State of the Art

Early Statin Therapy in Patients with Acute Coronary Syndrome

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Patients who survive an acute coronary syndrome (ACS; myocardial infarction [MI] or unstable angina) are at a high risk of recurrent events. In this context, recent data from observational, as well as from randomised clinical trials, support an early benefit from statins started during hospital admission for an ACS in addition to improving long-term compliance with statin therapy.[1,2]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study addressed the question whether early initiation of treatment with atorvastatin reduced the occurrence of major cardiovascular events (death, nonfatal acute MI, cardiac arrest with resuscitation or recurrent myocardial ischaemia requiring emergency rehospitalisation) in patients with ACS. Adults (n=3086) admitted for an ACS were randomly assigned to atorvastatin 80 mg/d or placebo 24 to 96 h after an ACS and were followed-up for 16 weeks. Treatment with atorvastatin reduced the incidence of recurrent myocardial ischaemia requiring emergency rehospitalisation in the first 16 weeks compared to placebo (6.2% vs. 8.4%, p=0.02), but there were no significant differences between the two groups in the incidence of death, nonfatal acute MI or cardiac arrest with resuscitation.[3,4]

In the Pravastatin in Acute Coronary Treatment (PACT) trial,[5] 3408 patients with an ACS were randomly assigned to 4 weeks' treatment with pravastatin (20 to 40 mg/day) or matching placebo within 24 h after the onset of symptoms. Pravastatin treatment resulted in a non-significant decrease (6.4%) in the incidence of the primary endpoint (a composite of death, recurrence of MI or readmission to hospital for unstable angina within 30 days of randomisation) compared to placebo.[5]

In the Lipid-Coronary Artery Disease (L-CAD) study,[6] patients were randomised, 6 days after an acute MI and/or percutaneous transluminal coronary angioplasty (PTCA) secondary to unstable angina, to either pravastatin (combined, when necessary, with cholestyramine and/or nicotinic acid) to achieve low density lipoprotein cholesterol (LDL-C) levels of ≤130 mg/dl (n=70), or to antilipidaemic therapy determined by their family physicians (n=56). After 2 years, significantly fewer patients (odds ratio 0.28, p=0.005) in the pravastatin group experienced a clinical endpoint (total mortality, cardiovascular death, nonfatal MI, need for coronary intervention, stroke and new onset of peripheral arterial disease) compared to the control group. Furthermore, minimal lumen diameter assessed by quantitative coronary angioplasty decreased by 0.18 ± 0.28 mm in the pravastatin group, whereas it increased by 0.13 ± 0.29 mm in the control group, p<0.001).[6] The LDL levels in the pravastatin and con-

trol groups at the end of the study were 125 and 167 mg/dl, respectively.

The Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA) trial[7] examined whether atorvastatin 40 mg/day for 7 days prior to elective coronary intervention would reduce procedure-induced myocardial injury. Atorvastatin pre-treatment was associated with a significant decrease in the detection of markers of myocardial injury (creatine kinase MB, troponin I and myoglobin levels) above the upper normal limit compared with the placebo group.[7]

In phase Z of the A to Z trial,[8] early initiation of an intensive statin regimen was compared with a delayed initiation of a less intensive regimen in patients with ACS. Three to four days after an ACS, patients were randomised to receive 40 mg/day of simvastatin for 1 month followed by 80 mg/day thereafter (n=2265) or placebo for 4 months followed by simvastatin 20 mg/day (n=2232). Patients were followed-up for 6-24 months and the primary end point was a composite of cardiovascular death, nonfatal MI, readmission for ACS and stroke. No significant difference was evident during the first 4 months between the two groups for the primary endpoint. At this stage the mean LDL cholesterol level in the simvastatin only and simvastatin plus placebo groups was 62 and 124 mg/dl, respectively. However, from the 4 months to the end of the study, the primary endpoint was significantly reduced in the simvastatin only group (hazard ratio 0.75, p=0.02) compared to the placebo plus simvastatin group.[8] Therefore, among patients with ACS, the early initiation of an aggressive simvastatin regimen resulted in a favourable trend (reduction of major cardiovascular events) compared with the delayed initiation of a less intensive simvastatin regimen.

