Statins before stents: Does an ounce of prevention improve outcomes?

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To prepare for a marathon, long-distance runners commonly carbohydrate load the day before as a means to optimize their glycogen stores and, hopefully, their endurance. To prepare for a percutaneous coronary intervention (PCI), accumulating evidence (1-4) suggests that it might be wise to preload with atorvastatin to reduce periprocedural myocardial injury and, hopefully, improve long-term outcomes. Runners debate the details of carbohydrate loading (should it be pasta or pancakes?) and analogously, several important questions remain unresolved about the details of pre-PCI atorvastatin use. The study by Sun et al (5) in this issue of *The Canadian Journal of Cardiology* is relevant to some of these questions.

WHAT DOSE?

In the original Atorvastatin for Reduction of MYocardial Damage during Angioplasty (ARMYDA) trial (1), atorvastatin pretreatment was given at a dose of 40 mg/day for seven days before PCI in a population of patients with stable coronary disease. In ARMYDA-Acute Coronary Syndromes (ACS) (2) and ARMYDA-RECAPTURE (3), the atorvastatin dosing schedule was 80 mg 12 h pre-PCI and an additional 40 mg just before the procedure. In the Novel Approaches for Preventing or Limiting Events (NAPLES) II trial (4), 80 mg of atorvastatin was given the day before elective PCI. In each of these four trials, atorvastatin significantly reduced post-PCI levels of markers of myocardial injury compared with placebo.

Sun et al (5) compared three loading doses of atorvastatin (80 mg given 12 h pre-PCI, 80 mg given 12 h pre-PCI plus 40 mg 2 h to 4 h pre-PCI, and 80 mg given 12 h pre-PCI plus 60 mg 2 h to 4 h pre-PCI) with placebo. All four treatment groups also received 80 mg of atorvastatin each night. The incidence of post-PCI elevations of creatine kinase (CK)-MB or troponin I levels greater than three times the upper limit of normal – the definition of myocardial infarction and the only component of the primary end point that occurred during the study – was significantly reduced with increasing loading doses of atorvastatin.

A major limitation of the study by Sun et al was the small number of patients – only 20 per treatment group, for a total of 80. The cardiology literature is replete with examples of small preliminary studies with encouraging results, followed by larger trials that failed to replicate the initial findings.

The range of loading doses (80 mg, 120 mg and 140 mg) seems too narrow to be expected to produce a difference in clinical outcomes. However, when we think about statin doses, we invariably relate them to the degree of low-density lipoprotein cholesterol lowering, and low-density lipoprotein cholesterol lowering is unlikely to be related to the mechanism of benefit of atorvastatin pre-PCI. The mechanism is largely unknown, but its effects could be linear such that a somewhat higher dose could at least theoretically make a difference for outcomes.

The maximal approved dose of atorvastatin is 80 mg/day, with 10 mg, 20 mg and 40 mg being approved starting doses. Loading doses of 80 mg to 140 mg were not reported to be associated with adverse effects in any of the three PCI trials in which they were used (2-5), with the exception of an elevated hepatic enzyme level in one case (5). A starting dose of 80 mg has been used in large clinical trials with no adverse

consequences (6,7). A total of 18,696 patients have been treated with atorvastatin 80 mg/day in clinical trials, usually for between four and five years, with an overall incidence of 1.43% for hepatic enzyme elevations greater than three times the upper limit of normal, and only four cases (0.021%) of CK elevations greater than 10 times the upper limit of normal (8). The number of patients treated with doses greater than 80 mg remains limited, and the safety at these dose levels is unclear, even though the high dose is limited to the pre-PCI setting.

WHICH STATIN?

The 80 mg dose of simvastatin is associated with an unacceptably high incidence of myopathy. In the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial (9), 52 of 6031 participants (0.9%) assigned to the 80 mg dose developed definite myopathy, defined as muscle symptoms plus CK levels greater than 10 times the upper limit of normal.

