Editorial

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# Pre-Treatment with Statins for Coronary Intervention: Pleiotropy of Statins or Effect of LDL-cholesterol Reduction?

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Statins inhibit hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMCoAR), consequently suppressing cholesterol biosynthesis. Animal studies, epidemiologic studies, and clinical trials all support the low-density lipoprotein (LDL) hypothesis. The benefit of these statin drugs has greatly impacted treatment of cardiovascular diseases in primary and secondary prevention. Data from the results of Cholesterol Treatment Trialists' (CTT) have proved that a reduction of 1 mmol/L in LDL cholesterol levels yields a consistent 23% reduction in the risk of major coronary events over 5 years. In addition, several clinical and basic science investigations have clearly demonstrated that statins may provide additional benefit besides LDL reduction. Statins exert a number of protective effects, including increasing nitric oxide bioavailability, improving endothelial function, stabilizing atherosclerotic plaque, reducing adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin), and decreasing circulating biomarkers of oxidative stress and inflammation, and inhibiting thrombogenic response, the so-called 'pleiotropic effects'.[1)]

Their beneficial effects have also been demonstrated in settings of coronary intervention by preventing periprocedural myocardial and renal damage, both are complications related to inflammatory pathogenesis.

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How do periprocedural statins protect myocardium? In stable clinical situations, statins can mediate their primary benefit mainly via low-density lipoprotein reduction (the LDL hypothesis). However, in acute situations, pure low-density lipoprotein reduction cannot fully explain cardiac protection.

Statins prevent the formation of cholesterol precursor mevalonate and produce important downstream non-lipid pleiotropic effects via inhibiting HMCoAR. Mevalonate depletion limits the production of isoprenoid and decreases the formation of Rho and Ras proteins involved in intracellular signaling pathways.

Endothelium-dependent vasodilatation in human coronary arteries correlates with the susceptibility of LDL to oxidation. Many factors influence the susceptibility of LDL to oxidation, including the size and composition of LDL and susceptibility to oxidative modification. Oxidative stress inactivates nitric oxide and decreases the expression of endothelial nitric oxide synthase (eNOS) by reducing the stability of eNOS mRNA. It has been shown that oxidized LDL can down-regulate eNOS in human coronary artery endothelial cells through an effect associated with up-regulation of lectin oxidized LDL (LOX-1) receptor. Oxidized LDL increases the expression and release of ET-1. Statins have been shown to be able to reduce pre-pro-ET-1 mRNA expression in vascular endothelial cells by inhibiting Rho geranylgeranylation and reduce fibroblast growth factor induced expression of endothelin receptors in rat aortic smooth muscle cells. In addition, statins inhibit angiotensin II mediated generation of reactive oxygen species by polymorphonuclear cells and aortic smooth muscle cells.

Therefore, statin treatment likely mitigates the inflammatory cascade by decreasing vascular reactivity and stabilizing plaque, both at the site of intervention and other "vulnerable" lesions.[2)]

There are numerous less clearly established mechanisms (new or old) accounting for the beneficial effect of statins. Blood viscosity has its greatest impact through reducing blood flow in small caliber vessels. Lowering concentrations of plasma lipoproteins and fibrinogen can reduce blood viscosity that may improve blood flow (particularly in the microvasculature) which can be important

in cardio- and cerebro- vascular diseases.[3] Plaque stabilization, changes to transmembrane ion channel conduction, antioxidant and antiproliferative effect, and decrease in the parasympathetic tone may potentially account for antiarrhythmic effect of statins. Circulating endothelial progenitor cells (EPCs) have important roles in the process of vascular repair by promoting re-endothelialization following injury. In preliminary results of Eisen, a trend of higher EPC CFU levels were found in patients treated with high-dose atorvastatin both before percutaneous coronary intervention (PCI) and after PCI. These findings could account for the beneficial effects of statins given to patients prior to PCI.[4]

These biological effects are thought to be the basis of periprocedural statin myoprotection.

Although a large body of convincing evidences exist, there are controversies about whether high dose statin administration before PCI can decrease peri-procedural microvascular injury.

Lee et al.[5] performed a prospective randomized study (RESIST-ACS Trial) to investigate the mechanisms and effects of pre-treatment with high dose atorvastatin on myocardial damage in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing PCI. They found that pre-treatment with high dose atorvastatin reduced peri-PCI microvascular dysfunction verified by post-PCI index of microcirculatory resistance (IMR) and exerted an immediate anti-inflammatory effect. Multivariable logistic regression analysis identified pretreatment with high dose atorvastatin as the only independent predictor for post-PCI microcirculatory impairment.

The Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA) study was the first randomized, placebo-controlled, and double-blind prospective study that demonstrated a beneficial effect of statins in preventing myocardial damage after coronary angioplasty in patients undergoing PCI for stable angina.[6] In the NAPLES II trial, even a single high-loading dose (80 mg) of atorvastatin administered within 24 h before stenting was effective in reducing the rate of periprocedural myocardial infarction (MI).[7] Considering the extensive use of statins in primary and secondary prevention, the majority of patients undergoing PCI are already on statin therapy at the time of the procedure. The ARMYDA RECAPTURE study's multivariate analysis identified atorvastatin reload as a predictor of decreased risk of major adverse cardiac events (MACE) at 30 days. High-dose (80 mg) atorvastatin load exerted significant anti-inflammatory short-term effect in patients with unstable angina or non-Q wave acute MI which was expressed by a reduction in C-reactive protein (CRP) levels. In vitro, statins increased endothelial nitric oxide synthase activity within 48 h of exposure, with a rapid augmentation of nitric oxide bioavailability, attenuating the extent of myocardial ischemia–reperfusion injury in vivo.