The most impressive results regarding the efficacy of the early administration of statins in patients with ACS came from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22).[9] Patients (n=4162) hospitalised for ACS within the preceding 10 days were randomly assigned to pravastatin 40 mg/day or atorvastatin 80 mg/day. The primary end point in this study was a composite of death from any cause, MI, documented unstable angina requiring rehospitalisation, revascularisation and stroke with a mean follow-up of 24 months. Atorvastatin treatment resulted in a 16% reduction in the hazard ratio of the primary end point compared with pravastatin (p=0.005).[9,10] Mortality from all causes was reduced by 28% in the atorvastatin group. Therefore, among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than a standard regimen. Surprisingly, the reduction in clinical events with the more intensive lipid-lowering therapy was apparent as early as 30 days after the start of therapy. This observation is similar to that reported in the MIRACL trial. Furthermore, the benefits derived from the intensive lipid-lowering therapy continue for at least 2 years after the ACS provided that the high-dose statin regimen is maintained. In PROVE-IT, the reduction in LDL-C was significantly (p=0.001) greater with atorvastatin (from 104 to 62 mg/dl) than with pravastatin (from 104 to 96 mg/dl) although pravastatin reduced LDL-C below the goal of 100 mg/dl that has been set by the National Cholesterol Education Program (NCEP) – Adult Treatment Panel III (ATP III). These findings indicate that such patients benefit from early and continued lowering of LDL-C to levels substantially below current target levels. The change in circulating C-reactive protein (CRP) levels was also more marked in those taking atorvastatin (from 12.3 to 1.3 mg/L) than in those taking pravastatin (from 12.3 to 2.1 mg/L).[11]

The reasons for the differences in the clinical benefit in the PROVE-IT and the A to Z trials are not well understood. One explanation is that the between-group LDL-C lowering was smaller in A to Z (66 mg/dl in the simvastatin only group vs. 81 mg/dl in the placebo plus simvastatin group at 24 months) compared to PROVE-IT (atorvastatin: 62 mg/dl vs. pravastatin: 96 mg/dl). Moreover, the CRP concentrations in the A to Z trial were similar in the two treatment groups at 30 days despite the difference in LDL-C levels. Therefore, simvastatin and atorvastatin may not have the same anti-inflammatory activity. This may have contributed to the lack of early clinical benefits in the A to Z trial. A significant (p<0.001) decrease in CRP levels was eventually seen in the intensively treated group (1.5 vs. 1.8 mg/l at 24 months) in the A to Z trial.

The early reduction in event rates in patients with ACS contrasts with the lag of approximately 1 to 2 years in statin trials conducted in patients with chronic atherosclerosis, such as 4S and HPS.

The underlying mechanisms for the beneficial effect of early and aggressive statin administration in patients with ACS may be related to the so-called pleiotropic effects of these drugs.[12,13] These effects may appear even before changes in lipid levels occur.[14] The

anti-inflammatory effects of statins (e.g. the decrease in plasma CRP levels) may stabilise vulnerable plaques which are responsible for the ACS. Indeed, statin use in patients with elevated CRP levels provides not only a larger but also a significantly earlier absolute survival benefit than statin use in patients with lower CRP levels.[15] Even a single dose of statins may significantly improve endothelial function,[16] and these drugs can reverse the coagulation and platelet abnormalities observed in patients with ACS[17] and acutely reduce myocardial reperfusion injury in vivo.[18] Furthermore, in patients with ACS in the MIRACL study, atorvastatin abrogated the risk of recurrent cardiovascular events associated with high soluble CD40 ligand levels.[19] In addition, early aggressive lipid-lowering therapy with atorvastatin for 6 months significantly reduced the plaque volume (as assessed by intravascular ultrasound) in the recent ESTABLISH study ($13.1 \pm 12.8\%$ decrease compared with $8.7 \pm 14.9\%$ increase in the placebo group, $p < 0.0001$).[20] In this study, the magnitude of plaque regression was positively correlated with the percentage of LDL-C reduction, regardless of the baseline LDL-C levels, implying that aggressive LDL-C lowering itself could be an important mechanism for event reduction by early statin therapy after an ACS.