This limitation makes simvastatin relatively unsuitable for high-dose loading pre-PCI. Nevertheless, in one study from China (10), 228 ACS patients were randomly assigned to 20 mg or 80 mg of simvastatin for seven days before PCI. Patients in the high-dose simvastatin group had better Thrombolysis in Myocardial Infarction flow grades, and lower levels of troponin and CK-MB post-PCI.

Contrast-induced nephropathy (CIN) is an important complication of PCI. Three studies (11-13) have examined the effect of atorvastatin on CIN and two of them (11,12) showed benefit. In one of the trials (11), CIN was a predictor of poor outcome over a four-year follow-up period, and patients without CIN who were pretreated with atorvastatin had the best outcome.

On the other hand, the recent PLANET trials (14) indicate that high-dose rosuvastatin is associated with substantial renal risk. In the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease (PLANET 1) involving patients with diabetes and proteinuria, five of 123 patients treated with rosuvastatin 40 mg/day developed acute renal failure, and nine developed acute renal failure or doubling of creatinine levels during the 52 weeks of treatment, compared with one of 110 patients in the atorvastatin 80 mg/day group. Atorvastatin improved proteinuria but rosuvastatin did not. Estimated glomerular filtration rate worsened significantly with rosuvastatin but not with atorvastatin. In the Prospective Evaluation of Proteinuria and Renal Function in Nondiabetic Patients With Progressive Renal Disease (PLANET 2), involving patients without diabetes, estimated glomerular filtration rate also worsened with high-dose rosuvastatin but not with atorvastatin.

These results suggest that high-dose rosuvastatin might not be a good choice for loading pre-PCI. Nevertheless, in a study from Korea (15) wherein 445 ACS patients were randomly assigned to 40 mg of rosuvastatin or to no statin treatment pre-PCI, troponin T and CK-MB levels post-PCI were significantly lower in the rosuvastatin group.

WHAT IS THE MECHANISM?

The mechanism whereby a statin protects from periprocedural myocardial injury is unknown. In the ARMYDA-Cell Adhesion Molecules

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(CAM) trial (16), a subset of patients had measurements of vascular cell adhesion molecule-1, intercellular adhesion molecule-1 (ICAM-1) and E-selectin levels at seven days pre-PCI, pre-PCI after seven days of treatment, and at 8 h and 24 h after the procedure. Levels of these biomarkers were similar in the atorvastatin and placebo groups before the intervention, but at 24 h post-PCI, ICAM-1 and E-selectin levels were significantly lower in the atorvastatin-treated patients. The authors concluded that a reduction in the post-PCI endothelial inflammatory response might explain the protective effect of the statin.

Similarly, in the trial with seven days of simvastatin pretreatment (10), levels of highly sensitive C-reactive protein, P-selectin and ICAM-1 were all significantly lower at 24 h post-PCI in the more intensively treated simvastatin group. Vascular inflammation was thought to play a major role in the response to vascular injury after PCI, even before the PCI statin trials were published (17). In addition to statins, other drugs used in this setting, including acetylsalicylic acid, clopidogrel, low molecular weight heparin and angiotensin-converting enzyme inhibitors, also contribute to modulating the inflammatory response to PCI (17).

DO MINOR POST-PCI ELEVATIONS OF CK-MB AND TROPONIN HAVE PROGNOSTIC SIGNIFICANCE?

The link between elevated CK-MB levels post-PCI and subsequent cardiac events is relatively strong. In one of several recent reviews (18),

18 of 32 studies with at least six months of follow-up using elevated CK-MB as a marker indicated increased long-term cardiac mortality. In comparison, only three of 28 studies using troponin T or I showed an increase in long-term mortality with elevations, although elevations were more often associated with recurrent chest pain or myocardial infarction. However, patients with troponin elevations after PCI exhibit new irreversible myocardial injury on delayed-enhancement magnetic resonance imaging, and the magnitude of this injury correlates directly to the extent of troponin elevation (19).

