22 Is Aggressive Lipid Lowering the Call in Era of Prevention of CAD?

Abstract: Ever since the publication of the 4S study, lipid management has been the center of preventive therapy for coronary artery disease.
Research over the last few years has focused on aggressive lipid lowering with statins/other combinations, with positive effects on cardiovascular outcomes and mortality in selected patient subsets.
This article discusses these issues in the current context and outlines the future directions.

INTRODUCTION

In the recent years, increasing emphasis has been placed on aggressive lipid lowering for the prevention of cardiovascular diseases, with statins at the center of the management of CAD.

In the context of Acute coronary syndromes (ACS) and stable coronary artery disease (CAD), various studies with outcome measures like major adverse cardiac events (MACE) and mortality have established the role of aggressive cholesterol reduction (LDL-C) with statins, in selected patient groups.

Goal posts for secondary prevention are also changing. Recent guidelines like the Joint British Society Guidance[1] and other prominent international authorities recommend inclusion of individuals with high vascular risk (i.e. 20% in 10 years) or Type 1 and 2 Diabetes mellitus, in the secondary prevention category, even if they have not had a previous primary atherosclerotic event. Hence, 'True' primary prevention would not be inclusive of such high vascular risk population who are as yet asymptomatic.

The following review looks at the role of statins and other agents, especially in the context of intensive therapy to aggressively lower the lipids (esp. LDL-C) and achieve maximum therapeutic benefits.

'The Beginning of a New Era….'

The **4S Study**[2] ushered a new era for role of statins in the prevention of cardiovascular diseases. In this study, 4444 patients with previous Ischemic heart disease and hypercholesterolemia (Total cholesterol 5.5–8.0 mmol/l) were randomised to double blind treatment with simvastatin or placebo and were followed up of 5.4 years. There was a clear and significant reduction in the primary end point for all cause mortality in Simvastatin arm with 30% relative reduction and 42% relative reduction in coronary death and reduced revascularization rate. This was followed by the **CARE study**[3] **(1996)** and **LIPID study**[4] **(1998)** to evaluate the benefit of statins in myocardial infarct patients even with relatively average lipid levels. Although level of risk reduction in CARE and LIPID were lesser compared to 4S study, it is likely to be due to relatively lesser average cholesterol levels in these studies and usage of other measures of secondary prevention in higher number of patients. (In LIPID study, 82% were on Aspirin compared to 31% in 4S study). Noticeably, in all these three studies, the statins were only commenced at least **three**

months after a coronary event. Further trials were undertaken to determine the benefits of an earlier introduction of statin.

'Statins are more beneficial when initiated at the time of admission'…

Evidence from Observational Study

The analyses of Swedish Register of Cardiac Intensive Care data[5] on patients admitted with an MI and other studies have demonstrated that statins, if commenced during admission with myocardial infarct, is associated with improved compliance and better outcome. Moreover, data published from US National Registry of Myocardial Infarction[6] consisting of 300,823 patients demonstrated that statins commenced within 24 hours of Acute MI admission is associated with significantly lower rate of early complications as well as inpatient mortality compared to a late introduction.

Evidence from Randomized Control Trial

The MIRACL Trial[7] published in 2001 enrolled patients with Unstable or Non-Q wave MI within 63 hours of admission to receive either Atorvastatin 80 mg daily or placebo. Primary composite endpoint (incidence of death, nonfatal acute MI, cardiac arrest with resuscitation or recurrent unstable angina) occurred in 17.4% of placebo group and 14.8% of the atorvastatin group (p=0.048) after 16 weeks follow up. Significance of primary endpoint was mainly due to reduction in symptomatic ischemia with admission but none of the other primary endpoint components were significantly reduced. This study demonstrated the benefit of statins initiated at the time of ACS admission irrespective of initial cholesterol level. The criticism was the short span of study, exclusion of patients who had undergone revascularization and whether such a high dose was warranted. Subsequent studies were performed to resolve these issues and compare benefits of intensive vs standard therapy following ACS admission.

Intensive versus Standard Statin Therapy during Acute Coronary Syndrome Admission

Intensive statin therapy instead of standard treatment following acute coronary event has been much debated and studied since the **MIRACL** study. The rationale behind the intensive therapy is to maximise the benefits in this group of patients, who are at the highest risk of recurrent events and death. The lipid lowering and other beneficial effects of statins have been tested to the best possible limits.

