INTRODUCTION

Lipids and lipoproteins are associated with atherosclerosis in general and coronary atherosclerosis in particular. CHD is a multifactorial disease. LDL-c is a strong and independent risk factor for CHD based on robust evidence from epidemiological data and lipid lowering trials. CHD still remains the single most prevalent cause of mortality not only in developed countries but also in developing countries including India. Clearly we must improve our ability to identify and intervene in controlling these risks. The question, of course, is how best to do it. Many CHD risk factors can be improved. Nonlipid risk factors and environmental factors must also be addressed. We have learnt many lessons from the lipid lowering trials particularly LDL lowering using statins in the last few decades.

NCEP-ATP III GUIDELINES

The current guidelines proposed by the National Cholesterol Education Program [NCEP].Third Adult Treatment Panel [ ATP III] recommend the use of LDL-c as the primary target of therapy based on robust evidence that LDL-c is a strong and independent predictor of CHD. ATP III also acknowledged the importance of hypertriglyceridemia and low levels of HDL-c as an important secondary consideration in optimizing lipid-related risk.[1]

ATP III advocated the use of non-HDL-c as a surrogate measure of risk associated with the dyslipidemia triad. In the stepwise algorithm advocated by ATP III, once LDL-c has been reduced to its target level, non-HDL-c should be determined if triglycerides are greater than 200 mg/dl, and then reduced to its corresponding target as a secondary goal of therapy.

STATIN TRIALS

The cholesterol hypothesis was finally definitively proven as a result of the clinical outcome trials with hydroxyl - 3 – methylglutaryl – coenzyme A (HMG-CoA) reductase inhibitors (statins). The concentration of LDL-c has been shown consistently in large epidemiological studies to be a powerful predictor of future CV events. Furthermore, therapies such as those with statins that reduce the level of LDL-c reduce the risk of future CV events. This is one of the most proven cases in modern medicine.

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4S : SCANDIVANIAN SIMVASTATIN SURVIVAL STUDY

4444 patients with CHD and elevated cholesterol were randomized to placebo or simvastatin 20 mg titrated to 40 mg as needed. Treatment with simvastatin was associated with a 30% relative risk reduction in total mortality and a 44% reduction in CHD death or MI. It is important that it was not only the subjects with the highest cholesterol levels who experienced a reduction in risk; the quartile with the lowest LDL-C levels at baseline had proportionately as much benefit from treatment as the highest quartile.

CARE STUDY : CHOLESTEROL AND RECURRENT EVENTS STUDY

4,159 patients who were post MI and had total cholesterol levels less than 240 mg/dl were randomized to placebo or pravastatin 40 mg daily and followed for an average of 5 years. Treatment with pravastatin was associated with a significant 24% reduction in relative risk.

LIPID: LONG-TERM INTERVENTION WITH PRAVASTATIN IN ISCHEMIC DISEASE.

9,014 patients with CHD and a broad range of cholesterol levels were randomized to placebo or pravastatin 40 mg daily and followed for an average of 6 years. Treatment with pravastatin significantly reduced CHD mortality by 24% and total mortality by 22%.

Conclusions from these three studies:

These three statin studies in patients with preexisting CHD reported in the 1990s definitively established the efficacy of statin therapy in reducing CV events and total mortality in patients with established CHD over a very wide range of baseline LDL-C levels.
Lessons Learnt From Lipid Lowering Trials: Our Future Approach

**WOSCOPS: WEST OF SCOTLAND CORONARY PREVENTION STUDY.**

Treatment with pravastatin was associated with a significant 31% reduction in relative risk of non fatal MI or CHD death.

**AFCAPS /TEXCAPS: AIR FORCE / TEXAS CORONARY ATHEROSCLEROSIS PREVENTION STUDY**

Treatment with lovastatin was associated with a 37% relative risk reduction in the primary end point of combined CV events.

**Conclusions:**

These studies confirmed that the benefits of cholesterol reduction extend to the primary prevention setting.

