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Scientific Update™

Targeted Cholesterol Reduction and Atherosclerosis: The Impact of Lower Targets for LDL Cholesterol on Atherosclerosis in Patients with Diabetes

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Reduction of low-density lipoprotein cholesterol (LDL-C) is associated with improved cardiovascular (CV) outcomes in patients both at risk for and with established vascular disease. Guideline targets for cholesterol lowering have steadily fallen; consequently, it has become more difficult to achieve the lower targets with statins alone. In patients who fail to achieve LDL-C targets with optimum statin therapy, the use of the cholesterol-absorption inhibitor, ezetimibe, is a strategy recommended by clinical guidelines to further reduce LDL-C. Recent trials have investigated the impact of a combination of ezetimibe and statin therapy on atherosclerosis in high-risk patients. The Stop Atherosclerosis in Native Diabetics Study (SANDS) indicates that achieving aggressive LDL-C lowering targets retards atherosclerosis more than using conservative targets. Furthermore, patients who require ezetimibe to achieve the aggressive LDL-C targets have similar protection from atherosclerosis as those who attain the same LDL-C goal on statins alone. This issue of *Cardiology Scientific Update* discusses strategies of optimal LDL-C reduction, diabetes and CV disease in the North American Indian population, and the implications of the SANDS trial.

Benefits of statin therapy related to achieved LDL-C

The Cholesterol Treatment Trialists' (CTT) collaboration meta-analysis[1] of 14 randomized statin trials using data from 90 000 subjects revealed that the proportional reductions of major coronary events, coronary revascularization, and stroke were linearly related to the LDL-C achieved on treatment. A meta-regression analysis[2] related CV outcomes to LDL-C reduction and demonstrated a linear relationship independent of the method to achieve LDL-C reductions. High-dose compared with low-dose statin therapy was found to provide an incremental reduction in CV events in patients at high risk. The TNT (Treat to New Targets) study[3] demonstrated that atorvastatin 80 mg compared with 10 mg daily resulted in LDL-C levels of 1.8 and 2.6 mmol/L respectively, a 2.2% absolute reduction of major CV events, and a 22% relative reduction in risk (hazard ratio [HR] 0.78; 95% confidence interval [CI], 0.69 to 0.89; $P<0.001$). In a recent visit to Toronto, Dr. John LaRosa discussed a *post hoc* analysis of the TNT study[4] finding that outcomes are related to LDL-C levels achieved after 3 months of treatment. This relationship was observed when the analysis was performed for both doses of atorvastatin. For the total group of TNT patients, there was a 0.7% relative risk reduction in major CV events for each 1 mg/dL reduction of LDL-C. However, the benefit of atorvastatin 80 mg compared with 10 mg was lost when adjusted for the on-treatment LDL-C level. These data support the hypothesis that the benefit of LDL-C reduction relates to on-treatment LDL-C levels and is independent of the way the reduction is achieved.

Lipid management in the patient with diabetes

Individuals with diabetes have a very high lifetime risk of developing atherosclerotic CV disease. Coronary heart disease is the leading cause of death in this population. Multiple clinical trials and a meta-analysis[5] have indicated that patients with diabetes have similar relative benefits from statin therapy as nondiabetic individuals. However, since the absolute risk for CV events is high in the person with diabetes, the absolute benefit is substantially greater. Furthermore, the Collaborative Atorvastatin Diabetes Study (CARDS)[6] demonstrated that atorvastatin (10 mg daily) reduced CV events in patients with diabetes, but no evident CV disease, with "normal" and low LDL-C (median 3.1 mmol/L). In the diabetes cohort of the TNT trial,[7] atorvastatin (80 mg) resulted in a 0.6 mmol/L lower LDL-C than in patients receiving 10 mg of atorvastatin (2.0 mmol/L vs

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2.6 mmol/L). Those receiving atorvastatin (80 mg) had a 25% lower CV event rate than the group receiving 10 mg. In patients with diabetes, the STENO-2 study[8,9] indicated that cholesterol reduction with statins contributed 70% of the reduction of CV outcomes;[10] whereas, other risk factors accounted for much smaller contributions to risk reduction (eg, blood pressure [BP] lowering [8%], and glycemic control [10%]).