The REVERSAL and the **ASTEROID** studies set the tone of intensive statin therapy. REVERSAL[8] (Reversal of Atherosclerosis with Aggressive Lipid Lowering) Trial compared the effect of Atorvastatin 80 mg or Pravastatin 40 mg on the size of atheroma as measured by Intra-vascular Ultrasound. It demonstrated significantly lower atheroma progression rate after 18 months in the high dose atorvastatin group. ASTEROID[9] went one step ahead and not only showed arrest but regression of atheroma following Rosuvastatin 40 mg on its own for 24 months.

The following two clinical outcome studies revealed significant findings:

The Pravastatin or atorvastatin evaluation and infection therapy trial (PROVE IT-TIMI 22)[10] trial was initiated by manufacturers of Pravastatin to show non-inferiority of this medication compared to intensive therapy with Atorvastatin. ACS patients were randomised within 10 days of their admission to receive 'standard' therapy with Pravastatin 40 mg or intensive therapy with Atorvastatin 80 mg. The composite primary endpoint included death from any cause, unstable angina requiring admission, revascularization rate and stroke with a follow up period of 24 months. Median LDL-C achieved in pravastatin group was 2.46 mmol/l as compared to 1.60 mmol/l in atorvastatin group with corresponding CRP difference. Reflecting this, there was a 16% relative reduction (p = 0.005) in primary endpoint favoring intensive therapy. All sub-

components of primary endpoint reached to significant level except for stroke. Benefit appeared as early as 30 days after initiating Atorvastatin. The greatest relative risk reduction of 34% occurred in those with baseline LDL-C of 3.23 mmol/liter or above as compared to 7% relative risk reduction in those with baseline LDL below 3.23 mmol/liter. Liver transaminases were elevated in 3.3% of the atorvastatin group as compared to 1.15 in pravastatin group.

A to Z Study[11]

In this study of ACS patients, the phase A of the A to Z study included mandatory treatment with tirofiban followed by either unfractionated or low molecular weight heparin. These patients along with previously not randomized myocardial infarct patients were included in the phase Z trial. Patients were randomized to receive either intensive therapy with Atorvastatin 40 mg daily for 30 days followed by 80 mg Atorvastatin or standard therapy of placebo for initial 4 months followed by simvastatin 20mg thereafter. Primary endpoint in this study composed of cardio-vascular death, nonfatal myocardial infarct or readmission with unstable angina and stroke. Up to 30% discontinuation rates were seen in both arms.

Trend favoring atorvastatin with 11% risk reduction in the primary endpoint was noted but this did not reach statistical significance (p=0.14). However, a significant 25% relative reduction in cardiovascular death (p=0.05) was observed. Notably the difference in Primary endpoint was only evident after initial 4 months. Unfortunately the study was terminated before reaching power since primary end points were more slowly accrued than expected. Ten patients in the atorvastatin group developed myopathy.

The evidence from the above two studies are contrasting. The PROVE-IT 22 study suggests benefit of intensive statin therapy with a relative reduction of coronary deaths by 14% and benefits across various other subcomponents except for stroke. However, all cause mortality despite showing a trend to support intensive therapy did not reach statistical significance. There is criticism that the study was short span compared to other major trials. This is especially important if one considers TNT study, a longer study with follow up of 4.9 years, which compared intensive and standard statin therapy in stable CAD patients. TNT study demonstrated slightly higher rate of non-cardiovascular death in the intensive therapy arm which in turn neutralized any cardiovascular mortality benefit of intensive therapy. Hence, this needs to be viewed carefully as well as to consider the slightly increased adverse effects encountered with intensive therapy. Also, the comparison of Atorvastatin 80 mg with Simvastatin 40 mg would have been more appropriate since simvastatin has much better efficacy than pravastatin, is more cost effective and consequently is the most frequently used statin world over.

In A to Z study despite the study design skewed favoring intensive therapy, it did not show benefit for intensive therapy as expected. The premature conclusion of this study, objectionable study design (initial phase with placebo for comparison group could be considered unethical) and short duration of follow up are negative aspects of this study.

A recent meta-analysis[12] of the above two trials involving about 8,500 patients followed up for 2 years has indicated that there is certainly an all-cause mortality benefit from high dose statin therapy (Simvastatin 80 mg vs 20 mg and Atorvastatin 80 mg vs Pravastatin 40 mg) in ACS scenarios and this should be the usual therapeutic strategy for such patients. Besides mortality benefit, major cardiac events and hospitalization rates are also reduced. Besides cholesterol reduction, the anti-inflammatory effects of statins are also thought to be the mechanism behind all cause mortality reduction in ACS patients. Hospitalizations due to heart failure were also reduced, possibly due to favorable effects of statins on infarct dimensions and remodelling.

