High-Dose Statins Prior to Percutaneous Coronary Intervention

A Paradigm Shift to Influence Clinical Outcomes in the Cardiac Catheterization Laboratory*

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Periprocedural myocardial infarction (MI), generally defined by consensus panels as creatine kinase-myocardial isoenzyme (CK-MB) elevation >3× the upper limit of normal (ULN), occurs in 5% to 15% of patients. It has been demonstrated that elevation of CK-MB post-percutaneous coronary intervention (PCI) is associated with increased long-term mortality, with a graded increase in risk according to the extent of elevation (1). Periprocedural MI is routinely used as an end point in clinical trials and increasingly as a quality performance metric (2). These factors have brought increasing focus on finding new methodologies to reduce periprocedural MI.

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The major etiologies of periprocedural MI include dissection, compromise of side branches due to plaque shifting, thrombosis, distal embolization, and no-reflow phenomenon. However, despite optimal management directed toward mechanical and thrombotic complications, the rate of periprocedural MI is still too high, and therapies directed to atherosclerotic and inflammatory processes in the vessel wall may provide additional benefit (3).

In that regard, in this issue of the Journal, Briguori et al. (4) report the results of the Naples II (Novel Approaches for Preventing or Limiting Events II) open-label study, which randomized 668 statin-naive patients (~10% of the population undergoing PCI from 2005 to 2008) undergoing PCI to 80 mg of atorvastatin the day prior to PCI versus no statin therapy. Patients were typical of subjects with stable angina presenting for PCI with modestly lowered low-density lipoprotein cholesterol (LDL-C) levels (124 mg/dl), advanced disease, and relatively complex procedures. A significant reduction in the primary end point, CK-MB >3× ULN, was present in the atorvastatin group compared with the control group (9.5% vs. 15.8%). The benefit was not due to an unusually higher number of complications in the control group, and likely not related to lowering plasma LDL-C levels which do not significantly decrease in 24 h.

As a result of iatrogenic plaque rupture during PCI, besides the risk of mechanical complications, many vasoactive and bioactive substances are released downstream into the microcirculation, leading to vasconstriction, endothelial dysfunction, myocardial ischemia, and necrosis. These include cholesterol clefts, thrombus, apoptotic bodies, microparticles derived from platelets and inflammatory cells, oxidized lipids (5,6), endothelin, angiotensin II, and other factors (7). In initial statin trials of primary and secondary prevention, restenosis, or acute coronary syndromes (ACS), the dosing of statin therapy was not linked to performance of PCI, and these studies did not evaluate periprocedural MI. Although it cannot be answered from this study, one has to speculate that the benefit of high-dose statins, particularly those that could accumulate deep within the plaque, is mediated by rapid and direct effects due to anti-inflammatory, antioxidative, antithrombotic, nitric oxide–sparing, immune-modulatory, and plaque-stabilizing effects on the vessel wall. These so-called pleiotropic properties of statins unrelated to changes in LDL-C have been demonstrated in vitro studies and in animal models, including showing that intravenous dosing of statins acutely reduces inflammation in a manner comparable to indomethacin (8). Removing or quenching the effects of these substances locally and downstream of the plaque would presumably result in lower ischemic events. In support of this concept, reduction in C-reactive protein and adhesion molecules has been demonstrated following PCI in subjects pre-treated with high-dose statins (9–12). However, although chronic pleiotropic properties cannot be easily examined in humans independent of statins’ lipid-lowering effects until more specific agents or molecular imaging techniques are developed, acute pleiotropic effects in humans may be easier to evaluate because LDL-C would not significantly change. Additional mechanistic studies should be performed to understand the acute effects of statins on vascular biology.

This study extends previous data in this field by demonstrating that even a single high dose of a potent statin given 1 day prior to PCI results in a 40% reduction in periprocedural MI. The 6 studies in Table 1 provide strong evidence that high doses of potent statins lead to reduction of periprocedural MI. The ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty study)
investigators (9–11,13), initially in stable angina patients, then in patients with ACS, and finally in patients already on statins, uniformly demonstrated an improvement in 30-day major adverse cardiac event (MACE) rates, which were primarily driven by a reduced rate of periprocedural MI. Furthermore, Yun et al. (14) recently showed in an open-label study that a single 40-mg dose of rosuvastatin resulted in similarly improved MACE at 30 days.

