LIPID MANAGEMENT: HOW AGGRESSIVE IS AGGRESSIVE?

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INTRODUCTION
We need to consider more aggressive LDL lowering for patients who have sufficiently elevated risk to benefit from more aggressive treatment. The third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP) identified an LDL goal <100 mg/dl for high-risk patients (those with clinical cardiovascular disease, diabetes, or 10-year CHD risk >20%). A subsequent 2004 report from the NCEP suggested an optional LDL goal <70 mg/dl for those at the higher risk, including those with established cardiovascular disease plus additional high-risk characteristics: diabetes mellitus, multiple cardiovascular risk factors, multiple risk factors of metabolic syndrome, or severe or poorly controlled risk factors, especially continued cigarette smoking. An LDL goal <100 mg/dl was also extended as an option to moderately high-risk primary prevention patients who had 2 or more risk factors and a 10% to 20% 10 year CHD risk as well as other indicators of increased risk.

The 2004 NCEP report also recommended at least 30% to 40% reduction in LDL in order to significantly lower cardiovascular risk. It should be noted, however, that many, if not most, patients will require at least a 50% reduction in LDL to achieve an LDL <100 mg/dl. This article will contain the trials which were conducted up to date particularly on aggressive lipid lowering, and safety issue.

HPS: THE HEART PROTECTION STUDY
The HPS was a more recent study in which 20,536 patients aged 40 to 80 years old with CHD, other atherosclerotic vascular disease, or diabetes were randomized to simvastatin 40 mg or placebo. For inclusion, total cholesterol needed only be greater than 135 mg/dl, ensuring that many subjects in this trial had average and even below-average cholesterol levels. Treatment with simvastatin was associated with a highly significant 24% reduction in major coronary events, 25% reduction in stroke, and 13% reduction in total mortality. Remarkably, the relative benefit of simvastatin therapy was similar across tertiles of baseline LDL-C, and even the group with LDL-C less than 100 mg/dl at baseline demonstrated benefit with simvastatin.

CONCLUSIONS
The results of HPS led to the widespread concept that there are benefits of statin therapy in high-risk individuals regardless of baseline cholesterol levels.

TNT: TREAT TO NEW TARGETS TRIAL
This was the first trial to directly compare two different doses of the same statin with regard to CV outcomes. A total of 10,001 patients with CHD and LDL-C less than 130 mg/dl were randomized to atorvastatin 10 mg or 80 mg daily. The higher dose of atorvastatin resulted in a mean on-treatment LDL-C of 77 mg/dl (compared with 101 mg/dl for the lower dose) and a significant 22% reduction in major CV events. This trial conclusively proved that a higher dose of atorvastatin reduced CV events to a greater extent than a lower dose. Persistent LFT elevations with 80mg warranted close monitoring in this study.

PROVE – IT/TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction – Lipid Lowering:
ACS patients were randomized to atorvastatin 80 mg or pravastatin 40 mg and followed for a mean of 2 years. The more intensive regimen of atorvastatin 80 mg (mean on–treatment LDL-C of 62 mg/dl) was associated with a significant 16% relative risk reduction in major cardiovascular events compared with the less intensive pravastatin 40 mg regimen (mean on–treatment LDL-C of 95 mg/dl).

Lower is better: First large scale trial to demonstrate an added clinical benefit of a more intensive lipid lowering therapy in post-ACS patients beyond current guidelines of LDL < 100 mg/dl. The studies from HPS to TNT moved the field toward a “lower is better” approach to reducing, LDL – C.

Individual trials and pooled analysis showing s highly significant 16% reduction in the risk of coronary death or myocardial infarction (p < 0.0001) Ref Figure 1.

The trials mentioned in the figure had clearly shown beneficial effects with aggressive lipid lowering, which had assumed high statistical significance.

JUPITER

Recently the results of the “Justification for the Use of statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin” were published. This study evaluated the safety, efficacy and outcomes of aggressively lowering LDL-C by 50% in 17,802 persons. The baseline LDL-C was within the normal range, that is under 130 mg/dl, and the patients were treated with 20mg of rosuvastatin per day as part of primary prevention strategy for the patients who otherwise would not currently qualify for lipid – lowering therapy. Among those randomized to rosuvastatin, there was a 50% reduction in LDL-C from 108 mg/dl down to 55 mg/dl. Approximately 50% of the treated participants achieved LDL-C of < 55 mg/dl and 25% achieved LDL-C under 44mg/dl. The study was terminated 3 years early because of strongly favorable results, that is a highly significant 44%, reduction in the primary endpoint (p<0.0001).The results of the JUPITER study further support the recommendations of this report for aggressive treatment of dyslipidemia to reduce the risk of CHD for persons at high risk.

