High Dose Statin Therapy in Asians: *Is* as Relevant as in Western Populations

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That statins should be prescribed for high-risk cardiac patients who present with an acute coronary syndrome (ACS) is a level 1A recommendation of most cardiac societies such as the Cardiac Society of Australia and New Zealand, and the American College of Cardiology. This level of recommendation is based on clinical trial evidence from several large trials like MIRACL, PROVE-IT, and A to Z. Whether high-dose statins should be used in all high-risk patients and whether this is relevant for all Asian populations is still a matter of debate.

Trials like MIRACL, PROVE-IT, and A to Z have investigated high-dose statin therapy in ACS, which represent the highest risk category of coronary heart disease (CHD) patients.

In the MIRACL trial, 3086 patients with unstable angina or non-Q-wave myocardial infarction were randomized within 4 days of the event to atorvastatin 80 mg/day or placebo and followed for 16 weeks. There was a 16% significant relative risk reduction in the primary composite endpoint (death, nonfatal MI, cardiac arrest, and worsening angina requiring rehospitalization) in the atorvastatin arm (P = 0.048) (1).

In the PROVE-IT trial, 4162 patients hospitalized with an ACS within the preceding 10 days were randomized to atorvastatin 80 mg or pravastatin 40 mg/day and were followed for a mean of 24 months. Again a 16% relative risk reduction was seen in the atorvastatin group (P = 0.005). A nonsignificant trend toward a reduction in total mortality was seen in the atorvastatin group (2.2% vs 3.2%, P = 0.07) (2).

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In the A to Z trial, simvastatin 40 mg/day was administered in ACS patients for 1 month followed by 80 mg/day thereafter, and compared with ACS patients receiving placebo for 4 months followed by simvastatin 20 mg/day. Follow-up was for at least 6 months, and up to 24 months was considered as primary endpoint. A total of 16.7% in the placebo plus simvastatin group experienced the primary endpoint compared with 14.4% in the simvastatin-only group (40 mg/80 mg). Cardiovascular death occurred in 5.4% and 4.1% patients in the two groups, respectively, but no differences were observed in other individual components of the primary endpoint. The trial concluded that although no treatment achieved the pre-specified endpoint, among patients with ACS, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of major CV events (3).

In a meta-analysis of 18,000 patients from randomized controlled trials treated with statins within 14 days of an ACS, early intensive statin therapy decreased death and CV events over 2 years (HR 0.81, 95% CI 0.77–0.87). The authors also found that the main benefit occurred between 4 and 12 months (4).

All these trials also showed that high-dose statin therapy is very safe and well-tolerated in patients with ACS across different populations.

An Important Question Is Whether These Findings Can be Expanded to Elderly Patients?

A post-hoc analysis from MIRACL compared benefits of 80 mg of atorvastatin in older (≥65 years) versus younger (<65 years) patients. Event rates were approximately two- to threefold higher in older than in younger patients. Treatment-by-age heterogeneity testing indicated no difference in treatment effect by age for any of the primary or secondary endpoints, and relative risk decreased in the primary endpoint with

atorvastatin versus placebo were similar in younger and older patients (22% vs 14%, respectively). The safety profile of atorvastatin was similar between the two age groups. These results and a greater immediate cardiovascular risk in older patients argue for early, intensive statin therapy as routine practice in older ACS patients (5).

Another Important Question Is the Mechanism of Benefit?

With regards to the mechanism of benefit of high-dose statin therapy in the setting of an ACS, we have to distinguish acute from chronic statin effects.

There is no doubt that the most important benefits are benefits of plaque stabilization due to LDL-cholesterol reduction, which is why the main benefit of statin therapy can be expected in the weeks, months, and years following an ACS. We and others have shown that plaque stabilization can be achieved with statins (6). This is especially important since there is evidence of multiple unstable plaques in patients with ACS (7). Even though the maximal lipid-lowering effect of statins occurs after weeks, some lipid-lowering effect of statin therapy occurs within 24 hours (8).

The second benefit of statins in this setting may be their acute benefits on vascular function and inflammation. Endothelial function has been shown to improve within 24 hours of therapy with atorvastatin, but also other statins (9). In addition, it is well-known that all statins reduce C-reactive protein, a marker of inflammation.

The next question is whether the benefits seen in Western populations can be extrapolated to Asian populations.

Results from many Japanese studies such as J-LIT (10), KLIS (11), MEGA (12), PATE (13), and JELIS (14) showed very similar results in Japanese subjects but it must be stated that the statin doses prescribed were generally lower because LDL levels and CV risk were lower in the Japanese population. From the results of all these trials, the Japanese guidelines recommend an LDL target of <100 mg/dL in high-risk patients which is consistent with western recommendations. Because the absolute CV risk is higher in some Asian countries like India, aggressive LDL reduction is even more likely to be relevant in those countries.

Several large studies have shown that statin therapy even at high doses is very safe in Asian population. DISCOVERY-Asia (15) was a randomized open label clinical trial with a 12-week duration and follow-up to establish the efficacy of a fixed starting dose of rosuvastatin and atorvastatin. Patients were predominantly from North Asia, mainly China. This trial showed that even large doses of atorvastatin and rosuvastatin are well-tolerated and safe in these populations.

The IRIS study (16) was a 6-week randomized clinical trial to document the efficacy of rosuvastatin compared to atorvastatin at fixed doses in South Asian population, living in the USA and Canada. This study showed that even high doses of these potent statins are safe in these populations.

Another study showed that various doses of rosuvastatin were effective and well-tolerated in 1007 Asian patients living in Singapore (17).

Conclusion

High-dose statins have been shown to be very safe and effective in Western and Asian populations.

Since a mortality benefit in pooled analysis of randomized controlled trials is apparent in high-risk patients, and very convincing data with high-dose statin therapy exists for short- and long-term CV event reduction, high-dose statin therapy should be considered in all high-risk patients in Asia.

It seems very important to achieve and maintain an LDL target of <100 mg/dL in high-risk patients, which can often only be achieved with higher dose statins and good patient compliance.

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