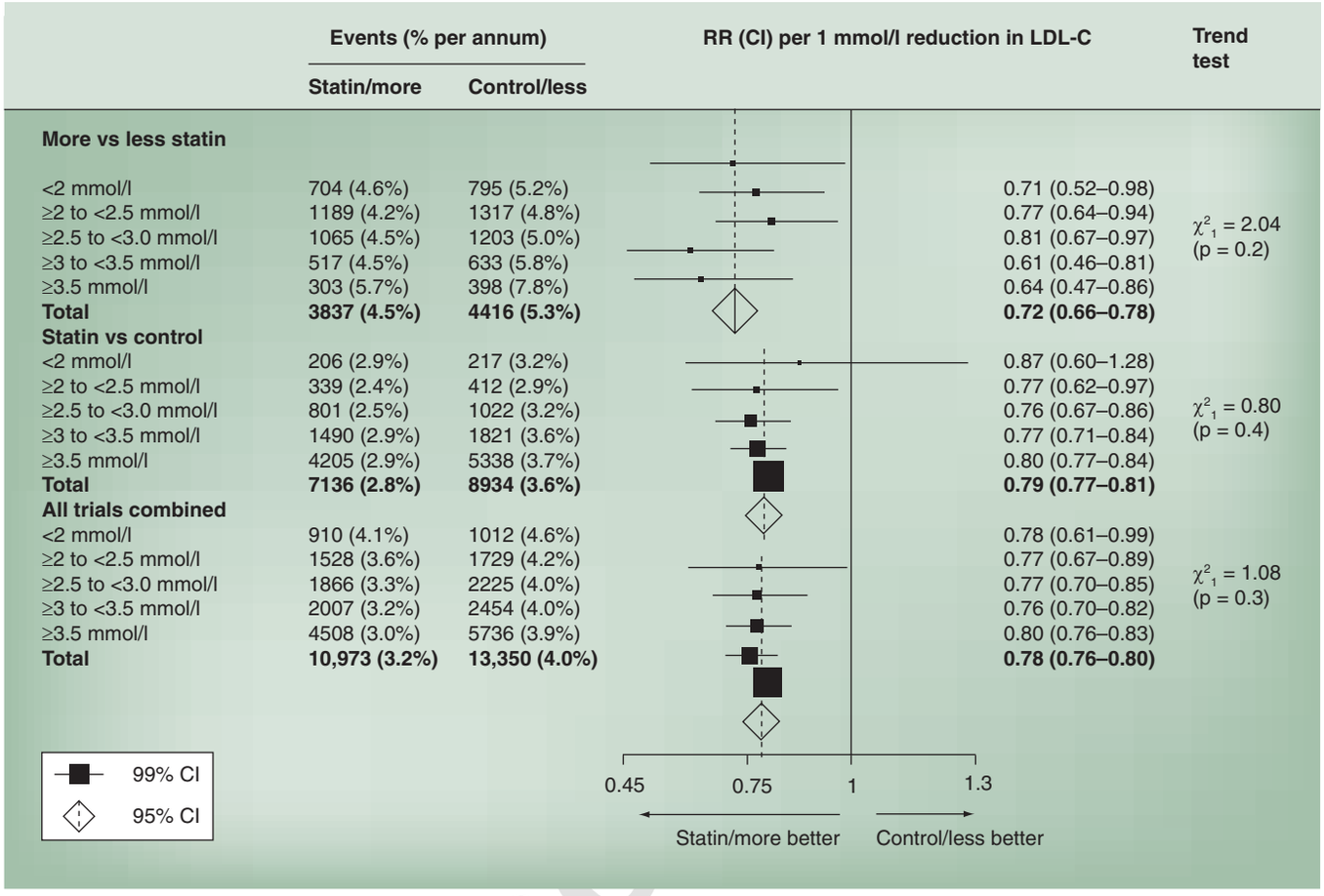

Figure 2. Effects on major vascular events per 1.0 mmol/l reduction in LDL-C, by baseline LDL-C concentration on the less intensive or control regimen. Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1.0 mmol/l LDL-C difference at 1 year. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs.
RR: Relative risk.
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events for every 38.6 mg/dl (1 mmol/l) additional decrease in LDL-C level **(Figure 2)**. Thus, for a large group of patients already considered to be the target LDL of less than 70 mg/dl (1.8 mmol/l), lowering their LDL further to approximately 50 mg/dl (1.3 mmol/l) resulted in further risk reduction. In the 26 trials collectively, the risk reduction per 1 mmol/l LDL-C reduction was 22%. Given the maintained linear relationship between LDL-C reduction and risk reduction, this would correspond to a 40% risk reduction for a 2 mmol/l decrease in LDL-C, and a 50% risk reduction for a 3 mmol/l decrease in LDL-C. These significant decreases in major vascular events provide a compelling basis for physicians to aggressively lower LDL-C beyond the currently stated goals.