AGGRESSIVE LIPID LOWERING THERAPY WITH COMBINATION AGENTS

Statin medications are safe and highly effective with a 25% to 60% reduction in LDL – C and non-HDL cholesterol achievable at maximum dose (atorvastatin 80 mg or rosuvastatin 40 mg /day). Lowering of LDL-C with statins reduces the risk of CHD by 30% to 45%. It is often not appreciated that the residual risk after LDL-C lowering therapy is still as high as 55% to 70%, possibly due to the concomitant presence of low HDL-C and other lipid and non-lipid abnormalities. Statin – niacin combination therapy has been shown to reduce the risk of CHD by 60% to 90% and may be particularly beneficial among Asian Indians who have multiple lipid abnormalities.

LESSONS LEARNT FROM LIPID LOWERING TRIALS

On LDL

Clinical endpoint trials with statins have been conducted in settings of primary prevention in people without CV disease and in settings of secondary prevention in those with CV disease. Lowering the concentration of LDL-c reduces fatal and nonfatal MI, stroke, unstable angina, and the need for revascularization procedures. The CV benefits associated with LDL-c lowering have been demonstrated beyond all reasonable doubt in men and women, in people with and without CV disease’ in young and old people, in those with ACS, in those who previously had ischemic strokes, in those with diabetes or the metabolic syndrome, and in those with hypertension. The results of these trials have been surprisingly consistent.

A recent meta-analysis of data from 90,056 participants in 14 randomized trials of statins concluded that for each 40-mg/dl (1.0-mmol/L) reduction in LDL cholesterol, there is a 12% reduction in all-cause mortality, a 23% reduction in the occurrence of MI or coronary-related death, a 24% reduction in the need for coronary revascularization, and a 17% reduction in the rate of fatal or nonfatal stroke. All of these reductions were highly significant. This analysis also concluded that the reduction in major vascular events is proportional to the magnitude of the reduction in LDL-c.

Hence, LDL cholesterol is now completely accepted as a target for therapy. To date, the trials reported have not identified a lower threshold below which LDL-c reduction is no longer of value.

Many current guidelines recommend an LDL-c target of less than 100 mg/dl (2.6 mmol/L) in people at high CV risk, although in the light of more recent evidence, the NCEP ATP III guidelines were updated with the recommendation that an LDL-c target of less than 70 mg/dl be considered as an
option in high-risk individuals. Importantly, support for this view is mounting with the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)[10] trial, and PROVE IT trial.

The “lower is better” hypothesis received further support from the TNT trial. The results of these trials support an LDL-c target of somewhere between 70 and 80 mg/dl in people at high risk of having a CV event.

On NON-HDL-C

Numerous reports from large databases, such as the Lipid Research Clinics Follow-Up Study, the Health Professionals’ Follow-up Study, the Nurses’ Health Study, the Women’s Health Study, the Third National Health and Nutrition Examination Survey (NHANES III) and the Framingham Study, now demonstrate convincingly that non-HDL-c is superior to LDL-c in reflecting CHD risk. This is not surprising since VLDL-c should be expected to add predictive power to LDL-c alone.

Non-HDL captures the cholesterol contained in all potentially atherogenic lipoproteins. The concentration of non-HDL-c is very simple to compute, being the difference between the plasma total cholesterol concentration and the HDL-c concentration.

Non-HDL-c was included as a secondary target in people with elevated triglyceride in the report of the NCEP ATP III, but the main focus of these guidelines has continued to be LDL-c. The most compelling case for considering non-HDL-c as a target has emerged from a recent analysis of the combined data set from the TNT and IDEAL studies in which a total target has emerged from a recent analysis of the combined data set from the TNT and IDEAL studies in which a total of 18,889 patients with established CHD were assigned to usual-dose or high-dose statin treatment and followed up for a median of just under 5 years. In univariate analysis, both LDL-c and non-HDL-c were strongly and significantly associated with major CV event. However, after adjustment for non-HDL-c, the significant relationship between LDL-c and CV events was lost, whereas the on treatment level of non-HDL-c remained predictive of events after adjustment for LDL-c levels. In patients with LDL-c below 100 mg/dl, non-HDL-c (but not LDL-c) remained a significant predictor of major CV events.10

It is most likely that non-HDL-c will eventually replace LDL-c as the primary target for cholesterol-lowering therapy. On the basis of available evidence, it is reasonable to recommend a non-HDL-c target of less than 100 mg/dl in very high-risk people and less than 130 mg/dl in those at lower risk.

On HDL

An inverse relationship between the level of HDL-c and the risk of developing premature CHD has been a consistent finding in large scale prospective population studies.

The importance of HDL-c as a potential therapeutic target has been strengthened by the observation that a low level of HDL-cholesterol remains highly predictive of CV events in people who are well treated with statins, even when the LDL-c has been reduced to levels below 70 mg/dl (Ref fig).

The results of fibrate trials have been mixed. In the Helsinki Heart Study, which used gemfibrozil as the active agent, it was concluded that a 1% increase in HDL-c was associated with a 2% to 3% decrease in CHD events that was independent of changes in levels of LDL-c. Recently published 18 year follow-up data of HHS indicated 33% reduction in all cause mortality, 71% reduction in CHD mortality (P < 0.001).