**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.

**PROSPER: PROSPECTIVE STUDY OF PRAVASTATIN IN THE ELDERLY AT RISK.**

In the PROSPER, 5,804 patients aged 70 to 80 years with vascular disease or risk factors were randomized to pravastatin 40 mg or placebo and followed for an average of 3.2 years . Pravastatin treatment was associated with a significant 15% reduction in a composite CV endpoint.

**Conclusions:**

Demonstrated the benefit of statin therapy in the elderly.

**ASCOT – LLA: ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL- LIPID LOWERING ARM.**

19,342 hypertensive patients with at least 3 other risk factors and with total cholesterol levels less than 242 mg/dL were randomized to atorvastatin 10 mg or placebo . The study was stopped early after 3.3 years when a highly significant 36 % relative risk reduction associated with atorvastatin was found.

**Conclusions:**

Statin therapy is beneficial over and above antihypertensive therapy.

**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 ower 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.

**AGGRESSIVE LIPID LOWERING THERAPY WITH STATIN**

**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 [2] and in settings of secondary prevention in those with CV disease [2,5]. 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 [6], in those who previously had ischemic strokes [5], in those with diabetes [2] or the metabolic syndrome [7], 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 [8]. 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 [9]. Importantly, support for this view is mounting with the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) 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[3] and IDEAL[4] 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[13].

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 APOLIPOPROTEIN B:

Another measure of the concentration of all atherogenic lipoproteins is apolipoprotein (apo) B. Because chylomicrons and their remnants, VLDLs and their remnants, and LDLs all contain one molecule of apoB per particle. apoB provides a direct measure of the concentration of all atherogenic lipoprotein particles.

Thus, the concentration of apoB should theoretically be superior to LDL-c concentration as an indicator of CV risk and a better surrogate as a target for therapy. The concentration of apoB has been shown in several studies to be highly predictive of future CV events, with some studies identifying apoB levels as more predictive than LDL-c[11,12]. In the analysis of the combined TNT and IDEAL studies, the on-treatment level of apoB was clearly superior to that of LDL cholesterol as a predictor of CV events, but it was not superior to non-HDL-c[13].

On the basis of available evidence, it is reasonable to recommend an apoB target of less than 80 mg/dl in very high-risk people and less than 90 mg/dl in those at lower risk[14,15].

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)[16]

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) [17]

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 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.

There is a need for additional research to determine whether the putative benefits of raising HDL-c in humans are dependent on the mechanism of the HDL-raising therapy and on the specific HDL subpopulations that are raised. There is also a need to determine whether the concentration of HDL-c is the best measure of the protective function of these lipoproteins. It is possible that an increase in a minor subpopulation of highly functional HDL particles (with little changes in the total HDL-c level) may be more effective than a larger increase of less functional particles. However there is currently insufficient knowledge to make recommendations.

**ON RATIOS:**

A number of population studies have identified various lipid and lipoprotein ratios as robust predictors of CV events. These ratios include TL-c/HDL-c and apoB/apoA-I. Both of these ratios provide estimates of the relative concentrations of atherogenic and antiatherogenic lipoproteins. The TL-c/HDL-c ratio has been shown in population studies to be protective of future CV events, with a power greater than either component of the ratio alone.

The other measure that reflects the relative amounts of proatherogenic and antiatherogenic particles is the ratio of apoB to apoA-I. This ratio has received much attention since publication of the Apolipoprotein-related Mortality Risk (AMORIS) [18], the INTERHEART [19] studies, in which it was an extremely powerful predictor of events. A potential advantage of using such a ratio is that a practicing clinician needs to act on the basis of only a single number rather than two numbers. However, a ratio that is predictive in a larger-scale epidemiological study may be less informative as a risk predictor in individual patients.

On the basis of the current evidence, it is likely that the apoB/apoA-I ratio will be incorporated into risk assessment that predict CV risk in future.

**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.

**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, 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. Genetic profiling of cardiovascular risk will be used routinely in clinical practice to guide lipid-modification therapy.

**REFERENCES:**


