Landmark Trials: Newer Insights in Lipid-lowering Therapy

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Various randomized clinical trials have shown that statins reduce cardiovascular (CV) event rates. The guidelines for CV disease prevention have increasingly emphasized that lowering low-density lipoprotein cholesterol (LDL-C) levels with statins is the primary goal of lipid-modulating therapy. The effect of statins extends across all ranges of LDL-C with no obvious lower threshold for benefit. Various imaging studies have shown that statins not only slow the disease progression but may also lead to disease regression in some patients.

There has been speculation on the extent to which various statins affect disease progression and if one is better than the other. There is a question mark if additional therapies, when given to patients with well-controlled LDL-C levels on statins, will further lead to risk reduction. Moreover, there has always been concern with regard to use of statins in mild to moderately increased liver enzymes and also regarding the potential long-term side-effects such as diabetes and cancer.

In addition to statins, other approaches for lipid lowering have also been under extensive investigation. Among them, cholesterol-ester transfer protein (CETP) inhibition has generated a lot of interest. CETP inhibitors are really the most potent high-density lipoprotein cholesterol (HDL-C) raising drugs that have been developed. Torcetrapib was the first CETP inhibitor to be tested in a large clinical trial [Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial]. Unfortunately, despite achieving powerful HDL-C reduction, torcetrapib resulted in increased overall mortality leading to the premature termination of the trial. The failure of this trial has put a question mark on the clinical utility of these agents. However, newer CETP inhibitors (anacetrapib dalcetrapib, evacetrapib, etc.) have been developed since then which appear to be free of the harmful side-effects thought to be responsible for the adverse outcomes seen with torcetrapib. The ongoing trials will tell whether this approach is indeed effective in improving CV outcomes.

Some recent trials on lipid modulation that have tried to address these unanswered questions are being discussed here.

AIM-HIGH (The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes Trial)

AIM HIGH Investigators. *N Engl J Med* 2011;365:2255–67.

This trial tested whether extended-release niacin added to intensive statin therapy (to maintain LDL-C of 40–80 mg/dL), as compared with statin therapy alone, would reduce the risk of CV events in patients with established atherosclerotic CV disease and atherogenic dyslipidemia (low levels of HDL-C, elevated triglyceride levels, and small, dense particles of LDL-C).

The AIM-HIGH Study was an investigator-initiated trial that was approved and sponsored by the National Heart, Lung, and Blood Institute (NHLBI). It was a multicenter trial that enrolled 3414 patients in USA and Canada. After 4–8 weeks of an open-label phase, patients were randomly assigned to niacin or matching placebo. Eligible patients were ≥ 45 years of age and had established CV disease, which was defined as documented stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease. All eligible patients had low baseline levels of HDL-C (<40 mg/dL for men; <50 mg/dL for women), elevated triglyceride levels (150–400 mg/dL), and LDL-C levels ≤ 180 mg/dL if they were not

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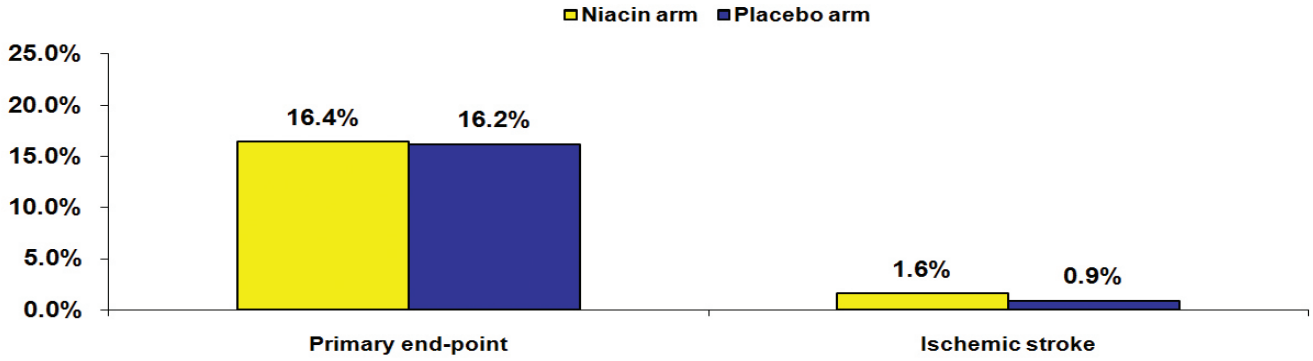

p= NS for both

taking a statin at entry. Patients who were screened were required to discontinue lipid-modifying drugs, except for statins or ezetimibe, at least 4 weeks before enrolment. Potential participants were excluded if, within 4 weeks before enrolment, they had been hospitalized for an acute coronary syndrome or had undergone a planned revascularization procedure or if they had a stroke within the preceding 8 weeks.

