DEBATE

High-Dose Statin Therapy in Asians: *Not* as Relevant as in Western Populations

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Our practice guidelines are based on randomized control trials. Although these guidelines are implemented/ formed on scientific evidence, many a times they do not address adequately the changes required for regional and racial differences. One such example is the use of statins for Asian versus Western population. In this article, we will discuss the reasons why high-dose statin may not be required in our population.

Higher Dose Is More Efficacious: Proven Beyond Doubt by RCT

Statins as a group is one of the most prescribed drugs across all nations for primary and secondary prevention of atherosclerotic cardio/ neurovascular diseases. Over the past decade, 17 large placebo controlled trials have established that statin therapy lowers the LDL cholesterol and prevents death and cardiovascular events in patients with established coronary artery disease or who are at higher risk for the same. Nine trials have shown that higher dose is more efficacious than the lower dose of statins in reducing the myocardial infarction /death by 16% and stroke by 18% in patients with coronary disease (1). However a close look at the data of these high doses reveals that the persons on high doses of statins also achieved a lower value of LDL cholesterol suggesting that the observed effect may have to be attributed to the lower LDL level with high dose.

For example in the TNT trial 80 mg of atorvastatin was compared with 10 mg. The LDL level achieved with 80 mg dose was 2 mmol/L versus 2.6 mmol/L with 10 mg. As a result, at 4.9 years of followup, only 8.7% of patients in the higher dose versus 10.9% in the lower dose group had primary events.

Another example is the IDEAL trial (2). In this trial, 80 mg of atorvastatin was compared with 20 mg of simvastatin. In the atorvastatin arm, the LDL level was brought down from 3.15 to 2.07 mmol/L, whereas simvastatin arm achieved only 2.58 mmol/L. Obviously in this study, persons on simvastatin did not achieve the target of 2mmol/L to get the maximum benefit.

In conclusion higher dose of statins achieves greater reduction in the events by virtue of the fact that they achieve lower levels of LDL and so the benefits are more. If so then all we need to is to achieve the target level of LDL as suggested in the guidelines and the cut points should be reached with titration of the doses.

Should Statin Dose Be Titrated to LDL Level?

In the 2004 National Cholesterol Education program, NCEP expert panel has recommended that physicians *should titrate* lipid therapy to reach LDL level of 1.81 mmol/L or 70 mg/dL for patients at very high risk for cardiovascular events. We have known that all the statins available in the market today reduce the cholesterol especially the LDL cholesterol. However, they all differ in their potency. For example 20 mg of simvastatin will be equal to 10 mg of atorvostatin and 5 mg of rosuvastain for the same amount of reduction of LDL. Currently there is no evidence to support assertion that a higher dose of any particular statin is more efficacious than higher dose of any other statins, assuming equipotent dosing and equal reductions of LDL cholesterol for clinical outcomes.

The most widely recommended approach to statin therapy is "level of LDL cholesterol" based, "treat to target" strategy, in which the drug dose is titrated to

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achieve the LDL cholesterol levels. This is the basis of National Cholesterol Education Program III guidelines. The second approach is to give the drug at a fixed dose and forget it—*fire and forget policy*—which is done for population-based studies especially for primary prevention. For example in the polypill that is given for primary prevention contains a fixed dose of statin and this is given for a prolonged period, irrespective of the LDL level that is achieved. The third method is the one called *tailored treatment approach*—the risk for next 5–10 years is calculated and a fixed dose is given. This tailored approach is not a new concept. It uses statistical modeling based on patient's overall risk.

Using simulation models, it was found that simple tailored therapy of statins given to persons between the ages of 30 and 75 was more efficient and prevented CAD morbidity and mortality substantially (3). *The point is that for primary prevention we need not do complex titration, but give some statin, based on overall risk assessment.* It is likely that many would not have reached the goals and others would have overshot the target and may actually be having low level of LDL.

LDL Lowering an Effective Surrogate for Magnitude of Clinical Benefits with Statins

It is well known that statins have multiple nonlipid lowering effects such as improvement in endothelial function, anti-inflammatory effects, plaque stabilization, antioxidant effects, etc. (4). These effects, which are also known as pleiotropic effects, are believed to play an important role in producing beneficial effects seen with statins. However, a large body of evidence suggests that the net benefit seen with statin therapy is still proportional to the magnitude of LDL lowering (5). Most statin trials have shown that there is a close relationship between the differences in total cholesterol in the two arms of lipid-lowering trials and differences in cardiovascular event rates achieved. For every 1% reduction in LDL levels, relative risk for major coronary events is reduced by approximately 1%, irrespective of the clinical presentation and the baseline LDL levels (5). In the PROVE-IT TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) study, 16% reduction in the primary end-point was achieved with high-dose atorvastatin therapy compared with standard-dose pravastatin therapy even when the standard therapy was able to attain LDL levels of <100 mg/dL in majority of the patients (6). In the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial also, substantial clinical benefit seen with rosuvastatin was accompanied by equally marked LDL reduction, despite almost "normal" baseline LDL levels (7). These findings suggest that irrespective of the mechanisms underlying benefit with statins, the magnitude of LDL lowering itself may serve as a reliable surrogate measure of the magnitude of clinical benefits achieved.