Carotid artery intima-media thickness as a surrogate measure for atherosclerosis

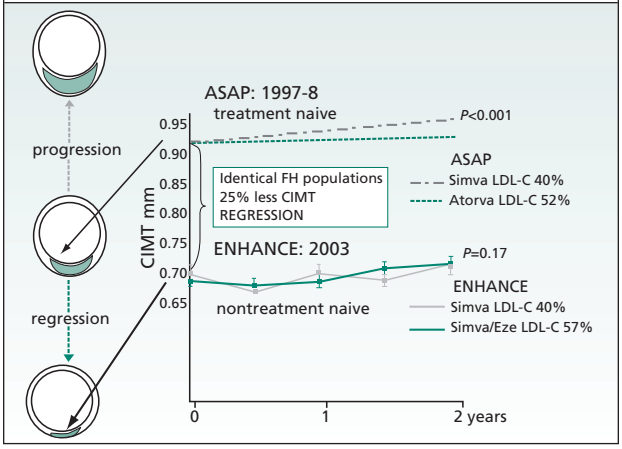
Carotid artery intima-media thickness (CIMT) is a well-established method of noninvasively assessing early atherosclerosis. CV event rates have been related to the level of CIMT;[11,12] furthermore, the rate of CIMT progression is well-characterized in patients with diabetes.[13] CIMT may regress or stabilize if LDL-C is substantially reduced. The Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial[14] in patients with familial hypercholesterolemia (FH) revealed that patients receiving atorvastatin (80 mg) had a 50.5% reduction in LDL-C that was associated with a 0.03 mm decrease in CIMT. However, the subjects receiving simvastatin (40 mg) had a smaller reduction in LDL-C (41%) with a resulting 0.036 mm increase in CIMT.

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial[15] was also conducted in FH subjects and failed to demonstrate any impact on CIMT from the combination of simvastatin and ezetimibe compared with simvastatin alone, despite an additional 17% reduction of LDL-C with the combination therapy. A significant problem in the ENHANCE design was the inclusion of patients who had been vigorously treated with statins, giving a baseline CIMT (0.69 mm) in the normal range. In contrast, the baseline CIMT of the ASAP trial was 0.9 mm. Consequently, it is not surprising that for the ENHANCE trial, the additional LDL-C reduction was unable to reduce a normal CIMT (Figure 1). The CASHMERE[16] (Carotid Atorvastatin Study in Hyperlipidemic post-MEnopausal Women: a Randomized Evaluation of atorvastatin versus placebo) trial, also in a patient population with baseline CIMTs in the normal range, failed to show any reduction in CIMT from atorvastatin compared with placebo.

Diabetes and CV disease in North American Indian populations

Extensive epidemiological evidence has revealed a very high incidence of both diabetes and CV disease in aboriginal populations; for example, the Strong Heart Study indicated a 50% overall prevalence of diabetes,[17] and up to 70% of women in these communities will develop diabetes.[18] The majority of these individuals develop insulin resistance and diabetes consequent to obesity and inactivity. Diabetes in this population confers an HR for the development of atherosclerotic CV disease of 6.3 in women and 3.1 in men, relative to individuals from the same population without diabetes. The population-attributable risk (the proportion of coronary heart disease that can be attributed to diabetes) is 76% in women and 55% in

Figure 1. Comparison of CIMT response to LDL cholesterol reduction in the ASAP and ENHANCE trials[14,15]



There was a 25% lower baseline for CIMT in the ENHANCE study with similar patient populations, suggesting that prestudy treatment had regressed CIMT to normal levels. CIMT = carotid-artery intima-media thickness; Simva = simvastatin; Atorva = atorvastatin; Eze = ezetimibe; FH = familial hypercholesterolemia

men, and these relationships are observed over all age ranges. There is a strong association in this population between LDL-C,[19] BP levels,[20] and the incidence of CV events. Consequently, it is important to determine whether a strategy that lowers both LDL-C and BP beyond current targets could help slow or regress CV disease progression in this very high-risk population.

SANDS

SANDS[21] investigated whether more aggressive reductions of BP and LDL-C compared with treatment to current goals would retard atherosclerosis. The study was carried out at 4 clinical centres in the United States and included American Indians as defined by the Indian Health Service Criteria. Patients recruited for this study included 548 men or women, ≥40 years old with type 2 diabetes, systolic BP >130 mm Hg, LDL-C >2.59 mmol/L, and no prior CV events. The ability to easily measure CIMT was an inclusion requirement. The study was a randomized, open-label study with blind endpoint assessment that compared the progression of subclinical atherosclerosis in individuals treated to reach aggressive LDL-C targets of ≤1.81 mmol/L, and systolic BP of ≤115 mm Hg versus standard targets of ≤2.59 mmol/L and ≤130 mm Hg. The algorithm for hypertension management was based on the recommendations of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) guidelines. The algorithm for achieving lipid targets was based on the recommendations of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III). If lifestyle modification did not achieve the LDL-C target, treatment was initiated with a statin and when statins failed to lower LDL-C below targets, combination treatment with ezetimibe was initiated. For patients failing to achieve the non-high-density lipoprotein cholesterol (HDL-C) target, treatment with fish-oil, fenofibrate, or niacin was recommended, but glucose control in both groups was left to the primary-care