Of course, it is well established that statin therapy should be given to all patients with cardiovascular disease and in particular those undergoing PCI. Therefore, one may wonder why there is increasing emphasis on optimizing the dosage and type of statin in the periprocedural period. First, although somewhat controversial, significant elevations of CK-MB are increasingly seen by interventional cardiologists, clinical trialists, regulatory bodies, and local and national quality performance committees as an adverse event that can be minimized. Second, a sizable minority of subjects are entering the cardiac catheterization laboratory without statin therapy, even those with stable angina, as noted in Naples II. Furthermore, subjects with ACS are now routinely catheterized within 24 h of admission and are often not on statins prior to admission or on presentation to the cardiac catheterization laboratory. For example, in the study of Yun et al. (14) and ARMYDA-ACS (10), 72% and 42% of patients, respectively, presented to the hospital without prior statin therapy. Third, CK-MB is increasingly used as a metric of PCI quality, which can either reflect well or poorly on the performing operators and hospitals. This has significant implications on a variety of levels, from local and national prestige, patient referrals, training programs, and perhaps to reimbursement in the future. Interestingly, data from the American College of Cardiology National Cardiovascular Database CathPCI Registry (ACC-NCDR) (2), reflecting 231,395 patients and 463 hospitals, demonstrates that the majority of U.S. hospitals are not routinely measuring CK-MB following elective PCI. In fact, <10% of hospitals routinely measured CK-MB in all patients undergoing elective PCI, and hospitals with less frequent measurements had higher rates of periprocedural MI when enzymes were measured, suggesting a significant underestimate of the true incidence when levels are not measured routinely. A level playing field in post-PCI measurement would be a welcome addition in defining the true incidence of periprocedural MI in clinical practice.

It is to be emphasized that the major benefit of pre-PCI statin therapy is a reduction in periprocedural MI, and no study thus far was powered to assess long-term, hard end points. Although the prognostic significance of very high elevations (≥5× ULN) of CK-MB has been demonstrated (15), it has not been determined whether modest elevations, which are often clinically silent, are directly related to the index event or instead, identify patients with a particularly high-risk substrate. A sophisticated analysis of the 7,773 patients undergoing PCI from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial...
(16) demonstrated that periprocedural MI occurs in 6.0% of patients and spontaneous MI in 2.6% over a 1-year follow-up period. In unadjusted analyses evaluating 1-year mortality, spontaneous MI (16.0%), and periprocedural MI (6.0%) had higher mortality compared with patients without MI (2.6%). However, after adjusting for clinical and procedural characteristics, periprocedural MI was no longer associated with increased mortality. Patients with periprocedural MI represent subjects with more risk factors and more extensive disease and complex plaque morphology. Nonetheless, the imperative to reduce periprocedural MI is strong, as it represents a patient at higher risk of future mortality.

Armed with this knowledge, how should clinicians treat patients potentially undergoing PCI? All patients should be treated with a high dose of a potent statin as outpatients, which should be continued until the performance of PCI, or as soon as possible on arrival at the hospital. In patients previously on statin therapy, it is not unreasonable to consider upstream use of high-dose, potent statins by reloading at least 12 h prior to PCI. Whether doses of statins substantially higher than standard lipid-lowering doses will result in even more benefit is an intriguing question that can be addressed in future clinical trials. Based on the current data, a rationale for further testing of higher “anti-inflammatory” doses in well-designed studies is present. Overall, these data have begun to generate a paradigm shift so that high-dose, potent statins should no longer be viewed for patients with ACS or as a discharge prescription, but instead should be given similar priority as aspirin and clopidogrel prior to patients undergoing PCI. In the final analysis, with validation of these data with larger outcomes studies, all interested parties will benefit from this extension of the remarkable therapeutic efficacy of statins.

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