Intensive Statin Therapy in Stable Coronary Artery Disease Patients

The *Heart Protection study*[13] showed benefits of LDL reduction up to 1.7 mmol/liter. This formed the basis of further randomised control studies to explore if intensive statin therapy that is

frequently required to achieve the ideal targets of LDL-C is more beneficial than modest dose of usual statin.

Treat to new targets study (TNT study).[14] Individuals with clinically evident CAD successfully completed a run in phase of 8 weeks receiving 10mg of atorvastatin before randomization to receive either 10mg or 80mg of atorvastatin with median follow up of 4.9 years. Primary efficacy outcome of major cardiovascular event (combining coronary deaths, non fatal MI, cardiac arrest with resuscitation and stroke) occurred in 8.7% in the intensive group and in 10.9% of 'standard' group with a relative reduction of 22% (p=0.001). However, the all-cause mortality was almost equivalent mainly due to small increase in non-cardiovascular deaths in the intensive therapy arm (p=0.06). Adverse effects were seen in 8.1% of intensive treatment arm vs. 5.8% in 'standard' treatment arm.

Incremental decrease in endpoints through aggressive lipid lowering (IDEAL study).[15] Subjects with previous definite myocardial infarct were randomized to receive either 80 mg of Atorvastatin or 20 mg of Simvastatin and were followed up to median of 4.8 years. The aim was to enquire if there was any incremental benefit with more intensive lowering of LDL-C to 100 mg/dl. Also, a provision was made to increase Simvastatin dose to 40 mg if by the end of 24 weeks the total cholesterol was greater than 5 mmol/liter. By the end of study 23% of Simvastatin group had required this escalation. The primary end point consisted of occurrence of major coronary event defined as any coronary death, nonfatal acute MI or cardiac arrest requiring resuscitation. A non-significant 11% reduction in the primary end point (p = 0.07) was noted. However, there was significant decrease in major cardiovascular events (if stroke was included) (p = 0.02) and nonfatal acute MI. But once again, all cause death was much the same in both arms (p = 0.81). There was a higher discontinuation rate with atorvastatin 9.6% vs Simvastatin 4.2% (p = 0.01). Interesting, although mean LDL-C were lower in Atorvastatin arm (81 mg/dl vs 104 mg/dl), levels of HDL were noted to be slightly higher in Simvastatin arm.

In the TNT study, intensive statin therapy accorded a significant benefit in cardiovascular endpoints including death but, a rather, unexpected finding of small increase in non-cardiovascular deaths was noted in TNT study that nullified any cardiovascular mortality benefit. IDEAL study was hence organised to clarify this issue. Although the primary endpoint of major coronary events did not reach to significance, there was significant difference in secondary endpoint of cardiovascular deaths. However, the issue of all cause mortality remained unresolved since there was no significant difference in both arms. Higher incidence of adverse effects with intensive therapy was noted in both studies. Again the 'standard therapy' in both the studies could be considered as weak, as the lowest dose of Atorvastatin (10 mg) was used in TNT and in IDEAL study lowest dose of Simvastatin (20 mg) was used instead of a more moderate dose.

A recent metaanalysis[12] of clinical trials involving around 20,000 patients with stable CAD has proved no mortality benefit with intensive (high dose) statin therapy. However, in this group as well, there was a significant reduction in major cardiac events and admissions with heart failure.

In conclusion, intensive statin therapy in stable CAD patients should be considered in those who are deemed as 'High Risk' and also, in those in whom target LDL-C levels is not achieved with standard statin therapy.

Safety Issues

As per the most recent meta-analysis[12] of trials involving 28,500 patients, intensive statin therapy is safe and associated with a threefold increase in adverse hepatic events from 0.4 to 1.4% and a trend towards increased adverse muscular events from 0.05 to 0.11%.

In practical terms these figures are acceptable and reassuring and should allow us to administer high dose statin therapy to the suitable patients, cautiously.

Aggressive Lipid Lowering: Statin Monotherapy Versus Statin/Ezetimibe Combinations

There is now plenty of evidence[16, 17] to show that greater LDL-C reduction can be achieved by Ezetimibe+ statin combination by the dual inhibition of cholesterol absorption (Ezetimibe) and production (statin). The incidence of statin side effects is also reduced with this strategy.

Unfortunately, no cardiovascular outcome data (MACE, mortality, etc.) are available with these agents till date but some large trials are underway, involving over 21,000 patients. These studies will investigate whether the lower LDL-C levels achieved with dual inhibition of cholesterol production and absorption are associated with a reduction in the progression of atherosclerosis or occurrence of cardiovascular or renal events. These trials include different clinical groups, ranging from hyperlipidemic patients to ACS (Table 1):

So What Target of LDL Cholesterol should We Aim for?