provider. The impact of the treatment strategies was assessed by CIMT and echocardiographic measurement of left ventricular mass, with measurements at 18 and 36 months. The primary outcome was the change in CIMT at 36 months.

Population characteristics

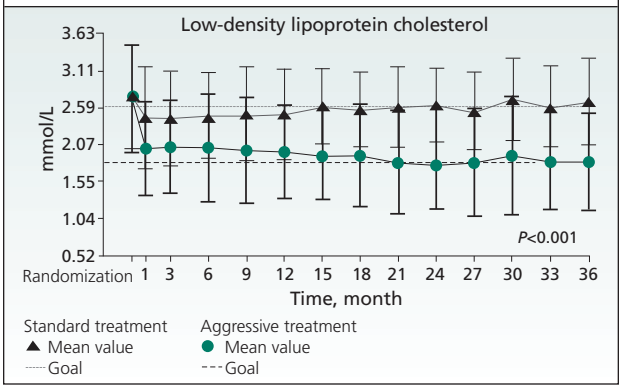
Women comprised 66% of the 548 subjects in the study, and the mean age for both sexes at baseline was 55 years for the aggressive-treatment group and 57 years for the standard-treatment group (P=0.05). The mean body mass index (BMI) was 34 kg/m^2 and 33 kg/m^2, respectively (P=0.77) and the mean systolic BP at baseline was 128 mm Hg for the aggressive-treatment group and 133 mm Hg for the standard-treatment group (P=0.003). There were no significant differences in lipid profiles at baseline between the groups; LDL-C was 2.7 mmol/L, HDL-C 1.19 mmol/L, triglycerides 4.1 mmol/L (aggressive treatment) and 4.2 mmol/L (standard group), and the non-HDL-C was 3.57 mmol/L and 3.62 mmol/L, respectively. There were approximately the same numbers of current smokers (22% and 20%, P=0.58); similarly, the baseline glycated hemoglobin (HbA_{1c}) was not significantly different (8.2% and 7.9%; P=0.45).

Results

During the 3-year trial period, treatment goals for both BP and LDL-C (Figure 2) were achieved, and 68% of the subjects achieved the aggressive LDL-C target of 1.81 mmol/L for >50% of the visits. During the last 12 months of the study, the difference in LDL-C between the standard- and aggressive-treatment groups was 0.83 mmol/L. However, to achieve these goals, 1.5±0.75 vs 1.2±0.73 (mean ± standard deviation [SD]) lipid-lowering agents were required for the aggressive- versus the standard-treatment groups and, in addition, 31% of subjects required ezetimibe to achieve targets. For systolic BP, 67% achieved the target of ≤115 mm Hg at >50% of the visits, and the systolic BP difference during the last year of the trial was 13 mm Hg. To achieve the BP goals the mean (SD) number of antihypertensive drugs used in the aggressive- and standard-treatment groups was 2.3 (1.3) versus 1.6 (0.73), respectively. Mean weight, BMI, waist circumference, and fasting glucose levels remained unchanged in both treatment groups.

Over the 36 months of the study, mean CIMT progressed in the standard-treatment group, and the mean increase was +0.038 mm (95% CI, 0.02-0.06); however, in the aggressively-treated patients there was a trend for CIMT regression, with a mean change of -0.012 mm (95% CI, -0.03 -0.0003). Therefore, at 36 months, there was a significant difference of 0.05 mm between the standard- versus aggressive-treatment groups (P<0.001). There were also significant differences in carotid arterial cross-sectional area that was 1.07 mm^2 lower in the aggressive-treatment group after 36 months (P<0.001). More individuals in the aggressive-treatment group had a decline in CIMT than in the standard group, but changes in systolic BP did not significantly relate to changes in CIMT. Nevertheless, there was a significantly greater decrease in left ventricular (LV) mass and LV mass index in the group with aggressive BP control.

Figure 2. Achievement of standard and aggressive LDL-C treatment goals[21]



The treatment goal in the aggressively treated group was only achieved in almost one third of patients after the addition of ezetimibe to statin therapy.