In the Veterans Affairs HDL Intervention Trial (VA-HIT) study the on-treatment HDL-c level was predictive of CHD events in both the active and placebo groups. Multivariate regression analysis showed that, of all of the variables measured, the increase in HDL cholesterol was the only one that predicted benefit.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, conducted in people with type 2 diabetes, used fenofibrate as the active agent. This study added little to the argument, because fenofibrate treatment resulted in an HDL-c increase of less than 2%, which may have been one of the reasons why the primary endpoint of this study was reduced by only 11% and was not statistically significant.

Niacin has long been used as a lipid modifying agent. It lowers plasma triglyceride by 40% to 50%, lowers LDL-c by 10% to 15%, and increases HDL-c by up to 30%. When co administered with statins, niacin promotes significant angiographic regression of atheromatous plaque and reduces clinical CV events.

ON TRIGLYCERIDE

Framingham Heart Study, Prospective Cardiovascular Munster (PROGRAM) Study and Helsinki Heart Study (placebo group) revealed that the level of plasma triglyceride was predictive of CV events only in those who also had an elevated level of LDL-c, a low level of HDL-c or both. To date
however, there is no definitive evidence that reducing the level of plasma triglyceride translates into a reduction in CV events. Thus, at this time, the presence of elevated plasma triglyceride supports the use of fibrates to reduce CV risk, but there is no current evidence to support plasma triglyceride as a therapeutic target.

SAFETY OF AGGRESSIVE LIPID MANAGEMENT

Since many patients with CHD or its equivalent will need a >50% reduction in LDL to achieve the LDL goal <100 mg/dl, it is reassuring that therapy with the highest doses of atorvastatin, simvastatin, and rosuvastatin appear to be well-tolerated in properly selected subjects. Low rates of serious musculoskeletal (<0.6%) or hepatic (<1.3%) adverse effects have occurred in randomized event trials with higher rates of persistent hepatic transaminase elevations occurring with atorvastatin 80mg and higher rates of myopathy and rhabdomyolysis occurring with simvastatin 80mg. Achievement of the more aggressive optional LDL goal <70 mg/dl should be reserved for the very highest-risk patients who are most likely to experience benefit and least likely to experience toxicity. Although high-dose statin therapy or combination treatment will most likely be necessary to achieve an LDL level <70 mg/dl, the long-term safety of other LDL, non-HDL, or triglyceride-lowering therapies added on to high-dose statin monotherapy has not been well established. Ezetimibe and coleselvelam appear unlikely to increase the risk of myopathy when used in combination with a high-dose statin; however, rates of hepatic enzyme elevation are slightly increased. Although the combination of niacin or fenofibrate with moderate-dose statins appears to be reasonably safe, the safety of combination with high-dose statins has yet to be determined. To enhance patient outcomes, clinicians need to be aware of specific patient characteristics, such as advancing age, gender, body mass index, diminished glomerular filtration rate, and other characteristics that predict muscle and hepatic statin toxicity, especially when considering the use of high-dose statin or combination therapy.

OUR FUTURE APPROACH

It is likely that the LDL-C and non-HDL-C goals will continue to fall for larger numbers of patients. Whether the LDL-C goal of less than 70 mg/dl in very high risk patients will fall even further is uncertain. It seems almost certain that the goal of LDL-C less than 70 mg/dl will no longer be ‘optional’ and will be formally extended to a larger number of patients, probably eventually to all CHD and CHD-risk-equivalent patients. Similarly, the goal of LDL-C less than 100 mg/dl will likely be formalized for all moderate-risk patients and may eventually be extended to all patients who are candidates for lipid-modifying drug therapy. The non-HDL-C goal will become more commonly used. The non-HDL-C goals will fall in parallel with the LDL-C goals, and a non-HDL-C of less than 100 mg/dl for patients with CHD / CHD-risk-equivalent status will become standard. The pressure to reduce LDL-C will drive the average dose of statin higher and result in substantial in the use of cholesterol-absorption inhibitors in combination with statins. There will be continued discussion of whether LDL-C and non-HDL-C should be replaced with a better marker of atherogenic particle number such as apoB or LDL particle number. As there is greater appreciation of the “residual risk” associated with statin mono therapy, coupled to the observation that statin-treated patients who have subsequent events are more likely to have elevated triglycerides and/or reduced HDL-C levels, –treated patients who have subsequent events are more likely to have elevated triglycerides and/or reduced HDL-C levels, –treated patients who have subsequent events are more likely to have elevated triglycerides and / or reduced HDL-C levels, further increases in combination therapy, particularly statin-fibrate and statin-niacin combinations will occur. This will be centered on higher-risk patients with existing CHD. If clinical trials designed to test the benefit of adding a fibrate or niacin to a statin demonstrate significant reduction in CV events, the use of combination therapy will become commonplace.

REFERENCES