The jury is still not out on what is the optimum level of LDL cholesterol one should aim for or, should we be using another better marker to monitor progress. The largest major Statin Trial; the Heart Protection Study[13] (HPS) showed outcome benefits up to LDL–C of 1.7 mmol/liter. HPS also demonstrated that for every 1mmol LDL Cholesterol reduction from 4 mmol up to 2 mmol there was a corresponding 25% decrease in major vascular event. This was confirmed in the meta-analyses carried out by cholesterol Trialists collaboration.[16]

Interestingly the ASTEROID study[9] with Rosuvastatin 40mg with a mean LDL Cholesterol level of 1.57 mmol/liter demonstrated corresponding benefits in atheroma regression.

In PROVE-IT TIMI 22 trial[10], about 11% of patients achieved LDL-C reductions to 1.0 mmol/l (40 mg/dl) and that intensive group had the lowest risk of MACE with no increase in adverse events. Some observational studies indicate that LDL-C of 1.3–1.9 mmol/l (50–75 mg/dl) is associated with improved longevity and an absence of atherosclerosis up to the seventh and eight decades of life. A recent meta-analysis of trials involving around 28,500 patients with ACS/Stable Angina indicated that achieving a mean LDL-C of 1.6-2.1 mmol/l (62-81 mg/dl) was safe and effective for reducing MACE.

For aggressive lipid lowering, the current usual recommendations[22] are to aim for Target LDL-C of 2 mmol/l (80 mg/dl) in those considered high risk and Target LDL-C of 1.8 mmol/l (70 mg/dl) in those who are perceived to be very high risk.

Statins and Ethnic Groups

Most of the prominent statin trials have been on European and North American Population. The only major trial that quoted a high proportion of black population (37%) was ALLHAT study[23] (mainly Primary prevention), which showed significant benefit of pravastatin compared to placebo in hypertensive black population despite not showing a significant benefit for non-black population.

Contrary to the belief of many physicians, ethnic Asian groups also require similar dose of statin as their western counterparts. Three secondary prevention studies, including Simvastatin Treats Asians to Targets Trial (STATT)[24], Singapore General Hospital Lipid Clinic Data[25] provide evidence in favor of this. In the SGH Lipid Clinic Experience, the magnitude of LDL-C reduction was similar to that seen in Non-Asian population of 4S, CARE and WOSCOPS[26] studies. The median statin dose in this study was 20mg Simvastatin and 50% required further upward titration of the dose to 40mg but even then the therapeutic target of LDL-C level of <2.0 mmol/l was achieved in only 25% of people. In STATT trials 72% required 20mg of simvastatin leaving them in a sub-therapeutic Target LDL-C of 2.6 mmol/l and further titration was required to reach therapeutic target.

A recent randomized study (IRIS)[27] trial in North American South Asian population has compared Rosuvatatin with Atorvastatin and as expected found higher LDL-C reductions to targets without any significant increase in side effects. An Indian study[28] has also investigated ezetimibe/simvastatin combination with similar results.

Is Under-Prescription and Compliance the most Important Issue?

In 4S and LIPID study, the significant reduction in mean LDL Cholesterol concentration compared to baseline, noted in the initial years, were not maintained in the subsequent years raising the doubts about compliance in the long-term, at least in a subgroup of study population. Many statin studies like TNT[14] and PROSPER[29] despite excluding non-compliant patients by run-in phase they still continued to have high discontinuation rate.

These findings have been replicated in several observational studies.[30] Moreover numerous studies have painted the picture of significant under prescription of statins even in those with high risk and especially in the elderly.[31] Also, a small proportion of Statin treated patients (about <10%) are intolerant to statins due to a non-severe adverse effect. A recent Study has shown that up to 65% of these individuals could tolerate an alternate statin if persevered but require a median of 2 switches in the statin type.[32]

In the real world, under-prescription and poor compliance may well be the biggest challenge in providing effective secondary prevention. Aggressive targeted measures and creating awareness is required to tackle this problem.

Summary of Current Status of Aggressive Lipid Lowering and Future Directions

Statin therapy has taken a long leap since the publication of 4S study. Investigators have studied various effects of this novel group of drugs in different clinical scenarios with gratifying results. There is an established role of these agents in the treatment of ACS/stable CAD, in addition to standard therapy with other agents, with proven reduction in MACE/ mortality benefits. There is enough evidence to show that "the lower the LDL, the better the long term outlook", in terms of MACE.