In a prospectively planned sub-analysis of the ARMYDA trial, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and E-selectin plasma levels were blindly measured in 38 patients pretreated with atorvastatin prior to PCI. Atorvastatin significantly attenuated ICAM-1 and E-selectin levels after PCI, confirming the protective actions of statins on endothelial function.

In summary, experimental data demonstrated that lipid-lowering action of statins only could partly explain their beneficial effects and the so-called 'pleiotropic effects' of statins could provide clinical benefit in the setting of percutaneous coronary intervention by preventing postprocedural incidence of myocardial and renal damage.

Observational studies and more recent controlled randomized trials such as the studies of the ARMYDA group demonstrated that pretreatment with statins before percutaneous coronary intervention could reduce periprocedural myocardial infarction even in the background of chronic therapy in patients with both stable and unstable syndromes. This evidence strongly supports an upstream administration of high-dose statins in patients undergoing percutaneous coronary intervention.

Assessment of functional coronary lesion severity using sensor-equipped guidewires has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization. Coronary diagnostic indices such as fractional flow reserve (FFR, pressure derived) and coronary flow reserve (CFR, flow derived) showed high agreement with non-invasive stress testing. These indices (FFR and CFR) are based on either intracoronary pressure or flow without differentiating hemodynamic status of the epicardial stenosis from microvasculature. Therefore, assessment of microvasculature is extremely challenging due to heterogeneous patient population, a large variety of pathogenetic mechanisms, poor anatomic resolution, and potentially patchy nature of the disease. Thus, assessment of the microvasculature is primarily functional, not anatomic.

The IMR has been validated in an animal model and stable angina patients. The advantages of IMR over current methods for assessing microvascular function are its relative ease in performance and interpretation, its independence of epicardial vessel stenosis, its reproducibility, and its quantitative nature.[8] The IMR has been used in humans to assess microcirculation in various clinical settings such as acute myocardial infarction, stable angina pectoris, and after cardiac transplantation.

Fujii et al.[9] have found that 1-month pretreatment with pravastatin is associated with reduced microvascular dysfunction induced by PCI. To determine independent predictors of microcirculation damage after PCI, they performed multivariate logistic regression


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analysis and tested the following variables: pravastatin, stent size, maximum balloon inflation pressure, diabetes mellitus, C-reactive protein level, IVUS plaque burden, and creatinine level. The only independent predictor ($p<0.03$) of a low IMR (<22) was the absence of pravastatin before PCI.[9]

Statin hypothesis is the concept that statins have unique efficacy (not shared by other lipid-modifying agents) for atherosclerotic vascular disease and that their ability to reduce LDL cholesterol levels is not their only beneficial effect. However, a number of questions remain. Eagle has addressed these questions in his editorial: [10] 1) Although data support high-dose statin therapy in procedural settings, is lower dose of statin is also effective? 2) Are certain statins better at procedural protection? Theoretically, agents with greater influence on Rho or Ras kinase(s) may be of particular value considering the pleiotropism hypothesis. 3) Is the benefit of pre-procedural statins limited to particular cohorts? The NAPLES II study showed that atorvastatin loading reduced periprocedural MI only in those with elevated CRP, but not in those with normal CRP levels. Thus, should CRP elevation guide statin pre-treatment? [10]

Whether it is "pleiotropic effects of statins" or "pleiotropic effects of cholesterol reduction" is still under debate. In this regard, we need to draw a distinction between the long-term effect and the short-term acute effect of statin. The results of IMPROVE-IT have implied that, in the long term effect, other non-statin interventions are also beneficial of reducing LDL cholesterol levels. Even LDL reduction obtained by a single LDL apheresis markedly reduced C-reactive protein and ameliorated the endothelial dysfunction of coronary arteries,[11] suggesting that LDL reduction by itself can rapidly translate into a variety of biochemical or clinical benefits. In this regard, ezetimibe and the recent development of PCSK9 inhibitors might be worthy of note. The latter agents can reduce LDL-receptor degradation, thereby enhancing LDL clearance from the circulation. They have been shown to be able to reduce LDL cholesterol levels by as much as 60%.[12] Definitive clinical outcome trials with these agents are ongoing.[12]

Based on our extensive knowledge about the different effect of statins, the recent NSTE-ACS and revascularization guidelines suggest that high-risk patients can obtain more benefit from early administration of a high-intensity statin therapy such as 80 mg atorvastatin to reduce events regardless of their initial cholesterol values, which lowered low-density lipoprotein cholesterol levels by ≥50% or below LDL-C goal of <70 mg/dL (<1.8 mmol/L). The implementation of high-dose statin before diagnostic catheterization has been shown to be able to reduce the incidence of contrast induced nephropathy. This should be considered as an additional preventive measure in patients without contraindications. No clear recommendations exist about the usage of statin before coronary intervention.

In summary, the available evidence creates a convincing argument for statin treatment before coronary procedures. The results from the RESIST-ACS Trial strongly support the general opinion that no patient should undergo coronary procedures without statin therapy unless clear contraindications exist.

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