The one-year mortality of 3585 patients who received statins after percutaneous coronary intervention (PCI) and stenting was compared with that of 935 patients who did not.[21] The mortality rate was 2.6% among patients who received statins and 5.6% among the control group. Statin therapy at discharge was associated with an odds ratio (OR) of 0.46 (95% CI = 0.33-0.65), indicating a 54% reduction in the risk of death at one year. Therefore, statin therapy improved survival after coronary artery stenting independent of patient baseline characteristics.[21]

In the Lescol Intervention Prevention Study (LIPS),[22] patients undergoing PCI were randomly assigned to receive treatment with fluvastatin 80 mg/day (n=844) or matching placebo (n=833) at hospital discharge for 3 to 4 years. Almost 50% of these patients had unstable angina at presentation. The median time between PCI and first dose of study medication was two days and median follow-up was 3.9 years. Major adverse cardiac event-free survival time was significantly longer in the fluvastatin group (p=0.01).[22]

Another important issue is the optimal time for statin administration in ACS patients. In a recent study, patients with an ACS who received statins within <24 h of presentation had a lower incidence of death,

stroke, reinfarction, heart failure and pulmonary oedema compared with delayed administration.[23] In an observational study[24] of 13871 patients receiving statins before hospital admission for a non-ST-segment elevation MI, 35.1% had treatment withdrawn during the first 24 h of hospitalisation. These patients (n=4870) had increased hospital morbidity and mortality rates relative to patients in whom therapy was continued, along with higher rates of heart failure, ventricular arrhythmias, shock and death.[24] Moreover, these patients were at similar risk compared to those (n=54635) not receiving statins before or during hospitalisation. Therefore, withdrawal of statin therapy in the first 24 h of hospitalisation for a non-ST-segment elevation MI is associated with worse in-hospital outcomes.

In a substudy of the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial in patients with ACS, those already taking statins had better short-term outcomes (decreased risk for death or nonfatal MI) than those not previously receiving statin therapy.[25] Statin therapy was associated with a reduced event rate at 30-day follow-up compared with patients without statins (adjusted hazard ratio 0.49, p=0.004). If the statin therapy was withdrawn after admission, cardiac risk increased compared with patients who continued to receive statins (2.93, p=0.005) and tended to be higher compared with patients who never received statins (1.69, p=0.15).[25]

In the Global Registry of Acute Coronary Events (GRACE) project (a large multinational observation study of patients with ACS, n=19537), patients who were already taking statins when they presented to the hospital were less likely to have ST-segment elevation or MI. Patients who continued to take statins in hospital were less likely to experience complications or die than patients who never received statins, while patients not previously taking statins who began statin therapy in the hospital were less likely to die than patients who never received statin therapy.[26] This large study shows that previous statin therapy significantly affects the severity of hospital presentation and that previous or early statin therapy favourably affects clinically relevant hospital outcomes. Interestingly, much of the observed effect associated with statin pre-treatment was lost if statin therapy was not continued during hospitalisation.

In an observational study[27] analysing data from two randomised trials (GUSTO IIb and PURSUIT), lipid-lowering treatment at hospital discharge was independently associated with a reduced short-term mortality after an ACS. Lipid-lowering therapy was

associated with a smaller proportion of deaths at 30 days (hazard ratio 0.44, p=0.001) and at 6 months (0.48, p<0.0001). After adjustment for lipid-lowering agents and other potential confounders, prescription of a lipid-lowering agent at discharge remained associated with a reduced risk of death at 6 months (0.67, p=0.023).[27]

Finally, patients enrolled in the Swedish Register of Cardiac Intensive Care who received statins at or before hospital discharge for acute MI experienced a 25% reduction in 1-year mortality compared with patients who were not receiving statins (p<0.001).[28]

Conclusions

In conclusion, barring contraindications, all patients presenting with an ACS should receive a statin as early as possible.[29] There is convincing evidence that this will not only reduce the short-term risk of events but will also result in long-term benefits. Among the latter is better compliance with statin treatment.

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