With regard to the safety of statin therapy, there were very low rates of rhabdomyolysis in the statin-versus-placebo trials as expected. However, myopathy and rhabdomyolysis are dose-dependent processes, thus the statin-versus-placebo studies are of limited utility since they generally studied low-dose statins. In the present analysis, the inclusion of high-dose statins in the more-versus-less subset of trials is more instructive when analyzed collectively. Individually, the Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE IT]-TIMI 22 [8], Treating to New Targets [TNT] [6], and Incremental Decrease in Endpoints through Aggressive Lipid Lowering [IDEAL] [7] trials each reported nearly equal and very low rates of rhabdomyolysis in low- versus high-dose statin arms (all <0.1%). The A-to-Z [16] and SEARCH [17] trials reported a small increase of 0.10–0.13% in rhabdomyolysis in the high-dose statin groups. Together, these findings underscore the exceptionally safe profile of high-dose statin therapy, which is comparable with less

intense regimens including placebo. However, some of the low rates of myopathy and rhabdomyolysis may partially reflect selection bias in the clinical trials for healthier participants, as well as exclusion of patients with a history of muscle symptoms on statins.

The concern that statin therapy may increase risk for malignancy was adequately addressed in the present study. Cancer was found to be of equal incidence (0.5% per annum) in statin/more and placebo/less treated individuals in all 26 trials (RR: 1.00; 95% CI: 0.96–1.04; p = 0.9), which was consistent with findings in substratified analyses of the statin-versus placebo-cohort and the more-versus-less-statin cohort.

The collective findings of a proportional risk reduction of major vascular events that corresponds directly to the absolute LDL-C reduction achieved without an increase in adverse effects, warrants physicians to more aggressively manage patients at risk for cardiovascular disease. Once the NCEP III goals have been met, the LDL-C level should continue to be a target of therapy with the goal of achieving the greatest absolute reduction possible. Importantly, in considering high-risk individuals, the relative risk reduction achieved represents a significantly larger absolute risk reduction with intensification of statin therapy. Therefore, it may no longer be acceptable for practicing physicians to maintain therapy once the LDL-C goal has been achieved, but instead to consider intensifying therapy whenever possible, particularly in high-risk individuals who are likely to have the greatest benefit.

Future perspective

This year, the USA will be releasing its updated NCEP-ATP IV guidelines on lipid management. It is anticipated that LDL-C and non-HDL-C will continue to be important cornerstones of lipid management. However, much debate remains regarding whether newer biomarkers should be included such as apoB, LDL particle number or C-reactive protein [CRP]. To date, new evidence suggests that non-HDL-C and apoB predict risk better than LDL in the general population and are better markers of residual risk after statin treatment [18]. Whether they will be considered or added as adjunctive therapeutic targets still remains speculative. Regardless of the updated NCEP IV panel results, statins will remain the main treatment in our pharmacotherapy armamentarium since they have the best evidence base for risk reduction. Based on the recent CTT meta-analysis, future guidelines will need to be re-evaluated and the goals of therapy may need to be revised with lower cutoff points for LDL goals. The use of more intensive statin therapy and the use of more potent statins will inevitably need to take place in order to meet new, more aggressive target goals. We advocate that practicing physicians move toward the intensification of therapy to achieve the greatest absolute reduction in LDL-C without increasing the known side effects of statins, which can interfere with long-term adherence.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

LDL-C in cardiovascular risk stratification & management

- LDL-C is the primary target of lipid-lowering therapy and statins are the most effective therapy to lower LDL-C and reduce cardiovascular events.
- Statins have been found to reduce major cardiovascular events including significant reductions in nonfatal myocardial infarction and coronary heart disease death, coronary revascularizations, ischemic stroke and total mortality.

LDL-C reduction beyond National Cholesterol Education Program goals

- Observational studies support that further reductions in LDL-C may have additional cardiovascular benefits.
- Randomized trials have individually and collectively demonstrated a direct linear reduction in cardiovascular risk that corresponds to the absolute LDL-C reduction achieved.

Safety & adverse effects

- High-dose and high-potency statins did not demonstrate any significant increased risk of rhabdomyolysis.
- High-dose and high-potency statins did not demonstrate any significant increased risk of any type of cancer as measured by incidence as well as mortality rates.

Executive summary

Moving forward

- Statins are underused based on available epidemiologic data and many high-risk patients remain above LDL-C goal
- Physicians must work with patients to achieve the greatest absolute LDL-C reduction that is possible without incurring significant side effects such as myalgia or myopathy.
- Existing evidence suggests that that even after the LDL-C goal has been achieved, additional LDL-C reduction will lead to further cardiovascular risk reduction.
- Patients with coronary heart diease and at high vascular risk warrant more aggressive therapeutic targeting of LDL-C since their greater absolute risk leads to greater absolute risk reduction.
- Given the proven benefits of statins in cardiovascular (CV) disease risk reduction, the use of more potent statins and statins at higher doses will result in greater CV risk reductions.
- New guidelines will need to reflect that no threshold level of LDL-C has been identified and that larger reductions in LDL-C will result in greater CV disease risk reductions.

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