In comparison to the standard (moderate: e.g. Simvastatin 20 mg/day or Pravastatin 40 mg/day) therapy, a high dose strategy (i.e. Simvastatin 80 mg/day or Atorvastatin 80 mg/day) leads to:

i. Higher reduction in LDL-C levels.
ii. Regression of coronary atheroma.
iii. Higher reduction in MACE across in ACS/stable CAD.
iv. Reduction in all cause mortality (approximately 25%) in ACS only.
v. Reduction in hospitalizations with heart failure in ACS/stable CAD.
vi. Higher but acceptable risk of hepatic /muscular side effects.

Based on current evidence, an aggressive lipid lowering strategy **(to aim LDL < 1.8 to 2.0 mmol/L, 70-80 mg/dl)** is recommended for following patient groups:

i. ACS.
ii. Stable CAD with high risk profile, i.e. diabetes.
iii. Post coronary angioplasty.
iv. Post coronary artery bypass surgery.

Currently, only **Atorvastatin 80 mg/day and Simvastatin 80 mg/day** have been tested in randomized outcome trials of intensive statin therapy with positive results. However, there is no reason to believe that **Rosuvastatin,** with most potent effects, would not yield similar benefits. Interestingly, there are no outcome data comparing the high Simvastatin or Atorvastatin doses with Simvastatin 40 mg/day or Rosuvastatin. There are some cardiovascular outcome trials under way looking at Ezetimibe/Statin combinations as well. Continuing lifestyle modification and other optimal medical therapy is also essential.

As the risk of adverse events increases with maximum statin doses, especially in patients on other drugs that may increase the statin concentration, it is important to initiate a reasonable statin dose followed by appropriate titration to the LDL-C goals.

However, even with optimal LDL-C lowering, there still remains a relatively high risk of MACE.

Also, it comes without saying that there is an acute need of robust cost effectiveness study to prove value of intensive therapy before its universal acceptance, even in the setting of the developed countries.

The focus now also seems to be on HDL-C, which seems to be a stronger predictor of risk than LDL-C (Each percentage increase in LDL-C increases risk by approximately the same; however, each percentage decrease in HDL-C is accompanied by a 2–3% increase in risk). The clinical strategy of simultaneously lowering LDL-C to reduce cholesterol deposition in the vessel wall, and raising HDL-C to promote reverse cholesterol transport, might produce considerable plaque regression.[33] Newer therapies are being investigated (beyond currently available agents) to stimulate HDL-C rise as much as possible, which could be the theoretical antithesis of this review and be labelled: "Aggressive lipid elevation!!!"

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MULTIPLE CHOICE QUESTIONS

1. **Which was the first outcome study in stable CAD showing benefit from high dose statin?**
   A. A to Z
   B. PROSPER
   C. TNT
   D. MIRACL

2. **Which two drugs have been investigated in the outcome studies with aggressive lipid lowering?**
   A. Pravastatin and rosuvastatin
   B. Simvastatin and atorvastatin
   C. Lovastatin and pravastatin
   D. Rosuvastatin and simvastatin

3. **What is the recommended LDL-C lowering target for "highest risk" patients?**
   A. 2.2 mmol/L
   B. 1.5 mmol/L
   C. 1.8 mmol/L
   D. 2.0 mmol/L

4. **Which agent causes maximum reduction in LDL-C?**
   A. Pravastatin
   B. Rosuvastatin
   C. Atorvastatin
   D. Simvastatin

5. **Which condition has mortality benefit from the use of high dose statin?**
   A. Stable angina
   B. Peripheral vascular disease
   C. Acute coronary syndrome
   D. Renal artery stenosis

6. **Adding Ezetimibe to a statin:**
   A. Increases liver side effects
   B. Enhances LDL-C reduction
   C. Reduces mortality
   D. None of the above

7. **Each increment in LDL-C by 1 mmol/l (40 mg/dl):**
   A. Increases the CAD risk by 10%
   B. Decreases the CAD risk by 5%
   C. Increases the CAD risk by 1%
   D. Decreases the CAD risk by 10%

8. **IMPROVE-IT is a trial comparing outcome data for:**
   A. Ezetimibe with rosuvastatin
   B. Ezetimibe+simvastatin with simvastatin
   C. Ezetimibe + atorvastatin with atorvastatin
   D. None of the above

9. **High dose statin therapy is known to:**
   A. Reduce all cause mortality in ACS
   B. Reduce admissions with heart failure
   C. Potential for increased side effects
   D. All of the above

10. **Each 1 mmol/L increase in HDL-C:**
    A. Reduces CAD risk by 1%
    B. Increases CAD risk by 2-3%
    C. Reduces CAD risk by 2-3%
    D. Increases CAD risk by 1%