Patients in the niacin group received niacin at a dose of 1500–2000 mg per day plus simvastatin. Patients in the placebo group received simvastatin plus a matching placebo that contained a small dose (50 mg) of immediate-release niacin in each 500-mg or 1000-mg tablet to mask the identity of the blinded treatment to the patients and the study personnel. The dose of simvastatin was adjusted to achieve and maintain the LDL-C level during treatment in the range of 40–80 mg/dL. Subjects in both the groups could receive ezetimibe, at a dose of 10 mg per day, to achieve the target LDL-C level.

The primary end-point was the composite of the first event of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

A total of 3414 patients were randomly assigned to receive niacin (1718) or placebo (1696). The trial was stopped prematurely (18 months ahead of schedule) after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL-C level from 35 to 42 mg/dL, lowered the triglyceride level from 164 to 122 mg/dL, and lowered the LDL-C level from 74 to 62 mg/dL. The primary end-point was similar in two groups and occurred in 282 patients in the niacin group (16.4%) and in 274 patients in the placebo group (16.2%) (hazard ratio 1.02; 95% confidence interval, 0.87–1.21; P = 0.79). Ischemic stroke occurred as the first event in 27 niacin patients (1.6%) versus 15 placebo patients (0.9%).

Perspective

Among patients with atherosclerotic CV disease and well-controlled LDL-C (levels < 70 mg/dL), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL-C and triglyceride levels.

The disappointing results of AIM-HIGH do not provide support for the use of niacin as an add-on therapy to statins in patients with stable CV disease who already have well-controlled LDL-C levels. However, there were several study-design-related issues which could have confounded the results of this study and have been a topic of lot of debate. Given these controversies, it is believed that the final verdict on niacin cannot be passed as yet and the results of other trials, particularly the HPS2-THRIVE (Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events), are eagerly awaited.

SATURN (The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin)

Nicholls SJ, et al. *N Engl J Med* 2011;365:2078–87.2011;361:1139–1151.

SATURN was a prospective, randomized, multicenter, double-blind clinical trial. The trial tested the effectiveness of the maximum doses of rosuvastatin (40 mg) and atorvastatin (80 mg) to determine any discernible differences in the effects on the progression of coronary atherosclerosis with serial intravascular ultrasonography.

Patients in age group 18–75 years were eligible if they had at least one vessel with 20% stenosis on clinical indicated angiography and a target vessel for imaging with less than 50% obstruction. Patients were required to have LDL-C > 80 mg/dL if treated with statins in preceding 4 weeks or >100 mg/dL if not treated with statins. After 2 weeks of initial treatment, patients with LDL-C < 116 mg/dL were randomized to full-dose treatment with either 40 mg rosuvastatin or 80 mg atorvastatin for 104 weeks. Intravascular ultrasound was performed at baseline and after 104 weeks. The primary efficacy end-point was change in percent atheroma volume (PAV) and secondary efficacy end-point was change in normalized total atheroma volume (TAV).

Over 104 weeks of therapy, patients on rosuvastain had lower levels of LDL-C (62.6 vs 70.2 mg/dL, P<0.001) and higher levels of HDL-C (50.4 vs 48.6 mg/dL, P = 0.01) as compared to atorvastatin group. The primary efficacy end-point, PAV, decreased by 0.99% with atorvastatin and by 1.22% with rosuvastatin which was not significant (P = 0.17). In terms of effect on normalized TAV, there was more favorable reduction of 6.39 mm3 in the rosuvastatin arm compared with a 4.42 mm3 reduction in the atorvastatin arm which was statistically significant (p=0.01).

Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV (P = 0.07) and 64.7% and 71.3%, respectively, for TAV (P = 0.02). Both agents in their maximal doses had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and CV events.

Perspective

SATURN demonstrated that maximal doses of both rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis, the largest observed in any clinical trial so far. Despite the lower level of LDL-C and the higher level of HDL-C achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups. However rosuvastatin led to more favorable effect on TAV.

Heart Protection Study: 11 Year Follow-up

Heart Protection Study Collaborative Group. *The Lancet* 2011;378:2013–2020.

Medical Research Council and British Heart Foundation (MRC/BHF) Heart Protection Study (HPS) randomly allocated between July 1994 and May 1997, 20,536 patients who were at high risk of vascular and nonvascular outcomes to either simvastatin 40 mg or placebo. Mean in-trial follow-up was 5.3 years. The trial provided immensely valuable data regarding use of statins in this group of patients and proved to be a landmark trial in the field of lipid-lowering therapy. Since then, continued follow-up of the surviving patients has yielded a mean total duration of 11 years of post-trial follow-up. The findings from this long-term follow-up are now presented. The primary outcome was first post-randomization major vascular event.