Asians Require Only Small Dose of Statins: Evidence

It is well known that south Asians are at higher risk for CAD compared to other populations such as US and UK. A study done in UK, on the dose of statins showed that those Asians living in UK required a very small dose to achieve the target LDL levels. *Overall, 81% achieved LDL target with 10 mg in 4 weeks time* (8). Dose titration to 40 mg was required in only one patient. This study confirms once again that doses need not be high and small doses can achieve the target especially in populations such as ours.

Another study from USA showed that 740 subjects having origin from India, Pakistan, and Nepal displayed significant reduction in LDL target with either doses of rosvuastatin 10 or 20 mg or atorvastatin 10 or 20 mg within 6 weeks (9).

Our personal experience in India is that doses such as 40 mg are rarely written in the outpatient clinics and the most common dose on sale is either 20 or 10 mg of a given statin. Once again it re-emphasizes the fact that if we want to achieve LDL target then we need to give the drug—titrate up the dose as needed and this dose is actually very low in Asian population such as India. We do not need to give a high dose to achieve the LDL target.

Unfortunately, no clinical trial till date has adequately evaluated the clinical benefits achieved with different doses of statins in Asians. However, as mentioned in the previous section, if the magnitude of LDL lowering could serve as a surrogate for the clinical benefits achieved with statins, a relatively low-dose statin in Asians, which lowers LDL significantly, should be able to produce proportional reduction in adverse cardiac event rate also. The MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult

Japanese) trial, which was the first clinical outcome trial of statin treatment in Asians, indirectly supported these assumptions. In this trial involving hypercholesterolemic patients with no previous cardiovascular disease, a significant 33% reduction in the risk of coronary events was seen with low dose pravastatin (10–20 mg/day) treatment (10).

High Dose of Statin Has Higher Side-Effects: Incident Diabetes

In a study done to assess whether statin does increase the incident diabetes by pooling five studies showed that intensive dose of statins *was associated with an increased risk of new onset diabetes* compared to moderate dose of statin therapy. In absolute terms, this means that there will be additional two cases of diabetes per 1000 patient years. It has also been shown that high-dose atorvastatin can worsen the diabetic control. These patients had higher HbA1c levels suggesting a potential dose effect.

Sattar and colleagues have calculated that the absolute risk of developing diabetes was one case per 1000 patient years of treatment (11). To put it in another way if you treat 255 patients for 4 years, one patient may develop diabetes. This also means that 5.4 deaths due to myocardial infarction would be avoided. In a comment written by Cannon points that the cardiovascular benefit definitely outweighs the risk of developing diabetes with the use of statins (12).

High Dose of Statin Has Higher Side-Effects: Liver Enzymes

A sample of three trials is given below with threefold increase in the liver enzyme then the normal with higher doses of statins (see Table 1). The long-term large randomized control trials of atorvastatin 80 mg daily compared with lower doses of statin or placebo confirm that the excess of persistent elevations of transaminases with this dose of atorvastatin and similarly some excess with simvastatin 80 mg but have not reported any hepatitis or liver failure (13). Other side-effects on muscle are not that important as shown in a meta-analysis (14).

Risk of Malignancies at Very Low Cholesterol Levels

Although the causal link has not yet been proven, several studies have demonstrated an increase in cancer mortality at very low total cholesterol and LDL levels, particularly in Japanese. In the JLIT (Japan Lipid Intervention Trial), which had evaluated only low doses of simvastatin, an increase in total mortality was seen in hyper-responders (18). The excess mortality was predominantly due to malignancies. Similar increase in cancer-related deaths was noted in some other studies also, such as MRFIT (Multiple Risk Factor Intervention Trial), PROCAM (Prospective Cardiovascular Münster), and a few Japanese studies (19–22).

Conclusion

All statins have more or less same efficacy so far as reduction in cardiac events are concerned and is based on the LDL target levels achieved. NCEP also recommends *treat to target*. To reach the target level recommended, we need only small doses in Asians, as seen in day to day clinical practice and in the studies. Higher dose has higher side-effects especially higher incident diabetes and liver enzyme abnormalities. If we can achieve the target level of LDL as recommended by the NCEP with smaller doses of statin then why give higher dose—get more side-effects and add cost to patients. We feel that a strong case can be made for lower doses in Asians for all clinical practice except the acute coronary syndromes and what we need is to do proper randomized controlled trials on low-dose statins in Asian population.

Table 1.

Liver Enzyme Abnormalities with Statin Higher Dose vs. Lower doses

Trial name	Dose of drug	Liver enzymes with higher dose vs low dose
PROVE IT (15)	Ator 80 mg vs 40 mg	3.3% vs 1.1%
Phase Z of A to Z trial (16)	Simvo 80 mg vs 20 mg	0.9% vs. 0.4%
TNT (17)	Ator 80 mg vs 10 mg	1.2% vs. 0.2%

Based on the current evidence, the use of higher dose statin therapy should be restricted to patients with established CAD, primarily acute coronary syndrome, at this time. In all others, especially the primary prevention group, we believe that the dose of statin should be titrated to achieve the LDL levels that are recommended by the societies concerned such as ADA or ACC/AHA.

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