Elevations in CK-MB and troponin post-PCI may be markers of a high-risk coronary anatomy and a poor long-term prognosis, and not causative of the poor outcome. If this were the case, suppression of the post-PCI increase in these markers would not be expected to improve the prognosis. Reliance on surrogate markers instead of hard outcomes has frequently led us astray.

A REASONABLE APPROACH

Based on the available data, a loading dose of atorvastatin 80 mg before PCI seems reasonable. The risk of such a treatment seems extremely small compared with the potential benefit. Higher doses may provide more benefit, but additional studies are required to confirm this. The study by Sun et al (5) should provide a stimulus for further investigations in this area.

As for the evening before the marathon, maybe just pick a very nice Italian restaurant to enjoy, without counting carbs.

REFERENCES

1. Pasceri V, Patti G, Nusca A, et al. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: Results from the ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) study. *Circulation* 2004;110:674-8.
2. Patti G, Pasceri V, Colonna G, et al. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: Results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 2007;49:1272-8.
3. Di Sciascio G, Patti G, Pasceri V, et al. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) randomized trial. *J Am Coll Cardiol* 2009;54:558-65.
4. Briguori C, Visconti G, Focaccio A, et al. Novel approaches for preventing or limiting events (Naples) II trial: Impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol* 2009;54:2157-63.
5. Sun Y, Qi G, Gao Y, et al. Effect of different loading doses of atorvastatin on percutaneous coronary intervention for acute coronary syndromes. *Can J Cardiol* 2010;26:481-5.
6. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effect of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A controlled clinical trial. *JAMA* 2001;285:1711-8.
7. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
8. Waters DD, Ku I. Early statin therapy in acute coronary syndromes. The successful cycle of evidence, guidelines, and implementation. *J Am Coll Cardiol* 2009;54:1434-7.
9. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Randomised comparison of more intensive LDL-lowering therapy with 80 mg versus 20 mg simvastatin daily in 12,064 myocardial infarction survivors. *Lancet* 2010. (In press)
10. Jia XW, Fu XH, Zhang J, et al. Intensive cholesterol lowering with statin improves the outcomes of percutaneous coronary intervention in patients with acute coronary syndrome. *Chin Med J (Engl)* 2009;122:659-64.
11. Patti G, Chello M, Pasceri V, et al. Usefulness of statin pretreatment to prevent contrast-induced nephropathy and to improve long-term outcome in patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2008;101:279-85.
12. Ozhan H, Erden I, Ordu S, et al. Efficacy of short-term high-dose atorvastatin for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. *Angiology* 2010;61:711-4.
13. Toso A, Maioli M, Leoncini M, et al. Usefulness of atorvastatin (80 mg) in prevention of contrast-induced nephropathy in patients with chronic renal disease. *Am J Cardiol* 2010;105:288-92.
14. De Zeeuw D. Different renal protective effects of atorvastatin and rosuvastatin in diabetic and non-diabetic renal patients with proteinuria. Results of the PLANET trials. 2010 European Renal Association – European Dialysis and Transplant Association Congress. Munich, June 27, 2010.
15. Yun KH, Jeong MH, Oh SK, et al. The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome. *Int J Cardiol* 2009;137:246-51.
16. Patti G, Chello M, Pasceri V, et al. Protection from procedural myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary intervention: Results from the ARMYDA-CAMs (Atorvastatin for Reduction of MYocardial Damage during Angioplasty-Cell Adhesion Molecules) substudy. *J Am Coll Cardiol* 2006;48:1560-6.
17. Kereiakes DJ. Adjunctive pharmacotherapy before percutaneous coronary intervention in non-ST-elevation acute coronary syndromes: The role of modulating inflammation. *Circulation* 2003;108(16 Suppl 1):III22-7.
18. Herrmann J. Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 2005;26:2493-519.
19. Selvanayagam JB, Porto I, Channon K, et al. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: Insights from cardiovascular magnetic resonance imaging. *Circulation* 2005;111:1027-32.