A further analysis of the SANDS data[22] examined the effect of aggressively lowering LDL-C and non-HDL-C on CIMT and other measures of carotid atherosclerosis with statins alone versus statins plus ezetimibe. The analysis aimed to address the question of whether the change in CIMT at 36 months was different between patients receiving statins alone or statin plus ezetimibe for the same degree of LDL-C lowering. In addition, it examined whether there were differences in CIMT at 36 months between the patients in the standard group and those in the aggressively-treated group who did and did not receive ezetimibe. Baseline characteristics of the standard group (n=204), and the aggressively-treated patients receiving ezetimibe (n=69) and no ezetimibe (n=154) were similar in age, gender, medications, renal function, and smoking status. The baseline lipid levels of the patients in the aggressive-treatment group receiving or not receiving ezetimibe were similar; however both systolic and diastolic BP were significantly lower in the group receiving ezetimibe.

The LDL-C reduction after 36 months of treatment was similar in the group receiving ezetimibe (-31.1%) and those not requiring ezetimibe (-32.3%); however, the LDL-C level in the ezetimibe-treated patients was slightly higher than in the non-ezetimibe group (2.02 mmol/L vs 1.76 mmol/L). Despite these small differences in LDL-C, both the aggressively-treated groups receiving and not receiving ezetimibe had significant reductions in CIMT compared with the group on standard treatment. There was no difference in the change of CIMT whether or not the patient had required ezetimibe to achieve the LDL-C target.

This analysis is not without limitations; since the study population was small, it was underpowered to examine clinical events. Most importantly, this was not a randomized comparison of statin plus ezetimibe versus a statin alone. Consequently, there were baseline differences between subgroups, for instance the significant difference in systolic BP between the aggressive- and standard-treatment groups. Although the smaller BP decline in the ezetimibe group might have biased the outcomes against ezetimibe yet, as noted above, systolic BP change did not influence CIMT. Finally, the study population of North American

Indians has, in some important ways, a different CV risk profile compared with other populations and the results of this study may not be completely generalizable to other groups.

The Vytorin on Carotid Intima-Media Thickness and Overall Arterial Rigidity (VYCTOR) study[23] was conducted in high-risk Mexican patients and examined the changes in CIMT with treatments targeting LDL-C to <1.8 mmol/L. Three lipid-lowering strategies were used: simvastatin (20 mg) with ezetimibe (10 mg); simvastatin (40 mg); and pravastatin (40 mg). If the LDL-C goal was not achieved, the pravastatin group received an addition of ezetimibe (10 mg), simvastatin alone was raised to 80 mg, and the simvastatin and ezetimibe combination became 40 mg with 10 mg ezetimibe. After 1 year, the LDL-C levels attained were statistically similar in the 3 groups and CIMT was reduced by similar amounts whichever lipid-lowering strategy was applied. This study appears to support the hypothesis that slowing atherosclerosis is dependent upon LDL-C reduction, whether achieved by statins alone or in combination with ezetimibe.

An analysis of 7 intravascular ultrasound studies[24] confirms that very low levels of LDL-C and normal systolic BP are associated with the slowest progression of atherosclerosis. This analysis, similar to the SANDS Study,[21] indicates that the impact of a very low LDL-C is likely greater than that due to lower BP.

The SANDS, in contrast to the ENHANCE study, suggests that the combination of ezetimibe plus a statin has essentially an identical beneficial effect on CIMT as a statin alone for similar changes in LDL-C and non-HDL-C. The SANDS is one of a few clinical studies that applied lipid-lowering therapy using a strategy recommended by clinical guidelines. The Canadian Diabetes Association Guidelines[25] recommend that combination therapy with ezetimibe, fibrates, or niacin be considered for patients with diabetes, who fail to achieve lipid goals on statin therapy at optimal doses. In the SANDS, statin therapy was optimized prior to initiating ezetimibe for individuals not yet at the goal. The results support the observation that benefits are achieved by LDL-C reduction. Whether LDL-C reduction is attained by bile acid sequestrants, ileal bypass surgery, or statins, the benefit relates both to the amount LDL-C is reduced[2] and the achieved level of LDL-C. The SANDS provides evidence demonstrating that if ezetimibe is required to achieve the LDL-C target, the benefit will be similar to that provided by the same level of LDL-C reduction with statins alone. Only ongoing clinical trials with outcome endpoints such as IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) will indicate whether the addition of ezetimibe to aggressive statin therapy translates into lower CV event rates.

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