During the in-trial period of 5.3 years, allocation to simvastatin yielded an average reduction in LDL-C of 1 mmol/L and a proportional decrease in major vascular events by 23% (95% CI 19–28; p<0.0001), with significant divergence each year after the first.

During the post-trial period (when statin use and lipid concentrations were similar in both groups), benefits persisted but no further significant reductions were noted in either major vascular events (risk ratio 0.95 [0.89–1.02]) or vascular mortality (risk ratio 0.98 [0.90–1.07]). During the combined in-trial and post-trial periods, no significant differences were recorded in cancer incidence at all sites (risk ratio 0.98 [0.92–1.05]) or any particular site, or in mortality attributed to cancer (risk ratio 1.01 [0.92–1.11]) or to nonvascular causes (risk ratio 0.96 [0.89–1.03]).

Perspective

Prolonged post-trial follow-up of participants in HPS shows that the substantial reduction in vascular mortality and morbidity produced during in-trial period with simvastatin persisted largely unchanged during the subsequent 6 years.

Moreover, even after study treatment stopped in HPS, benefits persisted without any evidence of emerging hazards. These findings provide further support for the prompt initiation and long-term continuation of statin treatment.

Long-term Statin Use and Abnormal Liver Tests in GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) Study: A Post-hoc Analysis

Athyros VG, et al. *Lancet* 2010;376:1916–1922.

GREACE was a prospective study that randomized 1600 patients of coronary heart disease to statins or usual care at a university hospital in Greece. The included patients had age <75 years, with serum concentrations of LDL-C >2.6 mmol/L and triglycerides <4.5 mmol/L. The primary outcome of the post-hoc analysis was risk reduction for first recurrent CV event in patients treated with a statin who had moderately abnormal liver tests (defined as serum alanine aminotransferase or aspartate aminotransferase concentrations of less than three times the upper limit of normal) compared with patients with abnormal liver tests who did not receive a statin. This risk reduction was compared with that for statin-treated patients with normal liver tests. Nonalcoholic fatty liver disease was the most likely reason of abnormal liver tests in the study patients.

Out of 437 patients with moderately elevated liver enzymes, 227 patients who were treated with statins had substantial improvements in their liver tests, whereas 210 patients who were not treated with statins had further increase in their liver enzyme concentrations ($p<0.0001$). CV events occurred in 10% of patients with abnormal liver tests who received statin and 30% of patients with abnormal liver tests who did not receive statin (68% relative risk reduction, $p<0.0001$). This CV disease benefit was greater ($p=0.0074$) than it was in patients with normal liver tests.

Perspective

In patients with mild to moderately elevated liver enzymes that are potentially attributable to nonalcoholic fatty liver disease, statin treatment is safe and can improve liver tests and reduce CV morbidity.

Effect of CETP Inhibitor Evacetrapib With or Without Statins on HDL-C and LDL-C

Nicholls SJ, et al. *JAMA* 2011;306:2099–2109.

It was a phase II multicenter trial conducted in United States and Europe to examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia. After a dietary lead-in, 398 patients with raised LDL-C or low HDL-C were randomly assigned to receive placebo, evacetrapib monotherapy (30, 100, or 500 mg) or evacetrapib (100 mg) in combination with statins for 12 weeks. The coprimary end-points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

As monotherapy, evacetrapib increased HDL-C levels from 53% to 128% (30–66 mg/dL), as compared with placebo, which decreased HDL-C levels by 3% (-0.7 mg/dL; $P<0.001$). Evacetrapib alone was also associated with decreases in LDL-C of 13–36% (-20.5 to -51.4 mg/dL) versus an increase with placebo of 3.9% (7.2 mg/dL; $P<0.001$). In addition, levels of triglycerides fell 16% at the highest dose of evacetrapib.

In combination with statin therapy, evacetrapib 100 mg produced increases in HDL-C by 78–88% (42.1–50.5 mg/dL; $P<0.001$) compared with statin monotherapy, and decreases in LDL-C of 11–14% (-67.1 to -75.8 mg/dL; $P<0.001$).

Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P <0.001$) but no greater increase in HDL-C ($P=0.39$). Although the study was underpowered, no adverse effects were observed.

Perspective

As already mentioned, the CETP inhibitors are really the most potent HDL-C raising drugs that have been developed. This trial confirms the same with yet another CETP inhibitor – evacetrapib. However, the effects of evacetrapib on CV outcomes and risk reduction require further investigation.